MICROSCOPY

Imaging Living Cells The Friendly Way

Researchers have found a new way to produce images of living cells' interiors without disturbing their biochemistry. The technique, described in the 17 May issue of *Physical Review Letters*, uses lasers to excite certain chemical bonds within the cells to emit light. Experts say it may be a useful addition to existing imaging techniques.

When biologists want to study microscopic structures within cells, they often flood them with fluorescent dyes that bind to certain molecules only. Next, they shine laser light on the sample, which makes the dyes light up. But this technique has its drawbacks: The dyes sometimes interfere with the cell's biochemistry—some are even toxic—and after a while, their fluorescence wears out. Harvard University physical chemist Sunney Xie and his colleagues, working at the Pacific Northwest National Laboratory in Richland, Washington, wondered if there was a less invasive way of producing similar images.

They used a technique called coherent anti-Stokes Raman scattering (CARS), first used for imaging in the early 1980s by researchers at the Naval Research Laboratory in Washington, D.C. In CARS, two laser beams are sent into a cell, at frequencies that differ by exactly the frequency at which a particular chemical bond in the cell vibrates. The photons from the two different lasers "mix," exciting the bond to vibrate and emit an optical signal of its own, at a frequency different from the lasers. Because the lasers can be focused to intersect in only a small volume of the cell, the technique can create a point-by-point chemical map of the cell—at least in principle.

Early experiments had produced poor-quality images, but team members Gary Holtom of Pacific Northwest and Andreas Zumbusch of the University of Munich used improved lasers to deliver ultrashort near-infrared pulses, tuned to the frequency of hydrogen-carbon bonds. They scanned the two lasers across samples of living cells. Some cell structures, like mitochondria and cell membranes, are rich in hydrogen-carbon bonds and respond to the laser; thus, they stand out in the resulting image. By tuning the two laser beams into other chemical bonds, like nitrogen-hydrogen, the team believes they can image the cellular distribution of molecules such as proteins as well.

Physicist Stefan Hell of the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany, sees CARS as a complement to fluorescence imaging techniques. "The images ... are very appealing," he says. But one drawback, says physicist Watt Webb of Cornell University in Ithaca, New York, is that it can take many minutes to produce an image with CARS. That will make it difficult to image rapid changes within cells, says Webb. **–MEHER ANTIA**

Meher Antia is a writer in Vancouver.

CREDIT: ZUMBUSCH ET AL., PRL

Portrait from life. Mitochondria glow within living cells, imaged by the CARS technique.

TECHNOLOGY TRANSFER

NIH Proposes Rules for Materials Exchange

Over the last 2 decades, scientists have witnessed the gradual erosion of a cornerstone of scientific progress: the free exchange of research materials such as reagents, antibodies, genes, cells, and animals. The principle that such tools should be shared still stands, but the invasion of commerce in biomedical research has meant that lawyers may haggle for months about conditions before a single test tube is shipped. Last week, the National Institutes of Health (NIH) proposed a new code of conduct aimed at curbing this legal wrangling and accelerating scientific discovery. The document, drawn up by NIH's office of technology transfer, has been put on the Web (www.nih.gov/welcome/forum) for comment.

The initiative comes at a time when contracts governing the exchange of research tools, so-called Materials Transfer Agreements (MTAs), are causing increasing frustration (*Science*, 10 October 1997, p. 212). Such contracts often contain far-reaching clauses to maximize profit and prevent proprietary materials from being used by competitors. Scientists often resent the legalese, and university licensing officers, meanwhile, are faced with the "terrible, terrible burden" of doing all the paperwork, says Louis Berneman, director of the technology transfer office at the University of Pennsylvania, Philadelphia. His office alone handles some 400 to 500 MTAs yearly.

NIH's housecleaning is targeted specifically at MTAs that might delay or prevent publication of research, or that seek so-called "reach-through rights"—a property claim on discoveries that arise from the use of shared materials. "Researchers are desperate to have the latest materials and often are willing to sign anything, promise anything," says Berneman. But NIH does not want grantees to give away tax-funded work.

NIH's proposed principles favor traditional academic values. Researchers are expected not to sign anything that unduly limits academic freedom or publication. Withholding of data is "unacceptable," as are reach-through rights. Conversely, NIH-funded research should be widely distributed, preferably on a nonexclusive basis.

The initiative is not the first attempt to clear out this legal thicket. Only 4 years ago, NIH led a group of institutes that drew up a simplified Uniform Biological Materials Transfer Agreement (UBMTA), reminiscent of the deeds that real estate agents use for selling homes. But even though 137 universities and institutes have now signed on to this idea, UBMTA is seldomly used in transactions. This time, NIH hopes to have more of an effect. "We're very serious about enforcing these guidelines," says Maria Freire, director of the agency's office of technology transfer. NIH may consider making them conditions of future grant awards.

> **"Researchers are desperate to have the latest materials and often are willing to sign anything, promise anything."**
>
> **—Louis Berneman**

Some welcome NIH's interference. "This is a very good example of the government exercising some kind of moral authority in balancing contrasting needs," says Terry Feuerborn, director of the University of California's office of technology transfer. But others disagree. Thomas Mays, a patent attorney at the Morrison and Foerster law firm in Washington, D.C., says universities and researchers should be able to decide for themselves whether to go along with restrictive contracts. "NIH appears to be attempting to go back decades, to a point where materials were freely available," he says. Yet Mays predicts that universities and small biotech companies, many of them dependent on NIH money, are unlikely to criticize the plan too harshly. "NIH is the 800-pound gorilla," he says. "No party really wants to go up against it."

–MARTIN ENSERINK