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SPECIAL TOPIC

Summary of Imaging in 2020: Visualizing the Future of Healthcare with MR Imaging

Brooke A. Corbin,[1] Alyssa C. Pollard,[2,3] Matthew J. Allen,[1] Mark D. Pagel[2,3]

[1]*Department of Chemistry, Wayne State University, 5101 Cass Avenue, Detroit, MI, USA*
[2]*Department of Chemistry, Rice University, 6100 S Main Street, Houston, TX, USA*
[3]*Department of Cancer Systems Imaging, The University of Texas MD Anderson Cancer Center, 1881 East Road, Houston, TX, USA*

Abstract
The Imaging in 2020 meeting convenes biannually to discuss innovations in medical imaging. The 2018 meeting, titled "Visualizing the Future of Healthcare with MR Imaging," sought to encourage discussions of the future goals of MRI research, feature important discoveries, and foster scientific discourse between scientists from a variety of fields of expertise. Here, we highlight presented research and resulting discussions of the meeting.

Key words: CEST, Contrast agent, Gadolinium, Imaging, MRI, PET–MRI

Introduction

From September 23 to 27 of 2018, more than 90 imaging scientists met at the Jackson Lake Lodge in the Grand Teton National Park to immerse themselves in presentations and discussions of cutting-edge research in magnetic resonance imaging (MRI) at the biannual Imaging in 2020 meeting (Fig. 1) [1]. Founded by Tom Meade and Dan Sullivan in 1999 (now led by Tom Meade and Jim Basilion), this meeting brought together imaging scientists, including chemists, physicists, radiologists, and clinicians from all over the world to build scientific relationships through unique and collaborative discourse on transformative research, while being surrounded by the beauty of the national park. The secluded setting and meeting format with large discussion periods paired with each talk enabled ample time to have debates that drive research forward. Topics in 2018 included discussions from the chemical functionalization of new contrast agents to the clinical translation and application of new MRI instrumentation and methodologies. In this review of the meeting, we summarize key points of the presentations and subsequent conversations, highlight important discoveries, and analyze the overall direction of the field. Imaging in 2020 in 2018 was somewhat different than meetings in prior years because the namesake year, 2020, is not so far into the future as it was in 1999. Therefore, although discussions were largely forward looking, some time was devoted to focus on the past to contextualize the likely issues with future research. With the "future" so close, how far have we pushed MR imaging, and how much further can we go?

Brooke A. Corbin and Alyssa C. Pollard contributed equally to this work.

Correspondence to: Matthew Allen; *e-mail:* mallen@chem.wayne.edu, Mark Pagel; *e-mail:* mdpagel@mdanderson.org

Gadolinium-Based Contrast Agents

The meeting started with a historical overview of clinically approved contrast agents for MRI and then expanded to include the current direction of new preclinical developments. Since the US Food and Drug Administration (FDA) approved the clinical use of gadolinium (III) (Gd^{III}) diethylenetriaminepentaacetate (Magnevist®) in 1988, Gd^{III}-based contrast agents have been workhorses in preclinical research and clinical MRI [2]. Since 1988, eight additional gadolinium-based contrast agents have been approved by the FDA. For comparison, three non-gadolinium agents have been approved, but manufacturing for these non-gadolinium agents has been discontinued due to lack of sales [2]. Other metals have been explored for use

Fig. 1 The Imaging in 2020 meeting was held at the Jackson Lake Lodge in the Grand Teton National Park, where the views of the Grand Tetons contributed to inspirational discussions about the future horizons of molecular imaging research.

as contrast agents for MRI, but the ability of Gd^{III}-containing complexes to enhance the relaxation rate of water and provide contrast has remained unmatched over a broad range of applications due to properties such as being highly paramagnetic and having fast water-exchange rates and high longitudinal relaxation rates [2–5]. Millions of patients with adequate kidney function have received imaging doses of Gd^{III}-based agents with no notable side effects; nevertheless, recent studies documenting gadolinium deposits in the skin, brain, and other internal organs have sparked questions regarding the safety of Gd^{III}-containing contrast agents, and these questions were discussed at the meeting [6–10]. In the early 2000s, some patients developed a rare but debilitating disease called nephrogenic systemic fibrosis (NSF) [11, 12]. Although this condition has largely been attributed to renal deficiencies in patients and is almost completely avoided today [13–15], these cases highlight the need for new contrast agents for patients with poor kidney function.

Following the first report of NSF in 2006, questions arose about the mechanism of toxicity, as discussed at Imaging in 2020 in 2018. While thermodynamic stability of contrast agents was a focus of much early research [16], kinetic inertness is a more critical aspect of toxicity that involves the dissociation of Gd^{III}*in vivo* [16–19]. Research showed that kinetic lability is more characteristic of linear complexes relative to macrocyclic complexes [13, 20], but few cases of NSF have occurred since the black box warning on some linear agents led to screening of patients for kidney dysfunction prior to imaging [15].

However, the need remains for new contrast agents beyond those currently in the clinic. Because the coordination chemistry of Gd^{III} relevant to T_1-weighted MRI is well-understood, the momentum of preclinical research for Gd^{III}-based contrast agents has shifted towards areas including responsive and targeted agents that have the potential to increase sensitivity and directly image biological events that correspond to diseases. To improve current contrast agents, investigators at the meeting presented strategies such as conjugating Gd^{III}-based complexes to biologically relevant scaffolds like DNA or proteins to increase relaxation rates and enable the use of lower doses [21]. To this effort, a collagen-targeting contrast agent with three Gd^{III}-containing moieties has been studied that produced a relaxivity 15 times higher than that of Magnevist® [22]. The large size and long correlation time of the collagen-targeted agent resulted in a relaxivity that enabled doses as low as 10 μmol/kg in rats with liver fibrosis [23]. Another example discussed at the meeting involved Gd^{III}-containing, protein-based contrast agents that target gastrin-releasing peptide receptors, which are overexpressed in many cancers. The protein-based agents were used to detect gastrin-releasing peptides in mouse tumors [24]. Linking contrast agents to new targeting moieties takes advantage of the well-established imaging properties of Gd^{III}-based agents and potentially eases clinical translation. As an example, both of the targeted agents discussed at the meeting are currently undergoing clinical studies.

Over the 30 years since the approval of Magnevist®, Gd^{III}-based contrast agents have dominated contrast agent research. Within the large body of investigations, the direction of research has shifted from the design and synthesis of new ligands to the study of new applications of Gd^{III}-enhanced, T_1-weighted MRI. Conversations at the meeting indicated the future direction of research for Gd^{III}-containing agents for MRI will focus on linking approved Gd^{III}-based agents to moieties that respond to or target biological phenomena. However, synthesizing kinetically inert Gd^{III}-containing complexes remains an objective.

Non-gadolinium Probes

Although Gd^{III}-based contrast agents are useful, presentations at Imaging in 2020 described research into other metals and non-metals to probe biological questions and disease states in new ways with MRI. One proposed alternative to Gd^{III} for T_1-weighted MRI is manganese (II) (Mn^{II}), which exhibits fast water-exchange rates, a high spin quantum number, and high relaxivities [25–27]. Only one agent containing manganese (Teslascan®) has been clinically approved [2] but concerns regarding toxicity and lack of sales led to its removal from use in both the United States and the European Union. However, research into new Mn^{II}-containing probes continues largely due to the diversity of chelating ligands. Also, unlike Gd^{III}, Mn^{II} has the potential to be used in metal-based redox-responsive contrast agents: a change in oxidation state leads to a change in MR contrast enhancement [28]. For example, a fibrin-targeting manganese-based contrast agent was discussed with relaxivities comparable to clinically approved Gd^{III}-based agents but without detectable dechelation and > 99 % clearance after 24 h [29]. To assess its clinical translatability, this agent was injected into baboons that were imaged at 3 T, and the resulting images were compared to images acquired using a clinically approved Gd^{III}-containing agent. While there was essentially no difference in the quality of the images or the pharmacokinetics of the two agents, the Mn^{II}-based agent exhibited mixed renal and hepatobiliary excretion, indicating that it could potentially be used in patients with poor renal function [30]. Although Mn^{II} serves as an alternative to Gd^{III}, there are reports of manganese toxicity upon overexposure and accumulation in the brain [31, 32].

Paramagnetic proton shift (PARASHIFT) imaging was another non-gadolinium technique featured at the 2018 Imaging in 2020 meeting. PARASHIFT imaging does not involve imaging of changes in bulk water, but directly images the proton signals of probes. Therefore, PARASHIFT probes need to be designed with equivalent fast-relaxing protons, such as homotopic *t*-butyl groups, and with resonances shifted well beyond endogenous water and fat (for example, shifts of ± 50 ppm or more) [33]. Chelation of fast-relaxing paramagnetic lanthanides to ligands that contain protons of interest for PARASHIFT imaging was shown to increase the sensitivity of desired signals. Further, the pseudocontact chemical shift of these protons is directly dependent on the choice of chelated lanthanide (Tb^{III}, Dy^{III}, Ho^{III}, Er^{III}, or Tm^{III}), and it is possible for one ligand to display shifts from water in opposite directions with the use of two different metal ions, enabling simultaneous imaging and co-observed signals under the same excitation conditions [33]. The 2018 meeting highlighted research that capitalized on this phenomenon; recently published probes simultaneously quantified pH and temperature in tissue using a ligand system containing pH-sensitive arylphosphonates with both Dy^{III} and Tm^{III} [33]. However, to move forward with this research, old theories need to be adapted to fit with new findings. Specifically, Bleaney's theory [34] falsely assumes the position of the principle magnetic axis is lanthanide-independent, leading to predicted trends inconsistent with experimental results. Recent developments presented at Imaging in 2020 rectify these inconsistencies and promise to guide the development of new PARASHIFT agents [35]. Further, this work demonstrates the importance of scientific discourse, and the fundamental role of scientists to critically examine old schools of thought and challenge dogmas.

A variety of other metals were discussed for use as probes for chemical exchange saturation transfer (CEST) MRI. In CEST MRI, contrast is produced through the exchange of saturated protons on a probe with bulk water [36]. CEST MRI can involve paramagnetic molecules with protons that have large chemical shift separations from water. Many exchangeable protons have pH dependencies, and this phenomenon can be used as a tool to report chemical information *via* images. For example, a cobalt-based agent was discussed that reports pH using a ratiometric approach with two protons with opposite pH dependencies [37]. Temperature is another biomarker that can be detected with appropriately designed paramagnetic complexes in combination with CEST MRI: for example, temperature measurements were discussed that were based on two spin crossover iron-based agents. The protons on the agents exhibited temperature-dependent chemical shifts, likely due to thermal conversion between high- and low-spin iron (II) [38]. Additionally, the first reported example of a Cu^{II}-based CEST agent was discussed. This agent introduced magnetic exchange coupling between two copper ions leading to a shortening of electronic relaxation time [39]. Preliminary results with this agent show that magnetic exchange coupling has the potential to expand the scope of metal ions used in CEST imaging and offer direction for future responsive agents.

Another way that CEST MRI can be used is through the detection of endogenous molecules such as metabolites, proteins, peptides, and membranes [40]. The use of highly abundant endogenous molecules can compensate for the low sensitivity of CEST and ensures biocompatibility because exogenous contrast agents are not needed. One variation of endogenous CEST MRI, known as amide proton transfer, detects amide protons present in peptides and proteins through selective saturation and subsequent exchange of these protons with bulk water [41]. Because the exchange rate of these protons is dependent upon biomarkers such as pH, changes in exchange rates can provide information relevant to the diagnosis of diseases, such as ischemic stroke [42]. Other metabolites that are commonly imaged with endogenous CEST are glutamate, which is a major neurotransmitter in the brain [43], and creatine that can be detected as it is formed from phosphocreatine by creatine kinase in myocardial tissue [44]. However, issues impede the routine use of endogeneous CEST including the need for new methods to resolve "dirty signals" composed of multiple contributors to the CEST signal and the need for clinical standards for how images are obtained.

Fluorine-containing probes for ^{19}F-MRI were also discussed at the meeting. These probes offer advantages over ^{1}H-MRI, such as a large range of chemical shifts and the absence of endogenous background signal [45–47]. Despite these promising features, examples of *in vivo* ^{19}F-MRI are limited, largely due to issues regarding sensitivity. To increase the sensitivity of fluorine-containing probes, researchers commonly increase the number of equivalent fluorine atoms and/or use paramagnetic ions to shorten T_1 and increase signal through rapid signal averaging. Because many paramagnetic probes can be fluorinated, fluorinated complexes of paramagnetic ions that also include exchangeable protons (for CEST MRI) were discussed as responsive multimodal imaging agents [48] or agents for pH-sensitive ratiometric imaging [49]. However, sensitivity barriers exist for small-molecule probes, resulting in limited examples of imaging *in vivo*. Recent advances discussed at the meeting also included nanoencapsulated perfluorocarbon emulsions functionalized with Gd^{III}-containing contrast agents in which enzymatic cleavage of the linker joining the paramagnetic Gd^{III}-containing complexes for the emulsion leads to a change in ^{19}F signal that can be correlated to caspase-3/7 or caspase-1 activity [46, 50]. Presentations of ^{19}F MRI acknowledged sensitivity as the most important current challenge, but the design of new small molecule probes and the integration of lanthanide-containing contrast agents with emulsions suggest a promising future for ^{19}F MRI.

Hyperpolarization is another approach proposed to overcome sensitivity issues regarding the MR imaging of metabolic processes relevant to diseases like cancer. Although many nuclei have been studied using hyperpolarized MRI [51], the 2018 Imaging in 2020 meeting highlighted research involving hyperpolarized ^{13}C-labeled metabolites. The dynamic nuclear polarization process amplifies the net spin population of ^{13}C nuclei, thereby increasing the sensitivity of ^{13}C MR imaging and spectroscopy by greater than 10,000-fold [52]. One popular variation of this research sparking heavy discussion at the meeting examines the distribution of hyperpolarized [^{13}C]-pyruvate and exchange to endogenous lactate to diagnose and monitor tumor responses to therapy [53–55]. Another hyperpolarized metabolite, [^{13}C]-glucose, can theoretically be used to image the entire glycolytic pathway [56]. In efforts to increase sensitivity, meeting attendants presented modifications such as deuteration of hyperpolarized metabolites to increase overall imaging times [56, 57], spin echo pulse sequences to combat distribution issues that influence exchange [53], excitation schedules to manage signal evolution, and the development of simulation models for improved quantification techniques [55]. To direct the field towards clinical use, discussions highlighted the need for improvements in acquisition techniques and coils, research into alternative technologies to hyperpolarize and store labeled metabolites, and more preclinical and clinical studies.

New Methodologies and Frontier Applications

Although MRI for *in vivo* research has been studied for nearly 50 years, new methodologies are continually emerging and revolutionizing the way that MRI can be used. One such method featured at Imaging in 2020 that has emerged over the last 5 years is MR fingerprinting [58]. This method promises simultaneous, quantitative measurements regarding multiple parameters in a similar time frame as a clinical MRI scan. Currently, MR images in a clinical setting are routinely used to acquire qualitative information because current quantitative techniques are time-consuming, limited by voxel size, or sensitive to experimental set-up. However, MR fingerprinting uses pseudorandomized acquisitions that are dependent on multiple sequence parameters, resulting in a specific signal evolution, called a fingerprint, that can be compared to a dictionary of predicted signals by pattern recognition software. Many parameters can be determined simultaneously from one fingerprint, including T_1, T_2, or proton density. Since its invention [58], MR fingerprinting has been adapted to examine a variety of biological phenomena, such as cerebral blood volume in microvascular systems and cardiac imaging [59], with more expected applications in the near future [60].

One recently developed application for MRI that was highlighted at Imaging in 2020 was simultaneous positron emission tomography (PET)–MRI. PET is often used in conjunction with X-ray computed tomography (CT) to provide anatomical images and attenuation correction. However, MRI has advantages for replacing CT including the lack of ionizing radiation in MRI and the wide variety of image contrast possible with MRI that provides both anatomical and functional information [61]. Additionally, the functional information gained from MRI is usually complementary to the functional information obtained from PET, and this relationship has been explored in brain imaging [62]. For example, [^{15}O]H_2O-PET was performed in succession with blood-oxygen-level-dependent functional MRI (fMRI) to monitor cerebral blood flow. Spatial discrepancies were found between the PET and fMRI signals because fMRI and PET detect increases in blood flow in different regions of the brain vasculature [63]. Brain imaging of rats using 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG)-PET and fMRI also had spatial and quantitative discrepancies upon stimulation [64]. This difference was attributed to the different time scales of the metabolic pathways probed by [^{18}F]FDG-PET and fMRI.

Although PET–MRI has tremendous potential for use in clinical imaging, presentations and discussions at the meeting raised issues that need to be addressed such as methods for attenuation correction, improved PET-compatible MR coils, better MR-compatible PET detectors, and new instrument geometries to improve sensitivity. For example, attenuation correction has recently been improved by using MR images to create pseudo-CT images through a combination of local pattern recognition and atlas registration [65]. The resulting MR attenuation-corrected images provided PET quantification in the brain with a mean error of 3.2 % compared to CT-based corrections. With PET–MRI being a relatively new area of research, there are many areas where this technology can be impactful. One of these areas that was highlighted at Imaging in 2020 was the possibility of performing dynamic PET–MRI using simultaneous functional [^{18}F]FDG-PET and fMRI.

Magnetic particle imaging (MPI) is another emerging imaging method that was discussed at Imaging in 2020. MPI uses low-frequency magnetic fields to image superparamagnetic-iron-oxide nanoparticles [66]. Although MPI experiments require a specially engineered scanner that is distinct from MRI scanners, the recent development of this technology has led to the commercial availability of MPI scanners [67]. As important benefits, MPI directly images the concentration of iron oxide nanoparticles and has a lack of background signal. Additionally, MPI experiments are largely unaffected by parts-per-million-level disturbances in magnetic field homogeneity, unlike MRI experiments [68]. For example, the ± 5 ppm magnetic field disturbance from alveoli in lungs confounds MR-imaging but does not hinder MPI, and the imaging of lung capillaries has recently been demonstrated *in vivo* with MPI [68]. To use this imaging modality in clinical applications, discussions during the meeting acknowledged the need to rectify gradients in transitioning from mouse to human studies. Additionally, nanotechnology researchers need to improve the physicochemical properties of iron oxide nanoparticles for MPI.

Presentations and discussions at the meeting highlighted MR microscopy to study phenomena too small to be visualized by typical MRI protocols including breakthroughs in understanding the microvasculature of the brain. The ability to differentiate angiogenesis using this technique promises to aid in quantitatively understanding pathophysiology of brain tumors and other critical targets [69]. Studies of connectomics also advance our understanding of brain structure by using imaging methods such as MRI tractography in combination with computational methods that probe the anisotropy of brain fiber connectivity using voxel-based probability calculations [70, 71]. Proposed clinical applications of connectomics include the diagnoses of neurologic and psychiatric diseases and presurgical planning [70]. This research highlights an important future direction of integrating systems biology into clinical diagnosis; however, many challenges need to be met, including the need for non-diffusion sampling protocols and large reference databases.

Finally, low-field MRI was discussed at the meeting, specifically in the context of new hardware for brain imaging. For example, a portable brain MRI scanner is currently in development using an electromagnet. With the low weight of the new scanner and lack of cryogens, this system is expected to be portable and relatively inexpensive compared to current scanners. The new scanner has the potential to be used in unique mobility experiments to analyze the motor cortex while enabling movement below the neck [72].

Conclusions

With the year 2020 within sight, a major talking point at the 2018 Imaging in 2020 meeting was where MRI research will take us in 2020 and beyond. The meeting began by examining the history, successes, and setbacks of Gd^{III}-based contrast agents that were approved for human use over a decade prior to the first Imaging in 2020 meeting. While it was largely agreed that toxicity issues have been managed, these issues brought a unique opportunity to produce new contrast agents. A recurring theme in these new agents was increased efficiency due to higher relaxivities, elevated sensitivity, targeting capabilities, or lower doses. More exotic MR techniques such as CEST, PARASHIFT, hyperpolarized MRI, MR fingerprinting, PET–MRI, MPI, MR microscopy, and low-field portable MRI have emerged, and presenters at Imaging in 2020 highlighted the clinical potentials of these methods. However, technological advances are still needed before clinical translation of these methods is achieved. While great progress has been accomplished since the first meeting in 1999, meeting participants were reminded of the challenges remaining in MRI research that will guide the field into the future. As one presenter poetically summarized: “In 2020, we will be doing the same old [stuff as today]; in 2030, who … knows”. With 2020 around the corner, the future for MRI is bright, and the research being done today will propel the field far beyond 2020.

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Compliance with Ethical Standards

Conflict of Interest

MDP has a relationship with Bristol Myers Squibb, Inc.

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