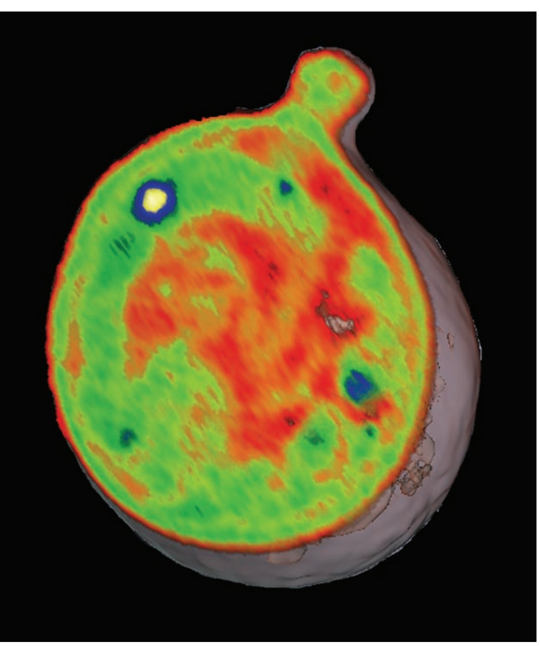
X-Ray Microscope Scans Cellular Machinery

At the National Center for X-ray Tomography, scientists have built a transmission X-ray microscope that can produce meticulous 3-D images of cells. Just as CT (computed tomography) scans provide a detailed view within the human body, X-ray tomography can generate high-resolution images of the internal structures of cells.

The X-ray microscope, located at the Lawrence Berkeley National Laboratory in California, uses X-rays created by a synchrotron—a circular particle accelerator that produces X-ray beams many orders of magnitude brighter than those from laboratory X-ray generators. The high intensity allows researchers to collect a complete data set for the 3-D image of a 10-micron-thick cell in a matter of minutes, compared to days or weeks for electron microscopes. This quick turnaround will allow scientists to accumulate a statistically significant volume of data within a relatively short time. Also, the high penetrating power of these bright X-rays, coupled with a near absence of refraction, makes them an ideal probe for determining the locations of labeled proteins in cells.

"A protein can have different functions depending on where it's spatially located inside a cell," says cell biologist Carolyn Larabell, the principal investigator for the new center. "Knowing where a protein is located throughout the cell cycle can be very important in determining its role." The new microscope offers the possibility of generating "tomographic atlases" that chart with high precision the locations of individual proteins at every state in the cell cycle, thus providing unique insights into the architecture and workings of cells.



This 3-D image, showing a yeast cell during cell division, was created using a high-powered X-ray microscope. X-ray microscopes produce high-fidelity images quickly and can help scientists study protein locations within a cell.

X-ray tomography helps to bridge the "gap" between light and electron microscopy. Traditional microscopy uses visible light and is preferred by many biologists, because it enables them to examine living cells in their natural state. Resolution, however, is limited to a wavelength of 200 nanometers, slightly shorter than the wavelength of visible light. Electron microscopy provides better resolution but requires dehydration of cells and elaborate preparation and staining—a technique that potentially alters the structure of cells. X-ray tomography is an emerging technology that combines some of the best features of light and electron microscopy by allowing whole-cell visualization at a sharper resolution of nearly 35 nanometers, without the elaborate specimen preparations. Future improvements may eventually sharpen the resolution even further to nearly 15 nanometers.

The National Center for X-ray Tomography was officially dedicated on October 11, 2006, and will undergo further testing in January 2007 before opening to the biomedical community. The center was developed with support from NCRR and the U.S. Department of Energy (DOE). Larabell received initial funding from the Office of Biological & Environmental Research at DOE and the National Institute of General Medical Sciences to develop the X-ray microscope technology.

The National Center for X-ray Tomography is one of 52 NCRR-funded Biomedical Technology Resource Centers around the nation. These centers provide scientists with access to a broad spectrum of technologies, techniques, and methodologies, including computational tools, optical and spectroscopic technologies, and advanced microscopy.

"The National Center for X-ray Tomography is the only resource of its kind in the United States," says Gerry McDermott, a research biophysicist at the center. "We believe it will offer a completely new way to explore cellular structure and function."

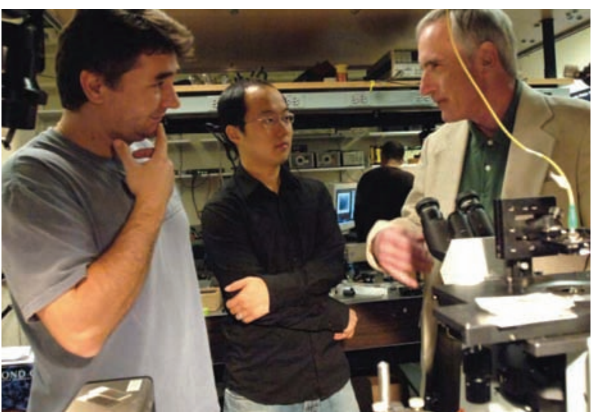
—AL STAROPOLI

TO GAIN ACCESS: The National Center for X-ray Tomography performs research in biological and biomedical imaging and cell biology. It houses the first soft X-ray microscope in the world designed specifically for biological and biomedical applications. The center is a joint program between the University of California, San Francisco, and Lawrence Berkeley National Laboratory. The National Center for X-ray Tomography is expected to become available to qualified biomedical researchers throughout the nation in Spring 2007. Researchers can gain access to the microscope and other resources by submitting a proposal to the center. To learn more or to submit a proposal, visit http://ncxt.lbl.gov.

IMAGE BY CAROLYN LARABELL AND MARK LE GROS, LAWRENCE BERKELEY NATIONAL LABORATORY AND UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Unique Partnerships Move Spectroscopy From Lab to Clinic

New laser-based instruments and techniques for visualizing biological tissues often show great promise in laboratory settings, but transferring these advances to the clinic can be an arduous process. Michael S. Feld, director of the Massachusetts Institute of Technology's George R. Harrison Spectroscopy Laboratory, has found the key to making the transfer possible: engaging physicians in a two-way street of education and collaboration. "A lot of clinicians are enthusiastic at first, but then a weeding out process occurs and only those who understand the research process remain," explains Feld. "The most successful collaborations have been with clinicians who are willing to roll up their sleeves and work with the staff scientists to determine jointly how to improve an instrument."



Michael Feld (right) at the MIT Laser Biomedical Research Center routinely collaborates with physicians to develop new imaging instruments.

Through the NCRR-funded Laser Biomedical Research Center (LBRC), which Feld founded in 1985 to exploit forefront applications of lasers, light, and spectroscopy to biology and medicine, he has enlisted a wide range of physicians—in specialties from pathology to cardiology and gastroenterology—to learn about the technical challenges they face in detecting the early stages of disease. At the same time, clinicians often seek out Feld's expertise to consider whether LBRC research may solve a clinical problem. "He selects collaborators who are scientists at heart, as well as physicians," says Maryann Fitzmaurice, associate professor of pathology, Case Western Reserve University, who is working with LBRC to develop a system to diagnose breast cancer.

The payoff is new instruments that improve patient care. One recent example is a diagnostic tool based on trimodal spectroscopy, a technique that combines three different methods to gather information, based on how light interacts with living matter. By coupling the technique with a tiny probe that shines laser light into patients' tissues through an endoscope, the new tool enables physicians to detect dysplasia, or precancerous cell changes, in the esophagus, mouth, colon, and cervix.

With input from the LBRC advisory committee, Feld and his LBRC colleagues choose which projects to pursue, based on whether a project's needs are compatible with the center's resources and how well a project fits the center's long-term goals. In some cases, ideas are so compelling that they lead to new goals. For example, although initial research at the center focused on coronary artery disease, it expanded its interests in 1989 when both staff and collaborators wanted to develop systems for detecting cancer. "Cancer detection, particularly the diagnosis of precancerous changes invisible to the eye, was seen to be a challenging scientific problem with important potential clinical applications," says Feld.

Once the LBRC team decides to take on a project, the collaborators begin an intense mutual education into both the fundamental science underpinning the project and the medical needs it will solve. Clinicians have input into every aspect of the project, including how instruments should be designed and used, the number and types of tissues or patients to study, how data are analyzed, and where and how clinical studies are performed. And when an instrument or technique is ready for clinical evaluation, which can take anywhere from several months to several years, Feld and his team piggyback on patient studies run by the clinician. "We're able to bring our instruments into a cath lab or endoscopy suite and integrate ourselves into the setting without getting in the way," he says.

Techniques conceived at LBRC have also enjoyed commercial success. An autofluorescence technique Feld's group developed to image and diagnose colon polyps became the basis for a high-resolution videoendoscope that detects subtle changes in lung tissue associated with the onset of lung cancer. Pentax Corporation, a major manufacturer of flexible endoscopes, began selling the instrument in Europe in 2006. Other potential products, including novel imaging systems and new types of microscopes, are in the pipeline. "Commercialization of our instruments and techniques is essential to getting them into widespread use, a step which is very important to us for improving patient care," explains Feld. **—SUSAN M. REISS**

TO GAIN ACCESS: Outside projects can be initiated by contacting Ramachandra Dasari, Associate Director of the Spectroscopy Laboratory. Once the scope of the project is defined, a Research Project Application must be filled out. There is no charge for using the facilities or equipment.

PHOTO BY DONNA COVENEY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY