imaging techniques. Nonetheless, high effective tissue concentrations can be achieved using "bulk carriers," such as vesicles and macromolecular constructs in which the number of paramagnetic species can be concentrated. Susceptibility agents based on iron oxide particles have a greater effective relaxivity but affect transverse relaxation rates ($1/T_2$), which are typically 10–30 times greater than longitudinal ($1/T_1$) rates. An alternative mechanism for affecting water MR signals is by magnetization transfer with labile protons on other species, notably amide groups in proteins or in agents designed to provide a large reservoir of exchangeable protons (such as dendrimers). The chemical exchange by saturation transfer (CEST) effect is interesting, partly because the contrast produced can be switched "on" and "off" in a controlled manner.

MR contrast agents proposed to date can be classified into the following categories:

(1) Nonspecific contrast agents, such as lanthanide chelates and intravascular blood pool agents, which have biodistribution and excretion routes that may vary but do not rely on specific targeting strategies.
(2) Targeted contrast agents, which usually are paramagnetic species attached to or part of specifically engineered molecules that are directed and taken up by specific molecular targets.
(3) Smart contrast agents, which change their efficacy (and therefore their effects on the MR signal) only in response to specific chemical processes, such as the presence of specific enzymes or a change in pH or other environmental variables.
(4) Cell labels, which may be either inside or attached to specific cells, that then rely on the trafficking of the cells to be localized. At high resolution in animals, single labeled cells have been detected using this approach.

Topical Issues

The potential applications of these different approaches are intriguing, but the practical success to date of detecting specific molecular targets has been limited. The prospects for achieving sufficiently high levels of contrast material to be seen reliably in clinical applications are poor compared with other modalities. Success will rely on combining improved designs for more effective relaxation agents and carrier vehicles that can deliver relatively large amounts of the agent to a target region. The advent of higher signal-to-noise at higher fields may also benefit these developments.

John Gore, PhD
Professor, Radiology and Radiological Sciences, Biomedical Engineering, Physics and Molecular Physiology, and Biophysics
Director, Vanderbilt University Institute of Imaging Science
Vanderbilt University
Nashville, TN

High-Resolution Optical Imaging: Progress and Perspectives

Unlike ionizing x-ray radiation, nonionizing electromagnetic waves, such as optical and radio waves, pose no health hazard yet can provide new contrast to medical imaging. Unfortunately, electromagnetic waves in the nonionizing spectral region do not penetrate biological tissue in straight paths as do x-rays.

Despite the high optical contrast, pure optical imaging is currently limited by either spatial resolution or imaging depth. High-resolution optical tomography, as demonstrated by confocal microscopy and 2-photon microscopy as well as optical coherence tomography, is limited to a depth of approximately 1 transport mean free path (~1 mm). Low-resolution diffuse optical tomography (DOT), by contrast, can provide near-infrared (NIR) functional imaging of the breast and brain. Light at approximately 700 nm in the NIR spectral region can penetrate multiple centimeters of biological tissue, because its 1/e penetration depth is on the order of 0.5 cm. However, recovering imaging information with high spatial resolution from diffuse photons remains a challenge, as does solving the ill-posed inverse problem for image reconstruction. As a rule of thumb, the spatial resolution of DOT is about 10% of the sample thickness.

High-resolution optical tomography has been developed for functional and molecular imaging by physically combining nonionizing optical and ultrasonic waves. Ultrasonic imaging provides good image resolution but poor contrast in early-stage tumors; in addition, it has strong speckle artifacts. Ultrasound-mediated imaging modalities combine optical and ultrasonic waves synergistically to overcome these problems. Two hybrid modalities are being actively developed: ultrasound-modulated optical tomography and photoacoustic tomography. The former uses a focused ultrasonic wave to encode diffuse laser light in biological tissue, which is analogous to the encoding mechanism in MR imaging. The latter uses low-energy laser pulses to induce ultrasonic waves in biological tissue. The hybrid

modalities yield speckle-free images with high optical contrast at high ultrasonic resolution in relatively large volumes of biological tissue.

Optical properties of targeted contrast agents can provide contrast for biomarkers in molecular imaging. Optical properties or bioluminescence of products from gene expression can provide contrast for gene activities. Furthermore, optical spectroscopy permits simultaneous detection of multiple contrast agents. Although several optical contrast agents are being utilized in animal studies, the number that have translated to human studies is limited. One challenge is to accomplish the translation of optical targeted contrast agents from concept to the clinic.

The major challenge in optical imaging will continue to be the limited penetration depth. To meet this challenge, radiofrequency-based photoacoustic tomography, also referred to as thermoacoustic tomography, is being developed because radiofrequency radiation is nonionizing yet capable of penetrating much deeper than light. Two important questions are:

(1) How quantitative will optical imaging be, and will optical tomography allow true quantification of the concentration of the optical probes?
(2) Because of the limited penetration depth, will optical imaging in humans be limited to tissues near the surface or to optical imaging utilizing various sensors that can be inserted into the body to image organs such as the prostate?

Lihong Wang, PhD
Royce E. Wisenbaker II Endowed Professor of Engineering
Texas A&M University
College Station, TX

Radiologic Approaches to Molecular Imaging

X-ray imaging methods based on plain-film recording and fluoroscopy are the most established of all medical imaging methods. The advent of CT in the early 1970s moved x-ray methods into the realm of more quantitative digital imaging with much better soft tissue contrast. All x-ray imaging methods rely on the ability to detect differences in the total x-ray attenuation coefficient which, in the diagnostic energy range (~10–150 keV), is dominated by photoelectric absorption and Compton scattering. These, in turn, depend on the atomic number and electron densities of tissues. Thus molecular imaging agents must be designed to modify the magnitudes of these gross x-ray interactions. As has been well known from conventional x-ray imaging, the most suitable agents for affecting x-ray attenuation are relatively heavy atoms with atomic numbers chosen such that photoelectric capture is optimized. This can be achieved when the binding energy of the K-shell electrons of the absorbing atoms falls close to the peak energy within the continuous bremsstrahlung spectrum of x-ray energies. This accounts for the current use of materials such as iodine, barium, and xenon as x-ray contrast media. It may be noted that the efficacy of x-ray attenuation is independent of the chemical environment of the absorbing atoms. In addition, x-ray imaging uses ionizing radiation, and the absorbed dose is ultimately a limitation on the ways in which imaging is performed.

Current State

The current principal role of CT in molecular imaging is to provide the structural/anatomical correlates by which the molecular species detected by other methods are localized to specific tissues and organs systems. Thus PET/CT and PET/SPECT are emerging as viable molecular imaging technologies in their own rights, with the molecular imaging modality providing the molecular "contrast" for CT.

The challenge for direct molecular imaging using x-ray detection methods can be reduced to the problem of delivering sufficient concentrations of the atomic reporter to target sites with reasonable specificity. Successful demonstrations of this approach have been achieved either by direct delivery of high concentrations of contrast material directly to a target compartment (e.g., vascular imaging) or by taking advantage of the selective uptake and concentration of the agent by tissue-specific transport systems (e.g., the high-capacity, receptor-mediated chylomicron remnant uptake system of hepatocytes). Both of these approaches have been shown using the same species of iodinated triglyceride contrast agent appropriately modified to remain in the intravascular space or to interact with the hepatocyte surface receptors mediating internalization and sequestration. The prospects of achieving molecular imaging based on specific ligand–receptor equilibrium binding interactions seem less promising. However, although only a few quantitative estimates of the likely success of targeting of x-ray agents have been published, strategies that make use of so-called bulk carrier vehicles such as vesicles and nanoparticles have sufficient promise to be worth further exploration. For example, current clinical CT scanners can detect small changes in absorption (on the order of 1%) at approximately