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Gadolinium(III)-based blood-pool contrast agents for magnetic resonance imaging: status and clinical potential

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Blood-pool MRI contrast agents have enormous potential to aid sensitive magnetic resonance detection and yield definitive diagnostic data of cancer and diseases of the cardiovascular system. Many attempts have been initiated to design macromolecular gadolinium (Gd[III]) complexes as magnetic resonance imaging blood-pool contrast agents, as macromolecules do not readily diffuse across healthy vascular endothelium, and remain intravascular. Although extremely efficacious in detecting and characterizing pathologic tissue, clinical development of these agents has been limited by potential toxicity concerns from incomplete Gd(III) clearance. Recent innovative technologies, such as reversible protein-binding contrast agents and biodegradable macromolecular contrast agents, may be valuable alternatives that combine the effective imaging characteristics of an intravascular contrast agent and the safety of clinically approved low-molecular-weight Gd(III) chelates.

1. Introduction

MRI is a powerful imaging modality for diagnostic radiology and biomedical research. MR images are produced based on the difference between proton relaxation rates of different tissues. MRI is largely used for anatomic imaging, but the technique can also produce valuable functional data. In general, MRI is advantageous for the detection and characterization of many diseases, including cancer, abnormalities of the CNS, cardiovascular and musculoskeletal systems, and dysfunctions of the liver, kidneys and spleen [1].

Although MR images can obtain contrast-based on manipulation of pulse sequences alone [2], contrast in an MR image needs to be optimized to give the best possible contrast between tissues, for more accurate diagnosis. Additional contrast enhancement requires the use of a paramagnetic contrast agent to decrease the T_1 and/or T_2 relaxation times of water protons proximal to the contrast agent. Depending on whether a T_1- or T_2-weighted data acquisition sequence is used, the signal of water proximal to the contrast agent will be increased or decreased, respectively, compared with water protons in surrounding tissues. Paramagnetic materials based on the Gd(III) and Mn(II) chelates, and iron oxide particulates are often used to facilitate proton relaxation [3,4]. However, the vast majority of clinical contrast-enhanced examinations use Gd(III)-based contrast agents; thus the focus here will be contrast agents developed using Gd(III) chelates. Reviews that describe in detail the physicochemical phenomena that render Gd(III) chelate an ideal material for contrast-enhanced MRI are given elsewhere [3,5,6].

Gd(III) ions cannot be administered directly because they are highly toxic in their ionic form, both acutely by interfering with calcium channels and protein binding

sites [7-9] and long-term by toxic bone accumulation [10,11]. Chelating Gd(III) to a ligand to form a stable complex greatly reduces its toxicity. There are two main categories of chelating ligands on which clinically approved contrast agents are developed: linear ligands based on diethylenetriaminepenta-acetic acid (DTPA) and macrocyclic ligands based on 1,4,7,10-tetra(carboxymethyl)-1,4,7,10-tetraazacyclodo-decane (DOTA) (**Figure 1**). For example, gadopentate dimeglumine, the first MRI contrast agent approved for clinical use in 1988 for CNS indications has a reported LD_{50} of 5.6 – 10.0 mmol/kg in mice, compared with 0.5 mmol/kg for $GdCl_3$ [11,12]. Since then, paramagnetic Gd(III) complexes have become an essential tool in the detection and characterization of many diseases. These low-molecular-weight Gd(III) complexes are most effective in diagnosing diseases of the CNS, in which there is a breakdown of the blood–brain barrier [13-15], representing neurodegenerative diseases such as multiple sclerosis [16], where the small contrast agents can permeate into the usually inaccessible tissue.

However, clinically approved MRI contrast agents are characterized by rapid elimination, rendering them inadequate for angiographic imaging. These contrast agents are classified as extracellular [5], meaning that the blood-pool concentration of these agents decreases rapidly after injection from both elimination and extravasation out of the vasculature [17,18]. As low-molecular-weight Gd(III) chelates rapidly diffuse across healthy vascular endothelium, T_1 shortening of surrounding tissue also decreases the overall image quality for angiographic images [17,19]. In addition, the rapid blood-pool clearance results in difficulty of exact timing between the contrast agent bolus and image acquisition [20]. As a result, the image resolution is greatly compromised, especially in MR protocols in which imaging of the blood pool is desired, for example in cardiovascular diseases and cancer.

To overcome the limitations of low-molecular-weight contrast agents, including rapid clearance from the blood pool, nonspecific extravasation into surrounding tissue, and subsequently unsatisfactory performance at reducing T_1 relaxation times in blood, macromolecular Gd(III) complexes have been proposed and designed for contrast-enhanced MRI. Unlike clinically approved low-molecular-weight contrast agents, macromolecules do not readily diffuse across healthy vascular endothelium. In fact, macromolecules tend to only diffuse across endothelium that has been compromised, and preferentially accumulate in tissues with leaky vasculature via the enhanced permeability and retention (EPR) effect [21,22]. This will occur wherever an inflammatory response is present, such as cancer, vascular disease and arthritis. In the case of diagnostic imaging, this gives desired preferential enhancement in the diseased tissue. In addition, macromolecular Gd(III) complexes typically have a higher relaxivity (i.e., more efficient contrast enhancement than low-molecular-weight complexes) [17]. Vascular confinement combined with more efficient contrast enhancement suggests that lower doses of Gd(III) are possible

with macromolecular Gd(III) complexes. These qualities make macromolecules the likely choice to overcome the limitations of presently available Gd(III) complexes for more effective MRI. This review outlines the design and development, physicochemical properties, and *in vivo* properties of several classes of blood-pool MRI contrast agents. In addition, their limitations are highlighted and recent innovations that have the potential for the clinical realization are also presented.

2. Macromolecular blood-pool contrast agents

The most straightforward method to increase the plasma circulation and promote vascular confinement of a contrast agent is to 'decorate' molecules that have minimal plasma clearance with Gd(III) chelates, such as biomacromolecules and biocompatible synthetic macromolecules. Initial efforts focused on using natural macromolecules. Later efforts have exposed the versatility of synthetic macromolecules, such as linear polymers and highly branched dendrimeric contrast agents. Each development has contributed greatly to the understanding of macromolecular blood-pool contrast agents.

2.1 Natural macromolecule-derived blood-pool contrast agents

Several macromolecular Gd(III)-based MRI contrast agents have been developed from natural biomacromolecule platforms, including protein conjugates, polysaccharides and dextrans. The first such agents consisted of Gd-DTPA covalently linked proteins, such as albumin [23], IgG [24], fibrinogen [25] and inulin [26,27], to amino acid residues containing a primary amine. Of these, the most comprehensively studied biomacromolecule is albumin. On average, the 19 – 35 Gd-DTPA molecules can be conjugated to albumin [23,28], resulting in a contrast agent with an apparent molecular weight of 92 kDa. The relaxivity of the agent is 14.9 $mM^{-1}s^{-1}$ at 0.25 T, significantly higher than clinically approved agents. The pharmacokinetics of this agent reveal that it is limited to the intravascular space, but due to extremely slow elimination [29], Gd(III) dissociation [24] and potential immunogenicity [30], it has been developed only as a prototype blood-pool contrast agent. Nevertheless, albumin-(Gd-DTPA)$_X$ has made an invaluable contribution to the understanding of macromolecular contrast agents with regard to noninvasive tumor characterization and has helped to expose the enormous clinical potential of macromolecular contrast agents [28,31-36].

Blood-pool macromolecular contrast agents have also been derived from other natural macromolecules, such as polysaccharides and their derivatives (**Figure 2**). For example, both DTPA and DOTA have been conjugated to polysaccharides [37], and DTPA has also been used as a cross-linking agent between polysaccharides [38]. The molecular weight of cross-linked polysaccharides is 17 – 150 kDa, and the T_1 relaxivity of these compounds is
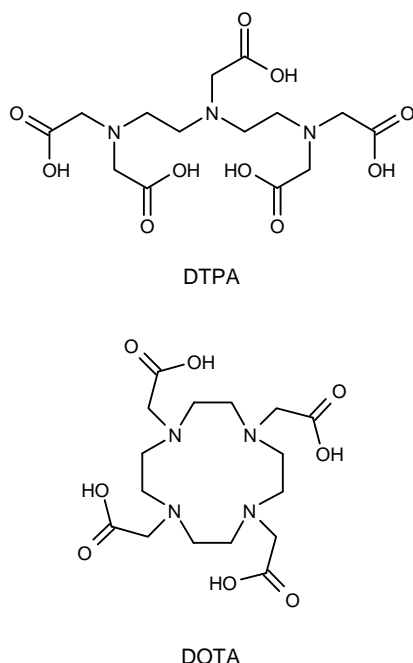
Figure 1. Chemical structures of Gd(III)-chelating ligands, DTPA and DOTA. These ligands and their derivatives when chelated to Gd(III) account for all clinically approved MRI contrast agents.

DOTA:1,4,7,10-tetra(carboxymethyl)-1,4,7,10-tetraazacyclododecane;
DTPA: Diethylenetriaminepentaacetic acid.

$5.3 - 6.5$ mM^{-1}s^{-1} [38]. Carboxymethyldextran-(Gd-DTPA) (CMD-[Gd-DTPA]) ranged in molecular weight from 42.7 to 158 kDa with T_1 relaxivity values from 6.5 to 7.3 mM^{-1}s^{-1} (20 MHz) [37,39,40]. CMD-(Gd-DOTA) of ~ 50 kDa had a longitudinal relaxivity of 10.6 mM^{-1}s^{-1} at 20 MHz [41]. Both CMD-(Gd-DTPA) and -(Gd-DOTA) showed better enhancement than a low-molecular-weight control for MR angiography, especially those relating to myocardium [39,41-43] and assessing liver disease [44,45].

2.2 Synthetic macromolecular blood-pool contrast agent

Synthetic macromolecular contrast agents for blood-pool MRI first appeared in the literature in 1990 [46-48] and are still an active area of research. Synthetic macromolecules for blood-pool MRI include conjugates of Gd(III) chelates to polyamino acids and dendritic polymers, and copolymers of Gd-DTPA and a diamine or a dialcohol (**Figure 3**). Due to the synthetic nature of these macromolecules, a wide variety of structures have been developed to fit specific MR applications.

Polyamino acids, especially poly-L-lysine (PLL), are routinely tested as therapeutic carriers for drug delivery due to their free amino groups, which allow convenient conjugation of a therapeutic entities to the polymer backbone. With respect to developing macromolecular MRI contrast agents, either Gd-DTPA or Gd-DOTA has been covalently linked to

the PLL backbone with a direct covalent bond of the carboxylate group of DTPA [49] or DOTA [46] or via linking groups [50] (**Figure 3A**). The T_1-relaxivity of these contrast agents was reported to be $10.9 - 13.6$ mM^{-1}s^{-1} at 0.3 T [48,49,51] – much greater than that of clinically approved low-molecular-weight agents, possibly due to a slower rotational correlation coefficient. PLL-based macromolecular contrast agents have been synthesized in a wide range of molecular weights with varying pharmacokinetics. In rats, PLL-(Gd-DTPA) of 36 kDa had a half-life in the blood of 64.9 min, and at 480 kDa of 428.6 min [51]. At 7 days postinjection of PLL-(Gd-DTPA) (48 kDa), > 3% of the injected dose resided in the liver, kidney and bone of rats [49]. In general, PLL-based macromolecular contrast agents have relatively low immunogenicity [30], but show relatively poor hemodynamic tolerance at higher doses [52].

The diagnostic applications of PLL-(Gd-DTPA) have been extensively investigated in preclinical studies. High-molecular-weight PLL-(Gd-DTPA) (407 kDa) showed higher and more sustained contrast enhancement in a mammary adenocarcinoma rodent model [53]. PLL-(Gd-DTPA) (40 kDa) was able to accurately differentiate between two causes of pulmonary edema (hydrostatic pressure and abnormal capillary permeability [54]) and, in another case, detected a pulmonary embolism [55]. Regarding myocardial infarctions, differential enhancement patterns of PLL-(Gd-DTPA) were effective in delineating the central and peripheral ischemic zones in cats [56] and differentiating acute, subacute and chronic myocardial infarctions in rats [57].

A second class of synthetic macromolecular contrast agents is the copolymers of the Gd-chelating ligand and an α,ω-diamine or -dialcohol, such as diamino-poly(ethylene glycol), diamino-poly(propylene glycol) or hexanediamine (**Figure 3B**) [58-61]. The molecular weight of copolymers of Gd-DTPA and either PEG or PPG is $10 - 83$ kDa with relaxivity values of 3.8 mM^{-1}s^{-1} (1.5 T) to 6.0 mM^{-1}s^{-1} (20 MHz) [59,61]. When an alkyldiamide is considered, the relaxivity increases with more methylene groups; values up to 20 mM^{-1}s^{-1} at 20 MHz have been reported, suggesting that hydrophobic interaction may limit molecular motion around Gd(III) [60], whereas free rotation occurs around PEG-DTPA copolymers [62].

From this class, poly[(Gd-DTPA)-*co*-1,6-diaminohexane] (19 kDa) has a T_1 relaxivity of 9.5 mM^{-1}s^{-1} at 20 MHz [63]. This contrast agent is characterized by a half-life of 98 min in rabbits with 4.91% injected dose remaining in bone after 7 days [58]. In a rabbit arterial stenosis model, the extended half-life of the agent produced stable enhancement for 2D and 3D time-of-flight magnetic resonance angiography images [64]. In other studies, a subcutaneous injection of poly[(Gd-DTPA)-*co*-1,6-diaminohexane] showed excellent popliteal nodal enhancement in a rabbit model. In mice with a human melanoma xenograft, dynamic enhancement of the copolymer was used to predict the efficacy of a macromolecular therapeutic [65].
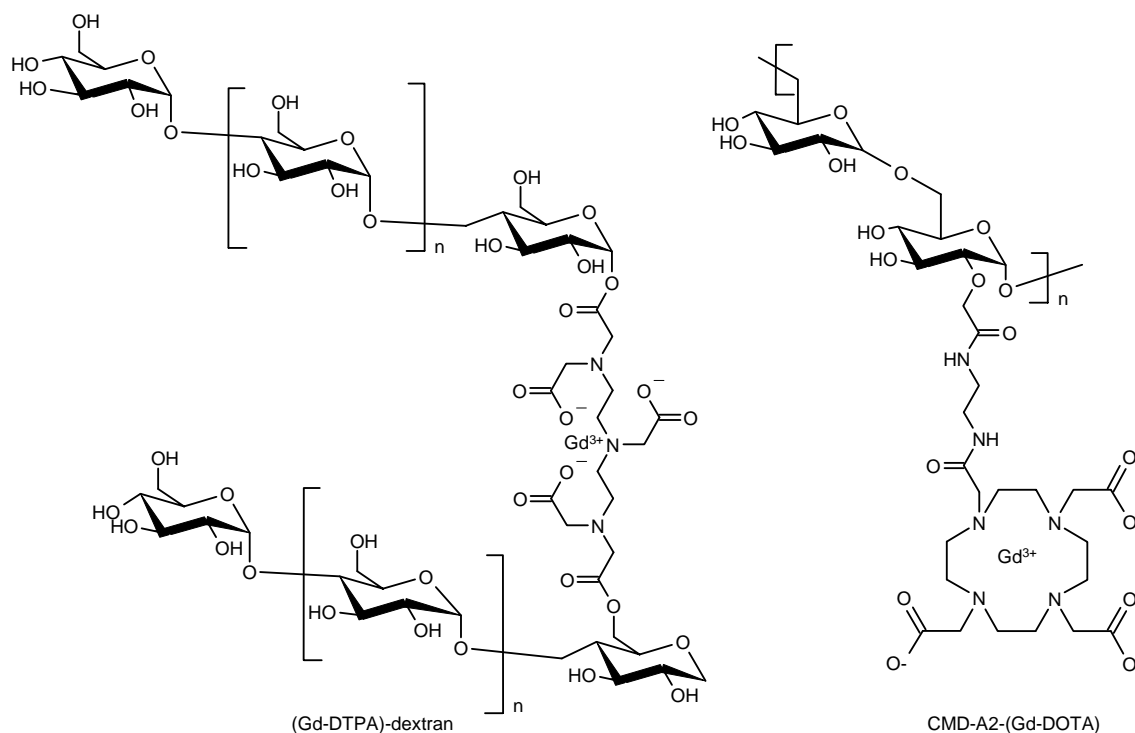
Figure 2. Chemical structures of cross-linked (Gd-DTPA)-dextran and carboxymethyldextran-(Gd-DOTA). These are two examples among several blood pool contrast agents that have been developed from naturally occurring macromolecules.
DOTA: 1,4,7,10-tetra(carboxymethyl)-1,4,7,10-tetraazacyclododecane; DTPA: Diethylenetriaminepentaacetic acid.

The third major group of synthetic macromolecular blood-pool agents is dendrimer-based paramagnetic complexes (**Figure 3C**). Dendrimers are highly branched polymers consisting of three fundamental components: a core, the branching units, and a layer of functional groups to be modified depending on the application [66]. There are several advantages of dendrimers for diagnostic applications, including uniform molecular weight distribution, relatively controlled structure compared with linear polymers, increased molecular weight compared with clinically approved agents, and typically higher relaxivity because dendrimers have a comparatively more rigid structure than linear polymers [67]. The first published reports of dendrimers for MRI applications were in 1994 by Adam *et al.* [68] and Wiener *et al.* [69]. Typical core types include, but are not limited to, ammonia, ethylenediamine, diaminobutane (DAB) and trimesoyl triamide. Branching units also have a wide variety of chemical structures, such as poly-amidoamine (PAMAM), polypropyleneimine and polylysine. Either Gd-DTPA or Gd-DOTA can be conjugated to the terminal amines. Detailed reviews have been published by several groups on the cores, structures, physiochemical properties, pharmacokinetics and various MRI applications of paramagnetic dendrimer complexes [66,70,71].

In brief, PAMAM-based dendrimeric contrast agents with molecular weights of 15 kDa (generation 2, 16 Gd chelates) to 3820 kDa (generation 10, 4096 Gd chelates) have relaxivity from 20 (generation 2) to 35 mM^{-1}s^{-1} per Gd chelate (generation 8, 954 kDa) at 1.5 T [71,72-75]. The dynamic enhancement pattern of PAMAM-based dendrimeric contrast agents depends significantly on the generation number, with generations 4 – 6 providing the best signal enhancement of small vessels [72], and an ethylene diamine core providing a more efficient signal enhancement than an ammonia core [76]. A comparison of different branching units, PAMAM versus polypropyleneimine diaminobutyl (DAB, r_1 = 12 to 29 mM^{-1}s^{-1} at 1.5 T), showed that DAB-based dendrimers had lower whole body accumulation compared with PAMAM, but significantly higher liver accumulation [73]. The selective accumulation of DAB dendrimers has led to their preclinical development as effective liver-specific imaging agents [77,78]. However, PAMAM dendrimers were effective in identifying tumor vasculature [79,80] and predicting herceptin internalization [81]. Both DAB and PAMAM dendrimers have shown efficacy in visualizing the lymphatic system in mice [74,82].

An agent in the dendrimeric group of contrast agents, which is in clinical development, is Gadomer-17 (Schering AG, Berlin, Germany). Gadomer-17 has a molecular weight of 17.5 kDa and has a relaxivity of 16.5 mM^{-1}s^{-1} at 20 MHz. This dendrimer has a trimesoyl triamide core and 18 lysine residues to bind 24 Gd-1,4,7,10-Tetraazacyclodo-decane-1,4,7-tris(acetic acid) (Gd-DO3A) chelates [67]. The molecule is large enough that its extravasation out of the
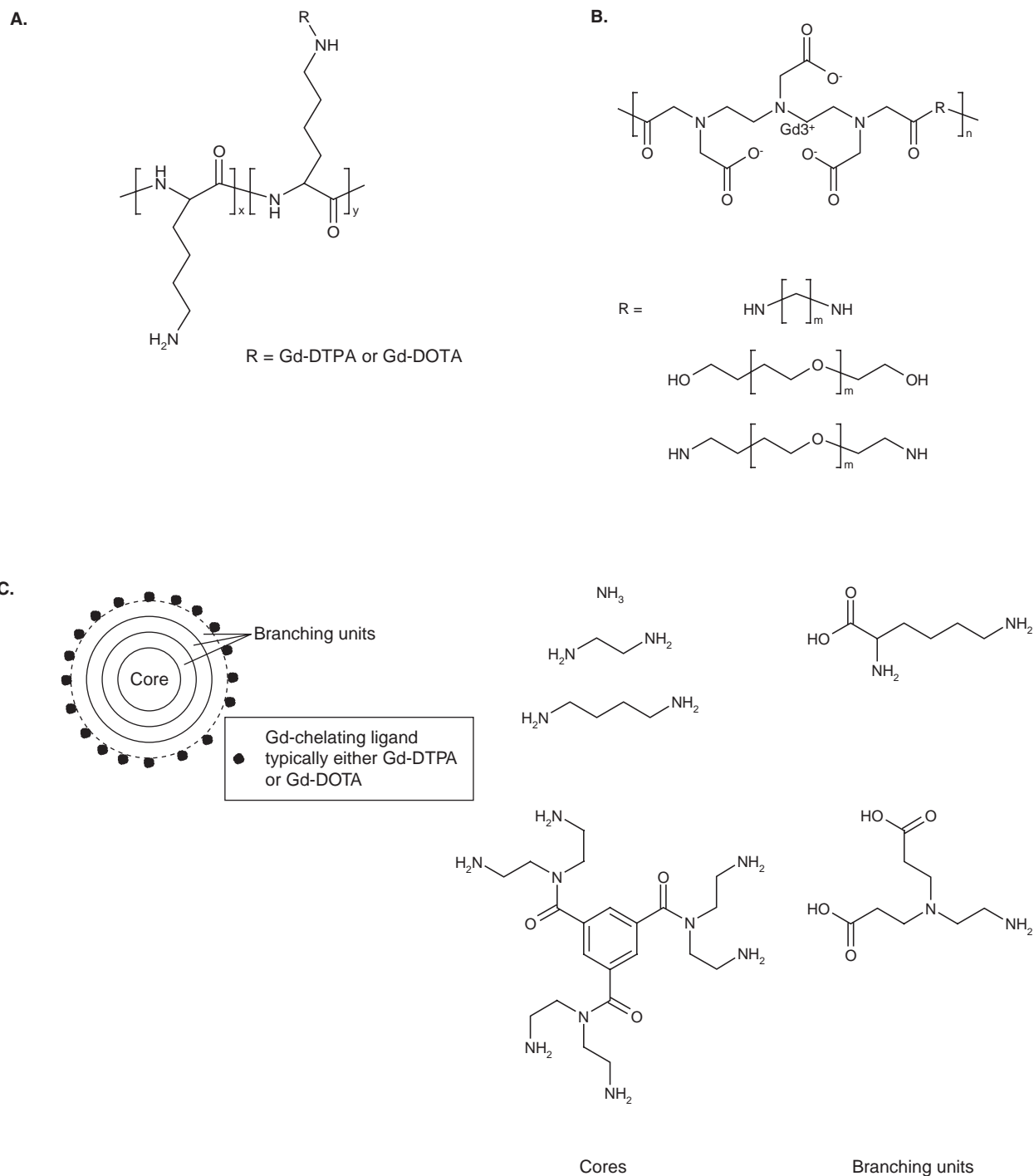
Figure 3. Synthetic macromolecular blood-pool MRI contrast agents. Polymeric contrast agents can have either Gd-DTPA or Gd-DOTA conjugated to a polymeric backbone (**A**). Gd-DTPA can also serve as a copolymeric unit with either a dialcohol or diamine (**B**). A third class of synthetic macromolecular contrast agents is dendrimers (**C**). These structures have a core, branching units and have a Gd(III) chelate conjugated at the surface. Gadomer-17, a clinically developed agent, has a trimesoyl triamide core, lysine branching units and Gd-DO3A as the paramagnetic chelate.

DOTA: 1,4,7,10-tetra(carboxymethyl)-1,4,7,10-tetraazacyclododecane; DTPA: Diethylenetriaminepentaacetic acid.

blood pool is reduced, but the molecule is still small enough that it is cleared via glomerular filtration, as characterized by a terminal phase $t_{1/2}$ of 10 min in rabbits [83]. This contrast agent has been tested with some success in several types of imaging, especially angiography. It has also been used to characterize tumor severity and angiogenesis [84].

2.3 Colloidal blood-pool contrast agents

Blood-pool contrast agents have also been developed from colloidal materials, such as liposomes and micelles. With respect to liposomes, Gd(III) complexes can either be encapsulated in the aqueous environment of the liposomal cavity or Gd(III) can be complexed at the polar end of amphiphilic DTPA derivatives. Liposomes encapsulating Gd-DTPA have been prepared from egg phosphatidyl-choline/cholesterol, dioleoylphosphatidylcholine/cholesterol and dipalmitoylphosphatidylcholine/cholesterol. The size of the particles are 20 – 400 nm for unilamellar vesicles [85,86] and > 10 μm for large multivesicular liposomes [87]. Unlike other proposed blood-pool agents, liposomes possess a relatively low T_1 relaxivity per Gd(III) chelate, dramatically lower than the relaxivity from Gd-DTPA itself. Unilamellar vesicle encapsulated Gd-DTPA had a T_1 relaxivity of 0.42 – 3.43 mM^{-1}s^{-1} at 0.5 T [85,88], and the relaxivity decreased with increasing particle size [85]. These findings were attributed to poor water flux across the lipid bilayer. Although liposome-encapsulated Gd(III) complexes have shown some utility for imaging of the reticuloenthothelial systems and the brain [87,89], the development of these particles for MRI has been severely limited due to toxicity concerns. The acute toxicity of these agents is similar to Gd-DTPA [86]. However, these agents resulted in significant deposition of Gd(III) (13 days) in the spleen, liver and lung [88,90]. Signs of toxicity included significant spleno-megaly, lymphocytopenia and hypergammaglobulinemia. Damage to cells of the spleen was the most significant of all the observed toxicities [91].

Amphiphilic Gd-DTPA derivatives, stearyl ester Gd(DTPA-SE), stearyl thiolester Gd(DTPA-ST), stearyl amide Gd(DTPA-SA) and decylamide Gd(DTPA-DA) (**Figure 4**) have been investigated to increase the relaxivity of liposomal Gd-DTPA by making the paramagnetic metal ion readily accessible to water [92-94]. When Gd-DTPA was part of the bilayer, some increase in T_1 relaxivity was observed, but as with liposomally entrapped Gd-DTPA, these agents also showed long-term Gd(III) accumulation in the reticuloendothelial system. At 12 days, Gd(DTPA-SA) liposomes had 62% Gd(III) retention in the liver and 10% in the spleen [94]. Gd(DTPA-SE) and Gd(DTPA-ST) resulted in 30 and 8% injected dose (ID), respectively, in the liver after 10 days, and Gd(DTPA-DA) showed 2% [92,94]. In the spleen, the accumulation from Gd(DTPA-SE) and Gd(DTPA-SA) was 6 and 5%, respectively, of the injected dose remaining after 10 days. Almost constant values were obtained from all time points measured over that interval, showing that this accumulation was indefinite [94].

Micelles have also been investigated for MRI applications. Gd-DOTA was conjugated to alkyl chains of different lengths [95]. The relaxivity of the micelles were 10.8 – 22.0 mM^{-1}s^{-1} (60 MHz), in which the shortest alkyl chain had the lowest relaxivity. Mixed micelle formulations showed good vascular enhancement in an MRA protocol [96]. A Gd(III) retention experiment of the mixed micelle showed that 8 – 10% of the injected dose remained after 7 days, and 5% remained after 28 days.

2.4 Targeted blood-pool contrast agents

Targeted blood-pool contrast agents have a potential to detect biomarkers in vasculature, tumors and other diseases with high specificity. Attempts to prepare targeted MRI contrast agents started as early as the mid 1980s. Initially, Gd-DTPA was directly conjugated to monoclonal antibodies. However, these paramagnetic antibody conjugates did not show significant targeted contrast enhancement in MRI because of the low loading of Gd(III) chelates on the antibody molecules [97,98]. Compared with nuclear medicine, contrast-enhanced MRI is much less sensitive, and a high concentration of contrast agent is required to generate significant contrast enhancement. In order to achieve a distinct increase of signal intensity, a large amount of the Gd(III) chelates is required in target tissues for effective tissue-specific contrast enhancement in MRI. Targeted MRI contrast agents have been prepared by incorporating targeting agents, including monoclonal antibodies and their fragments, and peptides, into macromolecular Gd(III) chelates and colloidal blood-pool contrast agents [99,100].

Monoclonal antibodies have been incorporated into PLL-(Gd-DTPA) conjugates to prepared targeted MRI contrast agents. The coupling of tumor-specific monoclonal antibody RA96 to PLL conjugate resulted in a 30% reduction of immunoreactivity, compared with the unbound antibody [101]. Prominent contrast enhancement in tumor tissue was observed with the targeted contrast agent, compared with a non-targeted blood-pool agent. The F(ab')$_2$ fragment of an anti-CEA monoclonal antibody was also incorporated into PLL-(Gd-DTPA) and PLL-(Gd-DO3A) with a retention of 80 – 85% immunoreactivity [102]. The immunoconjugates resulted in 10 – 15% tumor uptake in nude mice bearing human colorectal carcinoma LS 174T xenografts, and a 15 – 20% increase of relaxation rate at the tumor site with a reduced dose.

Targeted blood-pool contrast agents specific to angiogenesis biomarkers have been prepared for imaging of angiogenesis. Monoclonal antibody LM609 specific to $\alpha_v\beta_3$ integrin, was incorporated in to Gd(III)-labeled polymerized liposomes (300 – 350 nm) and tested in a rabbit model of squamous cell carcinoma for tumor angiogenesis MRI [103]. Significant tumor enhancement was observed 24 h postinjection. Anti-$\alpha_v\beta_3$ integrin monoclonal antibody DM101 was also incorporated into Gd-perfluorocarbon nanoparticles (~ 200 nm) for MRI of the neovasculature. The T_1 and T_2 relaxivities of the nanoparticles were 12 and 11 mM^{-1}s^{-1} per Gd. The targeted
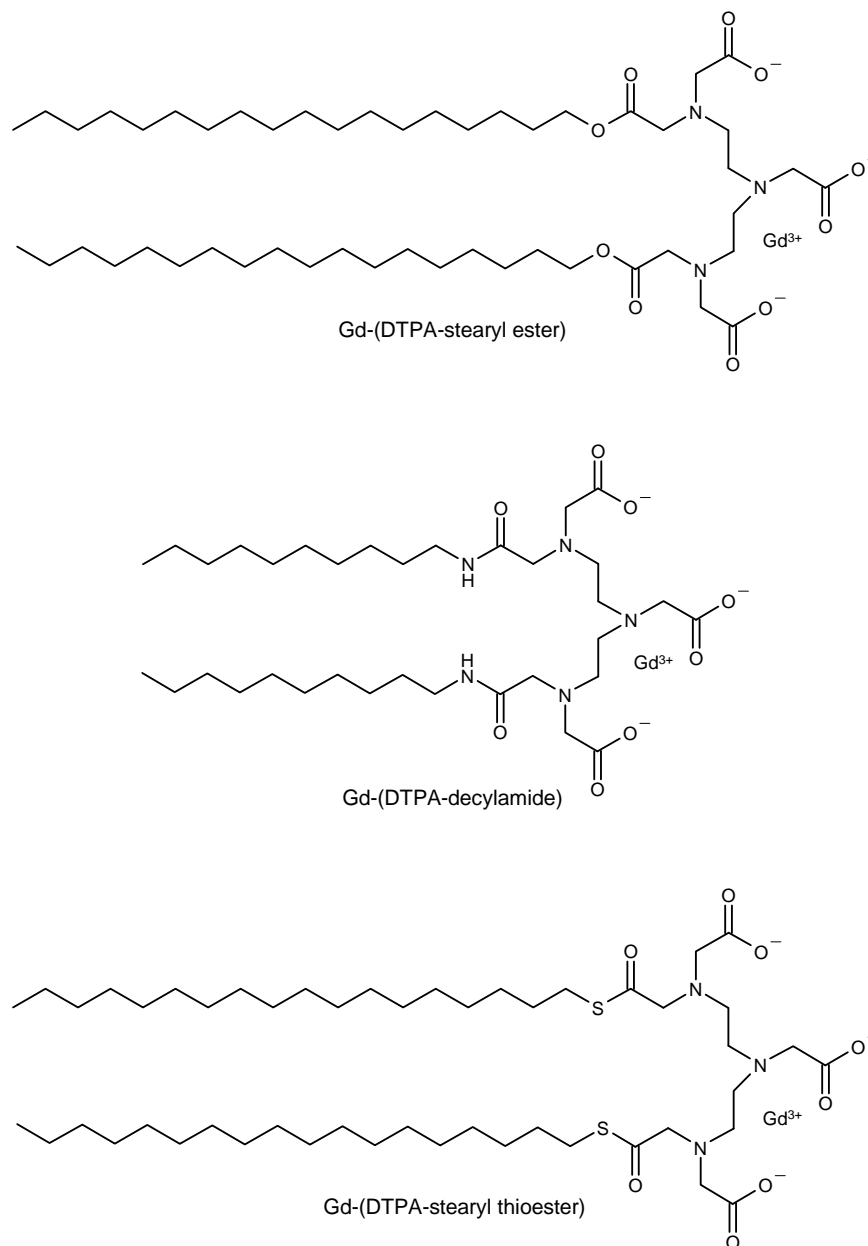
Figure 4. Examples of the amphiphilic Gd-DTPA-based ligands for liposomal blood-pool MRI contrast agents.
DTPA: Diethylenetriaminepentaacetic acid.

nanoparticles resulted in a 25% increase of MR signal intensity in the region of angiogenic capillary 90 min after injection, and no significant enhancement was observed with the non-targeted nanoparticles [104]. Arginine-glycine-aspartic acid (RGD) is a small peptide that can specifically bind to $\alpha_v\beta_3$ integrin. Incorporation of a relatively large amount of RGD peptide into the Gd(III) chelate-labeled liposomes, ~ 700 per liposome, resulted in a targeted contrast agent that specifically bound to activated tumor endothelium. Significant enhancement was observed in the tumor rim, which was rich in angiogenic blood vessels [105].

Targeted MRI contrast agents specific to the biomarkers of atherosclerosis have a potential to specifically detect vascular diseases. Paramagnetic immunomicelles targeting the microphage scavenger receptor were prepared and tested for detection of atherosclerosis in animal models. The micelles had a size of ~ 100 nm, with T_1 relaxivity ranging from $25 - 37$ mM^{-1}s^{-1} at 1.5 T. The immunomicelles were taken up by microphages and were useful for detection of microphage-rich plaques [106]. The immunomicelles resulted in significant enhancement in the aortic wall of atherosclerotic

plaques in ApoE-/- mice, at least twofold higher than nonspecific micelles [107]. Anti-fibrin monoclonal antibodies were also incorporated into Gd(III)-chelate-labeled perfluoro-carbon nanoparticles to develop fibrin targeted contrast agents for MRI of unstable atherosclerotic plaques. *In vitro* studies have shown that the targeted nanoparticles could bind to fibrin clots, resulting in strong contrast enhancement [108].

3. Limitations of macromolecular blood-pool magnetic resonance imaging contrast agents

Safety is the first priority in the development of any contrast agent for MRI. Clinically approved low-molecular-weight contrast agents are all rapidly eliminated by, for the most part, renal filtration. Therefore, potential toxicity from long-term Gd(III) accumulation is minimal. However, the rapid elimination from the vasculature by low-molecular-weight agents results in poor performance in blood-pool imaging applications. For more effective MRI, improvements are necessary to increase circulation time.

Macromolecular MRI contrast agents have definitive advantages, compared with low-molecular-weight agents, as shown above. The major reason for their efficacy is that their size limits blood-pool extravasation and renal filtration, normally when the molecule is greater than 20 kDa. Above 20 kDa, renal filtration depends on several physiochemical characteristics, including molecular structure, morphology, lipophilicity and polarity [109]. Macromolecular contrast agents of very large macromolecules (> 70 kDa) must be metabolized before being eliminated [17]. This increases the potential for cellular uptake of the contrast agent via endocytosis, and consequential Gd(III) release may occur due to the decreased pH in the lysozome and metabolism [110].

Gd(III) accumulation has in fact limited the clinical development of macromolecular MRI contrast agents. For example, the linear copolymer of Gd-DTPA and 1,6-hexane-diamine (19 kDa) had 4.91% ID in the bone at 7 days postinjection, which was 23-times higher than a control agent Gd-DTPA [58]. PLL-(Gd-DTPA) (42 kDa) had > 3% of injected dose each in the liver, kidney and bone at 7 days [49]. A second-generation polypropyleneimine dendrimer (7 kDa) resulted in 45% retention 14 days after injection [111]. A 9th-generation dendrimer was reported to have almost 60% retention 4 days postinjection [112]. Carboxymethylhydroxy ethylstarch-(Gd-DO3A)$_{35}$ (72 kDa) resulted in 47% of the injected dose remaining in the body after 7 days [113]. As stated above, the toxicity from liposomally entrapped Gd-DTPA is prohibitively high. In addition to concerns from long-term Gd(III) accumulation, the chemical structure of the contrast agent itself may also produce a toxic response. Several macromolecular contrast agents investigated have potential immunogenic responses [30], and incomplete ligand coupling to primary amines in the backbone of dendrimeric agents [75] may result in poor hemodynamic tolerance and accumulation of contrast agents in kidney.

In light of the potential toxicity from macromolecular Gd(III) complexes, several alternative approaches have been proposed to balance prolonged circulation and long-term Gd(III) deposition. Contrast agents have been synthesized with sizes below the renal filtration threshold, but larger than clinically approved agents; examples include Gadomer-17 [114], P760 [115] and P792 [116]. These so-called rapid clearance blood-pool agents potentially work better than clinically approved low-molecular-weight contrast agents, but they did not produce definitive data in a tumor model compared with larger macromolecules [117,118]. So far, none of these contrast agents have been clinically approved.

Chemical modification to existing macromolecular Gd(III) complexes has also been reported in the literature. PEG has been grafted to PLL-(Gd-DTPA) to help improve biocompatibility [119]. Dendrimeric contrast agents have also been PEGylated, resulting in decreased liver accumulation and increased renal excretion [120]. Dendrimeric contrast agents have also been co-administered with lysine [121] or biotinylated [122] to facilitate renal excretion. Recently, PEGylated liposomes were prepared and showed distribution to vasculature [123], but long-term Gd(III) retention studies with these agents have not been reported.

4. Potential alternatives

Clearly, blood-pool MRI contrast agents have great clinical utility. In order to make blood-pool contrast agents a clinical reality, there have been several investigations to design a contrast agent that has the intravascular imaging characteristics of a macromolecule and the safety of small clinically approved contrast agents. Two approaches to achieve this goal are presented in this review: protein binding contrast agents and biodegradable polymeric contrast agents.

4.1 Protein binding blood-pool contrast agents
This class of compounds is not comprised of high-molecular-weight agents, but of small molecules (MW < 1.2 kDa) with a hydrophilic Gd(III) complex and a hydrophobic region for reversible noncovalent binding to serum albumin [124]. In their unbound form, these contrast agents have relatively low relaxivity, but, when bound to albumin, the T_1 relaxivity increases from 25 to 35 mM^{-1}s^{-1} at 20 MHz. In addition, when bound to the protein, the contrast agent exhibits the properties characteristic of a macromolecular contrast agent, such as a long terminal half-life and confinement to the vascular pool.

The most well-studied contrast agent of this class is MS-325 [125], which is clinically approved in the EU and Canada and is awaiting clinical approval in the US. This agent has a DTPA derivative for Gd(III) complexation, linked via a phosphodiester bond to a hydrophobic diphenylcyclohexyl moiety for albumin binding (**Figure 5**). The binding of this molecule to albumin and its effect on relaxivity have been well studied. At physiologic conditions, ~ 88% of MS-325 is

bound to albumin, with a binding constant of up to 11.0 mM^{-1} [126]. The Gd(III) complex formed in MS-325 was determined to be more stable than a clinically approved agent, and significantly more chemically inert [127]. In preclinical and clinical experiences, MS-325 has shown application for angiographic experiments [128-131]. However, when MS-325 was applied to a chemically induced rat tumor, it was not as effective as a prototype macromolecular contrast agent (Gd-DTPA-albumin) at identifying tumor grade [132].

A second contrast agent from this group, gadocoletic acid trisodium salt (B-22956/1, **Figure 5**), has also shown potential. This contrast agent uses an analog of deoxycholic acid for albumin binding. The relaxivity of gadocoletic acid increases from 6.4 to 27 11.0 mM^{-1}s^{-1} at 0.47 T upon binding to albumin [133]. In human plasma, 94.5% is bound to albumin, slightly higher than the binding percentage for MS-325 under similar condition [134]. Gadocoletic acid has shown efficacy in coronary angiography [135].

4.2 Biodegradable macromolecular polydisulfide blood-pool contrast agents

To address the challenge of designing a contrast agent with the imaging attributes of a macromolecular MRI contrast agent, while achieving the favorable Gd(III) clearance profile of a low-molecular-weight chelate, novel biodegradable macromolecular contrast agents have been developed [136]. These contrast agents have disulfide bonds incorporated into a polymeric backbone. Potentially, these disulfide bonds can be readily reduced by the thiol-disulfide exchange reaction with endogenous or exogenous thiols facilitating the clearance of low-molecular-weight Gd(III) chelates.

The first such agent developed was Gd-DTPA cystamine copolymers (GDCC), which is a copolymer of Gd-DTPA and cystamine [137]. This contrast agent was synthesized by the copolymerization of cystamine and DTPA dianhydride in DMSO using TEA as the base, followed by Gd(III) complexation, and had a molecular weight of 15 – 60 kDa. The relaxivity of the complexes was 4.4 – 6.3 mM^{-1}s^{-1} at 3 T. Since the introduction of GDCC, several modifications of GDCC have been synthesized to examine the physico-chemical and imaging effects of the structural modification around the disulfide bond (**Figure 6**) [138-141].

Degradation of these compounds via the disulfide bond has been verified both *in vitro* and *in vivo. In vitro,* size exclusion chromatography showed the gradual breakdown of the original GDCC polymer into small degradation units in the presence of 15 μM L-cysteine. The degradation was shown to depend on the chemical structure around the disulfide bond. For example, modification of GDCC to Gd-DTPA cystine copolymers (GDCP) [138] or PEGylated GDCP [139,140] decreased degradation of the polydisulfide *in vitro*. In rats, after systemic administration of the polydisulfide contrast agents, GDCC and GDCP, low-molecular-weight and oligomeric Gd(III) complexes were identified in the urine

samples by MALDI-TOF mass spectroscopy, confirming *in vivo* degradation of the macromolecules and renal filtration of the contrast agents [137,138]. However, the *in vivo* metabolic degradation of the polydisulfide agents is much more complicated than thiol-disulfide exchange reaction. The pharmacokinetics of these agents reveal that they are excreted relatively quickly via renal filtration, but have an initially higher concentration of the contrast agents in the blood pool than the clinically approved low-molecular-weight chelates over a time period relevant to a clinical MR exam. To great benefit, compared with previously developed macromolecular contrast agents, the Gd(III) accumulation after 10 days was minimal for the polydisulfide complexes, and comparable to that of the clinical control [142,143].

MRI with novel polydisulfide contrast agents has showed great potential for the future development of these agents. Various studies in rodent models have demonstrated that polydisulfide Gd-based complexes with varying types of structural modification have all shown better contrast enhancement of the vasculature compared with a clinically approved contrast agent, Gd-(DTPA-BMA). In mice bearing MDA-MB-231 human breast carcinoma xenografts, GDCC, GDCP and GDCEP clearly depicted tumor periphery, and the tumors were poorly enhanced by the control [138]. Recently, GDCC was directly compared with MS-325 in an MR angiography experiment in a porcine model [144]. GDCC provided much clearer delineation of vessels in a coronary MRA protocol compared with MS-325. Excellent imaging capabilities combined with ideal pharmacokinetics give polydisulfide Gd(III) contrast agents great potential for further clinical development.

5. Conclusions

Almost a third of MRI exams are contrast-enhanced by low-molecular-weight stable Gd(III) complexes. These contrast agents aid in the diagnosis of a wide range of pathologies by enhancing the morphology and functionality of the tissue. These agents have little inherent toxicity because their small size allows them to be readily eliminated, mostly via renal filtration. Unfortunately, the rapid elimination that renders these agents safe for clinical use also results in undesirable pharmacokinetic performance, including inadequate blood-pool retention time for cardiovascular and tumor imaging.

Macromolecular Gd(III) complexes are an effective alternative to extravascular agents because the large size of macromolecules results in a long circulation half-life, confinement to the blood pool and increased signal intensity, all of which allow for a more complete data acquisition from the MR exam. Macromolecular contrast agents have been developed by the conjugation of Gd-DOTA, Gd-DTPA or their derivatives to synthetic polymers, such as PLL and dendrimers, biologic macromolecules or incorporation into colloidal particles. In preclinical studies, their use in assessing
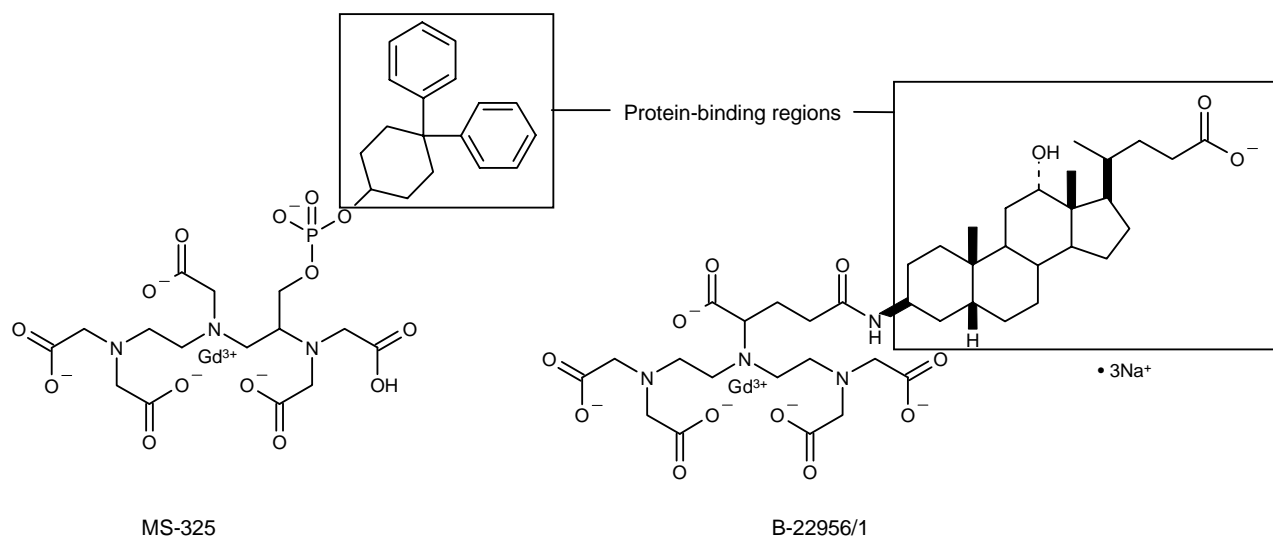
Figure 5. Chemical structures of MS-325 and B-22956/1. These are small-molecule blood-pool agents that possess a hydrophobic domain for reversible binding to plasma proteins.
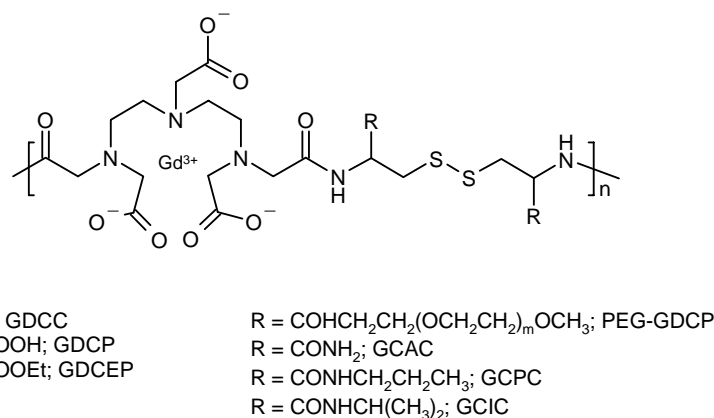

R = H; GDCC
R = COOH; GDCP
R = COOEt; GDCEP

R = COHCH$_2$CH$_2$(OCH$_2$CH$_2$)$_m$OCH$_3$; PEG-GDCP
R = CONH$_2$; GCAC
R = CONHCH$_2$CH$_2$CH$_3$; GCPC
R = CONHCH(CH$_3$)$_2$; GCIC

Figure 6. Biodegradable blood-pool MRI contrast agents based on polydisulfide Gd(III) chelates. Several examples of how the chemical structure can be modified around the biodegradable disulfide bond. These agents initially circulate as macromolecular blood-pool contrast agents and then are gradually degraded to small intact Gd(III)-chelates that can be cleared by renal filtration.

diseases of the cardiovascular system, tumors and other tissues has been clearly demonstrated. Unfortunately, the clinical development of these agents is limited because their slow clearance may result in a metabolic release of toxic Gd(III) ions, and other macromolecular contrast agents are potentially immunogenic. Alternative approaches, such as protein-binding agents, biodegradable polymeric agents, and continued innovation are required to realize the true clinical potential of a blood-pool contrast agent.

6. Expert opinion

The potential of macromolecular blood-pool contrast agents in actual clinical situations has remained relatively untapped. The lack of clinical development of these agents has one major

common denominator, potential toxicity either from their slow excretion or biocompatibility concerns of the macromolecules. This is not to say that results from preclinical studies highlighting efficacy are not promising. In fact, quite the opposite is true, as shown in this review. Macromolecular contrast agents have shown great potential from effectively defining the anatomy of concern in MRA examinations to quantitative characterization of benign versus malignant tumors and evaluating tumor response in anticancer therapies.

The key point is that no matter how efficient a macro-molecular Gd(III) complex is in preclinical studies, it will not be of clinical benefit unless it demonstrates safety comparable to clinically approved MRI contrast agents. Until this condition is met, the potential of a macromolecular MRI contrast agent cannot be realized. The development of novel blood-pool

contrast agents, such as polydisulfide-based biodegradable macromolecular Gd(III) complexes, introduces an innovative approach to achieve the maximum potential of a blood-pool contrast agent combined with the safety characteristics of a low-molecular-weight Gd(III) chelate. Not only do these agents have the potential to decrease the long-term accumulation similar to that of a clinically approved contrast agent, but they may also

be safer. In preclinical studies, polydisulfide contrast agents have outperformed clinical controls with less than a third to a half of the standard clinical dose. Therefore, novel biodegradable macromolecular MRI contrast agents may have the greatest potential, as they are more efficient at contrast-enhancing at lower doses, but would have a minimal long-term Gd(III) accumulation and a better safety profile.

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