From Discovery to Market

Making novel technologies commercially available leads to advances in research and medicine. **BY LISA CHIU**

From instruments that can peer deep inside cells and tissues, revealing previously unknown processes, to methods that can find signs of disease before any clinical symptoms arise, many tools and devices routinely used in the laboratory and clinic began their lives as challenging technical problems.

Researchers at NCRR-funded Biomedical Technology Research Resources (BTRRs) focus on finding solutions to such problems. Over the years, BTRRs have been the source of countless breakthrough technologies with wide applications in biomedical research and medicine. But as difficult as it is to develop a useful new method or instrument, it is also challenging to build it into a finished, easy-to-use product and put it in the hands of researchers and clinicians worldwide. This process sometimes requires collaborating with an established company or, in some cases, starting a new one.

Many BTRR discoveries have followed commercial paths. Two recent examples—a technique to enhance clinical imaging and another to detect changes in oxygen in different tissues—illustrate how some inventions make it to the clinic.

GETTING THE FAT OUT OF MRI

As a radiology resident at Stanford University School of Medicine, Scott Reeder set out to overcome a problem that had long vexed researchers working with magnetic resonance imaging (MRI).

MRI works by applying a strong, constant magnetic field to a sample and then measuring how the nuclei of hydrogen atoms—found in water, fat, and other body tissues—respond to a short burst of radio waves. The method can be thought of as ringing a bell: exposing the body to energy waves is the "ding," and the resulting echoes are used to construct an image.

The problem is that echoes from fat are very "loud" and can obscure those from tumors and inflamed or infected tissues.

■ Scott Reeder, currently at the University of Wisconsin–Madison, and colleagues at the NCRR-funded Center for Advanced Magnetic Resonance Technology at Stanford University, developed a new method for enhancing magnetic resonance imaging (MRI). Through a collaboration with General Electric (GE), the technology has been further developed into an easy-to-use option on many of GE's MRI instruments.

PHOTO COURTESY OF GENERAL ELECTRIC

AGREEMENTS WITH INDUSTRY

When academic scientists collaborate with industry, both parties draw up legal agreements that detail responsibilities for the work, ownership of intellectual property, communication of results, and other issues. Master Agreements, also referred to as "blanket" or "umbrella" agreements, are used when a company expects to sponsor multiple projects with an academic institution over a long period of time. In such cases, the legal terms and conditions are pre-negotiated. When a new project is proposed, the terms of the Master Agreement are incorporated by reference into the new agreement, considerably speeding up the negotiation process. Stanford University, home to the NCRR-funded Center for Advanced Magnetic Resonance Technology, has a Master Agreement for sponsored research with several companies, including General Electric.

(Source: www.stanford.edu/group/ICO/agmts/index.htm)

And although there are ways to eliminate fat signals from an image, they are difficult to implement in breast tissue, extremities, and the head and neck. As a result, these remain problem areas of the body for imaging.

To better distinguish between fat and other tissues, Gary Glover, head of the NCRR-funded Center for Advanced Magnetic Resonance Technology (CAMRT) at Stanford University, developed in 1991 a method that records MR signals at three different time intervals. Glover's technique provided considerable improvements to image quality in difficult areas, but it was not easy to implement routinely.

Reeder decided to work with CAMRT scientists to build on Glover's approach. "I wrote my first algorithm late at night while on call at the hospital, when the ER was slow," remembers Reeder. "We came up with a more general and flexible method to acquire and analyze the echoes."

COLLABORATING WITH A COMPANY

Reeder and colleagues took advantage of a collaborative research agreement established between Stanford University and General Electric (GE) to create a prototype of the algorithm that could be used with GE's MRI machines. (See sidebar "Agreements with Industry.") "When we have a new technology that may have broad applications, we work very closely with GE," says Brian Hargreaves, an assistant professor of radiology at CAMRT. "One of their strengths is making technologies work more reliably and efficiently so that any researcher can use them."

Today the technology that Reeder and colleagues at CAMRT developed with GE, dubbed IDEAL*, is being used by the Stanford group for a variety of applications, including to distinguish silicone from breast tissue; to image fatty tumors; and to suppress fat signals and improve imaging in the ankle, head, and neck.

And within a year, researchers and clinicians across the country will benefit from IDEAL technology as it becomes available as an easy-to-use option on many of GE's commercially available MRI devices. "It has taken a lot of communication between the groups to make IDEAL happen," says Reeder. "But the pace of development has been fantastic."

Reeder, who joined the University of Wisconsin–Madison Department of Radiology in 2005 as division chief of MRI, notes one key reason IDEAL will come so quickly to market was the research agreement in place with GE. "It is extremely important for an academic site to establish a comprehensive research framework with a collaborating company," he says. "The agreement needs to define intellectual property and other important principles that facilitate cooperation and ensure open communication."

MEASURING OXYGEN

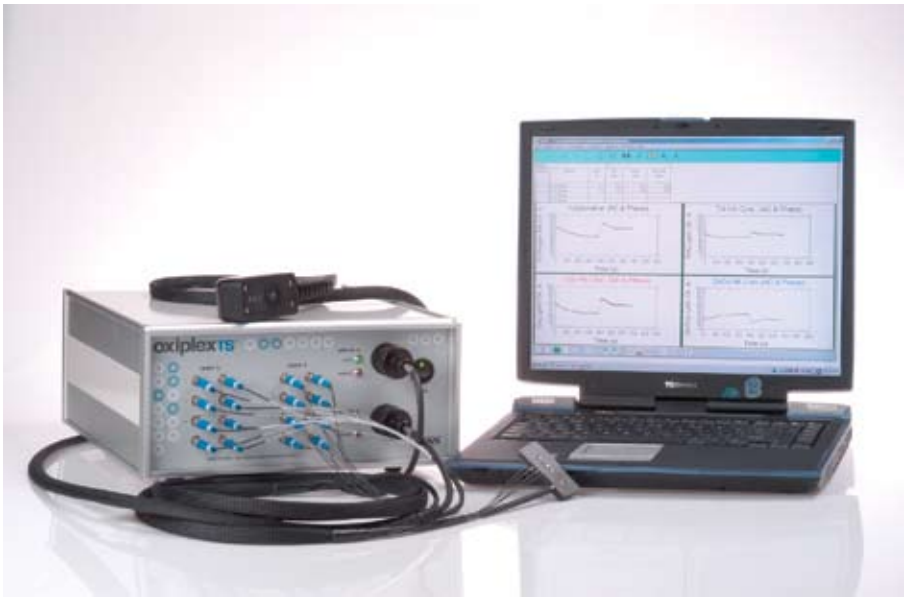
Enrico Gratton, head of the NCRR-funded Laboratory of Fluorescence Dynamics (LFD) at the University of California, Irvine, took a different track in bringing his discoveries to market. In 1984, Gratton founded the company ISS Inc. in Champaign, Ill., to make some of LFD's technologies commercially available.

One such technology, which has a broad range of applications in the clinic, grew out of a curious finding by the University of Pennsylvania's Britton Chance, a renowned expert in the field of optical imaging and a friend of Gratton.

In 1988, Chance's group was working with near-infrared lasers to understand how different tissues responded to laser light. Chance discovered that the light took a fair amount of time to pass through the brains of the graduate students in the lab, but it passed through very rapidly when the laser was pointed at his own head.

Chance was concerned that he might be witnessing the effects of aging on his brain. But Gratton had an insight: Brain activity results in an increase in blood flow and of oxygenated hemoglobin. Gratton realized that differences in the speed at which laser light traveled through the brain could be caused by changes in oxygenation. Further testing revealed that near-infrared lasers could be used to precisely quantify oxygen amounts in various tissues.

* Iterative Decomposition of Water and Fat with Echo Asymmetry and Least-Squares Estimation



■ ISS Inc., a company in Champaign, Ill., has developed numerous technologies from the NCRR-funded Laboratory of Fluorescence Dynamics (LFD), currently located at the University of California, Irvine. One of their products is OxiplexTS, a portable device to precisely measure oxygen levels in different tissues.

The finding put to rest Chance's worries and led to technological innovation. "Here we were helping a friend, and suddenly we have made a discovery that put us very far ahead in our field of research," says Gratton. "We could measure oxygenation of tissues in a quantitative way."

STARTING A COMPANY

ISS developed several instruments from this discovery, including OxiplexTS, a portable device that measures tissue oxygenation. Such measurements are useful because problems with oxygenation may reveal bad circulation or explain labored breathing.

Eighty OxiplexTS devices have been sold worldwide since the instrument came to market in 1998. They are used in research to study a variety of problems, from peripheral vascular disease and sleep apnea to the kinesiology of an exercising athlete. ISS is now in the process of filing a 510(k) application to the U.S. Food and Drug Administration (FDA) to use OxiplexTS in the clinic, specifically for use in patients with peripheral vascular disease. (See sidebar "Obtaining FDA Approval.")

Gratton has seen many of his discoveries benefit researchers and patients, but starting a company wasn't his first choice. "It was very time consuming to start a new company," says Gratton, who at the time he founded ISS was an assistant professor at the University of Illinois at Urbana-Champaign, where the LFD was located until 2006.

But Gratton was driven to this choice because he had not found anyone to commit to one of his first inventions: an instrument biochemists could use to measure fluorescence decay times to understand and quantify interactions among molecules. This product is now available through ISS and is used in many research laboratories.

Gratton left ISS in 1987 to focus exclusively on his academic career and remove any concerns about conflict of interest. But he still serves as a scientific advisor for the company.

Seeing their inspirations transformed into products that help researchers and improve health has been deeply satisfying to both Gratton and Reeder. "It is a really awesome feeling to know that I could think about the physics of a problem and see it become something useful in the clinic," says Reeder. "This has never happened to me before. Not all successful ideas result in helping patients." ■

TO GAIN ACCESS: NCRR supports 50 BTRRs across the United States. They develop new tools and applications and offer different types of services and training, free of charge, to qualified scientists. For more information, visit www.ncrr.nih.gov/BTRR.asp.

OBTAINING FDA APPROVAL

Before medical devices—such as surgical lasers, pacemakers, vascular grafts, as well as diagnostic tests—can be marketed for use in the clinic, they must be approved by the U.S. Food and Drug Administration (FDA). According to the Medical Device Amendments of 1976 and the Safe Medical Devices Act of 1990, manufacturers wishing to introduce a new medical device to the market may have to submit a pre-market application to the FDA and carry out the necessary clinical studies. But in some cases, clinical studies are not necessary. If a device is deemed to be "substantially equivalent" to another device marketed prior to the Amendments, the manufactured can file a 510(k) application. If the FDA agrees that the new device is substantially equivalent, it can be marketed immediately.

(Source: www.fda.gov/oc/ohrt/irbs/devices.html)

PHOTO COURTESY OF ISS, INC.