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Magnetic particle imaging for radiation-free, sensitive and high-contrast vascular imaging and cell tracking

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Magnetic particle imaging (MPI) is an emerging ionizing radiation-free biomedical tracer imaging technique that directly images the intense magnetization of superparamagnetic iron oxide nanoparticles (SPIOs). MPI offers ideal image contrast because MPI shows zero signal from background tissues. Moreover, there is zero attenuation of the signal with depth in tissue, allowing for imaging deep inside the body quantitatively at any location. Recent work has demonstrated the potential of MPI for robust, sensitive vascular imaging and cell tracking with high contrast and dose-limited sensitivity comparable to nuclear medicine. To foster future applications in MPI, this new biomedical imaging field is welcoming researchers with expertise in imaging physics, magnetic nanoparticle synthesis and functionalization, nanoscale physics, and small animal imaging applications.

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Introduction

Magnetic particle imaging (MPI) is a new tracer imaging technique first introduced by Philips, Hamburg [1]. MPI directly images the location and concentration of superparamagnetic iron oxide nanoparticle (SPIO) tracers with time-varying magnetic fields and has remarkably high sensitivity and contrast. Several SPIOs are clinically approved and currently on the market, including Feraheme (ferumoxytol), which is FDA approved for treatment of anemia in chronic kidney disease (CKD) patients [2]. Outside of the United States, SPIOs are available for patient imaging (Resovist), sentinel lymph node localization (Sienna) and hyperthermia (NanoTherm) applications [3–5]. Safe, radiation-free scanning in MPI combined with high-contrast, high-sensitivity imaging gives MPI fundamental advantages in vascular imaging and cell-tracking, which we discuss in this review.

The physics of MPI relies on the electronic magnetization of SPIOs [1]. When an excitation field is applied to SPIOs in the field-of-view (FOV), the magnetic dipoles reorient rapidly in response. Much like in MRI, the change in magnetization can be visualized via Faraday's law with a receiver coil. Unlike MRI, the change is of electronic magnetization, rather than nuclear magnetization. This results in a higher sensitivity for MPI, as the electronic magnetization of iron is 22 million times stronger than that of the nuclear magnetization of water at 7 Tesla [6]. To localize this signal, a large gradient field is used. Outside of a small region with a close to zero field, termed the field free region (FFR), the gradient locks SPIOs in place even if the excitation field is applied. Inside the FFR, the SPIOs reorient in response to the excitation field. By rastering this FFR across each point in the FOV, an image is created.

MPI sensitivity can be as low as nanograms of iron (corresponding to as few as ~200 cells for cell tracking applications), and resolution can be as fine as ~1 mm [7,8]. These specifications were obtained on academic prototype scanners. Commercial preclinical MPI scanners were only recently introduced by Bruker GmbH and Magnetic Insight Inc., and specifications are steadily improving. Theoretical work predicts that a human MPI scanner could have picogram sensitivity in a 1 s scan [9] and technical improvements have been made approaching this goal [10]. MPI has no view limitations, and it works robustly even in the lungs and bones, where MRI and Ultrasound routinely fail. For instance, Figure 3b clearly resolves SPIO-labeled stem cells in the lungs. Indeed, researchers have demonstrated proof-of-concept studies for MPI imaging of lung

perfusion and ventilation [11–13]. MPI also has no depth limitations, unlike optical imaging methods. Many molecular reporters employed in cell culture studies and small animals employ optical fluorescence or bioluminescence probes, which are fundamentally limited by optical scattering and attenuation to surface applications. Last, unlike radiotracers, the SPIOs reporter 'half life' is essentially infinite, enabling researchers to track the location of labeled cells even three months after introduction to a murine model [14]. This may be enabling since Nuclear Medicine reporters last for only hours (FDG 2 hours half life, Tc-99m 6 hours, In-111 2.8 days) while many pathophysiologic processes require weeks to manifest. Finally, MPI obtains a dose-limited sensitivity that is already competitive with Nuclear Medicine method on prototype MPI scanners.

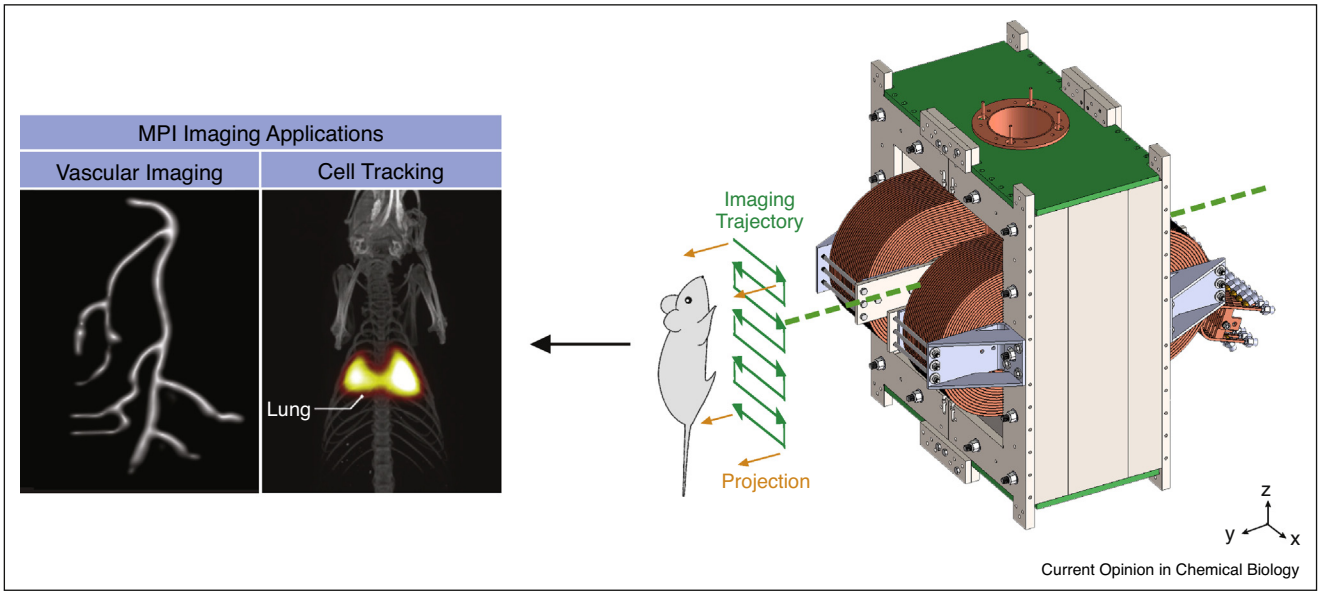
In this review, we discuss recent applications in MPI, broadly divided into vascular imaging and cell tracking, as described in Figure 1. Additionally, we discuss current needs in tracer development to enable future applications in MPI molecular imaging.

Vascular imaging

The earliest applications of MPI focused on vascular imaging with untargeted SPIOs, such as 3D imaging of a beating mouse heart using Resovist [15]. This early work emphasized some of the inherent advantages of MPI — three-dimensional, high-contrast and fast imaging. Both imaging speed and circulation time of the MPI tracers is crucial for vascular applications.

SPIOs used in MPI typically have a hydrodynamic diameter between 50 and 100 nm, and they remain in the bloodstream until cleared by the reticuloendothelial system [16]. Circulation time varies from minutes to hours depending on the nanoparticle coating. Early MPI researchers typically relied on ferucarbutran (also known as Resovist or VivoTrax), which is a cyclodextrin coated SPIO originally designed as a MRI liver imaging agent to highlight cancerous lesions [15]. It targets the liver within minutes [3]. The Krishnan group at University of Washington developed SPIOs with twofold better spatial resolution compared to Ferucarbutran and extended the circulation time of MPI SPIOs to 2+ hours in mice and 4+ hours in rats using polyethylene glycol coatings [17,18]. Alternative approaches to increasing MPI tracer circulation time include loading SPIOs into red blood cells [7,19,20]. These long-circulating tracers are crucial for applications like cancer imaging via the enhanced permeability and retention (EPR) effect [21••], brain imaging for traumatic brain injury (TBI) and stroke via visualizing cerebral blood volume and cerebral blood flow [22••,23], and gastrointestinal (GI) bleed imaging [24]. Each of these applications shown in Figure 2 requires imaging over hours or days, and hence long circulating SPIO tracers offer MPI an advantage over nuclear medicine techniques, in which radionuclide decay limits the

Figure 1



MPI imaging applications today. Broadly, MPI researchers have pursued vascular imaging and cell tracking. In vascular imaging, researchers have used both tracers that passively highlight the physiology of interest, or are specifically targeted via an antibody or other moiety. In cell tracking, researchers have imaged several types of stem cells, and more recently interest has grown in imaging immune cells for infection imaging, immunotherapy tracking and early-stage cancer detection. Scanner schematic adapted with permission from [24]. Copyright 2017 American Chemical Society. Vascular imaging phantom image courtesy of Justin Konkle. Stem cell tracking image courtesy of Bo Zheng. Image fusion of MPI (color) and CT (gray).