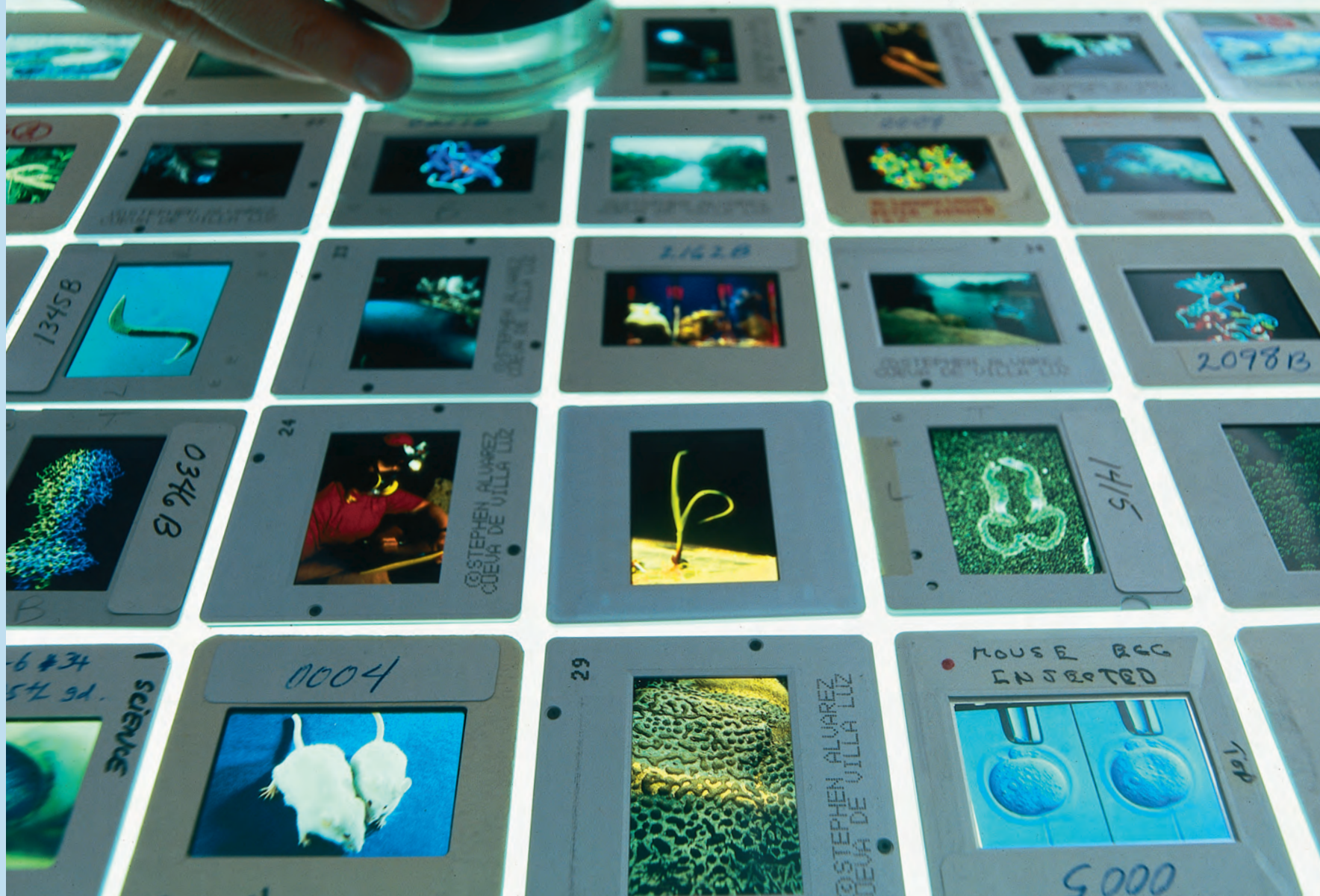


# HHMI

Howard Hughes Medical Institute Bulletin

## Cover Pursuits

A behind-the-scenes look at the lengths scientists will go to get their research on the cover of *Science*, *Cell* or *Nature*





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**On the Cover:** Cindy Smith, art director at Science, gives us a lesson in what goes into a good cover. Photograph by D.A. Peterson



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## NOTABLE

■ **Nancy C. Andrews**, an HHMI investigator at Children's Hospital, Boston, received the 2002 E. Mead Johnson Award from the Society for Pediatric Research.

■ **Randy L. Buckner**, an HHMI investigator at Washington University, St. Louis, received the 2002 Young Investigator Award from the Cognitive Neuroscience Society.

■ **Neil M. Ferguson**, an HHMI international research scholar at the Imperial College of Science, Technology and Medicine, London, England, was named an Officer of the Order of the British Empire for his efforts to help control the country's epidemic of hoof-and-mouth disease.

■ **Stephen J. Elledge**, an HHMI investigator at Baylor College of Medicine, Houston, Texas, received the 2002 National Academy of Sciences Award in Molecular Biology for his contributions to research in cell cycle regulation.

■ **Sankar Ghosh**, an HHMI investigator at Yale University School of Medicine, was named the 2002 American Association of Immunologists-PharMingen Investigator.

■ **Maxwell G. Heiman**, an HHMI predoctoral fellow at the University of California, San Francisco, received a 2002 Harold M. Weintraub Graduate Student Award for outstanding achievement in biological sciences course work. The international award is sponsored by the Basic Sciences Division of the Fred Hutchinson Cancer Research Center in Seattle.

■ **H. Robert Horvitz** and **Stanley J. Korsmeyer**, HHMI investigators at the Massachusetts Institute of Technology and the Dana-Farber Cancer Institute, received the first annual Wiley Prize in the Biomedical Sciences for their work in defining the genetic and molecular basis of programmed cell death. The prize is given by the Wiley Foundation.

■ **Richard P. Lifton**, an HHMI investigator at Yale University School of Medicine, won

the American Society of Hypertension's 2002 Richard Bright Award.

■ **Lee Niswander**, an HHMI investigator at Memorial Sloan-Kettering Cancer Center, was named one of two winners of the first Harland Winfield Mossman Developmental Biologist Award given by the American Association of Anatomists.

■ **Barbara A. Sawrey**, vice-chair of the Department of Chemistry and Biochemistry and HHMI program codirector at the University of California, San Diego, won the 2002 American Chemical Society Award for Encouraging Women into Careers in the Chemical Sciences.

■ **Michael F. Summers**, an HHMI investigator at the University of Maryland, Baltimore County, received the American Society for Microbiology's 2002 William A. Hinton Research Training Award for fostering research training in microbiology for underrepresented minorities.

■ **Roger Y. Tsien**, an HHMI investigator at the University of California, San Diego, received the 2002 American Chemical Society's Award for Creative Invention. It recognized the techniques he developed for studying cellular signaling.

■ **Jerry Waldvogel**, an associate professor at Clemson University in South Carolina and teacher in an HHMI-supported undergraduate program there, won the 2002 Outstanding Undergraduate Science Teacher Award from the Society for College Science Teachers.

■ **John D. York**, an HHMI investigator at Duke University Medical Center, received the 2002 Schering-Plough Scientific Achievement Award from the American Society for Biochemistry and Molecular Biology.

■ **William N. Zagotta**, an HHMI investigator at the University of Washington School of Medicine, won the 2002 Young Investigator Award from the Biophysical Society.

## LETTERS TO THE EDITOR

### Expand Bulletin Web site

I manage MiddleWeb, a large Web site dedicated to middle grades education. I'm also a freelance education writer and receive the *Bulletin* every quarter. It's a great publication, and I often find articles that I can link to MiddleWeb and promote through our weekly e-newsletter, which goes out to about 5,000 middle grades educators.

I was intrigued by "Building Interest in the Human Body" (December 2001, p. 30), which featured the program at Creighton University for middle school teachers and students who learn to "build a human." I was disappointed, though, when I found you had not included this article in your Web edition of the *Bulletin*.

Could I prevail upon you to add it? If you do, I'll make it available to our audience. I know that many middle grades science educators will enjoy reading it and stealing ideas from it.

JOHN NORTON

Editor, MiddleWeb: Exploring  
Middle Grades Reform  
[www.middleweb.com](http://www.middleweb.com)

Little Switzerland, North Carolina

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**Send your letters:** Via e-mail to [bulletin@hhmi.org](mailto:bulletin@hhmi.org) or to Letters, Office of Communications, Howard Hughes Medical Institute, 4000 Jones Bridge Road, Chevy Chase, MD 20815-6789. Letters will be edited for space and clarity. Please include your name, address (e-mail or postal) and phone number.

# Perambulating the Bounds

Some small New England towns have a tradition of perambulating the bounds—literally walking the town's boundaries to verify that they remain constant from year to year. The ritual, which has its origins in medieval England, reflects a profound human need for stability and reassurance. Science, however, has no such fixed boundaries that can be walked each year. And as scientists, we can offer little assurance to the public—the citizens of our “town”—about the direction in which our questions may lead.

I've been thinking about boundaries in the context of the ongoing national debate over research involving human embryonic stem cells. We have amassed extraordinary knowledge about the ways cells differentiate during the developmental process to create a fully functioning organism. Now, scientists throughout the world are working to tease apart that process in an effort to derive specialized cells that may some day be used to treat human disease.

This research occurs at the boundaries of the known and elicits concern—if not real fear. Confusion over vocabulary doesn't help. Reproductive cloning to create a new human being—which no responsible scientist supports—sounds pretty similar to therapeutic cloning, or what my colleagues and I are now trying to identify more accurately as somatic cell nuclear transfer technology. For those who are driven by fear or genuine philosophical differences, the distinctions between the two are not material and the confusion may even be helpful to their goals. But a new vocabulary would be beneficial for any informed discussion.

The lay public has every right to question those of us in the biomedical research community who seek to discover and use such knowledge, for whatever purpose. As responsible scientists, we have an obligation to consider the social and moral basis and the implications of the research we undertake. If we don't, we're little more than driven technocrats whose horizon is no broader than the next experiment.

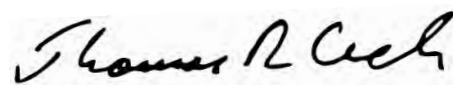
So where does this leave the Howard Hughes Medical Institute? Two years ago, I convened a group of leading ethicists and scientists to discuss human embryonic stem cell research as a first step toward deciding whether the Institute should support such research. After extensive review—and consideration of the many points of view shared at that meeting—the Institute agreed to support Douglas A. Melton at Harvard University in his quest to cure diabetes using human embryonic stem cells. Melton, whose research was profiled in the March 2002 *Bulletin*, collaborates with Boston IVF and colleagues at Harvard who work with stem cells derived from leftover frozen embryos created by in vitro fertilization. He hopes to coax the stem cells into becoming the insulin-producing beta cells that are lacking in individuals with juvenile diabetes.

The Institute will continue to evaluate requests from investigators to work with human embryonic stem cells on a case-by-case basis. In each instance, we will consider the potential for human health and the ethical implications of the research. As a private institution, we have an opportunity to fund research outside some of the restrictions placed on government-funded projects, but we have a concomitant obligation to carefully evaluate each new step.

The experience of thinking through the philosophical and humanistic aspects of Melton's research was so valuable that it has led us to create a Bioethics Advisory Board for HHMI (see page 37). Chaired by Laurie Zoloth of San Francisco State University, its members include Baruch Brody of the Baylor College of Medicine, LeRoy Walters of Georgetown University and Jonathan Moreno of the University of Virginia. Each has been an important contributor to national discussions about ethical issues in medical research. Members of the board are now immersing themselves in the essentials of basic biomedical research and participating in our regular meetings with investigators through formal programs, as well as informal office hours. They are also available to our scientists for consultations by telephone and e-mail.

Our expectation is that members of the Bioethics Advisory Board will help guide the Institute's thinking about the frontiers of biology. At the same time, they will be a resource for our investigators for planning new research studies. Finally, we envision a much-needed educational role for the ethicists on the board. Few good materials are available to today's scientists and graduate students—something I experienced firsthand while teaching a required course on the proper conduct of research at the University of Colorado in 1999. Working with Institute staff, the board will create teaching tools that will help inform the next generation of scientists, covering subjects that range from animal experimentation and genetic alteration to research involving human subjects and commercialization of discovery.

The boundaries of scientific discovery do not remain fixed in time or space. If we hope to break new ground in science, we must also break new ground in how we think about it. My expectation is that the Institute's Bioethics Advisory Board will be part of that process.



**Thomas R. Cech**

PRESIDENT

HOWARD HUGHES MEDICAL INSTITUTE



KAY CHERNUSH



# Up Front

## Chimps Yield New Clues to Origin of AIDS

*Scientists can now test wild chimps for SIV without disturbing them.*

A popular hypothesis among researchers studying the origin of AIDS is that human immunodeficiency virus (HIV) arose by cross-species transfer of a virus that infects chimpanzees in west central Africa. This simian immunodeficiency virus, SIVcpz, is thought to have jumped from wild chimpanzees (who do not appear to be harmed by the virus) to humans in the early part of the 20th century, perhaps when a hunter with an open wound came in contact with the blood of an infected chimp (see page 31).

Unfortunately, testing that hypothesis by studying the existence and spread of SIVcpz in wild chimps has been difficult; the animals are endangered and protected, so capturing or anesthetizing them to take blood samples is prohibited. Now, however, a new approach makes it possible to test for SIVcpz in wild chimps without touching or otherwise disturbing them. Using the new method, an international team of scientists identified for the first time a wild chimpanzee infected with SIVcpz. The work, done by Beatrice H. Hahn and her husband, HHMI investigator George M. Shaw, both at the University of Alabama at Birmingham, and a team that included renowned chimpanzee expert Jane Goodall, was reported in the January 18, 2002, issue of the journal *Science*.

The scientists analyzed urine and fecal samples from 58 chimpanzees living both in West Africa (Taï Forest in Ivory Coast) and East Africa (Kibale National Park in Uganda and Gombe National Park in Tanzania). All were in colonies that primatologists have studied so closely over the past several decades that they recognize individual chimps and know their life stories and daily habits—a boon for the HIV researchers.

“If we identified an infected chimp, we wanted to have the opportunity to go back to that very chimp for another sample, which required that the chimps be known to the people who study them,” Hahn explains. Once the primatologists were assured that no chimpanzees would be captured or disturbed, they were happy to help out, she says. “They were quite excited by the prospect that their work—which is painstaking—could help us decipher the origins, and

possibly the pathogenicity, of such a medically important group of viruses.”

The primatologists’ role, while vital, was far from glamorous. It was their job to collect chimpanzee urine and feces—no minor feat considering that the chimps roost in trees and the researchers had to keep track of which animal produced each sample. When the chimps arose each morning, the workers were waiting with buckets on the ground below, ready to catch whatever came their way. After collecting the material, the field teams sent the samples to Shaw and Hahn for analysis. Obtaining samples was only part of the challenge. “We needed to get a variety of information out of these samples,” says Hahn. “It took us two years to develop the methods [two highly sensitive immunological assays—one to detect antibodies and another to recover viral nucleic acids] that ultimately allowed us to do it.” The researchers first tested chimpanzee urine to detect infection. If a urine sample showed antibodies to the virus, the researchers then

*In Kibale National Park in Uganda, research assistant Ross Wrangham (below) catches urine from nesting chimpanzees like this mother and baby (top right) from Tanzania’s Gombe National Park. George Shaw and Beatrice Hahn (bottom right) used the specimens to test for SIVcpz.*



MARTIN MÜLLER



KARL AMMANN

isolated and analyzed viral RNA from the chimp's feces.

The 58 wild chimpanzees in the study belonged to the subspecies *Pan troglodytes verus* and *Pan troglodytes schweinfurthii*. Only one of these individuals—a 23-year-old male living in Tanzania's Gombe National Park—tested positive for SIVcpz. His strain did not resemble HIV as closely as some other strains of SIVcpz from west central Africa. Thus, it is unlikely that AIDS came from the Tanzanian chimpanzee population. Still, says Shaw, "while there were a number of clues and pieces of the puzzle that all led to the clear-cut conclusion that chimpanzees must be a natural reservoir for HIV-1, until now there had been no direct evidence for such a natural reservoir in the wild."

Now that the researchers know their techniques work, they can use them to test chimps in other parts of Africa, where evi-

dence from some of their earlier work suggests that SIVcpz made the chimp-to-human leap. In that research, the scientists analyzed SIVcpz strains from captive chimpanzees and concluded that the chimp subspecies *Pan*

*troglodytes troglodytes*, native to west central Africa, was the original source of the virus that led to human AIDS, because it harbored a virus most closely related to HIV-1.

The next step is to collect urine and fecal samples from chimpanzees in that region. "There, we won't have the luxury of knowing the individuals and going back to a particular chimpanzee for additional samples—we'll have to collect what we find on the forest floor," says Hahn. "But what we can do is determine the prevalence of the virus. And if we find a positive sample, we can genetically analyze the virus and compare it to known ones to further pinpoint geographic origins of the human viruses." The researchers are also continuing to study the virus isolated from the Gombe chimp, hoping to gain insights that can be used to develop a vaccine against HIV-1.

—NANCY ROSS-FLANIGAN



PAUL FETTERS



## Making Science Matter in Middle School

*Preteens need to know how science can change the world.*

The year is 2025, and the problems that plagued humanity at the turn of the century have all but disappeared. Scientists have repaired the ozone layer, discovered cures for most diseases and developed agricultural techniques that make it possible to feed all the people on earth.

Welcome to the world that Arizona middle school students would like to create, a world where science plays a central role in improving the quality of life. “We wanted to start with the real passions of kids and make that the driving force for a science program,” says Laura Martin, vice president for education and research at the Arizona Science Center in Phoenix. “So we asked 400 students from three middle schools what they would most like to be remembered for. They talked about ending war and poverty, and conquering disease. This age group is passionate about curing the ills of the world. Moral and ethical issues are vitally important to them.”

The Arizona Science Center’s creative approach couldn’t come at a better time in these children’s lives. Middle school, it turns out, is a now-or-never window for engaging youngsters in science. Students who greatly enjoy math and science in elementary school often grow apathetic in middle school because those subjects are no longer engaging or relevant to them, says Kit Peixotto, director of the Program on Science and Mathematics at the nonprofit Northwest Regional Education Laboratory in Portland, Oregon. In elementary school, she says, students learn science through appealing activities such as growing plants, constructing simple machines and measuring rainfall. By middle school, however, teachers tend to



GARY HOVLAND



abandon hands-on science in favor of lectures and exercises from books. As the curriculum gets dry, technical and remote, it loses pizzazz. It fails to intrigue. It's the *opposite* of fun.

#### TURNING POINT

If a student's interest in science fades in middle school, he or she may never recover it. The Third International Math and Science Study (TIMSS) of 1995 and 1999, published

At St. John's College in Annapolis, Maryland, faculty member Howard Zeiderman is pioneering a different solution to the middle school science slump. Because middle school students have a poor understanding of basic concepts in math and science—the kinds of problems that fascinated thinkers such as Aristotle and Galileo—Zeiderman and two other St. John's faculty members founded the Touchstones Discussion Project, a program designed to enrich science lessons by illuminating the

## *Middle school, it turns out, is a now-or-never window for engaging youngsters in science.*

by the National Center for Education Statistics, documents this slippage. While scores among U.S. fourth graders were well above the international average—only one country, Korea, outperformed the United States in both math and science—the scores of U.S. eighth graders were just average (with students from 20 of the 41 participating countries scoring higher). By the time U.S. students reached twelfth grade, their scores had plummeted—they outperformed only two other countries (Cyprus and South Africa).

According to TIMSS: "The better performance of U.S. fourth-graders . . . suggests that our children do not start out behind those of other nations in mathematics and science achievement, but somewhere in the middle grades they fall behind. These results point out that U.S. education in the middle grades is particularly troubled—the promise of our fourth-grade children (particularly in science) is dashed against the undemanding curriculum of the nation's middle schools."

With support from an HHMI grant, the Arizona Science Center is developing a hands-on biotechnology curriculum that will harness the youngsters' idealism, enthusiasm and openness to new ideas. "We want to introduce the kids to cutting-edge science, and we'd like them to build or do something that matters," Martin explains. "We want to excite them about their future."

Science center staff are collaborating with local teachers, as well as university and industry scientists, to design curricula that will allow students to develop ideas for new medical devices or implants or for genetically engineered crops to end world hunger.

ideas behind the facts and formulas.

Students use a short original text as a springboard. For example, they read a passage by Sir Isaac Newton before discussing why a ball keeps moving after it is thrown. Euclid's works introduce them to the idea of symmetry. The key to the program's success, says Zeiderman, is group discussion. Students hash out questions such as How straight is a straight line? Does the universe

### More in the Middle

Science is coming alive for middle school students and teachers at other HHMI-supported programs, including the following:

**Day in the Lab** Run by Hampshire College (Amherst, Massachusetts), this program brings middle school students and teachers to the college campus for hands-on science experiences. One of the sessions is especially designed to engage girls in science. For more information: [carbon.hampshire.edu/%7Estep](http://carbon.hampshire.edu/%7Estep)

**Kenyon Summer Institute** Kenyon College (Gambier, Ohio) invites middle school teachers to participate in research projects. The program also provides equipment and expertise to middle schools. For more information: [www2.kenyon.edu/depts/biology/HHMI/index.htm](http://www2.kenyon.edu/depts/biology/HHMI/index.htm)

**Water and Life** Headwaters Science Center in Benidji, Minnesota, takes research on water quality in two lakes at the head of the Mississippi into seventh and eighth grade classrooms. Hands-on activities use water and the local environment to teach the scientific method of inquiry. For more information: [www.hscbenidji.org/index.htm](http://www.hscbenidji.org/index.htm)

ever end? How does a scientist think?

"We've found that discussion is a real equalizer," he says. "The topics are not ones with correct or incorrect answers, so everyone's ideas are welcomed. Once they find themselves engaging in math and science discussions, students who were convinced they couldn't do math or science become much more confident."

To see how students from diverse backgrounds would respond, Touchstones was pilot tested in schools in Arizona, Connecticut, Maryland, New Mexico and Pennsylvania. Students in the pilot schools showed a dramatic improvement in their ability to think and write about mathematic and scientific concepts, Zeiderman says. This year, schools in New York, San Francisco, and Washington, D.C. have introduced the program and will act as regional centers to train educators to use the method.

#### QUANTUM LEAP

Kevin Williams, a science teacher at Frederick Douglass Academy II in Harlem, New York, has been using the program with his sixth- and seventh-grade classes. Through the discussions, he says, students have made a quantum leap in understanding. "The program allows them to form ideas and even to have the wrong idea. But they can then go back and figure out why it was wrong and what would be better," he explains. "We don't laugh at anything anyone says; no matter how wild and crazy it may seem, it may spark an idea in someone else. In our discussions, there is a lot of discovery going on."

In one class, for example, after students discussed a short passage by the scientist S.H. Scudder on the difference between seeing and observing, they spent an hour inspecting and drawing a leaf. They discovered that leaves are far more complex than they had realized, Williams says. More important, they learned the skill of scientific observation.

Now, instead of skimming the surface of subjects, Williams' middle schoolers observe the experimental process in depth, he says. Then, using the Touchstones principles, students formulate intelligent hypotheses based on their observations. They better understand the purpose and meaning of their studies. In the process, they are getting turned on, rather than turned off, to science.

—HELEN SILVIS

## Science Goes to Summer Camp

*A couple of weeks can turn apathy into enthusiasm.*

**B**efore she discovered science summer camp, 12-year-old Pa Nhia Lee thought science was boring. When a teacher nominated her to attend an HHMI-supported program sponsored by the Science Museum of Minnesota in St. Paul, Pa Nhia reluctantly decided to give it a try.

Born in Thailand of Laotian parents, Pa Nhia and her family emigrated to the United States when she was three years old. She grew up bilingual, often translating for her parents. Although she liked school, science was one of her least favorite subjects because it was taught from textbooks—not the greatest thrill for Pa Nhia, who preferred doing things to reading about them. The two-week camp was an altogether different story. She built models of a human heart and a cell, designed a prototype of a pain-relieving device and visited scientists at work in their labs at the University of Minnesota. “The experience completely changed my mind about science,” she says.

HHMI-supported summer programs across the country are having similar effects on students, and a hands-on approach appears to be the reason why. At Boston University School of Medicine’s CityLab Biotechnology Camp, for example, high school students were asked to imagine themselves as employees of a biotechnology company. Groups of three set out to produce a protein, starting with just a gene. In the process, the students learned—and taught each other—techniques for purifying and measuring the quantity of a protein such as one derived from an Amazon

rain-forest plant. They then tested the protein for its potential medicinal properties.

At the University of Nevada School of Medicine, ninth graders in the Summer of Discovery program learned about forensic science in a scenario involving a fictitious faculty member, Dr. Cutsalot, who had disappeared. “A judge from the Reno Justice Court came to hear the students present their analysis of forensic evidence that implicated a jealous employee in the doctor’s murder,” says Gina Sella, education-outreach coordinator. “He explained court procedures and asked questions about their findings. He was so impressed that he invited us to bring the following year’s students to his courtroom so they can see a real court case.”

In Minnesota, Pa Nhia used four soda bottles to construct a model of a human heart. She discovered that the model dou-

bled as an excellent squirt gun and also learned that the bottles represent the heart’s right and left atria and ventricles.

She used foods to build a model of a cell, with whipped cream as the cell membrane, grapes forming the cytoplasm and a small cake representing the nucleus. She incorporated peanuts as mitochondria, chocolate-covered nuts as Golgi bodies and raisins as RNA and DNA. After they finished studying their “cell,” the students dug in. “We couldn’t eat inside the lab,” Pa Nhia recalls, “so we took the cell outside and ate it sitting on the steps.”

She and her fellow “bioneers” did some practical things as well. They designed a device to help patients deal with the chronic pain caused by a sciatic nerve condition. The device massages a patient’s back when a button is pressed on a special bracelet. The students added a beeping signal to alert blind patients when batteries run low and a light to do the same for the hearing impaired.

Summer science camp is often just the beginning. Some students in the Boston program visit the university monthly during the school year to learn how to run sophisticated lab tests such as a Lowry assay (to measure the concentration of a protein in a solution)

and a polymerase chain reaction (which uses a sample of DNA to make more DNA). Their training may even continue through a second summer. Eight students who participated in the CityLab camp in 2000 and throughout the academic year returned to the Boston University School of Medicine the following summer for five-week internships in its research labs.

For Pa Nhia, the training may go on for years because she now wants to become a pediatrician. “When I learned how the human body works,” she says, “I started really thinking about a career in science. It’s the most important thing that has happened to me. —JOYCE BALDWIN



*Pa Nhia Lee changed her mind about science after a camp experience.*

DOUG KNUTSON





Science teacher Cindy Cook (left) and English teacher Elizabeth Henderson (right) have become comfortable in each other's professional worlds.

GIL FORD PHOTOGRAPHY

## Teachers Cross the Great Divide

*English and science teachers are working together like never before.*

Until recently, Elizabeth Henderson, an English teacher at Murrah High School in Jackson, Mississippi, steered clear of anything to do with science. The molecular biology topics that Cindy Cook taught in a classroom down the hall seemed arcane, a terra incognita well beyond Henderson's comprehension and her reach.

Now Henderson and Cook, as well as other Jackson-area teachers, are working together on science-related projects and even teaching each other's classes. Henderson teaches Cook's biotech students how, for example, the Lincoln-Douglas style of debating can shape discussions on hot topics such as embryonic stem cell research and genetic privacy. Cook, in turn, teaches Henderson's English students how to use the Internet for research, how to write science papers and how to make PowerPoint presentations of their findings.

Cook and Henderson have become com-

fortable in each other's professional worlds because they attended an unusual kind of summer institute at the University of Mississippi Medical Center (UMC), supported in part by a grant from HHMI.

"We did things that science students

*Biomedicine and biotechnology rely heavily on writing, reading and interpersonal skills.*

might do, such as collecting DNA by scraping our cheeks, then going through a procedure to make our own DNA fingerprints [the unique pattern of each person's DNA sequence]," says Henderson. The teachers also learned about infectious diseases and cancer and explored the ethics of science and medicine. The summer's reading list included *The Hot Zone*, the best-selling novel by Richard Preston about outbreaks of the lethal Ebola and Marburg viruses. "I

never would have thought that a science book would be accessible to an English teacher," says Henderson, who admits she enjoyed the book.

With the help of UMC faculty, Cook developed an interdisciplinary unit, dubbed the Sick School Project, in which students collect data about allergens that might be found in "sick buildings." She soon put it to use at Murrah. Biotech students inoculated a growth medium with dust samples they collected from various classrooms. When they identified the fungi that grew on the basis of color, filaments and spores, they found high concentrations of *Aspergillus* and *Penicillium*. Jan Gabrielle, a business and computer technology teacher, then helped the students set up data spreadsheets, and Kathy Bridges, an English teacher, helped design a tool for evaluating laboratory reports. Students in Bridges' English classes then reviewed the rough drafts of the "Sick School" reports written by the science students. This interdisciplinary project sparked an investigation in the school by local environmental officials.

At the summer institute, the teachers came up with the idea of exchanging classes. For Henderson, the exchange was a great morale booster: "When I go into Cindy's class, I am looking at students on a different academic track, most of whom I have never met. I feel energized just walking into their classroom, knowing that I have something important to share."

The summer institute is part of a program called Base Pair, which matches faculty at UMC with students and teachers in the Jackson Public School District to work

together on research projects. Director Robin Rockhold, a professor of pharmacology and toxicology at UMC, says one of Base Pair's goals is to achieve a "renaissance in science education" within the school district. He believes that biomedical and biotechnology issues are so pervasive, and rely so heavily on writing, reading and interpersonal skills for their resolution, that these subjects should not be taught in isolation from each other.

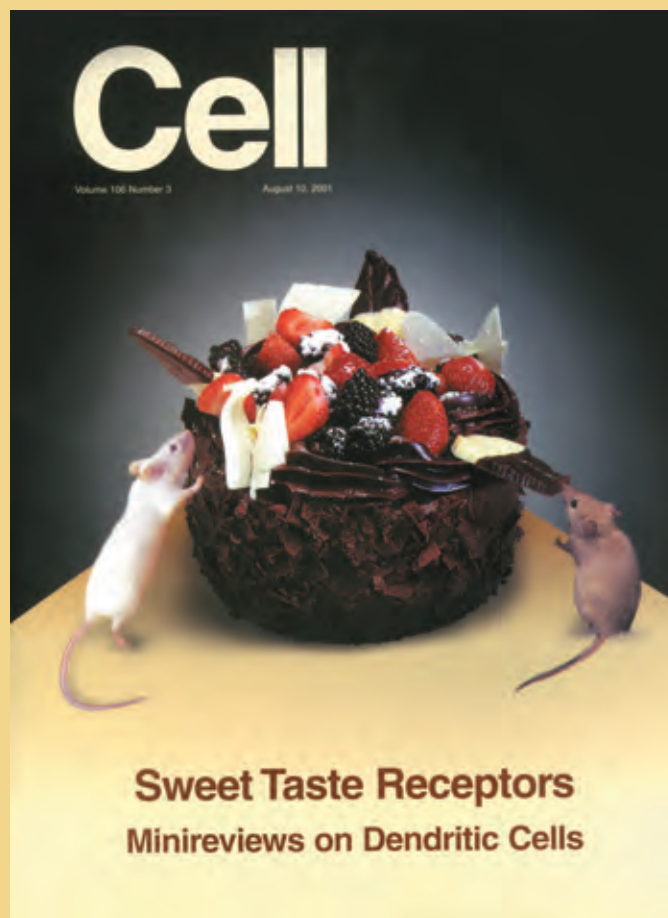
—JB



# Cover Calculations

TO WHAT LENGTHS WILL SCIENTISTS GO TO WIN COVER-STORY  
PLACEMENT IN SCIENTIFIC JOURNALS? **By Marlene Cimonis**





REPRODUCED WITH PERMISSION

TO THE BAKERS AT EXTRAORDINARY Desserts in San Diego, the behavior of HHMI investigator Charles S. Zuker must have seemed a little strange. He was looking for an uncommonly rich confection, but none of their cakes seemed decadent enough. He pointed to one extravagant pastry—could they possibly wrap an added layer of chocolate around it, and throw some cookies and fresh berries on top?

Of course, they said. What's the occasion?

"I'm going to feed it to a bunch of mice," he replied.

Zuker, a professor of neurosciences at the University of California, San Diego, laughs when he recalls last year's cake-shopping expedition, and how the bakers reacted when he told them his plans. "They freaked," he says.

Nevertheless, Zuker was on a serious mission. That luscious concoction—designed to entice the little rodents—was to play a major role in enticing certain bigger and smarter creatures as well. The journal *Cell* had just accepted a paper from Zuker's team on the functional

identification of mammalian sweet-taste receptors, and the scientists were out to create a photograph arresting enough to get their article featured on the cover.

"Science is an extraordinarily competitive endeavor," Zuker says. "We get two great pleasures out of it. One is to discover the undiscovered. The second is the recognition and respect of our peers. While it is the science that really counts, there's no question that getting on the cover... draws attention."

#### HOW SWEET IT IS

A cover appearance can indeed be a big deal, especially for young scientists trying to make a name in their field. "It can do their profile good," says Philip Campbell, editor of *Nature*. Although few believe that cover stories can make or break a career, covers nevertheless look good on a curriculum vitae and add heft to presentations at important scientific

meetings—plus they also look great on the office wall.

To this end, researchers often go to great lengths to create compelling and innovative images to accompany their submissions, hoping an editor will think “Cover!”

Zuker’s team found a photographer and brought some lab mice—and their newly purchased dessert—to his studio. There, they spent about seven hours shooting endless rolls of film. “It was extraordinarily difficult,” Zuker says. “You’d get one mouse to pose perfectly, and the others would scamper away—gone.”

The rodents weren’t even posing with the cake. With only that one precious confection, the team didn’t dare let the mice anywhere near it. Thanks to the wonders of computer technology, however, the final photograph—a seamless fusion of many shots—was flawless. It depicted a white mouse and a brown mouse, their forelegs reaching upward toward the delicacy, their noses sniffing the chocolate. It’s almost possible to imagine their whiskers twitching.

Readers of *Cell* saw it on the August 10, 2001, cover.

“We liked it,” says Deborah Sweet, a deputy editor at *Cell*. “Generally, we have scientific pictures. But we aren’t averse to having something less scientific from time to time, if it seems appropriate and looks good.”

### ICING ON THE CAKE

Scientific journals differ from mainstream publications when it comes to art. Most magazines arrange for photographs and other illustrations on their own, regardless of whether a piece is destined for the cover or not. Journals, however, suggest that researchers design and submit photographs and drawings to accompany their manuscripts and encourage the production of images that are high-tech, computer-generated, colorful and daring. A cover decision often will hinge on the quality of what the authors send.

Although most researchers will say it makes no difference to their careers, they nevertheless invest considerable time, effort and money trying to come up with ideas that will sell. “One of the tricks when you know your article is being published in a December issue, for example, is to make your art look Christmassy,” says HHMI investigator Thomas A. Steitz, a professor of molecular biophysics and biochemistry at Yale University. “For a submission to *Cell*, we had arranged one molecular structure, and I made sure it had red and green in it. In fact, it had a perspective that made it look a little bit like a Christmas tree.”

Cindy Smith, *Science*’s art director, is the editorial employee who comes under the most pressure from authors. “I’ve had people beg,” she says. “Postdocs have called and pleaded: ‘This would get me a job,’ or ‘This would get me a grant,’ if it landed on the cover. They’ve tugged at my heartstrings, and it’s always difficult for me to say no. So I never say no. I always say: ‘It’s still under consideration.’”

Steitz, who jokes that he “never had dreams of being a cover boy” as a young scientist, doesn’t believe his scientific future hinges on how often his work appears on a journal cover. But he doesn’t dismiss its value either—not for a moment.

“I don’t think anybody will get a job or be promoted because he or she had a cover; it’s what’s behind the cover that will get [a person] promoted,” Steitz says. “Still, it increases the impact factor—and that’s very important.”

HHMI investigator Christine E. Seidman, professor of medicine at



D.A. PETERSON

At *Science*, art director Cindy Smith and managing editor Monica Bradford look to the scientists for the art that adorns the covers of their journal.

Harvard Medical School, agrees. She and her colleagues made the cover of *Cell* last fall with their paper on Holt-Oram syndrome, a disorder that causes hand and heart deformities. The scientists introduced into mice the gene mutation that causes the syndrome, and they successfully reproduced the condition in the animals.

The cover featured a picture of a mouse heart with an atrial septal defect. “It’s a wonderful attraction to your article if it is represented on the cover,” she says. “Obviously, people will see it. People who are not necessarily inclined to read it otherwise will read it.”

Still, Seidman acknowledges that although “trainees and people writing the article are very invested in it being on the cover, the more senior people recognize that what is really important is the science. The discovery. Your experiments. The work. A cover, truly, is just the icing.”

In cases in which the cover potential of an article may be marginal, however, a dazzling piece of art can make the difference between prominence and burial. “It is often the case that a striking image determines the choice of what to run as the cover story,” *Nature*’s Campbell says. “But sometimes a paper is so important that we’ll know from the outset we want to highlight it whatever else is in the issue, and then develop the best cover that we can for it. Witness the February 15 [2001] human genome issue.”

### EYE OF THE BEHOLDER

Unlike newsstand magazines, the sales of journals do not depend on a strong cover. Most people who read journals are scientists who subscribe or who access them through libraries. “*Nature*’s cover is not driven by



a news agenda,” Campbell says. “However, we do want people to be as attracted as possible to opening it.”

Journal editors meet regularly, usually weekly, to talk about cover possibilities and available art. At *Nature*’s meetings, Campbell says, “all options for covers are displayed, and the cover chosen in an open discussion.”

Sometimes the choices are obvious—the human genome papers, for example. Those issues “are conceptual, and we often do [the covers] in-house or hire a freelancer,” says Monica Bradford, managing editor of *Science*.

“There are times when something has to be on the cover, but the scientist really has nothing interesting to offer,” art director Smith says. “I see that as a great challenge. Once I got an image that was a neuron, but you couldn’t see anything. It looked like a fluorescent dyed blob.”

Smith used special graphics software to bring out details in the image that couldn’t be seen on the original, making it more attractive. She was nervous about the changes she had made, so she ran it past the author. He was thrilled. “He said he was able to see things he hadn’t seen before,” Smith recalls. “It was all there. I was just bringing out more of it.”

But those times are rare. Usually, “if [the authors] can do the art, they’ve got a much better shot,” Bradford says, although “art is in the eye of the beholder—what some scientists think is beautiful, we don’t.”

The need to strike a balance among disciplines portrayed on the cover is another important factor, editors say. “We try to avoid an excess of covers with visually appealing subjects like furry animals or an excess of molecular structures,” Campbell says.

Sometimes that can’t be helped: for example, when two or more papers on similar subjects are published in the same time frame—and all are important enough to be on the cover. When that happens, editors try to use illustrations that tell the story without looking too much alike. *Science*, for example, produced two back-to-back covers featuring crystal structures (in the August 4 and 11, 2000, issues). “Both were very important papers, but the covers were strikingly different, considering they both were crystal structures,” Bradford says.

This may explain why Steitz—author of the August 11 paper, which described for the first time the structure of the large ribosomal subunit (part of the factory that makes proteins)—lost a bet with his colleagues over which of two art submissions the journal would select.

The winner was a computer-generated drawing that showed four representations of the ribosome “done like an Andy Warhol piece of art, with different colors in the background and different colors of the mol-

ecule,” Steitz says. “The one I was betting on was a single image, mostly in white and gray, with the proteins in yellow. It was stunning.”

It may have been stunning, but it was also too much like the picture that had run the week before. The corresponding paper described the work on rhodopsin, a light-sensitive protein, done by scientists at the University of Washington in Seattle and Japanese colleagues.

“I suspect what [Steitz] thought was simple and eloquent just looked too much like the August 4 cover,” Bradford says. “That’s what I mean. There are so many more things that go into these decisions than the author is even aware of.”

## BIGGEST BANG FOR THE BUCK

Some wonder whether the importance of cover placement has diminished in recent years with the rising popularity of online journals. But even that phenomenon hasn’t dampened scientists’ cover mania.

“It used to be that everyone opened their journals in the mailroom, and a great cover would hit you in the face and you would look up the article,” says HHMI investigator Chris Q. Doe, a biology professor at the University of Oregon who runs a lab at its Institute of Neuroscience. “Now I get most of my articles online and never even see the cover of a journal. All that said, I must admit that I try hard to get a cover every time, even now.”

Doe believes “great images are a good tool for introducing the science to a new audience. Also, I like having covers hanging in my office—they remind me of old students or projects. And I guess I can’t really accept the dawn of the e-publishing world and the lack of cover impact.”

The competition to get on the cover may be intense, but it usually doesn’t get nasty. No threats are involved. Money does not change hands, although an occasional box of chocolates from a grateful scientist may appear on an art director’s desk after the fact.

“It’s not hardball,” *Science*’s Bradford says. “But they do try to see how far they can go. It’s their big moment, being published, and they want to get the biggest bang for the buck. Some of the authors who have a very strong paper try to shop it around, as in ‘I can send it to you—if I get a cover—or to *Nature*. It’s like buying a car. They’re trying to make a deal.”

Zuker, however, jokes that it was easy to get *Cell*’s editors to use his photo on the cover. A piece of cake, one might say.

“I only had to promise them a slice,” he says, laughing.



REPRODUCED WITH PERMISSION

JOURNALS ENCOURAGE THE PRODUCTION OF IMAGES THAT ARE HIGH-TECH, COMPUTER-GENERATED, COLORFUL AND DARING. A COVER DECISION OFTEN WILL HINGE ON THE QUALITY OF WHAT THE AUTHORS SEND.



# A World Apart

A group of scientists with mammoth imaginations and the best biotech tools is piecing together a view of a prehistoric world where RNA ruled. This seemingly esoteric pursuit is generating modern-day approaches to fighting disease. >>

By Robert  
Kuska







# » Without a time machine,

biologists may never know for sure what created the first organisms roughly four billion years ago. Did life on Earth evolve, as some suspect, from self-replicating RNA molecules? In the hypothetical “RNA World,” a vision of the primordial Earth, precursors of modern RNA were responsible for storing genetic information and catalyzing biochemical reactions—functions primarily associated with DNA and enzymes.

While the theory is controversial, its implications transcend academic debate. In recent years, discoveries about the potential capabilities of primitive RNA have generated a wealth of new information about the structure, biochemistry and biological diversity of modern RNA. That, in turn, has served as the intellectual spark for a new and rapidly evolving species of the biotechnology world—companies that hope to develop and commercialize cutting-edge, RNA-based diagnostics and therapies for a range of human diseases (see page 18).

“I don’t think that we are ever going to prove evolutionary origins from work on the RNA World because it’s just too hard to do,” says Jennifer A. Doudna, an HHMI investigator at Yale University, who publishes frequently on RNA. “But I think that we can get some very interesting clues from these studies, and it makes the work exciting.”

Although the term was coined in 1986 by Nobel laureate Walter Gilbert at Harvard University, the idea behind the RNA World first appeared in the scientific literature in the 1960s. At the time, several theorists were bouncing around the relatively new concepts of codons and complementary base pairing in an effort to explain the relationship between DNA and proteins. Among the issues they raised was the ultimate chicken-and-egg question: Did proteins evolve before DNA, or vice versa? DNA, after all, requires enzymes to replicate, but enzymes are themselves proteins whose generation depends on “instructions” contained in DNA code.

The central dogma that emerged in molecular biology within a few years of Watson and Crick’s epochal description of the double helix in 1953 is that DNA leads to RNA, and RNA leads to protein. That is, sequence information from DNA in the chromosomes of all eukaryotic cells is copied to messenger RNA (mRNA) in a process called transcription; mRNA, in turn, carries its information to structures called ribosomes (see *Bulletin*, January 2001). Within these tiny “factories,” mRNA’s information is translated in the manufacture of proteins—the fundamental building blocks of cells, tissues and organs.

Elegant though this description is, it still leaves the chicken-egg problem. How could the complex DNA molecule have come into existence in the absence of enzymes? In 1968, Francis Crick, the legendary codiscoverer of the genetic code, offered a tentative explanation. Noting that the ribosome is composed largely of RNA, Crick proposed that RNA could have preceded both DNA and protein as the source of life. If so, in its earliest, most primitive state, RNA must have possessed both the capacity to store genetic information like DNA and the catalytic abil-

ity of an enzyme to power a rudimentary cell.

Though the idea sounded attractive, Crick and his colleagues faced a monstrous task in proving it. It was like strapping artificial wings on a horse and ordering it to fly like Pegasus—every molecular biologist knew that modern RNA was a messenger molecule, not an enzyme.

“We are really in the early days of RNA work, learning how RNA molecules fold, function and catalyze chemical reactions.”

—JENNIFER DOUDNA

JENNIFER DOUDNA



HAROLD SHAPIRO





JACK SZOSTAK

MARK WILSON

In the early 1980s, however, the horse sprouted wings. That's when two laboratories—one headed by current HHMI president Thomas R. Cech, the other by Sidney Altman at Yale University—independently and quite serendipitously discovered two distinct RNAs in the model organisms *Tetrahymena thermophila* and *Escherichia coli*. Under certain conditions, these RNAs were able to promote very precise cutting and joining of chemical bonds, thus acting like enzymes. In the often rigid, paradigm-driven world of biology, it was as unexpected as stumbling upon penguins nesting in the Florida Everglades. Jaws dropped.

The Nobel Prize-winning discovery of catalytic RNAs—now known as ribozymes—not only complicated the “DNA-RNA-protein” dogma, it added support to Crick's once tentative speculation. If mod-

ern living cells still lugged around fossils from an ancient RNA past, scientists might be able to dig them out and, in theory, develop a powerful model to explore the rudiments of primordial chemistry; Darwinian evolution; and, by inference, the biochemistry of modern RNA.

#### ARCANE VENTURES

Despite its obvious intellectual appeal, the RNA World was for the most part a quirky conceptual pastime in the years following the discovery of ribozymes. Though important new work dotted scientific journals, scientists unearthed only a half-dozen types of ribozymes that occurred naturally. This led many to believe that RNA World experiments had no practical applications.

“Ribozyme research was considered to be a very esoteric, ivory-tower sort of topic,” remembers Cech. “No one really dreamt of there being any commercialization or any practical spin-offs from the field at all.”

By the late 1980s, however, the theory of the RNA World began to attract the attention of researchers in biotechnology. As Cech observes, the field has never been the same since. “I went on Medline [the Internet database] a few weeks ago and saw that there were more than 2,000 articles that use the word ribozyme,” he says. “This is just a word that we invented in Colorado in 1981 for a lone example of a catalytic RNA. It has taken a worldwide effort to find other natural ribozymes [seven distinct structural classes and

more than 1,800 total examples have been described] and then to learn how to make unnatural ones for a full-fledged field to develop.”

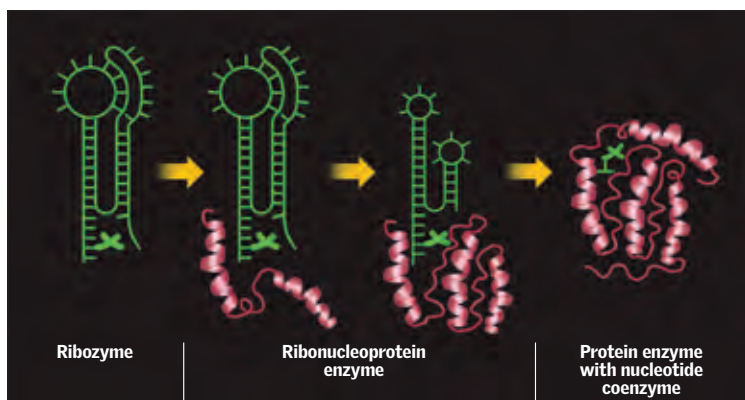
One of those leading the charge is HHMI investigator Jack W. Szostak, at Massachusetts General Hospital. Several years ago, Szostak and others believed the time was right to attempt to create ribozymes artificially by using a laboratory technique called *in vitro* selection. Szostak and colleagues begin their experiments with a test tube containing trillions of random-sequence RNA molecules. They screen this vast array of RNAs for some predetermined function, such as the ability to catalyze a specific chemical reaction or bind a target molecule. Those that don't make the grade are filtered out.

“Then we amplify the surviving molecules,” Szostak explains. At that point, the process is repeated, again and again. “The fact that this is an iterative process means that, in principle and actually in practice, you can start with a thousand trillion molecules in a little tiny tube. And you can find the one molecule in that tube that does a particular job.”

In short, Szostak and his colleagues crank up the forces of Darwinian selection to warp speed and then pull out the winner. “So many new ribozymes have been evolved from *in vitro* selection,” he says. “The range of chemistries these artificially produced ribozymes can catalyze has been greatly expanded. Yet we haven't observed this activity in living cells. It raises the interesting possibility that in an earlier era, ribozymes might have played a wider role than they do today.”

Like all laboratory techniques, *in vitro* selection is only a means to an end. For Szostak and others, the endpoint is not, as is sometimes reported, a bold attempt to recreate the RNA World, an epoch 50 times

“No one really dreamt of there being any commercialization or any practical spin-offs from ribozyme research at all.” —TOM CECHE



**The proposed transition** from the RNA World, where ribozymes performed all the catalysis needed for life. Later, RNA worked in concert with random chains of amino acids. When RNA evolved to synthesize specific proteins (as in today's ribosome), the role of proteins grew. In the modern world, catalysis is mostly performed by proteins (some still with RNA cofactors).

ADAPTED FROM A CONCEPT DEVELOPED BY HAROLD WHITE III

itive RNA; indeed, he says, "there probably never were any genetic fossils. The last common ancestor of life on this planet, it seems clear, was a pretty complicated organism. It had 300 protein genes—ballpark. It had ribosomal RNA; it had a full set of transfer RNA [which carried the appropriate amino acids to the ribosome to build new proteins]. Whoever the last common ancestor was, he and his contemporaries more or less ate the guys who were still in the soup. We don't have them to compare to anymore."

Why, then, this venture into the unknown? Why try to concoct a primitive RNA cocktail in a small glass tube? The answer is twofold. First, by performing in vitro selection experiments, scientists can learn to distinguish the biochemically possible from the impossible. As many point out, this nuts-and-bolts approach has direct applications in learning how to tweak the biochemistry of modern RNA and leverage its biochemical secrets to create new technologies to fight disease. "It is important to remember that we are really in the early days of RNA work, learning how RNA molecules fold, function and catalyze chemical reactions," says Doudna, noting that such fundamental work is

essential to develop effective RNA-based tools in medicine.

Second, the hypothetical RNA World serves as a unique model to study Darwinian evolution. Szostak would like to create a crude, RNA-based artificial cell that is capable of rudimentary metabolism. This would provide the first window to observe in real time the forces of Darwinian selection at work on primitive biomolecules. Through this window researchers could gain insight into key biological concepts

more ancient than the dinosaur era. The goal is to create a hypothetical model of a protobiotic Earth in which catalytic RNA might have evolved.

"It's all indirect in the sense that we really don't have an RNA World to study," Szostak says. "We just don't know the conditions that would have been relevant at that time. Basically, it's all possibility."

Sean R. Eddy, an HHMI investigator at Washington University School of Medicine in St. Louis, points out that there is no fossil record of prim-

## From the RNA World to the Real World

More than a half-dozen biotechnology companies have been launched to develop and commercialize ribozyme-based diagnostics and therapeutics. The pioneer was Ribozyme Pharmaceuticals, Inc. (RPI), of Boulder, Colorado. Founded in 1992 by current HHMI President Thomas R. Cech, the company was organized to pursue the discovery from Cech's laboratory that some types of RNA, called ribozymes, can cleave other RNA molecules. RPI is developing therapeutic ribozymes to target the messenger RNA (mRNA) of proteins implicated in specific diseases. Like all proteins, disease-related proteins are encoded by genes, whose instructions are carried to the ribosome

by mRNA. By synthesizing ribozymes that bind and cleave these mRNAs, RPI scientists are trying to prevent undesirable proteins from being produced.

After a decade of work, RPI has three ribozymes in early phase clinical studies to treat hepatitis C and cancers of the breast and colon. Another ribozyme is in clinical development to treat hepatitis B. Other companies that see promise in ribozyme-based therapeutics include Immusol, Inc., of San Diego; RiboTargets, of Cambridge, U.K. and Rib-X Pharmaceuticals, of New Haven, Connecticut, whose founders include HHMI investigator Thomas A. Steitz at Yale University.

Immusol uses ribozymes to "identify novel targets against which small-molecule-, antibody- or ribozyme-based drugs can be developed. Armed with a detailed knowledge of the structure of the ribosome and with techniques to screen large numbers of molecules at once, companies like RiboTargets and Rib-X are looking for ribozymes or other small molecules that will target the ribosome of a harmful bac-

terium and shut it down. In particular, they are targeting these potential antibiotic drugs to specific regions of the ribosome that don't seem to be susceptible to mutation. This means that the bacteria will be less likely to develop resistance to the drugs. RiboTargets is one of several firms also exploring the feasibility of using ribozymes to prevent or interrupt the process of replication in HIV, the virus that causes AIDS.

Still other young companies see ribozymes as the basis of new diagnostic tools. Archemix of Cambridge, Massachusetts, has licensed a technology developed at RPI to design a series of ribozymes whose activity is switched on or off by the presence of specific molecular targets. Called RiboReporters, these special ribozymes act as extremely sensitive biosensors. When they bind to target molecules, energy is generated that is detectable on various assays. According to Archemix, RiboReporters can be used to detect numerous molecules, ranging from ions to small molecules to proteins. —RK





DAVID BARTEL

KATHLEEN DOOHER

such as replication, translation, cellularization and metabolism.

Using in vitro selection, Szostak and other RNA Worlders have made tremendous progress toward this goal. Last year, David P. Bartel's laboratory at the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology produced a ribozyme that was capable of generating a complementary strand of other RNA sequences. Though Bartel says that the fidelity and length of the copy needs to be improved, the work nevertheless established that RNA can catalyze its own replication, a capability consistent with the RNA World hypothesis.

If in vitro selection is one vast chemical lottery, then the jackpot belongs to the laboratory that creates the first so-called replicase. A replicase is a still-theoretical ribozyme that would have catalyzed the replication of RNA molecules, including itself, in an RNA World.

“Nothing has led to thinking hard about ‘origins’ more than the RNA World hypothesis.” —ANDY ELLINGTON

Though a replicase has eluded scientists for years, most in the field say that its synthesis is only a matter of time. “It would be a very nice achievement, for sure, but it would not be completely shocking because we know it is possible to get an RNA to do the kind of chemistry that is necessary for a replicase,” says Doudna.

“It seems to me that the next step is getting the process to work, to copy long templates with better fidelity and to make molecules that are in fact functional,” she continues. “If you really are making a replicase, then you are making a molecule that is able to make a copy of itself. And that would be a remarkable achievement. If that were done, one could certainly imagine setting up a system in the laboratory to actually watch the molecule evolve. That would be pretty exciting.”

Bartel, whose laboratory seems to be the front-runner in the search for a replicase, agrees the payoff will be witnessing the forces of evolution leap into action. “If the replicase is just replicating any RNA that is in a solution, then there won’t be any selective advantage for it to replicate faster or more accurately,” he says. “It will just be replicating all of the RNA equally. But, if it preferentially replicates its relatives, then you get an evolutionary line going that takes over. That’s when the fun begins.”

#### TIME WASTED?

There remain many skeptics. Some doubt that pre-cellular RNA-based life would have had sufficient time to evolve into the most primitive bacterial cells that fossil evidence has revealed. The earliest date to about 3.8 billion years ago, leaving a fairly narrow 150- to 500-million-year span between the end of Earth’s bombardment by solar system fragments and the appearance of the first simple bacteria. Therefore, some scientists, including Francis Crick, have indicated a preference for a theory called Panspermia, which speculates that earthly life had an extraterrestrial source. Others have explored the possibility that humble crystals of terrestrial clay might have served as “scaffolds” upon which the first genomes assembled themselves.

If either of these theories or some other were to be proven true, would studies of the RNA World have been a waste of time—a scientific dead end?

“Oh, good Lord, no,” says Andy Ellington, a scientist at the University of Texas at Austin, who has studied the RNA World and recently joined forces with a colleague to start a biotech company that he describes as an indirect spin-off of the RNA World. In Ellington’s view, it’s something like the advances in miniaturization and integrated circuit development that were made as a result of the space program. They’ve profoundly changed the way we live, even though “we don’t go to the Moon anymore.”

“Nothing has led to thinking hard about ‘origins’ more than the RNA World hypothesis,” Ellington says. “Even if NASA scientists were to break the news that life began with cosmic ‘seeds,’ the ideas that have emerged as a result of the theory would not be irrelevant, just displaced to the next step in our history.” ■







# ACCOMPLISHED WOMEN

THE CLIMB TO THE  
TOP IS NOT EASY,  
BUT A NEW GROUP OF  
WOMEN IS MOVING  
INTO THE UPPER  
RANKS OF SCIENCE.  
THEY URGE YOUNG  
FACULTY TO AIM  
HIGH—JUST BRACE  
FOR THE INEVITABLE  
OBSTACLES.

BY KATHRYN BROWN

IN THE PAST THREE YEARS, Christine E. Seidman has served on three search committees for department chair or comparable positions at Harvard Medical School's Brigham and Women's Hospital. Each time, she's wondered where the women are. "I never saw more than one—sometimes zero—female candidates in each pool of 10 to 20 resumes." The school wasn't being aggressive enough to identify and actively solicit women with the credentials to compete for the jobs, she says.

"Although young women have more opportunities [than in the past], progress in getting to the top hasn't changed," says Seidman, a geneticist and HHMI investigator at Harvard Medical School. "The glass ceiling is more like cement."

A few institutions, such as the Massachusetts Institute of Technology (MIT) and the California Institute of Technology (Caltech) have been seriously studying the difficulties faced by women scientists in academia. While institutions take a look inside, a small cluster of women scientists have found their way into

ILLUSTRATIONS BY ALLISON SEIFFER

leadership positions at places like Princeton University and the Whitehead Institute. How did they do it and what will it take for others to follow?

#### FROM COAST TO COAST

At Caltech, which has more than 280 professors of varying rank, just 31 (11 percent) are women, according to a survey of its faculty released last December. These women, the survey reports, are paid less and have lower satisfaction at work than their male peers. Over half the female respondents said they were dissatisfied with or had reservations about the process for getting tenure—that official university stamp of approval and job security—compared with just 19 percent of the men.

About seven years ago, an MIT task force on women in science began studying the university's work climate. The team's 1999 report was bleak. Fifteen female scientists had tenure at MIT, compared with 197 men. Women were overlooked for jobs, paid less, given less lab space and assigned the worst teaching loads. Why

did they put up with it? "Basically, these were science junkies," says MIT biologist Nancy Hopkins, one of the study's authors. "Their passion for science was over the top, and that allowed them to endure some pretty hard and lonely times."

In fact, no matter what the school's size or status, female faculty continue to face classic challenges: cracking the upper echelons of fields dominated by men, balancing career and family and fighting the chronic battle against unequal pay. Some respond by finding other careers. "We've lost some awfully good talent," says microbiologist Rita R. Colwell, who became the first female director of the National Science Foundation (NSF) in 1998. According to NSF statistics, women currently earn roughly 35 percent of science and engineering doctoral degrees. Many of those women, however, opt out of academics, when they look down a long, competitive road that often favors men. "They don't see a level playing field," Colwell says.

Since the widely publicized MIT report was issued, Hopkins says, the tangible inequities—in salary, space allotments and administrative positions—have been corrected. Less-tangible biases, however,

## BABY ON BOARD

**F**or many female scientists, serious career dilemmas begin with thoughts of bringing up baby. Should you have a child before or after tenure? How will you find the time—not to mention the energy—to do it all?

In past decades, female scientists often gave up hope of having a family. But fewer are willing to do so today. "My life would have been empty without children," says Whitehead Institute Director Susan L. Lindquist, a mother of two teenage daughters. In fact, Lindquist says she would have opted for children over an academic career, if forced to choose. "I'm very happy I didn't have to make that decision."

Instead, she and other scientist-moms have perfected the art of time management. Take Erin M. Schuman, a neurobiologist and HHMI investigator at the California Institute of Technology. Since her daughter's birth in 1999, Schuman has become a master juggler. In the first two weeks of her daughter's life, she wrote a review for the journal *Neuron*. A few weeks later, she co-chaired a scientific conference with her child held close. Routinely, Schuman works at home two mornings a week. "It really is possible to be a good mom

and keep your lab running," she says.

Of course, there are always a few obstacles, obliging the woman to be a resourceful master juggler. Schuman recalls her own frustrations, from unhelpful meeting coordinators to a lack of childcare. She put her name on the waiting list for on-site day care at Caltech when she was just 5 months pregnant. More than two years later, when baby Charlotte had grown into a toddler, she finally got a spot.

"You have to be creative about problem-solving—flexible and yet organized," says Judith Kimble, a molecular biologist at the University of Wisconsin–Madison. Kimble was 38 and well on her way to tenure when she had a child—and only one. "I saw other women struggling with two or three kids, and I wasn't sure I was up for that," Kimble says. She also counts herself lucky to have a supportive spouse and community.

"I think we need a change in attitude," Schuman says. "A child needs the most focused attention for the first four years of life, so it's really not that much [of a professional setback] to spend a little less time in the lab and more time with a child. If we encouraged people to have families, women wouldn't drop out of science so much."

—KB

*When dusk is fast approaching but deadlines loom, Erin Schuman's daughter Charlotte "works"—with crayons and scissors—alongside mom.*





have been harder to erase. New reports released by MIT in March point to marginalization, for example female faculty being excluded from high-level decision making. Still, she says, the ranks of female faculty have grown by 50 percent (bringing MIT up to Caltech's 1 woman for every 10 men). At least a dozen women now work in science and engineering administration. "You've got to get women in positions of power, where they can offer support from above," Hopkins says.

### HOLD THE DOOR OPEN

Fields with plenty of senior women faculty, such as molecular biology, tend to attract far more female graduate students than male-dominated fields, such as physics. It's as though female leaders open the door, allowing others to follow. "The rich get richer," says former HHMI investigator Shirley M. Tilghman, who recently became the first female president of Princeton University (see page 25).

She points to x-ray crystallography, a field with a fair number of women. Decades ago, prominent x-ray crystallographer and Nobel laureate Dorothy Crowfoot Hodgkin trained women, who then went out and trained women, and so on, leading to today's vibrant field, with many female faculty. The same trend holds true in Tilghman's own specialty, mouse genetics. "There were great female founders in the field in the early 20th century who inspired generations of women, creating opportunities for women to thrive and reach National Academy of Sciences status," Tilghman says. "These were role models, catalysts." Unfortunately, she adds, the "female factor" has yet to reach physics, computer science and a variety of other fields.

Following in MIT's footsteps, Caltech's December report on female faculty offered some tangible suggestions for campus life, such as increasing the proportion of female faculty to 25 percent over the next decade, more carefully considering—and explaining—salary and tenure decisions and generally improving the work environment. Biologist Marianne Bronner-Fraser, chair of faculty at Caltech, says the report has prompted the school's academic divisions to adopt a formal mentoring process, designed to help both female and male assistant professors navigate the tenure track. Each division chair has also been asked to outline strategies for better recruiting and retaining female faculty. Finally, to make Caltech more family-friendly, a new committee will address childcare concerns, planning ways to help faculty, postdocs and graduate students gain access. "There are other issues that must also be addressed, but we are trying to take them in turn," Bronner-Fraser says.

### SLOW THE TENURE CLOCK

Many say that schools could do more by giving overextended parents a valuable gift—time. While the tenure process can be stressful for any junior faculty member, new mothers—already exhausted from coping with various other responsibilities—can find the process overwhelming. How much can you accomplish in 24 hours?

"It's not that women approach tenure any differently than men do," remarks Tilghman. "The problem is that your most likely child-bearing years and your tenure-track years are the same. My sense is that the shorter the tenure clock, the more intense the problem."



## GIRLS JUST WANT TO CURE CANCER

It was a slumber party like no other. The fifth- and sixth-grade girls gathered around to watch videos starring—not Britney Spears—but a biological anthropologist, a parasitologist and a wildlife biologist. Later on, the girls dissected the roundworm *Ascaris lumbricoides*. Before the night was over, they were searching for parasites on flea-infested dogs. The whole experience, they concluded, was way cool.

In 1998, educators in Lincoln, Nebraska, launched a series of sleepovers for grade-school girls based on the "Wonderwise" learning series, award-winning educational kits designed to encourage girls to pursue careers in science. Created by the University of Nebraska State Museum with a grant from HHMI, each kit features the life of a woman scientist and includes a video, CD-ROM and activity guide ([www.hhmi.org/wonderwise](http://www.hhmi.org/wonderwise)).

"Before the sleepover, I thought only a select few women made it all the way," says Hannah Weber, 15, who participated when she was 12 and 13. Watching the videos and meeting women scientists—including local science teacher Sara LeRoy-Toren, who led the worm dissection—dispelled that myth. "When I was younger, we learned about Louis Pasteur and Jonas Salk in school," she says. "The same names kept coming up, and very few were women."

The sleepovers helped reinforce Weber's interest in science. She is now a sophomore in the Lincoln Public Schools Science Focus Program, based at Folsom Children's Zoo and Botanical Gardens. She dreams of becoming a doctor or maybe a research scientist who discovers a cure for cancer.

Weber hopes that by the time she finishes medical and postgraduate training, women won't be confronted with all the obstacles that sidetracked her own mother, who aspired to be a scientist but finally opted for a more traditional female career as an arts administrator. For now, the teen is less concerned about how she'll juggle the competing demands of life as a woman scientist than about how to pay for her education. "I love science so much, I'll just work around all the obstacles," she says.

Her mother, Deb Weber, admires Hannah's passion and determination. "I support both my daughters—Hannah and 12-year-old Emily—in their natural curiosity about the world," she says, "and I encourage their confidence in their analytic abilities."

—JANICE KAPLAN



SAM OGDEN

*Nancy Hopkins has seen some progress at MIT since her study was published in 1999, but, she says, the less-tangible problems will take time to fix.*

Tilghman, a single mother of two, has pledged to review Princeton's tenure process. Others have also suggested extending postdoctoral funding for soon-to-be or new moms.

## PRACTICAL APPROACHES

The most successful female scientists often have mentors to thank. Colwell calls her (male) undergraduate adviser "a hero." Some 30 years ago, when her department chairman told an ambitious Colwell that he wouldn't "waste a fellowship" on a woman, she turned to her adviser, who promptly offered a genetics slot in his own lab. That left her with a powerful lesson: "Never give up," Colwell says. "If one opportunity falls through, find another."

Success stories like Colwell's suggest that women can, indeed, find their way in science—with the right attitude. "I was stubborn and determined and sometimes angry, and I was just going to have this career," Colwell remarks. Tilghman attributes much of her own success to

selective inattention. "I went through most of my career with massive blinders on," she says. "I didn't allow myself to see anyone trying to discourage me, actively or subtly." Indeed, she recommends that younger scientists brush right past callous remarks or minor annoyances, saving battles for post-tenure times. Molecular biologist Judith Kimble, an HHMI investigator at the University of Wisconsin–Madison, echoes that sentiment. "Don't think about being a woman," she advises. "Don't let it be an issue. Think about being a *scientist*."

Optimism helps. Former HHMI investigator Susan L. Lindquist, who last October became director of the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts, says that faith—and just a general optimism—carried her over the bumps in the scientific road. "I have a fundamental belief that most people are genuinely trying to do their best, and they may merely be unaware when they're inconsiderate or inappropriate," says Lindquist. "So over the years, if unfortunate incidents happened, I just licked my wounds and kept on going. I also worked like hell."

Looking back, Lindquist says she wishes she'd sought out a mentor—or at least female faculty friends—for inspiration and guidance. "It never occurred to me to talk with other faculty and get some advice," she says. "I felt I had to do it on my own." Today, Lindquist makes a point of mentoring women rising through the ranks. "Over the last 10 years, I've realized I can make a world of difference for other women." Some women approach her after seminars, others call. In just half an hour, she can offer empathy and practical pointers. "Don't hesitate to seek that kind of advice," she suggests. "Take the lessons women have learned and let them help you."

In the end, the best approach for ambitious scientists is a practical one, these women say. Do what you love. Ignore minor irritations. Fight for important changes. Harvard's Seidman suggests a focus on the process: What procedures are in place to actively recruit women for positions of power? Who is giving presentations at "grand rounds," for example, and how are the speakers chosen?

Finally, be realistic. When a female graduate student comes into Tilghman's office, anxious that she won't be able to juggle a normal family life and a scientific career, Tilghman hesitates. True, her heart goes out to the student. But she sprinkles her encouragement with caveats, keeping in mind all the free time—often with her kids—that she gave up to reach this point in her career. "To succeed at a high level in any profession requires some sacrifice," Tilghman says. "You have to be prepared to give up something—or be satisfied with lesser achievement. There's no free lunch here." **H**

## Medal Honors Female DNA Pioneer

The British government is boosting its efforts to help women scientists stay in the profession and gain recognition for their work. Patricia Hewitt, secretary for trade and industry and minister for women, announced in January the establishment of the Franklin Medal, named for Rosalind Franklin, whose research contributed to the discovery of the double-helix structure of DNA. Each year, the Franklin Medal and £30,000 (just over \$40,000 U.S.) will be awarded to a researcher for scientific innovation. Franklin, dubbed "the forgotten heroine" in the race to unravel the mystery of human DNA, died of ovarian cancer in 1958 at age 37.

Along with the medal, the British government is funding a mentoring program to help women scientists return to work after a career break. According to a January 2002 report, "Maximising Returns," 50,000 U.K. women with degrees in science, engineering or technology are not working at any one time, most having left the workforce to raise children. Of those who do return to work, only about 8,000 return to a job that makes use of their scientific training.



## A CONVERSATION WITH SHIRLEY TILGHMAN

# ADVOCATING FOR WOMEN

**M**olecular biologist Shirley Tilghman has always pushed science forward. As a postdoctoral researcher, she helped clone the first mammalian gene, a mouse beta-globin gene. As an HHMI investigator at Princeton University for 15 years, she unraveled molecular mysteries behind genetic imprinting, in which a gene's expression differs depending on whether the maternal or paternal form is inherited. All the while, Tilghman has been a vocal advocate for women in science—and the single mother of two children. Last year, she became Princeton's first female president.

*What's hardest about being both a scientist and a mother?*

**Shirley Tilghman:** Lack of time. You have to be disciplined about how you use those precious hours at work because they're limited. When you know you have to be out the door at six o'clock to pick up your kid at the day care center, it gets difficult. Related to that issue is guilt management. Too many women spend their time wishing they were someplace else, and that's just an intense waste of energy. You just have to have the self-confidence to say: "When I'm at work, I'm at work. When I'm at home, I'm at home. And each one of them is important."

*How have the challenges facing female scientists changed, and what barriers still exist?*

If you look at the life sciences, the challenge of my generation was how to be a minority—how to make your way in professions that were largely populated by men. That's not the case in those fields any longer; women are now in the mainstream. On the other hand, the more quantitative fields have had more difficulty attracting women. Many people believe you can trace that back to culture, to expectations in primary school and

high school. In education, setting high expectations is half the battle. If you set expectations very high for a group, the likelihood that they will meet them goes way up, as compared to telling a group, "Well, this is hard, and if you don't do well, we'll understand."

*You've said that it's time Princeton had a female president. How do you plan to encourage female scientists at the university, both formally and informally?*

I've established a task force that will explore Princeton's past record in hiring, promoting and retaining women, and it will make recommendations about how to improve those practices in the future. I would like to think that when I leave this job, we will have a far more diverse faculty. If we can find 1,100 new students a year who look like America, we should be able to find faculty who look like America. And I should say that I believe this can be accomplished without, in any measure, compromising excellence. We have done that with the

*Shirley Tilghman sees one common denominator among successful women scientists—they had unflagging support from their parents.*



student body: This year, our entering class of 2005 is more academically gifted than any class we've admitted, yet it's more diverse.

*How did you get around the hurdles you faced? Did you feel you had to work twice as hard as men?*

No. I had enormous self-confidence that was bred in me by my father. He encouraged me to be a scientist, he encouraged me to do math and he always set high expectations.

A few years ago, Rita Colwell and I went to a meeting of senior female scientists at Mills College in Oakland, California. Before the meeting, we were all sent a questionnaire asking us to describe our experiences as young women and as children. The responses showed one common denominator among all these incredibly successful scientists: Their parents believed in them. Their parents supported, encouraged and promoted them—without exception. Everything else was varied: Some women had great mentors, some had terrible mentors; some women had to fight like hell, some didn't have to fight at all. So what I really often worry about, as an educator, is that by the time I get my hands on these young women, they are either self-confident or they aren't. I can add around the edges, but I can't affect the core.

*What advice do you give female scientists and students?*

I urge them to focus. You will give up something. In fact, you'll give up a lot. I don't think we should kid young women that they can have it all. Focus on the most important thing to do that day; focus your research so that you're working on just two, not twenty, things; and focus on this time-management issue. That requires discipline.

Basically, you have two choices: You can sit around and feel victimized and feel as though you can't possibly do it. Or you can get on with business and make it happen. **H**

Robert Tjian's work on gene expression has revealed a DNA-reading machine run by meticulous commands.

BY INGFEI CHEN

**Robert Tjian doesn't eat breakfast or lunch.**

He claims he's watching his weight, but the truth, one suspects, is that food ranks low on his list of priorities. Tjian (pronounced "TEE-jen"), an HHMI investigator at the University of California, Berkeley, does confess to an all-consuming hunger, however. He's hooked—on data. "I have to have my hit of data every day," he says with a laugh.

Over the past three decades, this addiction to scientific discovery has driven Tjian to prominence in gene-regulation research. Since 1973, he has focused on transcription, the process by which cells "read" information from their DNA to make RNA and eventually proteins. His investigations tackle a fundamental mystery of life. Add sperm to egg, and nine months later, you've got a miraculous, wailing being with billions of specialized cells, from red blood cells to neurons. But what makes a neuron a brain cell, and not a blood cell? It all depends on which genes are switched on or off.

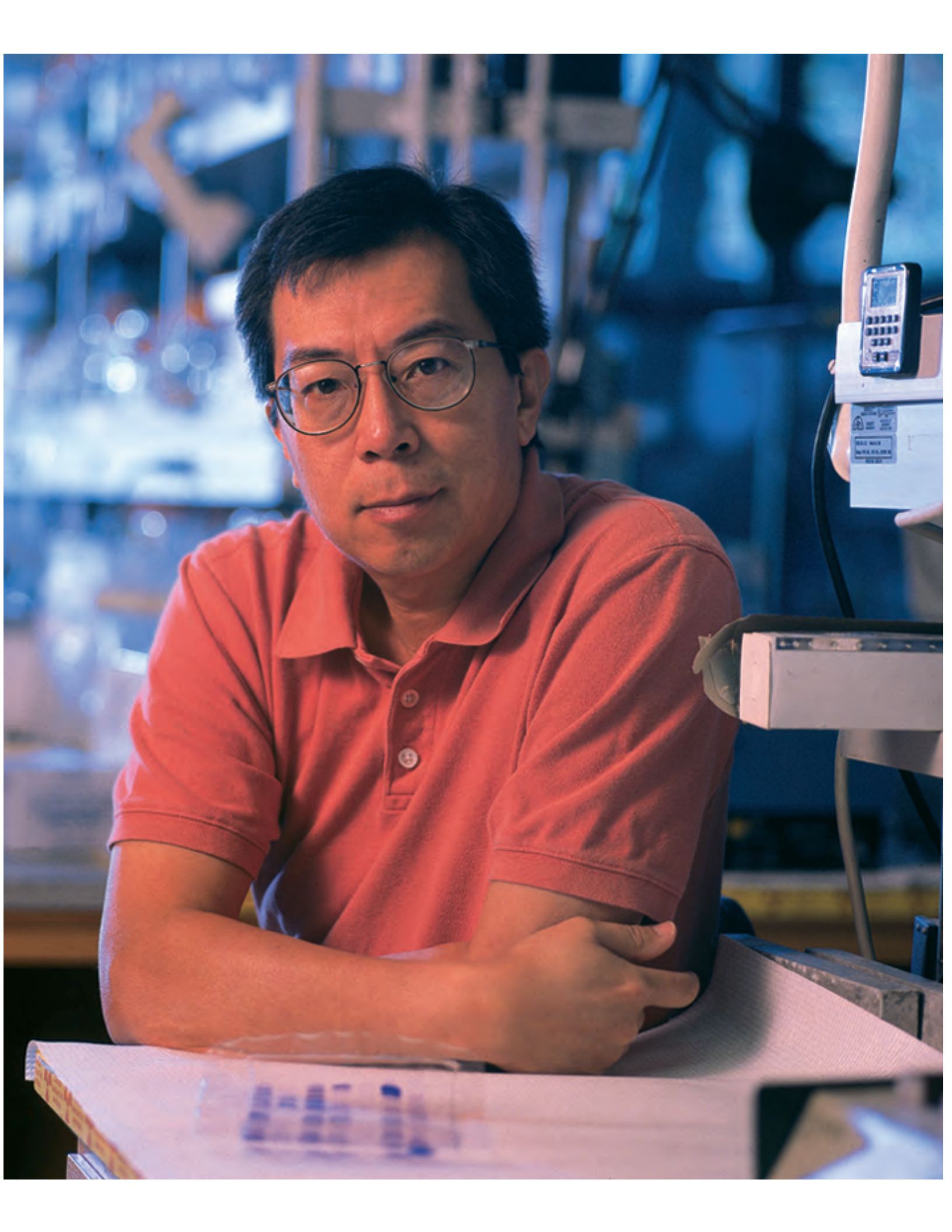
"Somehow, we [humans] have evolved a system that allows us a very detailed, extraordinarily elaborate readout of information from the genetic blueprint to not only make a human being but then to maintain life for 80-something years," Tjian says. "During that entire time, every cell in your body has to do the right job. And that all boils down to which genes are being transcribed." To make each of the myriad proteins that carry out life's chores, cells must retrieve the right bits of genetic information accurately and at exactly the right time.

When Tjian, now 52, began studying transcription in mammalian cells, this fundamental biological process was a black box. What little was known had been pioneered by biochemist Robert G. Roeder, who had discovered the enzyme RNA polymerase—the heart of the engine that drives the cell's DNA-reading machinery—in work he did at the University of Washington. Few other scientists thought transcription was worth studying. They figured that cells simply copied all of their genes into

# Peering Inside the Black Box

PHOTOGRAPH BY  
BARBARA RIES





an intermediary molecule—heterogeneous nuclear RNA (hnRNA)—and then just tossed out whatever wasn't needed. In other words, scientists envisioned the cell's DNA-scanning and RNA-making factory as largely automated and unregulated, with no direct role in specific gene expression.

That view has been shattered. Researchers have found that regulatory proteins, called transcription factors, guide RNA polymerase to scan only certain genes by telling the enzyme exactly where to start its work. The factory floor, it turns out, is teeming with more highly skilled laborers than anyone imagined. Drug makers now see the DNA-reading transcription machinery as a new target for treating illnesses such as asthma, cancer and heart disease, which arise in part from a shortage or excess of certain proteins. Novel medicines designed to tweak specific transcription factors could spur or inhibit the expression of genes for those proteins.

Tjian made his initial foray into the transcription field after finishing college at UC Berkeley in 1971 and spending a year at Oxford University. He began by exploring the DNA-reading process in bacteria during graduate school at Harvard University, earning a Ph.D. in 1976. He did postdoctoral research at Cold Spring Harbor Laboratory in

New York at the invitation of Nobel laureate James Watson. In 1977, Tjian gained a reputation as a hot young scientist by isolating the first nonbacterial DNA-binding protein and transcription factor, called T-antigen. Returning to California in 1979 to become an assistant professor at UC Berkeley, he undertook the work for which he is best known: He and his group discovered Sp1, the first gene-specific transcription factor ever found in human cells.

Tjian isolated the gene for Sp1 and showed how the factor directly attaches to and interacts with DNA at a specific target site, says Richard Losick, a gene-regulation researcher at Harvard University who was Tjian's Ph.D.-thesis adviser. "Those were electrifying experiments back in those early days," Losick says, especially when one considers that the techniques then available were primitive by today's standards. Since then, Tjian and his lab colleagues have hunted down and purified more than 100 transcription factors. "In my view," Losick adds, "the two stars of the transcription field in that era were Bob Roeder and Tj."

#### EAST TO WEST

"Tij" (pronounced "teej") is what friends call Tjian, who was born in Hong Kong in 1949, the youngest of nine children. After fleeing

## Spawning a Start-up

**Some people go fly fishing** to put their day-to-day cares aside, enjoy the outdoors and maybe even achieve some level of peace. Others go fishing and come back with a business plan. HHMI investigator Robert Tjian belongs to the latter group.

For more than 15 years, the biochemist at the University of California, Berkeley, has gone angling for salmon and trout all over the globe with his friend David Goeddel, a gene-cloning pioneer. In 1989, on a fishing trip in northern California, Goeddel told Tjian that he wanted to start his own biotech company and he asked his pal to join him.

At first, Tjian wasn't particularly interested. "I could see it would be a lot of work," he recalls. "I also didn't want to do it unless it was going to be different from [biotech giant] Genentech; there was no way you could compete with Genentech."

Still, he kept mulling it over. When Goeddel asked him again in the spring of 1991—while fishing on Christmas Island, 1,300 miles south of Hawaii—Tjian made up his mind. "I said, okay, it's now or never." It was during a third fishing excursion the following September, on Alaska's Tularik River, that the pair committed to the launch. That November, after enlisting biochemist Steven McKnight from the University of Texas

Southwestern Medical Center at Dallas as a third partner, they founded a company to propel research on gene expression—Tjian and McKnight's specialty—into the clinical realm.

The San Francisco-based firm, which the founders named Tularik, would pursue what was then a bold new approach: hunting for small molecules that could squeeze their way into cells and block or enhance the transcription of genes coding for disease-related proteins. Drugs based on such molecules would offer a major advantage over biotech drugs made of larger proteins: Patients could take them as pills instead of injections.

Tularik's first year was a whirlwind. Aside from honing the company's technological plan of attack, the founders had to raise money, hire the right people and build new labs from scratch. Tjian took a sabbatical from teaching but kept up his research activities at the university. As it turned out, securing money was relatively easy. "As soon as people found out Dave was a founder, it was kind of a no-brainer," says Tjian, who chairs Tularik's scientific advisory board.

Most biotech start-ups focus on one major product and go public within three years. Tularik, however, took a maverick route, chasing 10 to 20 promising drug candidates at once and going public only in



Tjian on the Dean River in British Columbia.

late 1999. Right now, the firm has four drugs in early-phase clinical trials—three to treat several different cancers and the fourth to work against cytomegalovirus. It's also pursuing more than 50 other leads, targeting disorders such as rheumatoid arthritis, diabetes and obesity.

The company still faces an upstream battle. It may be several years before Tularik finally gets a drug on the market, but the partners are confident that their efforts will prevail. "Goeddel, McKnight and I all have the same philosophy," says Tjian. "We don't mind working hard and taking risks." —IC



China during the Communist Revolution, his family bounced around Argentina and Brazil, and then moved to New Jersey in 1963. Six years later, as a UC Berkeley sophomore, Tjian boldly talked his way into the laboratory of biochemistry professor Daniel E. Koshland, Jr. Tjian visited Koshland and asked outright if he could join his research group. The scientist, already well known for his work on enzyme catalysis, said no—the kid hadn't even taken biochemistry yet. When Tjian persisted, Koshland gave him the weekend to read an advanced text called *Protein Structure*. Afterward, the professor quizzed him. "It was clear he hadn't just read it, he really understood it," Koshland recalls. "So I said, okay, you can be in my lab."

When Tjian graduated, the professor took him along on a year-long research sabbatical at Oxford. "He was very dedicated, a really hard worker," Koshland says. "He's a very inventive and imaginative scientist. He's willing to do new things, even if everybody else says it's risky."

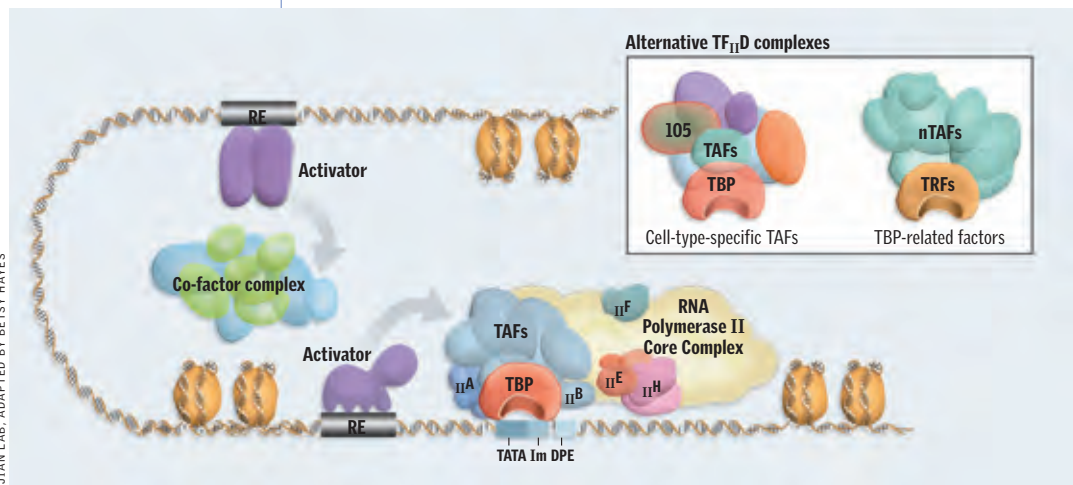
Those qualities, and a now-legendary technical prowess, sped Tjian through graduate school at Harvard in just three and a half years. "He's the most gifted experimentalist I've encountered," Losick says. "He was fearless and had a kind of special intelligence for making things happen on the bench-top."

#### FIND THE ACTIVATOR

As a young professor at Berkeley, Tjian began tackling the mystery of transcription in animal cells. His work focused on a nagging question. Scientists knew that RNA polymerase must touch down on a gene's "promoter"—a set of nucleotides punctuating the start of every gene—before chugging down the DNA track to read it and manufacture messenger RNA (mRNA). However, given that the polymerase can read any DNA it encounters, how was it able to choose the correct gene to read?

Tjian had already helped prove that in bacteria, proteins called sigma factors plugged into the RNA polymerase and preferentially instructed it to transcribe specific genes. Now, he and his research team began searching for a mammalian version of the sigma factors by studying how a virus called SV40 infects monkey and human cells. Like all viruses, SV40 replicates by hijacking the transcription machinery of the host cell. The researchers took a human cell extract containing the transcription apparatus and separated out its different proteins. When they mixed all the components back together with SV40 DNA in a test tube, they were able to recreate the virus's action: The host machinery was tricked into scanning viral, rather than human, DNA.

The scientists hoped to find the specific human transcription factor co-opted by the virus to pull off this stunt. So, in a series of experiments, they began testing the cell proteins one by one to see



**Highly Skilled Laborers** RNA polymerase, which copies DNA into the RNA that subsequently directs protein synthesis, is guided in its work by transcription factors. Some of these factors form multi-subunit complexes (co-factors) that serve as bridges between activators, which regulate the rate of transcription, and the RNA polymerase machinery. One class of cofactors, called TAFs, join with TBP (TATA-binding protein) to form the TFIIID complex, and attach to the TATA box DNA at the gene's promoter. All cells use an elaborate transcription apparatus to express genes, but some specialized cells (e.g., ovaries, testes, neurons) use alternative versions. For example, Tjian and colleagues have shown that TAF<sub>II</sub>105 (box) is specifically required for oocyte formation.

whether the same reaction would fail to occur if the protein wasn't added. "It's as if you have a whole bagful of stuff and pick out molecules from that pool one by one, asking, 'Can I throw that one away, or do I really need it?'" says Tjian. "It was just like looking for the needle in the haystack. It was really remarkable it even worked."

The culprit factor, Sp1, emerged from Tjian's lab in 1983 in work carried out by postdoc William Dynan. However, the protein wasn't what anyone expected. Unlike a sigma factor, it didn't bind to the polymerase. Instead, it stuck to a specific stretch of DNA called the GC box. Another year of studies revealed that Sp1 was an "activator," a transcription factor that speeds up the reading of specific genes. ("Repressors," on the other hand, slow or stop transcription.)

In 1985, another Tjian postdoc, James Kadonaga, purified Sp1 extracted from human cells—no mean feat, because cells contain vanishingly small quantities of transcription factors. Using a technique called affinity chromatography, Kadonaga, a chemist, attached copies of the GC box to tiny beads, which he then loaded into a glass cylinder. When he poured a crude protein extract through the column, only Sp1 stuck to the beads.

It was a breakthrough that galvanized efforts worldwide to find similar factors, says Losick. "Tjian's lab pioneered the methodology for hunting down these rare proteins and really set the standard for the entire field." Since then, many hundreds have been identified, and results from the Human Genome Project now suggest that anywhere from 2,000 to 3,000 of our approximately 30,000 genes code for such factors.

#### BUILDING A BRIDGE

With activator-protein Sp1 in hand, Tjian's group had yet another puzzle to solve. Given that the GC box lies upstream from the gene it regulates and RNA polymerase interacts directly with the gene, how

did Sp1 communicate with RNA polymerase?

By the mid-1980s, Roeder and his colleagues at The Rockefeller University had detected several other basic, or basal, components that, along with RNA polymerase, made up the core engine of the transcription machine. Scientists thought that cells of all types used this same engine to scan genes at a low level, like a car that can only move in first gear. To crank up or halt readout of particular genes, however, each different cell type would rely on its own, customized set of activators and repressors.

One critical basal transcription factor that Roeder's group found was TFIID. Its main ingredient was thought to be a protein—dubbed TBP—known to seek out and bind to the TATA box that lies within many gene promoters. As expected, when researchers put copies of purified TBP into a test tube with DNA, RNA polymerase and other basal components, transcription levels were low. In theory, adding an activator to the same mixture should have kicked transcription into high gear. A postdoc in Tjian's lab, B. Franklin Pugh, was the first to attempt this,

**“Every cell in your body has to do the right job. And that all boils down to which genes are being transcribed.”**

using Sp1. But in a flummoxing turn of events, it didn't work. Something was missing. “We called this missing thing a co-activator,” Tjian says.

Pugh and Tjian proposed in 1990 that co-activators were a third new class of transcription proteins that serve as a bridge between activators and the RNA polymerase. Other researchers were skeptical, but two years later, the Berkeley scientists purified a cluster of proteins called TAFs (TBP-associated factors) that work along with TBP—and, within this grouping, they found the first co-activators. These newly discovered helpers joined up with TBP at the promoter, forming what's now called the TFIID complex, which binds to the TATA box (see diagram, page 29). One end of Sp1 gloms onto the GC box while the other end makes contact with the co-activators. Dozens of co-activators have been identified in the decade since.

From there, Tjian pursued another hunch. He began pondering whether the so-called basal machinery was a misnomer. Maybe, he suggested, different kinds of cells or tissues had specialized versions of that machinery. Again, Tjian's intuition paid off. In studies of fruit flies, mice and humans, his team identified proteins that functioned similarly to TBP. Called TBP-related factors or TRFs, these new factors show up only in certain tissues, such as testicular and ovarian cells. And in separate work published in *Science* last fall (2001), the group showed that one kind of co-activator, named TAF<sub>II</sub>105, works selectively in ovarian tissue. When senior postdoc Richard Freiman and graduate student Shane Albright deleted the gene encoding for TAF<sub>II</sub>105 in female mice, they found that the mutant rodents were all infertile. DNA-screening tests showed that TAF<sub>II</sub>105 controls genes

responsible for proper oocyte formation.

Where do the layers of intricacy end? No one knows, but Tjian keeps digging. One of his current missions is to decipher the structures of TFIID and other co-factors to see exactly how they come together. Another is to learn how transcription factors navigate along and interact with DNA during normal cellular activity, in particular when DNA hasn't yet unwound from its naturally coiled-up state, chromatin. In 1999, collaborating with Berkeley biochemist and HHMI investigator Eva Nogales, Tjian's team created the first three-dimensional images of the transcription engine, the TFIID complex, by using the state-of-the-art techniques of electron microscopy and single-particle image analysis. This work showed that the TFIID complex is shaped like a squat, three-pronged pitchfork that can dock around DNA whether it is in chromatin or single-strand form.

#### NO HOLIDAYS

Given the wealth of data his group churns out, it might seem that Tjian commands an army of scientists. In fact, fewer than 20 researchers share the four large interconnected rooms of his lab in Koshland Hall, named after his former mentor. Somehow, he passes on his talents to his staff, Losick says. “They get beautiful data and are able to pull off very complicated experiments.”

Tjian himself is too busy these days to do hands-on lab work; his crammed schedule includes lecturing in undergraduate biology and chairing the chancellor's strategic-planning council for UC Berkeley's biological sciences programs. Nevertheless, postdocs and students say he's always available. “He expects the best of us and is extremely supportive,” says Andreas Ladurner, a senior postdoc from Italy.

At the same time, the professor is up-front about the level of work he expects from everyone in his lab. “The nine-to-five thing doesn't exist here,” he says. “Holidays don't exist. And they know that if I'm in town, I'm going to be here Saturdays and Sundays.” What do his wife, Claudia (an attorney), and two daughters (ages 22 and 16) have to say about his workaholic habits? “They think I'm nuts. They've had to put up with me forever like this.”

Tjian isn't all work, no play, however, and he does occasionally leave town. Every year, the biochemist spends several weeks pursuing his recreational passion—fly fishing—in such far-flung places as Russia and New Zealand. Often, he goes with close friend and biotech star David Goeddel, of Genentech fame. It was through fishing with Goeddel, in fact, that Tjian came to launch a biotech company, Tularik, Inc. (see page 28).

What Tjian relishes most about fishing is the thrill of the chase, he says. Much of the sport is about predicting what the slippery beauties will do. “One day you think you've figured it out. The next day, you go back and the fish are gone. You learn very quickly that you don't really know that much.” If this sounds reminiscent of his day job—fishing for data—Tjian concedes it is. “Fly fishing is like science,” he says. “You never get perfect at it, and you're always learning. That's how you get better.”

So which does he love more, fishing or science? Tacked on a bulletin board outside his office, a sheet of paper titled “Ancient Tj Lab Proverb” offers a clue: “If you wish to be happy for one hour, eat at Chez Panisse. If you wish to be happy for three days, get married. If you wish to be happy for eight days, work on transcription. If you wish to be happy forever, learn to fly fish.” ■



# Where AIDS and Conservation Intersect

*Alternatives to “bushmeat” must be found quickly—for ecological and health reasons.*

BY BEATRICE H. HAHN AND GEORGE M. SHAW

**T**he human AIDS pandemic—now afflicting more than 50 million people worldwide—appears to be the result of a single cross-species transfer of simian immunodeficiency virus (SIV) from a chimpanzee in west-central Africa. The precise nature of this transfer, which has led to one of the greatest medical challenges of our times, remains enshrouded in mystery. Our search for clues (see page 4) has brought us, unexpectedly, face-to-face with a socially and politically charged issue: the “bushmeat” trade.

Bushmeat is the flesh of wild or bush animals hunted and killed for food. Traditionally, it has been a source of sustenance for indigenous peoples of the tropical forests in Africa and elsewhere. But today, the bushmeat trade has grown into an international commercial enterprise generating \$50 million annually. Hunters now penetrate previously inaccessible forest areas, making use of modern weapons and newly built logging roads to obtain bushmeat in remote areas; from these outposts, the bounty is transported to major urban markets, mainly within Africa.

Conservationists have estimated that in a single year, 2,000 hunters will illegally shoot and butcher more than 3,000 gorillas and 4,000 chimpanzees. Thus, large-scale logging concessions, generally operated by companies from developed nations, are important, if unintentional, enablers of this illicit trade. Presuming that the killing continues at current or even greater rates, as many predict, what are the consequences likely to be? Are any solutions or alternatives in sight?

One consequence can be gauged in terms of human health. The most plausible account of how SIVs jumped from primates to humans is blood exposure resulting from bushmeat hunting and butchering. We are faced with the prospect that this process will continue, possibly resulting in the outbreak of new diseases or epidemics. Although the current HIV-1 pandemic can indeed be traced to a single viral jump from chimpanzee to human, this is not the only time SIV has crossed the species barrier. Less extensive outbreaks of HIV-1 have been caused by other chimp-to-human transmission events. A second human AIDS virus called HIV-2 is known to have resulted from crossovers of SIV to humans from the sooty mangabey monkeys of West Africa. Genetic analyses of the various HIVs and SIVs indicate that primates have transmitted SIV to humans on no fewer than 10 different occasions.

If chimpanzee and sooty mangabey SIVs have already crossed over to humans on multiple occasions, why not other SIVs? A recent survey

of bushmeat markets in Cameroon uncovered SIV infection in 20 percent of more than 700 primates screened, bringing to 30 the number of different primate species now known to carry a unique strain of SIV. A real risk thus exists that other SIVs, in addition to those from chimpanzees (SIVcpz) and sooty mangabeys (SIVsm) and not detectable by current HIV-specific blood tests, could be transmitted to humans. This scenario does not even contemplate the havoc that might result from transmission of other unrelated lethal viruses, including the Ebola virus.

The threat to human health is not our only worry. The expanding

bushmeat trade seriously threatens the survival of uncountable species, especially that of the great apes. Only 50 years ago, more than 2 million chimpanzees lived in a vast expanse of territory from Senegal in West Africa, across the rain forests of the Congo basin, to the western shores of Lake Tanganyika in East Africa. Today, fewer than 150,000 chimpanzees are believed to still exist.

Gorillas do not fare better. Current estimates predict that many primate species, including all of the great apes, will be all but extinct within 10 years.

The impact of this loss is incalculable.

Chimpanzees hold invaluable clues, not only to what makes HIV-1 pathogenic, but also to what it means to be human. Recent studies indicate that the chimpanzee, like all other primate species naturally infected by SIV, is largely resistant to the virus's devastating effects. Elucidating just how the chimpanzee deals with SIV could speed the development of innovative therapies for HIV/AIDS. In addition, studying chimpanzees infected with SIVcpz in their natural habitat may yield important insight as to where, how and why the virus made its jump to humans and whether similar events are preventable. Scientists are only beginning to unravel these complexities. Indiscriminate killing of chimpanzees and other primates for bushmeat robs us of this opportunity.

How can we combat the bushmeat crisis, yet find workable and locally acceptable solutions? Thus far, the biomedical and conservation communities have largely worked along separate trajectories. We believe that by coordinating educational programs in public health and conservation—while simultaneously investing in medical infrastructure within protected areas—public health experts, biomedical scientists and conservation biologists could forge truly meaningful relationships with governments and local peoples. Not only would such partnerships curb the spread of AIDS and other emerging infectious diseases, but they might also prevent the loss of our closest relative to poaching and ecological devastation. ■



KARL AMMANN

BEATRICE H. HAHN is professor of medicine at the University of Alabama at Birmingham (UAB). Her husband, GEORGE M. SHAW, is an HHMI investigator, also at UAB.

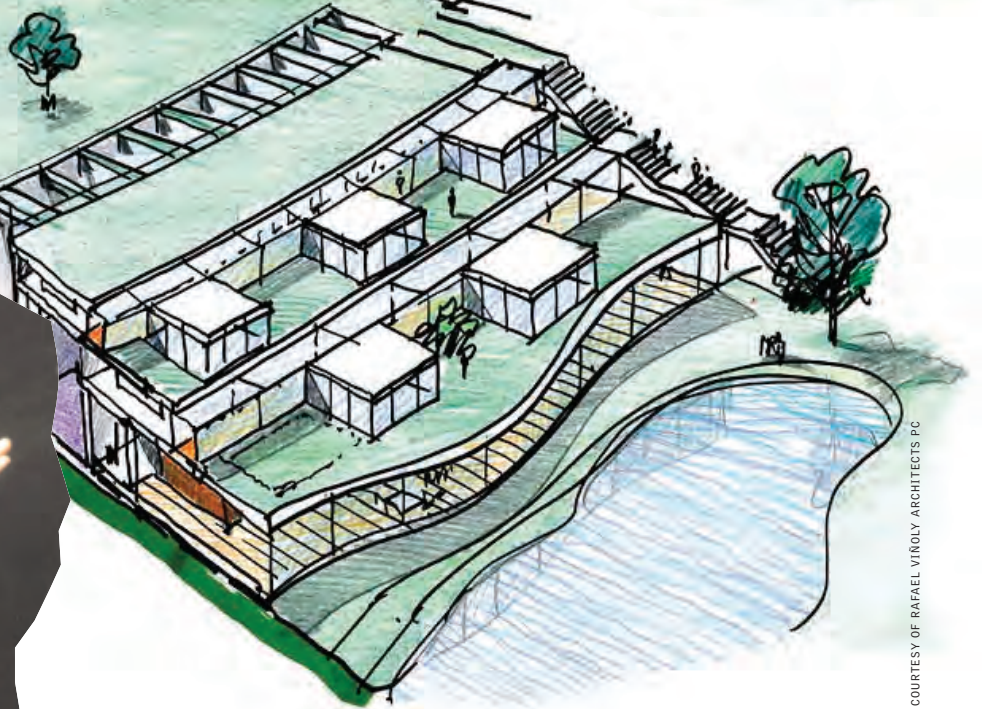
# NEWS & NOTES

## Renowned Architect Will Design Janelia Farm

**W**ith a plan for buildings that merge with the landscape, architect Rafael Viñoly has been chosen to design HHMI's Janelia Farm research campus. His vision for the site includes a low-rise, terraced structure built into a sloping hillside and several open areas to encourage interaction among scientists. "We are excited to be working with Rafael Viñoly, whose vision and experience with large-scale projects are a perfect fit," says HHMI President Thomas R. Cech.

In the next decade, the Institute anticipates spending about \$500 million to construct and operate the 281-acre campus, which sits alongside the Potomac River near Leesburg, in Loudoun County, Virginia, about 30 miles from HHMI headquarters. Janelia Farm will be a center for creating and disseminating the research tools needed for biomedicine in the 21st century, with an emphasis on collaborative research among biologists and scientists from other fields.

*Architect Rafael Viñoly (below) refers to his concept for HHMI's Janelia Farm research campus as a landscape building. His sketches for the site show buildings that work with the countryside and offices that engender interaction across disciplines.*



COURTESY OF RAFAEL VIÑOLY ARCHITECTS P.C.



Viñoly's 105-member firm, Rafael Viñoly Architects PC, is based in New York City. It was selected in February from a slate of distinguished architects who participated in a charette—a series of collaborative meetings between the architects and HHMI planning groups—held at the Institute last fall. Members of the Institute's Medical Advisory Board, HHMI investigators and other renowned scientists and science administrators had previously shared with the Institute their ideas about the research campus's architectural needs.

Founded in 1982, Rafael Viñoly Architects is an internationally recognized firm with offices in New York, Tokyo and Buenos Aires. The results of its projects are prominent in major cities in the United States, Japan, Korea, Europe and South America. They include the Cairo Financial Center, the Tokyo International Forum, the Lewis-Sigler Institute for Integrative Genomics at Princeton University, the Van Andel Institute (a foundation devoted to medical science and education) in Grand Rapids, Michigan, and the National Neuroscience Research Center, which will be located on the campus of the National Institutes of Health in Bethesda, Maryland.

HHMI's new facility will include research laboratories, a conference center and short-term housing for more than 100 visitors. The scientific staff will eventually number more than 200. Construction of the 750,000-square-foot space is expected to begin in 2003 and be completed early in 2006.

For the collaborative research activities on the new campus, the Institute will invite proposals from its own investigators as well as from the larger scientific community. It will seek to support research efforts with cutting-edge scientific and technological goals and will give preference to projects that bring together individuals with diverse expertise. Successful proposals will demonstrate originality, creativity and a high degree of scientific risk taking. An important feature of Janelia Farm activities will be the dissemination of information and technology to the broad scientific community. **H**



JOHN DOWNER/FPG INTERNATIONAL

*DNA fingerprinting may help track the origins of ivory poached from African elephants.*

## Teens Track Elephant DNA

**I**n the past, when Tom DeVries showed his students at Vashon Island High School near Seattle how to separate DNA molecules using a sophisticated biological technique, they were interested—up to a point. Then, DeVries reports, they always said, “So what? What difference does this make in the real world?”

Now he has an answer for them, thanks to a University of Washington professor who is working to use the same technique—gel electrophoresis—to track the origins of poached elephant ivory. Here it could make a *major* difference in the real world: Between 1979 and 1987, poachers caused the population of African elephants to drop from 1.3 million to 500,000, notes Samuel

Wasser, director of the university's Center for Conservation Biology.

“Using electrophoresis [the migration of charged molecules in an electrical field], we can tell the species, sex, geographical origin and individual identity of an elephant, using only a small sample of ivory,” says Wasser. “This has the potential to be enormously helpful in understanding the problem of poaching and in enforcing the law.” Although the technique has not yet been used in the field—Wasser and colleagues are still filling a few gaps in the genetic fingerprints of the ivory—it should be available within a few months. In the meantime, he has been working with forensic specialists at Interpol, the international police organization, to ensure that the technique will be useful to them.

It is already useful in the classroom. When Nancy Hutchison heard about Wasser's work with elephant DNA, she thought it could be a boon to science teachers and an

inspiration to their students. “What an incredibly rich topic,” says Hutchison, director of the Science Education Partnership (SEP), a professional development program for secondary school science teachers in Washington state, sponsored by the Fred Hutchinson Cancer Center and supported by a grant from HHMI. “In addition to giving meaningful context to the electrophoresis, elephant poaching raises many related, open-ended questions and shows how scientific tools are used to inform discussions of public policy.”

SEP assembled a team of five teachers, including DeVries, who turned Wasser’s research into a flexible curriculum to accompany electrophoresis kits. DeVries uses the elephant DNA in an environmental science unit, for example, while other teachers use it to teach genetics, population genetics, ecology, bioethics and conservation biology.

DeVries describes the students’ experience with electrophoresis—the heart of the unit—as “an obstacle course made of gelatin. We use an electrical charge that pushes the material through gelatin with microscopic holes. The molecules separate out depending on their sizes, charges and shapes. The small, compact ones race to the end. The big stringy molecules don’t get very far. A stain allows us to see and identify the different sizes.”

Twenty Seattle-area teachers have used the curriculum with almost 2,000 students, and the response has been overwhelmingly enthusiastic. For one thing, it shows them that teenagers can make some serious, grown-up contributions to science. “Who would have thought that a bunch of 15-year-olds would be able to do DNA fingerprinting like the professionals?” says Helen Huizenga, one of DeVries’ biology students. For another, it appeals to their sense of curiosity and adventure. “The mystery of where the confiscated ivory came from was intriguing,” says schoolmate Charlotte Skeffington. “I felt like Sherlock Holmes solving this case.”

“Even my special-needs kids do well in this unit,” says DeVries. “It’s also the kind of activity that will excite two or three percent of students enough that they’ll decide to become biologists or chemists.”

—MAYA MUIR

## Prize on the Eyes

Professional recognition sometimes comes early. It did for Ophelia Venturelli, one of 40 finalists in the Intel Science Talent Search—sometimes called the “junior Nobel Prizes.” The honor is the result of her research at the National Institutes of Health (NIH) as part of an internship in the HHMI-supported Student and Teacher Program, and it reinforces her career plans: to earn an M.D. in oncology and a Ph.D. in molecular biology. It also carries more immediate benefits: The 18-year-old senior at Walt Whitman High School in Bethesda, Maryland, will receive a \$5,000 scholarship and a computer. Plus, she and the Intel grand prizewinner, Ryan Patterson of Grand Junction, Colorado, had a brief run at stardom, appearing March 12 on “Good Morning America” with host Charlie Gibson.

Venturelli’s work at the National Eye Institute (NEI) could prove important to women with cataracts, the leading cause of blindness in the United States. She analyzed ocular lenses of female rats to determine whether the presence of estrogen can help prevent cataracts, an age-related degeneration of the lens of the eye. Preliminary results say yes. Venturelli and colleagues showed that adding estrogen to the lenses of 17-week-old and 9-month-old rats reduced expression of the alpha smooth-muscle



WILLIAM K. GEIGER

*Intel prize finalist Ophelia Venturelli will be a freshman at Stanford University this fall.*

actin gene, a known marker for cataracts.

Venturelli’s NIH mentor, Deborah Carper, chief of the section on molecular therapeutics in NEI’s laboratory of mechanisms of ocular diseases, describes her protégé as dedicated, extremely thorough and a quick study.

Venturelli says she became interested in science as a youngster living in Colorado. “I liked to immerse myself in the natural environment and just observe the wildlife,” she recalls. She plans to continue her research at NEI this summer, testing the findings on lenses from humans, which her mentor, Carper, says is the natural next step in the work.

—MELODY SIMMONS

## Reaching Out to Kids and Their Elders

Helping children and the grown-ups around them become conversant with science is a higher priority than ever, and biomedical research institutions have an increasingly important role to play. HHMI has invited more than 300 biomedical research institutions—including, for the first time, schools of veterinary medicine, dentistry and public health—to compete for almost \$12 million in grants to do science education outreach in their communities. Four-year grants of up to \$600,000 each will be awarded in 2003.

The new competition targets not only students from preschool through 12th grade and their teachers but their families and communities as well. To embrace a wider—as well as younger—perspective and broaden the professional training of scientists, the Institute is encouraging applicants to involve graduate students and postdoctoral fellows in their programs.

For the first time, approximately 10 percent of the overall budget will be earmarked for an HHMI-led evaluation project, including professional and peer evaluation. Two previous rounds of grants to biomedical research institutions totaled \$23.3 million. The science education outreach programs they supported have involved more than 350,000 students and nearly 16,000 teachers.

—JENNIFER BOETH DONOVAN



# Medical Student Aims Stem Cells at Multiple Sclerosis

**D**an Refai, 26, is panning the human bloodstream for stem cells—those biological nuggets that have the potential to develop into virtually any type of body cell—with a specific goal in mind. He wants to help reverse the destruction suffered by patients with multiple sclerosis (MS), a nerve-wasting disease that afflicts an estimated one million people worldwide and 350,000 people in the United States.

“There’s been a shift in the thinking about MS,” explains Refai, an HHMI–National Institutes of Health (NIH) research scholar. Scientists have long recognized the autoimmune component of the illness, in which the patient’s own immune system mysteriously attacks the myelin that insulates basic nerve circuitry. Researchers now are learning that MS has a second phase—a chronic, intermittent degeneration of nerve tissue. This erosion is what causes the worst effects of MS, such as loss of coordination, paralysis and eventual death. Some drugs have achieved partial successes against the autoimmune aspects of the illness, but “those treatments are more or less useless during later, chronic phases of the disease,” says neuroimmunologist Roland Martin, Refai’s mentor at the National Institute of Neurological Disorders and Stroke (NINDS) in Bethesda, Maryland.

Refai’s entry into the MS arena was serendipitous. “When I came to the NIH, the last thing I thought I’d ever do was immunology,” recalls the fourth-year University of Chicago medical student, who wants to pursue neurosurgery.

In October 2000, however, he happened

to pick up a current issue of *Nature Neuroscience* and come across an article by Angelo L. Vescovi’s group at the Stem Cell Research Institute in Milan, Italy. He was fascinated to read that the team had isolated stem cells from the brains of adult mice and from tiny ball-shaped human embryos and kept the cells alive in petri dishes for months. The researchers also had coaxed the stem cells to

wasting illnesses.

Impressed as he was, Refai had no connection with such work, so he filed away the information until the following March, when he overheard Martin discussing a vague idea with colleagues about using stem cells to treat MS. Martin proposed to repair the nerve deterioration by recruiting the patients’ own stem cells under the right conditions. Moreover, to avoid the ethical and political tangles of using stem cells from human embryos, he would try to coax adult hematopoietic (blood-forming) stem cells into becoming neural stem cells, which



PATRICE GILBERT

*Dan Refai, a fourth-year medical student, hopes to transform adult stem cells into neural cells and repair nerve damage.*

mature in vitro into skeletal muscle cells. Moreover, it appears that both the mouse and human stem cells could “walk the walk” in vivo: Upon transplantation into a group of muscle-injured rodents, the cells eventually made their way to the damaged sites and transformed themselves into muscle cells within regenerating fibers—the first step toward restoring muscle function. In short, the researchers were potentially developing a whole new way to treat muscle-

could then go on to produce neurons, glia and other cells of the central nervous system. Those, in turn, might repair the nerves’ frayed outer sheaths or build new connections within the central nervous system.

Refai immediately jumped in. “I want to do this,” he told Martin, who gave him a month to read up on the subject and put together a proposal. It was a convincing proposal, which blossomed into a plan that won a two-year, \$170,000 grant from

NINDS for Martin's laboratory and five collaborating laboratories.

Refaï obtained blood samples from healthy human donors who had been injected with a factor that helps enrich their blood supply of CD34-positive stem cells. He then fished out that scant supply (only 1 percent) of candidate cells with the help of a magnetic tag and grew the cells in petri dishes. As with most first-time investigators, Refaï's early months were slow going. He

lost all the stem cells on the first try because of a fluke in the isolation procedure, but by the second try, he was up and running. He can now get the cells to stay in culture for up to a week and is tinkering with conditions to see whether he can trick the cells into maturing into neural stem cells, which the team eventually hopes to inject into the central nervous systems of mice.

Refaï resumes his medical training in June, but he is so taken with the project

that he wants to return to it periodically over the next eight years as he completes neurosurgery training. That plan pleases Martin, who characterizes his protégé as the kind of young physician who is much needed in the research community. "It is actually a sad development," Martin says, "that fewer and fewer students who have chosen M.D. paths are eager to venture into the very difficult but very rewarding career of physician-scientist." —TRISHA GURA

## Gene Prevents Excessive "Grooming"—at Least in Mice

**T**alk about compulsive behavior. This group of mice didn't just lick themselves clean, as normal creatures do, but licked and bit themselves so continuously and vigorously that they became bald in some places and even developed open wounds. Joy Greer, a graduate student in Mario Capecchi's lab at the University of Utah, reported that the mice had body hair trapped between their teeth and gums, suggesting they had torn it off.

Why were these mice, all of whom lacked a gene called *Hoxb8*, so driven to groom themselves? "We initially thought they may have an itch," says Capecchi, an HHMI investigator who studied these animals with Greer. "We looked very carefully at their skin and all sensory inputs to the skin—sensitivity to pressure, temperature, pain, etc. Was there an irritation? An allergic response? We even gave them grafts of normal skin, but that didn't reduce the obsessive grooming. The skin appeared perfectly normal."

The researchers then set up infrared cameras to record what the mice did by night, when they are most active, as well as by day. Each mouse cage held a normal and a mutant mouse. After analyzing 24 hours of videotape, the researchers concluded that the mutant mice acted normally in almost every way. They ate, drank, climbed, hung upside down from the roof of the cage and built nests at the same rate as their normal counterparts. However, they spent nearly twice as much time licking and biting their bodies. They also groomed their cage mates.

All this activity kept them so busy that they slept about one hour less each day than the normal mice.

Intrigued, the researchers wondered whether the missing *Hoxb8* gene—one of 39 homeobox-containing (*Hox*) genes that play major roles in the early development of the body and brain—is normally expressed in the central nervous system of adult mice. They found that it is, and apparently, the protein produced by this single gene is required to prevent mice from compulsively grooming their bodies.

Because mouse genes are nearly identical to ours, Capecchi points out, this research very likely applies to humans as well. Thus his lab has become interested in people who suffer from trichotillomania—a condition in which people cannot stop pulling their hair out. As

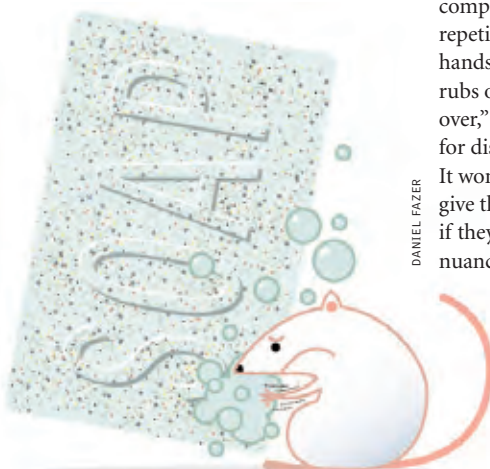
one patient reported to the Trichotillomania Learning Center, in Santa Cruz, California, "Talking on the phone for more than five minutes usually means that I won't have eyebrows or lashes when I hang up."

About 6 million Americans are estimated to have trichotillomania. What especially interests Capecchi is that identical twins share this trait 95 percent of the time and that it runs in families, suggesting some sort of genetic component. Could these people be suffering from a defect in *Hoxb8*?

Capecchi is determined to find out. He is collecting blood samples from approximately 150 patients in Utah and is planning to collect more samples nationwide. "We'll sequence the *Hox* genes from each patient," he says. "Besides *Hoxb8*, two other *Hox* genes may be involved. Obviously, if these genes are mutated in patients, we may find new targets for therapy."

If this project works out, other kinds of obsessive-compulsive disorders may benefit from studies of mouse genes. "Obsessive-compulsive disorders are associated with repetitive functions, such as washing one's hands over and over again until the skin rubs off, or lining up one's shoes over and over," Capecchi says. "We're going to look for displays of repetitive behavior in mice." It won't be easy, he admits. "Perhaps we'll give them some things to play with and see if they line them up. There are lots of subtle nuances to mouse behavior, and we'll have to keep our minds open. We're just beginning our analysis of what the *Hox* genes are doing in the adult brain." —MAYA PINES

» For movies of the mice grooming themselves, see: [www.hhmi.org/bulletin](http://www.hhmi.org/bulletin)



DANIEL FAZER



# HHMI Launches Bioethics Initiative

**R**esearchers today can no longer limit their attention to the nitty-gritty of science, especially when sensitive topics such as cloning or the use of embryonic stem cells are involved or when the boundary between the search for knowledge and the quest for profits becomes blurred. “One can’t think about basic research without the public asking—and in some cases insisting—that ethical concerns be at the fore of the discussion,” says Laurie Zoloth, professor

suggesting that if you don’t pay attention to the deeply held moral concerns raised in a democracy, you’ll be missing a critical piece of data,” says Zoloth.

Board members attend HHMI science meetings and maintain “office hours” via e-mail for the Institute’s 324 investigators and their trainees. In addition, the Institute is producing a series of educational videos in DVD format to address various topics on the ethics of laboratory research.

*“If you don’t pay attention to the deeply held moral concerns raised in a democracy, you’ll be missing a critical piece of data.”*

—Laurie Zoloth

of ethics and director of the Program in Jewish Studies at San Francisco State University.

Zoloth is chairing a four-member Bioethics Advisory Board to help HHMI scientists think through the ethical dimensions of their work. It’s part of the Institute’s recently launched bioethics initiative that, according to senior scientific officer James R. Gavin III, will bring the kind of thoughtful discussions to basic science research that have been part of clinical research and patient care for years. “Ethics of research—outside of human subjects—hasn’t been on anybody’s radar in any substantive way,” Gavin says. “HHMI is charting a new course.”

Thus the role of the Bioethics Advisory Board “is to listen to scientists struggle with substantive ethical and scientific issues and then reflect carefully on these issues with them,” explains Zoloth. “We all understand that ethical concerns are a part of the construction of the scientific process itself and of how the science is understood, applied and taught to a larger world. We are

In 2002, board members began presenting case studies at the science meetings. At a March session, for example, investigators reviewed a hypothetical case on scientist-created chimeras, or interspecies mixes, that seemed as far-fetched as Greek mythology. Yet, only days later, the reality came home with a lead story in the *Wall Street Journal*: “Furor over Cross-Species Cloning.” Protesters had confronted scientists in Seoul, South Korea, who were mixing human DNA with cow eggs to generate human embryonic stem cells for research.

For the chimera case study, board members helped scientists consider the source of the public’s discomfort. What are the boundaries? Just because scientists can do something, *should* they do it?

To HHMI investigator Eric Weischaus, a geneticist at Princeton University, the benefit of the session was clear. “Almost all of us scientists have to be part of the public debate on ethics. These sessions help us formulate our beliefs and refine the way we need to communicate so that others can understand.”

## BIOETHICS ADVISORY BOARD

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BARUCH BRODY

COURTESY OF BARUCH BRODY



JONATHAN MORENO

COURTESY OF JONATHAN MORENO



LEROY WALTERS

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LAURIE ZOLOTH

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## NAS Panel Tackles Data Sharing

**T**he “cumulative enterprise of science,” says Eric S. Lander, director of the Massachusetts Institute of Technology’s Whitehead Center for Genome Research, depends greatly on data sharing. “We maximize the total social product by promoting reuse of knowledge in new forms.”

Although few scientists would disagree, at least in principle, a study published in the *Journal of the American Medical Association* (January 23, 2002) reveals a different reality. In a survey of U.S. geneticists, twice as many stated that data sharing was on the decline than said it was increasing. Almost half of this polled group reported that at least one of their requests for data or materials regarding published research had been denied in the preceding three years.

This study confirms what already worries many scientists in this postgenome era, and they see the need for concerted action so that the trend does not continue unchecked. In that spirit, the National Academy of Sciences (NAS) has set up a panel, chaired by HHMI president Thomas R. Cech, to develop new standards for the sharing of data published in peer-reviewed journals. At a public meeting of the panel on February 25 in Washington, D.C., editors from *Science*, *Nature* and other journals joined industry researchers and academic investigators to begin hammering out this new set of principles.

Participants discussed a range of issues: Are there circumstances in which published data or materials may not be shared? Who should enforce such requirements? Does partial withholding of data that support a published paper seriously detract from the paper and impede scientific progress? Answers to these questions did not come easy.

Among the most contentious issues was whether corporate scientists should adhere to the same principles as academic scientists. There shouldn’t be a double standard, said Barbara Jasny, an editor at *Science*, “but

[industry] should have its considerations taken into account.” For *Science*, this meant going against tradition by publishing Celera’s draft of the human genome in February 2001 while Celera required those interested in accessing the data to agree to the company’s terms of use or pay it a subscription fee (see *Bulletin*, December 2001). Again, this April, *Science* agreed to special terms of data access to publish the rice genome.

Lander said he does not favor such allowances. With the complicated relation-

Medical School proposed a simple criterion in regard to large databases: If the data are central enough that they would normally be included in the paper itself, but space considerations and ease of access require them to be deposited in an independent database, they should be just as freely available as if they were included in the paper.

The NAS panel announced plans to publish its own proposed standards later this year after review by a wide array of biological scientists, both academic and industrial.

“I’m guardedly optimistic,” said Cech, that these “specific recommendations and concrete details of proper behavior will provide the basis for ongoing debate in the community.”

Lander urged the panel to be skeptical of attempts

by journals to change the system by allowing publication without data release: “This system [publication and credit in exchange for disclosure] has been in place since the British Royal Society instituted it in 1665. If we’re going to change it, we had better be careful.”

—Reporting by Jim Kling

*In a survey of U.S. geneticists, twice as many stated that data sharing was on the decline than said it was increasing.*

ships that exist today (consulting agreements, stock options, direct research support), distinguishing between academic and industry scientists is becoming increasingly difficult, “and it’s only going to get worse,” he says.

Participants were able to agree on one guiding principle: If any data or materials are integral to the scientific claim of the paper, they should be made freely available. But what is integral? Marc Kirchner of Harvard

» To listen to the meeting’s discussion, visit [www.nationalacademies.org/standards](http://www.nationalacademies.org/standards)

## New Grants Support Young Scientists in Central Europe

**S**ix outstanding young scientists in the Czech Republic, Hungary and Poland will benefit from a new four-year grant to the European Molecular Biology Organization (EMBO). The HHMI/EMBO Scientists Program will provide \$500,000 annually to help support researchers at the beginning of their careers.

The three countries are among those participating in HHMI’s International Research Scholars Program in the Baltics, central and eastern Europe and the former Soviet Union. At present, EMBO’s Young Investigator Programme supports promising young scientists in those countries with three-year awards of about 15,000 Euros (or \$13,000, at current exchange rates) annually. The new HHMI/EMBO program specifically targets young Czech, Hungarian and Polish researchers, who will receive 30,000 Euros a year (approximately \$26,450) for three years. They’ll be chosen by EMBO with the assistance of HHMI international research scholars in the three countries, who will also mentor the awardees.

“We hope that the new program, which leverages Institute support of international science by using the existing EMBO peer-review process, will help develop more first-rate researchers who can go on to become international research scholars,” says Jill Conley, HHMI international program director.

» For more information, see [www.embo.org/projects/yip/index.html](http://www.embo.org/projects/yip/index.html)



# HHMI LAB BOOK

RESEARCH NEWS FROM HHMI SCIENTISTS

## One Fish, Two Fish

**R**esearchers are using a freshwater fish to detail how many and what kinds of genetic changes it takes to evolve new traits. They've created a genetic map of the threespine stickleback that enables the tracking of chromosome regions responsible for evolutionary change. They hope to use this model to discover what is needed to evolve a new species.

Until now, the scientists say, it has been difficult to study the number and type of genes responsible for vertebrate evolution. To solve the problem, HHMI investigator David M. Kingsley and HHMI associate Catherine L. Peichel looked for natural populations that

evolved in isolated environments, "thousands of different lakes and streams represent thousands of independent evolutionary experiments."

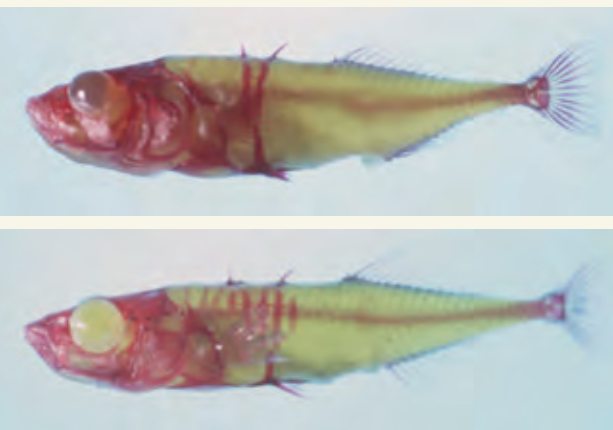
Kingsley's group designed a genetic-marking system to trace how various genes were passed from one generation to the next. To test this system, they crossbred two separate species of sticklebacks adapted to different environments in Priest Lake, British Columbia—a near-shore species and an open-water species. They watched how several physical traits were inherited in the next two generations; at the same time, they examined the inheritance of different chromosome regions. By comparing the types of physical changes with the types of chromosome regions inherited in these fish, they could determine which regions were responsible for the development of which

new traits.

"This method identified for the first time the location of major chromosome regions that control development of body armor, the length of spines and feeding modifications in the fish," Kingsley says. They also found that the stickleback species had a "flexible system for skeletal change," with different chromosome regions controlling the development of different parts of the fish skeleton.

Kingsley, Peichel and their coworkers at

Stanford University, together with colleagues at the University of Wisconsin–Eau Claire and the University of British Columbia, reported their results in the December 20, 2001, issue of *Nature*. The group hopes to use this genetic-mapping technique to tie behavioral and physiological differences among species of sticklebacks to changes in the genome.



**Isolated Evolution** The top panel shows a threespine stickleback that swims along the shore of Priest Lake in British Columbia. The bottom panel shows a separate species of stickleback from the center of the lake.

had evolved separately—and fairly recently—but could still be crossbred.

The stickleback, which has been extensively studied by biologists for more than 70 years, was a perfect choice, according to Kingsley. Species of sticklebacks evolved from marine to freshwater life only since the last Ice Age 15,000 years ago, a remarkably brief period of time, he says. Because the fish

## IN BRIEF

### Pinpointing the genetic trigger

Researchers are closing in on a genetic alteration that triggers a rare form of inherited pancreatic cancer. Studies of a family with a long history of the disease have led to a region of chromosome 4 that is the likely site of the mutated gene. Identifying the gene might reveal how the more common, sporadic form of pancreatic cancer arises—and therefore provide a potential target for new drugs.

Researcher: **Leonid Kruglyak**

[www.hhmi.org/news/kruglyak.html](http://www.hhmi.org/news/kruglyak.html)

### You must remember this

Some of the difficulties that elderly people have in remembering may be reversible. Researchers, using a powerful imaging technique, measured activity in the brains of young and old adults. They found that one type of memory-processing problem often seen in the elderly could possibly be improved by specific training.

Researcher: **Randy Buckner**

[www.hhmi.org/news/buckner2.html](http://www.hhmi.org/news/buckner2.html)

### Two for the price of one

A mouse gene that helps regulate the inflammatory response can exist in slightly different forms. Researchers have now learned that these alternate forms of the *Stat3* gene produce proteins that likely determine whether mice can stave off septic shock, a life-threatening condition in humans and other mammals. The findings may lead to a better understanding of inflammation-related diseases in humans—from autoimmune disorders to atherosclerosis—and to improved treatment.

Researcher: **Stephen V. Desiderio**

[www.hhmi.org/news/desiderio.html](http://www.hhmi.org/news/desiderio.html)

### Seeing the light

Scientists have discovered a second visual system that seems to detect light for the body's internal clock. They've also found that nerve cells involved in setting the clock almost certainly depend on melanopsin—a light-sensing pigment different from that found in the conventional >>

## IN BRIEF

visual system, which relies on rod and cone photoreceptors on the retina. The work is an important step in understanding how light resets the internal clock and may also help in understanding some sleep disorders. Researcher: **King-Wai Yau**  
[www.hhmi.org/news/yau.html](http://www.hhmi.org/news/yau.html)

**Move over colonoscopy** A non-invasive test that uses stool samples to detect a genetic trigger for colorectal cancer is on the horizon. The test detects a mutation in the tumor suppressor gene called *APC*. With anticipated improvements, the technique has the potential to find colorectal cancer early, when a cure is most likely.

Researcher: **Bert Vogelstein**  
[www.hhmi.org/news/vogelstein7.html](http://www.hhmi.org/news/vogelstein7.html)

**Hear no evil** The fruit fly protein, Hrs, may regulate cell growth by varying the number of receptors on the surface of cells. This finding is important because cells turn off their responses to outside growth signals by cutting the number of receptors available to pick up such messages. The comparable human protein could become a major new drug target for fighting cancer, a disease in which cells grow out of control.

Researcher: **Hugo J. Bellen**  
[www.hhmi.org/news/bellen.html](http://www.hhmi.org/news/bellen.html)

**Time flies** The life span of the nematode worm, *Caenorhabditis elegans*, can be extended by the removal of germ-line stem cells. When present, these gamete precursors are thought to regulate a steroid-dependent system that accelerates aging. Removal of these cells in fruit flies shows the same results, suggesting an evolutionarily conserved system.

Researcher: **Javier Apfeld**, former HHMI predoctoral fellow, University of California, San Francisco  
*Science* 2002 Jan 18;295:502-5.

**Salt control** Using x-ray crystallography, a team of scientists has determined the three-dimensional structure of the chloride ion chan-



*Catherine Dulac says pheromones help male mice distinguish between males and females.*

KAY CHERNUSH

## Love the One You're With

**P**heromones, those chemicals that kindle attraction between the sexes, are necessary for male mice to distinguish between other males and females. In a new study, male mice that lacked a gene to detect pheromones not only dropped their typical aggression toward other males, they tried to mate with them.

In mice, pheromones are detected by the vomeronasal organ (VNO)—a chemical-sensing structure that is found in the nasal cavities of many animals. It is distinct from the olfactory system. In humans, although anatomical traces of the VNO remain, the organ is thought to be inactive.

To find out more about how pheromones and the VNO influence behavior, molecular neuroscientist Catherine Dulac, an HHMI investigator at Harvard University, and her coworkers cut off pheromone activity in male mice by knocking out the gene for TRP2, an important ion channel thought to control pheromone detection in the VNO.

Dulac and her team put the knockout males with females, expecting to find that the males—unable to detect pheromones—would have no interest in mating. They were disappointed to find the male mice still mating with the females. Then they tested the knockouts' reaction to strangers, placing a new male into a

cage with knockout males. Males are normally territorial and ready to pounce on newly introduced male cage mates. Instead, the knockout males were docile and, unable to pick up the normal pheromone cues from the stranger, attempted to mate. Subsequent studies showed that the knockout mice also made the same courtship-related noises with males and females. The findings by Dulac, HHMI postdoctoral fellow Lisa Stowers and colleagues at Harvard were published in the February 22, 2002, issue of *Science*.

Their observations have several implications, Dulac says. If pheromones aren't needed for mating, then sensory cues—visual, auditory and olfactory—must be enough. However, she continues, “those sensory cues are gender-blind. Only pheromones can provide the brain with useful information about the sex of the animal.”

It also means that mating is the male's “default” behavior. “When a male mouse that can't detect pheromones encounters an animal of his own species, the first thing that happens is he attempts to mate,” she says.

Dulac thinks the key to this behavior is the VNO, which controls appropriate sensory cues to the brain. “How does the VNO do this?” she asks. “We don't know—it's the next step in our work.”



# Viruses: Enter Here

**S**cientists have produced the first images of the three-dimensional structure of bacteriophage T4, a virus that infects the common bacterium *Escherichia coli*. Solving the structure of the virus offers a clearer picture of a complex infection process and, according to the researchers, may eventually be a key to developing novel protein devices to deliver genetic material to human cells.

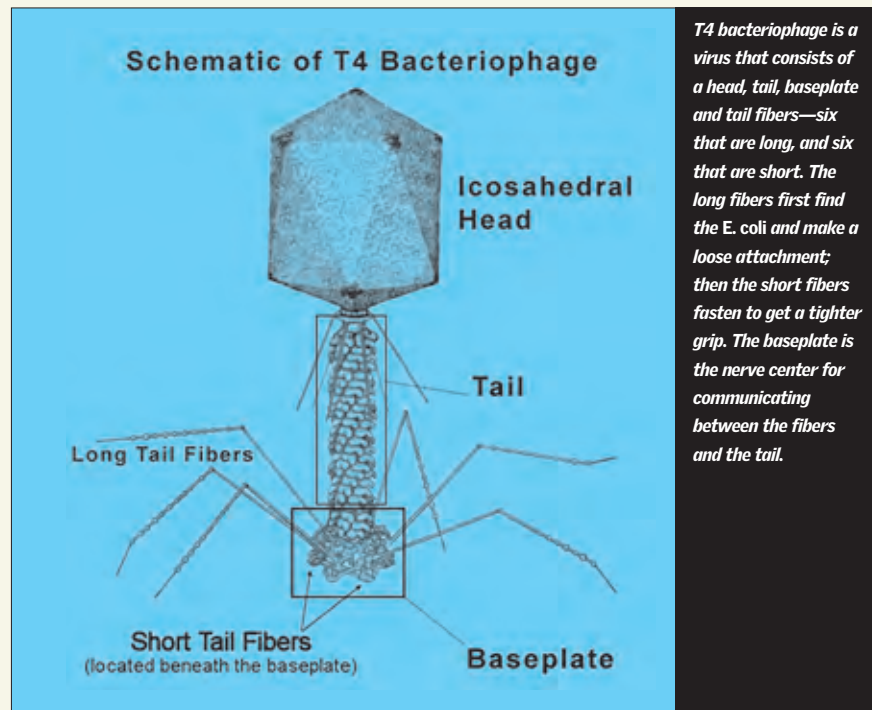
"By looking at the structure and knowing some of the functions, we are getting an idea of some of the initial stages of what happens when T4 lands on a host," says Michael G. Rossmann, a structural biologist at Purdue University, West Lafayette, Indiana, who led the work along with HHMI international research scholar Vadim V. Mesyanzhinov of the Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry of the Russian Academy of Sciences in Moscow. Rossmann, Mesyanzhinov and coworkers reported their findings in the January 31, 2002, issue of *Nature*.

Their work begins to reveal how the T4

virus, which resembles a lunar lander, invades bacterial cells in successive steps. It must first recognize and attach to the surface of the host; then viral machinery springs into action by puncturing the cell wall with a syringe-like protein spike and injecting its genetic blueprint into the *E. coli*. After this assault, the bacterium sets to work creating replicas of the virus. Such processes—and mechanisms—are shared among many viruses, says Mesyanzhinov.

The scientists used x-ray crystallography and high-resolution electron microscopy to create detailed three-dimensional images of the T4 virus, which consists of an elongated head that carries the virus' genetic material and a tail with a hexagonal baseplate and six long and six short leg-type structures.

The group analyzed—and reconstructed atom by atom—the structure of the virus baseplate. Serving as a "nerve center" and sending signals to and from the virus' head and "legs," it is the key component of the virus. While transmitting these messages, the baseplate machinery changes shape to inject viral DNA into the host cell. In the end, the infected bacterium bursts, releasing its manufactured viruses to invade other cells.



## IN BRIEF

nel. The images reveal an entirely new type of protein architecture that efficiently conducts chloride ions across the cell membranes. The work may provide insights into the behavior of these channels, many of which are involved in kidney and muscle disorders.

Researcher: **Roderick MacKinnon**  
[www.hhmi.org/news/mackinnon5.html](http://www.hhmi.org/news/mackinnon5.html)

**Memorable messages** Researchers have found a key protein involved in the transmission of chemical messages between nerve cells in the mouse brain. The protein, which specifically helps control changes in nerve signaling that affect learning and memory, provides a new opportunity to understand how and why neurotransmitters are released.

Researcher: **Thomas C. Südhof**  
[www.hhmi.org/news/sudhof2.html](http://www.hhmi.org/news/sudhof2.html)

**A wolf in sheep's clothing** A new mathematical study reveals that in Great Britain the risk of humans contracting bovine spongiform encephalopathy (BSE) from sheep—where it has not yet been found—is small but may now exceed that from cattle. This is due to more stringent control measures put in place in 1996 to reduce the risk from beef.

Researcher: **Neil M. Ferguson**  
[www.hhmi.org/news/ferguson.html](http://www.hhmi.org/news/ferguson.html)

**Protein protection** Using genetically altered fruit flies as a model for Parkinson's disease, scientists have shown that a class of proteins known as "molecular chaperones" can block the progression of neurodegenerative disease. The researchers have also found evidence that similar pathways may operate in humans, suggesting that these proteins could aid in treatment.

Researcher: **Nancy M. Bonini**  
[www.hhmi.org/news/bonini.html](http://www.hhmi.org/news/bonini.html)

**Evolutionary hero** Scientists have discovered that a single-celled microorganism has a type of molecular sensor usually found in multicellular animals. This is the first time that such a protein, called a receptor tyrosine kinase, has been found in a single-celled creature. This finding may provide a »

## IN BRIEF

glimpse of how these simple organisms made the evolutionary leap to multicellular life.

Researcher: **Sean B. Carroll**  
[www.hhmi.org/news/carroll2.html](http://www.hhmi.org/news/carroll2.html)

**The big turn-off** One of a female's X chromosomes must be taken out of action for an embryo to develop. Scientists studying "X-inactivation" have identified a protein, called CTCF, that appears to be central to regulating the process.

Researcher: **Jeannie T. Lee**  
[www.hhmi.org/news/lee.html](http://www.hhmi.org/news/lee.html)

**Double duty** A gene that helps control brain cell development has been shown to be involved in the development of intestinal cells. The gene, *Math1*, codes for a protein (called a transcription factor) that helps stem cells differentiate into three kinds of intestinal cells. A better understanding of the process may lead to new treatments for diseases such as irritable bowel syndrome and colon cancer.

Researcher: **Huda Y. Zoghbi**  
[www.hhmi.org/news/zoghbi4.html](http://www.hhmi.org/news/zoghbi4.html)

**Cellular gridlock** When certain Alzheimer's-disease-related proteins work incorrectly, an important cell-transport system breaks down and causes brain cells to die. Now researchers are inching closer to understanding what these proteins normally do in the brain and how they contribute to cell death. The results may help sort out which proteins play critical roles in Alzheimer's disease.

Researcher: **Lawrence S.B. Goldstein**  
[www.hhmi.org/news/goldstein2.html](http://www.hhmi.org/news/goldstein2.html)

**Leukemia revisited** By profiling the activity of thousands of genes in a drug-resistant form of childhood leukemia, scientists have uncovered a new form of the disease. They propose that it be called mixed-lineage leukemia because gene expression studies show that it is distinct and not a subtype of the more prevalent disease, acute lymphoblastic leukemia.

Researcher: **Stanley J. Korsmeyer**  
[www.hhmi.org/news/korsmeyer2.html](http://www.hhmi.org/news/korsmeyer2.html)

## Prostate Cancer's Two Hits

**T**he tumor-suppressor gene *p53* has been shown to play a major role in numerous cancers. Its role in prostate cancer, however, is much more limited. Now, a former HHMI medical student fellow has shown that mutations in a gene called Kruppel-like factor 6, or *KLF6*, which operates in a pathway parallel to that of *p53*, is involved in more than 70 percent of prostate cancer cases.

"This is the first gene to be implicated at a high frequency in prostate cancer," says Goutham Narla, who did this work in the laboratory of Scott L. Friedman at the Mount Sinai School of Medicine in New York City. Narla, now an M.D.-Ph.D. student in Friedman's lab, is lead author of the research paper on this study, published in the December 21, 2001, issue of *Science*.

Narla began looking at *KLF6* because it was implicated in the buildup of dense scar tissue, or fibrosis, in the liver, a focus of the Friedman lab. He succeeded in making transgenic mice that overexpressed the gene in the liver. Unexpectedly, the liver cells with the overactive gene grew more slowly. "This gene appeared to be involved in the regulation of cell growth," Narla recalls.

Previous work by Friedman and others had shown that the gene was located on chromosome 10, and other studies had indicated that loss of portions of this chromosome leads to the development of several types of cancer, including prostate cancer.

So, Narla and his collaborators tested tissue samples from 22 prostate tumors and observed that one copy of *KLF6* was missing in 77 percent. In addition, 71 percent of those tumors showed mutations in the retained copy of the gene. *KLF6* had the hallmarks of a tumor-suppressor gene. Meanwhile, additional studies by Narla showed that wild-type, or normal, *KLF6* works by turning on *p21*, a gene that acts to slow down cell division.

Friedman credits Narla with making the critical connection between *KLF6*, chromosome 10 deletions and cancer. He also says he was startled by the findings. The investigation, after all, began with the search for genes involved in liver fibrosis. Still, "you have to go where the science leads," Friedman says. "Much of my lab is now dedicated to looking at the role of *KLF6* in prostate and other cancers."

—CAMILLE MOJICA REY

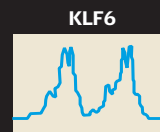
### Genetic analysis of the *KLF6* gene in prostate cancer

The top two panels show loss of one copy of the gene (the second peak is shortened in panel #2). This is known as the first hit in the "two-hit model" for tumor suppressor genes. The bottom two panels show that the tumor contains mutations in the remaining *KLF6* gene—the second hit required for cancer development.

Chromosome 10p15



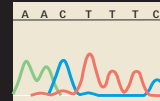
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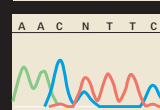
TUMOR



NORMAL



TUMOR



JOHN A. MARTIGNETTI

HHMI Lab Book written by Steven I. Benowitz



# Rebuilding Dresden

*A Conversation with Günter Blobel*

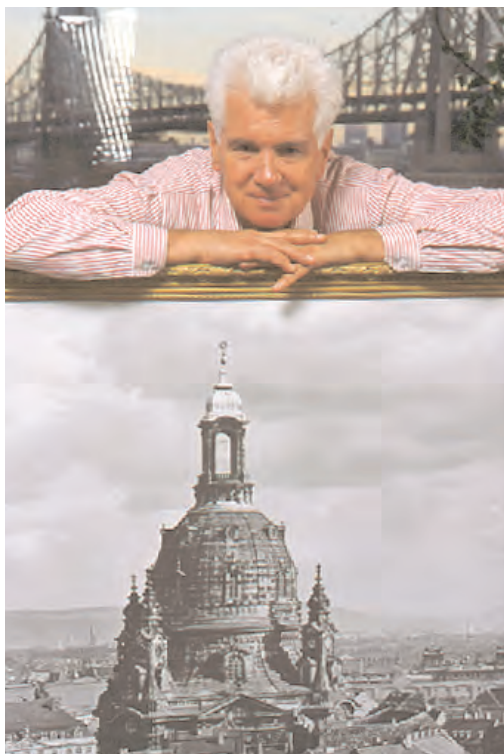
**G**ünter Blobel, an HHMI investigator at The Rockefeller University in New York City, discovered how the millions of newly made proteins within a cell find their appropriate destinations: through a special type of “zip code” system. The German-born scientist won the 1999 Nobel Prize in Physiology or Medicine for this work. Then he astounded everyone by giving his prize money away.

**Why did you give the money away?**

**Blobel:** Well, I could have bought a weekend house or something else that I don’t have, but I wanted to acknowledge my upbringing in what was then East Germany. I got my high school education there and then left, and I never did anything again for the people there. So I decided to donate the almost \$1 million from the Nobel Prize.

**The entire prize?**

**Blobel:** Yes. And I decided to give it to the city of Dresden because I saw it intact just two days before it was destroyed in 1945 in one of the most devastating fire-bombings of World War II. We were fleeing the advancing Russian Red Army, and my father briefly stopped the car on a hill. From there, I saw the whole city, with all the spires and the magnificent cupola of the Frauenkirche [Church of Our Lady], which was 100 meters high and very imposing. That silhouette of the city was famous, of course, but I’d never seen anything like it. To a nine-year-old who had never seen a large city, Dresden looked like a fairyland. At the end of the war, we tried to drive through Dresden again to go home. But there were no streets left in the old part of the city—just huge piles of rubble. It was a very, very sad sight.



*Günter Blobel in his Manhattan office with a pre-war photo of the 18th-century baroque cathedral that he is helping to rebuild.*

**When did you come to the United States?**

**Blobel:** In 1962. I had grown up in Silesia [now part of Poland] but it was impossible to return there after the war so we settled in Freiberg, an undestroyed medieval city. After high school, as I was not allowed to study in East Germany, I moved to West Germany, where I studied medicine. Then I went to the University of Wisconsin in Madison for my Ph.D. In 1967 I moved to New York City and have lived here ever since, but I never forgot Dresden. After the reunification of Germany in 1989, I heard that the citizens of Dresden wanted to rebuild the Frauenkirche. The rubble of this 18th-century baroque cathedral was still there—the stones could be reused—and two

huge arches were still left. But the church, the city and the state all said they had no money for rebuilding it. Then a citizens’ initiative in support of this enterprise had the idea to write to people all over the world and appeal for help.

**Did you reply?**

**Blobel:** I immediately formed a group in the U.S.—“Friends of Dresden,” with headquarters in New York City—to help them raise money. We collected about \$3 million over several years, but it was very hard work! Meanwhile, members of the Jewish community of Dresden decided to rebuild their synagogue, which was burned down by the Nazis in 1938 during Kristallnacht. They also needed to raise money, and I felt it would be only fair to give something to them, too.

**So what did you do?**

**Blobel:** When I got the Nobel Prize in 1999, I donated most of the prize money to both the church and the synagogue, in proportion to their construction costs. The Frauenkirche got about \$800,000, and \$50,000 went to the synagogue. The rest of the money I donated to other projects in Dresden, such as the reconstruction of the historic Neumarkt (the square and streets around the Frauenkirche), whose houses and palaces made Dresden the greatest baroque city of Europe. There was a big struggle about this because modern architects wanted to build in the modern idiom, while the citizens’ initiative wanted to restore the city as it was before it was bombed. I spent a huge amount of time writing many letters.

**Who won?**

**Blobel:** I finally persuaded the city council of Dresden to rebuild the area as it was. That’s about 10 percent of old Dresden. Of course, I’ve been criticized: “This wonderful Dr. Blobel knows about science, but he doesn’t appreciate modern architecture.” Actually, I like modern architecture very, very much. But I didn’t want the Frauenkirche surrounded by the kind of steel, glass and concrete buildings that you have all over the world. That would not restore the identity of Dresden.

**Are you happy you did it?**

**Blobel:** (smiling) It provides me with joy for the rest of my life.

—MAYA PINES

# A Better Way to Treat Heartburn

**A**s more consumers reach for drugs called proton-pump inhibitors to douse the flames of heartburn, one HHMI investigator is worried that long-term reliance on these medications may have unanticipated consequences. America's hearty appetite for these acid-reducing medications has made them the second biggest seller among prescription drugs, with \$10.8 billion in sales in 2001, according to the National Institute for Healthcare Management Foundation.

Overuse of acid reducers such as Prilosec and Prevacid can actually cause gastritis, or stomach inflammation, and can lead to more serious problems, according to HHMI investigator Juanita L. Merchant at the University of Michigan Medical School. In recent studies in mice, Merchant and her coworkers showed that the low levels of stomach acid

caused by proton-pump inhibitors can provide the perfect environment for harmful bacteria to flourish. The bacteria—which are normally kept in check by stomach acid—can trigger inflammation and ulcers that may ultimately lead to cancer. Their work was published in the January 2002 issues of *Gastroenterology* and *The American Journal of Physiology—Gastrointestinal and Liver Physiology*.

Although Merchant has raised questions about proton-pump inhibitors, which have been in use in the United States since the early 1990s, she acknowledges that they do have their place. “They are very effective medications, and they generally don’t have a lot of side effects. But we need to be cautious about leaving patients on these drugs for decades. There’s a reason why

we make stomach acid, and it’s not just to begin digestion. The production of stomach acid is a process that has evolved to protect us against bacteria in our environment.”

Reducing stomach acid can help speed ulcer healing, Merchant says, “but this should take no more than one or two weeks, depending on the depth of the ulcer.” Patients with recurrent ulcers or gastroesophageal reflux disease often take acid-reducing drugs for months or years, and the effects of long-term acid suppression have not been thoroughly evaluated in humans, she adds.

Ironically, Merchant’s group didn’t set out to evaluate proton-pump inhibitors. They were designing experiments to understand the molecular basis of acid secretion. The textbook explanation of hormonal regulation of acid secretion begins with the parietal cells in the stomach, which release the hormone gastrin when acid levels are low. Gastrin, in turn, boosts acid levels in the stomach by turning on an enzyme in parietal cells that produces hydrogen ions, or

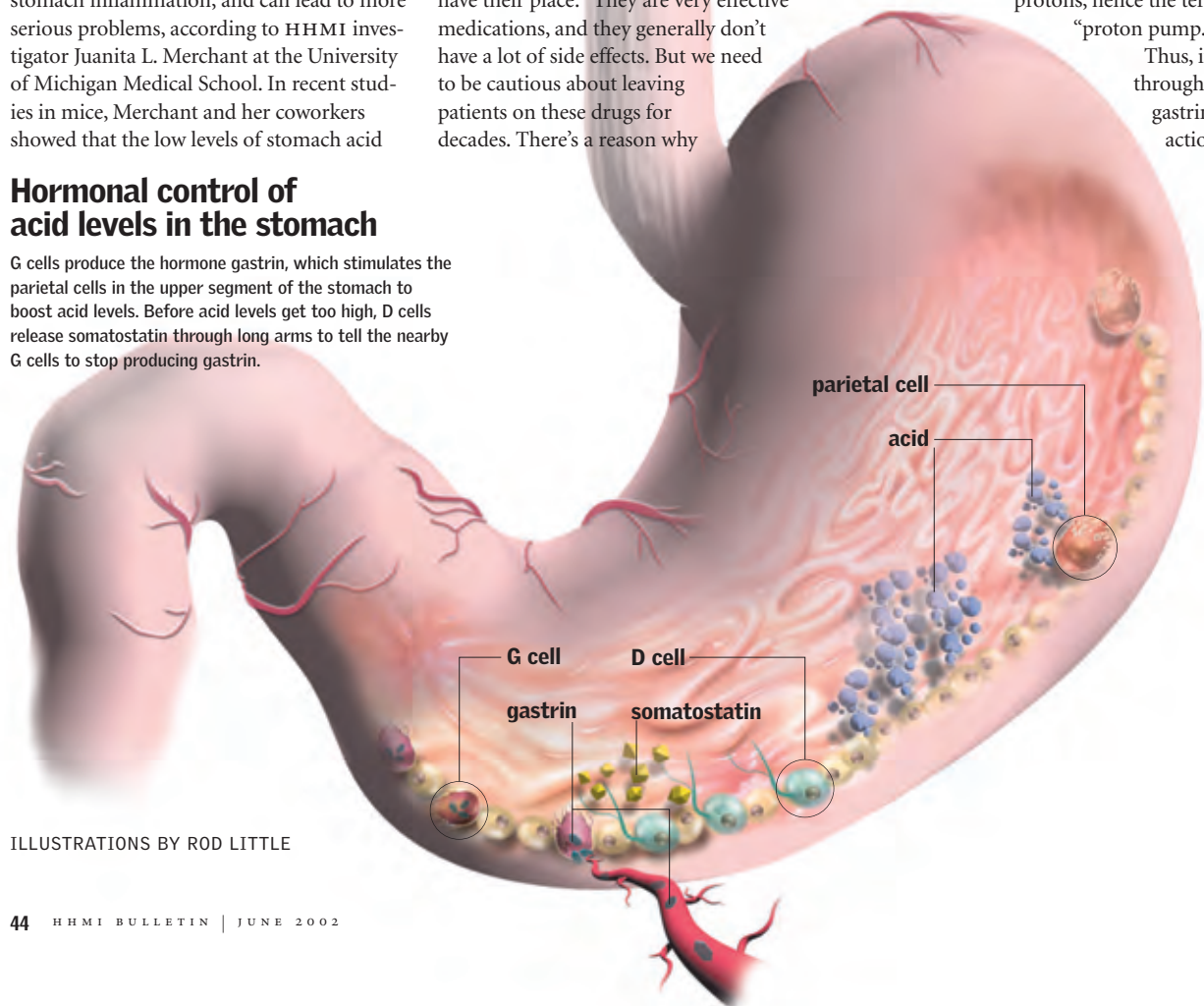
protons, hence the term

“proton pump.”

Thus, it is through gastrin’s action on

## Hormonal control of acid levels in the stomach

G cells produce the hormone gastrin, which stimulates the parietal cells in the upper segment of the stomach to boost acid levels. Before acid levels get too high, D cells release somatostatin through long arms to tell the nearby G cells to stop producing gastrin.



ILLUSTRATIONS BY ROD LITTLE



parietal cells that stomach acidity is restored to the proper level. A feedback mechanism is in place to inhibit additional gastrin production and acid secretion when proper acid levels are reached.

“However, that model doesn’t fit with what we see in patients who are infected with *Helicobacter pylori*, the major organism that infects the stomach,” says Merchant. In those patients, the stomach responds to the invader by pumping out protons, or acid, and the feedback mechanism doesn’t seem to operate. “Instead, patients develop pain from excess acid that then gets dumped into the duodenum. The excess acid can overwhelm the neutralizing capabilities of that organ, leading to ulcers.”

To better understand the role of gastrin in the formation of ulcers and cancer caused by *Helicobacter* infection, the researchers created transgenic mice that could not produce the hormone. “We planned to infect the animals with *Helicobacter* to see what would happen when there was no gastrin present,” says Merchant. “Would we still see ulcerations and inflammation?”

That’s when the researchers discovered that the mice they had planned to use for the studies showed signs of gastritis even though they had not yet been infected with

*Helicobacter*. The inflammation was caused by the overgrowth of other types of bacteria—*Lactobacillus*, *Enterobacter*, *Staphylococcus* and *Probionibacterium*—that are generally not associated with inflammation. When the researchers administered antibiotics to the mice, the inflammation subsided. This observation showed that *Helicobacter* isn’t the only culprit causing gastritis and ulcers, Merchant says.

Apparently, acid levels in the stomach determine which bacteria can thrive there, says Merchant. *Helicobacter* does well in highly acidic conditions, but other bacteria gain a foothold when acid levels are low.

Next, Merchant’s group treated normal mice with the proton-pump inhibitor omeprazole (trade name, Prilosec) for two months to block acid secretion. These animals, too, developed stomach inflammation as a result of bacterial overgrowth and showed signs of increased gastrin production. Instead of going down, acid levels in their stomachs rose. When the mice were given antibiotics, inflammation abated, bacterial numbers dropped and gastrin and acid production decreased.

“A key finding is that abnormally high gastrin levels could

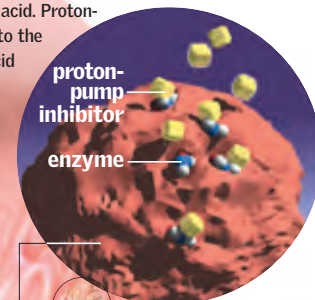
be reduced in omeprazole-treated mice just by giving them antibiotics,” says Merchant. Another important point—especially for patients and physicians—is that “you don’t want to block acid secretion over the long term just to treat *Helicobacter* infection, because that’s going to potentially allow other bacteria to grow,” says Merchant. Instead, patients should be treated with antibiotics, which will quell the infection and restore the normal acid-control mechanism, and with proton-pump inhibitors to prevent excess acid production during the 10 to 14 days it takes to get the infection under control. Once the bacteria are eradicated, she says, there is no reason to continue with acid reducers.

“*Helicobacter* has quite correctly been labeled a significant carcinogen,” says Merchant, “but our papers emphasize that other organisms can also cause chronic inflammation that may ultimately lead to cancer.”

—NANCY ROSS-FLANIGAN

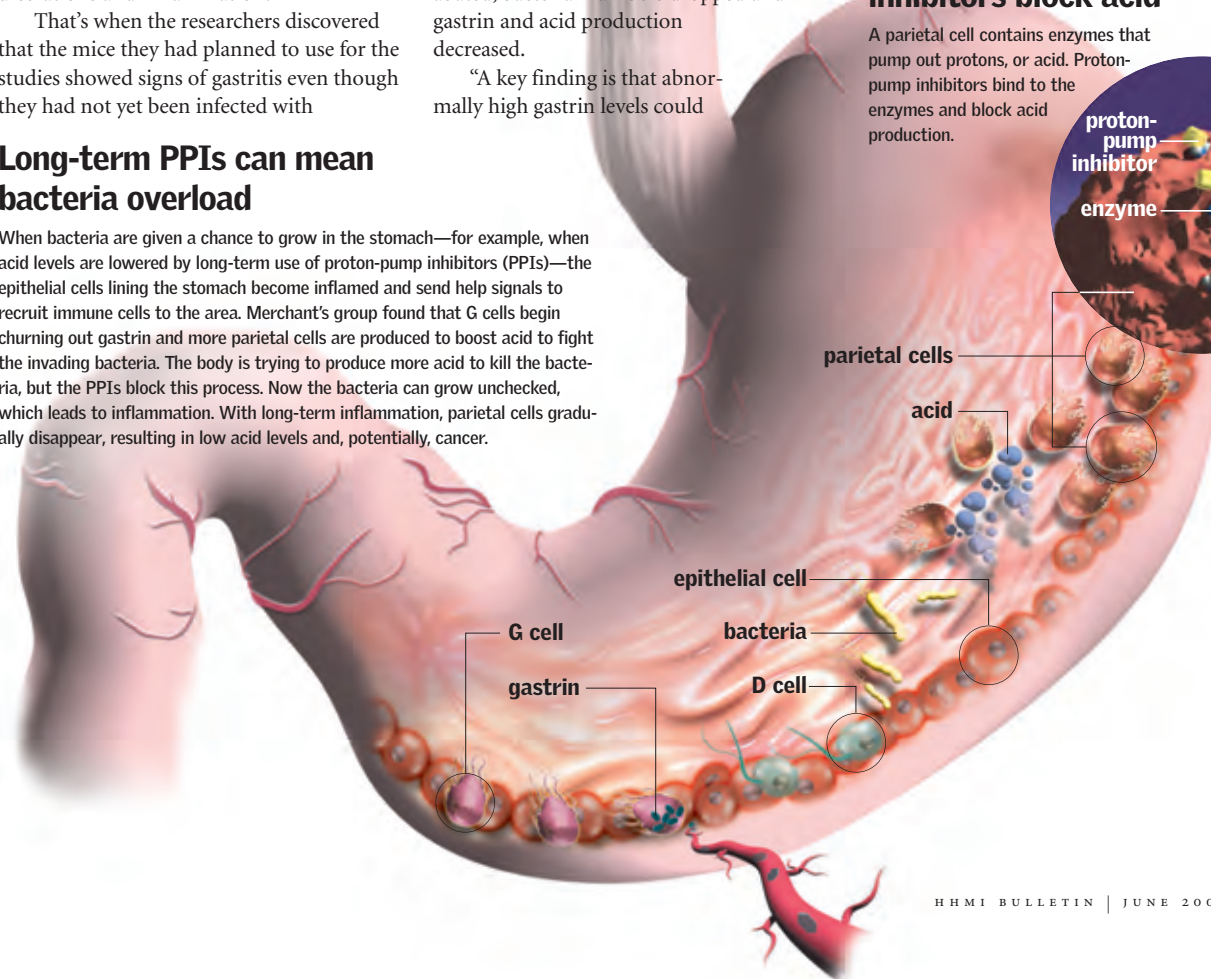
## How proton-pump inhibitors block acid

A parietal cell contains enzymes that pump out protons, or acid. Proton-pump inhibitors bind to the enzymes and block acid production.



## Long-term PPIs can mean bacteria overload

When bacteria are given a chance to grow in the stomach—for example, when acid levels are lowered by long-term use of proton-pump inhibitors (PPIs)—the epithelial cells lining the stomach become inflamed and send help signals to recruit immune cells to the area. Merchant’s group found that G cells begin churning out gastrin and more parietal cells are produced to boost acid to fight the invading bacteria. The body is trying to produce more acid to kill the bacteria, but the PPIs block this process. Now the bacteria can grow unchecked, which leads to inflammation. With long-term inflammation, parietal cells gradually disappear, resulting in low acid levels and, potentially, cancer.



# Models of Excitement

*Teachers use rapid prototyping to build protein structures.*

Discoveries normally take years to trickle down from the lab to the classroom. But a team of high school science teachers in Wisconsin has dramatically reduced the wait, while helping scientists see their work in new ways.

The teachers spent last summer creating sophisticated three-dimensional molecular models of the ribosome—the cell’s protein-making factory—based on atomic structures published less than a year before. Seeing, touching and manipulating the three-dimensional models “makes the molecular world real,” says Michael Patrick of the University of Wisconsin–Madison, who runs a summer enrichment program for science teachers in collaboration with the Center for BioMolecular Modeling at the Milwaukee School of Engineering. “It deepens understanding for the teachers, their students and even for researchers who know the molecules inside and out.”

Thomas A. Steitz, an HHMI researcher at Yale University who published the structure of the 50S ribosomal subunit (*Science*, August 2000), says he was amazed when he received the teachers’ version of his discovery. “I immediately showed it around the lab. We noticed a number of things we hadn’t appreciated about the molecule. For instance, it’s absolutely flat on the bottom. That fits with the fact that it sits on the [cell] membrane.”

“Every student I show them to gets very excited about the models,” Steitz adds. “Everybody wants to have one.”

The models are a product of *Genes, Schemes and Molecular Machines*, a teacher-development program partially supported by a grant from HHMI. Six Milwaukee-area teachers, who call themselves the 3D Translation Team, used the biomolecular modeling center’s rapid prototyping technology to produce several ribosomal subunits and complete ribosome models. Center director Tim Herman explains that recent software advances make it possible to use rapid prototyping—which is commonly

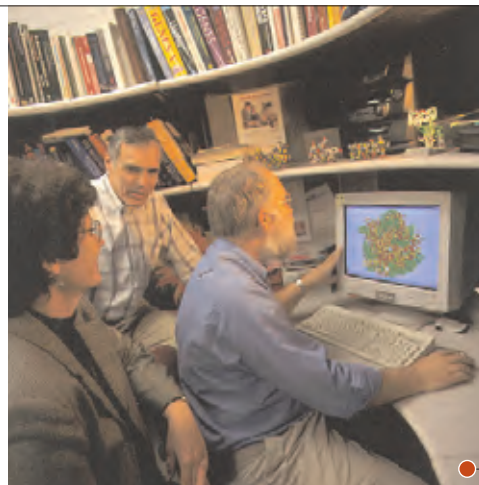
used for simulating auto parts and ships’ keels—to fabricate intricate molecular structures out of polymers, powder, ink and glue within a day.

The teachers first learned to use the prototyping equipment and then set themselves an ambitious goal: develop a complete protein synthesis kit, with models to demonstrate each step of the process in their classrooms.

The team’s first models were highly intricate. The teachers now feel that giving these to high school students is “like putting student drivers in a Porsche,” says Jon Knopp, who recently retired from Milwaukee’s Rufus King High School. The protein synthesis kit they plan to finish by fall 2002 will use simpler, more streamlined models. “The biggest stumbling block was discovering what we can do, then determining what level of sophistication is right for our students,” says Pete Nielsen of Kettle Moraine High School.

New teams of students and teachers have formed to build models. One team is modeling three proteins responsible for the toxicity of anthrax. Another is building a model of the p53 tumor suppressor protein, inactivated by the carcinogens in tobacco smoke, to use in an anti-smoking lesson.

Despite a steep learning curve at the start, the teachers have enjoyed immersing themselves in science. The original three-week program turned to six, and still the teachers kept returning to improve their models. Says Kettle Moraine’s Karen DeBoer, “What keeps us coming back is that we’re working on something cutting-edge and important.” —TONI SHEARS







■ Pete Nielson uses models of the 30S and 50S ribosomal subunits to demonstrate the details of protein synthesis to advanced placement biology students Stacy Weber, Eric Poweleit, Joe Yatzek, Jacob Schmidt and Tasha Shallow at Kettle Moraine High School in Wisconsin.

■ HHMI investigator Thomas A. Steitz (center) examines models of the 50S ribosomal subunit built by a team that included high school teachers Jon Knopp and Pete Nielson. Steitz's lab at Yale University determined the atomic structure of the 50S ribosomal subunit.



■ Wisconsin high school teachers built this three-dimensional model of the 50S subunit of the ribosome, which works as a protein-building factory.

■ The first step in molecular model-building is to download a computer file of the molecule's structure from the Protein Data Bank and create a design file that rapid prototyping equipment can use to fabricate the model. Wisconsin high school biology teachers Donna LaFlamme and Jon Knopp watch Tim Herman, director of the Center for BioMolecular Modeling at the Milwaukee School of Engineering, manipulate a computer image of the anthrax protective antigen protein.

■ High school teacher Karen DeBoer removes a finished model from a specialized color printer, one of five rapid prototyping technologies used to produce three-dimensional molecular models.

■ Donna LaFlamme, Jon Knopp, Tim Herman and Karen DeBoer put the finishing touches on their models to teach protein structure and function to high school students.



JAMES SCHNEPP (5), MICHAEL KIENITZ (STEITZ, ABOVE)

## A New Voice for HHMI

**A**vice A. Meehan has never worked for a philanthropy before. But anyone who thinks this might slow her down need only look at her history. New challenges have been the foundation of her career.

Meehan, HHMI's new vice president for communications and public affairs, spent plenty of time writing about politics but had never participated in a political campaign either—until she took on the job of communications director for Lowell P. Weicker, Jr. in his successful campaign to become Connecticut's first independent party governor. She went on to serve as Weicker's press secretary for nearly four years, a tumultuous period highlighted by the adoption of the state's first income tax.

When Weicker decided not to run for re-election, Meehan made another career leap, to the Memorial Sloan-Kettering (MSK) Cancer Center in New York City as vice president, public affairs. She was new to this field as well. "At the time, all I knew about cancer was that my mother had just been treated for it," she recalls. "But I did know how to manage a fast-moving communications agenda involving complex issues."

A governor's press office and the public affairs operation of a medical research center may seem worlds apart, but the common thread is Meehan's leitmotif: seeking a sense of mission and purpose. "I want to work for a place that is making a difference in people's lives," she explains.

As she learned the workings of a cancer treatment center that also conducts leading-edge research, Meehan says she gained a sense of the ways in which researchers and clinicians collaborate to advance scientific knowledge and alleviate the suffering caused by disease. "I feel blessed to have served an institution like Memorial Sloan-Kettering," she says. "I had the opportunity to work with incredibly talented scientists and physicians and to see the myriad ways in which



KAY CHERNUSH

*Avice Meehan will help HHMI inform the public and policy makers.*

research advanced the treatment of cancer."

She also learned to juggle challenging issues—from the impact of managed care on academic medicine and the ethics of clinical research to a major cancer center expansion—while managing an active media relations, Web and publications program. The experience sometimes made her years in journalism and politics look tame. For example, when New York's governor announced at a press conference last fall that anthrax had been detected in his office—which happened to be located in the same building as 1,200 MSK employees—Meehan and her colleagues scrambled to organize briefings for anxious staff as television cameras lined up on the street.

"At an institution that has as high a profile as Memorial Sloan-Kettering, anything can and does happen," she remarks.

"Fortunately, I also had the opportunity to think strategically about MSK's mission and how to support its long-term goals as one of the nation's leading cancer centers."

After nearly eight years in New York,

Meehan says she is thrilled about joining HHMI and having the opportunity to build on what's already a strong communications program. "I first learned about HHMI from Institute investigators at Memorial Sloan-Kettering. Through their work I began to see the many ways in which HHMI sets the standard in biological science—not to mention innovative teaching about science," she explains. "It's an honor to be part of this intellectual community and, even better, to have the opportunity to strengthen HHMI's role in informing the public and policy makers."

Meehan's first task will be to gain a more vivid sense of HHMI's mission and culture—the kind of perspective one can only gain by spending time

with those who know the Institute best. She's already thinking about the ways in which HHMI's 50th anniversary can be used to focus attention on the Institute's contributions while highlighting the challenges ahead in research, science policy and education.

In some ways, Meehan's move to Chevy Chase is a wrenching one. A born and bred Northeasterner, Meehan grew up in the tiny village of Goshen, New York. A graduate of Mount Holyoke College in Massachusetts, she earned a master's degree from New York's Columbia University Graduate School of Journalism and worked at newspapers in Massachusetts, Connecticut and New York. "I love Manhattan, but change is an essential part of my life," she says. "Having made so many friends and built so many connections there, I know I can do it again."

A few of those new friends may be four-legged. Meehan, a horseback rider, looks forward to living near horses and maybe even getting one of her own.

—JENNIFER BOETH DONOVAN



# Discovering Our Senses, This Time in Spanish

**S**eeing, Hearing and Smelling the World, one of HHMI's award-winning publications, is now available online in Spanish. Based on the positive response to the Spanish research news site ([www.hhmi.org/new/research-esp.html](http://www.hhmi.org/new/research-esp.html)), translating this publication—one of the most popular on the Institute's Web site—was almost a mandate. All the graphics and articles from the original print version are included, the navigation has been streamlined and a section titled “El progreso continúa” (“Progress Continues”) brings the reader up to date on the latest research about our senses.

Descubra cómo detectamos el mundo: [www.hhmi.org/senses\\_esp/](http://www.hhmi.org/senses_esp/)

**Netscape: Viendo, oyendo y oliendo el mundo**

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**UN INFORME DEL INSTITUTO MÉDICO HOWARD HUGHES**

**NUEVOS DESCUBRIMIENTOS AYUDAN A LOS CIENTÍFICOS A DARLE SENTIDO A LOS SENTIDOS**

**Viendo, Oyendo y Oliendo**

**ÍNDICE**

- Todo está en el cerebro
- Descifrando el código de los colores
- Cómo vemos las cosas que se mueven
- El conjunto de vibraciones que nos permite oír
- Localizando a un ratón por su sonido
- El misterio del olfato
- ¿Un sentido oculto en la nariz humana?
- Nuevas técnicas de procesamiento de imágenes muestran al cerebro en acción
- El progreso continúa

**Netscape: Juzgando un color**

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**Viendo, Oyendo y Oliendo el Mundo**

**UN INFORME DEL INSTITUTO MÉDICO HOWARD HUGHES**

**Descifrando el código de los sentidos... Juzgando un color**

¿Ver un color implica hacer comparaciones? “Un color que un conejo individual puede hacer su propio ‘mapa’ independiente de los receptores”, afirma Saito, “no dice nada acerca del color”.

Pero con un poco de ayuda, el cerebro puede comparar el estímulo entrante de diferentes clases de [www.hhmi.org/senses\\_esp/](http://www.hhmi.org/senses_esp/) y luego hacer muchas otras comparaciones.

El trabajo de juzgar un color comienza en la retina, la cual tiene tres capas de células. Las células de las capas más profundas de la primera capa son comparadas por las de las capas más superficiales, “separadas” por las de la segunda capa. Estas células “separadas” comparan el balance entre la luz roja y verde que viene de una parte determinada del campo visual. Ofrecen señales diferentes, entonces, cuando se ven los dos colores juntos con los reflejos combinados de los colores rojos y verdes.

En una etapa más avanzada, las comparaciones de las percepciones visuales de una imagen pueden ser comparadas individualmente por los colores como combinados, es decir, cuando están combinados simultáneamente.

Además, se están descubriendo las conexiones de esta “compleja red de sensores”, hechas por el sistema visual, al momento de la información y el poder de la comparación. ¿Qué y cómo?

Foto: Poynter.org - J. K. Koen Por Editorial Photo

# » » » » IN THE NEXT ISSUE

## » Creatures large and small

What can winged bats, hibernating squirrels and single-celled pond dwellers tell us about human development and disease?

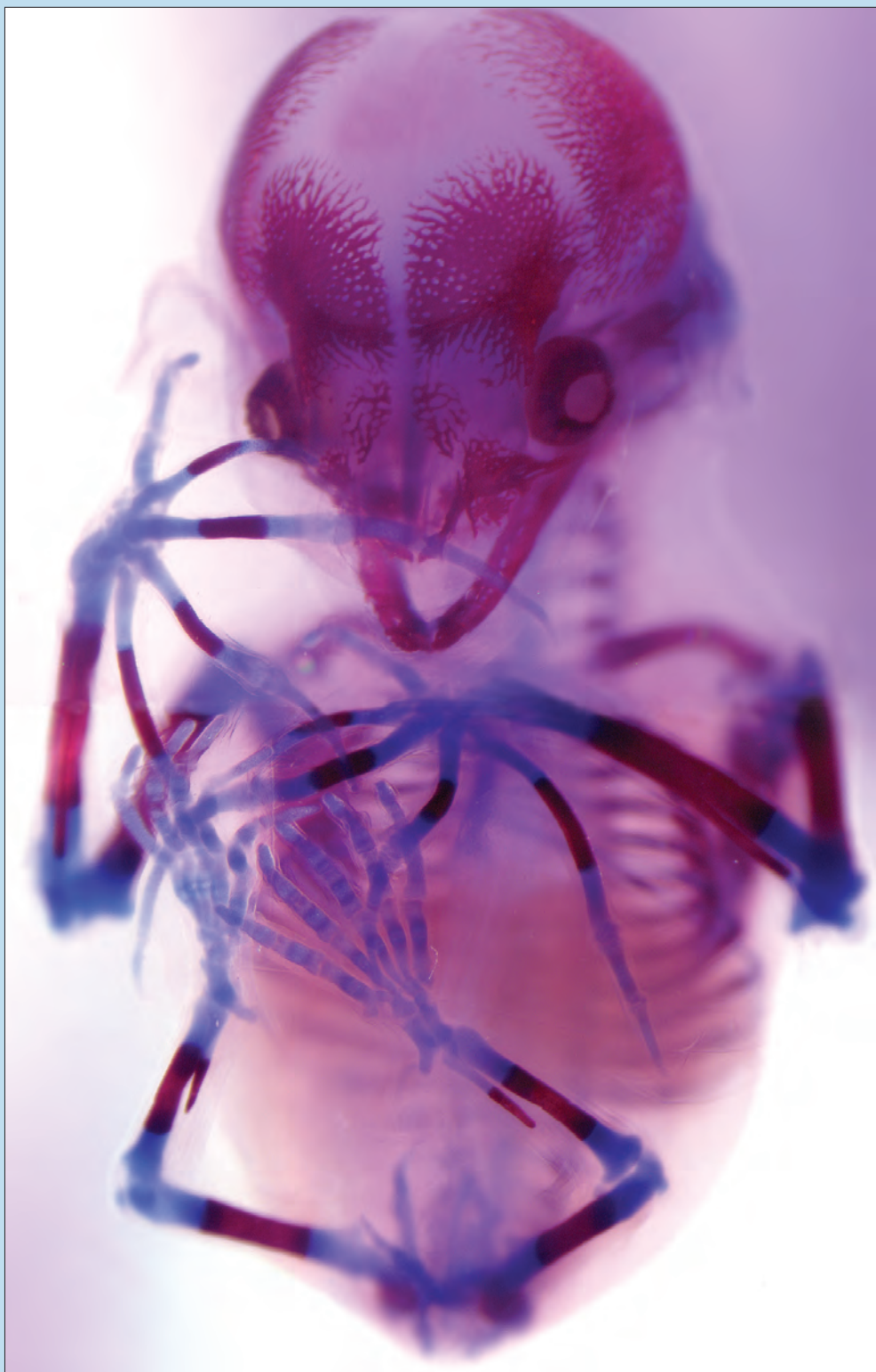
## » How intelligent a design?

Evolution may be losing ground in the classroom.

## » A foot in each camp

Physician-scientists who treat patients and do lab research get a boost from HHMI.

Bats, mice, chicks and humans share the same genes for limb development. As early embryos, the four look very similar, but differences in when and how certain genes are expressed lead each creature down a considerably different path. This image shows a bat embryo, about two-thirds of the way through gestation. The digits have grown very long to form its wings. The red-stained areas are bone; the blue are cartilage.



SCOTT WEATHERBEE, NISWANDER LAB



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