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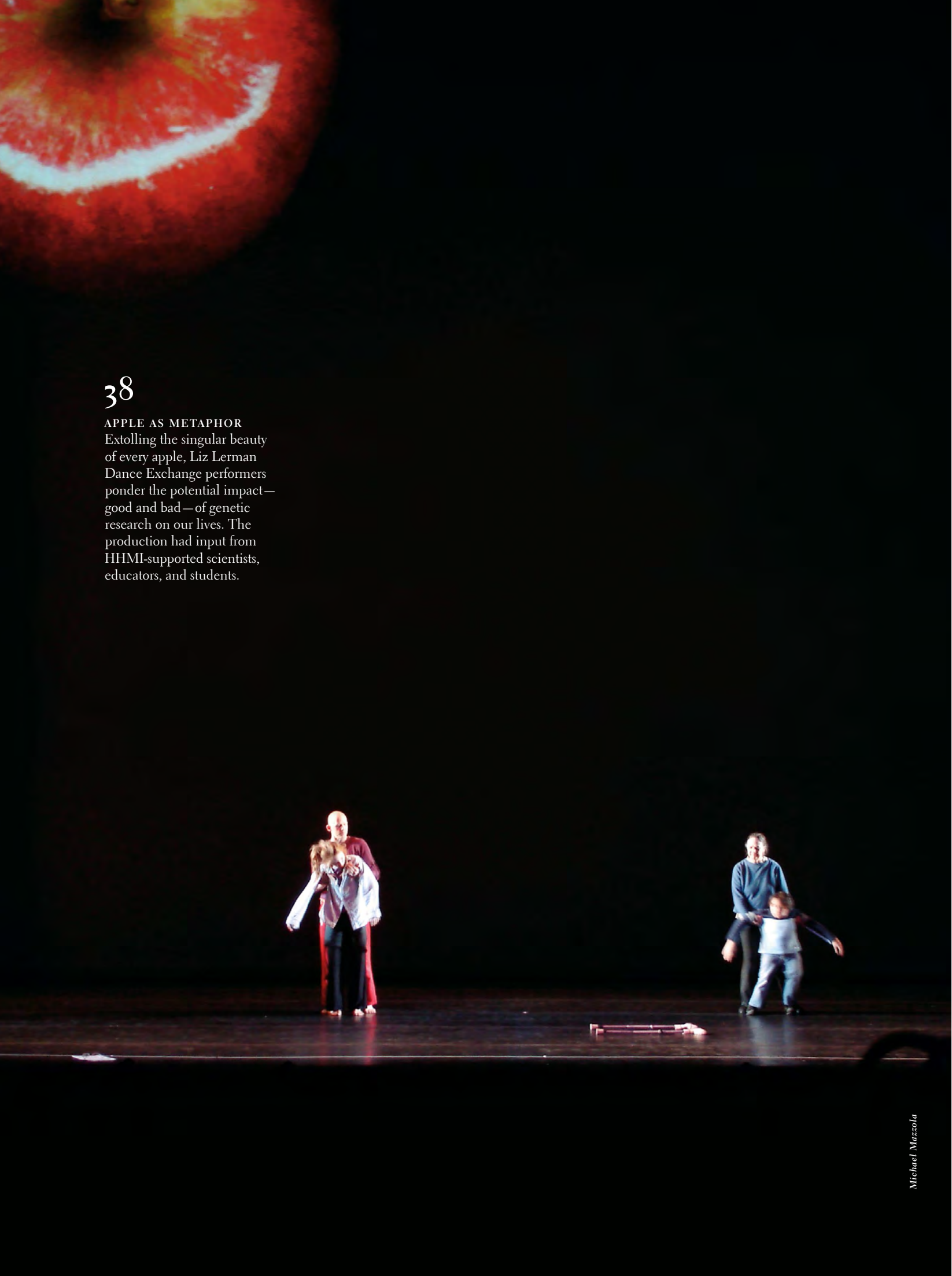
HHMI BULLETIN

Howard Hughes Medical Institute www.hhmi.org

action!

The dynamic—and unanticipated—choreography of the immune system



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APPLE AS METAPHOR
Extolling the singular beauty of every apple, Liz Lerman Dance Exchange performers ponder the potential impact—good and bad—of genetic research on our lives. The production had input from HHMI-supported scientists, educators, and students.

Michael Mazzola

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DEPARTMENTS

FEATURES

contributors


(1)

Marc Wortman's career demonstrates the lifelong value of a liberal arts education. Since earning a doctorate in comparative literature at Princeton, he gains a fresh education in the biomedical sciences each time he writes an article. He is an award-winning freelancer whose work has appeared in many national publications. His book, *The Millionaires' Unit: The Aristocratic Flyboys Who Fought the Great War and Invented American Air Power*, appeared in bookstores this month. (1)


(2)

After earning her doctorate in biochemistry at the University of Washington in Seattle, **Rabiya Tuma** launched a freelance writing career in 2001. Now based in Berkeley, California, she is a regular contributor to the *Economist* and a corresponding writer for *Oncology Times*, the *Journal of the National Cancer Institute*, and the *Journal of Cell Biology*. Her work has also been published in *CURE*, *Discover*, *O Magazine*, *SELF*, and *The New York Times*. (2)


(3)

An award-winning photographer who has covered stories from Iraq to Chiapas to Northern Ireland, **Jason Grow** has also photographed lots of really smart people in the worlds of finance, computers, software, medical research, and just about everything in between, for clients as diverse as *Time*, *BusinessWeek*, *Sports Illustrated*, and *Forbes*. A transplant to the East Coast from San Francisco, he now makes his home in Gloucester, Massachusetts, with his wife, Sarah, and three daughters, whose surfing skills are quickly surpassing his. Grow is a recently elected City Councilor for Gloucester. (3)


(4)

Karyn Hede is a science writer and editor based in Richland, Washington, who has written on topics ranging from the genetics of autism to how the Pacific atolls formed. Her freelance stories have appeared in *Scientific American*, *New Scientist*, and MIT's *Technology Review*, among other publications; she is currently a news correspondent for the *Journal of the National Cancer Institute*. A recent accomplishment of which she is exceptionally proud is helping to preserve a local mountain in its natural state. (4)

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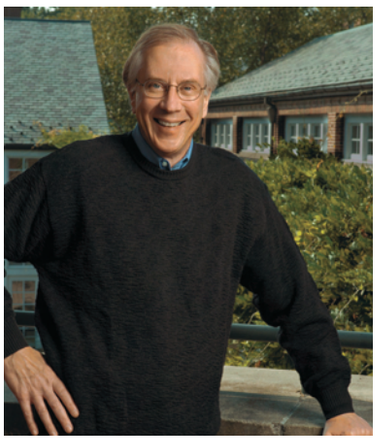
Photos courtesy of Marc Wortman, Rabiya Tuma, Jason Grow, and Karyn Hede

Reshaping the Landscape



Paul Fetters

"As in the literal landscape that's growing up around Janelia Farm, we do believe that the constituent parts will combine in surprising ways."

THOMAS CECH

MOTORISTS TRAVELING THIS SPRING THROUGH ASHBURN, Virginia, on Leesburg Pike might think that construction of HHMI's Janelia Farm Research Campus had just commenced, particularly if they happened to see numerous tractors crawling over the landscape moving massive dirt piles. No laboratory building is in plain sight and, after 4 years of furious activity, the most visible changes on the property are four squat, cylindrical towers sheathed in corrugated metal.

Appearances are deceptive. In fact, Janelia Farm is poised to begin operation, with the first group of neuroscientists, physicists, and computer scientists expected to move into their laboratories by midsummer. Some will aim to trace neuronal circuits responsible for complex behavior while their colleagues invent new microscopes for functional imaging to blaze the trail.

Inside the low-profile, terraced structure that looks out toward the Potomac River, the atmosphere has been anything but calm. Equipment, laboratory cabinets, and furniture have been pouring in for months, and are being installed by several hundred workmen.

A reshaped landscape is forming around the research building. More than 100 different types of plants and trees are being put in place, drawn from sources around the country and the world. They range from Little Bluestem prairie grasses (native to North America) and Dawn Redwood trees (presumed extinct until rediscovered in China) to three century-old spreading yews that once formed part of a maze in the State of Washington.

It's hard to believe that 7 years have passed since David Clayton, Gerry Rubin, and I first began discussing a possible new direction within HHMI's science program. After the initial scientific planning, Bob McGhee's steady vision and guidance as Institute architect have kept the project on track. He organized the writing of the initial program document we used to select Rafael Viñoly as the architect for the campus, and he consistently provides a mix of hard-edged project management and visionary ideas for laboratory design.

This issue of the *HHMI Bulletin* offers a behind-the-scenes glimpse at what it takes to equip a facility like Janelia Farm—as well as a look at the operational team, led by Cheryl Moore, that is charged with getting the campus up and running. Moore, the chief operating officer for Janelia Farm, has assembled an extraordinary team of experts in the areas of scientific support, information technology, facilities, conference services, finance, and human resources. Each team member is focused on creating an environment that will support the novel research culture at Janelia Farm.

As Moore has focused on the myriad operational details, Director Gerry Rubin and Kevin Moses, the associate director for science and training, have continued their recruiting efforts. To add to the eight group leaders who will move into Janelia Farm later this year, they have identified a new crop of candidate group leaders and fellows. Meanwhile, Moses has begun to shape a graduate program with our international partners, the University of Chicago and the University of Cambridge.

Participation by HHMI's university-based investigators has been—and will continue to be—essential to the success of our fledgling campus. They have worked with Rubin and outside scientists to shape the research program. They have spent countless hours helping review and evaluate candidates. We also expect them to be among the first—and most enthusiastic—visitors to Janelia Farm this coming fall when we hold a series of scientific meetings at the campus. In addition, as new microscopes and computational methods begin to emerge from the laboratories at Janelia Farm, our investigators will be among the first to have the opportunity to work with these tools and, we hope, will play a critical role in their development.

Janelia Farm represents a mix of the historical and the experimental. We've drawn inspiration from some long-famous institutions, including Bell Labs in Murray Hill, New Jersey, and the MRC Laboratory of Molecular Biology in Cambridge, England. Indeed, many of the physicists and biologists we have recruited have ties to Bell Labs or the MRC and are eager to return to an environment that supports small, highly interactive research groups. Yet Janelia Farm differs from its historical models and is based on what Gerry Rubin likes to describe as a working hypothesis, that its distinctive culture will foster unusually creative research.

We won't know for many years whether Janelia Farm will succeed in generating discoveries that will alter the scientific landscape. As in the literal landscape that's growing up around it, we do believe that the constituent parts will combine in surprising ways.

Flying Indoors

> "After accidentally crashing one into my wife's head when she was asleep on our couch, my first reaction was, 'Don't move!'"
>
> DAVID LIU

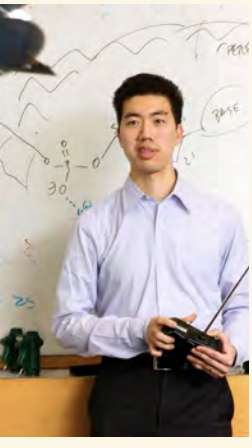
HHMI investigator David R. Liu admits he's sometimes a bit obsessed with his hobby of crafting ultralight radio-controlled airplanes. "After accidentally crashing one into my wife's head when she was asleep on our couch, my first reaction was, 'Don't move!'" says Liu, who realized his wife, Julie, posed a larger danger to the plane than vice versa. With good reason: His planes fly so slowly and are so light, weighing scarcely more than a half-dozen paper clips, that even a full-throttle impact is harmless.

Unlike typical remote-controlled planes, Liu's planes are meant to fly within small, indoor spaces. In fact, the challenge of designing an aircraft that can fly at a gentle enough pace to maneuver around a living room (1–2 mph), together with a childhood fascination with flight, is what propelled him to create his fleet of five ultralight planes. The realities of New England weather and long hours at work were also factors. Liu, a professor of chemistry and chemical biology at Harvard University, found that leaving the lab at 7 or 8 p.m., even during the summer, left hardly any daylight time for outdoor flying.

After several unsuccessful prototypes, Liu built a small squadron of planes that achieved in-home flight. The first, made in 2002 and dubbed "The Wisp," was among the first planes in the world documented to fly slowly enough to be controlled easily in a living room. The Wisp hums like an old-fashioned eggbeater, powered by a tiny, rechargeable lithium polymer battery commonly found in cell phones and pagers. Its three silver wings, each a foot wide, are made from 2-micrometer–thick Mylar film and dental floss. Slender tubes of carbon fiber provide support, and the dime-sized wheels are crafted from a special type of Styrofoam. A drop of Super Glue—which weighs a mere 5 milligrams once the volatiles evaporate—comes in handy for minor repairs.

Building these micro flyers shares some key similarities with one of Liu's

Photos: Jason Grow



research areas, in which he uses pieces of DNA to guide the synthesis of chemical compounds. Both endeavors entail a creative combination of basic and applied science, coupled with technology development. And both benefit greatly from collaboration. Liu's fellow hobbyists have been particularly generous, providing information and even materials for his planes. Knowing of Liu's goals, some even mailed him free samples of their latest designs of miniature gears or small electronic activators worth hundreds of dollars.

Such cooperation is, in a sense, a model for the collaborative approach to research fostered by HHMI, says Liu. As a chemist working among a group of world-class biologists, he feels fortunate to have the same sense of synergy in his professional life that he has realized with his hobby.
—Julie Corliss

FOR MORE INFORMATION: To learn more about Liu's research, visit http://evolve.harvard.edu/

Illustrations: Peter Arkle

Major-League Med Student

[1]

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Matthew McCarthy took an unusual detour after doing undergraduate research in the lab of HHMI investigator Joan Steitz and earning a degree in molecular biophysics and biochemistry from Yale University. He became a professional baseball player. We wrote about his unorthodox career move and published his baseball card in December 2002.

McCarthy is now out of baseball, but back with Hughes. He is on an HHMI research training fellowship for medical students, doing stem-cell studies in the laboratory of HHMI investigator Leonard I. Zon at Children's Hospital Boston of Harvard Medical School.

McCarthy pitched the full 2002 season for the Provo (Utah) Angels, a minor-league affiliate of the major-league Los Angeles Angels of Anaheim, but the organization released him from his contract at the end of spring training 2003. The blow was softened, however, by an acceptance letter from Harvard Medical School. "In the last game I ever pitched," McCarthy recalls, "three batters in a row hit the hardest shots I'd ever given up. Amazingly, all three balls were caught for outs. **I walked off the mound thinking, 'I should probably go to medical school.'**"

The HHMI fellowship allows McCarthy to take a year off from the textbooks and rounds to concentrate on research. He is working through early August on a project in the Zon group to explore the genetics of differentiation and development in blood stem cells. McCarthy's job is to irradiate zebrafish to knock out all their blood stem cells. "Then, after having the fish overexpress certain genes, I see how this cell population recovers," he explains. "**What we find could be useful for transplantation procedures** and in general provide a better understanding of stem-cell biology."

When asked if there was anything he learned from playing ball that helps with being a physician-scientist, McCarthy easily identified a common thread: "the need to put in the long hours—the thankless time—for the ultimate reward." He explains, "In baseball's off-season, pitchers do nothing but run and lift and throw. The reward comes when you get to show off your stuff on the mound." In a similar way, day-to-day life in the lab can be fairly mundane. "I inject hundreds of zebrafish embryos daily. But the reward is when you get that result and publish that paper."

At press time, McCarthy's former Yale teammate Craig Breslow was in spring training with the Boston Red Sox. If he makes the team, Breslow will room with McCarthy, whose apartment is just a 10-minute walk from Fenway Park. That continuing friendship has its perks: "**Not many stem-cell biologists get to hear the scouting report on Ken Griffey, Jr.,**" says McCarthy.

Is he staying involved in sports himself? "The intramural dodge ball team is heavily recruiting me," McCarthy jokes. And he's looking forward to this summer's surgery rotation, in sports medicine. One of the surgeons is team physician for the Red Sox, which means Doc McCarthy could soon have found his own unique route to the major leagues.
—Steve Mirsky

Into the Wilds—and Music

> "Seeing all the new and ancient lava flows, I was struck by the cycles of renewal at work."

MICHAEL EHLERS

For neurobiologist Michael D. Ehlers, scientific inspiration may strike as he's hiking a rocky trail or huddled in a tiny tent pitched in the woods. "I like to do a lot of outdoor stuff, especially backpacking and kayaking, and I've gotten some of my best ideas when I've managed to get away from the structures of normal life," says Ehlers, an HHMI investigator at Duke University Medical Center.

A prime example occurred when, about 5 years ago, his trekking led him to Iceland. "Seeing all the new and ancient lava flows, I was struck by the cycles of renewal at work," he recalls. "It dawned on me that the protein components of synapses in the brain also might undergo some kind of recycling. This general concept eventually led to experiments that have helped provide us with a better picture of how neurons store information and communicate with one another."

Ehlers' scientific sleuthing has yielded other rewards as well. In 2003, he received the Eppendorf & *Science* Prize for Neurobiology, an international award for outstanding recent research by a young scientist. "The scientific recognition was nice," he says. "But I also received $25,000 in personal prize money that I used to buy a new baby grand piano."

This new baby comes in handy because Ehlers is a concert-level pianist—he started playing at age five. "Right now, my goal is to add all of Rachmaninoff's preludes to my repertoire," he says. "It may take a while, but it's fun trying."

Ehlers also knows his way around a French horn, which he began playing to help fill a gap in his high school band in Nebraska. He went on to perform in symphony orchestras during his college years and is now principal horn in the Raleigh (N.C.) Civic Symphony. "Music is still a big part of my life," he says. "In fact, I once debated between music and science as a career. But my midwestern practicality won out, and I decided that it would be easier to be a scientist who plays music than a musician who does science."

There is another new baby on the scene as well—a son, Henrik, who is nearing his first birthday. "I've already taken him kayaking—in a safe way, honest!" Ehlers says. "And I'm sure we'll do more of that, if only to work off some of his amazing energy before he wears out his dad."

Starting this spring, Ehlers will spend a sabbatical at the University of Bordeaux, in France. In the lab, he will study single molecules within neuronal synapses. Away from the lab? "The Pyrenees are nearby," he says. "I can't wait to go exploring."—*Tom Burroughs*

FOR MORE INFORMATION: Learn about Ehlers' research by visiting http://www.ehlerslab.org/research.html

Illustrations: Peter Arkle Photo: Karen Tam/AP. ©HHMI.

MAY '06

upfront

It's sneezin' season again. If your drippy nose and watery eyes seem worse than usual this spring, you are not alone. Allergy specialists around the world say hay fever has reached "epidemic proportions." Pollen is often the culprit this time of year when trees, grasses, and weeds reawaken. Molecules on pollen's bumpy surface may be the key, according to some HHMI researchers. Understanding their role may open new avenues for preventing those irritating sniffles and the more serious health risks of asthma.

Where the Antigens Are

In allergy research, scratching the surface has made for a surprising advance.

Illustration: Brian Cronin

A PATIENT REPORTED AN ALLERGIC reaction after eating strawberries, yet came up negative on conventional skin testing. So the doctor tried something *un*conventional. He applied the juice of a fresh strawberry—as opposed to processed extracts—directly to the skin, and got the reaction his patient described.

HHMI investigator Daphne Preuss, a plant biologist, likes to share this story of her physician friend. "It tells us that we're missing something when it comes to allergies," she says. "We need greater diagnostic precision, and treatments that home in on the exact allergens involved in a reaction." Her work could make that happen. In collaboration with HHMI investigator Albert Bendelac, Preuss is identifying the molecular components of pollen cells that may hold the key to innovative detection and therapy for allergies.

Several years ago Preuss was investigating how female plant structures recognize a "fit" among the thousands of male pollen grains that arrive on the wind or are dropped by bees. In the process of identifying "recognition genes" that code for proteins on the outer surface of pollen cells, Preuss began to wonder if these extracellular surface proteins might also be involved in allergies.

Plant biologist Daphne Preuss and immunologist Albert Bendelac study why pollen triggers allergies.

If pollen's surface molecules have been overlooked as causative factors in allergies, it is largely because skin-testing extracts are "washed," a process that removes the outer coat. "Inadvertently, conventional preparations led to purification of mostly molecules *inside* the pollen cell," Preuss says. She arranged for her lab to receive unwashed batches of pollens. In the process of learning how to extract surface materials from many different pollen species, Preuss noted that pollen's outer coat carries many lipid compounds.

Enter Bendelac, an immunologist whose work has been instrumental in demonstrating that lipids are involved in inflammation, a biological phenomenon now understood to be a critical factor in such maladies as diabetes, heart disease—and asthma and allergies.

"Lipids are a major component of pollens," Bendelac says, "and when immune cells encounter lipids, they release hormone-like factors that orchestrate inflammation and immune responses." Bendelac has devised sensitive assay techniques that detect these immune responses to lipids—techniques that have proved integral to Preuss's research.

In addition to surface lipids, Preuss is exploring the allergenic properties of pollen surface proteins. HHMI investigator Arthur Weiss, a clinical immunologist based at the University of California, San Francisco, notes that "a vital aspect of Daphne Preuss's work is understanding the properties of pollen's surface antigens that make them so immunogenic. Knowing that might lead to a better understanding of why allergies develop in the first place, and why they develop in response to specific stimulants."

Preuss is indeed moving in this direction in the search for human genes associated with immune responses and the identification of plant cell fractions that contain allergens. As an alternative to current allergy testing, which screens for pollen allergies but doesn't usually tease out which species elicit allergic reactions in genetically predisposed individuals, she and her colleagues have designed a diagnostic chip that carries extracts of pollen material. "These extracts are primarily protein from 22 different species. We probe the chip with patient sera and can detect specific antibodies," Preuss says. "In the process of working out methods for purifying surface materials from many different [unwashed] pollen species, we've been able to demonstrate that humans create antibodies to pollen's outer coat. This is an exciting proof of concept."

"In the process of working out methods for purifying surface materials from many different pollen species, we've been able to demonstrate that humans create antibodies to pollen's outer coat."

DAPHNE PREUSS

Preuss presented her work at the annual meeting of the American Academy of Allergy, Asthma, and Immunology on March 3. "By discovering the specific antigens that elicit allergic responses," adds Weiss, "it may be possible to alter or prevent those responses." And at that point, adds Preuss, "We will be looking at new therapeutic opportunities." ■

–RICHARD CURREY

THE BIG PICTURE

Gesundheit!

RAGWEED IS ONE OF THE MOST prolific producers of allergy-causing pollen. A single ragweed plant can generate a million grains of pollen a day. And, no doubt about it, those light, dry grains can travel. Scientists have collected samples of ragweed pollen 400 miles out at sea and 2 miles high in the air, according to the National Institutes of Health. >> **FLAMBOYANT FLOWERS** usually aren't the culprits in seasonal allergies. The types of pollen that most commonly cause allergies are produced by the more unassuming—and abundant—plain-looking plants, such as trees, grasses, and weeds. When allergy-causing pollen lands on the mucous membranes of the nose, local mast cells release a chemical called histamine. As a result, small blood vessels in the nose dilate, nasal passages swell, and congestion results. Histamine also causes itching, irritation, and excess mucous production. Prostaglandins and leukotrienes play a role in allergy symptoms as well. >> **CURRENT ALLERGY TREATMENTS** work to block histamines, constrict blood vessels to reduce swelling, or inhibit mucous production. Most of those products have annoying side effects, such as drowsiness, while others take several days or weeks to work. Allergy shots—injected diluted extracts of pollen under the skin—are expensive and time-consuming (they have to be given many times with gradually increasing doses), and don't work for everyone.

Photos: Lisa Predko

Evolution of a Dance

Artists, scientists, and ethicists collaborate on a multimedia exploration of genetic science.

AT CENTER STAGE, MARTHA WITTMAN—A DANCER IN HER 70s—CONTEMPLATES a partially peeled apple that she holds in her hand. Noting the resemblance of the peel to the spiral shape of DNA, she reflects on the many varieties of apples, how different they look and taste, and the many wonderful ways her mother used to prepare them. ¶ A younger dancer bursts onto the stage in a wheelchair. Born with osteogenesis—an inherited disorder that causes bones to break easily—she dances defiantly on wheels, and then on crutches, whirling among Wittman and other more able-bodied members of the Liz Lerman Dance Exchange. The fury of the scene recedes, and Wittman wanders off the stage, admiring her apple and shaking her head at the thought of genetic manipulations that might render all apples uniformly red and tasteless. "No more tart surprises," she sighs.

Bonnie Bassler (left) and Liz Lerman collaborated to bring genetic science to the fore in an unusual way—on stage.

> "I just want people to leave saying, 'Oh, I can understand this. Big things are coming, and I can play a part in them."
>
> LIZ LERMAN

In *Ferocious Beauty: Genome*, choreographer Liz Lerman and HHMI investigator and fellow MacArthur Award recipient Bonnie Bassler have joined hands with artists, scientists, and ethicists across the country to tell the story of the human genome. A visual and auditory tapestry of dance, music, speech, costume, light, and video, the uncommon production premiered in February 2006 at Wesleyan University, in collaboration with HHMI's undergraduate science education program there.

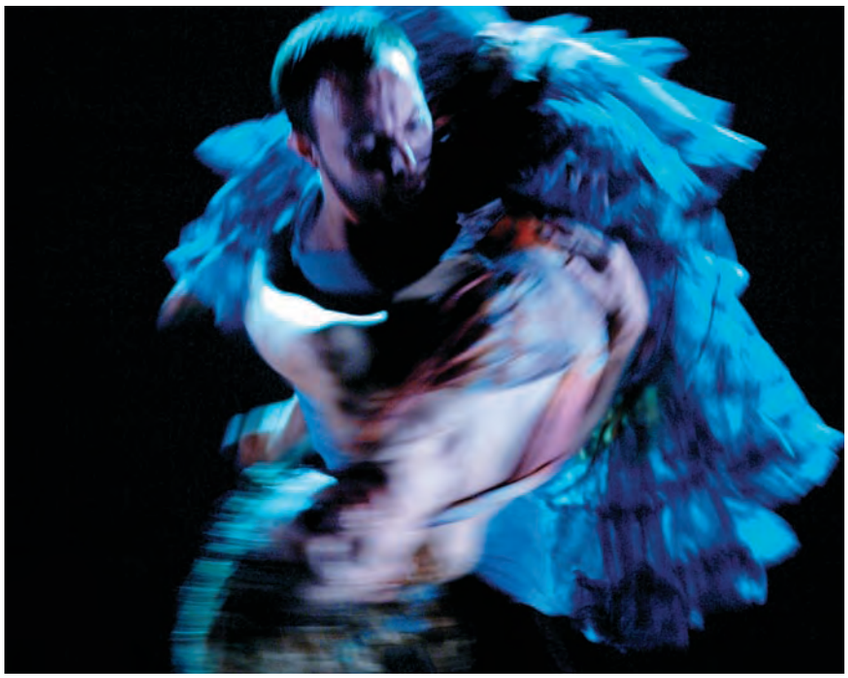
Three years in the making, the project was sparked in 2003 when Pamela Tatge, director of Wesleyan's Center for the Arts, saw Lerman's intergenerational modern dancers perform. Afterward, she heard the choreographer speak of her desire to develop a dance about genetic research and its implications for humanity. So Tatge arranged for Lerman to meet the then-dean of natural sciences and math at Wesleyan, Laura Grabel, who had been a professional dancer herself. Though Grabel had kept her dance and science separate for 30 years, noting, "There's not much call for a dancing biologist," she found Lerman's idea provocative.

After that meeting, Wesleyan invited the Dance Exchange, based in Takoma Park, Maryland, to establish a residency program at the university, using the Connecticut campus as home base for the genome dance project. Lerman immersed herself in the history of genetics and consulted with biologists at Wesleyan and elsewhere. She also learned from the students. An HHMI science education program at Wesleyan sponsored a student symposium where dancers and undergraduate scientists compared how they approach problems and do their work.

Bassler, a Princeton University researcher who studies how bacteria "talk" to one another, became an adviser to the project, initially spending a day with the performers to explain her research and watch them experiment with ways to express it in movement.

What if scientists were choreographers? Eight dancers glide and slide in and out of molecule-like formations—first intertwined, then breaking apart. On an enormous video screen behind them, Eric Jakobsson, director of the Center for Bioinformatics and Computational Biology at the National Institute of General Medical Sciences, ponders the question. "You could start by laying dancers out head to foot, end to end, head to foot...."

Shawn Henry



Ferocious Beauty: Genome *expresses the power, momentum, shape, and beauty of biology, as well as the sense of simultaneous connection—and separation—inherent in our genetics.*

Kevin Kennefick

Harris Lewin, a professor of immunogenetics at the University of Illinois, replaces Jakobsson, superimposed on the whirling dancers and supersized on the screen. "It's the genome shuffle," he suggests. "We're all very similar. The chromosomes are basically the same. We just reshuffle the pieces of our ancestors' genomes."

Bassler marks that day as one of the most fascinating of her life. "What they do is so different from what I do," she says, "and yet in some ways, it's so similar. Cells communicate with a chemical language, I communicate with spoken language, and dancers communicate with movement."

Lerman, whose "nonfiction dances" often have political and ethical themes, also consulted ethicists in creating *Ferocious Beauty: Genome*. The performance's first act deals with the rigor and wonder of scientific discovery, focusing on Gregor Mendel, the 19th-century monk renowned for his genetic experiments with peas. The shorter second act presents issues raised by genetic science, such as aging, the search for perfection, and our common ancestry.

Thomas Dwyer, silver-haired and gaunt, perches on a folding chair, hemmed in by brick walls that look a lot like microarrays. The soundtrack is a heartbeat. "New laws for old folks" flash across his walls: "Age 70—cease and desist wearing seat belts; Age 75—mandatory skydiving; Age 80—cross traffic on red light; Age 85—mandatory smoking…." Perturbed, depressed, frustrated, and finally angered by what he's losing and what he's lost, he circles his chair and explores the walls as scenes from his life flash across them.

Yet Lerman didn't want her production to become a soapbox. "It poses some small and large questions, but it doesn't attempt to answer them," she insists. "I just want people to leave saying, 'Oh, I can understand this. Big things are coming, and I can play a part in them.'"

Lerman and her dancers are taking *Ferocious Beauty: Genome* to stages at universities and performance centers across the country. Each audience will see a slightly different show. "Like biology, it will keep evolving," Lerman promises. "I'm still trying to understand the piece myself." ■

–JENNIFER BOETH DONOVAN

FOR MORE INFORMATION: For a schedule of performances, visit http://www.danceexchange.org/

A Few Good Neurons

Remembrances of things past do not necessarily involve a great many nerve cells.

Cornelia Bargmann joins forces with a tiny worm to study how the brain's wiring influences behavior.

Matthew Septimus

"We are watching the nervous system translate experience into its own language."

CORNELIA BARGMANN

IF YOU'VE HAD THIS UNPLEASANT EXPERIENCE, YOU WON'T FORGET IT: You ate something bad and got sick as a dog. Even years later, the thought of eating that particular food again makes your stomach turn.¶ This response, called conditioned taste aversion, is one of the strongest forms of learning in mammals, says Cornelia I. Bargmann, an HHMI investigator at the Rockefeller University. "All it takes is a single experience to form very long-lasting memories." And the process is not unique to mammals. Fish, snails, and the cuttlefish (a relative of octopus and squid) show a similar response. In the November 10, 2005, issue of *Nature*, Bargmann's team reported that *Caenorhabditis elegans*, a nematode with only 302 neurons, does too.

If a worm with so few neurons can learn such a sophisticated behavior, just how many neurons does it take to establish a memory? Theoretically, only two: a sensory neuron to detect a stimulus and a motor neuron connected to a muscle that will carry out a behavior. But in actuality, neural circuits are never quite this simple and invariably involve more—though not necessarily a great many—cells.

The laboratory of Eric R. Kandel, an HHMI investigator at Columbia University who won the 2000 Nobel Prize in physiology or medicine for his work on memory, has studied the sea slug *Aplysia*. This animal rapidly learns to associate a noxious stimulus, like an electrical shock, with an innocuous cue, such as a light touch on its siphon. It will subsequently withdraw its gill in a protective behavior in response to just the light touch.

The circuit that underlies such classical conditioning can be reduced to about 20 or 30 neurons if one focuses on only one aspect of gill movement, says Kandel. In the full-blown behavior, 50 to 60 neurons are likely to be involved.

Bargmann doesn't yet know what the circuit looks like that controls conditioned taste aversion in nematodes, but she estimates that, here too, some 60 neurons are involved. Significantly, her team used molecular tools to watch as one type of neuron in the circuit increased production of the neurotransmitter serotonin (which strengthens signaling between neurons) in response to bad food, in this case, toxic bacteria. When the scientists knock out the receptors for serotonin, they inhibit learning.

"We are watching the nervous system translate experience into its own language," says Bargmann. The worm experiences an infection from eating the wrong bacteria, and the nervous system transforms that experience into an increase in serotonin, a molecular language that the nervous system understands. The fact that it is the same neurotransmitter that Kandel's lab saw in classical conditioning in *Aplysia* leads Bargmann to suggest that scientists might be beginning to unravel the grammar of this molecular language common to all creatures.

So how many neurons do we humans need to remember a particular Rembrandt masterpiece or to recall a conversation we had with a close friend? There are no specific answers yet, but Kandel and others predict that the molecular aspects of memory storage in humans will be similar to those in *Aplysia* and other model systems. The size of the human brain, however, adds enormous complexity. Even simple circuits, such as those described above, will be layered many times over. And there will be a concomitant increase in combinatorial options to mix and match pathways. "We can't dissect out each bit yet," says Kandel, "but eventually we will." ■ —RABIYA TUMA

Table for One?

Have a question about nematode behavior? Ask Cornelia Bargmann. She's figured out what makes some of these 1-millimeter-long worms social eaters while others prefer to eat alone, and she can tell you how they know bad food when they smell it. The HHMI investigator at the Rockefeller University has also determined how the worms, known as *Caenorhabditis elegans*, can recognize and distinguish among thousands of odors in their environment. Their keen sense of smell and small number of neurons make *C. elegans* an ideal model for Bargmann and other researchers to understand the interface between genetics and experience. Since neuronal genes, like most other genes, are conserved among all animals, she expects that her research on the worm's brain will improve understanding of the human brain. The gene she found that determines whether a worm prefers a table for one or family-style dining, called *npr-1*, is related to human proteins involved in appetite and anxiety regulation.

Whittling Thousands to a Few

The key to identifying yeast proteins of interest is to get a handle on them.

KINASES CALL A LOT OF THE SHOTS INSIDE CELLS. THESE ESSENTIAL ENZYMES regulate a vast array of processes, such as whether cells grow normally or become cancers. But the functions of many of the more than 120 kinases that exist in yeast are mysteries—and no simple method exists to determine each one's modus operandi. Now, chemical and genetic engineering has allowed a team of researchers at the University of California, San Francisco, led by HHMI investigators Erin K. O'Shea (now at Harvard University) and Kevan M. Shokat, to pinpoint the protein substrates acted on by a yeast kinase called Pho85. "To understand the function of a particular kinase, we need to know what kinds of proteins it controls," says O'Shea.

> "We think the trick will be generalizable to almost every kinase."

KEVAN SHOKAT

The researchers expect their two-step method will prove useful for many kinases, especially because no one else has come up with a systematic approach to identifying a kinase's constellation of substrates.

Kinases activate proteins by grabbing the cellular energy–supplying molecule ATP (adenosine triphosphate), shearing off a phosphate, and adding it to the protein. Using radioactive ATP as a source of phosphate is one way to mark targeted proteins so that they can be identified amid a sea of others. But all 120 kinases exist in test tube extracts of yeast, and each of those can affix radioactive phosphate to proteins.

To get around this problem, O'Shea and Shokat developed the first step of their method—a molecular trick that allows only the kinase of interest to grab the radioactive ATP. They added a chemical tab to radioactive ATP and engineered Pho85 to have a slot to match the chemical tab, making them fit together much like pieces of a jigsaw puzzle. So only the Pho85 is capable of transferring a radioactive phosphate to its proteins.

THE BIG PICTURE

A Family of Overachievers

PROTEIN KINASES belong to a very large family of enzymes. The human genome contains about 500 protein kinase genes, or about 2 percent of the total. Kinases play a major role in controlling many key activities of the cell and are particularly prominent in transmitting signals within a cell and in coordinating the steps of cellular replication.>>**A PROTEIN KINASE MODIFIES** other proteins by chemically adding phosphate groups to them—a process called phosphorylation. The process usually results in a change in the target protein's activity, its location within the cell, or its interactions with other proteins. Each kinase can be a multi-tasker, having several substrates and acting as a substrate for other kinases.>> **PRECISE CONTROL** of protein phosphorylation is critical to normal cell behavior. Uncontrolled kinase activity is a frequent cause of disease. For example, in cancer, kinase-mediated regulation of many aspects of cell growth, movement, and death is disrupted. For these reasons, compounds that inhibit the activity of protein kinases are being studied as therapeutic agents. In fact, some kinase inhibitors are already available for treating patients, including the two anticancer drugs Gleevec (imatinib mesylate) and Iressa (gefitinib).

O'Shea: Christopher Jones Illustration: Joel Lardner

But how to find those proteins that Pho85 controls in yeast cells? Step two: The team designed yeast proteins to have unique molecular "handles." These antigenlike handles can be snagged with an antibody that recognizes them specifically and pulled out of the extract by a method called tandem affinity purification (TAP). Within a yeast cell, only one type of protein out of the multitude present is marked with a TAP handle.

The researchers then created 4,250 yeast strains, all identical except for the unique TAP-handled protein each strain makes. This bevy of strains represents a large percentage of all the proteins a yeast cell makes—and that a kinase can act upon. The importance of making such strains, says O'Shea, was to keep the kinase in an environment close to its natural habitat, thereby reducing the possibility that the kinase would behave in any way different from normal.

After adding Pho85 to a mash of pooled yeast strains, the team pulled out all the proteins displaying a TAP handle. The ones that showed up with a dab of radioactivity—from Pho85—could be investigated further. O'Shea and Shokat found 24 proteins that came through the steps radioactive, spotlighting two dozen possible Pho85 substrates. As an added bonus, one of the proteins had been previously reported to be under Pho85's control, affirming the value of their method.

Besides Pho85, Shokat has made more than 75 additional slotted kinases, all but three of which work well with the modified radioactive ATP. "We think the trick will be generalizable to almost every kinase," says Shokat. If so, this technique will help researchers move many kinases off the mystery list. ■ – MARY BECKMAN

"To understand the function of a particular kinase, we need to know what kinds of proteins it controls."

ERIN O'SHEA

Digital video vignettes of the immune system in action are opening scientists' eyes.

Lymphocytes, camera, action!

BY MARC WORTMAN

illustration by ***Jonathon Rosen***

"You can't understand complex, changing natural phenomena with just one snapshot....With video imaging,

In a laboratory at Stanford University School of Medicine, graduate students and postdocs spend a lot of time watching movies. Their mentor, HHMI investigator Mark M. Davis, doesn't mind a bit. In fact, he encourages them, and proudly shows off the product of a protégé's doctoral thesis, which he unofficially titles, "Immune System: The Movie." The student composed digital video recordings of immune cells going about their machine-like business—not unlike Hollywood's "Terminator"—of seeking out, recognizing, and destroying (or stimulating) other cells.

Davis calls up a video on his monitor showing the immune system in action. He watches three cells clump together, much like a basketball and two softballs lined up in a row. The largest of the three is a cancerous lymphoma cell. The two smaller cells—one blue, the other red—are components of the immune system scanning the unhealthy cell and communicating with one another about what they are "seeing."

The time-lapse images follow the two immune cells as their colors swiftly intensify and change to green. This color change is a laboratory-generated display of the internal biochemical changes the immune cells undergo when they recognize the lymphoma cell and signal to other nearby immune cells to mobilize against it. Their murderous business is swift and relentless. Nearly a dozen other cells charge in like a vengeful mob. With their colors intensifying and changing much like the first two cells, they cluster around the lymphoma cell and prepare to kill it.

Davis's team has recorded numerous videos of fluorescently tagged proteins on the surface of the immune system's T lymphocytes—the specialized white blood cells that move through the body with the flow of blood until they bump up against foreign or diseased cells. If the T cell's surface proteins link up with a sufficient number of counterpart proteins on the unhealthy cell, the T cell recognizes it as an enemy. At that point, the immune system swings into attack mode against the invader.

Only with recent advances in visual imaging systems have Davis and other investigators been able to generate these types of live-action videos. Their productions are changing the way scientists think about the immune system.

The imaging systems couple ultra-high–resolution microscopes with lasers (which send out pulses of light that illuminate fluorescently labeled protein probes, even deep within the intact tissues of living animals). These systems, known as multiphoton microscopes, include special video camcorders that produce layers of images at different microscopic depths as well as post-production software that recomposes the images into three-dimensional videos. Thus equipped, scientists like Davis can watch how the immune system works at the nuts-and-bolts level and observe what happens when it goes awry.

"You can't understand complex, changing natural phenomena with just one snapshot," says Davis. "We want to see where the molecules are, what they are doing, and how an organism responds to a threat. With video imaging, we can look at the gears turning and what cells do and how they do it."

MORE THAN ENTERTAINMENT

Microscopic observation of living cells on a slide (in vitro) or in a living organism, which goes by the general name of "intravital microscopy" (IVM), is not new. It was pioneered by German physiologist Rudolph Wagner in 1839. But the present sophistication of the process and the level of resolution now possible are indeed new, and filled with promise. When Davis and others began to generate videos in

FROM LEFT TO RIGHT:
Mark M. Davis, Dan R. Littman, Philippa Marrack



we can look at the gears turning and

***what cells do** and how they do it."* MARK DAVIS

the late 1990s, however, some in the field questioned their value. They were seen as a fancy way of showing what scientists already knew through static images.

Coming up against such attitudes, Davis had trouble finding a journal willing to publish his early papers. Editors feared they would be opening the doors to ridicule about the MTV generation taking over scientific research. "The convention was that videos were more about entertainment than information," he says. "It was almost impossible to persuade people that video can have much more information than a still image." Soon, though, as new knowledge began emerging from video microscopy, the same editors were clamoring for him to submit more video-based papers.

Now, those dramatic images have shown that the immune system is far more dynamic and actively choreographed than previous static-image studies had led scientists to believe. Davis and others are zooming in on that activity in molecular detail. Until moving images showed them otherwise, most biologists thought that the signaling process leading to an immune response required hours or even days of continuous communication between T lymphocytes and antigen-presenting cells (the cells that engulf cells infected with viruses and, through communication with T cells, initiate the process that will kill the virus).

Video microscopy revealed, instead, that these two fundamental immune-system components engage in a day-long minuet beginning with multiple short contacts. Each lasts only a few minutes, yet these fleeting encounters prove sufficient to activate the T cells. "Few people anticipated the enormous rapidity with which cells move," says Ulrich H. von Andrian, an immunologist at the CBR Institute for Biomedical Research, an affiliate of Harvard Medical School, and a leader in the use of video microscopy.

Many unstable cellular structures collapse when they are prepared for static observation. As a result, says von Andrian, static studies may have given scientists a false conception of living immune system mechanics. Studying the immune system in its natural state, he says, "provides an essential reality check for determining which phenomena are different in living animals and not faithfully reproducible" statically. Davis agrees: "It's like seeing an animal in its natural environment, rather than in a zoo. It's really important to see where they are and how they behave in different stages of their lives in their native habitat."

THE SECRET LIFE OF THE LYMPHOCYTE

Nearly all real-time knowledge of the immune system comes from studying T cells circulating in the blood. Yet, while a T cell typically spends only about 30 minutes in the bloodstream, it might spend hours or even days migrating through other organs, querying cells for antigens. Because "there is no evidence out there for what goes on inside an organ," says Dan R. Littman, an HHMI investigator at the New York University (NYU) Medical Center, only a small fraction of the life of the lymphocyte has ever been observed. He and others have begun to open up that hidden life.

In his laboratory, Littman, in collaboration with Michael Dustin at the Skirball Institute of NYU, uses IVM in mice to observe the living immune system within organs that are accessible by surgical procedures. He started with the liver, where natural killer T (NKT) cells, the immune system's sentinels against virus-infected cells, have long been known to concentrate. Scientists had observed NKT cells in the bloodstream, but little was known about how they functioned within the complex stew of nutrients, toxins, lipids, and other chemicals trapped in the labyrinth of microscopic

Davis: David Powers Littman: Chris Denney Marrack: Louie Psihoyos / Science Faction Images

Studying the immune system

in its natural state

"provides an essential reality check for

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vesicles that pervade the liver. By opening a flap in the membrane covering the organ, the researchers could deploy IVM to observe and record fluorescently labeled NKT cells going about their business.

Nothing in previous studies of NKT cells prepared the scientists for what they saw. Like other lymphocytes, NKT cells get pushed along by the blood's flow through the circulatory system. But inside the liver, their behavior is entirely different. The video images showed little self-propelled machines that crawled, amoeba-like, through the organ's tiny blood vessels. They moved swiftly yet seemingly at random, passing one another, changing direction, and even traveling against the flow of blood. Such apparently directionless, self-generated surveillance behavior—which continued until the NKT cells detected damage or infection and stopped in the vicinity of the problem to launch an immune response—had never before been observed.

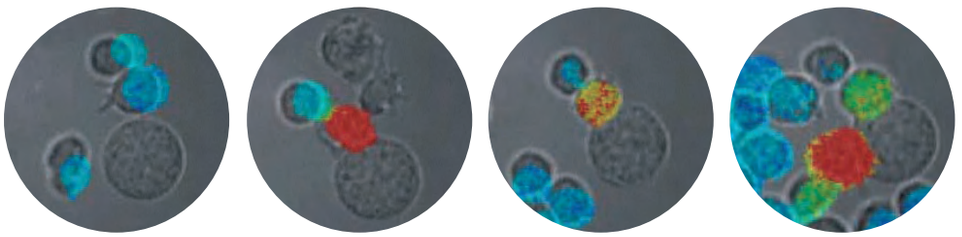
NKT cells are believed to play an important role in inflammation and may be involved in triggering chronic hepatitis. Now, says Littman, armed with knowledge about their normal movement in the liver, "We need to get at the mechanistic aspects of the NKT cells' surveillance behavior. Can we manipulate it in disease systems?" Developing ways to regulate that behavior could potentially lead to treatments that reduce the inflammatory response in hepatitis and other liver diseases.

Courtesy of the University of California, San Francisco

Attack of the hungry hookworm

Watching how the immune system responds throughout the body to a localized threat has provided new insights into autoimmune disorders, asthma, and allergies. Richard M. Locksley, an HHMI investigator at the University of California, San Francisco, has engineered a mouse with fluorescent probes in its immune-signaling system that light up when mucosal barriers, such as the intestinal lining or lung, come under attack. He introduced hookworms into the mouse's gut and then sliced and analyzed tissue from the entire mouse to find where the immune cells that signal such an attack, called effector cells, glowed. "This allowed us to find where every effector cell in the body ended up," Locksley says. As expected, certain known types of effector cells lit up in the intestinal lining where the hookworms bit. He was surprised, however, to find effector cells widely distributed, even in areas such as the lungs where the worms had not been. Watching these cells appear in such large numbers in the lungs in response to intestinal worms led Locksley to believe he had identified a response that overlaps with the lung's response to airborne irritants in asthma and other allergic disorders. He has made the mouse model freely available to the scientific community, encouraging others to use it to test new therapies for hookworms or other parasites, and to monitor effector cell activation and movement into unexpected places, such as the lungs and skin. "It's early days," he says, "but I'm convinced we're on the right track to show how these cells might contribute to chronic diseases like asthma. Eventually, manipulating the distribution and survival of these potent effector cells may provide new pathways for treating these diseases."

Still frames from a video of T cells interacting with GFP-labeled (green) antigen-presenting cells. Color overlaid on the cells highlights the intracellular calcium concentration of the T cells: Blue indicates low concentration; red is high. ***To watch the video, visit http://cmgm.stanford.edu/hhmi/mdavis/***



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ULRICH H. VON ANDRIAN

NEW PREDICTIVE POWER

The surface proteins, or ligands, on an invading cell must dock in a key-in-the-lock fashion with the T cell's own surface receptors for the T cell to launch an immune response. But Davis, who gained wide attention two decades ago for identifying and cloning T-cell receptor genes for the first time, observed that the binding of just one or two receptor-ligand pairs was not enough to signal the mobilization of an immune response. Because the videos that Davis's laboratory produces are so exquisitely precise that a viewer can literally count how many ligands a T cell must "see" before it reacts, he and his colleagues were able to observe that it takes at least 3, and typically around 10 ligands, for the immune system to spring into action.

"In the long term, [quantifying such interactions] is the way to determine that a certain input creates certain consequences for a cell," says Davis. "And you can only do this by imaging. That's how you get to the predictive power that has not been a part of cell biology before." As director of Stanford's Institute on Immunity, Transplantation, and Infection, Davis hopes this newfound capability will yield tools to outsmart cancer cells, improve organ transplantation, and devise better vaccines.

Using a different imaging technology—positron emission tomography (PET)—to scan the immune system, HHMI investigator Owen N. Witte has also been able to visualize—and quantify—the generation of an immune response deep in the body. In his laboratory at the University of California, Los Angeles, Witte and his team used PET to detect radioactive chemical tracers in immune cells of mice with a solid tumor. The PET studies could track the immune response throughout the mice's bodies. T cells normally remain relatively inactive in lymph nodes, which serve as T-cell reservoirs, but in his PET studies, nodes even some distance from a tumor showed T-cell activity at least 10 times higher than normal levels.

The tracers enabled the scientists to observe specific immune cells as they sprang into action in response to the cancer. "This lets us see not only how but where" the body is responding to disease, Witte explains. Eventually, he believes, such PET scans could allow clinicians to observe the ebb and flow of the immune system over the course of a disease, such as cancer or an autoimmune disorder, and to evaluate the effectiveness of treatment.

A COMPETITIVE EDGE

Meanwhile, HHMI investigator Philippa Marrack, a onetime doubter of the benefits of video recordings of the immune system in action, has been converted. Her team at the National Jewish Medical and Research Center in Denver will soon begin recording T cells to probe a phenomenon they discovered. They found that T cells compete with each other for antigens on a type of antigen-presenting cell called a dendritic cell. Dendritic cells gather antigens in tissue and then carry them into lymph nodes where they activate the T-cell response.

Now her laboratory is going to use multiphoton microscopy to find out if the T cells' competition leads the "winning" T cell to deny other T cells access to the antigen. This may prove important to the design of multivalent vaccines, which are composed of two or more antigens to stimulate a broader response to infection or a response to more than one type of disease. By recording the immune response in action when two antigens are present, she hopes to determine whether T-cell competition is undermining the immune response to multiple antigens. If so, perhaps this competition needs to be taken into account when designing certain types of multivalent vaccines, particularly complex DNA vaccines such as those being developed against HIV.

According to Davis, "You always have more questions to ask than the current state of the technology is capable of answering." But he believes the broadening array of video imaging studies will eventually lay out the molecular choreography of the immune system. Knowing just which steps and missteps occur in that biochemical dance may be key in improving health for all—from developing new vaccines to helping the body rid itself of cancer cells. ■

Courtesy of Davis lab


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Scientists need to store all of their data, not just what's published.

THERE'S GOLD IN THOSE ARCHIVES

BY KARYN HEDE // PHOTOGRAPH BY FREDRIK BRODÉN

In fall 2003, Beth Chen, a graduate student at the Watson School of Biological Sciences, Cold Spring Harbor Laboratory, went on a treasure hunt. Her quest was to fill knowledge gaps in the neural circuitry of the roundworm *Caenorhabditis elegans*—that ubiquitous experimental-model organism. Chen indeed "discovered" several new neural synapses and neuromuscular junctions, but she did it without so much as lifting a pipette or looking through a microscope.

The secret of her success was an archive of Sydney Brenner's work, a gold mine of many of the Nobel laureate's laboratory notebooks and thousands of his electron-microscopy (EM) images, mostly unpublished, on *C. elegans* anatomy. Chen spent several months poring over a dozen laboratory notebooks and more than 10,000 electron micrographs at the Albert Einstein College of Medicine's worm image archive, painstakingly reconstructing the neural connections that will inform her own research in the lab of Dmitri Chklovskii, an assistant professor at Cold Spring Harbor Laboratory and incoming group leader at HHMI's Janelia Farm Research Campus.

Chen prevailed because the Brenner archive was safely in the hands of David H. Hall, director of the Center for *C. elegans* Anatomy at Einstein, after it had sat moldering in boxes at the Medical Research Council (MRC) Laboratory of Molecular Biology in Cambridge, England, for more than 15 years. Hall had long cajoled people at MRC, convincing them to let him become the keeper of all that potentially useful worm image data.

There was a time when EM was a workhorse of biological research. But in the early 1980s, the genome revolution forced a radical change as scientists abandoned EM slides for DNA sequencing gels in a quest to get at the genetic secrets of *C. elegans*. Lost in this shift of resources was a massive amount of primary data, including maps of the complete neural circuitry of *C. elegans* collected mainly by Brenner and John G. White, now at the University of Wisconsin–Madison, while at MRC.

"By the mid-1990s, I was the only person left who could make sense of the records," says Hall, an expert on *C. elegans* anatomy. "It would

HELPFUL HINTS FROM THE PROFESSIONALS

With more than 45 years' experience helping scientists archive their life's work, the American Institute of Physics has put together a short guide to assist scientists in maintaining their personal archives: http://aip.org/history/source.htm ¶ For biomedical researchers searching for a home for their archives, Paul Theerman, head of images and archives at the National Library of Medicine (NLM)'s History of Medicine Division, suggests first contacting the library at your home institution. If that fails, NLM will try to work with you to find a permanent home for them (http://www.nlm.nih.gov/hmd/about/contactus.html). ¶ For advice on storing primary data, HHMI has put together a guide to managing the scientific laboratory: www.hhmi.org/labmanagement ¶ For more information about the Jackson Laboratory's Mouse Gene Expression Database, visit http://www.informatics.jax.org/mgihome/GXD/aboutGXD.shtml

"THERE IS NO WAY WE CAN HAVE THE F TO KNOW WHAT WIL IMPORTANT 10 OR 50 FROM NOW."

CONSTANCE CEPKO The challenge of storing the vast amount of data generated by her research has her searching for commercial solutions.

all have been lost. I took a personal interest to make sure that didn't happen. My data sets and the MRC data sets were extremely complementary. It just made sense to put them together in one place."

The research community has lately come full circle, however, because scientists are now eager to connect their molecular data to the detailed anatomical studies that Brenner, White, and their colleagues labored over for years. Researchers are flocking to access Hall's treasure trove of data; he gets 20 to 30 visitors and thousands of Web site hits per week. Hall is in the process of digitizing as many of the approximately 200,000 images as possible, with about 5,000 now available at his Web site (www.wormimage.org).

"We couldn't have done everything," says Brenner about cataloging the collection. "There was too much data there for the one project. But it testifies to the integrity of the result that it can be used over and over again. And it shows the importance of keeping primary data where others can use it."

Remarkably, no one besides Hall seems to have foreseen that the worm images would become so valuable. Although most scientists would agree that primary data should be saved, in some cases data can become outdated to the point that no one can interpret them.

"There will always be a need to go back and look at primary data," says John Spieth, group leader at the Genome Sequencing Center at Washington University in St. Louis School of Medicine. "There is no way we can have the foresight to know what will be important 10 or 50 years from now."

But saving data goes way beyond collecting a pile of graduate student notebooks and theses on a dusty top shelf. A quiet crisis looms in many labs as the volume of data generated by large-scale science grows at an alarming rate. Individual laboratories are struggling to find efficient and economical ways to store and retrieve key data. Many researchers have coped alone thus far, but some are now looking to large centralized archiving systems to bear part of the burden. And the rapidity of technology development, for example, has prompted Spieth to resequence parts of the *C. elegans* genome rather than rely on decade-old sequence data produced by technology that is now considered antiquated. Reacquiring data may work for large centralized data centers, but in individual labs, changing technology has often meant keeping antiquated equipment around so that data are not lost.

"Computer hardware and software quickly become obsolete, so that unless you hold on to your old computers the data you backed up with them may become difficult if not impossible to recover," says Terrence J. Sejnowski, a computational neuroscientist and HHMI investigator at the Salk Institute for Biological Studies in La Jolla. "It's something we have to live with."

ORESIGHT L BE YEARS

ARCHIVING LARGE DATABASES

Retaining all that material is easier said than done, however.

"It's a problem for everybody," says HHMI investigator Constance L. Cepko, a neurobiologist at Harvard Medical School who studies the structure and function of the eye in vertebrates. "In trying to link DNA clones, in-situ images, and microarray data, we can generate 30,000 data points in one experiment." She and her colleagues considered commercial data-management packages and high-tech start-up services for archiving such data, but none filled their needs. At present, an M.D.-Ph.D. student is setting up a customized relational database, but it is just a temporary solution.

Cepko says that because the volume of data her lab generates is rapidly filling servers, she is looking to a centralized archiving

Jason Grow

system, such as the Mouse Gene Expression Database at the Jackson Laboratory (TJL) in Bar Harbor, Maine, to take some of the data off her hands. TJL aims to make the database, funded by the National Institutes of Health, the leading archive of mouse genomic and proteomic data, and is actively soliciting and adding primary data to its curated, annotated database.

In much the same spirit, Sejnowski has an agreement with the San Diego Supercomputing Center, which maintains and archives all of his lab's large data sets. "You have to find a partner," he insists. "Data have become so unwieldy that managing them is too much for any one lab to handle on its own."

HHMI investigator Norbert Perrimon, who studies cell signaling at Harvard Medical School, found the solution to his data-management problems—at least, for the time being—by setting up a centralized public database to store the results of his lab's RNA interference screens in *Drosophila*. Its infrastructure was funded by a grant from the National Institutes of Health, which allowed him to hire two full-time programmers to get the job done.

But in the long run, the solution will depend on cheaper ways of storing data as well as being more selective, says Perrimon. "The issue that we are facing now is that we do not yet know what is worth keeping in these large-scale studies because the [RNAi] field is not very mature yet. We need to spend more time on data analysis to figure out what has real value in the data sets." So, for the time being, he is storing it all.

Paul W. Sternberg, an HHMI investigator at the California Institute of Technology, believes the answer may lie in more intelligent searching. "My general feeling is that we know a lot more than we think we do in biology," he says. "We aren't taking full advantage of what already exists out there. Digital storage is cheap. We should be archiving and making retrievable unpublished primary data." He is working on systems that will allow scientists to combine primary data from disparate sources, allowing them to develop new hypotheses by combining what he calls "weak hints," which tend to be overlooked when sources are assessed individually.

In the March 10, 2006, issue of *Science*, Sternberg and colleagues described how to apply such a computational approach to integrating published data on how genes interact with each other in roundworms, fruit flies, and yeast. "We now know that mining published and available data is valuable," Sternberg says. "Imagine what we could do if we could access the likely larger amount of unpublished information."

Sternberg believes this idea also extends to updating that laboratory mainstay, the lab notebook. "The new generation is more comfortable with electronic notebooks," he says. One of his graduate students keeps a personal blog on the lab's private intranet for recording observations and ideas. "I would have kept that kind of thing in a margin of my [paper] notebook," says Sternberg. "But then how would I ever find it again? In digital form, you can search and organize thoughts and ideas—and have instant recall."

A COMPLETE RECORD

In his 1965 Nobel Prize address, physicist Richard P. Feynman revealed one of the rarely uttered secrets of scientists. "We have a

When Articles and Data Go AWOL

JEREMY NATHANS If you're counting on your published articles serving as a record of your research, he warns, think again.

Jeremy Nathans, an HHMI investigator at the Johns Hopkins University School of Medicine, remembers searching for an article he considers to be a landmark publication. Citation in hand, he figured the fastest way to find it would be a quick PubMed search to link to the original article, which appeared in the journal *Nature* in 1978. He found nothing. The article had been missed in the process of adding pre–computer-era articles to the PubMed database, which includes citations and abstracts for virtually all published biomedical literature. ¶ Eventually, Nathans tracked down the article by contacting the author, who scanned the original print document and sent a grainy PDF file. But Nathans was still left with an uneasy feeling. Because scientists rely so heavily on PubMed searches, he reasoned, if it doesn't appear there "it's as if it had never existed." (*Nature* has since added that particular article to its electronic archive.) ¶ Research results can also disappear when they are relegated to the ranks of "supplemental data" when a journal article is published. These data are only available online, and do not always print out along with the main article. "A lot of us believe that the best way to store data is by publishing them," says Nathans. "But now journals are telling us to put so much in supplemental data, and that gets divorced from the published article." ¶ "This issue of supplemental data is becoming

Bill Denison

NORBERT PERRIMON A grant funded the centralized public database he set up to manage his RNA interference data.

habit," he observed, "in writing articles published in scientific journals to make the work as finished as possible to cover all the tracks, to not worry about the blind alleys or to describe how you had the wrong idea first."

Scientists are so acculturated to think of published literature as the ultimate archive of their life's work that they sometimes overlook the need to save the many other pieces. But science historians and archivists are often highly interested in, say, bumps in the road, which are often hidden in, or missing from, the clean and logical progression of ideas presented in the scientific literature. "Scientists have trouble understanding us," says R. Joseph Anderson, an archivist at the American Institute of Physics. "We want all their documents that are likely to have historical value. It's a matter of keeping a complete record."

Thus, scientists should keep materials such as early versions of manuscripts, correspondence, photos, minutes of scientific meetings, and especially correspondence and lab notebooks, which not only help scientific colleagues in their research but may also help science historians glean the thought processes that go into developing science policy.

"People think of archives as quaint," says Clare Flemming, curator of research collections at The Explorers Club, in New York City. "What curators at scientific collections do isn't splashy, but when you think about it, material without provenance is meaningless. If someone comes along later and disagrees with your result, and no one can find the data, what happens then? The whole foundation of science is predicated on information being able to be duplicated."

Still, "It's hard to know what's going to be helpful in the future," says Miriam Spectre, an archivist who organized and described the Barbara McClintock Papers at the American Philosophical Society in Philadelphia. Spectre says that while most of the 1983 Nobel laureate's laboratory notebooks describing her seminal work on transposable genetic elements survived, McClintock destroyed most of her correspondence before she died. "We sure would like to have had that," Spectre says. ■

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bigger and bigger," says Edwin Sequeira, policy coordinator for PubMed Central, an electronic complement to PubMed that offers free access to full-text journal articles at the National Library of Medicine. "I see it as an economic decision not to put all of the data into print, but I would argue that if the data are important enough to include at all, they are an integral part of an article and should be treated as such." ¶ Further, says Sequeira, not all journal publishers provide supplemental data when sending their articles for archiving. If a publisher goes out of business, there's no guarantee that those types of materials in its possession will survive. He thinks that as long as scientists are providing such supplemental materials, they should make sure the journals are supplying them to PubMed Central along with the article they complement. ¶ Traditionally, publishers have relied on libraries to maintain long-term archives, but in the digital age that role is in transition. Librarians, publishers, and the scientific community are grappling with how libraries will maintain the role of storing published articles and their supplemental data in the digital age. ¶ One potential solution is now being explored by a consortium organized by Stanford University Libraries. The system, called LOCKSS (http://lockss.stanford.edu) collects newly published content from participating publishers by using a Web crawler that compares the content it has collected with the same content collected by other LOCKSS users and repairs any discrepancies. The system, initiated by a small team of librarians and engineers, provides a mechanism to guarantee libraries long-term access to complete content by making multiple copies of published data stored at all participating sites. If one site has a technical problem, data can be restored from any of the other sites. Some scientific publishers have begun to buy into the system, which is still in its infancy. To date, 80 major research libraries in the United States and 25 in Europe, as well as others scattered around the world, are participating. *(continued on page 56)*

Jason Grow

Mitochondria are doing more than just keeping the cell's furnace stoked.

The Powerhouse—and Sentinel—of the Cell

by Karen F. Schmidt

LOOK UP "MITOCHONDRIA" IN ANY SCIENCE TEXT AND INVARIABLY THESE TUBULAR BAGS OF ENZYMES THAT FLOAT IN THE CELL'S INTERIOR ARE CALLED "THE POWER HOUSES OF THE CELL." OF COURSE, THE ROLE THEY PLAY AS CELLULAR FURNACES, converting nutrients and oxygen into energy, is immensely important. Every cell needs ATP—the chemical fuel generated by mitochondria—and some cells are particularly demanding: a muscle cell that pushes the leg into a sprint, a beta cell in the pancreas that synthesizes the hormone insulin, a brain cell that fires a signal to help create a thought. Each of these kinds of cells contains as many as 10,000 mitochondria, and it's no secret that those tiny organelles keep the home fires burning. • However, recent studies suggest that mitochondria do much more than generate energy. They are intimately involved in cell signaling, raising a red flag during times of cellular stress, such as when viruses invade or oxygen levels drop.

photograph by Mark Hooper

It now appears that subtle abnormalities in mitochondria contribute not only to rare metabolic disorders but also to many common diseases, including chronic hepatitis, cancer, and certain aging-related diseases, such as type 2 diabetes. Says Gerald I. Shulman, an HHMI investigator at Yale University School of Medicine whose area of expertise is diabetes, "We're moving into areas that affect large numbers of people—the 7 percent of the population with diabetes—and that gets a lot of attention."

These days, mitochondria often take scientists by surprise. "Researchers keep stumbling into mitochondria," says Gerald S. Shadel, a molecular biologist at Yale University School of Medicine who studies mitochondria and disease. "That probably reflects the fact that mitochondria are involved in many things besides what was historically assigned to them; people in many fields are now making important connections."

Signaling Immunity

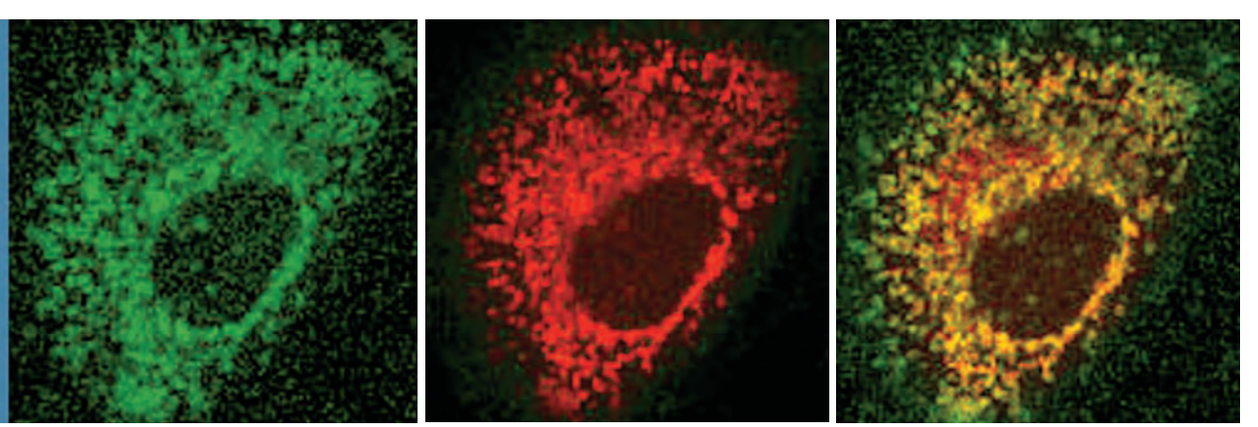
RESEARCH ON MITOCHONDRIA HEATED UP IN THE 1990s, WHEN STUDIES REVEALED THAT THEY PLAY A KEY ROLE IN SIGNALING PROGRAMMED CELL DEATH. In 1996, Xiaodong Wang, an HHMI investigator at the University of Texas Southwestern Medical Center at Dallas, made the surprising discovery that mitochondria release a molecule called cytochrome *c*, triggering a signaling cascade that leads to cell suicide, usually during embryonic development or in response to cellular stress or damage. Then, in 2001, the late HHMI investigator Stanley J. Korsmeyer reported that the activation of a pore in the mitochondrial membrane launches this process by enabling the cytochrome *c* signal to flow into the rest of the cell.

Now, another protein in the mitochondrial membrane has been discovered that for the first time links this organelle to the immune system. Zhijian "James" Chen, an HHMI investigator also at the University of Texas Southwestern Medical Center, found a protein in the mitochondrial membrane that contributes to viral defense. Chen wanted to know how cells detect and mount a response to infection by a virus—in particular, what activates the cell to produce important antiviral molecules called interferons (which are also used as medical therapies). His team searched for signaling proteins involved in antiviral immune responses and found a protein that appeared to activate two transcription factors known to trigger interferon production. They then engineered cells that express large amounts of this protein and grew them in culture with viruses. Monitoring to see what would happen, they found that the cells had gained antiviral immunity. Conversely, when they silenced the protein's expression, the resulting cells were swamped with replicating viruses.

The big surprise came when the group broke open the cells, spun them in a centrifuge, and found this protein not in the liquid extract but in the fatty membrane fraction. Using confocal microscopy, they pinpointed its location in the mitochondrial membrane and so decided to name it Mitochondrial Antiviral Signaling Protein, or MAVS. "It was quite surprising, but also very exciting," says Chen, because this was the first time anyone had found a protein involved in immunity that was part of the mitochondrion. In fact, several other groups had encountered the same protein but didn't figure out its cellular location, which, Chen's team found, is essential for the signaling function of MAVS.

The group reported their findings in the September 9, 2005, issue of *Cell*; soon after, *Science STKE* named the discovery of MAVS one of the "signaling breakthroughs" of the year. Eric A. Shoubridge, a human geneticist and HHMI international research scholar at McGill University, in Montreal, Canada, says, "Chen's work is pretty exciting stuff. Random bits of information had suggested that mitochondria might be involved in signaling and the immune system,

Confocal microscopy images show a cell stained with an antibody for the MAVS protein (left, green) and a mitochondria-specific dye (center, red). An overlay of the green and red images (right) indicates the mitochondrial localization of MAVS.



Courtesy of Rashu B. Seth and Zhijian "James" Chen

but this work is the clearest evidence yet—it's very convincing."

Once he discovered MAVS, Chen investigated whether some viruses could specifically target the protein to cripple a host's defenses. "After we found MAVS, we suspected maybe it was the long-sought-after target for the hepatitis C virus," he explains. Of the 170 million people in the world with hepatitis C, about 80 percent have persistent, chronic infections; their interferon production is suppressed. Sure enough, Chen's group discovered that the hepatitis C virus, using an enzyme called a protease, can clip MAVS off the mitochondrial membrane, effectively breaking the signaling pathway that triggers interferon production. The group reported these findings in the December 6, 2005, issue of the *Proceedings of the National Academy of Sciences*.

Chen's team further observed that a change in just one letter of the MAVS genetic code—the kind of simple mutation that typically distinguishes the DNA of one individual from that of another—protects it from being clipped by the viral protease. This observation may explain why some people are better than others at fighting off hepatitis C infection and suggests an important target for drug treatments. "If we could come up with an inhibitor of the viral protease, we could prevent viral replication and also restore [interferon production in] the host immune system—like killing two birds with one stone," says Chen.

A lot more remains to be learned about MAVS. Chen's group is exploring whether other viruses also target MAVS, whether other mechanisms can be used to cripple it, and whether MAVS serves any other functions in the cell. For instance, does MAVS ever talk to neighboring membrane proteins and tell them to trigger cell suicide? Theoretically, it would make sense for cells to use suicide as an additional antiviral strategy; plant cells are known to use it to limit the spread of infection for the benefit of the whole organism. "Maybe if a mammalian cell can't produce enough interferons, then it will need to die," Chen theorizes. However, any link between MAVS and cell suicide is still speculative, he says.

Low-Oxygen Alert

—IN MOST TISSUES, MITOCHONDRIA CONSUME 90 PERCENT OF THE OXYGEN THAT ENTERS THE BODY, SO IT MAKES SENSE THAT MITOCHONDRIA WOULD FUNCTION AS oxygen sensors as well. M. Celeste Simon, an HHMI investigator at the University of Pennsylvania *(continued on page 32)*

Numbers game: Is more better?

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SCIENTISTS HAVE *known for more than two decades that type 2 diabetes begins its development as "insulin resistance," in which tissues such as muscle respond poorly to the hormone insulin and, therefore, don't facilitate glucose transport out of the blood and into muscle cells where it is metabolized. It made sense to Gerald I. Shulman, an HHMI investigator at Yale University School of Medicine, that insulin resistance might be linked to mitochondrial function. After all, mitochondria convert glucose and fatty acids into energy—by a process called oxidation—and people with diabetes have too much unburned glucose in their blood, and too much fat in their muscle and liver cells.* • SO HIS GROUP *developed a novel method to tell how well mitochondria are functioning, using NMR methods to noninvasively measure rates of oxidation and ATP production. In 2003, Shulman's team reported evidence in lean, healthy, elderly volunteers that an age-related decline in mitochondrial function may contribute to insulin resistance. They hypothesized that reduced mitochondrial function predisposed these older people to accumulate fat in muscle and liver cells, and that, in turn, led to defective insulin signaling and then insulin resistance.* • IN AN INTERESTING *twist, however, Shulman's most recent study suggests that reduced mitochondrial function might also be caused by low overall numbers of mitochondria—at least in young, lean adults whose parents have type 2 diabetes. The researchers had previously studied this group and detected reduced rates of oxidation and ATP production in their muscle cells. Next, Shulman's team decided to take tissue samples and use an electron microscope to count the number of mitochondria. The samples—which already exhibited large amounts of intracellular fat, insulin resistance, and signs of impaired insulin signaling—had on average 38 percent fewer mitochondria than normal. The results of the study appear in the December 2005 issue of the* Journal of Clinical Investigation. *"Our data suggest that reduced mitochondrial function in this young group can be attributed to their low numbers of mitochondria," Shulman says. Now, the team is trying to determine whether intracellular fat accumulation might cause the low numbers, or vice versa. And how important are mitochondrial numbers? "Having more mitochondria might seem to be better, but it's probably not as simple as that," says Shulman.* • SCIENTISTS *still have much to learn about how the cell senses that it should make more mitochondria or has enough already, according to David A. Clayton, HHMI's vice president and chief scientific officer. "The Holy Grail in this field at every seminar is: How does the cell regulate the number of mitochondria? It's a challenging question." Researchers know that nuclear genes control the biogenesis of mitochondria (which have their own DNA), that tissues naturally have 100 to 10,000 mitochondria per cell, and that exercise increases the number of mitochondria in muscles. As scientists fill in the details, they expect to find many additional signaling pathways at the crossroads, Clayton notes.*

CELESTE SIMON *studies cellular responses to oxygen deprivation.*

"Understanding how oxygen levels are sensed and adapted to is fundamentally important to dealing with pretty much all of the major diseases that we encounter—atherosclerosis, autoimmune disease, stroke, and cancer."

CELESTE SIMON

School of Medicine, decided to explore this idea in 1997. "Understanding how oxygen levels are sensed and adapted to is fundamentally important to dealing with pretty much all of the major diseases that we encounter—atherosclerosis, autoimmune disease, stroke, and cancer," she says. For instance, solid tumors begin to grow outside the body's circulatory system, where oxygen levels are low, and they do so by turning on signals that tell tissues to sprout new blood vessels. Understanding how to disrupt this signaling might lead to new cancer treatments. Normal adult tissues, such as kidneys, can also experience low oxygen because of poor circulation and other dysfunctions. In that case, if doctors could enhance the signaling process, they might be able to promote blood vessel development and restore an organ's function.

Research on how cells respond to low oxygen, or hypoxia, took off in 1995, when a transcription factor named hypoxia-inducible factor, or HIF, was isolated and later shown to activate blood vessel formation and make cancer more aggressive. When Simon began her studies, a key question needed answering: What signals cause HIF to accumulate when oxygen levels drop? Some researchers theorized that HIF directly sensed oxygen, but Simon and others decided to look to mitochondria for signals. The first clue came when her research team suppressed mitochondrial metabolism in a cell culture and found that HIF no longer accumulated during hypoxia.

Now, after a series of experiments, Simon's group has strong evidence that metabolic by-products generated inside mitochondria called reactive oxygen species, or ROS, serve as important signals that stabilize HIF during hypoxia. The team reported its most recent findings in *Cell Metabolism* in June 2005.

For these studies, Simon's team developed a tool to measure extremely small changes in ROS in real time under the microscope. With this probe, they showed that ROS are produced in larger amounts in mitochondria during hypoxia. Next, the team tinkered with the cells to suppress the amount of ROS they could produce—first by knocking out an important gene and then by adding an enzyme that specifically scavenges ROS. In both cases, without ROS the cells could not launch the normal response to low oxygen. These results suggest that ROS is a necessary signal to cause HIF accumulation during hypoxia.

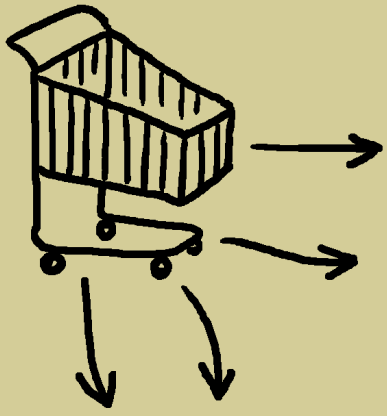
Simon's working hypothesis is that ROS are released into the fluid portion of the cell's interior, where they inhibit enzymes called HIF hydroxylases that lead to HIF degradation when oxygen levels are normal. Thus, HIF builds up and then sets in motion the cell's hypoxic response—activating the myriad genes that lead to blood vessel development and cell motility, for example. Yale's Shadel comments, "Simon has uncovered how this oxygen sensing has consequences beyond respiration—mitochondria are not just sensing oxygen for their own need but are telling the cell that it's low in oxygen and that it needs to initiate a response."

Some other labs have reported findings that support the theory that HIF hydroxylases (the enzymes leading to HIF degradation) serve as oxygen sensors. Simon reconciles the data by suggesting that two separate pathways may operate, one under extreme hypoxia (0.1 percent oxygen) and the other under modest hypoxia (1–3 percent oxygen). Her results indicate that when oxygen is nearly absent, mitochondria cease to be the dominant player and HIF hydroxylases become the oxygen sensor. However, she adds, cells in the body are more likely to encounter the conditions of modest hypoxia that she studies.

Understanding how mitochondria are involved in sensing and signaling may ultimately lead to new models for many diseases and their treatments. Researchers now know that mitochondrial dysfunction could affect more than just the cell's ability to produce energy, says Simon. "Many metabolites produced in the mitochondria have an impact on the rest of the cell, and these will be really important to consider in disease." As Shadel puts it, "The role of mitochondria in the cell is grossly underestimated, as is their role in human disease." ■

William Vazquez

The vision is set. The structures are built. Time to fill the empty spaces. Janelia Farm, HHMI's new research community in Loudoun County, Virginia, will be "a place for passionate, excited scientists to interact and collaborate, free from many of the distractions that make life in a modern university so hectic and scheduled," says Janelia Farm Director Gerald M. Rubin. Making that happen means hiring the staff and buying the supplies and equipment that will outfit the main campus building and its 21 labs, plus finding just the right amenities for the 96-room hotel and 53 apartments to make visiting scientists feel at home—and ready to work. No time to waste. Janelia Farm is slated to open its doors to research this summer.



EXTREMESHOPPING

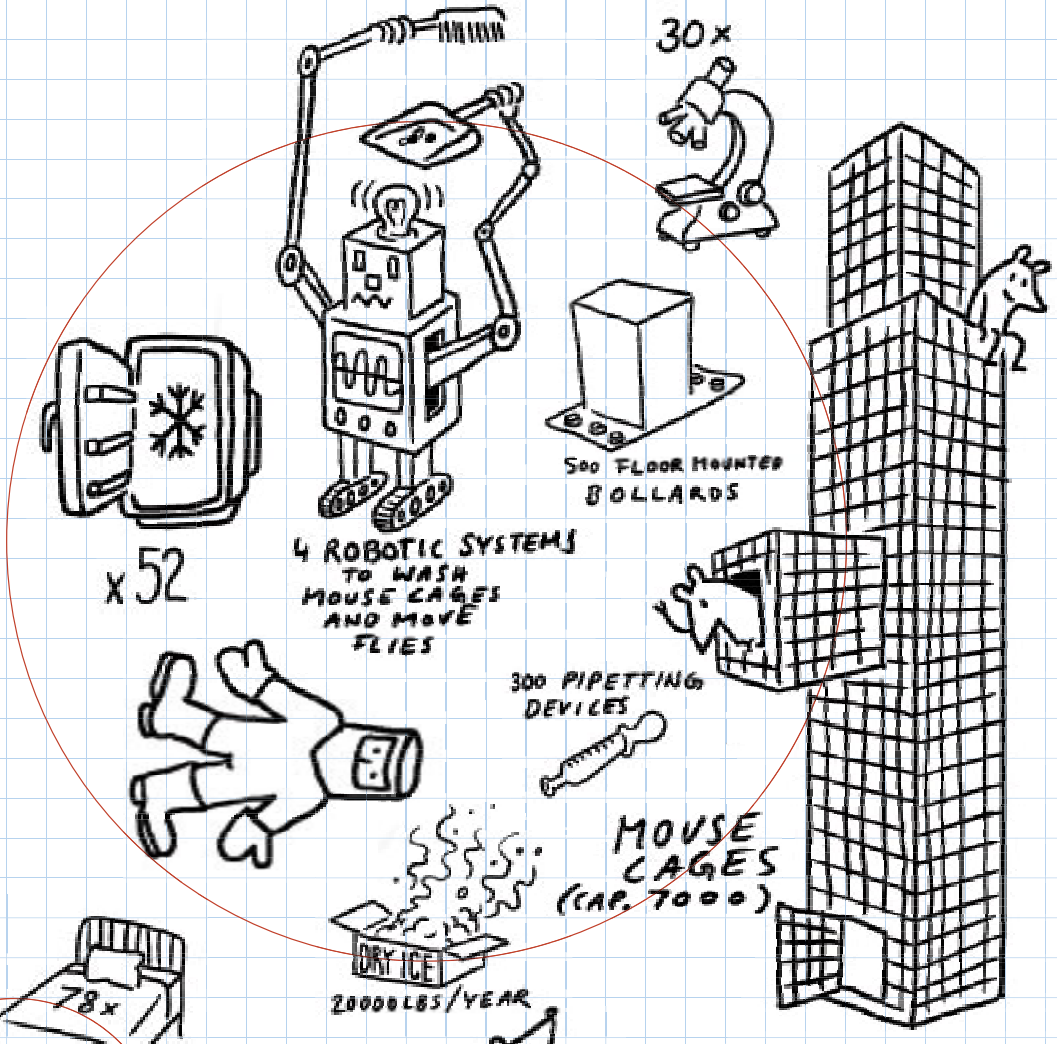
TO DESIGN, STOCK, AND STAFF THE JANELIA FARM RESEARCH CAMPUS, A HANDFUL OF CREATIVE PLANNERS ARE DOING SOME MAJOR PROCURING.

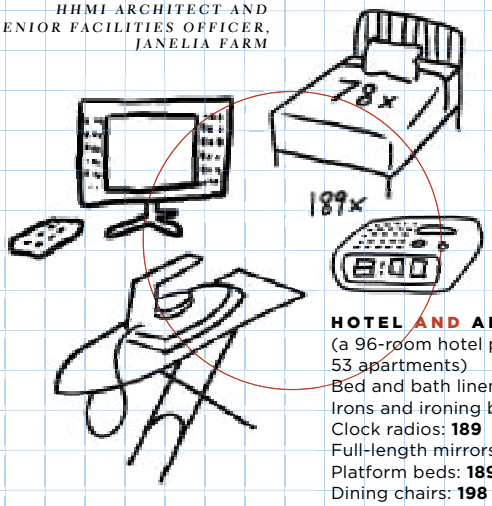
BY KATHRYN BROWN XXXXXX ILLUSTRATIONS BY CHRISTOPH NIEMANN

SCIENTIFIC EQUIPMENT (FOR 21 LAB AREAS)
Floor-mounted bollards (service pedestals): **500**
Industrial robotic systems to wash mouse cages and move flies: **4**
Lab robotic systems to sequence DNA, do molecular biology: **up to 5**
Freezers: **52**
Hoods (fume and biosafety): **30**
Computer-aided manufacturing tools to build machines: **3**
Transmission electron microscopes: **3**
Optical microscopes: **30**
Pipetting devices: **300**
Dry ice (est. lbs per year): **20,000**
Items in central laboratory supply stockroom (includes beakers, chemicals, bench-top centrifuges, etc.): **500**
Mouse cages (capacity): **7,000**

"Unlike any other lab in the country, the lab benches at Janelia Farm back up to floor-mounted bollards, or service pedestals, that look kind of like tombstones. The bollards—which include electrical power outlets, computer connections, and more—allow the labs to be dismantled and reconfigured for computer use, lab work, or other needs."

ROBERT H. McGHEE, HHMI ARCHITECT AND SENIOR FACILITIES OFFICER, JANELIA FARM



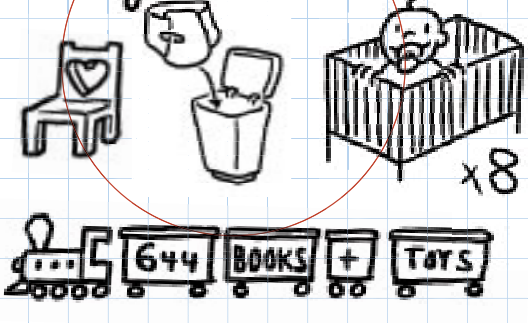


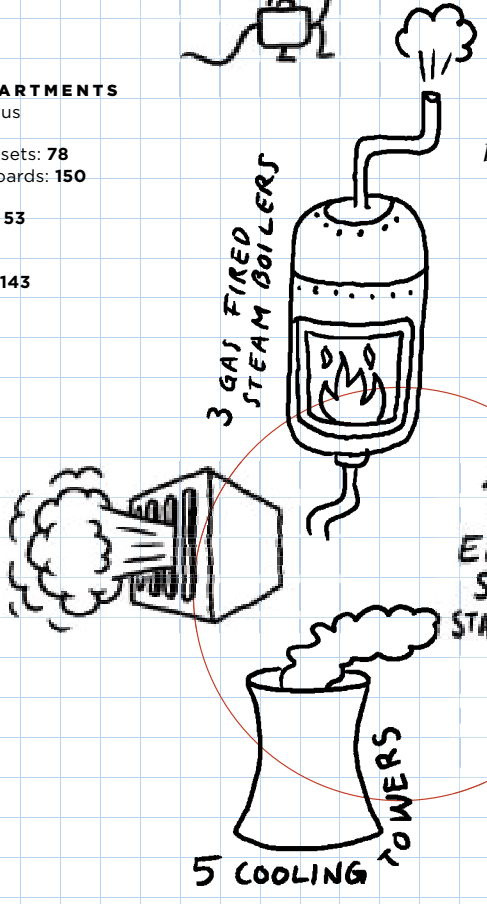
HOTEL AND APARTMENTS
(a 96-room hotel plus 53 apartments)
Bed and bath linen sets: **78**
Irons and ironing boards: **150**
Clock radios: **189**
Full-length mirrors: **53**
Platform beds: **189**
Dining chairs: **198**
Plasma televisions: **143**

"Getting the gigantic boilers to Janelia was quite an adventure. They came in on a 150-foot flatbed trailer. It took hours for crews to carefully navigate the stretch from Route 7 to Janelia's boiler room—which is probably no more than half a mile."

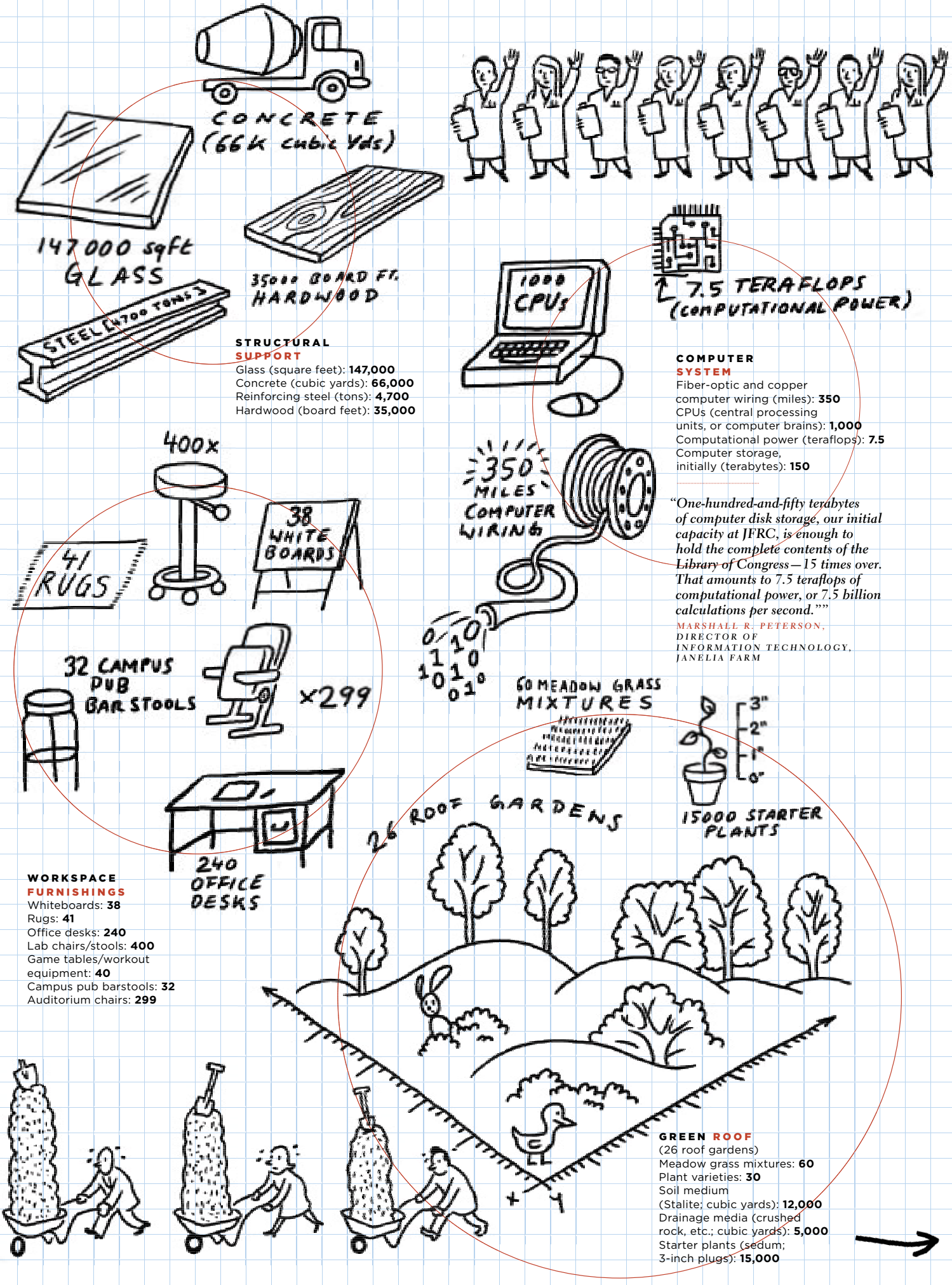
HOWARD MICHAEL DAY, DIRECTOR OF FACILITIES, JANELIA FARM

DAY CARE
(five classrooms for 50 children ages 5 and under)
Outdoor toys: **31**
Children's cots: **20**
Cribs: **8**
Wooden chairs: **22**
Books and indoor toys: **644**
Diaper pail: **1**





MECHANICAL GUTS
Gas-fired steam boilers (two 1500 hp, one 900 hp): **3**
Cooling towers (1,200 tons each): **5**
Chillers (1,200 tons each): **5**
Air handling units (45,000 cubic feet per minute): **15**
Electrical substations (35 kilovolt-amperes): **3**



STRUCTURAL SUPPORT
Glass (square feet): **147,000**
Concrete (cubic yards): **66,000**
Reinforcing steel (tons): **4,700**
Hardwood (board feet): **35,000**

COMPUTER SYSTEM
Fiber-optic and copper computer wiring (miles): **350**
CPUs (central processing units, or computer brains): **1,000**
Computational power (teraflops): **7.5**
Computer storage, initially (terabytes): **150**

"One-hundred-and-fifty terabytes of computer disk storage, our initial capacity at JFRC, is enough to hold the complete contents of the Library of Congress—15 times over. That amounts to 7.5 teraflops of computational power, or 7.5 billion calculations per second.""
MARSHALL R. PETERSON, DIRECTOR OF INFORMATION TECHNOLOGY, JANELIA FARM

WORKSPACE FURNISHINGS
Whiteboards: **38**
Rugs: **41**
Office desks: **240**
Lab chairs/stools: **400**
Game tables/workout equipment: **40**
Campus pub barstools: **32**
Auditorium chairs: **299**

GREEN ROOF
(26 roof gardens)
Meadow grass mixtures: **60**
Plant varieties: **30**
Soil medium (Stalite; cubic yards): **12,000**
Drainage media (crushed rock, etc.; cubic yards): **5,000**
Starter plants (sedum; 3-inch plugs): **15,000**

CHERYL MOORE: THE WOMAN BEHIND THE INFRASTRUCTURE

"CREATING AN EASY ENVIRONMENT IS NO EASY JOB."

CHERYL MOORE lives within 10 miles of her office, gets 8 hours of sleep most nights, and limits herself to one cup of coffee a day. Those numbers, she says, are "the only constant sanity" in her workweek.

As Janelia Farm's chief operating officer, Moore spends her time creating, from scratch, the environment that will greet Janelia Farm scientists when they arrive on the campus, which formally opens this summer. Decisions—from budgets and staffing to operations, and involving issues profound and mundane—dominate her days: How can HHMI ensure that scientists on campus frequently rub elbows, engaging in a social form of Brownian motion? Are we ordering the right supplies for the stockroom? How much should soda cost on campus?

Willowy and brisk, Moore, age 40, has a quick, confident laugh and an air of quiet focus. Her office is a cheerful yellow, evoking her previous home in sunny San Diego, California, where she served as senior vice president/chief operating officer for The Burnham Institute, a nonprofit organization devoted to biomedical research. Today, the view from Moore's office is decidedly mid-Atlantic, with a window framing the Virginia meadow that tops Janelia Farm's green roof.

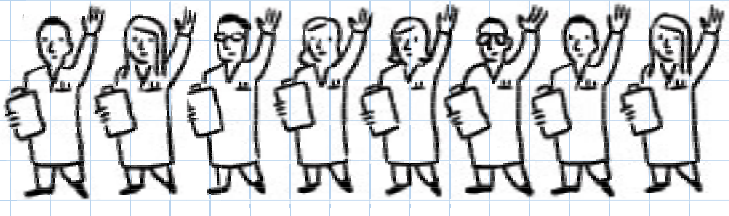
"Everything I am working on is designed to create a culture in which science can move forward, free from bureaucratic hassle," says Moore, who started planning for Janelia's opening 2 years ago. "If we succeed," she says, "scientists at Janelia will enjoy a kind of tunnel vision, focusing on their work in an environment of quiet comfort. My goal is to use common sense, rather than a detailed rule book, to respond to situations that arise. The trick is to make the complexity of federal, state, and Institute rules invisible to our researchers. They'll just need to explain to us what they're trying to do, and we'll figure out how to get them what they need. This is the type of customer service–driven support team we're building."

The difficult part of her job, Moore admits, is that "none of this exists yet." She begins each day by scanning her to-do list, which typically runs several pages, with a half-dozen must-do-immediately tasks and an additional 40 to 50 with a turnaround time of about a week. Although addicted to her BlackBerry and Microsoft Outlook, Moore says her favorite organizational tool is decidedly retro—a spiral notebook. In it, she reserves a page for each of Janelia Farm's five operational directors as well as for other staff—including Gerry Rubin (Janelia's director) and Kevin Moses (associate director for science and training). When an issue pops up, she jots a reminder on the indicated page to discuss that issue with the appropriate person. Then, during meetings or chance hallway chats, out comes the notebook.

And there are plenty of encounters, planned or otherwise. Every week, in addition to dozens of informal conversations, Moore holds an individual hourly meeting with Moses and with each Janelia Farm operational director. "About six or seven times a day, we'll have a quick stand-up meeting in the hall to brief those who need to know about a change that's just happened," she says. Rubin and Moore also share the occasional marathon planning session.

Until recently, Moore—a semi-vegetarian who favors ethnic dishes such as spicy black bean soup—typically worked through lunch, eating at her desk. But having noticed that most of Janelia Farm's current staff was doing the same, she began booking the conference room at noon to encourage everyone to come together and eat.

In much the same way, she is making nuts-and-bolts decisions aimed at enabling



Cheryl Moore: Paul Fetters

interaction among Janelia's future workforce. In fact, lunch is one example. When the campus formally opens for business, the cafeteria will offer a compressed lunch hour. The idea, Moore says, is to balance a scientist's desire to grab a quick lunch and return to work with HHMI's desire to foster brainstorming and bonding on campus. "We want to increase people's opportunity to bump into each other," she explains. But quickly feeding hundreds of scientists isn't a piece of cake, so to speak. To help make it work, Janelia Farm will implement a cashless purchase system in which staff members use swipe cards to pay for lunch, thereby speeding checkout.

To cultivate contact in the afternoon, the facility will host a daily 30-minute tea, with free snacks, in the campus pub. Rubin and Moore plan to attend.

Another item on the agenda is how to design orientation for Janelia Farm researchers. Moore and others have decided that incoming scientists will attend one full day of orientation that covers practical topics such as how to get a cashless charge card, how to order supplies, where the support labs are, and how to get a computer account as well as dozens of other issues big and small. "When they walk out of those sessions," she expects, "they'll be ready to hit the ground running."

A bigger and more immediate task for Moore is interviewing candidates for jobs at Janelia Farm. A comprehensive administrative and support staff will include individuals to run the campus machine shop, electronic library, shared scientific resources, computer network, and other services. When fully operational, Janelia Farm will employ an estimated 300 resident scientists, 100 visiting scientists, and 80 other staff.

"The details of each day vary, with different decisions to be made," Moore says. "But I'm always working on the same basic thing: infrastructure for creating an environment in which science can move forward. That means setting our top priorities, constantly reviewing them, and slowly working our way through the list." There are days when that list seems to stretch to the horizon. Thankfully, drugstores stock lots of spiral notebooks. ■

Photos: Paul Fetters

"SCIENTISTS AT JANELIA WILL ENJOY A KIND OF TUNNEL VISION."

MAKING IT HAPPEN

As Cheryl Moore assembled an operational team, she looked for staff who could fit the culture of Janelia Farm—working from minimal rules and maintaining their focus on the scientific mission. Her team includes:

Howard Michael Day

DIRECTOR OF FACILITIES

At Janelia, Day's job is to oversee the proper functioning of the lab, conference, and housing spaces. He brings 27 years of experience in supervising facilities—small (the 150,000–square-foot Carnegie Institution of Washington, Broad Branch Road Campus) and large (the 3.8 million square feet of educational spaces that constitute the Arlington, Virginia, public school system).

Jennifer L. Farris

DIRECTOR OF CAMPUS SERVICES

Short- and long-term housing, food, and fitness are Farris's domain. She most recently managed Northeastern University's The Warren Conference Center & Inn, located in Ashland, Massachusetts. Her goal at Janelia: "to create comfortable spaces that encourage creativity."

Reed A. George

DIRECTOR OF SCIENTIFIC SERVICES

Like Moore, George arrived at Janelia by way of California, where he helped found a biotechnology consulting business and worked in *Drosophila* genomics. He now directs Janelia's shared resource labs, including facilities for microscopy, instrument design, and molecular biology. George also heads up materials management and environmental health and safety.

Marshall R. Peterson

DIRECTOR OF INFORMATION TECHNOLOGY

Peterson is no stranger to big data and big ideas. He's a former vice president for Celera Genomics in Rockville, Maryland, a commercial organization that sequenced the human genome. He also has designed missile guidance systems and processed satellite data. Peterson is the brains behind the design, implementation, and support of Janelia's scientific computing infrastructure.

Joanne M. Theurich

DIRECTOR OF ADMINISTRATION AND FINANCE

Theurich has built, developed, and managed the finance and administrative functions of several start-up healthcare organizations. She will be responsible for the development and management of Janelia Farm's finance, purchasing, human resource administration, and library, and will oversee technology-transfer issues.

Liz Lerman

TO ENTERTAIN, STIMULATE, AND ENLIGHTEN

A CHOREOGRAPHER WITH A WIDE-RANGING CURIOSITY AND SOCIAL CONSCIOUSNESS TAKES ON THE HUMAN GENOME.

Paul Fetters

For 30 years, Liz Lerman has been creating dance performances that are at once joyful and thought-provoking. Through her company, the Liz Lerman Dance Exchange (based in Takoma Park, Maryland), she seeks to explore, in movement, concepts no less profound than nature, faith, identity, and ancestry. In her latest work, *Ferocious Beauty: Genome*, Lerman addresses challenges to humanity posed by the unlocking of the human genetic code.

IN THE SPRING OF 2002, I was asked to lead a public discussion on "Gene(sis)," an exhibit at the Henry Art Gallery in Seattle that revolved around genetic research—its discoveries, its potential, its implications. Preparing for the event got me thinking about my teenage daughter and the choices her generation might face. Soon after, when a radio interviewer asked me what my next project would be, I found myself saying I'd like to develop a project on the genome.

I often approach new areas of interest this way, as making dances gives me a platform on which to muse, to talk, to learn. It's a fabulous educational process.

During the development of *Ferocious Beauty: Genome*, I met with many wonderful scientists. At a lunch with science faculty at Wesleyan University, I asked them to think about how a performance piece might teach the public about the genome. Because they had to filter their remarks through a picture of what it means to present this knowledge theatrically, their answers were far different from their usual ones.

When the lunch was over, I thought to myself, "If nothing else happens with this project, at least we'll all go back to our laboratories newly energized. Both artists and scientists will be better off because we had this fresh thinking."

It has been a goal of mine to see whether people who may not know math or science, but who might be worried about genetics and the future, could walk away feeling that they have some understanding of this and maybe even do something about it. I don't want to scare the hell out of people or make them depressed. On the other hand, I don't want to make it an easy ride.

I must also say that once we entered the very large realm of genetics, genomics, and developmental biology, we realized we had tumbled into a place far deeper and stranger than where Alice landed after her fall down the rabbit hole. I soon realized that this project could be about capitalism, or religion, or nutrition, or population control. It could be about race and identity, or about ethics, or about policy and professionalism. It could be strictly about the mechanics of the genome, using dance to describe biological processes. It could be about the future. Ultimately, the piece poses small and large questions, but it doesn't try to address all the questions currently being generated by scientific research. No single work of art ever could.

The first act gives the audience some basic scientific information, through videos of scientists, text, and dance, and it spotlights the interaction of science and art. It is also when they're introduced to Gregor Mendel, who makes regular appearances and acts as kind of a spiritual guide. I think it's useful for us to be reminded that he was a religious figure doing science.

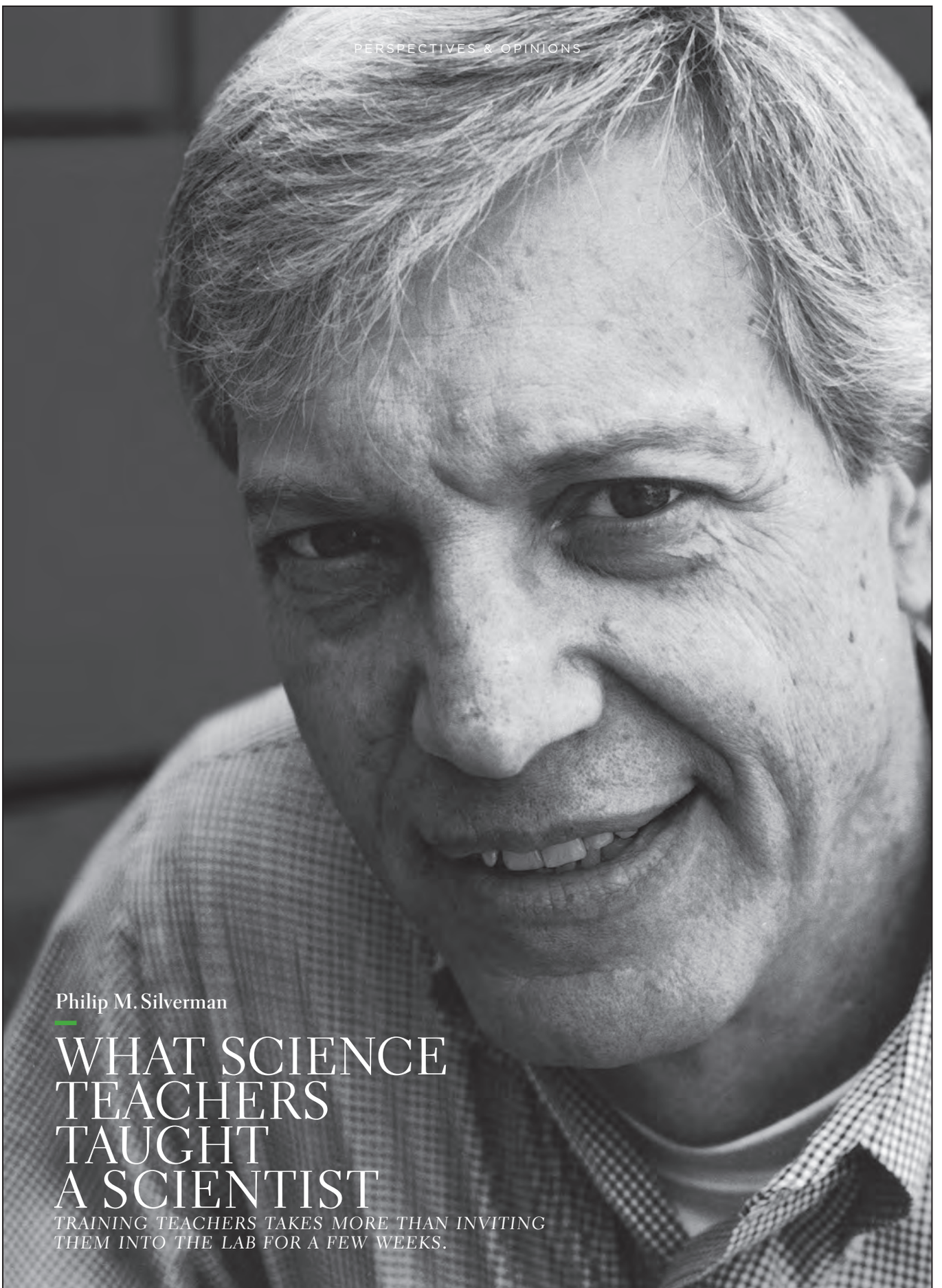
For the second act, I picked three issues: ancestry, the pursuit of human perfection, and the nature of aging and death and our desire for greater longevity.

I didn't mean for the piece to be so much about evolution, but of course it is. I thought I understood evolution before, but I didn't really get it. In the performance, we have a character who is full of angst and ennui. She doesn't know who she is at all. But Mendel leads her to the skeleton of a whale, which is shown through a video to be one of our (her) ancestors. It's a powerful moment.

I hope that the audience not only loves the performance but also, when they next read or hear about genetics, will have a little more insight. They don't have to feel numb about it.

One thing art can do is wake you up. I think that the piece begins to do this. ■

INTERVIEW BY ALICIA AULT *Liz Lerman's work has been commissioned by Lincoln Center, the American Dance Festival, BalletMet, and the Kennedy Center, among many others.*



Philip M. Silverman

WHAT SCIENCE TEACHERS TAUGHT A SCIENTIST

TRAINING TEACHERS TAKES MORE THAN INVITING THEM INTO THE LAB FOR A FEW WEEKS.

Misty Keasler

After 11 years as director of the Oklahoma Science Project, molecular biologist Philip M. Silverman has learned some lessons worth passing on. The Oklahoma Medical Research Foundation (OMRF) launched a program in 1988 to provide an 8-week summer research experience for Oklahoma public high school teachers. Some teachers were inspired by their experience but were left with nothing to take back to their students except enthusiasm, which quickly faded. Today, the program looks very different but is having its intended impact.

What were the obvious things that needed to change when you began observing the program?

The original program, called the Foundation Scholar Program, was based on the expectation that working on a cutting-edge project under the tutelage of a professional research scientist would somehow make the participants more effective science teachers. But science education and scientific research are separate activities. Teachers need research training they can take back and use in their classrooms, which can be hard to find in a high-tech research lab. How many high school laboratories have a DNA sequencer? How many even have gas for Bunsen burners? Additionally, the teachers worked in separate labs on different techniques and topics. They needed an environment that encouraged ongoing interactions—with their mentor and each other—to develop experimental skills and confidence, to model a research dynamic, and to work out ways to bring back what they were learning at OMRF to their students. They needed to be together in the same lab.

How did you decide on the right experiments to use?

It hit me when I was reading the second edition of *Phage and the Origins of Molecular Biology*, edited by John Cairns, Gunther Stent, and Jim Watson (expanded edition, Cold Spring Harbor Laboratory Press, N.Y., 1992). In the preface, Cairns wrote that all of the scientists who had done these fantastic phage experiments were dying off. He said, "The era of phage is over." When I read that, I thought, "Wait a minute. It's not over at all. The teachers would love these experiments." The science is fundamental and significant and the technology is cheap and simple. That's when I asked to try out my ideas with some teachers. I crowded a group of teachers into my laboratory, taught them the classic plaque assay for bacterial viruses, gave them some muddy lake water, and started them virus hunting.

Did it make a difference?

The teachers loved it. I grew up scientifically in the era of phage; I knew it intimately. I could convey the experiments themselves, but also the context and flavor of the times. The teachers loved that too. With passing summers we added new research topics (antibiotic resistance and regulated gene expression, for example). All of the experiments are derived from materials that the teachers (and later, their students) isolate themselves (livestock manure became the most popular and reliable source of bacteria and bacterial viruses), and from questions that the isolation generates in their own minds. Still, it wasn't translating to the classroom. I would get e-mails from the teachers when they went back to their schools about science fair projects but not about using the experiments in the classroom. By the second and third year, the teachers faded away. I stopped hearing from them.

What was missing?

Eight weeks wasn't enough. We give a grad student 5 years to do independent research and get a Ph.D., but we expect teachers to go through a transformation in 8 weeks? I began allowing teachers to return to the summer course for 4-week intervals as often as they wanted. This "Return to Science," as I called it, increased teachers' confidence and was certainly popular. It was kind of a circus, with new and returning teachers sharing lab space, but it was fantastic. Nevertheless, it didn't entirely solve the problem of classroom use.

Did you ever think, "This just isn't going to work"?

The idea entered my mind, but I immediately rejected it because I had 8 weeks with these teachers. I knew their abilities in the lab and how excited they were when they did these experiments. I just had to ask why this enthusiasm wasn't spilling over into the classroom, what other possibilities constituted barriers to classroom use. *(continued on page 56)*

INTERVIEW BY CORI VANCHIERI *Philip Silverman wants to help high schoolers pose questions and find answers through experiment.*

Q&A

How are you saving your lab notebooks and correspondence for posterity?

From those coveted eureka moments of insight to workaday data collection, scientists endlessly jot, note, print, and save. Today, researchers can catalog their typical science and occasional brainstorms in more ways than ever before. Here, several HHMI investigators share their strategies for preserving the details of their labors. — EDITED BY KATHRYN BROWN

Joseph DeRisi

ASSOCIATE PROFESSOR, BIOCHEMISTRY AND BIOPHYSICS, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

"For lab notebooks, **I still opt for the tried-and-true approach: a stuffed cabinet in my office.** Nothing fancy. We use our servers to back up e-mail, data, code, and more. True to biology, we're redundant. Once a year, we dump data onto DVDs. Ideally, these would be stored in an off-site location."

Erik M. Jorgensen

PROFESSOR, BIOLOGY, UNIVERSITY OF UTAH

"I am not saving my notebooks for posterity. I'm saving them for Stewart and Feder [self-appointed fraud investigators at NIH]. **The notebooks are in my office. I have them all**, going back to my report in fifth grade about the Komodo dragon, which is a lizard that grows up to 10 feet long and eats goats."

Christine E. Seidman

PROFESSOR, GENETICS AND MEDICINE, HARVARD MEDICAL SCHOOL

"While my desk gives the truest answer to this question (no wood is visible), our lab keeps important data on computer because Harvard Medical School (HMS) Department of Genetics has a really terrific backup system. **HMS also mandates keeping the data in lab books for 7 years**. When we moved into a new building almost 3 years ago, we faced the choice of pitching a lot of stored paper data. Despite the memories those lab books held, we simply didn't have space to keep them, and they were destroyed. We'd like to think that our published manuscripts provide the best legacy of what we did and why."

Roderick MacKinnon

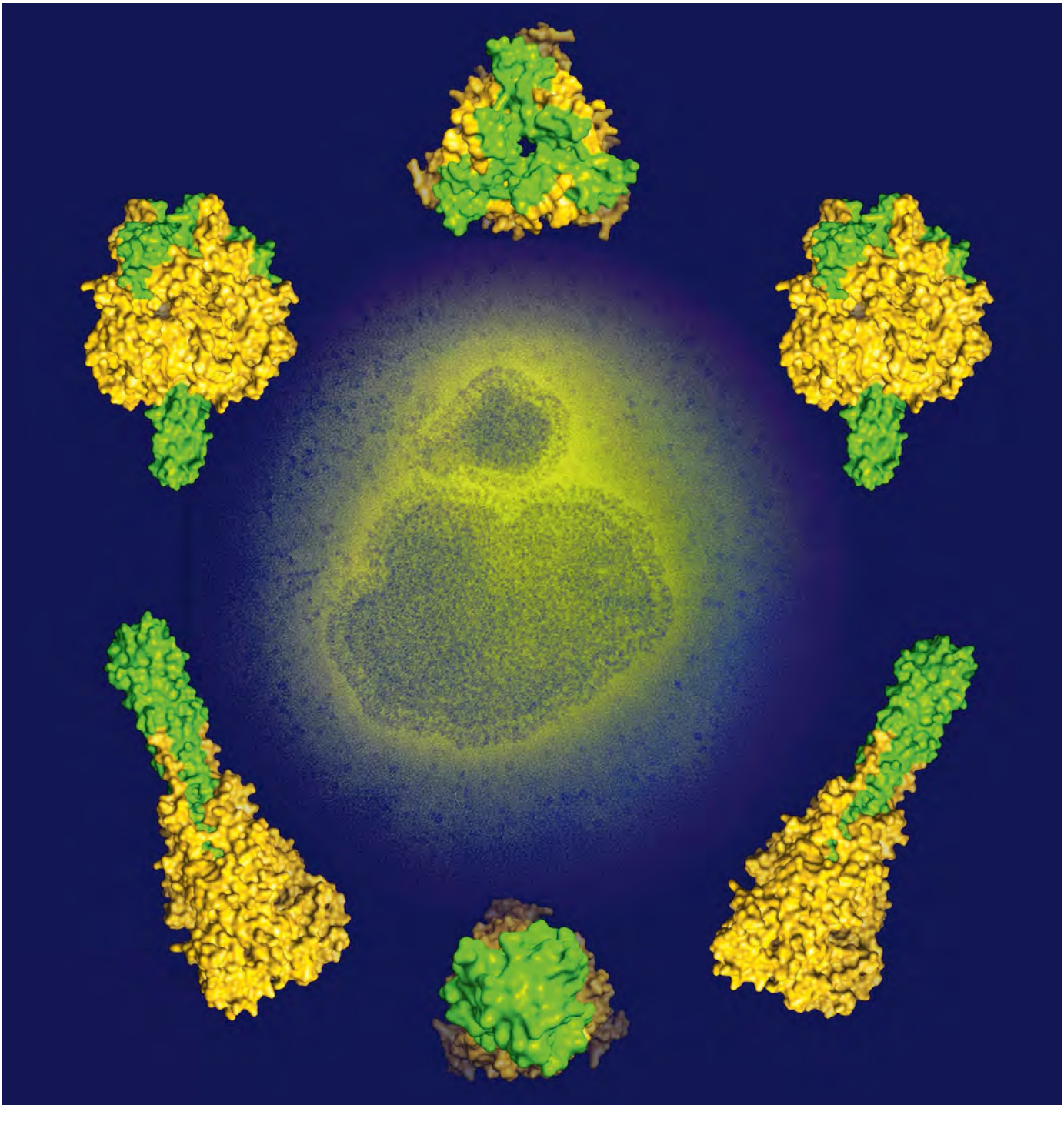
PROFESSOR, MOLECULAR NEUROBIOLOGY AND BIOPHYSICS, THE ROCKEFELLER UNIVERSITY

I generally don't save my correspondence, but I do hope the best and brightest information winds up in my scientific thinking! **I keep reams of synchrotron and electrophysiological data** on computer disks, tapes, and CDs. All of my biochemical data—dried gels, pictures, and chromatography profiles—go into notebooks."

DeRisi: George Nikitin/AP. ©HHMI. Jorgensen: Steve Wilson/AP. ©HHMI. Seidman: Justin Knight Photography MacKinnon: Robert Rathe

CHRONICLE

Even as this country's worst mumps outbreak in nearly 20 years spreads through the Midwest, a new finding by HHMI researchers gives insight into how the mumps virus is so successful at infecting its hosts (pg. 50).



Courtesy of Lamb lab

Creative thinking by undergraduate professors like Susan Wessler *(left) and* Scott Strobel *is inspiring a new generation of scientists.*

Twenty More Renaissance Profs

A NEW CLASS OF HHMI PROFESSORS—VISIONARIES IN RESEARCH AND TEACHING—AIMS TO ENERGIZE UNDERGRADUATE SCIENCE EDUCATION.

IMAGINE YOURSELF, as a college junior, exploring a rainforest to bioprospect for medically useful microbes, studying plant genomes to observe evolution in action, or analyzing your own DNA to determine the origins and wanderings of your ancient ancestors. That's just a taste of what the 20 recently chosen HHMI Professors are cooking up to tantalize undergraduates, fire their imaginations and develop their skills, and ultimately enhance the ranks of science.

The awardees—teacher-researchers all—will each receive $1 million over 4 years to test-drive ideas that depart from traditional curricula, which tend to emphasize fact memorization and laboratory experiments with predetermined "right" answers. Instead, the Professors will engage students in open-ended research projects using the techniques and tools of working scientists.

These 20 represent the A-team in pursuit of teaching innovations, but the talent pool was deep and their selection was not easy. "Every proposal I read gave me new insights and ideas on improving undergraduate science teaching," says Sharon R. Long, dean of the School of Humanities and Sciences at Stanford University and chair of the panel that reviewed 150 applications from 100 leading research universities.

New HHMI Professor Susan R. Wessler of the University of Georgia is a pioneer in the study of plant genomes' transposable elements, which reveal evolutionary history. Wessler will guide her students in computational and genetic analyses of such elements to see evolution in action. It's all the more important, she says, given that Georgia is enmeshed in controversy over the proposed teaching of "intelligent design" in schools. Scott A. Strobel, a professor of molecular biophysics and biochemistry at Yale University, believes that students can best be inspired by scientific research if they are given "ownership." He has designed classes so that instead of being "minor technical players in the big science of a typical laboratory, students will be completely vested in an original project in which they have full autonomy."

In each of the professorship's 4 years, Strobel and his father, Gary, a plant pathologist at Montana State University, will lead a dozen undergraduates on a spring-break expedition to one of the world's rainforests,

Wessler: Imke Lass Strobel: Amy Etra

where they will explore the ecosystem and collect biological samples. Then, in a summer laboratory course, the students will isolate, characterize, test, and potentially even name and patent the products of those rainforest organisms.

Winston A. Anderson, a professor of biology at historically black Howard University, in Washington, D.C., is creating an ambitious research-oriented academic program to give undergraduates a "competitive edge" for entering biomedical science careers. Active researchers will mentor the students in laboratory courses on genomics, proteomics, and metabolomics. Anderson is also planning summer exchange programs that will take undergraduates to African countries such as Ghana, Ethiopia, Mali, and Nigeria to learn about infectious tropical diseases and ethnopharmacology—the study of indigenous plants used for medicinal and other purposes.

Jasper Rine, professor of genetics and development at the University of California, Berkeley, wants to remodel introductory biology labs to "create a real interface between chemistry, math, computing, and biology." One area his students will explore is personal genetic information—often discussed in lectures as a societal issue, he says, but rarely addressed in laboratory curricula. Rine plans to have students' distinctive mitochondrial DNA sequenced commercially, whereupon they will each use computational tools to construct a "tree" of their heredity.

The 2006 Professors are successors to the original group of 20 selected in 2002 to show that productive scientists can also be committed, innovative teachers of undergraduates—a skill often undervalued at high-powered research universities. This goal was well met, says Stanford's Long, as the 2002 Professors "stimulated and transformed entire institutions, and have even facilitated new nationwide conversations on science teaching and mentoring." ■

–RICHARD SALTUS

> "[Instead of being] minor technical players in the big science of a typical laboratory, students will be completely vested in an original project in which they have full autonomy."
>
> SCOTT STROBEL

Robert Rathe

Undergraduates Abroad

WORKING WITH RESEARCHERS IN OTHER COUNTRIES ENRICHES STUDENTS' SCIENTIFIC AND CULTURAL OUTLOOK.

Zebras, hippos, and wildebeests; frenetic minibus rides through Johannesburg; Swaziland women doing the graceful, rhythmic Reed Dance—for Rokhsanna Sadeghi last summer, just leaving her dorm each morning brought a new adventure. Every day, she explored the tangled but beautiful web of science and culture in South Africa.

WITH WORLD-CLASS SCIENCE now being practiced on a truly worldwide basis, American scientists often spend time doing research in foreign lands. This is not the case for most students—especially undergrads—who rarely have the necessary resources or credentials. But for the past 5 years, an HHMI program has been pairing undergraduate students for summer research with the Institute's international research scholars. More than 40 students have been placed so far, from Mexico to India, and at least 20 more will have their chance this summer. Here, three undergraduates who participated during the summer of 2005 share their experiences of science and culture abroad.

When searching for an international research opportunity, Rokhsanna Sadeghi, a senior at Rensselaer Polytechnic Institute, in Troy, New York, looked for a location and a project that would allow her to learn laboratory-based biochemistry and directly connect her research to health issues in the local community. Working with Valerie Mizrahi in her lab at the University of the Witwatersrand and the National Health Laboratory Service in Johannesburg, South Africa, Sadeghi came to better understand how vitamin B_{12} regulates the production of methionine—an essential amino acid—which in turn affects the growth and virulence of bacterial strains that cause tuberculosis, a disease that wreaks havoc among HIV/AIDS patients in that region.

In her free time, Sadeghi sought out South African students and church groups

> "[Combining research and community service] renewed my faith that these are things I want to do and can do."
>
> ROKHSANNA SADEGHI

who brought food and medical care to homeless people. Accompanying them, sometimes to burned-out buildings on bitterly cold evenings, she helped medical students take patient histories and arrange for medical referrals among the people that her laboratory research might ultimately benefit. This combination of research and community service invigorated and inspired her, Sadeghi says. "It renewed my faith that these are things I want to do and can do."

Another student opted for an assignment north of the border in Canada, just 400 miles from his home base at Michigan's Kalamazoo College. Michael Glista, a senior, immersed himself in Alzheimer's disease research by spending his summer at Peter St George-Hyslop's University of Toronto lab. Throughout the summer, postdoc Hiroshi Hasegawa mentored Glista as they worked with recombinant proteins in an effort to reconstruct the molecular puzzle pieces that interact as cells produce the disease's telltale ß-amyloid plaques in the brain. His experience, Glista says, resulted in a published paper and a direction to pursue in his intended career as a researcher and clinician.

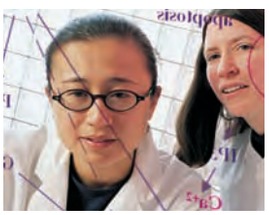
Although he didn't journey far for his research project, Glista says the international mix of colleagues in the St George-Hyslop lab—from Japan, China, Poland, and Canada—and their passionate commitment to their work left a strong impression.

Her summer in Ranulfo Romo's lab at Mexico City's National Autonomous University of Mexico allowed Egle Cekanaviciute, a junior at Harvard University, to explore neuroscience research with animals. She trained a rhesus monkey to respond differently when two distinct vibration frequencies were applied to its hands; then she watched her colleagues implant electrodes to understand how the monkey's brain distinguished between those stimuli. Sifting through detailed statistical analyses of the resulting data, she helped dispel the widely assumed notion that monkeys' brains sort and compare tactile information based on repeating patterns of stimulation.

Cekanaviciute also learned to appreciate working with these higher animals, especially compared with her previous efforts—with cell cultures. "Cells are not cute, they're not fluffy, and they're not smart," she says. "You don't get attached to them; you don't name them." Working with animals requires patience and emotional stamina, she says. "You are dependent on this whole set of circumstances: how smart the monkey is, how much it wants to be trained, and whether it stays healthy."

Overwhelmingly, her summer experience has deepened her love of Latin-American culture. In her free time, Cekanaviciute's growing fluency in Spanish allowed her to explore. She hiked through jungles and climbed pyramids in the Yucatan peninsula. She learned about the struggles of guerillas in the state of Chiapas and the poverty of young children selling flowers on the streets.

After she graduates next year, Cekanaviciute plans to spend a year south of the border, perhaps in Mexico or Peru, before pursuing graduate work. "It's very important to travel," she advises future participants. "It's a must to go and see everything you can." ■ —SARAH WEBB



Kay Chernush

Making It Relevant to Human Health

A NEW HHMI PROGRAM AIMS TO INCREASE THE NUMBER OF BASIC RESEARCHERS WHO ARE CLINICALLY LITERATE.

IT ALL COMES DOWN TO A FRAME of mind. The best physician-scientists have it. Their laboratory research is aimed directly at benefiting human health.

A new HHMI program aims to instill that sensibility in Ph.D. students to expand the pool of investigators steeped in rigorous scientific techniques but also familiar with clinical practice. HHMI's Med into Grad Initiative recently awarded $10 million over the next 4 years to 13 innovative graduate-training programs that combine medical knowledge with basic science.

"The goal is to integrate clinical science and medical information so the students are trained to think about the relevance of what they do to health or disease, and to emphasize an understanding of how things work in the human body," says Martha K. Cathcart, a cell biologist and director of one of the new training programs at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University. *(continued on next page)*

Awards Bring Science to the Community

***A new HHMI grant** initiative will harness the resources of biomedical research institutions to increase public understanding of science and broaden access to science for people of all ages. These outreach efforts will be aimed at improving science education for elementary, middle school, and high school students. "**Research institutions** have unique resources for sparking an interest in science and transforming science education," says Jill Conley, director of HHMI's Precollege Science Education Program. "For example, they have modern research facilities, cutting-edge scientific knowledge, and the ability to offer authentic research experiences to students." **HHMI has committed** $22.5 million to fund about 30 grants for 5-year projects. Almost 300 nonprofit U.S. institutions have been invited to apply. They include medical schools, academic health centers, independent research institutions, and schools of veterinary medicine, dentistry, and public health. To deliver their programs, the research institutions may collaborate with community-based organizations, including school systems and science centers. Two previous competitions have awarded 96 grants totaling $33 million. **The outreach programs** will be directed at teachers, students, families, and others in the community. Research institutions can design activities in a variety of areas, such as building students' scientific skills; supporting professional development for teachers; improving scientific literacy among parents, caregivers, and others; involving undergraduate and graduate students and postdoctoral fellows in K–12 education; and developing science education resources. "**We want to nurture** students' fascination with the natural world when they're young and curious," Conley says. "This may happen in school, but we've also seen a positive correlation between students' science proficiency and the importance placed on science outside school." **HHMI will announce** the awards for biomedical research institutions in June 2007.*

Mike Sands, Case Western Reserve University

This new medical school was established in partnership between Case Western and the Cleveland Clinic Foundation to train physician-scientists. HHMI will support a Ph.D. program in its Department of Molecular Medicine, where an intensive "core curriculum"—classes in the fundamentals of basic and clinical research—will be taught during the students' first 15 months. Advanced coursework can be taken there as well and on Case Western's nearby campus. Students will be assigned a clinical mentor and a research mentor.

If a student wished to do her thesis research on the molecular and cellular biology of cardiac ion channels and how they relate to human diseases, Cathcart explains, she would be mentored by a clinical researcher in the Cleveland Clinic's Department of Cardiovascular Medicine. The student would attend biweekly conferences sponsored by the clinic's atrial-fibrillation group—cardiologists, cardiac surgeons, radiologists, electrophysiologists, geneticists, cell biologists, nurses, and social workers who share a common interest in cardiac dysrhythmias—to discuss challenging cases and the latest advances in clinical and basic research.

At the end of the semester, the student would make a presentation to the group focused on a relevant translational-research problem—such as development of new targeted therapies directed against specific cardiac ion channels or the use of genomic tools to identify novel genetic changes associated with heightened risk of atrial fibrillation. And throughout the semester, her mentor would bring her to specific clinical sites to observe clinicians and clinical researchers engaged in activities related to a disease of current interest.

Houston's Rice University is working with neighbor University of Texas's M.D. Anderson Cancer Center to train future biomedical engineers in drug design for cancer therapeutics, tissue engineering for reconstructive procedures following surgery, and imaging tools for early cancer detection. Students take five courses and then do clinical rotations in specialties such as diagnostic imaging, radiotherapy, and bone marrow transplantation. "Our goal is to get students to understand the challenges physicians face in their practice and how bioengineering can be clinically useful," says Rebecca Richards-Kortum, a bioengineer and HHMI professor at Rice University who codirects the program.

At Stanford University, first-year graduate students take basic biomedical science classes alongside medical-school students. They also attend seminars in translational medicine and do an intensive 1- to 2-month clinical rotation. In their second year, students pick labs and mentors for their thesis research. "With only an extra year-and-a-half of training," says neurologist Ben Barres, the program's director, "we can generate a group of basic researchers who understand what goes on in the clinical wards."

Among the key elements emphasized at the program of the University of Alabama at Birmingham (UAB) are techniques of modern drug discovery. By working alongside scientists at Birmingham's Southern Research Institute, "Students can learn firsthand what it takes to get a drug to the marketplace," says Thomas Clemens, a pathology professor at UAB and the program director.

These programs, as well as the others supported by the Med into Grad Initiative, aim to provide graduate students in basic sciences with the skills to take their own research findings and apply them to clinical situations. In that way, translating basic scientific discoveries into new medical treatments will be not only better but faster. ■ —LINDA MARSA

"The goal is to integrate clinical science and medical information so the students are trained to think about the relevance of what they do to health or disease."

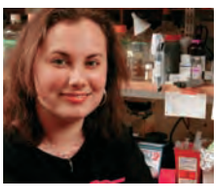
MARTHA CATHCART

Gilliam Fellowships Reward Determination

SIX YOUNG BIOMEDICAL RESEARCHERS who have battled adversity are winners of HHMI's 2006 Gilliam fellowships. These students all established impressive scientific credentials as undergraduates, marking them as promising research scientists. All of them also faced personal challenges that helped turn their sights toward careers in science. • Gilliam fellowships provide support for doctoral studies for disadvantaged students, including minorities underrepresented in the sciences. They are named for the late James H. Gilliam, Jr., a charter Trustee of HHMI who spent a lifetime fostering excellence and diversity in education and science. HHMI awarded Gilliam fellowships for the first time in 2005. • Gilliam fellowships are open to students who participated in HHMI's Exceptional Research Opportunities Program (EXROP) as undergraduates. EXROP students conduct research in the labs of HHMI investigators and HHMI Professors. These new Gilliam fellows will have leadership roles at EXROP meetings—speaking on panels, leading discussions of graduate student life, or chairing a scientific session—to enhance their own mentoring skills and to motivate upcoming EXROP students.

Jonathan Abraham
POSTBACCALAUREATE RESEARCH FELLOW
NATIONAL INSTITUTES OF HEALTH
After moving to Queens, New York, the Canadian-born Haitian became painfully aware of the misconception that Haitians were responsible for the spread of AIDS in the United States. Abraham plans to conduct infectious disease research and help dispel myths that degrade minorities.

John P. Cassady
GRADUATE STUDENT
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
Cassady switched from a major in nuclear engineering to biology and became committed to research on HIV while working with HHMI investigator Bruce Walker at Massachusetts General Hospital. Cassady's long-term goal is to develop a stem cell–based treatment for HIV infection.



Ana G. Cristancho
M.D.-PH.D. STUDENT
UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE
At age 11, Cristancho lost her father to brain cancer. She is determined to become a pediatric oncologist and cancer biologist. As an EXROP student, she helped develop a mouse model for the childhood cancer Ewing's sarcoma in the MIT lab of HHMI investigator Tyler Jacks.

Tam M. Nguyen
GRADUATE STUDENT
WAKE FOREST UNIVERSITY
Nguyen remembers her childhood in Saigon in the wake of the Vietnam War, walking past poor Vietnamese citizens suffering on the steps of hospitals, unable to get medical care. She hopes to establish a foundation to bring better medical care and equipment to her native Vietnam.

Kevin B. O'Brien
GRADUATE STUDENT
UNIVERSITY OF WISCONSIN–MADISON
O'Brien plans to study the viral pathogenesis of avian influenza virus, including its lingering effects on the immune system. His mother's autoimmune disease led him to focus on how acute and persistent viral infections may induce autoimmune disease later in life. He wants to help diversify research and teaching faculty.

Edwin H. Rodriguez
UNDERGRADUATE
STANFORD UNIVERSITY (GRADUATE SCHOOL UNDECIDED)
Watching his mother battle kidney disease—and recover with a kidney transplant—Rodriguez became interested in biomedical science. He is studying the effects of hypoxia, or low oxygen, on kidney cancer. "I want a life in academic medicine, treating patients and leading my own lab to new understandings of disease."

Jonathan Abraham: Tom Kochel John P. Cassady: Kathleen Dooher Ana G. Cristancho: David Graham
Tam M. Nguyen: David Graham Kevin B. O'Brien: David Nevala Edwin H. Rodriguez: Barbara Ries

Edward Palmerino Named Vice President for Finance and Treasurer

THE TRUSTEES OF THE HOWARD HUGHES MEDICAL INSTITUTE have elected Edward J. Palmerino as the Institute's new vice president for finance and treasurer. He assumed his new role in January.

Palmerino, 58, has served as the Institute's controller since 2001. He will oversee all of the purchasing, accounting, and business systems for the Institute, as well as internal audit and facilities management. HHMI's finance department oversees an Institute-wide annual budget of more than $660 million.

"Ed Palmerino has deftly streamlined many of the Institute's business practices during his years at HHMI," says president Thomas R. Cech. "His selection as head of the finance department ensures that the Institute's resources will continue to be used wisely in support of our mission of research and science education."

When Palmerino joined HHMI as assistant controller in 1986, his first task was to hire and train accounting and finance staff for relocation to the new headquarters site in Maryland. Since that time, he has been instrumental in ensuring the efficient management of the resources of the Institute, whose endowment had reached $14.8 billion by the close of fiscal year 2005.

Among the technological and operational changes introduced by Palmerino are the implementation of the first major computerized accounting system and the electronic storage of invoices and tax returns. He has developed procedures to ensure that the Institute's spending meets the government requirements for a medical research organization, and has also coordinated the borrowing of $500 million through tax-exempt bonds to finance the construction of the Institute's new Janelia Farm Research Campus.

Palmerino has a bachelor's of business administration degree in accounting from Nichols College in Massachusetts. Prior to joining HHMI, he was a financial director for the American Red Cross for 11 years, including 6 years as the national director of accounting.

Avian Flu: A Global Update

In March, HHMI and the Center for Strategic and International Studies (CSIS) presented a symposium on the global spread of avian flu and the preparedness of surveillance and public health systems to address that spread. The Capitol Hill event was headlined by a noted panel of speakers (above center), including Jeffery K. Taubenberger (left), Chair, Department of Pathology, Armed Forces Institute of Pathology; David Nabarro (center), Senior Coordinator for the United Nations System for Influenza Coordination; and Nancy J. Cox (right), Director, CDC Influenza Division, and Director, WHO Collaboration Center for Surveillance, Epidemiology, and Control of Influenza. HHMI investigator Robert A. Lamb of Northwestern University chaired the panel.

Photos: Paul Fetters

From Tree to Harpoon

SHAPE-SHIFTER PROTEIN GIVES A VIRUS DRAMATIC ENTRÉE TO ITS TARGET CELLS.

HIV, influenza, and other enveloped viruses infiltrate host cells by fusing their outer surface with the membrane of their target, then dumping their genetic material inside. Scientists from the labs of HHMI investigator Robert A. Lamb and Theodore S. Jardetzky, both at Northwestern University, have now provided a clear picture of how one protein—the F protein of the paramyxovirus—facilitates this fusion. It lies in wait until a target cell is nearby and then snaps into an entirely new shape to initiate infection.

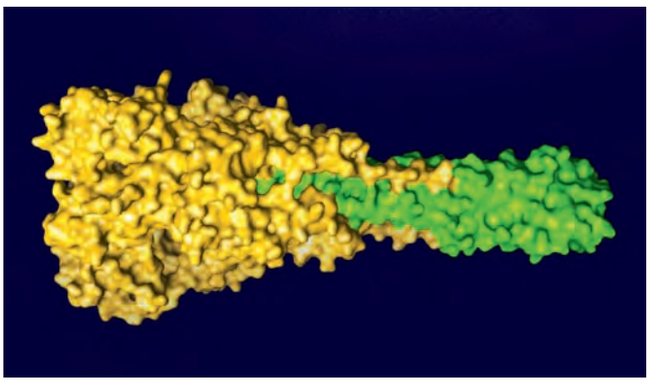
The reconfiguration of the F protein—responsible for measles, mumps, and a host of respiratory infections—is one of the most dramatic that scientists have observed in any protein. It starts out shaped like a tree, Lamb says, with its trunk anchored on the viral surface—a form that allows a great deal of energy to be stored. When the virus nears a susceptible cell, F uses its energy to extend like a harpoon into the target's membrane, then collapses on itself, drawing the two membranes together.

Scientists have known that viral-fusion proteins rely on a shape change to accomplish their task, but visualizing these structures has been challenging, in large part because the prefusion form is so eager to spring into action. "It's really sort of hair-triggered," Lamb explains. "It's sitting there ready to go, and if you disturb it, that's it." Moreover, he and his colleagues observed that removing the F protein from the membrane for structural analysis "was like releasing the spring. The whole thing unraveled."

The researchers' initial efforts to solve the prefusion structure of F were thus thwarted by its volatility. But they found that by adding a small piece of a foreign protein known to act as a kind of Velcro to the end of F, they could trick the mercurial protein into holding its prefusion shape. This allowed them to solve that elusive structure—and to envision F's dramatic remodeling during membrane fusion.

Understanding this viral-fusion process, which had previously been revealed only for influenza, should help in the design of drugs targeting the vast family of paramyxoviruses, Lamb notes. ■

– JENNIFER MICHALOWSKI



The virus that causes mumps and measles infects cells via its F protein, which adopts a harpoonlike shape to gain entry.

Courtesy of Lamb lab

IN BRIEF

HOW SPERM CRACK THE WHIP

Researchers have identified a key component of the mechanism spermatozoa use to abruptly convert their tail motion from a steady swimming undulation to the whip-cracking snap that thrusts them into an egg. The finding may help scientists recognize additional forms of male infertility and design contraceptives to thwart sperm entry into the egg.

What's more, the exquisitely delicate analytical technique the researchers used to eavesdrop on the electrical currents inside the squirming sperm cell could open a new window into its largely mysterious inner workings.

HHMI investigator David E. Clapham and his Harvard Medical School colleagues published their findings in the February 9, 2006, issue of the journal *Nature*.

According to Clapham, the finding represents the beginning of an important research pathway. "It's like opening a chamber in an ancient pyramid, because no one had ever seen inside sperm cells to measure all the currents that control their activity," he says. "We are already measuring many of these currents and beginning to answer questions about what they are and what they do."

MALARIA PARASITES DEVELOP IN LYMPH NODES

In the first quantitative, real-time imaging study of the travels of the malaria parasite *Plasmodium* through mammalian tissue, researchers at the Pasteur Institute in Paris found the parasites developing in an unexpected place: lymph nodes.

The parasites' presence in the lymph nodes almost certainly has implications for the mammalian immune response, says Robert Ménard, an HHMI international research scholar who led the study. Ménard and colleagues reported their findings in the February 2006 issue of *Nature Medicine*, published online on January 22, 2006.

Until now, researchers believed that, although both blood and lymphatic vessels take up *Plasmodium*, the parasites all end up in the liver. Says Ménard, "Nobody had proposed that they actually might stop" in the lymph nodes and develop there.

Understanding the intricacies of the mammalian immune response to *Plasmodium* infection might help scientists create better vaccines, including vaccines that target parasites before they develop in the liver. Their development in lymph nodes could be one reason why there is so much tolerance to these parasites, Ménard suggests.

WORMS MAY HELP REVEAL SECRETS OF PECULIAR TUMORS

HHMI researchers have developed a genetic model in the nematode *Caenorhabditis elegans* that may help scientists understand how a specific kind of tumor develops from germline cells.

The tumors are called teratomas, a name derived from *teroton*, the Greek word for monster. True to their name, teratomas are a monstrous mix of cell types—usually appearing with bits of hair, teeth, and bone wrapped into a metastatic ball.

Researchers have had a difficult time understanding how and why these tumors form. But an article in the February 10, 2006, issue of *Science* provides new clues to some of the genetic missteps that may occur. In the article, HHMI investigator James Priess and colleagues at the Fred Hutchinson Cancer Research Center in

Hamster Chill Time

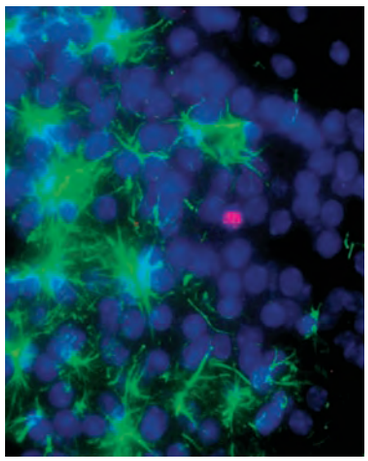
THE UPS AND DOWNS OF DAILY ACTIVITY ARE CONTROLLED BY A PROTEIN IN THE BRAIN.

Couch potatoes, take heart. That irrepressible urge to veg out might just be a matter of brain chemistry—at least, in hamsters, according to former HHMI predoctoral fellow Sebastian Kraves and his neurobiologist mentor Charles J. Weitz of Harvard Medical School. The researchers reported in the February 2006 issue of *Nature Neuroscience* their discovery of a brain protein that modulates rodents' daily activity patterns.

As anyone with pet hamsters knows, rodents lie low a good part of the day. That makes evolutionary sense, Kraves explains. Lest it become breakfast for a predator, for example, a rodent might do best to sit tight in its burrow if it doesn't have some good reason to be out and about. But what's behind those lulls?

By logging running sessions on an exercise wheel, scientists know that the timing of rodents' daily movement (locomotor) cycles repeats with a precision almost down to the minute. But if the rodent receives an injury to its suprachiasmatic nucleus (SCN), a tiny region in the brain that controls daily rhythms, this periodicity falls apart.

Drawing on prior research, Kraves and Weitz surmised that the SCN must release substances that trigger receptors in the brain to regulate locomotor cycles. They dug through piles of papers, searching for suitable candidates. After compiling a list of over 50 likely compounds, they put them through a number of behavioral and biochemical tests, and found one protein, called cardiotrophin-like cytokine (CLC), that seemed to fit the bill.



Having the CLC "laziness" protein (red) in its brain might be a hamster's signal for a siesta.

Kraves tested the protein directly by injecting it into the brains of lab hamsters and then keeping track of their wheel-running routines. Strikingly, the treatments completely abolished the animals' urges to run on their wheels during normal exercise periods. When Kraves stopped the protein administration, the hamsters resumed exercise right on schedule at their next cycle. What's more, blocking CLC's brain receptor—a protein called GP_{130}—spurred the hamsters to run at times when they normally would rest, indicating that CLC and GP_{130} work together to exert control on locomotor activity in rodents.

Though these proteins are also present in human brains, Kraves cautions, "We don't believe we're close to being able to extrapolate these results to humans." ■ – PAUL MUHLRAD

IN BRIEF

Seattle report that they switched off two genes in *C. elegans*, prompting gonad cells to grow into teratomas.

Similar to human ovarian teratomas, the nematode teratomas appear to result from germ cells that have entered but not completed meiosis, a specialized type of cell division in which chromosomes recombine before differentiating as sperm or eggs. "Although there's not a lot known about how teratomas form, we now have a relatively simple model for studying them," says Priess.

MOLECULE DOES MORE THAN SLICE AND DICE RNA

A team of HHMI scientists has peeled away some of the mystery about how cells are able to turn off genes selectively to control critical developmental events. The new insights arise from the first clear molecular images of the structure of Dicer, an enzyme that enables cells to dissect genetic material precisely.

The finding, reported in the January 13, 2006, issue of *Science*, came out of a study led by Jennifer A. Doudna, an HHMI investigator at the University of California, Berkeley. Doudna's research team used x-ray crystallography to assemble a detailed three-dimensional picture of Dicer. In cells, the enzyme jump-starts RNA interference, a process that causes genes to be turned off, which, in turn, prompts a host of key developmental events, ranging from brain development to stem-cell differentiation.

With the structure of Dicer solved, Doudna's group showed that the enzyme is more than a molecular cleaver—it also carefully measures and snips strands of RNA into precise increments. When Dicer cleaves large strands of RNA into smaller fragments, it initiates the process of RNA interference.

"The bottom line we've learned from the structure is that Dicer is a molecular ruler," Doudna explains. "It gives us a lot of insight into how the mechanism works."

FOLLOWING A HITCHHIKER FOR CLUES TO VIRAL SURVIVAL

HHMI researchers have discovered how the virus that has a causative role in Kaposi's sarcoma, a cancer associated with HIV infection, hitches a ride inside cells to ensure its survival.

The researchers said their findings promise greater understanding of how the virus, Kaposi's sarcoma-associated herpesvirus (KSHV), persists in the multiplying cells of growing tumors. More broadly, however, the researchers said their studies dramatically change how they view nucleosomes—beadlike structures of DNA and histone proteins that form the core of chromosomes. The new findings indicate that nucleosomes, once thought to be simple scaffolds around which DNA wound itself, are active docking stations for a number of regulatory molecules that affect gene function.

"This really changes the way we think about nucleosomes," Luger says. "Now, we see them as much more dynamic protein assemblages that can actually serve as binding platforms for all kinds of cellular factors."

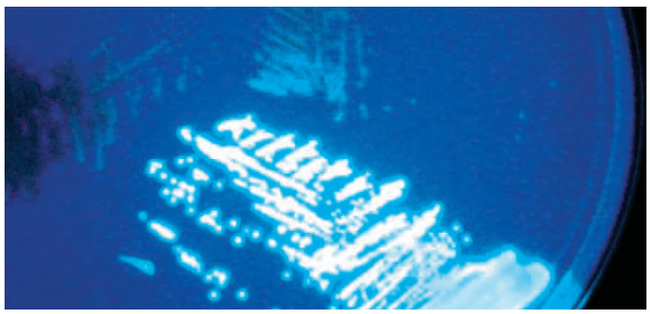
The research, published in the February 10, 2006, issue of *Science*, was a collaboration between the laboratories of Kenneth M. Kaye at Harvard Medical School and Brigham and Women's Hospital and Karolin Luger, an HHMI investigator at Colorado State University.

Shining Light on Vitamin B_{12}

AN HHMI PROFESSOR'S TEACHING STUNT LEADS TO A LONG-SOUGHT DISCOVERY.

Scientific discoveries sometimes emerge from the most unexpected places. HHMI Professor Graham C. Walker, for instance, never predicted that a classroom experiment with soil bacteria would uncover a missing link in the biochemical pathway for manufacturing vitamin B_{12}. Walker, a professor of biology at the Massachusetts Institute of Technology, studies the symbiotic relationship between certain bacteria and alfalfa plants. The microbes, called *Sinorhizobium meliloti*, invade the plants' roots, where they convert nitrogen gas from the atmosphere into a form that the plants, and animals that consume them, can tap for nourishment. In an ecological quid pro quo, the microbe, in turn, gets its required nutrients from the plant.

Years ago, while searching for engaging experiments for his undergraduate microbial-genetics course, Walker found that adding household laundry brightener to dishes containing *S. meliloti* caused some of the bacterial colonies to glow white under ultraviolet light, depending on the genes present. He thought the serendipity might make for a fun lab unit because "undergrads love glowing bacteria."



Under ultraviolet light, bacteria with a mutant bluB *gene outshine those without the mutation.*

The link between the bacteria and vitamin B_{12} surfaced when Walker's graduate student, Gordon R. Campbell, isolated *S. meliloti* mutants that fluoresced especially intensely in the laundry-brightener test. One of the brightest-glowing variants turned out to have a mutation in an uncharacterized gene, whose sequence was similar to that of a gene, called *bluB*, found in another bacterium. Scientists had implicated *bluB* in vitamin B_{12} biosynthesis.

Vitamin B_{12} is a large compound that requires more than 30 different enzymatic steps to assemble, Walker notes. The enzyme that catalyzes one of them—building a part of the molecule called DMB—had never been identified. The Walker team determined that *bluB* appears to be needed for that step. Their results were published in the March 21 issue of the *Proceedings of the National Academy of Sciences*.

"Many labs have been trying to figure out this missing part of the pathway for years," Walker says. "It was amazing to me to discover that there was something as basic as building a vitamin that wasn't completely known by 2006. Solving this mystery was a nice coming together of my interests in teaching and research." ■ – PAUL MUHLRAD

IN BRIEF

A NEW LOOK AT MOLECULAR MOTORS

An innovative method for categorizing myosins—one of the three types of molecular "motors" that produce movement in the cells of the body—has increased the information available about these essential proteins. The studies lay the groundwork for development of treatments for conditions ranging from certain kinds of blindness and kidney disease to neurodegenerative disorders and parasitic diseases such as malaria.

Researchers led by Dominique Soldati, an HHMI international research scholar at the University of Geneva, in Switzerland, developed a new system of classifying myosins. Up to now, researchers have studied only approximately 130 myosins at a time. The new system includes 250 myosins and increases the number of myosin subclasses from 18 to 24, enabling researchers to better understand each myosin's function.

"Myosins that belong to the same class work in similar ways but can have very different functions," explains Soldati. "We will have to discover the myosins' functions one by one, and the better we understand how they are related, the faster that will occur."

So far, molecular motors have been found in all organisms but bacteria, red algae, and the parasite *Giardia*. Soldati and her colleagues became interested in myosins after they discovered that the molecular motors enabled toxoplasmosis and malaria parasites to force their way into human cells. The new myosin classification system should help researchers make advances in a wide variety of fields, from veterinary medicine to tropical diseases.

The work appeared on February 6, 2006, in an advance online publication of the *Proceedings of the National Academy of Sciences*.

BOTULISM TOXIN'S INSIDIOUS ROUTE INTO NERVE CELLS

Botulinum neurotoxin A can be either the greatest wrinkle remover or one of the world's most potent biological weapons. To perform either job, however, the toxin must first find a way to enter cells.

Researchers have long known how botulinum neurotoxin A attacks the nerve cell's internal molecular machinery. But understanding how the toxin—one of seven neurotoxins produced by the bacterium *Clostridium botulinum*—enters nerve cells has proved elusive for scientists. Despite a decade-long search for the receptor by labs around the world, researchers came up empty-handed.

Now, a research team led by HHMI investigator Edwin R. Chapman reports that it has identified the cellular receptor for botulinum neurotoxin A. The University of Wisconsin–Madison group's work was published in the March 16, 2006, edition of *ScienceXpress*, which provides electronic publication of selected *Science* papers in advance of print. The finding offers important new insights that suggest how the toxin shuts down nerve cells with deadly efficiency.

The identification of SV2 as the neurotoxin A receptor raises the possibility of designing protective drugs that interfere with the toxin's action. Chapman plans to aid such efforts by focusing his research on developing a more detailed understanding of the molecular interaction between the toxin and its receptor.

Michiko Taga

Q.
Submitted by a U.S. high school student

Is it possible to "steal" the genes of successful performance horses—for example, by pulling a few hairs—and create genetic copies through cloning?

A.
Researched by Alexey Veraksa

Born on March 13, 2005, Paris Texas is a bay-colored colt and the first horse successfully cloned in North America. He was spawned from adult skin cells collected from a valuable performance stallion in Europe. The cloning was done at Texas A&M University by a research team led by Katrin Hinrichs, veterinarian and professor, and Young Ho Choi, associate research scientist, in collaboration with Eric Palmer, chairman of the French company Cryozootech. Horses have been cloned twice elsewhere; a number of other mammalian species have also been cloned.

Can genes be stolen in much the same way as, say, valuable documents? The fact that this cloning effort used adult cells tells us that the same method could be used for nefarious purposes. However, let me give a few reasons why I think we are not quite there yet.

First, cloning procedures—which proved especially difficult for the horse—still require state-of-the-art laboratories and years of experience. Our gene thief would need to find highly sophisticated collaborators.

Second, the success rate of these experiments remains low. The cells present in a few hairs probably would not be adequate, even after culturing, to get the number required to achieve successful cloning.

Third, even though the cloned horse was reported to be healthy, cloned animals are generally more prone to illnesses and weaker than naturally produced offspring. A cloned performance horse may not become a champion, because competitions test the extremes of what an organism can achieve physically.

"Cloning is not a way to produce competitors," notes Hinrich. "There is just too much variability in the environment that a cloned foal experiences, both in the uterus and after birth. Just the fact that he spent his first 7 days in an incubator can affect Paris Texas's growth rate after birth, and even his performance as an adult." On the other hand, Hinrich points out that, as a sire, Paris Texas should produce the same quality of foals as did the donor stallion, because the two carry identical sets of genes.

Finally, the breeding of performance horses is highly regulated. Professional associations of breeders recognized a potential for fraud some time ago, especially since performance horses can bring substantial amounts of money to their owners. One of those groups, the Jockey Club, monitors thoroughbred racing in North America and tightly controls breeding practices. The rules allow only natural breeding methods, not cloning or even artificial insemination. Horse breeders must submit DNA proof that their foals were bred naturally. DNA testing would reveal a cloned foal—it would be a duplicate of a single horse rather than a mix of two.

So, even if a horse were successfully cloned and raised into a healthy championship-caliber performer, there would be no possibility for it to participate in some types of competition, such as thoroughbred racing. However, a few biotechnology companies are seeking well-heeled customers interested in cloning their favorite horses.

RESEARCHED BY ALEXEY VERAKSA, *Assistant Professor, Biology Department, University of Massachusetts, Boston (former HHMI predoctoral fellow)*

The scientific process starts with a question. When a scientific inquiry piques the interest of a high school or college student and answers can't be found in class or in a textbook, students can turn to HHMI's Ask a Scientist *Web site. There, working scientists field a wide range of biomedical questions.*

TO SEE OTHER QUESTIONS
Visit *Ask a Scientist*, www.hhmi.org/askascientist

NICHOLAS D. ANDERSEN, an HHMI medical fellow at Harvard Medical School, won the 2005 Young Investigator Award from the International Society for Applied Cardiovascular Biology.

ELIZABETH AZZATO, a student supported by HHMI's undergraduate grants program at Washington and Jefferson College in Washington, Pennsylvania, was selected as a 2006 NIH-Cambridge University Scholar in Biomedical Research. Up to six scholars are named each year for the academic award.

Seven HHMI investigators, three Professors, and two board members were elected fellows of the American Association for the Advancement of Science in 2005. The investigators elected are TANIA A. BAKER, Massachusetts Institute of Technology; JOANNE CHORY, The Salk Institute for Biological Studies; HARRY C. DIETZ, The Johns Hopkins University School of Medicine; PHILIP GREEN, University of Washington; JOEL F. HABENER, Massachusetts General Hospital; STEPHEN C. HARRISON, Harvard Medical School; and MILAN MRKSICH, The University of Chicago. The Professors are LESLIE A. LEINWAND, University of Colorado, Boulder; SUSAN R. WESSLER, University of Georgia; and HUNTINGTON F. WILLARD, Duke University. Also elected were PETER C. AGRE, Duke University, who serves on HHMI's scientific review board, and BRUCE W. STILLMAN, Cold Spring Harbor Laboratory, who serves on HHMI's medical advisory board.

THOMAS R. CECH, president of HHMI, received the 2006 Award for Exemplary Contributions to Education by the American Society for Biochemistry and Molecular Biology. This is the inaugural year for the annual award.

DAVID E. CLAPHAM, an HHMI investigator at Children's Hospital Boston, received the 2006 Bristol-Myers Squibb Foundation *Freedom to Discover* Distinguished Achievement Award in cardiovascular research.

MICHAEL D. EHLERS, an HHMI investigator at Duke University Medical Center, was selected to receive a 2006 Fulbright Scholar Award. Ehlers will work at the Université Victor Segalen Bordeaux 2 in France.

DAVID GINSBURG, an HHMI investigator at the University of Michigan Medical School, won the 2005 Jeanette Piperno Memorial Award from Temple University School of Medicine for his work in the field of thrombosis.

LILY Y. JAN and YUH NUNG JAN, HHMI investigators at the University of California, San Francisco, each received a 2006 Distinguished Alumni Award from the California Institute of Technology.

WILLIAM G. KAELIN, an HHMI investigator at the Dana-Farber Cancer Institute, won the 2006 Richard and Hinda Rosenthal Foundation Award from the American Association for Cancer Research. Kaelin was honored for his discoveries related to the von Hippel-Lindau tumor suppressor gene.

M. YASHAR KALANI, an HHMI medical fellow at Stanford University School of Medicine, was recently selected as a Soros Fellow. The Paul & Daisy Soros Fellowships for New Americans are given "to provide opportunities for continuing generations of able and accomplished New Americans to achieve leadership in their chosen fields."

CODY J. LOCKE, a student supported by HHMI's undergraduate grants program at the University of Alabama, Tuscaloosa, was named to the 2006 *USA Today* College Academic All-Stars 1st Team.

JOAN MASSAGUÉ, an HHMI investigator at Memorial Sloan-Kettering Cancer Center, received the inaugural Vilcek Prize in Biochemical Research. The award is

SPOTLIGHT

Björkman Lauded by L'ORÉAL-UNESCO

PAMELA J. BJÖRKMAN

HHMI investigator **Pamela J. Björkman** at the California Institute of Technology won the 2006 L'ORÉAL-UNESCO For Women in Science Award for North America. The esteemed award, which honors female scientists who are leaders in their fields, also went to recipients in Africa, Asia/Pacific, Europe, and Latin America. ¶ Björkman was honored "for her lifetime commitment to decoding protein structures, one of the seminal accomplishments in immunology and a major step toward new HIV therapies." ¶ As a graduate student and postdoctoral fellow in the Harvard University laboratory of the late HHMI investigator Don C. Wiley, Björkman solved the crystal structure of a human histocompatibility molecule. She continued her postdoctoral training at Stanford University School of Medicine with HHMI investigator Mark M. Davis, where she worked on T-cell receptors. Currently, her Caltech laboratory is focusing on protein-protein interactions, particularly those mediating immune recognition.

Danny Turner

given by the Vilcek Foundation to honor outstanding creative achievement by immigrants to America. Massagúe was born in Barcelona, Spain.

CRAIG C. MELLO, an HHMI investigator at the University of Massachusetts Medical School, won the 2006 Paul Ehrlich and Ludwig Darmstaedter Prize from the Paul Ehrlich Foundation in Germany. Mello shares the award with Andrew Z. Fire, Stanford University School of Medicine, for the discovery of double-stranded small interfering RNAs (siRNAs) and their role in RNA interference (RNAi).

RAFAEL RADI, an HHMI international research scholar at the University of the Republic in Uruguay, was recently elected a Foreign Member of the Brazilian Academy of Sciences.

TRUDI SCHÜPBACH, an HHMI investigator at Princeton University, received the E.G. Conklin Medal from the Society of Developmental Biology for her contributions toward understanding fly development and for supportive mentoring of students and postdoctoral fellows

MARGARET SOMOSI SAHA, an HHMI undergraduate program director and professor of biology at the College of William and Mary in Williamsburg, Virginia, was one of 15 educators to receive a 2006 Outstanding Faculty Award from the Commonwealth of Virginia.

CHRISTINE E. SEIDMAN, an HHMI investigator at Brigham and Women's Hospital in Boston, is one of five individuals recently named by the National Institutes of Health to serve as a member of the Advisory Committee to the Director.

SARAH SIEGRIST, a graduate student in the University of Oregon laboratory of HHMI investigator Chris Q. Doe, was one of 16 graduate students from North America and Asia to receive the 2006 Harold M. Weintraub Graduate Student Award.

Evans: Misha Gravenor Steitz: Ethan Hill

SPOTLIGHT

LEFT TO RIGHT: RONALD M. EVANS AND JOAN A. STEITZ

Two Investigators Win Gairdner Awards

Ronald M. Evans, an HHMI investigator at The Salk Institute for Biological Studies, and **Joan A. Steitz**, an HHMI investigator at Yale University School of Medicine, are among the five researchers who are 2006 winners of the Gairdner International Award for Medical Research. ¶ The Gairdner Foundation recognized Evans "for his discovery and characterization of nuclear hormone receptors and their fundamental links with physiology, nutrition and disease, including diabetes, atherosclerosis and cancer." Steitz was honored "for her discovery of the reactivity of autoimmune sera with nuclear riboprotein particles and elucidation of the roles of small nuclear RNAs in gene expression." ¶ The Gairdner Foundation was created in 1957 by James Arthur Gairdner, a successful stock broker and industrialist. Gairdner's lifelong interest in the convergence of medical research and clinical medicine led to his conviction that the achievements of medical scientists should be tangibly recognized. The prestigious International Award is given to individuals from diverse fields for outstanding discoveries or contributions to medical science.

ROGER Y. TSIEN, an HHMI investigator at the University of California, San Diego, won the 2006 Lewis S. Rosenstiel Award for Distinguished Work in Basic Medical Science. He shared the award with Martin Chalfie at Columbia University for the development of tools that allow direct visualization of molecules in living cells. Tsien also won the 2006 ABRF Award from the Association of Biomolecular Resource Facilities for outstanding contributions to biomolecular technologies.

THOMAS TUSCHL, an HHMI investigator at the Rockefeller University, received the 2006 Molecular Bioanalytics Prize from Roche Diagnostics, based in Basel, Switzerland; the 2005 Meyenburg Prize, given by the Wilhelm and Maria Meyenburg Foundation at the German Cancer Research Centre in Heidelberg, Germany; and the 2005 Ernst Schering Prize from the Ernst Schering Foundation in Berlin, Germany.

AHMET YILDIZ, a postdoc in the University of California, San Francisco, laboratory of HHMI investigator Ronald D. Vale, was the GE Healthcare & Science Young Scientist Award grand prize winner, the highest prize given in the international competition. Yildiz's essay was titled, "Elucidating the Mechanism of Molecular Motor Movement."

YI ZHANG, an HHMI investigator at the University of North Carolina at Chapel Hill, won the 2006 Junior Achievement Award from the Society of Chinese Bioscientists in America.

LEONARD I. ZON, an HHMI investigator at Children's Hospital, Boston, of Harvard Medical School, received the 2006 Simon Gratz Research Prize for Jefferson Medical College alumni in recognition of his contributions to medical research of practical value to the care of patients.

CONTINUED FROM PAGE 27
(DATA GO AWOL)

"If publishers go out of business their online resources can vanish," says Michael Seadle, assistant director for information technology at Michigan State University and a LOCKSS user. "We want to make sure that scholars, 10 or 100 years from now, will still have access to these data. LOCKSS is a way to make sure that published information doesn't disappear, while respecting the publishers' copyright. It's a security policy for everyone."

CONTINUED FROM PAGE 41
(PHILIP SILVERMAN)

The answer?
They needed classroom support. It was naïve to expect the teachers to find time to pour 400 petri plates. It's so obvious when I say it, but it's amazing how long it took for this to sink in. So we asked the teachers to send us a shopping list. You need 400 petri plates? We'll pour them for you. You need filters to isolate your own phage? We'll send them. We send these kits overnight so they have them when they need them, and they are the key. Now we're getting repeats. Teachers are asking for this stuff year after year.

You plan to train other scientists to do what you do. What will you tell them?
I'll tell them you're not trying to turn these teachers into scientists but into better science teachers. Don't try to dazzle them with your intellect or with the cost of your toys.

Effective scientist-mentors will understand this perspective. I will also tell them that to fully engage teachers it really helps to be a bit of a ham—mentoring is part performance art. Finally, I will tell them that teachers are great about telling you what they think. Listen to them. They might even make you a better teacher. ■

Science News

At Your Fingertips

If you use an RSS news reader, you can now subscribe to the HHMI News feed to monitor articles describing the latest research discoveries by HHMI scientists, the activities of HHMI grantees, and announcements from the Institute.

Find out more about the HHMI News feed at: www.hhmi.org

Find out more about RSS at: www.whatisrss.com

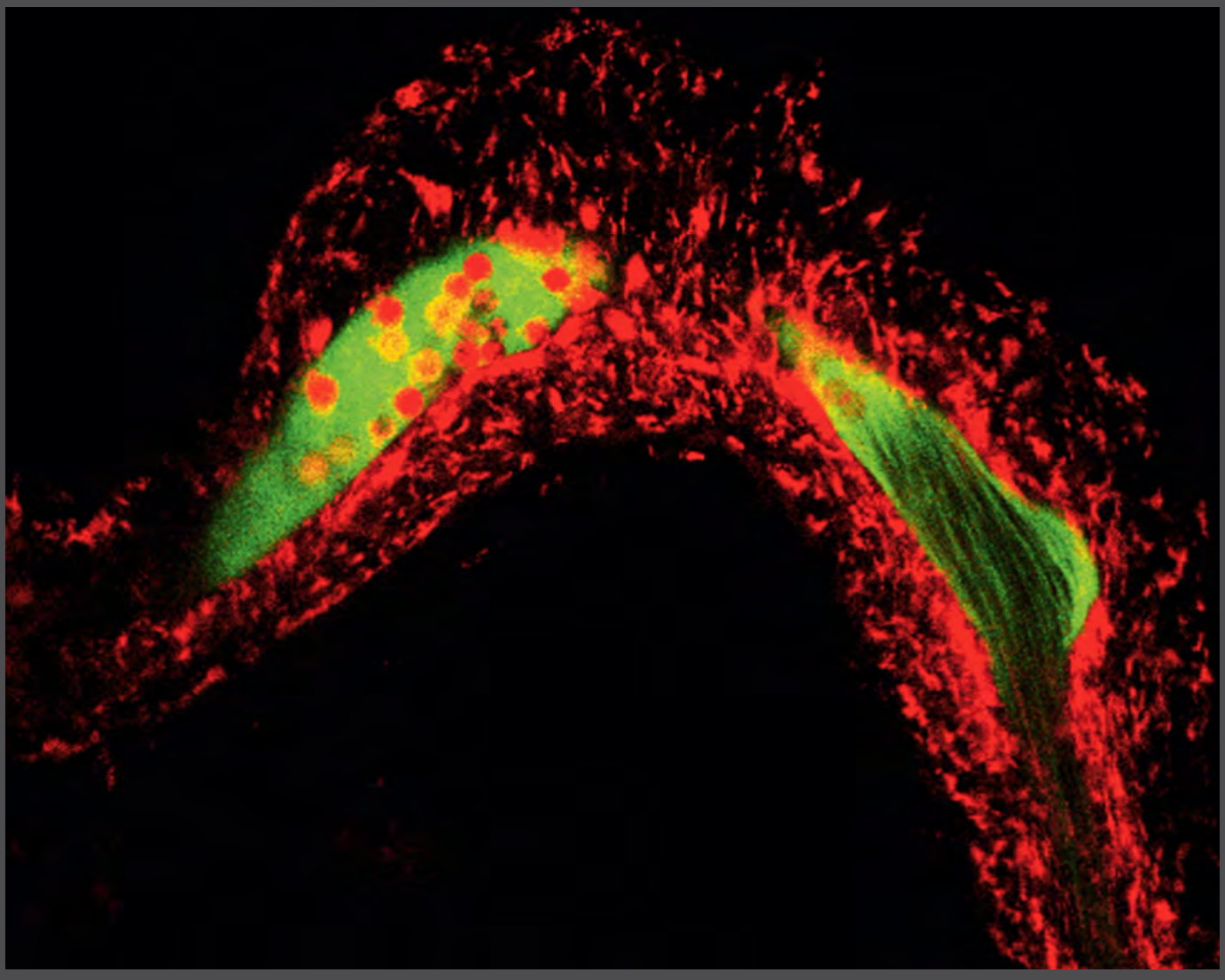
Answering Socrates

Knowing, from a career's worth of research, how faulty our memories really are, Columbia University neuroscientist Eric R. Kandel saved four decades of written correspondence, personal mementos, the minutes of every Society of Neuroscience annual meeting, and more. The HHMI investigator and Nobel laureate tapped deeply into that lode to write a memoir on his lifelong search for the physical basis of memory. Kandel donated his collected miscellany to the Columbia University library, which will curate his archives.

For biologists working on the brain, the mind loses none of its power or beauty when experimental methods are applied to human behavior. Likewise, biologists do not fear that the mind will be trivialized by a reductionist analysis, which delineates the component parts and activities of the brain. On the contrary, most scientists believe that biological analysis is likely to increase our respect for the power and complexity of the mind.

Indeed, by unifying behaviorist and cognitive psychology, neural science and molecular biology, the new science of mind can address philosophical questions first raised in Western thought more than twenty-five hundred years ago. Ever since Socrates and the early Platonists speculated about the nature of the human mind, serious thinkers have struggled with certain questions: How does the mind acquire knowledge of the world? How much of the mind is inherited? Do innate mental functions impose on us a fixed way of experiencing the world? What physical changes occur in the brain as we learn and remember? How is an experience lasting minutes converted to a lifelong memory? Such questions are no longer the province of speculative metaphysics; they are now fertile areas of experimental research.

Illustration: Shonagh Rae



Courtesy of Ulrich von Andrian, Katharina Engelke, and Harry Leung

Peering Into a Skull's Marrow

EVEN STATIC IMAGES OF A MOMENT CAPTURED IN TIME CAN SUGGEST MOVEMENT. IN THIS SECTION THROUGH A BONE MARROW CAVITY IN THE SKULL OF A LIVE MOUSE, RAPID BLOOD FLOW (GREEN) CAN BE SEEN IN THE UPPER PORTION OF THE VESSEL ON THE RIGHT. NUCLEI AND MITOCHONDRIA, STAINED RED, CAN BE SEEN IN THE BLOOD-FORMING CELLS THAT ADHERE WITHIN THE VESSELS. THE CAVITY IS ENCLOSED IN SOLID BONE, WHICH APPEARS BLACK.

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