

Molecular Imaging Modernizes Medicine

Remember when *Star Trek's* Dr. Beverly Crusher would pass a hand-held scanner over patients to find out what was wrong with them? With advances in molecular imaging, this technology is moving toward becoming a reality.

In many ways, we've left the fictional scanner in the dust. Molecular imaging is now not only capable of noninvasive diagnosing, but also of disease localization and characterization, monitoring of therapy and disease regression, and faster and more efficient drug development.

Think of molecular imaging as the latest in molecular biology — genetic testing combined with the newest clinical imaging technologies, such as single photon emission computerized tomography (SPECT), positron emission tomography (PET), and optical imaging. Molecular imaging promises to revolutionize diagnosis, but right now, it often is used in small animals like mice or Yorkshire swine.

"The images are spectacular," Eva Sevick-Muraca, PhD, enthuses. "You can actually watch the lymph flowing in the lymph channels in the pig." Recently, her research team also demonstrated lymph trafficking in humans.

Sevick-Muraca, professor of radiology and head of the division of molecular imaging at Baylor College of Medicine, in Houston, is talking about Sentinel Lymph Node Mapping Using a Fluorescent Contrast Agent and Near-Infrared Optical Imaging, the subject of current human trials funded by the

National Cancer Institute and the American Cancer Society. It's based on her team's successful work with mice and Yorkshire swine, whose lymphatic system is similar to that in humans.

Many cancers metastasize via the lymphatic system, but to see if cancerous cells have infiltrated a lymph node, it must be resected and sent to the pathology lab for analysis.

Sevick-Muraca's approach is to infuse an imaging agent labeled with a fluorescent near-infrared (NIR) dye and a radiotracer to detect cancer-positive lymph nodes noninvasively and intraoperatively. One of the six imaging agents in the developmental pipeline is trastuzumab (Herceptin) coupled to both an NIR dye and a radiotracer to bind with the HER-2/neu receptors in breast cancer cells. The area of interest is

scanned through the patient's intact skin with nuclear and optical cameras. With optical cameras, images are taken every 800 milliseconds. Superimposed on a "white light" image of the surgical field, the infrared images exactly pinpoint which nodes are candidates for resection and which are clear.

Trastuzumab is the first diagnostic probe tried by Sevick-Muraca's team; others are following. "We're trying to develop agents that are very specific to disease," she says.

"It's very difficult to perform nuclear imaging in the operating

room, so optical imaging seems like a natural way to move molecular imaging into the surgical suite," says Sevick-Muraca. Dual labeling with an optical and nuclear tracer, provides the sensitivity of gold-standard nuclear imaging techniques, and the ability to visually and molecularly guide surgery.

Some publicly traded and venture capital-funded companies are eager to cash in on molecular

imaging for breast cancer outside of the operating room. Molecular diagnostics company Spectros, in Portola Valley, Calif., is conducting studies on a portable optical sensor that doesn't need a contrast agent to diagnose and treat breast cancer, instead relying on angiogenesis markers. Industry giants General Electric Healthcare, Siemens, and Philips Medical are commercializing similar devices,

with and without contrast agents.

"Historically, the device without a contrast agent gets there first because the regulatory path is less steep," says David Benaron, MD, Spectros's CEO. "I'd be surprised if there isn't an FDA-approved device within two years. I would expect an optical sensor to be a routine part of diagnosing and treating breast cancer within five years."

BEST OF BOTH WORLDS

Imaging modalities such as magnetic resonance imaging (MRI) and computed axial tomography (CAT,

BY BOB
CARLSON,
MHA



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or CT) have been standard diagnostic tools for at least 10 years, as have the nuclear medicine modalities PET and SPECT. What's new about molecular imaging is using them with a variety of radioisotopes and contrast agents or physiological markers to image molecular pathways and events in vivo.

CT, X-ray, and ultrasound are most often used as *structural* imaging modalities to precisely locate an area of interest. PET, SPECT, and optical (bioluminescent or fluorescent) imaging are *functional* imaging methods that provide data about individual cells and processes, such as circulation and metabolism. MRI is used in both types of imaging.

"Structural and functional imaging are complementary, and that's why they are combined into hybrid PET-CT, PET-MRI, and SPECT-CT systems," explains Hossein Jadvar, MD, PhD, MPH, associate professor of radiology and biomedical engineering, and director of research, at Keck School of Medicine at the University of Southern California. "With hybrid systems, you have the best of both worlds."

FDG-PET, for example, is widely used to determine tumor metabolism by imaging uptake of glucose analog 2-fluoro-2-deoxy-D-glucose. Most tumors metabolize more glucose than normal cells, and hypermetabolic tumors usually result in a worse prognosis. Pre- and post-chemotherapy FDG-PET-CT scans determine whether chemotherapy lowered metabolic activity or decreased tumor size.

Diffuse optical spectroscopy, still going through NCI trials, uses annexin, conjugated to PET optical markers, to signal tumor cell death. If the trials succeed, it could supplement or replace the current standard of care for adjuvant breast

cancer therapy — structural MRI scan 6 weeks postchemotherapy.

"Instead of four noneffective courses of chemotherapy, you can get feedback right after the first course to tell whether you're on the right track," says Benaron.

Molecular imaging appears equally promising in drug development. A typical preclinical regimen for testing, say a chemotherapy drug, involves implanting cancer cells in hundreds of animals, a percentage of which are autopsied at predetermined intervals to measure the effect of different chemotherapy agents on tumor size.

Instead, cancer cells could be tagged with an optical marker pre-implantation, and an enzyme like luciferin, which makes tumor cells glow, could be given and the animals scanned as often as needed to monitor tumor therapy response. This scenario is less labor intensive and needs far fewer testers with no animal death. It also allows for more accurate cell counts, valuable longitudinal data, faster results, and tighter standard deviations.

A PARADOX

For now, getting new agents to market seems to be a choke point for the industry. Molecular imaging agents, or probes, as they are also called, are considered drugs by the FDA and have to jump through the typical regulatory hoops. This very costly proposition may keep promising agents from becoming widely available.

"This is actually the biggest challenge for molecular imaging," says Peter Martin, PhD, director of business development for molecular imaging at Philips Medical Systems. "We call it 'the molecular imaging paradox.'"

If molecular imaging is increasingly aimed at specific diseases, then the expense of bringing tar-

geted agents to market will be borne by fewer and fewer sales. In Martin's view, that's why nuclear medicine modalities such as PET and SPECT will continue to dominate molecular imaging in the near future. They use small doses of imaging agents that are less likely to cause unwanted side effects, which, according to Martin, often "kill off" drugs very late in the development cycle at great expense to the creator. To become cost-effective, he believes that targeted agents for other modalities, such as MRI, optical, and even ultrasound, will become cost-effective if aimed at common diseases, or if the FDA adapts its approval process to allow for lower cost approaches to proving agent safety and efficacy.

FDG was developed with support from the National Institutes of Health, and Martin says similar support is needed to develop new molecular imaging agents.

Martin sees a bright future for molecular imaging, but warns not to expect too much too soon. Benaron is more optimistic, noting that optical diagnostics and imagers already account for \$6 billion in sales annually.

"The old way of doing medicine is rapidly dying," says Benaron. "The new way will determine the patient's disease and treat it very specifically. Although more drugs will be targeted to smaller markets, prices will be good for the drug companies because everyone wants a drug that works."

Jadvar agrees.

"Molecular imaging will move to the center of patient care for diagnosis, treatment evaluation, and prognostication," he says. "We're only at the tip of the iceberg." **BH**

Contributing editor Bob Carlson writes exclusively about healthcare. He lives near Zionsville, Ind.