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SUMMER 2004

HHMI
Howard Hughes Medical Institute Bulletin

LIBERAL ARTS SCIENCE

In science and teaching—and preparing future investigators—liberal arts colleges earn an A+.

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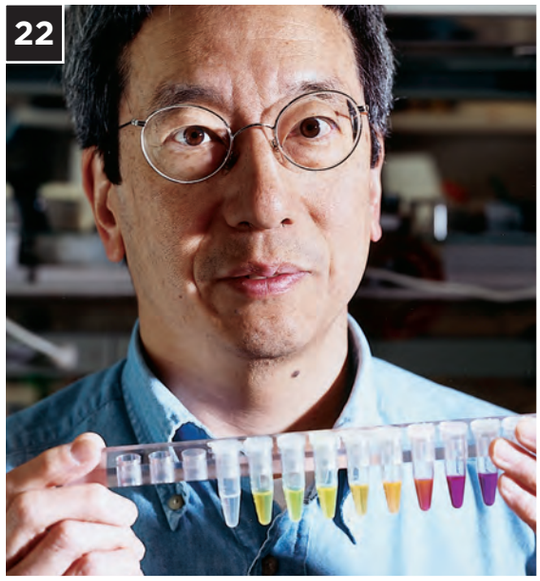

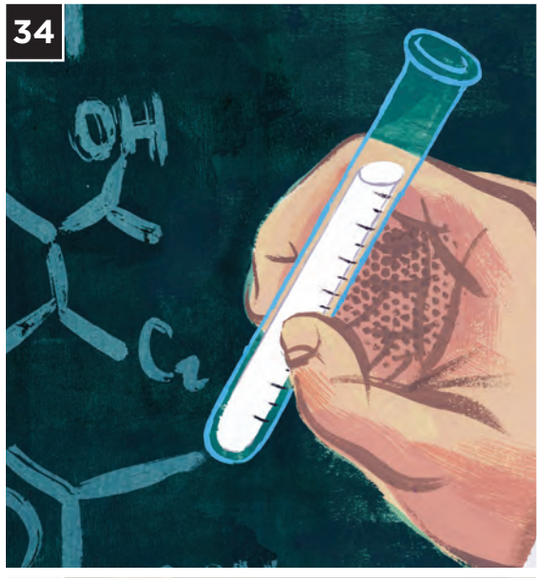

ON THE COVER: Nancy H. Kolodny (center), a professor of chemistry at Wellesley College, discovered her love for science as an undergraduate at Wellesley. Today she's a mentor to students, including Jae Young You (left) and Shivani Agarwal, both members of the class of 2005. PHOTOGRAPH BY JASON GROW

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Scott Gilbert (foreground), who teaches biology at Swarthmore College, encourages undergraduate students to conduct lab research. Students (clockwise from left) are Tyler Lyson, Sean Anderson, and Fraser Tan.

PHOTOGRAPH BY DAVID GRAHAM (ABOVE)

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The *Bulletin* is published by the HHMI Office of Communications and Public Affairs.

HHMI Announces New Investigator Competition

HHMI has invited nearly 200 universities, medical schools, and research institutions to nominate their best biomedical researchers for a newly launched national competition, with the expected result that between 30 and 50 scientists will be chosen to join the Institute in 2005 as HHMI investigators.

The Institute is looking for candidates from the full range of biological and biomedical inquiry who demonstrate exceptional promise early in their careers as independent researchers. "HHMI places a high value on innovation, and our distinctive approach to supporting biomedical research frees our scientists to use their creativity to extend the boundaries of scientific knowledge," says HHMI President Thomas R. Cech.

The competition represents a commitment by the Institute to invest as much as $350 million in additional support for biomedical research over the next seven years, Cech says. HHMI's annual research budget now stands at nearly $500 million a year.

Currently, the Institute employs 318 of the nation's most innovative scientists. They head Hughes laboratories at 66 universities, medical schools, and research institutes through long-term research collaboration agreements. These scientists and their research groups study a broad range of fundamental biological questions, including the causes of many human diseases such as Alzheimer's, diabetes, and AIDS.

Selection standards are high. More than 100 of HHMI's investigators are members of the National Academy of Sciences; 11 current or former investigators have received Nobel Prizes.

The new competition, the first since 2001, represents a continued expansion of the Institute's biomedical-research mission. "Recruitment of new investigators through a competition like this gives HHMI the ability to respond to emerging areas of scientific interest," says David A. Clayton, vice president and chief scientific officer.

In addition, HHMI will begin recruiting scientists this fall for the Janelia Farm Research Campus, the Institute's new and innovative facility located in Ashburn, Virginia. Representing an investment of $500 million, Janelia Farm—a multidisciplinary research environment for small teams of scientists—is scheduled to open in 2006 (see p. 28).

Undergraduate Science: $50 Million in New Grants

Colleges face many tough challenges in teaching science today. New fields that blur the lines between disciplines are emerging, and biologists, chemists, physicists, and mathematicians are forging interdisciplinary collaborations. Scientists trained to be outstanding researchers need to learn to be outstanding teachers. More minorities must be encouraged to pursue scientific careers.

To help colleges meet these challenges, HHMI is awarding $49.7 million in grants to 42 baccalaureate and master's degree institutions in 17 states and Puerto Rico. This brings HHMI's investment in undergraduate science to more than $606 million.

The four-year grants, ranging from $500,000 to $1.6 million, support a variety of programs to improve undergraduate science, from new courses in hot fields such as bioinformatics and computational biology, to fellowships for postdoctoral researchers that include teaching experiences, to a mobile teaching laboratory to bring science to remote areas.

Although its investigators conduct research at universities and medical schools, HHMI supports science at colleges because they also play a vital role, according to Peter J. Bruns, vice president for grants and special programs at HHMI. "Good science can be done in different settings, in colleges as well as universities," says Bruns. "Colleges are a better learning environment for some students, and they serve underrepresented minorities extremely well."

Undergraduate biology is not well-funded nationally, notes Stephen Barkanic, director of HHMI's undergraduate science education program. "Public and private funders tend to focus their support on research programs, infrastructure, and graduate training, but undergraduate biology tends to be neglected."

HHMI invited 198 public and private baccalaureate and master's degree institutions to compete for the new awards. They were selected for their record of preparing students for graduate education and careers in research, teaching, or medicine. A panel of distinguished scientists and educators reviewed proposals and recommended the 42 awards approved by the Institute's Board of Trustees on May 4.

NEW GRANTS AWARDEES

Amherst College (MA)	$1.3 million
Barnard College (NY)	$1.5 million
Bates College (ME)	$1.2 million
Bowdoin College (ME)	$800,000
Bryn Mawr College (PA)	$1.2 million
California State Polytechnic University, Pomona (CA)	$1.3 million
Canisius College (NY)	$800,000
Carleton College (MN)	$800,000
The City University of New York (CUNY) City College (NY)	$1.3 million
CUNY Hunter College (NY)	$800,000
CUNY Queens College (NY)	$800,000
The College of Wooster (OH)	$800,000
Davidson College (NC)	$1.3 million
Florida A&M University (FL)	$1.2 million
Grinnell College (IA)	$1.4 million
Harvey Mudd College (CA)	$1.2 million
Haverford College (PA)	$1.6 million
Hiram College (OH)	$1.2 million
Hope College (MI)	$1.5 million
Humboldt State University (CA)	$1.3 million
Kalamazoo College (MI)	$1.1 million
Kenyon College (OH)	$1.5 million
Knox College (IL)	$1 million
Mount Holyoke College (MA)	$1.2 million
Occidental College (CA)	$1.5 million
Point Loma Nazarene University (CA)	$800,000
Pomona College (CA)	$1.3 million
St. Olaf College (MN)	$1.4 million
Smith College (MA)	$1.3 million
Spelman College (GA)	$1.3 million
Swarthmore College (PA)	$1.5 million
Trinity College (CT)	$800,000
Trinity University (TX)	$1 million
Union College (NY)	$1.6 million
The University of Louisiana at Monroe (LA)	$1 million
University of Puerto Rico Cayey (PR)	$500,000
University of Richmond (VA)	$900,000
University of Texas-Pan American (TX)	$1.3 million
Wellesley College (MA)	$1.2 million
Wesleyan University (CT)	$1.3 million
Williams College (MA)	$1.6 million
Xavier University of Louisiana (LA)	$1.3 million

The Scientific Apprenticeship

KAY CHERNUSH

Biographies of molecular biologists, physicists, and chemists regularly outline the researcher's scientific ancestry—his or her tutors, influences, and guides from early schooling through graduate and postdoctoral training. The significance of the scientific lineage underscores the importance of mentorship in the training of young scientists. Moreover, it is during apprenticeship that one begins to develop a research focus and the approach one brings to working with colleagues.

However rich an experience it might be, though, an apprenticeship may not equip a promising postdoc with certain kinds of practical knowledge necessary for making a successful transition to running a lab. Scientific insight, experimental skill, and a passion for discovery are essential, but they provide no guarantee that a newly minted assistant professor will know the first thing about how to recruit and train lab personnel, motivate students, manage a budget, and win funding while maintaining a disciplined focus on his or her own research. This is especially an issue now that postdoctoral stints often persist for what many believe is too long a period of time; the average age at which a researcher first applies for an independent grant from the National Institutes of Health is now 36 or 37.

For young scientists—and, by extension, the entire scientific enterprise—to thrive, we need to rethink the nature of this apprenticeship and the training it provides. Fortunately, such rethinking is occurring.

At the macro level, National Institutes of Health Director Elias Zerhouni has asked the National Academy of Sciences to identify new ways to foster the independence of early-career scientists that will, as he put it, "shake the system in a testable way." I am chairing Bridges to Independence, as the NAS committee is called, and I am hopeful that we will be able to provide specific, concrete guidance to help the NIH meet this challenge.

New ventures such as HHMI's Janelia Farm Research Campus may help shake the system as well. For a small group of early-career scientists interested in applying interdisciplinary technology to biomedical questions, Janelia should provide an outstanding alternative research community—no tenure and no grant writing. Next year we will be searching for the initial cadre of Janelia scientists.

Here at the Institute, we have integrated career-enhancement opportunities for postdocs into each of our seven annual science meetings. We hope to continue enriching these programs with practical information about everything from leadership skills and career development to resolving conflicts and conducting science ethically. And as part of HHMI's ongoing commitment to graduate education, my colleagues and I are also thinking about ways to better prepare young scientists to thrive in an interdisciplinary research environment.

Over the next few months, we will also evaluate a new HHMI DVD, *Ethics in Biomedical Research*, to see whether it will be helpful to the broader scientific community as a teaching tool. The DVD, which focuses on animal research, genetic alteration, and scientific integrity, arose from discussions with our Bioethics Advisory Board and is intended to address the paucity of educational materials about ethical considerations that arise in biomedical research. I hope that our investigators and other scientists will use these materials to provoke thoughtful discussion in their labs as well as in the classroom.

Working within the existing apprenticeship model, leaders in the training of young scientists have also taken important steps to bolster the management skills of postgraduate fellows and new faculty. HHMI and the Burroughs Wellcome Fund (BWF), as well as the NIH, the National Academies, and professional societies, have developed courses, guides, and online resources to disseminate information about scientific management more broadly.

HHMI's collaboration with BWF, which began with a five-day course for 128 postdocs and starting faculty members in July 2002, has taken on a life of its own. The course materials were used as the basis for a nuts-and-bolts handbook entitled *Making the Right Moves: A Practical Guide to Scientific Management for Postdocs and New Faculty*. The book started with a relatively small print run but was made available online (see www.hhmi.org/labmanagement). To our pleasant surprise, *Making the Right Moves* was downloaded 10,000 times in the first month, and we quickly received more than 900 requests for hard copies.

Not only are we printing another 10,000 copies of *Making the Right Moves*, but HHMI and BWF are also planning a second course for July 2005. We'll use it as an opportunity to create a teaching guide and to train "missionaries" to replicate the course at their own institutions.

There's much more that can be done, and HHMI has a valuable opportunity to participate in this process through our own programs and as a catalyst for others. Given the recent wellspring of creative activities such as those outlined above, I am optimistic that we can identify, share, and implement constructive ideas that will improve the preparation of future scientists.

Thomas R. Cech
President
Howard Hughes Medical Institute

Up Front

New Discoveries Propel Stem Cell Research

Findings suggest new avenues to possible treatments.

By all accounts, the first half of 2004 proceeded at a record clip for HHMI investigator Douglas A. Melton. In March, Melton's research team at Harvard University unveiled 17 new human embryonic stem (ES) cell lines—just days after the announcement that Melton would codirect the university's new stem cell institute. In May, Melton's group discovered that insulin-producing beta cells in the pancreas are replenished through duplication of existing cells rather than through differentiation of adult stem cells. And in June, Harvard President Lawrence H. Summers announced that Melton would chair the university's Faculty of Arts and Sciences Life Sciences Council.

While Melton has become a public figure, his true passion is being in the laboratory, where he devotes as much time as his schedule permits to understanding human ES cells. Melton is among those who believe that these cells have the potential to yield treatments for devastating human diseases, as well as to enhance understanding of human development.

Melton made international headlines when he announced that he and colleagues had derived the 17 new human ES cell lines. Developed with funding provided by HHMI, Harvard, and the Juvenile Diabetes Research Foundation, the new cell lines have been made available to researchers around the world. The work was published in the March 25, 2004, issue of the *New England Journal of Medicine*.

THERAPEUTIC PROMISE

In 2001, Harvard, HHMI, and Boston IVF began a collaborative research effort that sought to realize the great therapeutic promise offered by human ES cells. Melton, Andrew P. McMahon, Chad A. Cowan, and colleagues at Harvard worked with Douglas Powers and scientists from Boston IVF to produce the supply of human ES cells.

Melton hopes that the availability of the new cell lines will speed research developments in the area of stem cell biology. "Consistent with the general practice among academic scientists, these cells are a reagent that will be shared," says Melton. "We hope that sharing these cells will quicken the pace of discovery."

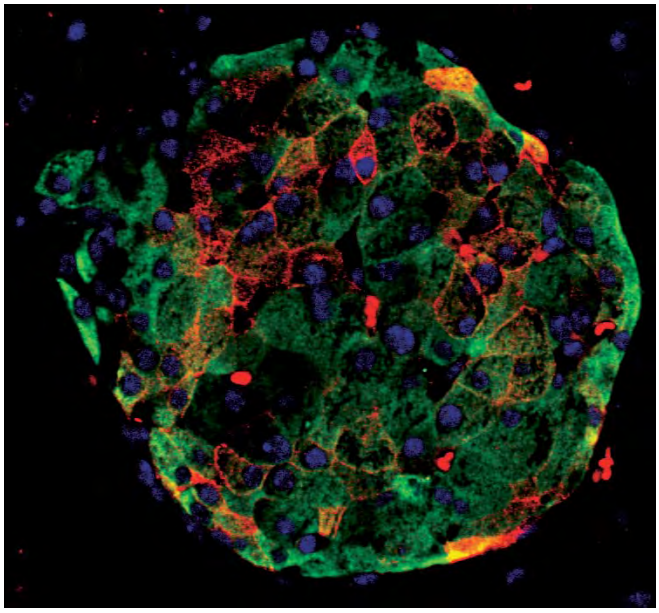
The availability of the cell lines should provide a boost to stem cell researchers worldwide. According to the National Institutes of Health, about 15 human embryonic stem cell lines are available for researchers in the United States who are doing federally funded research. The International Society for Stem Cell Research (ISSCR), an independent, nonprofit organization formed to foster the exchange of information about stem cell research, says the number of available human ES cell lines is a matter of some debate. The ISSCR Web site states that only about 8 to 10 cell lines in total are currently widely accepted as true human embryonic stem cells. Melton says that the cells that he and his colleagues developed "are robust, grow well, and are easy to handle."

The techniques Melton and his team used to derive the human embryonic stem cell lines were based, in part, on technology developed decades ago for mouse ES cells and on more recent work by Ariff Bongso at National University Hospital in Singapore and James A. Thomson and his colleagues at the University of Wisconsin–Madison. Melton notes, however, that in the course of his group's experiments, they discovered an easier way to tease stem cells free from surrounding tissues by using enzymes. "One of the things our paper shows is that it's possible to select for cells that can be easily grown by using enzymes rather than by the tedious process of hand-dissecting them," Melton says. "I would anticipate that in the future, researchers would use this method."

Distribution of the cell lines is being handled through Melton's HHMI laboratory at Harvard. Melton is impressed by the number of inquiries for the cell lines, and he is confident that his group is ready to meet the growing demand. "We are planning to distribute [the cells], to the extent possible, more or less the same way that we distribute any reagents we publish, be it a DNA clone or any other cell line," he says.

The availability of the new cell lines should also propel Melton's own research program, which uses a multipronged approach to understanding type 1 diabetes. His research team has been studying the insulin-producing pancreatic beta cells that are destroyed in patients with type 1 diabetes, a disease that commonly afflicts children. Melton's long-term goal is to learn how to direct the differentiation of human

Melton made international headlines when he announced that he and colleagues had derived 17 new human ES cell lines.



Douglas Melton's research includes study of the genetic lineage of beta cells in the pancreatic islet (left).

embryonic stem cells, so that they can generate pancreatic beta cells that can be used as a therapy for type 1 diabetes.

In May, Melton and his colleagues reported that the insulin-producing beta cells in the pancreas that are attacked in type 1 diabetes are replenished through duplication of existing cells rather than through differentiation of adult stem cells.

Although the experiments, which were done using mice, do not rule out the possibility that there are adult stem cells in the pancreas, the researchers say that they do suggest strongly that ES cells or mature beta cells may be the only way to generate beta cells for use in cell replacement therapies to treat diabetes. The findings were reported in the May 6, 2004, issue of the journal *Nature*. Melton's coauthors include Yuval Dor, Juliana Brown, and Olga I. Martinez, all from Harvard.

In cell culture, ES cells retain the properties of undifferentiated embryonic cells. ES cells have the capacity to make all cell types found in an adult organism. One of the most hotly debated questions in biology is whether adult stem cells, which have been isolated from blood, skin, brain, and other organs, have the same developmental capacity as ES cells.

Researchers have known for some time that ES cells can give rise to pancreatic beta cells during development. "But the more interesting question for us has been what happens in mature pancreatic tissue to both maintain the pancreas and regenerate it," says Melton. "Previous studies have suggested that there are sources of adult stem cells that might give rise to beta cells. However, those studies had largely depended on histological 'snapshots' of tissues." Those snapshots can only suggest the "geographic" origin of new beta cells and not the identity of the cells from which they arise, Melton notes.

Melton and his colleagues knew that they could finally put such questions to rest if they could tag beta cells in such a way that they could determine unequivocally whether the new cells were made from existing beta cells or from a different reservoir of stem cells. For these studies, they devised a "genetic lineage tracing" technique that involved engineering a mouse whose beta cells contained a telltale genetic marker that could be switched on by administering the drug tamoxifen to mice.

REPLICATIVE CAPACITY?

When the researchers applied their technique to the mice, they discovered that all the new beta cells they examined—whether arising in the usual process of renewal or during regeneration following partial removal of the pancreas—were generated from preexisting beta cells. According to Melton, the finding highlights a largely unappreciated capability of beta cells.

"No one has really paid much attention to the replicative capacity of the beta cell," he says. "And this work shows the cells to have a significant proliferative capacity that could be clinically useful."

According to Melton, the findings might have implications for developing treatments for type 1 diabetes, a disease that destroys beta cells. "If such people have residual beta cells, these findings suggest that a useful clinical direction would be to find a way to boost the proliferative capacity of those beta cells, to restore insulin production in such patients.

"On the other hand," he says, "if type 1 diabetics don't have any beta cells left, then these findings suggest that the only source of new beta cells is probably going to be embryonic stem cells, because there don't appear to be adult stem cells involved in regeneration."

The genetic lineage tracing technique can now be used to trace the origin of cells involved in the maintenance and repair of other types of tissue. Melton and his colleagues are already using the technique to determine the origin of new cells in lung tissue. And it should be possible to apply the technique to understand the origin of cancer cells in tumors and to understand the role of stem cells in such malignancies, Melton says.

—DENNIS MEREDITH and JIM KEELEY

Sleeper's Hold on Science

Inspired in part by Woody Allen, a scientific team clones a live animal from mouse-snout neurons.

Movie fans may remember the scene in the 1973 Woody Allen film *Sleeper* in which mock scientists foil a plot to clone a dead dictator from his nose. Thirty-one years later, in serious and fruitful experiments, real-life researchers have instead cloned mice using sensory neurons from a mouse's snout.

With a whimsical nod to *Sleeper*, HHMI investigator Richard Axel says, "It is important to credit Woody Allen's conceptual contribution. [He] first suggested this experiment." Axel, who studies the olfactory system and the brain at Columbia University College of Physicians and Surgeons, did the mouse-cloning work with collaborator Rudolf Jaenisch at the Whitehead Institute for Biomedical Research. Their accomplishments were reported in the March 4, 2004, issue of *Nature*.

These experiments are part of ongoing work to better understand the olfactory system. The findings are significant because they negate some assumptions about the limitations of cloning and about how neurons differentiate to acquire very specific functions. Moreover, they provide important new tools for better understanding the brain.

BANANAS AND TURPENTINE

As plain as it is on our faces, the nose remains a scientific mystery.

We detect smells using more than a million olfactory sensory neurons (OSNs) in the nasal passage's epithelial lining. Each OSN makes just 1 of about 1,500 possible olfactory receptors—the structures on the surface of OSNs that let them respond to specific odorants. While each receptor type detects only a few odorants, all neurons sharing that receptor type respond to the same chemicals and send signals to the same dot on the brain's olfactory bulb. Thus, bananas and turpentine, for instance, stimulate different sets of OSNs that connect to different areas of the olfactory bulb, creating diverse spatial patterns of neuronal activity. The brain then decodes these patterns, enabling us to sense and respond to the universe of smells.

To better comprehend how we are endowed with five senses, motor skills, and capacities to think, love, and dream, scientists are eager to understand how the nervous system diversifies. In particular, Axel wanted to know how OSNs decide which receptor to make.

One theory has held that an irreversible genetic change somehow activates one receptor gene and permanently silences the others. That's how the immune system's B cells, for example, choose to make just one of countless possible antibodies. Could OSNs use the same kind of genomic rearrangement to produce their myriad receptors?

An alternative theory suggests that olfactory-receptor choice results from a reversible influence that nudges the cell to notice one gene and ignore others, while leaving all genes intact—as happens in most gene regulation. Could this account for the striking diversity and broad distribution of OSNs?

"We wanted to design a test of these models in which a negative answer would be as significant as a positive one," says Axel. The perfect tool was cloning. If an irreversible change does occur, mice cloned from an OSN would inherit only one functional receptor gene and could detect a very limited range of smells.

But it would be hard to pick a more obstinate cell for this effort than the OSN. For cloning to work, the donor cell's nucleus must divide, but mature neurons have stopped dividing and have never been shown to resume cell division. Further, the newly divided cloned cells must continue to differentiate to make the body's various tissues. Only the most immature, undifferentiated cells—the "totipotent" embryonic stem cells—have that ability, while highly

specialized OSNs are just the opposite; they are terminally differentiated and cannot become another cell type. Conceivably, clones seemingly derived from adult cells might come instead from undetected embryonic stem cells lurking in the tissue. Such concerns even plagued scientists regarding Dolly, the famous cloned ewe.

Similar doubts shadow efforts to clone from mature neurons. Kristin Baldwin, who was then an HHMI associate and postdoctoral fellow in Axel's lab, explains that under a microscope mature neurons cannot be distinguished from other cells in a sample of nasal epithelium tissue. In previous studies, samples were 90 to 95 percent mature—not good enough to prove that cloned mice really derived from nondividing cells.

MICE GLOWING GREEN

Axel knew that Jaenisch had recently cloned mice from terminally differentiated B cells and that, as expected, the clones expressed only one antibody. Axel wanted to do a similar experiment with OSNs. As it turns out, Jaenisch also wanted to tackle the highly specialized, nondividing neuron. (B and T cells, while terminally differentiated like neurons, still divide, especially during infections.) In fact, Kevin Eggan, who was a graduate student in Jaenisch's lab, was working on cloning mice from OSNs, but he was stuck on how to select only mature neurons. He needed neurons that were genetically marked so that he could identify them and later prove that he had not used less specialized, dividing cells.

Meanwhile, Axel's team had generated mice in which OSNs produce a visible green fluorescent protein (GFP) when they reach terminal differentiation, making them easily distinguishable under the microscope from cells that can still divide. A natural collaboration soon formed that combined Axel's techniques for selecting and marking mature OSNs with Jaenisch's methods for cloning from terminally differentiated cells.

The collaborators essentially wanted to know whether a mature OSN could be reprogrammed to generate a mouse clone and, if so, whether the mouse would express the entire repertoire of olfactory receptors or just the one of its parent cell.

For their first experiment, the researchers randomly selected GFP-expressing OSNs with unidentified receptors. Eggan transferred nuclei from the GFP-expressing OSNs into oocytes from which nuclei had been removed. Astonishingly, he managed to coax the resulting eggs to divide and generate embryonic stem cells—a first in science for neurons. The team then transferred the resulting embryos to surrogate mothers and awaited the births.

"It was so exciting to see live mouse pups glowing green," Baldwin recalls. "Then we saw that they were nursing, and mice that cannot smell their mother don't nurse. We had a hint right away that their olfactory system was normal. But we needed to confirm this through a series of careful experiments to compare their olfactory systems with those of normal mice."

The Axel lab then tested whether the mice expressed one receptor either exclusively or in overabundance and whether specific odorants relayed an abnormal pattern to the olfactory bulb. All signs indicated a normal sense of smell.

But was there any genetic rearrangement? To find out, the researchers needed to know which specific olfactory sensory receptor was expressed by the donor neuron so that they could examine that receptor's genetic sequence. In a new experiment, they used a line of mice in which only the neurons expressing one specific odorant receptor, the well-known P2 receptor, were tagged with GFP. They then used the neurons expressing P2 (which they could isolate because they alone glowed green) to generate cloned embryonic stem cells and mice. Again, the cloned babies expressed the full spectrum of odorant receptors without any preference for the P2 receptor that the donor neuron had expressed exclusively. Importantly, because they knew the P2 gene's DNA sequence, they could look for changes in and around the clones' P2 genes. "We found nothing," Baldwin says, though they are now exploring other areas of the clones' genome.

Meanwhile, the researchers could make some firm conclusions. "Our experiments demonstrated that mature OSNs expressing only one receptor are totipotent and can generate mice that express the entire repertoire of odorant receptors," Axel observes.

Taking the genetic-change model off the list of usual suspects narrows the investigation into the mysteries of the olfactory system. "Now," says Axel, "given that there appear to be no irreversible changes in DNA, we ask: What mechanism ensures that a cell will make only one type of receptor?" Additional experiments are planned.

Still, Axel also simply wants to know more about the nose. "People often view smell as an aesthetic sense that elicits enduring thoughts and memories," he says. "But it's also a primal sense, the primary way most animals interact with the external world and identify food, predators, and mates. Without it, they could not survive."

So why is smell important in humans? For one thing, Axel suggests, "perhaps it's the way you choose your mate."

—CATHRYN M. DELUDE

Woody Allen (above center, with Diane Keaton, in the movie Sleeper*) inspired Richard Axel (left) in recent research, and mice cloned from neurons (above, with associate research scientist Kristin Baldwin) was just one result. It's all part of Axel's ongoing work to better understand the mysteries of the olfactory system.*

OPPOSITE AND MIDDLE: JENNIFER ALTMAN; TOP: GETTY IMAGES

Ask a Scientist

Responding online to student questions can also tutor the teacher.

Why is life cellular in nature? Is cloning possible from a piece of hair or any other body part? Why are some species rare while others are abundant?

When questions like these pique the interest of high school or college students, and answers can't be found in class or in a textbook, who better to turn to than a working scientist? That's what HHMI's Ask a Scientist Web site is all about. "We want to help satisfy people's honest curiosity about the world around them," says Dennis Liu, program director of the Institute's public science education initiatives. "We want to answer the questions that fall outside the curriculum."

More than 100 scientists have volunteered their time to answer the 50 to 100 questions submitted to the Web site every week. "The scientific process starts with a good question," says Alexey Veraksa, a former HHMI predoctoral fellow who is now a postdoc at Harvard Medical School, "so we should really encourage all students to ask questions." Lucy Godley, a former HHMI medical student fellow who is currently an assistant professor of medicine at the University of Chicago, points to the pedagogical value of the student-scientist connection. "It's important to give young people access to people doing science in the lab," she says. "It can really make a big difference and inspire them."

After a quick review, program staff send student questions to a volunteer scientist who has relevant expertise. The scientist generally responds within a couple of weeks. Questioners receive an answer directly. Each week, particularly interesting questions and answers are posted online. They are then archived for later reference by other students.

There are other similar services, but Ask a Scientist's approach is unique. "Some of the other sites will collect a hundred questions and then pick only one or two to answer and publish on the Web," says Liu. "What distinguishes our program is that we provide a detailed response, and sometimes more than one response, to almost 90 percent of the questions." Questions not answered by Ask A Scientist are referred to other sources.

GENE FOR CHOCOLATE MILK

Participating scientists are recruited mainly from HHMI's pool of current and former fellows from one of the Institute's graduate or medical student programs. Volunteers have the option to accept a question or suggest that it be sent to someone else. The choice depends on whether the topic falls within the scientist's area of expertise, whether it grabs his or her interest, and, of course, whether the researcher's schedule can accommodate it. "Not all questions take a long time to answer," says Veraksa. "A lot of them are about techniques—how to do a ligation, how to do a PCR [polymerase chain reaction, a technique used to copy fragments of DNA]—and this is what I do every day in the lab. So I don't need to think long and hard about the answers."

But some questions require reflection—and a search through the relevant literature. One questioner asked, Could you take the gene that gives the cocoa bean its flavor and put it in cows, thus giving you a cow that would produce chocolate milk? "I had a lot of fun answering that one," says Veraksa, "and I learned a lot about the chocolate-making process." Veraksa spends up to two hours a week on Ask a Scientist.

Other volunteers also enjoy mixing the mundane and the sublime. "I like simple questions about my favorite topic of neuroscience," says Michael Tri Do, a former HHMI predoctoral fellow who is now a postdoc at Harvard Medical School. "But I also like the ones that are more general because it can get me into the philosophical aspects of doing science. For example, a while back I got this question: 'Basically, we are made of atoms. How do they work together to create our thoughts and our awareness of life?' I thought that was a great question." Do, who majored in religious studies, crafted a 1,300-word answer with several references for further reading.

Although staff try to match questions to participating scientists by field, some Ask a Scientist volunteers are willing to spend a few hours doing research into a topic not directly relevant to their area of expertise, simply because it can be interesting and helpful to them. "Once I got a question about bird physiology even though I work on insects," says Jayatri Das, an HHMI predoctoral fellow at Princeton University. "I ended up learning something new by interviewing a scientist who is an expert on birds."

Curious Minds Want To Know

A sampling of recent questions fielded by HHMI's Ask A Scientist and an answer to one:

- **How does diabetes cause blindness?**
- **Why is it an advantage to have different cells specialized to carry out particular functions?**
- **Why has no one found a cure for the common cold?**
- **What are the differences in the structures and effects of "good" and "bad" cholesterol?**
- **What is the role of the p53 gene in cancer genetics?**

Q. How did the discovery of cells lead to the germ theory of disease?

—Michael, a middle school student from Miami, Florida

Do has had similar experiences. "I went to hear a talk on the sleep-wake cycle by HHMI investigator Masashi Yanagisawa. As I was listening to the talk I realized that most of what I knew about the topic came from a question I had answered for Ask a Scientist."

SAVVY QUESTIONERS

Volunteer scientists also report that the questions students ask these days are surprisingly astute. "There is a greater awareness among high school students than what I had when I was in high school, and it wasn't that long ago!" says Tom Rutkowski, an HHMI postdoctoral fellow at the University of Michigan Medical Center.

Godley has had similar impressions. "It's striking to me that someone in high school is asking some of the questions being debated in the scientific literature," she says. "One student, confused about how many genes humans possess, asked, 'I have read different numbers. Why is there no simple answer?' What a great question. This person really was thinking very hard, and not unlike scientists involved in the Human Genome Project."

For their part, the students asking the questions appreciate the hard work of the volunteer scientists. "They have no qualms about answering questions, no matter how frivolous; the way in which they answer them makes learning a pleasure; and understanding and conceptualizing things discussed in a textbook become very easy as a result," says a student from South Africa who has been submitting questions for more than two years and who sometimes even requests that specific scientists answer his queries.

Not all of the program's volunteers are junior scientists, however. Nicholas R. Cozzarelli, professor of molecular and cell biology at the University of California, Berkeley, and editor-in-chief of the Proceedings of the National Academy of Sciences, has been answering Ask a Scientist questions for several years. "I love communicating science as much as I did when I was a college student—probably more," says Cozzarelli, who credits his daughter Laura, a primary-school teacher, with getting him interested in reaching out to younger people.

Viewing Ask a Scientist as a valuable part of scientific training, HHMI encourages its fellows to participate. Peter J. Bruns, HHMI's vice president for grants and special programs, says the program cuts two ways: "It helps with the public understanding of science," he says, "and it also broadens what the trainees are exposed to." Maryrose Franko, the program officer who oversees HHMI's fellows programs, adds that Ask A Scientist gives fellows "an opportunity to communicate science and get connected to the outside world."

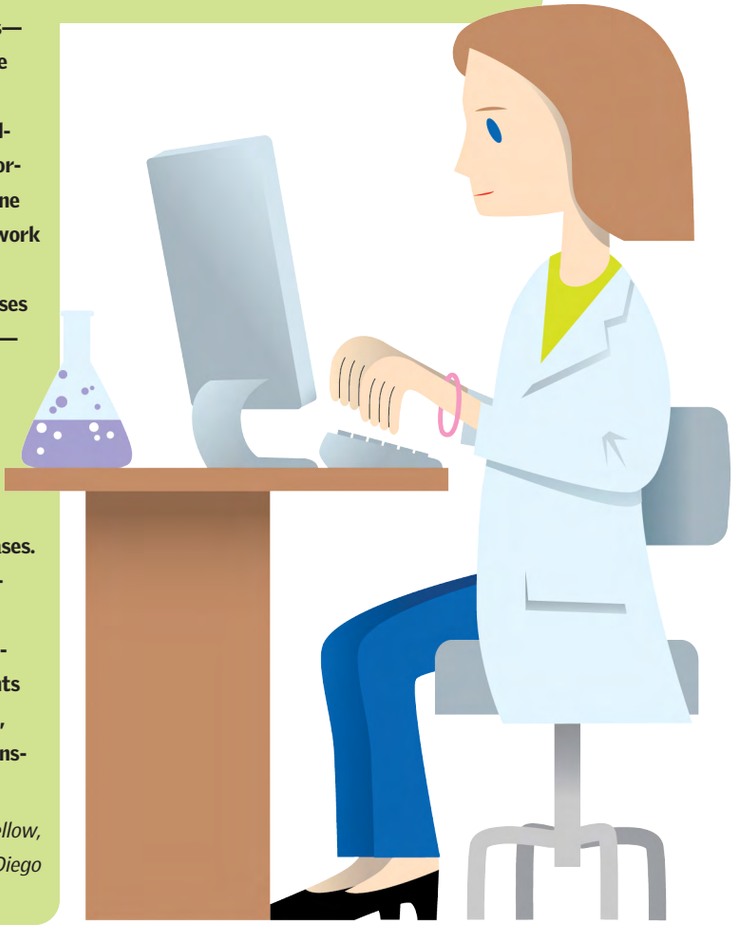
Das, a relatively recent volunteer, wholeheartedly agrees. "Ask a Scientist is a great program," she says, "and I plan to keep on doing it."—**LAURA BONETTA**

Ask a Scientist is located at www.hhmi.org/askascientist.

A. Anton van Leeuwenhoek discovered cells in the 1670s when he invented the first simple microscope and observed the organized structure of cork cells. Through his simple microscope, he also observed the first microorganisms, single-celled creatures too small to be seen by the naked eye. It wasn't until about 200 years later that Louis Pasteur definitively showed that microorganisms in the air were the cause of contamination and responsible for the process of fermentation (for example, turning grape juice into wine). In his experiments, he sterilized liquid broth by boiling it and then left some in a flask exposed to the air and some in a sealed flask. The exposed flask eventually became contaminated, and the sealed flask remained free of contamination. Pasteur's work was the first step toward the germ theory of disease, which says that disease is caused by exposure to microorganisms. From the mid-1870s to early 1880s, Robert Koch furthered the germ theory by showing that specific diseases—anthrax, tuberculosis, and cholera—were caused by specific microorganisms.

The germ theory of disease is considered by many to be one of the most important contributions to science and medicine (if not the most important). Before the work of van Leeuwenhoek, Pasteur, Koch, and others, most doctors believed that diseases were caused by spontaneous generation—that is, infections arose from nonliving material. And since it was believed that microorganisms could arise from nonliving substances, scientists and doctors of that time saw no purpose in trying to discover ways to prevent diseases. In fact, before the germ theory was proposed, doctors would actually perform autopsies on people who died of an infectious disease and then go care for patients without washing their hands in between, not realizing that they were actually transmitting the disease themselves!

— Kendall Powell, HHMI predoctoral fellow, University of California–San Diego



DANIEL FAZER

A WELLSPRING OF SCIENTISTS

When it comes to producing science Ph.D.s, liberal arts colleges are at the head of the class. By CHRISTOPHER CONNELL

PHOTOGRAPH BY TODD BUCHANAN

WHEN IT WAS TIME TO DECIDE ON A COLLEGE, future Nobel laureate David Baltimore turned down Harvard and Cornell and elected to earn his undergraduate degree at Swarthmore College, a small Quaker school in Pennsylvania. ¶ Nobelist Harold E. Varmus graduated from Amherst College in central Massachusetts. ¶ And HHMI President Thomas R. Cech, who won the Nobel Prize in chemistry in 1989, says that "the intellectual cross-training" in the humanities and arts that he received at Iowa's Grinnell College made a profound difference in his life. ¶ Every scientist follows his or her own path, but how likely is it that future Nobelists will track in the footsteps of Cech and company to pursue undergraduate studies at liberal arts colleges? Judging from the trends, very likely. ¶ Liberal arts colleges have a long, prolific history of sending students on to graduate school and careers in science, both as front-line researchers and to serve as the next generation of faculty. They enroll about 1 in 12 undergraduates, but turn out almost 1 in 6 future Ph.D.s in science and engineering. Oberlin, Reed, Swarthmore, Williams, Wellesley, and similar schools that concentrate on undergraduate education and award few if any degrees beyond the bachelor's take pride in their ability to train future scientists—despite, or perhaps because of, their small size. "We have open doors," says A. Malcolm Campbell, a biologist who teaches and conducts genomics research at Davidson College in North Carolina. "The students come in, they ask questions, we get them into our labs. The students are not afraid of their teachers. Teaching is highly valued here,

"Intensity and fervor." *James Gentile (center left), with student scientists at Hope College, says the passion for teaching at liberal arts colleges mirrors enthusiasm for research at large universities.*

as is the mentoring and the hands-on access to research opportunities. It's the right mix."

"The cutting-edge science is done at the R-1 [Research 1, or major research] universities. No one would quibble with that," says James M. Gentile, recently appointed president of the Research Corporation, who has served as dean for the natural sciences at Hope College in Michigan. Regardless, Gentile says, "there are wonderful liberal arts colleges across the country where the intensity and fervor of teaching" is akin to the passion that scientists bring to the lab at research universities.

THE BRIGHT AND THE (NOT SO) BOLD

Skeptics suggest that liberal arts colleges' success in turning out scientists is attributable more to their admissions offices than their science faculty. At Reed College in Oregon, for example, the median SAT score for the class of 2007 was 1,359 (out of 1,600 points). The national average for entering freshman was 1,026. "It's not like we turn coal into diamonds. They come in bright," says Peter J. Russell, a Reed biology professor. "Basically we channel them … [and] stimulate them to perform at their highest level."

Channeling is an important function of the liberal arts colleges. With small student-faculty ratios and courses in which professors know every student by name, these schools are adept at steering students into the sciences and other rigorous majors.

What liberal arts colleges may do best is to open a path for students too diffident to push their way forward. Consider molecular biochemist Manju M. Hingorani, who joined Connecticut's Wesleyan University in 2000. She specializes in DNA replication and repair, publishes regularly, and collaborates with HHMI investigator Michael E. O'Donnell at the Rockefeller University in New York. Hingorani says the attention that faculty lavish on the undergraduates at Wesleyan is unimaginable at a research university. "I'm here all the time. I'm here at 7 in the morning. I'm here at 8 at night. I'm here on weekends. It's not just me, it's most professors," says Hingorani. The undergraduates whom she remembers from her teaching assistant days were "the ones with initiative, willing to knock down the professor's door if that's what it took. At Wesleyan, we have so many students who are a bit more tentative—bright, even brilliant, students who maybe just need to be in a class with only 10 students so that they can speak up and say, 'OK, I have an idea.'

New worlds. *Wellesley chemist Nancy Kolodny found her career path as an undergraduate at the college.*

"The bright and bold," says Hingorani, "they'll do great anywhere. It's the others who are bright but maybe not so bold who benefit the most from places like this."

Small colleges often turn students on to research. "Students here often don't know about research as a career," says Nancy H. Kolodny, a professor of chemistry at Wellesley College in Massachusetts. "It's our responsibility that they find out about it as early as possible." A Wellesley alumna, Kolodny took chemistry to fulfill a distribution requirement, then spent

SMALL COLLEGES MAKE BIG INVESTMENTS

Rather than compete head-on with the major research universities, small colleges cultivate a unique niche.

Liberal arts colleges often spend hundreds of thousands of dollars to set up new science-faculty hires. Manju M. Hingorani, a molecular biochemist at Wesleyan University, says that the college lavished upwards of $300,000 on her equipment and a similar amount on renovating her lab, inherited from a retiring researcher. But Wesleyan's investment quickly paid off when Hingorani won a five-year, $1 million grant from the NIH.

Wellesley College President Diana Chapman Walsh says that steep start-up costs are a fact of life for liberal arts colleges serious about having science faculty combine teaching with research. "We need to help them get started because we know it's harder here" to land large research grants. The Wellesley College Science Center, which underwent a major renovation in 1991, boasts two nuclear magnetic resonance spectrometers, microcalorimeters, two electron microscopes, and a high-powered laser—all kept in steady use by faculty and undergraduates. Walsh says that the success of Wellesley's science faculty in securing research grants "has affected the larger culture of the college. The social scientists have gotten wind of it and now they want to do more hands-on research mentoring of students."

Many small colleges, in much the same spirit, have replaced cramped science buildings that dated from the Sputnik era. Williams College opened a new science center in 2000. Haverford College opened its new Koshland Integrated Natural Sciences Center in 2002. In 2003, Mount Holyoke College completed Kendade Hall, which cleverly links existing lab space and other academic buildings into a unified science center. A similar center at Swarthmore, which opened this past spring, connects the science and math departments. All these centers cost their colleges tens of millions of dollars.

It's a fact of life, however, that research universities are always going to have the advantage of newer, bigger, and better equipment, simply because "research-intensive universities are fundamentally different from small liberal arts colleges in their mission and focus," says Shirley M. Tilghman, president of Princeton University and a former HHMI investigator.

Nevertheless, if they wish to do science well, small colleges "must decide whether they are willing to make the investment in infrastructure to provide the environment for science to prosper," says Tilghman. "If not, they cannot turn around and expect the faculty to be competitive." —CC

JASON GROW

two summers in a lab with other Wellesley students, courtesy of the National Science Foundation. "If I hadn't gone to Wellesley or another small liberal arts college, I never would have gone into research," says Kolodny.

REAL SCIENCE

Access to faculty is easier at small liberal arts campuses than at most R-1 universities, says molecular biologist Shirley M. Tilghman, the president of Princeton University and a former HHMI investigator. "In addition," she says, "students in small liberal arts colleges aren't spending their time with disgruntled eight-year graduate students terrified they won't get their Ph.D.s and five-year postdocs terrified they won't get a job."

When A. Malcolm Campbell was finishing graduate studies at the Johns Hopkins University, a professor bluntly warned him, "Don't go into teaching. You'll go brain dead." Campbell ignored the advice, headed to Macalester College in Minnesota, and later joined the faculty at Davidson College, where he has found a balance between the classroom and the laboratory.

While most newly trained scientists emerging from Ph.D. programs and postdoctoral fellowships at major research campuses elect to stay within that universe, scores make the decision that Campbell made.

> **"Every science course I took at Swarthmore—and there were a lot—had a lab associated with it. That is unheard of."** —Joseph Takahashi

Teaching at top liberal arts colleges allows them to do important research, although at a slower pace than in the hothouse R-1 university world.

Reed College avidly recruits faculty with such interests. With 1,340 students—a quarter of whom major in math, science, or engineering—Reed hires faculty with a research interest as well as a passion for teaching, then provides the infrastructure that allows them to do both, according to biology professor Peter Russell. "We have a fully fledged stockroom and two assistants to prepare our labs," he says. That means Russell, who experiments with budding yeast, can spend time in the lab talking with students about "the serious stuff, not telling them how to pour gels."

At California's Harvey Mudd College, all 700 undergraduates study science or engineering and are eager for collaboration. "I've had students from four departments in my lab—biologists, chemists, physicists, and engineers," says Elizabeth J. Orwin, a professor of engineering and biology. In her research on growing cells that may one day constitute replacement corneas, "I've got students not only working on the tissue, but also trying to get the matrix material. We've got engineers building a bioreactor so we can grow these things with the same physical, mechanical, and chemical stimuli that they have in the eye."

"At a bigger campus, I couldn't take any risks or do anything that would lead to my not publishing," Orwin says. "A place like [this] gives you the opportunity to explore things you might not do at an R-1 university."

One by-product of professor-student collaboration is that faculty scientists often publish papers with undergraduates as coauthors in peer-reviewed journals. Because most liberal arts colleges have few if any graduate students or postdocs, "we have to bring undergraduates into that niche" for laboratory research, says Scott F. Gilbert, a professor of biology at Swarthmore. Admittedly, it's a slower process. "It takes a long time before you get a paper out," says Gilbert.

Thomas Wenzel, a professor of chemistry at Bates College in Maine, says that "the research I am doing at Bates is of similar quality to the work I did during my Ph.D. thesis at the University of Colorado, and the students are not frustrating me. They make my job worthwhile." Wenzel advocates getting undergraduate students involved in research right away. "I do semester-long projects in my first semester general chemistry class right off the bat instead of weekly, boring three-hour experiments. That way, they get really engaged."

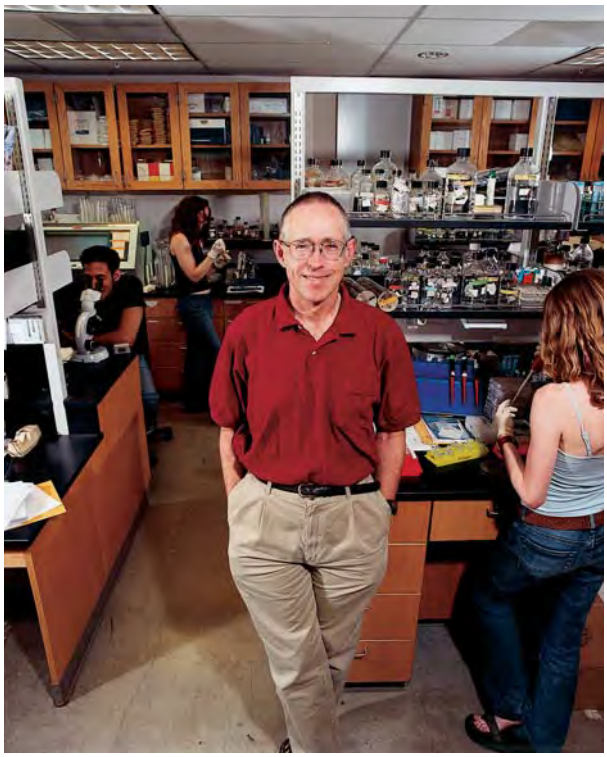
PREPARATION FOR LIFE

For some students, that engagement turns into a lifelong passion. Renowned scientists who are alums of liberal arts colleges often remember their undergraduate days with fondness, and they speak highly of the education that prepared them for life in the laboratory and the public arena. HHMI's Cech attributes part of his scientific success to his study of the humanities and arts at Grinnell. "In addition to whatever exposure one gets to undergraduate research at these places," he says, "maybe it's the liberal arts education as a whole that gives you the broad-based education needed to be an imaginative scientist."

David C. Page, an HHMI investigator at the Whitehead Institute for Biomedical Research, remembers Swarthmore's honors program and seminars as key to his personal and professional growth. "You were given a topic and some suggested readings and expected to show up and discuss the topic intelligently. That meant we needed to be completely comfortable with the library and with critically analyzing and digesting the scientific literature without someone holding your hand. This made me better able to take on new intellectual pursuits with minimal supervision."

Another HHMI investigator, neurobiologist Joseph S. Takahashi at Northwestern University, is still struck by the fact that "every science course I took at Swarthmore—and there were a lot, like 16—had a lab associated with it. That is unheard of." In a course taught by physiologist Kenneth Rawson, Takahashi became fascinated with circadian rhythms, a topic he pursues to this day.

Harold Varmus, president of Memorial Sloan-Kettering Cancer Center, in an article written more than



ROBBIE MACLAREN

Faculty hires. *Biologist Peter Russell says Reed College recruits faculty who want to blend research and teaching.*

a decade ago for an Amherst publication, said that in a small liberal arts college students can learn "the arts of exposition and criticism that scientists often wait too long to learn. Most scientists spend an extraordinary amount of time reading, writing, and speaking, for which imagination, critical analysis, and clarity of expression become more important than any technology."

Varmus, who majored in English at Amherst and also obtained a master's degree in literature at Harvard University before finding his way to medical school, called himself "a confirmed proponent of prolonged adolescence and career indecision."

David Baltimore, now president of the California Institute of Technology, agrees that it's better to devote a good part of one's undergraduate years to unconstrained exploration, which is a bit more likely, even expected, at a small liberal arts school: "This is one time in your life

WHERE DO FUTURE PH.D.s COME FROM?

The National Science Foundation (NSF) keeps track not only of how many doctorates U.S. institutions award each year, but also where the recipients earned their undergraduate degrees. The NSF's latest tally shows that liberal arts colleges continue to excel at this enterprise. Although they enroll approximately 8 percent of four-year college students, from 1996 to 2002 their graduates earned 15.5 percent of the Ph.D.s awarded.

The top 25 research universities, meanwhile, produced five times as many Ph.D.s as the top 25 baccalaureate institutions—but they also enrolled five to ten times as many students.

For example, the University of California, Berkeley, which reserves prime parking spaces on campus for the eight Nobel Prize winners on its faculty, produced 2,234 undergraduates who earned science and engineering Ph.D.s from 1996 to 2002, more than any other institution. Berkeley enrolls almost 24,000 undergraduates. Oberlin College, which led the baccalaureate schools with 417 science and engineering Ph.D.s, enrolls fewer than 2,900.

The NSF data also show that the same highly selective four-year colleges remain at the head of the class in producing science Ph.D.s. Indeed, these schools have become even more productive since the NSF's 1996 report, *Undergraduate Origins of Recent (1991-95) Science and Engineering Doctorate Recipients* (NSF 96-334). From 1991 to 1995, graduates from the top 25 baccalaureate colleges earned 3,686 science and engineering Ph.D.s, for an average of 737 a year, and from 1996 to 2002 graduates from these schools earned 5,648 science and engineering Ph.D.s, or 807 a year. The accompanying charts tell the story in raw numbers.

—CC

Top 25 "research universities" that were baccalaureate origins of 1996–2002 science and engineering (S&E) doctorate recipients, ranked according to total S&E doctorates

Rank	Name	S&E total	Physical sciences
1	University of California, Berkeley	2,234	1,794
2	Cornell University, all campuses	1,730	1,362
3	University of Illinois at Urbana–Champaign	1,488	992
4	University of Michigan at Ann Arbor	1,478	1,143
5	Massachusetts Institute of Technology	1,331	821
6	Pennsylvania State Univ., main campus	1,256	889
7	University of Wisconsin–Madison	1,237	1,030
8	Harvard University	1,213	1,160
9	University of California, Los Angeles	1,139	958
10	University of Texas at Austin	1,134	893
11	University of California, Davis	1,031	876
12	Texas A&M University, main campus	961	725
13	Stanford University	939	786
14	University of Minnesota–Twin Cities	903	669
15	Purdue University, main campus	901	557
16	University of California, San Diego	860	737
17	Michigan State University	831	687
18	University of Florida	818	610
19	Virginia Polytechnic Institute and State Univ.	805	521
20	University of Pennsylvania	783	639
21	Yale University	781	731
22	Princeton University	780	631
23	University of Washington–Seattle	768	613
24	Rutgers the State Univ. of NJ New Brunswick	765	610
25	University of Virginia, main campus	763	603
Total, top 25		26,929	21,037
Total, all "research universities"		50,631	40,244
Top 25 as a percent of all "research universities"		53.2	52.3

Top 25 "baccalaureate colleges" that were baccalaureate origins of 1996–2002 science and engineering (S&E) doctorate recipients

Rank	Name	S&E total	Physical sciences
1	Oberlin College	417	417
2	Swarthmore College	368	368
3	Carleton College	357	357
4	Wesleyan University	319	319
5	Williams College	292	292
6	Wellesley College	257	257
7	Reed College	251	251
8	Smith College	235	235
9	St. Olaf College	228	228
10	Grinnell College	227	227
11	Pomona College	216	214
12	Bucknell University	213	213
13	Bryn Mawr College	196	196
14	Vassar College	196	190
15	Colgate University	189	187
16	Amherst College	187	187
17	Haverford College	185	185
18	Mount Holyoke College	179	178
19	Franklin & Marshall College	175	175
20	Barnard College	174	174
21	Macalester College	171	170
22	Bowdoin College	166	166
23	Bates College	154	154
24	Allegheny College	150	149
25	Furman University	146	144
Total, top 25		5,648	5,633
Total, all "baccalaureate colleges"		17,097	16,313
Top 25 as a percent of all "baccalaureate colleges"		33.0	34.5

Source for tables: National Science Foundation, Division of Science Resources Statistics

ERRATUM: In each table on page 14, the right column is mislabeled. The label should read "Sciences only."

The tables below, from the National Science Foundation, tell a more complete story. The first table shows the top 25 baccalaureate colleges in producing science and engineering Ph.D.s during the years 1996-2002, sorting their graduates who went on to earn doctorates in the sciences by field of study. The second table reports similar data for research universities.

Top 25 baccalaureate colleges that were baccalaureate origins of 1996-02 science and engineering (S&E) doctorate recipients, ranked according to total S&E doctorates, by field of doctorate

Baccalaureate-origin institution	S&E total	Total sciences	FIELD OF SCIENCE: Physical sciences	Earth, atmospheric, & ocean sciences	Mathematics	Computer science	Agricultural sciences	Biological sciences	Psychology	Social sciences	Total engineering
Oberlin College	417	417	50	24	15	15	5	111	68	123	0
Swarthmore College	368	368	36	8	15	8	2	104	50	110	0
Carleton College	357	357	77	45	14	3	7	64	51	85	0
Wesleyan University	319	319	25	13	9	5	0	65	81	114	0
Williams College	292	292	47	17	11	12	5	63	53	76	0
Wellesley College	257	257	28	5	10	2	0	75	66	67	0
Reed College	251	251	53	6	24	6	9	84	15	50	0
Smith College	235	235	14	10	5	2	2	56	72	73	0
St. Olaf College	228	228	49	7	23	1	5	62	28	36	0
Grinnell College	227	227	43	2	13	1	4	58	37	58	0
Pomona College	216	214	16	14	18	2	2	44	50	61	2
Bucknell University	213	213	24	5	3	7	3	69	41	32	0
Bryn Mawr College	196	196	29	9	7	0	2	38	37	70	0
Vassar College	196	190	18	1	7	3	1	35	80	49	6
Colgate University	189	187	24	17	4	2	4	42	43	45	2
Amherst College	187	187	26	12	7	4	2	52	35	44	0
Haverford College	185	185	34	10	6	6	5	45	27	43	0
Mount Holyoke College	179	178	15	6	0	4	4	83	33	30	1
Franklin & Marshall College	175	175	38	16	2	3	1	32	35	39	0
Barnard College	174	174	7	2	2	3	0	37	76	45	0
Macalester College	171	170	21	13	3	1	2	39	27	60	1
Bowdoin College	166	166	38	7	4	5	4	53	19	32	0
Bates College	154	154	26	11	2	1	2	46	28	29	0
Allegheny College	150	149	23	7	6	3	2	48	30	18	1
Furman University	146	144	48	5	6	6	2	33	28	13	2

Top 25 research universities that were baccalaureate origins of 1996-02 science and engineering (S&E) doctorate recipients, ranked according to total S&E doctorates, by field of doctorate

Baccalaureate-origin institution	S&E total	Total sciences	FIELD OF SCIENCE: Physical sciences	Earth, atmospheric, & ocean sciences	Mathematics	Computer science	Agricultural sciences	Biological sciences	Psychology	Social sciences	Total engineering
University of California, Berkeley	2,234	1,794	311	59	80	77	21	587	227	432	440
Cornell University, all campuses	1,730	1,362	188	37	43	68	85	499	228	214	368
University of Illinois at Urbana-Champaign	1,488	992	183	21	32	37	54	378	162	125	496
University of Michigan at Ann Arbor	1,478	1,143	131	36	46	38	25	311	313	243	335
Massachusetts Institute of Technology	1,331	821	295	29	76	93	4	230	24	70	510
Pennsylvania State University, main campus	1,256	889	133	47	35	22	57	322	141	132	367
University of Wisconsin-Madison	1,237	1,030	158	38	32	24	52	322	183	221	207
Harvard University	1,213	1,160	181	46	87	56	7	337	109	337	53
University of California, Los Angeles	1,139	958	126	31	26	28	3	294	280	170	181
University of Texas at Austin	1,134	893	128	32	28	31	8	237	242	187	241
University of California, Davis	1,031	876	113	33	20	21	53	424	114	98	155
Texas A&M University, main campus	961	725	83	27	19	13	103	263	119	98	236
Stanford University	939	786	83	37	30	48	10	246	120	212	153
University of Minnesota-Twin Cities	903	669	105	24	18	26	53	198	108	137	234
Purdue University, main campus	901	557	103	24	21	28	56	200	80	45	344
University of California, San Diego	860	737	103	31	34	17	5	297	157	93	123
Michigan State University	831	687	76	16	22	26	64	183	147	153	144
University of Florida	818	610	87	13	28	10	42	143	181	106	208
Virginia Polytechnic Institute and State University	805	521	94	19	25	18	53	191	70	51	284
University of Pennsylvania	783	639	58	19	21	29	2	184	162	164	144
Yale University	781	731	96	37	33	30	8	215	129	183	50
Princeton University	780	631	128	23	48	42	4	177	53	156	149
University of Washington-Seattle	768	613	92	32	16	22	28	177	122	124	155
Rutgers, The State University of New Jersey, New Brunswick	765	610	63	34	9	20	29	225	123	107	155
University of Virginia, main campus	763	603	87	29	20	16	5	174	126	146	160

Source (both tables): National Science Foundation, Division of Science Resources Statistics, Survey of Earned Doctorates.

when you can get broad experience and develop those things that are not standard scientific capabilities."

NIFTY FIFTY

Intellectual hothouses such as Swarthmore, Reed, and Oberlin have produced science Ph.D.s in significant numbers for decades, and more recently other liberal arts colleges have been doing so as well. Some benefited from a buyer's market for new science Ph.D.s in the 1970s and 1980s, when limited opportunities at the major research universities led more young academics to consider careers at smaller colleges, where they could combine teaching with research.

When Oberlin College organized a group of liberal arts colleges in 1985 to seek more government and foundation support for their science programs, they were dubbed the "Nifty Fifty." That number has since grown. When the Research Corporation released its 2001 *Academic Excellence* study of undergraduate science research, it counted 136 public and private colleges that were endeavoring to combine serious research with committed teaching.

The approach of getting undergraduates into labs with faculty, not only as mentors but also as research partners, no longer is exclusively the province of highly selective, private liberal arts colleges. It has now caught on with a growing number of other private and public colleges as well.

Mark Jacobs, long a star on the biology faculty at Swarthmore College, was wooed by Arizona State University (ASU) in 2003 to become dean of its Barrett Honors College. ASU's honors students "are just as smart as the Swarthmore kids," says Jacobs. "You've got to invent a way to get the kids into labs, and that's what we're trying to do." Few universities offer labs with every science course the way Swarthmore does, and fewer still have full professors teaching those labs, he notes. "Undergrads are a lot more ready and willing to embrace real research than lots of older-style professors would ever believe. The old conception that students are bothersome fleas that have to be flicked off the professor's hide is breaking down," says Jacobs.

California State University at Fullerton and Western Washington University also exemplify public colleges that engage their undergraduates in research. After three decades at the University of Colorado at Boulder, Arlan Norman became dean of the College of Sciences and Technology at Western Washington University, which has 12,000 undergraduates. Norman says Western Washington endeavors to get science majors "working side by side with faculty who are experienced teachers and researchers. There is not the hierarchy of mentorship that often exists in primarily research institutions, where the undergrad works with a grad student, much of the grad student's work is supervised by a postdoc, and the postdoc reports to the faculty lab director."

So the liberal arts college model of science education and research is spreading. At Wesleyan, Manju Hingorani says of her 14-hour days in class, office, and lab: "I am very tired, but I am so happy. I see the faculty and students committed to science and more research money around me, and at many other institutions as well. It is a very exciting time."

Cancer researcher Thomas R. Tritton, president of Haverford College, once suggested that an inexpensive way to gauge the vitality of scientific research on a campus was to walk by the labs at 11:30 p.m. and see how many lights were on. For now, liberal arts colleges are keeping their laboratories' lights burning. H

JASON GROW

FACULTY ROLE-MODEL

A Mentor and Four Students

There is no "middleman" in the science labs at Wellesley.

Is this heaven? *When Mary Allen joined the Wellesley faculty, she marveled at how much time colleagues spent with undergraduates.*

Microbiologist Mary M. Allen works with Wellesley College undergraduates unraveling the mysteries of cyanobacteria, perhaps the oldest oxygen-producing organisms on earth. "There's no middleman in our laboratories—no postdocs or graduate students between me and my students," says Allen. For decades, Wellesley has produced more scientists than all but a handful of other liberal arts colleges.

When Allen joined the Wellesley faculty in 1968, she marveled at how much time colleagues spent with undergraduates. "I thought I had died and gone to heaven. It was just fantastic," she recalls.

The faculty-student collaboration process at Wellesley requires patience. "The undergraduates take three years to do what a postdoc probably could do in a year, but the quality is the same," says Allen, a past president of the Council on Undergraduate Research. Three of her students became Beckman Scholars—recipients of $17,600 scholarships from the Arnold and Mabel Beckman Foundation for research over two summers and the senior year. In interviews, three Wellesley graduates and a senior spoke about their mentor.

Keren Lisa Witkin '98 graduated this spring from UC Berkeley with a Ph.D. in molecular and cell biology. She didn't envision a career in science when she entered Wellesley, "but in my first year I took 'Intro to Cell Biology' and loved it." The summers in Allen's lab were "a lot of fun," Witkin recalls. "We were a tight group. Mary was always encouraging." She calls Allen "a phenomenal mentor."

Witkin wrote her undergraduate thesis on heat-shock response in cyanobacteria, and she and Allen presented a poster on that work at the VI Cyanobacterial Workshop in Pacific Grove, California, in July 1998.

"That was one of the best parts about doing research as an undergraduate," Witkin says. "It was very unusual to go to meetings with undergraduates. Mary took two of us. We got to present our research in front of all these real scientists. The experience was amazing."

Jean Jing Huang '01 arrived at Wellesley knowing she wanted to study biology. "I had great mentors in a public elementary school in Brookline, Massachusetts. A friend and I won the science fair in sixth grade," she says. "We developed a test for lead in paint, and we went around town testing the paint in the library and other places."

Huang worked in Allen's lab during the summer after freshman year, looking at acid shock. Allen "was there when I needed help, but she wasn't telling me what to do. That was the best part, because I developed confidence," says Huang. The students even had keys to the lab, allowing them to work with a buddy late at night and on weekends.

"This project was very forgiving," she says. "I tried a lot of experiments. I'd take a course and learn about some technique, then try it with the cyanobacteria. Since we weren't looking for any one result, it could develop in all these different, interesting ways. We used NMR [nuclear magnetic resonance] spectrometers and all sorts of instruments, and we collaborated with other labs on campus." Huang, who became Allen's first Beckman Scholar, wound up presenting a paper at a microbiology conference in Barcelona and was the lead author of a paper published in the *Archives of Microbiology*.

"I really saw the best of what science was all about at Wellesley," says Huang, a third-year graduate student in biology at the California Institute of Technology. "The only model I saw was a successful professor." [HHMI, recognizing that graduate students and postdoctoral fellows may also serve as mentors, supports programs that train them in teaching as well as research at both colleges and universities.]

> **"I really saw the best of what science was all about at Wellesley. The only model I saw was a successful professor."**
>
> **—Jean Jing Huang**

Katie Shea '03 was bursting to do science, thanks in part to mentoring from her high school biology teacher, when she arrived at Wellesley from rural New Hampshire. She became Allen's second Beckman Scholar. (The third, Sogole Moin, class of 2005, received the honor just this spring.)

Allen "had an open-door policy. If things weren't going right, you'd ask her questions. She was floating in and out of the lab all the time," says Shea. Allen and other professors also met jointly each week with the students working in their labs, sharing progress reports and offering suggestions on how to deal with bottlenecks.

Shea took up the acid-stress work in her junior year, presented posters at American Society of Microbiology meetings in Salt Lake City and Washington, D.C., and graduated *summa cum laude*. She is now at Dartmouth Medical School, with her cap set toward pediatric oncology.

"I definitely want research to be part of my career," says Shea. "That's one aspect of oncology—your research can coordinate well with your clinical skills."

Tam-Linh N. Nguyen '04 came to Wellesley from Pennsylvania as a premed major, but soon switched to biology. When the opportunity came to work in Mary Allen's lab, Nguyen embraced it. "I found that I really, really liked being in the lab, I liked working with instruments, I liked doing science," she says.

Nguyen picked up the acid-stress work where Katie Shea left off. "They've already done so much work on this, I am a successor," she says. "But I feel like I'm contributing something to their project." If things fall into place, eventually a paper will be published with all the participants' names on it.

The young researcher says "Professor Allen is so approachable and so down-to-earth, she doesn't intimidate any of the students. I can talk with her about my problems. I talk to her about all sorts of things." They even discuss the progress of her sister Michelle, who just finished her freshman year at Wellesley.

Perhaps Allen has an eye on Michelle for the lab, too? "Possibly—or my sister has an eye on her," Nguyen replies. "If you want a mentoring relationship like that, you can't just sit around waiting for it to come to you. You have to go out and find it." —CC

CAMPUS CULTURE

The Faculty's Greatest Passion

At Swarthmore, the road to a Ph.D. starts in Bio 1 and 2.

SWARTHMORE COLLEGE, FOUNDED during the Civil War by Quakers who wanted a coeducational alternative to Haverford College, has always been fertile ground for training scientists. Among liberal arts schools, it was second only to Oberlin College in the number of science Ph.D.s produced between 1920 and 1976. The latest statistics from the National Science Foundation (NSF), for 1996–2002, show that Oberlin and Swarthmore are still first and second.

Some science Ph.D.s, no doubt, are born. But others are made, and a visitor to this campus can practically watch them being hatched in Bio 2—or, more formally, "Biology 002: Introduction to Organismal and Population Biology"—as Julie Hagelin, an expert on how birds use plumage ornamentation to attract mates, lectures on natural selection and how insects decide their optimal group and territory size. Between slides, she peppers the audience with questions. At the lecture's start, Hagelin tosses cotton into an aquarium containing a colleague's Siberian hamsters. At the end of class, she flips a switch so that an overhead camera projects the result of the animals' industry: a cozy nest built of fluffy cotton and pine shavings. While some students slam notebooks and bolt for the exits, others in this class of 100—gargantuan by Swarthmore standards—stream up the aisles for a closer look or to pose additional questions.

Hagelin team-teaches Bio 2 with three other biology professors; each also spends one afternoon a week in the lab with the students. In much the same manner, four other biologists team-teach "Biology 001: Cellular and Molecular Biology" in the fall. Students emerge from this pair of courses not only familiar with biological concepts from genetics to microbiology to ecology to behavior, but also on a first-name basis with most of the biology faculty.

Some students enter Swarthmore with physics or philosophy or political science in mind until Bio 1 or 2 essentially realigns their brain cells. And this is clearly a long-lasting realignment, as almost half of the college's biology majors go on to obtain doctorates in science.

For example, Aaron Strong, now a junior, arrived from Maine thinking about astrophysics, "but that changed the first week I was here." When Hagelin mentioned last year she was looking for students to do summer fieldwork studying crested auklets on an island in the Bering Sea off Alaska, Strong needed no second invitation. "He sent me an e-mail saying, 'I've wanted to go to the Arctic since I was five years old,'" recalls Hagelin. "I could see right away he was passionate about what he does. That's just the kind of student you want at a field site, where things don't always go the right way."

Strong spent winter break at Auburn University in Alabama, learning how to isolate bacterial DNA from bird feathers, and is one of three students working alongside Hagelin this summer on St. Lawrence Island, inhabited by a few hundred Siberian Yup'ik Eskimos and hundreds of thousands of birds, including the crested auklet, a monogamous seabird that produces a tangerine scent during courtship.

The Bio 1 and 2 experience tends to realign faculty brain cells as well, with similarly positive results. These classes are a far cry, says Hagelin, from "the cattle-call courses" at a large state university where she taught as a postdoctoral fellow, "with the cell phones going off and people reading newspapers during class. Here it's almost like they are little goldfish nibbling at my feet, wanting more and more and more."

DAVID GRAHAM

Teamwork. *Swarthmore students do lab work in groups, says Amy Cheng Vollmer, "because complex problems are solved by teams."*

PARKING EGOS AT THE DOOR

Swarthmore President Alfred H. Bloom says that the college hires faculty with a passion for combining teaching and research, and helps them stay current by granting paid sabbaticals every seventh semester.

> **"We've developed a culture of making sure our students have research experiences."**
>
> **—Carl Grossman, Swarthmore College**

Professors must tailor their research, however, to fit the fabric of a liberal arts college. "You can't do certain types of projects that require a full graduate team," notes Bloom, "and you can't do projects that require unbelievably costly equipment. But you can do a lot of exciting, important, and innovative interdisciplinary research." Toward that end, the school opened a new $77 million science center this spring.

Biology chair Amy Cheng Vollmer says that Swarthmore faculty are "willing to park their egos at the door" and see their success in their students' triumphs. Physics professor Carl Grossman agrees. "We've developed a culture of making sure our students have research experiences," says Grossman. He chooses experiments for his nonlinear-optics research lab "that combine entry-level work and get students thinking about what they can do in graduate school."

Two recent physics majors were able to extend that thinking on Rhodes scholarships. Matthew Landreman '03 spent two college summers in labs at the University of Minnesota and the Santa Fe Institute, courtesy of the NSF's Research Experience for Undergraduates program; his next two summers were spent in the spheromak (plasma ring) lab of Swarthmore plasma-physics professor Michael R. Brown. Now at Oxford, Landreman remembers not only exciting experiments in the lab, but also "a great number of excellent barbeques" at Brown's home. "I got to know other faculty well, even those with whom I never had a class," he says.

Jacob J. Krich '00 is pursing a Ph.D. in physics at Harvard, after three years studying mathematics during his Oxford sojourn. Krich's mentor was physics professor Peter Collings, who has done pioneering work in liquid crystals. "He explained advanced concepts of physics to me in a wonderful, patient manner," Krich recalls. "He was always a bright spot in the lab. Peter helped me through the hard parts and got me farther than either of us expected." Krich won an Apker Award from the American Physical Society for physics undergraduate research.

Even students who ace advanced placement science are encouraged to take one of the introductory biology courses, if only to hone an ability to write lab reports as though they were being submitted to the journals *Cell* or *Nature*. They also do this lab work in groups, says Vollmer, "because complex science problems are solved by teams rather than by single people."

The cutthroat competition often found on college campuses, especially in courses frequented by premeds, is less evident at Swarthmore, says cell biologist Elizabeth A. Vallen: "The kids here are driven internally, but they are amazingly kind and helpful to each other." Not once has a student asked Vallen if a topic covered in class would be on an exam.

"Students get excited any time I talk about what the end of knowledge is," says neurobiologist Kathleen Siwicki. "Our students sense that there's plenty of interesting science to be done"—in her own lab, for example, where she works with *Drosophila melanogaster*, or fruit flies. "We study learning and memory, and changes in the brain that are responsible for changes in behavior. We're working at a slower pace, naturally, because the students have lots of other commitments and don't work full-time in the lab," says Siwicki. "The most exciting part of the teaching experience here are those afternoons in seminar. The students select the papers and literature they want to read. Something goes on in those seminars that empowers them to think of themselves as scientists."

Several of Siwicki's students paid tribute to their mentor at the most recent Darwin's birthday party, an annual biology department event, by decorating cupcakes with icing that depicted two *Drosophila* a-courting.

FRUITS OF RESEARCH

To other institutions wishing to emulate Swarthmore's success at grooming scientists, President Bloom urges them to hire faculty "who treasure the work with undergraduates, and to change the criteria for promotion and tenure so that inspired teaching is rewarded."

Too often, the value of such teaching "is discounted as contrary to the seriousness of a research institution," says Bloom.

Five honors seniors bring their slides one morning to summarize their projects for a visitor. Seeta Sistla plans to pursue a Ph.D., while Stephanie Cross, Emily Ford, Matthew Goldstein, and Renuka Nayak aim to acquire joint M.D.-Ph.D. degrees.

"I'll be over 35 before my first job," says Cross, one of the cupcake decorators. "I knew from the start that I wanted to do biology. But there's a passion here at Swarthmore. It's in the professors and students."

Ford worked with biology professor Colin Purrington on a study of the evolutionary bias of handedness in twining vines; 90 percent of vines advance in a counter-clockwise manner.

In a Stanford lab last summer, Goldstein studied the potential of statins (cholesterol-lowering drugs) to suppress proliferation of T cell lymphoma. He is also a left-handed pitcher with a close-to-90-miles-per-hour fastball who cocaptained the Swarthmore baseball squad.

Nayak said studying *Drosophila* (fruit flies) "helped me see how research is done. It's all about asking questions. I came in really shy. Research has given me more confidence."

Seeta Sistla, of Albany, New York, arrived intending to major in philosophy but was converted by Bio 1 and 2. She hopes to publish with Purrington and plant physiologist Mark Jacobs (now dean of Barrett Honors College at Arizona State University) results of her research on plant vascular regeneration. **—CHRISTOPHER CONNELL**

THE STUDENT EXPERIENCE

Striving to Succeed

Traditionally minority and majority colleges alike offer benefits to students, and faculty, of color.

Erica Martin earned her undergraduate biology degree at Spelman College, a small, historically African American college for women in Atlanta. The 32-acre campus wasn't crawling with famous research scientists, and some specialized courses the M.D.-Ph.D. student wishes she could have taken—anatomy, for example—weren't offered. But Martin wouldn't trade her undergraduate years at Spelman for anything.

"We were nurtured and challenged there," she says. "We learned hands-on, with constant feedback. They taught us to pay attention to details and to think outside the box. Academically, it was as rigorous as any research university. It was also like a family. Everybody knew my name."

After Spelman, Martin finished two years of medical school at the University of Maryland, Baltimore (UMB), when she switched to a neuroscience graduate program there, and is now in her third year of that program. After she earns her Ph.D., Martin will return to the university's medical school to complete her M.D. She wants to do clinically oriented research on the effects of ischemia, or reduced blood flow to the brain, which often occurs during cardiac arrest and stroke.

Medical school was quite an adjustment for Martin after four years at Spelman, where her largest class had 40 students. At UMB, she found herself in classes of 150. Some of her classmates from research universities had already taken

Fast track. *On course to earn her Ph.D. and M.D., Erica Martin says she got a strong start in science as an undergraduate at Spelman College.*

CHRIS HARTLOVE

courses in anatomy, histology, and electrophysiology.

But Martin took it all in stride. "Spelman prepared me mentally to do the work," she explains. "I understand how to use resources to find things out—how to learn. And maybe most important, it gave me self-confidence. So if a professor here doesn't know my name, I'll walk right up and introduce myself and ask a question."

Martin participated in a math and science magnet program at Montgomery Blair High School in Silver Spring, Maryland. For college, she considered two branches of the University of Maryland system, including the flagship at College Park, before settling on Spelman. "At historically minority colleges and universities, you are among other minorities who are striving to succeed," says Martin, adding that Spelman is known for its dedication to helping minority females succeed.

"Academically, [Spelman] was as rigorous as any research university. It was also like a family. Everybody knew my name."—Erica Martin

Martin almost went to College Park because she loved to play soccer and they had a good women's team, while at Spelman there was none. Instead, she chose Spelman and spearheaded a women's soccer program there. "So I got the best of both," she says with a grin.

A friend's younger sister now is facing the choice Martin made nine years ago. "She's considering Spelman or New York University, and I'm offering my advice, whether she wants it or not. I've told her she should go to Spelman."

TOUGH CHOICE

With two undergraduate degrees from two very different kinds of schools—Morehouse College and the Georgia Institute of Technology—Keith Howard knew he wanted to teach at a small liberal arts college. "The mentorship I received and my interactions with professors were much more meaningful at Morehouse than at Georgia Tech," he recalls.

For Howard, the tough choice after graduate school (at Vanderbilt University in Nashville, Tennessee) was whether to teach at a historically minority institution like Morehouse or one where his African American face tended to stand out.

"I had offers from both predominantly white and predominantly black institutions," the mathematician recalls. "My final decision was based on where the resources were available that would enable me to further my research interest in mathematical modeling."

He chose Kenyon College in Gambier, Ohio, a school where only 12 percent of the 1,550 students are minorities. Not only did Howard receive the necessary resources from Kenyon, but he also knew the territory. Having worked there for a year as a dissertation fellow, he says, "I had already integrated myself into the department and the institution."

Howard has found that being one of only a few minority faculty members has nurtured collegiality with other colleagues of color. And, both a plus and a minus, he is asked to serve on numerous committees dealing with diversity issues. "These are labors of love, but they are also very time-consuming," he observes.

At a historically minority college such as Morehouse, undergraduates find themselves in a familiar community, and the faculty serve as role models. Colleges such as Kenyon lack the numbers of black students necessary for a sizeable subculture to emerge, creating an environment that can be intimidating to the few black students there, Howard says.

Yet, in a way, that makes his role even more significant. "At a school like Kenyon, every faculty member of color has a huge impact on students," the assistant professor of mathematics points out.

—JENNIFER BOETH DONOVAN

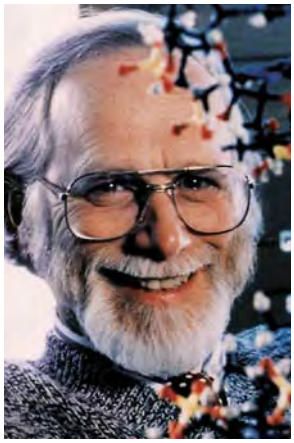
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

THE NOBELIST

Expect the Unexpected

An eminent investigator's perspectives on the best preparation for a life in science.

J. Michael Bishop, chancellor of the University of California, San Francisco (UCSF), gave his 2003 autobiography the wry title *How to Win the Nobel Prize: An Unexpected Life in Science*. Bishop, who shared the 1989 Nobel Prize in physiology or medicine with Harold Varmus, grew up in rural Pennsylvania, a minister's son, and went to Gettysburg College. "Every new subject that I encountered in college proved a siren song. I imagined myself a historian, a philosopher, a novelist, occasionally a physician, but never a scientist (in part because I then had no idea of what a scientist might do)," he wrote. He saw "nothing of research. Gettysburg was a small liberal arts college that valued creativity, but in those days provided no opportunities for laboratory research, nor did it occur to me at the time that it should."



Value added. *J. Michael Bishop says that liberal arts colleges "know how to prepare science students for graduate school."*

Nevertheless, "it was adequate preparation, a suitable stepping stone to the next level of sophistication that I encountered at Harvard Medical School," he says in an interview. "But recall that I was starting from a primitive base. That was a long time ago. It appears to me that the contemporary liberal arts colleges of first rank know how to prepare science students for graduate school, and offer much more to boot."

A liberal arts education is "a wise course of action, both as a credentialing device and a test of motivation."—J. Michael Bishop

But are graduate students from the liberal arts colleges as well prepared as those who studied, say, across the bay at UC Berkeley, when they come to UCSF, an institution that ranks among the country's leaders in biomedical research?

"By and large, yes," replies Bishop, "especially if they have worked in a competent research lab during summers. Some colleges have alliances with research-intensive universities to facilitate this. And some students take a year or two after college to obtain extensive experience in a research lab before applying to graduate school."

The chancellor says that he remains "a great fan of liberal arts education. By all indications, this is a wise course of action, both as a credentialing device and as a test of motivation. Such students seem always to do well in our programs at UCSF. I recommend it."

—CHRISTOPHER CONNELL

THE PROFESSOR/RESEARCHER

Right Where They Belong

Combining the pleasures of teaching and research at small liberal arts colleges.

Roberta R. Pollock is a product of research universities. As an undergraduate, she studied biology at Emory University in Atlanta, graduating *summa cum laude*. She went on to earn a Ph.D. in immunology at Harvard University and did postdoctoral fellowships at Albert Einstein College of Medicine and Columbia University's College of Physicians and Surgeons. But since 1989, Pollock has been teaching biology at Occidental College, a liberal arts campus in Los Angeles with about 1,900 students and 135 faculty.

Nurturing. *Roberta Pollock says "I love teaching undergraduates in small classes, and playing a role in their intellectual growth."*

The author of some three dozen papers, Pollock has continued her research in immunology and at last count had authored seven papers since joining Occidental, three of them with undergraduate coauthors. An HHMI grant to Occidental helped the college equip her lab. "My research has progressed much more slowly than it would at a research university," she admits, "but I love teaching undergraduates in small classes, getting to know them, and playing a role in their personal and intellectual growth."

Pollock also likes the accessibility of colleagues from other scientific disciplines, as well as those in the humanities and social sciences. She values the college's willingness to let her work half-time when her children were very young, and its support for innovative ideas. With help from Occidental's HHMI grant, Pollock developed a course on gender and science in which she explores the historical role of women as scientists, the status of women in science today, and whether women and men conduct science differently.

After 15 years, Pollock is sure that she's right where she belongs. "I wanted to combine teaching and research and have them both count toward tenure," she explains. "Occasionally, when I go to a professional meeting, I regret that I am not accomplishing as much in research as I would if I had chosen to be at a research university. But I am helping students decide what they want to do with their lives, and that is so satisfying."

At Occidental, Roberta Pollock likes the accessibility of colleagues from other disciplines, in the sciences and beyond.

THE BEST JOB EVER

Barely more than half Pollock's age and just finishing his first year on the biology faculty at Austin College in Sherman, Texas, Lance Barton couldn't stay out of the classroom even during his graduate school days at the University of Cincinnati College of Medicine, where the focus was firmly on research.

Barton found time to teach undergraduate biology at Cincinnati's College of Mount St. Joseph and to instruct middle school students in the Saturday Science Academy, an HHMI-supported outreach program at the University of Cincinnati.

As long as he stayed productive in the lab, Barton's mentor, HHMI alumni investigator John J. Monaco, Jr., didn't object to the graduate student's teaching activities, but others in his department "didn't think you could do both," Barton recalls. When he won the department's scientific award and an academic achievement award, "I think I changed a lot of attitudes," he says with a smile.

When Barton began looking for a faculty position, the largest school to which he applied had an enrollment of 2,200. He accepted an offer from Austin College, home to 1,300 undergraduates, because he liked the interdisciplinary nature of the faculty and their devotion to their students.

Barton is taken with a required course called "Integrated Science," cotaught by scientists and faculty from other disciplines, and with Austin College's January Term, three weeks between the fall and spring semesters when faculty and students can let their academic imaginations run wild.

He is also continuing his research on T cell immune response to viruses by collaborating with colleagues from the University of Cincinnati, and his students have opportunities to do research as well. He says that the faculty at the University of Texas Southwestern Medical Center at Dallas, home to four active Nobel laureates and only 70 miles away, "love Austin College students because they can think and have good lab skills."

If Barton had any doubts about his career choice, they vanished when he visited his undergraduate alma mater, Dickinson College in Carlisle, Pennsylvania, last year, and told biology chair John H. Henson that he too had decided to teach at a liberal arts college. "I told you when you were here that this is the best job ever," Henson replied.

"I only took three classes from Dr. Henson. He wasn't even my adviser, and I graduated five years ago," says Barton. "But he remembered me and my name."

—JENNIFER BOETH DONOVAN

DANNY TURNER

DAVID MCLAIN/AURORA

Alliances. *To extend her research, Hadley Horch (above) crafts strategic collaborations.*

THE PARTNERSHIP

Collaboration in the Name of Science

A college-university alliance proves to be win-win-win.

A product of Swarthmore College, Hadley Wilson Horch always wanted to teach at a liberal arts college. But as an assistant professor of biology and neuroscience at Bowdoin College, she found she missed the interaction with colleagues and the fast pace of discovery that characterized her graduate and postdoctoral days. She felt she needed to reconnect to the larger research community while carving out a productive niche for her own research.

She's solving these problems by linking up with Cornell University neuroscientist Ronald R. Hoy, an HHMI professor and Horch's postdoctoral adviser. Now Hoy and his former postdoc are collaborating to bring the tools of modern cellular and molecular biology to one of Hoy's pet projects, the regeneration of auditory neurons in crickets. Together they—and their undergraduate students—are revisiting questions that Hoy's research raised nearly 20 years ago, when the tools were not yet available to answer them.

It's a win-win-win situation. Horch gets to continue the research she began as a postdoc. In fact, she just won a $150,000 grant from the National Institutes of Health to pursue the regeneration work. Her students get to meet regularly with Hoy and the students in his lab, to do real science, and to see themselves as intellectual partners in a larger research project. And Hoy gets help with the molecular aspects of his research, freeing him to use the sophisticated equipment at Cornell to focus on the physiology of cricket neuronal regeneration. He also gets the stimulation of a dynamic dialogue with Horch about teaching undergraduates.

"I'm hoping to link up with several more faculty like Hadley to form alliances to build challenging research practices into undergraduate pedagogy," says Hoy. In 2002, he was named as one of 20 HHMI professors nationwide. Each HHMI professor receives $1 million over four years to develop innovative approaches to teaching undergraduate science.

Horch sounds a note of caution, though. "I think this collaboration works wonderfully with someone like Ron, who is truly interested in teaching and working with undergraduates. It might work less well collaborating with someone who rarely interacts with undergraduates." **— JENNIFER BOETH DONOVAN**

PRIVATE FINANCIAL SUPPORT

HHMI and Liberal Arts Science

$600 million in support of undergraduate science education.

HHMI supports undergraduate science education at major research universities and liberal arts colleges through separate invitation-only competitions. These competitions award four-year grants of up to $2.2 million to launch or sustain efforts to lure more students, especially minorities, into biology and other sciences; to get more undergraduates into laboratories; and to convince top scientists to bring to teaching the same passion and creativity they apply to their research.

In May, HHMI awarded almost $50 million to 42 baccalaureate and master's degree institutions—including many that are top producers of future science Ph.D.s. Two summers ago, it divided $80 million among 44 research universities for efforts to bridge the gulf between the lab and the classroom. The Institute also provides extensive support for K–12 science education, and two years ago it named 20 Hughes professors—prominent researchers who are each receiving $1 million over four years to practice and encourage great teaching.

HHMI has invested more than $600 million in undergraduate science education since 1988, making it the country's largest private source of such support. Why has the Institute—best known for the nearly $500 million in biomedical research it spends each year—made education such a priority as well?

"We saw a real need to connect science and the scientific community—hence research—more carefully with teaching," says Peter J. Bruns, vice president for grants and special programs. "With Hughes' name on it, this program challenges the community to think about education in the way that we think about science."

Bruns himself became a believer in 1989, when as a professor of molecular biology and genetics and director of the division of biological sciences at Cornell University, he was asked to lead the school's first Hughes undergraduate education grant. "Until that time I was pretty much the usual faculty member," Bruns recalls. "I did my teaching and enjoyed it, though it was not a major focus; I didn't develop programs or plans beyond my own course. But putting together the Hughes education proposal got my attention." Bruns and colleagues created the Cornell Institute for Biology Teachers, which enables faculty to work with high school instructors across New York State. That institute, with steady support from Hughes, is still flourishing and now also works with elementary teachers. Bruns left Ithaca in 2000 to lead HHMI's grants programs.

The liberal arts colleges that receive funding from HHMI tend to be repeat customers too. Most of the 42 liberal arts colleges that shared this year's nearly $50 million in awards were also selected in the 2000 round, and 10—Bates, Carleton, Haverford, St. Olaf, Smith, Swarthmore, Wellesley, Wesleyan, Williams, and Xavier of Louisiana—are five-time grant recipients. But 12 percent were chosen for the first time, and 29 percent were funded previously but not in 2000. The mix, Bruns says, "reflects the wisdom of an external, peer-review panel: We don't throw away the current people the next time we do something, and we're also not a closed shop." He added, "We recognize there are some things, like strong outreach to teachers, where it's important just to keep the wheels turning." **—CHRISTOPHER CONNELL**

Cells A GLOW

Combining aesthetics with shrewd science, Roger Tsien found a better way to look at cells—and helped to revolutionize several scientific disciplines.

BY DIANA STEELE

PHOTOGRAPHS BY JOE TORENO

INSIDE AN INSTITUTIONAL-GRAY scientific laboratory, it can be startling to find brilliant, paintlike fluorescent colors. But in one San Diego lab, bacterial colonies in bright hues of green, blue, magenta, yellow, and orange dot agar plates and linger in discarded microcentrifuge tubes. This eccentric biological palette is the work of HHMI investigator Roger Y. Tsien, and his "studio" is a pharmacology lab at the University of California, San Diego (UCSD).

"I like pretty colors," Tsien says. His casual comment belies the fact that his artistic sensibilities—combined with shrewd scientific instincts—helped foment a revolution in cell biology and neurobiology.

Tsien is renowned for having created colorful dyes to track the movement of calcium within live cells—and without having to poke holes in them, the traditional way to do such tracking. Tsien also engineered the jellyfish green fluorescent protein (GFP) to glow more brightly in the visible part of the spectrum and created color variants in brightly fluorescent yellow, blue, cyan, yellowish green, orange, and red. These multicolored fluorescent proteins (FPs) aren't just for making pretty pictures—although Tsien's students and postdocs have been known to draw with them—but are more like a set of molecular biologist's crayons. They can be used to monitor gene expression or see biological processes inside living cells, and having more than one color available means that scientists can study more than one interacting process at a time.

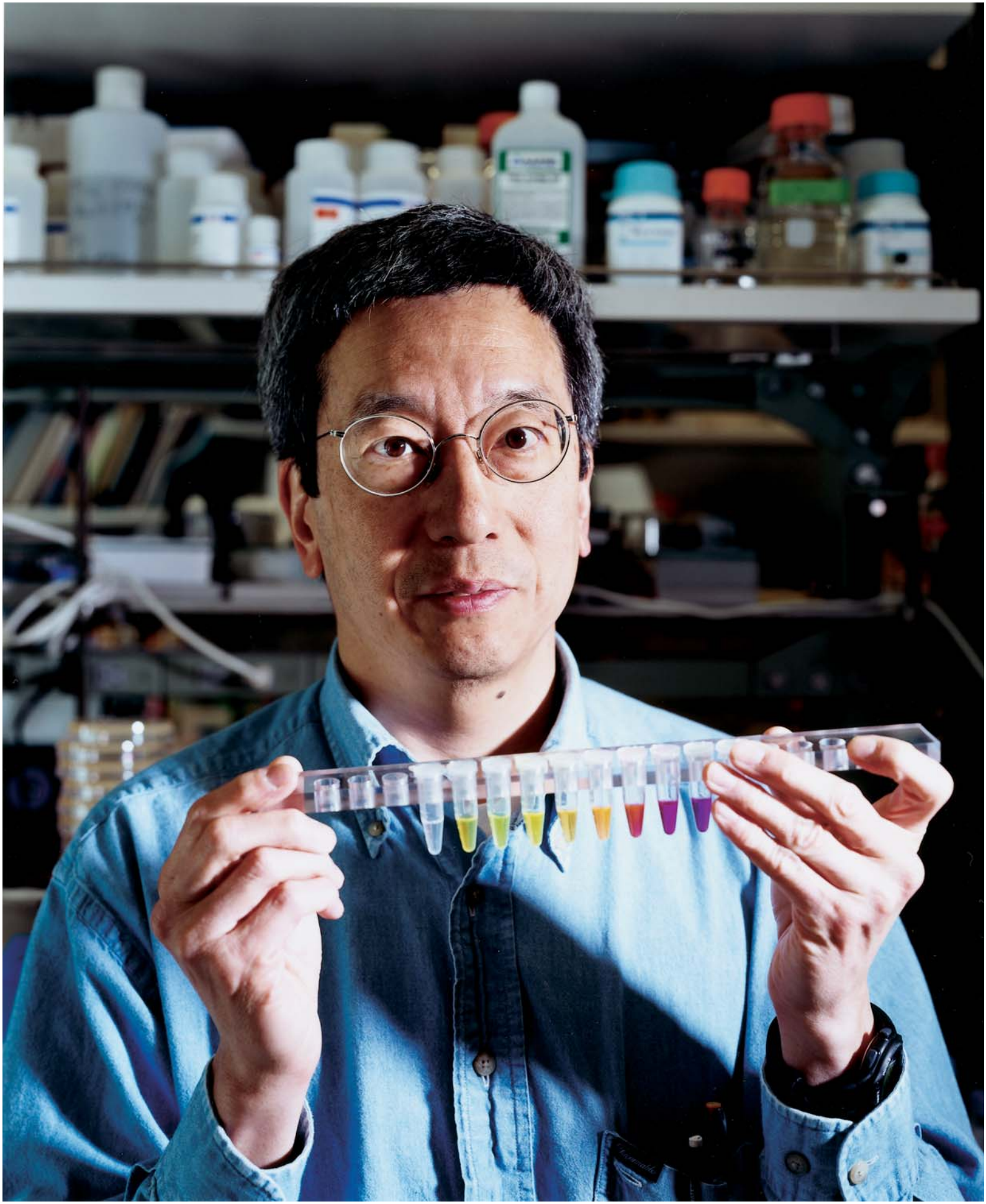
"GFP has revolutionized the fields of cell biology and neurobiology," says Jennifer Lippincott-Schwartz, who heads the section on organelle biology at the National Institute of Child Health and Human Development at the National Institutes of Health. Tsien, she says, "stands out as probably the single person who most facilitated that revolution through his techniques, his insights, his contributions—in terms of creating reagents and showing how they can be used creatively to address important questions."

Tsien's contributions haven't gone without official notice. In January, he was awarded the prestigious Wolf Prize in Medicine for his "seminal contribution to the design and biological application of novel fluorescent and photolabile molecules to analyze and perturb cell signal transduction."

"DOOMED BY HEREDITY"

Tsien has always appreciated color, not just for its scientific potential, but also in a sensual way. He is drawn more to Henri Matisse's vivid colors, for instance, than to the brown, gray, and black tones of Georges Braque in his cubist phase. Imaging with pretty colors has always been close to his heart. "Your science should ideally feed the deeper parts of your personality, to pro-

Roger Tsien created dyes to track the movement of calcium within live cells.



vide some intrinsic pleasure to tide you over the inevitable periods of discouragement," he says.

Born in New York City in 1952, Tsien grew up in Livingston, New Jersey. His family was chock full of engineers. Tsien's father was a mechanical engineer. His mother's brothers were engineering professors at the Massachusetts Institute of Technology. Tsien, who calls his own work *molecular* engineering, says, laughing, "I'm doomed by heredity to do this kind of work."

His father's cousin Tsien Hsue-Shen was a rocket scientist and professor at the California Institute of Technology until he was accused in 1950 of being a Communist. Put under house arrest for five years, he was finally deported to China, where he subsequently fathered that country's ballistic-missile program.

Roger became interested in the chemistry of pretty colors as a youth—partly because his older brothers weren't. "Younger siblings tend to try wild and crazy things because older siblings occupy certain ecological niches," Roger says. His brother Richard (known as Dick)—seven years older and now a noted cellular physiologist at Stanford University School of Medicine (and member of HHMI's scientific review board)—recalls that Roger had asthma as a child and was often obliged to stay indoors while his two older brothers were out doing sports. Roger studied and performed chemistry experiments in the basement, one time charring a table-tennis table in a gunpowder experiment gone awry.

But for the most part, he put the time to productive use. At age 16 he won first prize in the Westinghouse Science Talent Search with a project investigating how metals bind to thiocyanate. With a National Merit Scholarship, he attended Harvard College, graduating at age 20 with a degree in chemistry and physics.

A Marshall Scholarship then took him to the "other" Cambridge, in the United Kingdom, where he earned a Ph.D. in physiology and stayed on to complete a postdoctoral fellowship.

CHEMIST INTERLOPER

"Dick pointed out that neurobiology was the cardinal unsolved problem of all biology and perhaps philosophy," Roger Tsien recalls. For Roger, certain mental lightbulbs began to flash when "I found out that chemistry could be applied to neurobiology."

Dick recalls that Roger didn't have an easy time in Cambridge: "His attempts at always doing things in a chemical way seemed a bit strange to them, but I think it was the beginnings of the realization that his chemical knowledge could be of great importance to biology."

When life-science experiments require a new biological macromolecule, says Roger, biologists will just go out and make it. "But if it's a chemical molecule you can't order from a catalog, they usually figure 'Well, forget about it. Let's find another way of doing the experiment or scrap it altogether.' " The fear and loathing that most biologists have for chemistry, he says, "creates a niche for those of us who are willing to do it."

As a graduate student, Roger started to develop a better indicator dye for intracellular calcium, which is an important messenger in numerous biological systems. It plays a critical role in neuronal regulation, muscle contraction, and fertilization, just to cite a few examples.

In those days, the only way to measure calcium inside a cell was to use microelectrodes or inject through the cell's membrane a luminescent calcium-binding protein called aequorin, which comes from jellyfish and glows when it binds calcium. But those techniques had several disadvantages, including having to work with big, sturdy cells, and only one at a time.

Tsien thought there ought to be a method for measuring calcium that is less damaging to cells. He developed organic dyes that twist their necks when they bind calcium. Such twisting drastically changes the dyes' fluorescence or ability to re-emit light of a different color. Equally important, he found a temporary masking cloak to help the molecules sneak across a cell's membrane, only binding and reporting calcium once they shed the cloak inside the cell—kind of like an army going over a wall in the middle of the night and then springing into action.

The practical result: no more injections, and the ability to work with all kinds of cells, including small cells. For the first time, scientists could study calcium easily inside a plethora of live cells. Tsien's career—of using chemistry to devise methods to study what biologists had only been able to study indirectly—thus began in earnest. Nevertheless, the British government decided not to pursue any patents, deciding that calcium inside cells was insufficiently important. The same agency had just turned down monoclonal antibodies, which subsequently earned other Cambridge scientists a Nobel Prize and launched a major segment of the biotechnology industry.

> "The basic idea didn't come from us," Tsien says, "but we maybe helped lots of people appreciate the stuff that wasn't quite as easy to appreciate in its original form."

Tsien's work is simple in some respects, but its overall impact on science has been extraordinarily powerful.

Tsien landed a job at the University of California, Berkeley, in 1981, where he spent the next eight years developing and applying better dyes for calcium and other ions. The University of California was eager for patents, so Tsien got his first in 1986, and now holds more than 60.

But by that time, Tsien wanted to "get out of the calcium box," he says. "The problem with calcium is that it sounds too chemical, it's a small inorganic ion, and famous biologists, especially at Berkeley, were very snooty about calcium." They thought ions were insignificant compared to the really important biological molecules such as DNA, RNA, and proteins.

WORKING THE GOLDMINE

So Tsien turned to studying the next-most-important universal messenger inside cells—cyclic AMP. At that time, there was no means of imaging it in a live cell; the state of the art was to grind up cells in order to isolate the cyclic AMP contained within.

Tsien and his colleagues eventually figured out that they needed to hijack a protein that was a natural sensor for cyclic AMP—in particular, cyclic-AMP-dependent protein kinase (PKA). That realization led Tsien to move his lab in 1989 to San Diego in part to be near biochemist Susan S. Taylor, an HHMI investigator at UCSD who is an expert on PKA. By attaching a fluorescent dye to PKA, the Tsien and Taylor labs eventually made a protein that changed color when it bound cyclic AMP.

This was a major advance over destroying cells. But the protein still had to be injected. "It was the dissatisfaction with having to make the protein in bacteria, put fluorescent dyes on it, purify it, and inject it back into cells—and then only into big cells—that led me to think we desperately needed a way to encode the fluorescent indicator by genetics," says Tsien. Tsien realized that there was a need to have cells produce fluorescent markers directly, by molecular biology. From his work with organic calcium dyes, Tsien was familiar with the literature of the competing dye, the protein aequorin. He vaguely remembered a contaminant of aequorin, a naturally green fluorescent protein. "I typed 'green fluorescent protein' into MEDLINE and was amazed that somebody had just cloned it," Tsien recalls. This was biologist Douglas Prasher, who cloned GFP in 1992.

Tsien telephoned Prasher, who was working at the Woods Hole Oceanographic Institute. Prasher offered to give Tsien the clone. He had run out of funding and wasn't planning to work on GFP any more. "He was sitting on a goldmine," Tsien says, "but he had run out of steam and resources just short of the finish line."

Prasher warned, however, that there wasn't yet any evidence that any organisms other than jellyfish knew how to make GFP.

One other person, Martin Chalfie, at Columbia University, noticed the GFP clone at just about the same time. "I was the first to ask Prasher," Tsien says, "but Marty was ready to start working first." Tsien didn't even have a molecular biologist in his lab and had to wait until a new colleague, Roger Heim, arrived from Switzerland.

Chalfie soon demonstrated that other organisms—in his case, *Escherichia coli* and *Caenorhabditis elegans*—could, in fact, make GFP just like jellyfish; the protein doesn't need any special enzymes or cofactors to make it glow. The gene sequence for GFP can be inserted into an organism's genome and butted up against the sequence for almost any protein a biologist wants to study. When the organism expresses that protein, it does so with a fluorescent tag attached to it—like a reindeer with a glowing nose. All the biologist has to do is follow the glow to find the protein.

Early GFP was difficult to see. Heim—following some suggestions from Tsien that Tsien calls "misguided"—modified the amino acid sequence of GFP to successfully improve its visibility. The lab eventually produced user-friendly fluorescent proteins of different colors ranging from blue to red. Most applications of fluorescent proteins now use versions pioneered by the Tsien lab.

The result of this work is simple in some respects, but its overall impact on science has been extraordinarily powerful: Researchers using FP tags can now see inside live cells with a light microscope and watch molecular processes in motion. And they can easily track where and when certain genes are expressed in cells or even in whole organisms.

CONSPIRACY DETECTION

Although Tsien was instrumental in helping to make GFP the incredibly useful molecular-biology tool it is today, he is conscious that nature made the protein in the first place and that he played what he considers the relatively minor role of tuning it up for research.

"In a way it's like somebody who turns an obscure novel into a popular film," Tsien says. "The basic idea didn't come from us, but we maybe helped lots of people appreciate the stuff that wasn't quite as easy to appreciate in its original form."

Tsien's modesty aside, GFP is a blockbuster. MEDLINE indexes only half a dozen papers on "green fluorescent protein" before 1992. And a search for papers with the acronym "GFP" in 1990 and 1991 turns up only nine papers—in which GFP stands for six different things, from "gonadal fat pads" to "Ghanaian traumatic fracture patients," but not "green fluorescent protein."

Prasher published the sequence of GFP in 1992, and Tsien reported his blue version two years later, in 1994—the same year that Chalfie published research using GFP as a marker for gene expression. Since then, more than

14,000 papers have been published that mention green fluorescent protein or its acronym GFP.

With GFP and other agents, Tsien's particular blend of biological insight and chemical and physical knowledge has allowed him to play a unique role. For example, he wasn't content merely to expand GFP's color palette. Like a skillful painter who achieves a new shade with a careful blending of hues, Tsien engineered two colors to illustrate what no single color could represent on its own.

If one protein is tagged with cyan GFP and another with yellow GFP, a researcher using a light microscope is able to follow the cyan and yellow fluorescence and learn whether the proteins have arrived in the same general vicinity. But to see whether the proteins are actually interacting with each other—which is far beyond the resolution of a light microscope—something much more sensitive is needed.

Tsien uses the analogy of electronic monitoring bracelets for criminals. If, say, the spatial resolution of the bracelets was half a mile, a monitor could tell whether two criminals were in the same vicinity but not whether they might be conspiring. However, if their bracelets interacted with each other in a special way when the criminals got to within a few feet of each other, then a signal could be sent back to headquarters.

"Zing! Conspiracy!" says Tsien.

That special signaling is exactly what happens when the two different colors of GFP overlap. In a quantum-mechanical handoff of energy, one GFP absorbs light of a certain wavelength and transfers the energy to the other GFP, which emits light of a different wavelength. So, for instance, light that would ordinarily cause a GFP to glow cyan makes it glow yellow instead. Anything in the biochemistry of a cell that changes the distance between the GFPs, or their relative orientation, sends a conspiracy signal back to headquarters.

Tsien does acknowledge that FPs sometimes have their downsides. "There are times when GFP is too big, and it really does mess up the protein you put it on," he says. "Sometimes you have to switch to something completely different." To that end, he says, "we have several alternatives to GFPs, including tags that are much smaller."

Apart from fine-tuning FPs, though, Tsien also has his eye on some new research directions.

NEXT TARGET: CANCER

The chemical technique by which two differently colored fluorescent proteins emit that special signal when they are in close proximity to each other is called fluorescence resonance energy transfer (FRET). An early application of FRET that Tsien explored was monitoring the action of enzymes, called proteases, that cleave proteins. In a short sequence of amino acids, he bound two FPs together so that they showed the FRET signal. When the amino acid chain was cleaved by a protease, the signal went away. Nearly any biochemical signal that can shift one FP relative to another can now be monitored inside living cells.

Aspects of this work appear to have given Tsien new ideas to dream about. Cancer cells, unlike normal cells, have protein cleavers on their surfaces. These proteases help cancer cells break down connective tissue that would otherwise prevent them from escaping and metastasizing.

Tao Jiang, an HHMI research associate in Tsien's lab, has built peptide molecules basically shaped like horseshoes. One end of the "U" likes to enter cells and carries a payload—such as an imaging molecule or a chemotherapeutic agent. The other end covers up the first, preventing the payload from sticking to or entering cells. That is, until a cancer cell's protease cleaves the bottom of the U, unleashing the sticky half with the payload to enter the nearest cell.

Vials with a variety of fluorescent proteins.

"When you have really sticky tape, it usually comes with nonstick backing paper so that you can handle it," Tsien says. "It doesn't stick down until you peel the halves apart." Similarly, the peptide carrying the radioactive isotope or the cancer drug won't stick to normal tissue but only to cancerous tissue. "The dream is that in the morning, we would put a tiny tracer dose into the cancer patient" and then look to see where it stuck. "If you see a good image, then in the afternoon you come in with a bigger dose" of the toxic agent that's designed to kill the cancer.

Far in the future, Tsien imagines, doctors might use as a payload a sensitizing agent that leaves cancer cells susceptible to X-rays or neutrons. Healthy tissue, however, which lacks the sensitizing agent, is left intact even though it's exposed to the beam.

In this pursuit, Tsien is conscious of his limitations—for one thing, he has not yet done clinical experiments in his lab. "Obviously, cancer has defeated an awful lot of researchers," he says. "I'm very conscious that there's an enormous failure rate, but one still has to try."

Tsien says one good thing about prizes—such as his Wolf Prize—is that it allows the honoree to tie a bow around an old research area and have the confidence to move into a new field. "It's very hard to give up an area in which you are one of the world's experts and try something where you are like a graduate student again," he says. "But we're having a try, it's fun, it's new, and we'll see." H

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ROBERT CAMPBELL & PAUL STEINBACH

INTERVIEW

Toward Détente on Stem Cell Research

A conversation with LeRoy Walters.

LeRoy B. Walters, a member of HHMI's bioethics advisory board, likes to wrestle with broad, compelling issues—such as whether it is ever justifiable to kill another human being, and if so, when? But in the past three years, Walters, a professor of ethics and philosophy at Georgetown University's Kennedy Institute of Ethics in Washington, D.C., has become increasingly absorbed by specific questions involving the use of human embryonic stem (ES) cells in medical research. He is fascinated by the rapidly changing, often-contradictory policies on this research in the United States and abroad.

His goal is to clarify the options and then propose thoughtful solutions. With his gentle manner in the face of heated arguments, he can be firm without giving offense. "In the end," Walters says, "we have to make public policies that try to reach an accommodation among a wide variety of religious and nonreligious viewpoints."

In research on human ES cells, is the United States the world's most conservative nation?

Walters: Maybe not, but we're close. The world has changed a great deal since August 9, 2001, when President Bush announced his policy of limiting federal spending for human ES cell research to cell lines that were established at that time. Unfortunately, there are only 19 approved ES cell lines, as opposed to NIH's original estimate of about 60, and even some of these do not grow well.

Meanwhile, more and more countries in Europe, the Middle East, and Asia have been liberalizing their policies on human ES cell research—even on cloning for medical research. The United Kingdom has always been quite liberal in this regard; so have China and Israel. India and Belgium also accept cloning for research purposes.

Unfortunately, in the United States the issue of human ES research has become tied up with the abortion question, which is not as much in the forefront of debate in other countries. Consequently, the U.S. is running the risk of falling behind in this area of research.

Do you think it's ethical to do research on human ES cells when this requires damaging very early human embryos?

Walters: In my view, the argument that all early embryos should be protected from harm is not convincing. We know that they can split into two, becoming twins, or that two embryos can combine into one. We also know that in natural human reproduction only about 35 percent of early embryos develop to maturity in the mother's womb, while the others die. On the positive side, ES cells have become integral to the understanding of human development and disease. In the long run, they may open up new pathways to therapy for such devastating illnesses as juvenile-onset diabetes, Alzheimer's, Parkinson's, or for spinal-cord injuries.

To argue against ES cell use, one needs to introduce religious premises—especially about the endowment of the embryo with a soul at the time of fertilization.

What role should the government play in all this?

Walters: When I had the chance to talk with President Bush about this question three years ago, I suggested that he set up a special advisory committee of scientists and bioethicists—some 8 to 12 people—to help keep our human ES cell research policies fresh and flexible. If such a committee had been in place in 2002 or 2003, it could have indicated how few established ES cell lines there really were. Or perhaps the president's advisers could have pointed to new data about adult stem cells that show such cells are not as promising as some people had hoped.

The president did in fact establish a council on bioethics with a much broader mandate. In its first report, a narrow majority of this council proposed a four-year ban on cloning for biomedical research. This action would have been disastrous for basic research, in my view, and the U.S. Senate has wisely rejected such proposals. A subsequent council report was unduly optimistic about the prospects for research with adult stem cells. Because Congress has not taken any action on this issue, it has fallen to the states to set their own policies for human-embryo research. Given that only 11 states prohibit such research, most state legislatures are more liberal than the federal government on this subject. Evidently, 39 states see the possibilities opened up by research on human ES cells and don't want to miss out on them.

Would you place any limits on research with human ES cells?

Walters: The United Kingdom provides an excellent model for public oversight. Each year its licensing authority issues a public report on the institutions that are doing research on human embryos, who the investigators are, and what topics they are studying. The authority also keeps statistics on how many embryos are being used in research. That's the kind of transparency we need. I think the balance is strongly in favor of going forward with this research. At the same time, however, I think that U.S. researchers should be willing to participate in a moderate, flexible system of public oversight.

—MAYA PINES

LeRoy Walters seeks accommodation in stem cell policies.

WILLIAM K. GEIGER

NIGHT science

Like to take risks and tackle intractable problems? As construction motors on at Janelia Farm, the call is out for venturesome scientists with big research ideas.

By MARY BETH GARDINER

Day science calls into play arguments that mesh like gears, results that have the force of certainty.… Conscious of its progress, proud of its past, sure of its future, day science advances in light and glory. By contrast, night science wanders blind. It hesitates, stumbles, recoils, sweats, wakes with a start. Doubting everything, it is forever trying to find itself, question itself, pull itself back together. Night science is a sort of workshop of the possible where what will become the building material of science is worked out.

—FRANÇOIS JACOB
Of Flies, Mice, and Men

BESPECTACLED AND BEARDED, clad today in shirt and tie instead of his trademark black turtleneck and trousers, Gerald M. Rubin doesn't look much like a biblical figure. But in his role as director of Janelia Farm Research Campus, Rubin has been called a modern day Noah, readying his "ark" and rounding up the best and brightest scientists—of every stripe—to fill it.

"Gerry is not trying to populate Janelia Farm with all the world's best chemists," says HHMI investigator Stuart L. Schreiber, a chemical biologist at Harvard University and a core faculty member of the interdisciplinary Broad Institute recently founded by Harvard University, MIT, and the Whitehead Institute for Biomedical Research. "He'd like to have a couple of them, though. It's like Noah's ark—he wants a healthy mix of very different kinds of scientists."

As girders and rebar give shape to Janelia's physical aspects, and as the process for recruiting scientists unfolds, Rubin and colleagues continue to sculpt the conceptual underpinnings of the science that will take place there.

SAFE HAVEN

Located in Loudoun County, Virginia, HHMI's Janelia Farm

PAUL FETTERS

Where now one sees girders, rebar, and cranes, one will soon find a community of scientists: the Janelia Farm Research Campus.

Research Campus will house a multidisciplinary, collaborative community of scientists. But how does one build such an environment? "Suppose someone said you could build a new research institute and there were no rules—you could do anything you want," Rubin ventures. "How would you decide what to do?" It's a challenge he accepted with relish. "Janelia is going to be unique, not because we pick problems that are seen as outside the mainstream, but because of the way we approach those problems."

The plan for Janelia Farm grew out of an acknowledgment by HHMI leaders that while most biomedical problems are handled well in a university setting, there are some that might be better addressed in a place where small groups of researchers with different skills can work together without the barriers typically encountered at a university. Development of new tools to facilitate biological discovery, for example, can require diverse expertise, such as that of engineers, physicists, and computer scientists. But at universities, scientists from different fields are often compartmentalized, and demands placed on researchers by home departments may restrict collaboration outside those walls. "A physicist who wants to work on a biological problem would likely not get tenure in a university physics department," says Rubin.

In developing the concept for Janelia, Rubin, HHMI President Thomas R. Cech, Vice President and Chief Scientific Officer David A. Clayton, and their advisers aimed high: They sought to create an environment where researchers from a variety of disciplines will work together with the freedom to apply their collective talents to tough biological questions, the kinds of questions that can't be answered in the three to five years that most federally funded grants cover. The Janelia campus, Rubin says, will provide a "safe haven for a unique subset of researchers." Freed from most of the administrative, grant writing, and teaching duties that consume time at a university, Janelia's scientists will be "functioning scientists" who will be able to spend the bulk of their days working at the bench or engaging in collaborative discussions.

The campus and its scientific program will closely complement HHMI's longstanding investigator program. That program currently consists of more than 300 researchers at 66 uni-

versities, medical schools, and research institutes throughout the United States who have the freedom and flexibility to push the bounds of knowledge in some of the most important areas of biomedical research.

As director of Janelia Farm, Gerald Rubin has his sights set on research questions that are on science's horizon. Below, Janelia takes shape.

FOLLOW YOUR NOSE

The concept for Janelia, Rubin points out, evolved out of tried-and-true best practices. "You make a list of the most successful research institutions," he says, "and look for common principles."

A handful of places stood out. Eventually, Rubin focused on two of the world's most highly regarded institutions, the Medical Research Council (MRC) Laboratory of Molecular Biology in Cambridge, England, and AT&T's Bell Laboratories in Murray Hill, New Jersey. Funded by the British government, the MRC hosted no more than 300 scientists at any given time during its heyday, yet it spawned a string of notable discoveries, including the structure of DNA, protein crystallography, DNA sequencing, monoclonal antibodies, and the *Caenorhabditis elegans* model system for genetic studies. Bell Labs, with a staff of about 3,000, was similarly productive in the fields of solid-state physics and electronics—for example, it was there that the transistor and the laser were developed.

Though the two labs were different in many ways, they did have several things in common. Both institutions kept research groups small, and principal investigators worked at the lab bench. All funding was provided by the single sponsor—applying for outside grants was not allowed—and good support services and infrastructure were in place. Notably, says Rubin, both institutions evaluated their own people rather than rely on expert opinions from outsiders. That was important, he says, because the scientists needed an environment "where they could tackle difficult problems without making the kind of progress that would be visible to someone 3,000 miles away looking at their CV."

Similarly, Rubin sees Janelia Farm as a place that will appeal to self-directed scientists just starting their careers who are looking for independence, and also to established scientists who want to explore new scientific questions. Charles V. Shank, a member of Janelia's advisory board, supports that notion. Shank signed on at Bell Labs just out of graduate school and ended up staying 20 years. Currently director of the Lawrence Berkeley National Laboratory and a professor of physics and chemistry at the University of California, Berkeley, Shank says his time at Bell Labs had a "huge impact on my career. I had an opportunity to pursue science in a way that didn't fit into the narrow box one would see in a university." Shank's degree was in electrical engineering, but at Bell, his interest shifted to chemistry and physics. "In science, people reinvent themselves on a regular basis," he says. "Over that 20 years, I was given the opportunity to go where my nose led me."

The nature of such pursuits implies that few of the scientists who come to Janelia Farm will spend their entire career there, says Rubin. "Unlike a lot of institutions that want to hold on to their people, we want turnover in order to ensure a fresh flow of ideas. If you're worried about tenure, you're probably too risk-averse to function well in a Janelia-like environment."

"There's another advantage of scientists spending 5 to 10 years at Janelia and then moving on," adds Tom Cech. "When they move back to academia, they'll be ambassadors for the frontier technology developed at Janelia. We want to spread the instruments and computational tools created at Janelia around the world, and these alumni of the Farm will provide one mechanism for dissemination."

Nancy M. Bonini is an HHMI investigator at the University of Pennsylvania School of Medicine. Asked if she might have forgone her traditional postdoctoral training path if a stint at Janelia Farm had been an option, Bonini's response was immediate: "Why wouldn't I have applied to a place like that? I want a vibrant, interactive, intense environment where it will be fun to do science and that will give me the freedom to do the kind of science I want to do."

ACCIDENTAL LANDINGS

Creating such a collaborative atmosphere where exploration and risk taking are encouraged will be key to Janelia Farm's success, Rubin says. "If you're wandering around in the unknown, you'll

PAUL FETTERS (TOP & OPPOSITE); STEWART BROTHERS PHOTOGRAPHERS (BOTTOM)

often land at the cutting edge—not intentionally, but because you've made some accidental observation," he says. "That's the way a lot of important discoveries happen."

Something that Rubin and his advisers felt would promote collaboration and collegiality at Janelia Farm was to level the playing field. In lieu of the typical university hierarchy of assistant, associate, and full professor, the more egalitarian designation of "group leader" will be given to scientists regardless of career stage, from those just finishing postdoctoral training to senior researchers. One other researcher category, "fellow," could be an individual just out of graduate school looking for an alternative to traditional postdoctoral training, or he or she could be a more advanced researcher who wants to change fields or move, say, from industry to academia. As with the group leaders, fellows will be independent—"essentially free agents," says Rubin—able to control their own resources and ally with collaborators of their choosing.

To promote interaction, group size at Janelia Farm will be small—between two to six lab members for each group leader and one to two per fellow. With scientists spending less time at their desks and more time in the lab, opportunities for discussion and mentoring within and between lab groups will arise more frequently.

Postdoctoral trainees and graduate students will also be a part of the culture at Janelia, though integrating predoctoral students into the mix will be more complex, since they require affiliation with a degree-granting institution. Rubin is exploring the idea of tapping into HHMI's network of international research scholars to recruit students from abroad, where graduate programs typically include little coursework. "I want to ensure that Janelia Farm has an international flavor, and I think this will work," he says. "They would be close to Washington, a very international city. And this will appeal to people who have an adventurous spirit, which is what we're looking for."

One of the most innovative elements of the plan for Janelia Farm is to make it a place where researchers can come as visiting scientists to work on short-term individual or group projects. Building into the program this "research hotel" concept is unique to Janelia, says Stuart Schreiber, and an idea whose time is due.

"One of our inspirations was what happened in the yeast field, when two geneticists and a molecular biologist went on sabbatical at Cold Spring Harbor Laboratory in the mid-1970s to work together in a shared lab," says Rubin. "What they accomplished greatly accelerated the development of the yeast molecular genetics field. Few places today, however, have the physical or financial resources to accommodate independent visitors."

At Janelia Farm, external scientists will be able to put in a group application for funding and space, including housing. "This will be for novel, collaborative projects," says Rubin, "some of which may involve other researchers at Janelia, but not necessarily." A more conventional use will be sabbatical visits. "A number of our investigators would never consider moving to Janelia, but they might want to come for a year—we'd be able to offer housing for them and their families," he says. "We hope to have two or three investigators at Janelia at any given time."

Even shorter-term visits will be possible—for example, a scientist might send a postdoc to use special instrumentation unavailable back home. As Cech points out, the setup is ideal. "With Washington Dulles International Airport just a few miles away and short-term housing available on the campus, a visiting scientist will be able to fly in and get right to work."

VOLUNTARY ASSEMBLIES

With so many of the organizational decisions already made, and construction well under way, Rubin's attention is now focused on two other critical

PARTNERING WITH LOUDOUN COUNTY

Local school kids will rub shoulders with scientists at Janelia Farm.

With the sun barely clearing the pines that rim the construction site, a group of Loudoun County Public Schools (LCPS) teachers and administrators as well as community and business leaders joined HHMI officers and staff at Janelia Farm this past March for breakfast and an announcement that had the guests "hovering just a little above the floor," according to LCPS Superintendent Edgar B. Hatrick.

The group had gathered for the formal announcement of an HHMI commitment to invest at least $1 million per year in support of science education in the LCPS system. Though the Institute has funded science education since the inception of its grants program in 1988—more than $1.4 billion have been invested thus far in a range of activities for students of all ages—this partnership marks the first time that HHMI will work directly with recipient schools.

College scholarships, each worth $7,000 per year, have been established for two outstanding seniors at every Loudoun County high school. In addition, HHMI will bolster two programs already in the county budget: the start-up of a district-wide science academy at the recently built Dominion High School and the development of a new middle school science curriculum.

Space for a public academy was built into the plan for Dominion, says Hatrick, though the nature of the academy had been undefined. "Through our work with the Institute, what was a somewhat cloudy vision at first is becoming much clearer," he says. Developing a science academy with a cross-pollination of activities at both Dominion and Janelia Farm will "create opportunities for science education that will be unbeatable anywhere in America."

Guests from Loudoun County survey a model of the Janelia Farm Research Campus.

Modernizing the middle school curriculum will involve the creation of hands-on activities to pique interest at this "prime time" in a student's development, says Peter J. Bruns, HHMI's vice president for grants and special programs. HHMI will hold a summer workshop to familiarize teachers with the new tools as well as a two-day booster class just before school begins. To further ensure success, a group of long-time HHMI grantees from Pennsylvania—who developed the nationally renowned "LabLion" program for elementary schools—will provide support throughout the school year.

It is the national and international network of HHMI grantees and scientists, and not just dollars, that makes the value of the partnership so immense, says HHMI President Thomas R. Cech. The well of experience of the more than 200 grantees at research universities across the United States should prove a major resource for innovative ideas for Loudoun County teachers. And, says Hatrick, the value to students of the proximity of the Janelia Farm campus cannot be underestimated. "For them to have the chance to rub elbows with researchers who are opening the world of science to things we can't imagine right now, the potential is boundless."

—MARY BETH GARDINER

MOORE TAPPED AS JANELIA COO

In March, HHMI named Cheryl A. Moore as associate director and chief operating officer of the Janelia Farm Research Campus. Helping to develop an administrative and management structure for the research facility, Moore will oversee all fiscal and administrative services at the 281-acre campus.

Moore comes to HHMI from the Burnham Institute, a private, nonprofit life-sciences research center in La Jolla, California, where she has been senior vice president, chief operating officer, and chief administrative officer. A graduate of the University of San Diego and a member of the American Institute of Certified Public Accountants, she has held top-level management positions with an international financial services firm and two managed healthcare companies.

"My goal is to work with Gerry Rubin to create a uniquely creative research environment free of bureaucratic hassles, in an atmosphere of openness, support, and freedom," Moore says. "My goal in managing the business of research is to remove as many impediments to the advancement of science as I can, to help our researchers move more quickly toward scientific discovery. I will know that Janelia Farm is successful when people comment on how much fun it is to work there because of the sense of teamwork and intellectual stimulation."

dimensions: pinpointing the kinds of biological problems that Janelia's scientists will tackle and recruiting the right people to work on them. "Those two tasks are completely linked," he says, "because whatever we decide to do, we only want to do it if we can attract some subset of the best people in the world for that problem."

Rubin knows very well that Janelia offers an extraordinary opportunity to extend scientific knowledge. Accordingly, the questions he's considering for Janelia's core work are on science's horizon—the kinds of problems, he says, that are too premature to warrant funding from the National Institutes of Health or similar sources.

For guidance about specific areas, Rubin has organized a series of workshops (see sidebar below) that engage many of today's leading scientists in wide-ranging discussions about scientific problems and opportunities. To help attendees think beyond typical short-term project timelines, Rubin challenges them with what he calls the "thousand-person-year problem." He instructs them to "imagine you were given the resources to assemble a group of 100 people and to support that group for 10 years. The rules are that the problem has to be really important, but you must make a convincing case that you have at least a 20 percent chance of solving it."

Outcomes from the workshops are "exceeding expectations," says Rubin. "There have been lively and open exchanges, and eventually there was some loose consensus on what people thought were the main issues." David J. Bishop, a 26-year veteran of Bell Labs who is now its vice president of nanotechnology research, participated in the workshop on the biochemistry of the single cell. "There are certain classes of problems, such as this one, where a principal investigator and three postdocs and graduate students just can't make headway," he says. "You have to have multidisciplinary teams going after them." They are the kinds of problems, Bishop says, that have won Bell Labs scientists eleven Nobel Prizes and nine U.S. National Medals of Science over the years.

When fully staffed, the research campus will host 20 to 30 group leaders. Though two-thirds of them will likely focus on two central projects, that doesn't translate into a loss of independence for the researchers. Rubin anticipates that those who come to Janelia will be drawn by the diversity and the opportunity to work on a problem larger than any single lab can tackle. "We hope that the project teams will self-identify—creating 'voluntary assemblies,' if you will—as we recruit," he says.

"The question is, do you simply hire the brightest people, irrespective of research field, hoping that the mix will create synergy?" he continues. "Or, because you need computational biologists, instrument builders, and cell biologists for a particular problem, do you specifically hire from those fields to work on it together? We're trying to strike that balance."

Building flexibility into Janelia's approach is key, says Rubin. "Undoubtedly, there will be a lot of details that we don't get right. We look at this not as a set of rules that define how Janelia is to be run forever, but as a working hypothesis," he says. "We will evolve as we go." H

FIELDS OF INTEREST

Janelia Farm's research agenda will be not proscribed, but evolutionary. There will be a strong focus on developing new tools—experimental methods, computer software, and scientific instruments—needed to advance research capabilities. The aim is to identify important biomedical problems for which future progress requires technological innovation and then nurture the development of integrated teams of venturesome biologists and tool builders.

To narrow the focus to three to five ideas for initial research, Gerald Rubin and colleagues are organizing a series of workshops with leaders in several fields of interest. While not pinpointing future Janelia research, the topics here hint at broad directions for Janelia's science:

- *Perception and behavior,* organized by HHMI investigators Cornelia I. Bargmann and Richard Axel. Neuroscience, imaging, and computation.
- *Biochemistry of single cells,* organized by HHMI investigators Robert Tjian and Gerald R. Crabtree. Methods required to study biochemical reactions and processes in single cells.
- *Membranes, membrane proteins, and membrane-associated molecular machines,* organized by HHMI investigators Roderick MacKinnon, Eric Gouaux, and Tom A. Rapoport. Overcoming the unique challenges limiting experimental study of cellular processes that occur at or within membranes.
- *Functional imaging in living systems,* organized by HHMI investigators Roger Y. Tsien and Eric R. Kandel and Max Planck Institute directors Winfried Denk and Nikos K. Logothetis. Emerging methods for monitoring gene activity, protein modification and subcellular localization, ion fluxes, and other metabolic activities in living cells.
- *Imaging cellular structures,* organized by HHMI investigators David A. Agard and Eva Nogales and Max Planck Institute directors Wolfgang Baumeister and Stefan W. Hell. Emerging methods in light and electron microscopy for determining the structure of cellular components.

MARY KRISTEN PHOTOGRAPHY

Extending HHMI's Global Outreach

HHMI is stepping up its commitment to fostering international biomedical research with two new grant competitions for more than $30 million. The Institute will select approximately 80 scientists from outside the United States to receive five-year awards of $50,000 to $100,000 annually. Since 1991, the Institute has awarded more than $100 million in international grants, supporting the work of scientists in 32 countries.

One competition is for researchers from 13 countries in the Baltics, Eastern and Central Europe, Russia, and the Ukraine. Eligible countries include Bulgaria, Croatia, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Russia, Romania, the Slovak Republic, Slovenia, and the Ukraine. The grants will encourage talented scientists to remain in their own countries, helping reverse the brain drain and build the scientific capacity of those nations.

Many countries in this region have a strong tradition of scientific research but such limited resources that scientific progress is severely challenged. "HHMI wants to help keep those scientific traditions alive," says Jill Conley, director of HHMI's international program.

The other competition targets scientists who are on the front lines of the fight against emerging and established infectious diseases such as malaria, Chagas disease, and tuberculosis. These researchers may be from any country except the United States and the United Kingdom, and their research must focus on basic biological processes or disease mechanisms in parasitology or infectious diseases.

In countries with limited economic resources, even a fairly small research grant can have a broad impact. According to Conley, such support may simultaneously provide training opportunities for students; electronic-journal subscriptions for colleagues in the scientist's home institution; equipment for use by others, both there and in neighboring institutions; opportunities for collaboration; travel to scientific meetings; and salary support for the researcher and his or her laboratory personnel.

Two previous rounds of grants in 1995 and 2000 to scientists from the Baltics, Eastern and Central Europe, Russia, and the Ukraine have enabled talented researchers to remain in—or return to—their home countries to do their research. An example is Tamás F. Freund, a Hungarian scientist. "The first HHMI grant played a major role in my making a decision to stay in Hungary in spite of prestigious job offers from the West," he says. "The second 5-year grant allowed me to build up a relatively large, well-equipped, internationally competitive lab, which provides training and ideal working conditions for many graduate students, postdocs, and undergraduate student researchers."

In HHMI's first infectious diseases and parasitology research competition in 2000, 45 scientists in 20 countries received grants to study the basic biological mechanisms underlying diseases that disproportionately affect the world's poorest people. Approximately half of the grant recipients were from developing or middle-income countries. Annual meetings of the international research scholars have led to productive collaborations between researchers in less and more developed countries as far apart as Mexico and Australia.

Both new competitions will accept applications as well as nominations by other scientists, and HHMI is encouraging qualified applicants to apply. Deadlines are in September and November 2004. Awards will be made in 2005.

Institute Awards Two Grants for Science Education Programs

HHMI is teaming up with biomedical research institutions, science museums, and school systems in seven states to help two specific groups—parents who homeschool their children, and preschoolers.

The Cable Natural History Museum in rural Cable, Wisconsin, will spearhead an effort to train parents who homeschool to do hands-on, inquiry-based science education for kids in grades 4 through 12. Those parents will in turn train others in their communities. Inquiry-based approaches teach students the scientific method of asking questions, formulating and testing hypotheses, analyzing results, and drawing conclusions.

The Science Museum of Minnesota in St. Paul will add an urban perspective to the Cable Museum's rural experience. Together, the museums plan to conduct workshops for 10 parents from Wisconsin and 10 from Minnesota, using kits developed by the project's biomedical research partners, the Genetic Science Learning Center at the University of Utah and the Lovelace Respiratory Research Institute in Albuquerque. All four institutions already operate HHMI-supported science education programs.

Partners in the preschool science project are the Fairchild Tropical Botanic Garden in Miami, the Cognitive Learning Institute of Pennsylvania, and the Loudoun County (Virginia) Public Schools. They too run HHMI-supported programs.

The goal is to foster critical thinking, problem-solving ability, and literacy in preschoolers and children in the early elementary grades. Research has shown a clear relationship between the skills with which children enter school and their later academic achievement, the program's directors say. Research also suggests that raising parents' comfort level in science can help them create a more educationally rich home environment.

The preschool program will use hands-on activities that teach information processing; mathematical concepts such as "greater than" and "less than"; and science concepts such as gravity, density, weight, and light. Family science activities—"family health nights," for example—will also be held regularly to further parents' involvement with their children's science learning. The program will take place in three geographically and ethnically diverse regions: Harrisburg, Pennsylvania; Sterling, Virginia; and Miami, Florida.

Both new programs, funded with grants of $50,000, are pilot projects that are expected to serve as models for similar activities in other places.

—JENNIFER BOETH DONOVAN

Web-based applications for the international competitions are at **www.hhmi.org/grants/gcs**. *The login ID is* **guest** *and the password is* **register**.

Additional information about HHMI's international program can be found at **www.hhmi.org/grants/office/intlprog**.

Bye-Bye Bio 101

Why we should teach science the way we do science.

It has long been clear that university-level science education needs reform. Yet, although effective alternatives have been available for years, scientists who teach have tended to resist changing their teaching methods. A group of persistent reformers, however, is now raising scientists' awareness of successful new approaches and providing the tools to implement them. In particular, they note in their policy-forum article published in the April 23, 2004, issue of *Science*, "There is mounting evidence that supplementing or replacing lectures with active learning strategies and engaging students in discovery and [the] scientific process improves learning and retention of knowledge."

Lead author Jo Handelsman, an HHMI professor and plant pathology researcher at the University of Wisconsin (UW)–Madison, and her coauthors—including Peter J. Bruns, vice president for grants and special programs at HHMI, and Shirley M. Tilghman, president of Princeton University and a former HHMI investigator—argue that outcomes assessments demonstrate that students taught this way have better problem-solving ability, conceptual understanding, and success in subsequent science courses in comparison with students who learned in traditional passive ways.

The other coauthors of the policy-forum article are Jim Gentile, president of Research Corporation and former dean of natural sciences and HHMI program director at Hope College; William B. Wood, University of Colorado at Boulder; Diane Ebert-May, Michigan State University; Robert Beichner, North Carolina State University; Amy Chang, American Society for Microbiology; Robert DeHaan, Emory University; and James Stewart and Sarah Lauffer, both of the UW–Madison.

The publisher for the article was carefully selected, says Handelsman. "Most scientists don't read reports on education, but they do read *Science*. So this was the place to reach our colleagues."

Numerous reports—such as "Science for All Americans," published in 1989 by the American Association for the Advancement of Science, and "Bio 2010: Transforming Undergraduate Education for Future Research Biologists," issued in 2002 by the National Research Council of the National Academies and funded in part by HHMI—have called for a shift to "scientific teaching," defined as science education using the techniques of science itself. These include asking questions, formulating hypotheses, designing and conducting experiments, collecting and analyzing data, drawing conclusions based on evidence, and writing up the results.

The shift is already beginning. In their own teaching, Handelsman and other pioneer reformers are spearheading fundamental changes in the way scientists teach and understand how graduates learn science. And those changes to the curriculum are based on scientific evidence. In other words, they are teaching science scientifically.

"It's the science community that needs to reform," says Bruns. "We are calling for change from within."

CHALLENGE OF LEARNING

Widespread reform has been slow to catch on, however, partly because many scientists are unaware of data that demonstrate the approach's effectiveness, are intimidated by the challenge of learning new teaching methods, or fear that focusing on teaching will hurt their credibility as researchers, say the authors of the *Science* essay.

"It's the science community that needs to reform," says Bruns. "We are calling for change from within."

A few institutions are endorsing and supporting such efforts, including HHMI through its HHMI Professors initiative. In 2002, the Institute awarded $20 million to 20 recognized researchers at universities nationwide to develop innovative ways for undergraduate science teaching to mirror the methods and rigors of research science at its best.

Toward the goal of having scientific teaching replace lectures and "cookbook" labs in which the results are already known, the policy paper offers several specific recommendations:

- Revamp introductory lecture courses to include active participation by students
- Teach science graduate students how to teach
- Change the reward system at universities to reflect the importance of good teaching

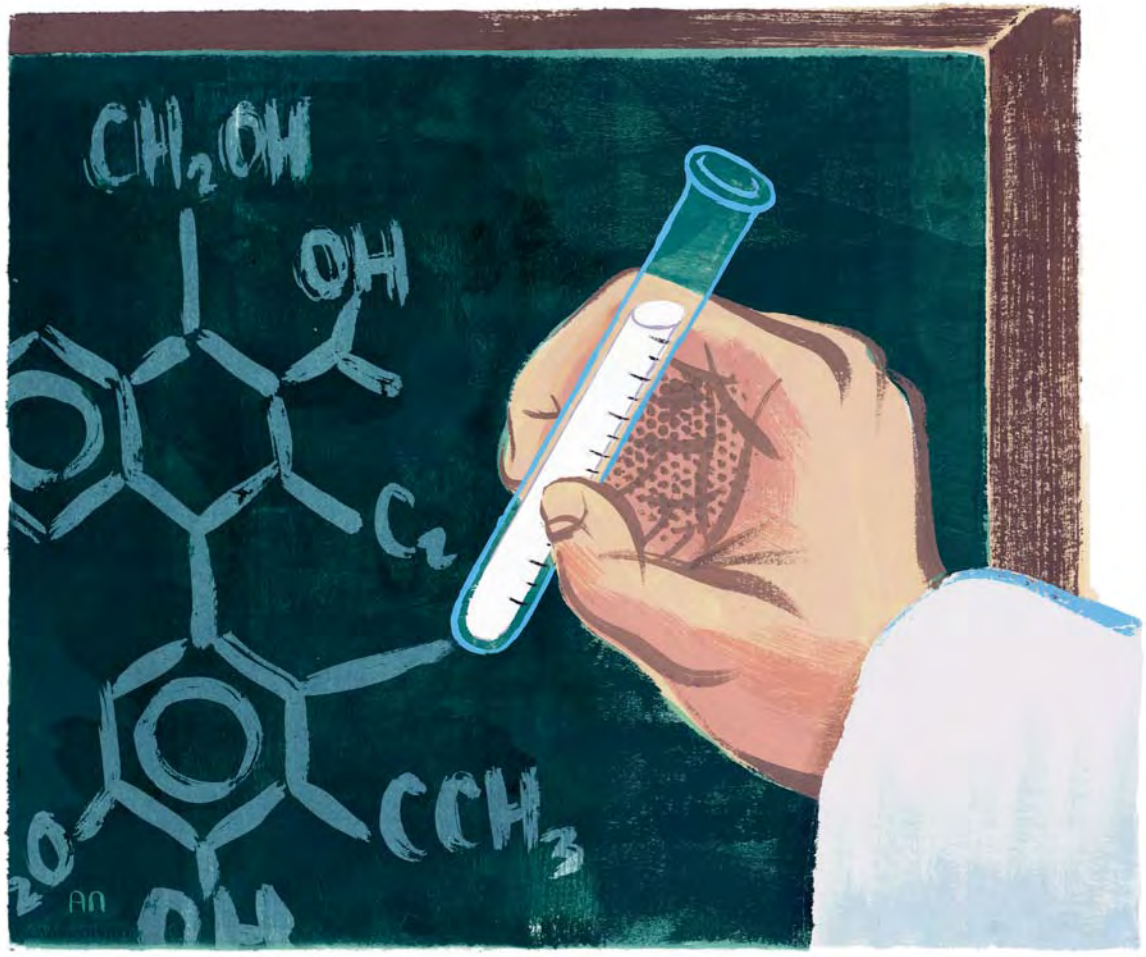
"We need to dispel the notion that excellent teaching is incompatible with first-rate research," says Bruns. At research universities, the reward system—tenure, sabbaticals, pay raises, and promotion—is based on success in research. "We need to encourage and reward excellence and innovation in teaching as well."

There are signs that the message is starting to be heard and taken to heart. For example, the UW–Madison—Handelsman's campus—has rewritten its guidelines for tenure, sabbaticals, and merit pay raises to emphasize teaching.

Handelsman and her colleagues have introduced a course at UW–Madison in which nonscience majors develop hypotheses, design and conduct experiments, and interpret data. "Initially, many colleagues were skeptical of it," she recalls. "Some raised their eyebrows when they passed a lecture hall filled with 120 students talking to each other, and one called it 'biology for poets.' But when they saw the results, which included students flocking to enroll and evidence that the students were grappling with real science and tough problems, many became excited, and quite a few of them now teach the course."

The HHMI-supported program at Madison also focuses on training scientists to teach. "We introduce them to the education literature to encourage them to become scientific teachers who demand data to make educational choices," Handelsman says. "We provide opportunities for them to practice teaching, using methods that have been shown to help

"It's the science community that needs to reform," says Bruns. "We are calling for change from within."



ALEX NABAUM

students acquire knowledge and learn to think and reason about science." She herself offers a mentoring course to teach graduate students and postdocs how to supervise undergraduates in research more effectively. "We hope to send into the world a new generation of teachers who are committed to engaging undergraduates in science both in the classroom and in the research lab," the HHMI professor explains.

TOOLS FOR TEACHING

To help give science faculty members at research universities the tools to do what the policy paper's authors recommend, an annotated collection of more than three dozen online resources accompanies the paper. They include tested and effective teaching methods for reaching a diversity of students, inquiry-based labs, Web-based programs to enhance classroom teaching, experiments and data about teaching methods, assessment tools, and workshops for science educators. "In addition to being a passionate call for action, we hope [the paper] provides educators with a comprehensive, yet accessible, set of outstanding materials that will help them start their own revolution," Handelsman says.

In 42 new undergraduate science education grants totaling nearly $50 million that HHMI recently awarded (see page 2), one of the themes was helping postdoctoral fellows in the sciences to learn to teach undergraduates. A number of funded programs include teaching fellowships for postdocs.

To help further disseminate information about this innovative way of teaching science, the Institute is supporting a new peer-reviewed, Web-based journal called *Cell Biology Education: A Journal of Life Science Education*. HHMI, together with the National Academy of Sciences, is also sponsoring a summer institute on undergraduate education in biology at UW–Madison, where 36 faculty who teach large introductory science courses will develop new instructional materials that apply tested teaching methods. The 2004 course is codirected by two of the policy paper's authors, Handelsman and Wood.

"Many students attend research universities because of the strength of the science being performed there, but they get turned off in introductory courses and never look back," says Bruns. "We need those bright young minds. We want to encourage more students to become scientists, and we want to send non-science majors into society knowing how to confront issues that require analytical and scientific thinking."

"To achieve scientific literacy in society," Bruns suggests, "we need to teach people how science is done, which means engaging them in science, asking them to be scientists, as part of their university education."

—JENNIFER BOETH DONOVAN

Saving the Children

This Brazilian scientist wants to break a chronic affliction's persistent grasp. The answer may be inside us.

In the poorest regions of Brazil, such as the Northeast, malnutrition and inadequate sanitation are commonplace, and many infants and young children die from persistent diarrhea. HHMI international research scholar Aldo A. M. Lima is determined to find new ways to save their lives.

He may well have found a remedy, right inside our own bodies, in glutamine—an amino acid important to protein synthesis, cell proliferation, and cell death, and a major fuel for rapidly dividing cells, such as those lining the intestine. "Persistent diarrhea is commonly associated with childhood malnutrition, and glutamine is known to improve intestinal mucous repair and function in these cases," says Lima. "The intestine can better absorb the food, breaking the cycle of diarrhea," thereby helping patients to recover.

A professor at the Federal University of Ceará (UFC), Lima has been addressing this problem for 25 years, ever since his graduation from the UFC Medical School in Fortaleza, capital of Ceará state. He recalls that in his internship at Albert Sabin Children's Hospital, also in Fortaleza, "I was the infectious-disease resident, responsible for the diarrhea cases, and I saw lots of kids with diarrhea." There was only so much he could do for them, though. "I remember using the best antibiotics available, together with rehydration solution, but without success. Few of them survived, and I became really disturbed by the overall situation."

Ceará has an elevated infant mortality rate. According to a 1999 study in the *International Journal of Epidemiology*, the infant mortality rate varies substantially among municipalities in the state of Ceará, from 14 per 1,000 live births—not bad by Brazilian standards—to 193 per 1,000 live births, but they are far higher than the rate in countries such as the United States (6.7 per 1,000) and France (4.0 per 1,000).

Lima's aim is for his glutamine treatments to help close the gap. Natural glutamine has some disadvantages, including being unstable under acid conditions. For example, Lima says, "you can't dilute it in pineapple juice." Lima's lab developed a variant called alanyl-glutamine that is much more stable and has shown good results in studies with malnourished children.

Aldo A. M. Lima

In one study involving youngsters from poor communities within Fortaleza, Lima showed that 53 children treated with the oral supplement were able to gain weight and repair mucosal damage faster than a control group not receiving glutamine (both groups were following a diet recommended by the World Health Organization). In an earlier study, 57 children were given only glutamine oral supplement or glucose for five days. Those who got the glutamine compound had a weight gain of 200 grams, while the control group showed no significant weight change.

Encouraged by these and similar results, Lima expects to see the glutamine oral supplement on the market within two years. Nutrasol, an emerging company in northeast Brazil, has started to develop such products.

"The discovery that glutamine helps to repair the intestinal mucosa is one of the most important discoveries I've seen relating to infectious diseases and the intestine mucous membrane," says HHMI international research scholar Edgar M. Carvalho, a professor at the Federal University of Bahia in Salvador, Brazil, who has been following Lima's work. In a low-income country such as Brazil, Carvalho explains, "the method developed by Dr. Lima can be widely used because it is so low-cost."

Thanks to one scientist's determination to break persistent diarrhea's virulent cycle, Brazil's poor may one day see at least one of their challenges eased—and ultimately, perhaps, erased.

—ALESSANDRO GRECO

Tranquil here, the Amazon floods seasonally, as do other Brazilian rivers, abetting the spread of disease.

WOLFGANG KAEHLER/CORBIS (LEFT); KENT KALLBERG, KALLBERG STUDIOS (TOP)

Six Antigens at a Time

To combat malaria, British researchers experiment with a broad-spectrum vaccine.

Every year, malaria infects up to 500 million people worldwide. In the developed world, the disease can generally be treated with prescription drugs or prevented outright via insecticides.

In Africa, however, malaria kills more than 1 million people a year—most of them children under the age of five. Lack of access to medicine is only part of the problem. The continent must also endure a particularly virulent species of malaria parasite, *Plasmodium falciparum*, that has thwarted all attempts to control it.

Working in Africa and in England, HHMI international research scholar Adrian V. S. Hill and his colleagues are pursuing intriguing new approaches to preventive vaccines against *P. falciparum*—and their ideas have drawn the attention of their scientific colleagues.

Hill's team is field-testing one candidate vaccine with human volunteers on both sides of Africa—in Kenya in the east and The Gambia in the west. That vaccine uses a "prime-boost" strategy: First a fragment of *P. falciparum* DNA "primes" a type of immune cell, called a T cell, to recognize the *P. falciparum* antigen, and then the DNA fragment is inserted into a harmless modified virus (called modified vaccinia virus Ankara, or MVA), which expresses the antigen protein and boosts that T cell response. It's a novel approach in that it stimulates the cellular arm of the immune system rather than production of antibodies—the traditional strategy of vaccine design, which doesn't seem to work against malaria.

In their lab at the University of Oxford, the British researchers have been busily testing a new and possibly better vaccine in mice. Hill and his colleagues have strung together DNA encoding six antigens from *P. falciparum* and delivered it to mice inside a virus that has been modified so that it can't replicate or cause disease. At 10 kilobases in length, says Hill, "we think it's the largest string of antigens that's ever been published as an insert in an engineered vaccine."

Because it uses six antigens instead of one, the vaccine theoretically could protect more effectively against malaria because of its broader repertoire. The potential improvement afforded by the six antigens comes at a cost, however. "It's relatively straightforward to string them together," says Hill, who has been working on the project for four years now. "The challenge is to have something that large be expressed as a protein that will then generate an immune response after vaccination."

As Hill explains, the antigen DNA has to be carried into the host cell, where it is expressed and eventually displayed on the cell's surface to attract the attention of any passing T cells. At first, using the MVA approach that had worked with one antigen alone, the research team failed to achieve this objective; the MVA vector simply wasn't efficient at transporting such a large packet of DNA into cells. But when they tried again, using MVA in tandem with a second modified poxvirus, they achieved an immune response as strong as that seen with their existing vaccine. They published this result in January 2004 in the *Proceedings of the National Academy of Sciences*.

Hill's next concern was that the response would be to one antigen only, and that the other five would prove redundant. But that's not what occurred. Instead, in different strains of mice, different antigens served to trigger the strongest immune response. "Our guess is that not only is this what happens in humans when you vaccinate them," he says, "but it's also probably what happens when they are naturally exposed to malaria."

Because most of the people who receive the vaccine will already have been exposed to malaria, Hill believes that it will simply boost the immune response that is naturally strongest in each individual. "What these poxviruses are particularly good at doing is not so much starting off an immune response, or priming it, as boosting an immune response," he says. "You're taking something that's barely there, or barely detectable, and amplifying it to very high levels."

Zarifah Reed of the World Health Organization's Initiative for Vaccine Research says she will be interested to see if six antigens are indeed better than one. "There is controversy as to whether combining all these antigens will actually increase immune response," she says, adding that some researchers believe the combinatorial approach could even afford *lower* protection, the result of competition between antigens. "The bottom line is that until it goes into human trials, it's hard to tell."

The Oxford group began work on its new construct before the sequencing of the *P. falciparum* genome was completed in 2002, so they were limited to a fraction of the parasite's antigens that are now known. If the combinatorial approach does turn out to be more effective, says Hill, it's possible that vaccines based on many different combinations of antigens may be created in pursuit of optimal response under different conditions.

—LAURA SPINNEY

GRAHAM TROTT

Adrian Hill pursues intriguing new approaches to preventive vaccines.

The Emergence of Resistance

Researchers find clues about how cholera and other infectious diseases outsmart antibiotics.

In 1992, after finishing his clinical training in infectious diseases and working as a postdoc in the laboratory of Harvard researcher John Mekalanos, Matthew K. Waldor came across two letters written in *The Lancet* that changed the course of his career. They described a new strain of the bacteria that causes cholera, a severe and sometimes lethal diarrheal disease raging in India and Bangladesh. This strain was resistant to four common antibiotics, and it carried a mysterious piece of genetic material that no one had yet characterized. By 1993, this genetic element had shown up in almost all forms of *Vibrio cholerae*, the bacteria that causes cholera in Asia, forcing doctors there to abandon previous treatments.

When Waldor, now an HHMI investigator at Tufts University School of Medicine in Boston, began studying these newly emerged cholera-causing bacteria, he discovered a transferable block of chromosomal DNA that allows the microorganisms to resist destruction by antibiotics. Now his group at Tufts has found that ciprofloxacin ("cipro")—the antibiotic that gained much attention during the anthrax scare—actually hastens the spread of antibiotic resistance by prompting exchange of this DNA among bacteria.

Waldor and his colleagues showed that the chromosomal antibiotic-resistant genes were transmissible by conjugation, a form of microbial sex where the organisms shimmy up to each other, touch cell membranes, and exchange segments of DNA through pores at the contact point. But what code was in the DNA that the microorganisms might be trading? John W. Beaber, a student in Waldor's lab at Tufts, sequenced many stretches of bacterial DNA and uncovered the culprit: a section of DNA, dubbed SXT, that holds at least 88 genes. SXT encodes the machinery for bacterial conjugation, and for chromosomal integration and excision, and it also confers resistance to four different antibiotics.

To understand the mechanisms that control SXT transfer, Waldor focused on one of the genes in SXT—one that resembled a gene used by viruses that infect bacteria to enforce inactivity during their stay in the host—ultimately discovering that it was a repressor gene. Called *setR*, this gene encodes a protein (SetR) that switches off at least two other proteins, both of which are products of SXT genes. The researchers found that SetR ordinarily inhibits the excision and transfer of SXT.

Two letters in* The Lancet *changed the course of Matthew Waldor's career.

ASIA KEPKA

Waldor's group also found, however, that when damage to the bacterial chromosome activates what's called the "SOS response," the repressor protein becomes inactive, triggering SXT to replicate itself and spread from the damaged bacterium. The SOS response can be activated by environmental stimuli such as ultraviolet radiation and by certain classes of antibiotics. Hence, damage to bacteria can trigger faster spreading of antibiotic resistance. The work was published in the January 1, 2004, issue of *Nature*.

Waldor says his team's research shows how antibiotic use can "promote the evolution of new antibiotic-resistant organisms that have obtained their resistance genes from other species. This new understanding of the mechanism of transfer is very worrisome, for it shows how indiscriminant antibiotic use can promote the dissemination of antibiotic resistance." The researchers also emphasize that their findings about how bacteria transmit antibiotic resistance further underscore the hazards of widespread, chronic use of antibiotics in humans and animals.

"It's a very scary era," says Jo Handelsman, HHMI professor at the University of Wisconsin–Madison. "There is more resistance to more antibiotics and a wider range of antibiotic-resistant genes turning up." At the same time, she adds, very few new antibiotics are coming out. Pharmaceutical companies are focusing on more lucrative chronic conditions such as diabetes and obesity; drug companies have often neglected to do the basic research that would support taking a new bacteria fighter through the risky and expensive phases of development.

The vagaries of the marketplace don't deter Waldor, however, who remains committed to an ambitious research agenda of his own. He wants to understand the environmental conditions as well as the molecular mechanisms that control the transfer of genetic information among bacteria. He would also like to understand the host range of mobile DNA—for example, which other infectious agents can pick up SXT or related elements, thereby conferring resistance to common antibiotics. He has already found that *Escherichia coli*, *Salmonella*, and *Pseudomonas* are all susceptible.

Waldor and his colleagues are studying other genes in the SXT system to learn more about their machinations in the rugged world of evolving microbes. "It could ultimately help us to prevent the emergence of resistance," Waldor says, "as well as of new [disease-causing] microorganisms."

—TRISHA GURA

Hidden Potential

Brain cells once considered secondary are found to work as stem cells.

Researchers have found an unexpected source of stem cells in the adult human brain. They have demonstrated for the first time that certain human astrocytes—starlike cells of the central nervous system classically thought to play more of a supportive role for the neuron—can actually function as stem cells. These astrocytes form a ribbonlike structure lining the ventricles—inner cavities of the adult human brain—and are capable of generating all three types of mature brain cells (neurons, astrocytes, and oligodendrocytes). The finding opens the possibility that such human stem cells could be used one day to regenerate damaged areas in the adult central nervous system.

"This ribbon of human astrocytes represents a significant departure from other species," says Nader Sanai, a former HHMI medical student fellow who is currently a neurosurgery resident at the University of California, San Francisco (UCSF). Sanai led the work with Arturo Alvarez-Buylla, professor of neurological surgery at UCSF. "The differences we see imply that this region in the human brain doesn't necessarily do the same things as its primate and rodent counterparts," Sanai adds. Stem cells from a comparable area in the rodent brain follow a distinct path from their place of origin to the olfactory bulb (a brain region that processes smells), where they create new neurons. In humans, "this cell population does not appear to serve this purpose, but has the potential to regenerate other parts of the brain, though it's not clear which regions those may be." With millions of dollars invested in animal models of stem cells, he says, the team's findings might call into question the fidelity of those models in predicting the human brain. Sanai, Alvarez-Buylla, and colleagues reported their findings in the February 19, 2004, issue of *Nature*.

These findings are provocative because astrocytes have traditionally been considered simple helper cells, Sanai says. "This speaks to the plasticity of the human brain. Certain cell types may have hidden potential." And because these subtypes of astrocytes appear no different from any other astrocytes, he says, "it's possible that other astrocytes, in other regions of the brain, have the same potential."

Other research, by scientists at the Salk Institute for Biological Studies in La Jolla, California, has shown that neurons are generated in the adult human hippocampus, says HHMI investigator Sean J. Morrison at the University of Michigan Medical School. As a result, there's at least the possibility that stem cells in the human subventricular zone (the source of these astrocytic neural stem cells) "could well be giving rise to new neurons in the adult human brain, at least at a low rate, and the rate of neurogenesis by these stem cells could increase in response to injury," says Morrison.

Nader Sanai found an unexpected source of stem cells.

Sanai and colleagues want to know still more about astrocytes' work as stem cells. "We know the cells are dividing," says Alvarez-Buylla, "yet it leaves us with the question: What are these cells doing if they are not going to the olfactory bulb?" The researchers now plan to better characterize this region of the human brain and investigate potential relationships between these stem cells and brain tumors.

—DENNIS MEREDITH

Remembering Santiago

The family and friends of Nestor V. Santiago, the Institute's vice president and chief investment officer until his death in 2003, gathered in a courtyard at HHMI headquarters for the dedication of a granite sculpture in his memory (right). At the ceremony, HHMI President Thomas R. Cech presented a check for $107,060.77 to the Santiago Fund, established by Santiago and his siblings in 2000 to benefit the Nueva Ecija National High School in the Philippines. The gift resulted from contributions by HHMI employees, business associates, Trustees, and members of HHMI's investment advisory committee, with a matching contribution from the Institute. Santiago had attended Nueva Ecija, in a province approximately 70 miles north of Manila, where he was valedictorian of his class in 1965. After the government abolished tuition at public schools, enrollment at his alma mater at first grew rapidly, but government funding for the school did not keep pace. Crowded conditions, a shortage of materials, and a gradual decline in the quality of education led affluent students and well-qualified teachers to seek better schools, leaving talented but needy students at Nueva Ecija with limited educational opportunities, particularly in science and math. Under Santiago's leadership, he and his siblings created a fund to provide resources and well-qualified faculty for a special science school within the high school. HHMI's contribution will help endow the salary of a highly qualified science teacher, who will have the title Nestor V. Santiago-HHMI Teacher of Science. The first Santiago Teacher is expected to be named later this year.

—JENNIFER BOETH DONOVAN

TIM ARCHIBALD (TOP), PAUL FETTERS (BOTTOM)

Models and Mentors

Kids give up their Saturdays to travel to Georgetown University—and a world of new opportunities.

Every Saturday morning, a band of determined middle and high school students make their way from the mean streets of Washington, D.C.'s Deanwood neighborhood—where in May this year an 8-year-old girl was killed by a stray bullet during a streetfight—to Georgetown University. Both literally and metaphorically, it's a long trip. Some students leave home before 7 a.m. and have to take two or three buses to get there. For some, the trip across town takes them as far west as they have ever gone.

What motivates these students to give up their Saturdays? The promise of a brighter future, for one. And two exceptional role models, Thomas Bullock and Charlene Brown-McKenzie, who inspire students' minds and spirits and help turn their lives around.

Bullock, a mathematician who grew up in D.C.'s Capitol Heights section, the son of school teachers, heads Georgetown's Institute for College Preparation (ICP), which has been supported by HHMI since 1992. Brown-McKenzie, a clinical social worker, is the program's only other paid staff member. Yet, with the help of dedicated volunteer faculty and students from Georgetown, determined parents from Deanwood, and alumni of the program itself, they have managed to send 92 percent of the more than 100 students who have participated in the ICP to college—from a school district where only one out of two students graduates from high school.

Once enrolled, an impressive number of ICP students stay to complete college. Of the program's first class, which finished high school in 1995, 85 percent have earned a college degree.

How do Bullock and Brown-McKenzie do it?

For one thing, "we make ourselves part of their communities, part of their lives," Brown-McKenzie says. They go to Deanwood's christenings, weddings, and funerals. They meet with parents and visit homes. They tutor seventh-graders at Ronald H. Brown Middle School, and Brown-McKenzie meets with seventh-grade teachers and special-education teachers there to help them design interventions for other at-risk students.

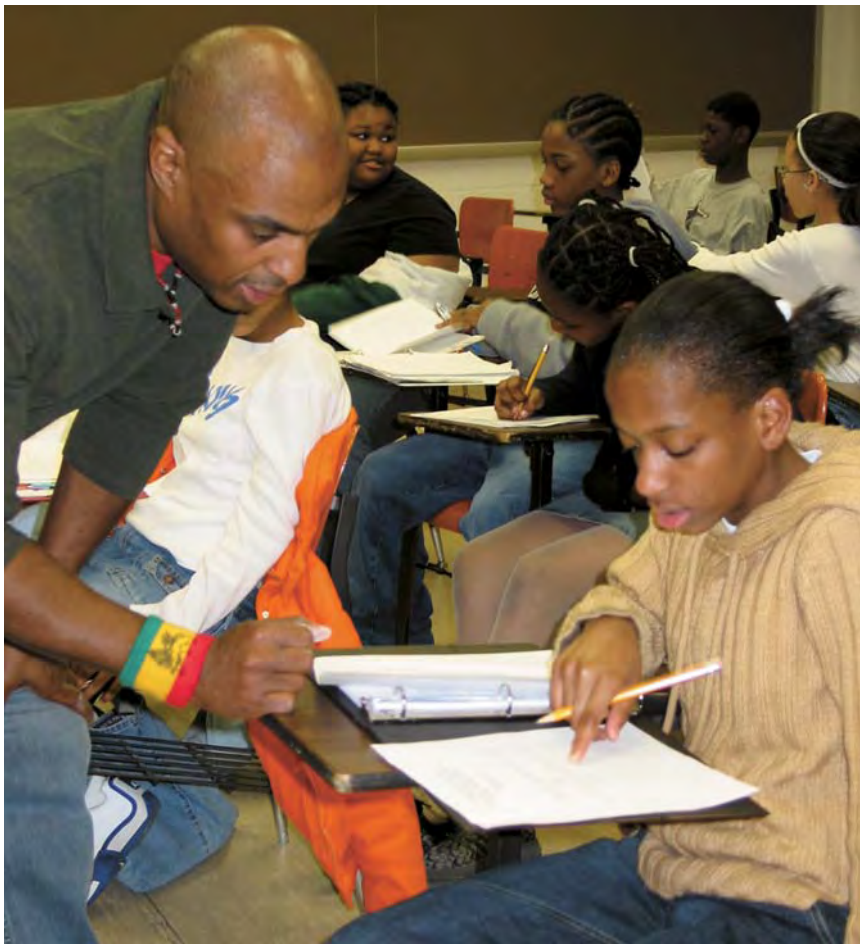
ICP's leaders inspired a Georgetown biology professor and her class to partner with the science teachers at the middle school. Twenty-five Georgetown sociology students are working with the middle schoolers to do what sociologists call "community asset mapping"—combing Deanwood for assets that might help it attract businesses and improve real-estate values. Two such assets are that the neighborhood is near a river and sits on a hill, much like affluent Georgetown. "What happened to Georgetown can happen to Deanwood too," Bullock tells them.

Basically, "the students see an environment around them that feels hopeless," says Bullock. "We give them hope."

At the ICP Saturday Academy, students study English, math, Spanish, chemistry, and Washington, D.C., history. In the class Success Skills, they learn how to manage their time, take notes, and apply for college and get financial aid. Once a month, parents attend the ICP, so that they can learn how to help their children prepare for, get into, and succeed in college. "We are trying to help parents face their fears and anxieties, to understand that college is a good and possible thing for their children," Brown-McKenzie explains.

Bullock and Brown-McKenzie, too, are willing to do whatever it takes to get "their" kids into college. When Christina Olukunle was accepted to Bennett College in North Carolina, her mother, a single parent with a younger daughter at home,

MATH MAPPING. ***African American mathematician Benjamin Banneker surveyed the land that is now the District of Columbia, laying out the streets on a grid similar to the x and y axes of the graph of an algebraic equation. That's the lesson that Tom Bullock, director of Georgetown University's Institute for College Preparation, shares with Gabrielle Alston, a student at Ronald H. Brown Middle School, during a Saturday Academy math class on the university campus.***



JENNIFER BOETH DONOVAN

lacked the resources to transport her there. So Bullock and Brown-McKenzie rented a van and drove Olukunle, accompanied by her mother and sister, to Greensboro. Now Christina has completed her junior year, and her sister Alice just finished her freshman year at Bennett. "We got two to college for the price of one," Bullock says with a grin.

If they stick with ICP—and most participants do—teenagers who have rarely ventured beyond their neighborhood go abroad during the summer between tenth and eleventh grades. One class went to Ecuador and another to Belize, where they studied biology, language, and culture. Now one student is applying for a music internship in Russia, another has traveled to Ghana, and a third is planning to enter the foreign service. "These are kids who had never been on a plane," says Bullock. "But now their career interests have just exploded."

ICP also takes students and their parents on college tours. Often they are hosted by ICP alumni, such as Nolen Wren, a junior at North Carolina Agricultural and Technical State University, and Cedric Southerland, a junior at Hampton University in Virginia.

DeAngelo Rorie is one of ICP's many success stories. When he was growing up in Deanwood the only thing Rorie knew about Georgetown University was that it had a good basketball team. Now he's a graduate of Georgetown, mentoring another generation of D.C. kids, and planning to apply to the police academy.

"The students see an environment around them that feels hopeless. We give them hope."

—Tom Bullock

Latonya Bell grew up in the same neighborhood. She attended Ronald H. Brown Middle School, where at least once a week a teacher's car was vandalized or stolen, and the playground faced a street where drugs regularly changed hands. By sixth grade, she had developed a "why bother?" attitude and was earning Ds and Fs. Now a junior at Georgetown, Bell is majoring in sociology and gaining fast on a 4.0 grade-point average. She spends one afternoon a week at her old middle school, working with seventh-graders.

Bullock and Brown-McKenzie, who see what they are doing as a successful model for urban school reform, are now hoping to use it to change an entire school system. Their plan is for nine of the D.C. members of the Consortium of Universities of the Washington Metropolitan Area to each adopt two high schools and their feeder middle schools. Partnering with businesses and philanthropies, they will spread the ICP model to all of the D.C. schools.

"We want D.C.'s kids to realize that they can go to college," says Bullock. "We want them to go. We want them to stay. We want them to graduate. And we want them to help the next generation do the same thing."

—JENNIFER BOETH DONOVAN

Tracking the Transgenic Fly

In a Harvard lab, local high school students learn—and teach.

It's an overcast March morning in Harvard Square—and a great day to go play with flies. In a darkened lab at Harvard University, a swarm of seniors from suburban Needham High School suck mutant *Drosophila* into cotton-plugged hoses. "Suck harder," urges one young investigator. "No, *you* do it," insists another. "Eww, gross," says a third.

It's not exactly standard chitchat for the lab, but then, this is not your standard lab session. The students are visiting Harvard to take part in an HHMI-sponsored outreach program run by the university's department of molecular and cellular biology (MCB). Over the course of three weeks, the MCB Outreach Program brings nearly 500 students from 31 high schools in Massachusetts, Rhode Island, and New Hampshire to Harvard for hands-on laboratory experiences.

Conducting experiments on fruit fly behavior, the Needham High students investigate whether *Drosophila* gravitate toward light—and, if so, whether they can be trained to do otherwise. The procedure involves loading the flies into mazes that allow assessment of the creatures' hypothesized preference for light, hence the need for the rubber transfer hoses (plugged with cotton because, as program coordinator Tara Bennett explains, "you can only swallow so many transgenic flies").

In addition to the fly lab, this year's students participate in workshops on the polymerase chain reaction (PCR), where they analyze their own DNA from cheek swabs, and workshops on cardiac physiology, where they dissect calf hearts and examine their own EKGs before and after doing jumping jacks and other exercises.

These experiences are structured to mesh with the high school curriculum, says Robert A. Lue, executive director of undergraduate education and senior lecturer at Harvard, who is the founder and director of the university's biology outreach program. Jennifer Woo, a teacher at Needham High who signed up her advanced-placement biology class to work with flies, uses the experience to supplement lectures on genetics and behavior. "It's a nice change of pace," she says of the outing, "and it exposes the students to science in the real world."

And real-world science it is. "This is the cutting edge in fly behavior," says Benjamin de Bivort, a second-year graduate student and outreach program teaching fellow. The experiments performed in the morning fly lab are virtually identical to those that de Bivort is doing for his Ph.D. thesis with Harvard professor Sam Kunes. The Needham students place flies in mazes that were designed by de Bivort and assembled just weeks before the workshop. "When we started, we weren't sure the experiments would actually work," says Kunes, who talked to the students about the biology of vision and then helped them analyze their experimental results.

Lue sees the program as a way to spark young people's imaginations, and its exercises in an actual lab give them access to materials and equipment that they might otherwise lack. "We don't have a single PCR machine in our lab," says Woo. Most of all, the class enjoys seeing how science happens "for real, in person," says Vicky Banchevsky, one of the Needham seniors. "It was so much better than biology class in school."

The program also benefits the Harvard students, postdocs, and faculty who run the labs. "The experience really enriches their view of teaching," says Lue, "and it gives them an opportunity to

improve their communication skills." Catherine Linnen, a graduate student who presents a primer on animal behavior at the start of the fly lab, says she is delighted by the high schoolers' enthusiasm and that the experience teaches her a lot about how to keep young students engaged—even at the dreadfully early hour of 9 a.m.

Among other outreach programs, Harvard offers paleontology and cell biology labs for grade school kids conducted by Harvard students and postdocs. And in a 10-day workshop on immunology and infectious disease this summer, high school teachers and curriculum directors will attend lectures and work with animators to develop multimedia materials for use in the classroom.

As for the fly lab, the students decide that normal fruit flies do indeed flock toward light, confirmed by their observation that blind flies show no such preference. But they fail to show that *Drosophila* can be taught to avoid light. Their conclusion? As one student summarized it: "Our flies were dumb."

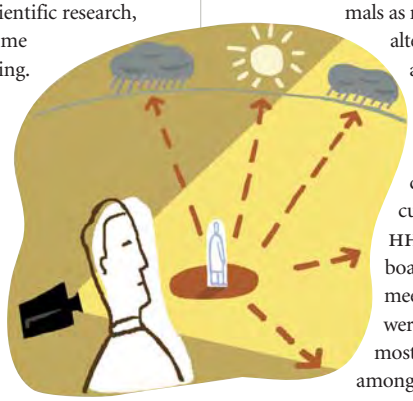
The workshop, however, was anything but. "I thought it was fun," says Banchevsky. "I love hands-on things." Could a morning with flies lure her toward a career as a *Drosophila* biologist? "No," she answers without hesitation. "I didn't love it *that* much." —KAREN HOPKIN

In addition to offering programs for high school students, Harvard's biology outreach program also serves students in other grades. This past fall, for example, the program brought students from five Cambridge elementary schools to Harvard labs—which prompted a visit as well from the city's mayor, Michael A. Sullivan. The mayor lauded the program for its contribution to town-gown connections and for its role in helping students experience the world outside the walls of their classroom. Sullivan's interest is also economic—he stated that science literacy is increasingly important in light of Greater Boston's growing biotechnology industry.

Conduct Beyond Reproach

DVD aims to prompt discussion of ethics in biomedical research.

Scientific research has always been fraught with controversy. Issues such as the use of animals or humans as research subjects, for example, have long been fodder for debate. As scientists' knowledge of biology deepens and technological capabilities grow more sophisticated, decisions as to what is right and what is wrong in the conduct of scientific research, and how far is too far, become increasingly more challenging. Uninitiated scientists just starting their careers may find themselves unprepared for the ethical situations they encounter.



"I don't think the internal ethic is sufficient to provide a compass for people entering research," says Ronald M. Green, a professor of ethics and director of the Ethics Institute at Dartmouth College. "I think we need to talk about these things and recognize the problems ahead and the pitfalls."

In an effort to prompt such dialogue among beginning scientists and their mentors, HHMI has produced *Ethics in Biomedical Research*, a DVD containing three short videos on the use of animals as research subjects; genetic alteration, including cloning and the use of stem cells; and scientific integrity in conducting and reporting on research. Ideas for content came from discussions led by members of HHMI's bioethics advisory board at investigators' science meetings; the selected topics were those that generated the most interest, especially among postdocs and graduate students. The DVD includes interviews with many HHMI investigators who, according to HHMI President Thomas R. Cech, "have given thoughtful consideration to the broader ethical implications of their work."

"We also intentionally included people from the public sector and ethics community who have different points of view," says W. Emmett Barkley, director of HHMI's office of laboratory safety and leader of the DVD project. "The purpose is not to say these are the steps you can take to get to the right answer—I don't think that exists. The idea is to create an environment where these very important points of view can be discussed."

Discussion among scientists of the ethical issues inherent in biomedical research "has never been more important than it is today," says D. Gary Gilliland, an HHMI investigator at Brigham and Women's Hospital and Havard Medical School, whose use of animal models is fundamental to his research on blood-borne cancers. "Open discussion and transparency between the scientific and lay communities are also critical," he says.

Scientists early in their career generally do

STEPHANIE MITCHELL/HARVARD NEWS OFFICE (TOP); JUD GUITTEAU (BOTTOM)

not fully appreciate the importance of ethical considerations, says Ronald Green. "They are preoccupied with career building, and what they don't realize is that ethical mistakes can be the single, most serious source of difficulty in the development of a career, and can even lead to career-ending moves."

Faye C. Austin, senior vice president for research at the Dana-Farber Cancer Institute, is active in ensuring that regular, open discussions about ethical issues are part of the training program there. If an ethical issue in research arises at Dana-Farber, she says, it's usually a case of a researcher making a hurried decision or taking the easier road. "Had they thought about the consequences and understood, they never would have done it," she says. "In most cases I've seen, there was no attempt to deceive or do harm, but the pressure of getting things done by a deadline often results in some issues being overlooked. So it's important that this awareness becomes an ingrained part of how scientists work."

Cech has asked HHMI investigators to critique the DVD's effectiveness as a teaching tool and to pilot test it in their labs this summer. Their suggestions will help guide a planned revision later this year that will also include an overview on the history of bioethics in research and medicine.

—MARY BETH GARDINER

The 1918 Flu: Case Solved

Researchers now know what made the influenza virus so deadly.

The rapid spread of a dangerous flu virus in 1918 caused one of the worst pandemics in history. The outbreak likely started at a military base in the Midwest and was spread by soldiers deployed to Europe during World War I. The flu killed some 675,000 people in the United States. Worldwide, at least 20 million people died, and some researchers believe the death toll was actually as high as 50 million.

It took 85 years, but researchers now believe they know why the 1918 influenza spread so effectively: It was abetted by the unique structure of a protein, called hemagglutinin, on the virus's surface. This newly determined structure shows that the protein underwent subtle alterations that enabled it to bind with deadly efficiency to human cells while retaining the basic properties of the protein of the avian virus from which it evolved.

The findings are the result of a long-term collaboration between the late Don C. Wiley, an HHMI investigator at Harvard University who died in 2001, and Sir John J. Skehel of the Medical Research Council's National Institute for Medical Research in London. Their studies were published in the March 19, 2004, issue of the journal *Science*.

Although the researchers state that their findings do not apply to the new and virulent strain of avian flu that is currently threatening to spread, they do emphasize that subtle alterations in today's avian flu could spawn a major epidemic.

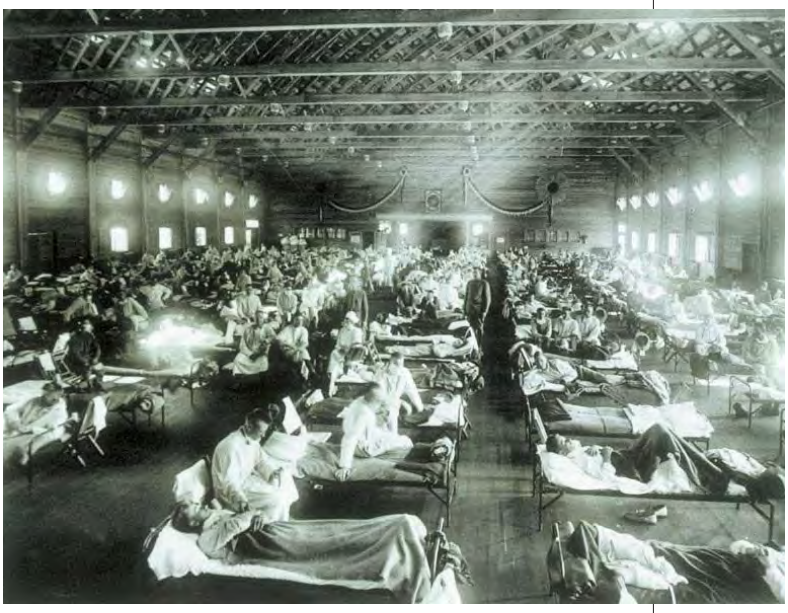
In their research, Wiley and Skehel sought to understand the structure of the hemagglutinin protein, which covers the surface of the influenza virus and is known to initiate the first stages of viral infection. The protein does so by recognizing and binding to receptors on the cell surface that contain molecules called sialic acids. After hemagglutinin binds to these receptors, it causes pores to open in the human cells, allowing the virus to pass through.

The hemagglutinin in the 1918 virus was designated H1, and the influenza viruses that caused later pandemics had distinctively different hemagglutinin structures—designated H2 for the Asian influenza, which began in 1957, and H3 for the Hong Kong strain, which started in 1968. "What was interesting," says Skehel, "was that although all three of these subtypes came from birds, H1 was quite different from H2 and H3, having hardly changed from what it was in the avian virus."

The researchers set out to analyze this difference by using DNA-sequence information that other researchers, who worked with viral material isolated from preserved 1918-pandemic autopsy samples, had obtained. Such scientific detective work was necessary because the virus had apparently become extinct and had not been included among stored specimens of that era.

Using these sequence data, Wiley, Skehel, and their colleagues synthesized the gene for H1 and used it to produce the protein itself. They then crystallized the protein, and with the aid of x-ray crystallography were able to determine its structure.

"The structure revealed how this H1 group could still resemble the avian binding site but nevertheless infect humans," says Skehel. "We found basically that two sides of the hemagglutinin receptor binding site are in slightly different positions in the 1918 hemagglutinin, in comparison with the Hong Kong protein," he reports. "This subtle difference allows the human receptor to bind in an antigenically favorable way."



Emergency hospital during 1918 influenza epidemic, Camp Funston, Kansas.

According to Skehel, the hemagglutinin of the current strain of avian flu, which has killed people in Asia who were exposed to infected birds, is closer to that of the Hong Kong flu. "But presumably what's blocking this current flu from spreading person-to-person," he says, "is that its hemagglutinin structure has not yet evolved such that it can efficiently infect humans."

By contrast, the researchers conclude that the hemagglutinin structure they uncovered for the 1918 virus may well have been a key contributor to its deadly spread.

—DENNIS MEREDITH

NATIONAL MUSEUM OF HEALTH AND MEDICINE

HHMI LAB BOOK

RESEARCH NEWS FROM HHMI SCIENTISTS | *By* STEVEN I. BENOWITZ

The Inner Life of Proteins

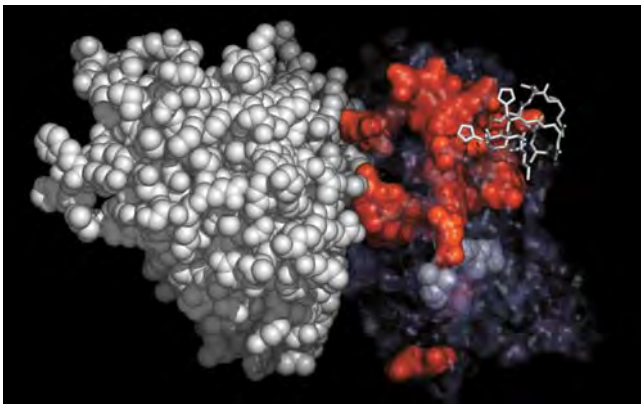
Taking some cues from the process of evolution, researchers have developed a statistical tool to predict the makeup of biological networks that proteins use to talk to themselves and to each other.

Researchers have known for some time that an internal communication system transmits signals across a protein—such as when a molecule, called a ligand, attaches to a receptor on the protein's surface—through changes in the protein's individual amino acids. But it was not known how.

To find out, a team led by HHMI investigators David J. Mangelsdorf and Rama Ranganathan at the University of Texas Southwestern Medical Center at Dallas used statistics to analyze the evolutionary process. "Evolution is constantly carrying out random mutagenesis on proteins," says Ranganathan. "The basic idea is that if one site communicates with another site on the protein, they then coevolve, and the coevolution of pairs of amino acid residues should tell us about the functional interactions between amino acids in the protein."

The researchers statistically compared amino acid sequences of a large family of receptor proteins related to the retinoid X receptor (RXR). Normally, RXR links with a protein similar to itself to form a structure called a heterodimer. The team wanted to see if evolutionary variation of any single amino acid was statistically coupled to variation in another, which would suggest that the two amino acids had coevolved.

Using a method called "statistical coupling analysis" (SCA), the team predicted a network of coevolving amino acids that connected the protein's functional surfaces and also seemed to bridge the two parts of the heterodimer. When the researchers altered individual amino acids in the network, they found that the communication system was disrupted in most cases.



Party-line call *Crystal structure of the human retinoid X receptor (RXR) protein showing a SCA-predicted communication network (depicted in solid red) linking RXR with a second protein and with two bound residues. RXR (slate gray) has formed a heterodimer with the human PPAR-γ protein (white). Bound coactivator peptide appears as white stick bonds and bound ligand as white spheres within RXR.*

COURTESY OF MANGELSDORF LAB.

"This means that for the first time we can meaningfully predict the ways in which amino acids and regions of protein structures talk to each other," says Ranganathan. "In many instances, we couldn't predict these just by looking at crystal structures." The team reported its findings in the February 6, 2004, issue of *Cell*.

IN BRIEF

Bacteria Blocker

Scientists have discovered a protein in mice that prevents bacteria from invading the urinary tract. The protein, called TLR11, which recognizes bacteria that cause infections of the bladder and kidney, is thus "an important arm of the immune system," says HHMI investigator Sankar Ghosh at Yale University School of Medicine, who led the work.

But the discovery was at first perplexing: If such a powerful bacterial-recognition system exists, asked Ghosh, why do some seven million urinary-tract infections occur every year in the United States alone? When the researchers looked in humans, they found their answer in a truncated version of the protein, which appears to have lost normal function.

The team hopes to identify the molecular pattern of the urinary bacteria that TLR11 recognizes, thereby leading to potential drug targets.

Ghosh, HHMI investigator Richard A. Flavell, and colleagues reported their findings in the March 5, 2004, issue of *Science*.

Genome Comb

Using the new science of RNA interference (RNAi), HHMI investigator Norbert Perrimon at Harvard Medical School and his colleagues developed a screening technique that enabled them to characterize the roles of nearly all the genes in the fruit fly genome.

In RNAi, double-stranded RNA (dsRNA) degrades matching messenger RNA in a gene, wiping out the gene's function. Perrimon and his colleagues created a library of dsRNAs that correspond to nearly all of the more than 16,000 known *Drosophila* genes. Adding each of these dsRNA molecules to *Drosophila* cell cultures, they were able to identify genes involved in general cell growth, the cell cycle, cell survival, and other functions.

"Ours is the first high-throughput, full-genome screening method that allows a systematic interrogation of the function of every gene," Perrimon says. He and his colleagues described their technique in the February 6, 2004, issue of *Science*.

Perrimon believes that the technique can be applied to any organism, including humans, and will eventually become a standard way to screen gene function—and perhaps drugs as well.

Resistance Movement

Physicians typically treat prostate cancer patients with anti-androgen drugs to lower their levels of testosterone, which drives tumor growth. But drug treatment frequently fails, despite early success, when the patient's tumor becomes resistant. Now, researchers may have discovered why: a change in a testosterone-receptor gene.

HHMI investigators Charles L. Sawyers at the University of California, Los Angeles, and Michael G. Rosenfeld at the University of California, San Diego, and their colleagues used a technique called xenografting to produce

The statistical technique might also help pinpoint new drug targets—those sites on a protein that selectively affect particular functions—in order to avoid undesirable side effects. "SCA will give researchers the ability to make mutations that affect the activity of one ligand but not another," notes Mangelsdorf. "This will offer a potential screening strategy for drugs that affect one response pathway over another."

Chromosome Dynamics

Regulation of gene expression across large chromosomal territories—a process that happens in all organisms—is mysterious," says HHMI investigator Barbara J. Meyer at the University of California, Berkeley. For example, how do cells adjust the level of gene activity on X chromosomes so that males, who have only one of them, end up with the same level of gene expression as females, who have two?

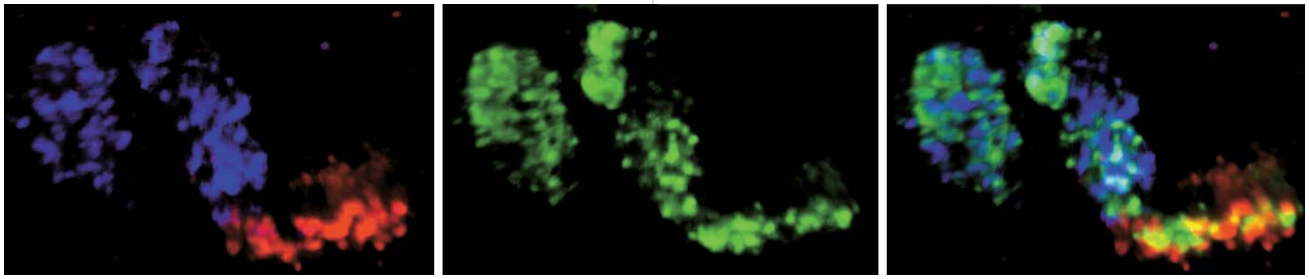
This process, known as "dosage compensation," apparently uses certain regulatory proteins—called the "dosage compensation complex" (DCC)—to control X-chromosome gene expression, though how the DCC attaches itself to X chromosomes has been poorly understood.

To investigate how dosage compensation works, Meyer and her colleagues turned to the roundworm *Caenorhabditis elegans*, essentially "mapping" its entire X chromosome to determine which DNA segments could recruit the complex. Snipping out bits from along the chromosome's entire length and assessing whether the DCC recognized a specific segment, they discovered that certain discrete sites attract the DCC and engineer the spreading of the complex to other parts of the chromosome that lack such sites. "These 'recognition sites' are the landing pads of the complex," Meyer explains. Once it lands on such a site, the DCC is able to attach itself to nearby DNA, thereby spreading throughout the chromosome step-by-step.

"Spreading of regulatory protein complexes is essential in a number of processes in biology, such as X inactivation in mammals, position-effect variegation in flies, and gene silencing in yeast," Meyer notes. Her group reported its findings in the February 20, 2004, issue of *Science*.

As the researchers continue to search for more DCC-recognition sites on the *C. elegans* X chromosome, they hope to learn more about spreading—where and when the DCC proteins touch DNA directly, for example, or if they possibly recruit other cellular proteins to implement dosage compensation. The Meyer team is also trying to understand the molecular mechanisms by which the complex, under certain conditions, can turn down DNA transcription by as much as 50 percent.

Spreading the wealth ***Recruitment of the dosage compensation complex (green) to both a detached segment of an X chromosome (red) and the remainder of X (blue) demonstrates the presence of multiple X-recognition elements.***



COURTESY OF MEYER LAB.

hormone-sensitive human prostate cancers in mice. The scientists treated mice to lower their hormone levels, eventually making them as drug-resistant as some human cancer patients.

Using DNA microarrays to compare gene-expression patterns, the research team unexpectedly found a single consistent difference between hormone-sensitive and hormone-resistant cancers—an increase in the androgen-receptor gene's expression.

The researchers described their findings in the January 1, 2004, issue of *Nature Medicine*.

Power Shortage

Mitochondria—the body's power plants—convert glucose and fatty acids into energy. But when they don't work, the fatty acids build up in muscle, leading to insulin resistance and potentially to diabetes. Now, researchers have found that defects in cells' mitochondria may also lead to insulin resistance in children of individuals with type 2 diabetes.

The scientists, led by HHMI investigator Gerald I. Shulman at Yale University School of Medicine, compared young, lean volunteers who were insulin-resistant and who had a parent with type 2 diabetes to a group of healthy age-, weight-, and activity-matched volunteers who were insulin-sensitive. As expected, they found that the insulin-resistant subjects had higher levels of fat in their muscle cells. Upon examining the mitochondria in those cells, the researchers found defects in lipid metabolism and a 30 percent drop in overall mitochondrial activity.

The team reported its findings in the February 12, 2004, issue of the *New England Journal of Medicine*.

Hotspot Mutations

Sequencing a gene previously implicated in diverse diseases, researchers have uncovered mutations that suggest new avenues for future therapies and diagnostics. The gene, *PIK3CA*, is part of a family of genes encoding lipid kinases, enzymes that play a role in cell growth, survival, and motility—pathways important in cancer development and other diseases.

When HHMI investigators Bert Vogelstein at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University School of Medicine and Sanford Markowitz at Case Western Reserve University School of Medicine and their colleagues sequenced all members of the lipid kinase family, they found a high percentage of mutations in one member, *PIK3CA*, in several cancers, including those of the colon, brain, and stomach.

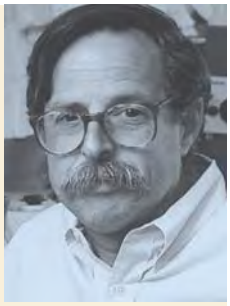
"It's surprising because members of this gene family have been known for more than a decade and are involved in diverse pathways implicated in a variety of diseases, including cancer," says Vogelstein. "No one until now appreciated that these kinases themselves are mutated."

The mutations are clustered largely within two DNA "hotspots," he says, making them easy targets for inhibitors and diagnostic tests.

The researchers reported their findings in the April 23, 2004, issue of the journal *Science*.

Horwich Wins Gairdner Award

SPOTLIGHT



Arthur L. Horwich, an HHMI investigator at the Yale University School of Medicine, is one of five scientists awarded a 2004 Gairdner Foundation International Award, which honors medical scientists whose contributions tangibly improve quality of life. Horwich's award—shared with Reginald John Ellis, emeritus professor at the University of Warwick in Coventry, UK, and Franz Ulrich Hartl, managing director of the Max Planck Institute for Biochemistry in Martinsried, Germany—recognizes "seminal contributions in establishing the principles and discovering the key mechanisms and pathways in cellular protein folding."

Gairdner Foundation President John Dirks says the discoveries "have direct relevance to diseases such as Alzheimer's disease, cystic fibrosis, an inherited form of emphysema, and even many cancers that are believed to result from protein misfolding."

In 1987, Horwich identified a mutant yeast strain in which proteins are imported normally into mitochondria—structures responsible for a cell's energy production—but then misfold and clump into aggregates. Investigating why the misfolding occurred, the lab discovered a specialized protein, called a chaperone, which is critical to the folding process. Understanding how chaperones and related assemblies of such proteins, known as chaperonins, figure in normal folding pathways has occupied the Horwich lab ever since. One current project looks at how protein misfolding causes amyloid plaques, which are implicated in a variety of neurodegenerative diseases.

Several HHMI investigators, a professor, a trustee, and a former international research scholar were elected to the American Academy of Arts and Sciences.

The investigators are **Tania A. Baker** and **Mark F. Bear**, both at the Massachusetts Institute of Technology; **Catherine Dulac**, Harvard University; **Scott D. Emr**, University of California, San Diego; **Paul L. Modrich** and **Joseph R. Nevins**, both at Duke University Medical Center; and **Donald Ganem** and **Erin K. O'Shea**, both at the University of California, San Francisco.

The HHMI professor is **Graham C. Walker**, Massachusetts Institute of Technology.

Also elected were HHMI Trustee **Anne M. Tatlock**, Fiduciary Trust Company International, and former international scholar **Anthony J. Pawson**, University of Toronto.

Catherine Brinkley, a recent graduate of Wellesley College, and **Tara Martin**, who graduated from Harvey Mudd College, are 2 of 50 graduating seniors in this country to win a Thomas J. Watson Fellowship, a one-year grant for independent study and travel outside the United States. Brinkley's senior thesis work was supported by HHMI through the labs of Barbara Beltz (biology) and Nancy H. Kolodny (chemistry) at Wellesley. Martin was supported by HHMI in 2001, when she worked at the University of Washington with Raymond B. Huey, and in 2003, in the research lab of Catherine McFadden at Harvey Mudd.

Patrick O. Brown, an HHMI investigator at Stanford University School of Medicine, won a *WIRED* Magazine Rave Award together with Harold E. Varmus of the Memorial Sloan-Kettering Cancer Center and Michael B. Eisen of the Lawrence Berkeley National Laboratory and the University of California, Berkeley. They were honored for founding the Public Library of Science, publisher of the first open-source peer-reviewed journal, *PLoS Biology*.

Jilda Caccavo, a student at Midwood High School at Brooklyn College, won a 2004 Neuroscience Research Prize from the American Academy of Neurology. Caccavo participated in the HHMI-supported precollege science education program at the Rockefeller University by doing research in the laboratory of geneticist Jürg Ott.

Mark M. Davis, an HHMI investigator at the Stanford University School of Medicine, received the 2004 Paul Ehrlich and Ludwig Darmstaedter Prize from the Paul Ehrlich Foundation. Davis shared the award with Tak W. Mak, University of Toronto, for outstanding achievements in the field of immunology.

Johann Deisenhofer, an HHMI investigator at the University of Texas Southwestern Medical Center at Dallas, received the 2004 German International Röntgen Award (known as the Röntgen-Plakette) together with fellow Nobel laureates Robert Huber and Hartmut Michel.

Waterman Award Goes to Tissue Engineer

SPOTLIGHT

In recognition of her groundbreaking work in biomaterials used for tissue repair and replacement, HHMI investigator **Kristi S. Anseth** at the University of Colorado at Boulder received the 2004 Alan T. Waterman Award of the National Science Foundation. Criteria for the $500,000 award, which recognizes a young researcher in science or engineering supported by the National Science Foundation, include originality, innovation, and impact on the field.

Anseth applies her chemical engineering training, together with a knowledge of biology, to the development of synthetic scaffolding material that guides and organizes cells into forming complex three-dimensional organs. The material is injected in liquid form, but when activated by light, it becomes gel-like, providing a damaged area, such as a knee, with stability and strength while also promoting regrowth of tissue. This process could fabricate replacement body parts for a host of medical conditions, providing an alternative to surgery. Currently, Anseth is refining her biodegradable scaffolding while designing new biomaterials; two applications of particular interest to her lab are heart-valve and cartilage-tissue engineering.

Anseth is the first engineer to have been named an HHMI investigator.

HAROLD SHAPIRO (HORWICH); GEOFFREY WHEELER (ANSETH)

Theodore Drivas, an undergraduate at the Johns Hopkins University who participated in the HHMI-supported precollege science education program at the Rockefeller University from 2001 to 2003, won a Woodrow Wilson Undergraduate Research Fellowship. Drivas, who worked in the laboratory of HHMI investigator and Nobel laureate Günter Blobel while at Rockefeller, will use his award to return to the Blobel lab this summer.

B. Brett Finlay, an HHMI international research scholar at the University of British Columbia, won the 2004 Michael Smith Prize in Health Research from the Canadian Institutes of Health Research (CIHR). Finlay was hailed by CIHR as "a national treasure [who] has made important contributions to the molecular understanding of *Salmonella, E. coli* and *H. pylori*."

Two HHMI international research scholars were named Outstanding Scientist in the doctor of science/biology category by the Russian Academy of Sciences. The researchers are **Mikhail Gelfand** of the Research Institute for the Genetics and Selection of Industrial Microorganisms and **Andrey Zaraisky** of the Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry. Both institutes are located in Moscow.

Mario Godoy Gonzales, a high school teacher in Royal City, Washington, who participated in the HHMI-supported precollege science education program at the Fred Hutchinson Cancer Research Center in Seattle, was honored with the 2004 Gustav Ohaus Award for Innovation in Science Teaching by the National Science Teachers Association.

Hanna H. Gray, chairman of the HHMI Trustees, received the 2004 Harvard College Women's Professional Achievement Award for her "trailblazing service in academia."

David Haussler, an HHMI investigator at the University of California, Santa Cruz, was named corecipient of the 2003 Allen Newell Award by the Association for Computing Machinery (ACM), along with Judea Pearl of the University of California, Los Angeles. ACM cited Haussler as possibly the most influential contributor to the field of computational biology.

Lily Y. Jan and **Yuh Nung Jan**, both HHMI investigators at the University of California, San Francisco, were jointly awarded the 2004 K.S. Cole Award from the Membrane Biophysics Subgroup of the Biophysical Society. The award recognizes substantial contributions to knowledge of membranes.

Simon W.M. John, an HHMI investigator at the Jackson Laboratory in Bar Harbor, Maine, received the 2004 Cogan Award from the Association for Research in Vision and Ophthalmology for his contributions to the development, analysis, and use of mouse models for genetic and therapeutic studies of glaucoma.

Lauren Kernochan, an HHMI-National Institutes of Health research scholar and medical student at the Yale University School of Medicine, won the 2004 Saul R. Korey Award in Experimental Neurology from the American Academy of Neurology.

Stanley J. Korsmeyer, an HHMI investigator at the Dana-Farber Cancer Institute, won the 2004

Eleven Investigators Elected to NAS

SPOTLIGHT

Eleven HHMI investigators were elected in April to the National Academy of Sciences. The researchers are **Kevin P. Campbell**, University of Iowa Carver College of Medicine; **Barry Honig**, Columbia University College of Physicians and Surgeons; **Richard L. Huganir**, Johns Hopkins University School of Medicine; **Mark T. Keating**, Children's Hospital, Boston; **Dan R. Littman**, New York University School of Medicine; **Stephen L. Mayo**, California Institute of Technology; **Erin K. O'Shea**, University of California, San Francisco; **Peter Walter**, University of California, San Francisco; **Xiaodong Wang**, University of Texas Southwestern Medical Center at Dallas; **Huda Y. Zoghbi**, Baylor College of Medicine; and **Charles S. Zuker**, University of California, San Diego.

Top to bottom, left to right:
KEVIN P. CAMPBELL
BARRY HONIG
RICHARD L. HUGANIR
MARK T. KEATING
DAN R. LITTMAN
STEPHEN L. MAYO
ERIN K. O'SHEA
PETER WALTER
XIAODONG WANG
HUDA Y. ZOGHBI
CHARLES S. ZUKER

CREATIVE MEDIA GROUP, COURTESY OF ROY A. AND LUCILLE J. CARVER COLLEGE OF MEDICINE (CAMPBELL); COURTESY OF COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS (HONIG); COURTESY OF THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE (HUGANIR); JOHN TELFORD (KEATING); JUDY WALGREN, NYU SCHOOL OF MEDICINE (LITTMAN); MARK HARMEL (MAYO); LISA CISNEROS (O'SHEA); EL MERCURIO (WALTER); UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER AT DALLAS (WANG); PAM FRANCIS (ZOGHBI); BARBARA RIES (ZUKER)

Three Researchers Win GM Cancer Research Awards


SHERR


STILLMAN


KELLY

One HHMI investigator and two advisory board members have been honored by the General Motors (GM) Cancer Research Foundation.

SPOTLIGHT

Charles J. Sherr, an HHMI investigator at St. Jude Children's Research Hospital, won GM's 2004 Charles S. Mott Prize, given for outstanding contributions related to the cause or prevention of cancer. Sherr was cited for the discovery and characterization of key genes and proteins that control cell division and are thus frequently involved in cancer cases when their processes go awry.

Sharing the 2004 Alfred P. Sloan Prize for notable contributions in basic science related to cancer are **Bruce Stillman**, a member of HHMI's Medical Advisory Board, and **Thomas J. Kelly**, a member of the Scientific Review Board. Stillman, who is president and CEO of the Cold Spring Harbor Laboratory, and Kelly, director of the Sloan-Kettering Institute at the Memorial Sloan-Kettering Cancer Center, each lead research programs on regulatory mechanisms for DNA replication in mammalian cells and yeast.

Katharine Berkan Judd Award from the Memorial Sloan-Kettering Cancer Center. The award recognizes outstanding contributors from a wide range of basic sciences and clinical medicine whose work applies to cancer.

■ Two HHMI-supported students are among 32 American men and women to receive 2004 Rhodes Scholarships. **Pooja Kumar**, now a medical student at Harvard University, was an HHMI undergraduate research fellow in the lab of Margaret A. Pericak-Vance at Duke University in 1998. **Wen Shi**, an undergraduate at the Johns Hopkins University, was funded as a Johns Hopkins-HHMI summer research fellow in Kathleen Gabrielson's lab in 2002.

■ Two HHMI investigators have been named Distinguished Scientists by the American Heart Association in honor of their "extraordinary contributions to cardiovascular and stroke research." The researchers are **Robert J. Lefkowitz** of Duke University Medical Center and **Christine E. Seidman** of Brigham and Women's Hospital in Boston.

■ **William T. Newsome**, an HHMI investigator at Stanford University School of Medicine, is corecipient of the 2004 Dan David Prize. Newsome, together with Robert Wurtz of the National Eye Institute (at the National Institutes of Health) and Amiram Grinvald of the Weizmann Institute of Science, was recognized for his contributions to the scientific understanding of the brain's visual system. The researchers share a $1 million prize that is endowed by the Dan David Foundation and administered by Tel Aviv University in Israel.

Fenway Feels Tonegawa's Heat

As a guest of the Boston Red Sox on May 7, HHMI investigator **Susumu Tonegawa** had the honor of throwing out the game's first pitch. Pitching enthusiasts speculated that the molecular biologist and neuroscientist from the Massachusetts Institute of Technology elected to throw a splitter. And while there's no word on how this moment of glory compared to another in Tonegawa's life—winning the Nobel Prize in 1987—Fenway's centerfield scoreboard screened a supersized image of the eminent scientist post-pitch, as he tipped his glove to the crowd and beamed with delight.

■ Two HHMI investigators were honored by the American Association of Immunologists (AAI). **Michel C. Nussenzweig**, the Rockefeller University, received the 2004 AAI-Huang Foundation Meritorious Career Award, and **David G. Schatz**, at the Yale University School of Medicine, won the 2004 AAI-BD Biosciences Investigator Award.

■ **Norbert Perrimon**, an HHMI investigator at Harvard Medical School, received the 2004 George W. Beadle Award from the Genetics Society of America, given for innovative contributions to the fields of molecular biology or genetics. Perrimon studies signaling pathways involved in the fruit fly's development and morphogenesis.

■ **Daphne Preuss**, an HHMI investigator at the University of Chicago, was named a lifetime National Associate of the National Academy of Sciences in recognition of her pro bono service to programs of the National Research Council and Institute of Medicine.

■ **Sally Stoll**, a high school teacher in Vermillion, South Dakota, who participated in the HHMI precollege science education program at the University of South Dakota School of Medicine, received a 2004 Presidential Award for Excellence in Mathematics and Science Teaching from the National Science Foundation.

STEVE JONES (SHERR); BILL GEDDES (STILLMAN); COURTESY OF SLOAN-KETTERING INSTITUTE (KELLY); COURTESY JULIE CORDERO/BOSTON RED SOX (TONEGAWA)

Dollars and Sense

When he was a boy, Landis Zimmerman would sometimes go to work with his chemist parents and gaze in bewildered wonder at the racks of tiny test tubes and other laboratory paraphernalia. His visits never kindled a desire to follow in his parents' footsteps, but growing up around researchers makes coming to work at HHMI, after some 20 years on Wall Street and in the halls of academia, feel a little like coming home.

While he knew early on that research wasn't his destiny, Zimmerman does give credit where credit is due. "I've always enjoyed mathematical, quantitative problems," he says. "Scientists are analytically rigorous, so that's probably the piece of the gene that's gotten through—not the one for scientific inquiry or curiosity."

As HHMI's new vice president and chief investment officer, Zimmerman is responsible for managing the Institute's endowment, valued on the day we spoke at about $12.6 billion. That's a task that most of us cannot begin to fathom, but the prospect doesn't rattle Zimmerman. "It's a tremendous amount of money," he admits. "But if you think about an investment strategy, it has everything to do with allocating money to appropriate markets. And that decision you can make whether it's your own IRA or $12.6 billion."

The very first strategic decision that any investor makes is how much to hold in equities and how much in bonds, says Zimmerman. "We need the equities, but they're risky. The bonds, though safer, provide less return." Figuring out the best way to deploy a strategy, he says, is the hard part. But he has some expert assistance. Under Zimmerman's leadership, management of the portfolio is divvied up among a team of seasoned financial managers; some of them are in-house, though most work for outside firms.

Zimmerman combines the risk-management part of his job, which he sees as "highly quantitative and analytical," with the "softer, more judgmental" aspect of evaluating whether an investment manager's performance is the result of luck or skill, and if it's skill, whether it's sustainable. Making a good judgment about the people who manage HHMI's assets, he says, "requires asking tough questions and the experience of having evaluated hundreds of investment managers over time."

Before joining HHMI earlier this year, Zimmerman had been chief investment officer at the University of Pennsylvania, where he managed a $3.6 billion endowment. He was named Penn's first chief investment officer in 1998, and while there, he orchestrated a restructuring of the endowment's asset allocation and a reorganization of the office of investments. Zimmerman received his undergraduate degree in economics from Penn and an MBA from the Wharton School before heading to New York City and Wall Street.

The activities he engaged in for nearly 15 years on Wall Street were "not just run-of-the-mill," he says. While many drawn to work in that financial district deal strictly in bonds or equities, Zimmerman was interested in more complicated financial products and financial engineering, including the derivatives market—a broad constellation of investment strategies that help investors take on wanted risk or hedge unwanted risk. "This combination of experiences blends into a pretty interesting background for managing $12.6 billion," he says, "because it's all about being opportunistic in identifying and taking advantage of market anomalies, but also being aware of managing the risk involved."

Zimmerman left Wall Street behind, he says, "because after a while you look around and wonder why you even bother." The work he did at Penn, and now at HHMI, yields a different kind of reward. "At the risk of sounding Pollyannaish, I feel lucky to have found a path that led me here where I've found this combination of an intellectually stimulating and fun job, a great bunch of people to work with, and an institution that has a real purpose and plays a fundamental and important role in society."

PAUL FETTERS

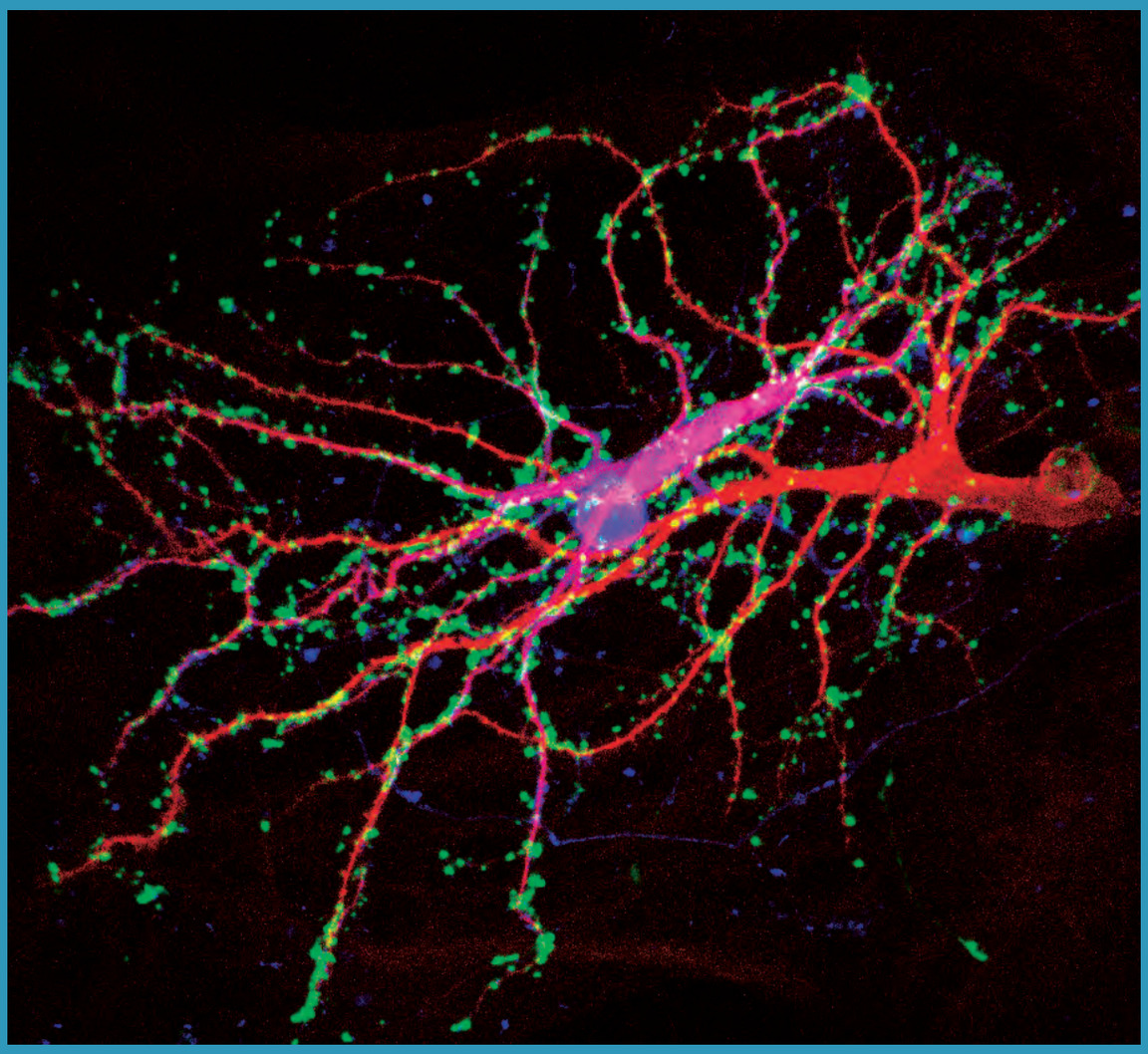
Managing HHMI's endowment, Landis Zimmerman looks for opportunities but keeps a close eye on risks.

Zimmerman brings with him from Pennsylvania his wife and two daughters, ages 10 and 13, who are into so many things, he says, it's hard to keep up. As his first daughter enters her teens, his strategy is to stay engaged—at least on the squash court. "I've gone from being the hero dad who knows everything to the big dope that just doesn't get it," he says. "But for 45 minutes on the squash court, we can have a fun relationship. I'm hoping that will remain a fun way for us to be together."

As for the financial wisdom he shares with his daughters, we might all do well to take it to heart: "Save your allowance," he advises. "Don't fritter it away on candy."

—MARY BETH GARDINER

IN THE NEXT ISSUE



KIMBERLY HARMS AND ANN MARIE CRAIG

STUDY IN SYNAPSES. Two rat neurons from the brain's hippocampal region, fluorescently stained to identify functional parts. Each green spot represents one synapse. The dendrites, which receive messages, appear red. Blue staining on one of the neurons reveals part of the fine caliber axon, which is involved in the transmitting process.

Synapses

Thanks to recent productive research on synapses in the brain, neuroscientists believe they are on the verge of taking on some of the toughest problems in science—such as how brain malfunctions contribute to mental diseases, and how nerve cells produce emotion, reasoning, and consciousness itself.

Oklahoma's Investigator

Meet Charles Esmon, HHMI's sole investigator in the state of Oklahoma. In his jeans and plaid shirt, he could pass for a rancher. But minutes into a conversation with him, it's clear that his home is not on the range, but in the lab. Esmon's success in the lab extends now over three decades.

A Student's Big Science

Few students witness the birth of a new scientific discipline, but in Krishna Roskin's case, he even participated in the delivery. "I got this grandiose e-mail saying, 'How would you like to join the greatest scientific project of all time?'" Roskin recalls. He found the offer too intriguing to resist.

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