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THE MAGAZINE OF DISTINCTION IN RADIOLOGY
VOL. 18 NO. 5
MAY 2017

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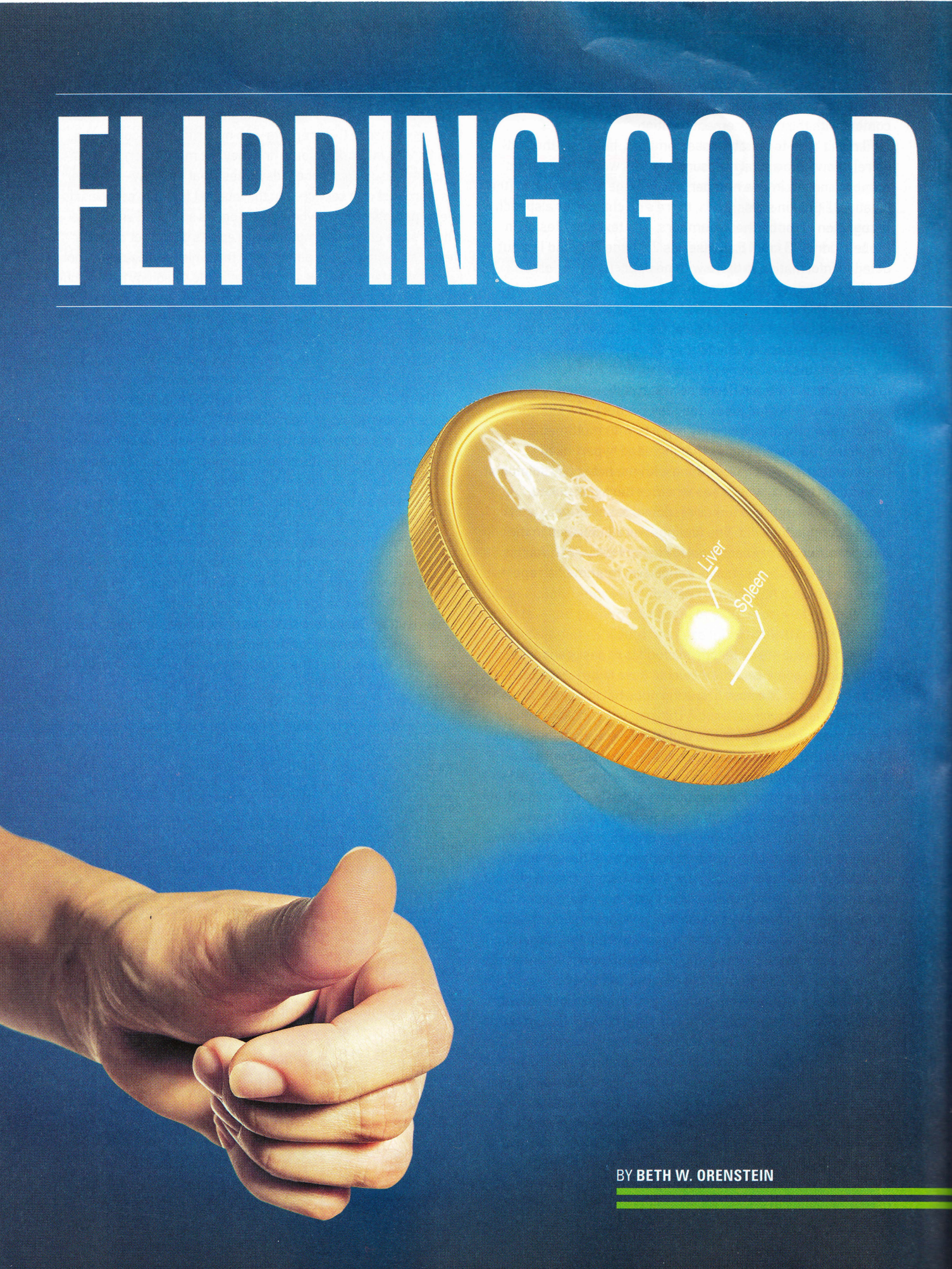


BY **BETH W. ORENSTEIN**

IMAGING

Magnetic particle imaging offers an exciting new option for medical diagnostics and treatment.

Researchers worldwide are excited about what is likely to be the first completely new imaging modality to come to medicine in three decades. That new modality is magnetic particle imaging (MPI), and, while it's not yet available for humans, many are actively pursuing it. Two companies are manufacturing preclinical MPI scanners: Magnetic Insight in Alameda, California, founded by a team from the University of California at Berkeley, and Bruker Corp, in Ettlingen, Germany. A third company, LodeSpin Labs LLC, founded by a team from the University of Washington in Seattle (UW/LSL), is developing high-performance, biocompatible magnetic nanoparticle tracers that are critical to the translational success of MPI.

"MPI is still in its very early stage," says one of the researchers, Max Wintermark, MD, chief neuroradiologist at Stanford University in Stanford, California. "At this point, we're limited to animal imaging. But we're dealing with a completely new imaging modality. It's not a CT scan. It's not MRI. It's something completely different, and that's quite rare and terribly exciting."

MPI is similar to MRI in that it uses magnetic fields, but that's where the similarity ends, Wintermark says. MPI, a tomographic imaging technique, uses iron oxide nanoparticles as tracers. Patrick Goodwill, PhD, cofounder and chief technology officer of Magnetic Insight, explains: "There's one spot where all these iron oxide nanoparticles will rotate called the field-free region (FFR). The way we produce an image is we take the FFR and rapidly transition it across what we wish to image. Any magnetic particle will flip as the FFR passes over it. Whenever a particle flips, it sends a signal that we can turn into a 3D image instantly."

Nanoparticles detected in MPI are comparable to the radionucleotides detected in nuclear imaging, Goodwill notes. MPI detects tracers and not contrast agents, which are detected by anatomical imaging modalities such as MRI and X-ray/CT.

"This flipping of a nanoparticle gives you high contrast and sensitivity because all you see is the nanoparticle," adds Anna Christensen, PhD, president and CEO of Magnetic Insight. "The added advantage is that we count all the nanoparticles, and so we actually have a very quantitative approach to imaging as well."

MPI does not directly show anatomical details; it only provides functional imaging, ie, the tracer distribution over time. To coordinate its findings with the tracer's location in the body, another structural imaging study would be needed. To overcome this lack of structural information, it has been shown in the research labs of Bruker and Steven Conolly, PhD, a professor at UC Berkeley and a cofounder of Magnetic Insight, that MPI could be combined with a second modality providing complementary data.

"By combining MPI and MRI into one fully integrated hybrid scanner, we have demonstrated the benefits of acquisition of complementary 3D and 4D datasets in a single, seamless multimodal study without any ionizing radiation," says Jochen Franke, MSc, project manager of MPI for Bruker. "Hybrid imaging systems will allow clinicians to precisely plan MPI examinations on the basis of morphological information, in addition to a precise coregistration of the complementary data sets, and thus provide deeper insight into pathology and the outcome of therapies." Magnetic Insight is currently integrating a low-dose CT option into its instrument, which allows for dedicated MPI performance with anatomic context.

Long Time Coming

MPI has been in the works for more than 15 years. Two physicists, Bernhard Gleich and Jürgen Weizenecker at the Philips Research Laboratory in Hamburg, Germany, conceived the idea in 2001. Before coming to Philips, Gleich and Weizenecker had worked independently on the principles of magnets and paramagnets, Gleich at the University of Ulm and Weizenecker at the University of Karlsruhe.

In January 2005, Gleich and Weizenecker published a two-page paper in ***Nature*** in which they reported on the first MPI images and the feasibility of the modality. They wrote about its promise for detecting vascular diseases and cancers.

"That was pretty much the start of the field when they published their paper in ***Nature***," Goodwill says.

Philips has since decided to focus in areas outside of MPI and licensed its version to Bruker Corp. In a close collaboration with Philips, Bruker designed the world's first commercially available preclinical MPI scanner, the MPI 25/20 FF system. Its first installation was in 2014 at the University Medical Center Hamburg-Eppendorf, Germany. Since then, three more sites within Europe have been equipped with a Bruker preclinical MPI scanner.

Magnetic Insight also has developed an MPI scanner that focuses on sensitivity and high-resolution imaging using X-Space reconstruction methods and a magnetic geometry that allows for higher sensitivity using computerized tomography approaches similar to those used in X-ray and CT. These features are targeted towards quantitative monitoring of cells for therapeutic development. MPI is being used to advance applications in

cancer, diabetes, vascular disease, and inflammation by more than 10 American research groups including several at Stanford, Massachusetts General Hospital, UW/LSL, MD Anderson, Dartmouth, Case Western, the University of Florida, and UC Berkeley. Magnetic Insight will be developing MPI scanners for human use starting with one for use in brain imaging. It's expected to be ready in a few years, Christensen says.

Many Advantages

MPI uses no ionizing radiation, which researchers see as a significant advantage over existing imaging modalities. Radiation is a growing concern in medical imaging, and it is believed that up to 2% of future cancers could be induced by radiation from medical imaging modalities such as CT and fluoroscopy. Nonionizing technology holds much promise, Franke says.

Although MRI does not use ionizing radiation either, some MRI studies require the contrast agent gadolinium to obtain clear images. In the last two years, the FDA has expressed some concern that gadolinium may remain in the brain, bones, and other organs long after the MRI scan is completed, and the long-term effects of residual gadolinium are still not known.

"We've been getting a lot of interest from radiologists to see where MPI is going, not only with pressures of reducing radiation but also reducing the amount of gadolinium usage," Christensen adds.

"That MPI potentially could have a future as an alternative to gadolinium-enhanced MRI has me particularly excited," Wintermark says.

The iron particles themselves are generally considered safe for use in humans. First, Christensen says, "the amount of iron that we use is much less than what is currently clinically used for anemia treatment. We detect iron oxide at such small amounts that the dose of iron we need to image is very, very low, which helps with safety concerns." Also, she says, iron oxide gets processed in the liver, not in the kidneys, and eventually becomes free iron for the body.

In addition to safety, MPI is seen as having advantages over other modalities in speed, sensitivity, quantitative signal, and flexibility, Franke says. MPI can image in milliseconds. According to Bruker's literature, "being able to image up to 46 volumes per second, MPI ranks among the fastest ways to image molecular tracers and allows for real-time-like imaging for most biological processes."

MPI also yields no background signal. As a result, Bruker says, its sensitivity can be up to a hundred times better than MRI with a comparable dose of contrast agent. MPI generates a positive signal that increases linearly with the tracer concentration. This means that researchers can obtain absolute quantitative images with a positive signal, making comparison between experiments easier and more reliable, even among different research sites. Finally, the magnetic tracer can be functionalized to selected targets, as long as the magnetic nanoparticle does not prevent the probe from reaching the site of recognition, Franke says.

Most MPI research to date has been done using three related tracers: Resovist (Bayer-Schering), FeraSpin R (nanoPet), and VivoTrax (Magnetic Insight). Resovist is approved in a number of clinical markets in Asia and Europe for use with MRI for imaging liver carcinomas, while FeraSpin R and VivoTrax are for research use only. Because Resovist is not optimized for MPI, a number of research groups are developing particles tailored specifically to the modality.

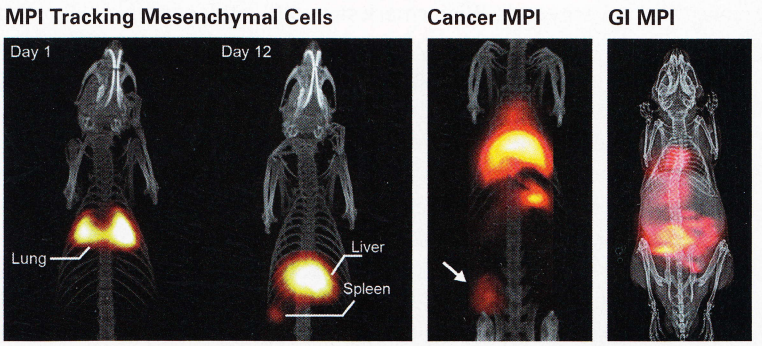
"The main issue for us is to get a matching tracer and a human scanner," says Kannan Krishnan, PhD, who is leading the group at UW/LSL. "Right now, we're working with animals and an animal scanner, but we are convinced—and we have convinced a lot of people—that the tracer for use in humans is very much there, and we can take it toward human work reasonably soon."

Indeed, Krishnan's group has already demonstrated that the tracer LS-008 has four times better signal in vivo than Resovist. LS-008 has also demonstrated long circulation time, approximately one hour, in rodent models.

Going With the Flow

Although mainstream clinical applications of MPI are still some years away, researchers are focusing on developing it for use in cardiovascular applications, perfusion studies, cell tracking, oncology, and neurology studies. Krishnan's group and LodeSpin Labs, in collaboration with the UC Berkley MPI scanner group, have already demonstrated in animals MPI's potential as the best imaging modality for monitoring blood flow and blood pool imaging. Franke says MPI's unmatched speed makes it a terrific modality to characterize the heart without the need for triggering and gating.

"By using MPI, it was proven recently to allow for 4D flow estimation with a total data acquisition time in the range of seconds," Franke says.



(Left) MPI Stem Cell Tracking: This is a 10-minute 3D MPI scan, shown as a maximum intensity projection image, with an X-ray CT anatomic overlay. These UC Berkeley data used the Resovist MPI tracer labeled to 3 million mesenchymal cells. MPI scans were performed for 12 days following tail vein injection of the labeled stem cells. The MPI scans show that cells were trapped in the tight lung capillaries on Day 1 and then naturally cleared to the liver on Day 12. MPI quantitatively tracks cells for months, even in the lungs, where MRI and ultrasound are not completely robust.

(Middle) Cancer MPI: This is a 10-minute 3D MPI scan, displayed as a maximum intensity projection, with X-ray overlay. These UC Berkeley data used untargeted MPI tracers from LodeSpin Labs (LS-008). The MPI scan, performed six hours after tail vein injection, shows preferential extravasation of tracer from the neovasculature of the tumor (arrow).

(Right) Gastrointestinal Bleed MPI Scan: This is a 2D MPI projection scan, displayed as a maximum intensity projection, with X-ray anatomic overlay. These unpublished UC Berkeley data used LS-017, LodeSpin Lab's long-circulating MPI tracer. This MPI scan shows blood loss in the large intestine of a mouse model of Familial Adenomatous Polyposis. This demonstrates MPI's promise as a sensitive and zero-radiation complement for RBC-Tc99m nuclear medicine studies, which are often used to detect subtle gut bleeds following trauma.

IMAGES COURTESY OF THE STEVEN CONOLLY LAB AT UC BERKELEY

MPI's contrast allows for functional perfusion imaging, Goodwill adds. Conolly says his group at Berkeley, in collaboration with others, recently demonstrated the first preclinical MPI scans of MPI ventilation perfusion scanning using macroaggregated albumin tagged to iron nanoparticles as well as traumatic brain injury imaging via cerebral blood volume/cerebral blood flow. Conolly believes the MPI ventilation-perfusion (VQ) study, for example, would be an attractive, zero-radiation complement to VQ scans now done in nuclear medicine or to CT pulmonary angiography to diagnose pulmonary embolisms, and they can be done in a few minutes, he says.

MPI is also seen as an ideal tool for imaging vasculature, whether the heart, lung, or liver, because of its ability to finely characterize the arrangement of blood vessels in an organ or part of the body. MPI could someday enhance the study of lung diseases, especially improving treatment response assessment, Franke says. Liver studies could benefit, as well, from better quality perfusion data, he says. Currently, the liver, like the heart, is challenging to image, and some patients have allergies to iodine-based contrast agents.

In addition, MPI allows for quantitative cell tracking with unprecedented sensitivity, Conolly says. Conolly and UC Berkeley colleagues published the first two papers on in vivo MPI stem cell tracking in ***Nature Scientific Reports*** in 2015 and in ***Theranostics*** in 2016 with first author Bo Zheng, in which they found that MPI could be used to see 200 mesenchymal stem cells over periods of up to three months. They showed that MPI can even track cells in the lung.

"It tracked exquisite images of stem cells to the lung and followed them 12 days later to the liver, which is very hard to do with any other imaging modality, since MRI and ultrasound both have well-known physics challenges due to the presence of air in the lungs," Conolly says. "We expect to improve MPI cell sensitivity, perhaps down to three to 10 cells, in the near future by using optimized MPI scanners and optimized MPI tracers."

"You can use the iron tracer to label a specific molecule or specific type of cell, and you can track those that have been labeled when they are circulating in the body," Wintermark explains.

Growing Interest

MPI is also drawing interest for other applications. One sign of that interest is its recent selection as a Special Interest Group for the World Molecular Imaging Society.

"I think it will be very interesting to see how it develops in the next few years," Wintermark says.

For example, UW/LSL tracers have a surface functionalization platform that allows for the conjugation of cancer targeting antibodies and molecules, Krishnan says. In collaboration with the UW/LSL group, the Conolly lab recently published the first untargeted in vivo MPI cancer imaging in ***ACS Nano Letters***, with first author Elaine Yu, a UC Berkeley engineering graduate student.

Because minute amounts of iron are visible, MPI could facilitate earlier detection of cancers when they are in their most curable stages, Christensen adds. Researchers see MPI as complementary to PET scans, providing new diagnostic information. Conolly says MPI shows great promise for cancer imaging because of its superb contrast, sensitivity, safety, and ability to image anywhere in the body.

In addition to detecting cancers, MPI might also be able to deliver live images during surgery, Franke says. The live images would afford physicians insights into the effects of therapies such as manipulation or drug injections in real time.

Wintermark sees great potential for MPI in neurology studies, as well. Neurologists are interested in stroke-related inflammation and how that information can help with recovery, he says.

"We can baste macrophages, a type of white blood cells, with iron particles and inject them in the blood stream of rodents," says Wintermark. "With MPI, we can track the macrophages as they migrate to the area of [interest in] the brain, see what they do over time in stroke, and correlate that with the recovery process."

Inflammation also plays a role in other diseases that affect the brain, including Alzheimer's, mild traumatic brain injury, brain tumors, and multiple sclerosis, Wintermark says. "If MPI were to allow us to directly study inflammation, monitor that inflammation, and see how it's evolving over time and how it responds to specific treatment, that would be something extremely valuable," he says.

Christensen says MPI allows physicians to see neuroperfusion at the capillary level. "This ability translates to looking at neurovascular diseases and, potentially, brain tumors," she says. "It really opens the world to different types of neurovascular diagnostics."

Franke says MPI may also hold potential for therapeutic interventions. A Philips paper in ***ScienceRobotics*** claims, "Magnetic micromachines can be controlled remotely inside the human body by application of external magnetic fields" while a combination with the real-time imaging capability of MPI could be exploited, too. Initial experiments of spatially selective magnetic manipulations have been conducted on Bruker MPI systems, demonstrating possible utility as a tool for minimally invasive local therapy delivery, Franke says.

MPI's properties make it a promising candidate for imaging theranostic agents, which have both diagnostic and heat-induced therapeutic properties, Franke says. MPI can easily monitor the distribution of drug-tracer bundles over time with great sensitivity and specificity, he explains.

"And once the site of interest is reached, one could thermoactivate the drug," Franke says. "In some cases, it could also be combined with thermotherapy approaches to destroy the tumor or to control the release of another molecule of interest."

However it ends up being used, the new modality's possibilities have generated tangible excitement. "There's a lot of interest in MPI because of its potential in many translational applications in medicine," Krishnan says. "As MPI gets more established and people become more and more aware of the technique, [that interest] will only increase."

— Beth W. Orenstein of Northampton, Pennsylvania, is a freelance medical writer and regular contributor to *Radiology Today*.