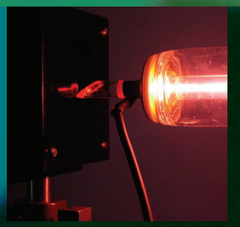
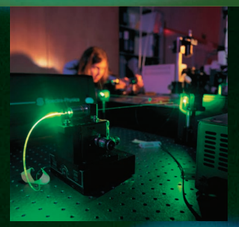




SHEDDING LIGHT ON LIFE

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 now made a little easier by a state-of-the-art facility for CBST within a new building adjacent to the UCD Medical Center in Sacramento, Calif. Dedicated in 2006, 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 is expected to be commercialized with the help of an industrial partner and a research instrumentation grant from the NSF.

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. One research area focuses on interactions of DNA and proteins—an effort that may shed light on cancer, aging, and how genetic damage is recognized and repaired.

Another direction is understanding atherosclerosis, the artery-clogging disease. Despite the fact that atherosclerosis is the main cause of death in the U.S., the exact molecular mechanisms by which dietary fat and cholesterol lead to injury of arterial walls and ultimately to the formation of atherosclerotic plaques has been poorly understood. But how to reduce an inherently complex and dynamic system into manageable parts for study? Some of the key components include the membrane of the cells that line artery walls, conglomerates of fat and protein called lipoproteins, and components of the immune system.

One approach is the lipid microarray developed by Atul Parikh of the UCD Department of Applied Science and colleagues. These "membranes on a chip" allow researchers to observe and analyze in a well-controlled manner the molecular events that normally occur on a cell membrane.

"I am a bio-physical-chemist-materials-science type of a person," laughs Parikh, "and before the center, had no direct connection with clinical scientists. There was never a clear-cut reason why they would be interested in talking to us," he says. "The center enabled a lot of us to work together, so we ended up interacting with someone who was a practicing M.D. whose main research interest was to identify biomarkers for early events in atherosclerosis."

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

Center support gave Parikh and colleagues the time and "breathing space" they needed to do the high-risk fundamental work that contributed, in part, to getting a 4-year, $1.65-million NIH grant on how lipoproteins interact with endothelial cells that line the artery walls. Outcomes of these efforts are contributing to the notion currently gathering momentum that lipids are not mere passive players but rather play an active role in regulating protein function in biological processes.

Parikh is cofounder of a CBST spin-off company called Cherrimetrix, Alexandria, Va., an early-stage venture focused on the development of sensors, lipid microarrays, and other tools for biological research. This is just one of many startups and affiliated companies that have benefited from center expertise. □

A CONVERSATION WITH THE DIRECTOR

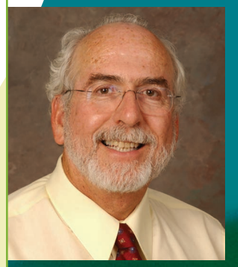
Dennis Matthews

"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 reward. 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. The National Institutes of Health had a meeting on this subject a few years ago, and this was one of the primary conclusions: 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

NSF INSTRUMENTATION GRANT FOR ADVANCED IMAGING PROJECT

In August 2006, CBST received a $600,000, two-year NSF Major Research Instrumentation award to develop an ultra-high resolution light microscope in collaboration with a company called Applied Precision (AP), Issaquah, Wash.

The project, led by Thomas Huser, chief scientist at CBST and a UCD professor of internal medicine, aims to develop and commercialize a high-resolution, structured-illumination fluorescence microscope system.

The effort builds upon a design developed with center funding at the University of California, San Francisco (UCSF) called OMX (Optical Microscope eXperimental). The prototype OMX system at UCSF has demonstrated a typical resolution of 100 nm, the highest resolution of any wide-field light microscope—nearly a factor of three better than existing instruments.

A commercial prototype of the new system is expected at CBST's facility at the Oak Park Research Building in late 2007. The final product would hit the market in the 2009 time frame, notes Joe Victor, senor vice president of life sciences at Applied Precision.

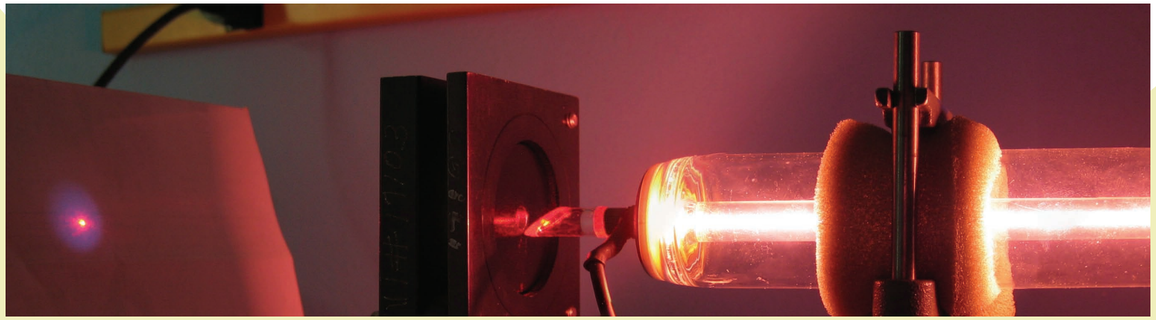
OMX fills an existing gap in microscopy. It covers the intermediate length scales between standard fluorescence microscopes and electron microscopy. Researchers expect to target important biological applications in this range, such as resolving subcellular structures, studying the organization of chromosomes, assembling large protein complexes, studying viral structure, and exploring processes affecting cellular organelles. In addition to its use in research, the OMX system will be used in the training of students as part of CBST courses in advanced microscopy.

"We hope to tackle samples that could not be analyzed with existing optical microscopes—for example, the entry and exit of viruses from cells. Current images of viruses are based on electron microscopy, "but it's static," says Huser. "Ideally, we want to study this dynamically and follow the replication of the viral particle. The new system allows us to make sequences of images over time to see a sort of movie." This kind of live cell imaging is done at multiple wavelengths and is a capability that distinguishes the new system.

In addition to Huser, the principal investigator of the grant; the inventors at UCSF; and researchers at UCD and Lawrence Livermore National Laboratory, the project involves the help of a graduate student and a postdoctoral research associate. The main engineering work will be done at AP.

"The center and AP have amazing synergy," says Victor. "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 beyond this one," he adds.

AP has been in operation for about 20 years and has grown to 180 employees. With business areas in life sciences imaging instrumentation and in semiconductor metrology, a large part of AP's customer base is academic labs. "We value our relationships with universities," says Victor. "They help us to stay current with the latest technologies and to track where the boundaries are. And they provide a great opportunity to move technology into practice."



Helium Neon laser. *Photo: Marco Molinaro*

NEWS WATCH

LASER TRAP RAMAN SPECTROSCOPY TAKES THE MOLECULAR "FINGERPRINT" OF CELLS

Current methods used to study individual cells and to differentiate normal from abnormal ones are often time consuming, nonspecific, and destructive. CBST is developing a rapid technique that can accurately and non-destructively identify and sort cells for the diagnosis and potential treatment of cancer.

Center researchers have combined micro-Raman spectroscopy with optical trapping to sort and study cells while leaving them intact. This is all done 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."

A BETTER WAY TO "SEE" THE STRUCTURE OF SINGLE BIOMOLECULES

Much of scientists' knowledge about the structure of biomolecules has come from X-ray crystallography, that is, X-ray studies of molecules in the crystalline state. But because it's so hard to produce high-quality crystals, only a small fraction of the biologically important molecules have yet been determined. And some biomolecules can't be crystallized at all.

CBST researchers are developing an X-ray diffraction method to determine the configuration of single biomolecules without needing to crystallize them. In this approach, a stream of individual biomolecules passes through an X-ray beam from a laser or synchrotron source. X-rays diffracted from each molecule are collected, and although a few molecules alone wouldn't be enough, a "running total" from many molecules yields a diffraction pattern with a high enough signal-to-noise ratio to allow the structure to be analyzed.

Matthews notes that tests are currently being conducted at facilities around the world, but in the future, they plan to use the coherent light source at Stanford University when it is completed. The work may lead to a new high-resolution method for obtaining structure information for proteins, protein complexes, and viruses.

Pictured in background:
Cells in Raman trap

Center director Dennis Matthews with a group of high school students from Center High.

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."