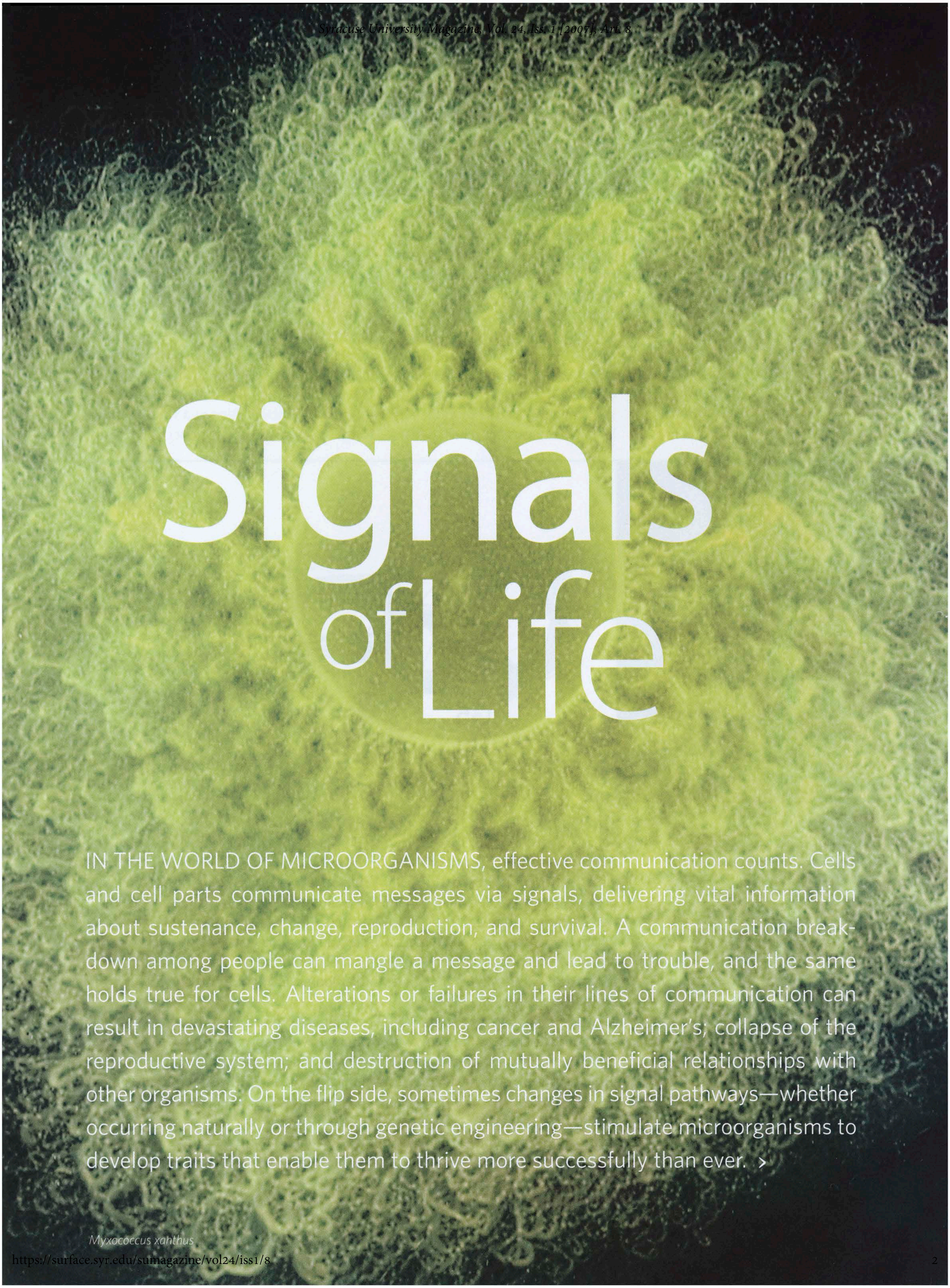
SU RESEARCHERS sharpen their focus on cell signaling, studying how cells communicate, interact, and change amid all sorts of circumstances

By Margaret Costello

Above: Biology professor Roy Welch with postdoctoral researcher Kimberly A. Murphy; photos by Susan Kahn



Signals of Life

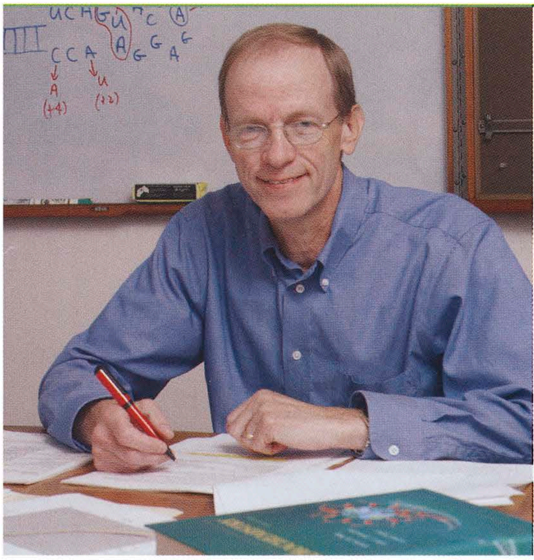
IN THE WORLD OF MICROORGANISMS, effective communication counts. Cells and cell parts communicate messages via signals, delivering vital information about sustenance, change, reproduction, and survival. A communication breakdown among people can mangle a message and lead to trouble, and the same holds true for cells. Alterations or failures in their lines of communication can result in devastating diseases, including cancer and Alzheimer's; collapse of the reproductive system; and destruction of mutually beneficial relationships with other organisms. On the flip side, sometimes changes in signal pathways—whether occurring naturally or through genetic engineering—stimulate microorganisms to develop traits that enable them to thrive more successfully than ever. >

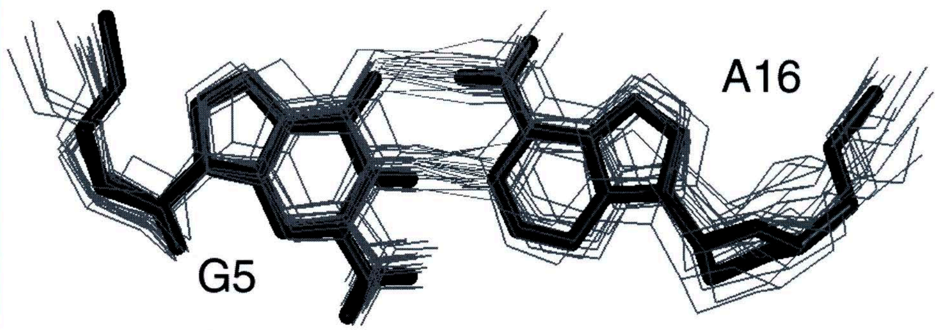
Myxococcus xanthus

Controlling molecular changes requires expertise in cell signaling, a growing area of study that seeks to understand the mechanisms used by cells to communicate. Syracuse University scientists are performing innovative research in this area, advancing scientific knowledge of antibiotics and cancer chemotherapies; of the effects of environmental toxins on fertility; and of how viral infections, including AIDS, spread within an organism. This research also points the way to new solutions for early detection of bioterrorism substances and increased production of food crops resistant to pests and other environmental threats. In the long term, it may help solve some of the mysteries of molecular evolution. "The more we learn about cell signaling, the more patterns we see emerging," says Professor John Russell, biology department chair, who is studying a strain of the herpes virus that causes the human host cell to greatly enlarge, rupture, and spread the virus. "Eventually, a person interested in plant pathogen signaling should be able to understand a person studying viral signaling because the concepts are the same, even though the details may be different. Using cell signaling as an umbrella, we have developed a robust area for cross-collaborative study."

Chatterbox Cells

Cell signaling—whether in bacteria, plants, or eggs—occurs in a basic sequence of actions. The process begins with a cell perceiving a stimulus or signal, which may be natural, such as a hormone, neural signal, light, heat, or sound; or artificial, such as the introduction of a virus or chemical compound by a researcher. The cell then trans-





Professor Philip Borer works with three-dimensional structures of RNA and RNA-protein complexes from HIV and other retroviruses.

Inhibiting the HIV Virus

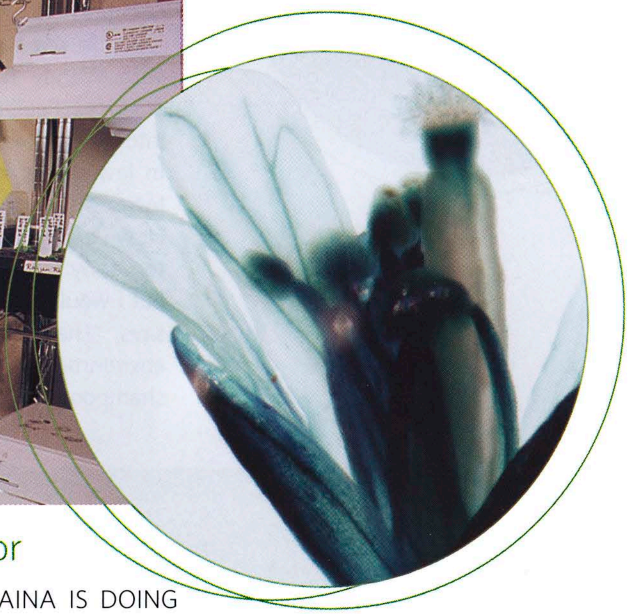
APPROXIMATELY 40 MILLION PEOPLE WORLDWIDE ARE INFECTED WITH HIV, THE virus that eventually leads to AIDS. While many scientists are trying to find a vaccine to prevent the virus's spread, biochemistry professor Philip Borer is making strides in finding new medicines to treat those already infected. After studying the molecular mechanisms by which the virus enters and infects a T-cell (an immune cell) and spreads to another, Borer and his students replicated the relevant molecules in the lab, flagging part of an RNA strand of the virus with a marker that glows under fluorescent light. The glow goes out when a viral protein attaches to the RNA.

He is currently testing some 80,000 compounds to see if any interrupt or inhibit the protein from attaching to the RNA, which would prevent replication of the virus. When he finds a compound that can displace the HIV-protein and make a dark strand glow, he marks it for further testing by chemists at pharmaceutical companies. "We're on the front end, putting new drug candidates into the pipeline that leads to future treatments for people with HIV," Borer says. "Medical doctors currently treat HIV with a 'cocktail' of drugs, but because the virus continually mutates, there are resistant strains of the virus for every one of these drugs. By adding new drugs to the cocktails, doctors can better treat their patients."

Photo courtesy of SU Department of Chemistry lates that signal into an intracellular signal or a cascade of signals by producing proteins capable of carrying out the response. SU researchers examine different stages of this process to identify and isolate the cell parts involved in perception, translation, protein production, and response transmission. Because each stimulus may set off the production of a different series of proteins or other actions, identifying and matching each stimulus-protein relationship is a crucial, if arduous and time-intensive, task.

The chances of successfully identifying these proteins are enhanced by approaches incorporating techniques from biology, chemistry, physics, and engineering. "Applying a physics equation to a cell signaling question complements what a biologist brings to the same issue," physics professor Ed Lipson says. "Many advances in structural biology, including Watson and Crick's discovery of the DNA double helix, have been made through the application of physics techniques, such as X-ray diffraction." In addition to facilitating solutions to specific problems, interdisciplinary work is often personally rewarding for researchers. "Working with people from other disciplines helps me see how my work fits into the broader picture and what others think are the critical challenges facing science today," says chemistry professor Chris Boddy.

The following vignettes are a sampling of research projects at SU that seek to address some critical cell signaling questions.



Arabidopsis, a small flower plant of the mustard family

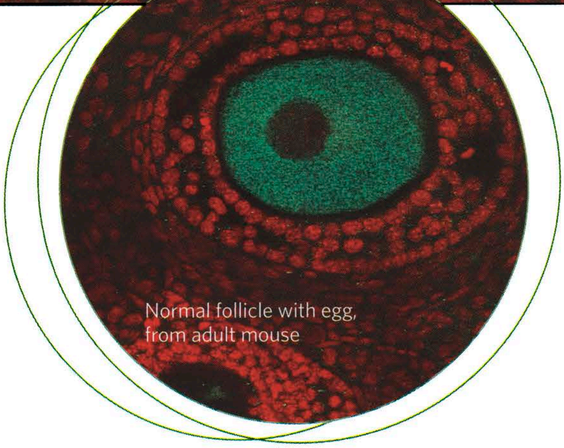
From Mustard Plant to Danger Detector

AS A MOLECULAR BIOLOGIST, PROFESSOR RAMESH RAINA IS DOING research that could make agricultural plants more resistant to pests, disease, and extreme environmental conditions through genetic engineering. "To fix a car, you have to understand how all the parts work and which ones are causing the problem," he says. "The same is true for biological systems. If we can understand how plants respond to extreme cold, for example, then we can develop cold-tolerant plants and save farmers from losing crops to frost." Raina's current research on cell signaling in *Arabidopsis*, a small flower plant of the mustard family, is funded by the National Science Foundation's Arabidopsis 2010 project, which aims to determine the function of every one of the approximately 28,000 genes in this plant. "While the entire genome of the plant has been sequenced, we know very little about what each one of its genes does," he says. "That's a big challenge for us now."

The second major project in Raina's lab, funded by the U.S. Department of Defense, is to understand molecular mechanisms involved in perception and signaling of environmental stimuli in plants. These studies have potential to develop plants that can be used as sentinels capable of detecting chemical or biological weapons. "We're hoping to engineer plants that can induce a predictable response [visible to passersby] upon exposure to certain chemical and biological agents," he says. Such plants could sense dangerous substances in public places, including airports, government buildings, shopping malls, and playgrounds.

Photo of Ramesh Raina by Schmitt Shoots!! Inset photo courtesy of Ramesh Raina

Multiple egg follicle, from adult mouse



Normal follicle with egg, from adult mouse

Mixed Signals

BIOLOGY PROFESSOR MELISSA PEPLING RECENTLY PUBLISHED A PAPER in *Biology of Reproduction* about the possible dangerous effects of soy products on female fertility. She based the hypothesis on her research concerning oocytes (egg cells), which respond to genistein, a naturally occurring estrogen found in soy-based infant formula and adult dietary supplements. Working with Wendy Jefferson of the National Institute of Environmental Health Sciences, Pepling discovered that genistein prevented eggs from separating into single cells at birth and caused them to remain clustered in adult mice. In low doses, introduction of genistein resulted in fewer pregnancies and fewer offspring per litter, while higher doses caused infertility in the mice. Now Pepling wants to identify how genistein signals the cells to cluster. "It's too early to draw any conclusion about soy products' effects on humans, but I would caution pregnant or nursing women to avoid too much soy," she says. "The preliminary results open up areas of related research on other environmental toxins and synthetic hormones, which are in everything from shampoos and lotions to beef and chicken."

Students Attracted to Research Work and Interdisciplinary Programs

SU HAS TRADITIONALLY ENCOURAGED INTERdisciplinary study and has established many degree programs in the sciences that cross several fields, including biochemistry, biophysical science, bioengineering, and chemical engineering, as well as a doctoral program in structural biology, biochemistry, and biophysics (SB3). The University has strong partnerships with scientists and science programs at SUNY Upstate Medical University and the SUNY College of Environmental Science and Forestry, both adjacent to campus. "These kinds of connections are crucial, because we cannot afford to hire 100 biologists to teach in the life sciences," says biology professor and department chair John Russell. "Collaborators in other departments and at other institutions expand our resources and enrich the learning experiences of our faculty and our students."

Biochemistry professor Philip Borer, director of the SB3 program, says the caliber of students entering the program has grown impressively since the University committed itself to increased support for interdisciplinary programs. "We simply wouldn't have attracted some of these students in the past," he says. "We have also been able to recruit top-notch faculty because of these interdisciplinary and inter-institutional collaborations."

Brett Spurrier G'06, who earned a master's degree in mechanical engineering, is grateful for the opportunity he had to enhance his engineering skills in a biology lab. "I wanted to learn how to use biology to aid engineering and how to apply engineering to advance medical biology, so that I can really have an impact on people's lives," he says. "What better way to do that than to be part of a team of cancer biologists fighting one of the world's worst killers?"

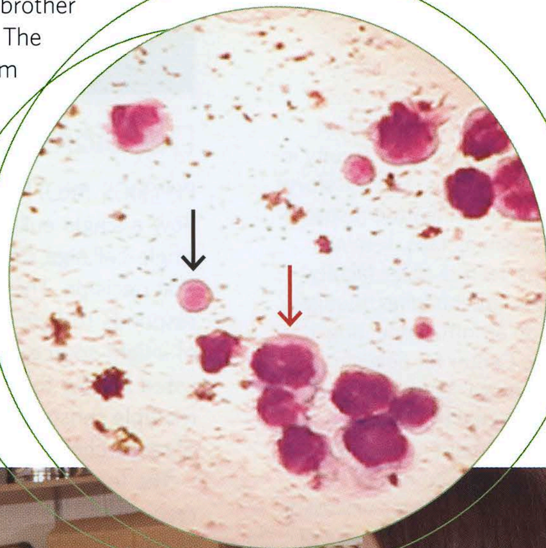
The eagerness of life sciences faculty members to work on their research projects with undergraduates is

Follicle cell photos courtesy of Melissa Pepling

Ultrasound Blast

FOR THE PAST 45 YEARS, PROFESSOR TOM FONDY HAS STUDIED CELL BIOLOGY, focusing much of his work on cancer treatments. Currently, he is investigating the use of ultrasound to treat chronic myelogenous leukemia, a bone marrow cancer. To help calculate the effectiveness of sound waves in killing the cancer cells, Fondy recruited Brett Spurrier G'06, then a graduate student in mechanical engineering. "There are countless approaches to this problem, and we are investigating the ones that work best," Spurrier says. "The physics of ultrasound was taught to me in engineering courses, so my involvement was a good check and balance for the biologists. Viewing the same puzzle from two sides of the table, the bigger picture is easier to put together."

The results have inspired the researchers, especially Fondy, who lost a brother to lymphoma in 2005, after twice donating stem cells for transplants. The researchers discovered if they treat cancer cells with molecules taken from molds called cytochalasins, they can induce the cancer cells to produce multiple nuclei, which make them bigger, easier targets for treatment. The sound waves cause the enlarged cells to burst at levels too low to affect normal cells, which are less susceptible than leukemia cells to damage by cytochalasins and do not become enlarged and multinucleated. "We already use ultrasound to treat kidney stones, and it appears the technique might also work for treatment of these large, multinucleated cancer cells," Fondy says. "Maybe it can make a difference for some patients, and that's why we're doing this—so someday we can say to someone with cancer, 'We know what we can do to help you.'"



Human myelocytic leukemia cells—mononucleated (black arrow); and multinucleated, with at least four nuclei (red arrow).

Professor Tom Fondy, with biology majors Arthur Kapalanga '07, Lacien Blake '07, and Shannon Dubois '07, who assist him with his lab research

particularly appealing to students. Ashley O'Hara '06, a biochemistry major who won the Lundgren Award for outstanding research in biology, was first drawn to SU by the opportunity to conduct research. She worked with biology professor Melissa Pepling, studying a gene in mice that plays a role in the development of an egg. "Performing research in a lab allowed me to apply a lot of the techniques that I learned in my classes," says O'Hara, now a medical student at the University of Rochester. "My coursework and research have greatly contributed to my preparation for medical school. I have a solid base in research, and I learned to think critically."

Biology major Kathryn Gold '06 says working in biology professor Tom Fondy's lab on a project designed to make leukemia cells more vulnerable to treatment expanded her knowledge base and taught her important life skills. "The experience really brought home the importance of perseverance and determination—two qualities essential for conducting research," says Gold, now a doctoral candidate in cell biology and molecular genetics at the University of Maryland. "Science is ever-changing, and I am well prepared to be part of its future."

Leukemia cell photo courtesy of Tom Fondy; lab photo by Susan Kahn

Life Sciences: > A University Priority

TO SUPPORT THE GROWING interest in cell signaling and life at the molecular level, the University broke ground last April on the $107 million, 210,000-square-foot Life Sciences Complex. The new facility, scheduled to open in 2008, will house programs in biology, biochemistry, and chemistry under one roof, making cross-disciplinary collaborations easier, and facilitating communication among students and faculty in these programs. The six-story structure will feature research and teaching labs, seminar rooms, lecture halls, faculty offices, greenhouses, lounges, and an atrium connecting it to the Center for Science and Technology. "Syracuse is part of a national trend of increasing investment in education and research in the life sciences," says physics professor Eric Schiff, associate dean of mathematics and sciences at the College of Arts and Sciences. "Federal funding for research in the life sciences has more than doubled in the last 15 years, and there are good reasons for this surge of interest in the life sciences. A confluence of new tools and concepts has created a period of takeoff. It is absolutely essential for Syracuse to improve its facilities and strengthen its faculty in the life sciences if we are to fulfill our responsibilities as educators and creators of knowledge."

Decisions, Decisions

PHYSICS PROFESSORS KENNETH FOSTER AND JUREE SARANAK WANT TO KNOW how a single eukaryotic cell makes decisions based on multiple inputs. They study how a single-cell alga, *Chlamydomonas*, decides which direction to swim and how it then carries out that decision. The cell swims in a "breast stroke" with a pair of cilia. The organism normally responds to light by swimming toward, away, or perpendicularly, relative to the direction of a light source; stopping and backing up; or "diddling" around. "We are particularly interested in how the choice of swimming behavior is made by the nonlinear processing of its multiple sensory inputs," says Foster, who leads a multidisciplinary, multi-institutional team of researchers.

The team is further investigating how the decision is signaled to the two cilia, which are responsible for moving and steering the cell. Specifically, they wish to know how the cilia change their breast stroke to steer the cell, carrying out the cell's decisions. Understanding this process in the single-cell organism could lead to knowledge of the human genome, as approximately 3 percent of the human genome is devoted to cilia and their control in the multiple tasks of sensing fluid flow, light, sound, gravity, smell, touch, and taste; and of moving fluids that aid reproduction, development, and the cleaning of respiratory tracts.

A related project asks how light triggers rhodopsin, a light receptor in the alga's eye similar to the visual receptors in a human's eye. "Understanding how these receptor proteins are activated is particularly important, because 5 percent of human genes are variants of these receptors and 50 percent of medicines involve these gene products," Foster says. "By studying these receptors in simple to more complex organisms, we can better understand how vision has evolved."

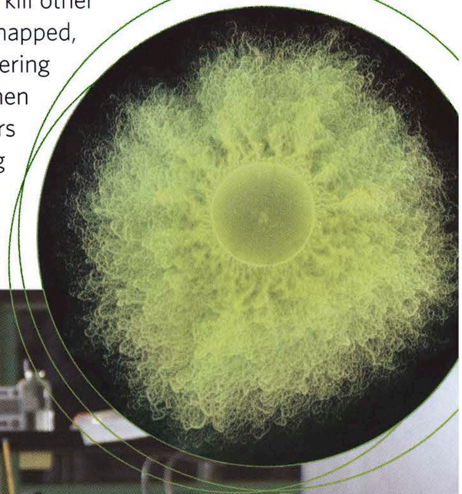
Chlamydomonas reinhardtii

Photo by Susan Kahn

Physics professor Kenneth Foster (right) studies how a single-cell alga directs its cilia to move in different directions.

Hunting Season for Bacteria

CHEMISTRY PROFESSOR CHRIS BODDY HAS TEAMED WITH BIOLOGY PROFESSORS ANTHONY Garza and Roy Welch to study how *Myxococcus xanthus*, a bacterium, creates toxic molecules that kill other bacteria and single-cell organisms on which it feeds. Most of *M. xanthus's* 10,000 genes have been mapped, enabling them to identify the 30 or so genes involved in this process. "The biologist's approach of altering a gene to alter an outcome works well when there's only one gene involved," Boddy says. "But when you have 10 genes involved in a process, changing one may have little effect because the nine others may compensate to do the same job. That's where chemical genetics can help. Instead of changing the genes, we chemically synthesize different molecules and see how each affects the outcome." If the researchers succeed in stimulating the production of these toxic molecules, the discovery may lead to the creation of new antibiotics or anti-cancer medicines.



Susan Kahn

Sharing the Same Evolutionary Story

Biology professor Roy Welch (above) is part of an interdisciplinary team investigating *Myxococcus xanthus* (inset).

TO STUDY THE YUCCA PLANT, BIOLOGY PROFESSOR KARI SEGRAVES MUST STUDY THE YUCCA moth because the two have evolved together, depending on each other for survival. "Their reproductive interests are entirely linked," Segraves says. "They are the textbook example of mutualism." The female moth has developed specialized mouthparts to purposefully pollinate the plant, and the moth larvae feed on some of the seeds that the female creates by pollinating. In this way, the plant reproduces at the cost of a few seeds. Studying what molecular genetic and developmental processes occur to create these unique parts provides a basis for understanding how traits evolve.

In the lab, Segraves investigates her field observations. For instance, a predatory beetle is feeding on the yucca plant's pollen and reducing its fertility. So what happens to the pair when one experiences environmental changes? Will the yucca moth's mouth revert to its earlier, less specialized version for survival? If so, how does that process occur? Would the plant find other pollinators if something were to happen to the yucca moth over generations? "Some say when a species becomes super-specialized, it becomes a stronger candidate for extinction," Segraves says. "Others say the species could revert back and become more generalized. It's a question we can answer."

Biology professor Kari Segraves examines the relationship between the yucca moth and yucca plant (inset).

Segraves photo by Steve Sartori; yucca moth (inset) by National Geographic/Getty Images