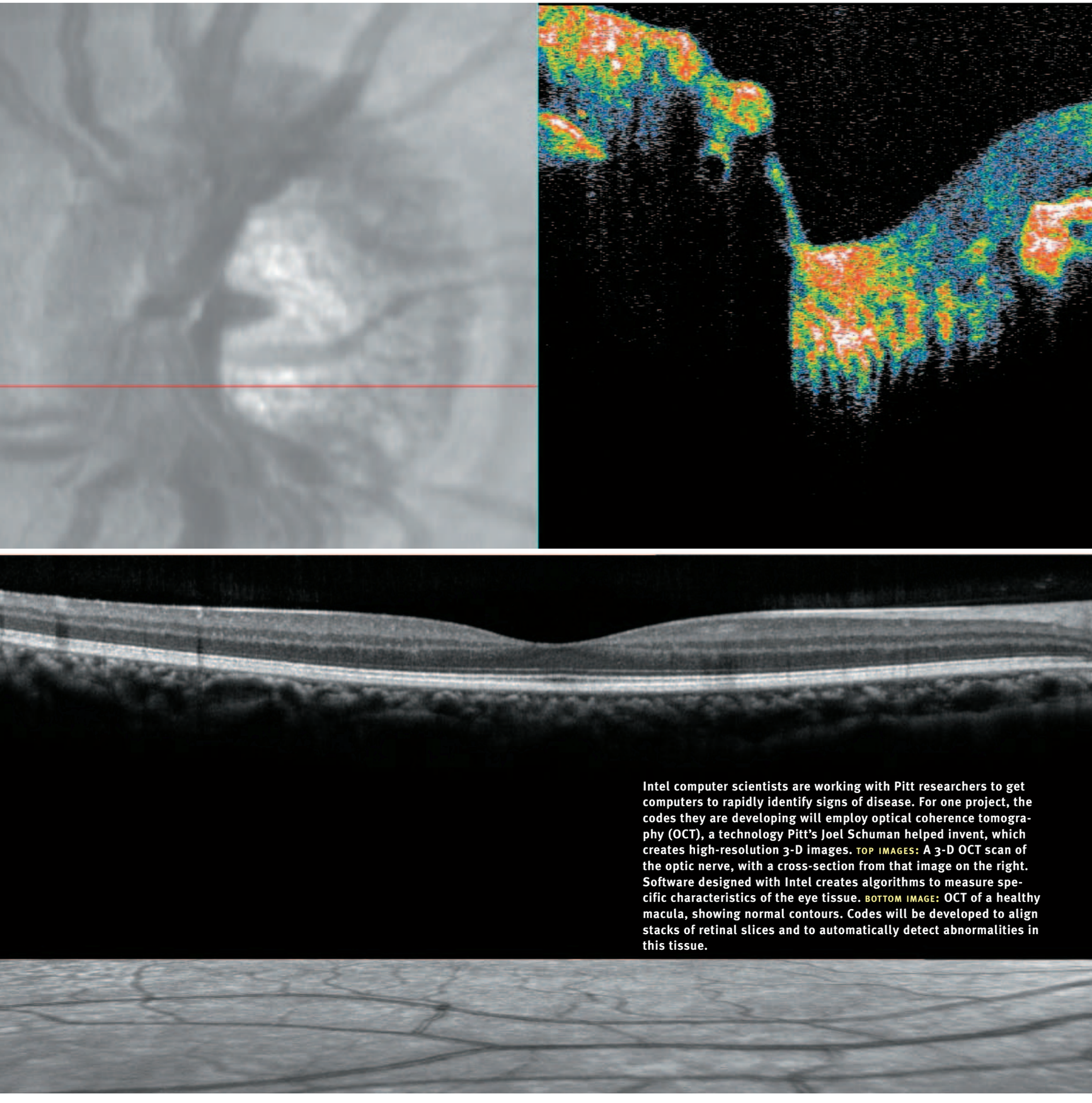


Intel computer scientists are working with Pitt researchers to get computers to rapidly identify signs of disease. For one project, the codes they are developing will employ optical coherence tomography (OCT), a technology Pitt's Joel Schuman helped invent, which creates high-resolution 3-D images. TOP IMAGES: A 3-D OCT scan of the optic nerve, with a cross-section from that image on the right. Software designed with Intel creates algorithms to measure specific characteristics of the eye tissue. BOTTOM IMAGE: OCT of a healthy macula, showing normal contours. Codes will be developed to align stacks of retinal slices and to automatically detect abnormalities in this tissue.

THE PIXELATED STETHOSCOPE

AT INTEL LABS PITTSBURGH, COMPUTERS CAN SEE WHAT DOCS CAN'T

BY REID R. FRAZIER

Among the many talents of Leonard H. "Bones" McCoy, *Star Trek*'s inimitable, sharp-tongued physician, were his capabilities with what looks like a medical ray gun. Pointing a saltshaker-like sensor at a patient, McCoy could detect brain waves, sense blood abnormalities, and identify pathogens like "Saurian virus."

It remains a far-fetched idea, this business of point-and-shoot diagnostics, but it turns out the technology needed for a McCoy-worthy medical sensor (or "medical tricorder," in Trekkie-speak) might arrive considerably sooner than the 23rd century if a group of Pittsburgh scientists has its way.

University of Pittsburgh researchers are working with computer scientists at Carnegie Mellon University and Intel, the world's largest maker of chips, to develop computers that will assist doctors in diagnosing and treating disease. In 2002, Intel established a foothold in Pittsburgh, on the CMU campus, building one of three such "lablets" to pull together top researchers in biomedicine, robotics, and computing.

The lab's unique collaborative arrangement allows scientists to put their heads together on some killer apps that would make McCoy proud.

"Everything we do is basic, 'far-out' research," says David O'Hallaron, Carnegie Mellon associate professor of computer science and electrical and computer engineering and director of Intel Labs Pittsburgh. Projects under way include developing catoms—tiny, programmable machines that may one day be able to glom onto one another to form 3-D objects that walk, talk, and do jobs we can't or won't do, as well as video recognition technology that can tell what a person is doing. A branch of the outfit is involved in "computational health"—harnessing the computer's incredible powers of organization, especially finding things that are like other things—to solve wide-ranging medical dilemmas.

Doug Weber and Wei Wang are hoping to read people's minds. The Pitt assistant professors of physical medicine and rehabilitation are sifting through magnetoencephalography (MEG) data with Intel and CMU computer scientists. MEG measures magnetic fields produced by brain activity The idea is to get a computer to recognize brain patterns when people think of specific words. This application could eventually help patients who have difficulty verbalizing—perhaps because of neurodegenerative disease, spinal cord injury, or stroke—to "talk" through a computer. The team can determine, with 80 percent accuracy, whether a person is thinking of, say, a hammer or a stalk of celery.

When analyzing images of patients, doctors already use a computer to form diagnoses—the one between their ears, that is. They compare a clinical scan—perhaps an X-ray or CT—to the hundreds of others they've already seen. But inevitably, unfamiliar shapes or shadows pop up on film or screen. What if docs could compare their referent image to millions or billions of other images? That's one possible use of Diamond, a program created by Intel scientists Rahul Sukthankar and Larry Huston with Mahadev Satyanarayanan, founding director of Intel Pittsburgh and Carnegie Group Professor of Computer Science at CMU.

A few years ago, Satyanarayanan wondered whether he could create an application that could search images in the same way that Google looks through reams of text on the Internet. When Pitt medical researchers heard about his idea, they quickly lined up to help create a version of Diamond for docs. "Imagine if, at the point of care, you have the world's fattest textbook, which can home in on the three or four most relevant cases," says Satyanarayanan.

Computers could also solve a glitch common to 3-D medical imaging. These systems require a computer to collate stacks of cross-sectional "slices" of organs and tissue. If the object moves (as when a retina shifts), the slices can become skewed. Mei Chen, an Intel computer scientist, has been keeping busy developing codes with a number of Pitt researchers that would allow a computer to reposition each slice after an imaged object has moved. Friedrich Knollmann, associate professor of radiology, and Athanassios Argiris, professor of medicine, want a code to follow blood flowing through a lung tumor (as they breathe, lungs don't really "sit still" for the camera). Joel Schuman, chair of ophthalmology, wants a similar program for optical coherence tomography (OCT), a 3-D eye-mapping system he helped invent. With Chen, his group is creating an automated diagnostic application, eye* (pronounced "eye star"), that would "proofread" the OCT image, compare it with a database of known eye diseases, and give a preliminary diagnosis. "If it sees tissue abnormalities, it will say, 'Oh, that's glaucoma,' or 'That's macular degeneration,' or 'That's diabetes,'" Schuman says.

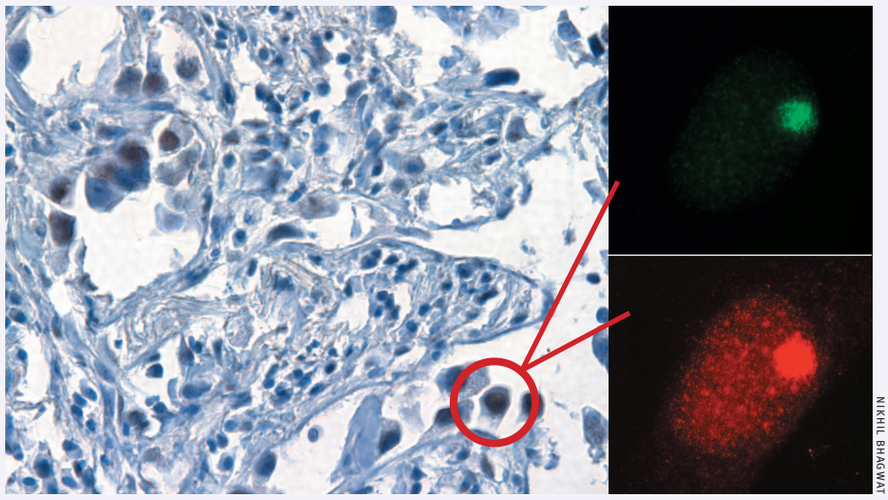
So, could a machine take a doctor's place one day? Probably not. But Schuman notes: "We have a technology that creates a 3-D image of the back of the eye. Wouldn't it be great if a computer could tell you if that eye is all right?" ■

COURTESY OCULAR IMAGING LABORATORY

ONE STEP CLOSER TO PERSONALIZED MEDICINE

A CHEMOTHERAPY BREAKTHROUGH

BY MELINDA WENNER



NIKHIL BHAGWAT

We may one day be able to predict drug response by testing tumors for a DNA-repair complex (green) that makes patients less likely to respond to chemotherapy. (The red stain shows an area of DNA damage in lung cancer cells.)

As if the devastating side effects of chemotherapy weren't enough, another problem cancer patients face is drug resistance. Nearly one-third of ovarian cancer patients fail to respond at all to platinum-based therapies, which form the cornerstone of many chemotherapy regimens. Those who do typically stop responding within several years, often causing their cancer to return. Although oncologists have long tried to understand and predict this resistance, a new study by Laura Niedernhofer, an associate professor of microbiology and molecular genetics at the University of Pittsburgh Cancer Institute, suggests that they may have been using the wrong tools to do it. Her study, published in September 2009 in *Cancer Research*, raises major questions about the way scientists have studied cancer drug resistance and presents a new method that may ultimately help save lives.

Platinum-based chemotherapies like cisplatin work by damaging the DNA inside cancer cells. If the injury is drastic enough, the cell dies, Niedernhofer explains. But our bodies also have built-in repair mechanisms to fix the minor DNA damage that we accrue over a lifetime. Some scientists have speculated, then, that the people who grow resistant to chemotherapy are those who have the strongest repair mechanisms.

One of the ways researchers have tested this idea is by assessing the activity of an innate cellular repair complex called ERCC1-XPF, the only enzyme complex known to be involved in addressing all of the types of damage that platinum drugs cause. If patients who do not respond to therapy have better repair mechanisms, they should, in theory, have higher levels of ERCC1-XPF in their tumor cells—so by measuring how much of the complex resides inside these cells, it might be possible to predict whether patients will respond to drugs.

For years, scientists have measured ERCC1-XPF levels by flooding cells with a fluorescently tagged antibody called 8F1 that is known to bind to the repair complex. But Niedernhofer and coauthor Richard Wood, formerly a University of Pittsburgh biologist now at the University of Texas M.D. Anderson Cancer Center, wondered whether 8F1 was actually specific to ERCC1-XPF. In other words, could it be binding to other cellular proteins, too? If so, then even if the antibody seemed to show high levels of ERCC1-XPF in tumor cells, the cells weren't necessarily chock full of it, because the antibody could be binding to something else instead.

Niedernhofer and Wood's hunch was correct. With the help of colleagues, including Pitt postdoc Nikhil Bhagwat, they showed that 8F1 binds to several proteins.

"There must be about 400 papers out there measuring ERCC1 levels. A lot of times [investigators were measuring levels] with an antibody that we demonstrated was not specific for ERCC1," Niedernhofer says. As a result, scientists who thought they were seeing evidence of ERCC1-XPF were sometimes seeing something else. This may have led "a lot of people in the wrong direction," she says.

Niedernhofer next checked whether any of the other 11 commercially available antibodies known to bind to ERCC1-XPF actually are specific to it—or if they, too, bind to other proteins. To do so, she and her colleagues looked for antibodies that got "hits" when added to cells that had ERCC1-XPF but did not when they were added to mutant cells that lacked the complex. In addition, Niedernhofer scouted for antibodies that bound only inside the nucleus, where ERCC1-XPF resides. Eventually, the researchers identified three antibodies that appear to be specific to ERCC1-XPF, and Niedernhofer showed it was possible to use these antibodies to identify the complex in fixed, paraffin-embedded tissue, which is how most doctors preserve tumor specimens after surgery.

Now, the researchers are using the three specific antibodies to test whether ERCC1-XPF levels do, in fact, correlate with drug response. But even if they do, there is still a long road ahead:

"All tumors are not created equal," Niedernhofer says. What predicts drug response in one type of tumor might not in another.

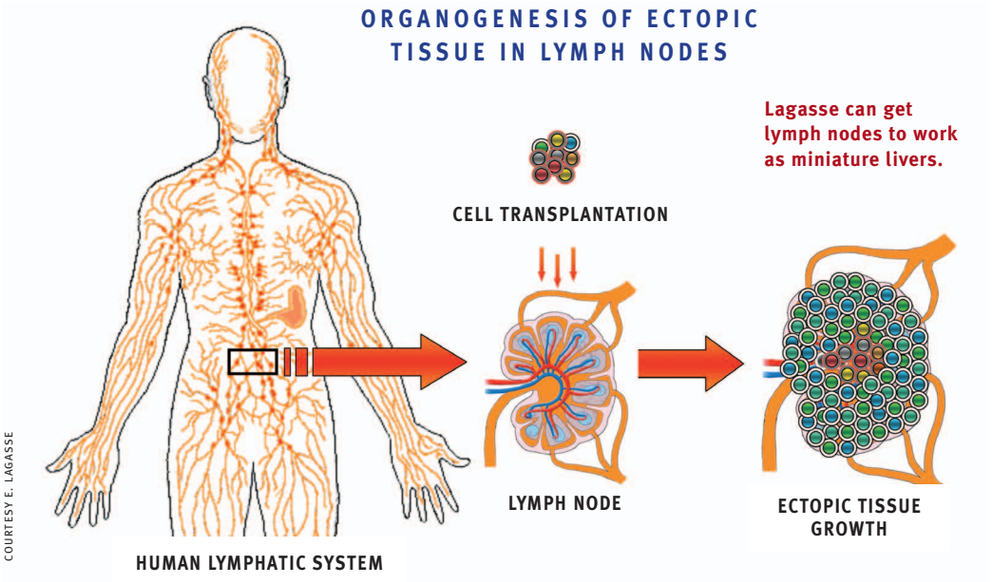
"It's not like you'll be able to go buy a kit to measure ERCC1 levels and that will predict, for every tumor type, whether or not they'll respond to cisplatin therapy," she says.

Still, Niedernhofer's findings bring doctors closer to being able to tailor cancer treatments to individual patient needs. It's a first step toward personalized medicine, she says. ■

LYMPH NODES

SPROUT LIVERS

BY MICHELE BAUM



WHERE THE WILD ORGAN GROWS

Eric Lagasse wants to fight liver disease by gaming the system—the lymphatic system, that is.

Lagasse, associate professor of pathology and director of the Cancer Stem Cell Center at the Pitt-UPMC McGowan Institute for Regenerative Medicine, is exploring a concept so revolutionary that, in September 2009, the National Institutes of Health (NIH) awarded him a five-year, $2.9 million Director's Transformative R01 grant. He is searching for ways to co-opt some of the body's 500 lymph nodes into doing double-duty as miniature livers. Different from standard R01 grants—R01 refers to "individual research project," and such grants are known as career-making benchmarks in themselves—transformative grants are designed "to fund high-risk research that will create new or challenge existing paradigms," according to the NIH. The Lagasse grant was one of 42 awarded in 2009.

The fact that the lymphatic system will host functioning colonies of hepatocytes "is a spectacular finding," says George Michalopoulos, Maud L. Menton Professor and chair of pathology at Pitt, who studies liver cancer and liver cell biology.

"Nobody had even thought about this before."

Lagasse foresees an alternative to transplantation, currently the only effective treatment for end-stage liver disease. Transplantation remains a costly option fraught with risks, not only from the surgical procedure, but also because of lifelong drug therapy to suppress the immune system.

"This is the first step of a complex idea that could lead to organogenesis," says Lagasse.

Among the can't-live-without-it major organs, the human liver is unique in that it regenerates. After a live-donor transplant, two complete organs will grow from the components of just one, typically within six months. Even with this quality, however, the organ can be so impaired by disease or injury that liver failure becomes inevitable.

Enter something Lagasse calls black magic.

"We have found that when you inject liver cells into the peritoneum [the abdominal lining] of a mouse, they will migrate to the lymph nodes.

"Large nodules then form in the stomach and gut region, and we found out that they were essentially mini-livers," explains Lagasse.

For the experiments submitted to NIH in support of his grant application, Lagasse used mice genetically engineered with liver defects as models of progressive liver failure. The animals' livers were endangered by tyrosinemia, a genetic enzyme deficiency. Yet the old black magic of that very failure appears to be a key component, Lagasse says, of his experiment's success, perhaps signaling the transplanted cells to take root, grow, and work.

"If you inject cells into an animal without liver failure, the cells die," he says.

"We want to give the cells an opportunity to find the right location and expand as needed, and we have found that they can expand dramatically," he says. Injecting mice with liver cells appears to result in localized migration of hepatocytes to lymph nodes without affecting the function of other, neighboring nodes. In the mice with tyrosinemia, transplanted liver cells functioned robustly—enough to rescue the animals from liver failure.

A healthy liver removes toxins and waste from the bloodstream and also works to aid digestion and regulate metabolism. There are many kinds of liver disease, yet the most common diagnosis leading to a transplant is cirrhosis, a scarring of the liver often related to long-term alcohol use. Cirrhosis may lead to liver cancer. Liver failure also can be tied to drug interactions, viral infections such as hepatitis C, or chemical poisoning.

"About 100,000 people in the United States have end-stage liver disease," notes Lagasse. "At least 20,000 are on a transplant waiting list."

"Every now and again there are really huge leaps of faith that occur in science, and this is one," says Alan Russell, director of the McGowan Institute as well as a Pitt University Professor of Surgery with appointments in chemical engineering, bioengineering, and rehabilitation sciences and technology. He names whole-organ transplantation as another leap-of-faith example.

"For decades, people have been injecting cells of one kind or another. But it's an extraordinary leap to think that you can take cells from one organ, inject them into another, and have [those cells] take on the characteristics of the first.

"Not only that—it works." ■