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Revolutionizing Imaging and Diagnostics: Harnessing Metallic Nanoparticles and Nanocarriers for Cutting-Edge Theranostics

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ABSTRACT

The field of medical diagnostics and therapeutics is currently undergoing a transformative revolution, driven by the rapid advancements in nanotechnology. This paper explores the promising potential of metallic nanoparticles and nanocarriers in the realm of theranostics, a fusion of therapy and diagnostics, offering unprecedented opportunities for precision medicine and patient care. The integration of metallic nanoparticles and nanocarriers into medical applications has opened new frontiers for non-invasive imaging and targeted therapy. This review provides an in-depth analysis of metallic nanoparticles, including gold, silver, and magnetic nanoparticles, highlighting their unique physicochemical properties that make them ideal candidates for imaging and therapeutic purposes. Additionally, we discuss the evolution of nanocarriers, such as liposomes, micelles, and dendrimers, and their role in enhancing drug delivery, bioavailability, and treatment specificity. The versatility of metallic nanoparticles and nanocarriers in both imaging and therapeutic applications is showcased through their utilization in areas such as cancer diagnosis, drug delivery, and the management of neurological disorders. Furthermore, their potential to enable real-time monitoring of treatment responses and disease progression is explored, empowering clinicians with essential tools for personalized medicine. Challenges and considerations related to toxicity, biocompatibility, and regulatory hurdles are also discussed, shedding light on the need for further research and collaboration between scientists, clinicians, and regulatory bodies. As metallic nanoparticles and nanocarriers continue to evolve, they promise to revolutionize the landscape of medical diagnostics and therapy, ultimately improving patient outcomes and enhancing the effectiveness of healthcare practices. This paper serves as a comprehensive overview of the current state and future prospects of these groundbreaking technologies, contributing to the advancement of theranostics and its wide-reaching implications for the healthcare industry.

Keywords: *Theranostic; Gold nanoparticles; Carbon tubes; Quantum dots; Imaging agents; Therapeutic agent; Patents.*

Introduction

Theranostic agents represent a cutting-edge innovation capable of not only diagnosing but also precisely targeting treatment. Their unique ability to simultaneously conduct imaging and therapeutic

functions has given rise to an emerging scientific discipline known as theranostics. Ongoing research explores their potential applications in the diagnosis and treatment of a wide array of diseases, including cancer, diabetes, tuberculosis, and more [1]. Theranostics offer a promising alternative to the existing heterogeneous approaches to disease treatment, which often face limitations at various stages of the disease progression. Much like how the introduction of nanotechnology has bridged the gap between diagnosis and therapy, similar to its role in fostering the development of nanophytomedicines, nanotechnology has brought about a convergence of diagnostic and therapeutic functions [2].

In recent years, nanoparticle-based theranostics has emerged as a distinct and burgeoning field of study, expanding upon the foundations of traditional theranostic agents. This extension emphasizes co-delivery and the added benefit of conducting imaging not only before or after treatment but also during the therapeutic process. Many nanomaterials already serve as diagnostic agents, and this existing capacity can be leveraged to transform them into theranostic agents. The critical requirement of effectively targeting the affected area for both therapy and imaging has united these two disciplines, making theranostics based on nanoparticles a thriving field of research [3,4] (Figure 1).

Nanoparticles stand out due to their unique property: a higher surface area-to-volume ratio, enabling them to carry diagnostic and therapeutic substances on their surfaces with remarkable efficiency [5]. While some nanoparticles possess inherent imaging capabilities, others can be customized to fulfill therapeutic functions and vice versa [6].

Various imaging modalities, including optical imaging, MRI, ultrasound, nuclear imaging, and positron emission tomography (PET), have harnessed the potential of theranostic nanoparticles. To be effective, a theranostic nanoparticle must be meticulously designed to synergize with a specific imaging modality, facilitating the conversion of photosensitizers or other light-sensitive compounds into potent therapeutic agents [6]. Nanoparticles can be deployed independently to enhance photothermal treatments or loaded with biologics and small molecule medications to achieve the desired imaging effect.

Recent strides in nanotechnology and the growing interest in personalized medicine have significantly influenced the field of nanoparticle theranostics [7]. In this article, we provide a comprehensive overview of metallic nanoparticles employed as theranostic agents and those utilized for imaging purposes. Additionally, we delve into the current patents associated with metallic nanoparticles as theranostic agents.

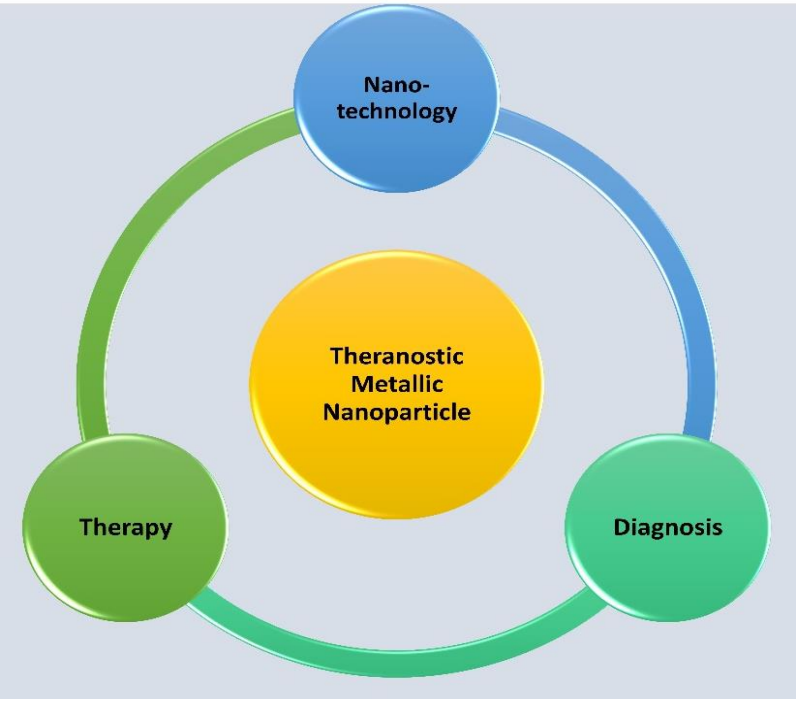

Figure 1: Diagrammatic representation of application of nanotechnology to bring therapy and diagnosis together.

Metallic nanoparticles as theranostic agents

Recent years have witnessed a surge in interest surrounding metallic nanoparticles, primarily due to their distinctive physicochemical attributes that render them promising contenders for an array of biomedical applications. A particularly exciting domain of study revolves around the utilization of metallic nanoparticles as theranostic agents, enabling them to fulfill both diagnostic and therapeutic roles.

The classification of metallic nanoparticles as theranostic agents hinges on several pivotal factors, including composition, size, shape, surface functionalization, and surface plasmon resonance (SPR). These factors serve as the bedrock for categorizing and harnessing the potential of metallic nanoparticles in this burgeoning field.

1. **Composition**: Metallic nanoparticles, fabricated from materials such as gold, silver, iron oxide, and platinum, are differentiated based on their elemental composition. Each metal offers distinct qualities that can be leveraged in theranostic applications, including optical, magnetic, and catalytic properties.
2. **Size**: The size of metallic nanoparticles plays a pivotal role in determining their biological activity. Nanoparticles can be classified as ultra-tiny (less than 10 nm), small (10-100 nm), or giant (larger than 100 nm), each size range influencing their interactions with a diverse array of biomolecules.
3. **Shape**: The geometric form of nanoparticles is another influential factor in their functionality. Shapes like spheres, rods, triangles, and cubes provide unique advantages for various purposes, making them valuable tools in theranostic procedures.
4. **Surface Functionalization**: Metallic nanoparticles can have their surfaces tailored by attaching an array of biomolecules, including antibodies, peptides, and nucleic acids. This functionalization enhances their biocompatibility, target selectivity, and therapeutic effectiveness.
5. **Surface Plasmon Resonance (SPR)**: Surface plasmon resonance refers to the resonant oscillation of conduction electrons in response to light. It is an important aspect in categorizing metallic nanoparticles. The SPR characteristics of nanoparticles, influenced by their shape and composition, can be harnessed for both imaging and therapy.

These considerations, among others, form the intricate matrix of factors used to categorize metallic nanoparticles as theranostic agents. A profound understanding of these attributes equips researchers with the knowledge needed to tailor metallic nanoparticles effectively for diagnostic and therapeutic applications, paving the way for innovative advances in healthcare.

Metallic nanoparticles based theranostic agents

Iron oxide nanoparticles as theranostic agents

Iron oxide nanoparticles (IONPs) have garnered substantial attention in recent years due to their unique attributes, positioning them as promising candidates for theranostic applications. With a magnetic core, IONPs serve multiple functions, including acting as contrast agents in MRI scans and serving as a source of heat in magnetic hyperthermia therapy. Moreover, the surface of IONPs can be functionalized with various biomolecules like antibodies, peptides, or nucleic acids, facilitating targeted delivery to specific cells or tissues.

IONPs exhibit the remarkable capacity to function as theranostic agents, seamlessly blending the diagnostic and therapeutic dimensions of treatment. This is achievable because a single IONP encapsulates both diagnostic and therapeutic capabilities, enabling real-time assessment of treatment progress and the flexibility to make necessary adjustments. Notably, IONPs, trackable through MRI, can be programmed to release therapeutic drugs in response to environmental cues, such as changes in pH or temperature.

Numerous preclinical studies have substantiated IONPs' potential as theranostic agents. For instance, IONPs have been employed to enhance the therapeutic effectiveness of chemotherapeutic drugs while reducing systemic toxicity, especially in the targeted delivery to cancer cells. Additionally, IONPs have been shown to sensitize cancer cells to radiation, thereby augmenting the efficacy of radiation therapy.

In the realm of treating diseases like cancer and heart disease, IONPs demonstrate remarkable promise as theranostic agents. Nevertheless, further research is essential to fully explore their potential and determine the most effective strategies for translating this promise into clinical practice.

Information on the production of iron oxide nanoparticles is readily available in written form. The most common method for synthesizing these nanoparticles involves the co-precipitation of Fe(II) and

Fe(III) precursors in water. The inclusion of hydrophilic polymers in the particle synthesis process enhances colloidal stability, safeguarding the nanocrystal surface from aggregation, and promoting their optimal functionality.

Iron Oxide Nanoparticles in the Role of Theranostic Agents

Bleul et al. harnessed micromixer technology to synthesize magnetic single-core iron oxide nanoparticles. These particles, with an average core diameter of 30 nm, displayed promise as a magnetic particle imaging agent, as their stability was confirmed through analytical centrifugation investigations. Furthermore, relaxometry studies established their potential as a T2-weighted magnetic resonance imaging contrast agent for multimodal in vivo imaging in theranostic applications. These particles also exhibited therapeutic potential in magnetic fluid hyperthermia, and researchers found no evidence of cytotoxicity or poor biocompatibility in the particles they created [8].

Bleul and their team utilized micromixer technology to craft magnetic single-core iron oxide nanoparticles with an average core diameter of 30 nm. Analytical centrifugation investigations indicated the stability of these particles, suggesting their utility as magnetic particle imaging agents. These nanoparticles also exhibited potential as T2-weighted magnetic resonance imaging contrast agents, enabling multimodal in vivo imaging for theranostic purposes. Furthermore, they held promise for use in magnetic fluid hyperthermia, and researchers confirmed their excellent biocompatibility and the absence of cytotoxicity [9].

Amirshaghabhi et al. employed the oil-in-water method to create chlorin e6 (Ce6)-coated superparamagnetic iron oxide nanoparticles (Ce6-SCs). These nanoparticles were used in photodynamic therapy and dual-mode imaging in mice with tumors. Ce6 effectively solubilized stable nanoclusters of hydrophobic superparamagnetic iron oxide nanoparticles without requiring carriers or amphiphiles. Optical and MR imaging confirmed the localization of Ce6-SCs within tumor cells due to enhanced permeability and retention. The researchers observed a significant slowdown in tumor progression in mice treated with Ce6-SCs [10].

Yoon et al. engineered ultra-small supermagnetic iron oxide nanoparticles loaded with epirubicin using an iron oxide nanoparticle core and a poly-aspartic acid graft copolymer. The proposed formulation demonstrated a high encapsulation efficiency and sustained release of epirubicin. EPI-P-IONP (Epirubicin poly-aspartic acid iron oxide nanoparticle) exhibited a high relaxivity value and more than a twofold contrast enhancement compared to commercially available contrast agents. These engineered particles effectively induced the death of cancer cells through the release of epirubicin. Subsequent experiments confirmed the potential of P-IONP as a theranostic agent, demonstrating nuclear uptake of epirubicin from EPI-P-IONP [11].

Shen et al. developed extremely small magnetic iron oxide nanoparticles (ES-MIONs) loaded with doxorubicin (DOX) and grafted with Poly(ethylene glycol) methyl ether (mPEG) conjugated to Dimeric RGD peptide (RGD2). These multifunctional theranostic nanoparticles exhibited promise as T1-weighted magnetic resonance imaging contrast agents and effective chemotherapeutic agents. The ES-MIONs were identified as optimal T1-weighted magnetic resonance contrast agents. They selectively targeted cancer cells, as demonstrated through laser scanning confocal microscopy and flow cytometric analysis. Nanoparticles containing DOX@ES-MION3@RGD2@mPEG3 showed potential for high-resolution T1-weighted magnetic resonance imaging and targeted cancer cell treatment [12].

Wang et al. employed a focused ultrasonic method guided by magnetic resonance to create superparamagnetic iron oxide nanoparticles. These nanoparticles were loaded with anti-epidermal growth factor receptor monoclonal antibodies to enhance targeted delivery for lung cancer treatment. The theranostic drugs were tested in an in vitro model of human lung cancer and an in vivo rat xenograft model of human lung cancer (H460). The study not only improved MRI contrast at the tumor site but also demonstrated enhanced targeting of H460 tumor cells with PEGylated SPIO NPs targeted with anti-EGFR mAb. The study also provided evidence of the usefulness of various contrast-enhanced MR techniques, including T1-weighted, T2-weighted, and diffusion-weighted imaging, in tracking treatment success in rat models treated with magnetic resonance-guided focused ultrasound [13].

Xu et al. effectively produced Ps 80 superparamagnetic iron oxide nanoparticles (Ps 80-SPIONs) loaded with doxorubicin hydrochloride (DOX). The presence of a magnetic field significantly increased the absorption of DOX@Ps 80-SPIONs by C6 cells, resulting in greater cytotoxicity in in vitro experiments. Magnetic targeting and Ps 80-mediated endocytosis successfully delivered DOX@Ps 80-SPIONs to tumor cells in vitro and in

vivo, as confirmed by ex vivo DOX fluorescence assays and prussian blue staining. Under the influence of a magnetic field, DOX@Ps 80-supramagnetic iron oxide nanoparticles completely suppressed malignant growth in vivo 28 days after treatment. This therapeutic effect was attributed to magnetic targeting and Ps 80-mediated endocytosis. The study concluded that, in combination with a magnetic field, DOX@Ps 80-SPIONs effectively suppressed glioma growth in vivo at day 28 following treatment [14].

Ali et al. developed new erlotinib-conjugated iron oxide nanoparticles (FeDC-E NPs) designed for the intracellular delivery of drugs directly to cancer cells with overexpressed EGFR. Cellular uptake and intracellular accumulation of FeDC-E NPs were validated through Prussian blue staining, transmission electron microscopy (TEM), and magnetic resonance imaging (MRI). In in vivo xenograft tests with BALB/c nude mice, researchers confirmed the ability of FeDC-E NPs to successfully inhibit tumor growth [15].

Lai et al. created superparamagnetic iron oxide nanoparticles (STM-SPIO NPs) for use in theranostics, mimicking the stem cell membrane. The formulation was developed using a gentle sonication approach that was both straightforward and effective. STM-SPIO NPs, known for their high magnetic properties, were proposed as a novel MRI contrast agent. When exposed to an alternating magnetic field, STM-SPIO NPs induced cancer cell death through magnetic hyperthermia [16].

Utilizing Quantum Dots for Theranostic Applications

Nanocrystals, known as quantum dots (QDs), possess unique optical properties due to their composition and size, which can be precisely controlled to fine-tune their optical characteristics [17]. These QDs are typically crafted from semiconductor materials drawn from groups III-V, II-VI, or IV-VI, along with metalloids, primarily around elements from groups 4 and 6. Among the extensively studied QDs, those based on cadmium (Cd) are notable for their broad excitation range, limited emission spectrum, high brightness, quantum yield, and excellent photostability. However, Cd-based QDs are associated with toxicity, which can induce cell damage, including DNA impairment. Consequently, there has been growing interest in alternative QDs made from materials such as silicon and carbon. Carbon-based QDs encompass a diverse range of materials, including carbon dots, carbon nanotube dots, graphene QDs, graphene oxide, nano-diamonds, polymer dots, and more [18].

Quantum Dot Nanoparticles in the Role of Theranostic Agents

Exploring Quantum Dots Coupled with Hyaluronic Acid for Theranostic Applications Yang and colleagues developed a multifunctional theranostic agent for cancer using hyaluronic acid-coupled magnetic Prussian blue@quantum dot nanoparticles. This involved coupling hyaluronic acid to the surface of magnetic Prussian blue nanoparticles coated with bovine serum albumin-coated CuInS2-ZnS (copper indium sulfide conjugated zinc sulfide) quantum dots. The resulting nano-agent demonstrated effectiveness as a contrast agent, enhancing sensitivity in both MRI and NIR scans. Notably, the combination of hyaluronic acid, acting as a CD44 ligand, and the magnetic core significantly improved the uptake of the nano-agent by CD44-overexpressed HeLa cells when subjected to an external magnetic field. In vivo MR imaging and NIR fluorescence studies confirmed the achievement of a high concentration of nano-agents, underlining their excellent CD44 receptor/magnetic dual-targeting capabilities [19].

Thakur and colleagues developed a cancer theranostic system by loading berberine hydrochloride into multi-fluorescent graphene quantum dots. These graphene quantum dots were synthesized using microwave heating in a single container. The researchers discovered that process parameters, such as ionic strength and heating time, influenced the photoluminescence properties. Berberine hydrochloride was loaded onto graphene quantum dots using cysteamine hydrochloride, resulting in an 88% drug loading efficiency. Cytotoxic assays, including trypan blue and MTT-based assays, confirmed the potent cytotoxic effect of the GQDs@Cys-BHC (graphene quantum dot complexed with cysteamine hydrochloride-berberine hydrochloride) complex against various cell line models, including MDA-MB-231 breast cancer cells and HeLa cervical cancer cells [20].

Additionally, a similar system was developed by Thakur et al., featuring multi-fluorescent graphene quantum dots loaded with berberine hydrochloride. These graphene quantum dots were synthesized through microwave-assisted heating in a single container. The study revealed that process parameters such as ionic strength and heating duration could affect photoluminescence properties. Berberine hydrochloride

was conjugated to graphene quantum dots using cysteamine hydrochloride, resulting in a high drug loading efficiency of 88%. Cytotoxic assays using trypan blue and MTT confirmed the potent cytotoxic effect of the GQDs@Cys-BHC complex against various cancer cell lines, including MDA-MB-231 and HeLa cells [21].

Shao and colleagues developed a non-invasive theranostic imaging system for HSV-TK/GCV suicide gene therapy in liver cancer. Their system utilized folate-targeted quantum dot-based liposomes, resulting in the successful formulation of a folate-modified theranostic liposome (FL/QD-TK). This liposome incorporated the herpes simplex virus tk suicide gene covalently linked with near-infrared fluorescent CdSeTe/ZnS (cadmium selenium tellurium complexed zinc sulfide) core/shell quantum dots. The specificity and safety of FL/QD-TK for liver cancer were validated through in vitro and in vivo experiments. The study reported enhanced tumor imaging and potent inhibition of Bel-7402 mouse xenografts that overexpressed folate receptors when using the FL/QD-TK system, without any systemic effects [23].

Furthermore, Bansal et al. developed an innovative fluorescent theranostic tool for cancer using a biosurfactant-conjugated graphene quantum dot system. They synthesized graphene quantum dots through a bottom-up method involving the pyrolysis of citric acid. These dots were subsequently conjugated with folic acid and biosurfactant. The study found that this new formulation effectively targeted tumor cells while sparing healthy cells. Biosurfactant-conjugated graphene quantum dots exhibited a 50% reduction in cellular viability within 24 hours, as confirmed by cytotoxic assays using trypan blue and MTT. Drug internalization tests using confocal laser scanning microscopy showed that folic acid conjugation improved the tumor cell specificity of the bioconjugated graphene quantum dots [24].

Gold Nanoparticles for Theranostic Applications

Gold nanoparticles have garnered significant attention in various fields, such as surface-enhanced Raman spectroscopy and computed tomography, due to their unique properties. These nanoparticles can be tailored into various shapes, including rods, spheres, cages, cubes, and wires, each influencing their imaging capabilities based on physical characteristics. Surface changes on gold nanoparticles are often facilitated through the strong interaction of thiol groups with gold. Bifunctional molecules with amine/carboxyl terminations and thiol-terminated portions are commonly used, with the thiol-terminated section binding to the nanoparticle surface and the exposed amine/carboxyl-terminated portion available for conjugation. In some cases, the entire particle can be prethiolated to enable biomolecule loading. Monodentate thiol is often used to ensure stable attachment of gold via ligand. Figure 2 illustrates a typical gold nanoparticle loaded with a drug and featuring a radiodiagnostic agent [25].

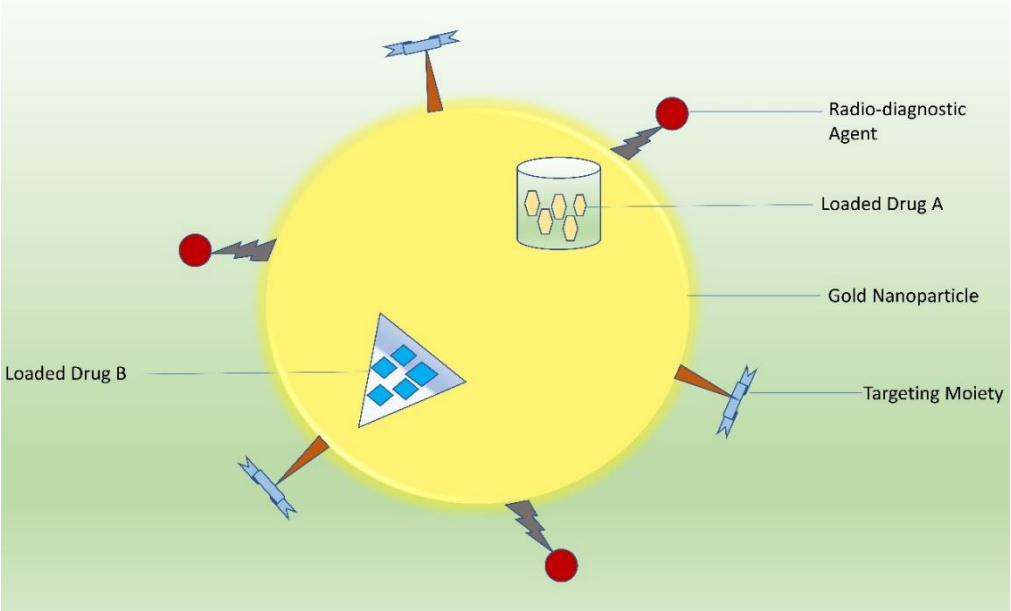

Figure 2: A typical gold nanoparticle fabricated with radio-diagnostic and therapeutic agents.

Theranostic Applications of Gold Nanoparticles

The study by Theodosiou et al. focuses on the development of theranostic agents for drug delivery and imaging using gold nanoparticles. The researchers designed and manufactured gold nanoparticles loaded with a pH-sensitive polymeric material, P(MAA-co-MBA-co-AA) (methacrylic acid-co-N,N′-Methylenebis (acrylamide)-co-acrylic acid). They accomplished gold nanoparticle loading and in situ synthesis through distillation precipitation copolymerization. These gold nanocrystals included doxorubicin, a chemotherapy drug. The survivability of these gold nanoparticles, doxorubicin-loaded gold nanocrystals, and doxorubicin alone was assessed using HEK-293 human embryonic kidney cells and MCF-7 breast cancer cells. The results indicated that gold nanocontainers were localized in the cytoplasm of MCF7 cells after 1 hour of treatment, whereas gold nanocontainers loaded with doxorubicin were situated in the cell nucleus [25].

Davidi et al. introduced cisplatin-conjugated gold nanoparticles as potential multifunctional agents for medication delivery, radiosensitization, and tumor imaging in head and neck tumor treatment. In vitro experiments were conducted to evaluate the cytotoxicity and tumor cell penetration of gold nanoparticles loaded with cisplatin and glucose. In vivo imaging and assessments of tumor growth were performed. The researchers found that this new formulation exhibited effective tumor cell penetration and cytotoxicity, suggesting an increased anti-tumor effect when radiation was combined with cisplatin and glucose-loaded gold nanoparticles [26].

Heo et al. developed gold nanoparticles loaded with paclitaxel, biotin receptors, and rhodamine B conjugated to beta cyclodextrin for their application as theranostic agents in cancer treatment. Paclitaxel was complexed with beta cyclodextrin and then conjugated to gold nanoparticles. Various surface functionalized gold nanoparticles were created and tested for their efficacy against cancer cell lines, including A549, HeLa, and MG63. Cell viability testing, fluorescence-activated cell sorting (FACS), and confocal laser scanning microscopy (CLSM) supported the researchers' conclusion that these gold nanoparticles exhibited significant theranostic potential in cancer therapy and diagnosis [27].

Bogdanov Jr. et al. employed methoxy polyethylene glycol-graft (MPEG) grafted poly(L-lysine) to stabilize gold nanoparticles. The produced gold nanoparticles remained dispersed within endosomes even after exposure to blood proteins and phosphate. These stabilized gold nanoparticles exhibited low toxicity to endothelial cells and dose-dependent toxicity to epithelioid cancer cells. The labeling of these nanoparticles with 99mTc aided in imaging their biodistribution, revealing dose-dependent blood circulation. The researchers found that these particles were biocompatible, did not aggregate, and had potential applications in biomedical theranostic cancer therapy and imaging [28].

Suvarna et al. devised a unique glucose-capped gold nanoparticle system using a simple room-temperature approach. Various characterization techniques, including transmission electron microscopy, Fourier transform infrared spectroscopy, dynamic light scattering, selected area electron diffraction, and ultraviolet-visible spectroscopy, were employed to assess the produced gold nanoparticles. Cytotoxicity of these nanoparticles was evaluated across different cell lines using a 3-(4, 5-dimethylthiozol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay [29].

To enhance ultrasound/MR imaging, photothermal imaging, and photodynamic therapy for breast cancer, a unique formulation of Her2-functionalized gold nano-shelled hybrid magnetic nanoparticles was created by an undisclosed team. This formulation included perfluorooctyl bromide, SPIONs, PLGA nanoparticles coated with a gold nano-shell, and anti-Her2 antibodies. Cell-targeting tests confirmed the specific binding of these nanoparticles to Her2-positive human breast cancer SKBR3 cells. The formulation also exhibited a dual-modal imaging effect at the cell level, and it was shown to be effective in targeted photothermal cytotoxicity, killing SKBR3 cells when exposed to a near-infrared laser [30].

Gao et al. developed a hybrid gold nanoparticle on graphene oxide for guiding photothermal therapy (PTT) using fluorescent and photoacoustic imaging. The matrix metalloproteinase-14 substrate was linked to a near-infrared dye (Cy5.5), enhancing the photothermal effect in the graphene-gold hybrid. After intravenous injection of the complex in SCC7 tumor-bearing mice, high fluorescence and photoacoustic signals were detected in the tumor region. Laser irradiation further confirmed its biological potential as a cancer theranostic agent, demonstrating excellent tumor suppression [31].

Review of Carbon Nanotubes-Based Theranostic Agents

Carbon nanotubes offer versatile applications in theranostics, encompassing photoacoustic imaging,

Raman spectroscopy, and drug delivery. The utilization of extreme oxidative conditions for creating anchoring sites often results in surface flaws on carbon nanotubes. Their aromatic and hydrophobic properties make them an ideal platform for non-covalent compound attachment. Various salts have been explored for forming homogeneous aqueous solutions with carbon nanotubes, with sodium dodecylbenzene sulfonate emerging as an effective choice. Biocompatibility and efficiency have driven extensive research into ligands, particularly PEGylated phospholipids.

Liu et al. devised an effective theranostic agent by modifying polyethylene glycol with mesoporous silica-coated single-walled carbon nanotubes for cancer treatment. Doxorubicin, an anticancer drug, was applied to the porous surface. Near-infrared stimulation released doxorubicin, leading to anticancer activity. In vivo experiments confirmed the accumulation of the compound in tumor cells after intravenous injection, supported by magnetic resonance and photoacoustic imaging, demonstrating synergistic anti-tumor activity [32].

Wang et al. developed carbon nanotubes coated with manganese oxide, showing potential as lymph mapping agents for photothermal therapy of tumor metastasis. T1-weighted magnetic resonance mapping of manganese oxide effectively identified regional lymph nodes following local injection. Near-infrared imaging revealed metastatic lymph nodes, confirming the compound's multifunctionality as a theranostic agent for mouse models of lymph node metastases [33].

Liang et al. created dye-conjugated single-walled carbon nanotubes for near-infrared-guided photothermal treatment in breast cancers. These carbon nanotubes exhibited stability and low cytotoxicity, with effective tumor suppression in both in vitro and in vivo experiments using near-infrared imaging to guide photothermal therapy [34].

Xie et al. employed evans blue to formulate a single-walled carbon nanotube complex for fluorescence imaging and photodynamic therapy of cancer. The complex contained albumin/Chlorin e6, enabling photoacoustic and fluorescence imaging. The combination of photodynamic therapy and photothermal therapy proved effective in tumor ablation and reduced recurrence [35].

Delogu et al. explored a novel functionalized multiwalled carbon nanotube as an ultrasonic contrast agent, demonstrating its long-lasting ultrasonic contrasting properties, superior to single-walled carbon nanotubes or pristine multiwalled carbon nanotubes made from graphene oxide. The carbon nanotubes were found to be highly echogenic and non-toxic in ex vivo experiments in pigs [36].

Chen et al. enhanced the biocompatibility and stability of single-walled carbon nanohorns using poly(maleic anhydride)-alt-1-octadecene-poly(ethylene glycol). The complex exhibited improved photothermal and photoacoustic imaging, attributed to high near-infrared absorption. Its prolonged circulation time, penetration, and retention action led to tumor accumulation, allowing effective photothermal tumor ablation without major complications [37].

Zhang et al. produced and tested multi-walled fluorescent magnetic carbon nanotubes for achieving photothermal and dual-modal imaging and chemotherapy of cancer cells in vivo. The nanocomposites, containing doxorubicin, served as a drug delivery system with heat-induced drug release, NIR and pH-responsive drug delivery. The complex exhibited synergistic photothermal and chemotherapeutic tumor eradication, demonstrating its potential for targeted cancer treatment upon near-infrared irradiation [38].

Review of Silica Nanoparticles-Based Theranostic Agents

Silica has long been recognized in the medical field for its potential as an implant material due to its reputation for safety. Precise manipulation of morphological factors allows for the creation of optimized silica nanoparticles. While silica nanoparticles are not imaging agents on their own, they serve as a versatile foundation for loading molecules with both imaging and therapeutic capabilities. The common methods for producing silica nanoparticles involve the condensation and hydrolysis of tetraethyl orthosilicate. Co-precursors like mercaptopropyl methoxysilane or aminopropyl trimethoxysilane can be coagulated with tetraethyl orthosilicate to introduce thiol or amine groups on the particle surface during the silica functionalization process. Additional functionalization can be achieved by grafting compounds like Gd-DTPA and organic dyes onto the silica particle matrix to create magnetic or optically active agents.

Ho Hong et al. developed an activatable theranostic agent by loading indocyanine green onto mesoporous silica nanoparticles. Singlet oxygen production and near-infrared fluorescence were used to return the complex to its initial state. Energy transfer via fluorescence resonance played a role in indocyanine

green's extracellular non-fluorescent and non-phototoxic behavior. Upon endocytosis into cancer cells, the nanoparticle became highly phototoxic and fluorescent, enhancing its theranostic efficacy in cancer therapy [39].

He and colleagues encapsulated a ruthenium polypyridyl complex within mesoporous silica nanoparticles for targeted cancer imaging and treatment. The addition of the RGD peptide enhanced cellular uptake and selectivity between normal and malignant cells. The complex exhibited high toxicity to cancer cells that overexpressed the integrin receptor. Once internalized, the nanoparticles released ruthenium polypyridyl into the cytoplasm, triggering cancer cell apoptosis. Ruthenium polypyridyl's autofluorescence allowed for direct monitoring of drug delivery, supporting its theranostic application [40].

Mignot et al. used a top-down approach to synthesize multifunctional gadolinium-based silica nanoparticles. Various characterization techniques were employed to confirm the dissolution of the oxide core and the chelation of gadolinium to the DOTAGA complex. The study's findings suggested that this complex holds promise for image-guided radiation therapy [41].

Milgroom et al. investigated mesoporous silica nanoparticles encapsulating the monoclonal antibody Herceptin® for ultrasound imaging and targeted therapy against breast cancer. The nanoparticles exhibited tumor-specific cytotoxicity and targeted binding to HER2+ cancer cells, demonstrating their stability, biocompatibility, and theranostic potential in breast cancer cells [42].

Kempen et al. explored mesoporous silica nanoparticles with theranostic properties, enhancing stem cell survival and delivering insulin-like growth factor after ultrasound or magnetic resonance imaging. These nanoparticles improved cell survival and could be guided into the peri-infarct zone for implantation, providing a promising avenue for treatment [43].

Pasha et al. investigated a novel platinum(II) based aggregation-induced emission chemical encapsulated in mesoporous silica nanoparticles for potential use as a cancer theranostic agent. The compound was designed with an anti-EpCAM aptamer on the surface for efficient targeting of malignant cells. This newly created compound exhibited increased apoptotic cell death and improved intracellular fluorescence [44].

Chan et al. created multifunctional mesoporous silica nanoparticles for potential theranostic use. These nanoparticles exhibited both magnetism and fluorescence when doped with gadolinium and europium. The addition of folic acid facilitated targeted delivery to malignant cells, and the inclusion of camptothecin provided anti-cancer activity with regulated drug release. In vitro and in vivo studies supported the promise of this system for dual imaging and targeting [45].

Utilizing Metallic Nanoparticles for Imaging

Metallic nanoparticles hold significant promise in various imaging modalities, including Magnetic Resonance Imaging (MRI), Optical Imaging (OI), Computed Tomography (CT), Ultrasound (US), Positron Emission Tomography (PET), and Single Photon Computed Tomography (SPCT). These nanoparticles can be paired with intrinsic therapeutic properties or engineered to carry therapeutic agents for effective theranostic applications, as illustrated in Figure 3.

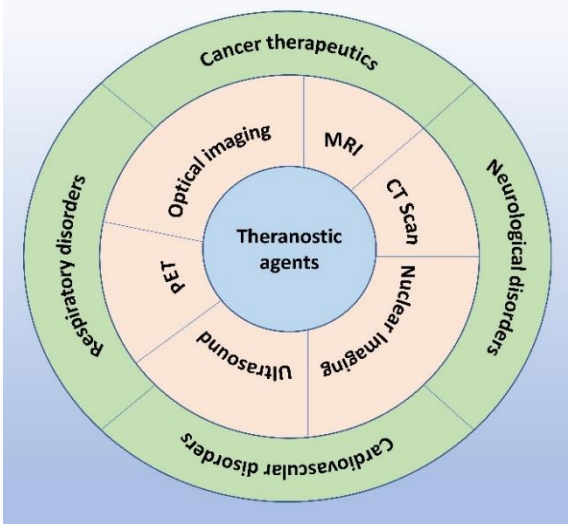

Figure 3: Application of theranostic agents in different diseases and diagnostic purposes.

Optical Imaging:

Optical imaging is a cutting-edge noninvasive method for high-resolution imaging of organs and tissues, down to the cellular level. This technique detects photon emissions from Raman and fluorescent bioluminescence probes in the visible and near-infrared spectrum, offering a safer and cost-effective alternative to X-rays. Optical imaging can be performed at various wavelengths and resolutions, often in conjunction with other imaging modalities. Near-infrared imaging, specifically between 700 and 900 nm, is commonly

used for in vivo imaging of metallic theranostic nanoparticles to overcome limitations like limited penetration depth and interference by heme groups, proteins, and water.

Prigodich et al. conducted research on nanoflare gold nanoparticles loaded with antisense oligonucleotides targeting the cancer-fighting gene survivin's messenger RNA (mRNA). This approach demonstrated increased fluorescence in the presence of the target, highlighting its potential to block mRNA translation effectively.

Huang et al. developed a silica-based hyaluronic acid nanoparticle for multimodal imaging of tumor targeting. This system employed labeled mesenchymal stem cells and successfully demonstrated its ability to target tumors through optical, PET, and MRI imaging.

Magnetic Resonance Imaging (MRI):

MRI is a low-risk imaging method based on the relaxation of hydrogen nuclei in water under an external magnetic field. Functionalizing nanoparticles with gadolinium can reduce relaxation times, providing high spatial resolution and sensitivity. This technique has been valuable for tracking cell treatments and monitoring drug responses.

Kaittanis et al. created iron oxide nanophores loaded with cancer drugs and found a direct correlation between the drug amount and T2 and T1 nuclear magnetic resonance proton relaxation periods. The release of doxorubicin and fluorophores was successfully monitored in a prostate cancer cell line.

Crisci et al. investigated the use of supramagnetic iron oxide nanoparticles in dendritic cells to induce functional immune responses in pigs. They confirmed the tracking and immunization of dendritic cells using magnetic resonance imaging in pigs.

Ultrasound:

Ultrasound is known for its reliability, speed, and affordability as an imaging option. It involves the transmission of high-frequency sound waves through the skin, which are then recorded as echoes from internal organs. Ultrasound is commonly used for intravascular ultrasonography to locate internal organs.

Gao et al. utilized ultrasound to create MnO2 nanoparticles for photodynamic therapy, targeting cancer cells with the production of reactive oxygen species upon exposure. This approach has shown potential for image-guided cancer treatment.

Kempen et al. explored mesoporous silica nanoparticles loaded with insulin-like growth factor for cardiovascular disease therapy, demonstrating enhanced cell tracking and imaging resolution using ultrasound and MRI.

Nuclear Imaging:

Nuclear medicine imaging employs radio-labeled tracers or radionuclides for procedures like SPECT and PET, recording gamma rays emitted by these radionuclides to create 3D images.

Xie et al. developed functional iron oxide nanoparticles capable of PET, MRI, and near-infrared fluorescence imaging, showcasing their potential for imaging and therapy in a tumor area.

Computed Tomography (CT):

CT scans are often used in conjunction with other imaging modalities, and they rely on x-ray attenuation properties of tissues. High-atomic-number nanoparticles like gold, iodine, and bismuth are studied as CT contrast agents.

Kim et al. designed gold nanoparticles coated with glycol-chitosan for use as a CT contrast agent to image and treat thrombi. They targeted tissue plasminogen activator to enable imaging and treatment of cerebrovascular thrombi.

Recent Patents:

Metallic nanoparticles as theranostic agents have gained substantial attention, leading to numerous patent applications. These patents cover the use of metallic nanoparticles in various theranostic applications, including imaging and therapy. Notable examples include using gold nanoparticles modified with a DNA hairpin to release medication upon target molecule hybridization and the development of nanoprobes for overcoming multidrug resistance in cancer. These patents reflect the ongoing innovation and research in the field of metallic nanoparticles as theranostic agents (Table 1).

Patent Developments in Metallic Nanoparticle-Based Theranostic Agents

A range of patents highlights the advancements in metallic nanoparticle-based theranostic agents and their applications in various fields:

1. **Patent US10568970B2 (Boston University)** discusses theranostic compositions. It involves coating a Janus nanoparticle with a microbubble

capable of ultrasonography or magnetic resonance imaging and loading it with a therapeutic agent like nucleic acid [63].

2. **Patent US20200383929A1 (University of California)** describes mesoporous silica nanoparticles with a lipid bilayer coating for payload delivery. The lipid bilayer provides structural integrity and traps the payload agent within it [64].
3. **Patent US20200271655A (Arizona Board of Regents of ASU)** introduces folic acid-functionalized copper sulfide nanoparticles designed for ovarian cancer cell flow detection. These hybrids are employed in photoacoustic flow cytometry to detect ovarian cancer cells [65].
4. **Patent US20200230071A1 (University of California)** outlines methods for producing hollow metal nanospheres. These nanospheres, created from a cobalt-based nanoparticle nucleus with a metallic shell, can be oxidized to form hollow metal nanospheres [66].
5. **Patent US20200206358A1 (Leland Stanford Junior University)** focuses on long-circulating theranostic agents designed for diagnosing and imaging metastatic tumors. These agents incorporate a TMTP1 peptide conjugated to an albumin-binding moiety, allowing for the conjugation of a metal ion with diagnostic properties [67].
6. **Patent US20200101177A1 (Northwestern University)** discusses magnetic nanocomposite compositions with a supramagnetic nucleus and a shell of ferrites featuring varying magneto-crystalline anisotropy [68].
7. **Patent US20200101176A1 (University of Michigan)** describes small, highly homogeneous nanomedicine compositions for therapeutic, imaging, and theranostic applications. These compositions can be visualized with magnetic resonance imaging and are tailored to target F3-cys [69].
8. **Patent US20190317167A1 (Mars Sciences Ltd.)** explores superparamagnetic particle imaging and its applications in quantitative multiplex stationary phase diagnostic tests. These nanoparticles can send and receive information and incorporate a hybrid point-of-care chip [71].

Table 1: List of recent patents, publication title, inventor/assignee and year of publication of patents on metallic nanoparticles based theranostic agents since 2016.

Publication numbers	Current Assignees	Inventors	Title	Publication dates	Reference
US20160243254A1	Massachusetts Institute of Technology	Natalie Artzi, João Conde, Nuria Oliva	Theranostic Nanoprobes for Overcoming Cancer Multidrug Resistance and Methods	2016	[62]
US10568970B2	Boston University	Joyce Y. Wong, Ragnhild D. Whitaker, Nelson Ruiz-Opazo, Victoria L. M. Herrera	Theranostic compositions and uses thereof	2016	[63]
US20200383929A1	University of California	Andre E. Nel, Huan Meng, Xiangsheng Liu	Mesoporous silica nanoparticles with lipid bilayer coating for cargo delivery	2020	[64]
US20200271655A	Arizona Board of Regents of ASU	Barbara Smith, Joel Lusk	Folic acid functionalized copper sulfide nanoparticles for the detection of ovarian cancer cells in flow	2020	[65]

US20200230071A1	University of California	Sarah Lindley, Jin Zhang	Methods of producing hollow metal nanospheres	2020	[66]
US20200206358A1	Leland Stanford Junior University	Yesen Li, Zhen Cheng	Long-circulating theranostic agents for diagnosing and imaging metastatic tumors	2020	[67]
US20200101177A1	Northwestern University	Vikas Nandwana, Vinayak P. Dravid	Magnetic nanocomposite compositions	2020	[68]
US20200101176A1	University of Michigan	Thomas Hopkins, Scott D. Swanson, Raoul Kopelman	Small Highly Uniform Nanomedicine Compositions for Therapeutic, Imaging and Theranostic Applications	2020	[69]
US10786582B2	Northwestern University	Thomas J. Meade, Matthew W. Rotz, Robert J. Holbrook	d(III)-dithiolane gold nanoparticle conjugates	2019	[70]
US20190317167A1	Mars Sciences Ltd	Ronald T. LaBorde, Yu Ge, Kevin N. Walda	Superparamagnetic particle imaging and its applications in quantitative multiplex stationary phase diagnostic assays	2019	[71]

Conclusion and Future Perspectives

While significant progress has been made in developing theranostic agents inspired by metallic nanoparticles, several challenges must be addressed to bring these innovations to clinical applications. Although metallic nanoparticles have demonstrated promise in preclinical trials, there is still a gap to be bridged before successful clinical trials are achieved.

Recent advancements allow for the precise loading of drugs onto metallic nanoparticles, enabling targeted delivery and controlled release in conjunction with diagnostic and imaging capabilities. Nevertheless, further research is needed to enhance the development and safety of metallic nanoparticles in clinical applications.

Designing metallic nanoparticles as theranostic agents presents challenges, including ensuring stability and controlled drug release, addressing potential toxicity associated with nano-sizing, and mitigating behavioral, physiological, and metabolic complications. Nonetheless, with cutting-edge methodologies, researchers are successfully developing metallic nanoparticles that incorporate therapeutic agents and diagnostic capabilities.

The substantial number of patents filed each year for nanoparticle-based theranostic agents reflects the global interest in this evolving field. Metallic nanoparticles' dual potential for diagnosis and therapy continues to gain traction worldwide.

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