With new imaging technology, scientists and clinicians can visualize biological systems

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A picture may be worth a thousand words. But new imaging technology that harmonizes mighty and distinctive microscopes may tell a complex story about a disease or condition – how it develops and how it can be treated precisely.

In UCSF's Bioengineering and Biomaterials High Resolution Correlative Imaging Facility, researchers examine a variety of biological specimens from bone, kidney, cartilage, blood vessels, teeth and other body tissues.

"The facility integrates traditional high resolution light with electron and X-ray microscopy techniques to visualize biological systems from atoms to tissues to organs – linking structure to function," said Sunita Ho, MS, PhD, director of the facility and professor of preventive and restorative dental sciences. "It is the aperture through which pathologic processes can be discovered."

While an electron microscope can magnify up to 2 million times to analyze a specimen's structure, a light microscope is better for viewing live cells, their movement and functions. The facility—located on the eighth floor of the Health Sciences West Building on the Parnassus campus – combines the best of the three microscopy techniques into a single instrument to produce exquisite images and detail for clinicians and scientists.

"It's greater than the sum of its parts," she said. "By integrating the microscopes we obtain significantly greater information than the complementary information that we would get from individual pieces."

Ho likens the imaging concept to Google Earth technology, which can offer a mile-high view of an entire city, zoom on one neighborhood and home in on a single building. But on an even tinier scale, correlative imaging may be more powerful and precise. It can get into the building – its biological target – and see what's happening inside the walls and basement.

The new technology that combines the best of X-ray, electron and light microscopy modalities also is more convenient and practical. Imaging in most laboratories requires moving a specimen from one microscope to another, which can be labor intensive and risky. One correlative workflow avoids that labor and risk. Also, with correlative imaging, scientists don't have to cut specimens to get a detailed inside look at their targets/regions of interest.

"The ability to image the same specimens at a macro and a nano scale is very exciting and provides a whole new dimension to research at UCSF," said John D.B. Featherstone, dean of the School of Dentistry. "I am so pleased to see this campuswide facility come into operation, and am very excited that the School of Dentistry laboratories were able to house the facility and to provide substantial support for it."

At the correlative imaging facility, operated by the School of Dentistry, researchers analyze tiny tooth fragments to understand damage from bacteria, grinding teeth and how ligament mineralization affects gum and bone near the teeth.

But the imaging technology has application and value far beyond oral health. One of Ho's collaborators is Marshall Stoller, UCSF professor of urology and nationally recognized leader in treating kidney disease. Their NIH-supported biomineralization studies are shedding light on how urinary stones form. They hope the research will guide novel treatments for a disease that is on the rise worldwide.

The underpinnings of how biominerals and plaque form in human tissue have not been well-studied, said Ho. But the advanced imaging at the facility is producing new pictures of their structure and role in penile calcification (Tom Lue, Department of Urology), knee osteoarthritis (Daniel Bikle, Departments of Medicine and Dermatology), artery disease (Michael Conte, Department of Surgery) and a variety of other diseases related to ectopic mineral formations within organs/tissues.

"The state-of-the-art imaging is needed to confirm processes that lead to the pathophysiology of many and varied diseases," said Ho. "It provides the framework to address unmet clinical challenges for individual patients and can be the backbone to develop newer personalized medicine algorithms.

"The technology supports our UCSF mission of advancing health care—from diagnostics to therapeutics," she said.

The novel technology also aids UCSF's research mission by creating new collaborations among scientists of many departments and disciplines.

"UCSF is a world-class institution that traditionally has been divided into silos – the School of Dentistry is unique, yet separate from the School of Medicine for example," said Ho. "There is a need to bring varied disciplines and professions together to work as inter- and trans-disciplinary working groups. Cross fertilization among varied fields will further push understanding of disease processes and lead to novel therapeutic interventions."

That sentiment is supported by the substantial investments made in the correlative imaging facility by the Dean's Office of the School of

Dentistry and by the Office of the UCSF Executive Vice Chancellor and Provost's office.

"The correlative imaging system allows us to register images based on tissue biochemical properties, tissue ultrastructure and tissue microarchitecture into the same coordinate system," said Thomas Lang, associate dean for research for School of Dentistry. "It gives us a new lens with which to study biology and by its nature supports UCSF's goal of promoting collaboration between scientists with differing interests and expertise, across UCSF and the UC system."

The facility already hosts users from UCSF's Schools of Medicine and Pharmacy, as well as Dentistry. So, there is some chipping of the silos noted by Ho.

"Cutting edge tools are an essential element for breakthroughs in science, and I could not be more pleased about the multidisciplinary, collaborate effort that has gone into creating this core facility," said Dan Lowenstein, M.D., executive vice chancellor and provost.

Eventually, correlative imaging technology at UCSF could be offered to other Bay Area institutions and colleges, said Ho. "High school, medical and other professional students and post-docs will have the ability to visualize pathology at multiple scales," she said.

"I congratulate Sunita for leading the initiative over several years to bring correlative imaging to UCSF and the Bay Area," Dean Featherstone added.

Making the technology widely available "could help integrate UCSF with our surrounding community," said Ho. "An electron image has much less relevance to the lay community; however, with correlative microscopy, high resolution images can be put into context to better understand disease processes that the UCSF community is trying to investigate."

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