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APPLICATIONS OF GADOLINIUM NANOPARTICLES IN MAGNETIC RESONANCE IMAGING: A REVIEW ON RECENT ADVANCES IN CLINICAL IMAGING

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Abstract

Magnetic Resonance Imaging (MRI) is a powerful imaging technique in clinical diagnostics. Magnetic nanoparticles (MNPs) have shown a promising potential as contrast agent in MRI techniques for in vivo assessments of anatomy, function, and metabolism. Gadolinium (Gd) nanoparticles have been widely used in MRI techniques especially in molecular imaging. This paper aims to comprehensively review the applications of Gd nanoparticles in different techniques of MRI especially in molecular imaging. In addition, the main features of Gd nanoparticles as contrast agents and their contrast enhancing characteristics in MRI are discussed. Improvements in the stability, relaxivity, and safety of Gd nanoparticles make them appropriate contrast agents.

Today, Gd nanoparticles are used as CA to improve image quality of MRI technique. Despite plenty of research has been conducted on Gd, there is serious concern in patients with renal failure. Iron oxide nanoparticles are a good alternative for these patients. Other types of paramagnetic and superparamagnetic nanoparticles have been developed to overcome these weaknesses, but still Gd nanoparticles are the most common contrast agent in MRI.

Key words: Gadolinium, Magnetic Resonance Imaging, Contrast Agents, Advances, Nanoparticles, Gadolinium, Manganese nanoparticle.

1. Introduction

Magnetic resonance imaging (MRI) is one of the most useful diagnostic imaging techniques with various applications in clinical medicine because of its excellent spatial resolution, noninvasive and nondestructive nature [1]. Noninvasive study of internal organs of a human body has always been a challenge to medicine [2]. Advances in nanoparticle technology over the last decade have shown that some of these materials have the potential to play an

important role in the diagnosis and treatment of cancers [3-6] [4, 7-10]. The development of MRI to one of the most powerful techniques in clinical diagnosis is accompanied by the progress in the design of contrast agents (CAs)[11]. Advances in nanoparticle technology over the last decade have shown that some of these materials have the potential to play an important role in the diagnosis and treatment of cancers [4, 7-10]. The development of MRI towards one of the most powerful techniques in clinical diagnosis is accompanied by the progress in the design of CAs, which enhance image quality [11]. MRI CAs provide a high sensitivity for the early detection of different pathologies and the tracking of magnetically tagged cells in vivo through molecular and cellular imaging [12]. MRI CAs improve diagnostic accuracy in some conditions such as inflammation and infectious diseases of the brain [13], spine [14], and soft tissues [15]. Various CAs have been developed for cellular and molecular imaging using MRI [16]. Among the broad spectrum of nanoscale materials being investigated for biomedical applications, Magnetic nanoparticles (MNPs) have gained significant attention due to their intrinsic magnetic properties, which enable tracking through the radiology cornerstone, MRI. Currently, CAs are used with a diameter of 50 to 350 nm [17]. Today there are great two class of MR CA: T1 and T2CA. T1 and T2CAs generate contrast enhancement in MR images via longitudinal and transverse relaxation processes, respectively [18]. Lowering the longitudinal (T1) or transverse (T2) relaxation times of the nuclear spins of water protons in tissues would enhance the efficiency of MRI CAs [19-21].

2. MRI and Contrast Agents

MRI is an imaging modality which is primarily used to construct images of the NMR signal from the hydrogen atoms in an object. In medical MRI, radiologists are most interested in looking at the NMR signal from water and fat, the major hydrogen containing components of the human body [22]. MRI utilizes the strong static homogenous magnetic field generated by the magnet. When the high frequency magnetic field is applied to the subject placed in the homogeneous static magnetic field, it excites proton nuclear spins within the patient's tissues. The excited proton spins rotate at a rate dependent upon the static magnetic field. As they flip, they emit radio frequency signals, referred as magnetic resonance signals [23]. The signal intensity of a volume element, a voxel, composing the slice depends not only on the quantity of protons present in this voxel but also on the ability the protons have to return to the equilibrium state after being excited with the radio frequency pulse, that means their relaxation properties [24, 25]. The return of excited nuclei from the high-energy state to the low-energy or ground state is associated with loss of energy to the surrounding nuclei [26]. Macroscopically, relaxation can be characterized by the longitudinal return of the magnetization to its ground state in the direction of the main magnetic field. The MR relaxation times include T1

and T2. The T1 longitudinal relaxation time is the time for the magnetization to return to 63% of its original value also is called spin-lattice relaxation. Spins are considered completely relaxed after 3-5 T1 times. T2 is a time at which transversal component has lost 63% of its excited state energy. During this period, energy is transported form one spin to nearby spins [27, 28]. For this reason, this decay constant also is named spin-to-spin relaxation. MRI is a clinical diagnostic imaging modality and works mainly on the differences in the longitudinal and transverse relaxation rates (1/T1 or 1/T2) of water protons in different tissues [29].

3. Contrast Agents in MRI

MRI signal strength depends on the longitudinal (T1) and transverse (T2) relaxation time of water protons, the difference in the relaxation times causes different contrasts in MRI images [30]. To maximize image quality, MR CAs are often needed to decrease T1 and T2 relaxation times [31]. Several materials have been recently developed to enhance the image contrast and diagnostic accuracy of MRI [32-34]. MRI CAs can be divided into two main categories of paramagnetic and super paramagnetic compounds. Paramagnetic CAs, also called T1 or positive CAs, are usually composed of Gadolinium^{3+} or Mn^{2+}, which generates positive signals on T1-weighted images. Superparamagnetic CAs, also called T2 or negative CAs, are usually constructed with iron oxide, which generates negative signal on T2 weighted images [35].

T1 CAs with reducing spin-lattice relaxation time leads to a stronger signal on T1 weighted images. T2 CAs reduce the signal on T2-weighted images by both shortening the spin–spin relaxation time (T2constant) and out-of-phase adjacent protons (by modification of their precession angular velocity). Therefore, Depending on the type of CA, by increasing (paramagnetic T1CA, mainly Gadolinium-based) or decreasing (superparamagnetic T2 CA, mainly iron-oxide-based) the signal in MRI revealed a molecular target [36].

4. Paramagnetic

Currently paramagnetic metal ions use as CA in MRI. These materials are metals with unpaired electrons in their outer shell (transition and lanthanide metals). The contrast material of this class can be named of Gadolinium and manganese, which are widely used in MRI [37].

4-1. Gadolinium (Gd): Paramagnetic

Although different metal ions can be used as CAs in MRI but the gadolinium (Gd^{3+}) ion is by far the most commonly used. This is due to a right combination of large number (seven) unpaired electrons combined with a long electron spin relaxation time which makes this metal a very efficient relaxation enhancing agent [38, 39]. The five MRI CAs,

approved by FDA for clinical applications are based on the Gd(III) ion, the material has high ability to catalyze the relaxation of the water signal and create positive contrast in MRI [40].

4-1-1.Gd-based magnetic resonance contrast agents (GBCAs) for molecular imaging

- **Gadolinium Gd(III) chelates:** This agent enhances T1 relaxation rate (1/T1) and commonly used as T1 CAs, producing a positive image contrast. Because of the toxic even at low concentrations free Gadolinium, it is bound to a chelate (usually a low-molecular weight organic molecule such as DTPA5 (diethylene triamine pentaacetic acid)) [41]. Both gadolinium and the ligands alone can't be used because of the toxicity [42]. To date, Gd(III) chelates the property due to strong paramagnetism, strengthening relaxation, stability and inertness in the body, are the most widely used CAs in MRI [43]. Gd(III) chelates compound, by altering the relaxation rate of the surrounding water protons to allow for more effective MRI contrast enhancement [40]. The Gd(III) chelate for clinical applications, has been divided into two major groups of cyclic (The macrocyclic ligands, e.g. DOTA and DO3A) and acrylic (The acryclic ligands, e.g. DTPA and DTPA-BMA) [44].
- **Macromolecular Gd(III) complexes**: Small molecular Gd(III) chelates have a relatively low relaxivity and extravasate non selectively from blood into the interstitium of both normal tissue and tumor, which has been a major limitation for their clinical applications. Attaching Gd(III) chelates to macromolecules slows down the rotational motion of the complexes, thus increases relaxivities [45]. For example Gd^{3+}-hexanedione NPs(GdH-NPs) produce stronger signal intensity than Gd-DTPA, probably because the larger Gd complexes with high molecular weight in GdH-NPs cause the slow tumbling rate of GdH-NPs [46]
- **Dendrimer**: Imaging the use of dendrimers as scaffolds to prepare MR CAs has received tremendous interest in the scientific community. This is largely due to the well-defined architectures, multivalent surfaces, and nanoscale sizes of dendrimers. Many research groups have explored the use of dendrimers as a new class of T1 positive MR CAs [47, 48], Typically Gd(III) conjugated with DPTA [49], DOTA [50], or their derivatives for T1 MR imaging applications [51]. Besides the discussed T1 MR CAs, dendrimers can also be used as stabilizers to form iron oxide NPs [52].
- **Gadolinium-Based Hybrid Nanoparticles**: recently Gadolinium-based hybrid (GH) nanoparticles were developed as a positive MR CA [53]. Gadolinium-based hybrid (GH) nanoparticles used to blood pool CAs. They showed much higher longitudinal relaxivity and transverse relaxivity (r1 and r2) than Gd–DTPA which are commonly used for clinical MRI. The GH nanoparticles can use as liver specific CA [54]. Luminescent hybrid

nanoparticles with a paramagnetic Gd_2O_3 core were also applied as CAs for MRI. These particles can be followed up by fluorescence imaging [55] .

- **Biodegradable macromolecular**: These new agents can act as macromolecular CAs for in vivo imaging and excrete rapidly as low molecular- weight agents. The polydisulfide Gd(III) is a biodegradable macromolecular, complexes have a great potential to be developed as safe, effective, biodegradable macromolecular MRI CAs for clinical applications [56, 57].
- **Liposomal particles**: Gd(III) complexes including Gd-DTPA [58, 59], Gd(DTPA-BMA) [60] and Gd-DOTA [61] have been encapsulated in the core of liposomes to prepare nanosized MRI CAs [62].
- **Targeted contrast agents**: The use of targeted CAs can improve contrast and provide information about specific biomarkers [63, 64], (e.g. Tumor-targeting with small molecular, protein, dendrimer, liposomal-based Gd CAs) [43].

4-1-2.Types of gadolinium contrast agents:

Gadolinium (III) CAs can be divided into three groups of the extracellular fluid agents and blood pool and Organ-specific agents.

- **Extracellular fluid agents:** Of extracellular fluid agents that are currently used, include: Dotarem, Magnevist, Omniscan, OptiMARK, and Prohance [65]. When these agents inject intravenous, randomly distribute within the vascular and interstitial ECF space and then excreted rapidly in their unchanged forms through the kidney glomerular filtration in the kidney [42]. All approved GBCAs are administered intravenously, distribute into accessible extracellular spaces with a distribution half-life about 10 min, and are excreted through the kidneys with a plasma half-life typically about 90 min in healthy human adults [66]. In case of malfunction of the kidneys, CA plasma elimination can be Considerably prolonged, with a half-life that may exceed 30 hour in some individuals [67].
- **Blood pool agents (intravascular agents):** The first-generation MR CAs was based on this design and have been used to image ruptures in the blood–brain barrier(BBB) [68]. This unique type of CAs refers to a diversity of CAs that are confined by purpose to the intravascular space and allocated exclusively to cardiovascular applications [69]. This property of blood-pool (BP) can be find out by controlling the distribution and elimination of the CAs, which in turn by their size relative to the permeability of the capillary endothelium in various organs determined. Although BP CAs are limited partially or entirely in passing through the endothelial membrane bound, they can still be excreted through the kidneys [42].These agents are designed in two ways: by connecting the Gd^{3+} ions to a

macromolecular polymer formed during the synthesis [70] or combination of Gd^{3+} with plasma proteins to form macromolecules in blood after injection [71]. Modification the structure of polydifulfide Gd(III) complexes can lead to biodegradable macromolecular CAs with various reinforce profiles in the blood pool. Polydisulfide Gd(III) complexes have relatively long blood circulation time are gradually into small compounds that are rapidly excreted through the kidney filtration converted. The use of biodegradable macromolecular CAs in MRI imaging cardiovascular disease and cancer, and to evaluate the response to treatment [72-74]**.**

- **Organ-specific agents:** Organ-specific agents are designed to specifically accumulate in a given organ or tissue. The diagnosis of hepatic lesions continues to be a problem even though many diagnostic methods are available [75]. Although the more commonly used MR contrast media are gadolinium (Gd) chelates, they are relatively non-specific due to the rapid accumulation in the liver [76]. Many efforts have been made to serve Gd^{3+}as specific CAs, small unilamellar liposomes used as carriers for gadolinium chelates. This chelates Trap in aqueous volume of liposomes and has the potential not only as a specific CA for the liver and spleen, but also for imaging vascular system [77]. Tetra-*P*-aminophenylporphyrin (TPP) was conjugated with gadolinium diethylenetriaminepen-taacetic acid (DTPA) ($Gd_2(DTPA)_4TPP$) could be a useful in MR imaging CA with an specific tumors CA [78]. A new class of metal-loaded nanoparticles has developed that have potential as CAs for medical imaging. In this case, the nanoparticles are loaded with Gd^{3+} to provide contrast in magnetic resonance (MR) imaging. The Gd^{3+}-loaded nanoparticles have a diameter of 120 nm, and provide excellent contrast when used to image the heart and gastrointestinal tract in a rat animal model [79].

4-1-3. Safety of gadolinium contrast agents

One of the important properties of MRI CAs in clinical uses is safety. Because Gd(III) ions are very toxic in ionic form, extremely interfering with calcium channels and protein binding sites, they cannot be administered directly [80, 81]. Free Gd ions accumulate in the liver, spleen, kidney, and bones. To reduce the side effects of toxic ions and prevent tissue interaction, Gd(III) ions are combined with chelating ligands. However, toxic Gd(III) ions may still be released of some chelates via transmetallation with other metal ions such as Zn^{2+}, Ca^{2+} and Cu^{2+} in the body and protonation of the ligands in the pH low which may cause the separation of scheelite within the body [82, 83]. Nephrogenic fibrosing dermopathy (NFD) is an idiopathic disorder in Kidney patients. In most patients with NFD, dialysis for kidney failure occurs [84, 85]. It often affects middle-aged. The Gd–DTPA is a small compound that is easily released from the pores of the vessels. Gd-containing CAs in patients with normal kidney function are rapidly

excreted from the kidney with a half-life of about 2 hours, however, in patients with chronic renal failure have a long half-life and may be greater than 120 to 30 hours. If immediate after MR angiography dialysis be inadequate markedly prolongs Gd clearance [86]. The combination of metabolic acidosis and insufficient clearance of Gd-containing agent is present in renal failure [87, 88]. Patient dehydration, old age, use of concomitant nephrotoxic drugs, multiple myeloma, heart failure, and liver disease are other risk factors [89-92].

4-1-4.Relaxivity of gadolinium contrast agents

The ability of a CA in changing water proton relaxation rates is called relaxivity. The relaxivity is defined as the ratio of the inverse relaxation time and the concentration of the CA nanoparticles [93]. It is often reported as the parameter r_2/r_1 (r_1 is longitudinal relaxivity and r_2 is transverse relaxivity) that gives an indication as to whether CAs are employed as positive or negative (CAs) [94-96], High relaxivity of a CA is acute for effective contrast enhanced MRI [97, 98]. Many attempts have been made to produce efficient CAs with high relaxivity [99, 100]: for example ligands based on hexadentate hydroxypyridinone (HOPO) and the polyaminocarboxylate based CA [Gd(AAZTA)]−1 are agents with greater relaxivity than DTPA and DOTA [101, 102]. When the high water exchange rate, relaxivity of chelated Gd has also been improved [103].

6. Conclusion

Gadolinium nanoparticles have been widely used in MRI especially in molecular imaging. Improvements in the stability, relaxivity, and safety of Gd nanoparticles make them appropriate contrast agents. Today, Gd nanoparticles are used as CA to improve image quality of MRI technique. Despite plenty of research has been conducted on Gd, there is serious concern in patients with renal failure. Iron oxide nanoparticles are a good alternative for these patients. Other types of paramagnetic and superparamagnetic nanoparticles have been developed to overcome these weaknesses, but still Gd nanoparticles are the most common contrast agent in MRI.

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References:

1. Mankoff, D.A., *A definition of molecular imaging*. J Nucl Med. 2007 Jun;48(6):18N, 21N.
2. Azhari, H., et al., *Noninvasive quantification of principal strains in normal canine hearts using tagged MRI images in 3-D.* American Journal of Physiology-Heart and Circulatory Physiology, 1993. **264**(1): p. H205-H216.

3. Ali, Y., et al., *Applications of Upconversion Nanoparticles in Molecular Imaging: A Review of Recent Advances and Future Opportunities*. Biosci., Biotech. Res. Asia, 2015. **12**(Spl.Edn.1): p. 131-140.
4. Ali, Y., et al., *Dye-Doped Fluorescent Nanoparticles in Molecular Imaging: A Review of Recent Advances and Future Opportunities*. Material Science Research India, 2014. **11**(2).
5. Yadollahpour, A., *Magnetic Nanoparticles in Medicine: A Review of Synthesis Methods and Important Characteristics*. Oriental Journal of Chemistry, 2015. **31**(Special Issue 1 (2015)): p. 271-277.
6. Yadollahpour, A. and S. Rashidi, *Magnetic Nanoparticles: A Review of Chemical and Physical Characteristics Important in Medical Applications.* Oriental Journal of Chemistry, 2015. **31**(Special Issue 1 (2015)): p. 25-30.
7. Park, J.Y., et al., *Paramagnetic ultrasmall gadolinium oxide nanoparticles as advanced T 1 MRI contrast agent: account for large longitudinal relaxivity, optimal particle diameter, and in vivo T 1 MR images.* ACS nano, 2009. **3**(11): p. 3663-3669.
8. Frias, J.C., et al., *Recombinant HDL-like nanoparticles: a specific contrast agent for MRI of atherosclerotic plaques*. Journal of the American Chemical Society, 2004. **126**(50): p. 16316-16317.
9. Hadjipanayis, C.G., et al., *Metallic iron nanoparticles for MRI contrast enhancement and local hyperthermia.* Small, 2008. **4**(11): p. 1925-1929.
10. Ali, Y., et al., *Applications of Upconversion Nanoparticles in Molecular Imaging: A Review of Recent Advances and Future Opportunities.*
11. Waters, E.A. and S.A. Wickline, *Contrast agents for MRI.* Basic Res Cardiol, 2008. **103**(2): p. 114-21.
12. Vuong, Q.L., et al., *A universal scaling law to predict the efficiency of magnetic nanoparticles as MRI T(2)-contrast agents.* Adv Healthc Mater, 2012. **1**(4): p. 502-12.
13. Saleh, A., et al., *In vivo MRI of brain inflammation in human ischaemic stroke.* Brain, 2004. **127**(7): p. 1670-1677.
14. Rudwaleit, M., et al., *Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group.* Annals of the rheumatic diseases, 2009. **68**(10): p. 1520-1527.
15. Garcia-Diez, A., et al., *MRI evaluation of soft tissue hydatid disease.* European radiology, 2000. **10**(3): p. 462-466.

16. Lee, Y.C., et al., *The use of silica coated MnO nanoparticles to control MRI relaxivity in response to specific physiological changes.* Biomaterials, 2012. **33**(13): p. 3560-7.
17. Waters, E.A. and S.A. Wickline, *Contrast agents for MRI.* Basic research in cardiology, 2008. **103**(2): p. 114-121.
18. Feldmann, V., et al., *Synthesis, characterization and examination of Gd[DO3A-hexylamine]-functionalized silica nanoparticles as contrast agent for MRI-applications.* J Colloid Interface Sci, 2012. **366**(1): p. 70-9.
19. Stanisz, G.J., et al., *T1, T2 relaxation and magnetization transfer in tissue at 3T.* Magnetic Resonance in Medicine, 2005. **54**(3): p. 507-512.
20. Qin, J., et al., *A High- Performance Magnetic Resonance Imaging T2 Contrast Agent.* Advanced Materials, 2007. **19**(14): p. 1874-1878.
21. Mlynárik, V., S. Gruber, and E. Moser, *Proton T1 and T2 relaxation times of human brain metabolites at 3 Tesla.* NMR in Biomedicine, 2001. **14**(5): p. 325-331.
22. Ward, K., A. Aletras, and R. Balaban, *A new class of contrast agents for MRI based on proton chemical exchange dependent saturation transfer (CEST).* Journal of magnetic resonance, 2000. **143**(1): p. 79-87.
23. Bushong, S.C. and G. Clarke, *Magnetic resonance imaging: physical and biological principles*. 2013: Elsevier Health Sciences.
24. Kobayashi, S., H. Ikeda, and T. Yoshimoto, *A clinical and histopathological study of factors affecting MRI signal intensities of pituitary adenomas.* Neuroradiology, 1994. **36**(4): p. 298-302.
25. de Graaf, R.A., et al., *High magnetic field water and metabolite proton T1 and T2 relaxation in rat brain in vivo.* Magnetic Resonance in Medicine, 2006. **56**(2): p. 386-394.
26. Lee, V.S., *Cardiovascular MRI: physical principles to practical protocols*. 2006: Lippincott Williams & Wilkins.
27. Brown, M.A. and R.C. Semelka, *MRI: basic principles and applications*. 2011: John Wiley & Sons.
28. Kuperman, V., *Magnetic resonance imaging: physical principles and applications*. 2000: Academic Press.
29. Lu, Z.R., et al., *Polydisulfide Gd(III) chelates as biodegradable macromolecular magnetic resonance imaging contrast agents.* Int J Nanomedicine, 2006. **1**(1): p. 31-40.
30. Brasch, R., et al., *Magnetic resonance imaging of transfusional hemosiderosis complicating thalassemia major.* Radiology, 1984. **150**(3): p. 767-771.

31. Kuperman, V.Y. and M.T. Alley, *Differentiation between the effects of T1 and T2* shortening in contrast- enhanced MRI of the breast.* Journal of Magnetic Resonance Imaging, 1999. **9**(2): p. 172-176.
32. Tromsdorf, U.I., et al., *A highly effective, nontoxic T 1 MR contrast agent based on ultrasmall PEGylated iron oxide nanoparticles.* Nano letters, 2009. **9**(12): p. 4434-4440.
33. Rieber, A., et al., *MRI in the diagnosis of small bowel disease: use of positive and negative oral contrast media in combination with enteroclysis*. European radiology, 2000. **10**(9): p. 1377-1382.
34. Liu, Y., et al., *Gadolinium-loaded polymeric nanoparticles modified with Anti-VEGF as multifunctional MRI contrast agents for the diagnosis of liver cancer.* Biomaterials, 2011. **32**(22): p. 5167-5176.
35. Burtea, C., et al., *Contrast agents: magnetic resonance.* Handb Exp Pharmacol, 2008. **185**(1): p. 135-65.
36. Gauberti, M., et al., *Molecular magnetic resonance imaging of brain-immune interactions*. Front Cell Neurosci, 2014. **8**(389).
37. Runge, V.M., et al., *Paramagnetic agents for contrast-enhanced NMR imaging: a review.* American journal of roentgenology, 1983. **141**(6): p. 1209-1215.
38. Brasch, R., *Work in progress: methods of contrast enhancement for NMR imaging and potential applications. A subject review.* Radiology, 1983. **147**(3): p. 781-788.
39. Brasch, R.C., *6.5 Contrast-enhanced NMR imaging: animal studies using gadolinium-DTPA complex.* Classic Papers In Modern Diagnostic Radiology, 2005: p. 423.
40. Caravan, P., et al., *Gadolinium(III) Chelates as MRI Contrast Agents: Structure, Dynamics, and Applications.* Chem Rev, 1999. **99**(9): p. 2293-352.
41. Raty, J.K., et al., *Non-invasive Imaging in Gene Therapy.* Mol Ther, 2007. **15**(9): p. 1579-86.
42. Ni, Y., *MR Contrast Agents for Cardiac Imaging*, in *Clinical Cardiac MRI*, J. Bogaert, et al., Editors. 2012, Springer Berlin Heidelberg. p. 31-51.
43. Zhou, Z. and Z.R. Lu, *Gadolinium-based contrast agents for magnetic resonance cancer imaging.* Wiley Interdiscip Rev Nanomed Nanobiotechnol, 2013. **5**(1): p. 1-18.
44. Huang, C.H. and A. Tsourkas, *Gd-based macromolecules and nanoparticles as magnetic resonance contrast agents for molecular imaging*. Curr Top Med Chem, 2013. **13**(4): p. 411-21.
45. Botta, M. and L. Tei, *Relaxivity Enhancement in Macromolecular and Nanosized GdIII- Based MRI Contrast Agents*. European Journal of Inorganic Chemistry, 2012. **2012**(12): p. 1945-1960.

46. Tseng, C.L., et al., *Gadolinium hexanedione nanoparticles for stem cell labeling and tracking via magnetic resonance imaging.* Biomaterials, 2010. **31**(20): p. 5427-35.
47. Qiao, Z. and X. Shi, *Dendrimer-based molecular imaging contrast agents.* Progress in Polymer Science, 2014.
48. Margerum, L.D., et al., *Gadolinium (III) DO3A macrocycles and polyethylene glycol coupled to dendrimers Effect of molecular weight on physical and biological properties of macromolecular magnetic resonance imaging contrast agents.* Journal of alloys and compounds, 1997. **249**(1): p. 185-190.
49. Pálinkás, Z.n., et al., *Kinetics of the Exchange Reactions between Gd (DTPA) 2−, Gd (BOPTA) 2−, and Gd (DTPA-BMA) Complexes, Used As MRI Contrast Agents, and the Triethylenetetraamine-Hexaacetate Ligand.* Inorganic chemistry, 2011. **50**(8): p. 3471-3478.
50. Lauffer, R.B., *Paramagnetic metal complexes as water proton relaxation agents for NMR imaging: theory and design.* Chemical Reviews, 1987. **87**(5): p. 901-927.
51. Kobayashi, H. and M.W. Brechbiel, *Nano-sized MRI contrast agents with dendrimer cores.* Advanced drug delivery reviews, 2005. **57**(15): p. 2271-2286.
52. Strable, E., et al., *Synthesis and characterization of soluble iron oxide-dendrimer composites.* Chemistry of materials, 2001. **13**(6): p. 2201-2209.
53. Hifumi, H., et al., *Gadolinium-based hybrid nanoparticles as a positive MR contrast agent.* J Am Chem Soc, 2006. **128**(47): p. 15090-1.
54. Zhang, B., et al., *Bioinspired synthesis of gadolinium-based hybrid nanoparticles as MRI blood pool contrast agents with high relaxivity.* Journal of Materials Chemistry, 2012. **22**(29): p. 14494-14501.
55. Bridot, J.L., et al., *Hybrid gadolinium oxide nanoparticles: multimodal contrast agents for in vivo imaging.* J Am Chem Soc, 2007. **129**(16): p. 5076-84.
56. Xu, R., et al., *In vivo evaluation of a PAMAM-cystamine-(Gd-DO3A) conjugate as a biodegradable macromolecular MRI contrast agent.* Experimental Biology and Medicine, 2007. **232**(8): p. 1081-1089.
57. Lu, Z.R., et al., *Extracellular biodegradable macromolecular gadolinium (III) complexes for MRI.* Magnetic resonance in medicine, 2004. **51**(1): p. 27-34.
58. Unger, E.C., et al., *Hepatic metastases: liposomal Gd-DTPA-enhanced MR imaging.* Radiology, 1989. **171**(1): p. 81-85.

59. Unger, E.C., et al., *Liposomal Gd-DTPA: effect of encapsulation on enhancement of hepatoma model by MRI.* Magnetic resonance imaging, 1989. **7**(4): p. 417-423.
60. Bui, T., et al., *Novel Gd nanoparticles enhance vascular contrast for high-resolution magnetic resonance imaging*. PLoS ONE, 2010. **5**(9): p. e13082.
61. Hak, S., et al., *A high relaxivity Gd (III) DOTA-DSPE-based liposomal contrast agent for magnetic resonance imaging*. European Journal of Pharmaceutics and Biopharmaceutics, 2009. **72**(2): p. 397-404.
62. Mulder, W.J., et al., *Lipid- based nanoparticles for contrast- enhanced MRI and molecular imaging.* NMR in Biomedicine, 2006. **19**(1): p. 142-164.
63. Hengerer, A. and J. Grimm, *Molecular magnetic resonance imaging.* Biomed Imaging Interv J, 2006. **2**(2): p. 1.
64. Achilefu, S., *Lighting up tumors with receptor-specific optical molecular probes.* Technol Cancer Res Treat, 2004. **3**(4): p. 393-409.
65. Laurent, S., L.V. Elst, and R.N. Muller, *Comparative study of the physicochemical properties of six clinical low molecular weight gadolinium contrast agents.* Contrast media & molecular imaging, 2006. **1**(3): p. 128-137.
66. Caravan, P., et al., *Gadolinium (III) chelates as MRI contrast agents: structure, dynamics, and applications.* Chemical reviews, 1999. **99**(9): p. 2293-2352.
67. Grobner, T. and F.C. Prischl, *Gadolinium and nephrogenic systemic fibrosis.* Kidney Int, 2007. **72**(3): p. 260-4.
68. Räty, J.K., et al., *Non-invasive imaging in gene therapy.* Molecular Therapy, 2007. **15**(9): p. 1579-1586.
69. Bjørnerud, A. and L. Johansson, *The utility of superparamagnetic contrast agents in MRI: theoretical consideration and applications in the cardiovascular system.* NMR in Biomedicine, 2004. **17**(7): p. 465-477.
70. Dunand, F.A., et al., *Lipari-Szabo approach as a tool for the analysis of macromolecular gadolinium (III)-based MRI contrast agents illustrated by the [Gd (EGTA-BA-(CH2) 12)] n n+ polymer.* JBIC Journal of Biological Inorganic Chemistry, 2001. **6**(3): p. 247-255.
71. Martin, V.V., et al., *Gadolinium (III) di-and tetrachelates designed for in vivo noncovalent complexation with plasma proteins: a novel molecular design for blood pool MRI contrast enhancing agents.* Bioconjugate chemistry, 1995. **6**(5): p. 616-623.
72. Lu, Z.-R., et al., *Polydisulfide Gd (III) chelates as biodegradable macromolecular magnetic resonance imaging contrast agents.* International journal of nanomedicine, 2006. **1**(1): p. 31.

73. Zong, Y., et al., *Structural effect on degradability and in vivo contrast enhancement of polydisulfide Gd (III) complexes as biodegradable macromolecular MRI contrast agents.* Magnetic resonance imaging, 2009. **27**(4): p. 503-511.
74. Zong, Y., et al., *Effect of size and charge on pharmacokinetics and in vivo MRI contrast enhancement of biodegradable polydisulfide Gd (III) complexes.* Journal of controlled release, 2006. **112**(3): p. 350-356.
75. Geraldes, C.F. and S. Laurent, *Classification and basic properties of contrast agents for magnetic resonance imaging*. Contrast media & molecular imaging, 2009. **4**(1): p. 1-23.
76. Niesman, M.R., et al., *Liposome encapsulated MnCl2 as a liver specific contrast agent for magnetic resonance imaging.* Invest Radiol, 1990. **25**(5): p. 545-51.
77. Schwendener, R., *Liposomes as carriers for paramagnetic gadolinium chelates as organ specific contrast agents for magnetic resonance imaging (MRI).* Journal of Liposome Research, 1994. **4**(2): p. 837-855.
78. Hindré, F., et al., *Tetra- p- aminophenylporphyrin conjugated with Gd- DTPA: Tumor- specific contrast agent for MR imaging.* Journal of Magnetic Resonance Imaging, 1993. **3**(1): p. 59-65.
79. Reynolds, C.H., et al., *Gadolinium-loaded nanoparticles: new contrast agents for magnetic resonance imaging.* Journal of the American Chemical Society, 2000. **122**(37): p. 8940-8945.
80. Lansman, J.B., *Blockade of current through single calcium channels by trivalent lanthanide cations. Effect of ionic radius on the rates of ion entry and exit.* The Journal of general physiology, 1990. **95**(4): p. 679-696.
81. Biagi, B.A. and J.J. Enyeart, *Gadolinium blocks low-and high-threshold calcium currents in pituitary cells.* American Journal of Physiology-Cell Physiology, 1990. **259**(3): p. C515-C520.
82. Laurent, S., et al., *Stability of MRI paramagnetic contrast media: a proton relaxometric protocol for transmetallation assessment.* Investigative radiology, 2001. **36**(2): p. 115-122.
83. Greenberg, S.A., *Zinc Transmetallation and Gadolinium Retention after MR Imaging: Case Report 1.* Radiology, 2010. **257**(3): p. 670-673.
84. Cowper, S.E., et al., *Nephrogenic fibrosing dermopathy.* Am J Dermatopathol, 2001. **23**(5): p. 383-93.
85. Swartz, R.D., et al., *Nephrogenic fibrosing dermopathy: a novel cutaneous fibrosing disorder in patients with renal failure.* Am J Med, 2003. **114**(7): p. 563-72.

86. Joffe, P., H.S. Thomsen, and M. Meusel, *Pharmacokinetics of gadodiamide injection in patients with severe renal insufficiency and patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis.* Acad Radiol, 1998. **5**(7): p. 491-502.
87. Grobner, T., *Gadolinium--a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis?* Nephrol Dial Transplant, 2006. **21**(4): p. 1104-8.
88. Vorobiov, M., et al., *Iron-mobilizing properties of the gadolinium-DTPA complex: clinical and experimental observations.* Nephrol Dial Transplant, 2003. **18**(5): p. 884-7.
89. Ledneva, E., et al., *Renal safety of gadolinium-based contrast media in patients with chronic renal insufficiency.* Radiology, 2009. **250**(3): p. 618-28.
90. Finn, W.F., *The clinical and renal consequences of contrast-induced nephropathy.* Nephrol Dial Transplant, 2006. **21**(6): p. i2-10.
91. Parfrey, P., *The clinical epidemiology of contrast-induced nephropathy.* Cardiovasc Intervent Radiol, 2005. **28**(2): p. S3-11.
92. Kuo, P.H., et al., *Gadolinium-based MR contrast agents and nephrogenic systemic fibrosis*. Radiology. 2007 Mar;242(3):647-9. Epub 2007 Jan 9.
93. Hifumi, H., et al., *Gadolinium-based hybrid nanoparticles as a positive MR contrast agent.* Journal of the American Chemical Society, 2006. **128**(47): p. 15090-15091.
94. Josephson, L., et al., *The effects of iron oxides on proton relaxivity.* Magnetic resonance imaging, 1988. **6**(6): p. 647-653.
95. Koenig, S.H. and K.E. Kellar, *Theory of 1/T1 and 1/T2 NMRD profiles of solutions of magnetic nanoparticles.* Magnetic resonance in medicine, 1995. **34**(2): p. 227-233.
96. Kellar, K.E., et al., *'NC100150', a preparation of iron oxide nanoparticles ideal for positive-contrast MR angiography.* Magnetic Resonance Materials in Physics, Biology and Medicine, 1999. **8**(3): p. 207-213.
97. Allen, M., et al., *Paramagnetic viral nanoparticles as potential high- relaxivity magnetic resonance contrast agents.* Magnetic Resonance in Medicine, 2005. **54**(4): p. 807-812.
98. Livramento, J.B., et al., *High Relaxivity Confined to a Small Molecular Space: A Metallostar- Based, Potential MRI Contrast Agent.* Angewandte Chemie International Edition, 2005. **44**(10): p. 1480-1484.

99. Lu, Z.R., et al., *Extracellular biodegradable macromolecular gadolinium(III) complexes for MRI.* Magn Reson Med, 2004. **51**(1): p. 27-34.

100. Ladd, D.L., et al., *Polymeric gadolinium chelate magnetic resonance imaging contrast agents: design, synthesis, and properties.* Bioconjug Chem, 1999. **10**(3): p. 361-70.

101. Aime, S., et al., *[Gd-AAZTA]-: a new structural entry for an improved generation of MRI contrast agents.* Inorg Chem, 2004. **43**(24): p. 7588-90.

102. Werner, E.J., et al., *Highly soluble tris-hydroxypyridonate Gd(III) complexes with increased hydration number, fast water exchange, slow electronic relaxation, and high relaxivity.* J Am Chem Soc, 2007. **129**(7): p. 1870-1.

103. Avedano, S., et al., *Maximizing the relaxivity of HSA-bound gadolinium complexes by simultaneous optimization of rotation and water exchange.* Chem Commun, 2007. **7**(45): p. 4726-8.