Gadolinium(III) based nanoparticles for $T_1$-weighted magnetic resonance imaging probes

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The development of magnetic resonance imaging (MRI) contrast agents with delicate sensitivity and advanced functionalities has recently received extensive interest. Nanoparticle MRI contrast agents have been synthesized for various potential applications because of their unique properties, such as large surface area, surface modifications for multifunction, contrast enhancement, and conjugation with biomolecules for therapeutic and diagnostic applications. This review summarized the recent progress on Gd-based nanoparticles as $T_1$-weighted MRI contrast agents including inorganic crystalline Gd(III) nanoparticles and Gd(III) chelate-grafted macromolecular nanoparticles. The recent development of Gd(III)-based nanoparticle as multimodal contrast agents including $T_1$-weighted MRI/computed X-ray (CT) and $T_2$-weighted MRI/optical were also included.

Introduction

Magnetic resonance imaging (MRI) is a complementary molecular imaging modality that provides images with high spatial resolution and anatomical details without exposure to radioisotopes such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT). Contrast agents have been introduced to differentiate the hydrogen nuclei situated at diverse environment under an applied magnetic field, highlight the part of interest by means of contrast difference resulted from the alternation of the signal intensity. Gd(III) possesses seven half-filled f orbitals unpaired electrons, leading to a favorable large magnetic moment (spin-only $\mu_{\text{eff}} = 7.94$ BM) and the spin of which perturbs the proton relaxation in water results in an efficient shortening of longitudinal relaxation times and increase the MR signal intensity. Therefore, Gd(III)-based agents are the constituent of most MRI contrast agents which provide with positive signals and perform as high efficiency $T_1$-weighted agents as they have ideal physicochemical, pharmacological properties such as thermodynamic and kinetic stability, good water solubility, high relaxivity, in vivo stability, low toxicity, etc.  

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Nanomaterials form a convenient platform that can carry highly specific targeting biomaterials, antibodies, drugs and combine different clinically relevant properties in a single unit for bioimaging probes. Nanomaterial-based MRI contrast agents have been synthesized and developed to increase MRI sensitivity, and to adjust the biodistribution of the contrast agents for tissue-targeting purpose. Novel nanomaterials MRI contrast agents with a therapeutic component as theranostic nanomedicines have been reviewed for monitoring drug delivery, drug release and drug efficacy.

Gadolinium is a highly toxic rare earth metal in the unbounded form. Exposure to the unchelated Gd(III) is associated with nephrogenic systemic fibrosis (NSF) which is known to inhibit the calcium channels and has considerable cardiovascular and neurologic toxicity. When the Gd(III) ions are chelated, the toxicity can be enormously reduced and the LD₅₀ increases 100-fold after chelation. In 2009, the World Health Organization (WHO) issued a restriction on use of several current commercial available Gd(III) chelates contrast agents in patients with severe kidney problems, or with who have recently received a liver transplant.

The Gd(III) based nanomaterial as effective contrast agents in preclinical and clinical applications has been extensively studied. There is a need to evaluate the potential toxicity of these Gd(III) based nanomaterial, and to investigate their bioaccumulation and clearance properties. The toxic effects were evaluated through the biological interaction between Gd nanoparticles with various mouse and human cells. The studies on Gd₂O₃ nanoparticles injected in mice showed the particles were naturally eliminated by renal excretion after a few hours with low cytotoxicity. The potential toxicity of Gd based nanoparticle depends on its constituent materials, on the chemical properties of its surface coating and on the size of the particles. Through the surface modifications, size selection and interior chemistry the Gd₂O₃ nanoparticles would enhance their biocompatibility with satisfactory cytotoxicity, minimal immunotoxicity and optimal pharmacokinetics and excretion characteristics.

This review focuses on development of Gd(III)-based nanoparticles contrast agents including Gd(III) containing inorganic crystalline nanoparticles and Gd(III) chelate-grafted macromolecular nanoparticles for T₁-weighted MRI, multimodality imaging contrast agents. Synthetic methods, surface modification, physicochemical properties of Gd(III) containing nanoparticles for T₁-weighted MRI contrast agent are summarized. This review also highlighted the functionalization of the Gd-based nanoparticle as multimodal contrast agents including T₁-weighted MRI/computed X-ray (CT) and T₂-weighted MRI/optical for therapeutic and diagnostic applications.

Inorganic crystalline Gd(III) nanoparticles

Inorganic crystalline Gd based compound nanoparticles are considered as a new generation T₁ contrast agent because a rigid crystal environment could effectively prevent the free Gd(III) ions release from nanoparticles. These Gd based nanoparticles can be used as efficient T₁-weighted contrast agents because of their large paramagnetic properties with a small r₂/r₁ values. The preparation of monodispersed ultra-small nanoparticles with size uniformity and large surface area is of highly importance as only the Gd close to the surface contributes to the contrast effect. Added T₂ contrast materials to the T₁ contrast nanoparticles would lead to T₁/T₂ dual contrast agent. For example, Gd(III)-labeled magnetite nanoparticles obtained by modifying Gd-DTPA chelates on the surface of T₂ magnetic iron oxide nanoparticles were reported by Bae et al. and Yang et al. However, proper design of nanostructure is needed in order to separating the T₁ contrast materials and T₂ contrast layers to prevent the magnetic coupling between them.

Nanomaterials gadolinium oxide (Gd₂O₃), gadolinium fluoride (GdF₃), inorganic fluoride nanoparticles K₃GdF₄ and NaGdF₄ (ref. 57) have been extensively explored as promising T₁ contrast agents with improved T₁-weighted MR contrast enhancement. Lanthanide doped inorganic fluoride KGdF₄ and lanthanide doped GdPO₄ nanocrystals have been investigated as potential optical/magnetic multimodal imaging probes. Several methods have been developed to synthesize small sized Gd₂O₃ nanoparticles for the application in MRI contrast agents. Gd₂O₃ nanoparticles were synthesized from three different Gd(III) precursors by refluxing each of them in tripropylene glycol under O₂ flow. The r₁ value 9.9 mM⁻¹ s⁻¹ can be achieved when the Gd₂O₃ particle diameter is 1.0 nm. The high relaxivity of the particles is possibly because several surface Gd(III) ions interact with the water proton cooperatively and thus induce the longitudinal relaxation of water proton as shown in Fig. 1. Rahman’s experiments on 7T showed that there is an optimum Gd₂O₃ nanoparticle size of 2.3 nm with highest spin-lattice relaxation rate of the water protons.

Preparation from Gd precursors in the presence of stabilizers such as polyethylene glycol or its derivatives results in stable
Gd₂O₃ colloidal solutions with particle size ranging from 2 to 15 nm.⁶⁰ Polyethylene glycol as a capping agent on Gd₂O₃ nanoparticles could prevent aggregation, and enhance the blood retention, and facilitate the cell uptake of the nanoparticles, etc. The impact of the polyethylene glycol on the relaxivities and signal intensity of ultrasmall Gd₂O₃ nanoparticles was investigated by Fortin et al.⁷⁹ Functional Gd₂O₃ surface treatment with a stabilizing PEG-silane, the obtained PEG-silane–Gd₂O₃ exhibited enhanced proton relaxivities and high signal intensity. PEG-silane could prevent aggregation of the oxide cores and PEG chains could potentially be used as binding sites for targeting molecules. Stability, biocompatible coatings and nanocrystal functionalization of the PEG-coated Gd₂O₃ nanoparticles can be achieved for positive MR contrast agent. Same group also investigated the impact of agglomeration on the relaxometric properties of aqueous suspension of paramagnetic diethylene glycol (DEG) coating ultra-small Gd₂O₃ nanoparticles.⁶⁰ Roux et al. reported ultrasmall Gd-based nanoparticles (GBNs) can be used for contrast MR enhancement and dose enhancement of X-ray microbeams.⁶² Since GBNs induce both a positive contrast for MRI and a radiosensitizing, when the Gd content is high enough in the tumor and low in the surrounding healthy tissue, radiosensitizing effect of GBNs can be activated by X-ray microbeams for image-guided radiotherapy. Ultrafine Gd₂O₃ nanoparticles were synthesized from Gd-acetate clusters inside single-wall carbon nanoborns was reported by Miyawaki et al. Decomposition of Gd(OAc)₃ encapsulated in single wall carbon nanotubes produces Gd₂O₃ nanoparticles with a small particle size of 2.3 nm.⁶³ The ligand-size dependent proton relaxivities of ultrasmall Gd₂O₃ nanoparticles was reported by Kim et al. Both of r₁ and r₂ values decreased with increasing ligand size.⁷¹

For the preparation of ultra-small metal oxides, the organic synthesis route has been proved to be able to produce very good particle quality with a controlled size and narrow distribution. This method includes the decomposition of metal precursors in a non-polar organic solvent with the presence of oleic acid (OA) or trioctylphosphine oxide as the capping agent.⁷²–⁷⁴ However, most studies have reported that maintaining OA on the nanoparticles surface keeps the water molecules away from the Gd₂O₃ core, and thus seriously affects the magnetic influence of Gd⁴⁺ to the relaxation of protons. We have adopted the organic synthesis route with an improved procedure to synthesize monodispersed ultra-small Gd₂O₃ nanoparticles.⁷⁵ The OA capped Gd₂O₃ nanoparticles were phase transferred into hydrophilic through bilayer coating and ligand exchange methods (Fig. 2). In the bilayer coating method, OA was maintained by applying another surfactant layer of cetyltrimethylammonium bromide (CTAB) with its ammonium group facing outwards forming a hydrophilic surface. Through the ligand exchange, OA on Gd₂O₃ nanoparticles was replaced by a hydrophilic polymer polyvinyl pyrrolidone (PVP). The influence of different surface coating on Gd₂O₃ nanoparticles was then investigated based on their performance in reducing T₁ relaxation time. After successful ligand exchange with PVP, the Gd₂O₃–PVP showed a high r₁ value as a potential effective T₁ contrast agent, while Gd₂O₃–OA–CTAB showed a very low r₁ possibly due to the bi-layer long hydrophobic chains effectively prevent the water protons from approaching the Gd in the core of the nanoparticles. The in vitro cell viability and in vivo experiment were carried out to evaluate their cytotoxicity and application to T₁-weighted MR imaging.

Four different sizes between 2.5 and 8.0 nm of thermodynamically stable β-NaGdF₄ nanoparticles were synthesized by modifying nanoparticle growth dynamics as T₁-weighted contrast agents was reported by van Vegge et al.⁶⁷ The synthesized β-NaGdF₄ were exchanged the oleate ligands with biocompatible polyvinyl pyrrolidone in water. The r₁ relaxation increased with decreasing particle size and with increasing the surface-to-volume ratio demonstrated the surface Gd⁴⁺ ions on the particles are mainly contributed the relaxivity enhancement (Fig. 3). Moreover, the surface Gd⁴⁺ ions on a large particle affect the relaxivity stronger than those on a small particle. The ultrasmall β-NaGdF₄ nanoparticles can be doped with Yb⁴⁺/Tm⁴⁺ as potential bimodal probes.
Hou and co-workers synthesized differently sized NaGdF4–PEG–mAb nanoprobes, NaGdF4 nanocrystals conjugated to anti-EGFR monoclonal antibody (mAb) via “click” reaction both on the maleimide residue on particle surface and on thiol group from the partly reduced anti-EGFR monoclonal antibody (mAb) (Fig. 4). The biocompatibility and binding specificity of NaGdF4 nanocrystals (NaGdF4-PEG–mAb) with narrow particle size distributions were evaluated through in vitro and in vivo experiments. The NaGdF4-PEG–mAb probes exhibited promising tumor-specific targeting ability and enhanced MRI contrast effects.

Poly-(acrylic acid)-coated gadolinium hydrated carbonate nanoparticle (GHC-1) with ultrasmall size (2.3 ± 0.1 nm) through a simple strategy was developed by Liang and co-authors (Fig. 5). The obtained GHC-1 showed a high longitudinal relaxivity of 34.8 mM⁻¹ s⁻¹ at 0.55 T and low $r_2/r_1$ ratio of 1.17, highly dispersible and stable in aqueous solution because of the hydrophilic polymer coating. The biodistribution in organs and in vivo MRI studies demonstrated that GHC-1 could be a potential candidate as a $T_1$-weighted contrast agent. Lin’s group developed the gadolinium hexanedione nanoparticles (Gdh-NPs) as a cell tracking agent. Experiments demonstrated Gdh-NPs were nontoxic for human mesenchymal stem cells (hMSCs), the Gdh-NPs labeled stem cells have had better signals in cellular MRI assay. The Gdh-NPs could be as a potential MRI contrast agent for stem cell tracking.

Mesoporous silica nanoparticles doped with Gd can be potentially used for MRI contrast agents because of their characteristic uniform porous structure. The advantages of mesoporous silica nanoparticles, such as easy surface modification, good biocompatibility, make them being easily functionalized for cellular labeling, or bioconjugation with biomolecules for drug delivery, gene therapy. But most of studies focus on their preparations and physicochemical properties. Recently Gd$_2$O$_3$-assembled silica nanocomposite Gd$_2$O$_3$@MCM-41 was reported by Li et al. as an effective targeted probe for in vivo molecular imaging of cancer with systematic pre-clinical studies (Fig. 6). The biocompatibility of these nanoparticles is crucial for their clinical applications.
includes *in vitro* cell viability assessment, and *in vivo* study on immunotoxicity and acute toxicity test of the nanocomposite. Biodistribution and excretion studies of the nanocomposite were carried out for pharmacokinetic profile. MRI nanoprobe demonstrated a larger water proton relaxivity $r_1$ and a better $T_1$-weighted MR imaging when compared to Gd-DTPA.

Gadofullerenes are Gd-containing metallofullerenes, a new class of $T_1$-weighted MRI contrast agents. Gadofullerene derivatives such as Gd@C$_{60}$[OH]$_x$, Gd@C$_{60}$[C(COOH)$_2$]$_{10}$ and Gd@C$_{82}$[OH]$_x$ demonstrated high relaxivity as potential MRI contrast agents. Superparamagnetic gadonanotubes derived from ultrashort single-walled carbon nanotubes in which Gd(III) have been loaded are high-performance contrast agents. Water-soluble gadonanotube derivative that underwent a dramatic response to pH change at physiologically relevant conditions is a pH-activated smart contrast agent (Fig. 7). The relaxivity of the gadonanotubes response dramatically from 40 mM$^{-1}$ s$^{-1}$ (pH = 8.3) to 133 mM$^{-1}$ s$^{-1}$ (pH = 6.7) at 37 °C, especially approximately 40 mM$^{-1}$ s$^{-1}$ change between pH 7.4 and 7.0. With the dramatic response around physiological pH, the gadonanotubes could be promising for the development of clinical agents for the early detection of cancer as the extracellular pH of cancerous tissues is less than 7.0.

Fillmore and co-authors reported a tumor-specific peptide IL-13 peptides was conjugated with the carboxyl functionalized metallofullerene Gd$_3$N@C$_{80}$[OH]$_{24}$[CH$_2$CH$_2$COOH]$_{16}$. The obtained metallofullerene showed an enhanced specificity for the human glioma cells expressing IL-13Ra2. In addition, experiments demonstrated significant uptake of the targeted metallofullerene into brain tumor tissue in an orthotopic rodent model and the targeted metallofullerene could be used for delivering imaging and therapeutic agents to tumor cells.

**Gd(III) chelate grafted macromolecular nanoparticles**

Gadolinium complexes, Gd(III) ions chelated with a low molecular weight acyclic or cyclic ligand are the only Gd-based contrast agents used for clinic and will continue to be the most widely used. Macrocyclic-based gadolinium complexes have a number of advantages such as pharmacokinetics and pharmacology due to the tight binding Gd(III) to the macrocyclic chelator. While various compounds have been evaluated as MR contrast agents, the high relaxivity and stability of Gd(III) chelates are the two important requisites for the development of contrast agents. Most of these small molecular contrast agents distribute throughout the intravascular and interstitial space, and excreted rapidly via renal filtration. Both small doses and low release of free Gd(III) ions are the most concerns as they will reduce the toxicity. Some strategies have been reviewed to increasing the relaxivity of Gd(III) chelates as MRI contrast agents.

![Fig. 6](a) The average loading H$_2$O of simulated models (left vertical axis) versus the water adsorption of experimentally measured samples (right vertical axis) in MCM-41 silica assembled with different additions of the Gd$_2$O$_3$ molecule. Comparison of the proton relaxivity $r_1$ (b) and $T_1$-weighted phantom MR image (c) between Gd$_2$O$_3$@MCM-41 silica nanocomposite and the commercially available Gd-DTPA (ref. 87).

![Fig. 7](a) A pictorial representation of the gadonanotubes. Small, superparamagnetic clusters of Gd(III) ions reside within the sidewall defects of the nanotube (chloride counteranions omitted for clarity). (b) $r_1$ relaxivity (per Gd(III)) as a function of the pH for the gadonanotubes at 1.41 T and 37 °C (ref. 94).
nanoparticles, human mesenchymal stem cell are strategies to increase the relaxivity of contrast agent as nanoparticles exhibit a high relaxivity per particle. Though simply increase the overall size of the nanoparticle will lead to a corresponding increase in the relaxivity per nanoparticles, there is an optimal nanoparticle volume or molecular weight.

Gold nanoparticles can be used as carriers for Gd(III) chelates with a dithiolated derivative of DTPA (DTDTPA) in which gold core of the nanoparticle coated with Gd(III) chelate. Gold nanoparticles with a size of 2–2.5 nm were prepared by reducing a gold salt in the presence of new chelator. The immobilization of a large number of DTDTPA-Gd chelate on each particle contribute to a very high relaxivity \( r_1 = 585 \text{ mM}^{-1} \text{s}^{-1} \) compared to 3.0 mM\(^{-1}\) s\(^{-1}\) for DTPA-Gd) of the particle which make them as contrast agents for MRI. In addition, the biocompatibility of gold offers its applications in living organisms for MRI and/or hyperthermia therapy. The DTDTPA chelator could be conjugated to a biomolecules for other applications such as specific targeting. A nanoconjugate contrast agent made from covalent attachment of Gd(III) to thiolated DNA followed by surface conjugation on to gold nanostars (DNA-Gd@stars) was reported recently by Rotz et al. The study showed the nanoparticle shape and surface structure play an important role for relaxivity of the nanoconjugate as they affected the organization of the conjugated DNAs on the particle surface and thus to affect the water molecules in the proximity of the Gd(III) complex. (DNA-Gd@stars) improve Gd(III) delivery and maintain biocompatibility when incubation with pancreatic cancer cells. A gold nanoparticles conjugate (DNA-Gd@AuNPs), that is functionalized with deoxythymidine oligonucleotides containing Gd(III) chelates and a red fluorescent Cy3 moiety which can be used to visualize in vivo transplanted human neural stem cells was reported by Nicholls and coworkers [Fig. 8]. Through the in vitro assays to determine cell uptake, potential cytotoxicity and cellular relaxivity, the stable DNA-Gd@AuNPs can be used to visualize the distribution of human neural stem cells by MRI with optimal imaging parameters and exhibited an improved \( T_1 \) relaxivity and excellent cell uptake.

Gd-DOTA derivative conjugated self-assembling peptide amphiphiles (PACAs) form the nanofiber networks was synthesized and their in vitro MR evaluation was carried out by

![Fig. 8](image_url)

**Fig. 8** DNA-Gd@AuNP synthesis and stability. Particles consist of a gold nanoparticle core loaded with DNA to which the Gd-HPDO3A and Cy3 moieties are attached (A). Transmission electron microscopy (TEM) of conjugated DNA-Gd@Au nanoparticles for size determination (B). Particles retain their relaxivity properties at 1.41 T over more than 2 weeks (C). There is a small amount of Gd(III) loss at 37 °C, amounting to <5% of total Gd(III) over 2 weeks. However, loss is negligible (<0.4%) when particles are stored at 4 °C (D) [ref. 118].
The peptide amphiphiles contain three parts: a headgroup, body, and an alkyl tail. The headgroup is made up of an epitope for specific cell interaction. The body is functional in which hydrogen bond formed between molecules is the driving force for fiber formation (Fig. 9). The alkyl palmitoyl tail of the PA initiated a hydrophobic collapse in an aqueous environment. Self-assembling PAs forms nanofiber, varying the position of the Gd(III) chelate with DOTA derivative on the PAs leads to the changes in the molecule’s relaxivity. Novel design of MRI active supramolecular structures to noninvasively track PA gel scaffolds in vivo, provides a possible three dimensional MR images for the fate mapping of these new biomaterials. Kobayashi et al. reported Gd(III) complex Gd-EDTA (EDTA = ethylenediaminetetraacetic acid) entrapped in mesoporous silica nanoparticles Gd-EDTA/SiO$_2$. (3-Aminopropyl)trimethoxysilane was introduced on the silica particles at pH 3 to make NH$_2$/SiO$_2$. Then immobilization of Gd-EDTA on the NH$_2$/SiO$_2$ particles at pH 5, the obtained Gd-EDTA/SiO$_2$ particle colloid solution was concentrated to certain Gd concentration with centrifugation. High contrast $T_1$-weighted MR images and high $r_1$ relaxivity of the Gd-EDTA/SiO$_2$ particles indicated their application to MRI.

Polymer-based nanoparticle MRI contrast agents have demonstrated optimal pharmacokinetics and blood half-life, increased tolerance to enzymatic degradation, good physical and chemical stability which improve their clinical and therapeutic value. Polymeric macromolecular nanoparticle contrast agents can be considered as an alternative to blood pool agents because blood pool agents have following shortcomings: enhancement of interstitial space while enhancement of blood, prolonged retention in liver and bone, cardiac toxicity, etc. Attention has been put on Gd(III) chelates conjugated onto dendrimers, liposomes, micelles, core cross-linked star polymers and hyperbranched polymers.

Kobayashi and Brechbiel reviewed and developed the nano-sized MRI contrast agents with different dendrimer cores such as polypropylenimine diaminobutane (DAB) (Fig. 10). Different nano-sized molecular contrast agents in diameter behave differently in the body. Various size contrast agents up to 15 nm altered vascular wall permeability in the blood, excretion pattern, and recognition by the reticuloendothelial system. The different sizes and various properties of dendrimer-based macromolecular MRI contrast agents provide sufficient contrast enhancement for various applications. The

Fig. 9 Structures of the PA molecules with the black circles representing the Gd(III) ion. (1) is an example of a filler PA and does not contain the Gd(III) chelate. (2) and (3) are the PACA molecules used in this study containing Gd(III) (ref. 110).
**in vitro** and **in vivo** experiments on the dendrimer core Gd(III) chelate contrast agents demonstrated that they have much higher relaxivity compared to a single chelate unit. These contrast agents could be used for intravascular contrast-enhancing.

Dendrimers have been prepared as multifunctional nanomaterials for diagnostic and therapeutic agents. Gd(III) chelates conjugated to dendrimers with functional groups could be used as targeting contrast agents, as carriers for target-specific delivery of drugs. Gd-DTPA conjugated dendrimer nanoclusters were reported as a _T_1-weighted MRI contrast agent for tumor-targeting by Tsourkas and coworkers. The dendrimer nanoclusters (DNCs) were prepared by crosslinking G5 PAMAM dendrimers through a bifunctional amine-reactive crosslinker NHS-(PEG)5–NHS-(BS(PEG)5). Gd-DTPA chelates were then conjugated to DNCs and further functionalized with the folic acid for tumor-targeting and the optical imaging dye fluorescein isothiocyanate (FITC) (Fig. 11). The _r_1 relaxivity of Gd(m) chelate conjugated DNCs is higher than that of Gd-DTPA.

**In vivo** studies of DNCs on folate-positive KB tumor mice showed significant contrast enhancement at 4 h to 24 h post-intravenous injection of DNCs. A tumor targeting biodegradable dendrimer MRI contrast agent FA-PEG-G2-DTPA-Gd was synthesized and evaluated for enhanced blood pool and tumor imaging by Shen and Tang groups. Both PEG chains with distal folic acid and Gd-DTPA chelates were conjugated to a polyester dendrimer.

**Fig. 10** Scheme of the dendrimer core used for contrast agents (ref. 135).

**Fig. 11** The preparation of paramagnetic targeted dendrimer nanoclusters (DNCs) (ref. 141).
MRI have been incorporated into nanodevices to enable preclinical and clinical applications. Gd-DTPA was incorporated into DACHPt-loaded micelles by utilizing the reversible complex formation between DACHPt and Gd-DTPA, leading to slow molecular reorientation and decrease the mobility with increase relaxivities (Fig. 13). The obtained Gd-DTPA/DACHPt-loaded micelles have a longitudinal relaxivity $r_1$ 80.5 mM$^{-1}$ s$^{-1}$. Animal experiments revealed that Gd-DTPA/DACHPt-loaded micelles accumulated effectively in subcutaneous murine colon carcinoma and orthotopic human pancreatic adenocarcinoma models, and specifically enhanced the signal at the tumor site for a prolonged time. Contrast-enhanced MRI exhibited that Gd-DTPA/DACHPt-loaded micelles could be applicable for the measurement of the volume of orthotopic pancreatic tumors in the abdominal cavity, and for the noninvasive evaluation of their enhanced antitumor activity.

Nanoscale micelles based on biodegradable poly(L-glutamic acid)-b-poly(lactide) with Gd-DTPA conjugated to the shell layer (Fig. 14) was reported by Li et al. as a potential nano-sized MRI visible delivery system with a high $r_1$ relaxivity. Polymeric micelles composed of polysuccinimide (PSI) derivatives incorporating methoxy-poly(ethylene glycol) (mPEG) were conjugated with DTPA-Gd, and showed better contrast on in vitro phantom compared to that of Omniscan. However, the pharmacokinetics of these polymeric micelles needs to be done before assessing their potential applications for in vivo MRI study. Liu et al. reported a new multifunctional pH-disintegrable micellar nanoparticles prepared from star copolymers containing asymmetrically functionalized β-cyclodextrin (β-CD) were covalently conjugated with doxorubicin (DOX), folic acid (FA), and DOTA-Gd moieties. The obtained micellar nanoparticles exhibited considerably enhanced $r_1$ relaxivity compared to that of the small molecule counterpart. In vivo MR imaging studies found considerable uptake of micellar nanoparticles at rat kidney.

The drawbacks for synthesis of dendrimers are challenging multistep synthesis and purification. There are issues for indirect assembly strategies to prepare micelles utilizing amphiphilic block copolymers as they are not very stable on dilution,
leading to uncertainty during in vivo studies; the additional micelle cross-linking increases the inherent complexity. There is a need for the development of more versatile and efficient synthetic routes to polymeric nanoparticle MRI contrast agents such as core cross-linked star and hyperbranched polymer nanoparticles.

Gd-loaded nanoparticles (GdNPs) have been attractive as MRI theranostic applications in imaging-guided drug delivery, drug release, monitoring the treatment efficacy and personalized administration, etc.\(^\text{159}\) The ideal theranostic GdNPs should possess following properties: biodegradable and non-toxic of NPs carrier materials; efficient delivery of GdNPs to target tissue or organ; active targeting and sensitive to diagnosis; therapeutic efficacy of drug; optimal excretion pattern of Gd molecules to reduce toxicity [Fig. 15]. GdNPs as drug carriers to co-deliver the therapeutic drugs and Gd are normally lipid-based,\(^\text{151,152}\) polymeric,\(^\text{151}\) micelles,\(^\text{154}\) and silica\(^\text{155}\) nanoparticles. Nanocarrier liposomes co-encapsulated doxorubicin and Gd was reported as a dual functional diagnostic and chemotherapeutic agent, and target-specific carriers for clinical applications.\(^\text{171}\) An interesting temperature-induced liposomal system encapsulated doxorubicin and Gd-HPDO3A was developed as a theranostic agent for chemotherapeutics under MRI guidance.\(^\text{152}\) Mesoporous silica nanoparticles can be useful for theranostic applications as silica nanoparticles could gradually release therapeutic drugs and diagnostic contrast agents at the targeting area. A pH-dependent biodegradable silica nanotubes derived from Gd(OH)\(_3\) nanorods was reported by Hu et al.\(^\text{155}\) The released Gd(\(\text{III}\)) ions from the Gd(OH)\(_3\) nanorods were chelated by the pre-modified DOTA, obtained Gd-DOTA then grafted onto silica nanotubes. The Gd-DOTA grafted silica nanotubes loaded with doxorubicin exhibit enhanced \(T_1\) imaging contrast and anticancer activity.\(^\text{155}\)

Core cross-linked star and hyperbranched polymer nanoparticles were reported as MRI contrast agents by Li et al. with significant advancements in their preparations.\(^\text{152,153}\) The macromolecular architecture and precise molecular location of Gd(\(\text{III}\)) chelate has a significant impact on relaxivity and efficacy of contrast agents. When compared to the traditional micellar approach, one of the key advantages of core cross-linked star and classic hyperbranched polymer nanoparticles is the inclusion of cross-linking during the polymerization process. These polymer nanoparticles required to load hydrophobic guest molecules. Liu et al. reported that star copolymers covalently anchored with polycationic PDMA (PDMA = poly(N,N-dimethylaminoethyl methacrylate)) arms and conjugated with DOTA-Gd chelate at the lower and upper rim of toroidal \(\beta\)-cyclodextrin (\(\beta\)-CD) cores were synthesized (Fig. 16).\(^\text{156}\) The obtained cationic star copolymer could effectively bind negatively charged anionic plasmid DNA (pDNA) via electrostatic interactions, thus a dramatically increased \(r_1\) relaxivity (10.9 mM\(^{-1}\) s\(^{-1}\)) was found compared to that of small molecule contrast agents. Same group recently also reported the synthesis of hyperbranched polyprodrug amphiphiles (hPAs) via reversible addition-fragmentation chain transfer (RAFT) copolymerization.\(^\text{154}\) Reduction-activatable camptothecin prodrugs and Gd-DOTA derivatives chelate conjugated onto hPAs through the click reaction in the hydrophobic cores, the nanoparticles were then decorated guanidine onto hydrophilic coronas. The hPAs nanoparticles exhibited cell penetration potency, prolonged blood circulation, synergistic activation of therapeutic efficacy and MR imaging contrast enhancement. MR imaging contrast performance on guanidine-decorated hPAs demonstrated prolonged blood circulation with a half-life up to ~9.8 hours.\(^\text{154}\)

We presented the direct synthesis of stable Gd(\(\text{III}\))-chelated branched copolymer nanoparticles, started from novel monomers via reversible addition-fragmentation chain transfer
(RAFT) polymerization without the self-assembly techniques. The resulting branched copolymer nanoparticles comprise a hydrophilic corona and a hydrophobic covalently cross-linked core. This synthetic approach does not require post-polymerization modification to incorporate macrocycle functionalities. The structural advantages of branched copolymer nanoparticles have been demonstrated by encapsulated the hydrophobic dye Nile within the hydrophobic core of N2(Gd) without precipitation for three months. The stability and structural advantages of loading hydrophobic guest molecules within the nanoparticles cores, without any significant loss in relaxivity, offer the potential for simultaneous bioimaging and drug delivery. The cytotoxicity testing using HK-2 cells established their negligible toxicity profile. In vitro and in vivo MRI studies of the N2(Gd) nanoparticles showed that they have a high relaxivity and a long blood retention time. The dynamic contrast imaging on SCID mice bearing U87MG human glioma xenograft tumor demonstrated that they are promising intra-vascular MRI contrast agents and are able to perfuse and passively target tumor cells. The bifunctional hydrophobic cores are able to simultaneously conjugated to Gd(III) chelate and noncovalently encapsulate hydrophobic guest molecules, that combine the properties of micellar assemblies with the synthetic advantages of core cross-linked star polymers.

### Bimodality probes for MRI and other imaging modalities

A series of nanostructured materials have been developed as novel multimodal bioimaging agents for applications in diagnostics and therapy as they overcome the limitations of either imaging modality used alone. The integration of MRI and fluorescence imaging (FI) techniques provides new opportunities for cancer diagnosis, drug delivery, and therapy by taking advantages of the superb spatial resolution of MRI and high sensitivity of FI. Chemistry synthesis strategies have been developed extensively for this regard. Hyeon et al. designed the multifunctional nanomedical platforms as cancer-targeted, dual modality imaging probe including MRI and optical imaging, and drug delivery. The multifunctional polymer nanoparticles was composed of four moieties (Fig. 17): biodegradable poly[D,L-lactic-co-glycolic acid] (PLGA) nanoparticles as vehicles for loading and release of therapeutic agents into cells; superparamagnetic magnetite nanocrystals for magnetically guided delivery and T2 MRI contrast agent and semiconductor nanoparticles (CdSe/ZnS quantum dots) for optical imaging; doxorubicin for cancer therapy; PEGylated folate for active cancer cells. Same group later prepared multifunctional nanoparticles by assembling Fe3O4 nanocrystals on uniform dye-doped mesoporous silica nanoparticles for enhanced MRI and FI dual modalities. The in vivo study showed the composite nanoparticles accumulated at the tumor site.

Gd2O3 core embedded in a polysiloxane shell which is comprised of organic fluorophores and carboxylated PEG to form hybrid nanoparticles as contrast agent for both in vivo FI and MRI was reported by Bridot et al. It was found that the longitudinal relaxivity per particle enormously increases with the decrease in the particle size. Kryza and co-workers reported hybrid gadolinium oxide particles as a multimodal SPECT/MRI/optical imaging and theranostic agent. The particles prepared by encapsulating Gd2O3 cores within a polysiloxane shell, which contains organic fluorophore (Cy 5), coated by a hydrophilic carboxylic layer were used for biodistribution and pharmaco-kinetics studies. Various iodine compound coated Gd2O3 nanoparticles were synthesized as T1-weighted MRI and CT dual imaging probes for cancer. Efforts have been made to transfer these Gd2O3 nanoparticles from hydrophobic into hydrophilic for bio-applications. Petoral et al. synthesized Tb(III)-doped ultrasmall Gd2O3 nanocrystal for combined fluorescent labeling and MRI contrast agent. The nanocrystals were stabilized by PEGylation. Since Tb(III) attributed to the fluorescent property, the capacity of the Tb(III)-doped nanoparticles for fluorescent labelling of living cells was investigated. A facile synthetic strategy for fabrication of rare earth Tb(III), Y(III) and Er(III)-centred labelling of living cells was investigated. A facile synthetic strategy for fabrication of rare earth Tb(III), Y(III) and Er(III)-centred labelling of living cells was investigated. Oleylamine stabilized the particles and prevent the aggregation of these particles. Interactions of oleylamine on the nanoparticles lead to the formation of the extended chain, which fuse longitudinally and recrystallize to nanorods (Fig. 18). The rare earth-doped Gd2O3 nanorods demonstrated a tunable down- or up-conversion fluorescent and promising T1-weighted MRI contrast agent.

Rare earth ions doped upconverting nanoparticles have extensive applications in biomedical imaging. Inorganic GdF3 or NaGdF4 nanoparticles doping with other lanthanides to integrate optical and MR contrast effect into dual modality probes have been explored. NaGdF4:Er(III),Yb(III)/NaGdF4 core/shell upconverting particles can be used as a new type of both optical and MRI bimodal probe was investigated by...
Without adding any other moieties, the nanoparticles exhibit multimodality on their own nanocomposites. The optical property of the particles is attributable to Er(III) or Yb(III) located on the crystal lattice of the NaGdF₄ host. Chen et al. reported amine-functionalized and biocompatible KGdF₄:Ln(III) nanocrystals were synthesized through a facile one-step solvothermal route (Fig. 19). The nanocrystals conjugated to biomolecules through amino groups on the capping ligand polyethylenimine to be functional bioprobes. The KGdF₄:Ln(III) showed as a sensitive bioprobe in time-resolved fluorescence resonance energy transfer (TR-FRET) assays to quantitatively detect avidin protein. In the meantime, KGdF₄ possess a relatively large longitudinal relaxivity.

Rare earth ions contained upconverting nanomaterials displayed excellent luminescence, unique MR and strong X-ray attenuation, thus they can be used as high performance contrast agents for luminescence, MR and CT imaging. Rare earth ions contained upconversion nanomaterials displayed excellent luminescence, unique MR and strong X-ray attenuation, thus they can be used as high performance contrast agents for luminescence, MR and CT imaging. Rare earth ions contained upconversion nanomaterials displayed excellent luminescence, unique MR and strong X-ray attenuation, thus they can be used as high performance contrast agents for luminescence, MR and CT imaging. Rare earth ions contained upconversion nanomaterials displayed excellent luminescence, unique MR and strong X-ray attenuation, thus they can be used as high performance contrast agents for luminescence, MR and CT imaging. 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complex, followed by complete acetylation of the remaining dendrimer terminal amines (Fig. 21). The $r_1$ relaxivity and X-ray attenuation property of Gd–Au DENPs enable the nanoparticles to be used as dual CT/MRI contrast agents for in vivo imaging. In vivo biodistribution studies on major organs of rats and mice showed the Gd–Au DENPs have an extended blood circulation time. Europium-doped (GdS:Eu(III)) opto-magnetic nanoparticles prepared from sonochemistry method was reported by Jung and coworkers. Gadolinium sulfide constitutes the core with Gd replaced by Eu dopant. The sulfur from 1-dodecanethiol at the core also serves as a surface capping ligand which is replaced by 3-mercaptopropionic acid (MPA) for bio-application (Fig. 22). The photophysical property is induced by Eu(III) ions dopant. The nanoparticles were internalized into the cytoplasm of breast cancer cells (SK-BR-3). The photoluminescence and paramagnetic properties of the nanoparticles enable them to be used as a dual probe for in vitro cell imaging and in vivo $T_1$-weighted MR imaging. Strong positive contrast enhanced blood vessels and organs of mice and the confocal images of breast cancer cells containing GdS:Eu(III) nanoparticles demonstrate the dual-mode imaging capability of the GdS:Eu(III) nanoparticles.

Gd(III)-conjugate AuNP microcapsules was developed to visualized pancreatic islet cells for treatment of type 1 diabetes and enable multimodal cellular imaging of transplanted islet cells. Multifunctional dendrimer-entrapped Gd(III)-conjugate AuNP have been used for CT/MR dual mode imaging of tumors. Lipid Gd-DOTA functionalized AuNPs@PDA nanohybrid containing core–shell structure with the polydopamine coating gold nanoparticles as the inner core, the indocyanine green (ICG) as a phototherapeutic agent and lipids modified Gd-DO3A and lactobionic acid (LA) showed potential as theranostic agents for photothermal therapy to ablate cancer. Lux and coworkers reviewed the Gd-based nanoparticles developed for theranostic applications and more precisely on irradiations guided by MRI. Gd-based nanoparticles can act as effective radiosensitizers under different types of irradiation such as radiotherapy. These new therapeutic modalities pave the way to therapy guided by imaging and to personalized medicine. Same group also summarized the advantages of Gd-based ultrasmall nanoparticles versus molecular Gd chelates for radiotherapy guided by MRI for glioma treatment. Fast accumulation and strong resident time in the brain tumor of Gd-based nanoparticles was found compared to commercial chelates. The biodistribution profile is suitable for an optimal radiosensitization.

Design of Gd(III) chelate coated gold nanoparticles for both X-ray and MRI were reported by Roux et al. The Gd(III) chelate coated gold nanoparticles were obtained by encapsulating gold nanoparticles inside the polymeric microcapsules made of PLGA (poly(lactic-co-glycolic acid)) and PLGAs with different molecular weights (Fig. 21). The PLGA microcapsules were then functionalized with the Gd(III) chelate and the nanoparticles were then coated with gold nanoparticles. The resulting nanoparticles showed high relaxivity and a strong positive contrast effect in MR imaging.

![Fig. 21](image1.png) Schematic illustration of the designed nanostructure (a) and the synthesis procedure (b) of the Gd–Au DENPs. TEA and Ac₂O represent triethylamine and acetic anhydride, respectively (ref. 184).

![Fig. 22](image2.png) (A) Detailed structure of Eu-doped GdS (GdS:Eu(III)) opto-magnetic NPs (B) cell imaging via fluorescence emission of GdS:Eu(III) NPs at 614 nm. (C) Biocompatible GdS:Eu(III) NPs as a strong positive contrast agent for the MR imaging of blood vessels and various organs (ref. 185).
cores within a multilayered organic shell made from Gd(III) chelates bound to each other through disulfide bonds (Fig. 23). The *in vitro* imaging experiments demonstrated that Au@DTDTPA-Gd (DTDTPA = dithiolated derivative of diethylenetriaminepentaacetic acid) nanoparticles have a positive contrast enhancement at kidney in T₁-weighted images. The contrast enhancement in MR images is contributed by Gd(III) ions which are chelated by DTDTPA in the organic shell, whereas the gold core provides X-ray absorption. The Gd(III) chelate functionalized gold nanoparticles can be applied as contrast agents for both MRI and X-ray. The other examples of gold nanoparticles coated with Gd-chelate as potential CT/MRI bimodal contrast agents were reported by Kim *et al.* The chelator L = a conjugates of DTPA-bisamide (DTPA = diethylenetriaminepentacetic acid) with cysteine or 4-aminothiophenol. These well-dispersed spherical GdL@Au particles are obtained by substituting gadolinium chelate (GdL) for citrate on the gold nanoparticle surfaces. *In vitro* MRI showed GdL@Au nanoparticles have very high relaxivity (∼104 mM⁻¹ s⁻¹) and the r₁ relaxivity per [Gd] is as high as 10 mM⁻¹ s⁻¹. These particles also exhibit low cytotoxicity, indicating they can be further applied for preclinical studies (Fig. 24).

Gd(III) complex contrast agents have been incorporated to develop dual MRI/optical imaging probe. Dendrimer-based MRI/FI dual modality nanoprobe has been prepared by covalently incorporating Gd(III) complex and organic dyes. The first dendrimer-based dual MRI-FI agent is a novel PAMAM-based nanoprobe G6-(Cy5.5)₁₂₅(1B4M-Gd)₄₅ which composed of PAMAM dendrimers with covalently attached Gd(III)-DTPA chelates and units of NIR fluorescent dye, Cy 5.5. It should be noted that since FI possess much higher sensitivity compared to MRI, the number of Gd(III) chelate units on the dendrimer surface must be exceed the number of fluorophore units to obtain the performance in equilibrium for both imaging modalities. In the meantime, increase concentration of dye moieties on the surface lead to partial self-quenching of the FI due to lanthanide ions located in a close proximity to the optical probe. *In vivo* studies of the nanoprobe by both MRI and FI modalities demonstrated that the sentinel lymph nodes in mice can be visualized by MRI and can be detectable by FI with as little as 0.5 nmol of Cy 5.5. The combination of MRI and FI of the nanoprobe could be suggested to provide the complementary information by mapping the sentinel nodes with MRI prior to surgical resection and then FI could be used for the surgeon to the appropriate sentinel nodes during surgery. Same group further reported a novel synthetic approach to prepare a biotinylated dendrimer-based MRI agent conjugated to fluorescently labeled avidin that a unique disulfide bond in the core of the Gd[III]-1B4M-DTPA chelated to G2 PAMAM dendrimer as a biotin-targeted, lectin-targeted dual MRI/FI probe.

Core cross-linked (CCL) polymeric micelles covalently conjugated with DOTAGd and green-emitting fluorescent dye NBD fluorophores within pH-responsive cores were developed by Liu and co-workers. Due to pH-responsive core swelling and the associated hydrophobic–hydrophilic transition of CCL micelles, CCL micelles exhibit mildly acidic pH-triggered enhancement of signal intensities for both MR/FI imaging modalities. Tsien *et al.* reported activatable cell penetrating...
peptides linked to dendrimeric nanoparticle labeled with dye Cy5, and Gd(III) chelates for in vivo visualization of matrix metalloproteinase (MMP) activities by MRI and FL. The activatable cell penetrating peptides (ACPPs) are short polycations attached via protease-cleavable linkers to neutralizing polyanions which for in vivo fluorescence localization of active MMP-2 and MMP-9 in xenograft and transgenic tumor models. Each ACPP-conjugated dendrimers (ACPPDs) consists of a dendrimer conjugated to the polycationic segments of several ACPPs. The proteases such as MMP-2 and MMP-9 in tumors cut the linkers, releasing polyanions and leaving polycationic ACPPDs go into cells around the protease. The both Cy5 and Gd labeled “dual” ACPPD provide a good contrast for protease activity as dual probes for in vivo FI/MRI. However, these probes demonstrated the intrinsic shortcomings of commercial dyes, such as small Stokes shift, poor photo-stability and dye self-quenching.

Semiconductor quantum dots (QDs) are a new class of materials for bioimaging because of their fluorescence, photo-stability, and narrow and tunable emission spectrum. QDs with a paramagnetic coating, Gd(III)-functionalized, Mn(II) doped core/shell have been reported for multifunctional probes for bioimaging. Annexin A5-functionalized QDs with a paramagnetic lipidic coating for detection of apoptotic cells with both MRI and FI in vivo was reported by van Tilborg. The other group also reported annexin A5-functionalized QDs with biotinylated Gd-DTPA for optical and MR imaging of cell death and platelet activation.

Near-infrared (NIR) QDs can be used for FI to visualizing target objects in deep tissues with a low background signal. Jin et al. reported Gd(III)-DOTA functionalized NIR emitting QDs (CdSeTe/Cds) as a dual modal imaging probe for in vivo FI and MRI. Fig. 25 is a schematic representation for preparing Gd(III)-functionalized NIR-QDs. Hydrophobic CdSeTe/Cds QDs capped with trietylphosphine (TOP), trietylphosphine oxide (TOPO), and hexadecylamine (HAD) were replaced with a surface coating agent glutathione (GSH, a tripeptide (γ-L-glutamyl-L-cysteinylglycine)). The resulting GSH-QDs conjugated with Gd(III)-DOTA complex to add the T1-weighted MRI contrast ability.

Silica-based nanoparticles have been explored for molecular imaging and biomedical applications with improved biocompatibility and pharmacokinetics. Silica particles coated with equal amounts of both PEGylated (PEG-DSPE = 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(poly(ethylene glycol))-2000]) and Gd-DTPA-based Gd-DTPA-DSa = Gd-DTPA-bis(stearylamine) lipids (Q-SiPaLCs, Fig. 26) make it hydrophilic materials as a dual probe for FI and MRI. The bio-applicable lipid coating silica particles showed an increased blood half-life time and a favourable tissue distribution profile compared to the bare silica particles. Another hybrid silica nanoparticles for multimodal imaging was reported by Lin.
et al. The hybrid silica nanoparticles containing a luminescent \([Ru(bpy)_3]Cl_2\) core (bpy = 2,2'-bipyridine) and a paramagnetic monolayer coating of a silylated Gd-DTPA chelate. The efficient uptake of these hybrid nanoparticles by monocyte cells is demonstrated with their multimodal in vitro imaging.

Biodegradable polysorbate 80-coated poly(n-butyl cyanoacrylate) (PBCA) nanoparticles can be used to deliver targeted fluorophores, which is blood–brain barrier (BBB) impermeable, into the brain to allow in vivo optical imaging of cellular and neuropathological structures, and to deliver BBB permeable MR contrast agents Gd-DTPA into the brain of living mice by using endogenous lipapatidated apolipoprotein E particles to facilitate BBB crossing. Guccione et al. reported a novel fluorescent and paramagnetically labelled polymerized gadolinium–rhodamine nanoparticles (Gd–Rd-NPs), a dual modality imaging probe, can be used for serial monitoring of cell trafficking in vivo MRI/optical imaging.

Development of multimodal positive contrast agents is mostly based on Gd-DTPA terminated dendrimeric nanoparticles, Gd(III) chelate based lipid coating silica nanoparticles, Gd(III) chelate immobilized on QDs as mentioned previously. The potentials of Gd2O3 nanoparticles have been evaluated as multimodal contrast agents for in vivo imaging. The hybrid gadolinium oxide nanoparticles were prepared by encapsulating Gd2O3 cores by a polysiloxane shell containing organic fluorophores and covalent grafting of carboxylated PEG. The coating polysiloxane is porous for water molecular to contact the surface of crystalline core.
Gd(III) nanocarriers with fluorophore, strong photo-bleaching resistance and low toxicity are ideal for dual-modal imaging. Liu et al. developed a new approach to prepare Gd(III)-decorated hyperbranched polyglycerol (HPG) with a fluorescent polyhedral oligomeric silsesquioxane core (POSS-HPG-Gd) as a single molecular imaging probe for MRI/FI (Fig. 27). Hyperbranched molecules such as HPGs, added to hybrid nanodots composed of a rigid polyhedral oligomeric silsesquioxane (POSS) core surrounded by cationic conjugated oligoelectrolyte arms, then conjugated with DTPA-Gd to form hyperbranched architecture. The obtained hyperbranched molecules demonstrated excellent water solubility, low cytotoxicity and high biocompatibility. Fluorescent cell imaging of MCF-7 cancer cells demonstrated POSS-HPG has been successfully internalized into cytoplasm. Combined with MR imaging study, the POSS-HPG-Gd demonstrated a promising nanoprobe for FI/MRI. Further work from the Liu’s group focused on the development of FI/MRI nanoprobes with targeting ability, such as cancer detection in live animals, cancer metastasis study.

Conclusion and outlook

Extensive research on development of Gd(III) based nanoparticle-based has been carried out to overcome the limitation of traditional Gd chelate-based contrast agents. These novel nanoparticle MRI contrast agents including inorganic crystalline Gd(III) contained nanoparticles and Gd(III) chelate-grafted macromolecular nanoparticle certainly offer delicate sensitivity and specific functionality in diagnostic and therapeutic applications such as diagnosis of cancer and metastasis. Various Gd(III) containing multifunctional nanomaterials can be used as multimodal imaging probes for introducing a paradigm shift in clinical applications.

Several fundamental issues are remained, such as polar solvent-based synthetic method, surface modification for sophisticated nanoparticles, physicochemical properties such as chemical composition, shapes and sizes in order to accommodate biocompatibility and imaging properties; the major challenges in this field are functionalization of the multifunctional nanoparticles and the in vivo biological behavior of the nanoparticles such as their targeting efficiency, physiological stability and pharmacokinetics; obstacles still exist on integrated technology of combined MR and other imaging modalities for more therapeutic and diagnostic applications. All these challenges need to be addressed with an interdisciplinary collaboration between chemist, biologist, engineer and clinician.

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References


