SHEDDING LIGHT ON LIFE

Extract a lot of information, but use a gentle touch. That's biophotonics: studying the interaction of light with biological materials and systems.

Because light can be used to analyze living tissues in a minimally invasive manner, advances in the field of biophotonics will be key to new clinical tools and biomedical instruments.

This is the challenge facing a band of scientists, engineers, biomedical researchers, clinicians, and instrument developers at the Center for Biophotonics Science and Technology (CBST), headquartered at the University of California, Davis (UCD) under the leadership of center director Dennis Matthews.

It's a job that is facilitated by state-of-the-art facilities, equipment and instrumentation for CBST within a dedicated building adjacent to the UCD Medical Center in Sacramento, Calif. The $20-million, 40,000-sq-ft Oak Park Research Building also houses laboratories for the study of aging, infectious disease, and cancer research.

CBST is "pushing the envelope" of imaging science and filling gaps in existing technology. Tools such as X-rays, computerized tomography (CT scans), and light microscopy are able to image life down to the level of tissues and cells. On the other hand, recent advances in studying the human genome have revealed much about the structure of biological systems at the atomic and molecular scale. But in between these two scales, a critical gap exists in the ability to image at the level of groups of biomolecules and structures within the cell.

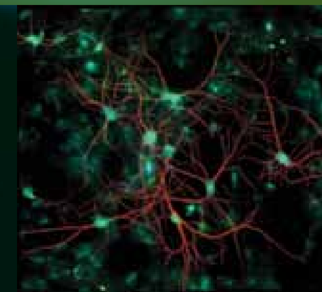
That's why CBST is supporting several research projects aimed at new bioimaging tools. These projects include work to develop X-ray lasers to enable diffraction imaging of single biomolecules, new gene based optical labels for fluorescence imaging, and unprecedented levels of resolution with light microscopy.

"We have come up with the capability to use optical illumination to image something that's ten times smaller than the wavelength of the light we're using," explains Matthews. "We can basically look at objects 50 nanometers in size and resolve them using 500-nanometer light." Related research was commercialized with the help of Applied Precision, Inc. and a research instrumentation grant from the NSF, with second-generation Optical Microscope eXperimental (OMX) instruments already under development.

CBST is developing a host of new gadgets not only to study single cells in the lab but also to characterize tissues in living organisms. For example, professor Laura Marcu's group has developed tissue diagnostic systems for in vivo detection of disease and has worked with physicians to test them in animals and in patients. A portable, endoscopic microscopy system based on fluorescence lifetime imaging makes it possible to non-invasively characterize tissues and diagnose diseases during an operation. The group developed an instrument for diagnosing head and neck tumors based on changes they can detect in the biochemical composition of tissues between pre-cancerous and cancerous states using a kind of laser spectroscopy called time-resolved laser induced fluorescence. Professor Marcu and collaborators also developed a multimodal tissue diagnostic system that combines several methods of imaging using light and sound waves to perform structural and chemical analysis of tissue.

Over the last few years, CBST scientists have developed laser trap Raman spectroscopy, a non-destructive, accurate, and label-free technique that records the molecular fingerprint of cells. Center researchers have combined micro-Raman spectroscopy with optical trapping to sort and study cells





CBST education director Marco Molinaro, second from right, with students.

while leaving them intact, without fluorescent tagging. “We can study cells in their native state, getting a molecular fingerprint,” says Matthews. “This capability is going to be important for treating cancer, and we’re focusing initially on pediatric leukemia patients.”

CBST scientist James Chan and his collaborators are currently developing a way to use laser beams much like ultra tiny tweezers to hold individual cells in place or maneuver them precisely in order to make Raman spectroscopic measurements on them. Laser tweezer Raman spectroscopy has been applied to research in cancer, stem cells, infectious disease, and cardiovascular applications. Most recently, the technology was used to distinguish cells from the lining of the aorta from those of veins. That capability will be critical in order to sort and purify engineered stem cells for medical therapy. □

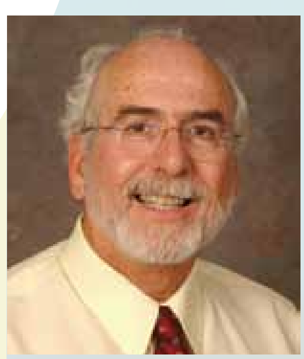
A CONVERSATION WITH THE DIRECTOR
Dennis Matthews

“Team science is the only kind of science I’ve been involved with for a very long time,” says center director Dennis Matthews. “In graduate school, I worked in a nuclear physics laboratory, and in order to get anything done, you soon found out you had to go charm a bunch of people to work with you.

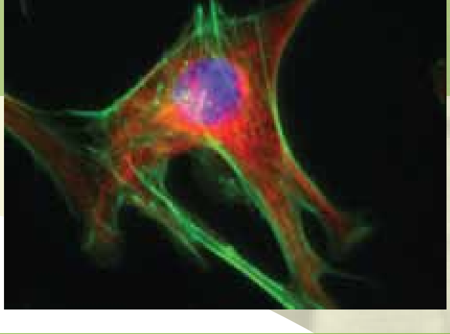
“Then, working at Lawrence Livermore National Laboratory, every project there was a team science and engineering project—it’s too complicated to pull off in the single investigator model. You’ve got to get a team of experts to work with you to accomplish the objectives.

“The academic way of life in the past has used the merit system as a way of providing rewards. The merit system is based on individual performance—being PIs on a grant, being the first author on a paper, and so forth. That system is evolving to reward people for working in a team science approach. This is not new. All major agencies, including the National Institutes of Health and the National Science Foundation, recognize that the academic environment should reward team effort.

The academic department is the fundamental unit of governance for professors. Getting departments to change their procedures is hard, but I think it’s going to come, as people see more and more reward for it. Universities are changing some of the ways they are organized—for example, an office of research having its own faculty lines to allocate for interdisciplinary work.”



Dennis Matthews, director of the Center for Biophotonics Science and Technology



RESOLVING CELLULAR STRUCTURES ON THE NANOSCALE WITH LIGHT MICROSCOPY

Biological structures previously too small to be resolved using optical microscopy can now be revealed using structured illumination and other super-resolution techniques. Scientists at the University of California, San Francisco invented a new technique, called Structural Illumination Microscopy (SIM), with funding from CBST and other sources.

Previously, CBST chief scientist Thomas Huser, a UC Davis professor of internal medicine, led an NSF Major Research Instrumentation award to develop the first commercial Optical Microscope eXperimental (OMX) system, in collaboration with Applied Precision, Inc. (API) of Issaquah, Wash. Recently, API was acquired by GE Healthcare.

A second-generation system has already been co-developed by CBST and API scientists, culminating with CBST implementing the first such system in the U.S. at the time of this writing in mid-2011.

"The center and API have amazing synergy," says Joe Victor, CEO of Applied Precision. "Both organizations are very engineering oriented. That doesn't mean they aren't science oriented as well—but what you find often in a lot of academic organizations is a heavy weight on the science side and not too heavy on the engineering side. What you see at this center is really a core competency in both. We see a potential for multiple collaborations." he adds.

OMX fills an existing gap in microscopy. It covers the intermediate length scales between standard fluorescence microscopes and electron microscopy. Since the first commercial OMX system was installed at CBST, researchers have been targeting a number of important biological applications in this range.

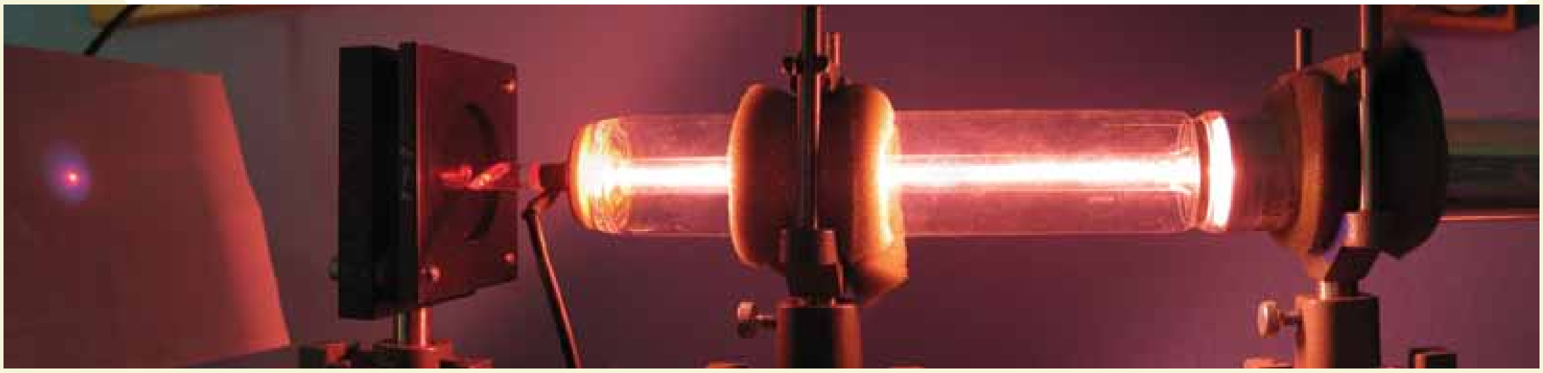
In a highly successful collaboration among physicists, physicians, engineers, and other researchers from Mount Sinai School of Medicine in New York and CBST, scientists produced the first evidence of direct cell-to-cell transfer of HIV. High-speed tracking of the HIV virus revealed several unique modes of motion, suggesting that HIV transport occurs not simply by passive diffusion, but through more active mechanisms of motion, such as virological synapse formation.

Center scientists imaged HIV-1 virus particles inside infected T cells, and applied super-resolution microscopy and spinning disk confocal microscopy to visualize the location at different time points of individual viruses. Research now indicates that HIV virus particles are transmitted from infected to uninfected cells via virological synapses, which are clusters of virus at the point of host cell-to-target cell contact. This research is expected to lead to more effective HIV vaccines.

In another project, CBST scientists are collaborating with physicians to study the mechanisms of HIV1 pathogenesis in the gut mucosa. As the main physical barrier protecting the body from the environment, the gut mucosa is the primary interface where viral infection initially occurs, and it is widely believed to sequester HIV during the latent phase of infection.

Super-resolution microscopy was also used to investigate the role of autophagy, i.e. programmed intracellular recycling, in response to traumatic brain injury (TBI), with the goal to determine whether this process can be monitored as a prognostic indicator for recovery after TBI. CBST researchers teamed up with neuroscientists as well as a small company to collaborate on this project, which can have important implications for more than 1.5 million people affected by TBI annually in the U.S. alone.

Other applications in cancer, liver disease, and regenerative medicine also have been explored. In addition to its use in research, the OMX system is being used in the training of students as part of CBST courses in advanced microscopy.



Helium Neon laser. *Photo: Marco Molinaro*

NEWS WATCH

ECOSYSTEM FOR BIOPHOTONICS INNOVATION

CBST has received a $1 million, two-year grant from the NSF to develop an "Ecosystem for Biophotonics Innovation" program and to accelerate commercialization of biomedical technologies developed by Center researchers. The grant is matched at least one to one by third-party investments from CBST partners.

The ecosystem will be nurtured by an educational and business alliance between CBST, the Sacramento Area Regional Technology Alliance (SARTA) and its MedStart initiative, third-party investors, a pediatric cancer foundation, and a national laboratory. The goal is to foster the commercialization of innovative bioinstrumentation and medical technology while educating students and postdoctoral researchers in entrepreneurship, product design, and development. Among the technologies proposed for commercialization are an ultra-short pulse laser scalpel; a home blood-testing device; a 3-D wide-field super-resolution optical microscope that improves upon existing OMX technology; and single-cell Raman spectroscopy systems.

"We are very excited to develop the Ecosystem for Biophotonics Innovation (EBI) program as a unique alliance of committed partners," says CBST Director Dennis Matthews, principal investigator of the grant. "This program will enable faster translation of research-based technologies into start-ups or existing firms, leading to new jobs and economic growth, while also providing hands-on training and learning opportunities in entrepreneurship."

UNIVERSITY OF CALIFORNIA BIOPHOTONICS ALLIANCE

CBST has worked with university and government partners to establish the University of California Biophotonics Alliance (UCBA). The goal of the alliance is to capitalize on the significant research in biophotonics that occurs on all the UC and California-based national laboratory campuses, in order to accelerate biophotonics discovery and innovation, for the benefit of bioscientists, physicians and patients.

UCBA will organize a UC Biophotonics Industry Forum in January 2012 to connect biophotonics faculty, students, and other researchers with colleagues from California companies, leading to collaborative research, knowledge transfer via licensing, scientist exchanges, and student internships and jobs.

CBST Spring Science Workshop 2011

Pictured in background: Cells in Raman trap

TEAM SCIENCE 101

The bell rings as the last few students filter into the seminar room and take their seats. One of the instructors begins to speak.

"As a research physician in a top-ranked medical research institution, you are aware of the need for improved technology to measure narrowing of carotid arteries. At a seminar, you discover that a brilliant faculty member in the physics department may have such a technology—a supersensitive wide-bandwidth microphone—but he hasn't filed a patent for his concept nor has he any known interest in applied research or medicine or anything but single-investigator, discovery-based research.

"You are given the challenge of putting together a multidisciplinary team to translate this technology into medical practice, and bring it to Phase II clinical trials in only two years. How should you proceed?"

The scenario is used in a course actually taught by CBST director Dennis Matthews, Marco Molinaro, and Frank Chuang at the University of California, Davis, in conjunction with the NIH-funded Mentored Clinical Research Training Program.

Not the typical chalkboard talk you might associate with graduate or medical school, the course tackles real-world problems that transcend traditional academic departments. It's one of the ways that the center is transforming the graduate educational experience.

"Students can be woefully underprepared for the team working environment, especially if they go into industry, where it is very team-oriented," says Matthews. "With our students, what our center tries to do is to instill in them the value of working together with other disciplines."

BIOPHOTONICS