Substantia
An International Journal of the History of Chemistry

Firenze University Press
www.fupress.com/substantia

Research Article

Paramagnetic Contrast Agents in MRI: A Review

Jack S. Cohen[1,*], Silvio Aime[2]

[1] *Visiting Professor, Chemistry Department,Ben Gurion University, Beer Sheva, Israel*
[2] *IRCCS SDN SynLab Via E. Gianturco 113, 80143 Napoli, Italy*
Corresponding author email: cohen.jack@yahoo.com

Abstract. Magnetic Resonance Imaging (MRI) is a powerful, non-invasive imaging technique widely used in medical diagnostics. However, its inherent inability to differentiate between certain tissues can limit its diagnostic capabilities, especially when distinguishing between subtle tissue differences. To overcome these limitations, contrast agents are employed to enhance the images produced by MRI and improve the clarity and accuracy of the results. This review delves into the role, types, and advancements of paramagnetic contrast agents in MRI.

Keywords: MRI, Contrast Agents, Paramagnetic

OPEN ACCESS

Citation: Cohen, J.S., Aime S. (2026) Paramagnetic Contrast Agents in MRI: A Review. *Substantia* 10(1): 51-61. doi: 10.36253/Substantia-3538

Received: Jun 10, 2025

Revised: Aug 31, 2025

Just Accepted Online: Sep 26, 2025

Published: Mar 31, 2026

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Competing Interests: The Author(s) declare(s) no conflict of interest.

1. PARAMAGNETISM

Paramagnetism refers to the magnetic behavior of substances that are attracted to an external magnetic field due to the presence of one or more unpaired electrons in their atomic or molecular orbitals. These unpaired electrons possess intrinsic magnetic moments (spin angular momentum), which interact with external magnetic fields, resulting in a net magnetic moment. Unlike diamagnetic materials, which are repelled by a magnetic field due to paired electrons and a negative magnetic susceptibility, paramagnetic materials exhibit a positive magnetic susceptibility, though typically small and only observable in strong magnetic fields (1).

The magnitude of paramagnetism in a substance depends on the number of unpaired electrons and their spatial distribution. According to Curie's Law, the magnetic susceptibility of paramagnetic materials is inversely proportional to temperature (2). This relationship reflects the thermal agitation that disrupts the alignment of magnetic moments at higher temperatures, reducing net magnetization.

Common examples of paramagnetic substances include transition metal ions such as $Fe^{2+/3+}$, $Mn^{2+/3+}$, and Cu^{2+}, as well as molecular oxygen (O_2) in its ground triplet state. In solid-state physics and chemistry, paramagnetism is frequently analyzed through techniques such as electron paramagnetic resonance (EPR), which detects the energy transitions of unpaired electrons in a magnetic field (3).

Paramagnetism is a quantum mechanical phenomenon fundamentally rooted in the Pauli exclusion principle and Hund's rules, which govern the occupancy of electron orbitals in atoms and molecules. The presence of unpaired electrons creates localized magnetic dipoles that, although randomly oriented in the absence of a magnetic field, tend to align parallel to an applied field, generating a weak attraction.

2. INTRODUCTION TO MRI CONTRAST AGENTS

Magnetic Resonance Imaging (MRI) contrast agents (CAs) are specialized compounds administered to patients—usually intravenously—to enhance the visibility of internal anatomical structures and pathological conditions during MRI scans. These agents work by altering the relaxation times (T_1 and T_2) of nearby hydrogen nuclei (protons), thus modifying the intensity of the MRI signal in affected regions. The result is improved signal contrast between different tissues, which helps distinguish normal anatomy from abnormalities such as tumors, inflammation, vascular malformations, or ischemia (4,5).

Contrast agents primarily fall into two categories: T_1-weighted (positive) agents, which shorten the longitudinal relaxation time and appear bright on T_1-weighted images, and T_2-weighted (negative) agents, which shorten the transverse relaxation time and appear dark on T_2-weighted images (6). The most widely used MRI contrast agents are based on gadolinium (Gd^{3+}), a paramagnetic lanthanide ion with seven unpaired electrons that significantly enhances the T_1 relaxation rate of surrounding water protons. Because free gadolinium is highly toxic, it is administered as a chelated complex (e.g., Gd-DTPA or Gd-DOTA), which safely sequesters the metal ion while retaining its magnetic efficacy (7) (Figure 1).

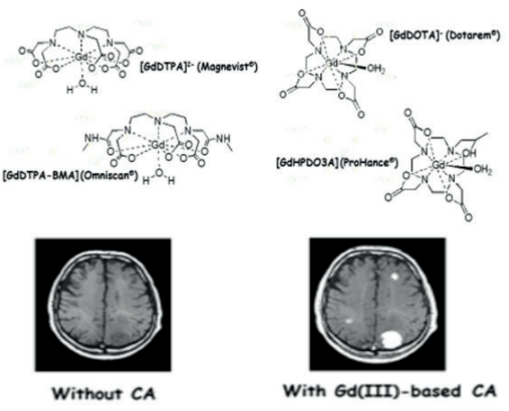

Figure 1. Chemical structures of Gd3+ complexes used in clinical practice. They yield a marked hyperintensity in the anatomical region where they distribute. The presence of tumour lesions is clearly highlighted thanks to the vascular leakeage of neo-formed vessels.

In addition to gadolinium-based contrast agents (GBCAs), iron oxide nanoparticles are used as T_2 agents, particularly in imaging the liver, spleen, and lymph nodes, due to their strong magnetic susceptibility and ability to induce signal loss in surrounding tissues (8). More recently, research has expanded into new classes, like the relaxation enhancing manganese(II)- and iron(III)-based agents, as well as systems exploiting heteronuclei such as fluorine-based agents (9). Furthermore, the field has been further widened by exploiting routes to change the MRI response based on the saturation of exchanging protons (10). Moreover much attention has been devoted to the design of smart (responsive) contrast agents, which are activated in specific physiological environments or in response to particular biomarkers (11).

Contrast-enhanced MRI plays a critical role in clinical diagnostics, enabling early detection and precise localization of lesions, vascular pathologies, and neurodegenerative conditions. However, safety concerns, especially regarding nephrogenic systemic fibrosis (NSF) associated with certain GBCAs in patients with renal impairment, have led to ongoing development of safer and more efficient agents (12,13).

3. MECHANISM OF ACTION OF PARAMAGNETIC MRI CONTRAST AGENTS

MRI contrast agents primarily function by modulating the behavior of water protons within biological tissues, thereby enhancing image contrast and improving diagnostic clarity. The underlying mechanism centers on the effect of contrast agents on proton relaxation times, particularly the longitudinal relaxation time (T_1) and the transverse relaxation time (T_2). These relaxation times govern how quickly protons return to their equilibrium states after being excited by the MRI's radiofrequency pulse. Contrast agents typically contain paramagnetic or superparamagnetic substances, which interact with the magnetic moments of nearby hydrogen nuclei (water protons), altering the local magnetic environment (4,5).

Paramagnetic contrast agents, such as those based on gadolinium (Gd^{3+}), contain unpaired electrons that create fluctuating local magnetic fields, which increase the efficiency of energy transfer between protons and their surroundings. This accelerates longitudinal (T_1) relaxation, leading to brighter signal intensities on T_1-weighted images—hence, these are often referred to as positive contrast agents (6,7). In contrast, superparamagnetic agents, such as iron oxide nanoparticles, generate strong microscopic magnetic gradients that accel-

erate transverse (T_2) relaxation, causing rapid dephasing of proton spins. This leads to signal loss and darker images on T_2-weighted sequences, classifying them as negative contrast agents (8).

The efficiency of a contrast agent in altering relaxation times is quantified by its relaxivity (r_1 and r_2), which reflects its capacity to enhance the relaxation rates ($1/T_1$ and $1/T_2$) per unit mM concentration. Relaxivity depends on several factors, including the molecular structure of the agent, the coordination geometry of the metal ion, the number and exchange lifetime of inner-sphere water molecules and rotational correlation time (4) (Figure 2). Additionally, the local tissue environment—such as pH, temperature, and the presence of macromolecules—can modulate the relaxivity and hence the contrast enhancement efficacy.

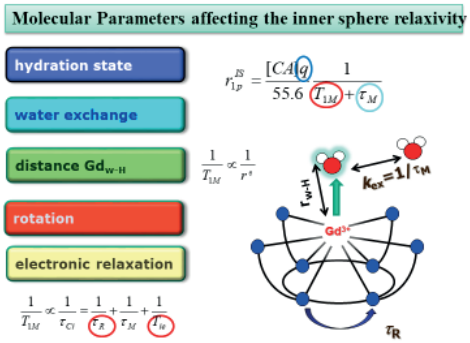

Figure 2. The performance of Gd-based MRI contrast agents has been improved by acting on their molecular structure and on their dynamics.

In clinical imaging, the choice of contrast agent and imaging sequence (T_1- or T_2-weighted) is tailored to the diagnostic objective, such as detecting tumors, assessing vascular integrity, or visualizing inflammatory processes. Advances in contrast agent development are increasingly focused on creating targeted or responsive agents that selectively accumulate in pathological tissues or change their magnetic properties in response to physiological triggers (11).

4. TYPES OF MRI CONTRAST AGENTS

MRI contrast agents are critical tools in enhancing the diagnostic capabilities of magnetic resonance imaging. They work primarily by altering the relaxation times of nearby hydrogen nuclei, thereby enhancing image contrast between different tissues. Among the broad classes of paramagnetic contrast agents used in clinical and experimental imaging, the most prominent include gadolinium (Gd)-, manganese (Mn)-, and iron (Fe)-based complexes, iron oxide nanoparticles, and paramagnetic chemical exchange saturation transfer (paraCEST) agents.

(i) Gadolinium-Based Contrast Agents (GBCAs)

Gadolinium-based contrast agents are the most widely used in clinical MRI. Gadolinium (Gd^{3+}), a lanthanide metal, possesses seven unpaired electrons, making it highly paramagnetic. This property allows GBCAs to significantly reduce the longitudinal relaxation time (T1) of nearby water protons, resulting in brighter signal intensities on T_1-weighted images. GBCAs are particularly valuable in imaging vascular structures, tumors, and regions with compromised blood-brain barrier integrity (14,15).

To mitigate gadolinium's inherent toxicity—as free Gd^{3+} ions are toxic due to their interference with calcium biochemistry—GBCAs are formulated as chelates, where the Gd^{3+} ion is tightly bound to organic ligands. These ligands are primarily classified as linear or macrocyclic, based on their chemical architecture.

- **Linear GBCAs**: These have an open-chain chelating structure. While they are effective at enhancing signal intensity, their kinetic stability is lower, which increases the risk of gadolinium dissociation, especially in patients with impaired renal function. Examples include gadodiamide and gadopentetate dimeglumine (16,17).
- **Macrocyclic GBCAs**: These agents encase the gadolinium ion in a rigid ring-like structure, providing greater thermodynamic stability and kinetic inertness. This arrangement significantly reduces the release of free Gd^{3+} ions, thereby lowering the risk of adverse effects such as nephrogenic systemic fibrosis (NSF). Widely used macrocyclic agents include gadobutrol, gadoterate meglumine, and gadoteridol (18,19). Recently Gadopiclenol (a system with two water molecules in the inner coordination sphere) has been introduced (20)
- Much work has been done to get an in-depth understanding of the structural, electronic and dynamic parameters that control the observed relaxivity of Gd-containing agents (21) (Figure 2).

(ii) Manganese (Mn)- and Iron (Fe)-Based Complexes

Manganese and iron are emerging as biocompatible alternatives to gadolinium due to their status as essential trace elements in the human body. Although these ions have fewer unpaired electrons (Mn^{2+} has 5; Fe^{3+} has 5), they are still paramagnetic and capable of T1 signal

enhancement, especially when appropriately chelated or incorporated into nanoparticle structures.

- **Manganese-Based Agents**: Manganese, often used in the form of manganese chloride ($MnCl_2$) or chelates like Mn-DPDP (mangafodipir), enters cells via calcium channels and can serve as a surrogate biomarker for cellular viability or activity (22,23). Its use is being revisited in manganese-enhanced MRI (MEMRI), particularly in neuroscience and cardiology research. However, concerns about neurotoxicity at high doses have limited its widespread clinical use (24).
- **Iron-Based Complexes**: Iron-based MRI agents include ferric iron chelates and iron oxide nanoparticles. While superparamagnetic iron oxide nanoparticles (SPIONs) are more traditionally associated with T2-weighted imaging (discussed below), iron3+ chelates are being explored for their potential T1 contrast capabilities. These agents benefit from endogenous metabolic pathways for clearance and storage, reducing concerns about long-term deposition (24).

The use of Mn and Fe as alternatives to Gd is under intense scrutiny, especially in preclinical settings, due to their potential to offer safer, biodegradable options with low systemic toxicity, particularly important for vulnerable populations such as children, pregnant women, or patients requiring frequent imaging.

(iii) Metalloporphyrins:

Paramagnetism is often associated with the presence of metal ions at the center of the porphyrin ring. Metalloporphyrins are highly relevant due to their diverse roles in biological systems, such as in hemoglobin, cytochromes, and chlorophyll, and their use in various applications including catalysis and sensors. The metal center in a metalloporphyrin can significantly influence the electronic structure, which in turn impacts the magnetic properties of the compound. The metal ion can either contribute unpaired electrons to the system, inducing paramagnetism, or alter the electronic environment to promote coordination with ligands that can lead to distinct magnetic behaviors. For instance, iron (III)-containing metalloporphyrins (e.g., ferriprotoporphyrin IX) are typically paramagnetic due to the presence of unpaired electrons in the d-orbitals of the iron ion. Similarly, manganese (III) porphyrins exhibit paramagnetism due to the partially filled d-orbitals of manganese. The magnetic susceptibility of these systems can be influenced by factors such as the ligand field around the metal, spin-state splitting, and temperature, among others (25).

The paramagnetic behavior of metalloporphyrins is particularly useful for understanding their interactions with other molecules, such as in enzyme catalysis or electron transfer processes. For example, studies on the paramagnetism of cobalt (III) porphyrins have revealed insights into their role in oxidative catalysis and their ability to activate molecular oxygen (26). The understanding of the magnetic properties of these systems is not only crucial for biological systems but also for their potential application in materials science, The paramagnetic behavior of metalloporphyrins is particularly useful in the development of novel magnetic sensors or drug delivery systems. Additionally, their magnetic properties make them suitable candidates for use in magnetic resonance imaging (MRI) as contrast agents (27).

(iv) Iron Oxide-Based Contrast Agents

Iron oxide-based contrast agents, particularly superparamagnetic iron oxide nanoparticles (SPIONs) and ultrasmall superparamagnetic iron oxides (USPIOs), are an important class of negative contrast agents in MRI. These agents work by shortening the transverse relaxation time (T_2 or T_{2^*}), leading to a decrease in signal intensity (darkening) on T_2-weighted images. The core of these nanoparticles typically consists of magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3), surrounded by a biocompatible coating (e.g., dextran, PEG) to enhance stability and reduce immunogenicity (28,29).

SPIONs are especially effective in imaging the reticuloendothelial system (RES), including the liver, spleen, and lymph nodes, because macrophages rapidly phagocytose the particles. This allows for detection of lesions or tumors that do not take up the agent, appearing as hyperintense (bright) areas against a darkened background (30). Additionally, SPIONs have shown promise in cell tracking, magnetic drug delivery, and theranostic applications, owing to their ability to be functionalized with targeting ligands or drugs (31).

Despite their advantages, SPIONs have faced regulatory and commercial setbacks. For example, Feridex® and Resovist®, two clinically approved SPION agents, were withdrawn from the market due to limited clinical demand and high production costs, though a superparamagnetic iron oxide nanoparticle that has been approved in the United States, Europe, and Canada for intravenous iron supplementation research continues robustly in this area (32). Currently the off-label use of Ferumoxytol (a superparamagnetic iron oxide nanoparticle that has been approved in the United States, Europe, and Canada for intravenous iron supplementation) appears as an efficient replacement in these applications (33).

(v) Eu2+ Contrast Agents

Some attention has been devoted to Eu2+ based agents because the number of unpaired electrons in this ion is the same as the one of Gd3+ (i.e. 7 unpaired electrons). The most attractive application appears to look at them as reporters of the tissue oxygenation state as the transformation from Eu2+ to Eu3+ causes a marked reduction of the relaxivity being the latter almost "silent" as relaxation enhancer for water protons (34).

(vi) ParaCEST Contrast Agents.

Paramagnetic Chemical Exchange Saturation Transfer (paraCEST) agents represent a novel and versatile class of MRI contrast agents. Unlike tradition1al T_1 or T_2 agents that rely on altering relaxation times, paraCEST agents generate contrast through a frequency-selective saturation transfer mechanism. A radiofrequency (RF) pulse is applied at the resonance frequency of exchangeable protons saturating their magnetization. These saturated protons then exchange with bulk water protons, causing a reduction in the bulk water signal, which is detectable in the image (35).

One major advantage of paraCEST agents is that their contrast can be turned on or off "at will" by adjusting the RF pulse, allowing for tunable and multiplexed imaging—multiple agents can be selectively visualized based on their chemical shift. ParaCEST agents often incorporate lanthanide ions like Eu^{3+}, Tm^{3+}, or Yb^{3+}, which induce a large paramagnetic shift in the exchangeable proton resonance, enabling selective excitation and efficient contrast (36).

A leading figure in the development of paraCEST agents is A. Dean Sherry, whose pioneering work introduced the use of lanthanide-based DOTA-tetraamide complexes as responsive MRI contrast agents (37). His research demonstrated how paramagnetic ions could create large chemical shifts in exchangeable protons, facilitating the design of highly specific and tunable probes. Sherry's lab further developed molecular imaging agents responsive to biological variables such as pH (38), glucose (39), and metal ions like Zn^{2+} (40), significantly enhancing the functional imaging potential of MRI. He also contributed to the advancement of imaging methodologies such as frequency-labeled exchange transfer to improve in vivo detection of these agents (41).

An exciting development in this field is the creation of LipoCEST agents, which consist of liposomes encapsulating paramagnetic shift reagents within their aqueous cores. These systems confine the paraCEST agent, improving sensitivity and enabling compartmentalized contrast. LipoCEST agents are being explored for molecular and responsive imaging, such as detecting pH, enzyme activity, or temperature changes in localized tissue environments (42,43).

Furthermore, paraCEST agents are under active development for use as biosensors, particularly in cancer and neurological imaging, where they can provide functional information—such as changes in tumor microenvironment or enzyme expression—that goes beyond traditional anatomical imaging (44,45).

(vii) Effects of Paramagnetic Agents on the Endogenous MR-CEST contrast

CEST (Chemical Exchange Saturation Transfer) is an emerging modality in MRI. As anticipated above reporting on paraCEST agents, it relies on the transfer of saturated magnetization to the bulk water signal upon the RF irradiation of the absorption of mobile protons of a given solute in slow/intermediate exchange regime with water. In biological tissues, the exchangeable pool of protons is provided mostly by N-H and O-H functionalities on endogeneous proteins, creatine, free aminoacids and alcoholic groups. Basically, the endogenous CEST effect increases with the concentration of mobile protons and their exchange rate (still remaining in the slow/intermediate exchange regime) and decreases with the shortening of the water proton relaxation time. T_1 of water protons can be markedly decreased by the addition of paramagnetic agents.

It has been deemed of interest to exploit the effects of paramagnetic agents on the endogenous CEST response (46). The T_1 shortening causes a decrease of the Saturation Tranfer thus allowing to track phenomena reporting on the local biodistribution of the GBCAs and on the dynamics of the water molecules "labelled" by the interaction with the paramagnetic agent. Interestingly, since the endogenous CEST effect arises essentially from intracellular molecules, it follows that this experiment allows to map the differences in the permeability of cell membranes. The cycling of water molecules across the cell membrane reports about the activity of transporters that are overexpressed/up-regulated in tumor cells i.e. in turn on the cell metabolism (Figure 3). By applying this procedure one may generate maps reporting on the changes in water permeability of tumour cell membranes *via* the modulation of the endogenous (intracellular) CEST response by the decrease of water proton T_1 affected by the presence of a Gd-contrast agent in the extracellular space.

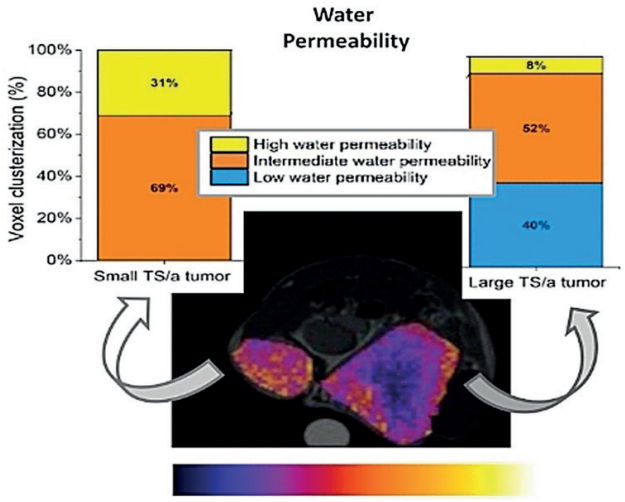

Figure 3. Map of the tumour regions reporting the changes of the endogenous CEST response upon the administration of a Gd-containing agent. The paramagnetic agent distributes in the extracellular space causing a shortening of T_1 of the water protons in this compartment. The transfer of these "labelled" water molecules to the intracellular compartment (where the endogenous CEST response is generated) causes a reduction of the CEST effect that is dependent on the differences in water permeability of the tumour cells. The heterogeneity in the distribution of voxels representing low, intermediate and high membrane permeability reflects changes in number and type of membrane transporters, i.e. a tool to get more insight into the differences in cell metabolism.

5. CLINICAL APPLICATIONS OF MRI CONTRAST AGENTS

MRI contrast agents—particularly gadolinium-based contrast agents (GBCAs)—play a pivotal role in enhancing diagnostic accuracy across multiple organ systems by improving tissue contrast and highlighting pathological changes. Their utility spans several major clinical domains:

- **Neuroimaging**: In brain imaging, GBCAs are essential for detecting and characterizing intracranial tumors, multiple sclerosis (MS) plaques, stroke, and infections. Under normal conditions, the blood-brain barrier (BBB) restricts the entry of contrast agents into the brain parenchyma. However, in areas of pathology where the BBB is disrupted—such as in gliomas or inflammatory lesions—contrast agents can accumulate, enhancing these regions on T_1-weighted MRI (47,48). This selective enhancement is critical for delineating lesion boundaries, assessing disease activity in MS, and guiding neurosurgical planning.
- **Oncology**: MRI contrast agents are widely employed in cancer diagnostics, staging, and treatment monitoring. Tumors typically exhibit increased vascular permeability and abnormal angiogenesis, allowing contrast agents to preferentially accumulate within malignant tissues—a phenomenon exploited in dynamic contrast-enhanced MRI (DCE-MRI) (49,50). This technique provides valuable information about tumor perfusion, vascular density, and response to therapy. GBCAs, as well as experimental agents like metalloporphyrins, have shown promise for targeting tumor-specific microenvironments and enhancing tumor-to-background contrast (11).

Paramagnetic metalloporphyrins have emerged as promising agents in cancer imaging and therapy due to their unique physicochemical properties and biological behavior. One of their most notable characteristics is their natural tendency to accumulate in tumor tissues, a phenomenon attributed to both the enhanced permeability and retention (EPR) effect and the specific affinity of porphyrin structures for cancerous cells (51,52). Leveraging this tumor-selective uptake, paramagnetic metalloporphyrins—such as those incorporating manganese or iron—have been investigated as magnetic resonance imaging (MRI) contrast agents. Studies have demonstrated their efficacy in enhancing the visibility of tumors in vivo, especially in preclinical models using human tumor xenografts in mice (53-56). These agents offer high relaxivity and favorable biodistribution profiles, with some formulations showing minimal aggregation or dimerization in aqueous environments, which further improves their imaging utility.

Recent advances have also explored the structural modification of metalloporphyrins to improve their pharmacokinetics and imaging specificity. For instance, conjugation with targeting ligands or incorporation into liposomes or nanoparticles can enhance their accumulation in tumor tissues and reduce off-target effects (57-59). Furthermore, dual-modality imaging using metalloporphyrin-based agents that combine MRI with fluorescence or positron emission tomography (PET) has been developed to provide complementary diagnostic information (60,61).

Beyond diagnostics, paramagnetic metalloporphyrins are gaining attention in therapeutic applications, particularly in the development of magnetically guided drug delivery systems. By attaching therapeutic agents to metalloporphyrin complexes, researchers have engineered multifunctional constructs that respond to external magnetic fields, thereby enhancing drug localization at tumor sites and minimizing systemic toxicity (62,63). This dual-function approach holds promise for integrat-

ing imaging and therapy—so-called theranostics—into a single platform. Moreover, the ongoing development of nanoparticle-based delivery systems incorporating metalloporphyrins is anticipated to further increase targeting specificity and therapeutic efficacy while reducing adverse side effects (64,65). These innovations represent a significant advancement in precision oncology, facilitating both the early detection and effective treatment of malignant tumors.

- **Cardiovascular Imaging**: MRI contrast agents are instrumental in evaluating myocardial perfusion, ischemia, and viability. In cardiac MRI, GBCAs help visualize coronary arteries, detect myocardial infarction, and assess fibrosis or scar tissue using late gadolinium enhancement (LGE) techniques (66). Additionally, contrast-enhanced MR angiography (CE-MRA) provides noninvasive visualization of vascular abnormalities such as aneurysms, stenoses, and congenital heart defects (67).
- **Musculoskeletal Imaging**: In musculoskeletal (MSK) applications, contrast agents enhance the detection of inflammatory, infectious, and neoplastic conditions. They are particularly useful in evaluating synovial inflammation in rheumatoid arthritis, soft tissue abscesses, osteomyelitis, and soft tissue tumors (68,69). Contrast-enhanced MRI can also differentiate between viable and necrotic tissue in cases of trauma or postoperative complications, aiding clinical decision-making.

These diverse clinical uses underscore the versatility of MRI contrast agents in modern diagnostic imaging. The continued development of novel contrast materials, including targeted, biodegradable, and theranostic agents, promises to expand their utility even further.

6. SAFETY AND RISKS

While MRI contrast agents—particularly gadolinium-based contrast agents (GBCAs)—are widely regarded as safe and well-tolerated in the general population, their use is not entirely without risk. Millions of doses are administered annually with a low incidence of acute adverse reactions, which are usually mild and include nausea, headache, dizziness, or injection site discomfort (70). However, more serious concerns have emerged, particularly in relation to renal impairment and gadolinium retention. In principle, also Mn2+ and Fe3+ based Contrast Agents too own some risk. For the former ones, the main concern deals with the in vivo release of manganese ions that may interfere with the homeostasis of this essential metal ion. For Fe+ based systems, main risks appear to be associated to the potential formation of OH radicals and ROS in the case water molecules enter its inner coordination sphere (Fenton reaction).

One of the most significant complications associated with GBCAs is nephrogenic systemic fibrosis (NSF), a rare but debilitating disorder that can occur in patients with severe renal dysfunction (glomerular filtration rate <30 mL/min/1.73 m^2). NSF is characterized by progressive fibrosis of the skin, joints, and internal organs, often leading to severe disability or death. The condition was first linked to gadolinium exposure in 2006 (71), and subsequent studies confirmed that certain linear, nonionic GBCAs pose a higher risk due to their lower kinetic stability and greater likelihood of releasing free gadolinium ions (Gd^{3+}) in vivo (72,73).

In response, regulatory agencies such as the FDA and EMA issued safety guidelines restricting the use of high-risk GBCAs in at-risk populations, especially those with chronic kidney disease (CKD) or acute kidney injury. Today, macrocyclic GBCAs, which have a more stable and inert chemical structure, are preferred in clinical practice for their lower propensity to release gadolinium and their association with a significantly reduced risk of NSF (12,74);

A second area of concern involves the retention of gadolinium in brain tissues—notably in the dentate nucleus and globus pallidus—even in patients with normal renal function. This issue was first observed via increased T_1 signal intensity on non-contrast MRIs in patients who had received multiple doses of GBCAs (18). Follow-up studies confirmed that both linear and macrocyclic agents could lead to gadolinium deposition, although the extent and persistence appear to be greater with linear agents (75,76). While no clinical consequences have yet been established to date, the long-term effects of gadolinium accumulation remain under intense scrutiny, prompting precautionary approaches in pediatric, pregnant, and repeat-scan populations.

To cope with these concerns, contrast agents manufacturing companies have recently introduced Gd-based contrast agents endowed with higher relaxivities that provide the same diagnostic response of the first generation systems at markedly lower administration doses.

Moreover, hypersensitivity reactions, although rare, have been reported. These include mild allergic responses and very infrequent anaphylactic reactions, with incidence rates estimated between 0.01% and 0.1% (77). Informed consent, appropriate screening for renal function (typically via eGFR), and risk-benefit evaluation remain essential components of safe GBCA administration.

Continued research is underway to develop non-

gadolinium-based contrast agents and biodegradable nanoparticles, aiming to reduce safety risks while preserving diagnostic efficacy (78). Such advances may further improve the safety profile of MRI contrast agents in the future.

7. RECENT ADVANCES IN MRI CONTRAST AGENTS

In recent years, research into MRI contrast agents has shifted toward the development of next-generation agents that not only enhance imaging quality but also improve safety profiles, enable molecular targeting, and even combine diagnostic and therapeutic functions. These innovations aim to overcome the limitations of conventional gadolinium-based contrast agents (GBCAs), particularly concerns related to gadolinium deposition and non-specific tissue enhancement, while enhancing the ability to visualize complex biological processes at the molecular and cellular levels.

- **Targeted Contrast Agents**: A major frontier in MRI contrast development involves the creation of target-specific agents that can recognize and bind to biomolecular markers associated with particular diseases, such as cancer, inflammation, or neurodegeneration. These agents are typically conjugated with ligands—such as antibodies, peptides, or small molecules—that bind to overexpressed receptors (e.g., HER2, integrins, or folate receptors) on pathological cells. For example, agents targeting vascular endothelial growth factor (VEGF) or matrix metalloproteinases (MMPs) have shown promise for imaging tumor angiogenesis and metastasis (79,80). This molecular-level imaging may enable early detection, risk stratification, and monitoring of treatment response, moving MRI closer to personalized medicine. A major obstacle in these applications is represented by the low sensitivity of MRI contrast agents. Often the number of targeted epitopes is too low to yield sufficient change in the detected contrast-to-noise ratio in the acquired MR images. In the case of Gd-base agents, the local concentration has to be in the microM range, i.e. the number of Gd per cell has to be of the order of 10^9/relaxivity. However, these tasks continue to be challenged either pursuing systems endowed with marked relaxation enhancements and by applying supra-molecular approaches able to bring a large number of contrast agent units at the targeting sites.
- **Multifunctional (Theranostic) Agents**: Another cutting-edge approach involves theranostic nanoparticles—agents that combine diagnostic imaging and therapeutic delivery in a single platform. These hybrid systems often integrate contrast-generating components (e.g., gadolinium, manganese, or iron oxide) with chemotherapeutics, gene therapy vectors, or photothermal agents. Upon accumulation at the target site, such as a tumor, these agents enable real-time imaging and simultaneous localized therapy (81). For example, iron oxide nanoparticles functionalized with doxorubicin and tumor-targeting ligands have demonstrated dual capabilities for imaging and cancer treatment in preclinical models (82).
- **Reducing Gadolinium Toxicity**: To address the growing concerns regarding gadolinium retention in tissues, researchers have developed more stable gadolinium chelates—especially macrocyclic ligands—that tightly bind gadolinium ions and exhibit minimal *in vivo* dissociation (19). Furthermore, entirely gadolinium-free agents are being actively explored. Alternatives include manganese-based agents (which mimic calcium in biological systems and have natural clearance pathways) and iron oxide nanoparticles, which are biodegradable and pose a lower risk of long-term deposition (83). These developments represent important steps toward safer and more sustainable MRI contrast technologies. In this context, among the classes of non-metal containing agents, it is worth to mention diaCEST systems and hyperpolarized molecules as they are often based on naturally occurring species or compounds endowed with a high biocompatibility. Much attention is currently devoted to heteronuclear detection of hyperpolarized C-13 labelled molecules whose *in vivo* chemistry reports on ongoing enzymatic transformations at cellular level. This opens the way to investigate in real time important steps of cell metabolism as it has been shown in applications based on the use of hyperpolarized substrates like C-13-labelled pyruvate and fumarate.

Overall, these advances reflect a broader trend toward precision imaging, wherein MRI contrast agents not only enhance anatomical detail but also provide functional and molecular information critical for diagnosing and treating complex diseases.

8. CONCLUSION

Contrast agents are indispensable tools in the field of MRI, enhancing the diagnostic power of the imaging technique. They cause a marked signal enhancement in

the regions where they distribute providing clearer, more detailed images of internal structures. Nowadays these CAs are used in about 30-40% of the MR scans acquired at clinical settings.

While there are risks associated with their use, ongoing advancements in contrast agent technology continue to improve both the safety and effectiveness of these agents. As research progresses, we are likely to see even more sophisticated agents that are safer, more targeted, and more efficient, further cementing MRI's role as a cornerstone of modern medical diagnostics.

Acknowledgement: JSC thanks his host at BGU, Prof. Barak Akabayov and Chemistry Department Head Prof. Maya Bar-Sadan, for their support.

REFERENCES

1. Earnshaw, A. (2001) *Introduction to Magnetochemistry*. Dover Publications.
2. Curie, P. (1895) Propriétés magnétiques des corps à diverses températures. *Annales de Chimie et de Physique*, **5**, 289-405.
3. Weil, J.A., Bolton, J. R., & Wertz, J. E.. (1994) *Electron Paramagnetic Resonance: Elementary Theory and Practical Applications.* Wiley.
4. Caravan, P., Ellison, J. J., McMurry, T. J., & Lauffer, R. B. . (1999) Gadolinium(III) Chelates as MRI Contrast Agents: Structure, Dynamics, and Applications. *Chemical Reviews*, **99**, 2293–2352.
5. Runge, V.M. (2018) *Contrast Media in Magnetic Resonance Imaging: Basic Principles and Clinical Applications*. Springer.
6. Weinmann, H.J., Brasch, R. C., Press, W. R., & Wesbey, G. E. (1984) Characteristics of gadolinium-DTPA complex: A potential NMR contrast agent. *American Journal of Roentgenology*, **142**, 619–624.
7. Shokrollahi, H. (2013) Contrast agents for MRI. . *Materials Science and Engineering C*, **33**, 4485–4497.
8. Bulte, J.W.M., & Kraitchman, D. L. . (2004) Iron oxide MR contrast agents for molecular and cellular imaging. *NMR in Biomedicine*, **17**, 484–499.
9. Hequet, E., Henoumont, C., Muller, RN., Laurent, S. (2019) Fluorinated MRI contrast agents and their versatile applications in the biomedical field. *Future Med Chem.*, **11**, 1157-1175.
10. Wu, B., Warnock, G., Zaiss, M. et al. (2016) An overview of CEST MRI for non-MR physicists. *EJNMMI Phys*, **19**, 3.
11. Zhou, Z., Lu, Z. R. (2019) Gadolinium-based contrast agents for magnetic resonance cancer imaging. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, **11**, e1518.
12. Grobner, T. (2006) Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrology Dialysis Transplantation*, **21**, 1104–1108.
13. Thomsen, H.S. (2006) Nephrogenic systemic fibrosis: A serious late adverse reaction to gadodiamide. *European Radiology*, **16**, 2619–2621.
14. Runge, V.M. (2016) Safety of the gadolinium-based contrast agents. *Top Magnetic Resonance Imaging*, **25**, 137–143.
15. Aime, S., & Caravan, P. (). . (2009) Biodistribution of gadolinium-based contrast agents, including gadolinium deposition. *Journal of Magnetic Resonance Imaging,*, **30**, 1259–1267.
16. Perazella, M.A. (2009) Current status of gadolinium toxicity in patients with kidney disease. *Clinical Journal of the American Society of Nephrology*, **4**, 461–469.
17. Thomsen, H.S. (2013) Nephrogenic systemic fibrosis: History and epidemiology. *Radiologic Clinics of North America,*, **47**, 827–831.
18. Kanda, T., et al. . (2014) High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: Relationship with increasing cumulative dose of a gadolinium-based contrast material. *Radiology*, **270**, 834–841.
19. Gulani, V., Calamante, F., Shellock, F. G., Kanal, E., & Reeder, S. B. (2017) Gadolinium deposition in the brain: Summary of evidence and recommendations. *The Lancet Neurology*, **16**, 564–570.
20. Maimouni, I., et al. (2025) Gadopiclenol: A q = 2 Gadolinium-Based MRI Contrast Agent Combining High Stability and Efficacy. *Investigative Radiology*, **60**, 234-243.
21. Wahsner, J., Gale, EM., Rodríguez, A., Caravan, P. (2019) Chemistry of MRI Contrast Agents: Current Challenges and New Frontiers. *Chem. Rev.*, **119**, 957-1057.
22. Silva, A.C., Lee, J. H., Aoki, I., & Koretsky, A. P. (2004) Manganese-enhanced magnetic resonance imaging (MEMRI): Methodological and practical considerations. *NMR in Biomedicine*, **17**, 532–543.
23. Koretsky, A.P. (2012) Manganese-enhanced MRI of the heart and brain: What does the future hold? *NMR in Biomedicine*, **25**, 660–664.
24. Widerøe, M., Ravna, A. W., & Larsen, B. R. (2011) Manganese-enhanced MRI: Biological specificity and toxicity. . *NeuroImage*, **54**, 2316–2327.
25. Bau, R., Purtell, J. E., & Powell, M. S. (2014) Magnetic properties of metalloporphyrins and related compounds. *Journal of Inorganic Biochemistry*, **129**, 39-46.

26. Sjöblom, S., et al. (2019) Magnetic properties and catalytic activity of cobalt (III) porphyrins. *Journal of Catalysis*, **377**, 100-107.
27. Kuhn, H., et al. (2013) Metalloporphyrins as contrast agents in magnetic resonance imaging. *Journal of Magnetic Resonance Imaging*, **38**, 727-735.
28. Na, H.B., Song, I. C., & Hyeon, T (2009) Inorganic nanoparticles for MRI contrast agents. *Advanced Materials*, **21**, 2133–2148.
29. Lee, N., Hyeon, T. (2011) Designed synthesis of uniformly sized iron oxide nanoparticles for efficient magnetic resonance imaging contrast agents. *Chemical Society Reviews*, **41**, 2575–2589.
30. Wang, Y.-X.J. (2013) Superparamagnetic iron oxide based MRI contrast agents: Current status of clinical application. *Quantitative Imaging in Medicine and Surgery*, **1**, 35–40.
31. Gupta, A.K., & Gupta, M. (2005) Synthesis and suRFace engineering of iron oxide nanoparticles for biomedical applications. *Biomaterials*, **26**, 3995–4021.
32. Sharma, A., Rao, H., & Politi, L. S. . (2021) Iron-based T1 contrast agents for magnetic resonance imaging: A new era of safer clinical diagnostics. *Contrast Media & Molecular Imaging*, **I**, 1–14.
33. Adams, L.C., et al. (2023) Ferumoxytol-Enhanced MRI in Children and Young Adults: State of the Art. *American Journal of Roentgenology*, **220**, 590-603.
34. Lewandowski, E.C., et al. (2024) Europium(ii/iii) coordination chemistry toward applications. *Chemical Communications*, **60**, 10655-10671.
35. Zhou, J., & van Zijl, P. C. M. (2006) Chemical exchange saturation transfer imaging and spectroscopy. *Progress in Nuclear Magnetic Resonance Spectroscopy*, **48**, 109–136.
36. Tóth, É., Helm, L., & Merbach, A. E. (2014) *Paramagnetic NMR Relaxation Theory and Applications. The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging*. 2nd ed. Wiley-VCH.
37. Zhang, S., Winter, P., Wu, K., & Sherry, A. D. (2001) A novel europium(III)-based MRI contrast agent. *Journal of the American Chemical Society*, **123**, 1517–1518.
38. Wu, Y., et al. (2006) pH imaging of mouse kidneys in vivo using a frequency-dependent paraCEST agent. *Magnetic Resonance in Medicine*, **55**, 843–848.
39. Yadav, N.N., et al. (2014) Imaging glucose metabolism using dynamic glucose-enhanced (DGE) MRI. *Magnetic Resonance in Medicine*, **72**, 823–832.
40. Esqueda, A.C., et al. (2009) A new Gd^{3+}-based MRI zinc sensor. *Journal of the American Chemical Society*, **131**, 11387–11391.
41. McMahon, M.T., et al. (2008) Quantifying exchange rates in chemical exchange saturation transfer agents using frequency-labeled exchange transfer. *Magnetic Resonance in Medicine*, **60**, 1049–1057.
42. Aime, S., & Castelli, D. D. (2005) Liposomal MRI agents: SuRFace functionalization and targeting. *NMR in Biomedicine*, **18**, 461–469.
43. Liu, G., et al. (2019) LipoCEST: A platform for sensitive molecular MRI. *Advanced Healthcare Materials*, **8**, 1801332.
44. Chan, K.W.Y., et al. (2013) Responsive paraCEST MRI contrast agents for sensing pH and enzyme activity. *Accounts of Chemical Research*, **46**, 2080–2090.
45. Ferrauto, G., et al. (2011) Imaging tumor acidosis with a paramagnetic CEST MRI contrast agent. *Angewandte Chemie International Edition*, **50**, 10762–10765.
46. Di Gregorio, E., et al. (2024) A Magnetic Resonance Imaging-Chemical Exchange Saturation Transfer (MRI-CEST) Method for the Detection of Water Cycling across Cellular Membranes. *Angew Chem Int Ed Engl.*, **63**, e202313485.
47. Essig, M., et al. . (2006) Perfusion MRI: The Five Most Frequently Asked Clinical Questions. *American Journal of Roentgenology*, **187**, 792–804.
48. Rovira, À., Wattjes, M. P., et al. (2015) Evidence-based guidelines: Use of MRI in multiple sclerosis—Clinical implementation in the diagnostic process. *Nature Reviews Neurology*, **11**, 471–482.
49. Tofts, P.S., et al. (1999) Estimating kinetic parameters from dynamic contrast-enhanced T1-weighted MRI of a diffusable tracer: Standardized quantities and symbols. *Journal of Magnetic Resonance Imaging,* **10**, 223–232.
50. Padhani, A.R., et al. (2002) Dynamic contrast-enhanced MRI in clinical oncology: Current status and future directions. *Journal of Magnetic Resonance Imaging,*, **16**, 407–422.
51. Chen, C.-W., Cohen, J. S., Myers, C. E., and Sohn, M. (1984) Paramagnetic Metalloporphyrins as Potential Contrast Agents in NMR Imaging,. *FEBS Lett.*, **168**, 70.
52. Patronas, N.J., et al. (1986) Metalloporphyrin Contrast Agents for Magnetic Resonance Imaging of Human Tumors in Mice. *Cancer Treat. Rep*, **70**, 390.
53. Hambright, P., et al. (1987) An Iron (III) Porphyrin that Exhibits Minimal Dimerization in Aqueous Solution. *Inorg. Chim. Acta*, **128**, L11.
54. Lyon, R.C., et al. (1987) Tissue Distribution and Stability of Metalloporphyrin. *Mag. Res. Med.*, **4**, 24-33.
55. Megnin, F., et al. (1987) On the Mechanism of Selective Retention of Porphyrins and Metalloporphyrins by Cancer Cells. *Biochim. Biophys. Acta*, **929**, 173-181.

56. van Zijl, P.C.M., et al. (1990) Metalloporphyrin magnetic resonance contrast agents: feasibility of tumor-specific MRI. *Invest. Radiol.* , **25**, S69-S70.
57. Place, D.A., et al. (1992) MRI contrast-dose relationship of manganese(III)tetra(4-sulfonatophenyl) porphyrin with human xenograft tumors in nude mice at 2.0 Tesla. *Magn. Reson. Imaging*, **10**, 919-928.
58. Ethirajan, M., Chen, Y., Joshi, P., and Pandey, R. K. (2011) The Role of Porphyrin Chemistry in Tumor Imaging and Photodynamic Therapy, Chem. *Soc. Rev.*, **40**, 340–362.
59. Zhao, X., et al. . (2021) Multifunctional Porphyrin-Based Nanoparticles for Tumor Imaging and Therapy. *Coord. Chem. Rev.*, **429**, 213616.
60. Zhang, L., Wang, D., Yang, K., et al. . (2013) Manganese Dioxide Nanoparticles as a MRI Contrast Agent and an Enhancer for Photodynamic Therapy in Cancer Cells. *Chem. Commun.* , **49**, 5573–5575.
61. Zhang, X., Xiao, Y., and Qian, X. (2014) A Dual-Modal Probe for Simultaneous Fluorescence and MRI Tumor Imaging. *J. Mater. Chem. B*, **2**, 5662–5667.
62. Huang, Y., et al. (2015) Paramagnetic metalloporphyrins in targeted cancer therapy. *Biomaterials*, **45**, 35-46.
63. Zhang, R., Lu, G., Sun, Z., et al. (2016) Theranostic Nanoplatforms Based on Porphyrin Derivatives for Multimodal Imaging-Guided Phototherapy. *Chem. Commun.*, **52**, 10588–10605.
64. Lovell, J.F., Jin, C. S., Huynh, E., et al. (2011) Porphysome Nanovesicles Generated by Porphyrin Bilayers for Use as Multimodal Biophotonic Contrast Agents. *Nat. Mater.*, **10**, 324–332.
65. Yang, X., Wang, D., Mao, D., and Wang, S. (2022) Porphyrin-Driven Smart Nanomedicines for Cancer Theranostics. *Acta Pharm. Sin B*, **12**, 1885–1905.
66. Kramer, C.M., et al. (2008) Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2008 update. *Journal of Cardiovascular Magnetic Resonance*, **10**, 35.
67. Prince, M.R., & Yucel, E. K. (1993) MR imaging of the vasculature with gadopentetate dimeglumine. *Journal of Magnetic Resonance Imaging,*, **3**, 761–767.
68. van der Heijde, D., et al. (2002) Magnetic resonance imaging of the wrist in early rheumatoid arthritis. *Annals of the Rheumatic Diseases*, **61**, 844–849.
69. Malghem, J., et al. (2001) Magnetic resonance imaging of musculoskeletal infections. *Radiologic Clinics of North America,*, **39**, 183–201.
70. Prince, M.R., Zhang, H., Zou, Z., Staron, R. B., & Brill, P. W. (2011) Incidence of immediate gadolinium contrast media reactions. *American Journal of Roentgenology*, **196**, W138–W143.
71. Kuo, P.H., Kanal, E., Abu-Alfa, A. K., & Cowper, S. E. (2007) Gadolinium-based MR contrast agents and nephrogenic systemic fibrosis. *Radiology*, **242**, 647–649.
72. Cowper, S.E., Robin, H. S., Steinberg, S. M., Su, L. D., Gupta, S., & LeBoit, P. E. (2006) Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. *Lancet*, **356**, 1000–1001.
73. Kanal, E., et al. (2007) ACR guidance document for safe MR practices. *American Journal of Roentgenology*, **188**, 1447–1474.
74. EMA. (2017) European Medicines Agency recommends restrictions on the use of gadolinium contrast agents. *Retrieved from https://www.ema.europa.eu*.
75. McDonald, R.J., et al. (2015) Gadolinium deposition in human brain tissues after contrast-enhanced MR imaging in adult patients without intracranial abnormalities. *Radiology*, **275**, 772–782.
76. Radbruch, A., et al. (2017) Gadolinium retention in the brain: A radiologic concern? . *Radiology*, **285**, 901–902.
77. Runge, V.M. (2001) Safety of approved MR contrast media for intravenous injection. *Journal of Magnetic Resonance Imaging,*, **14**, 486–491.
78. Li, W., Min, Y., Niu, G., et al. . (2021) Gadolinium-free contrast agents for magnetic resonance imaging: Recent progress and future perspectives. *Chemical Society Reviews*, **50**, 5650–5671.
79. Rogosnitzky, M., & Branch, S. (2016) Gadolinium-based contrast agent toxicity: A review of known and proposed mechanisms. *BioMetals*, **29**, 365–376.
80. Caravan, P., Farrar, C. T., & Frullano, L. (2020) Molecular MR imaging: The road to clinical translation. *Journal of the American Chemical Society*, **142**, 12709–12722.
81. Chen, H., Zhang, W., Zhu, G., Xie, J., & Chen, X. (2017) Rethinking cancer nanotheranostics. *Nature Reviews Materials*, **2**, 17024.
82. Qin, S.Y., Cheng, Y. J., Sheng, Y. H., Zhang, A. Q., & Zhang, X. Z. (2018) Biomedical applications of iron oxide nanoparticles: Current insights into novel therapeutic strategies. *Nanomedicine*, **13**, 1435–1450.
83. Zhou, Z., Lu, Z. R. (2021) Gadolinium-free contrast agents for magnetic resonance imaging: Current trends and future directions. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, **13**, e1654.