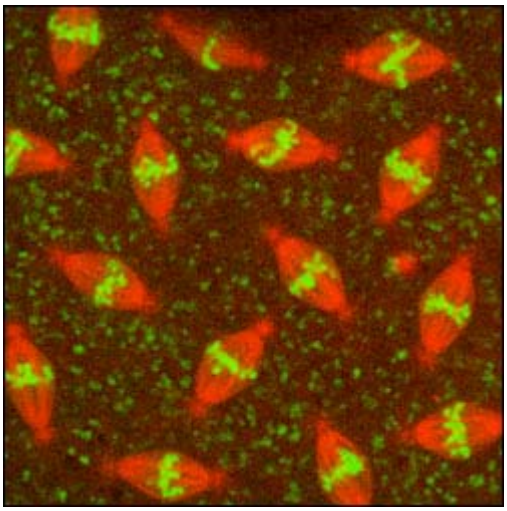
‘Guide Stars’ Improve Adaptive Optics-Based Tissue Imaging

SANTA CRUZ, Calif., Aug. 3, 2011 — Inspired by adaptive optics (AO) technology for telescopes, researchers are developing novel microscope techniques that can deeply image living cells and tissues.

Funded by a $1 million grant from the W.M. Keck Foundation, the new W.M. Keck Center for Adaptive Optical Microscopy at the University of California, Santa Cruz, builds on efforts begun in 2006 by a multidisciplinary group of biologists, astronomers and optical engineers.

Principal investigator Joel Kubby has worked on AO systems for large telescopes as well as for biological imaging. In astronomy, AO systems correct the blurring in telescope images caused by turbulence in the Earth's atmosphere. In microscopy, blurring is caused by the flowing cytoplasm of living cells.



Chromosomes labeled with green fluorescent protein are about to separate in this frame from a movie of dividing cells at the surface of a fly embryo. With adaptive optics for deep-tissue imaging, biologist William Sullivan hopes to extend his observations to cells below the surface of the embryo. (Images: W. Sullivan)

"We can get beautiful images of cells close to the surface of the tissue, but if you want to go deep, you're out of luck because of the degradation of the image. That was the motivation for this project," said co-investigator William Sullivan. "For cell biologists, anything that improves imaging is a big deal, and this has the potential to open up vast areas of cell biology that have been opaque to us."

In stem cell research, for example, an important bottleneck in efforts to develop therapies has been the inability to follow injected cells and monitor their fates below the surface of the tissue. AO microscopy could solve this problem, and the California Institute for Regenerative Medicine has provided support for the work at the Santa Clara campus, including funding that led to the development of the team's first AO microscope.

Co-investigator Yi Zuo plans to use AO microscopy to extend her research on synaptic reorganization in the brain during development and learning. "So far, most of our understanding of synaptic remodeling in living brains has been limited to the superficial cortical layers," she said. "AO

microscopy will allow us to explore the structural and functional plasticity of synapses in the deeper cortex."

Graduate student Oscar Azucena (left) and undergraduate Ziah Dean helped develop the adaptive optics system for a wide-field microscope at the University of California, Santa Clara. (Photo: J. Kubby)

AO systems for telescopes use a point-source of light — either a bright star or a laser-based artificial guide star — as a reference beacon for measuring atmospheric blurring. The system calculates the corrections needed to counteract the distortion of the image, applies the correction by bouncing the incoming light off a deformable mirror, and repeats the whole process hundreds or thousands of times per second.

The UC Santa Cruz project is the first effort to apply this approach to microscopy. "Other groups have tried to do AO microscopy using image optimization and other techniques. Our unique angle has been to develop a biological guide star as a reference beacon for the AO system so that we can measure the wavefront aberration the way they do so successfully in astronomy," Kubby said.

To develop the AO microscopy system, the researchers used fluorescent dextran beads injected into fly embryos to serve as guide stars. For a more versatile system, however, the team is developing genetically engineered fluorescent proteins as biological guide stars. The ideal protein would be compact — providing a point source of light — and would be located on or near the structure of interest. For images of chromosomes in fly embryos, for example, Sullivan is tagging proteins within the centromere to serve as a guide star, while the arms of the chromosomes are tagged with a different color.

"When you label the centromere, it's like a big bright dot in the middle of each chromosome," he said. "We'd also like to find a guide star that works well for neurons and other tissue types. Eventually, we will want to have a whole kit of guide stars for different tissues."