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Efficacy of Metallic Nanoparticles and Nanocarriers as an Advanced Tool for Imaging and Diagnosis: Insight into Theranostic Applications

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ABSTRACT

The development of nanotechnology has brought diagnosis and therapy closer together, making theranostic compounds a promising area of study. Theranostic substances can both diagnose and treat a patient's condition. For their potential use in treating a wide range of ailments, including cancer, TB, diabetes, etc., metallic nanoparticles are currently the subject of intensive research. Modern nanotechnology allows for the precise assembly of medicinal chemicals onto metallic nanoparticles, which can then be used for targeted drug delivery, illness detection, and even imaging. Problems that must be solved before metallic theranostic agents can be successfully implemented in clinical settings include their complicated design, instability, toxicity, drug release regulation, mass production, and the potential for behavioral, psychological, and metabolic side effects. This article reviews the recent progress made in using metallic nanoparticles like gold, carbon, and iron oxide nanoparticles as theranostic agents. We also provide a brief summary of the various imaging properties of metallic nanoparticles. Finally, this in-depth analysis discusses new patents associated with metallic nanoparticles as a theranostic agent.

Keywords: *Gold nanoparticles; Iron oxide nanoparticles; Carbon nanotubes; Quantum dots; Imaging agents; Patents.*

Introduction

Theranostic agents can perform diagnostic testing in addition to targeted treatment. Due to their capacity to simultaneously perform imaging and therapeutic activities, theranostics have recently emerged as a new scientific discipline. Research into their potential use in the treatment and diagnosis of diverse diseases as cancer, diabetes, tuberculosis, etc. is ongoing [1]. Theranostics offer a promising alternative to the current heterogeneous disease treatments, which have limitations at various points in the disease's course. Similar to how it encouraged the creation of nanophytomedicines, the advent of nanotechnology has brought diagnosis and therapy closer together [2]. Nanoparticle-based theranostics have emerged as a distinct field of study in recent years. In reality, it is an expansion of classic theranostic agents, with an emphasis on co-delivery. It adds the benefit of imaging not just before or after therapy, but also during it. Many nanomaterials are already in use as diagnostic agents, and this fact could be utilised to their advantage by

transforming them into theranostic agents. The fact that effective accumulation in the sick area is necessary for both therapy and imaging has united the two disciplines. Theranostics based on nanoparticles is currently a flourishing field of study [3,4].

Nanoparticles are special because their larger surface area to volume ratio makes it possible for them to carry both diagnostic and therapeutic substances on their surfaces [5]. The imaging properties of many nanoparticles are inherent, and others can be tailored to carry out therapeutic tasks and vice versa [6].

Optical imaging, MRI, ultrasound, nuclear imaging, and positron emission tomography (PET) are only few of the imaging modalities that have made use of theranostic nanoparticles. For a theranostic nanoparticle to work, it must be designed to work in tandem with a specific imaging modality to convert photosensitizers or other light-sensitive molecules into highly poisonous compounds [6]. Nanoparticles can be employed to enhance photo thermal treatment on their own, or they can be loaded up with biologics and small molecule medicines to provide the desired imaging effect.

Recent developments in nanotechnology and rising interest in personalized medicine have had a significant impact on the study of nanoparticle theranostic [7]. In this article, we present a comprehensive overview of metallic nanoparticles used as theranostic agents and metallic nanoparticles used for imaging. Finally, the study discusses current patents involving metallic nanoparticles as a theranostic agent.

Classification of metallic nanoparticles as theranostic agents

In recent years, metallic nanoparticles have received a great deal of attention because their distinctive physicochemical features make them promising candidates for a wide range of biomedical uses. The use of metallic nanoparticles as theranostic agents, which may perform both therapeutic and diagnostic tasks, is an exciting new area of study.

Composition, size, shape, surface functionalization, and surface plasmon resonance (SPR) can all be used to categorize metallic nanoparticles as theranostic agents. Nanoparticles made of metals including gold, silver, iron oxide, and platinum can be categorized according to their composition. Different metals have different qualities that can be used in theranostic procedures, such as optical, magnetic, and catalytic ones. Metallic nanoparticles' biological activity is highly dependent on their size because of the wide variety of biomolecules they can interact with. According to their size, nanoparticles are either ultra-tiny (less than 10 nm), small (10-100 nm), or giant (more than 100 nm). Metallic nanoparticles' biological activity may also be affected by their form. Nanoparticles can be generated in many different geometric forms, including spheres, rods, triangles, and cubes. Different shapes can be used for various purposes due to their individual advantages. Metallic nanoparticles can have their surfaces functionalized with a wide variety of biomolecules, including antibodies, peptides, and nucleic acids. Their biocompatibility, target selectivity, and therapeutic efficacy may all improve after this functionalization. Surface plasmon resonance (SPR) is the resonant oscillation of conduction electrons in response to light, and it can be used to categorize metallic nanoparticles. Nanoparticles' shape- and composition-dependent SPR characteristics can be utilized for imaging and therapy.

Considerations of composition, size, shape, surface functionalization, and SPR characteristics are just few of the many that go into categorizing metallic nanoparticles as theranostic agents. Researchers can better tailor metallic nanoparticles for therapeutic and diagnostic uses if they have a firm grasp of these characteristics.

Metallic nanoparticles based theranostic agents

Iron oxide nanoparticles as theranostic agents

Due to their distinctive features, iron oxide nanoparticles (IONPs) have attracted a lot of interest as a potential theranostic agent in recent years. Due to its magnetic core, IONPs can be employed as contrast agents in MRI scans and as a heat source in magnetic hyperthermia treatment. Targeted distribution to specific cells or tissues is further made possible by the fact that the surface of IONPs can be functionalized with different biomolecules including antibodies, peptides, or nucleic acids. IONPs have the potential to function as theranostic agents, which combines the therapeutic and diagnostic aspects of treatment. This is possible because a single nanoparticle combines diagnostic and therapeutic capabilities, allowing for continuous evaluation of treatment outcomes and adjustments to be made in real time. IONPs, which can be monitored using MRI, can be programmed to release therapeutic drugs in response to environmental cues such shifts in pH or temperature.

Multiple preclinical investigations have established that IONPs have the potential to act as a theranostic agent. For instance, IONPs have been employed for improved therapeutic efficacy and less systemic toxicity in the transport of chemotherapeutic medicines to cancer cells.

Furthermore, IONPs have been demonstrated to enhance the efficacy of radiation therapy by boosting cancer cells' sensitivity to radiation.

When it comes to treating diseases like cancer and heart disease, IONPs are showing impressive promise as a theranostic agent. However, more study is required to determine their full potential and determine the best way to translate that promise into clinical practice. Information on how to create nanoparticles of iron oxide is easily accessible in written form. The most frequent method for producing iron oxide nanoparticles is the co-precipitation of Fe(II) and Fe(III) precursors in water. Incorporating hydrophilic polymers into the particle creation process improves the particles' colloidal suspendability, which in turn aids in the passivation and protection of the nanocrystal surface from particle aggregation.

Review of Iron oxide nanoparticles as theranostic agents

Using micromixer technology, Bleul et al. synthesized magnetic single core iron oxide nanoparticles. The produced particles, with an average core diameter of 30 nm, were determined to be a promising magnetic particle imaging agent based on analytical centrifugation investigations confirming their stability. Their feasibility as a T2-weighted magnetic resonance imaging contrast that could facilitate multimodal imaging of particles in vivo during its application as a theranostic drug was further established by relaxometry studies. In magnetic fluid hyperthermia, these particles were said to offer therapeutic promise. Researchers also found no evidence of cytotoxicity or poor biocompatibility in the created particles [8].

Magnetic single core iron oxide nanoparticles were created by Bleul et al. utilizing micromixer technology. The produced particles, with an average core diameter of 30 nm, were found to be stable after analytical centrifugation investigations, suggesting they could be a useful magnetic particle imaging agent. As a theranostic agent, multimodal imaging of particles in vivo may be possible thanks to measurements confirming their potential as T2-weighted magnetic resonance imaging contrast. The use of these particles in magnetic fluid hyperthermia has been cited as having medicinal promise. The absence of cytotoxicity and the excellent biocompatibility of the produced particles were also confirmed by the researchers [9].

To create chlorin e6 (Ce6)-coated super paramagnetic iron oxide (SPION) nanoparticle (Ce6-SCs), Amirshaghabhi et al. used the oil-in-water approach. Mice with tumors underwent photodynamic therapy and dual-mode imaging to study the effects of the treatment. Chlorin e6 was found by the researchers to be effective in solubilizing stable nanoclusters of hydrophobic superparamagnetic iron oxide nanoparticles without the need of carriers or amphiphiles. Ce6-SCs were detected by optical and MR imaging to be localized within tumor cells due to enhanced permeability and retention. Researchers found that PDT dramatically slowed the progression of tumors in mice bearing the Ce6-SCs gene [10].

Using an iron oxide nanoparticle core and a poly-aspartic acid graft copolymer, Yoon et al. created an ultra-small, supermagnetic iron oxide nanoparticle loaded with epirubicin. The proposed formulation demonstrated a high encapsulation efficiency, with a sustained release of epirubicin, according to the study's authors. The high relaxivity value and greater than 2-fold contrast enhancement impact of EPI-P-IONP (Epirubicin poly-aspartic acid iron oxide nanoparticle) relative to commercially available contrast agent were further validated. Researchers discovered that cancer cells were killed by the epirubicin produced by the engineered EPI-P-IONP. The promise of P-IONP as a theranostic agent was validated by later experiments, which showed nuclear uptake of epirubicin from EPI-P-IONP [11].

Extremely small magnetic iron oxide nanoparticles (ES-MIONs) loaded with doxorubicin (DOX) grafted with Poly(ethylene glycol) methyl ether (mPEG) conjugated to Dimeric RGD peptide (RGD2) were used by Shen et al. for the development of multifunctional theranostic nanoparticles, which showed promise in T1 - weighted magnetic resonance imaging and chemotherapeutic agent. The produced ES-MIONs were determined to be optimal as a T1-weighted magnetic resonance contrast agent, according to the study's authors. The proposed formulation was shown to selectively attack cancer cells by means of laser scanning confocal microscopy and flow cytometric analysis. Nanoparticles containing DOX@ES-MION3@RGD2@mPEG3 show promise as agents for high-resolution T1-weighted magnetic resonance imaging (MRI) and targeted treatment of cancer cells [12].

Wang et al. created superparamagnetic iron oxide nanoparticles using a focused ultrasonic method guided by magnetic resonance. The above developed nanoparticles were loaded with anti-epidermal growth factor receptor monoclonal antibodies to enhance lung cancer targeted delivery. The theranostic drugs were tested on an in vitro model of human lung cancer and an in vivo (H460) rat xenograft model of human lung

cancer. In addition to improving MRI contrast at the tumor site, the study demonstrated that PEGylated SPIO NPs targeted with anti-EGFR mAb had improved targeting capability to H460 tumor cells. The study's author also provided evidence that T1-weighted, T2-weighted, and diffusion-weighted imaging, among other contrast-enhanced MR techniques, were useful for tracking treatment success in rat models treated with magnetic resonance guided focused ultrasound [13].

Ps 80 superparamagnetic iron oxide nanoparticles (Ps 80-SPIONs) loaded with doxorubicin hydrochloride (DOX) were effectively created by Xu et al. The authors showed that C6 cells were able to absorb much more DOX@Ps 80-SPIONs in the presence of a magnetic field, leading to a greater cytotoxic effect observed in in vitro experiments. Magnetic Ps 80-supramagnetic iron oxide nanoparticles and encapsulated doxorubicin were successfully targeted to tumor cells in vitro and in vivo using 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 was attributable to magnetic targeting and Ps 80-mediated endocytosis. Under the influence of external magnetic fields, encapsulated DOX and magnetic Ps 80-supramagnetic iron oxide nanoparticles were transported to the malignant cells, as shown by ex vivo DOX fluorescence assays and prussian blue staining. Furthermore, the authors concluded that the presence of a magnetic field, in combination with the produced DOX@Ps 80-SPIONs, totally suppressed glioma growth in vivo at day 28 following treatment [14].

New erlotinib conjugated iron oxide nanoparticles (FeDC-E NPs) were developed by Ali et al. Drugs can be delivered intracellularly via these clever targeted devices, directly to cancer cells where EGFR is overexpressed. Prussian blue staining, transmission electron microscopy (TEM), and magnetic resonance imaging (MRI) further validated the cellular uptake and intracellular accumulation of FeDC-E NPs. Using in vivo xenograft tests with BALB/c nude mice, the researchers verified that FeDC-E NPs successfully limit tumor growth [15].

For use in theranostics, super paramagnetic iron oxide nanoparticles (STM-SPIO NPs) were developed by Lai et al. to mimic the stem cell membrane. The formulation was created with a gentle sonication approach that was both easy and effective. Due to their high magnetic properties, STM-SPIO NPs have been proposed as a new MRI contrast agent. Using an alternating magnetic field, STM-SPIO NPs were able to cause cancer cell death by magnetic hyperthermia [16].

Quantum dot as theranostic agents

Nanocrystals with light-emitting capabilities called quantum dots (QDs) are created from semiconductor materials with unusual optical properties and a restricted emission range. Controlling QDs' composition and size allows for fine-tuning of their optical properties. [17].

They often consist of elements from groups III–V, II–VI, or IV–VI, as well as metalloids. Around members 4 and 6. Due to their wide excitation, limited emission spectrum, brightness, quantum yield, and good photostability, Cd-based QDs are one of the most studied quantum dots. Cd-based QDs have great electrooptical characteristics, but their toxicity leads to cell death through DNA damage. There has been a lot of interest in novel QDs made from silicon and carbon. Carbon-based QDs cover a wide range of materials, from carbon dots to carbon nanotube dots to graphene QDs to graphene oxide to nano-diamonds to polymer dots, and so on [18].

Review of quantum dot nanoparticles as theranostic agents

Using hyaluronic acid coupled magnetic prussian blue@quantum dot nanoparticles, Yang et al. created a multifunctional theranostic agent for cancer. Hyaluronic acid was coupled to the surface of magnetic pussian blue nanoparticles coated with bovine serum albumin-coated CuInS2-ZnS (copper indium sulfide conjugated zinc sulfide) quantum dots. The created nano-agent was proven to be an effective contrast agent since it improved sensitivity in both MRI and NIR scans. Hyaluronic acid, a CD44 ligand, in combination with the magnetic core significantly enhances the absorption of the nano-agent by CD44 overexpressed HeLa cells subjected to an external magnetic field. In vivo MR imaging and NIR fluorescence studies demonstrated that high concentration of nano-agents was achieved due to their outstanding CD44 receptor/magnetic dual targeting capacity [19].

As a cancer theranostic system, berberine hydrochloride-loaded multi-fluorescent graphene quantum dots were developed by Thakur et al. Graphene quantum dots were produced with the help of microwave heating applied to a single container. It was discovered that process parameters like ionic strength and heating time affected the photoluminescence property. Graphene quantum dots were loaded with berberine hydrochloride using cysteamine

hydrochloride. Drug loading efficiency of 88% was observed in the formulated formulation. Using trypan blue and MTT based cytotoxic assays, the researchers confirmed that the GQDs@Cys-BHC (graphene quantum dot complexed with cysteamine hydrochloride- berberine hydrochloride) complex had a potent cytotoxic effect against various cell line models, including breast cancer cells like MDA-MB-231 and cervical cancer cells like HeLa cells [20].

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Multi-fluorescent graphene quantum dots produced from milk and doped with berberine hydrochloride were developed as a cancer theranostic system by Thakur et al. Graphene quantum dots were produced using microwave-assisted heating in a single container. It was discovered that ionic strength and heating duration are two of the process parameters that can affect the photoluminescence property. Cysteamine hydrochloride was used to bind berberine hydrochloride to graphene quantum dots. The medication loading efficiency of the formulated product was determined to be 88%. The GQDs@Cys-BHC (graphene quantum dot complexed with cysteamine hydrochloride- berberine hydrochloride) complex had a potent cytotoxic effect, as confirmed by trypan blue and MTT based cytotoxic assays, against various cell line models, including breast cancer cells like MDA-MB-231 and cervical cancer cells like HeLa cells [22].

Non-invasive theranostic imaging of HSV-TK/GCV suicide gene therapy in liver cancer was developed by Shao et al. using folate-targeted quantum dot-based liposomes. Successful formulation of a folate-modified theranostic liposome (FL/QD-TK) containing the herpes simplex virus tk suicide gene covalently coupled with near-infrared fluorescent CdSeTe/ZnS (cadmium selenium tellurium complexed zinc sulfide) core/shell quantum dots. The biotargeting specificity and safety of FL/QD-TK for liver cancer were verified in in vitro and in vivo experiments. Increased targeted tumor imaging and potent inhibition of folate receptor-overexpressed Bel-7402 mouse xenograft were reported using the created FL/QD-TK, without any systemic effects, according to the study's authors [23].

An innovative fluorescent theranostic tool for cancer was created by Bansal et al. based on a biosurfactant-conjugated graphene quantum dot system. The bottom-up method was used to synthesise graphene quantum dots by pyrolyzing citric acid. Additionally, carbodiimide chemistry was used to conjugate it with folic acid and biosurfactant. Researchers found that their new formulation effectively targeted tumor cells without having a discernible effect on healthy cells. Biosurfactant coupled graphene quantum dots, the study found, reduce cellular viability by 50% in just 24 hours. The results of drug internalization tests using confocal laser scanning microscopy indicated that folic acid conjugation improved the tumor cell specificity of bioconjugated graphene quantum dots [24].

Gold nanoparticles based theranostic agents

In the fields of surface enhanced raman spectroscopy, computed tomography, etc., gold nanoparticles have been investigated extensively because of their unique properties. Rods, spheres, cages, cubes, and wires are just some of the shapes that can be produced while working with gold nanoparticles. The capacity to image the generated goods depends on their physical qualities, which in turn are affected by the shape of the gold nanoparticles used in the development process. Since the thiol group interacts strongly with the Au (gold), thiolated compounds are frequently used to make substantial surface changes. Most often, amine/carboxyl-terminated bifunctional molecules are used, with the thiol-terminated portion immobilized on the surface and the amine/carboxyl-terminated portion exposed for conjugation. However, the particle as a whole can be prethiolated, allowing for the loading of biomolecules. If you want to induce stable attachment of gold via ligand in the case of gold nanoparticles, monodentate thiol is your best bet. Figure 1 shows a typical gold nanoparticle loaded with drug and fabricated with radio-diagnostic agent.

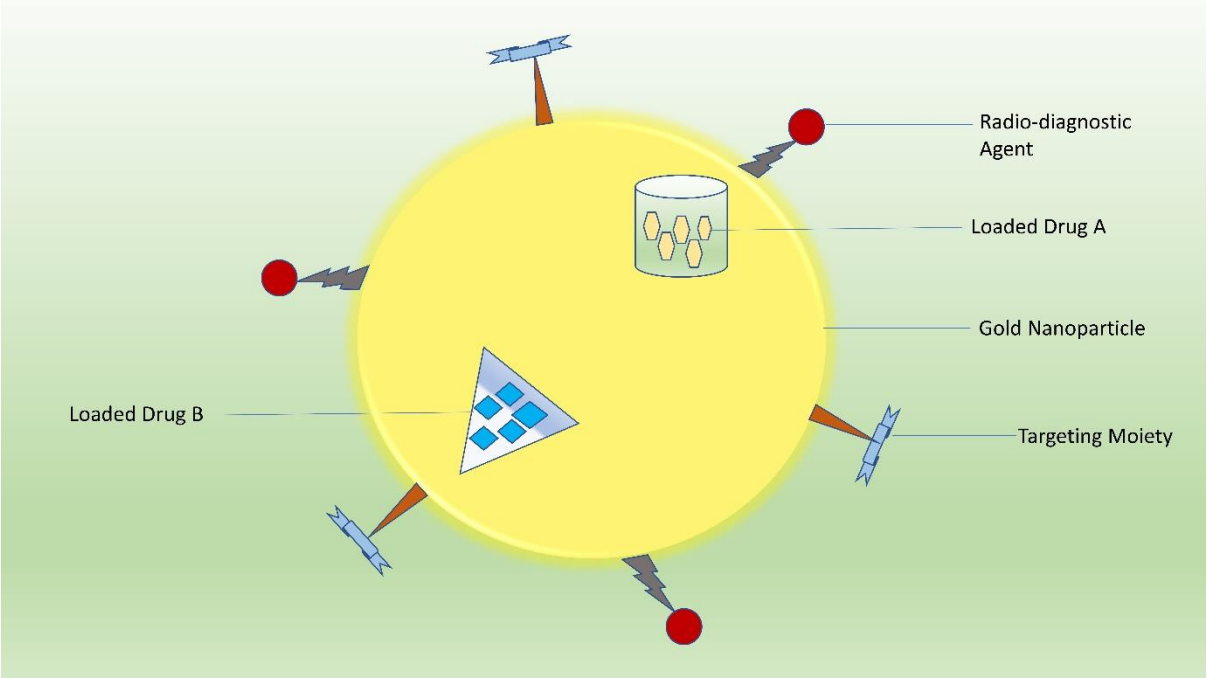

Figure 2: A typical gold nanoparticle fabricated with radio-diagnostic and therapeutic agents [72].

Review of gold nanoparticles based theranostic agents

For a theranostic effect in drug delivery and imaging, Theodosiou et al. designed and manufactured gold nanoparticle loaded on to pH-sensitive polymeric P(MAA-co-MBA-co-AA) (methacrylic acid-co-N,N′-Methylenebis (acrylamide)-co-acrylic acid). The gold nanoparticle loading and in situ synthesis were carried out via distillation precipitation copolymerization. The gold nanocrystal contained doxorubicin. Using HEK-293 human embryonic kidney cells and MCF-7 breast cancer cells, the researchers examined the survivability of gold nanoparticles, gold nanocyrstals loaded with doxorubicin, and doxorubicin alone. The scientists concluded that after 1 hour of treatment, gold nanocontainers were positioned in the cytoplasm of MCF7 cells, while gold nanocontainers loaded with doxorubicin were located at the nucleus, where it is most [25].

The cisplatin conjugated gold nanoparticle discovered and synthesized by Davidi et al. has the potential to serve as a medication carrier, radiosensitizer, and tumor imaging agent in the treatment of head and neck tumors. In vitro investigations were used to assess the cytotoxic effect and tumor cell penetration of gold nanoparticles loaded with cisplatin and glucose. Imaging and effects on tumor growth were assessed in vivo. The new formulation was found to have effective tumor cell penetration and cytotoxicity, the authors stated. The study's authors also noted an increased anti-tumor effect from using radiation in tandem with cisplatin and glucose-loaded gold nanoparticles] [26].

Gold nanoparticles carrying paclitaxel, biotin receptor, and rhodamine B coupled beta cyclodextrin were produced by Heo et al. for use as a theranostic agent in cancer treatment. Together with -cyclodextrin, paclitaxel was able to generate an inclusion complex, which was subsequently conjugated to a gold nanoparticle. PEG, rhodamine B linked -cyclodextrin, and other PEG, biotin, and rhodamine B linked -cyclodextrin surface functionalized gold nanoparticles were produced and tested for their efficacy against the cancer cell lines A549, HeLa, and MG63. Cell viability testing, fluorescence-activated cell sorting (FACS), and confocal laser scanning microscopy (CLSM) all supported the researchers' conclusion that gold nanoparticles exhibited considerable theranostic action in cancer therapy and diagnosis [27].

Methoxy polyethylene glycol-graft (MPEG) grafter poly(L-lysine) was used to stabilize gold nanoparticles that were manufactured and created by Bogdanov Jr. et al. Researchers found that the produced gold nanoparticles remained disseminated within endosomes even after being exposed to blood protein and phosphate. Researchers found that gold nanoparticles stabilized with methoxy polyethylene glycol (MPEG) grafter poly(L-lysine) were stable and exhibited low toxicity to endothelial cells while demonstrating dose-dependent toxicity to epithelioid cancer cells. Imaging of biodistributed gold nanoparticles was aided by

labeling them with 99mTc, and researchers found a dose-dependent blood circulation. The team determined that the particle was biocompatible, did not aggregate, and might be used in biomedical theranostic cancer therapy and imaging [28].

A unique glucose-capped gold nanoparticle system was devised and manufactured by Suvarna et al. using a straightforward room-temperature approach. Developed gold nanoparticles were characterized using a wide variety of techniques, including transmission electron microscopy, Fourier transform infrared spectroscopy, Dynamic light scattering, selected area electron diffraction, and ultraviolet-visible spectroscopy. During surface enhanced Raman scattering experiments, the produced gold nanoparticles demonstrated Raman signals up to 50 times the background level utilizing 2DG. Different cell lines were tested for their cytotoxicity utilizing a 3-(4, 5-dimethylthiozol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay [29].

It was determined to create and synthesize Her2-functionalized gold nano-shelled hybrid magnetic nanoparticles for use in ultrasound/MR, photothermal imaging, and photodynamic therapy of breast cancer. The active ingredients in the formulation were perfluorooctyl bromide, SPIONs, PLGA nanoparticles coated in a gold nano-shell, and anti-Her2 antibodies that had been attached to the particles. Cell-targeting tests, the researchers said, verified the agent's specific binding to Her2-positive human breast cancer SKBR3 cells via the receptor. The proposed formulation was also said to have a dual-modal imaging effect at the cell-by-cell binding it was designed for. Live/dead cell assays and targeted photothermal cytotoxicity showed that Her2-GPH NPs functioned as an effective photo-absorber, killing SKBR3 cells when exposed to a near-infrared laser [30].

In order to guide PTT using fluorescent and photoacoustic imaging, Gao et al. built a hybrid gold nanoparticle on graphene oxide. Matrix metalloproteinase-14 substrate was coupled to a near infrared dye (Cy5.5). The photothermal effect was improved in the graphene-gold hybrid. High fluorescence and PA signals were found in the tumor region after intravenous injection of the complex in a study of anti-tumor efficacy in SCC7 tumor-bearing mice. Its biological potential as a cancer theranostic agent was validated by further laser irradiation, which exhibited excellent tumor suppression [31].

Carbon nanotubes based theranostic agents

Photoacoustic imaging, Raman spectroscopy, and drug delivery are just a few of the many uses for carbon nanotubes. Extreme oxidative conditions are used to build mounting sites, which result in flaws on the nanotubes' surface. Carbon nanotubes' aromatic and hydrophobic properties also make them an ideal anchor for non-covalent compounds. Various salts, such as sodium dodecylbenzene sulfonate and sodium dodecyl sulfate, are used to create a homogeneous aqueous solution containing carbon nanotubes. It has been discovered, however, that sodium dodecylbenzene sulfonate is more effective than its analogue in creating a suspension of carbon nanotubes. The biocompatibility and efficiency of carbon nanotubes have led to extensive research into the use of ligands, with particular focus on PEGlyated phospholipids.

Review of carbon nanutubes based theranostic agents

Polyethylene glycol modified with mesoporous silica coated single walled carbon nanotubes was created and produced as an effective theranostic agent by Liu et al. for the treatment of cancer. The doxorubicin anticancer medication was applied to the porous surface. Anti-cancer action was discovered after doxorubicin was liberated from the complex upon near infrared stimulation. After being injected intravenously into mice, the produced compound accumulates within tumor cells, as confirmed by magnetic resonance imaging and photoacoustic imaging. In vivo investigations using a mouse tumor model verified the synergistic anti-tumor activity [32].

Carbon nanotubes coated in manganese oxide were produced by Wang et al., and they show promise as lymph mapping agents for photothermal therapy of tumor metastasis. Researchers found that T1-weighted magnetic resonance (MR) mapping of manganese oxide clearly indicated the regional lymph nodes following a single local injection and lymph draining. Under the direction of dual modality mapping, near infrared imaging revealed metastatic lymph nodes. Multifunctionality of the created compound as a theranostic agent was verified in mouse models of lymph node metastases [33].

Dye-conjugated single-walled carbon nanotubes were produced by Liang et al. for the purpose of triggering near-infrared guided photothermal treatment in breast cancers. Near infrared imaging was used to precisely pinpoint the tumors, which were subsequently irradiated with a laser. Single walled carbon nanotubes were shown to be highly stable and exhibit low cytotoxicity in both in vitro and in vivo investigations. In vivo research using near-infrared imaging to direct

photothermal therapy with Cy5.5-conjugated single walled carbon nanotubes shown effective tumor suppression in mice. The created compound demonstrated considerable breast tumor suppression, the researchers reported, leading them to infer that it has great potential as a theranostic drug for breast malignancies [34].

Xie et al. used evans blue, a novel single wall carbon nanotube dispersion agent, to formulate a single walled carbon nanotube complex for fluorescence imaging and photodynamic treatment of cancer. Albumin/Chlorin e6 was reported to be bound to the complex, which enabled both photoacoustic and fluorescence imaging to be performed. Synergistic photothermal therapy and photodynamic therapy were shown to be effective in ablating tumors. In addition, the study's authors found that combining photodynamic therapy with photothermal therapy increased tumor damage and effectively reduced recurrence [35].

For their use as an ultrasonic contrast agent, Delogu et al. looked into a novel functionalized multiwalled carbon nanotube. The researchers verified the proposed formulation's long-lasting ultrasonic contrasting characteristics. It was also shown that the ultrasonic signal from a functionalized multiwalled carbon nanotube was greater than that from a functionalized single walled carbon nanotube or a pristine multiwalled carbon nanotube made from graphene oxide. Ex vivo experiments in pigs indicated that the produced carbon nanotubes were highly echogenic in heart and liver. It was discovered that tubes could be seen at a variety of frequencies. In addition, the scientists stated that carbon nanotubes were found to be non-toxic [36].

With the use of poly(maleic anhydride)-alt-1-octadecene-poly(ethylene glycol), Chen et al. created single-walled carbon nanohorns with improved biocompatibility and stability and theranostic capabilities. Both the photothermal and photoacoustic imaging characteristics of the developed complex were significantly improved. The high near-infrared absorption accounted for these characteristics. The complex accumulated at the tumor site due to its ultra-long bold circulation time and its improved penetration and retention action. After 24 hours of i.v. injection, the concentration was at its highest, which is when 808 nm laser treatment is most effective. It was also mentioned that photothermal tumor ablation can be achieved without major complications down the road [37].

To accomplish photothermal and dual modal imaging and chemotherapy of cancer cells in vivo mice, Zhang et al. produced and examined multi-walled fluorescent magnetic carbon nanotube. Nanocomposites containing doxorubicin were used. The complex was put to use as a drug delivery system for cancer treatment. The complex was found to have heat-induced drug release, as well as NIR and pH-responsive drug delivery, according to the study's authors. In addition, the complex was shown to successfully eradicate tumor by photothermal and chemotherapeutic synergistic action in in vitro and in vivo investigations, proving its potential to deliver the anti-cancer agent to the targeted cancerous cell upon irradiation by near infrared rays [38].

Silica nanoparticles based theranostic agents

The medical community has long recognized silica for its potential as an implant material. They enjoy a reputation for being risk-free. Optimized silica nanoparticles can be made by precisely manipulating the morphological factors. They are not imaging agents on their own, but they provide a great foundation for loading molecules with imaging and therapeutic abilities. Condensation and hydrolysis of tetraethyl orthosilicate are the usual methods of producing silica nanoparticles. Co-precursors, such as mercaptopropyl methoxy silane or amino propyl trimethoxy silane, are coagulated with tetraethyl orthosilicate to introduce thiol or amine groups to the particle surface during the silica functionalization process. To create a magnetic or optically active agent, Gd-DTPA and organic dyes are grafted onto a silica particle matrix.

Review of silica nanoparticle based theranostic agents

In order to create an activatable theranostic agent, Ho Hong et al. loaded indocyanine green onto a mesoporous silica nanoparticle. In order to return the created complex to its initial state, singlet oxygen production and near infrared fluorescence were used. Energy transfer via fluorescence resonance was found to be responsible for this quality in indocyanine green. This renders the compound extracellularly non-fluorescent and non-phototoxic. Once within the cancer cell via endocytosis, the nanoparticle reportedly becomes highly phototoxic and fluorescent, guaranteeing a more potent theranostic effect in cancer therapy [39].

Cancer can be targeted and directly imaged with the help of the ruthenium polypyridyl complex that He and colleagues encapsulated in mesoporous silica nanoparticles. The created nanoparticles' cellular absorption was enhanced by the addition of the RGD peptide, which also helped with selectivity between normal and malignant cells. The created compound was

shown to be highly hazardous to cancer cells that overexpressed the integrin receptor, the researchers stated. Nanoparticles, once internalized, release ruthenium polypyridyl into the cytoplasm, where it triggers apoptosis in the cancer cell by regulating phosphorylation of AKT, MAPKs, and p53. Direct monitoring of drug delivery is made possible by ruthenium polypyridyl's autofluorescence, guaranteeing its theranostic applicability [40].

In order to create an effective theranostic agent, Mignot et al. used the top-down approach to synthesize multifunctional, ultra-small gadolinium-based silica nanoparticles. The dissolution of the oxide core was confirmed by means of electron paramagnetic resonance, transmission electron microscopy, and photon correlation spectroscopy, all of which were used to characterize the formed complex. Additional characterization techniques, including diffusion ordered spectroscopy, fluorescence spectroscopy, mass spectrometry, inductively coupled plasma mass spectrometry, and 1H NMR, verified the created nanoparticle's composition. To further verify that gadolinium is highly chelated to the DOTAGA (1,4,7,10-tetraazacyclododecane-1-glutaric anhydride-4,7,10-triacetic acid) complex, potentiometric titrations were also performed. According to the study's findings, the complex is a promising option for image-guided radiation [41].

Mesoporous silica nanoparticles were investigated by Milgroom et al. as a potential theranostic agent for use against breast cancer cells. The monoclonal antibody Herceptin® was encapsulated in silica nanoparticles, and the resulting compound was found to be an effective ultrasound contrast agent. Researchers reported tumor-specific cytotoxicity of mesoporous silica nanoparticles using in vivo experiments, confirming their targeted binding to HER2+ cancer cells. The created formulation was judged to be stable, biocompatible, and to have effective theranostic property in breast cancer cells by the authors [42].

After ultrasound or magnetic resonance imaging and stem cell survival enhancement medication delivery, mesoporous silica nanoparticles with theranostic properties were examined by Kempen et al. The produced mesoporous silica nanoparticles have been shown to boost cell survival by releasing insulin like growth factor, and the researchers have revealed that they can be guided into the peri-infarct zone for implantation using MRI or ultrasound signal. In around 3 weeks, the compound was gone from the cell [43].

For its prospective use as a cancer theranostic agent, a novel platinum(II) based aggregation induced emission chemical encapsulated in mesoporous silica nanoparticle was investigated by Pasha et al. Analytical techniques such as infrared spectroscopy, nuclear magnetic resonance, mass spectrometry, and single crystal X-ray structure were used to learn more about the developed complex. The peak of the aggregation-induced emission was reported by the researcher to be at 497 nm. The compound was encapsulated in mesoporous silica nanoparticles that have an anti-EpCAM aptamer incorporated into their surface for efficient targeting of malignant cells. Increased apoptotic cell death and improved intracellular fluorescence were reported for this newly created compound [44].

For possible theranostic use, Chan et al. created and analyzed multifunctional mesoporous silica nanoparticles, characterizing them for in vitro and in vivo dual mode imaging. Magnetism and fluorescence were discovered in the nanocomplex when gadolinium and europium were doped onto the mesoporous silica nanoparticle. The addition of folic acid to the combination helps direct the mesoporous silica nanoparticle to the malignant cell by attaching the folic acid to the cell membrane. By linking camptothecin to the nanoparticles with a disulfide bond, we can give them anti-cancer activity and make them capable of regulated drug release. The system's promise for dual imaging and targeting is supported by reports from in vitro and in vivo studies of functionalized mesoporous silica nanoparticles [45].

Metallic nanoparticles as an imaging agent

Magnetic resonance imaging (MRI), optical imaging (OI), computed tomography (CT), ultrasound (US), positron emission tomography (PET), and single photon computed tomography (SPCT) are just few of the imaging modalities that could benefit from using metallic nanoparticles. To achieve the desired theranostic results, imaging modalities are typically paired with the nanoparticle having intrinsic therapeutic property or the nanoparticle is engineered to embed a therapeutic medication onto the nanoparticle.

Optical imaging

It's a cutting-edge noninvasive method for clinically-accurate imaging of organs and tissues down to the cellular level. This method detects the photon emission from Raman and fluorescent bioluminescence probes in the visible and near infrared spectrum. Optical imaging uses non-ionizing radiation, giving it a safer and more

cost-effective alternative to X-rays. Optical imaging can be done at a variety of wavelengths and resolutions, and it can also be used in conjunction with other imaging modalities. It can be used in tandem with other imaging modalities. Drug release and uptake from nanoparticles can be tracked using methods like fluorescent lifetime imaging microscopy [46]. The limitations of optical imaging include noise, limited depth of penetration, and absorption by heme groups, proteins, and water. For in vivo imaging of metallic theranostic nanoparticles, the near infrared region, between 700 and 900 nm, has been employed to circumvent these restrictions [47,48].

Detecting and targeting messenger RNA (mRNA) of the cancer-fighting gene surviving was the focus of research by Prigodich et al., who examined nanoflare gold nanoparticles loaded with antisense oligonucleotides. The produced gold nanoparticle was given an antisense strand and tagged with Cy5 oligonucleotides by the researchers. In the absence of target, low fluorescence was seen. In the presence of a still-alive target, the fluorescence is said to rise. Scientists came to the conclusion that their mRNA-targeting theranostic chemical could effectively block the translation of any remaining mRNA [49].

Using labeled mesenchymal stem cells, Huang et al. created and investigated a silica-based hyaluronic acid nanoparticle that conducted multimodal imaging for tumor targeting. Author demonstrated that complex internalization into mesenchymal cells was improved by nanoparticle delivery. Optical, positron emission tomography, and magnetic resonance imaging all validated the targeting of the complex to the tumor site following intravenous injection in the glioblastoma model, paving the way for further research [50].

Magnetic Resonance Imaging

It's an imaging method that has a low risk of negative effects. Hydrogen nuclei in water relax in response to an external magnetic field, providing the basis for the resulting pictures. Reductions in relaxation time can be achieved by functionalizing nanoparticles with gadolinium [51]. MRI has excellent spatial resolution, but its imaging sensitivity is restricted. [52]. This imaging technique has been used well in the fields of cell treatment tracking and drug response monitoring.

In a work conducted by Kaittanis et al., iron oxide nanophores containing the cancer drugs taxol and doxorubicin were created. T2 and T1 nuclear magnetic resonance proton relaxation periods were shown to be directly proportional to the amount of drug put into nanophores. Release of doxorubicin and fluorophores was suppressed and recovered in the LNCaP prostate cancer cell line in a manner comparable to that of an empty nanoparticle. These results imply that iron oxide nanoparticle load carrying capacities can be determined using relaxation measurement [53].

Researchers Crisci et al. studied the efficacy of a dendritic cell line derived from monocytes that contained a supramagnetic iron oxide nanoparticle in inducing functional immune responses in pigs when exposed to rabbit haemorrhagic disease virus particles containing a T-cell epitope derived from foot and mouth disease virus 3A protein. The complex's viability was tested in vitro and found to be satisfactory. Subcutaneous injection of the complex followed by magnetic resonance imaging to trace the movement of dendritic cells through the lymph nodes was then performed. The study verified the tracking and immunization of dendritic cells in pigs [54].

Ultrasound

Ultrasound is often regarded as a reliable, quick, and inexpensive imaging option. Here, a transducer sends high-frequency sound waves through the skin and records the echoes that are reflected back from the interior organs [55]. Internal organs can be located with the help of intravascular ultrasonography.

The use of ultrasound to create MnO2 nanoparticles for photodynamic treatment is something that Gao et al. H2O2 and other reactive oxygen species are produced and used to trigger apoptosis in the exposed cancer cells. Researchers took advantage of the fact that cancerous tissue produces more H2O2 by using MnO2 nanoparticles, which combine with H2O2 to form reactive oxygen that specifically targets the tumor. To enhance biocompatibility, tumor binding capacity, and MnO2 release, hyaluronic acid was included into the combination. For nuclear imaging resonance laser triggered photosensitization, indocyanine green is additionally included into the complex. The study's authors concluded that these intricate nanoparticles could be useful for image-guided cancer treatment [56].

Researchers Kempen et al. investigated the potential of mesoporous silica nanoparticles loaded with insulin-like growth factor as a theranostic therapy for cardiovascular disease. Researchers found that the mismatch at the tissue-silica particle interface facilitated better cell tracking and molecular imaging in in vivo tests. Gadolinium was also loaded onto the nanoparticle, helping to improve imaging resolution and enable dual-modality imaging. Nanoparticles are implanted into the left ventricular wall after being taken up by human bone

marrow mesenchymal stem cells in hairless mice. Improved backscatter was confirmed by ultrasound images, and the cell count dropped from 100,000 to 10,000, both of which are detectable by MRI [57].

Nuclear Imaging

For nuclear medicine imaging, radio-labelled tracers or radionuclides are injected for procedures like single photon computer tomography and positron emission tomography. The camera records the gamma rays given off by the injected radionuclides, which are then processed to create a three-dimensional image. For many years now, nuclear imaging has come to rely heavily on single-photon computer tomography. The cost-effective radioactive isotope technetium-99m (99mTc) is utilized for this. Nuclear imaging and gamma-ray emission at 140 keV are just two of its helpful capabilities. Numerous studies have looked into the feasibility of using 99mTc in the form of a liposomal nanoparticle as a nuclear imaging agent for the detection of malignant cells and sentinel lymph nodes [58].

To generating two γ-ray emissions of 511keV in opposite directions, PET is a nuclear imaging technique that uses positron emission. These photons are measured to be 1800 femtoseconds apart using a scintillation ring for positron emission tomography. A sensitive and quantitative method, although with low resolution. Because of its high biocompatibility, fast pharmacokinetics, and optimal biodistribution, copper-64 (64Cu) has been included as a positron emission tomography tracer [59].

Positron emission tomography, magnetic resonance imaging, and near infrared fluorescence were all achieved through the development of functional iron oxide nanoparticles in a work by Xie et al. Iron oxide nanoparticles had their surfaces modified with dopamine, resulting in nanoconjugates that could encapsulate human serum albumin matrices. Labels of 64Cu-DOTA and Cy5.5 were used to mark the hybrid that was created. The U87MG xenograft mouse model was used for the research. To conclude the hybrid complex's theranostic potential to give imaging and therapy of tumor area, the researchers confirmed its capacity to provide positron emission tomography, magnetic resonance imaging, and near infrared fluorescence images [35].

Computed Tomography

The majority of CT scans are performed in conjunction with other imaging modalities, rather than as a standalone procedure. Autonomic images are created by compiling tomographic images obtained from computer-processed x-rays. Tissues have varying degrees of x-ray attenuation because of their electron density and atomic number. So, high-atomic-number nanoparticles like gold, iodine, and bismuth are extensively researched as CT contrast agents.

Gold nanoparticles covered in glycol-chitosan were analyzed by Kim et al. It was coupled with peptides that target fibrin for use as a CT contrast agent. The formulation was created so that tissue plasminogen activator, a thrombolytic agent, could be imaged and used to treat thrombi in the cerebrovascular system. The only treatment for acute ischemic stroke licensed by the US Food and Drug Administration is tissue plasminogen activator. The thrombi can be lysed by them. However, careful observation is necessary to prevent hemorrhagic consequences. Using a mouse model of embolic stroke, the researchers employed gold nanoparticles coated with fibrin targeting peptides and saw distinct differences between targeted and non-targeted nanoparticles on cerebral computed tomographic images [60].

Recent patents on metallic nanoparticles based theranostic agents

Nanoparticles that have the potential to be used for both imaging and therapy have attracted the attention of scientists all over the world [61]. There is a high volume of patent applications for research on theranostic compounds every year. The authors of this review have made an effort to compile a database of patents that cover the use of metallic nanoparticles as a theranostic agent, including information about the patent's title, number, publication year, and inventors/assignees. The study surveyed publications published in 2016 and after. Only US patents are included in the table. The authors used Google patents to conduct their literature review. The search was narrowed down to within the previous 5 years by using only one term, ‘theranostic metallic nanoparticle’. Table 1 tabulates publication title, patent number, year of publication and inventor/assignee of the patent related to metallic nanoparticle based theranostic agents.

The methodologies and theranostic nanoprobes for overcoming multidrug resistance in cancer are discussed in patent US20160243254A1 assigned to the Massachusetts Institute of Technology. Gold nanoparticles modified with a DNA hairpin were used in the nanoprobes. Upon DNA-hairpin hybridization with the target molecule, the theranostic nanoprobes are programmed to release the medication [62].

Patent US10568970B2 assigned to Boston University discusses theranostic compositions and their applications. Coating a Janus nanoparticle with a microbubble capable of ultrasonography or magnetic resonance imaging and carrying a therapeutic agent such as nucleic acid [63].

University of California-assigned patent US20200383929A1 describes mesoporous silica nanoparticles with lipid bilayer coating for payload delivery. The nanocarrier has a lipid bilayer coating, and a payload trapping agent is located within a phospholipid bilayer. The phospholipid bilayer provides structural integrity and seals pores [64].

Patent US20200271655Aassigned to Arizona Board of Regents of ASU describes folic acid-functionalized copper sulfide nanoparticles for ovarian cancer cell flow detection. The developed hybrid was reportedly capable of detecting ovarian cancer cells via photoacoustic flow cytometry [65].

In the University of California-assigned patent US20200230071A1, methods for producing hollow metal nanospheres are described. The nanospheres were manufactured with a predetermined level of surface abrasion. Cobalt-based nanoparticle nucleus with a metallic shell. This was oxidized further to create hollow metal nanospheres [66].

Long-circulating theranostic agents for diagnosing and imaging metastatic tumors are discussed in patent US20200206358A1 assigned to Leland Stanford Junior University. It was composed of a TMTP1 peptide conjugated to an albumin-binding moiety that could prolong circulation time and permit the conjugation of a metal ion with diagnostic properties to theranostic agent. Consequently, the theranostic agent could be conjugated to a radionuclide suitable for positron emission tomography or a paramagnetic metal ion suitable for magnetic resonance imaging [67].

The Northwestern University-assigned patent US20200101177A1 discusses magnetic nanocomposite compositions. It possesses a supramagnetic nucleus and a shell of ferrites with varying magneto-crystalline anisotropy [68].

Small, extremely homogeneous nanomedicine compositions for therapeutic, imaging, and theranostic applications are discussed in patent US20200101176A1 that is assigned to the University of Michigan. It may be visualized with magnetic resonance imaging and is tailored to target F3-cys [69].

University of Michigan's patent US20200101176A1 describes tiny, homogeneous nanomedicine compositions with medicinal, imaging, and theranostic uses. It may be visualized by MRI and was developed with F3-cys in mind [70].

Superparamagnetic particle imaging and its uses in quantitative multiplex stationary phase diagnostic tests have been discussed in a patent (US20190317167A1) that is assigned to Mars Sciences Ltd. The supramagnetic nanoparticles were sensitive, responsive, and able to send and receive information. It is also possible to incorporate a hybrid point-of-care chip inside the supramagnetic nanoparticle [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 [72].

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

Many new types of theranostic agents have been developed in part because of the inspiration provided by metallic nanoparticles. However, in order for innovative theranostic agents to be produced in a way that they can reach the clinics, it is necessary to address various limitations of traditional theranostic agents. Metallic nanoparticles have shown promise as theranostic agents in a number of preclinical trials, but there has yet to be a successful clinical trial. Modern techniques allow for the precise synthesis of drugs onto metallic nanoparticles for targeted delivery and sustained release in conjunction with diagnosis and imaging. According to the literature, metallic nanoparticles' clinical applications might benefit from further research into their development and safety. Designing metallic nanoparticles as theranostic agents presents a number of challenges, including stability and control of drug release, large-scale manufacturing, some toxicity concerns related to nano-sizing, and the potential for behavioral, physiological, and metabolic complications. With the advent of cutting-edge methods, researchers

are developing and studying metallic nanoparticles successfully manufactured with medicinal medicament and diagnostic agent. Nanoparticles are the subject of substantial research and development. The remark that this developing science of dual potential of diagnosis and therapy has gained appeal around the globe is supported by the large number of patents submitted each year for nanoparticle-based theranostic medicines.

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Conflict of Interest

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