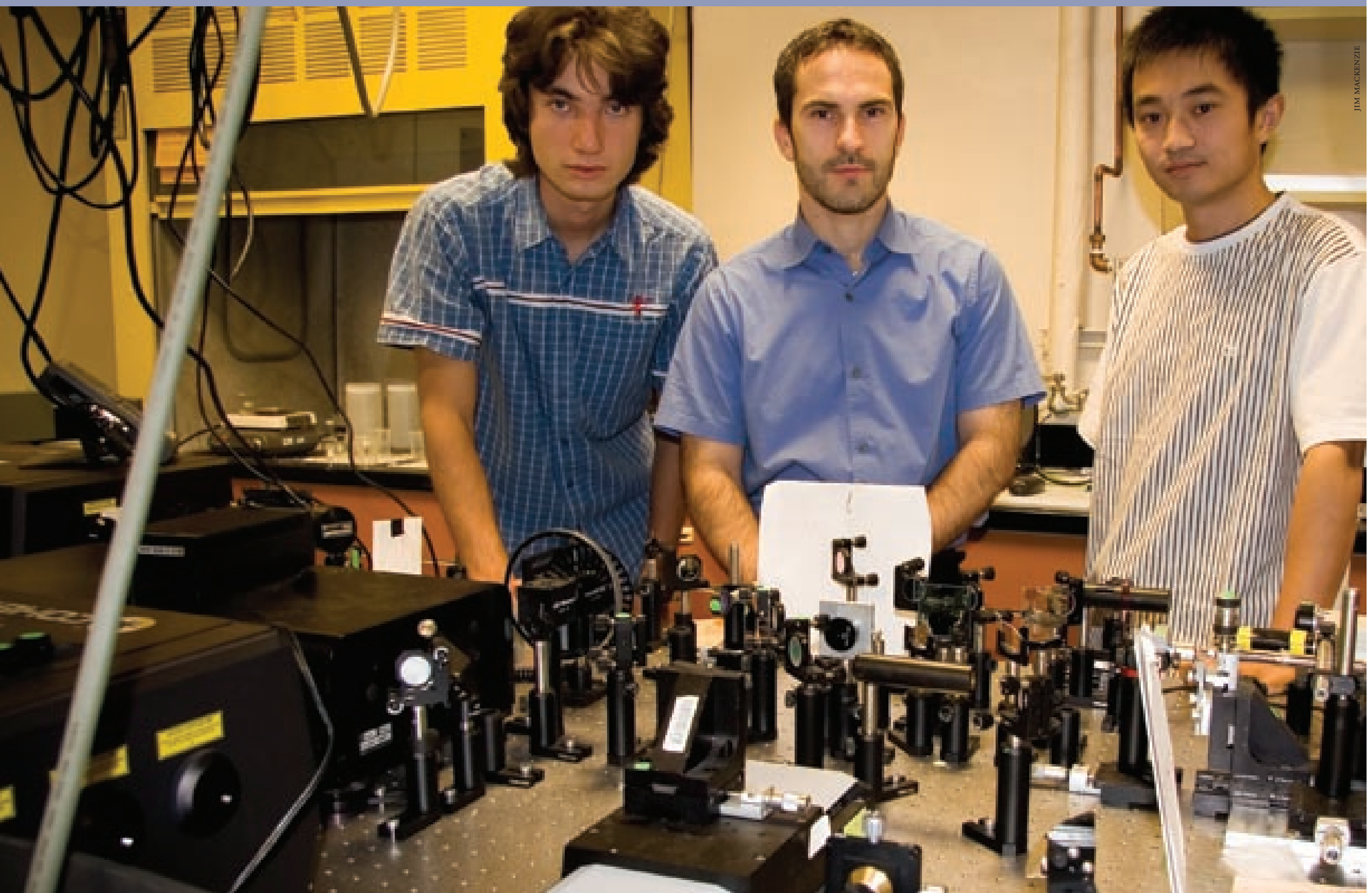
when Nano meets Bio

By Tim Stephens

An interdisciplinary team of UCSC scientists is developing a tiny tool to analyze disease organisms one molecule at a time.



JIM MACKENZIE

The 'Nano' side of the team: Electrical engineer Holger Schmidt and graduate students Mikhail Rudenko (left) and Dongliang Yin (right) in Schmidt's optical lab

In 2004, UCSC engineer Holger Schmidt reported an exciting advance in optical technology. His team had found a way to build onto a silicon chip a mechanism for guiding light through tiny volumes of liquid or gas. Schmidt, an associate professor of electrical engineering, knew that this technology held great potential for a wide range of applications, including highly sensitive chemical and biological sensors.

Since then, Schmidt has teamed up with faculty in other departments at UCSC and won a $1.6 million grant from the National Institutes of Health to develop new sensor technology for biomedical applications.

"We aim to develop a new type of instrument that can do both electrical and optical sensing of single biomolecules, with all the components of the sensor ultimately integrated onto a chip," Schmidt says. Collaborators on the project include David Deamer, professor of chemistry and biochemistry, and Harry Noller, Sinsheimer Professor of Molecular Biology.

The new instrument could prove valuable for basic research in molecular biology and biochemistry, as well as for medical diagnostic testing and other applications. Used to detect viruses, for example, the instrument could allow rapid diagnosis of patients infected with a new strain of the flu virus in the event of a pandemic.

"The idea is that you would be able to take a throat swab from a patient and detect the virus within 10 minutes instead of hours," Deamer says.

Initially, however, the researchers will test the new sensor platform on ribosomes, the complex biomolecular machines that serve as the protein factories in all living cells. Noller, a leading authority on ribosomes, says he hopes the project will help him realize a long-sought goal: to make a movie of the ribosome in action as it translates the genetic code from messenger RNA and makes proteins.

"Studying ribosomes is just one application for this device," Noller says. "It has tremendous potential."

At the heart of the device is Schmidt's invention, a new type of "optical waveguide" that transmits light through a hollow core that can be filled with liquid or gas. The optical fibers that have revolutionized the telephone system, cable TV, and the Internet are solid-core waveguides that transmit signals over long distances. Guiding light waves through liquids and gases is a challenge because they lack crucial properties that make the solid core of an optical fiber effective.

"But if you can guide light through water and air, all of the fields that rely on nonsolid materials can take advantage of integrated optics technology. Liquids and gases are the natural environment for molecules in biology and chemistry," Schmidt says.

A major advantage of his hollow-core waveguides is that they are made using the standard silicon fabrication technology used on an industrial scale to make computer chips. As a result, the waveguides can be integrated into a silicon chip along with electronics, fiberoptic connections, and other components. A compact, affordable device based on the hollow-core waveguide could perform optical analyses that currently require expensive and bulky microscopes set up on a laboratory benchtop.

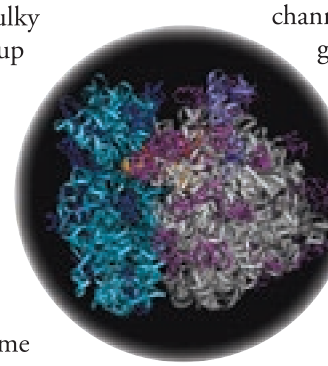
Fabrication of the waveguides is done at a facility at Brigham Young University by Schmidt's longtime collaborator Aaron Hawkins.

The 'Bio' side of the team: Biochemist David Deamer and molecular biologist Harry Noller

Shortly after he had developed the hollow-core waveguide, Schmidt visited Deamer's lab, where researchers have pioneered the development of "nanopore" devices for electrical sensing of single molecules. Soon, Schmidt and Deamer were making plans to combine their two devices.

A nanopore is a tiny hole with dimensions on the order of nanometers (a nanometer is one billionth of a meter). The researchers plan to incorporate a nanopore into the waveguide, using it to feed samples into the core one molecule or particle at a time for optical analysis. Schmidt's group has already demonstrated optical detection of single molecules using hollow-core waveguides on a chip.

"The nanopore will act as a smart gate for entry of individual molecules into the channel of the waveguide," Schmidt says.

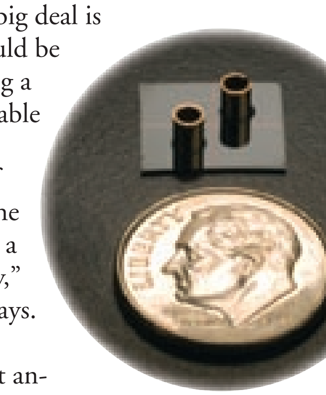


The Target: The sensor will be used to study the dynamics of the ribosome, a complex biomolecular machine that manufactures proteins in living cells.

As molecules pass through the nanopore, they produce an electrical signal that can be captured and analyzed, giving the device the capacity for both electrical and optical characterization of single molecules.

The optical analysis will rely on fluorescence methods that are commonly used in molecular biology and biomedical tests. To detect viruses, for example, fluorescent tags can be attached to antibodies that bind to specific viral proteins.

"What makes our approach a big deal is that it could be done using a little portable machine, instead of sending the sample to a laboratory," Deamer says.



The Technology: A prototype of Schmidt's dime-sized sensor device integrates two fluid reservoirs, microfluidic channels, and intersecting optical waveguides.

Noller points out another noteworthy aspect of the project—it highlights the kind of interdisciplinary interactions that UC Santa Cruz seems especially good at fostering.

"This is the sort of thing that people talk about all the time, but in most universities it never really happens," says Noller. "I think Santa Cruz may be a place that attracts creative people who are interested in working with people in other disciplines. It's an environment that's very inspiring."

PHOTOS: PAUL SCHRAUB (TOP AND RIGHT), COURTESY HARRY NOLLER (BOTTOM)