A hybrid magnetic-resonance/fluorescence imaging system aids identification and study of tumors.

Conventional medical imaging devices such as x-ray, magnetic resonance imaging (MRI), and ultrasound can detect abnormal tissue. Yet they provide little insight into whether a suspicious lesion may be malignant or benign, much less how best to treat the disease. As our understanding of the underlying mechanisms of disease evolves and therapies become more sophisticated, both doctors and medical researchers require images that reveal how living tissue functions, especially on a molecular level. Such images would not only advance the understanding of disease and aid in developing new therapies, but also help identify appropriate treatments for a particular patient and provide rapid-response monitoring of the treatment’s efficacy. The recent introduction of fluorescent probes targeted to specific molecular processes1–6 is a significant move towards this goal and has facilitated development of devices capable of imaging drugs in living tissue.

Fluorescence molecular tomography (FMT) uses fluorescent probes to image the distribution of molecules associated with diseased tissue, such as cancer. This approach has been studied for over a decade, and a number of systems have been introduced to image research animals, such as mice and rats,7–10 as well as the human breast.11–13 Light in the near-IR window (700–950nm) penetrates 10cm of tissue, and therefore fluorescence imaging is feasible through even relatively thick tissue volumes. Typically, a suitable dye is administered, excited with light, and fluorescence emission is measured at different points on the tissue surface. Sophisticated algorithms calculate the distribution of fluorescence activity, thus locating the targeted molecular feature.

Several physical realities make FMT in tissue challenging. Light diffusion through tissue and relatively sparse data sampling result in poorly resolved, blurry images, especially compared with those produced by x-ray and MRI devices. In addition, nonspecific tissue autofluorescence contaminates the measured emission signal. Our FMT scanner overcomes these challenges by mating to a conventional MRI scanner and introducing spectrally resolved optical detectors. The optical detection component consists of 16 Acton Research Insight spectrometers with cooled CCD detectors, shown in Figure 1(a). Each spectrometer is coupled to long optical fibers that reach inside the MRI bore, as shown in Figure 1(b).12 Custom-designed MRI coils accommodate the optical fibers that deliver light to and collect light emitted from the tissue surface. We acquire MRI and FMT data simultaneously. We use the magnetic-resonance (MR) images to define the outer boundary of the interrogated tissue and delineate its internal anatomical structure. We use this in turn to guide the image recovery of fluorescence activity. This technique produces images that are more quantitatively accurate and highly resolved than those produced without the supplemental MR images.14–17 Tissue autofluorescence is decoupled from the measured optical signal using spectral fitting routines that extract the targeted drug-specific signal. This also facilitates imaging multiple fluorescent drugs simultaneously to explore different molecular processes.

We are currently imaging different types of cancerous tumors in hairless research mice. The experiments begin by implanting brain tumor cells through a hole in the animal’s cranium. After 2–3 weeks, the cells proliferate into a malignant tumor. Prior to imaging, we inject a fluorescent dye targeted to a protein receptor that is overexpressed in some types of cancer. The dye binds...
to the protein receptor and, over time, much of the unbound dye is cleared from the body. Two days after injection the animal is scanned in the MRI-FMT system (see Figure 2).

Figure 2(a) shows an anesthetized mouse in the optical-MRI coil. The ring formation of eight fibers is visible in a single plane around the animal’s head. Figure 2(b) shows a 3D rendering of the head using MR images. The intersecting plane illustrates the location of the optical-fiber plane. The corresponding combined MRI/fluorescence image is displayed in Figure 2(c) and shows increased fluorescence in the tumor region, which is associated with the abundance of the protein receptor specific to the tumor. We recently used this approach to distinguish between mice tumors that overexpress the protein receptors and those that do not. Many new cancer drugs coming to market target similar protein receptors, and so the ability to determine which tumors have a receptor overabundance is valuable in planning treatment.

In summary, we developed a technique for detecting small molecular changes in tumors early in a treatment course. This is important for developing and testing new treatments as well as monitoring patient response. We are currently investigating our system’s sensitivity to these changes in several types of cancer. Preliminary results indicate that our approach is sensitive to changes caused by a therapeutic drug targeted to the same receptor as the fluorescent probe, although it is unclear if this is due to competitive binding to the receptor or slower growth of treated tumors. We are conducting another preclinical study using MRI-FMT to track the effects of photodynamic therapy (PDT) in pancreatic cancer. This aims to enhance our understanding of the metabolic changes induced by the therapy and thus help guide PDT dosage and follow-up therapy.

Our system can also accommodating human subjects and will be used in an upcoming study of breast-cancer patients. Currently, very few fluorescent probes have been approved for use in humans, and those have limited specificity to tumor cells. Therefore, routine clinical realization of MRI-FMT in humans may be years in the future and depends heavily on the availability of safe and effective imaging drugs. However, fluorescent-probe development is both a broad and expanding area of research,1–6 and we aim to have an exceptionally capable system in place as new, targeted imaging agents become available.

This research was funded by the National Institutes of Health (grants RO1 CA109558, RO1 CA69544, and U54 CA105480), Philips Research Hamburg, and Department of Defense Breast Cancer pre-doctoral fellowship BC051058. We acknowledge the critical input of Summer L. Gibbs-Strauss, Kimberly Samkoe, Julia O’Hara, Hamid Dehghani, Subhadra Srinivasan, and Keith D. Paulsen.

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