

CHEMISTRY

Toward Molecular Imaging with Xenon MRI

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When it comes to molecular imaging—the burgeoning discipline of visualizing biological processes at the cellular and molecular level in living organisms—magnetic resonance imaging (MRI) is low on the list of favored techniques (1). The receptors and gene expression products that

we aim to observe by molecular imaging are present at minuscule concentrations (around

10^{-6} to 10^{-12} mole per liter) in the body. Yet the nuclear magnetic moments that provide the signal in MRI are tiny, and lots of them are needed to generate an image. MRI is thus limited to detecting concentrations of 10^{-3} to 10^{-5} mole per liter. In contrast, radioisotope imaging methods such as positron emission tomography and single photon emission tomography can detect probe molecule concentrations of 10^{-9} to 10^{-12} mole per liter. These techniques have been the natural choice for molecular imaging, although they lack the spatial and temporal resolution of MRI and make use of ionizing radiation.

On page 446 of this issue, Schröder *et al.* (2) report an important step toward changing this conventional wisdom by introducing a new technique, dubbed HYPERCEST, that could make MRI competitive in the molecular imaging game. By combining elements of atomic physics, synthetic chemistry, and magnetic resonance trickery, the authors create the compelling vision of a comprehensive MRI examination that provides diagnostic information at the molecular, functional, and anatomic levels.

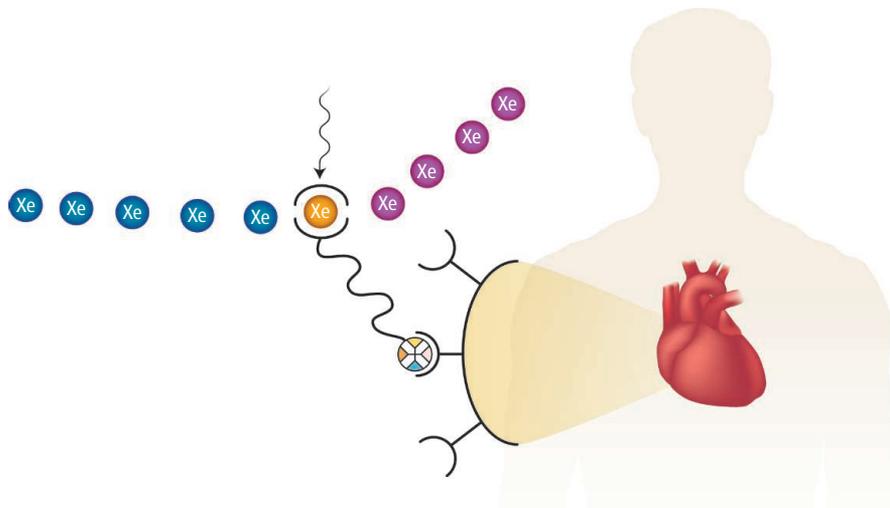
To increase the sensitivity of MRI, the authors use hyperpolarized ^{129}Xe gas, so named because the nuclear alignment (polarization) of the ^{129}Xe atoms is five orders of magnitude higher than that achieved by the MRI magnet (3). The resulting 100,000-fold signal enhancement makes it possible to image the inhaled ^{129}Xe gas in the lungs with exquisite resolution, even though it is less

dense than water (the usual MRI signal source) by a factor of 3000.

When hyperpolarized ^{129}Xe is inhaled into the lungs (or injected in a carrier fluid), it dissolves in the blood and is circulated throughout the body, where it could be imaged in all tissues. However, although the signal enhancement achieved through the use of ^{129}Xe is an impressive start, it is not sufficient to enable molecular imaging. Further sensitivity enhancement is needed, and a means is required to obtain specificity to particular molecular targets of interest. To

Biosensors that include xenon as the signal source dramatically increase the sensitivity of magnetic resonance imaging and may have extensive clinical application.

^{129}Xe atoms are continually diffusing in and out of the cage of the biosensor. During their millisecond-long stay in the cage, the ^{129}Xe atoms experience a unique shift in their resonance frequency, which makes them readily identifiable. Continuous application of radio-frequency radiation at this frequency causes the signal from any ^{129}Xe atom that enters the cage to be erased. Because irradiation can take place for many seconds, thousands of ^{129}Xe atoms can be affected. By imaging the distribution of ^{129}Xe after irradiation, the presence of accumulated biosen-



The future of MRI. Xenon biosensors may provide a means to use magnetic resonance imaging to visualize molecular binding events in the body at minute concentrations.

address these remaining issues, Schröder *et al.* turned to xenon biosensors.

Xenon biosensors are supramolecular constructs consisting of a cage, a linker, and a targeting moiety such as an antibody or ligand that causes the sensor to bind to a specific biological target in the body (see the first figure). This specific molecular binding lets the sensors accumulate in the type of pathology they were designed to find, such as tumors or atherosclerotic plaques. Ironically, the way to detect the presence of such bound sensors is by using them to extinguish the hard-won signal from the hyperpolarized ^{129}Xe gas. An enormous sensitivity gain arises from the fact that one biosensor can snuff out the signal from potentially thousands of nearby ^{129}Xe atoms.

sors (and thus pathology) is manifested as a dark region in the ^{129}Xe image.

The vision, then, is this. A patient, who is predisposed to heart troubles, comes to the hospital and is injected a few hours before imaging with a low concentration of biosensors designed to bind to a marker associated with atherosclerosis. The biosensor may, for example, bind to matrix metalloproteinases, which are elevated in plaques that are vulnerable to rupture (4). The patient is then placed in the MRI scanner and inhales a lungful of hyperpolarized ^{129}Xe , which distributes throughout his body. While it distributes, the ^{129}Xe is irradiated at its unique biosensor-bound frequency. Subsequently, the remaining ^{129}Xe distribution is imaged, and regions where biosensors have accumulated in vulner-

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able plaque appear as dark spots. In the same exam, a high-quality image of blood flow through the coronary arteries and anatomical landmarks of the heart can be made using conventional MRI techniques. On the basis of this comprehensive study, the physician can prescribe a treatment plan that is tailored to the individual patient. Moreover, such noninvasive imaging procedures, once validated, could be used to quickly test the efficacy of novel therapeutic compounds in much smaller numbers of patients than required in current clinical trials.

Schröder *et al.* report a promising path toward nanomolar-sensitivity molecular imaging. However, imaging ^{129}Xe in tissues beyond the airspaces of the lung is in its infancy. As ^{129}Xe moves from lung to blood and tissues, its concentration is reduced by a factor of 10 or more, making imaged correspondingly more challenging. Recently, the lungs of living rats were imaged to reveal the ^{129}Xe distribution at the micrometer scale in the airspaces (see the



second figure) and at the millimeter scale in the pulmonary blood and tissues (5).

Progress from imaging ^{129}Xe in the tissues of rats to imaging ^{129}Xe in the tissues of humans will require larger volumes of hyperpolarized ^{129}Xe to be produced and delivered. Ruset *et al.* recently reported a ^{129}Xe polarizer prototype

Imaging with xenon. This ^{129}Xe MRI image shows the lungs of a rat at a resolution of 300 μm (5).

that produces several liters of ^{129}Xe in 10 min (6). Such production, once routine, would be more than enough to meet this challenge.

Finally, biosensor formulations for specific molecular targets must be developed, and their biodistribution and safety validated. Much remains to be done, but it is not every day that a favorite imaging technique gains three orders of magnitude in sensitivity.

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SIGNAL TRANSDUCTION

Prelude to an Anniversary for the *RAS* Oncogene

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In 1981, groups led by Robert Weinberg, Michael Wigler, and Geoffrey Cooper discovered that small fragments of DNA taken from human cancer-derived cells could endow malignant characteristics on normal mouse fibroblast cells. Within a year, the same groups, along with that of Mariano Barbacid, established that the active ingredient in transforming DNA from a human bladder cancer cell line was the cellular homolog of H-*RAS*, an oncogene found in the Harvey rat sarcoma retrovirus. They thus demonstrated for the first time that human tumors contained activated oncogenes, related to those picked up by retroviruses from their host genomes. Within a few months, the same groups further found that the difference between the normal human H-*RAS* gene and the oncogenic form found in tumors was a single point mutation. It soon became clear that a very high proportion of human tumors contain such activating mutations in *RAS* oncogenes (1). Thus

began the burgeoning area of research into the three closely related proteins, H-, K-, and N-*RAS*, henceforth collectively referred to as *RAS*. The imminent quarter-century anniversary of the identification of the first human oncogene was marked by a recent conference in Glasgow (2).

With so much work on *RAS* behind us, what has been achieved and where are we heading? The realization that mutations in *RAS* oncogenes play a causal role in more than a quarter of human cancers has kept *RAS* and the signaling pathways it controls firmly in focus as therapeutic targets (3). They are small GTP-binding proteins that, when acted upon by specific factors, cycle between an activated and inactivated form—*RAS*-GTP and *RAS*-GDP, respectively. *RAS* proteins are tethered to the inner cell membrane, coupling growth factor receptors to downstream signaling pathways that control cell growth, proliferation, survival, and transformation (see the figure).

Blocking the activity of *RAS* by means of farnesyltransferase inhibitors, which prevents membrane localization, has proved disappointing in the clinic. Other ways of

A recent conference focused on the role of *RAS* in cancer, nearly a quarter of a century after its identification as the first human oncogene.

targeting *RAS* itself have not been developed. However, there is currently much excitement surrounding drugs that inhibit downstream signaling cascades controlled by *RAS*. These include the RAF–mitogen-activated protein kinase kinase (MEK) pathway and the phosphatidylinositol 3-kinase (PI3K)–AKT pathway, both of which control cell growth. In addition to *RAS*, two direct effectors, the B-RAF isoform and PI3K (specifically, the p110 α subunit), are frequently activated by point mutation in human cancers (4). Potent inhibitors of MEK, the direct target of RAF, are showing promise in clinical trials, although it is not clear that B-RAF or *RAS* mutational status correlates with outcome.

“Oncogene addiction,” the notion that tumor cells become reliant on the continued function of activated oncogenes, is an attractive hypothesis for drug developers but clearly does not always hold true. During the complex evolution of a tumor, the total set of acquired mutations will no doubt affect the degree of continued dependence on early oncogenic events such as *RAS* activation. Other drugs targeting the RAF-MEK path-

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