

# HHMI

Howard Hughes Medical Institute Bulletin



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**On the Cover:** An embryologist at Boston IVF adds liquid nitrogen to a tank of frozen embryos. Photograph by Kathleen Dooher

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Howard Hughes Medical Institute Bulletin

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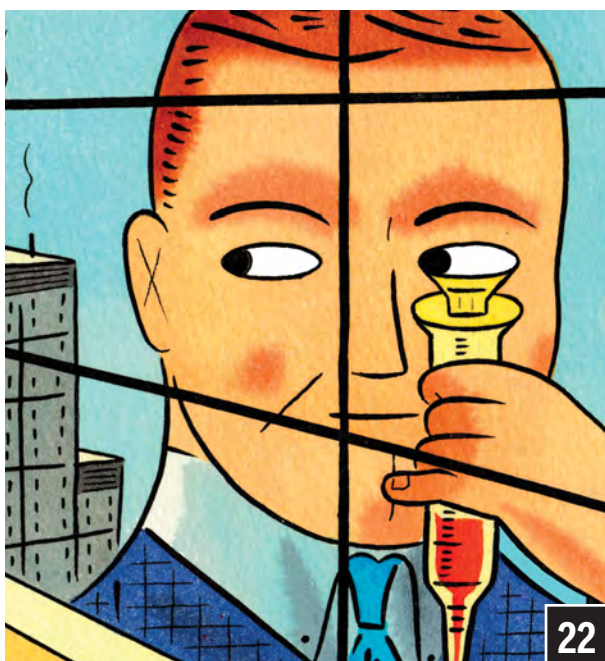
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■ Eight HHMI investigators have been elected 2002 fellows of the American Association for the Advancement of Science (AAAS). **Philip A. Beachy**, The Johns Hopkins University School of Medicine; **Linda B. Buck**, Fred Hutchinson Cancer Research Center; **Mario R. Capecchi**, University of Utah; **Sean B. Carroll**, University of Wisconsin–Madison; **David Ginsburg**, University of Michigan Medical School; **Lawrence C. Katz**, Duke University Medical Center; **Joseph S. Takahashi**, Northwestern University; and **Marc Tessier-Lavigne**, Stanford University, were inducted at the AAAS annual meeting in February. Fellows are chosen for their contributions to science.

■ Two science teachers from programs supported by HHMI science education grants were chosen for *USA Today's* All-USA Teacher Teams. **Betsy Berg**, Corvallis High School, was nominated by Oregon State University's program, and the program at the University of Arizona nominated **Cecelia Valenzuela Gee** of Davis Bilingual Magnet School.

■ **Günter Blobel**, an HHMI investigator at The Rockefeller University, was named Academician of the Pontifical Academy of Sciences by Pope John Paul II.

■ **Kevin P. Campbell**, an HHMI investigator at the University of Iowa College of Medicine, received the 2001 Elsevier Science Award at the 6th International Congress of the World Muscle Society.

■ Three HHMI investigators were among four scientists who shared the first Paul Marks Prize for Cancer Research. **Stephen J. Elledge**, Baylor College of Medicine; **William G. Kaelin, Jr.**, Dana-Farber Cancer Institute and Harvard Medical School; and **Xiaodong Wang**, University of Texas Southwestern Medical Center at Dallas, received the honor for their contributions to cancer research.

■ **Joachim Frank**, an HHMI investigator at

Health Research, Inc., at the Wadsworth Center, received a Scientific Merit Award from the New York State Department of Health for his discovery and development of a novel method for visualizing large biomolecules. The one-time award recognized the New York State researcher who made the most important scientific contribution during the last quarter of the 20th century.

■ Three HHMI investigators have been named 2002 fellows of the Biophysical Society. **Joachim Frank**, Health Research, Inc., at the Wadsworth Center; **Wayne A. Hendrickson**, Columbia University College of Physicians and Surgeons; and **H. Ronald Kaback**, University of California, Los Angeles, were honored for their contributions to expanding the field of biophysics.

■ **Jeffrey M. Friedman**, an HHMI investigator at The Rockefeller University, received the 2001 Bristol-Myers Squibb Award for Distinguished Achievement in Metabolic Research.

■ **Stanley J. Korsmeyer**, an HHMI investigator at the Dana-Farber Cancer Institute, received the Leukemia & Lymphoma Society's de Villiers International Achievement Award & Grant for his research on the role of apoptosis, or programmed cell death, in lymphomas and other cancers.

■ **Tian Xu**, an HHMI investigator at Yale University School of Medicine, was the first recipient of the Tuberous Sclerosis Alliance's Rothberg Award for Courage in Research, for his identification of genes associated with tuberous sclerosis, a genetic disorder.

■ **The Wildlife Conservation Society's Bronx Zoo** received the 2001 National Science Board Public Service Award for organizations for its education programs, supported in part by an HHMI science education grant. The National Science Board is the policy-making body of the National Science Foundation.

### Logistical Nightmare

In "Quantifying Uncertainty" (*HHMI Bulletin*, September 2001), author Laura Spinney writes of the United Kingdom's 2001 hoof-and-mouth disease (HMD) epidemic: "Almost 2.5 million animals were slaughtered in 11 weeks, requiring burial pits equivalent to 200 Olympic-size swimming pools." That is an average of 12,500 animals per "swimming pool," and an enormous number of beasts.

Ms. Spinney also writes that 2,000 troops and 1,000 police officers were involved in the eradication. Does this mean that they shot on average more than 800 animals each?

I am curious about these logistics because HMD or foot-and-mouth disease (FMD) virus could well be introduced into the United States by terrorists. The disease in the U.K. required the killing of about 4 million animals; more than 80% were sheep. The disease in the U.S. would affect mostly cattle and hogs. The U.S. Department of Agriculture's draft plan for FMD states that animals should be buried in a trench 7 feet wide and 9 feet deep. How many miles long must such a trench be to hold, say, one million head of cattle? My calculations indicate 500 miles!

JOSEPH M. CUMMINS, D.V.M., Ph.D.  
Amarillo, Texas

Laura Spinney responds: *The statistics I quoted came from a Cabinet Office paper published in May 2001, at the height of the epidemic. The paper described one mass burial site in Throckmorton, Worcestershire, that had the capacity to accommodate more than 430,000 sheep (the paper did not give the pit's dimensions). Of course, animal carcasses were burned as well; by May, 15,000 vehicles had been used for transporting the carcasses to burial pits and funeral pyres.*

*The police officers involved in the eradication did not shoot animals; they handled general duties in support of the operation—for example, restricting movement to and from infected areas. Military marksmen were deployed for the rapid culling of pigs in open fields—hoof-and-mouth disease was particularly virulent in those animals.*

**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.

## Seeing the Opportunities

**D**uring my first two years as president of the Howard Hughes Medical Institute, I have often been struck by the need for researchers and institutions to act decisively when new opportunities arise. A scientist may shift his focus in response to a new lead, for instance, and end up solving an entirely different problem than originally planned. An institution may suddenly see a new way to make a real contribution to science.

One of the most interesting new initiatives for the Institute is the development of Janelia Farm, the research campus that will soon be built along the Potomac River near Leesburg, Virginia, about 30 miles from HHMI headquarters. The campus will provide 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.

In February, the Institute selected Rafael Viñoly as the architect for the campus. Viñoly, who heads a 105-member architectural firm based in New York City, was chosen from a slate of distinguished architects who participated in a charette, a series of collaborative meetings between the architects and HHMI planning groups where participants shared and discussed ideas about the project. The charette capped months of hard work by the architects, as well as the Institute's Janelia Farm Advisory Committee, which included members of our Medical Advisory Board, HHMI investigators and other renowned scientists and science administrators.

A native of South America, Viñoly, the son of a prominent theater director and filmmaker, considered a career as a concert pianist before deciding to become an architect. His firm's diverse projects are found in many major cities in the United States, Japan, Korea, Europe and South America, and include the Cairo Financial Center, the Tokyo International Forum, the Lewis-Sigler Institute for Integrative Genomics at Princeton University, the Van Andel Institute in Grand Rapids, Michigan, and the National Neuroscience Research Center, which will be located on the National Institutes of Health campus in nearby Bethesda, Maryland.

One of Viñoly's tasks at Janelia Farm will be to create a research facility that will offer scientists the flexibility to shift quickly into new areas of scientific interest. We will have more on this exciting initiative, including a look at the conceptual design, in the next issue of the *Bulletin*.

One HHMI investigator who saw an opportunity and shifted gears is William Dietrich, featured in this issue (see page 4). He moved from genome mapping to host-pathogen interactions when he arrived at Harvard Medical School six years ago. Dietrich studied several different microbes before settling on anthrax. In the wake of

last fall's anthrax attacks, Dietrich's laboratory at Harvard became a virtual sound stage as information about the risks of anthrax and how to address them made Dietrich a valuable resource for numerous television and print journalists.

Of course, Dietrich was not alone in responding to journalists. Many scientists, including other HHMI investigators, readily shared their expert knowledge. Some of those interviewed were in the audience at an HHMI science meeting on infectious diseases in November—one of eight to ten meetings that the Institute holds on scientific topics each year. At that session, participants heard about promising research on the pathogens that cause tuberculosis, Legionnaire's disease, malaria and many other human illnesses. The progress being made on those deadly pathogens gives us hope that Bill Dietrich and his colleagues will continue to make impressive leaps in understanding anthrax.

I'd like to end by sharing some personal observations on the celebration of the 100th anniversary of the Nobel Prizes held in December 2001. As one of 200 Nobel laureates who returned to Stockholm for the event, I was keenly aware that I was in the company of some of the most scientifically talented and knowledgeable people in the world. It was especially remarkable to see how many of the attendees were associated with HHMI—not just the five current investigators who are already Nobelists, but many others who were invited to attend or make presentations about their work (see page 48).

Another aspect of the Nobel Centennial that remains vivid in my mind is the number of students, representing many different countries, who were invited to the festivities by the Nobel Foundation. Links between education and high quality research have always been an important aspect of higher education in the United States—and a prominent part of the Institute's programs—so I was gratified to see this vital connection acknowledged on such an august occasion.



**Thomas R. Cech**  
PRESIDENT

HOWARD HUGHES MEDICAL INSTITUTE



KAY CHERNUSH

# Up Front

## Can We Become Resistant to Anthrax Toxin?

*William Dietrich faces the media spotlight for his discovery of a gene that makes some mice immune to anthrax.*

For the better part of two days last fall, journalists practically stood in line to interview HHMI investigator William F. Dietrich, turning his lab at Harvard Medical School into a backdrop for TV tapings and photo shoots. The sudden media interest was triggered by an eerie coincidence: Dietrich had discovered a gene that confers immunity to anthrax toxin in certain mice, and his work was published during the same week that the first of the deadly anthrax attacks-by-mail began spreading fear across the nation.

Scientists tend to be ambivalent about the media even in the best of times, and Dietrich is no exception. He welcomed the attention to the science, but he had qualms that he might be seen by colleagues as “taking advantage of horrible circumstances to further my own personal and professional agenda.” Other scientists, in fact, did not see Dietrich that way, although they—and he—were “bemused at the [VIP] treatment I was receiving,” says Dietrich. For the 36-year-old geneticist, it was a wholly unexpected turn of events: “Never in my dreams did I imagine that I would be on the six o’clock news.”

The spotlight also worried him on a personal level. “I was concerned that I had made myself, my family and my colleagues targets for criminals intent on making very newsworthy anthrax attacks,” says Dietrich, a tall, broad-shouldered man with a gentle manner. He is married, with children ages 7 and 2.

Dietrich’s paper, published in the journal *Current Biology*, marks a milestone in his major research interest, which is studying the interrelated mechanisms by which microbes attack and hosts defend against them. As part of that quest, he investigates why some individuals are better than others at fighting off bacteria. Previously, Dietrich

and others had observed that certain strains of mice quickly fall ill and die when exposed to anthrax toxin, while other strains can shrug off even high doses. Dietrich has now pinpointed the gene that controls this life-or-death trait. If it turns out that such a genetic quirk exists in humans, he says, “We can begin to think ‘What if we could manipulate this process? How might that help people resist the disease?’”

### A DANGEROUS OVERREACTION

Dietrich came to Harvard six years ago, following a postdoctoral fellowship at the Massachusetts Institute of Technology, where he worked on genome mapping projects at the Whitehead Institute for Biomedical Research. At Harvard, he decided to investigate the effects of bacterial infections in host cells in order to learn more about the pathogens. He was initially interested in classes of microbes such as *Rickettsia* and *Chlamydia*, which cause important human diseases. “But they were hard to study using typical microbial genetic techniques (because of issues with their life cycles),” he says. “In the end, I realized I could probably contribute more by looking at the host response, and that I should leave it to the experts to dissect the pathogens themselves.”

His first studies were of *Legionella pneumophila*, the microbe that causes Legionnaire’s disease. Subsequently, he decided to include anthrax, inspired by a colleague at Harvard Medical School, R. John Collier, a noted expert on anthrax.

Anthrax, or *Bacillus anthracis*, is a bacterium that dwells in the soil, where it forms hardy spores capable of surviving for years. Anthrax has long been known to devastate animal herds and occasionally to afflict, and



kill, humans. They may become infected while working around animals—people who handle wool or animal hides are at high risk—or by eating contaminated meat. Cases are rare, however, especially in industrialized countries. Until the attacks in October, there hadn’t been a case of inhalation anthrax—its deadliest form—in the United States since 1976, according to the Centers for Disease Control and Prevention.

Dietrich’s lab harbors no anthrax microbes. The team works with two of three

*William Dietrich studies why some individuals are better at fighting off bacteria than others—and how this information could help people resist disease.*



ASTIA KEPKA

protein components of the anthrax toxin, each of which is harmless in itself but forms a potent poison when combined with the others. The researchers manufacture these proteins (in separate batches, of course) in the lab by using cultures of *Escherichia coli* bacteria. The anthrax toxin, which they administer in small amounts to mouse cells in culture, specifically targets macrophage cells—blood cells that ordinarily recognize, engulf and destroy foreign invaders.

When the anthrax bacteria enter the cells

of a victim, macrophages rush to the scene—only to become victims themselves. Once inside the macrophages, the bacteria release a toxin, containing lethal factor, or LF, which chops up one or more of the cell's proteins. By this time, the victim is in serious trouble.

The action of LF prompts the macrophages to counterattack by releasing a cascade of potent molecules that cause inflammation. The anthrax toxin's crafty assault, however, somehow triggers an overreaction by the macrophages, which pour inflammatory molecules into the bloodstream in such a burst that blood pressure drops precipitously, causing shock and filling the lungs with fluid. At this point, anthrax is almost untreatable. Ironically, "it seems that the macrophages are complicit in the death of the patient," says Dietrich.

#### A LIFE-OR-DEATH DIFFERENCE

Such a sequence is not inevitable, at least in mice; the anthrax toxin fails to undermine some animals' immune systems. Dietrich reasoned that if he could determine what trait dif-

fered between the resistant and the vulnerable strains of mice, it should be possible to home in on the genetic mechanism that controls the unleashing—or the incapacitation—of the toxin.

In a previous collaboration, Dietrich and Collier had identified additional strains of mice that were either vulnerable or immune to anthrax. The two researchers then used genetic mapping methods to identify a region on chromosome 11 of the mouse that they believed could contain the responsible gene.

Nearly five years ago, Dietrich's team began sifting through the DNA in this chromosomal region, with graduate student James Watters carrying out much of the bench work. They had to sequence all of the DNA in this region of chromosome 11 until they came upon a gene whose sequence differed between toxin-resistant and toxin-susceptible cells.

They found one mouse gene with the variation—*Kif1C*, a member of a family of genes that code for widely distributed motor proteins called kinesins. The variation was modest, but its effect profound. A difference of just one amino acid, caused by a base change in the *Kif1C* sequence, produced enough of a functional disparity in the proteins to account for vulnerability or invulnerability to anthrax in the mice.

One form of the *Kif1C* protein enabled macrophages to deflect the toxin's attack; the other form rendered the macrophages helpless. The scientists then inserted the protein's resistant form into the genetically susceptible macrophages (with the aid of a retroviral vector that expressed only modest amounts of the protein). Thereafter, the cells were more likely to survive when exposed to the toxin.

Why is this protein able to make a life-or-death difference to the macrophage? Dietrich's group is trying to find out. So far, they can say what the protein does *not* do, having ruled out the possibility that *Kif1C* prevents uptake of the toxin by the macrophage. They also know that it does not deter the toxin from destroying its target proteins inside the cell.

It's clear, however, that the macrophage can withstand the toxin's invasion only if *Kif1C* is performing its normal function well. The Dietrich team tentatively assumes that this function involves transporting proteins around the cell, because that is what kinesins ordinarily do.

The findings also invite speculation that there may be individuals in the human population who are not susceptible to anthrax infection. Studying such individuals could provide clues for the eventual immunization of those who otherwise would be susceptible. Until then, there's another possible payoff: In a mass anthrax attack, doctors could reserve treatment for victims whose genetic makeup renders them vulnerable to the bacteria.

—RICHARD SALTUS

## Town-Gown Partnership Unites Birmingham

*With a little help from University of Alabama scientists, Birmingham offers high school students a hands-on genetics course.*

Until three years ago, high school science teachers in the public schools of Birmingham, Alabama, taught genetics in the traditional way—by having their students draw grids on paper to trace inheritance of observable characteristics. Now students breed generations of fruit flies in the lab, extract DNA, run gels and isolate proteins—and those are just a few of the hands-on activities in an elective course offered in all nine of Birmingham’s city high schools.

This genetics course is one of the first to be added to an entire school system’s curriculum with the help of its hometown medical school, and the program’s popularity is growing fast. Since 50 students in two high schools went through a pilot program during the 1999–2000 school year, this year’s enrollment in the nine-week course has grown to 400 students throughout the school system.

The unusual collaboration between the public schools and the University of Alabama at Birmingham (UAB) grew out of an HHMI-supported program called BioTeach. In the nine years since BioTeach began, 158 Alabama teachers have completed a summer course—which gives them laboratory training in molecular biology and lectures on genetics, parasitology and neurobiology—and they’ve used its kits of hands-on experiments to teach students throughout the school year.

“Science in our classrooms was driven by textbooks,” says Spencer Horn, director of science for the Birmingham school system. “Now a textbook will only be used as a resource.”

In 1998, Stephen Hajduk, UAB professor of biochemistry and molecular genetics, had been a Birmingham resident for 20 years, and he liked this down-to-earth, livable city where his home was within walking distance of his lab. However, he was being wooed away by

other institutions. Ann Reynolds, the university’s new president, asked him what it would take to make him stay.

Hajduk, who had been concerned about a disconnect between the university and its city, didn’t hesitate for a minute: He asked for a broad commitment by UAB to a community outreach effort. “We have a renowned medical center and an undergraduate campus of 14,000 students with good faculty, but we aren’t doing much for Birmingham,” he told Reynolds. He knew that the city’s public schools faced more than their share of problems: “White flight” out of Birmingham had resulted in an inner-city student population that was 97 percent minority, a financially strapped system and a divided school board.

Reynolds was former chancellor of the City University of New York, where close community ties are highly valued, and she sympathized. Soon Hajduk, an expert in cellular differentiation in parasitic organisms, was made director of UAB’s new Center for Community Outreach Development (CORD), a multifaceted initiative to improve local public education. Today, he needs three flowcharts and a computer calendar to keep up with all the interconnected programs that CORD oversees. Its 400-member volunteer corps tutors students in math and reading, but it is in science that the group has the most to show: hands-on science classes for elementary school students, biology training for middle school and high school teachers, laboratory space in a city science museum for teachers and students and the new genetics elective for high school students. In addition, a general high school physical-science program is being developed.

CORD has also created the “GENEius Laboratory” at Birmingham’s science museum, the McWane Center. Teachers statewide

who graduate from BioTeach can bring their students to the fully equipped GENEius Lab to extract and examine their own DNA, or to study sickle-cell hemoglobin at the protein and DNA levels, assisted by UAB graduate students and postdoctoral fellows. Last year, 2,800 students participated. The lab is supported by UAB, HHMI, the National Institutes of Health (NIH) and the National Science Foundation (NSF).

It is the high school genetics course, however, that pulls all the pieces together. CORD’s two-week summer Genetics Institute, developed with funding from NIH and NSF, offers high school teachers their own class and laboratory, with on-site assistance from UAB graduate students. Of the institute’s nine lab experiments—everything from “*Drosophila* Genetics” to “You’re Having My

**Stephen Hajduk, shown at Birmingham’s McWane Center, brings University of Alabama resources to inner city students.**





Zygote!”—two are held in the GENeius lab at the McWane Center. The city pays teachers a stipend to attend. CORD is now developing a similar Microbiology Institute.

This town-gown collaboration—the broadest such initiative that Hajduk knows of in the country—pays big dividends to teachers and students alike. “My students could walk into anyone’s freshman college class and do well,” says teacher Thelma Davis, who took the training, helped develop a lab manual with UAB and now teaches the high school genetics course. “They use technology usually available only in a research lab.”

Hajduk says that CORD’s success is largely the result of open minds and mutually respectful attitudes at the university and the public school system. About the time that Reynolds took the reins at UAB, a new Birmingham school superintendent, Johnny Brown, emerged as a strong and energetic leader who supported UAB’s outreach efforts. So did his troops, says Shirley

Sanders Ginwright, CORD’s administrative and program director. “The school system here is hungry for this, and a large part of the motivation is coming from teachers.”

For their part, Hajduk, Ginwright and other UAB administrators have been relentlessly collegial in their approach to the public schools. “We asked the superintendent what he needed, and we always make sure to bring teachers and principals on board,” says Hajduk.

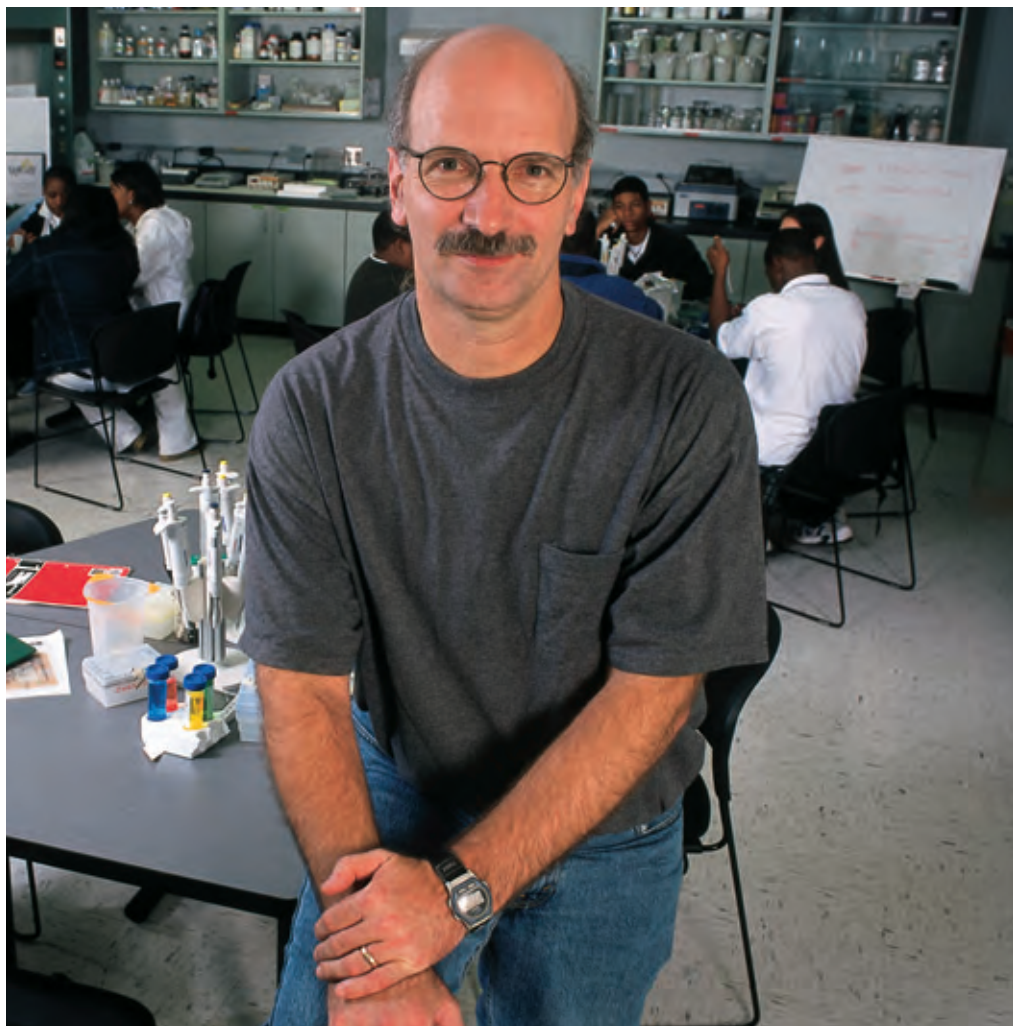
Ellen T. Wilson, a research associate at the University of Utah who helped create a Web-based genetics-education program for Salt Lake City schools, agrees that a sensitive touch is crucial to developing a symbiotic relationship with teachers. “A lot of science-education programs are created by well-meaning people from a science background who believe that all they need to do is offer lectures about a subject, and then teachers and their kids will suddenly understand,” she says. “Teachers know their craft. It’s difficult for scientists to create something for

them to use in a classroom that works without teacher input.”

The evolution of the HHMI-supported High School Human Genome Program at the University of Washington’s School of Medicine shows that to be true. “One of our original goals was to work with districts on developing curriculum frameworks that integrated the teaching of genetics concepts into their biology curriculum. When we started meeting with local school districts, it became clear that they viewed the development of curriculum frameworks as their responsibility,” says Maureen Munn, director of the Washington program. So, Munn’s program shifted gears to designing classroom activities to teach genetics at different grade levels and providing professional development for teachers, working to complement several other school-based biotechnology programs in Seattle. “We didn’t try to design classes for the teachers; we tried to help them make the curriculum work better for them.”

That kind of approach has made fervent allies for CORD among teachers and administrators in the Birmingham school system. Science director Horn says he has never seen anything before like this collaboration with UAB, but he hopes to see it again as it’s duplicated for the benefit of other communities. “I think it could be a national model for any urban system with a research institution in its midst,” he says.

But Hajduk warns that what has worked in Birmingham may not be appropriate elsewhere. “Each school system and university population has its own set of strengths and weaknesses,” he says. “It is not a matter of adapting someone else’s program but of finding what fits your own community’s needs.” —RENEE TWOMBLY



MIKE CLEMMER

#### FOR MORE INFORMATION

- » The University of Alabama at Birmingham’s CORD program: [www.uab.edu/cord](http://www.uab.edu/cord)
- » The University of Washington’s GENETICS project: [chroma.mbt.Washington.edu/outreach/genetics](http://chroma.mbt.Washington.edu/outreach/genetics)
- » The University of Utah’s Genetic Science Learning Center: [gslc.genetics.utah.edu](http://gslc.genetics.utah.edu)
- » HHMI’s precollege science education biomedical initiative: [www.hhmi.org/grants/precollege/overview/biomed.htm](http://www.hhmi.org/grants/precollege/overview/biomed.htm)

## Undergrads Learn to Write Clearly About Science

*Professional writers give science majors some valuable tips.*

Writing labs at universities around the country are making it more likely that the students who emerge from university science programs will later be able to describe their scientific work clearly. The undergraduates who take these courses interact with professional science writers, which should also improve their ability to communicate about science to a lay audience.

Aaron Robison, a senior at the California Institute of Technology, says that writing a feature article on the Ebola virus gave him an entirely new perspective. “Many of the concepts have to be simplified and streamlined in order to be understandable,” Robison says. He also felt it necessary to “spice things up, adding a bit of melodrama to the mix to keep it interesting.”

There is no lack of melodrama in Robison’s lead paragraph: “In July of 1976, a Sudanese storekeeper known simply as Yu G. became the first recorded victim of a terrifying new hemorrhagic fever that had emerged from its lair in the rain forests of central Africa. The virus that killed him eventually became known as Ebola.” Robison wrote the Ebola article for a science writing lab required of all undergraduates. “The faculty here recognized the need for students to excel at writing about their work as well as at doing it,” says Gillian Pierce, coordinator of the course. “It is important for scientists to be able to tell people what they do and why it is relevant.”

With nearly all Caltech students majoring in science, Pierce understands that they begin the class “speaking science as their first language”—one that is largely unintelligible to the general public. As the class progresses, however, she sees students start to shed the dry, academic tone of scientific papers and become more aware of what they can and cannot expect nonscientists to know. For example, says Pierce, “We don’t know the

periodic table by heart.”

Much of Caltech’s writing course is taught one-on-one rather than in a lecture format. Pierce, who is a former editor, and her staff work with students on writing style, and a faculty adviser oversees scientific content. For the Ebola paper, Robison went right to the top; his scientific consultant was Nobel laureate and Caltech President David Baltimore.

Robison says his greatest challenge was striking the right balance between technical detail and simplicity. While one adviser—the scientist—was urging Robison to give highest priority to making things more precise, a second adviser—the writer—was encouraging him to shorten his descriptions and simplify them (though not at the expense of accuracy).

*As the class progresses, students start to shed the dry, academic tone of scientific papers.*

Because “good writing is rewriting,” says John Travis, who taught science journalism at the University of Arizona last year, science majors in his course at the Tucson campus spent a lot of time editing and revising. Science students often have no idea how to improve a paper, says Travis, so it is a good lesson for undergraduates to learn early that the first draft is not the final draft. In his class, students received guidance not only from him, but from classmates, who critique each other’s pieces.

Travis came to Arizona on a sabbatical from *Science News*. He expected that journalism students would show the most interest in his class and was surprised to see twice as many biology majors enroll.

Amanda Jaksha, an ecology and evolutionary biology major, was one of them. “I thought John’s class would be something interesting, something different,” she explains. “It would get me away from boring

journal writing.” She was not disappointed.

One of Jaksha’s first assignments—to write a news article for the public based on a paper in a scientific journal—won her a trip to the American Association for the Advancement of Science annual meeting in San Francisco in 2001. Her spirited style turned a technical anthropology piece that might have been tedious for a general audience into a reader-friendly article that evoked images of Wilma Flintstone and leopard-skin dresses. The course made Jaksha realize that she actually likes writing, which she believes will be useful in the public policy career she plans to pursue after graduating this year.

When public policy and science intersect, as in the Human Genome Project, the need for articulate scientists is pressing. The researcher has “an obligation not just to do the job, but to explain it to the public,” says Bruce Lewenstein, a science journalism professor at Cornell University. “In the real world, science and technology depend on public support.”

Cornell’s Laurel Southard, director of the HHMI-supported program in biology research for undergraduates, describes one

of the university’s mechanisms for helping science students improve their writing. Each student is required to write an article about another student’s research—for nonscientific readers. The best articles are published in an abstract book and submitted to the Cornell News Service for publication.

Writing for the public as part of the course was suggested to Southard by a Cornell undergraduate, Torrie Hanley. Hanley arrived at Cornell with a passion for science and a love of writing. “When I came to Cornell, I was torn,” she explains. “But it turns out I didn’t have to decide between the two.” Hanley, now a double major in biology and English, spent two summers doing environmental research in the Cornell–HHMI program. She hopes to combine her science and writing talents as an environmental journalist.

—DIANE NAUGHTON

# Canada's Quieter Stem Cell Debate

*A Conversation with Janet Rossant*

**T**he public debate over stem cell research has been less stormy north of the border. Janet Rossant, a developmental biologist at Mount Sinai Hospital in Toronto and an HHMI international research scholar, recently chaired a working group of scientists, ethicists and lawyers that provided guidance on the issue to the Canadian Institutes of Health Research, the country's lead federal agency for this area. The panel called for funding of embryonic stem cell research—with some important restrictions.

**How has Canada's experience differed from that in the States?**

**Rossant:** There's been a consensus in Canada that embryo research is acceptable under strict ethical guidelines and for specific goals. Although there is certainly opposition, it hasn't led to legislative blockage. Opposition groups here aren't as organized politically, lobbying is less important and the government has a strong majority in parliament. I think Canada is staking out the middle ground and being quite pragmatic. Our working group proposed that the use of existing cell lines and, where necessary, the generation of new cell lines should be allowed. We're proposing to *not* allow the use of cloning technology for the generation of stem cells or the creation of embryos specifically for stem cell research, or the combining of human embryonic stem cells with animal embryos and vice versa.

**Why did your report say that people should not be allowed to create embryos specifically for research purposes?**

**Rossant:** Our feeling is that this would be a step toward the "commodification" of the human

embryo, raising serious ethical questions. Also, at this time, there seems no reason to generate new embryos when there are a relatively large number available at in vitro fertilization clinics.

**How has the debate differed in the two countries?**

**Rossant:** I think the debate has been open in both countries, although the outcomes may be different. In the end, that is simply a reflection of the different political systems. Canada is not like the States; we're less polarized.

**What do you think will be the effect of that polarization?**

**Rossant:** I worry that it may cause scientists and other people who support stem cell research to hype its potential as they put forward the strongest case and bring out high-profile celebrities with degenerative diseases and injuries. We have to be careful that we don't get into a situation where stem cell research is seen as something that is going to get Christopher Reeve out of his wheelchair tomorrow. There really is enormous potential in stem cell research, but it's unknown how soon it will have a real impact on diseases.

**Can scientists around the world help each other on this issue?**

**Rossant:** Yes, I think so. For example, there's a real need to compare different cell lines and research approaches. Canada is setting up a national stem cell network of "centers of excellence"—researchers across the country working on all aspects of stem cells, and people looking at the ethical, legal, social and patenting issues. It's the sort of concept we could try internationally.

**What has it been like personally to get involved in such a contentious issue?**

**Rossant:** On the whole, it's been good, although obviously it puts you in the public eye and in potential conflict with those who truly believe that any research with human embryos is morally wrong. I think there are times when scientists have to get involved. I really do believe that stem cell research, whether with embryonic or adult stem cells, is an exciting and novel frontier in medicine. It will have real impact in the next 10 years or so. Therefore, I feel it's incredibly important that we get the best people doing the best research under the most clearly regulated, peer-reviewed systems.

—DAVID JARMUL



*Rossant favors allowing research on new ES cell lines where necessary.*


KENT KALLBERG



# Are Stem Cells the Answer?

Researchers hope to coax human stem cells into becoming pancreatic cells to cure diabetes.

By Maya Pines

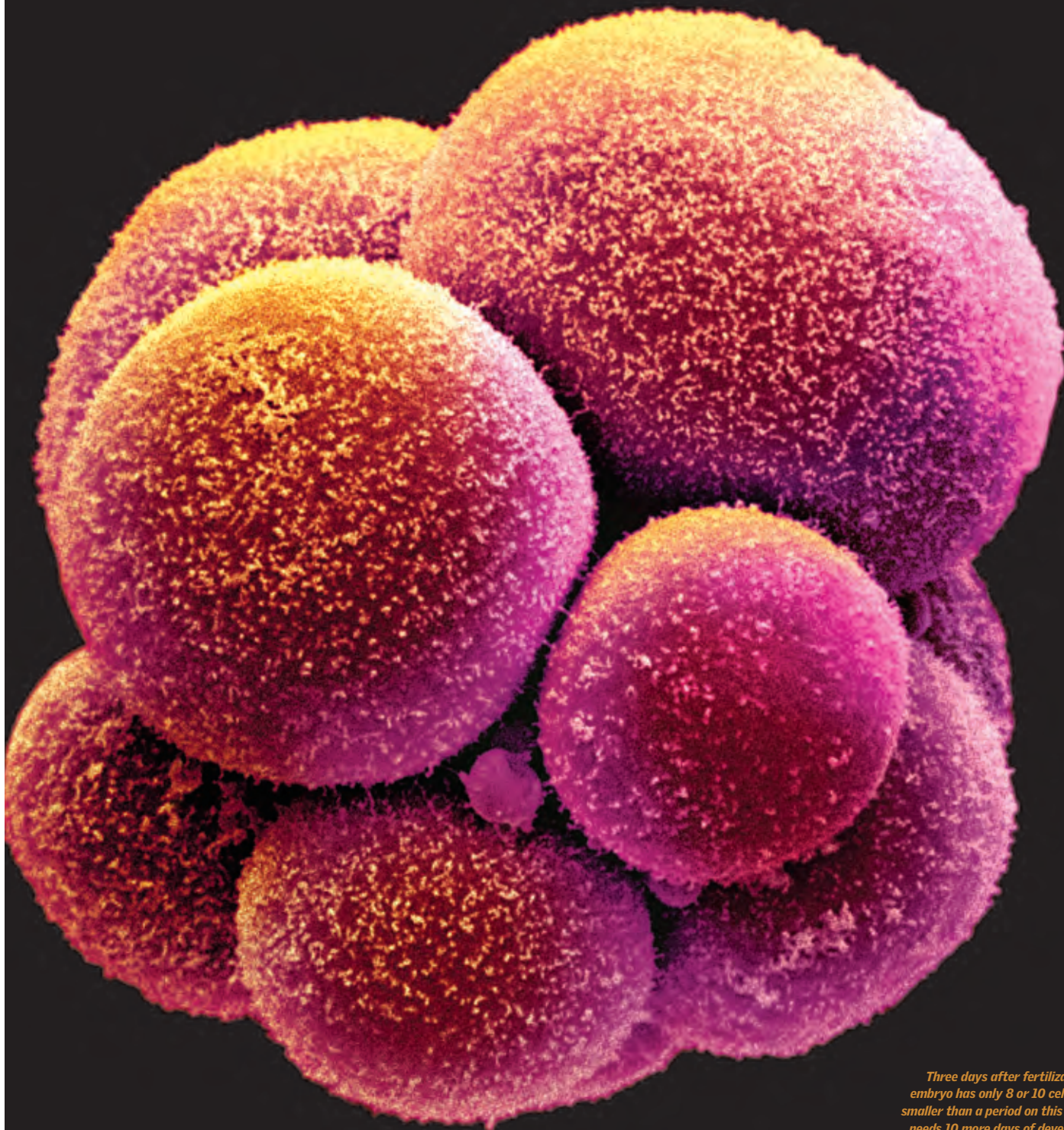


DOUGLAS A. MELTON HAS A SINGLE, OVERRIDING goal: finding a cure for his nine-year-old son, Sam, and millions of others with type I (juvenile) diabetes. This is why Melton, an HHMI investigator at Harvard University, stopped focusing on the early development of frogs, in which he had done pioneering studies, and started research on mouse development. It's also why he is now leading a major drive to turn human embryonic stem (ES) cells into the special kind of pancreatic cells, called beta cells, that supply what diabetics lack: insulin.

First, of course, he needs human ES cells. As Melton explained during a September U.S. Senate committee hearing, only ES cells have “the remarkable capacity to make any kind of cell in the body”—skin, bone, brain, liver or other specialized cells, including pancreas. Because ES cells also reproduce themselves, they could actually become factories for specialized cells to replace those lost through disease or injury.

Millions of patients with conditions such as Alzheimer's disease,

Y. MIKASSTONE



*Three days after fertilization, an embryo has only 8 or 10 cells and is smaller than a period on this page. It needs 10 more days of development to become a 100-cell blastocyst that can be implanted in a woman's body.*

Parkinson's disease, cancer, osteoporosis and spinal injuries, as well as diabetes, might benefit from such therapy. "Every family in America has been touched by these diseases and conditions, and now we have the opportunity to offer them real hope," declared Representative James R. Langevin of Rhode Island, a quadriplegic with a damaged spine, when he testified before the same committee. Most scientists believe it will take at least 5 to 10 years, however, to solve the problems involved in translating such hopes into treatments.

*Douglas Melton embarked on this quest a decade ago, when his son was diagnosed with type I diabetes.*

From Melton's point of view, the hardest part of the job will be learning how to coax primordial ES cells into becoming just one specific kind of cell—in this case, the beta cells of the pancreas that secrete insulin in response to blood sugar (glucose). Next, the new beta cells will have to be implanted into patients and continue functioning there. Finally, researchers must find ways to prevent a recipient's immune system from destroying the new cells. Only then can they hope "to transplant these cells into diabetics and effectively cure them by keeping their blood sugar under control," he says.

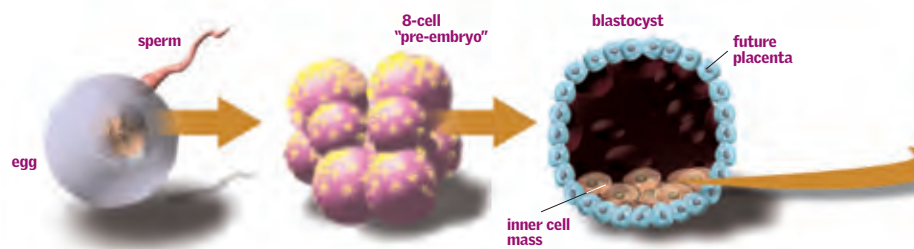
Melton embarked on this quest nearly a decade ago, when his son was diagnosed with type I diabetes—a debilitating disease in which the body's immune system destroys the insulin-producing beta cells. No one can live without insulin, which enables the body to use glucose as a basic fuel. People who cannot make their own insulin are totally dependent on daily injections of it. Melton's son, for example, routinely needs seven blood checks and insulin injections per day to maintain a safe balance between his food intake (which raises the level of glucose in the blood), physical activity (which lowers it) and insulin.

"Many times, particularly when he's playing soccer, we double that number of checks to avoid a crisis," says Melton. Diabetics suffer crises both when their glucose level is too high (this may cause lethargy or unconsciousness and may be life-threatening) and when it is too low (this "insulin shock" develops without warning; it may cause shakiness, confusion, seizures or unconsciousness). They may also face complications such as heart disease, stroke, blindness or kidney failure or require amputation, and their life spans are considerably shorter than average.

Before turning his attention to pancreatic development, Melton had won fame for his work on how the frog's body plan is established early in the life of the embryo. One of his best-known discoveries involved the frog's nervous system; he showed that this most complex part of the body forms simply by default, when a biochemical signal to make skin is lacking. Not surprising-



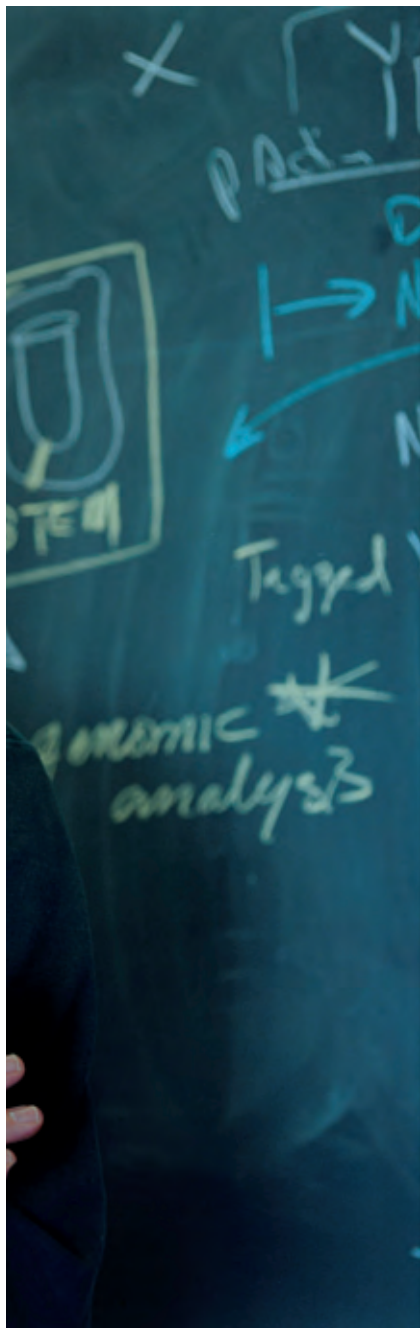
## Harvesting Human ES Cells and Their S



**1.** A human sperm fertilizes an egg.

**2.** The fertilized egg grows into a ball of 8 uniform cells.

**3.** The clump of cells develops into a blastocyst containing about 100 cells (the inner cell mass) surrounded by a transparent shell (the future placenta).



KATHLEEN DOGHER

ly, his first studies of pancreatic development were carried out in frogs. Then he moved on to mice, which are genetically much closer to humans. Scientists already had accumulated decades of experience with mouse ES cells, and Melton expected to limit his studies to these. The plan changed in the late 1990s, when James A. Thompson of the University of Wisconsin, Madison, and others devised ways to make human ES cells grow in the lab almost as well as mouse ES cells did.

The news of this achievement galvanized Melton. He knew what he had to do: work with human ES cells. But how? Only a few self-perpetuating colonies, or "lines," of human ES cells had been reported in scientific papers, and most of them belonged to private companies that held the patents for them.

At first he collaborated with other scientists on experiments with human ES cells. "This [work] showed that, like mouse ES cells, the human ES cells respond to various growth factors and differentiate," Melton says. "But we could not find a growth factor that made all the ES cells differentiate into a single type of cell. They would differentiate willy-nilly. This implies that we will not find a growth factor, or even a cocktail of factors, that will cause them all to become beta cells. We will need a different method."

Finding this method will require great effort and, most likely, many different ES cell lines, he believes. "I'm especially concerned because we know from mouse work that some ES cell lines are better than others for making endoderm, the embryonic layer from which the pancreas develops. We don't want to take the chance of being restricted to just a few lines, some of which clearly don't grow well."

● **A NEW PARTNERSHIP**

At a friend's barbecue about four years ago, Melton, who was then chair of Harvard's department of molecular and cellular biology, met R. Douglas Powers, a professor at Boston College and the scientific and laboratory

## Panel Says More ES Cell Colonies Are Needed

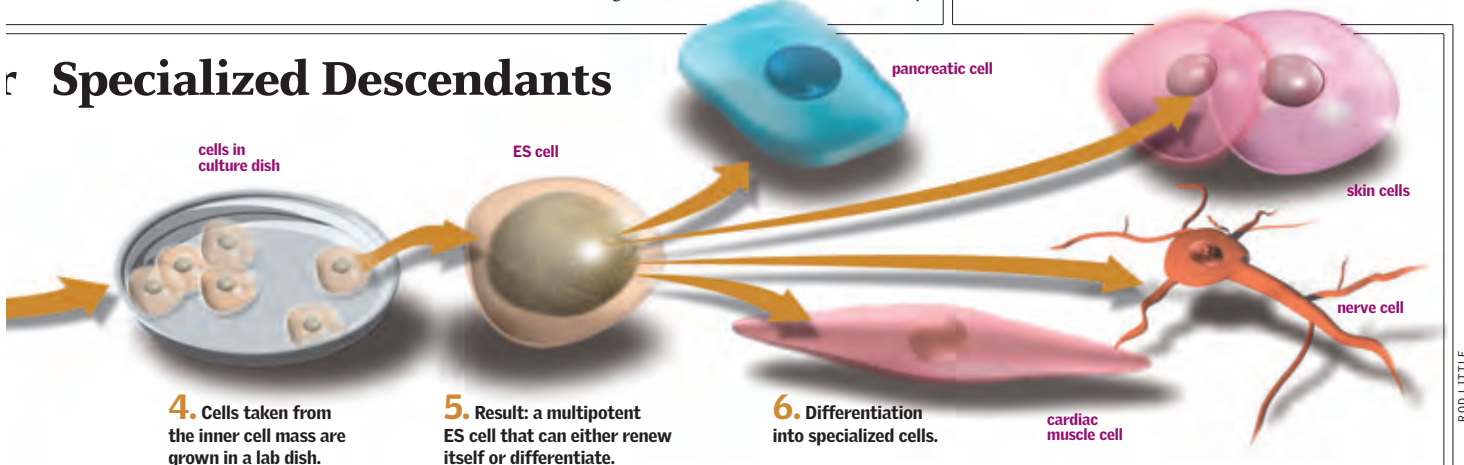
Additional colonies of human embryonic stem (ES) cells will be needed if "regenerative medical therapies" are to fulfill their promise, a panel of the National Academy of Sciences recently concluded. "The human ES cell lines that are already available should be very useful for learning more about the biology of stem cells and answering basic questions about them," commented Bert Vogelstein, an HHMI investigator at The Johns Hopkins University School of Medicine, who chaired the panel. "But in the long run they won't be enough. New lines will need to be developed to replace existing ones that become compromised by age, and to address concerns about [growing the stem cells] with animal cells and serum that could result in risks for humans, as well as to fully explore potential medical applications."

The panel, which strongly endorsed federal financing of research and the government oversight that comes with it, consisted of senior biomedical researchers who were not personally involved in stem cell research and had no conflicts of interest. Vogelstein was joined by Barry R. Bloom, dean of the Harvard School of Public Health; Corey Goodman, a neuroscientist and now president and CEO of Renovis; Patricia King, a medical ethicist at the Georgetown University Law Center; Myron Weisfeldt, chairman of the department of medicine at The John Hopkins University School of Medicine; and Guy McKhann, professor of neurology at The Johns Hopkins University School of Medicine. —MP

director for Boston IVF (an in vitro fertilization clinic). Melton told Powers about his work with mouse ES cells and his attempts to learn how these cells make a pancreas. "It's a kind of decision tree," he explained. "We want to know what genes and cells are involved in each decision so we can learn how to direct the cells' differentiation down that pathway."

They also talked about the then-recent discovery that human ES cells could be grown in culture. This led to a discussion of the need for more human ES cell lines. Powers then revealed that his clinic had thousands of

## Specialized Descendants



ROD LITTLE

frozen preimplantation embryos left over from couples' efforts to produce a pregnancy and that these extra embryos were slated for destruction. When Melton asked Powers whether he would be willing to collaborate with him in using such embryos to produce new human ES cell lines for his research, Powers readily agreed.

Last year, Melton approached Tom Cech, the new president of HHMI, with the proposal he had discussed with Powers. Boston IVF, one of the nation's largest fertility clinics, would supply frozen embryos that were left over from fertility treatments, with the donors' consent. The Boston IVF scientists would then gently thaw these very early embryos, still at the eight-cell stage, and prepare them to be grown in a lab dish.

Then, a few days later, when the embryos have grown into slightly larger blastocysts with a hollow core, Andrew McMahon, newly appointed chair of the department of molecular and cellular biology at Harvard, would do his part. Using his experience in deriving many lines of mouse ES cells, he would tease out some cells from the inner cell mass of the human blastocysts and try to turn them into new lines of self-reproducing human ES cells. This process would take at least six months, including a stage during which the cells' biological characteristics would be identified and confirmed. Finally, Melton would experiment with various combinations of growth factors or other molecules in an effort to prod the ES cells into becoming active beta cells that churn out insulin.

At HHMI, Melton found a receptive audience. "Our primary mission is to carry out the very best in biomedical research, and Doug is one of our researchers," says Cech. "He came to us and said he had the opportunity to do some very exciting and potentially very important research. We evaluated it carefully. Then we decided to fund it, as long as it remained legal and passed review by the Harvard Institutional Review Board. We also entered into an agreement with Harvard and Boston IVF covering the proposal.

"We are comfortable with our decision on all grounds—medical, scientific, ethical," Cech declares. "In fact, considering the potential for human health, we think it would be unethical not to proceed."

### ● REASONS FOR OPTIMISM

The collaboration between Harvard, Boston IVF and HHMI is just beginning. Renovation of a laboratory dedicated to the stem cell project has just been completed. It will enable Melton to study, in great detail, the various steps in the development of insulin-producing beta cells in humans.

Melton points out that he'll benefit from the experience of National Institutes of Health (NIH) scientists who recently succeeded in coaxing mouse ES cells to develop



## A Fertility Clinic Offers Its Help

Thousands of frozen human embryos, floating in culture fluid in hundreds of thin plastic vials, are stored in insulated tanks at Boston IVF, one of the nation's largest fertility clinics. Each embryo consists of only eight cells and is considerably smaller than a period on this page.

HHMI investigator Douglas Melton refers to the eight-cell clumps as "pre-embryos." At the time they are frozen, three days after in vitro fertilization, they are still several steps away from becoming the 100-cell blastocysts that, under the right circumstances, are implanted in a woman's body about 10 days later. Yet these microscopic balls of cells are an essential resource for Melton and his colleagues at Harvard, who plan to produce new colonies of human embryonic stem (ES) cells for research. Melton hopes to turn such ES cells into pancreatic beta cells,

which secrete insulin, to replace those that are missing in people with juvenile diabetes.

The embryos come from the many eager couples, about 20 a day, who stream into Boston IVF's clinic in Waltham, Massachusetts, for help in having a baby—specifically, by the in vitro fertilization process from which the clinic takes its name. Despite repeated attempts, all these couples have failed to achieve a pregnancy "the old-fashioned way," as R. Douglas Powers, Boston IVF's scientific and laboratory director, puts it. Now they rely on the clinic to unite their sperm and eggs in a dish.

The couples are greeted by a team of blue-smocked young technicians and embryologists who pad about in blue paper shoe covers and caps as they move in and out of labs and operating rooms. One of the most important procedures the





KATHLEEN DOOHER

**R. Douglas Powers, scientific and lab director of Boston IVF, gives couples the option to donate their extra embryos for research on stem cells.**

lab carries out is semen analysis. If the semen proves suitable, the husband's sperm may be processed. First, however, the woman's eggs must be removed from her ovaries, which requires a minor operation. Only one egg normally matures in the ovaries every month, but a single egg is extremely unlikely to result in a successful pregnancy. Thus, to avoid repeat operations, the woman receives hormones that stimulate her ovaries to produce many more eggs. The physicians can then collect 10 to 20 eggs at one time.

"Assume we have obtained 15 eggs," says Powers. "We put the eggs in a culture medium in a dish, and then we drop the sperm on top of

the eggs. The sperm swim around; about 80 percent of the time they actually attach to the eggs and penetrate them. So maybe 13 eggs will get fertilized in vitro. Any eggs that were not fertilized are discarded right away.

"Probably 10 of the 13 eggs will go on to develop into fairly good looking embryos," says Powers, explaining that he chose the term "good looking" deliberately. "We have no test that can tell us reliably which embryos are the best," he says. "So we just look at them with a microscope and try to judge them on their appearance."

Several of these 10 embryos will then be put into the woman's uterus. "With the current state of infertility treatments," Powers explains, "we can't guarantee that if you put only one embryo back she'll have a high probability of getting pregnant. So usually, depending on her age, somewhere between two and four embryos are placed back—fewer embryos for younger women and more for older women.

"Assuming you put 3 of the 10 embryos back, you've still got 7 left over," he says. "That's where the freezing comes in. If the woman doesn't get pregnant the first time, she can come back for another attempt. At that point, we thaw out some more of her embryos and try again."

If the couple is lucky, the woman will get pregnant after one or two attempts of in vitro fertilization and have a healthy baby. She might even have a second child later. But eventually the couple may not want any more children, even though some of their frozen embryos remain stored in liquid nitrogen. Or, if the woman does not get pregnant, the couple may sooner or later cease trying. "That's why the number of embryos we have in storage slowly grows and grows," Powers explains. "We freeze about 8 embryos a day, and we probably thaw out 3 embryos every day. Since 1989, we have built up a large bank of embryos." In fact, he says, the clinic now has about 3,000 frozen embryos under lock and key.

Powers teaches embryology at Boston College and was one of the founders of Boston IVF. "We've been responsible for the birth of 9,000 babies," he notes proudly. In the past, when a couple decided they had finished their fertility treatments, they were given the choice of leaving the remaining embryos in storage or discarding them. Now, Powers says with satisfaction, "we can offer them an additional choice: donating their embryos for research."

—MP

into pancreatic cells that make insulin. "The cells self-assemble to form three-dimensional clusters similar... to normal pancreatic islets," reported Ron McKay, chief of the Laboratory of Molecular Biology at the National Institute of Neurological Disorders and Stroke, and his associates in the May 18, 2001, issue of *Science*. "When these cell clusters were exposed to glucose, they released small amounts of insulin. They continued to function even when injected into diabetic mice"—although at levels too low to make a real difference in the health of the mice.

Melton intends to reproduce these findings and extend them to human ES cells. He is convinced that if he succeeds in producing human beta cells that pump out enough insulin, he'll be able to implant these cells into diabetics and cure them. The evidence comes from Canada, he says. Last year, a group of physicians in Edmonton took pancreases from cadavers, obtained islets from them and then transplanted the islets (which contain beta cells as well as three other kinds of pancreatic cells) into patients who had very hard to control diabetes. "The results are extremely encouraging," says Melton. "All of the patients are doing well. They are no longer taking insulin injections."

The procedure is not perfect, however. "The patients have to be kept on immunosuppressant drugs so they won't reject the foreign islets," Melton explains. "For this reason, you would not at this point treat a child with such implants, since it's unknown whether taking daily insulin injections and having imperfect glucose control is better or worse than having perfect glucose control but taking immunosuppressants all your life."

The problem of immunity will be solved, Melton believes, when "some clever immunologists figure out how to induce tolerance and block rejection. Or maybe scientists will develop a special net to enclose the transplanted beta cells and keep them away from the body's immune system."

But there is another big problem: supply. "There just aren't enough cadavers to treat the one million type I diabetics in the U.S., plus another million type II [adult-onset] diabetics who take insulin," he says. "The very best estimates say that there are only 1,000 to 2,000 pancreases available from cadavers in any one year. Why? Because the pancreas is exquisitely sensitive to the loss of oxygen.... You only really have access to patients who first of all are organ donors and, secondly, who you know are about to die."

For this reason, Melton places his hopes on the production of fresh beta cells from a renewable source, human ES cells. He envisions two promising outcomes. First, if functioning beta cells are implanted into type I diabetics, such as his son, the cells will squirt out just the amount of insulin each patient needs. This will occur internally, elim-

inating both the need for injections and the fear of crises.

Second, as scientists learn which signals tell the ES cells to become beta cells, they may be able to mimic these signals with drugs and stimulate patients' own stem cells to make more beta cells. If this is possible in type I diabetes—if these patients still have some pancreatic precursor cells to stimulate—“you would need to combine such therapies with some block to the immune system,” Melton warns. “Otherwise, the person would get more beta cells, but the immune system would be there saying ‘whack, whack,’ and just killing them off. But in type II patients, where there is no autoimmune attack, a stimulus to the patients' own cells might provide a cure.”

### ● A NEED FOR ADDITIONAL ES CELL LINES

Melton knows that the clock is ticking, that he must work rapidly and that the hunt for a cure would be speeded up considerably if he and other scientists were studying human ES cells. Until recently (August 2001), however, the majority of U.S. bioscientists—those who receive funds from government agencies—were forbidden to use the funds to work with human ES cells; some legislators were concerned that human embryos, which are potential life, would be destroyed in the process of deriving these cells.

There was much discussion about possible alternatives—using stem cells from adult tissue such as blood or bone marrow, for instance, or those derived from umbilical cords or placentas. Such cells can generate several kinds of specialized cells and are certainly worth pursuing, Melton says, but he warns that because these cells have already started down a particular path, they cannot generate all of the estimated 200 types of cells of the human body. Besides, he points out, adult stem cells “are very rare and difficult to find, and in most cases, no one can get them to grow outside the body. An ES cell, by contrast, has no trouble growing in a culture dish.”

On August 9, 2001, President Bush tried to settle the controversy about federal financing of research on human ES cells by allowing it to proceed only as long as the cells came from human embryos that were left over from fertility treatments and that were already destroyed by the day of his speech. These constraints were apparently meant to ensure that government funding of stem cell research was kept separate from, and did not encourage, the further destruction of human embryos.

NIH then produced a list of 64 human ES cell lines that already existed or were in various stages of development in the United States, Australia, Sweden, Israel and India. At the Senate hearing called by Senator

Edward M. Kennedy a few weeks later, however, new issues were raised.

Senator Arlen Specter argued, “many of the lines cited are not robust, viable or usable.” He also pointed out that because all the human ES cell lines produced so far were grown on layers of mouse feeder cells, they may be unsafe for human use. Melton added that the August 9 cutoff date “was not chosen for scientific reasons, and its arbitrary selection will have an effect on the progress of research.”

Although ES cell lines may live indefinitely, Melton said, “decades of experience with mouse ES cells” have shown they can lose their full potential with increasing age. For example, the cells can lose their ability to remain in the undifferentiated state. In addition, they can become contaminated in the lab or accumulate harmful mutations. Thus, under the President's restrictions, Melton told the Senate committee, by the time research on human ES cells advances to the point at which clinical applications can begin, “the viability of the existing cell lines will have been exhausted.”

“If we can turn human ES cells into pancreatic beta cells, we would want to use additional, new ES cell lines,” he emphasized. In that quest, he hopes that the privately funded HHMI-Harvard-Boston IVF collaboration can help him along. **H**

**Adult stem cells are very rare and difficult to find, and in most cases, no one can get them to grow outside the body. An ES cell, by contrast, has no trouble growing in a culture dish.**

*Krissy Jones, an embryologist at Boston IVF, adds liquid nitrogen to a tank containing hundreds of frozen embryos.*



# A Global Struggle to Deal with Human ES Cells

Policies on human embryonic stem (ES) cell research are as diverse as the global community itself. Some countries' regulations are highly restrictive toward such research, while others allow almost total freedom. This is an area of rapid change, however, and many governments are reviewing their policies. What follows is a brief status report on eight countries and two international bodies, compiled with the help of LeRoy B. Walters, a bioethicist at Georgetown University and a member of the HHMI Bioethics Advisory Board. Web site addresses are provided, where available, for obtaining updates.

**AUSTRALIA** The law regarding human embryo research varies from state to state, but that situation may soon change. In August 2001, a federal parliamentary committee called for the legalization of research using ES cells derived from spare embryos and for the creation of a national licensing body to regulate all ES cell research. In the meantime, the committee proposed a three-year moratorium on therapeutic cloning (the use of ES cells created through nuclear transfer for research or transplantation). Six cell lines in Australia meet President Bush's criteria, making them eligible for research supported by U.S. federal funds.

» Australian House of Representatives Standing Committee on Legal and Constitutional Affairs: [www.aph.gov.au/house/committee/laca](http://www.aph.gov.au/house/committee/laca)

**FRANCE** Although human embryo research is currently prohibited in France, in January 2002 the Assembly of the French Parliament passed a bill that would permit research on leftover embryos from fertility clinics. Prime Minister M. Lionel Jospin had initially advocated the creation of embryos through nuclear transfer for such purposes, but negative feedback from two advisory groups showed that legalizing research on spare in vitro fertilization (IVF) embryos alone had a far greater chance of legislative success.

**GERMANY** The Nazi era haunted discussions of bioethics in Germany for many years, causing a public reaction against anything that hinted at eugenics. Thus, existing embryo-protection legislation (1990) bans fertilizing an ovum for any purpose other than reproduction. Public sentiment is changing, however, and Chancellor Gerhard Schroeder supports a liberalization of the current law. In January 2002, the German Bundestag voted to allow the importation of stem cells derived from embryos that had already been produced by the time of the vote.

**ISRAEL** A 1998 law prohibits reproductive cloning but allows leeway for human embryo research. Talmudic law places distinct value on the embryo only after implantation and deems it to have achieved the status of a "formed" human only after 40 days. In August 2001, a national bioethics committee approved the derivation of ES cells and research into therapeutic cloning. Israel has four cell lines that meet U.S. government guidelines for federal funding.

» Israel Academy of Sciences and Humanities: [www.academy.ac.il](http://www.academy.ac.il)

**JAPAN** A law passed in November 2000 allows experiments with human embryos and cloned embryos in vitro, but it prohibits placing any cloned embryos into a uterus. An expert panel on bioethics recommended in August 2001 that research to derive human ES cell lines from spare embryos be permitted. In September 2001, the Ministry of Education, Science & Technology

released guidelines to implement the panel's recommendations.

» English translation of the law passed in 2000: [www.mext.go.jp/english/shinkou/index.htm](http://www.mext.go.jp/english/shinkou/index.htm)

**THE NETHERLANDS** The lower house of the Dutch parliament approved an Embryo Bill in October 2001 that would allow the use of left-over human embryos for research. The creation of embryos for research purposes would be permitted only through a royal decree and concurrence by the parliament. Action by the upper house is expected early in 2002.

» Ministry of Health, Welfare and Sport: [www.minvws.nl/english/index.html?folder=3](http://www.minvws.nl/english/index.html?folder=3)

**SWEDEN** In December 2001, the Swedish Research Council published guidelines that reaffirm Sweden's traditional policy of permitting research on surplus embryos. Although the Council did not approve the creation of embryos for research through IVF, it declared that creating embryos through somatic cell nuclear transfer "can be ethically defensible." However, this step would require that the Swedish government take steps to ensure it is legally permissible. Sweden is home to the largest number of ES cell lines (24) that meet Bush administration criteria for federal funding.

» English translation of the Swedish Research Council's report: [www.vr.se/medicin/index.asp](http://www.vr.se/medicin/index.asp)

**UNITED KINGDOM** For the past decade, British researchers have been allowed to use spare human embryos, and also create embryos, for research purposes. A 1990 law initially limited such work to contraception, infertility and congenital diseases. But its scope was extended in early 2001, when Parliament adopted regulations that permit human embryo research for "developing treatments for serious disease." A clear goal of these regulations was to permit the creation of embryos for research through somatic cell nuclear transfer, and in January 2002, the Court of Appeal ruled that the 1990 law does in fact cover embryos created in that way. Since 1990, more than 53,000 human embryos have been used in research in the United Kingdom.

» Human Fertilisation and Embryology Authority: [www.hfea.gov.uk/](http://www.hfea.gov.uk/)

**EUROPEAN UNION AND COUNCIL OF EUROPE** Trans-European bodies have consistently supported the use of leftover embryos in research but have opposed the creation of human embryos for research purposes. In November 2000, the European Commission's European Group on Ethics in Science and New Technology concluded that using spare human embryos from IVF clinics for stem cell research is acceptable, but that creating embryos for research was not currently necessary. The European Parliament's Temporary Committee on Human Genetics recommended in November 2001 that the European Union ban all EU funding for human ES cell research; however, this recommendation was decisively rejected by the Parliament, which has budgeted substantial funds for such research from 2002 through 2006.

» European Group on Ethics in Science and New Technology: [europa.eu.int/comm/european\\_group\\_ethics/](http://europa.eu.int/comm/european_group_ethics/)

» Temporary Committee on Human Genetics: [www.europarl.eu.int/committees/genetics\\_home.htm](http://www.europarl.eu.int/committees/genetics_home.htm)

—PETER MOORE

# Iron Devotion

Nancy Andrews takes her fight against iron-related disorders from lab to patients and back again.

BY NANCY ROSS-FLANIGAN

JUST BACK FROM A SPEAKING engagement in Philadelphia, Nancy Andrews is itching to make the rounds of her Harvard Medical School lab—to get updates from postdoctoral fellows and graduate students on the latest experiments, to celebrate their successes or ease their disappointments. A glance at her calendar, however, shows that she won't be lingering long over lab benches today. By mid-morning, she must be off to another building to review plans for a student-faculty retreat; then at midday, she'll grab a sandwich and share insights with students in Harvard's M.D.-Ph.D. program. Seminars, committee meetings and other such duties will fill the rest of her afternoon.

That's life as usual for this HHMI investigator. In a typical day, Andrews switches among her roles as associate professor of pediatrics, director of the M.D.-Ph.D. program and attending physician at Children's Hospital in Boston, pausing just long enough to exchange e-mail with collaborators or to coordinate family schedules with husband Bernard Mathey-Prevot, a researcher at the Dana-Farber Cancer Institute.

Although it would be distracting and exhausting to some, Andrews actually thrives on this varied, chock-full schedule. Her knack for seamlessly changing gears—and sometimes even direction—helps explain the researcher's success, and that of her team, in helping to unlock the mysteries of iron-metabolism disorders.

## A SUDDEN CHANGE OF DIRECTION

ANDREWS MADE HER FIRST MAJOR gear change in the early 1990s while she was a postdoc in HHMI investigator Stuart Orkin's lab at Harvard Medical School, where she researched globin gene transcription. A seemingly temporary assignment to help a medical student with a literature review on iron metabolism soon became a major new interest and research area for her.

"I knew nothing about iron metabolism," she recalls, "but I was asked to work with him because our lab studied red-cell biology, and iron and red cells are always important to each other" (Iron must continually be recycled in the body to replenish red cells' hemoglobin.) To the medical student, Mark Fleming, the

project was no mere academic exercise. His father-in-law had a heritable iron-metabolism disorder, and, coincidentally, a member of Fleming's family had been recently diagnosed with an iron-metabolism disorder.

Together, Andrews and Fleming delved into iron's intricacies and soon realized that even though medical scientists had been studying iron metabolism for nearly a half-century, "some big pieces of the puzzle were missing." Various labs had spent decades trying to identify the proteins involved in iron transport, but the approach used—purifying target proteins—wasn't panning out, probably because the critical transporters were present in very small amounts. When it came time for Andrews to set up her own research program, she and her lab group (which included Fleming as a postdoctoral fellow) decided to take a different tack.

"We figured genetics would give us a different way to get at these missing pieces," says Andrews. "We could isolate transporters by studying mice that were anemic due to mutations disrupting iron transport: We'd simply track the anemia in the animals and the mutations in their DNA and then find transporter genes based on their positions in the genome, rather than their function. This approach bypassed the biochemical step, which was difficult, and took advantage of emerging techniques in gene mapping."

It was a bold decision: Andrews was essentially rejecting the protein-purification techniques in which she was well schooled from her graduate and postgraduate work, to embrace molecular genetics methods in which she was relatively unschooled. What's more, she was still a newcomer to the study of iron-related disorders. The change of course paid off, however. In the seven years since they began exploring the subject through molecular genetics and clinical observations, Andrews and her cowork-

Photographs by  
Asia Kepka





ers have made several important contributions, such as identifying a key protein (DMT1) that ferries iron across membranes and discovering a mutation that interferes with the expression of transferrin, another important iron transporter. (Indispensable as it is, iron is curiously inept at getting itself into and out of cells; it relies on transporters to shuttle it where it needs to go.) At present, the researchers are investigating the roles of other proteins and modifying genes in iron transport and accumulation.

### AVOIDING IRON OVERLOAD

AT THE MOST BASIC LEVEL, iron-related disorders are easy to understand—they result from either too much or too little iron in the body. Too little iron leads to the pallor and lethargy of iron-deficiency anemia, a condition that one in ten people will experience some time in life. Genetic defects are rarely to blame; iron deficits usually occur

when people don't get enough iron in their diets or when blood loss or intestinal parasites deplete their iron stores.

Iron overload is a bit more complicated. Although iron is essential—it helps hemoglobin carry oxygen through the bloodstream to all the tissues of the body—too much of it can be toxic. Balance is clearly all-important, but avoiding overload is a tricky task.

"There's no pathway for getting rid of iron in the liver or the kidneys," explains Andrews. A smidgen is lost every day through the normal sloughing of skin and intestinal-lining cells, and premenopausal women lose some in menstrual blood, she says, but "for the most part, the iron you take in—either through diet or blood transfusion—is what you have forever."

Like a remote island where castaways must cleverly conserve precious resources in order to survive, a healthy body uses finely tuned mechanisms to continuously recycle iron. The body has strict controls on the

uptake of iron in the digestive tract and its subsequent distribution to organs. If something goes awry with the control mechanisms, however, the delicate balance is upset and iron builds up in the body, with harmful consequences. When it accumulates in the liver, for example, the likely results are cirrhosis, liver failure or liver cancer. In the heart, irregular beat and reduced ability to pump blood may result. Excess iron can also cause diabetes and problems in sexual development when it collects in the endocrine tissues.

Still, patients with iron-overload disorders aren't doomed to deteriorating health. When recognized, the problem can be treated by regularly removing blood from the body—a process called phlebotomy. "It's a simple, safe and effective treatment that's been done for more than 50 years," says Andrews. There's just one problem, she notes: "Patients hate it." Clearly, learning how to prevent or treat the disorders—rather than just managing iron buildup—could improve the lives of millions of affected people.

In one line of research, Andrews and her colleagues are gaining new insights into an ancient iron-overload disorder, HFE-associated hemochromatosis, that originated some 2,000 years ago as a mutation at a single point on a gene carried by a Celtic man or woman. The mutation, which produces a defective form of a protein called HFE (see page 44), spread throughout the world along routes of Celtic migration, eventually becoming common in the British Isles, Australia, the northwestern coast of France and the United States.

Today, in the Andrews lab, the use of mice with the same mutation is helping to show exactly how the gene defect leads to the disease. Experiments with these mice have revealed, for example, that iron buildup in the animals is caused by increased iron flux through the usual absorption pathway and not by the activation of some alternative pathway—information that could eventually prove useful in devis-

## Student Support System

STUDENTS IN HARVARD MEDICAL SCHOOL'S M.D.-Ph.D. program have a lot going for them: a state-of-the-art medical education, research training in the labs of top investigators, preparation for distinguished careers—and Nancy Andrews.

Andrews, the program's director since January 2000, has deep feeling for the aspirations of student physician-scientists and a direct knowledge of their ups and downs, having lived them herself. She is an alumna (1987) of the program, an experience she says has served her well.

"Survival skills that I learned from my training—organizing time and being able to jump back and forth from one way of thinking to another—have been tremendously useful," says Andrews. "You're always encountering new situations, so you have to figure things out as fast as you can. You learn to be comfortable with feeling uncomfortable, and I think that's part of what has made it easier for me to take risks in science."

The goal of the M.D.-Ph.D. program is to give students grounding in both scientific investigation and clinical medicine. Some graduates go into research, bringing a clinical perspective to their work; others become innovative clinicians, using the tools and techniques of basic science to better serve patients.

The program begins each July with a course called Molecular Biology of Human Disease, which runs concurrently with the students' first laboratory rotation. The summer course is also the first step in a community-building process that Andrews especially values. Bonds formed among classmates during that first summer are regularly reinforced throughout the program. An annual retreat, which offers poster sessions, guest speakers, hikes, a lobster bake and a DJ-hosted dance, is the event of the year.

During the first two years of the program, students follow one of two medical curricula: the more-or-less traditional Health Sciences and Technology or the alternative, New Pathway in General Medical Education, which emphasizes self-directed, problem-based learning. While completing lab rotations and choosing a thesis laboratory, students also take graduate courses. After a core clinical rotation in medicine or pediatrics during the third summer, students concentrate on finishing the Ph.D. first, and then the M.D.

Combining two demanding degree programs can be daunting to students just starting out, as the pressures on that career track appear intense. Not so, says Andrews. "I'd say the pressures are *different* from those of doing just one or the other, but I wouldn't say that they're *greater*." The rewards, however, may well be greater—and not just to the physician-scientists themselves, but to those who benefit from their work.

"Clinical medicine and science are very different kinds of specializations, so to be able to speak both languages—think about things in both ways, see things from both perspectives—shapes your approach," says Andrews. It also shapes attitude. "My work means more to me," she adds, "knowing that it's the first step toward something that, down the road, will improve patient care in some way." —NRF

“The fact that Nancy is a physician—that she sees patients and goes to conferences and hears about these problems—really keeps us on track.”

—Doctoral student Angel Custodio

*A 2-year-old patient with a blood disorder, Andrew Tham, gets special attention from Nancy Andrews after his surgery.*

ing treatment strategies. The researchers also are zeroing in on genes that influence the severity of the disease.

Strains of mice with this and other mutations—both natural and engineered—are helping the Andrews team tease out the details of iron metabolism. Yet the researchers always keep human patients in mind.

“The fact that Nancy is a physician—that she sees patients and goes to conferences and hears about these problems—really keeps us on track when it comes to addressing questions that are the most relevant,” says Angel Custodio, a doctoral student in the Andrews lab. “My conversations with her in the laboratory put my experiments in the context of what’s happening in the clinic. Without that, it would be easy to invest time following avenues that wouldn’t take us to the answers we really want.”

“The ‘why’ [of research] can’t just be that ‘it’s interesting,’ or ‘it’s a major biological process,’ although I think those things are very important,” explains Andrews. Part of the ‘why’ also has to be ‘how does this help advance medicine?’”

#### FROM PATIENTS TO MICE AND BACK AGAIN

ANDREWS’ DUAL ROLES AS PHYSICIAN and scientist not only help her students and postdocs avoid blind alleys, but also lead to whole new paths to explore. For about a year, for instance, postdoctoral fellow Cindy Roy had been trying to develop a mouse model of an iron-deficiency disorder called anemia of chronic disease—the most common type of anemia in hospitalized patients. “Certain cells in the body—called macrophages—are responsible for recycling iron,” says Roy, “but in chronic disease, the macrophages hang onto the iron instead of recycling it back to developing red blood cells.” So although there’s plenty of iron in the body, anemia results because much of the iron is trapped inside the macrophages, and there’s not enough available for making new red blood cells. Roy realized that she had to breed mice genetically predisposed to this condition; trying to induce it in standard mice was “difficult to do without making them super sick,” she says.



Meanwhile, as Roy labored in the lab, Andrews was learning from clinician colleagues about young patients with a metabolic disease that causes them to develop benign liver tumors. The intriguing connection to Roy’s work was that patients who developed the liver tumors showed symptoms just like those seen in people with anemia of chronic disease. “Even if you give these patients intravenous injections of iron, they still can’t make enough red blood cells,” says Roy. “But if the tumor is removed, the anemia corrects very quickly.”

The liver tumors, it seemed, were producing something that interfered with iron absorption and recycling, and the researchers speculated that this same substance might have a role in anemia of chronic disease as well. Comparing samples of tumor tissue with normal tissue, Roy found that the tumors contained abnormally high levels of a particular protein—one known to be involved in regulating iron absorption. Apparently, the tumors produce so much of the protein that iron recycling and absorption are completely shut off.

Armed with that knowledge, Roy now has a “candidate” protein—a handle on the fundamental cause of the condition—to look for in her mouse model system, once she establishes it. “It’s kind of backwards,” she laughs. “Usually the mice help us figure out what’s going on in the patients, but in this case, the patients have helped us with the mice.”

Whatever the order, progress has been made. Patients are a step closer to better health. Once again, shifting gears has helped Andrews and her lab move forward. **H**

# The Lure of Industry

BY STEVE MIRSKY

Why are a growing number of accomplished researchers moving into industry and leaving academic positions that are the envy of many of their colleagues? A major part of the answer is the pull of so-called translational research, or translational medicine, which seeks to apply the knowledge generated in basic biological research to actual therapies or vaccines for human diseases. >>>

Illustration by Michael Klein



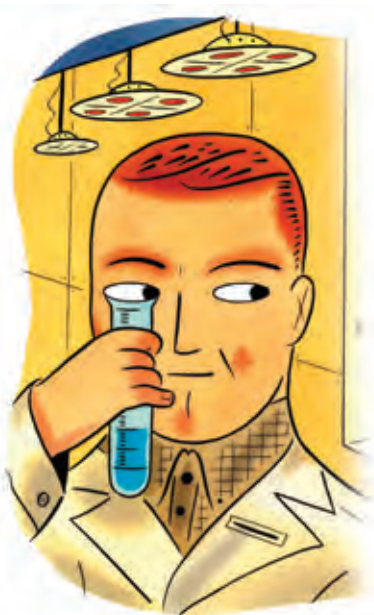






**“I wanted to help with unmet medical needs by applying my scientific knowledge in a more direct way. ...”**

**—Richard Scheller**



Take former HHMI investigator Richard Scheller, for example. A member of the National Academy of Sciences, Scheller left Stanford University in January 2001 to become senior vice president of research at Genentech. His reasoning reflects the thinking of most biologists who go from campus to company: “I wanted to help with unmet medical needs by applying my scientific knowledge in a more direct way than through fundamental biochemical research.” Scheller’s work at Stanford focused on the organization and fusion of cellular membranes. He hopes that his intimate knowledge of the cell surface will contribute to the creation of agents that attack tumor cells specifically.

Some researchers, such as Andrew Chan, hold the combined M.D.-Ph.D. degree, indicating a long-standing interest in direct patient care. Chan left Washington University School of Medicine in St. Louis last August to join Genentech as senior director of immunology. He thus joins Scheller both in venue and motivation. “At this particular point in my life,” says Chan, “I saw in industry the potential to do more translational medicine and to have a significant impact on developing therapeutics or understanding certain disease processes at a deeper level.” He plans to direct his major research interest—the signaling mechanisms that regulate T and B lymphocyte function—toward therapies that might interfere with autoimmune reactions.

Corey Goodman, also a member of the National Academy of Sciences, left the University of California, Berkeley, last September to become president and chief executive officer of Renovis, a biopharmaceutical company he cofounded in February 2000. “I’ve had a lab for 23 years,” he notes, “and it was very satisfying. But as you get older you start to think that it would be nice to push along those applications for human health.” Goodman’s observations of axon guidance and brain wiring in fruit flies will now inform such areas as human spinal cord injury and neurodegenerative disease.

Ask Peter S. Kim why he decided to leave the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology and the question seems almost obtuse, considering that the position he assumed in February 2001 is executive vice president of research and development at Merck & Co. “You didn’t just leave academia for industry,” a visitor says, “you were offered the chance to manage the Yankees!” Kim laughs at the comparison. “Well,” he responds, “I’m a Boston Red Sox fan, but I understand the analogy.” Kim, a member of the National Academy of Sciences and its Institute of Medicine, says that when this opportunity came along, “I leapt at it. It was a real chance to have a tremendous impact on human health.” One such application may derive from Kim’s studies of the molecular basis of viral infection, which have obvious potential for pharmaceuticals. “In the past, I used to say that if my work led to the development of a real drug or a real vaccine, I would view that as one of my major accomplishments in life,” he says.

Joan S. Brugge, a National Academy of Sciences member who studies signal transduction, left the University of Pennsylvania School of Medicine in 1992 to become scientific director of ARIAD Pharmaceuticals, a Cambridge, Massachusetts, company she cofounded. “I felt that ARIAD was going to pursue research that was important to me, that my energy could be devoted to translating those discoveries into therapeutics, and that it would be a really worthwhile effort,” she recalls. She also looked forward to reclaiming the energy that had been diverted by the various nonresearch duties of the academic scientist: lecturer, student adviser and multiple-committee member, for example. “I liked these responsibilities,” she says. “But I wasn’t able to control my time.”

“Time for a change” is another motivating factor for many who make the switch. “Twenty years at Stanford was absolutely terrific, 10 years with Hughes was terrific, and another 20 years would have also been terrific,” says Scheller, “but I wanted new challenges.” Goodman, who in the 1980s had the laboratory next door to Scheller’s at



**“I saw in industry the potential to do more translational medicine and to have a significant impact on developing therapeutics. ...”**

**—Andrew Chan**



**“I’ve had a lab for 23 years. But as you get older you start to think that it would be nice to push along those applications for human health.”**

**—Corey Goodman**

BOB BOSTON (CHAN), BARBARA RIES (GOODMAN), KAY CHERNUSH (KIM), COURTESY OF JOAN BRUGGE LAB (BRUGGE)

Stanford, echoes his former neighbor. “Had I gone through my entire life just doing the same kind of basic research,” he says, “I would have always wondered whether I had lost an opportunity. I thought that if I didn’t do it, I was going to regret it.”

## » Blurring the Lines Between Academia and Industry

Because Brugge took the industrial turn almost a decade ago, she has more data on the aftermath of her decision than do researchers who made this change more recently. Applying her research, ARIAD quickly identified three potential molecular targets against which therapies might be deployed. However, “we couldn’t afford to continue to go after new targets because we needed to pursue the targets we’d already identified,” Brugge says. “At the same time, in order to have capital to fund the pursuit, it was important for the company to form partnerships with pharmaceutical companies and get additional funding resources from investors.”

Brugge thus found herself reliving the academic experience of being pulled away from her research efforts—this time to keep investments flowing. “I think that in one 18-month period, I gave 140 talks,” she recalls. Brugge eventually decided to return to academia.

When she joined Harvard Medical School in 1997, she was pleasantly surprised to find that academia had started to emulate the research structure originally developed in industry—the collaborative, multidisciplinary research teams whose function is to funnel scientific discovery into the creation of drugs or vaccines. Similar academic groups now exist, or are being planned, for translational medicine. “So I have become much more involved in translational efforts than I ever was before,” Brugge says. For example, she is now a committed member of the Dana-Farber/Harvard Cancer Center, which describes itself as a “collaborative entity dedicated to the translation of research discovery into the eradication of cancer.”

The creation of such campus facilities—other notable examples include the James H. Clark Center for Biomedical Engineering & Sciences at Stanford and the Health Sciences Initiative at Berkeley—may be academia’s way of immunizing itself, keeping the trickle of researchers who leave for industry from becoming a stream. Or it may simply mark the natural evolution of the structure of campus biological research, a general response to changing environmental conditions.

“Industry and academia are different,” says Goodman, “but they’re still evolving. And the lines between them are getting more blurred. At Berkeley, we used to talk about how having the individual lab completely self-contained might not be the best model any more and how we needed to take a lesson from the private sector. The way things are often done in industry—core facilities with accessibility to different kinds of teams, and multidisciplinary approaches—was something that one needed to think about in the future design of academic laboratories. Look, for example, at what HHMI is doing with its new campus.” (See “HHMI Unveils Long-Range, \$500 Million Plan for Collaborative Research Campus,” [www.hhmi.org/news/020101.html](http://www.hhmi.org/news/020101.html), or “Janelia Farm,” *HHMI Bulletin*, July 2001, p. 10.)

The blurring of the lines between academia and industry also reflects another new reality: The stigma once faced by biologists who took industrial positions seems to be disappearing, making it easier for them to consider taking the plunge. “There is still clearly a bias against scientists going into industry, but the acceptance is greater compared with 10 or 20 years ago,” Chan says.

Kim agrees. “When I was in graduate school in the early ’80s,” Kim recalls, “you were not considered a success if you went into industry. Today we’re finding that many of the really good students and postdocs are in fact attracted to, and being attracted by, opportunities in industry. There’s also a shift in that you are seeing premier academic scientists moving into industry, and I think in many cases, it’s driven by a desire to direct their science at solving unmet medical needs.”

These are people who perceive new challenges as exciting rather than daunting and who want their work to improve the human condition. Where and how they do that work may ultimately be far less important than the fact that they do it. **E**

“If my work led to the development of a real drug or a real vaccine, I would view that as one of my major accomplishments in life.”

—Peter S. Kim



“I felt... that my energy could be devoted to translating discoveries into therapeutics, that it would be a really worthwhile effort.”

—Joan S. Brugge, on move to industry in 1992



“I have become much more involved in translational efforts than I ever was before.”

—Joan S. Brugge, after her return to academia in 1997



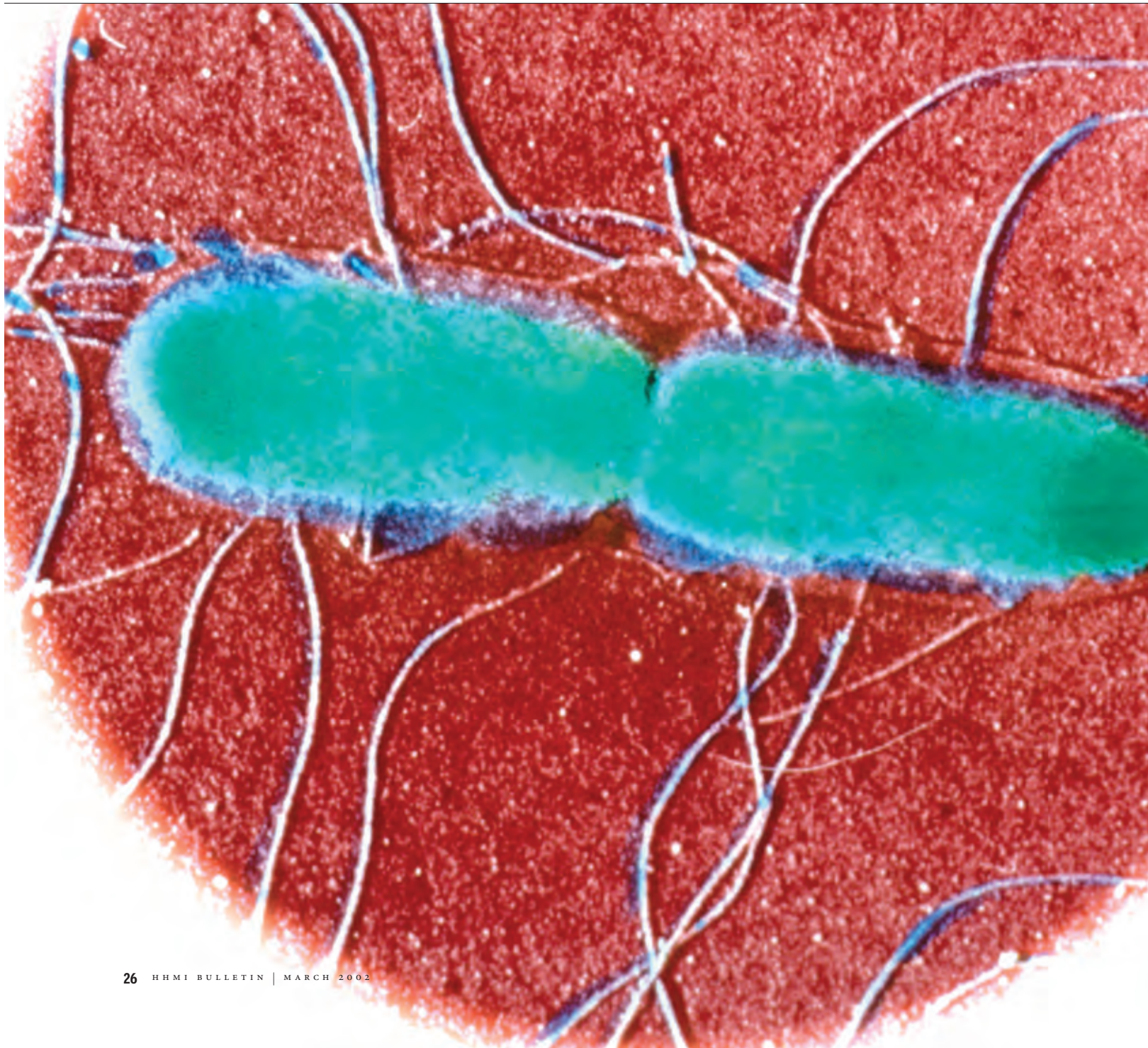
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# MICROBES VS. HUMANS:

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AS MICROBES LEARN TO AVOID OUR DEFENSES, SCIENTISTS TRY NEW TACTICS TO DEFEAT THEM. | BY STEVE OLSON

# WHO'S WINNING?

A standard character in science fiction is the foe that continually changes shape, so that a protagonist's victories are always temporary. To biomedical researchers studying human pathogens, this scenario is depressingly familiar.

"Bacteria are constantly changing," says B. Brett Finlay, an HHMI international research scholar at the University of British Columbia, who studies pathogenic strains of the common intestinal microbes *Escherichia coli* and *Salmonella*. "And when they find something that works, they hang onto it—at least until their enemies develop new weapons and the bacteria need to change again."

The ability of pathogens to adapt to changing environments has made them a tenacious opponent. Worldwide, infectious diseases remain the single greatest cause of death, killing more than one third of all human beings. Even in the developed world, newly emergent diseases, growing antibiotic resistance and the ever-present threat of bioterrorism haunt populations that have otherwise come to expect good health.

Along with a new recognition of the power of microbial adaptation, however, has come a great optimism among researchers. "By understanding how microorganisms such as the tuberculosis bacteria have evolved ways to persist," says William R. Jacobs, an HHMI investigator at the Albert Einstein College of Medicine, "we should be able to develop new therapies against them."

## A DANGEROUS VERSATILITY

Infectious diseases have not always been treated with the respect they deserve. In the 1960s, new antibiotics and vaccines seemed about "to close the book on infectious disease," as U.S. Surgeon General William Stewart famously predicted. His confidence was woefully misplaced. The sudden appearance of AIDS and Legionnaire's disease in the final three decades of the 20th century served dramatic notice that the age of infectious diseases was far from over.

Meanwhile, research advances revealed the ability of pathogens to live in a wide range of environments. Think about a *Salmonella enterica* bacterium that has just traveled on an undercooked

piece of chicken into someone's stomach. First it must survive the stomach's extreme acidity. Then it must endure the low oxygen levels and digestive juices of the intestines. Next it must penetrate the wall of a cell in the intestine and keep itself from being dissolved by the cell's lysosomes, which are constantly on the lookout for bacterial invaders. Finally, it must exude its progeny from the cell so that they can infect new hosts.

Any organism with such a complex life cycle must be quite a sophisticated survivor. "Microbes can't anticipate," says Eduardo A. Groisman, an HHMI investigator at the Washington University School of Medicine. "They react to the environment. Those like *Salmonella* that live in multiple environments have the means to gather information about changes in their environment and use this information to activate or repress certain subsets of genes at the right time."

Microbes that spend their lives in less varied environments do not require such elaborate genetic controls, Groisman points out. "If you're just eating soup, you only need a spoon—not a knife and a fork." Many of these organisms have shed parts of their genomes over

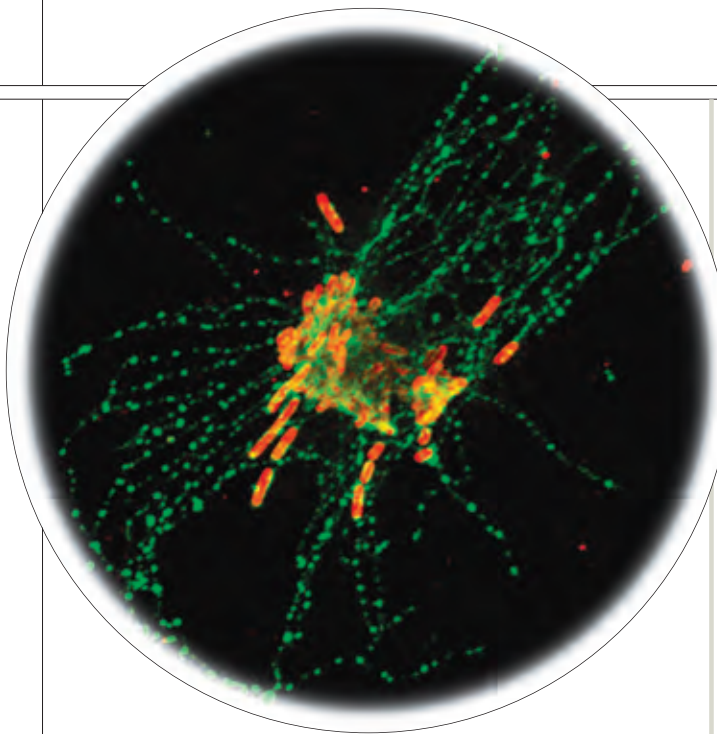
**ESCHERICHIA COLI BACTERIA** are generally harmless, but can become dangerous by acquiring new bits of DNA from other organisms.



**SALMONELLA BACTERIA** (left), a common cause of food poisoning, move through the intestines using long, thin flagellae.

© CNRI/PHOTOTAKE

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**How Salmonella Hijack a Cell** When a *Salmonella enterica* bacterium (orange) enters a human cell, it squirrels a protein called PipB (green) that forces the cell to do what's best for the bacterium. This protein is encoded within one of at least five pathogenicity islands that have been identified in the DNA of *Salmonella*. As shown in Brett Finlay's lab, the bacterium's virulence depends on "cross-talk" between genes encoded within three of these islands.

time and rely on their hosts for essential metabolites, while organisms that live in more complex environments have larger genomes and a greater percentage of their genomes is devoted to regulatory functions. "This trend toward more complex regulation goes hand in hand with versatility," says Groisman.

Many pathogens also have evolved an ability to manipulate their hosts to maintain a favorable environment. HHMI investigator Ralph R. Isberg and his colleagues at the Tufts University School of Medicine have been studying how the bacterium *Legionella pneumophila*, which causes Legionnaire's disease pneumonia, avoids the normal defense mechanisms in the lung. They've found that the bacterium produces a set of proteins that allow it to live within human macrophages and not be exposed to the antimicrobial agents with which macrophages normally kill bacteria.

*L. pneumophila*'s ability to survive in different environments has contributed greatly to its pathogenicity, Isberg says. Until humans began constructing machines that harbored dark, warm reservoirs of water, the microbe was probably a harmless freshwater dweller. The man-made reservoirs gave the bacteria a new place in which to grow, and when water from these reservoirs was sprayed into the air, the microbe found its way into human lungs. "Now most sources of infection are from aerosols from plumbing systems that are inadequately cleaned or air-conditioning systems that aren't working properly," says Isberg.

### BEWARE OF THE BACTERIAL INTERNET

Microbes have a critical asset, a genetic flexibility unknown in multicellular organisms, that they can use in colonizing new environments. Because bacteria multiply very quickly—once every 20 minutes for the

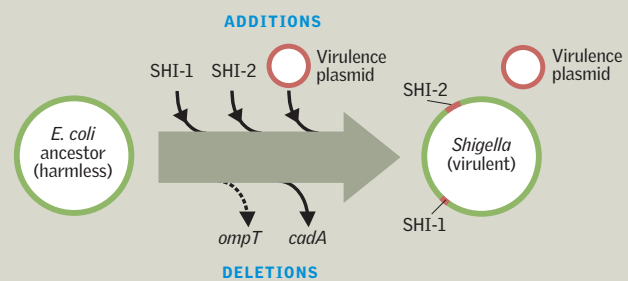
common laboratory microbe *E. coli* in optimal conditions, compared to once every 20 or so years for humans—they must repeatedly copy their DNA. Mistakes in the copying process introduce genetic changes that can alter the structure or expression of bacterial proteins. As a consequence, the microbes are continually spinning off new genetic variants that have multiple copies of genes, genetic deletions or altered patterns of gene expression.

These variants then are exposed to an especially stringent form of natural selection. If a particular variant is disadvantaged in competition with others, it will die and that genetic lineage will eventually be lost; but if the variant has an advantage in that environment, it quickly begins to make copies of itself. Furthermore, when a microbe reproduces, it does not have to dilute its genes with those of a partner, as do organisms that reproduce sexually. It can keep making copies of itself until an environmental niche is filled, at which point it can begin looking for new niches.

Many microbes combine the ability to generate new microbial mutants with another key asset: They can acquire DNA directly from other organisms. Sometimes this DNA travels in viruses or across cytoplasmic bridges between bacteria. In other cases, a bacterium simply laps up DNA that lies exposed in the environment, whether from a decomposing microbe or even from a plant or animal cell. This "horizontally acquired" DNA can range in size from short snippets of genetic material to what are called pathogenicity islands—long stretches of DNA containing many genes that encode potent virulence factors. "Bacteria have their own Internet," says the University of British Columbia's Finlay. "They can download each other's genetic sequences."

These downloads can have dire consequences. In 1982 an outbreak of severe bloody diarrhea sometimes accompanied by kidney failure was traced to undercooked hamburger from a particular fast-food outlet, and examination of meat samples revealed the culprit: a new and highly virulent form of *E. coli* dubbed O157:H7. The new strain differed from the laboratory strain of *E. coli* in two main ways. "One was that it had a classic pathogenicity island," explains Finlay. "The other change was the acquisition of a stretch of DNA that codes for a Shiga toxin, found in *Shigella dysenteriae*. The Shiga toxin kills cells that then plug up the kidneys, so the victim gets kidney hemolytic uremic syndrome. This was a bacterium that had put two preexisting virulence

**From Harmless to Virulent** A benign *E. coli* bacterium becomes a virulent *Shigella* by adding some genes and deleting others. Two of the added genes, *SHI-1* and *SHI-2*, become part of the new microbe's chromosome. *Shigella* also makes good use of an acquired virulence plasmid (an independent, self-replicating ring of DNA that can be transferred from one cell to another). At the same time it gets rid of two genes that normally make *E. coli* harmless, *ompT* and *cadA*.



BRETT FINLAY AND LEIGH KNODLER

factors together to yield a new pathogen.”

Finlay has been studying how O157 subverts the normal functions of human cells to its own ends. It uses a “type III secretion system” to inject proteins, including its own receptor, into the epithelial cells of the intestine. As the bacterial proteins hijack the human cell, they cause it to erect pedestals on which the pathogenic microbes sit, spewing toxins. Surprisingly, these type III secretion systems are common not only in human pathogens but in animal and even plant pathogens, suggesting that they have been passed from microbe to microbe through horizontal gene transfer.

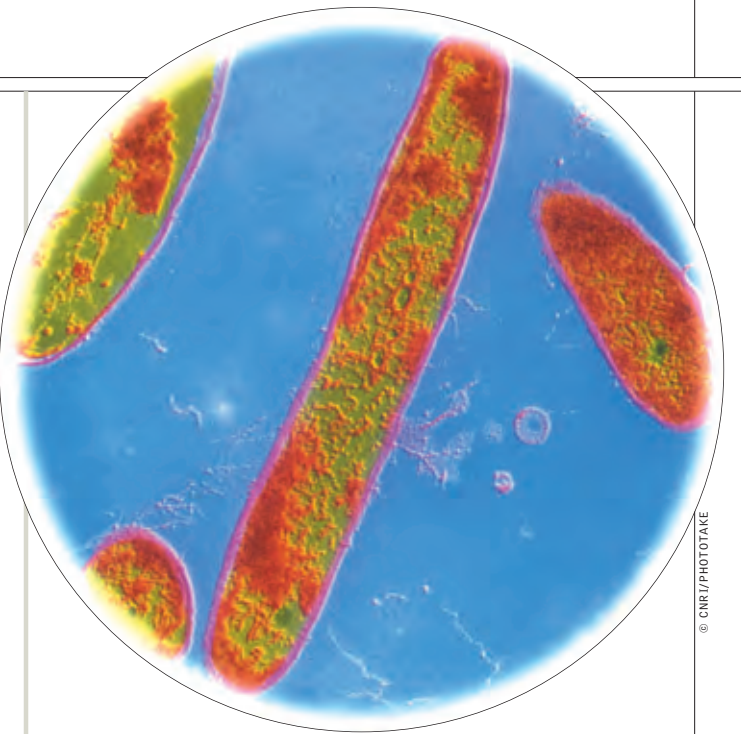
Horizontal transfers of DNA were recognized decades ago, in part because antibiotic resistance was spreading among microbial strains far too quickly for that resistance to be evolving *de novo* each time. But only in the past few years have microbiologists come to recognize the extent to which horizontal gene transfer has shaped the microbial world. “We used to think that evolution was a slow, constant process—you’d change a base at a time and one protein would slowly segue into another,” says Finlay. “What really turned the tide was the recognition of pathogenicity islands, these huge chunks of DNA with virulence factors lined up side by side. Slow evolution is still occurring as these systems are tried and improved in various places before being transferred around. But the recognition of large-scale chromosomal changes gave us a new view of how evolution works.”

Researchers are now in a position to gauge the degree of horizontal gene transfer through the use of a powerful new tool: the ability to sequence the complete genomes of microbes. They have found such transfers to be surprisingly extensive. For example, Pascale Cossart, an HHMI international research scholar at the Pasteur Institute in Paris, has devoted her career to studying *Listeria monocytogenes*, a foodborne pathogen that causes hundreds of deaths and miscarriages in the United States each year. Recently, she and her colleagues compared the complete genome of *L. monocytogenes* with that of the related strain *L. innocua*, a harmless microbe also found in food and the environment. The pathogenic form of the microbe, they discovered, has 270 genes that the nonpathogenic form does not, clustered in 100 islands scattered across the genome. The nonpathogenic *L. innocua*, in contrast, has 149 genes that are not shared with its pathogenic cousin. “Multiple episodes of gene acquisition and deletion” must have occurred to produce this genetic collage, Cossart concludes.

Complete genome sequences also are revealing the much deeper evolutionary relationships among microbes. For example, Washington University’s Groisman and researchers Howard Ochman of the University of Arizona and Jeffrey Lawrence of the University of Pittsburgh have been studying the evolutionary process by which various microbes have descended from a common ancestor. “People have been saying that we can’t trust phylogenies because of lateral gene transfer,” Groisman says, “but I don’t think that’s the case. If you look at conserved genes, you can still derive phylogenies that are pretty accurate.”

These evolutionary relationships are of more than academic interest, researchers say. Uncovering the historical links among pathogens is likely to produce many new ways to diagnose, treat and prevent infectious diseases.

At the Albert Einstein College of Medicine, for example, Jacobs has been seeking to exploit the evolutionary history of *Mycobacterium tuberculosis*, the respiratory pathogen responsible for more deaths worldwide than any other microbe. “The amazing thing about tuber-



© CNR/PHOTOTAKE

**LEGIONELLA BACTERIA** cause Legionnaire's disease pneumonia through aerosols from plumbing or air-conditioning systems.

culosis is that it has evolved the ability not only to grow in the lungs but to hang out once it encounters an immune response,” Jacobs says. “If you’re a pathogen, you don’t want to be wiping out all the humans in the world, because there goes your host. A more effective strategy is to go in, dance with the immune system and stay for a lifetime.

“I had an uncle, 84 years old, who died last week of TB. He probably had been infected for 50 years. Then he got a lymphoma that wiped out his immune system and, boom, his tuberculosis was reactivated. Once the immune system starts to go, the pathogen knows that it has to find somewhere else to hang out. So it causes an overt infection that leads to coughing, and someone nearby is infected.”

The tricks that microbes use to infect hosts and exert their effects often suggest new treatments, Jacobs says. For example, he and his colleagues have developed a mutant strain of *M. tuberculosis* that lacks the ability to construct the elaborate surface molecules the pathogen uses to confuse the human immune system. “By understanding how TB keeps itself from being killed by an immune response, we should be able to design novel interventions—vaccines or therapies—that will be able to eliminate TB.”

Furthermore, the therapeutic approaches developed through such research may be widely applicable. Because many pathogens have shared their genetic secrets through horizontal gene transfer, new treatments may work for multiple pathogens. For example, Finlay has been examining the type III secretion system as a possible target for controlling many different kinds of infectious agents. “Ten years ago this field was in chaos because we thought that different bacteria did things completely differently,” he says. “Now we’ve come to realize that pathogens often use common processes.”

Still, no one expects that we’ll win the war against infectious diseases anytime soon, if ever. Evolution will continue to produce new genetic variants—and surprises. “We’ll never get rid of infectious diseases,” says Finlay. “There will always be new ones.” **H**

# Choices in

# G R A Y

**Science** is not a morally neutral endeavor,  
and undergraduates are learning that ethical decisions  
are rarely a matter of black and white.

BY  
FRAN SMITH

Illustrations by Brad Yeo

Peggy wants to use a few genetically engineered mice developed by her colleague Jim, but this won't be so simple to arrange. She refuses to sign an agreement required by a drug company, Jim's sponsor, on the grounds it would restrict her use of the resulting data. Jim knows that Peggy needs the mice to complete her protocol. He appeals to a company executive, who will not bend.

Last summer, 39 undergraduates and their faculty mentors at Santa Clara University watched a videotape of these fictitious scientists' dilemma, then debated what Jim should do. Just say no? That might jeopardize a valued colleague's research, as well as their relationship. Should he leave Peggy alone with the mice, giving her a chance to "borrow" them? That might not be ethical, or even legal.

The discussion was part of the university's Ethics in Science program. Supported by an HHMI grant, it reflects a nationwide trend to incorporate such issues into curricula. At Santa Clara, a Jesuit school in Silicon Valley, all undergraduates are required to take an ethics course. Thus, students receive more than just hard-core training in their fields; they learn some of the rules of professional conduct and start developing the ability to make ethical decisions.

The summer ethics class encourages students—and faculty—to think beyond public controversies such as stem cell research and consider the day-to-day dilemmas that scientists face. "Ethics isn't always those big-headline issues," says Margaret R. McLean, director of biotechnol-





ogy and healthcare ethics at the university's Markkula Center for Applied Ethics. "Most of the time, it's the little decisions we make every day."

One afternoon a week, the undergraduates gather with their mentors to role-play and debate ethical choices that range from the profound to the mundane. For example, Should I sign a restrictive agreement, as Jim did? What should I do if I discover that a colleague fudged data? If I overslept Saturday morning and didn't feed the rats until noon, must I record the delay? Why bother, if it won't affect my data? (Then again, maybe it will.)

Making ethical decisions requires sensitivity, judgment and the ability to identify the stakeholders as well as the benefits, costs and consequences of any action. Moral imagination helps, as does compassion.

Perhaps compassion cannot be taught, but bioethicists believe that judgment can. Besides, learning to recognize and think about ethical questions may be as important as coming to consensus on answers. Leading scientific organizations, such as the National Institutes of Health, have recommended broad instruction in proper research conduct.

Traditionally, formal education about the ethics of science did not begin until graduate school—if then. A growing number of educators, however, believe it needs to start earlier, before students develop deep-rooted research styles and standards. "College is where many young people abandon earlier habits, ways of thinking and aspirations, and acquire new ones. So it is an especially fertile environment for teaching ethics," says Elizabeth Kiss, director of the Kenan Institute for Ethics at Duke

University. As part of the liberal arts curriculum, Duke requires every undergraduate to complete two courses in ethical inquiry.

This can be a real challenge, teachers report. Students—especially science majors—often feel uncomfortable discussing deeply felt values and analyzing motivations and consequences. "We're not talking about memorizing a chemical cascade," Santa Clara's McLean observes, "we're talking about the kind of person you are."

Another barrier is that undergraduates often assume science is a morally neutral endeavor, says Jeremy Sugarman, a professor of medicine and philosophy at Duke. "They need to see that science is not value-free. There are norms and standards that need to be learned."

In Sugarman's course on ethics in the process and application of science, students are paired with mentors from the medical center's Institutional Review Board. Each pair reviews protocols actually under consideration by the board and attends a board meeting together. Then students write papers about what it is like to judge another scientist's protocol and how the board's deliberations compare with the ideal standards and procedures discussed in class.

The students also examine real cases with chairs of the Committee on Institutional Animal Care and Use and the group that investigates allegations of research misconduct. They also spend time in labs, teasing out some of the ethical questions that arise in the course of doing research. Visiting the lab of an Alzheimer's disease researcher,

## Theologians Meet Genetics

How do people wrestle with the novel bioethical issues raised by modern genetics? Many turn to their clergy for advice, but find them too uninformed to help. In a new course called *God, Adam and Eve: Theology and Science in the Genome Age*, theology students in Chicago are exploring the interface of science and religion in order to better address their future congregations' concerns.

The class at Chicago Theological Seminary on the city's South Side is taught by faculty members from both the seminary and neighboring University of Chicago; the collaboration is supported in part by a grant from HHMI. Because the seminary's students include Protestants from various denominations as well as Catholics and Jews, and because they are preparing for a variety of professions—some are ministers or plan to be; others work in helping professions such as social work, and the Ph.D. graduates often become community and denominational leaders—the course is nonsectarian and could have far-reaching effects. The class will publish a Web-based bioethics course for public use.

The syllabus includes some controversial topics: "gay genes," genetics and violence, and genetic determinism and human freedom. Sessions on key concepts in classical genetics and modern issues in genetic research, such as genetic similarities and differences among races, or genetic testing for diseases that can't be treated effectively, provoked lively discussion among the first class's 19 students, most of whom are working toward advanced degrees.



The students are not the only participants to profit from the course. "This class has been a learning process for me too," says Lainie Ross, associate professor of pediatrics at the university and one of the instructors. "The premises of some religions are entirely different from mine, and ethical choices flow from these premises. These premises also help define one's world view." Or as Laurel C. Schneider, associate professor of theology, ethics and culture at the seminary and another course instructor, puts it: "Religion is a lens for viewing the world; science is another lens. The lens you are using helps determine the choices you make."

The University of Chicago already teaches bioethics to life sciences majors (both undergraduate and graduate) and medical students, but that's just scratching the surface as far as the life sciences faculty is concerned. "We wanted to have a broader impact," explains José Quintán, professor of pathology and director of HHMI programs at the university. "This course is taking the mystery out of science for nonscientists." He wants to develop a similar course for journalism students to help them better communicate bioethical issues to their future audiences.

Susan B. Thistlethwaite, president of the seminary and one of the bioethics course teachers, is as enthusiastic about the experiment as Quintán. "It's important to break down the literal and figurative walls between science and religion," she says. "We have things to teach each other."

—JENNIFER BOETH DONOVAN

» For more information, see [www.CTSSchicago.edu](http://www.CTSSchicago.edu) and [bscd.bsd.uchicago.edu/GenTheo/index.html](http://bscd.bsd.uchicago.edu/GenTheo/index.html)

for example, they discovered how deeply the work was influenced by considerations of informed consent. “It’s one thing to read a textbook that spells out the ethical issues,” Sugarman says. “It’s much harder to recognize those questions when they come up as science is actually happening.”

Arizona State University and the University of Arizona cohost an annual three-day retreat for science majors, supported by HHMI. The theme is lofty—what makes science ethical?—but the discussions are down-to-earth. In a session on medical ethics, for instance, the students consider the inequitable distribution of organs and end-of-life care. In a genetics workshop, they talk about “designer children.”

The closer a problem comes to their own lives, the more excited and engaged the students become, says James Collins, chairman of biology at Arizona State and co-organizer of the retreat. One of the most popular workshops explores questions of laboratory ethics: Who owns the lab notebook? What constitutes plagiarism? What’s the relationship between the lab head and postdocs, between postdocs and graduate students, between all of them and undergraduates? “Those questions are real to students,” Collins says. “That’s when we really begin to see light bulbs go on.”

Students respond well to playing the role of ethical decision maker by applying what they’ve learned in their ethics courses. At the start of Santa Clara’s Ethics in Science seminar, Amy Shachter, associate dean of the College of Arts and Sciences, conducts an ethics “inventory” in which students write a short response to several scenarios. For example, “You are a journal editor who learns that a reviewer is disregarding confidentiality guidelines. What do you do?” Shachter scores the essays on sensitivity (how well the student goes beyond facts to express values and weigh benefits and costs to others), judgment (whether the student expresses moral principles and reasoned justifications beyond mere opinion) and commitment (the student’s willingness to take action after determining the possible consequences).

At summer’s end, Shachter repeats the test. In 1999—the most recent year for which data were analyzed—sensitivity scores started high and remained fairly constant: 75 percent in June, 78 percent in August. Judgment improved dramatically, however—from 44 percent to 78 percent—and commitment also increased measurably, from 67 percent to 78 percent.

“Students and even faculty grow in their ability to say, ‘This is wrong and ought not to be done,’” says McLean. This growth is not linear, however, for there is a paradox in ethics education: The more one learns about the relationships among the players, the range of possible actions and the far-reaching consequences, the more difficult it becomes to make a decision. “Many ethical issues appear at first to be black and white,” Shachter says, “but when you understand more, everything turns out to be gray.”

To guide students through this murkiness, Shachter uses a simplified version of the Ethical Decision-Making Framework, a step-by-step approach to analyzing ethical problems that was designed by the university’s Markkula Ethics Center. The tool first helps the user to define the ethical issue at hand; then to identify stakeholders, describe relationships, list possible actions and predict consequences; and, finally, to find ways to resolve problems resulting from the user’s chosen action.

At first, the students and their faculty mentors rely heavily on the framework to analyze ethical issues and come up with solutions. But by summer’s end, they do it without the framework, which vanishes like a map discarded once the journey becomes familiar.

## Bioethics Goes to High School

Ethics education is reshaping high school science. Just ask Carla Calogero, a 10th grade biology teacher at Nathan Hale High School in Seattle.

Calogero used to consider ethics a “tag-along to the curriculum” or “icing on the cake” to capture student attention. Now, ethical inquiry is a substantive part of her five-week unit on genetics.

The class begins by playing a version of the game *Scruples*. Calogero presents scenarios. For example, a close friend wants to crib your answers on a test. Students must respond to questions such as, Do I help my friend cheat? How do I decide? Who is affected? A heated but enlightening discussion often ensues as they debate their answers.

The teacher then segues into science ethics. Students do assigned exercises that help them make connections between scientific advances—genetic testing, for example—and the dilemmas facing researchers, doctors and families. Finally, teams of students produce “magazines” about topics such as pharmacology or forensics. Each magazine must cover both scientific details and ethical implications, and also present conflicting points of view. “It’s easy for students to catch on to the issues,” Calogero says, “and as they learn more about the science, the technology and the ethical problems, their understanding really increases.”

Calogero began to rethink her curriculum two summers ago, when she took a week-long workshop for teachers at the GENETICS Project, a University of Washington School of Medicine program supported by an HHMI grant. Workshop leaders encouraged the teachers to include bioethics instruction in their classrooms.

Some teachers found this “preposterous,” Calogero recalls. “A few objected that bioethics is values-based instruction that has nothing to do with science.” Most, however, had already begun discussing ethics informally in class—usually because students brought it up. “I was shooting in the dark, letting the kids take sides and argue,” says Paul Ladniak, a biology teacher at Seattle’s Chief Sealth High School.

In the workshop, teachers learned a more systematic approach. “They gave us a framework,” says Ladniak. “You look at the scientific facts; you identify the stakeholders and their values; you discuss possible outcomes; you keep the discussion narrowly focused.” Ladniak thinks that such structured ethics lessons will be more comfortable for him and more valuable to his students than free-wheeling debates. —FS

» For more: [chroma.mbt.washington.edu/outreach/genetics/index.html](http://chroma.mbt.washington.edu/outreach/genetics/index.html)

Ethics in Science began in 1996 with chemistry faculty and students. Last year, Shachter and McLean added HHMI-supported biology students and their mentors, which produced a few surprises.

Chemists and biologists look at issues very differently, McLean discovered. Remember the conflict between Jim and Peggy over the genetically engineered mice? In past summers, the chemists agonized over finding a satisfactory solution: Giving her the mice seemed wrong, but refusing didn’t seem right either. The biologists, however, came up with an answer immediately.

“The biologists said, ‘All he has to do is sacrifice the mouse and give her the organs. That’s all she really needed in this case,’” McLean recalls. This solution, of course, raised other ethical questions for the class to ponder. **H**

# Lesson from September 11

*We urgently need a truly functional public health system.*

BY BARRY R. BLOOM

As the recent anthrax attacks have made clear, this country is woefully unprepared to deal with bioterrorism. We need—but do not presently have—a fully functional public health system that can bring together expertise from a wide range of disciplines—epidemiology, biostatistics, molecular genetics, economics and social sciences—to anticipate risks to health and then translate that knowledge into effective preparation and response.

It is only since September 11 that the American public and Congress seem ready to seriously contemplate long-term investments of this sort. To deal with bioterrorism, in contrast to nuclear threats, what is most needed is not hardware but “software”—people, training and communications.

Consider the case of a deadly biological agent that we can predict with assurance will kill 20,000 Americans in the next year—despite the fact that we have a very good vaccine. (By contrast, anthrax has thus far caused disease in 22 people, of whom 5 have died.) This agent is the influenza virus, an interesting example because it represents one of the great successes in public health, as well as one of the great failures.

The world—or at least the industrialized world—has decided it wants to be prepared and not have a deadly epidemic each year. Flu epidemics, after all, have the potential to become giant pandemics, such as the one that killed more than 20 million people worldwide in 1918. An extraordinary network for global collaboration has been created to prevent such a disaster: More than a hundred World Health Organization influenza centers around the world look at the spread of new flu strains in Asia and report them to a group of scientific experts who, with the help of historical experience and epidemiological modeling, make a best guess as to what the three major strains will be each year. The vaccine companies immediately go into action. With remarkable speed and efficiency, they produce the vaccines, obtain regulatory approval, and distribute the new products each year in time to protect against the anticipated strains. By the time the flu arrives at our shores, we are prepared with vaccines to immunize the people at greatest risk of severe or fatal illness.

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BARRY R. BLOOM is Dean of the Harvard School of Public Health. Until 1998, he was an HHMI investigator and chairman of the department of microbiology and immunology at the Albert Einstein College of Medicine.



LISA BLALOCK

That's public health prevention of infectious disease at a very sophisticated level. Yet because we lack a fully effective public health *system* and are unwilling to spend the resources required to have one, those vaccines do not reach all the people who are most at risk. Last year, an ordinary year, 20,000 Americans needlessly died of influenza.

Why is it that we don't have a public health system that can deal effectively with 22 cases of an emergent infection, or save the lives of 20,000 people for whom we have an appropriate vaccine? The simple answer is that the basis of our health system is to treat disease after it occurs, rather than to prevent it. Despite the fact that for most illnesses, prevention is far less expensive in both human and monetary terms than treating people who are already sick, we tend not to respond until a disaster or crisis has occurred.

We have many of the key elements of a public health system, but they are underfunded and not really integrated to make a system. The Centers for Disease Control and Prevention is a unique institution, and its scientists and epidemiologists were exemplary in tracking down all of the suspected cases of anthrax, despite being deluged by almost 10,000 telephone calls that they had to respond to and hundreds of samples that were spurious but had to be tested. The scientific staff of the U.S. Army Medical Research Institute of Infectious Diseases at Fort Detrick, our major institution for defense against germ warfare, has vast experience and is extraordinarily professional but underappreciated. The state and municipal health departments have some heroically dedicated and effective people, but most often have inadequate personnel, facilities, communications technology and training. In sum, the public health system lacks the support to be a functional and integrated system that can respond to bioterrorism or to virtually any other major health threat to populations.

An obvious example is the issue of surge capacity. Suppose that instead of 22 patients with anthrax, 200,000 people had been exposed to anthrax at a stadium or in a subway system or, as in a recently modeled terrorist attack, that they were exposed to a few people infected with smallpox. Our health care system has prided itself on reducing the number of beds and cutting everything it can to the barest bones in order to hold down costs. As a result, we have almost no surge capacity. We would have to throw patients out of hospital beds in a crisis caused by a highly contagious agent such as smallpox. We would have to quarantine hospitals, doctors and staff

and even whole cities. Obviously, we haven't begun to think through, much less prepare for, health crises of that magnitude.

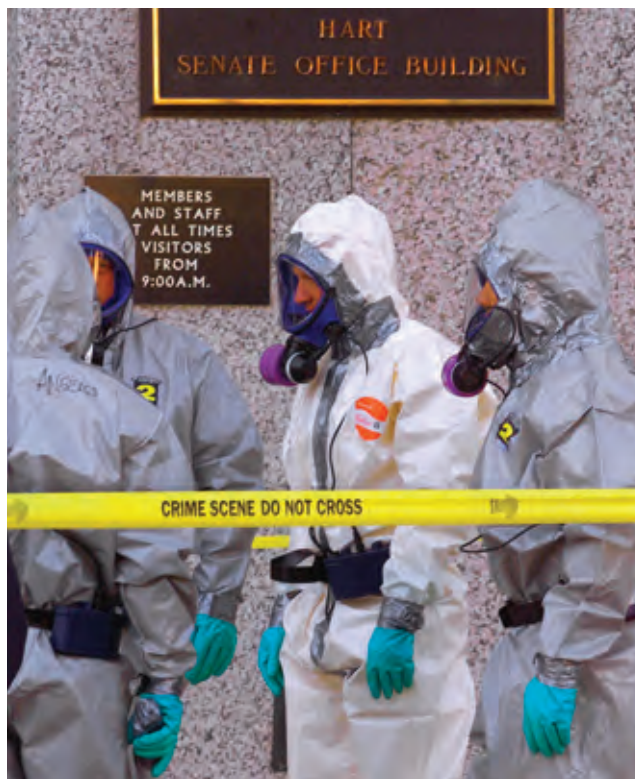
At the technical level, we don't have enough qualified laboratories capable of handling 10,000 biohazard samples, let alone 200,000 samples. And multiply that number by 100 for the frivolous samples that would inevitably be proffered in any kind of terrorist attack—the aim of such an attack, after all, is at least as much to terrorize as it is to kill people.

Beyond the problem of surge capacity, the country lacks critical coordination and communication functions—not just between politicians and the press but between the research, medical and public health communities and the people on the front lines, that is, primary-care doctors (particularly in emergency rooms), police, fire fighters, school nurses, pharmacists and postal workers.

In addition, we need early-warning systems—local, and perhaps regional and national—that would check the number of cases of fever, rash, hemorrhage or spots on a daily basis and be able to notice any sudden increases. Such a surveillance of symptoms would provide the very first tip-off that something unusual or dreadful is happening. Although this type of system is already in place in three or four cities in the United States, it needs to be more sophisticated and to be implemented in all major cities (or in all States).

Besides early warning, county and local public health and law-enforcement agencies need an effective rapid-response capability. Yet about 20 percent of county health departments are not able to send e-mail, 50 percent can't send faxes to multiple recipients to announce an emergency and many are technologically unable to use the Internet!

My strong hope is that the September 11 and anthrax attacks have awakened the country and prompted our leaders to invest in improving the public health system now—not only to prepare for biological terrorism and warfare, but also, on a more routine basis,



*Hazardous materials workers prepare to enter the U.S. Senate building.*

PAUL J. RICHARDS/AFP PHOTO

TO DEAL WITH BIOTERRORISM, IN CONTRAST  
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more virulent or better able to evade immune responses.

We urgently need to invest in new technologies that can detect and identify infections much more rapidly than growing bacteria in culture allows. Growing bacteria usually takes days or weeks—and sometimes is not even possible. The genomes will provide tools for early diagnosis. Individual bugs have individual DNA sequences, and DNA chips could be developed to identify each pathogen's “signature.” Also, each pathogen induces unique changes in infected hosts. Potentially, one might be able to deduce within just a few hours after testing a drop of blood with a DNA chip whether an individual is infected and, if so, by which infectious agent.

To do all this, our country needs to engage the scientific community at all levels. We must ensure that government leaders have access to scientists' most creative and effective approaches to dealing with, as well as preventing, biological terrorism. **H**

to prevent infectious diseases and to improve the health of everyone. The same networks, surge capacity, education, training, analytical skills and communications are needed to fight emergent infections (whether from biological weapons or naturally arising, such as drug-resistant tuberculosis, which could come from Eastern Europe, or an HIV-like infection that jumps species and infects humans) or any kind of disaster.

At the same time, we need specialized help from biomedical scientists in preparing to deal with new kinds of pathogens. The genomes of all the major existing pathogens are now on the Web, or soon will be. The DNA sequence of the plague bacillus, for instance, was published just a few months ago, and anthrax is now done. Moreover, the genes for resistance to all the major antibiotics are known. Unfortunately, we can be sure that this information has been—or will be—applied to perverse and inhumane purposes to create new and highly lethal infections. The genie of recombinant DNA technology is out of the bottle; it can be misused for inserting genes from one pathogen into another to render the pathogen

## Sailing to Victory in the Lab and on the Sea

**M**ark Bear believes that scientists and sailboat racers have a few things in common. Both are driven by the desire to reach the goal first. Both experiment, change course in response to results and pick up subtle cues that guide them in the right direction. The best scientists, he says, like the best sailors, can “see things others don’t see” in a given situation.

Bear should know. Not only is he Brown University’s—and Rhode Island’s—first HHMI investigator, he’s also a competitive sailor who won the New England Laser championship in 2001.

As a neuroscientist, Bear seeks to understand how the developing brains of young animals are shaped by sensory experiences. The biological processes he and his colleagues study are thought to be at work during early development and throughout life, forming the underpinnings of learning and memory. “The big question we’re interested in,” he says, “is how experience modifies the brain.”

Increasing the strength of synapses (the connections between nerve cells) is widely believed to be a memory mechanism. Scientists call this process long-term potentiation, or LTP. A significant contribution of Bear’s laboratory was to characterize the opposite process, long-term depression (LTD), which researchers had largely ignored. Many scientists were skeptical of its significance in the cerebral cortex, the seat of the brain’s most complex functions, and some doubted LTD’s existence altogether. But it made sense that LTD would also be used in memory, he says, because “if memories are stored in a pattern of synaptic change, a *decrease* in synaptic strength as a result of experience has as much information as an increase.”

The phenomenon of LTD was established first in living slices of the cerebral cortex. To find evidence that the same mechanisms are at work in vivo, Bear’s group

followed up on some famous experiments by David Hubel and Torsten Wiesel, who shared the Nobel Prize in Physiology or Medicine in 1981 for their work on visual processing.

Hubel and Wiesel temporarily closed one eye in young animals and discovered that when the eye was reopened, some neurons in the animals’ visual cortex had stopped responding to stimulation. The temporary lack of visual experience had evidently modified their synapses so powerfully that it caused a form of blindness.

Bear’s group decided to investigate whether LTD had contributed to this process. They temporarily deprived young animals of sight in one eye in two different

ways: either by anesthetizing the retina or by closing the eyelid and allowing the retinal cells to continue firing nerve impulses randomly, which occurs any time an eye is closed. A few days later, after the anesthesia wore off and the closed eyes were reopened, the scientists showed visual patterns to each eye and measured brain activity with the help of electrodes.

They found that in animals whose eye had simply been closed temporarily, preserving spontaneous activity, nerve cells in the brain responded more strongly to input from the open than from the closed eye. The synapses had weakened while the eye was visually deprived. In animals whose retina had been anesthetized, however, the brain responded about equally to stimuli from both eyes. The experiment had not altered their synapses. These findings suggest that synaptic strength declines not through inactivity, as once believed, but



Sailing “gives you the opportunity to reboot your brain,” says neuroscientist Mark Bear.

through the active process of LTD.

Studies of this sort can be carried out effectively only in young animals whose nervous systems are still developing. Bear notes, however, that his research and that of many other neuroscientists around the world are revealing that the processes of LTP and LTD are used to shape the brain's functioning throughout life. "Many aspects of development are reused in the adult, usually in a more subtle form, to underlie information storage," he says. "Over the years, we've become more and more convinced that the changes we're studying are relevant to adult synaptic processes underlying learning and memory."

The exhilaration and physical demands of competition on the water provide a crucial respite from laboratory work and life's other concerns, Bear says. He has been racing sailboats since he was a teenager in the Washington, D.C., area. As an undergraduate at landlocked Duke University, his sailing was limited to running a summer program in Cleveland. But his move to graduate school at Brown in 1979 brought him happily to coastal Rhode Island, a major sailing center.

Bear sails his 14-foot Laser year-round, and claims he most enjoys "frostbite sailing" in the winter months. "It's exciting because in the winter, all the superstar sailors—who in the summer are being paid to sail all sorts of different boats—show up in their dinghies," he says. "You get to sail against the top people."

The most significant milestone in Bear's racing career was turning 35, when he became eligible to compete in the masters division. Although the age divisions were created to allow middle-aged and older adults to compete separately from young people, Bear notes that in New England, aside from the occasional Olympic athlete, "the masters sailors are at the top of most of the regattas." Bear won a silver medal at the 1998 Nike World Masters Games in Portland, Oregon, and took third place in his age category at the 2001 Laser Masters North American Championships in San Francisco.

Sailing "gives you the opportunity to reboot your brain," he says. "When you're racing, you're not thinking about anything else—you have to be 100 percent focused on what you're doing." —TOM REYNOLDS

## The Mad Scientist Tells All

**W**hy is the sky blue? Why do frogs pee on you when you pick them up? How much wood could a woodchuck really chuck if a woodchuck could chuck wood?

Answers to these and more than 25,000 other questions can be found on the Mad Scientist Network Web site, just one of the science-education services that Washington University in St. Louis provides through its Young Scientist Program (YSP). Started in 1991 by a group of university-student volunteers and now supported by grants from HHMI and the Washington University School of Medicine Alumni Association, YSP takes science from the university's labs to the city's high school classrooms.

The program is designed to pique curiosity and foster science literacy. For example, when a team of university students gave a neuroscience lesson at Roosevelt High School in St. Louis, they brought a real human brain and spinal cord. "None of the students had seen anything like this before," says Vaughan Morrill, head of the science department at Roosevelt and a teacher for more than 29 years. "I heard 'ooohs' and 'aaahs' all around. Many students jockeyed for a closer look—others backed away—but they were all 100 percent engaged."

The university volunteers don't care whether the teens are attracted or repelled, as long as they're intrigued. "We hope that our hands-on lessons will encourage students to pursue careers in science," says Stephanie Strand, YSP director and a graduate student in microbiology. "But we also try to emphasize that science permeates every aspect of life, from politics to medicine, whether people are scientists or not."

YSP does more than bring science to the students: It also brings students to science. To follow up on their exposure to the teaching teams and the Mad Scientist Network, high school juniors can apply for the Summer Focus program, an eight-week science internship. The young interns work with

graduate-student mentors on real research projects and get to observe medical procedures in the school of medicine. "Last summer, the students were able to watch an actual neurosurgery while a physician explained what was going on," says Strand. "Only one became woozy."



The Mad Scientist's Web site answers a question about why we can recognize octaves easily, but not 3rds, 5ths or other chords.

YSP also works with teachers. It recently developed the Summer Research and Curriculum Enrichment program, similar to Summer Focus for students, in which teachers work with scientists in their labs and then develop new curricula based on what they learn.

"As a teacher, this was one of the most challenging—and rewarding—experiences that I've had," says Morrill, who participated last summer. "I had the chance to do proteomics research, at the cutting edge of medicine, and bring what I learned to my students." YSP even donated electrophoresis equipment so that he could teach his students how to identify various proteins.

In St. Louis and around the world, students, teachers and anyone else can surf the Mad Scientist Network Web site ([www.madsci.org](http://www.madsci.org)) and indulge their curiosity. By the way, in case you are wondering, the Network's answer to that perpetual woodchuck question is, about 700 pounds over its lifetime.

—TRENT STOCKTON

>> For more: [medicine.wustl.edu/~yvsp](http://medicine.wustl.edu/~yvsp)

## Science, Science Everywhere

**C**indy Lins' fourth-grade physical education class is standing in the schoolyard at Spark M. Matsunaga Elementary School in Germantown, Maryland, squinting into the sun. It is a clear, nearly cloudless morning.

The children are studying the position of the sun and how it moves across the sky. They are trying to determine whether the sun's position affects athletic performance. Each child tries to catch five pop flies while facing the sun and again while facing away from it. Then they do the same experiment while shooting foul shots with a basketball.

Recording their results in journals, the students agree that the sun's glare made it difficult for them to see. It was much easier to see with the sun behind them. They will do the experiment again in other seasons, graph their data and take digital photos of the sun to chart its daytime journey across the sky.

Is this a PE class or a science class?

Actually, it's both. Matsunaga students are participating in a new program designed by science educators in Montgomery County, Maryland, with support from HHMI. The school will integrate science into its entire curriculum—including classes that in the past contained virtually no science. The goal is to engage students in science by showing how it pervades their lives.

For example, in the study of the sun's position, Lins asks her fourth graders to imagine that they are trying out for an outdoor sports team. The tryouts run from 9 a.m. to 9 p.m., and each student can schedule his or her own tryout time. "When we finish, you will be able to pick the time that will give you the best opportunity to be successful," she says.

Almost all of Matsunaga's teachers are participating in the program. They took two weeks of training last summer with 27 scientists to broaden their knowledge of science and help them design inquiry-based experiments. The scientists "explained their research and how they do it, and how teachers and kids can think and act like scientists," says Sharon Kahl, a Montgomery County Public Schools science specialist for kindergarten through



PATRICE GILBERT

*Fourth graders Ida Yu and Sharon Sun classify cloud formations during their study of the sky.*

eighth grade. Many elementary school teachers are not sufficiently trained in science "in part because they have to focus on five different subjects in a day," Kahl observes.

"This [program] takes science, blends it into all academic areas and adds many more hands-on experiences," says Judy Brubaker, Matsunaga's principal. For example, students in reading teacher Sherry McQuillan's class read about bulbs and grow a bulb garden. Jennifer Chizik's first graders investigate whether a hamster has a favorite food; they build mazes with different foods at the ends and record the hamster's choices.

Brubaker says the program does not steal time from other subjects because science is incorporated into reading, language arts, math and other studies. The school gives teachers paid time to attend the training. They also receive \$400 to purchase supplies.

The county will evaluate the program's impact by looking at student scores on the Maryland School Performance Assessment Program tests, which use questions that combine reading, math and science to measure skills. "My guess is that our kids will do very well," says Brubaker.

—MARLENE CIMONS

## New Focus on Evaluation and Curriculum Design

**H**HMI's precollege science education program has awarded two \$50,000 minigrants for projects to improve science curricula and enhance evaluation of programs for students and teachers from kindergarten through 12th grade. One grant goes to the Genetic Science Learning Center at the University of Utah to design and conduct a workshop on science-curriculum development, in collaboration with the University of Washington School of Medicine and the Missouri Botanical Garden.

The other grant will help Boston University School of Medicine's CityLab create an online resource center for evaluating science-education programs, which all HHMI grantees could use. CityLab will work in collaboration with the Robert C. Byrd Health Sciences Center of West Virginia University, the University of Washington, the University of Cincinnati College of Medicine, the Partners in Health Sciences program at the University of Arkansas for Medical Sciences, Baylor College of Medicine and Washington University in St. Louis.

The two-year grants were designed to help grantees work together on creative ways to address challenges faced by science educators. The funding enables them to develop projects that are outside the scope of their individual grants. Eleven programs competed for the awards. **LI**



# Taking Advantage of a New Imaging Technique

**D**an Fernandez, a medical student at the University of South Florida, is developing applications for a new imaging technique that gathers both chemical and spatial information from tissue samples. He and his mentors hope that this technique, termed Fourier transform infrared (FT-IR) spectroscopic imaging, will provide new approaches to the diagnosis of cancer and other diseases.

For the past two years, Fernandez has been in the HHMI–National Institutes of Health Research Scholars Program, working in the laboratory of Ira W. Levin, chief of the section on molecular biophysics at the National Institute of Diabetes and Digestive and Kidney Diseases. Fernandez will earn his Ph.D. there before returning to medical school.

Most scientists who use infrared spectroscopy focus on a single point in a sample and record a single spectrum whose peaks reveal information about the chemical bonds defining the molecules at that point. “What we do, however, is to collect many spectra within a field of view simultaneously,” Fernandez explains. The new system integrates an interferometer, an infrared microscope and a state-of-the-art infrared array detector. The detector conceptually resembles the chip in a digital camera, but it is sensitive to infrared radiation instead of visible light.

The interferometer is used to modulate the infrared radiation, which is focused over the sample area by the microscope. The radiation is then

transmitted through the sample and recorded digitally on the detector. Finally, the information is processed by a computer and translated into color-coded images.

The technique requires no stains or dyes; as a result, the sample retains its original characteristics. It’s fast as well. What used to take 40 hours, for example, now takes only 5 minutes. Fernandez and his colleagues are devising ways to make the technology even more efficient without sacrificing signal quality.

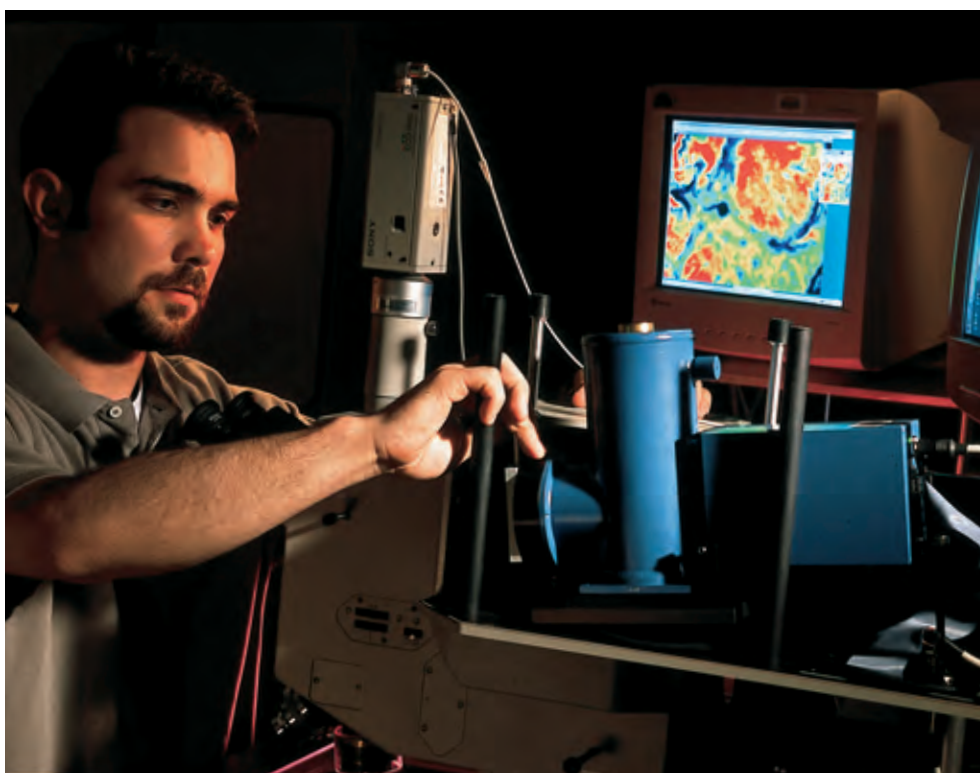
FT-IR imaging may prove useful in drug development by allowing scientists to examine polymer systems, which might one day encapsulate medications and then slowly dissolve, so that drugs could be safely released over a long period of time. Currently, Fernandez is studying images of nor-

mal and cancerous prostate tissue to identify spectral characteristics that distinguish one sample from the other.

“I’ve done several small studies that have shown real promise,” he says. “Now I’m gearing up for a large study using prostate tissue, and possibly also ovarian, kidney and esophageal tissue.” In addition, Fernandez is examining tissue microarrays—blocks containing hundreds of different tissue samples prepared identically—to minimize the differences that might result from diverse ways of preparing the samples. This would enable scientists to study thousands of spectra and do statistical analyses of their results on a large scale.

Will FT-IR ever become commonplace in cancer diagnosis? “Right now, the cost of the instrument is probably prohibitive,” says Fernandez. “The detector alone costs close to \$100,000. I don’t see this as a tool that every pathology lab is going to purchase. I envision it as primarily a research tool for the next several years.”

—NANCY VOLKERS



Dan Fernandez, a medical student, adjusts equipment for a new study of the differences between normal and cancerous tissues.

KAY CHERNUSH

## Big Payoffs from College Students' Research

The research that Diana C. Hargreaves performed while still an undergraduate at Haverford College has taken her a long way, literally and figuratively. She was invited to travel from her college in southeastern Pennsylvania to a national gathering of immunologists at Asilomar near Monterey, California, to present her work. While there, she landed a job at an HHMI investigator's lab at the University of California, San Francisco (UCSF), and she hopes her research experience will help open doors to graduate school and an immunology career.

Hargreaves is one of a growing number of undergraduates who not only conduct research, but have the opportunity to make formal presentations about it alongside full-fledged scientists. Over the past five years, more than 5,700 undergraduates have received HHMI support to participate in this way at scientific meetings.

Hargreaves took her first step on the research ladder as part of an interdisciplinary program supported by an HHMI grant. The chemistry major's project was to help Haverford biology professor Judy Owen design a more efficient system for isolating certain regulatory regions of genes that are expressed after B-cell activation. Because Owen believes that students who have made major contributions to the work of her lab should be invited to accompany her to scientific meetings, Hargreaves found herself, at the age of 21, presenting a poster at the 2000 Mid-Winter Conference of Immunologists at Asilomar.

"I was pretty scared," she recalls. "I was the youngest person there by a long shot. But it was really good to be part of that scientific community, to get feedback on a national level and to be exposed to what was going on in the field of immunology as a whole."

The Federation of American Societies for Experimental Biology (FASEB) 2001 meeting in Orlando, Florida, made a similar impression on Hesham Attaya. Now a junior majoring in biochemistry at Texas Tech University, he presented a poster on his research into human metastatic pancreatic cancer-cell

expression of a particular enzyme, plasmalemmal vacuolar type proton ATPase. "It was amazing to me how principal investigators, postdocs and graduate and undergraduate students from around the world come together to talk about science," he says. He was impressed with the lack of condescension. "Many people came to see my poster and talked to me as a peer, not a student."

"My laboratory encourages undergraduates to present their work at national and international meetings," says Raul Martínez-Zaguilán, a professor of physiology and Attaya's mentor. "Hesham's poster won one of the top 10 undergraduate research awards in a competition organized by the Society of Biochemistry and Molecular Biology at the FASEB meeting in Orlando, and that is a major accomplishment." Attaya says his par-

*"My lab encourages undergraduates to present their work at national and international meetings."*

—Raul Martínez-Zaguilán

ticipation in the meeting inspired him to pursue an M.D.-Ph.D. and a research career.

Texas Tech sends several undergraduates on similar adventures every year. Larry Blanton, biology professor and director of Texas Tech's HHMI-supported undergraduate program, calls presenting at scientific meetings "one of the most meaningful parts of an undergraduate's research experience. Participating in these meetings makes them realize that they are active participants in the creation of knowledge rather than passive recipients of delivered facts."

Such presentations also help students clarify their thoughts about research, notes Washington University in St. Louis biology professor Sarah Elgin, director of a similar program there. "They must understand and explain their choice of research problem and experimental approach, and report on the outcomes," she says.

Scheduling trips to scientific conferences can pose problems for undergraduates, but

they aren't insurmountable. Elgin recalls a student who would have to miss a mid-term exam in one of her classes in order to present his research at a national meeting. Instead, she faxed the exam to the student's mentor, who served as proctor while the student took the exam during the meeting, hundreds of miles from St. Louis. The mentor returned it to Elgin by fax in time for grading with the rest of the class. "The faculty shares a strong commitment to undergraduate research, so we are happy to work with students to make meeting participation possible," Elgin explains.

At the University of Delaware, where a dozen or more undergraduates present research at professional meetings each year, biochemistry professor and HHMI program director Hal White explains, "Our objective is to provide an undergraduate track to a research career." Delaware senior Mike Usher is speeding along that track. Presenting his research into the biochemical mechanisms underlying targeted gene repair at the 2001 FASEB meeting, he won a Pfizer summer research fellowship. The meeting,

he says, gave him a taste of the way scientists from different disciplines can nurture each other's work. "I look at things from a biochemical viewpoint, and there I was talking to a molecular biologist about bacterial genetics," Usher recalls. "We both took home some new ideas." Usher wants to earn an M.D.-Ph.D. and do clinical research.

Remember Hargreaves at Asilomar? One of the scientists who visited her poster was HHMI investigator Jason G. Cyster of UCSF. He was looking for a research assistant, and Hargreaves was looking for a job after she graduated in May 2000. "I was impressed by the enthusiasm Diana showed as she took me through her poster and by the good understanding she demonstrated of the work she had been doing," Cyster recalls. Hargreaves has worked with Cyster ever since. She was first author on a paper published in the *Journal of Experimental Medicine* in 2001, and she is now applying to graduate school.

—JENNIFER BOETH DONOVAN



Guided by David Page, students use vegetables to model how genetic traits are transmitted.

## Y or Why Not?

Teens and adults from the Washington, D.C., area participated in a research study to measure and compare testosterone levels in males and females of different ages. Each participant contributed a saliva sample to be analyzed by a commercial laboratory.

Approximately five milliliters of saliva from each person told the tale, which HHMI investigator David C. Page recounted during the 2001 Holiday Lectures on Science, this year titled *The Meaning of Sex: Genes & Gender*. Testosterone levels in males averaged three to four times higher than those in females, and levels in both sexes tended to decline with age. Individuals varied widely, however, with some females showing higher levels of the so-called male hormone than males their age, and levels in some older adults exceeding those of the teenagers.

“Did some of you expect that all the males would have more testosterone than all the females?” Page asked students from high schools in Maryland, Virginia and the District of Columbia. “Your data raise some interesting questions, as the results of scientific experiments often do: What makes a person a male, and what genes on the Y chromosome contribute to maleness?”

Page, from the Massachusetts Institute

of Technology, and Barbara J. Meyer, an HHMI investigator at the University of California, Berkeley, have devoted their research careers to such questions. Instead of focusing on humans, however, Meyer studies sex determination in the tiny roundworm *Caenorhabditis elegans*, which has two sexes: male and hermaphrodite (a female that produces both eggs and sperm). The hermaphrodite can mate with a male or self-fertilize.

“Worms provide a powerful experimental system for studying many biological processes because they are easy to grow in the lab and can be genetically manipulated,” Meyer explained. “By eliminating or altering genes in an organism, scientists learn how these genes function.”

Sex determination in worms is one of nature’s simpler designs: One X chromosome makes a male and two Xs make a hermaphrodite, Meyer told 200 high school students who attended the Holiday Lectures at HHMI headquarters and others watching a live Webcast worldwide. However, because hermaphrodites have two Xs, they also have a double dose of every gene on the X. Genes make proteins, so hermaphrodites produce twice as much X-encoded protein as males. Such genetic imbalance can be harmful to any organism; in humans, Down syndrome is caused by an extra copy of chromosome 21. For worms, the extra X can be lethal, but

hermaphrodites have found a way to survive by cutting in half the amount of protein produced by genes on the X chromosome, a process called dosage compensation. This process evolved from chromosome segregation, in which chromosomes move apart during division.

Page chronicled the evolution of the human X and Y chromosomes. About 300 million years ago, after mammals and reptiles diverged, “an irrepressible gene called *SRY* commandeered a perfectly ordinary autosome—a chromosome not involved in sex determination—and started it on the path to becoming the Y chromosome,” he said. Part of the Y chromosome houses a handful of genes that make a male a male, but the Y also has genes unrelated to sex determination, with counterparts on the X. These are living fossils of the genes on the original autosomal chromosomes from which the X and Y evolved, he explained. Page, who also conducts research on human infertility, added that deletions on the Y chromosome are the most common known cause of low sperm counts in males.

A recorded Webcast of the 2001 Holiday Lectures on Science can be viewed at [www.holidaylectures.org](http://www.holidaylectures.org)

—JENNIFER BOETH DONOVAN

## Research Awards Go to Canadians and Latin Americans

HHMI has awarded \$16.25 million in new grants to 43 biomedical researchers in Canada and five Latin American countries: Argentina, Brazil, Chile, Mexico and Venezuela. The five-year awards will support research in genetics, epidemiology, virology and neuroscience, among other fields. The grants include funds for laboratory personnel, equipment and supplies; for travel to visit research collaborators or attend scientific meetings; and for the scholars’ home institutions. HHMI supports international research scholars in 29 countries.

» For more: [www.hhmi.org/news/011502.html](http://www.hhmi.org/news/011502.html)

# H H M I L A B B O O K

RESEARCH NEWS FROM HHMI SCIENTISTS

## IN BRIEF

**Clues to how the pancreas grows** The discovery that blood vessels send chemical instructions to embryonic cells to trigger the development of the pancreas has researchers speculating that similar biochemical signaling systems will be found for other organs. The signaling mechanism for the pancreas may aid scientists' efforts to one day use embryonic stem cells as a source of the insulin-producing cells that are depleted in people with type I diabetes. Researcher: **Douglas A. Melton**  
[www.hhmi.org/news/melton2.html](http://www.hhmi.org/news/melton2.html)

**How our internal clock talks** Scientists have taken an important step in understanding how the brain's internal clock—which helps control sleep and wake cycles as well as body temperature and other functions—communicates with the rest of the body. A team of researchers has discovered that the fruit fly gene *Nf1*, which is related to the human gene involved in the nerve disorder neurofibromatosis type 1, also helps regulate a cellular switch that's important in the communication process. Researcher: **Amita Sehgal**  
[www.hhmi.org/news/sehgal2.html](http://www.hhmi.org/news/sehgal2.html)

**Cancer gene's dual role** A gene previously implicated in several cancers may also control the growth of stem cells in the brain and central nervous system. Researchers have shown how the absence of *PTEN*, a tumor suppressor gene, disrupts the growth and proliferation of brain stem cells. Understanding how the protein expressed by the gene promotes proliferation could aid efforts to use these cells in treating neurological disorders. Researcher: **Hong Wu**  
[www.hhmi.org/news/wu.html](http://www.hhmi.org/news/wu.html)

**A genetic thermostat** In tracking the cause of a rare genetic disorder that produces brittle bones, scientists have discovered a genetic "thermostat" that appears to control how individuals accumulate bone mass. This finding could help reveal why many people don't

## Attacking the "Chaperones"

Scientists have produced the first images of a class of molecules called bacterial chaperones, which help many of the most dangerous bacteria infect cells. Scientists have known for several years that bacteria such as *Salmonella*, *Pseudomonas* and *Shigella* use "molecular syringes," known as "type III secretion systems," to inject harmful bacterial proteins across cell membranes and into a host cell. These proteins in turn hijack the cell, manipulating and sometimes even killing it. The type III chaperones are an integral part of this injection process, although how they get enough bacterial protein across cell membranes to take over a cell remains a mystery.

"There are several possible roles for these chaperones," says HHMI international research scholar Natalie Strynadka at the University of British Columbia in Vancouver. "Do they keep the bacterial proteins in an unfolded state? Or do they act like molecular bodyguards to prevent the proteins from interacting with each other before they get into the host cell?" Strynadka, in collaboration with HHMI interna-

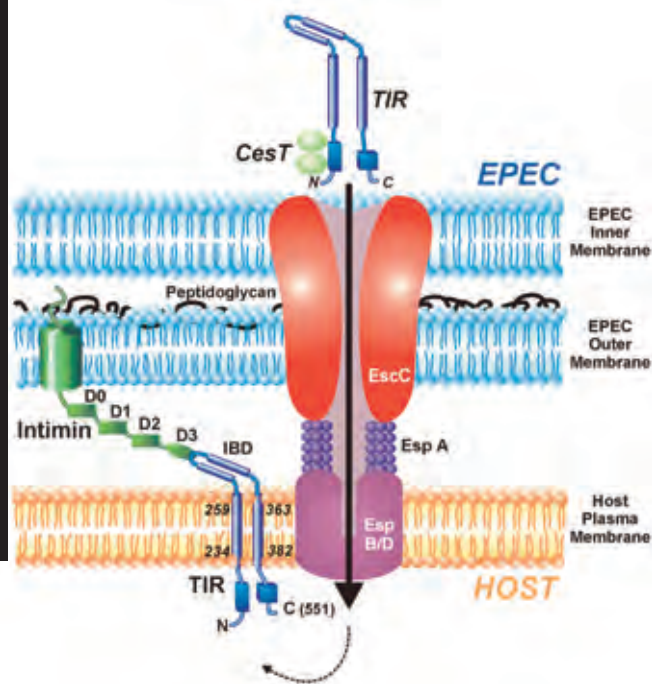
tional research scholar Brett Finlay, also at the University of British Columbia, decided that the answers might lie in the shape of the chaperone itself.

Strynadka and her colleagues used x-ray crystallography to image two type III chaperones, one from a strain of *Escherichia coli* that causes intestinal bleeding and the other from a strain of *Salmonella*. The group reported its findings in the December 2001 issue of the journal *Nature Structural Biology*.

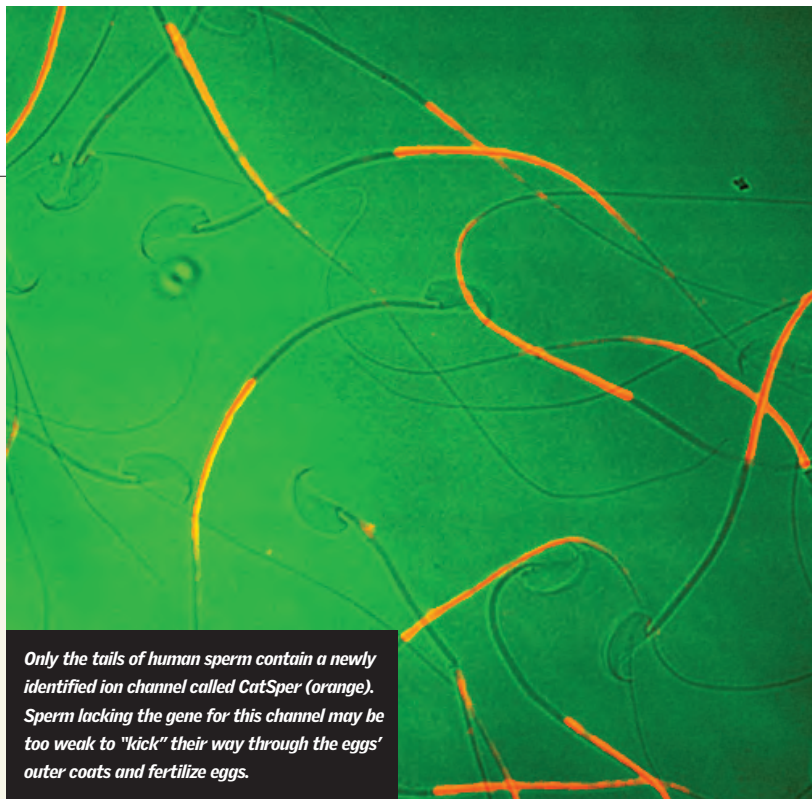
The structures and accompanying biochemical analyses revealed that type III chaperones have unusual hydrophobic surfaces, Strynadka says, which are critical for recognizing and interacting with particular proteins. Even though the four type III chaperone structures known to date all look alike, their surfaces are very different, probably to match up with specific proteins.

Questions remain, however. When researchers know more about how the bacterial proteins get through the secretion apparatus and into the target cells, they may be able to design specific inhibitors of that process and thwart particular infectious bacteria.

Some of the most dangerous bacteria infect cells by means of a "molecular syringe" (red) that injects harmful bacterial proteins (such as TIR) into the cell. This operation requires help from a chaperone dimer (green balls) whose structure has just been solved by Strynadka's team.



STRYNADKA LAB



Only the tails of human sperm contain a newly identified ion channel called CatSper (orange). Sperm lacking the gene for this channel may be too weak to "kick" their way through the eggs' outer coats and fertilize eggs.

NATURE 413:603-609, FIG. 3A, (2001) © MACMILLAN PUBLISHERS LTD.

## IN BRIEF

develop enough bone mass during the first three decades of life, a significant risk factor for the development of osteoporosis later on.

Researcher: **Matthew L. Warman**  
[www.hhmi.org/news/warman.html](http://www.hhmi.org/news/warman.html)

**How the nose knows** Researchers are closer to understanding how the brain tells the difference between various odors. In studies in mice, scientists showed how chemical signals from different odor receptors are arranged in the brain's olfactory cortex, which processes odors. In detailing a precise sensory map of the olfactory cortex, researchers also showed that this map is virtually identical in different mice.

Researcher: **Linda B. Buck**  
[www.hhmi.org/news/buck3.html](http://www.hhmi.org/news/buck3.html)

**The many births of a ribozyme** For years, scientists have known that RNA can be a biological catalyst, or "ribozyme." Now they have evidence that a type of ribozyme that actually cleaves itself may have evolved independently in organisms ranging from plant viruses to cave crickets. Understanding the nature of ribozymes is becoming more important as researchers try to harness them for use in treating some human diseases.

Researcher: **Jack W. Szostak**  
[www.hhmi.org/news/szostak2.html](http://www.hhmi.org/news/szostak2.html)

**RNA stop sign** Scientists have developed a new technique that selectively blocks messenger RNA from leaving the cell nucleus to enter the cytoplasm. The technique, which uses peptides that can pass through the cell to ferry inhibitory molecules inside, offers a new opportunity for targeting drugs to certain types of cells.

Researcher: **Joan A. Steitz**  
[www.hhmi.org/news/jsteitz.html](http://www.hhmi.org/news/jsteitz.html)

**Let there be light** A global survey of varieties of a single plant species indicates that genetic variation in certain light-sensing proteins may regulate how plants that grow in different parts of the world respond to light. Plants in northern climes, for example, are more sensitive to light than are their counterparts closer to the equator. Tracking the source of this natural variation should help scientists better understand the underlying molecular machinery.

Researcher: **Joanne Chory**  
[www.hhmi.org/news/chory4.html](http://www.hhmi.org/news/chory4.html)

# How Sperm Wiggle, Then Kick

Researchers have discovered how sperm get where they're going and deliver the goods. The key appears to be an ion channel protein that regulates the flow of calcium into the sperm's tail. Without that ion channel, sperm cannot swim strongly enough to penetrate the tough outer shell of the egg and fertilize it. As a result, this ion channel could be a new target for contraception, both for women and men.

HHMI investigator David E. Clapham and his colleagues at Harvard Medical School discovered the channel while performing a general screen of the human gene database for novel calcium-selective ion channel genes. One gene caught their eye because its sequence resembled other ion channels known to be important in cell motility. The researchers subsequently pinpointed the protein produced by the gene by using antibodies in mouse and human tissue. Surprisingly, Clapham says, they found the ion channel only in sperm, and what's more, only in the sperm tail—in a part known as the principal piece, which is specialized for swimming. Clapham and his colleagues reported their findings in the

October 11, 2001, issue of the journal *Nature*.

To find out what the protein—which they named CatSper, for "cation channel of sperm"—actually did, the scientists created "knockout" mice lacking the gene. They found that although the mice appeared normal and the female knockout mice were fertile, the male mice couldn't fertilize eggs. When the researchers mixed the sperm with eggs lacking their outer coat, called the zona pellucida, the sperm could fertilize the eggs normally. Without CatSper, Clapham speculates, the swimming sperm might be too weak to generate a final "kick" to break through the zona pellucida.

That might be the case in some forms of male infertility: Defects in CatSper may result in weakly swimming sperm. The finding is important, Clapham points out, because ion channels are common targets for therapeutics. "Since we know that 100 percent of the mice are infertile without the ion channel in the sperm tail, blocking the channel in humans might be effective in preventing conception."

*HHMI Lab Book* written by **Steven I. Benowitz**

# Getting Fooled by Mother Nature

*Pamela Bjorkman finds some exceptions to a general rule.*

In biological science as in architecture, form is said to follow function. Biologists generally assume that a molecule's form—its structure—dictates its function. When the three-dimensional structure of DNA was solved, for example, it immediately suggested how the molecule could serve as a template for replicating genes.

It turns out, however, that the form-follows-function aphorism can sometimes be misleading. Research by HHMI investigator Pamela J. Bjorkman at the California Institute of Technology shows that proteins with surprisingly similar three-dimensional structures can have radically different roles.

Bjorkman's lab studies members of a family of proteins related to major histocompatibility complex (MHC) class I molecules, the so-called "MHC homologs." Real MHC class I molecules serve as ID tags on every cell in the body, identifying the cell as "self" by displaying peptides derived from proteins within it. When a virus invades a cell, the cell chops up the invader into fragments and the MHC class I molecules "present" these fragments on the cell surface, where they serve as a red flag for the immune system's killer T cells. The T cells then destroy the infected cell.

The roles of MHC homologs may be quite different, however. Some homologs act within the immune system but do not present peptides, while others appear to have no role within the immune system at all.

For example, an MHC homolog called HFE is mutated in patients with hereditary hemochromatosis, a defect in iron metabo-



## MHC Class I

MHC Class I proteins serve as the cell's ID cards and are vitally important to the immune system. They present fragments of self proteins and alien proteins to the immune system's killer T cells. Upon detecting a peptide derived from a dangerous organism, the T cells bind to the infected cell and destroy it.

### FcRn

The immune function of FcRn is different from that of typical MHC class I proteins. FcRn transports immunoglobulin G from mother to offspring, giving the newborn temporary immunity to pathogens that the mother has encountered.



### HFE

HFE helps regulate the entry of iron into cells. Problems in this regulation can result in either anemia or iron-overload disorders.



### ZAG

ZAG causes fat depletion in cachexia, a wasting syndrome seen in terminally ill patients.



lism that causes iron overload (see page 18). HFE competes with transferrin, a molecule that transports iron into cells, to bind to the transferrin receptor on the cell membrane. If HFE binds to the receptor first, less transferrin—and less of the iron it carries—will enter the cell. Bjorkman's studies of the three proteins indicate that they may form a mechanism that regulates iron's entry into cells. This is relevant for understanding both iron overload and iron deficiency.

By merely looking at HFE's structure, however, one would never guess that it was involved in iron transport. "When the HFE gene is translated into the protein sequence, it is clearly similar to class I MHC sequences," Bjorkman says. Although conventional wisdom pointed toward HFE having an immune function, "there's no evidence that hereditary hemochromatosis is an autoimmune disease."

In mice that lack the HFE gene, "you can't find any immune defects."

A second MHC homolog with no known role in the immune system is Zn- $\alpha_2$ -glycoprotein (ZAG), a protein involved in the breakdown of lipids. It was isolated 30 years ago, but researchers only recently discovered that it causes fat depletion in cachexia, a wasting syndrome found in terminally ill patients. Curiously, the structure of ZAG revealed an occupant, presumably a lipid, in a position similar to that of peptides that bind MHC proteins. Most other MHC homologs have unoccupied grooves.

The neonatal Fc receptor (FcRn), a third MHC homolog, does have an immune role, but it is not related to the typical MHC function. Rather than present peptides to immune cells, FcRn is a receptor for a large macromolecule, immunoglobulin G, which

it transports from mother to offspring, thereby transferring maternal immunity.

An even greater mystery surrounds the functional roles of class I MHC homologs produced by cytomegalovirus, Bjorkman says. "No one understands what they do, but they're probably a sort of decoy class I MHC designed to fool the immune system in some way." This could indicate either that the protein template is extremely ancient or that the viruses essentially stole MHC molecules to confuse the vertebrate immune system.

Although Bjorkman's results undermine some assumptions about the tight link between protein form and function, they may provide a fresh perspective on the evolutionary relationships among the many organisms that produce MHC homologs.

—DAVID TENENBAUM

## A Diplomat's Touch

He's an ambassador, a coach, a cheerleader. He's also a number cruncher, a strategic planner, a computer troubleshooter and a human resources specialist. In other words, Rod Hargraves is a manager of administrative services at an HHMI field office. To 18 investigators and 130 of their employees at The Johns Hopkins University School of Medicine, the University of Maryland Baltimore County and the Carnegie Institution of Washington, he is HHMI.

"This office is the center of the HHMI universe for them," says Hargraves. "We may be only 40 miles from headquarters, but that can seem like 400 miles. Most of our employees here have never been to Chevy Chase." That's why he does what he can to establish a sense of community—from throwing parties and holding meetings to planning a field trip to the Institute's new campus at Janelia Farm. "I want HHMI to be more than a name on a paycheck," Hargraves explains.

That's not easy to do when you work at a remote site. "It's analogous," he says, "to the New York Yankees playing their home games at Camden Yards in Baltimore."

Sports analogies come easy to a man who spent his high school years hoping to play professional basketball. However, the only basketball scholarship he was offered was at a military college whose rigid style appealed to Hargraves about as much as its mediocre team record. "That was a reality check," he says with a grin.

So he went to James Madison University in Harrisonburg, Virginia, not far from his Orange County home, where classes in human resources and management especially intrigued him. "I saw how one person can play a role that inspires and leads others," he recalls.



Rod Hargraves gets things done in Baltimore without ruffling feathers.

to answer that question. Hired as a project specialist in research administration, he was assigned to work with Robert H. McGhee, the Institute's architect and senior facilities officer, on construction projects and occupancy issues. McGhee, known for his tactful handling of dicey situations, found and nurtured the natural diplomat in Hargraves. "He was fresh out of school, but he had a gentle, yet persuasive, style," McGhee recalls. "He could figure out how to get things done without ruffling feathers. He knew how to pay attention to the host institution's concerns and still watch out for HHMI's interests."

In 1995, Hargraves got his chance to put that diplomat's touch to work as manager of administrative services in his own field office. "I have an open door," he announced when he arrived at Hopkins. "If you have issues, come in and let's talk about them."

It didn't take long. Hopkins faculty pay half-price undergraduate tuition for their children, a popular perk that HHMI investigators weren't getting because they are paid by HHMI, not Hopkins. The investigators protested, however, that the Institute's collaboration agreement with the university promised "full faculty benefits." Following rounds of meetings

Hargraves stayed to complete a master's degree in business administration and had a job lined up with the federal General Accounting Office—"the people who find out why a 25-cent screw costs the government 25 dollars," he quips—when one of his professors heard that HHMI was looking for a freshly minted M.B.A. to work at its headquarters. He thought Hargraves would be a good fit.

The graduate had heard of Howard Hughes the man, but not the Institute. "What do they do?" he asked. "They give money to scientists," the professor replied. The young man persevered: "And what happens when the money's gone?"

Since May 1987, Hargraves has been working to help ensure that no one ever has

between Hargraves and Hopkins administrators, the tuition break was extended to investigators. How did he turn the situation around? "Reasonable people can usually come up with a reasonable solution," Hargraves says with an enigmatic smile. "Remember, the word 'collaboration' comes from the Latin, com (together) and laborare (to work)."

The scientists also love Hargraves' skill at solving the myriad problems that can interrupt and delay their projects. "When our research requires something unusual or unique," says Bert Vogelstein, an HHMI investigator at Hopkins, "Rod always seems to figure out how to make it happen, and happen fast." —JENNIFER BOETH DONOVAN

BILL DENISON



# Don C. Wiley

DON WILEY WAS ONE OF THE PIONEERS WHO TRANSFORMED the specialty once known as “protein crystallography” into the discipline we now call “structural biology.” He helped to create how we picture molecular organization at the cell surface. His two monumental contributions, the structures of influenza virus hemagglutinin (HA) in its various states and the structures of class I and class II major histocompatibility (MHC) molecules in combination with peptides, superantigens and T cell receptors, redefined molecular virology and immunology.

Don and I were recruited by the Harvard Department of Biochemistry and Molecular Biology in 1971. When Don accepted his appointment, a few months after I accepted mine, he came to propose that we set up our laboratories together. He had joined the Harvard faculty immediately upon completing his degree—an unusual step that circumvented the conventional postdoctoral route. The lack of a transitional period within which to find a worthy research goal was the source of considerable stress, as Don recounted in an interview with Sondra Schlesinger (see [medicine.wustl.edu/~virology/wiley.htm](http://medicine.wustl.edu/~virology/wiley.htm)), but by 1974, he had found a direction that would dominate the rest of his career. He seized upon the study of viral surface glycoproteins—the influenza virus HA in particular—as a route toward unraveling the molecular mechanisms of cell-cell recognition.

Don’s eventual long-term collaborator and friend, John Skehel, had published in 1972 a report on purification and apparent crystallization of HA. Don contacted Skehel in 1974, and in 1976 he spent six months in Skehel’s laboratory in Mill Hill, pushing the HA project forward. They spoke on the telephone at least weekly during the ensuing decades. The HA structure was completed in 1980, and papers describing the molecule and its antigenic properties were published in *Nature* in 1981. It redefined in molecular language the three central properties of the protein—receptor binding, antigenic variation and membrane fusion. Almost overnight, vast areas of virology had become chemistry.

Skehel’s finding in the following year, that HA undergoes a dramatic conformational change at low pH, led to the second phase of work on HA—efforts to define the structural transformations that accompany viral entry. Don regarded the discovery of the low-pH transition as a key moment. For him, “discovery” had a special meaning—not just a completed observation, however important and however hard-won, but rather a qualitative insight, preferably formulated in a few simple sentences, or in a simple drawing.



KAY CHERNUSH

Don’s collaboration with Jack Strominger’s laboratory at Harvard led to an even more celebrated discovery. The HLA major histocompatibility antigen, originally identified as the principal determinant of transplant rejection, was by 1980 known to be a crucial component of the T cell-mediated immune response. Pamela Bjorkman, a graduate student (now an HHMI investigator at Caltech), undertook to crystallize it and to determine its structure. The outcome in 1987 was a turning point in immunology. Various lines of evidence had led to the notion that major histocompatibility molecules like HLA would bind antigen-derived peptides and “present” them on the cell surface. The structure showed how. For sitting between two alpha-helical “rails” on the outer surface of the molecule was the now famous “extra density,” promptly ascribed to bound antigenic peptide.

During the decade and a half since the 1987 paper, Don and his laboratory turned that first glimpse of what the T cell receptor really sees into an entire library of concepts and images. Recognition and prizes came in abundance (the Louisa Gross Horwitz, Gairdner, Lasker and Japan Prizes, to name a few), but Don remained strikingly unaffected by the glamour, his thoughts still fixed on what discoveries might come next. When in the right mood, Don could hold forth at teatime for an hour or more, with his laboratory members (and mine) arrayed around him like iron filings near a magnet. He was a superb mentor of graduate students, and from 1980 to 1992 he chaired the biophysics program that had once granted him a Ph.D.

When Don married Katrin Valgeirsdottir, he learned Icelandic, and Iceland became an adopted second home. He cared very much about his family. He was also deeply conscious of his scientific family—his current and former students and postdoctoral fellows, his collaborators, his mentors. I would wander into his office at the end of almost every day that we were both in town, to talk about our science and to seek or give advice. I will miss those remarkable encounters, just as the rest of Don’s extended scientific family will miss—probably more than any of us yet realizes—his powerful yet unpretentious intellectual presence.

—STEPHEN C. HARRISON

HHMI Investigator, Harvard University

*Don C. Wiley joined HHMI in 1987. He died at age 57 in an accident in Memphis on November 16, 2001.*

# Celebrating a Centennial

**H**HMI President Thomas R. Cech was among the past and present Nobel laureates who traveled to Stockholm in early December to attend the Nobel Prize award ceremony and other festivities held in conjunction with the Nobel Centennial.

Since 1901, the Nobel Prizes have been presented at ceremonies on December 10, the anniversary of the death of Alfred Nobel, the Swedish industrialist for whom the prizes are named. At the Centennial, the laureates and invited guests were fêted with a week-long series of lavish banquets, receptions, lectures and concerts that culminated in the Nobel Prize award ceremony for the 2001 laureates, a group that included HHMI Scientific Review Board member Leland H. Hartwell.

As the photos on this page indicate, HHMI was well represented in Stockholm. Of special note was the three-day symposium, called "Beyond Genes," which was held at the Karolinska Institute. Many of the speakers at the symposium have close ties to HHMI, including Hughes investigators Günter Blobel, Linda Buck, Mark Davis, H. Robert Horvitz, Eric Kandel and Roger Y. Tsien and HHMI Medical Advisory Board members Joseph L. Goldstein, Tony Hunter and Harold Varmus. Other HHMI investigators in attendance in Stockholm included Johann Deisenhofer, Kathleen Gould, James Maller, Trudi Schüpbach, Thomas and Joan Steitz, Susumu Tonegawa and Eric Wieschaus.

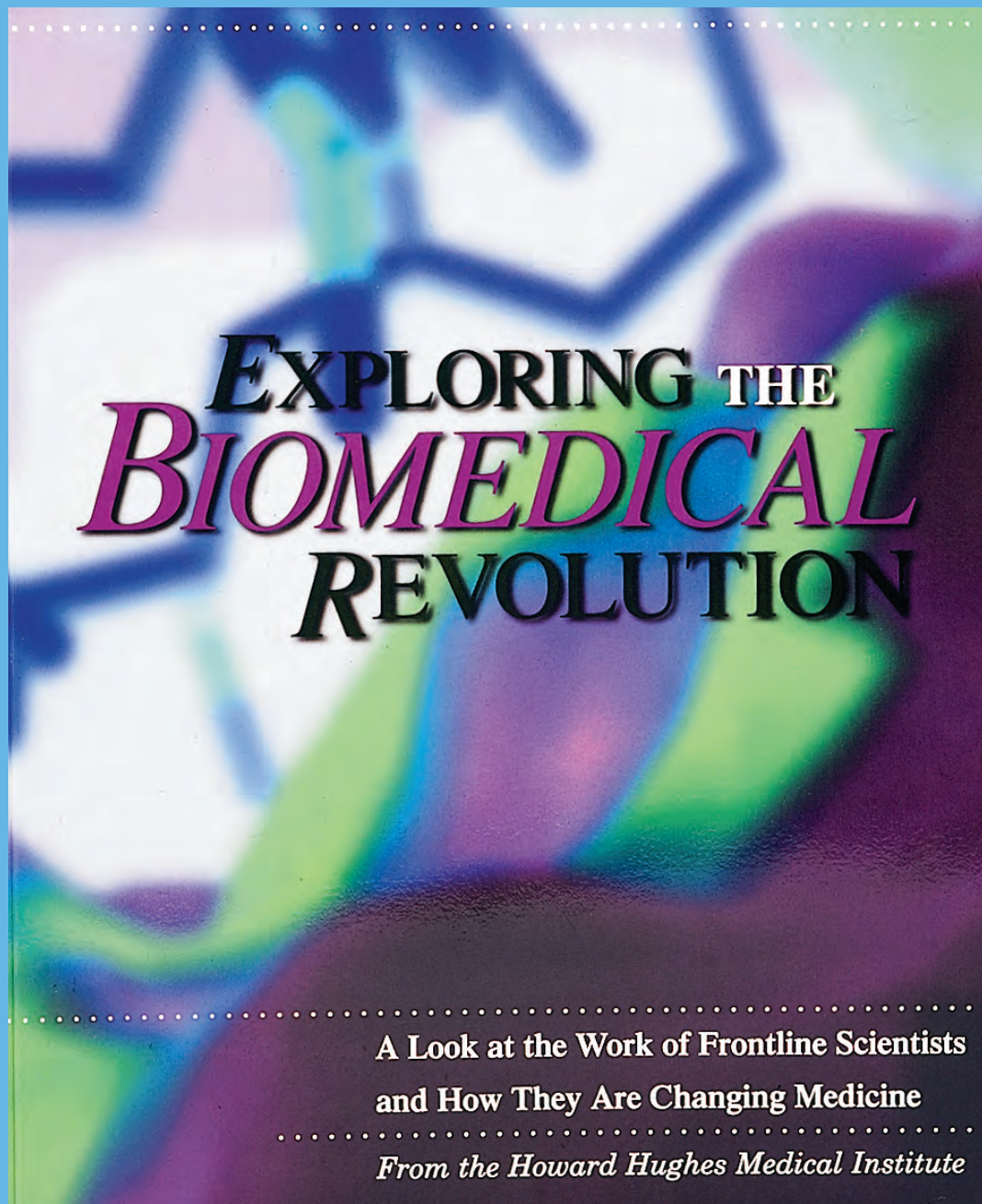


*Tom Cech snapped these photographs during a week of special events commemorating 100 years of Nobel prizes. At top, the lights of Stockholm shimmer on the harbor during the December celebrations. At left, recent Nobel laureates, HHMI's Günter Blobel (1999) and Eric R. Kandel (2000), enjoy the festivities. Harold E. Varmus and J. Michael Bishop (bottom left) shared a Nobel prize in 1989. Below right are HHMI investigators Thomas A. and Joan A. Steitz.*



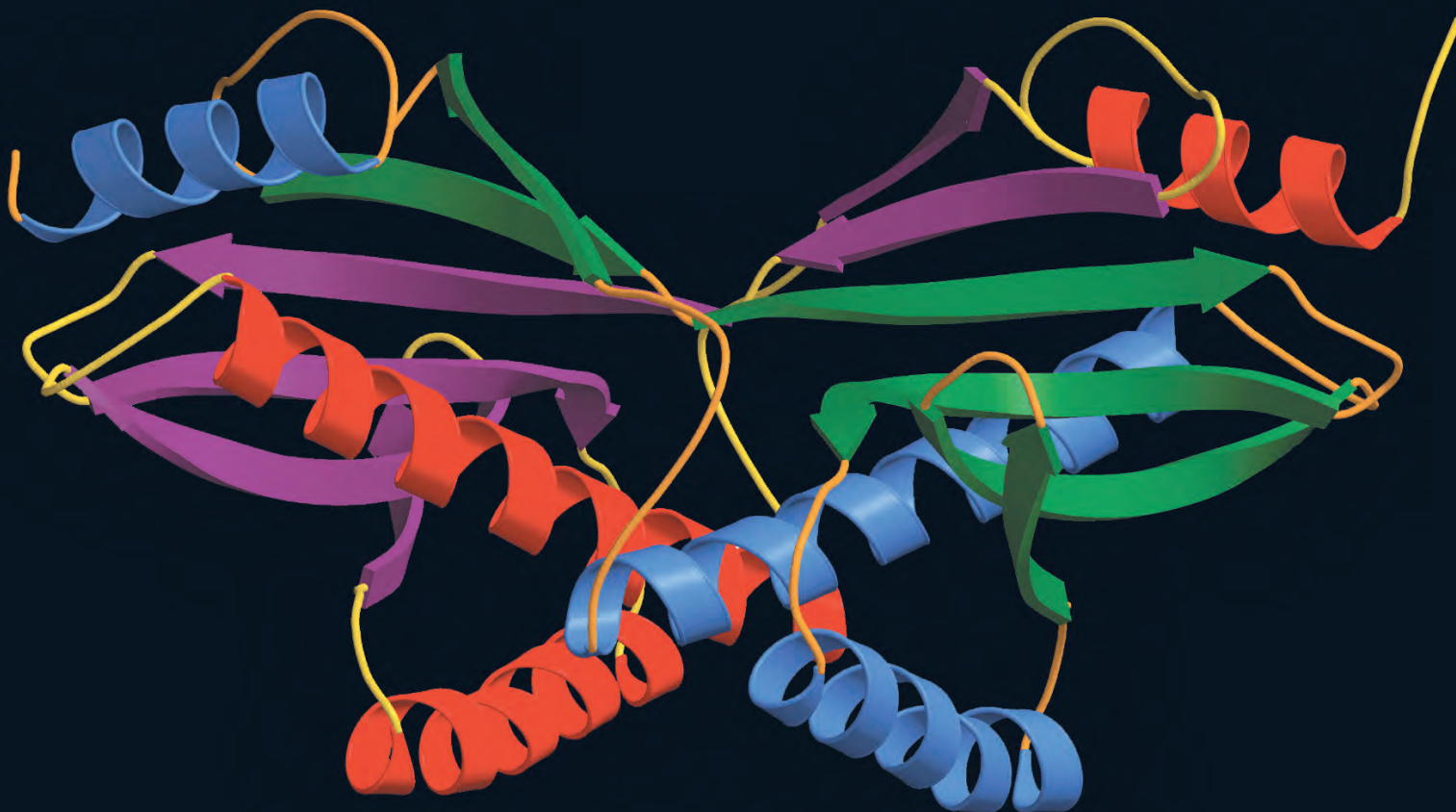
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This ribbon diagram shows the newly solved structure of a bacterial chaperone that helps dangerous *E. coli* bacteria inject their own proteins into human cells. The structure consists of two interacting parts, one colored in red/purple and the other in blue/green. See Lab Book, page 42.

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