

## MRI Technology Breaks New Ground in Molecular Imaging

*Nuclear medicine continues to make strides.*

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Researchers with the U.S. Department of Energy's Lawrence Berkeley National Laboratory and the University of California at Berkeley have developed a new technique for magnetic resonance imaging (MRI) that allows for detection of signals from molecules present at 10,000 times lower concentrations than conventional MRI techniques. Called HYPER-CEST, for hyperpolarized xenon chemical exchange saturation transfer, this new technique holds great promise for molecular imaging, in which the spatial distribution of specific molecules is detected within an organism. Ultimately, HYPER-CEST could become a valuable tool for medical diagnosis, including the early detection of cancer.

In two papers published in the journals *Science* and the *Journal of Magnetic Resonance*, the team of researchers reports on a technique in which xenon atoms have been hyperpolarized with laser light to enhance their MRI signal, incorporated into a nanoscale cage biosensor, and linked to specific protein or ligand targets. These hyperpolarized xenon biosensors generate highly selective contrast at sites where they are bound, dramatically boosting the strength of the MRI signal and resulting in spatial images of the chosen molecular or cellular target. This research was led by Alexander Pines, Ph.D., and David Wemmer, Ph.D.

"Our HYPER-CEST molecular MRI technique makes optimum use of hyperpolarized xenon signals by creating a strong signal in regions where the biosensor is present, allowing for easy non-invasive determination of the target molecule," said Pines. Wemmer added, "Other molecular MRI contrast agents provide small changes in big MRI signals, making the changes difficult to detect when the amount of contrast agent binding is small. Our HYPER-CEST contrast agent provides a big change in the xenon MRI signal, which means it is much easier to detect even though the xenon MRI signals are rather small."

In addition to its intrinsically higher contrast, another advantage with the HYPER-CEST technique is that its effects can be "multiplexed," meaning that the polarized xenon biosensors can be targeted to detect different proteins at the same time in a single sample. This capability, which is not shared by most conventional molecular MRI contrast agents, opens up a number of possibilities for future diagnostics. For example, as a diagnostic tool for the detection of cancer, with HYPER-CEST physicians could perform multiple virtual biopsies on a single tissue sample, using different biosensors to screen for each potential form of cancer.

As a diagnostic tool for cancer, HYPER-CEST would be extremely sensitive, able to detect the presence of cancer-related proteins at micromolar (parts per million) concentrations. The sooner that the presence of cancerous cells is detected, the better the chances are for successful treatment. In addition to high sensitivity and target specificity, HYPER-CEST MRI is also unique from other molecular imaging techniques in that it provides both spatial and biochemical information. This technique points to a wide range of biomedical applications far beyond cancer diagnostics.

MRI is well established as a powerful technology for biomedical imaging. It is a painless and radiation-free means of obtaining high quality three-dimensional tomographical

images of internal tissue and organs, particularly useful for opaque samples. However, the application of MRI to molecular imaging has been limited by sensitivity issues.

MRI, like its sister technology, nuclear magnetic resonance (NMR) spectroscopy, is based on a property of atomic nuclei with an unpaired proton or neutron called "spin." Such nuclei spin on an axis like miniature tops, giving rise to a magnetic moment, which means the nuclei act as if they were bar magnets with a north and south pole. When exposed to an external magnetic field, these spinning "bar magnets" attempt to align their axes along the lines of magnetic force. Since the alignment is not exact, the result is a wobbling rotation, or "precession," that's unique to each type of atom.

If, while exposed to the magnetic field, the precessing nuclei are also hit with a radiofrequency (rf) pulse, they will absorb and re-emit energy at specific frequencies according to their rate of precession. When the rf pulse is combined with magnetic field gradients, a spatially encoded signal is produced that can be detected and translated into images.

Obtaining a spatially encoded MRI signal from a sample depends upon the spins of its precessing nuclei being polarized so that an excess points in one direction, either "up" or "down." Because the natural excess of up versus down spins for any typical population of atomic nuclei is only about one in 100,000, conventional MRI techniques are designed to detect nuclei that are highly abundant in tissue, usually the protons in water. Clinicians use contrasting agents to induce detectable changes in the MRI signal from a sample that can reveal the presence of anomalies. However, even though some of these contrasting agents will bind to specific biomolecular targets, the sensitivity is usually too low for molecular imaging.

In earlier studies, Pines and his group exploited the fact that zapping rubidium vapor with a beam of polarized laser light creates a "hyperpolarized" effect that can be transferred to nuclei of xenon, an inert gas whose nuclei naturally feature a tiny degree of spin polarization. This process, called "optical-pumping," vastly increases the proportion of spin-up nuclei, producing a population of xenon atoms with nearly 50 percent of their nuclei in the up state. Pines and his group also developed techniques for transferring this hyperpolarization from xenon nuclei to other molecules, and methods to probe the environments of the xenon atoms and their movement.

Working with the Pines group, Wemmer and his group subsequently used a nanoscale molecular cage, called a cryptophane, that they adapted to hold hyperpolarized xenon atoms. With the addition of a biochemical "linker" that makes the nanocage soluble in water, they created a novel agent that binds to a specific target molecule and associates the hyperpolarized xenon with it. These sensitive and versatile xenon biosensors can then be used to selectively alter MRI signals.

In the new research papers, the Pines and Wemmer team reported their work aimed at combining the xenon biosensors with CEST technology, which was developed as a contrast method for boosting the MRI contrast from protons. CEST is based on the exchange of protons that takes place between water molecules and other molecules in the body. While effective under certain conditions, CEST is limited by the fast relaxation time of protons, which necessitates the need for large magnetic fields to decrease relaxation effects and increase the difference between saturated and non-saturated MRI signals. It also requires a relatively large amount of the CEST agent to generate significant contrast enhancement.

Hyperpolarized xenon has a much longer relaxation time than protons, which means that the enhanced MRI signal is not only stronger, but lasts much longer. The MRI signal obtained directly from the xenon biosensors is hundreds of times smaller than the easily detected signal obtained from a pool of free xenon dissolved in the rest of the sample. The HYPER-CEST images are based on the free xenon signal rather than direct detection of the biosensors that leads to the high sensitivity of the technique.

This work is detailed in two papers. The first, published in Science, is titled, “

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