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HHMI BULLETIN

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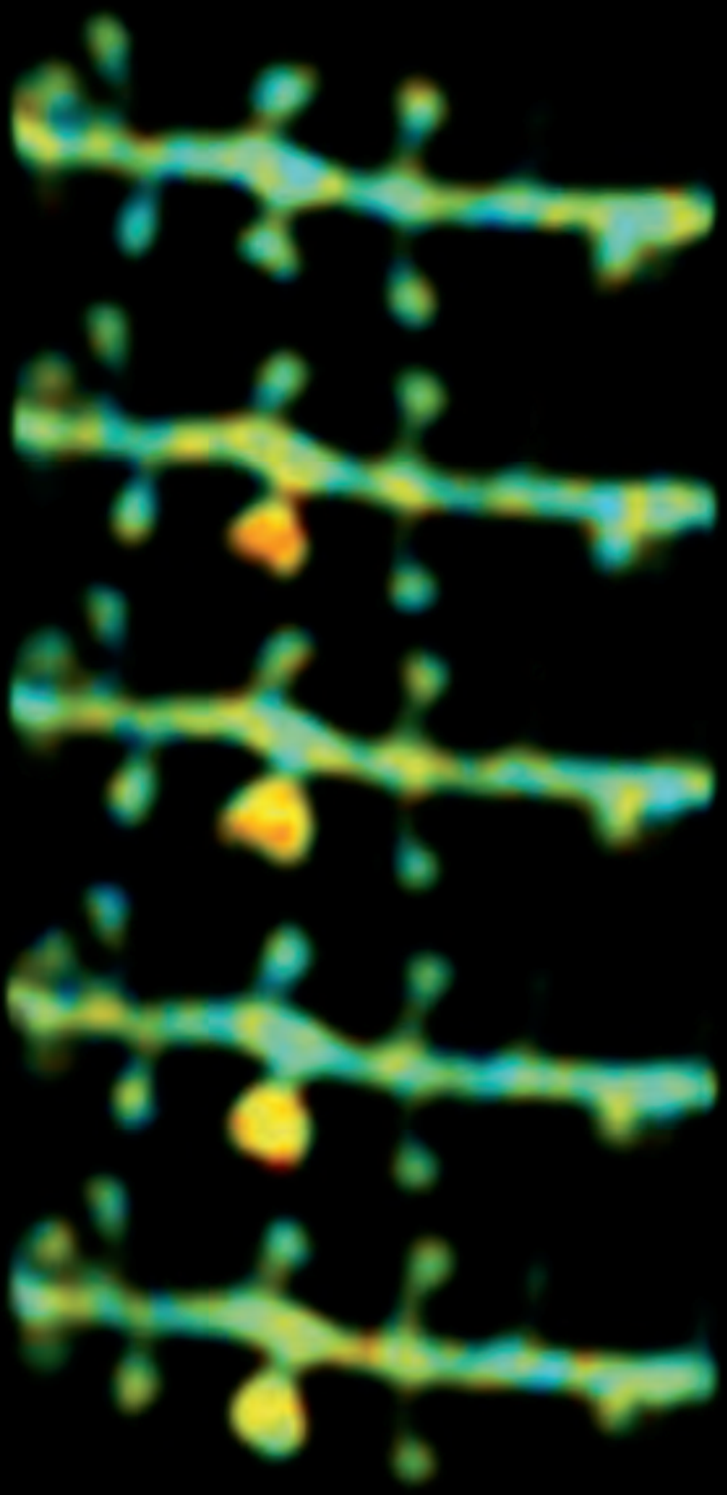

Web Only Content

When neurons fire in the brain, they exchange signals through tiny buds known as spines. Signaling strength can fluctuate rapidly, but some changes lasting minutes or longer are thought to encode long-term memories. To better understand what's happening in those extended moments, biophysicist Yasuda Ryohei images living spines as signaling occurs, as seen in this series of photos. Read more in "Lasting Memories" at www.hhmi.org/bulletin/aug2011.

Yasuda lab

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Web Only Content

- Drink in the sights and sounds of Baltimore's crowd-rowdy Kinetic Sculpture Race.
- Travel through a 30-year timeline of discovery in the field of gene therapy.
- Learn how the Summer Institute inspired radical change in one science educator's approach.
- Immerse yourself in heavenly wonders through the lens of Fred Eiserling's telescopic camera.
- Join us at www.hhmi.org/bulletin/aug2011.

Features

Departments

A native of São Paulo, Brazil, graphic designer and illustrator **RUBENS LP** ("Seeing is Believing," page 18) has worked with companies worldwide, including Microsoft, Nike, Absolut Vodka, Sony Ericsson, Coca-Cola, MTV, Folha, Editora Globo, and Ride Snowboards. When not at his desk, he enjoys nature, art history, movies and books, video games, beauty, friendship, and—most of all—life. (1)

LAURA PUTRE ("Evolution of the Textbook," page 12) is a freelance journalist from Cleveland whose articles have appeared in *Miller-McCune*, *O Magazine*, *The Root*, and the *Chicago Reader*. She loves walking on the beach, spending time with friends, and narrative journalism and wishes she'd had an interactive science textbook when she was in college. (2)

Freelance writer **VIRGINIA HUGHES** ("Seeing is Believing," page 18) lives in Brooklyn, New York, where she partakes in Brooklyn-y things like book readings, coffee cuppings, and dog sitting. She likes to write about brains, drugs, and genes, sometimes all at once. Her articles appear in *Nature*, *Popular Science*, *Scientific American*, and a quirky science blog called *The Last Word on Nothing*. (3)

California-born, Brooklyn-based designer and illustrator **KEENAN CUMMINGS** (cover and "Evolution of the Textbook," page 12) enjoys working for a roster of clients from large organizations and brands to small publishing houses. In his personal projects, he explores themes and ideas he cares about: education, health, science, and the creative process. (4)


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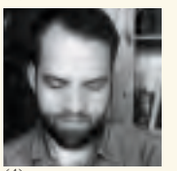
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Rubens LP, Laura Putre, Virginia Hughes, Keenan Cummings

Journal: Scientists at the Heart

James Kegley

EARLIER THIS SUMMER, LEADERS OF THE WELLCOME TRUST, MAX Planck Society, and the Howard Hughes Medical Institute met in London to make a significant announcement: our decision to join forces to launch a top-tier scientific journal. We expect the first issue to publish a year from now under the leadership of Randy Schekman, a distinguished HHMI investigator who has agreed to serve as editor in chief. Over the coming months, Schekman will be responsible for recruiting an editorial team composed of active, practicing scientists and for bringing this exciting new venture to life as an independent scholarly publication.

Our plan is bold: to publish the highest-quality research across the full spectrum of the life sciences. We expect the journal to become self-sustaining over time, but our first priority is to develop a rapid, efficient, and transparent editorial process. The new journal will seek submissions from scientists around the world; it will be open to the scientists supported by our three organizations, but they will remain free to publish in the journals of their choosing. We will define success by the influence the journal has within the scientific community—rather than by impact factor, the numerical score assigned to journals based on the number of times its articles are cited. I can offer one practical indicator that makes sense to me: Is this journal THE place where the best graduate students and postdocs want to publish their best work?

> "Our plan is bold: to publish the highest-quality research across the full spectrum of the life sciences."
>
> ROBERT TJIAN

As one might expect, a few observers have posed an obvious rhetorical question: does the world need yet another scientific journal? The leadership of HHMI, the Wellcome Trust, and the Max Planck Society believe the answer to that question is yes. The world does need another scientific journal, albeit one with a distinctive model that puts scientists at the heart of the decision-making process about what gets published. After all, the work of science isn't complete until the results are shared through publication. As funders who support the research of some of the world's leading scientists and their collaborators, we are prepared to play a positive, active role in bringing the work to completion.

Our organizations have already invested considerable thought and resources to encouraging creative thinking in scientific publishing and believe we can do more. The Wellcome Trust and the Max Planck Society have long supported fundamental change in scientific publishing and the adoption of open access policies. HHMI provided early support for the Public Library of Science, a pioneering open access publisher, and adopted policies to ensure rapid dissemination of research results. But institutional policies cannot, in and of themselves, address the frustrations of many practicing scientists as they navigate between the world of research and the world of publishing.

We certainly heard plenty at a workshop held last December at HHMI's Janelia Farm Research Campus when we brought together journal editors and a group of scientists from a range of disciplines for a conversation. Key themes emerged: a belief that selectively engaging active, practicing scientists can add value to the publishing process, and that both editors and reviewers should be appropriately compensated for their work; a desire to address repeated cycles of review that delay publication and often generate too many additional experiments that do not necessarily advance the work but result in articles laden with supplemental data; a conviction that science is well served by diverse publishing options; and a commitment to a fully online, open-access model that enables wide sharing of information.

Our plan for the new journal reflects these important themes. But I would like to focus on another aspect that exemplifies a significant goal of the new journal: redefining the size of the publishable unit. Just how many years of work should a single paper represent? This is a real and important question that confronts many labs, including my own. If a postdoc or graduate student spends six years rigorously documenting a new discovery, should he or she then be required to conduct numerous additional experiments to satisfy reviewer comments? Where should the line be drawn? What is reasonable? I for one would like to see articles—that is, publishable units—reflect the fact that science itself is a continuum, that you can never have a complete story. You can, however, describe a compelling story of discovery that sets the stage for directing future inquiry and experimentation. That is what HHMI and its partners, the Wellcome Trust and Max Planck Society, seek to achieve in an efficient and timely manner without sacrificing originality, novelty, or rigor.

Sink or Swim

At dusk on May 5, 2011, a dozen Janelia Farm scientists and staff gathered at a remote corner of the 689-acre campus to set their hand-crafted amphibious vehicle on its maiden voyage. They needed to know if it was ready for the annual Kinetic Sculpture Race in Baltimore, Maryland.

The vehicle—a hulking aluminum chassis with 32-inch all-terrain tires, powered by five recumbent pedaling stations at the front and rear—did not look like something that would float. But its riders proved otherwise, pedaling confidently downhill and into the murky water. The spectators, most of whom had a hand in the vehicle's design and construction, cheered.

"It felt like sliding on glass," recalls Jason Osborne, an instrument design specialist at Janelia Farm for whom the test was especially rewarding. A year earlier, he had attended the annual race of human-powered art projects, sponsored by Baltimore's American Visionary Art Museum. Captivated by the participants' creativity (a 15-foot-tall pink poodle dominated the day) and the spirit of the event (official rules include a "mandatory fun regulation"), he came to work the next Monday with a mission: to recruit a team and enter the following year.

The Kinetic Sculpture Race is something of an anti-race. Teams must cross 15 miles of highway, water, mud, and sand on human-powered vehicles in and around Baltimore's inner harbor. The grand prize goes to the team that finishes in the middle, and rule-breakers escape penalty with bribes.

Beyond that playfulness is a serious mission—to honor collaboration, creativity, and community. Osborne submitted a proposal and recruited a core team of more than two dozen people.

They solicited ideas ("Should it be a fly? Should it be a rat? Should it be a fly chasing a rat?" recalls neuroscientist Roian Egnor) and then settled on the closest thing to a common denominator at Janelia Farm: the brain. By January they had a design, and by March, a shell. Ultimately, more than 100 scientists, students, and administrative and operational staff contributed ideas and labor. They called themselves the Lobe Trotters.

On race day, bystanders peered into the brain's cubbyhole-like "portals" each containing artwork and found objects depicting a state of mind such as fear, absent-mindedness, and addiction. Postdoctoral researcher (and race-day DJ) Andy Seeds was stationed inside the brain to run a music and light show.

At the starting bell, costumed teams dashed to their vehicles, among them a monocled blue caterpillar, a beehive, a Viking ship, and the Janelia team's brain. Some vehicles broke down immediately, creating a traffic jam that "probably didn't matter because our vehicle was rather slow," confesses mechanical engineer Brian Coop. With five riders pedaling at full capacity, the brain's max speed was two miles per hour. Then came the hill … and a broken chain.

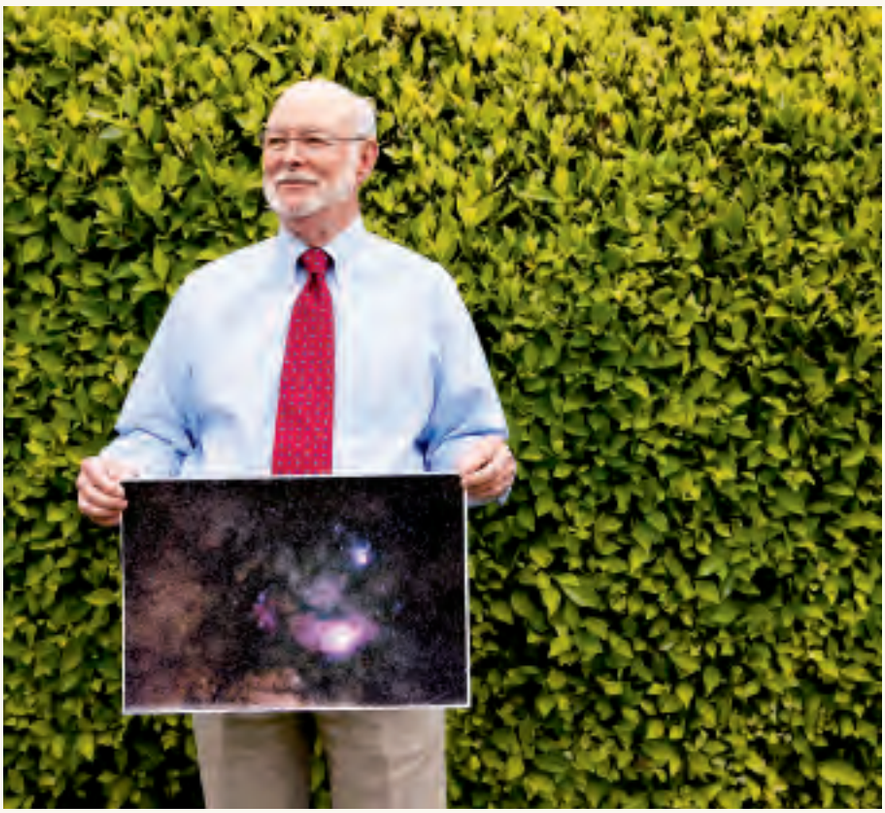
"Then *we* were the traffic jam," admits Coop.

By the time they reached the water challenge, the Lobe Trotters were in last place. But once they rolled down the ramp and into Baltimore's inner harbor, their secret weapon—125 empty illy coffee cans hidden inside the chassis for flotation—prevailed. Having seen a number of vehicles falter, sink, or simply drift away, the massive crowd roared.

In the end, the Lobe Trotters took home the Worst Honorable Mention award, in recognition of a tortoise-like pace on land but a flawless finish in the water. With new ideas already bubbling to the surface, they might not be able to resist doing it again. —*Sarah Goforth*

WEB EXTRA: For a glimpse at race day mayhem, see our slideshow at www.hhmi.org/bulletin/aug2011.

Ping Zhu



Darcy Hemley

The Night Sky

For decades, Fred Eiserling squinted through electron microscopes to study bacteriophages—viruses that infect bacteria—on the scale of millionths of millimeters.

In his free time, however, he photographed faraway galaxies and nebulae measuring light-years across—a hobby he continues to pursue today.

"It allows me to really put the universe in perspective after having stared at viruses for a few years," says Eiserling, an HHMI undergraduate program director and associate dean of life sciences at University of California, Los Angeles (UCLA).

Among the most gorgeous objects in the sky, according to Eiserling, are nebulae—billowing clouds of mostly hydrogen gas that represent the births and deaths of stars. With a telescope, he can even capture the colors of different stars. Hot ones glow blue; cold ones appear red. The resulting photographs look like wads of brightly hued, otherworldly cotton candy.

Like children gazing at clouds, astronomers and astrophotographers name these hydrogen clouds for their silhouettes. Eiserling has photographed the Horsehead Nebula, which dangles off the belt of the constellation named for the hunter Orion. And the Dumbbell Nebula, in the fox-shaped constellation Vulpecula, which looks like exercise equipment for the gods.

Eiserling is aiming toward the so-called Needle Galaxy. It's not actually skinny, but it looks that way to Earthlings because it appears edge-on in our skies. That point of view makes it hard to discern much about the galaxy's three-dimensional layout. Eiserling wants to find out how far he can push his equipment—a camera bolted to the telescope, mount, and guider to follow objects that move with the Earth's rotation, all tethered to a computer—to get the maximum detail.

Astrophotography is no point-and-shoot pursuit; plenty of things can go wrong in the process. "It's getting more technical as I try to get better and better pictures," Eiserling says. He has to find the stellar object he's after, focus properly, track it across the sky, and collect several pictures. Later, at his home computer, he fits the individual pictures together into one stunning photograph.

Because so much artificial light spills into the skies around Los Angeles, Eiserling can't practice his hobby at home. So once a month, when the moon is new, he and his wife, physician Phyllis Guze, make the seven-hour drive to much darker territory, the shore of Baja California in Mexico. There Eiserling and his brother built a small observatory, like a storage shed with a roll-off roof, to house their five-foot-long telescope.

Eiserling fell for the stars when he was 12 during a class trip to the local Griffith Observatory. Soon after, he joined fellow sky enthusiasts in the observatory's basement, where he hand-ground the mirror for his first homemade telescope. "It wasn't the greatest," he recalls, "but it was mine."

When Eiserling was a student at UCLA in the 1950s, advisors told him there were no jobs in astronomy—the university didn't even have a Ph.D. program in the subject. So he turned to bacteriology.

He indulged in one astronomy course, and in 1957, he and fellow students plotted the course of a little Russian orbiter known as Sputnik. Within a few years, the space race was on and, as Eiserling recalls, "They couldn't find enough astronomers!"

He has no regrets, however, about pursuing nanoscale biology. "I discovered that there were these incredible tools … that allowed you to see things at the level of molecules," he says. "I found that to be tremendously exciting."

Back at UCLA, Eiserling focuses on what he calls his "experiments" in education for about 200 undergrads: most recently, turning dull "cookbook" labs into real experiments in which students discover new viruses or pursue other novel data. Some students get to take home electron microscope portraits of bacterial viruses they've discovered in class.

And on a dark evening, you can still find him staring up at the sky.

—Amber Dance

WEB EXTRA: To see a slideshow of Eiserling's astrophotography, visit www.hhmi.org/bulletin/aug2011.

The Tao of Science Fairs

As a kid in Brazil, Dayan (Jack) Li played in the citrus groves of the experimental fruit farm where his dad did field research. He enjoyed poking the occasional poisonous toad to watch the oil ooze from its blistered back, but he never envisioned winning accolades at a prestigious international science fair.

Li didn't know what a science fair was until he moved to Laurel, Maryland, and participated in one as a seventh grader. By the time he entered Eleanor Roosevelt High School, the HHMI-funded science and technology magnet, he was hooked … and winning. He graduated from Harvard University this summer.

Growing up in Moorestown, New Jersey, Maria Elena (Ellen) De Obaldia delighted in working on kitchen table science projects with her sisters. For one experiment, the girls even talked their dentist into irradiating fruit flies with his x-ray machine. De Obaldia, also a Harvard grad, went on to win elite science competitions, where students develop innovative projects in fields as diverse as encryption, human behavior, cancer, and astronomy. Today she is a graduate student at University of Pennsylvania (Penn), where, as part of the HHMI Med into Grad Program, doctoral students get exposure to principles of medicine and disease.

Li's and De Obaldia's paths to success were wildly different, but both occasionally wished they could have had more guidance along the way. So they jumped at the chance in 2008 to work with three other Harvard students to write a book—*Success with Science: The Winners' Guide to High School Research*—published in January. (See Observations, inside back cover.)

"There is incredible value in hearing the advice from peers who have so recently experienced the same thing," says Michele C. Glidden, director for science education at the Society for Science and the Public, the long-time organizer of elite science competitions. "The book shows the good nature of scientists and the importance of sharing best practices and research."

The brainchild of Shiv Gaglani, a 2010 Harvard graduate, the book aims to demystify the process of finding a mentor, initiating a project, and competing in high-caliber science fairs. Gaglani recruited fellow science fair winners among Harvard undergrads, and they divvied up 24 chapters, culling the wisdom of about 50 science fair winners. De Obaldia focused on personal development, scientific method, and keeping a log book.

"No one wanted to write the chapter about documenting your work, but I did!" she laughs, remembering the fun she had with her log book and how she personalized it. "I used photographs to document things like how I set up tubes and what materials I bought."

In his chapters, Li encourages students to approach the lab as a foreign country, noting, "some people are surprised that it takes time to get used to the environment and the rhythms and norms of behavior." He also touts the value of internships with financial support as a help for finding research mentors. Li did his Intel project work as a summer intern in the research lab of David Roberts at the National Institutes of Health.

Having smoothed the journey for those following in their footsteps, Li and De Obaldia are moving forward on their career paths. Li will be pursuing an M.D./Ph.D. in the Harvard/MIT Medical Science Training Program. De Obaldia is a Ph.D. candidate in immunology at Penn. Ultimately, she wants to be a professor with her own research lab.

"Science fairs gave me the chance to be creative and then show what I had accomplished," De Obaldia says. "The process builds so much confidence and that influences everything else I do."
—Lisa Chiu

WEB EXTRA: To marvel at the science honors achieved by each of the book's coauthors, go to www.hhmi.org/bulletin/aug2011.

Ping Zhu

upfront

WEB ONLY CONTENT

LASTING MEMORIES
Measuring molecules at a single synapse gives clues to how memories become long term. Read the story at *www.hhmi.org/bulletin/aug2011*.

Scientists are an inherently curious bunch. If they need a new tool to find answers, they often figure out a way to build it. Like a microscope to observe the what, where, and how of protein interaction at a synapse. Or small molecules to explore the tight regulation of cell death in cancer and wound healing. Even designing nanoparticles to learn how to make immune cells better pathogen fighters isn't too far a stretch. Who says science isn't a creative pursuit?

The Goldilocks of Cells

Too much or too little cell death can lead to disease. Scientists are learning how to find the range that's just right.

EVERY DAY, BILLIONS OF CELLS IN THE HUMAN BODY UNDERGO A quick and painless suicide called apoptosis. Self-destruction of the right cells—those that are old and slow, have mutations, or are damaged by a virus, for example—keeps the rest of the organism alive. But when too many healthy cells die, the body suffers.

"Apoptosis is one of the most tightly regulated pathways in cells," says HHMI investigator Hermann Steller, "because if you make a mistake, you can't undo it. Dead cells can't come back to life."

Steller, at the Rockefeller University, has spent the past three decades trying to understand these strict levels of regulation. Now, he's translating those findings into developing small molecule drugs for two diametrically opposed purposes: healing wounds and treating cancer. Abrasions and burns heal faster, he's found, when cellular suicide is turned down. By turning up apoptosis, however, he can treat cancers by killing off the cells that drive their growth.

At the crux of Steller's research is a family of proteins called IAPs (inhibitors of apoptosis proteins) that put the brakes on cell death. In humans, there are eight IAPs, with different effects throughout the body so that long-living cells, like neurons, don't die as easily as those with a short lifecycle, like skin cells. Other proteins, in turn, regulate the IAPs: in humans, Smac and ARTS do the job; in fruit flies, it's the aptly named reaper, hid, and grim, discovered in part by Steller's lab group in the 1990s. ARTS, reaper, hid, and grim all encourage cell death by blocking IAPs.

"These are the brakes and the accelerators of cell death," Steller says. "They hold the keys to controlling the whole pathway."

Scientists studying acute lymphoblastic leukemia had found that in many instances of the disease, ARTS expression was diminished. Steller wanted to know whether a lack of ARTS was sufficient to cause cancer, so he blocked expression of the protein in mice. A third of the mice developed leukemia or lymphoma within 15 months, his lab group reported in *Genes & Development* in October 2010. Without the cellular suicide pathway kicking in, their low apoptosis threshold allowed cancer cells to thrive. But when the researchers also blocked expression of a key IAP protein, the effect was reversed—apoptosis could proceed, killing off cancer cells.

"The ideal cancer drug would block the IAPs, as ARTS normally does, or restore ARTS expression," says Steller. With his sights set on such a drug, he's collaborated with clinical scientists to find out how ARTS is silenced in leukemia and to develop molecules to block IAPs. In work published September 2010 in the *Journal of Cell Biology*, Steller and his colleagues concluded that reaper and hid—the functional equivalents of ARTS in the fly—work by clustering on the mitochondria, a cellular organelle critical to apoptosis. Now they're

Emily Robertson

developing a small molecule based on a conserved region of reaper and grim, and they're tacking on a protein sequence that sends the molecule to mitochondria. A version to treat cancer is in early animal trials.

"The rationale for these drugs seems strong and the promise great," says H. Robert Horvitz, an HHMI investigator at the Massachusetts Institute of Technology who also studies the cellular suicide pathway.

Turning up apoptosis, however, has a drawback. When Steller blocked ARTS expression in mice, the tumor-ridden animals had one health advantage over their cancer-free counterparts: speedy wound healing. With impaired apoptosis, wounds heal faster—good for healing nasty cuts and burns. Likewise, Steller has shown that when cell death is increased, wounds heal slower.

"This means if people have a major wound, you can stimulate pathways to heal them faster," says Steller. "But in a cancer patient you want to diminish those same pathways. It's this slider between cancer and regeneration."

But the dividing line may not be so clear-cut, he's found. When a cell undergoes apoptosis, it also sends out signals to nearby cells encouraging them to divide, Steller has found. "The cell is saying 'look, I'm going to die, you need to replace me,'" he explains. For wound healing, this means some level of apoptosis actually helps the process of healing. But in cancer, it introduces a problem: more apoptosis may increase the signals that tell nearby cells—including cancerous ones—to multiply.

This may mean that radiation therapy (which kills cancer through inducing widespread apoptosis) or one of Steller's new small molecule compounds could force a cancer to spread at the same time it's killing a primary tumor. If researchers like Steller can tease apart these growth-causing signals—called mitogens—from the rest of the apoptotic pathway, they'd be able to pick and chose which ones to turn on. For cancer, the ideal mix would be more apoptosis with no mitogens. For healing, the goal would be less apoptosis and a surplus of mitogens.

"Steller's recent work," says Horvitz, "is novel, important, and intriguing in the context of possible novel therapeutics."

And whether or not his findings lead rapidly to therapeutics, his research is helping scientists understand how to control a cell's most fundamental decisions: whether to live or die. ■ –SARAH C.P. WILLIAMS

T-Cell Booster Kits

A bioengineer remodels cell surfaces to prod the immune system.

Darrell Irvine is focusing his engineer's mind to boost the body's defenses against cancer. He's also working on ways to deliver drugs directly—and only—to the cells that need them.

Matt Kalinowski

T CELLS FROM THE IMMUNE SYSTEM CAN BE REMOVED FROM A cancer patient, trained in a laboratory dish to recognize and attack tumor cells, and then returned to the patient ready for battle. In some clinical trials, up to 70 percent of patients with advanced melanoma have seen their tumors shrink with this experimental immunotherapy.

These tumor-hunting T cells don't remain active for long, however, unless the patient receives sustained doses of stimulatory interleukins such as IL-2. These powerful immune stimulants can cause low blood pressure, flu-like symptoms, nausea, diarrhea, and dizziness. For some patients, this adjuvant drug treatment makes T-cell therapy too dangerous.

But what if the T cells could carry their own tiny supplies of interleukins, just enough for their own needs?

HHMI investigator Darrell Irvine has found a way. In his laboratory at the Massachusetts Institute of Technology, he and his colleagues make nanoparticles filled with interleukins and attach these immune "booster kits" to the surface of T cells. They're so minuscule that 100 booster kits can fit on just 3 percent of the cell's surface area, where they slowly release their contents to the cell.

By "getting the drug just to the cells that need it," says Irvine, "we're looking for the extra nudge that could take immune-cell therapy from working [only] in a subset of people to working in nearly all patients."

Irvine and postdoctoral research associate Matthias Stephan mounted booster kits containing IL-15 and IL-22 onto T cells extracted from metastatic melanoma tumors implanted under the skin of mice. The T cells were "educated" in laboratory dishes to recognize and destroy the melanoma cells. When infused back into the rodents, the enhanced T cells rapidly proliferated and accurately zeroed in on the metastatic tumors, according to the researchers' report in the September 2010 *Nature Medicine*. Importantly, the enhanced cells remained viable longer than untreated T cells and increased the survival rates for the cancer-ridden mice receiving them.

Remodeling the surface of cells with synthetic materials for therapeutic ends reflects Irvine's merger of materials science and immunology. He studied engineering in college and materials science in graduate school. "I became attracted to life science and problems in medicine, and how someone with an engineering background could have a role in those fields," he says. In particular, he became fascinated with the immune system and its complex regulatory actions that control the body's defenses.

Improving Cell Therapy

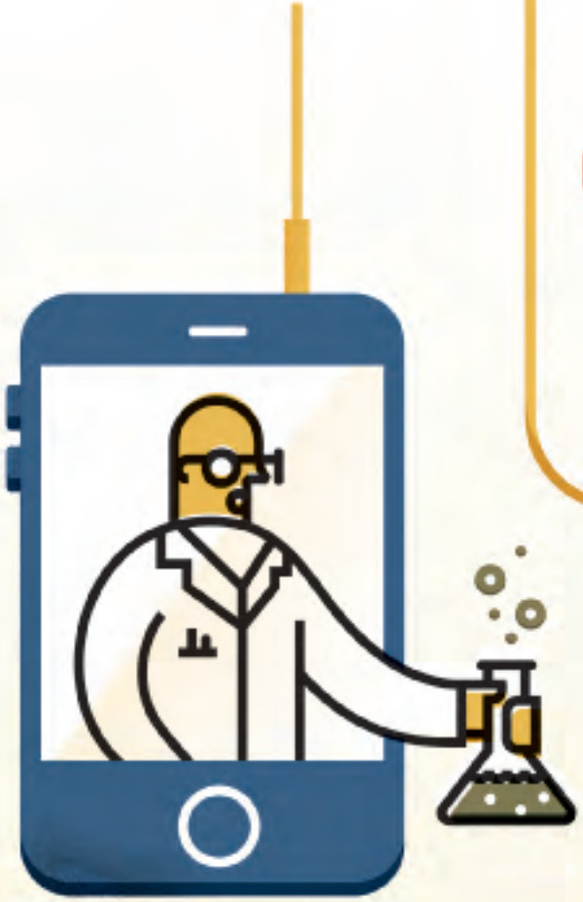
Irvine found success when he turned a standard approach on its head. For several decades, researchers have explored the possibilities of using cells directly as therapy (stem cell transplants, for example) or as transporters. One research group was developing T cells as vehicles to infect tumors with cancer-killing viruses. "Instead of using the T cell as a ferry for a virus," Irvine says, "we started thinking about putting synthetic drug particles onto T cells to make them function better."

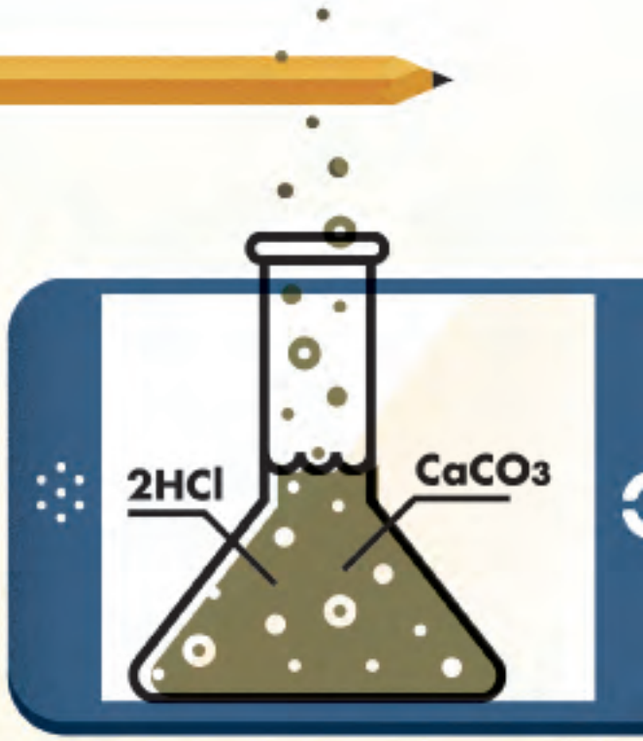
First Irvine's group had to overcome a difficult challenge: because components of the T-cell surface are recycled over periods of hours to days, particles placed on the plasma membrane would rapidly be swept into the cell's recycling bins and inactivated. After some trial and error, Irvine found he could shackle the booster kits to small reactive sulfur groups, called thiols, which remain stable on the cell surface, allowing the nanoparticles to survive for at least a week. "I think this linkage is somehow stabilizing the material on the surface," Irvine says.

The bioengineer envisions an array of additional applications. In a related experiment described in the *Nature Medicine* paper, Irvine attached drug-filled nanoparticles to blood stem cells. When transplanted into mice lacking blood-forming cells, the enhanced stem cells restored the bone marrow more quickly than stem cells without the drug boost. He'd also like to try transporting small molecule drugs such as vaccines or contrast agents into patients. Another possibility is using T cells to carry antiretroviral drugs into the deepest recesses of HIV/AIDS patients' immune systems.

Transferring cells in and out of the body along with the necessary lab work makes T-cell therapy costly and time-consuming. Ever the engineer, Irvine is brainstorming possible shortcuts, aiming for "strategies where you could deliver drug agents, like interleukins, directly to specific cells within the patient," he says.

Meanwhile, his group continues to develop the booster kit method, filling the particles with IL-2 and testing them in more clinically relevant melanoma mouse models. The researchers look forward to a day when patients undergoing T-cell therapy may be spared any toxic side effects. ■ –RICHARD SALTUS





Eraser

BY:
Laura Putre

ILLUSTRATION BY:
Keenan Cummings


EVOLUTION
of the
TEXTBOOK
Publishers are beginning to go digital with textbooks, pushing boundaries to give students a personalized, interactive experience.
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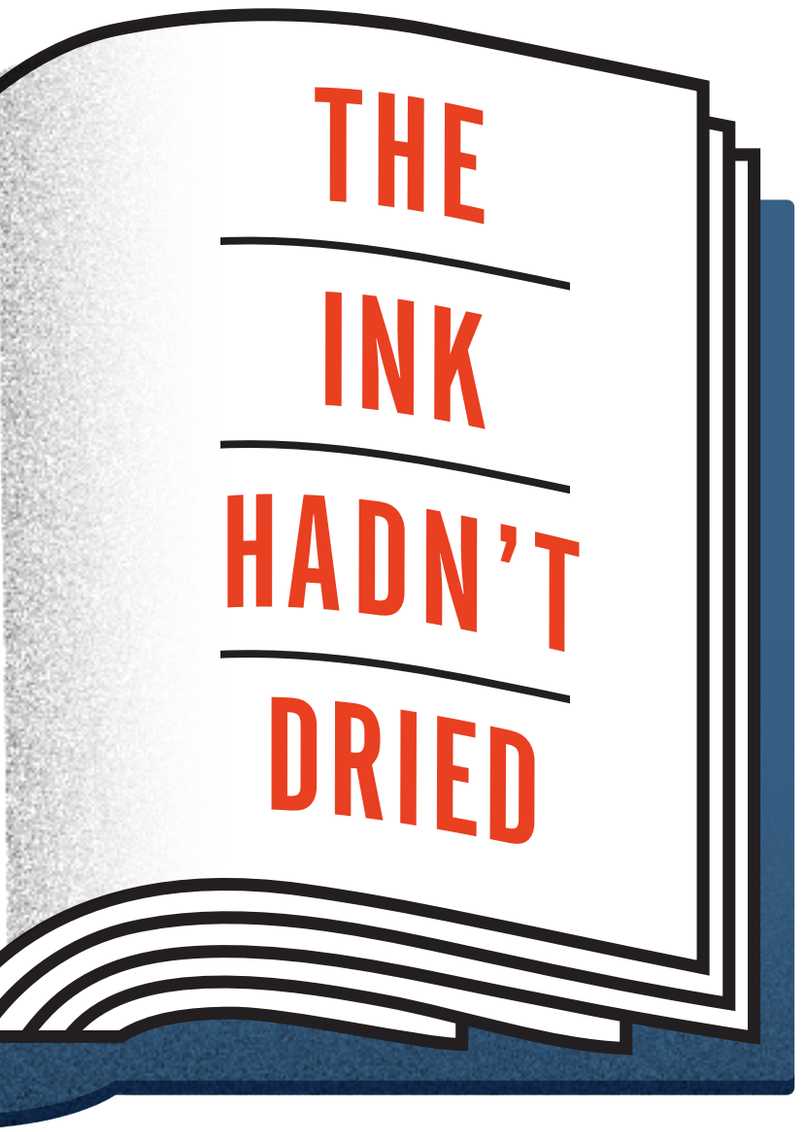


on the first edition of *Molecular Biology: Principles and Practice* when its scientist authors began dreaming up ideas for the second. They would go way beyond words on the page to give students a front row seat to science in action.

It was the summer of 2010, and the collaborators had just met with Adam Steinberg, the book's artist. On his newly minted iPad, Steinberg showed them a splashy periodic table application called *The Elements: A Visual Exploration* that rocked their world.

The app included cleverly worded facts and scintillating periodic table trivia. But its real impact was visual. Its creator, scientist Theodore Gray, had gathered a mini-museum's worth of fascinating objects to represent each element—from an iridescent hunk of bismuth to a dimestore dragon figurine made of copper. App users could see the objects in 3-D and rotate them, front to back and front again, with the swipe of a finger.

It wasn't quite holding an object and turning it over in your hand, but it was pretty close.

Jennifer Doudna, an HHMI investigator at University of California, Berkeley, and coauthor of the textbook, marveled at how the app transcended the traditional boundaries of a textbook. "When I was in college and learning [molecular biology] for the first time myself, I found the textbook approach very dry," she says. "It really did not give a sense at all of science being a living, breathing, growing, changing kind of field."

In the first edition of *Molecular Biology*, Doudna and her coauthors Michael M. Cox and Michael O'Donnell had set out to humanize their subject matter almost entirely within the confines of the printed page. For instance, they opened each chapter with a first-person vignette from a scientist talking about a moment of discovery.

But Steinberg's tablet computer demonstration got them dreaming about adding video versions of the vignettes that students could tap into as they read. They imagined 3-D animations and virtual experiments where students could choose their data sets and follow them through to the outcome.

"We have ideas and the ground is definitely shifting quickly," says O'Donnell, an HHMI investigator at Rockefeller University. "We're all thinking about it and we're all very excited."

So what will college science textbooks look like in five years? A decade? The boundaries have already stretched beyond the physical page to incorporate animations of molecular processes, videos of scientists talking about discoveries, and social networking between researchers and students around the world. Publishers are offering content that teachers can customize as they see fit. However, a flock of unknowns is circling—Will the iPad prevail? Will the cost for developing spectacular apps be more than students are willing to pay?

Jonathan Crowe, an editor in chief at Oxford University Press who works with science authors, predicts the textbook industry will change more in the next few years than it has in the past 50 or 100. And plenty of new and traditional publishers are moving fast to stake a claim to that future.

STILL A SMALL MARKET

College textbooks are big business. Higher education textbooks sales were $4.58 billion for 2010, an increase of 7.8 percent since 2009, according to U.S. publishers' net sales revenue released by the Association of American Publishers in February.

"WHEN I WAS IN COLLEGE AND LEARNING [MOLECULAR BIOLOGY] FOR THE FIRST TIME MYSELF, I FOUND THE TEXTBOOK APPROACH VERY DRY. IT REALLY DID NOT GIVE A SENSE AT ALL OF SCIENCE BEING A LIVING, BREATHING, GROWING, CHANGING KIND OF FIELD." *—JENNIFER DOUDNA*

Digital textbooks, however, make up roughly 5 percent of the textbook market, says Vikram Savkar, publishing director at Nature Publishing Group (NPG), which will soon launch its second college-level digital initiative. Other numbers bear this out: for John Wiley and Sons, a major publisher of science textbooks for the higher education market, $10 million of its $290 million in higher-education revenue last year came from digital-only sales (titles not packaged with a print textbook)—that's 3.5 percent of the company's higher-education revenue.

"Everybody in the market says it's time to go digital, yet year after year people still spend most of their money on print textbooks," says Savkar. "I personally believe that's because there haven't been digital projects that have come out yet that are really exciting to the market and that are designed to be effective replacements for textbooks."

A NEW ENTITY

Matt MacInnis, CEO of an interactive publishing company called Inkling, says "textbook" is too narrow a term for the new kind of learning content his company is developing. An alumnus of Apple's international education division, MacInnis envisions traditional print textbooks being replaced by a new generation of media-rich learning platforms.

Inkling, which was born in 2009, takes existing textbooks (and their supplemental online content like animations and self-assessment quizzes), "gently disassembles" them, and then reassembles them for multitouch tablet devices like the iPad. For example, Inkling's version of *Hole's Human Anatomy and Physiology* features 400 interactive "exhibits" embedded in the text, including 3-D animations, anatomical diagrams where students can make the labels disappear and test themselves, and interactive quizzes that give instant feedback. Students can highlight passages with a finger swipe, swap ideas onscreen with friends on blue "sticky notes," and read handy annotations, in purple, from their teachers.

Brown University School of Medicine recently bought into the Inkling concept. Its incoming first-year students, 108 of them, will be required to purchase an iPad and will use six Inkling titles as their textbooks for core preclinical classes.

NPG, publisher of the journal *Nature*, is finding ways to make scientific instructional content more accessible to students. In January 2009, NPG unveiled a free collaborative learning site called Scitable, "as a personal research space for undergrads and high school students with a deep love of science," Savkar says. Users can access a growing library of original content as well as previously published material from *Nature*, mostly in genetics, cell biology, and ecology.

"Eventually it will have coverage across all of biology," he adds. Instructors can assign readings, asking students to explore them at their leisure, plus students can log on and ask questions of scientists, communicate with students in other parts of the world, and read student-written blogs on topics like global warming and neuroscience.

The second NPG project is a $49 interactive digital *Principles of Biology* textbook that will debut in September 2011 at three California state university campuses. *Principles of Biology* sets out to combine the scientist-produced content and high-quality illustrations of a print textbook with primary literature from *Nature*, as well as animations, assessment tests integrated into the lessons, and interactive simulations of concepts that students can manipulate.

"Wherever possible, we try to get the student actively engaged," Savkar says. A "Build a Fly" module, for example, allows students to choose different types of genetic material for a fly and then see how the phenotype changes with their choices.

Students can access the material on a desktop, laptop, smartphone, or tablet. They can also print one color copy of the textbook for free. If teachers want to customize the content—as 25 to 35 percent of instructors have indicated to NPG—the digital textbook will automatically rearrange itself as requested.

Free updates will come continually, after review by an editorial board. "We're looking at this as a living edition," says Savkar.

AN INVESTMENT

Issues of price, always a hot topic among cash-strapped college students, are complicated. E-textbooks cost about half the price of print. Inkling's titles generally cost 15 percent more than e-books, but students can pay as they go for the content at $2.99 per chapter. Teachers can pick and choose chapters for a course, so if they need only 15 chapters, students pay $45 instead of $180 for the full 60-chapter book.

Still, students will need to shell out the $500 or more for the tablet device. And interactive publishers who develop iPad content may save on printing and paper, but they will have higher development costs for the multimedia features, says Alison Pendergast, senior vice president and chief marketing officer at Jones and Bartlett Learning, a large U.S. college textbook publisher.

"I don't necessarily think technology is going to drive down the cost of textbooks," says Pendergast. "If anything, it's going to

keep them priced where they are. All of those additional components—animations, simulations, and interactivity—are expensive to develop.

"We're continuing to try to find business models that keep the resources affordable for students but at the same time are cutting edge. It's hard to do this stuff cheaply—and in order to do it well, there has to be investment."

The nonprofit E.O. Wilson Biodiversity Foundation estimates it will need $10 million to develop a 59-chapter digital biology textbook called *Life on Earth*. But the foundation plans on paying for it with money from private and public donors and making the textbook available to the public for free.

HHMI investigator Matthew Scott, a professor at Stanford University and coauthor of *Molecular Cell Biology*, is a fan of another nonprofit site with free content, Khan Academy. Developed by an MIT graduate named Salman Khan, the site offers upward of 2,000 video tutorials that consist of scrawled notes and colored doodles on an electronic blackboard, with Khan's voice explaining it all. The content leans heavily toward precollege math and physics but also includes dozens of higher-level biology and organic chemistry videos. Teachers can have their students log on as a class, then direct them to particular videos and assessment exercises and track their process.

"It's enormously well done," says Scott. "I use it, my kids use it, and friends who are Stanford faculty use it."

EFFECTIVE TEACHING

At Harvard University, students may be fused to their iPads in their off hours, but they're not using them in their undergraduate biology classes yet. Instead, teachers rely on the latest in interactive technology such as animated movies that illustrate cellular processes and handheld clickers to gauge the class's understanding of a particular concept and drive discussion.

"After watching an animation of, say, the transport of proteins across a nuclear envelope, we'll have a discussion of the core process that's being shown," says Robert Lue, a professor of molecular and cellular biology and director of Life Sciences Education at Harvard University as well as an HHMI undergraduate program director. "But then we'll have a discussion in the context of a living cell—what are some of the things we didn't show and how are they going to affect the process we're talking about?

"It becomes a real teaching tool, not like a passive look at something," says Lue, who runs Harvard's Biovisions program for digital animations.

The landscape of textbooks is changing rapidly, says Lue, but he's less interested in whether it brings the latest whizbang interactive features to a nearby screen than in how it's changing to meet teachers' increasingly well-defined and precisely planned pedagogical goals. Textbook authors used to focus just on clearly explaining concepts, but "authors now have to spend a lot of time thinking not just about how to present something but about how to teach it," says Lue.

"In the past, textbooks were simply laying out the information in the written word with still diagrams that were clear. But there is so much we have learned about how best to teach material, how best to use interactivity and activity-based learning methods," he says. For example, students in biology, computer science, and visual art courses can work together to develop their own scientific animation.

"It's not just the material between two covers," Lue says. "It's also a whole program in terms of how to teach more effectively."

"The textbook is always there as a framework," says Dennis Liu, who heads HHMI's education resources group, which produces materials to supplement textbook content for HHMI's BioInteractive website (www.hhmi.org/biointeractive). "We have to be mindful of what teachers are teaching now while also exposing them to new content and ideas and helping them to inject cutting edge research into their curricula." Liu hopes to see BioInteractive animations, some of which are being adapted for smart phones and the iPad, become incorporated as digital assets in new textbook-like products. "I can imagine future partnerships with authors and publishers to custom design some of our media to match new digital textbook content," says Liu.

NONSTOP UPDATES

One dilemma in the life sciences is how to distill into a single course the "enormous explosion" of information that has come with breakthrough discoveries in the past 20 to 30 years. "It's both a very rapidly expanding area and one where there are still a lot of things that haven't been settled yet," says Lue. "That means the life sciences courses and textbooks are constantly responding to revisions of fundamental paradigms."

With two or three competing models for a particular idea, Lue says the current challenge for textbook authors is to assess the entire spectrum of materials and choose which examples best illustrate fundamental principles. "We have to help instructors use the material most effectively, rather than just handing it over," says Lue.

"IT'S BOTH A VERY RAPIDLY EXPANDING AREA AND ONE WHERE THERE ARE STILL A LOT OF THINGS THAT HAVEN'T BEEN SETTLED YET," SAYS LUE. "THAT MEANS THE LIFE SCIENCES COURSES AND TEXTBOOKS ARE CONSTANTLY RESPONDING TO REVISIONS OF FUNDAMENTAL PARADIGMS."

(l-r) The second edition of the molecular biology textbook co-authored by Jennifer Doudna and Michael O'Donnell will likely include virtual experiments and conversations with practicing scientists to help make science come alive for students. Matthew Scott, also a textbook author, is already a fan of one teaching website packed with 2,000 video tutorials on math and science topics. Robert Lue notes that cool interactive features are less important than figuring out how to use interactivity to teach more effectively.

Doudna: Michael Marsland / Yale University O'Donnell: Rockefeller University Scott: Matthew Scott Lue: Harvard University

For HHMI investigator Matthew Scott, a particularly compelling part of textbook authorship is distinguishing discoveries that are of enduring value from those that are merely in vogue.

"You don't want to put in too many of the latest hot things that are perhaps wrong or less important than they may seem at the moment," he says. "Yet you want the book to seem up to date, so you're doing a balancing act."

Oxford University Press's Jonathan Crowe says with the ability to change digital content at will, it will be "fascinating" to see whether authors will be constantly updating things to keep pace with the latest discoveries, or stick to the old way of curating.

"In theory, their task could never end," he says. "The molecular biology team I work with, at least they've got a couple of years without me breathing down their necks. I could be on them every month, and it could never stop."

He suspects there will be incremental updates rather than constant ones, and then new editions every three years. For more topical matters, "that's where things like social networking could come in," says Crowe. "You could have a Twitter feed associated with the book if a discovery comes in. Anybody who's following that feed will see it has happened and then go have a look at this journal for this particular advance." And then when the new version of the textbook comes along, "the authors can build it into the narrative."

THE BEST OF BOTH

So while authors and educators wend their way through the digital morass, will the paper textbook soon go the way of cave drawings and illuminated manuscripts? Or will students cling to the textbook because sitting in the grass and highlighting a page with a yellow marker is just simpler than highlighting electronically?

The best print textbooks, especially for upper-level courses, will probably not go away as fast as people anticipate, says Pendergast. "It's still a pretty functional tool."

"When you're trying to learn math or chemistry or physics, and this stuff is really hard, I think people use the textbook as a life vest. It's insurance—you grab onto it and hope that it's going to provide the explanation you need to understand the concepts you're trying to learn."

The advantage of digital content, she says, is that it personalizes the learning experience, so students can process information at their own pace and use visuals to enhance their understanding of the material.

"Instead of reading 20 pages on the Civil War or Civil Rights Movement, they could go on a website and see a video of Martin Luther King," she says. "They could see and read original text from MLK and JFK and get a much more visual experience over time."

The iPad is a physical object, too—and one that weighs a mere 1.35 pounds, making the textbook seem more like a millstone than a life vest. In the second edition of *Molecular Biology: Principles and Practice*, Doudna hopes to fuse the best of print and digital. "I doubt there will be less text, frankly, because we've found that faculty want quite a high level of discussion about experimental findings.

"But expanding into other kinds of media like the iPad will allow us to give people more options. We could pick any sort of topic in molecular biology and have an application that would allow students to get real-time information about that concept. We could have discussions with practicing scientists kept very up to date with interviews as new discoveries are made.

"Or it could be a hands-on demonstration of the discovery, showing them data and walking them through how one does the experiment."

Doudna hopes to have all that out in three years. "We just had our booksigning party [for the first edition], and our publisher said, 'Don't relax. In a few months I'm going to be calling you.'" ■

WEB EXTRA: To learn more about digital supplements to textbooks, visit www.hhmi.org/bulletin/aug2011.

SEEING IS BELIEVING

SCIENTISTS ARE CAUTIOUSLY BRINGING
GENE THERAPY OUT OF THE DARK.

BY VIRGINIA HUGHES
ILLUSTRATION BY RUBENS LP

AT AGE 8, COREY HAAS STOOD AT SQUARE ONE OF A FLOOR MAZE AT THE CHILDREN'S HOSPITAL OF PHILADELPHIA.

Black and white squares covered the ground, with an arrow on each to show him the correct path. He took a few steps and then paused. "This is being really hard," he told the adults in the room. After about a minute, they nudged him in the right direction. After a couple more timid steps, he stopped again, frustrated. "I can't even see anything."

Corey has Leber's congenital amaurosis (LCA), a rare inherited disease in which a genetic glitch damages cells in the retina, causing blindness. On that fall day in 2008, he was tackling the maze as the youngest of 12 patients who had received an experimental therapy for LCA. Ninety days before, a surgeon had injected a healthy version of a gene called *RPE65* into the back of Corey's left eye. His eye cells began pumping out the protein that he was born without, allowing him to see.

In that first, frustrating maze, Corey was relying on his untreated eye, wearing a patch over the newly treated left eye. About an hour later, he did the maze again, this time using his left eye to guide him. He cruised through it in about 20 seconds. The spectators burst into applause.

The trial's participants ranged from 8 to 44 years old, and the therapy worked, to varying degrees, for all of them. When the results were published, in November 2009, it was a boon to the gene therapy field, which has had highly publicized ups and downs since its debut in the late 1980s (see Web Extra gene therapy timeline). The general pattern: scientists would see fantastic results when testing gene therapy on animals. But when they used it on people, they came up against two major obstacles: the new gene would be expressed only for a short time or the immune system would reject the therapy outright.

Today, researchers are tackling both problems by finding clever ways to deliver long-lasting, healthy genes without triggering a serious immune response. One promising approach is to repair a gene in the patient's cells outside the body and then put the cells back after the gene has fully integrated into the genome. Another tactic is to tweak the vehicles that deliver the gene so that they aren't as easily seen by the immune system.

Then there's the strategy behind the LCA trial: targeting parts of the body—such as the eye or brain—that are somewhat isolated from the immune soldiers in the blood. A leader of this study is Katherine High, a gene therapy pioneer and HHMI investigator at Children's Hospital. High has her hands in many lines of gene therapy research, but so far the LCA trial has produced the most dramatic outcomes. At a conference in May 2011, her team announced the latest results: 3 of the original 12 patients have received the therapy in their second eye, and their vision has improved further. The researchers plan to launch a phase 3 trial—the last step on the long road to regulatory approval—this fall.

After two decades in this controversial field, High has difficulty wrapping her head around this medical miracle. "It's almost Biblical," she says. "I still can't quite believe that something like this could actually happen."

BEYOND DOGS

High has been fascinated with the idea of gene therapy since she launched her first laboratory, at the University of North Carolina, in 1985. She had spent years pinpointing the genetic glitches responsible for bleeding disorders called hemophilias. Most of these mutations damaged clotting factors, enzymes that help the blood clot. "From there, it's not a very far leap to ask if there's a way we can use the gene to go into a person with hemophilia and correct their disease," she says.

Those were the glory days of gene therapy, when researchers were seeing their first successes in animal models and declaring that the treatment could one day cure thousands of genetic diseases. The first human clinical trial, launched in 1990, treated a rare immune deficiency, dubbed SCID, in a 4-year-old girl.

Researchers removed some of the girl's blood, used a retrovirus to insert a healthy version of the broken gene into her white blood cells, and then infused the altered cells back into her body. The therapy seemed to work: four years later, the girl carried the healthy gene in half of her white blood cells. From 1989 to 1998, some 275 other gene transfer protocols were listed in U.S. regulatory registries, according to the NIH Office of Biotechnology Activities.

By the late 1990s, High's team and a group at Stanford University, led by Mark Kay, had independently cured hemophilia B in dogs. Both groups used a new delivery method: they used part of a virus, called adeno-associated virus (AAV), and its outer shell to carry the factor IX gene, which codes for a clotting factor, into the dogs' cells. AAVs were thought to be safer than retroviruses, which integrate themselves into the host's genome and could potentially turn on cancer genes. In contrast, these modified AAVs almost always unload their genetic packages outside the host's genome.

High and Kay collaborated to bring this therapy to human clinical trials. But eight months after they published their dog data, the field took a major hit. In 1999, a gene therapy trial for a rare metabolic disease at the University of Pennsylvania caused the death of an 18-year-old named Jesse Gelsinger.

Gelsinger's death unleashed a mountain of scrutiny from the press and regulatory agencies. The Food and Drug Administration temporarily suspended two other studies using the same viral vehicle—adenovirus—that was used to deliver Gelsinger's therapy. (Despite the similar name, adenovirus is very different from AAV.) Within months, the agency issued more stringent regulations on gene therapy clinical trials and the University of Pennsylvania (Penn) stopped all clinical trials at its Institute for Human Gene Therapy.

High's hemophilia trial at Children's Hospital, just down the road, used the AAV vector and was not delayed or shut down. Still, she says her work was affected in a broader sense. "It raised questions about the safety of gene therapy, and that had broad ramifications for the field," she says. "It reduced the interest of pharmaceutical companies in pursuing gene therapy and heightened the perception that it was somehow dangerous."

In the summer of 2001, High and Kay began a trial in which they injected factor IX into the liver of volunteers with hemophilia B. One participant, a 31-year-old man, had a baffling reaction. At first, the therapy worked exactly as it had in dogs: levels of clotting protein in his blood rose dramatically. But after four weeks, his factor IX levels dropped, while liver enzymes—a sign of liver injury—began to rise. By 12 weeks, his enzyme levels were back to normal, and he had no detectable factor IX in his blood.

The liver enzymes were a sign that the man's immune system was killing all the cells that had received the new gene. As High and Kay later figured out, the patient's immune system was reacting not to the new gene itself but to proteins, called capsids, that make up the shell of the AAV vehicle (known as a vector).

"This was totally unexpected," says Kay, now professor of pediatrics and genetics at Stanford. "There had been tests in dogs, monkeys, rabbits, rodents—nobody had seen this response in animals." After hearing the news, Avigen, the California biotech company that was providing High with AAV vector, pulled out of the research. In short order, High convinced her hospital's leadership to build its own multimillion dollar, industry-grade vector manufacturing facility. It was up and running by the summer of 2005, and two years later the National Institutes of Health chose the facility to be the sole provider of all the AAV clinical trials it funded.

With an ample supply of AAV, High extended her work to other diseases. For years, she had wanted to collaborate with one of her Penn colleagues, ophthalmologist Jean Bennett, who she had gotten to know because their daughters ran on the same track team. Bennett had used AAV gene therapy on dogs with LCA, and all of them showed improved vision. High had tried to convince Avigen to begin an LCA clinical trial, but the company did not want to invest in such a rare disease.

With the new AAV manufacturing facility, High and Bennett could do it themselves. "Jean had done 35 dogs—it was clear that it worked," High says. It was time to test it on people.

SEEING SUCCESS

LCA is an untreatable group of diseases that crop up in about 1 in 80,000 people. The condition is caused by mutations in any of 13 known genes, including *RPE65*, which leads to the breakdown of

"IT'S ALMOST BIBLICAL," SHE SAYS. "I STILL CAN'T QUITE BELIEVE THAT SOMETHING LIKE THIS COULD ACTUALLY HAPPEN."
KATHERINE HIGH

cells in the retina, the light-sensing film that lines the back of the eye. (See Web Extra sidebar, "RPE65: A Blinding Gene.")

"These kinds of inherited retinal degenerations are just devastating—patients end up blind at a very young age," notes Joan Miller, chair of the ophthalmology department at Harvard Medical School. Although some patients benefit from implantation of artificial retinas, "it would just be wonderful to restore a more natural vision to these patients," she says.

After the disappointing hemophilia trials, High began to brainstorm ways to avoid the body's immune response to gene therapy. The eye, she thought, might be an ideal spot: it's a small and contained area—it would need only a small amount of AAV—and it is relatively easy for surgeons to access. The eye is also somewhat isolated from the peripheral immune system.

Between October 2007 and June 2009, the five children and seven adults in High and Bennett's eye study underwent a 90-minute surgery to receive the gene therapy. The surgeon, Albert Maguire (Bennett's husband), had done all the canine eye surgeries in Bennett's earlier work.

Maguire injected a tiny amount of liquid holding the AAV package into a pocket of space under the retina. The vector would migrate into retinal cells and release its DNA contents: the healthy *RPE65* gene. The DNA would then invade the nucleus and be expressed just like a normal gene.

For three months after the surgery, the 12 patients returned to the hospital several times for various vision tests, from eye charts to measuring the range of peripheral vision to navigating floor mazes. All the participants showed improvement in at least one of the tests. Their pupils showed a 100-fold or greater response to light. Four patients are no longer classified as legally blind.

High is professorial and intense when she discusses the molecular tricks of gene therapy. But she gets emotional when talking about LCA patients. Her favorite anecdote concerns the oldest participant, 44-year-old Tami Morehouse, whose daughter is a star softball player. Before the treatment, Tami would sit in the bleachers at her daughter's games, in near darkness, hanging on every word of a play-by-play from her husband.

HE KNEW THE SURGERY WAS THE RIGHT DECISION FOUR DAYS AFTER COREY LEFT THE HOSPITAL, WHEN THE FAMILY TOOK A TRIP TO THE ZOO AND COREY SAID THAT THE SUN WAS HURTING HIS EYES. "THAT HAD NEVER HAPPENED BEFORE. IT WAS A PRETTY BIG DEAL."
ETHAN HAAS

"After she had this procedure, she was sitting in the stands one day. She couldn't see the outlines of her daughter's face, but she saw the person on third base steal home. And that was her daughter," High says, tearing up. "It's very, very hard to fully comprehend that kind of thing happening."

Tami's improvement is impressive, but the younger participants showed even better results. Corey, for instance, now age 10, can read the blackboard at school if he sits in the front row. He plays outfield on a Little League baseball team and rides his bike independently. "There are a lot of differences in colors now," Corey says. "When I go outside, my pupils will shrink right down."

At the same time as the Penn trials, research groups in London and Florida were doing similar AAV therapy for LCA. Patients in all three groups saw gains in vision after the treatment. And, perhaps best of all, none had an immune reaction to the therapy.

"The ophthalmology field was very excited because this was such a huge advance," says Harvard's Miller. The findings, which received a lot of media attention, also helped gene therapy's reputation. "Gene therapy had taken a major hit before this," Miller says. "So this [research] was a huge push for gene therapy of any kind."

EVADING THE ALARM SYSTEM

There are dozens of viable approaches to gene therapy, and High has, at some point, worked on most of them. For example, the vector manufacturing facility at Children's Hospital produces not only AAV viral vectors but also lentiviral vectors. Lentiviruses—retroviruses of which the most famous is HIV—work by quietly slipping their contents into the host's genome, so that every time the host cell replicates, so does the virus. This is one reason why HIV is so destructive—and why lentiviral gene therapy has much promise.

Retroviruses were used in the first gene therapy trial and now, 20 years later, several groups are making headlines for treating blood diseases with the same approach. Researchers first harvest blood stem cells—which can give rise to any type of blood cell—from the patient's bone marrow. In the lab, they mix the stem cells with a lentivirus that delivers a healthy version of the broken gene. Finally, patients receive an infusion of their own repaired stem cells. If all goes well, their daughter cells will carry working copies of the gene.

With this so-called ex vivo approach, "immunity is not a big issue," notes Luigi Naldini, director of the San Raffaele Telethon Institute for Gene Therapy in Milan, Italy, who has worked on lentiviral vectors for 15 years. The lentivirus delivering the new gene is cleared away before the cells are infused back into the body, so the immune system has nothing to pounce on. "You prevent the alarm system from going off," he says.

Starting in 2006, French researchers performed ex vivo lentiviral gene therapy on two boys with X-linked adrenoleu-

RESEARCHERS KATHERINE HIGH (LEFT) AND JEAN BENNETT COLLABORATED TO MOVE GENE THERAPY FOR A BLINDING EYE DISORDER FROM ANIMAL STUDIES TO HUMAN CLINICAL TRIALS, WITH PROMISING RESULTS. THIS FALL THE RESEARCHERS PLAN TO LAUNCH A PHASE 3 TRIAL, THE LAST STEP TO REGULATORY APPROVAL.

kodystrophy, a fatal brain disease caused by loss of the *ABCD1* gene. This gene plays an important role making myelin, the fatty sheath that insulates neurons. Without *ABCD1*, the brain can't send electrical messages properly.

The boys received a transfusion of their own modified blood stem cells. Two years after the therapy, about 15 percent of their blood stem cells carried the fixed version of *ABCD1*. Their brain cells had started making insulated neurons and the damage ceased. Although the boys still have some cognitive difficulties, the therapy saved their lives.

In 2007, some of the same researchers used the approach on an 18-year-old man with ß-thalassemia, a genetic disease that prevented him from making healthy red blood cells, which carry oxygen throughout the body. The man had received a blood transfusion every month since he was 3 years old.

After receiving the gene therapy, he started making his own healthy blood. "He has not received one drop of blood for three years," says Philippe Leboulch, professor of medicine and cell biology at the University of Paris and visiting professor at Harvard Medical School, an investigator in both studies. "He has a full-time job as a cook in a Paris restaurant, he has a girlfriend, he feels good." Leboulch plans to transplant a second ß-thalassemia patient this fall.

THE RIGHT VECTOR FOR THE JOB

Every gene therapy strategy has pros and cons. So far, ex vivo approaches haven't run into a major immune response. But because their vectors are permanently inserted in the host's genome, they could inadvertently turn on cancer genes.

In the ß-thalassemia trial, for example, the lentivirus turned on expression of a protein called HMGA2, which has been linked to benign and malignant cancers. "It's something that the field is well aware of and that we need to improve upon," Leboulch says.

Cancer is less of a concern with the AAV vector used in the eye trials because most of it stays outside the genome. Because it doesn't integrate into the DNA, however, it's not useful in cells that constantly divide, such as those in the blood, skin, and intestine. And, of course, AAV's capsid envelope brings about that unwanted immune reaction.

Several groups are at work fine-tuning the AAV vector so that it's more efficient, delivering more of the target gene with less exposure to the viral capsids. High's group, for example, is collaborating with researchers from St. Jude Children's Research Hospital, Stanford University, and University College London to test a modified AAV vector that may reduce the immune response in people with hemophilia.

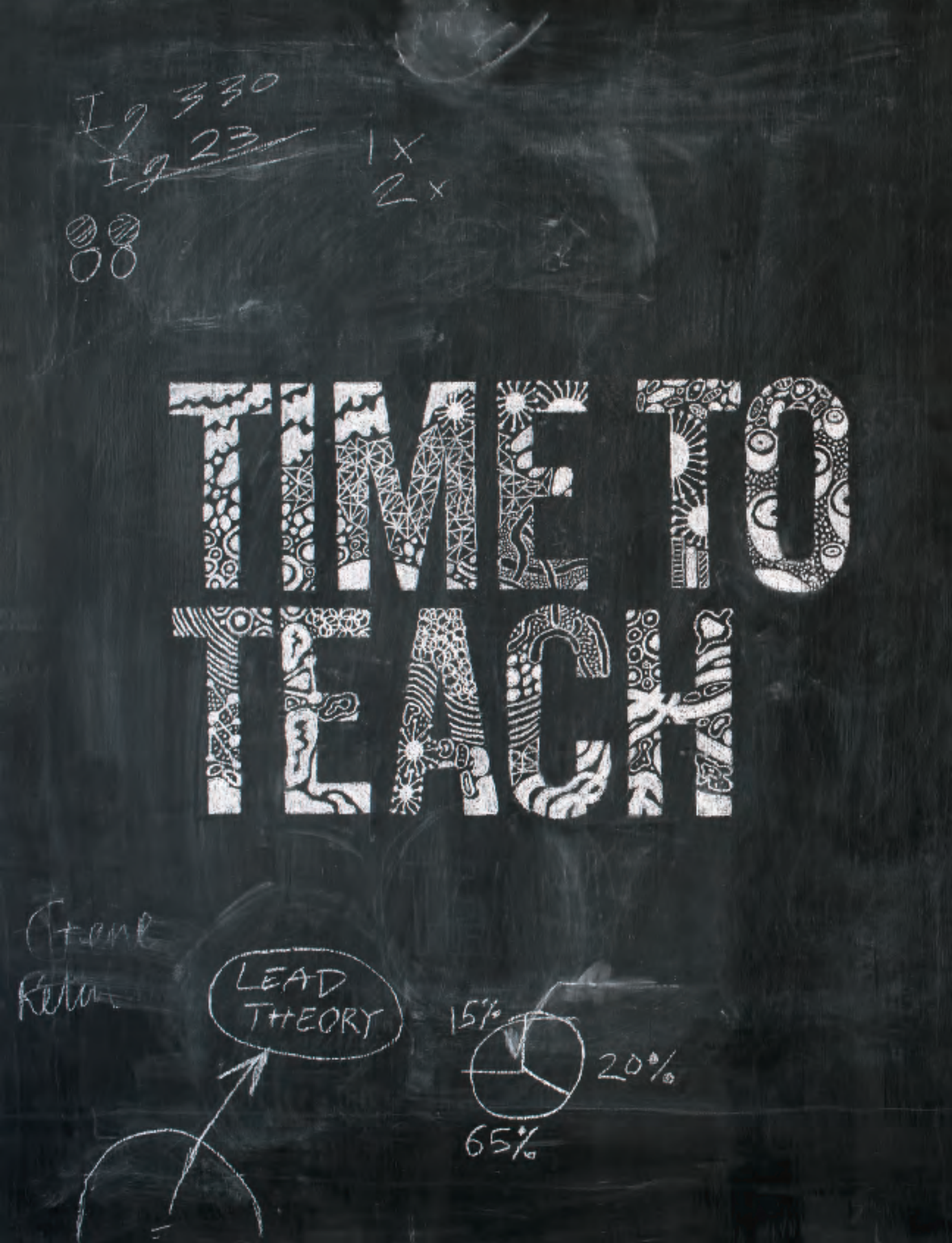
She's also working on a different approach in which, rather than adding a healthy gene, a molecular knife—called a zinc finger nuclease—corrects the broken gene. These fingers have received much attention in the past couple of years, since High's colleagues at Penn began using them to alter an immune system gene ex vivo in blood cells of patients with HIV. In a study of mice with hemophilia, published June 26, 2011, in *Nature*, High's group reported the first demonstration that zinc fingers can also work their magic inside a living animal.

"Zinc fingers have several advantages over AAVs," High says. Perhaps most notably, they correct genes inside the stretch of the genome where they belong, meaning that normal cellular cues will be able to turn them on and off when necessary.

Still, High says that in the short term, hemophilia patients are more likely to benefit from AAV approaches. "I know how long it is from a mouse study to a clinical trial that works," she says.

(continued on page 48)

High: Universitat Autònoma de Barcelona Bennett: Daniel Burke Photography


TIME TO
TEACH
LEAD
THEORY
15%
20%
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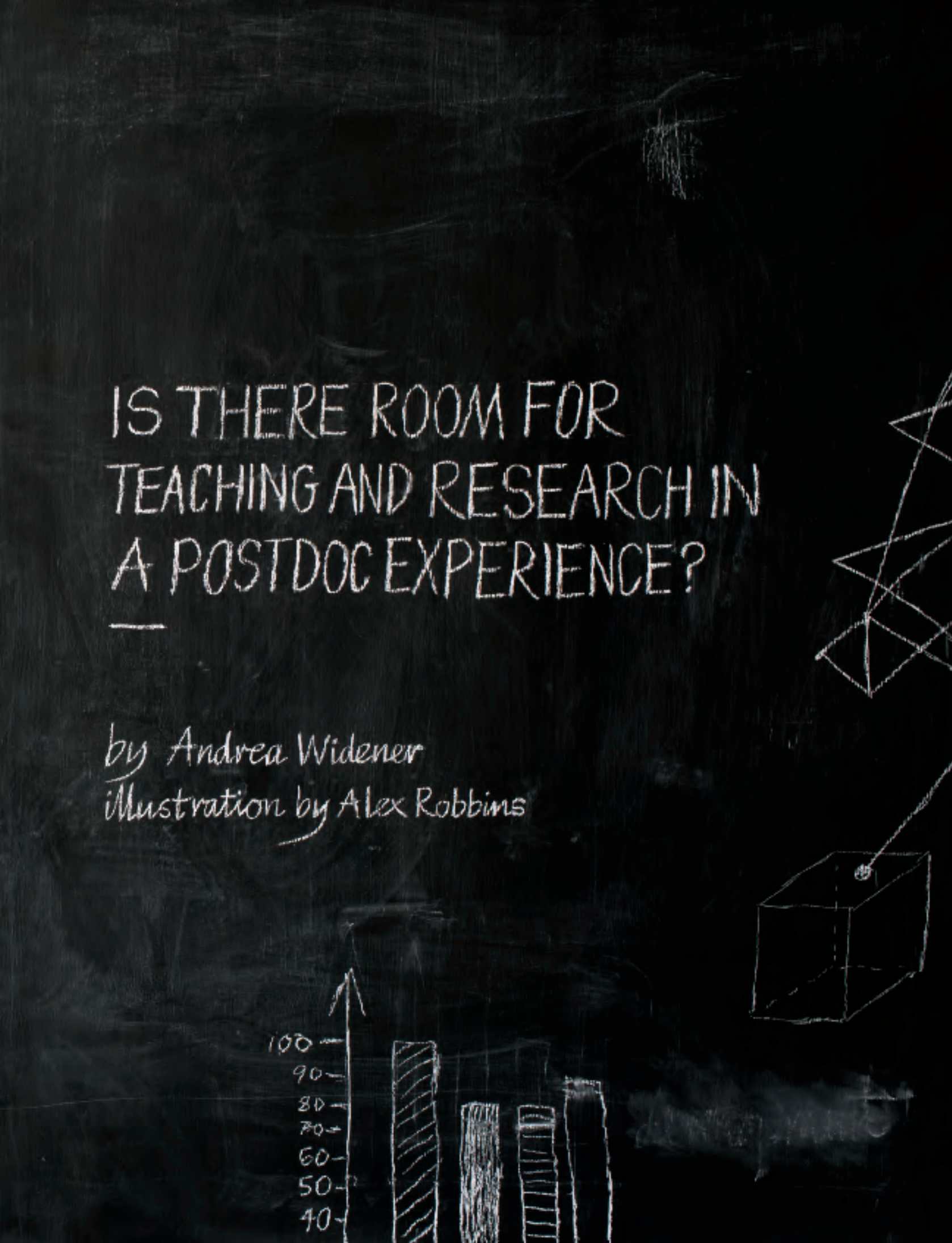
IS THERE ROOM FOR TEACHING AND RESEARCH IN A POSTDOC EXPERIENCE?

by Andrea Widener
illustration by Alex Robbins



As she faced the end of grad school, Karmella Haynes wasn't sure what direction to take. "I couldn't think of a research project that got me really excited," says the graduate of Washington University in St. Louis.

Haynes thought she might want to teach. But, like many modern grad students and postdocs, she didn't have enough experience teaching to know if she liked it—or if she could get a job doing it.

Science educators say teaching experience is vital for postdocs, many of whom are going to be teaching as part of their faculty duties someday. But a lot of schools are struggling with how to prepare graduate students and postdocs to teach, and there is no consensus on the best approach.

"For someone truly interested in becoming an academic scientist, traditional training usually won't offer lessons in pedagogy or how to teach," says David J. Asai, director of HHMI's precollege and undergraduate education programs. "I think teaching experiences for postdocs are a great idea if someone can be patient, get their research solid, and do a postdoc where they can learn to teach and mentor undergraduates in their own research lab."

Few postdocs are getting teaching experience now. Greater than 60 percent have 21 or fewer hours of teaching experience, and almost a third have no experience at all, according to an ongoing longitudinal study of science graduate students from Arizona State University, the University of Washington, and the University of Wisconsin–Madison.

Postdocs who want some teacher training will find a handful of training opportunities, and the numbers are increasing. They range from formal teaching postdocs to programs that expose postdocs to teaching while they work in a traditional research position.

To land a job when the training is over, however, a student must strike a fine balance between research and teaching, and few positions offer that balance. Teaching experience isn't always seen as a plus by hiring institutions, especially research universities. Many faculty discourage graduate students or postdocs from going after teaching experiences because they fear that time away from the lab will mean fewer publications—and more difficulty getting a job.

Haynes's mentor was Sarah Elgin, an HHMI professor who created the Genomics Education Partnership and is intensely involved in developing better ways to teach genomics. Haynes recalls Elgin strongly encouraging her to take a traditional research postdoc at first. But Haynes was persistent, so Elgin pointed her toward a teaching postdoc position at Davidson College in North Carolina.

Haynes thought it might be a chance to find out about life at a liberal arts college while exploring whether she liked teaching. She chose Davidson's postdoc over other teaching opportunities because it provided a mix of education and research—just in case she changed her mind.

"I was very aware of the fact that I was taking an alternative path," Haynes says. "A bad move would have been to jump into the first teaching position I saw. I was really careful to make sure the course of the fellowship left me with my options open."

TEACHING AND RESEARCH MIX

A focus on research appears to be the hallmark of many of the successful teaching postdocs at liberal arts colleges and research universities. Many also include formal education mentoring by current faculty members or seminars on how to best teach so students learn. The duration of teaching postdocs is traditionally shorter than a typical biology research postdoc (two or three years, rather than five or more).

At Davidson, Haynes spent the first year of her two-year postdoc doing research in a new field, synthetic biology, with mentor Malcolm Campbell. Working at a college research lab was completely different from her grad school experience. "It was very small, in a wash-your-own-glassware, stuff-your-own-pipette-box way," she says.

Campbell taught her how to design projects that were easy for undergrads to jump into. "His approach was setting up student-accessible science, rather than bringing the students up to the science," Haynes explains. The lab focused on bacteria, which are easy for students to work with themselves, instead of using animals or complicated equipment. "They were pretty big impact projects but there wasn't this big hurdle of technical difficulty."

"I WAS VERY AWARE OF THE FACT THAT I WAS TAKING AN ALTERNATIVE PATH." —KARMELLA HAYNES

The group published a research paper in the *Journal of Biological Engineering* describing how they engineered the bacterium *Escherichia coli* to solve a mathematical problem. The publication landed Haynes on National Public Radio's *Science Friday*. "It was just really cool how this paper with undergraduates—not coming from a big, powerful research university—got us a lot of attention," she says. The research also allowed Haynes to attend an international synthetic biology conference—her first professional trip overseas—and meet some prominent scientists in the field.

In her second year at Davidson, Haynes focused on teaching. She redesigned a bioinformatics course to overcome its intimidating reputation among students. They were no longer left on their own to navigate databases and new software; instead, she walked students through the complex material in class—a method she affectionately calls "synchronized swimming exercises"—before making them go solo. She also taught an introductory biology course that had even nonmajors doing polymerase chain reaction and biochemistry.

But the very experience she thought would cement her desire to teach instead drew her back to research. She decided to follow her two-year postdoc with a traditional research postdoc in synthetic biology at Harvard University.

"When I immersed myself in teaching there were some things I missed, like being able to mentor grad students and postdocs," Haynes says. "So I wanted to make sure I was competitive for a small liberal arts college job or a research university job."

THE COLLEGE MYTH

Haynes made a wise choice. Schools at all levels—liberal arts colleges, regional public universities, and major research institutions—look first at research, says Jo Handelsman, an HHMI professor and national education leader who runs a science education training program for graduate students and postdocs at Yale University.

"If people want to go into academic positions, a pure teaching postdoc can be fatal," Handelsman explains. "There is a myth out there that you don't need a research postdoc if you are going to a predominantly undergraduate institution, but many of them expect a strong research program."

Chris Himes learned that lesson the hard way.

As a graduate student at the University of Washington, Himes sought out teaching opportunities and eventually won his university's teaching award for co-developing a course that teaches study skills to students from groups traditionally underrepresented in the sciences. When it came time to graduate, Himes had an offer for a traditional research postdoc, but he decided to take a two-year teaching postdoc position at Williams College in rural western Massachusetts instead. "I wanted to see how

Haynes: Jared Leeds Himes: Jen Judge

KARMELLA HAYNES AND CHRIS HIMES ENJOYED FORMAL TEACHING POSTDOCS. BOTH, HOWEVER, WENT ON TO A SECOND POSTDOC TO GET THE RESEARCH EXPERIENCE THEY THEY'D NEED TO GET A GOOD FACULTY POSITION.

research is done at a college, see how teaching is done, and learn what a liberal arts college is like."

The two-year postdoc was set up to include both research and hands-on teaching experience, but because of his interests—and the shock of being in such a different environment, with so few colleagues at his level with similar scientific interests—he did more teaching than research. He taught in a whole range of settings: labs, seminars, and large lecture courses.

Himes had a great experience at Williams and learned a lot about teaching. He may even want to work at a liberal arts college someday. But when he looked for a job after the first year of his postdoc, he didn't get a single offer. Williams had an open position in his area; he applied but didn't even get an interview. "That was an eye opener for me," Himes says. "Here I am doing the work at a liberal arts college that I would be expected to do later, but I wasn't considered for the job."

Wendy Raymond, who oversaw the postdoc program at Williams, says the school doesn't emphasize teaching experience when hiring faculty. Any postdoc with only two years of experience would be in the same boat as Himes, she says. "We wouldn't hire a teaching postdoc for a faculty position without a strong research record," she says.

Himes doesn't regret going to Williams, but he does wish he had had different priorities. "My advice: even if you are going to do a teaching postdoc, focus on research and take the teaching experience as a plus," says Himes, who is now in a second teaching postdoc with a stronger emphasis on research. "At the end of the day, it is the publication record that will get you the interview, then the job."

Many in the academic community have a negative view of teaching postdocs and other teaching positions for newly minted Ph.D.s. Rather than helping postdocs become better teachers or get better jobs, they think schools just use them to fill teaching slots. "All too often teaching postdocs are primarily … to teach a class or two to relieve a faculty member from his or her teaching duties," says Chris Craney, an Occidental College chemistry professor. "We didn't want to do that."

Occidental has had a teaching postdoc in the sciences for almost 20 years. When the college redesigned the program in 2004, the focus was on a postdoc's future. "We thought, what would this postdoc have to demonstrate to make them a top candidate at a place like Oxy?" explains Craney, who led the program through the changes.

The school settled on a two-year postdoc for a single Ph.D. graduate that focuses primarily on developing the capacity to combine teaching and research. Both a teaching mentor and a research mentor, or one person filling both roles, commit to guiding the postdoc in everything from balancing teaching and research to college politics.

The trainee spends the first year working in the lab, choosing a research project and learning how to create a research program that can work for undergraduates. In a twist from other teaching postdocs, no classes are directly assigned to Oxy's postdocs. Instead, they coteach courses with their teaching mentor during the second year, while continuing to do research.

Craney and Eileen Spain, who runs the program now, say this model of teaching and research works, and the proof is in the jobs that have come later. Their postdocs, eight in all, have landed the jobs they wanted, including tenure track positions at places like the College of Charleston, Mount Holyoke College, Loyola Marymount University, even Occidental itself.

For those seeking a job at a liberal arts college, "the game has changed from 20 years ago," Spain says. "The bar is higher, the expectations are higher. They need to come to the table with a robust plan for how they can do their research with undergraduates and a clear understanding of what it is like to be at a liberal arts college."

Like Occidental, schools that offer teaching postdocs need to keep those larger goals in mind. "It is a big responsibility," Asai says. "It's not, let's hire a teaching postdoc so that my workload goes down. In fact, when done right it will likely increase your workload because you have the added responsibility of mentoring the teaching postdoc."

POSTDOCS NEED TO FOCUS ON RESEARCH FIRST, TEACHING SECOND, SAYS JO HANDELSMAN (LEFT). BUT THEY DO NEED TO LEARN HOW TO TEACH, SAYS DIANE EBERT-MAY, AND THE EARLIER THE BETTER.

Handelsman: James Kegley Ebert-May: Peter Baker

TEACHING ON THE SIDE

While not going as far as a formal teaching postdoc, some programs help traditional research postdocs at major colleges and universities get teaching experience.

The largest is the federally funded Institutional Research and Academic Career Development Awards (IRACDA), which

> **"THE MIXED TEACHING AND RESEARCH POSTDOC IS THE IDEAL FOR THE GREATEST DEPTH OF ACADEMIC JOBS... THEY ARE GETTING SUPERVISORY EXPERIENCE, THEY ARE GETTING MULTI-TASKING EXPERIENCE."** —JO HANDELSMAN

support traditional postdocs at research-intensive universities who also teach at nearby predominantly minority institutions. The awards currently fund around 180 three-year postdocs at 17 research universities across the country. In addition to their research positions, the postdocs teach classes with help from mentors and get formal instruction in the science of teaching and learning.

Clifton Poodry, director of the division of minority opportunities in research at the National Institute of General Medical Sciences, designed the program in 1997 when he saw a golden opportunity: postdocs told him they wanted teaching experience and minority-serving institutions expressed the need for more research-active faculty to help update their courses. The trainees spend 75 percent of their time on research and 25 percent on career development, including teaching, Poodry explains.

"Initially there was real concern that this would be a burden on postdocs. How could they be competitive if they are teaching a quarter of the time?" Poodry remembers. Assessment of the program showed that the postdocs (500 to date) do as well or better than their peers and publish as much as or more than their peers. They have gotten jobs at research universities, liberal arts colleges, minority-serving institutions, and industry, says Shiva Singh, who currently directs IRACDA. "For people who believe data, the idea that teaching experiences are hurting these postdocs should be dispelled," Poodry says.

When Himes finished his postdoc at Williams and didn't get a job, he started an IRACDA postdoc at the University of New Mexico in Albuquerque. He says the structured split of research and teaching has been a good fit. He also values the formal teacher training seminars—his mentorship at Williams was more freeform—and his interactions with other postdocs who face the same challenges and concerns.

Even in his first year, "the goal of the program is clear," Himes says. "They want us to get this teacher training but they also recognize that the primary goal of this postdoc is research."

Several other programs that offer teaching as a supplement to research postdocs have the same approach. The University of Wisconsin and Emory, Stony Brook, and Yale Universities have programs that provide postdocs and grad students interested in teaching with formal courses, mentored teaching opportunities, or both. "Some of the students say getting a break 10 hours a week actually makes them more excited to go back to their research," says Pat Marsteller, who runs a program at Emory. "And they learn how to get the work done for both things—research and teaching—which they will have to do as faculty."

Diane Ebert-May from Michigan State University runs a program recently funded by the National Science Foundation called FIRST IV that is available to postdocs in biology from any university. The idea for the program grew out of Faculty Institutes for Reforming Science Teaching (FIRST), which showed that the longer faculty teach, the less likely they are to adopt student-centered teaching techniques. This prompted her to target future faculty for the FIRST IV program to help them learn how to teach from the get-go.

The two-year program began in the summer of 2009 when the first 100 postdocs were selected for intensive training. The postdocs then went back to their home institutions to use what they learned to teach or coteach a course. The following summer, they came back together to share what they learned in the classroom, review videos of their teaching, and revise their courses. "We confirmed that learning how to teach is better at the outset of a career," says Ebert-May, whose second cohort of FIRST IV postdocs began training this summer.

Around 25 percent of the first cohort have finished their postdoc and moved into jobs, and Ebert-May thinks their participation in FIRST IV gave them a competitive edge. For the most part, they have been able to land the types of jobs they want at the types of institutions they are interested in. Those who have faculty jobs now "are becoming change agents in their departments and are influencing their peers' approaches to teaching."

The biggest challenge for someone who wants to apply to FIRST IV and many other university teaching programs is getting their lab head's permission, which is required.

But she is optimistic that scientists' attitudes toward teaching and learning are changing. Most applicants don't have a problem getting their lab heads to sign off, and she thinks that it is important for faculty mentors to support postdocs who want to develop not only as researchers but also as teachers.

ADVICE FOR THE FUTURE

Emory's Marsteller hopes that awareness will lead to expanded teaching opportunities for postdocs. "I think it is unconscionable for universities to not prepare people for the jobs that they want to do," Marstellar says. "We are way past the time where we should be thinking that we can just throw people into a classroom if they can give a good lecture."

More fellowships that allow teaching or other professional development as part of a postdoc would better train these students to balance the mix of demands they will face as faculty members, says Handelsman at Yale. "We as a scientific community need to be thinking about what the goals for postdocs are and what the opportunities should be, " she says. "The mixed teaching

(continued on page 48)

Let's Get Small

Janelia researchers are working their way up from simple to more complex organisms to measure brain activity.

by Helen Fields | photo illustration by Fredrik Broden

To Tim Harris, understanding the brain is like understanding a building—a really big building—from the vantage point of the sidewalk. "The brain is the Empire State Building, and it's opaque. You're standing there looking at the outside and wondering: is the hot water faucet on the third sink of the 65th-floor restroom on the left or the right?"

This is the situation neuroscientists find themselves in, Harris says. They can see your head, they can see you sensing your environment and doing things, but they have only the murkiest sense of your brain's inner workings. Harris, a physicist at HHMI's Janelia Farm Research Campus in Ashburn, Virginia, develops tools neuroscientists can use to measure the brain's activity, to give them a quantitative view inside the elaborate structure of the brain.

Harris spent the early part of his career at Bell Labs, where he developed optical methods for studying semiconductors. Later, at Helicos Biosciences and elsewhere, he became interested in biological measurements that generate huge amounts of data. He sees neuroscience as one big measurement problem. All science depends on good measurements. But the unbelievably complex brain makes measuring particularly challenging. The human brain has more than 80 billion neurons, and each neuron can have 10,000 connections to other neurons. There's no way to measure the whole thing at once.

Taking it apart, however, isn't the answer. The brain is a live, working system; cut out a piece and you're left with a blob of goo. Then there's the problem of the unyielding skull. Cutting a hole in it opens a window to the electrical signals that carry information but offers only a limited view: "If I punch a hole in a wall and look through the hole, I can see many things. I'm not sure what fraction of them are engaged in my problem and what fraction are not relevant to my problem," Harris says.

To study the brain, he adds, "the question is, where did the electricity go and when did it go? The essence of all neuroscience is summed up in that one thing." Since it's impossible to work out the entire human brain at once, Harris and the other instrument experts at Janelia help neuroscientists figure out what they can measure and how to do it. They're getting at the brain by studying simpler animals, like nematodes and fruit flies, with tools that can measure electricity either directly, with an electrode, or indirectly, with proteins that light up when an electrical pulse goes by.

Start Simple

One way to understand a behemoth like the Empire State Building, Harris says, is to first figure out the workings of a one-room, mud-brick hut. In neuroscience, that's the nematode *Caenorhabditis elegans*. The tiny, see-through worm has 302 neurons—much easier to study than a human brain. Rex Kerr, a fellow at Janelia Farm, is trying to understand how worms do what they do. And one of the tools he's using to measure the worm's brain was developed at Janelia by group leader Loren Looger's team: GCaMP3, a protein that lights up in the presence of calcium and is now used in labs throughout the world.

Neurons make their electrical impulses by moving ions around. One of the main ions is calcium. GCaMP3 is a kind of protein known as a genetically encoded calcium indicator, or GECI. The cell is engineered to express GCaMP, so when a blue light is shined on it, the GCaMP lights up—giving off green light—when it detects calcium. These proteins let neuroscientists see electricity in the brain, with the help of a microscope.

"The challenge here is that we have neurons in three-dimensional space," Kerr says. A worm's brain is tiny and clear, but it's still 3-D, with cells stacked on top of each other and intertwined. With instrument design experts at Janelia, Kerr developed a microscope that can image the whole brain. A laser sweeps through the brain over and over, lighting it in sheets from the side. As the laser beam touches each level, it hits the GCaMP3 proteins and they fluoresce, sending light to the waiting microscope to record which neurons are active.

Kerr can measure neuron activity in live worms while they are sensing the environment. An individual worm is placed under the microscope lens and herded into a wedge-shaped chute like a sheep waiting for a vaccination. A researcher uses a setup of syringes to squirt chemicals past it—and then watches to see how neurons that have been engineered to make GCaMP3 react to, for example, a scent that the nematode associates with food.

For now, the worm has to be stuck in a chute to line up its brain just so with the laser and microscope lens. But Kerr's dream is to be able to take a dish of free-swimming worms, "and tell the scope, 'Follow that worm! Tell me what it's thinking wherever it goes.' Or tell me what that small subset of neurons is doing wherever it goes." He's working on a system to do this—it involves putting the dish on a platform that tracks the worm's movement and moves the plate so the worm's head stays centered under the lens. He already has a system that can track worms as they squirm around under a microscope (see Web Extra, "Follow that Worm").

Kerr thinks it might be possible to learn how a worm does what it does in the next decade or so. And those lessons could be applied to understanding more complicated animals.

Moving on Up

It's still just a worm, but Tim Harris says that's a good start. "Learning how to build a one-story, mud building is a pretty good idea," he says. "Then people think, 'ok, so, mud is never going to get us to the Empire State Building. We've got to learn how to build using bricks and do plumbing and all that jazz.' So that's now another measurement problem that's even harder."

A fruit fly brain is a lot easier to study and less complex than a human brain, but more complicated than a worm brain. When dealing with a lot more neurons, you want more measurements. It's possible to buy a probe from a supply company with many tiny wires on the end. Ease it into the brain and the tip of each wire records the electrical impulses around it. The probe can record data for many neurons at once, Harris says. "But, you're still poking a stick into a brain. You've probably caused some damage. We'd rather have a magic microscope that could see through the brain and measure the electricity, but we don't know how to make that."

Instead, he's making better probes. Along with fruit fly researcher Vivek Jayaraman, Harris and Mladen Barbic in his group have developed smaller, skinnier probes for fly brains. Because they're 10 times narrower than commercial probes, they destroy less tissue on the way in, and the tips of the wires are tiny, suited to flies' small neurons.

Like Kerr, Jayaraman wants to measure neuron activity in flies living in a sort of virtual reality arena. An individual fruit fly is glued by its head to a bracket and then allowed to fly or to walk on a ball, like a treadmill. Meanwhile, the researchers display moving patterns on a U-shaped bank of light-emitting diodes designed by Janelia group leader Michael Reiser. The fly sees and reacts to those patterns, trying to walk or fly toward a fixed line or fly straight when it seems the world is moving to the left.

Crucially, the top of the fly's head is open and bathed in saline under a microscope; a researcher removes a smidgen of the fly's cuticle, and nudges a probe into the working brain. Harris's improved probes should help Jayaraman get better measurements from neurons and understand more about how the brain makes decisions.

Kerr: James Kegley Harris: Paul Fetters

REX KERR (LEFT) CAN MEASURE NEURON ACTIVITY IN WORMS AS THEY SENSE CHEMICALS IN THEIR ENVIRONMENT. TIM HARRIS SAYS WORMS AND FRUIT FLIES ARE A GOOD START FOR EVENTUALLY ANSWERING QUESTIONS ABOUT THE BRAINS OF LARGER ANIMALS.

Illuminating Windows

The next step on the way up to the Empire State Building, Harris says, is the mouse. "The mouse brain is even bigger, with even more neurons. So you have to study smaller parts of it to understand what's going on."

Karel Svoboda, a group leader at Janelia Farm, studies mouse brains. His team builds a tiny glass window into each animal's head. This doesn't seem to bother the mice, and the researchers can follow one mouse for months as its brain changes to accommodate its new knowledge.

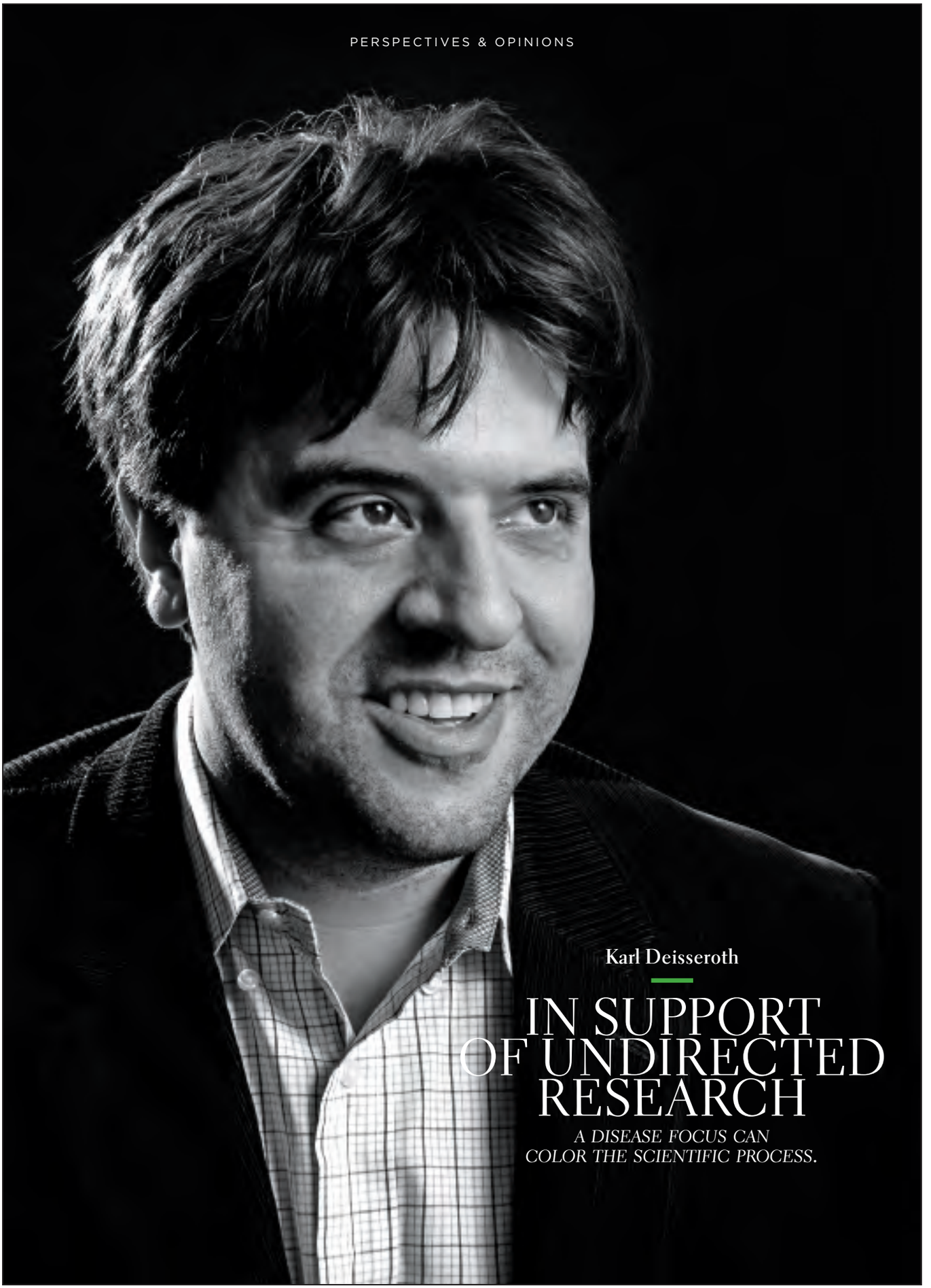
He uses GCaMP3 and other tools to measure electrical activity in mouse brains. But he says the tools available to do neuroscience today still aren't good enough. "In brain research, we make up a lot of stories based on incomplete information," Svoboda says. "We're still looking at large populations of neurons, but we have only probed a small part of the brain. In many ways we're still very much limited by measurements."

As part of the GECI project at Janelia, Svoboda, Jayaraman, and Kerr are working with protein engineer Looger to develop improved versions of GCaMP3. The new proteins should be better at binding calcium, so they will respond when there's less calcium. They hope newer versions will also light up sooner after calcium rushes into the cell. And while the current version can impair cells when it builds up, the next proteins may do less damage.

"The major discoveries of neuroscience in the modern era correlate directly with advances in measurement technology," Svoboda says. Around the turn of the 20th century, Spanish physiologist Santiago Ramón y Cajal perfected a technique for looking at slices of brains and determined that brains were made of cells. Neuroscientists figured out some basics about how the visual cortex works because they invented a technique for recording electrical signals from cells.

This work continues at Janelia Farm, as its neuroscientists keep working to understand the brain. Harris thinks neuroscientists won't understand the human brain for a thousand years, at least; but with new tools, they can keep chipping away at the problem—and make a little bit more sense of what goes on inside our heads. ■

WEB EXTRA: To learn how scientists quantify worm behavior and study salamanders at dinner, visit www.hhmi.org/bulletin/aug2011.



Karl Deisseroth

IN SUPPORT OF UNDIRECTED RESEARCH

A DISEASE FOCUS CAN COLOR THE SCIENTIFIC PROCESS.

Ramin Rahimian

Karl Deisseroth surprised his neuroscience colleagues at a February 2011 panel discussion by defending the legitimacy of doing science for its own sake rather than being motivated solely by the need for cures. In recalling that moment, the HHMI early career scientist at Stanford University—a practicing psychiatrist, neuroscientist, and bioengineer—urges public and private funders to diversify their portfolios when they invest in science and biomedicine.

At that AAAS symposium in Washington, D.C., panelists were invited to discuss neuroscience research. After we presented our work, the moderator, Story Landis, head of the National Institute of Neurological Disorders and Stroke, observed that every speaker had tried to link their work to a brain disease. She asked, was this necessary?

That was a provocative question. Do we neuroscientists always have to justify what we do in a disease context, or can we make a sufficiently compelling argument for the intrinsic excitement of doing biology?

As the only practicing physician on the panel, I was expected to advocate for tying research to disease, but I took the opposite viewpoint. I argued that we must support work that is not related to disease models and value completely undirected research with no implications for health.

That answer may seem surprising, because I still practice psychiatry and have always had a translational motivation. In the 1990s, I went through an M.D./Ph.D. program at Stanford and became fascinated by psychiatry. The patients were suffering severely, and I felt a need to develop methods to understand their diseases. My psychiatry colleagues were brilliant, thoughtful, and caring but lacked tools to probe the brain with precision, and our interventions often lacked specificity. So when I set up my lab in July 2004, I wanted to create targeted approaches for understanding brain disease, which led to my development of optogenetics.

In optogenetics, we take genes encoding light-responsive proteins from microbes and introduce them into neurons, even within freely moving mammals. Using a variety of proteins, we have shown that we can stimulate or inhibit neurons with millisecond-precision flashes of light. By switching specific populations of neurons in the brain on or off to define what they do, we've obtained insights into neural circuit function relevant to Parkinson's disease, anxiety, substance abuse, depression, narcolepsy, and autism.

But the roots of the field extend to 1971 when the first light-responsive microbial opsin protein, bacteriorhodopsin, was identified. Scientists studying microbes for their own sake characterized more opsins in 1977 and 2002. They did not give a thought to neuropsychiatric disease; attempts to link their work with psychiatry would have been laughed at. These researchers were simply studying an elegant biological system. No disease-driven donor or agency would have funded them.

Yet we now stand on their shoulders. Based on that history, I offer a challenge. Let's make the explicit absence of a potential disease justification—a health relevance of zero—a priority when evaluating scientific programs supported by funding agencies, even those with a disease mission.

Disruptive, landscape-shifting ideas that enhance our understanding of disease processes will likely come from research with little apparent disease connection. Talented young scientists will always choose problems that illuminate the complexity of the biological world. How an organism turns light into ion flow—now *that* is an interesting question! But if in 1971 a funding agency had called for new ideas to study Parkinson's disease or anxiety, the likelihood of supporting bacteriorhodopsin work would have been zero. It took decades of poking around algae and bacteria for us to understand how light-sensitive channels work, followed by the unlikely step of putting them into neurons.

Donors interested in funding high-impact science should know the optogenetics story. Its lesson is that we don't know enough to guide research fully and should instead seek to understand the complexity of the natural world.

Scientists constantly think about how to fund their research, and many funding agencies favor a clinical justification. Nobody wants to criticize those agencies, because funders have their own reasonable constraints. Making a disease-related justification has become almost an instinctive part of science culture, particularly in the United States.

As it becomes universal, students come to see this disease-relevance aspect as essential to the scientific process, and the resulting value judgments color the scientific process and guide national and global priorities. But I have long made it a point to underscore to my students and postdocs the importance of undirected research.

For me the question of basic versus applied research is not a choice. Translational work is essential. But every funding agency—even those with a disease focus—should examine its portfolio, and if all is translational or even disease inspired, this should be viewed as a serious weakness. Despite shrinking budgets, undirected basic science funding must be preserved and even encouraged if we are to reach our disease-curing goals.

INTERVIEW BY ELISE LAMAR. *Karl Deisseroth is a member of the Institute of Medicine.*

Q&A

What can you measure today that you never dreamed of being able to quantify when you became a scientist?

In elementary school, children learn to measure things they can see in inches, milliliters, gallons. In biomedical science, measurement has moved into the infinitesimal. Four HHMI scientists weigh in.

—EDITED BY SARAH C.P. WILLIAMS

Vivian Cheung

HHMI INVESTIGATOR
THE CHILDREN'S HOSPITAL OF PHILADELPHIA

"As a child, I loved to name animals. On car rides, instead of tracking license plates, I looked for animals. Was it a chipmunk, ground or flying squirrel? There are over 10 million living species in the world. The child who loved animals became a geneticist just at the right time. We can now "measure" the diversity of living organisms not just by the colors of their fur but also by their DNA sequences! I am enchanted by our ability to measure this phenotypic variation from the anatomical to the molecular level."

Jeff Magee

JANELIA FARM GROUP LEADER

"We are able to measure activity in the smallest parts of neurons in awake brains. With genetically encoded indicators and two-photon microscopes we can measure signals from the tiniest dendrites, spines, and axon terminals while mice perform simple tasks."

Edward De Robertis

HHMI INVESTIGATOR
UNIVERSITY OF CALIFORNIA, LOS ANGELES

"Back in the dark ages, we thought of a cell as a bag of enzymes; if we could purify each one we would understand the whole. I never imagined enzymes zipping in and out of cellular organelles, let alone that we could quantitate this. With green fluorescent protein fusions came a revolution in cell biology: we could measure the movement of proteins. My lab is measuring how a cytoplasmic enzyme called GSK becomes incorporated inside membrane-bounded organelles when the cell is stimulated by a growth factor. Quite amazing."

Michael Laub

HHMI EARLY CAREER SCIENTIST
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

"I would say global measurements of RNA abundance using new deep sequencing methods—i.e., RNA-seq. I remember as an undergrad (which wasn't all that long ago) running and rerunning Northern blots for weeks just to determine the level of a single RNA. Now you can measure every RNA transcript in a genome in about a week. I certainly couldn't have imagined such a technology existed when I was an undergrad. It would have spared me a lot of hassle."

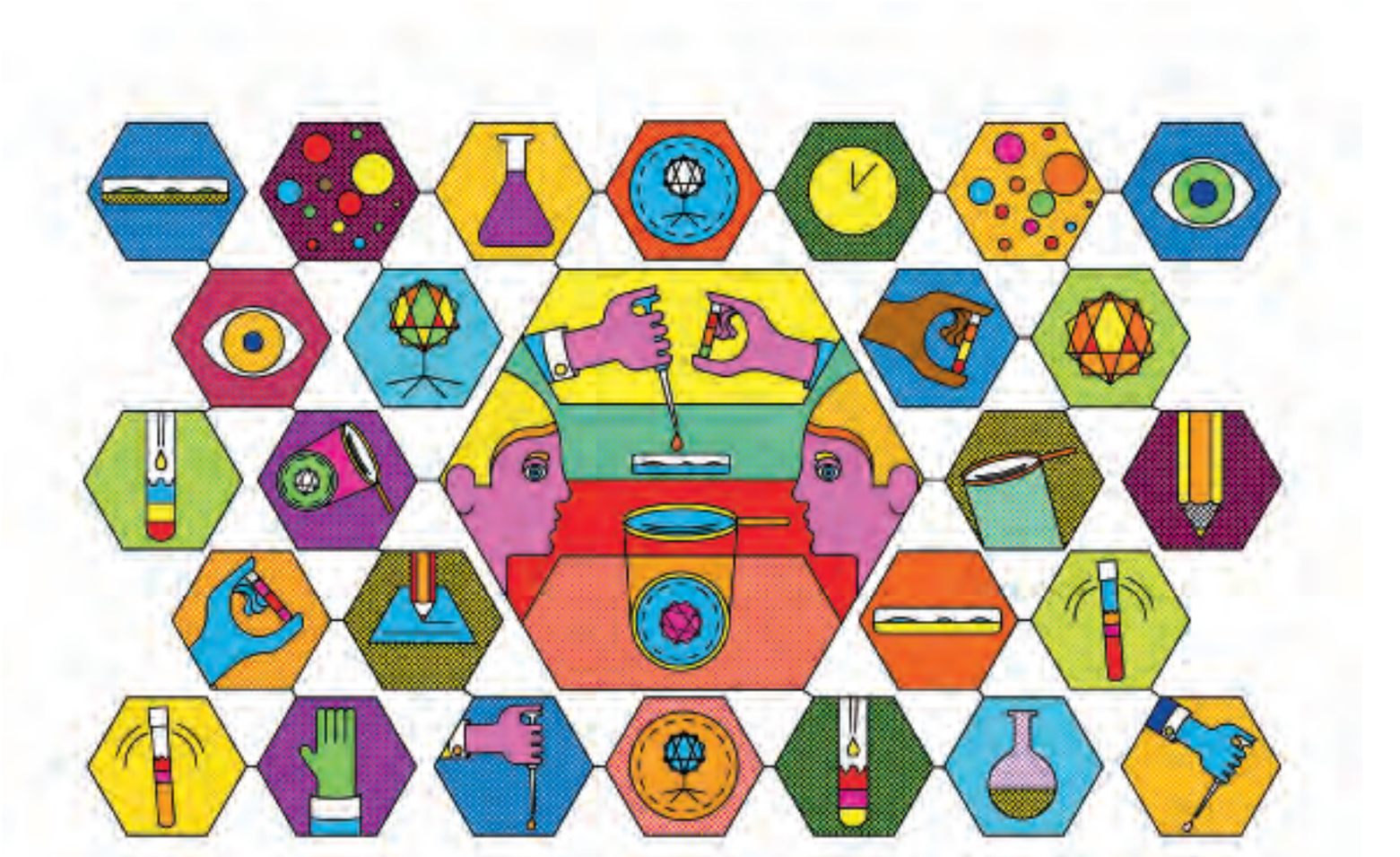
Cheung: Peter Wodarczyk / PR Newswire, ©HHMI Magee: Tom Kleindinst De Robertis: Ana De Robertis Laub: Donna Coveney / MIT

chronicle

There had to be a faster way to silence genes in skin stem cells. Elaine Fuchs managed to do it, carving years off the process, by using a well-timed injection of lentivirus—loaded with an RNA hairpin—into a mouse amniotic sac.

The virus infects the embryo's outer layer of skin cells, which differentiate into the multilayered epidermis and hair follicles. One or more target genes in the resulting skin stem cells are silenced through this method. This image shows the fluorescently labeled viral payload reaching the inner skin cells, confirming specificity of delivery. To read about the method and its many uses, visit www.hhmi.org/bulletin/aug2011.

Fuchs lab



Going Viral

SEA'S HANDS-ON LAB APPROACH TAKES ON LIFE OF ITS OWN.

WHEN BIOLOGY PROFESSOR ANN FINDLEY FIRST CONSIDERED teaching a research course to freshmen at the University of Louisiana at Monroe, she wasn't certain they could meet the challenge. Coming from rural school systems, many of the students had never set foot in a science lab.

"Not only have they stepped up, they've soared and become peer leaders on campus," says Findley. The assumption was that a research-based program would succeed only at elite universities or among honors students. "We've been able to prove that even truly novice students can do research at a very high level and benefit from it in exciting ways we never could have imagined."

Participants from the 10 other colleges and universities that pioneered HHMI's phage course, formally known as the National Genomics Research Initiative, share Findley's enthusiasm. So much so that even though their three years of HHMI support are ending, each of these schools has committed to continuing to offer the course. The introductory bio lab course thrusts freshmen into the world of research instead of parking them in the more traditional bio lab of "experiments" with preordained outcomes.

This first cohort of schools (the fourth cohort starts this fall) is working to offer the course to more freshmen, expand research opportunities to upperclassmen at their own institutions, and spread the program to other colleges.

"We really want to go viral with this idea of early research experiences; it's just so exciting and valuable," says professor Louise Temple of the Integrated Science & Technology Department at James Madison University in Harrisonburg, Virginia. Temple is leading the effort with 17 other institutions—7 of them from the first cohort; 6 from the second—to secure a National Science Foundation grant to create a network that supports the expansion and diversification of the phage course model to include other organisms and other universities and colleges.

Jamie Cullen

The phage course is a relatively simple concept based on work by HHMI professor Graham Hatfull at the University of Pittsburgh. Students isolate novel viruses that infect bacteria, called bacteriophages or phages, from soil, and then purify them, isolate their genomic DNA, and send it away for DNA sequencing. When the sequence comes back, the students employ bioinformatics tools to annotate and characterize their new-found phages.

From start to finish, there are no guarantees of success or right answers. Students endure the pitfalls of true research, such as contaminated bacterial plates and inscrutable results, along with the thrill of discovery and eureka moments small and large. "Just because something is effective, doesn't mean that it's always a comfortable experience to go through," says Grant Hartzog, a professor at the University of California, Santa Cruz. "These [students] are getting pushed to think hard in ways that they aren't used to."

And the phage course is effective. As the first initiative of HHMI's Science Education Alliance (SEA), which now encompasses 67 schools, participants have been documenting their experiences: students participating are more likely to continue in science courses and perform significantly better in lecture courses than peers in traditional laboratories, says Tuajuanda Jordan, former director of SEA who was instrumental in getting the program off the ground. Jordan notes, "We are born naturally curious and the SEA course engages that curiosity and really helps students develop higher thinking skills."

The quality of those thinking skills and the significance of the science produced was on full display in the January 27, 2011, issue of the peer-reviewed journal *PLoS One* where 192 coauthors composed of students from the first cohort of SEA schools and from the University of Pittsburgh identified and characterized 18 previously unknown phages. At the time, their work represented a fifth of all bacteriophage genomes characterized.

The ability to adapt the course to best fit the students and curricula of an individual school is part of what makes it so effective at institutions ranging from elite universities to regional colleges, according to Jordan.

While the course has been built around phages that infect *Mycobacterium smegmatis*, a cousin of the bacterium that causes tuberculosis, some schools are switching to different organisms because they are less expensive or easier to work with or represent "uncharted" territory. For example, the University of Mary Washington, in Fredericksburg, Virginia, through a collaboration with the Naval Surface Warfare Center at Dahlgren, will look for phages that infect spore-forming bacillus bacteria—common and easily maintained organisms that could inform the Navy's work on anthrax bacteria.

At the College of William & Mary in Williamsburg, Virginia, the biology department will institute a *Helicobacter pylori* genomics lab course and the environmental science and neuroscience departments will explore the effect of mercury on embryonic development in frogs.

One of the most exciting ways the phage course is evolving takes the effort to upper classmen. The first cohort of schools faced a "problem" when students were eager to continue pursuing questions arising from the phage course work and the schools had nothing to offer them.

"Once you've sequenced and annotated a phage genome, this is just the beginning of discovery," says associate professor Aaron Best of Hope College in Holland, Michigan. The annotation process sheds light on new avenues of exploration that truly engaged students want to pursue. "We had a student at the end of the course throw up her hands and ask if this was *IT*?" laughs William & Mary biology professor Margaret Saha. Like most of the first cohort of schools, Hope and William & Mary are developing courses for upperclassmen designed to explore gene expression patterns in the phages they've annotated.

"People always ask how we afford to offer this experience," Saha says. "It's really not that expensive when you consider what it gives the students and the institution. It's mostly time and it just works so well." ■ –LISA CHIU

2011 HOLIDAY LECTURES ON SCIENCE

BONES, STONES, AND GENES: THE ORIGIN OF MODERN HUMANS

Some 150 years after Charles Darwin proposed that we have a common ancestor with great apes, human evolution remains one of the most debated topics in all of science. In HHMI's 2011 Holiday Lectures on Science, three world experts will delve into millions of years of evidence that scientists use to study human evolution and the fact and fiction of this important topic. ¶ John J. Shea of Stony Brook University will explain how ancient stone tools provide evidence of problem solving. Sarah Tishkoff of the University of Pennsylvania will examine the genetic heritage of modern humans and human evolution. And Timothy D. White of the University of California, Berkeley, will describe the fossil evidence that links modern humans to our earliest relatives. ¶ This year's lecture series—*Bones, Stones, and Genes: The Origin of Modern Humans*—will take place in front of an audience of high school students October 6–7 at HHMI's headquarters in Chevy Chase, Maryland. Sign up now for the live webcast at www.hhmi.org/biointeractive.

Rosenfeld To Lead HHMI Documentary Initiative

MICHAEL ROSENFELD WILL LEAD HHMI'S LEAP INTO DOCUMENTARY filmmaking. The former president of National Geographic Television joined the Institute in July as head of television and film.

HHMI's $60 million documentary film initiative, announced in February, aims to bring high-quality, compelling science features to television. The initiative will extend the Institute's science education outreach to a global TV viewership.

As president of National Geographic Television, Rosenfeld oversaw the production of more than 130 hours of television documentary programming a year, which aired on National Geographic Channel, PBS, and worldwide. Over two decades, he held various supervisory writing and production positions at National Geographic. He has won—or led teams that won—nearly 40 news and documentary Emmy Awards.

"Good science films capture the passion of discovery," Rosenfeld says. "At their best, they give viewers a vicarious sense of what it is like to be a scientist and to be on an adventure. Through film we can help people imagine—in a vivid way—what it would be like to make a discovery themselves."

HHMI has supported television projects, including the public broadcasting series *NOVA scienceNOW* and science reporting on *PBS NewsHour*. But this is its first experience with documentary filmmaking. The HHMI film division's priority will be to tell intriguing science stories that grab the viewer, says Sean Carroll, HHMI's vice president for science education. The films will cover all areas of science, especially biology and medicine, but will go beyond the work of HHMI's own researchers.

HHMI's educational resources group and others will work with the documentary team to repackage the film footage into materials for teachers and students at the high school and college levels.

"My goal will be to find projects that can have an impact on the way people think about science and the world they live in," Rosenfeld says. "We will develop our own ideas but will also look for proposals from broadcasters, producers, and filmmakers who share our excitement about doing great science television."

Rosenfeld is the second Michael Rosenfeld to join HHMI. Michael G. Rosenfeld, known to his friends as Geoff, is an HHMI investigator at University of California, San Diego, who studies transcription and cell signaling. ■

HHMI Teams Up for Open Access Journal

HHMI, THE MAX PLANCK SOCIETY, AND THE WELLCOME TRUST intend to launch an open-access journal for biomedical and life sciences research that breaks the mold set by traditional scientific journals. The three organizations announced the journal in June and the first issue is expected to be published in the summer of 2012. The journal's tenets include a fast review process, online publishing, and an editorial team made up of active scientists.

The plans for the yet-to-be-named journal were developed after a workshop in 2010 at HHMI's Janelia Farm Research Campus attended by a number of leading scientists. The participants concluded that there was a need for a model of academic publishing that better suits the needs of researchers.

"The message from the research community was clear," says HHMI president Robert Tjian. "We are fortunate to have many excellent journals, but there is need for a different, more appropriate, and efficient publishing model."

Editorial decisions for the planned journal will be made by a team of highly regarded, experienced, and practicing scientists who will ensure a transparent peer-review process aimed at limited revision and rapid publication. Accepted articles will be published online along with anonymous reviewers' comments.

"This will be a journal for scientists edited by scientists," says Sir Mark Walport, Director of the Wellcome Trust. "The ethos of the journal will be to avoid asking authors to make extensive modifications or perform endless additional experiments before a paper can be published."

As the journal will exist only in digital form, it offers an opportunity to exploit the potential of new technologies to present data, share content, and directly engage the reader.

Randy Schekman, currently editor of the *Proceedings of the National Academy of Sciences*, has been named founding editor in chief. Schekman is an HHMI investigator and a distinguished cell biologist at the University of California, Berkeley. ■

James Keglev

Plant Science Gets a Boost

IMAGINE WHEAT ENGINEERED TO BE RESISTANT TO DISEASE AND packed with extra, essential nutrients. Now picture a mustard plant that reveals biology's secrets—secrets that pertain to plants and humans—of gene regulation and gene silencing.

These scientific achievements are a reality, thanks in part to the work of 15 researchers who have been chosen to join a new initiative supported by HHMI and the Gordon and Betty Moore Foundation (GBMF). The investment provides much needed funding for research in fundamental plant science.

HHMI and GBMF are supporting this initiative at $75 million total, offering 5-year, potentially renewable grants to the 15 investigators so they have the flexibility to move their research in creative directions. Despite funding constraints that have plagued plant researchers for decades, this group of scientists has made impressive discoveries, opening up new research fields and improving crop engineering. They represent 13 institutions from across the United States and were selected on the basis of individual scientific excellence from a group of 239 applicants.

"We think the creation of our joint program underscores the importance of investing in fundamental plant science and we hope it will encourage others in the United States to make analogous commitments," said HHMI President Robert Tjian. "We are as excited as these scientists are to begin putting their best ideas into action."

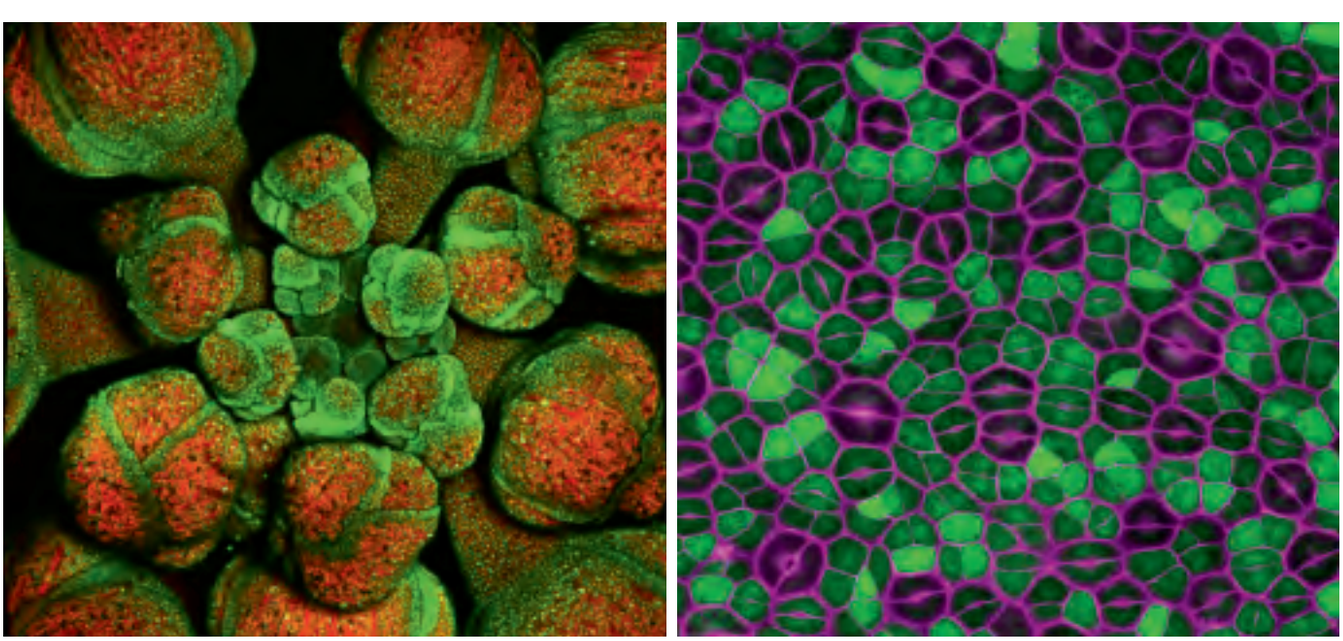
"GBMF and HHMI believe the research will generate high-impact discoveries with implications for a range of intertwined concerns facing society: food production, human health, protection of the environment, and identification of renewable energy resources," says Vicki L. Chandler, chief program officer for science at GBMF.

"People in the developed world have sort of lost touch with how, every day, plants are part of their lives—from food, shelter, clothing, and fuel to the simple beauty of a garden," says Jeff Dangl, of the University of North Carolina at Chapel Hill. His appointment as an HHMI-GBMF investigator will help him recruit smart and creative young scientists to his lab to tackle what he considers the big questions and exciting problems in plant biology. ■

THE HHMI-GBMF INVESTIGATORS

PHILIP BENFEY, PH.D. *Duke University*
DOMINIQUE BERGMANN, PH.D. *Stanford University*
SIMON CHAN, PH.D. *University of California, Davis*
XUEMEI CHEN, PH.D. *University of California, Riverside*
JEFF DANGL, PH.D. *University of North Carolina at Chapel Hill*
XINNIAN DONG, PH.D. *Duke University*
JORGE DUBCOVSKY, PH.D. *University of California, Davis*
JOSEPH ECKER, PH.D. *Salk Institute for Biological Studies*
MARK ESTELLE, PH.D. *University of California, San Diego*
SHENG YANG HE, PH.D. *Michigan State University*
ROBERT MARTIENSSEN, PH.D. *Cold Spring Harbor Laboratory*
ELLIOT MEYEROWITZ, PH.D. *California Institute of Technology*
KRISHNA NIYOGI, PH.D. *University of California, Berkeley*
CRAIG PIKAARD, PH.D. *Indiana University at Bloomington*
KEIKO TORII, PH.D. *University of Washington*

FOR MORE INFORMATION: To learn more about the scientists and their work, visit www.hhmi.org/news/plantscience20110616_list.html.



Left: Adrienne Roeder, PLoS Biology, 8, e1000367 Right: Kylee Peterson / Torii lab

Scientists study pattern and orientation of plant cells, which is often predictable and tied to function. In the mustard plant's flower, the patterns and proportions of cells develop progressively from the center outward (left). Stomata, valve-like structures on the underside of the plant's leaves that regulate exchange of gas and water, are typically spaced at regular intervals. When activity of a genetic transcription factor is elevated, all epidermal cells become stomata (right).

The Buzz on Bee Viruses

TECHNOLOGY DESIGNED FOR HUMAN VIRUSES IS HELPING SOLVE A BEE RIDDLE.

In 2006, bee colonies started failing at a rate never seen before. Entire colonies died. Farmers feared a shortage of bees to pollinate their crops. The cause of this phenomenon, known as colony collapse disorder, remains a mystery despite intense effort. HHMI investigator Joe DeRisi is using his expertise on viruses to tackle the problem.

"Attempts to examine the cause of the bee colony collapses were confounded by the fact that very little was known about viruses in bees, period," says DeRisi.

So DeRisi and his colleagues at the University of California, San Francisco, decided to follow a convoy of semitrailer trucks with 70,000 beehives as it drove around the country during its annual trek to pollinate crops. With the help of experienced commercial beekeepers, bee samples from 20 designated hives were collected each week throughout the year. Using a specially designed microarray that allows rapid screening for viruses and other pathogens of insects, they monitored pathogen incidence at different times of year in different hives.

"We were leveraging a lot of the same skills and technology that we use to look at human medicine and veterinary medicine," says DeRisi, "and now applying that to insects."

By the end of the year, the team had tracked all known bee viruses and identified four more, they reported in *PLoS One* on June 7, 2011. Two in particular stood out. The scientists named them Lake Sinai virus 1 and 2, after a South Dakota lake near where the bees were collected. Surprisingly, Lake Sinai virus 2 was found to be the most abundant pathogen in the bees, reaching levels of greater than 1 billion copies per bee in the winter.

The data collected by the DeRisi lab don't solve the mystery of why bees are dying. But they offer a baseline for scientists who continue to track bee viruses. "This study provides a foundation from which to work," says DeRisi. Now the team can continue following bees and begin correlating viruses with colony collapse to better understand current and emerging threats. It's a step toward keeping bees healthy. ■ –SARAH C.P. WILLIAMS

Understanding the pathogens that normally inhabit beehives provides a baseline to look for the cause of colony collapse disorder.

Mark Bowler / Photo Researchers, Inc.

IN BRIEF

WHEN COPIES DON'T MATCH

For a cell to function properly, it needs to copy DNA—the most basic blueprint of proteins—to RNA strands that encode proteins. It's long been assumed that RNA must code for the protein in exactly the same way as its complementary DNA for this process to work smoothly. Mistakes at any step were always thought to be detrimental—and rare. Now, new research suggests that DNA blueprints aren't always followed to the letter.

"The idea that RNA and protein sequences are nearly identical to the corresponding DNA sequences has not been questioned in the past," says Vivian Cheung, an HHMI investigator who led the study. To investigate this question, Cheung and her colleagues at the University of Pennsylvania School of Medicine analyzed the DNA and RNA sequences from B cells, a form of white blood cell, in 27 individuals.

The team found more than 10,000 differences in base pairs—the letters that make up genes—between the DNA and RNA. The RDDs (RNA-DNA differences) were found in about 40 percent of genes and often led to a change in protein sequence. The researchers repeated the experiment in skin and brain cells of infants and adults to rule out the effect of age and cell type on the phenomenon. They found similar results, they reported May 19, 2011, in *Science* Express.

Known RNA-editing molecules could explain only about half of the RDDs the scientists found. Their next step is to explain how the rest arise, why the cell lets these sequence differences persist, and whether the RDDs in different individuals contribute to variations in disease susceptibility.

HOMING IN ON AUTISM GENES

A team of HHMI researchers has identified new gene mutations linked to cases of autism spectrum disorders (ASDs). The findings suggest that 20 percent of cases of sporadic autism—where neither parent of an affected child has a family history of the disorder—can be explained by spontaneous gene mutations.

ASDs cover a wide range of defects in language, social ability, and movement and vary widely in severity and symptoms, making them hard to study as a group. Scientists at the University of Washington School of Medicine led by HHMI investigator Evan Eichler looked at 20 affected children in their latest study. They compared the genes of the children with those of their parents to find mutations that were unique to the child.

The team turned up 21 spontaneous mutations, 11 of which altered protein sequences. In four children, the researchers pinpointed severe mutations that have been linked to autism, intellectual disability, and epilepsy. The findings, published in the June 2011 issue of *Nature Genetics*, hint that the same mutations can manifest themselves in different ways in different individuals. They support the idea that having more than one mutation can change or worsen symptoms of ASDs.

"The idea that multiple genes are coming together in what's called an oligogenic model of autism is, I think, an exciting but also daunting prospect," says Eichler.

A DELICATE BALANCE PROTECTS AGAINST LEUKEMIA

When it's turned up too high, the cellular Notch signaling pathway causes leukemia. Now, HHMI researchers have found

Memory Cells at the Ready

SPECIAL NEURONS GIVE RODENTS A LEG UP WHEN FACING UNFAMILIAR TERRITORY.

As a rodent navigates an environment, its brain forms a mental map by firing a few select cells in the memory-forming region called the hippocampus. Janelia Farm group leader Albert Lee and colleagues found that these cells, which represent 25–50 percent of the total, are primed to take charge of the next piece of information destined for memory storage.

The cells, known as place cells, are considered analogous to cells in the human brain that store memories of people, places, facts, and events. Since most hippocampal neurons act as place cells in certain environments but remain silent in others, Lee was curious about what determines which cells take charge of new spatial memories. To find out, his group compared the electrical activity inside place cells with that in neighboring silent cells.

For a neuron to fire, inputs from neighboring cells must push its membrane potential (a difference in voltage between the interior and exterior of the cell) above a certain threshold. When Lee measured the electrical activity inside hippocampal cells as a rat explored a new maze, he found that place cells received more excitatory inputs than silent cells, but surprisingly they also had a significantly lower threshold for firing. Even before an animal enters a maze, its future place cells behave differently than others, responding to stimulation with a distinctly different firing pattern.

This memory-forming hippocampal neuron was recorded in a freely moving rat.

These results, published in the April 14, 2011, issue of *Neuron*, suggest there is some predetermination of place cell identity even before a new environment is encountered. "[The brain] has a certain pattern that it wants to have for the next memory that it gets," Lee says. "It doesn't care so much about the particular details of that thing, it just wants to assign it." Since there is evidence that the human hippocampus also associates discrete sets of neurons with specific bits of information, Lee suspects this model of memory formation could help explain how those patterns are formed. ■ –JENNIFER MICHALOWSKI

Doyun Lee and Brenda Shields / Lee lab

IN BRIEF

that when Notch is turned too low, it also encourages a form of leukemia. It's one of the first examples of a pathway that can both cause and suppress disease in a single tissue.

Iannis Aifantis, an HHMI early career scientist at New York University, was looking at Notch's role in the immune system. The protein is already known to have roles in embryonic development, tissue renewal, and cancer. When Aifantis eliminated Notch signaling from blood stem cells, mice developed a form of leukemia called chronic myelomonocytic leukemia (CMML). CMML is a rare but deadly form of leukemia that mainly affects adults over age 65. The average survival time after diagnosis is less than two years.

"This was a big surprise," says Aifantis. "Usually if you delete an oncogene you get no tumor."

When Notch is overactive in blood stem cells, it causes cancer in T cells. CMML, on the other hand, is a cancer of myeloid blood cells. But both are cancers of the blood.

To determine whether Notch has the same effects in human cells as in mice, the researchers sequenced all members of the Notch pathway in human CMML. They found mutations that inactivate the Notch pathway, leading to development of disease, the team reports in the May 12, 2011, issue of *Nature*. The next question: how can researchers coax cells to have perfect levels of Notch?

ANIMAL MODEL OF GLAUCOMA

Until now, researchers have struggled to find the genes and molecules responsible for one of the most severe forms of glaucoma. HHMI researchers have now turned the tables, developing a mouse model of the disease.

Angle-closure glaucoma (ACG) occurs when the cornea and iris of the eye meet at too narrow of an angle, blocking drainage from the eye and allowing fluid to build up. It is responsible for approximately half of the cases of blindness due to glaucoma.

Researchers led by HHMI investigator Simon John at The Jackson Laboratory first observed ACG symptoms in a mouse with an unknown gene mutation. The team then mapped the mutation to a gene that encodes a protease—an enzyme that breaks down other proteins. Patients with ACG often have relatively small eyes and the team found that the ACG gene also causes a human condition characterized by very small eyes known as microphthalmia.

"This gene is going to give us new insight into pathways for understanding these conditions," says John. The results, which appear in the June 2011 issue of *Nature Genetics*, will allow the scientists to study how the disease progresses and to screen affected mice for drugs that help treat the disease.

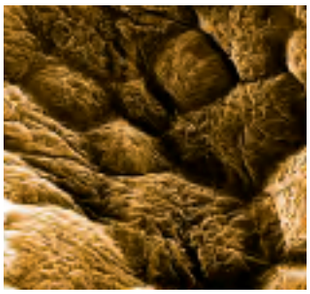
VIRAL TAKEOVER OF DEFENSES

It's not the first time that a virus has been found to hijack a cell's inner workings, but it's the latest example of a viral takeover. HHMI investigator Peter Cresswell and his colleagues at Yale University have discovered how human cytomegalovirus (CMV) uses a cell's own antiviral defenses to enhance infection.

Cresswell's lab first identified the antiviral protein, viperin, in the late 1990s. They found that the immune system switched on the protein in response to infection. But they and other researchers later discovered that CMV can directly turn on viperin.

Leading a Double Life

PROTEINS THAT GUIDE EMBRYO DEVELOPMENT ALSO REPAIR ORGANS.



Developmental signaling proteins appear to play a role in repair of cells lining the bladder.

Lucky for us, the organs in our bodies come with a self-repair kit. Though regularly bombarded by harmful bacteria, more often than not they manage to heal themselves. How this happens has puzzled scientists, but now there may be some answers.

A study led by HHMI investigator Philip Beachy of Stanford University reveals that the Hedgehog and Wnt protein families, well known for regulating embryo development, also contribute to bladder repair in adult mammals.

Beachy and his collaborators exposed adult mice either to a strain of *Escherichia coli* that infects the urinary tract and damages the bladder or to a chemical that harms the organ. The researchers identified stem cells in the lining of the bladder and noticed that in response to either type of injury their proliferation and their levels of the protein Sonic hedgehog increased; Wnt pathway activity also increased in multiple cell types.

When they did the same experiment with mutant mice lacking the Gli1 protein, a component of the Hedgehog pathway, cell replication was delayed and reduced, and the mice's kidneys accumulated tenfold more bacteria than normal. The results indicate that not only is Hedgehog-dependent proliferation required for bladder regeneration, it also prevents microbes from invading other organs.

The researchers observed that Sonic hedgehog protein expression in the bladder lining triggers increased Wnt protein expression in an underlying cell layer, which then stimulates growth of new cells to replace damaged ones. "This may have implications for medical problems that involve the restoration of tissues," says Beachy.

According to Beachy, the results, published April 7, 2011, in *Nature*, suggest that "signaling proteins with important roles in establishing cell pattern during embryo development are redeployed to help restore pattern in adult organs during regeneration."

Beachy wants to find out if these molecules promote tissue repair in other organs and, conversely, if they promote tumor growth when inappropriately activated. "That's an area we'll be exploring in the future, which could provide some insights into how to design better therapies for cancer patients," he says. ■ –JANELLE WEAVER

IN BRIEF

In their latest work, published May 27, 2011, in *Science*, the team shows that CMV not only turns on viperin production, it also sends the protein to the mitochondria of the cell, where it sabotages energy production. The cell can no longer efficiently produce ATP—a molecule that transports chemical energy within cells.

When Cresswell's team created cells that lacked viperin, CMV could no longer infect cells as well. The virus needed viperin to turn down the cell's energy to give it an edge.

NEW MIDDLE MOLECULE IN SCHIZOPHRENIA PATHWAY

When people without schizophrenia take a drug that blocks the action of a specific brain cell receptor—the NMDA receptor—they develop symptoms of the disease: hallucination, disordered thinking, inner voices. The observation led scientists to hypothesize that in schizophrenia, the activity of the NMDA receptor is dialed down. New research by HHMI international research scholar Michael Salter is now refining that explanation.

Salter and his colleagues at the Hospital for Sick Children in Toronto wanted to know the effects of two proteins previously implicated in schizophrenia—neuregulin and ErbB4—on the NMDA receptor. They thought signaling by these molecules could account for low NMDA activity in the disease.

But Salter's team instead found that a molecule called Src is to blame. Neuregulin and ErbB4 turn down Src activity, which in turn squelches NMDA receptor activity. They reported their results in the April 2011 issue of *Nature Medicine*.

The relationship between these molecules held true in two different regions of the brain, the hippocampus and the prefrontal cortex, and the researchers plan next to investigate whether it occurs in other regions.

AORTIC ANEURYSMS IN MARFAN SYNDROME EXPLAINED

Mouse experiments using a drug called losartan have suggested that it decreases aortic aneurysms in cases of Marfan syndrome, a connective tissue disorder that can lead to heart problems. But the exact mechanism of aortic aneurysm in Marfan patients—and how losartan alters it—wasn't clear. Now, research by HHMI investigator Harry C. Dietz, of the Johns Hopkins University School of Medicine, is spelling out the connection.

It was already known that a molecule called TGF-beta drives aneurysm progression in a mouse model of Marfan syndrome. Losartan blocks TGF-beta signaling. But TGF-beta works through a handful of different signaling pathways, and researchers didn't know which one was linked to aneurysms.

Dietz and his colleagues pinpointed two signaling molecules, called ERK and JNK, that rely on TGF-beta. When the scientists blocked either molecule in a mouse model of Marfan syndrome, they reported in the April 15, 2011, issue of *Science*, the abnormal aortic growth that causes aneurysms was suppressed. The new finding, Dietz says, offers new, and more specific, targets for drugs to halt aneurysms.

"I really think we're going to be able to make more informed choices regarding which medication to use now [to protect against aortic aneurysm], and which medications to test in the future," he says.

David M. Phillips / Photo Researchers, Inc.

Q A

Can stimulants exercise your heart and make it stronger, just like lifting weights will make your body stronger?

Asked by Ryan, a high school student from Massachusetts

The best place to start answering this question is to discuss what makes a strong heart. A useful measure of the heart's efficiency is cardiac output: how much blood the heart can deliver to the body with each heartbeat. At rest, about 5 liters of blood are pushed out of the heart every minute. During aerobic exercise like running and swimming, the heart can increase its cardiac output to 25 liters per minute to deliver more oxygenated blood to the body.

Exercise can certainly make your heart stronger, but it also optimizes the way the heart functions. The heart is a specialized type of contractile muscle, best visualized as sets of muscles encircling a series of chambers; contraction of the left ventricle of the heart squeezes blood into the circulation like toothpaste from a tube. The volume of blood that can be delivered to the circulation per beat depends primarily on the volume of blood that fills the chamber while the heart is relaxed and the fraction of blood that is ejected during contraction. The heart can optimize these two parameters by maximizing contraction to eject more blood from the ventricle, followed by rapid relaxation to allow the ventricle to refill with oxygen-rich blood. With consistent exercise the heart becomes a more efficient pump for greater cardiac output per minute.

What about heart rate and conditioning? Long-term aerobic training in fact slightly decreases heart rate, as a rapid heartbeat may not give the left ventricle enough time to fill with an optimal volume of blood. But increasing the volume of blood the heart pumps, even without changing heart rate, can increase cardiac output by up to 40 percent, clearly reflecting a stronger and more efficient heart.

Stimulants such as amphetamine and cocaine increase heart rate by increasing the stimulation of the heart through neurons from the brain, which also occurs during exercise and even in anticipation of exercising. This so-called sympathetic stimulation increases both the heart's output volume and its rate and therefore increases cardiac output. Long-term use of stimulants, however, may lead the heart to become less sensitive to the signals of sympathetic stimulation, possibly making it more difficult to initiate an appropriate response to true exercise. At high doses, some stimulants can increase heart rate to such a degree that they increase the risk for heart attacks and seizures.

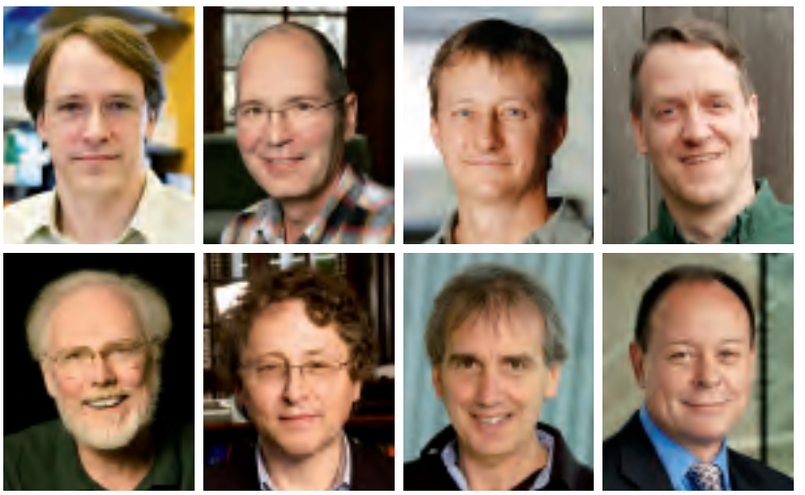
With the exception of judicious use for treating conditions like attention deficit hyperactivity disorder (ADHD), the potential adverse effects of using stimulants exceed their short-term benefit. Cardiologists use drugs that modify the heart's contractile force to help individuals whose hearts are intrinsically failing. But the best conditioning for the heart will always be aerobic exercise, which enables the heart to adapt over time in the context of the changing physiology of the entire body—no drug will likely ever be able to precisely mimic that.

ANSWER RESEARCHED BY JEFFREY T. EHMSEN, *an M.D./Ph.D. student in neuroscience at the Johns Hopkins University School of Medicine.*

Science is all about asking questions, exploring the problems that confound or intrigue us. But answers can't always be found in a classroom or textbook. At HHMI's *Ask a Scientist* website, working scientists tackle your tough questions about human biology, diseases, evolution, animals, and genetics. Visit www.hhmi.org/askascientist to browse an archive of questions and answers, find helpful Web links, or toss your question into the mix. What's been puzzling you lately?

SPOTLIGHT

Eight Elected to National Academy of Sciences



TOP ROW: BARTEL, DIETZ, JACOBSEN, KINGSLEY
BOTTOM ROW: McCAMMON, NUSSENZWEIG, KORNBLIHTT, PARADA

Six HHMI investigators, one international research scholar, and one member of HHMI's scientific review board have been elected to the National Academy of Sciences. The investigators are **David P. Bartel**, Massachusetts Institute of Technology; **Harry C. Dietz**, The Johns Hopkins University School of Medicine; **Steven E. Jacobsen**, University of California, Los Angeles; **David M. Kingsley**, Stanford University School of Medicine; **J. Andrew McCammon**, University of California, San Diego; and **Michel C. Nussenzweig**, The Rockefeller University. The international research scholar is **Alberto R. Kornblihtt**, University of Buenos Aires. The board member is **Luis F. Parada**, University of Texas Southwestern Medical Center at Dallas.

Eight HHMI investigators are among 212 fellows elected to the American Academy of Arts and Sciences. The investigators are RAYMOND J. DESHAIES, California Institute of Technology; DAVID C. PAGE, Massachusetts Institute of Technology; KEVAN M. SHOKAT, University of California, San Francisco; DAVID P. COREY, Harvard Medical School; AMITA SEHGAL, University of Pennsylvania School of Medicine; GEORGE Q. DALEY, Children's Hospital Boston; DANIEL A. HABER, Massachusetts General Hospital; and KATHERINE A. HIGH, The Children's Hospital of Philadelphia.

IANNIS AIFANTIS, an HHMI early career scientist at New York University, received the 2011 McCulloch and Till Award from the Society for Hematology and Stem Cells. Aifantis studies the role of the ubiquitin-proteasome complex in regulating the balance between physiological stem cell differentiation and malignant transformation.

The University of North Carolina at Chapel Hill named HHMI investigators CORNELIA I. BARGMANN, of the Rockefeller University, and CATHERINE DULAC, of Harvard University, co-recipients of the 11th Perl/UNC Neuroscience Prize. The award recognizes the scientists' contributions to the discovery of chemosensory circuits that regulate social behaviors.

HHMI investigator PAMELA J. BJÖRKMAN, of the California Institute of Technology, was featured as one of *Working Mother* magazine's Most Powerful Moms in STEM (Science, Technology, Engineering, and Math). Björkman uses x-ray crystallography, electron tomography, and biophysical methods to study proteins and cells in the immune system.

HHMI investigator AXEL T. BRUNGER, of Stanford University, received the American Society for Biochemistry and Molecular Biology's inaugural DeLano Award for Computational Biosciences. The award honors creators of computer technology that enhances research in molecular biology. Brunger was chosen for developing the software suite CNS, a data refinement program used by x-ray crystallographers.

PETER J. BRUNS, who retired as HHMI vice president for grants and special programs last year, received the American Society for Cell Biology's Bruce Alberts Award for Excellence in Science Education. Bruns was recognized for his leadership in catalyzing revolutionary changes in biology education.

The Jewish Guild for the Blind named CONSTANCE L. CEPKO, an HHMI investigator at Harvard Medical School, recipient of its 2011 Bressler Prize in Vision Science for her research on retinal degeneration.

HHMI investigators JOANNE CHORY, of the Salk Institute for Biological Studies, and THOMAS A. STEITZ, of Yale University, were elected as foreign members of the Fellowship of the Royal Society in recognition of their exceptional contributions to science. CARLA J. SHATZ, a member of the Janelia Farm Advisory Committee, was also selected.

HHMI investigator ELAINE FUCHS, of the Rockefeller University, was one of three scientists to receive the 11th annual Albany Medical Center Prize in Medicine and Biomedical Research. Fuchs shares the prize with James A. Thomson, of the University of Wisconsin–Madison, and Shinya Yamanaka, of Kyoto University and the Gladstone Institute of Cardiovascular Disease. The scientists were honored for advancing understanding of the potential of stem cells to treat or reverse diseases and conditions.

PALOMA T. GONZALEZ-BELLIDO, a research associate in the lab of Janelia Farm group leader Anthony Leonardo, was awarded the 2011 International Society for Neuroethology Capranica Prize. The award recognizes Gonzalez-Bellido's article (*PNAS*, March 8, 2011) on the anatomy and physiology of the

Bartel: Kelly Lorenz Dietz: Paul Fetters Jacobsen: John Hayes / AP, ©HHMI Kingsley: Davis Tower Kingsley McCammon: Paul Fetters Nussenzweig: Paul Fetters Kornblihtt: David Rolls Parada: UT Southwestern Medical Center

eyes of two species of flies, which was judged to be most scientifically significant publication in the field of neuroethology in 2010.

HHMI investigator **TAEKJIP HA**, of the University of Illinois at Urbana–Champaign, received the 2011 Ho-Am Prize in Science from the Ho-Am Foundation of Korea. Widely regarded as the Korean equivalent of the Nobel Prize, the award went to Ha for his work using fluorescence resonance energy transfer techniques to control and visualize the movements of single biomolecules.

DAVID HAUSSLER, an HHMI investigator at the University of California, Santa Cruz, was chosen by the University of Oxford to receive the 2011 Weldon Memorial Prize, a prestigious award that recognizes the work of biomathematicians. Haussler is a leader in the field of bioinformatics, which applies advanced computational techniques to complex problems in biology.

HHMI investigator **ERIC R. KANDEL**, of Columbia University College of Physicians and Surgeons, won the University of Rochester's Eastman Medal, given to honor individuals who embody the university's ideals through their achievement and service. Kandel studies how neurons store information and how the brain's cellular and circuitry systems process and manage that information over time.

HHMI investigator **ROBERT J. LEFKOWITZ**, of Duke University, was awarded the highest honor of the Association of American Physicians: the George M. Kober Medal. Lefkowitz was honored for his research on G protein–coupled receptors and related enzymes, proteins, and signaling pathways.

WILLIAM T. NEWSOME, an HHMI investigator at Stanford University School of Medicine, was elected to the American Philosophical Society, the oldest learned society in the United States. Newsome's research focuses on understanding how higher mammals acquire, process, and respond to sensory information.

DAVID C. PAGE, an HHMI investigator at the Massachusetts Institute of Technology, won the 2011 March of Dimes Prize in Developmental Biology. Page shares the award with Patricia Ann Jacobs, of Southampton University Medical School and the Wessex Regional Genetics Laboratory, for their studies on X and Y chromosomes.

HHMI investigators **STEPHEN R. QUAKE**, of Stanford University, and **XIAOWEI ZHUANG**, of Harvard University, are recipients of the 2011 Raymond and Beverly Sackler International Prize in Biophysics from Tel Aviv University. Quake was honored for developing microfluidic techniques used in biophysics and structural biology; Zhuang received the accolade for her development and application of super-resolution microscopy.

The American Society for Cell Biology presented **RANDY W. SCHEKMAN**, an HHMI investigator at the University of California, Berkeley, with the E.B. Wilson Medal, its highest honor for science. Schekman shares the award with Stuart Kornfeld, of the Washington University School of Medicine, and James E. Rothman, of Yale University, for their pioneering research on protein transport. Schekman also recently received the Arthur Kornberg and Paul Berg Lifetime Achievement Award in Biomedical Sciences from Stanford University.

CHRISTINE E. SEIDMAN, an HHMI investigator at Brigham and Women's Hospital, was awarded the Jay and Jeanie Schottenstein prize in cardiovascular science from Ohio State University. Seidman received the biannual award for her research on gene mutations that cause human heart disease.

HHMI investigator **JOAN A. STEITZ**, of Yale School of Medicine, won the Robert J. and Claire Pasarow Foundation's 2011 Annual Medical Research Award for Extraordinary Achievement in Cancer Research. Steitz studies the roles played by noncoding RNA–protein complexes in gene expression in vertebrate cells.

HHMI investigator **WILFRED A. VAN DER DONK**, of the University of Illinois at Urbana–Champaign, was recently elected a fellow of the American Academy of Microbiology. Van der Donk uses genomic approaches to discover natural product antibiotics.

The German Society for Biochemistry and Molecular Biology will award the 2011 Otto Warburg Medal to **PETER WALTER**, an HHMI investigator at the University of California, San Francisco. Walter studies protein localization and the regulation of organelle abundance in the cell.

SPOTLIGHT

Medzhitov Wins Shaw Prize

Chris Jones

RUSLAN M. MEDZHITOV

In June, HHMI investigator **Ruslan M. Medzhitov**, of Yale School of Medicine, became one of three scientists to receive the 2011 Shaw Prize in Life Science and Medicine. He shares the $1 million prize with Jules A. Hoffman of the University of Strasbourg and Bruce A. Beutler of the Scripps Research Institute, for their discovery of the molecular mechanism of innate immunity, the first line of defense against pathogens. Medzhitov's research has expanded our understanding of the key roles Toll-like receptors play in infection control, chronic inflammation, and the growth of tumors.

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(SEEING IS BELIEVING)

Down the line, it's likely that the field will be choosing from a range of vectors and using both in vivo and ex vivo approaches, depending on the disease, according to Kay. "There's not going to be one vector that's going to be perfect for all applications. They all have their niche." (See Web Extra sidebar, "Taking Down Bad Genes.")

The AAV procedure, for example, transformed Corey's life. His father, Ethan Haas, knew the surgery was the right decision four days after Corey left the hospital, when the family took a trip to the zoo and Corey said that the sun was hurting his eyes. "That had never happened before. It was a pretty big deal," Ethan recalls. But best of all, he says, was the day Corey tried out the maze. "To see him navigating this obstacle course without difficulty—it was the most dramatic thing."

In the two years since, Haas says he's been pressing the researchers to repeat the procedure in Corey's other eye. He's slated for surgery this fall. ■

WEB EXTRA: For more about the work described here and to see a timeline of events in the field of gene therapy over the last 30 years, visit www.hhmi.org/bulletin/aug2011.

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(TIME TO TEACH)

and research postdoc is the ideal for the greatest depth of academic jobs.... They are getting supervisory experience, they are getting multitasking experience."

That's how it turned out for Haynes.

After three years as a research postdoc at Harvard University, she starts a tenure-track faculty position at Arizona State University in the fall. She interviewed at several institutions and believes her teaching experience was a key factor in her appeal.

Her advice? "Find a place that has top notch research facilities but cares enough about teaching that it will not count against you," Haynes says. "Those universities do exist." ■

WEB EXTRA: Postdocs can learn to be science education researchers too. Visit www.hhmi.org/bulletin/aug2011.

Jing Wei

A GUIDING LIGHT

A motivated group of Harvard undergrads—all winners of elite high school science fairs—decided to give back and share their advice and experiences as competitors. Their book is half encouragement and half how-to. Early on, they reassure readers that scientists no longer fit the stereotypical mold of "old, beaker-carrying men." In fact, successful female and male scientists range from 10 to 90 years old. Today's researchers are younger—more secondary students than ever are conducting scientific experiments—and their projects are becoming progressively more sophisticated.

Some students may not be content with just memorizing and regurgitating scientific facts. Others may never blindly agree with what they learn in the classroom. What do these students have in common? A pleasure in discovering something for themselves. Being able to contribute to the pool of human knowledge is more rewarding than other high school activities, such as getting straight A's or earning a Varsity letter (though by no means are these mutually exclusive!). The motivation to do research has to be much stronger than that, however, if we are to account for the tens of thousands of high school students who do research each year.

By no means is research easy: it can be a substantial time commitment and quite frustrating at times. At the same time, though, it can be the most fulfilling activity of your high school career. The stoichiometric relationship between research and class work is close to 1:3. That is, in one month of research a student can often learn as much as he or she would in three months of schoolwork. Unlike homework, research does not just provide book knowledge. It also enables one to develop important life skills such as giving presentations, writing research papers and applications, networking and making professional boards and posters.

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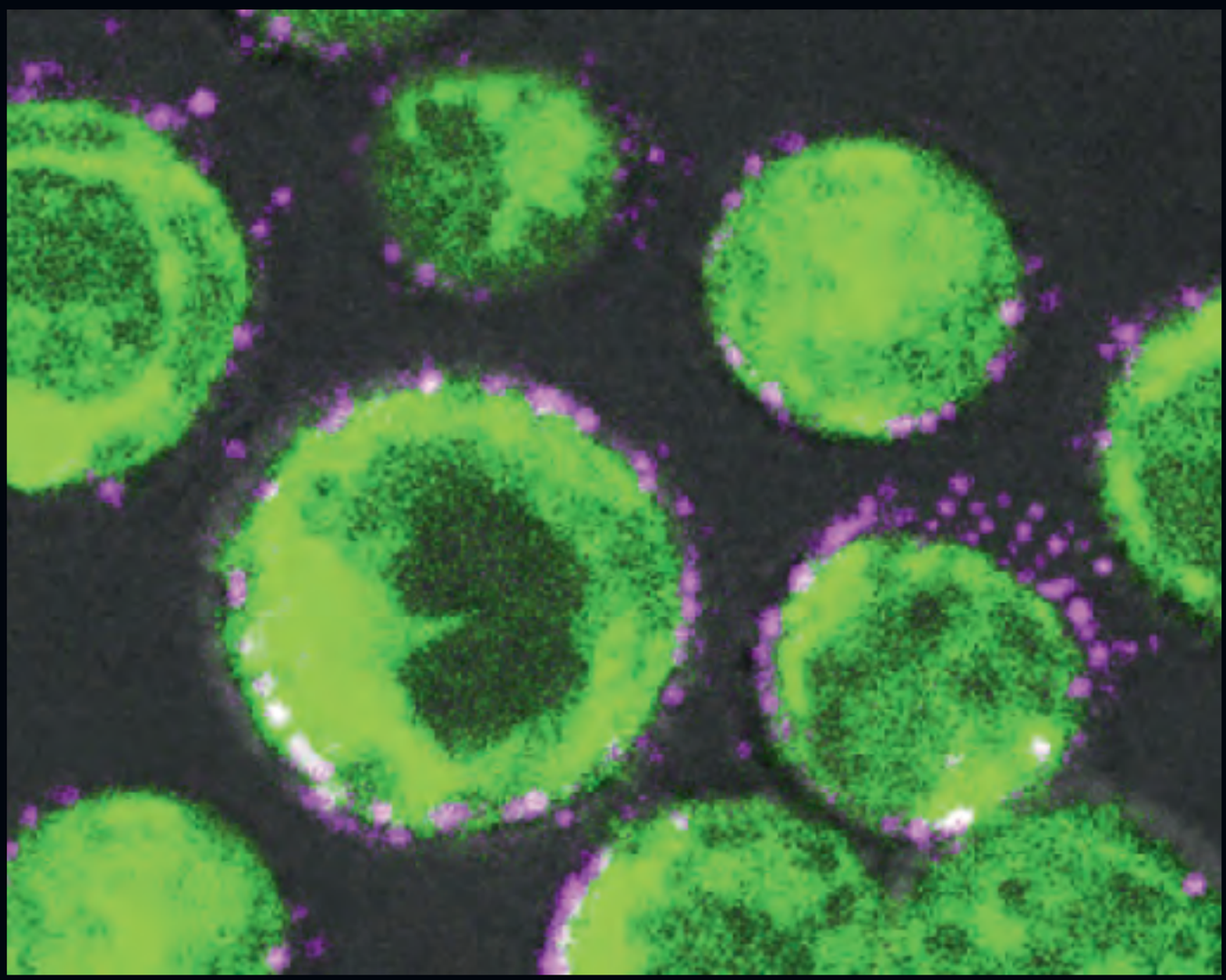
Special Delivery

What if a cancer patient's own immune cells could be loaded with tumor-fighting drugs? Engineer and materials scientist Darrell Irvine has found a way. Irvine's lab group has devised tiny drug-loaded nanoparticles and strapped hundreds of them to the surface of T-cell lymphocytes. When tested in mice with metastatic melanoma, the enhanced T cells rapidly reproduced, moved through the body, and zeroed in on the spreading tumors. The tumors shrank and the mice lived longer than untreated mice. The team has also used the technique to send drug-studded blood stem cells to restore depleted bone marrow in mice. Fascinated by the complexity of the immune system, Irvine is working to remodel the surface of cells with synthetic materials to treat disease and reduce treatment side effects, with more applications in sight (see "T-Cell Booster Kits," page 10).



Matthias Stephan / Irvine lab