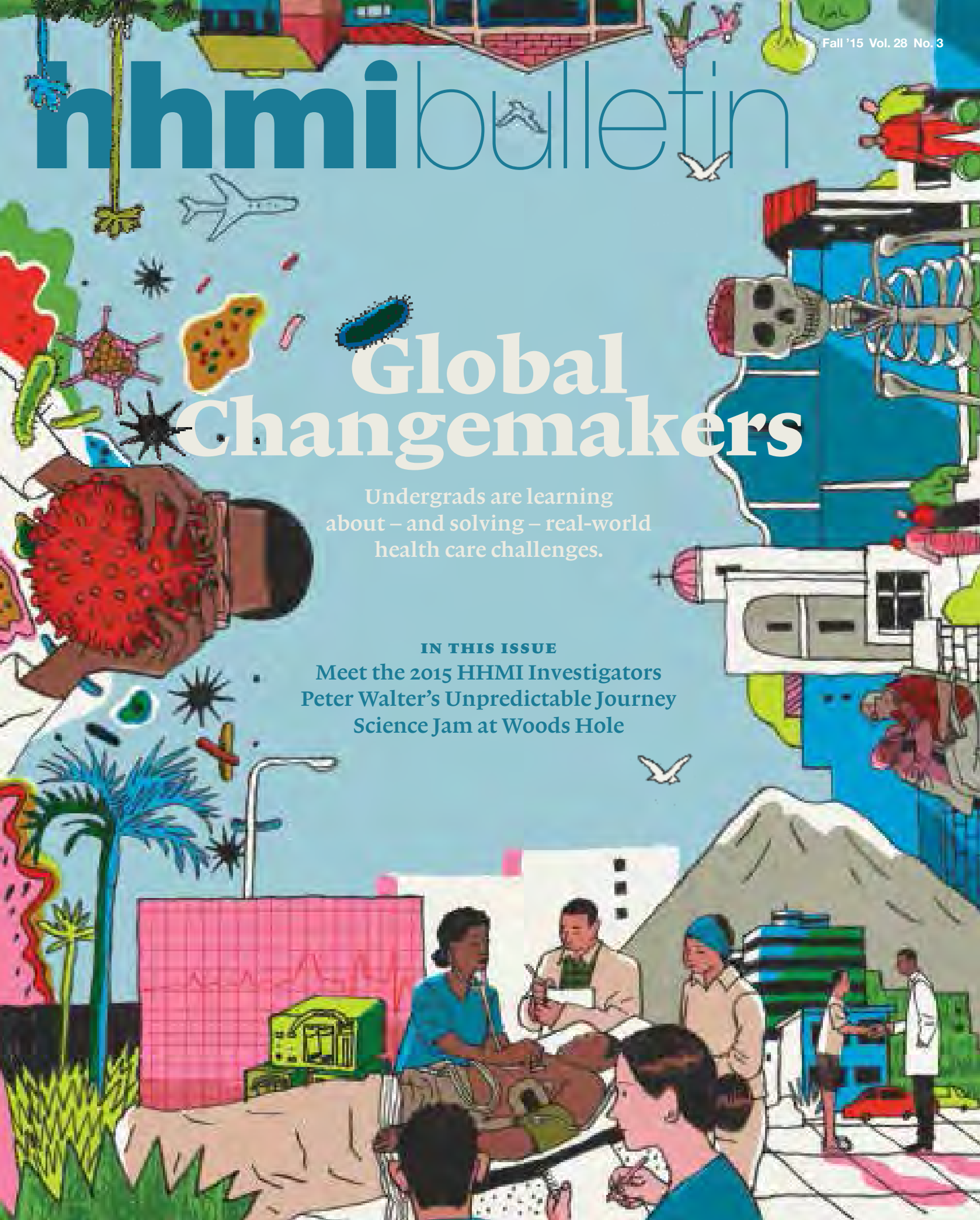
hhmi bulletin

Fall '15 Vol. 28 No. 3



Global Changemakers

Undergrads are learning about – and solving – real-world health care challenges.

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There's more to this image of the mycobacteriophage Corndog than meets the eye – even more than its whimsical name. Look closely and you'll see the faces of the student and faculty "phage hunters" from HHMI's SEA-PHAGES program. Interwoven in this mosaic are snapshots of bacteria-infecting viruses, called phages, whose genomes are themselves a mosaic of modular components. Launched in 2008, SEA-PHAGES – Science Education Alliance Phage Hunters Advancing Genomics and Evolutionary Science – has given thousands of undergraduates a taste of lab work by having them analyze the genomes of phages they find in local soils. Pooling that data has allowed a team led by HHMI Professor Graham Hatfull to compare the genomes of 627 different bacteriophages – including Corndog – found in the soil-dweller *Mycobacterium smegmatis.*

Welkin Pope and Graham F. Hatfull

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Jake Stangel

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- **Learn what drives the newest cohort of HHMI investigators.**
- **Travel to Africa to see how undergraduates are making an impact on global health.**
- **Experience the windswept Arctic landscape that forms the cornerstone of David Marchant's research program.**
- **Go along with scientists as they collect stickleback fish from the lakes and streams that dot Vancouver Island.**

www.hhmi.org/bulletin

Cover illustration: Josh Cochran

Editor's Letter

Turning Point

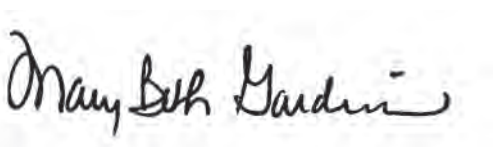
SHORTLY AFTER I JOINED HHMI in 2004, I was given a writing assignment that would change my life. Newly hired as assistant editor of the *HHMI Bulletin*, I was sent to cover an early-morning breakfast meeting in Loudoun County. As the sun rose that day, local teachers, school administrators, and business leaders gathered with HHMI executives and staff members in an office building overlooking the busy construction site that was then Janelia Research Campus. Amid the clatter of knives and forks, HHMI formally announced a commitment to invest $1 million per year in support of science education in the Loudoun County Public School system. As if that wasn't heady enough for this newbie, the event was also where I met my future husband.

Paul Fetters

To say that day was memorable is now an understatement. But its serendipitous effects weren't yet evident as I went on to write that story, and many more, for the *Bulletin*. Then, two years later, against my wildest dreams, I was named editor. And what a ride it's been. The magazine has become, as my boss puts it, "a storytelling machine" – an orchestrated effort by a cast of talented writers, editors, illustrators, photographers, and designers to capture the rich texture of the stories behind the remarkable people and work supported by HHMI. Our ability to tell those stories has grown ever more dynamic over time with the addition of video, animation, and multimedia to our online and iPad editions.

So for me, it's somewhat bittersweet to acknowledge that this issue of the *Bulletin* will be the last ever published. But as we move away from the magazine format, we promise that the storytelling won't abate: we plan to dive headlong into the swirl that is today's communications frontier. You can look for continuing stories from HHMI, both online and through social and other digital media. And your favorite *Bulletin* articles from the past will still be available as well, archived indefinitely on our website. Some of them may even resurface from time to time, as the stories of scientific discovery are often by their very nature incremental and evergreen.

We hope you'll stay with us as we make this pivot into a more nimble future. With Janelia now approaching its 10th anniversary, and newly funded scientists – such as the latest HHMI investigators introduced in this issue – coming on board on a regular basis, there is a deep vein of stories yet to mine. We will do our best to share the treasure with you.



hhmi Howard Hughes Medical Institute

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www.hhmi.org

President's Letter

James Kegley

A New Chapter

I IMAGINE EVERY generation of scientists is struck by the pace of change. Today, it's definitely the case that HHMI researchers are breaking long-held scientific barriers, from limits in light microscopy and data analysis to worn publishing dogma and outdated funding silos. Since 2009, it's been my privilege to watch these walls come tumbling down, and to play my part in driving science forward as HHMI president. It has also been a pleasure and honor to recruit and work with a superb executive team and other colleagues at HHMI headquarters, the Janelia Research Campus, and in our field operations.

As I head into my eighth year in this role, I've announced my intent to step down at the end of 2016 and return to the University of California, Berkeley, where I can devote more time to exciting new lab research opportunities. In this column, I'd like to reflect on some of the changes we've made at HHMI in recent years.

Collaboration at HHMI is on the rise – not only at Janelia, where small teams of scientists work side by side as a rule, but also in our philanthropic support of science. To combat a weak funding environment for basic research and to leverage HHMI's investments, we've deepened our partnerships with like-minded funders. Working with the Gates Foundation and the Simons Foundation, HHMI is supporting early-career scientists in the U.S. and internationally. We've also partnered with the Gordon and Betty Moore Foundation to share our newly developed advanced imaging technology with academic scientists and to fund plant scientists, who contribute more to biomedical knowledge than you might realize. In addition to these research-funding collaborations, HHMI has begun partnering with other nonprofits to increase outreach to philanthropists who can invest in the next generation of science. Across all this work, our goal is to deepen and extend our impact by supporting basic discovery research, the bedrock of U.S. science.

"I'm confident that the Institute has a bright future, fueled by passionate scientists and educators who believe deeply in the power of science to change our world."
—ROBERT TJIAN

More subtly, we've worked to increase our impact by adapting our programs and operations to be flexible, efficient, and sustainable. For instance, we've developed a "phase-out" option for experienced HHMI investigators who are prepared to leave the Institute. We've also reshaped our field operations to ensure that we're supporting science sustainably and consistently in our labs, coast to coast as well as internationally.

To catalyze a culture shift in scientific publishing, we provided funds to launch the open-access journal *eLife*, in partnership with Wellcome Trust and the Max Planck Institute. Since 2012, the online-only *eLife* has published more than 1,000 research papers, with an emphasis on three important principles: making scientific results available to everyone; offering a fair, constructive, and expedited peer-review process; and embracing the power of digital media. The acceptance rate at *eLife* is currently 15 to 18 percent, and the editors have an ambitious agenda for growth, which currently stands at over 500 submitted manuscripts per month.

One thing that hasn't changed during my tenure in HHMI leadership is our commitment to identify and catalyze bold thinkers, allowing them to do rigorous research that reveals fundamental truths about how biology works. This effort extends from experienced scientists to postdocs, and even undergraduate and high school students, who benefit from hands-on lab experiences and educational media supported or developed by our science education staff. We have also launched new efforts to enlighten society as a whole about the process of discovery by producing captivating and scientifically informative documentary films.

It's been my honor to lead HHMI, working closely with our Board of Trustees and other senior leaders. I'm confident that the Institute has a bright future, fueled by passionate scientists and educators who believe deeply in the power of science to change our world. I look forward to doing my part, back at the bench and in academia.

Evolution of a Magazine

As the HHMI Bulletin retires, the editors take a look back at its journey from newsletter to widely read science magazine.

SINCE IT WAS FIRST PUBLISHED IN 1988, the *HHMI Bulletin* has assumed many guises. The magazine started life as a no-frills, four-page newsletter, meant solely for the HHMI community. Over the ensuing 25-plus years, its appearance has evolved; it has expanded (and occasionally contracted) in size; its content has assumed a more narrative tone; and the text has increasingly been complemented by artful illustrations and captivating photographs. In 2005, an equally artful *Bulletin* website went live, and 2011 saw the launch of an iPad edition – making the *Bulletin* one of the first science magazines offered through the iTunes store.

As the magazine evolved, so did its readership. Individuals from outside HHMI – including science educators, scientists-in-training, and science aficionados – began subscribing in ever-growing numbers, drawn by the compelling stories of scientific discovery. More than 37,000 copies of this issue will come off the printing press, to be mailed to subscribers and passed along to other readers, and the magazine's online and iPad editions will eventually be seen by thousands more.

Now, with this last issue, we are retiring the *Bulletin* as we move away from the magazine as a communications medium. But that doesn't mean the storytelling will end: Look for vibrant coverage of HHMI's work and people online and through social media in the days, weeks, and years ahead. Science is ongoing, and the way it's conducted – and communicated – will continue to evolve.


THE
Bulletin
Published for the Howard Hughes Medical Institute Community
Newsletter plays role in rapidly growing HHMI
New headquarters to be built on "serene campus"
Kingsbury joins HHMI

August 1988
Vol 1, No 1


Howard Hughes Medical Institute Bulletin
Closing the gender gap in science

May 1991

Flash Forward
First edition's news still resonates today

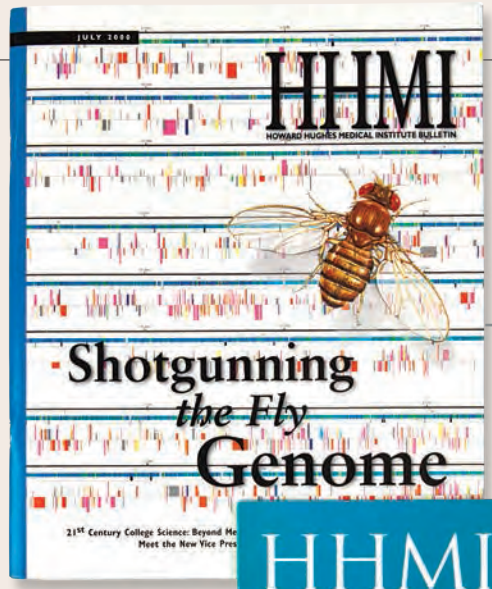
Then...
Top graduate, **medical students win support** *the first HHMI doctoral fellowships in the biological sciences

...Now
From this first class of fellows, three – **Abby Dernburg**, **Julie Theriot**, and **Geraldine Seydoux** – went on to become HHMI investigators, and one – **Scott Strobel** – became an HHMI professor.

Then...
Institute scientists receive **national awards**

...Now
HHMI Investigator **Eric Kandel's 1988 National Medal of Science** (NMS) presaged his 2000 Nobel Prize in Physiology or Medicine, while Nobelist **Joe Goldstein**, also an NMS winner that year, went on to become chairman of HHMI's Medical Advisory Board and later an HHMI Trustee, a position he still holds.

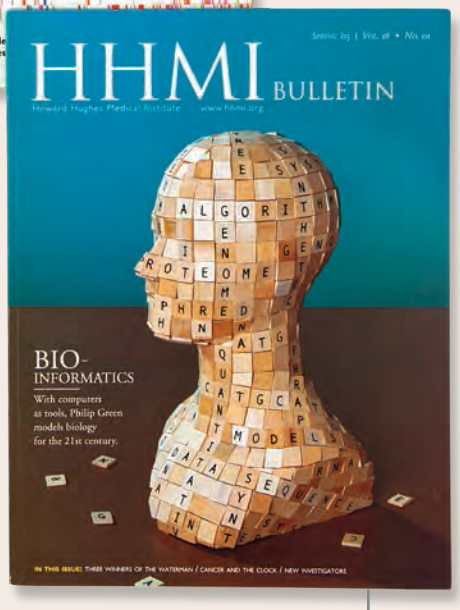
To trace the evolution of the *Bulletin* from a simple newsletter to an artful science magazine, go to hhmi.org/bulletin/fall-2015.



July 2000

April 1998

February 1996



Spring 2005

Fall 2013

Then...
Ten investigators join research staff *raising total number to **178**

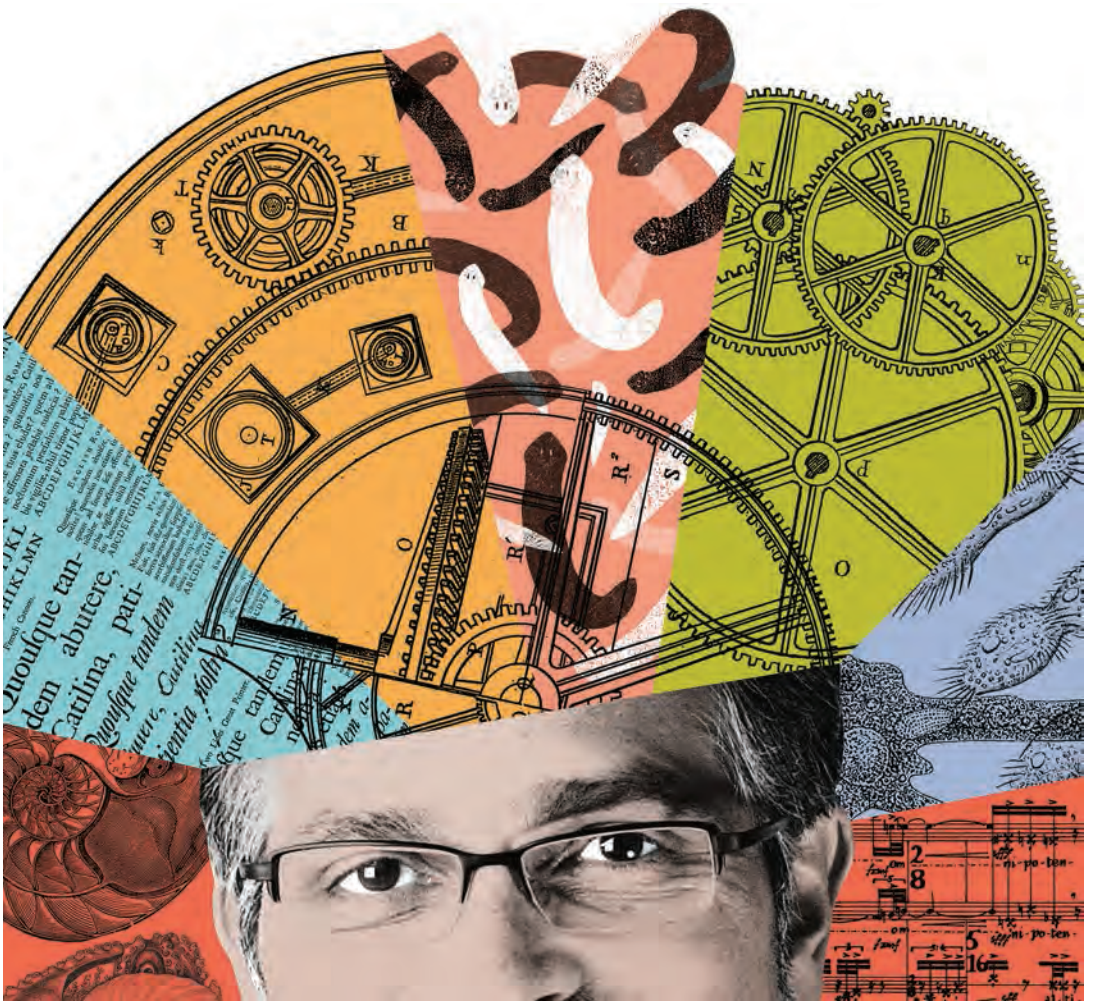
...Now
Out of this group of 10 appointees, five are still HHMI investigators, and one – **Tom Cech** – went on to win the **Nobel Prize** in Chemistry and to become HHMI's fourth president.

Then...
Grants go to **44 liberal arts, historically black colleges** *among the first major efforts of a 10-year, $500 million grants program

...Now
Science education grants provided **$77 million** of support in fiscal year 2014 through a variety of programs. Recent initiatives, such as the **Meyerhoff Adaptation Project and Inclusive Excellence**, aim to encourage colleges and universities to increase the diversity of students engaged in science.

Then...
New headquarters and conference center to be built on "serene campus" in **Chevy Chase, Maryland**

...Now
Headquarters opened in 1993, and a new wing was added in 2010. HHMI also launched the Janelia Research Campus, near **Ashburn, Virginia**, in 2006 and has established field operations supporting laboratories nationwide.



A Curious Mind

CURIOSITY MAY HAVE killed the cat, but it's Alejandro Sánchez Alvarado's *raison d'être*. "I don't have hobbies per se," he admits, "unless thinking counts. I've always wanted to understand where things come from: music, language, ideas. It's what got me into trouble as a kid and what led me to learn the classical guitar. It's still a driving force."

For instance, he remembers wondering as a boy why doors have locks, doing research at the library about the origin and history of locks, and then – to satisfy his curiosity – grabbing a screwdriver and dismantling the lock on his family home's front door (not realizing that, like Humpty Dumpty, it couldn't easily be put together again). His questioning mind also led him, upon seeing a van Leeuwenhoek sketch, to build his own microscope, sacrificing his mother's hairpins to "see the unseen." Spying his first "animalcule" – a *Paramecium* or *Euglena*, he recalls – was thrilling, even if "no one else in my family was terribly interested." (To this day, his mother has a hard time understanding how her son – an expert in planarian flatworms at Kansas City's Stowers Institute for Medical Research – makes a living studying worms.)

Sánchez Alvarado is especially captivated by the history of science. While teaching embryology the past few summers at the Marine Biological Laboratory (MBL) in Woods Hole, he's spent time in MBL's archives, trying to learn who coined the term "stem cell." It's not everyone's cup of summer fun, he owns, but "exceedingly attractive to me." He's unearthed references as far back as the mid-1800s and is intrigued that "this concept likely came from botany, not animal biology."

He's also been pondering the Lophotrochozoa superphylum, a diverse group of animals that includes mollusks and flatworms. "They have complex, plastic body plans that are generally underappreciated," observes Sánchez Alvarado, an HHMI investigator who almost single-handedly established the freshwater planarian *Schmidtea mediterranea* as a model to study regeneration. "I want to know more," he adds, so the last two summers he's conducted plankton tows near Woods Hole to understand the habits, life cycles, and natural history of this diverse group of animals. "I've become really good at reading tides," he says – flood tide being best for collecting samples of these organisms (which he's now cataloging).

In many ways, Sánchez Alvarado would have been right at home during the Renaissance, when inductive inquiry, or curiosity-driven observation with few to no assumptions, was the norm. "Imagine how much fun it would have been to have discussed the world with Laplace and Kepler, or Lavoisier – he was an engaged citizen as well as a scientist. All were thinkers who saw things others didn't necessarily see."

These days, he worries that hypothesis-driven research has all but shoved aside inductive inquiry. "If we paid more attention to the history of science," he says, "we'd see that innovation has always involved both. We're able to generate data like never before, but it's mostly knowledge without much understanding. How about taking a step back: Can we distill new first principles from these vast data?"

This, though, will require changes in how scientific productivity is rewarded. "I adore curiosity-driven research, but in the current biomedical research climate it doesn't necessarily pay the bills," Sánchez Alvarado says. "Still, science will be better served if we establish mechanisms to promote such inquiry, as will humankind."

A shift in that tide may be a while coming. In the meantime, he'll keep diving down intellectual rabbit holes – perhaps remarking, like young Alice, "Curiouser and curiouser!" *–Alissa Poh*

Eda Akaltun

To see more of David Marchant's Antarctica, go to hhmi.org/bulletin/fall-2015.

Ice Bound

BUNDLED IN FIRE-ENGINE–RED PARKAS, a handful of researchers pick their way across a parched, high-altitude Antarctic valley swept by howling winds. Beneath their puffy white boots, the oldest ice on Earth lies buried under boulders and sand.

Led by David Marchant, a geologist who directs the Boston University (BU) Antarctic Research Group, they take photographs, collect samples of volcanic ash, and search for sites where ice unchanged for millions of years lies near the surface. Some carry spades to expose the ice and then use specialized drills to retrieve ice cores for analysis back in Marchant's lab.

The scientific prize they're after is bubbles of atmospheric gases that were trapped within the ice cores during the Pliocene epoch several million years ago, when the Earth was warmer and sea levels were 30 to 300 feet higher than they are now. Marchant explains that measuring carbon dioxide levels in the bubbles could help predict global responses to today's rising CO_2 levels and temperatures.

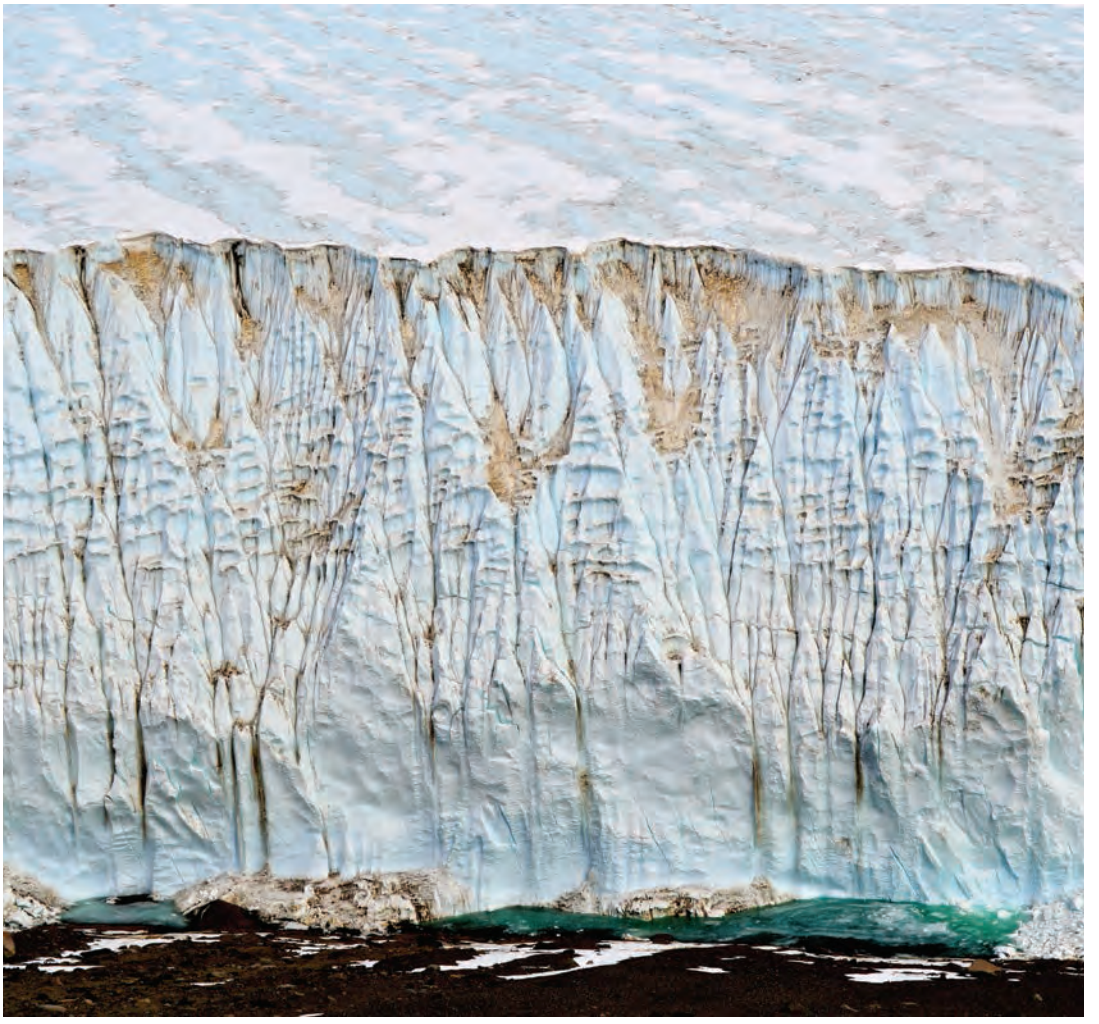
This frigid scene is displayed on wall-sized monitors in the comfort of Marchant's BU lab. This and other expedition videos are also posted online. Marchant, who became an HHMI professor in 2014, places a high priority on public outreach as part of a curriculum he created for undergraduates to "seed a cultural change in STEM education" by emphasizing early and consistent research, communication, and education.

Marchant has a genial manner and the look of an outdoorsman – bearded and tanned from 20 polar expeditions since being "captivated" by his first trip some 25 years ago. "It's cold and it's hard and it's physically demanding," he says. "And trying to 'read' the dynamic landscape is a mental challenge." But he's driven by the thrill of discovery. "We know we can find things in a single excavation pit that have global significance," he says.

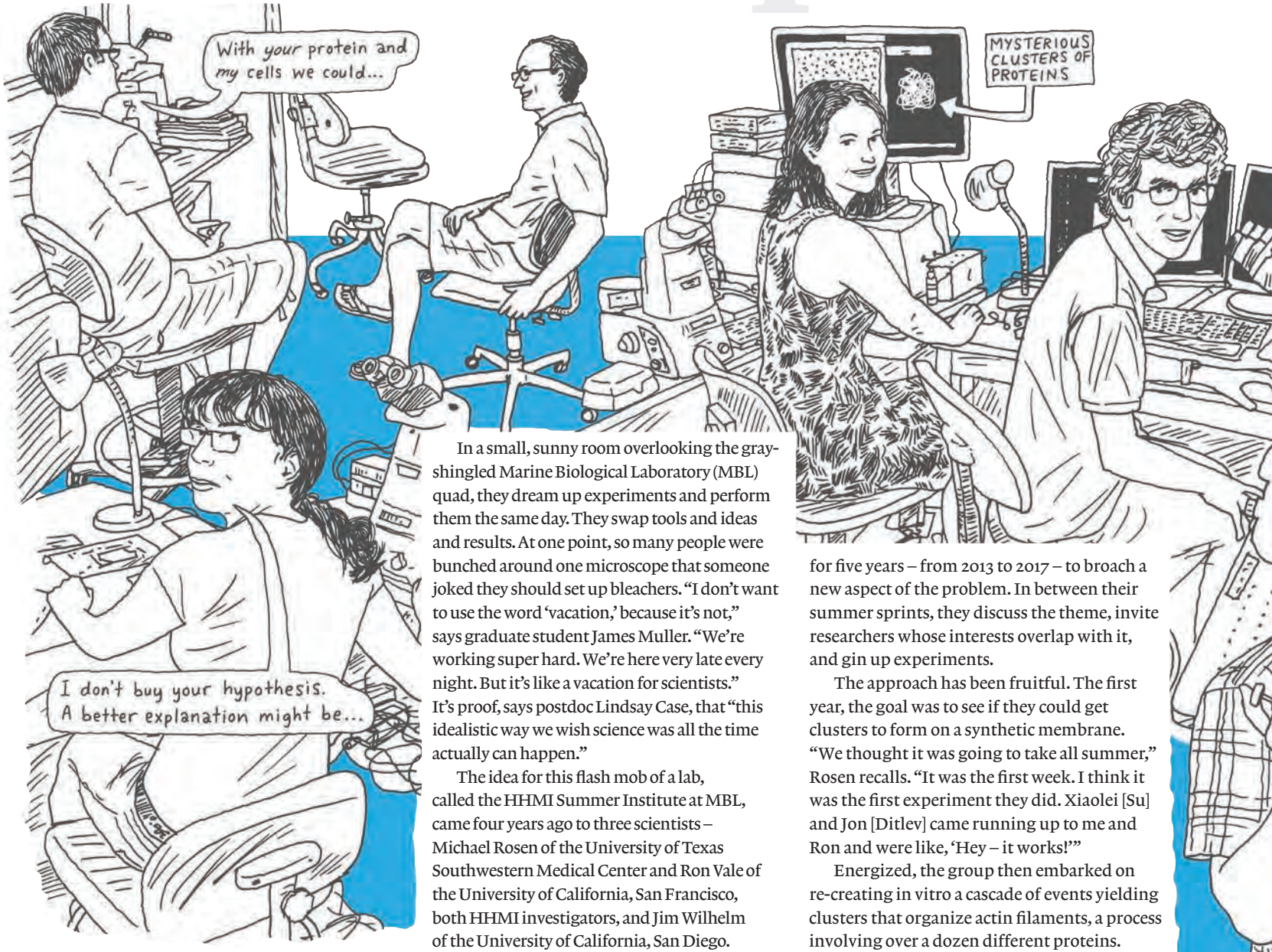
Marchant's group is preparing for another field excursion, from November 2015 through January 2016, the Antarctic summer. Three undergraduates will join the expedition for up to three months' work on the West Antarctic Ice Sheet, which has been melting so rapidly that recent scientific reports warn it may be doomed to complete disintegration, raising sea levels by several feet. The team will map geological features that mark the ice sheet's changing margins over the past 18,000 years. Their aim is to develop a long-term glacial and atmospheric record "that can tell us what to expect in the future," says Marchant.

Students remaining at the BU lab will use high-resolution photos and videos to create "virtual field trips" and analyze landscape patterns and will perform geochemical analyses of the volcanic and ice samples. They'll also work with middle-school teachers to translate lab results into lesson plans and produce communication materials for the public.

For those who travel with Marchant to Antarctica, he says, the experience will have a lasting impact. "When the first storm hits, the new people will wonder if they're going to make it through the night," Marchant says with a grin. But the fast pace and steep learning curve transform students into confident researchers in a few short weeks, he says. "You can see it when they're back on campus, too. There's nothing you can give them after this experience that they'll fail at. They'll just keep trying until they get it." *–Richard Saltus*



Andrew Christ



Science Jam

A pop-up laboratory in Woods Hole takes on daring biology research in an unusual setting.

OVER THE WINTER, the scientists gather gear, manufacture extra proteins, and bone up on obscure aspects of biochemistry. In June, they descend on the beach town of Woods Hole, Massachusetts – 18, 19, 20 of them from around the world – for six or so feverish weeks of research.

In a small, sunny room overlooking the gray-shingled Marine Biological Laboratory (MBL) quad, they dream up experiments and perform them the same day. They swap tools and ideas and results. At one point, so many people were bunched around one microscope that someone joked they should set up bleachers. "I don't want to use the word 'vacation,' because it's not," says graduate student James Muller. "We're working super hard. We're here very late every night. But it's like a vacation for scientists." It's proof, says postdoc Lindsay Case, that "this idealistic way we wish science was all the time actually can happen."

The idea for this flash mob of a lab, called the HHMI Summer Institute at MBL, came four years ago to three scientists – Michael Rosen of the University of Texas Southwestern Medical Center and Ron Vale of the University of California, San Francisco, both HHMI investigators, and Jim Wilhelm of the University of California, San Diego. They realized they'd all encountered the same phenomenon in their research: large, mysterious clusters of proteins. At first glance, the clusters could be mistaken for detritus floating around in the cell, but they're not. They coalesce in response to diverse cues, littering the cell with wads of enzymes, signaling proteins, and even RNA, and then disappear. There were tantalizing clues that they helped activate immune cells and control the production of proteins from RNA.

Studying the clusters didn't fall squarely under any of their research grants, but a Hughes Collaborative Innovation Award gave the trio a platform from which to tackle the challenge. The awards go to large-scale projects of unusually ambitious scope; this one calls for the scientists to meet every summer for five years – from 2013 to 2017 – to broach a new aspect of the problem. In between their summer sprints, they discuss the theme, invite researchers whose interests overlap with it, and gin up experiments.

The approach has been fruitful. The first year, the goal was to see if they could get clusters to form on a synthetic membrane. "We thought it was going to take all summer," Rosen recalls. "It was the first week. I think it was the first experiment they did. Xiaolei [Su] and Jon [Ditlev] came running up to me and Ron and were like, 'Hey – it works!'"

Energized, the group then embarked on re-creating in vitro a cascade of events yielding clusters that organize actin filaments, a process involving over a dozen different proteins. Su, Ditlev, and Darius Köster, all postdocs in different labs, put the final experiment under the microscope at 1:00 a.m. just a few days before they were to leave Woods Hole. In the morning, they had a video that shows blue clusters appearing out of the gloom, then a web of red filaments blooming and spreading. It was a beautiful vindication of the summer's work. "I kept watching the video on the plane, instead of movies," Su says.

It was an experiment they'd never have attempted back home. "There really is almost no way you can say to a new student or postdoc in your lab, 'Hey, you're going to make 13 proteins, and it's going to take two years, and it probably won't work at the end,'" Rosen says. But at the Summer Institute, with a few

Peter Arkle

"We're working super hard. We're here very late every night. But it's like a vacation for scientists."
—JAMES MULLER

proteins made beforehand by each lab and everyone in the same room to troubleshoot, it became possible.

Last year, they examined how clusters that include RNA form. This year, the goal was to understand how the assemblies modulate signals and whether the signals that trigger cluster formation are the same in different kinds of immune cells. During a lab meeting, results from past experiments and ideas for future ones flew, while sounds of tourists and seagulls wafted through the open window. They now have only hunches about why the clusters exist. But, speculates Jay Groves of the University of California, Berkeley, when their role is finally understood, it may prompt a fundamental change in thinking about molecular organization in cells – a shift akin to researchers' realization that proteins' complex structures are key to their function; Groves, an HHMI investigator, participated in this year's gathering.

It's hard work, and there are lows as well as highs. Not every tack is as successful as the first year's re-creation experiment. And if there's a problem with materials brought from home, it's not easy to make more.

But the scientists, both junior and senior, say it's worth it. Grad student Kyle Begovich traces his dissertation directly to his work at the Summer Institute. Su, Köster, and Ditlev, who plan to continue collaborating, say the model forges lasting relationships. "You can meet someone at a conference, and that's one thing," agrees Muller. "But to meet someone here and to really get to know them – to break bread, share a beer, share pipettes – that leads to long-lasting collaborations that are not just transient interactions." It helps that the sessions are hosted by the MBL, which has a collaborative culture, dorms, a dining hall, and other visiting researchers.

Do they ever make it to the beach? They're on Cape Cod, after all. Lindsay Case laughs at the mere idea. She's working so intently she's lost track of the day of the week. *After* the Institute, she might take some time off. For now, there's work to do. *–Veronique Greenwood*

Bench Report

Steady On

Throughout his decades-long career, physician-scientist Michael Welsh's focus on cystic fibrosis has never wavered.

WHEN MICHAEL WELSH was a medical student, in the 1970s, textbooks described cystic fibrosis as a lethal genetic disease affecting children.

Cystic fibrosis, or CF, disrupts the ability of cells lining the body's cavities and surfaces to manage chloride and bicarbonate, key components of salt. This has particularly devastating effects in the lungs, causing thick, stringy mucus to clog the airways.

But thanks in part to Welsh and his colleagues, treatments have improved and today's textbooks read very differently. "Our CF clinic now has more adults than children," says Welsh, an HHMI investigator at the University of Iowa.

A soft-spoken native Iowan, Welsh is passionate about studying CF. He has focused on the disease, which is caused by inheriting a mutated *CFTR* gene from each parent, for nearly three decades.

Making Headway

The *CFTR* gene was discovered in 1989. Welsh was already studying CF and caring for patients with the disease. Armed with the new genetic knowledge, he and colleagues discovered that the CFTR protein forms a channel, or pore, in the cell's outer membrane through which chloride and bicarbonate flow. They also showed that a "gate" in CFTR controls salt flow by opening and closing the channel.

By the early 1990s, Welsh was looking at how mutations mangle the CFTR channel. He knew that the *CFTR* gene's most common mutation, found in more than half of individuals with the disease, produces a misshapen channel. The cell's quality control machinery recognizes the mutant and rejects it. His team showed that the mutant fails to appear on the cell surface, leaving no pathway for chloride flow.

So Welsh was puzzled by a 1991 paper by Francis Collins, then an HHMI investigator at the University of Michigan. Collins's lab reported that the common mutant did, in fact, form a channel on the cell surface. But, Welsh noted, Collins had studied mutant CFTR in frog eggs kept at room temperature, while his own lab had studied it in mammalian cells at a much warmer 37 degrees centigrade. So Welsh's team ran the experiments again at a lower temperature.

"Boom! There it was – a channel that conducts chloride, albeit not as well as a healthy protein," Welsh says. "Too often, researchers worry when their results differ from those obtained by others in their field. It can be good to explore why results differ, as that can lead to important insights."

Today, this decades-old research underpins work on a handful of emerging CF therapeutics, including Orkambi. The drug, which mimics the effects of lower temperature to facilitate repair of the ion channel, was approved by the U.S. Food and Drug Administration in July 2015.

When Pigs Fly

Welsh also set the stage for new ways of unraveling precisely how *CFTR* mutations cause the disease in 2008, when he and colleagues reported in *Science* that they'd developed a pig model of CF. Until then, researchers had created mice with *CFTR* mutations; however, mice don't develop the same symptoms as humans.

Pigs, much closer to humans in terms of biochemistry, physiology, and size, were an attractive alternative. But the mouse was the only mammal ever engineered to reproduce a human disease. The idea of a CF pig seemed so far-fetched that members of Welsh's team hung a winged pig above the lab bench of the postdoc working on the project.

> **"I don't think CF has to be a lethal disease."**
> —MICHAEL WELSH

But the idea worked. Now, Welsh says, "the model is letting us ask new questions about the origins of the disease." It's shown how CF wreaks havoc on the lung; in a July 2012 paper in *Nature*, Welsh and colleagues reported that CF throws off the pH balance in the lung's airways, crippling the lung's infection-control mechanism. And it's revealed how CF disrupts the lungs' natural self-clearing action; Welsh and colleagues reported in August 2014 in *Science* that this disruption is due to unusual acidity and decreased fluid production in the lung's submucosal glands.

Welsh says these insights would have been impossible without the pig model, whose usefulness seems likely to endure.

A Changing Landscape

Welsh jokes that he chose the pig as a model "because I am from Iowa." He believes the state possesses a unique and subtle beauty often missed by those from the coasts. He's restored several acres of prairie surrounding the farmhouse where he lives, just minutes from campus but out of sight of any neighbors. "Put that in the article," he says, laughing. "It might help me recruit people from Boston, the Bay Area, and New York."

The land had been farmed hard before he bought it. "It was like looking at a hard, old face scarred by the weather," says Welsh, a fan of former U.S. poet laureate Ted Kooser, who often writes about the Midwest landscape.

Welsh's acreage now boasts prairie grasses and wildflowers "that were here before white people came." Its transformation is not unlike the change in the outlook for those with CF. According to the Cystic Fibrosis Foundation, "Today the life expectancy of a person with CF is 41 years of age. This is a dramatic improvement from the 1950s, when a child with CF rarely lived long enough to attend elementary school."

Welsh believes the dramatic improvements will continue. "I don't think CF has to be a lethal disease," he says. – *Geoff Koch*

Lucy Hewett

Through genetics and porcine modeling, Michael Welsh is improving the lives of patients with cystic fibrosis.

World Class

Global health curriculum initiatives encourage undergraduates to embrace – and solve – real-world problems.

BY MEGAN SCUDELLARI

ILLUSTRATIONS BY JOSH COCHRAN


PHARMACY

REBECCA RICHARDS-KORTUM couldn't get the four tiny newborns, crowded shoulder to shoulder in a single plastic crib, off her mind.

It was 2005, and Richards-Kortum, a bioengineer and HHMI professor at Rice University, was returning home from Malawi, a landlocked African nation and one of the world's least-developed countries. While there, she'd visited the neonatal intensive care unit at Queen Elizabeth Central Hospital. It was an institution that lacked sufficient space, adequate resources, and equipment to perform even the most basic medical tests and treatments.

When she got back home to Houston, Richards-Kortum challenged her students to help babies like those four newborns. Jocelyn Brown, a senior bioengineering major, and four other undergraduates accepted the challenge and spent the next year researching and designing a device that the pediatricians at Queen Elizabeth had requested: a bubble Continuous Positive Airway Pressure (bCPAP) system, which blows an oxygen-rich air mixture into the lungs of premature babies to help prevent the respiratory problems that often afflict preemies.

As an undergraduate at Rice University, Jocelyn Brown helped engineer a device to ease respiratory problems in premature infants.

Hospitals in the United States use a $6,000 bCPAP machine, but that price tag wasn't feasible for a Malawian hospital. Brown and her teammates constructed a prototype for less than $200 that offered the same therapeutic flow and pressure as the systems used in Houston hospitals. "I knew students had the skills to design technologies that could truly improve health care," says Richards-Kortum. "That was the start of it."

Today, Rice is home to one of several HHMI-funded programs that incorporate global health in undergraduate curriculums. The need for such programs is great, says HHMI Professor Muhammad Zaman, a bioengineer at Boston University (BU). Many engineers and scientists have knowledge that is deep but not broad, so they may be unaware of how their work can apply to and affect the real world, especially in resource-poor settings. "Global health education is an opportunity to understand how policy, social and cultural barriers, religion, and the structure of society affect health," says Zaman. "All of these things are connected, and that's important for our engineers and scientists to know."

Such programs not only support the development of solutions to critical global health problems, but also engage students in real-world problem solving, says David Asai, senior director of undergraduate and graduate programs for HHMI. "Given the internationalization of everything we do these days, leading schools will be thinking more and more about what's going on in the whole world."

Breath of Life

Brown continued to work on the bCPAP project after graduating in 2010. She traveled with the machine to Malawi and demonstrated it to physicians and nurses, who offered feedback. With that input, she improved the design and then returned to Malawi to conduct a nine-month clinical trial in 89 infants to test the effectiveness of the machine.

The student-designed bCPAP device improved the average survival of premature infants with respiratory distress syndrome from 24 percent to 65 percent, says Brown. "It was absolutely exciting and validating to know that we had developed this device, it could be used, and it worked well."

The bCPAP device was the first of many technologies to come out of Rice's Beyond Traditional Borders (BTB) initiative, an undergraduate biomedical engineering design program founded by Richards-Kortum and her colleague Maria Oden under a 2006 HHMI science education program grant.

In 2013, BTB won the $100,000 Lemelson-MIT Award for Global Innovation. Richards-Kortum and Oden donated the prize money toward the construction of a new neonatal ward at Queen Elizabeth Central Hospital.

Today, the BTB program – which incorporates coursework, design challenges, internships, and outreach programs – has trained more than 10 percent of all Rice's undergraduates since the program's inception. And BTB

Tommy LaVergne/Rice University

undergraduates have built and tested an estimated 116 prototypes for use in the developing world.

Last year, for example, a group of freshmen designed a handheld device that accurately and quickly measures respiratory rates in children – a critical parameter for diagnosing pneumonia. "Using just a microprocessor and a couple of LEDs, they did a lot of great engineering," says Richards-Kortum. Those students were in Malawi this past summer, demonstrating the device to nurses. With their input, the students will spend the coming academic year improving the device and planning a clinical trial.

Other technologies under development in the program include a liquid-medicine dosing syringe for children with HIV/AIDS, a solar-powered autoclave, a hand-powered centrifuge, and a battery-powered fluorescence microscope.

As for the bCPAP device, Rice licensed the machine to 3rd Stone Design, a California company where Brown now works. With funding from the United States Agency for International Development (USAID), the company distributed devices to all 27 hospitals in Malawi and now is preparing to mass-produce it to sell in other developing countries.

"For myself and my classmates who have gone through the program, it is really exceptional to make things that will actually be used in the world," says Brown. "It is compelling to know, as a young engineer, that I can make a huge impact on health."

"It is compelling to know, as a young engineer, that I can make a huge impact on health."

—JOCELYN BROWN

Leading by Example

On a quiet street tucked behind Boston University's bustling urban campus, Muhammad Zaman says goodbye to four undergraduates and a postdoctoral student also eager to make an impact on health. The five are headed to the airport to catch a plane to Zanzibar, an archipelago off the coast of East Africa, where they will spend six weeks living with host families and working with local students to brainstorm health-care technologies needed in the region.

After seeing them off, Zaman, who became an HHMI professor in 2014, walks back through a door leading to his two laboratories. In the lab to the right, he studies how cancer cells interact with their environment. In the lab to the left, he focuses on global health.

Zaman grew up in a developing country, Pakistan, and experienced firsthand the poverty and lack of medical technology that are endemic to such settings. As a boy, Zaman tagged along with his mother whenever she trekked across town to pick up medications. She never went to the pharmacy on the corner by their house, Zaman recalls. For the longest time, he thought that was just the way it was done – you traveled across town for medicines. "Then I came to America and realized that's not how it should be," he says. Zaman realized his mother's long trips were necessitated by her distrust of the quality of the medicines at the corner store.

In 2011, with funding from USAID's Promoting Quality of Medicine Program, Zaman began developing an inexpensive, portable kit able to detect counterfeit and substandard drugs. An estimated 10 to 30 percent of the drugs sold in parts of Africa, Asia, and Latin America are counterfeit, and a whopping 30 to 50 percent of all antimalarials are estimated to be substandard. The prototype kit, which Zaman calls PharmaChk, is a black plastic container about the size of a carry-on suitcase. It's a laboratory-in-a-box, complete with tiny test tubes, fluorescent probes, a microfluidics chip, and more.

In 2013, *Scientific American* hailed PharmaChk as one of 10 "World Changing Ideas." With the device, Zaman hopes to ensure that medicines are safe at all points along the supply chain – from manufacturers to distributors to corner stores in Pakistan.

As he was building PharmaChk, Zaman discovered that his students were as passionate about global health as he was. "This is the Facebook generation; people are getting more connected and are socially conscious," he says. The interest from his undergraduates, combined with his own origins in a developing country, led Zaman to embrace and become a model for incorporating global health into science courses. In one of his current undergraduate courses at BU, for example, Zaman uses burn injuries and postpartum hemorrhage to teach the concepts of heat, mass, and momentum transfer in living systems.

To see photos from Richards-Kortum and Zaman's travels to Africa, go to hhmi.org/bulletin/fall-2015.

> **"A program that teaches science or engineering and neglects the social implications is an incomplete education."**
>
> —DAVID ASAI

Today, Zaman is working to help other professors at BU do the same thing. With students, he has built a university-wide online repository where anyone – student or professor alike – can propose a global health topic. Once an idea is suggested, his team converts the concept to useful, bite-size nuggets, such as exam questions or project ideas. Faculty can then pull from that list for lessons and assignments, and Zaman and others will help them tailor the example to their lesson – be it chemistry, history, literature, or some other topic.

Muhammad Zaman is spearheading an effort to incorporate global health studies into the curriculum at Boston University.

The goal is to incorporate global health examples into as many types of classes as possible, says Zaman. For now, the resource is internal to BU, but he hopes to eventually make the system accessible to other universities.

In addition to infusing undergraduate classes with global health material, Zaman is ramping up the globalization of BU's engineering department. A biomedical engineering program called Quality, Exposure, Policy, Innovation and Implementation in Context, or Q-EPIC, includes a brand new, spring 2016 course called Engineering for Global Development. Q-EPIC will also incorporate global health problems into a yearlong sophomore lab taken by every engineering major at BU, and the summer program in Zanzibar will be available to seven or eight students annually.

"As students graduate and go into the real world, whether or not they stay in engineering, they will always retain this idea of how engineering transforms the real world," says Zaman. "If there is one thing I want them to come away with, that is it."

Reaching Out to the World

Not only are large research universities like Rice and BU developing global health programs, but so, too, are smaller liberal arts colleges. For example, three colleges in Pennsylvania recently launched HHMI-funded global health programs.

When Allegheny College in Meadville, in northwestern Pennsylvania, announced a new major in global health for the 2013-14 school year, the response was "rather alarming," says Lee Coates, a professor of biology. With a 2012 HHMI education grant, Coates and colleagues had spent a year developing the curriculum; as soon as it was announced, nine graduating seniors instantly came out of the woodwork and registered for the major. Freshmen, sophomores, and juniors enrolled in the program as well. "We had faculty interest, and now there was this incredible student interest," says Coates, project director of the Global Health Studies program.

Kevin Crooks, a sophomore biology major, immediately signed up for a minor in global health. "It was a new area of study, and I knew I wanted to jump right in," he recalls. Soon Crooks was adding classes in community health assessment and global health transitions to his packed schedule of molecular and cell biology classes.

This year, 18 seniors are enrolled in Allegheny's Global Health Studies program, and Coates expects it to soon enroll 25 to 30 majors per year. That rapid growth is a testament to the interest in the field and also to Allegheny's unique approach to global health, through four "pillars": science, health, and the environment; ethics and social responsibility; policy, resources, and economics; and cultures and society.

"This is a liberal arts approach to global health – it's bigger than just medical treatment," says Caryl Waggett, chair of Allegheny's Global Health Studies program. "Using these broader ways of thinking, students' skill sets are much better refined when they graduate."

In addition to coursework, many students in the program participate in either U.S.-based or international internships. About 40 students took part this year in initiatives ranging from a project to encourage breastfeeding in Pennsylvania workplaces, conducted in collaboration with the Women, Infants, and Children federal nutrition program, to internships in Mysore, India, where six students are currently working at health-care–related nonprofits.

Crooks spent six weeks after his junior year at an orphanage in Kenya, performing a systematic analysis of best practices at that orphanage and two others nearby. He found that the ratio of caregivers to children had a huge impact on the children's lives. "In the larger orphanage, there were 90 children to one or two caregivers," says Crooks. "It set the children back."

Since graduating, many of the first nine global health majors have taken positions with service agencies or entered

Paul Morigi

medical or public health school. Crooks had originally planned to go to medical school, but his experience in the Global Health Studies program changed his mind. Today, he is working on a master's in public health at Tulane University's School of Public Health and Tropical Medicine, while also spending two years in the Peace Corps. "I know now I can make an impact, not just be an observer," he says.

Southeast of Allegheny, another Pennsylvania college boasts a global health initiative. At Ursinus College, located on a 170-acre campus in suburban Philadelphia, biology professor Rebecca Kohn and colleagues saw a need greater than just pumping out biology majors and premeds. "We want to make sure students are thinking about their impact beyond their career as a doctor or in a research lab," says Kohn. "We want them to think about how they impact society, how they impact the world."

With an HHMI education grant awarded in 2012, Kohn and other Ursinus professors initiated the Center for Science and the Common Good, aimed at encouraging science majors to reflect on the role of science in society. Since its inception, the center has introduced new courses, internships, a speaker series, and student research programs, infusing the school's traditional science courses with ethics and global health topics.

Senior biology major Kathryn Yoo heard about the center from a teaching assistant in a chemistry class and thought it would give her a chance to travel internationally. It did far more than that. "I used to get so wrapped up in talking science, science, science – I didn't think about how it relates to other people, how it affects their lives," says Yoo. "Now, I do." It was the courses she took through the center, she says, that made the difference.

One such course, Science and the Common Good, examines the ethical, political, and religious implications of current scientific developments such as genome sequencing. Another course emphasizes how social, economic, and political forces influence sickness and treatments around the globe. Students like Yoo can also become fellows of the center, which involves intensive advising, a suite of specialized courses, and internship funding. Yoo spent five weeks in Peru working at a clinic for disabled children. "In the U.S., some of these kids would live at home and just go to physical therapy, but because of the structure of Peru's health-care system, these kids have no choice but to live in this clinic," she says. "It was shocking."

Because of her experiences, Yoo now plans to pursue an MD-MPH dual degree rather than just an MD. "I now know it's not just the medical side, but a lot of policy, that has an impact on health care. I want a background in that."

Almost 200 miles west of Ursinus, a trio of professors at Juniata College, a liberal arts school in the small town of Huntingdon, Pennsylvania, has dedicated an entire arm of their HHMI-funded Genomics Leadership Initiative to science's broad ethical, legal, and social implications – or ELSI, as they call the program.

ELSI thrives on breaking down academic silos at Juniata through interdisciplinary classes such as the Social History of Medicine, taught by a historian, and Doctors and Medicine in Literature, taught by James Roney, a professor of Russian literature and international studies, who co-leads ELSI. "A lot of these students are majors in the sciences who then do independent research, combining their scientific knowledge with work on ethics, global health, and the environment," says Roney.

At all three colleges, the focus is not only on the students but also on the faculty. At Juniata, the ELSI program hosts well-attended faculty lunches where professors in different departments talk about issues related to genomics. The program also hosted a January conference on teaching ELSI in the classroom. And over the last two summers, 12 faculty members attended an intensive two-week summer workshop that involved reading and discussing 10 books related to science and society, and developing genomics sections to include in courses across a range of disciplines.

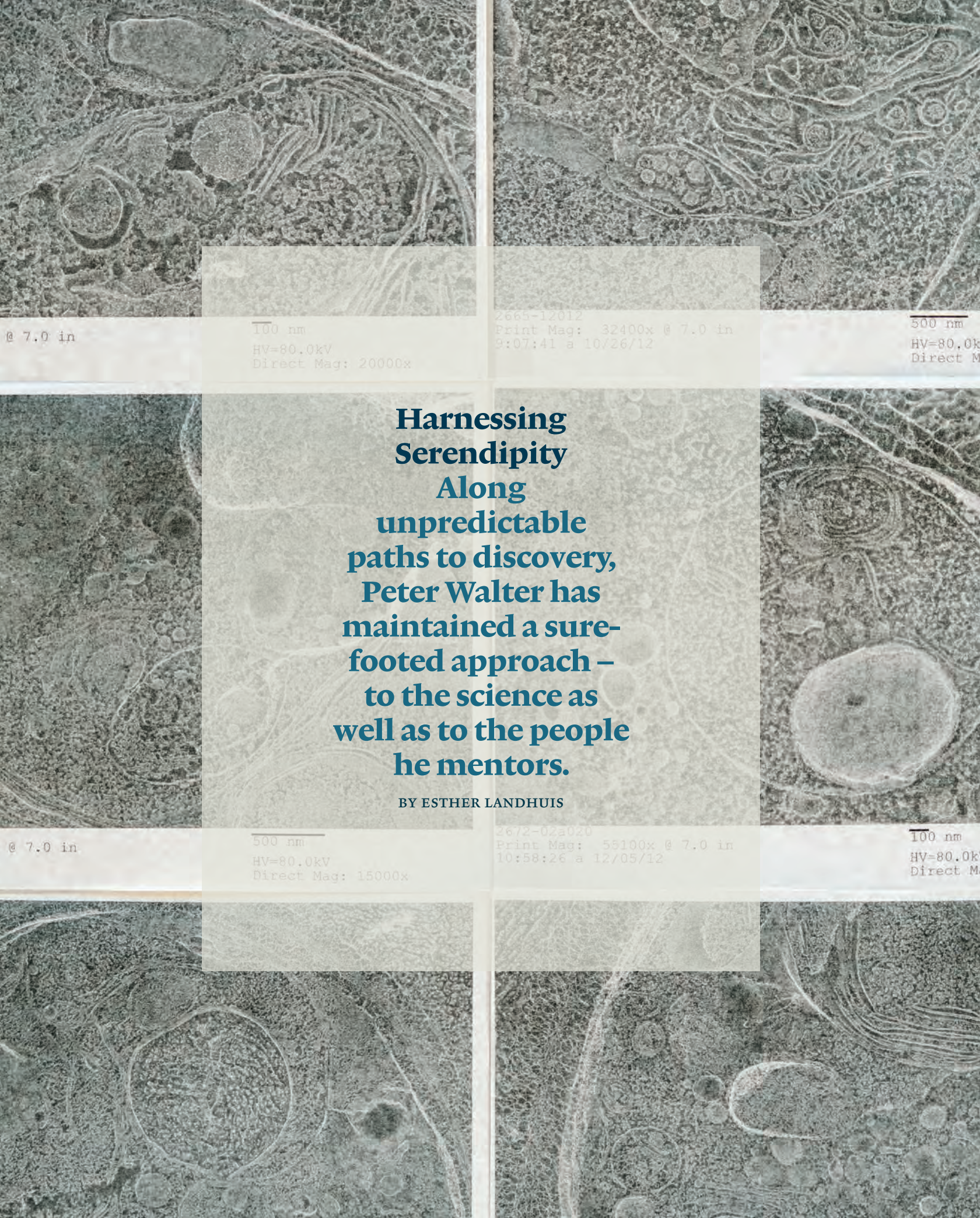
"It can be too easy to sit in your own office and critique how scientific research might lead to social inequality," says Roney. "Those of us who have been through these workshops take science much more seriously. I'm personally excited about this kind of model for what a liberal arts education can be, for both undergraduates and for faculty."

At Allegheny this summer, the Global Health Studies program hosted 38 faculty members from other schools in the U.S. and abroad to discuss and share global health courses and curriculums. "We had to develop our major from scratch," says Coates, "so we are always interested in sharing ideas with other folks and learning from them."

More and more schools are clamoring for global health programs, according to Richards-Kortum, who regularly receives requests from colleges interested in starting their own. And they should, adds HHMI's David Asai. "A program that teaches science or engineering and neglects the social implications is an incomplete education," he says. "I'm glad to see these top schools engage and expose their students to the real world." ■

After completing coursework at Ursinus College's Center for Science and the Common Good, Kathryn Yoo is set on making a difference in global health care.

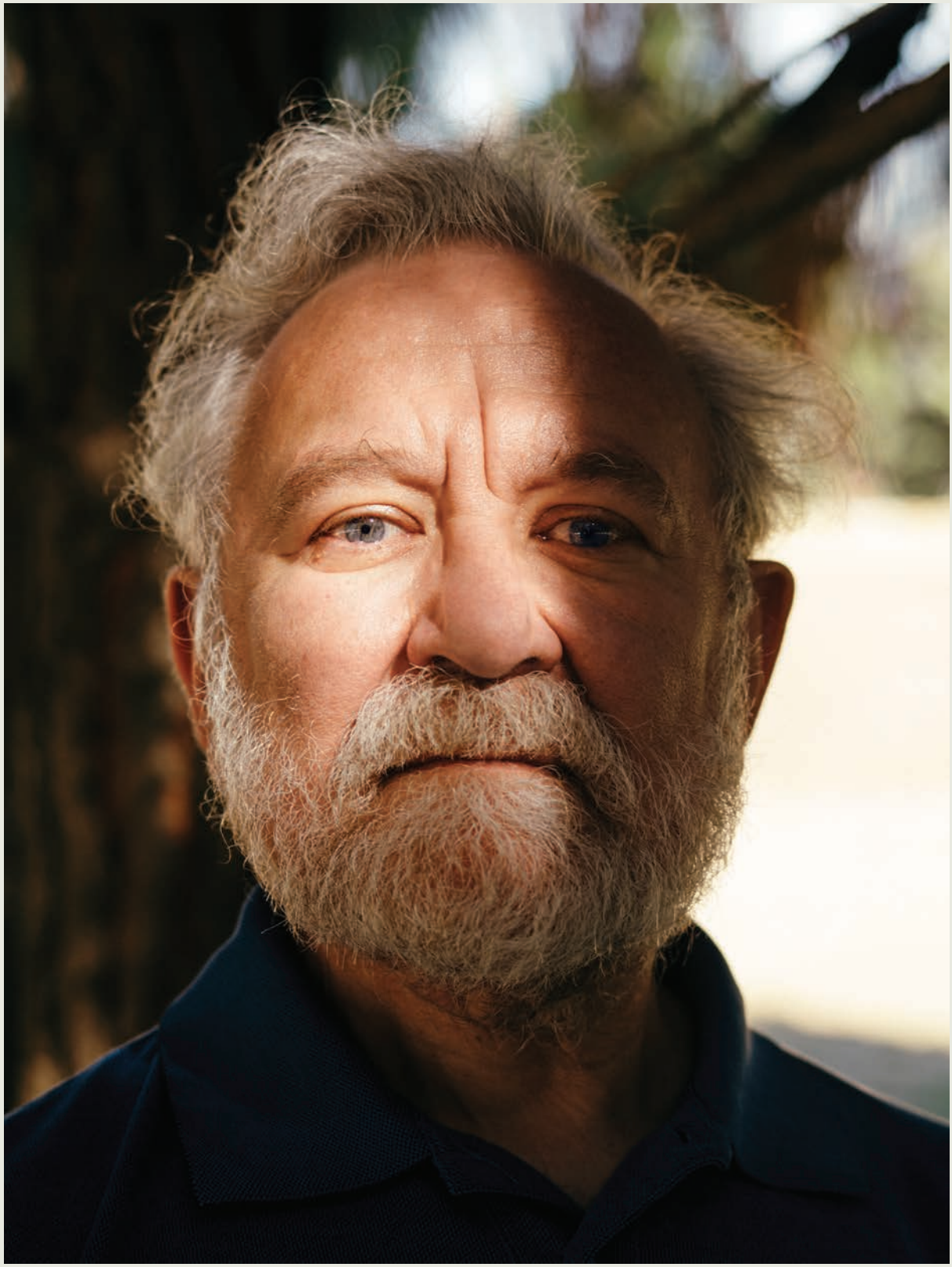
Gene Smirnov



Harnessing Serendipity

Along unpredictable paths to discovery, Peter Walter has maintained a sure-footed approach – to the science as well as to the people he mentors.

BY ESTHER LANDHUIS



PHOTOGRAPHY BY JAKE STANGEL

For a video about Peter Walter – and a glimpse of his lab's mascot – go to hhmi.org/bulletin/fall-2015.

IT'S A CREATURE OF LEGEND, a rare symbol of the inscrutable and unattainable. Yet in Peter Walter's large, third-floor office at the University of California, San Francisco (UCSF), a dazzling white specimen sits in plain view. "She's our lab mascot," says the German-born scientist, gesturing at the stuffed unicorn perched on a swivel chair beside bulging bookcases. "She represents the mystical things we discover."

The unicorn – a BigPlush.com purchase – stands three feet tall and has ink sketches of the group's most beloved molecules taped to her chest and brow. The lab presented Walter with the endearing monstrosity last fall, at a boat party celebrating his most recent awards. Walter's prize-worthy research has unveiled fundamental pathways in the cell that control how proteins are made and where they go. Imbalances in these systems can lead to a variety of diseases.

Why a unicorn? The one-horned icon harkens back to an article Walter shared with the lab, as he often does, to spur dialogue about topics of interest beyond his Genentech Hall quarters. This article's author was taking a jab at big-data science – likening the hunt for discoveries within huge data sets to the arcade game where you try to grasp small toys by maneuvering an electronic "claw," usually to no avail. The story had an amusing photo of a claw machine loaded with plush unicorns – prizes "most people can never grab," notes postdoctoral fellow Margaret Elvekrog. "But Peter did."

Walter doesn't come across as a go-getter. At a recent lab meeting, the white-bearded biochemist greeted group members with smiles and an occasional hug. His outfit that July morning consisted of a loose, blue button-down with khakis and Birkenstocks. During brief interjections, the professor's tone conveyed confidence and light-heartedness. But his interruptions were few. For most of the presentation, Walter peeled an orange and listened intently, brow furrowed.

An HHMI investigator since 1997, Walter has a tried-and-true approach: pose a single, simple question and probe it painstakingly. As a graduate student, Walter explored how a cell's proteins know where to go. What he found – the molecular machinery that brings nascent linear peptides to the intracellular factory that fashions them into three-dimensional proteins – helped propel his advisor, Günter Blobel, to the 1999 Nobel Prize in Physiology or Medicine.

The discovery also landed Walter his own lab at UCSF. There, the young scientist continued to study protein trafficking but shifted his gaze. His new focus: the signals that tell the nucleus when the cell's protein-folding factory – a maze-like structure called the endoplasmic reticulum (ER) – is overloaded. By the early 1990s, Walter's team uncovered the set of molecules that transmits this information. Called the "unfolded protein response" (UPR), this quality-control system senses when misfolded proteins accumulate and spurs the cell to make more ER. The UPR "makes life-or-death decisions for cells," says Walter. But if things go awry, it can prompt neurons to die inappropriately, leading to neurodegenerative disease, or keep alive menacing cells, causing cancer.

Through a 2008 Hughes Collaborative Innovation Award – a program designed to support team projects of ambitious scope – Walter and colleagues synthesized small molecules that can regulate the UPR. Now the researchers are probing how the UPR functions in various disease models in the hope of one day tweaking the system to help patients. One compound made recent headlines because it enhances cognition in mice. This molecule is undergoing further development at Calico, a Bay Area biotech firm devoted to fighting age-related diseases.

Walter's pioneering research on the unfolded protein response has earned him a growing list of accolades – including a Shaw Prize and a Lasker Award in 2014, and this year's Vilcek Prize in Biomedical Science, which recognizes creative contributions of immigrants.

Chasing Freedom

Walter's path toward success began in the 1960s, when he was a curious lad tinkering with chemicals at his parents' *Drogerie* (a store that sells nonprescription medicines and household products) in West Berlin. Those playful experiments produced a few explosions, admits Walter, "some of which my parents never knew about."

The "ignorance is bliss" mantra likely applies. His explorations in the family shop led Walter to decide by age 12 that he would major in chemistry. However, the science training he got as an undergraduate at Free University in Berlin was unsatisfying. The lab experiments were too prescribed, Walter recalls.

Determined to improve his English so he could read important biochemistry papers, Walter applied for a Fulbright scholarship to study abroad. He was rejected. But thanks to a different fellowship, Walter was able to pack his bags and fly to Nashville, Tennessee, where he spent nine months working on the biosynthesis of a fungal alkaloid in Tom Harris's lab at Vanderbilt University. "I got two papers out of that," says Walter. "And I picked up some English."

But most of all, he relished the independence. "As a lowly student, I was given tremendous freedom to play and use sophisticated instruments," says Walter in his lilting German accent. "I was immersed in real research rather than having to follow a curriculum and do experiments that zillions of students had done before."

That appreciation for unbridled freedom carries through to this day, as Walter manages two dozen technicians, students, and scientists in his lab at UCSF. "He gave us freedom to follow our passions," says Carmela Sidrauski, a former PhD student and postdoc in the Walter lab. "He's not scared to go into areas he hasn't yet explored. He will take the journey with you."

Walter compares the journey of a scientist to that of an artist. "It's not enough to do the same thing over and over and do it perfectly," he explains

Given his travel schedule, Walter appreciates the fact that the succulents on his office windowsill tolerate erratic watering.

during a drive across town to his two-story brick home, whose garage he's converted into a woodshop. "In science and art, the essence is doing something no one has done before."

That principle permeates gatherings of his lab team. Years ago, at one of the group's annual retreats, Walter brought canvases and acrylics and had everyone paint their own project. "I wasn't sure if that would go down like a lead balloon," he says. "But everyone got into it." Holiday parties at the Walter home include a "Secret Santa" gift exchange where lab members give each other homemade books, board games, and such. One travel-heavy year, Walter received a Waldo-style "Where's Peter?" map.

Now that grant writing and traveling leave the senior scientist little time to tinker in the lab, Walter tools around in his home woodshop. Some creations are whimsical – for example, a garden sculpture of cubes giving birth, or a six-foot-long twisted copper fountain. Others are highly practical – like the clock he plans to give his younger daughter for her October wedding. "I like creating things with my hands," Walter says. "I'm constantly inventing little tricks and solving problems."

The Detergent Trick

Of course, persistence and ingenuity also pay off at the lab bench. Six years before Walter started his PhD at Rockefeller University in New York in 1977, his advisor, Blobel, had proposed a controversial theory. He hypothesized that proteins destined for the ER carry a signature sequence – an address tag that lets the cell know where that protein needs to go. The idea was intriguing, but without direct evidence many scientists dismissed it. They figured proteins simply drifted to the ER by thermodynamic forces, not through a specific targeting mechanism. To prove the latter, Blobel, an HHMI investigator since 1986, would need to isolate this targeting machinery.

As a first step, Blobel worked out a system for studying protein assembly in a test tube. That was quite a feat in and of itself. But there was a nagging problem: when Walter, as a new graduate student, tried to purify an agent responsible for transporting new peptides to the ER, its activity seemed to fizzle out in one of the wash steps.

Puzzled but captivated, Walter repeated the experiment again and again, adjusting the conditions meticulously. Instead of discarding "dead" wash fractions, he stashed them in the fridge. He was "waiting for the day they would wake up," Blobel says.

Sure enough, Walter discovered he could revive the samples with a dash of nonionic detergent. Now he could use conventional procedures to purify the molecular assembly that brings fledgling proteins to the ER. Dubbed the signal recognition particle (SRP), this complex gloms onto a sequence of amino acids on some newly forming peptides. The SRP then ferries the peptides to the ER by docking at a specific surface receptor.

Fast Fame

Walter described the purification of SRP in a landmark 1980 paper. His findings provided the first evidence that proteins reach the ER not by chance but through a controlled process governed by dedicated

"He gave us freedom to follow our passions. He's not scared to go into areas he hasn't yet explored. He will take the journey with you."

—CARMELA SIDRAUSKI

Peter Walter, who's won both the Shaw Prize and a Lasker Award, has been on the UCSF faculty since 1983.

targeting machinery. He became "instantly famous," Blobel says. Walter soon made an even bigger splash – and reeled in job offers – after a serendipitous mishap lifted the veil on one of SRP's most intriguing features.

Walter routinely measured the concentration of his samples of purified SRP on the lab's spectrophotometer. This machine shines ultraviolet light through a solution and calculates how much gets absorbed. Assuming SRP to be a protein complex, Walter set the spectrophotometer to read at 280 nanometers – the wavelength for detecting proteins. However, one day a lab member doing a different experiment had calibrated the device to 260 nanometers instead of 280. When Walter came along later with his SRP sample, the signal was twice as high as he was used to seeing.

"He could have said, 'Oh well, this was an accident,'" Blobel says. Instead, Walter pondered the data and realized something else was going on. The SRP is no ordinary protein complex – it contains a previously undetected RNA. (Unlike protein-containing samples, which are read at 280 nanometers, nucleic acid solutions are measured with the spectrophotometer set to 260 nanometers.)

Happenstance might have nudged the SRP-RNA discovery. However, "luck is only recognized by those who are prepared," notes Blobel. Walter "is an incredible detective," he says. "From the tiniest bit of evidence, he pursues and eventually finds what is beautifully hidden."

One of Walter's current graduate students, Aaron Mendez, is glad nothing escapes his mentor's scrutiny. "Often you get blinded when you see a negative result," Mendez says, recalling a perplexing experiment where a manipulation that was supposed to help his cells live longer instead made them drop like flies. "It was demoralizing," he says. "Peter helped me get out of my tunnel vision. Sometimes it's the things that don't work that end up opening new avenues."

In that case, Walter guided his student through a rough patch by reminding him of the bigger picture. Other times, Walter brings focus to students' work.

"Peterizing"

When Sidrauski wrote her first paper as a graduate student in the lab two decades ago, she appreciated Walter's steel-trap mind. Scrolling through the manuscript line by line, "he would 'Peterize' the text – *What does this mean? Why did you do the experiment?* – translating it so someone without the background could understand," recalls Sidrauski, who now works at Calico. "You could always tell when Peter had revised a manuscript."

Though long and arduous, writing papers together was one of the things Sidrauski loved most about working with Walter. She brought papers to his home on weekends – the only time he wasn't booked – and they would pore through them over a glass of wine. "Sometimes it got so late I'd stay for dinner with his wife and family," says Sidrauski.

Walter met his wife, Patricia Caldera, at a party while both were working on their PhDs in New York. A native of Mexico, Caldera helped coordinate UCSF's outreach to local science teachers until retiring a few years ago. The couple raised two daughters; Gabriela is an architect in San Francisco, and Sylvia is a schoolteacher in Portland, Oregon.

Walter considers the lab his "second family." Its members are close-knit and supportive. In between experiments, many bustle around the lounge that joins the lab to Walter's office, gulping coffee or chatting over lunch. The group includes musicians, artists, and athletes from all corners of the world. Yet the diverse crew carries on like a well-oiled machine, even when Walter travels for weeks at a time. Some think the secret is Walter's knack for attracting highly motivated free spirits like himself. (Walter himself says he looks for "endless curiosity and independence" in prospective lab members.)

"Each person has a strong personality," says postdoc Diego Acosta-Alvear. "A lot of us have creative passions." Acosta-Alvear, for example, plays the electric bass. He's also building one. On sporadic weekends Acosta-Alvear carefully cuts, sands, and laminates wood pieces in Walter's garage woodshop. Construction of the five-string fretless "baby" began about two years ago, before Acosta-Alvear's wife gave birth to a real one – their daughter Ana Sofia.

The bass project grew out of conversations with Walter during a painful turning point in Acosta-Alvear's research. "I had to leave a main project I'd been working on for a couple of years. It was a hard time for me," recalls Acosta-Alvear. "Peter offered his home, his shop, and his help so I could have something to do outside of lab, to help me regroup and refocus."

"It's not enough to do the same thing over and over and do it perfectly. In science and art, the essence is doing something no one has done before."

—PETER WALTER

UPR and Beyond

When Walter arrived at UCSF in 1983 to set up his own lab, he, too, made a deliberate shift from the research he had previously pursued at Rockefeller. "I wanted to start something new," recalls Walter, gazing out his office window. On a knoll below stands *Dreamcatcher*, a 50-foot-tall steel sculpture by Mark di Suvero installed by the university to inspire innovation.

Back in the 1980s, scientists knew that when misfolded proteins accumulate, the cell makes more ER. It was also clear that this compensatory activity is triggered by changes in the expression of genes in the cell's nucleus. But how does the nucleus know what's going on in the ER? "We wondered how that information travels between different compartments," Walter says.

To find out, two of his graduate students, Jeff Cox and Caroline Shamu, set up a yeast genetic screen. They wanted to identify molecules responsible for ER-to-nucleus communication – a pathway now known as the unfolded protein response. They discovered Ire1, a sensor molecule embedded in the ER membrane. However, unlike a typical membrane receptor – which activates a cascade by transmitting a signal to another protein, which in turn hands it off to another protein, and so forth, until the signal reaches the nucleus – Ire1 behaves like a bunch of different proteins bundled into one package. Its sequence of actions triggers a splicing event that signals the nucleus to turn on genes that will boost the cell's ER resources. "As the story progressed, it became super exciting," says Walter. "Every bit of this pathway is bizarre."

But here's the clincher – the essential UPR features that were discovered in yeast are also found in mammals. The mammalian UPR is more complicated, though: it has three branches, each controlled by a different sensor (Ire1, ATF6, or PERK), whereas yeast just have Ire1.

Collaborating with several groups, Sidrauski and others in the Walter lab identified small molecules that modulate the activity of each UPR branch in mammals. One of these modulators, ISRIB, makes cells insensitive to a particular chemical change – phosphorylation of the eIF2 molecule. Normally, this phosphorylation event puts a brake on memory consolidation.

Nahum Sonenberg, a biochemist at McGill University in Montreal and an HHMI senior international research scholar, had a mutant mouse in which this phosphorylation event is partially blocked. Those mutants outperformed normal mice in tests of cognition. Walter surmised that giving mice ISRIB would be the pharmacological equivalent of the genetic tampering that made Sonenberg's mutants smarter. Indeed, when the team injected ISRIB into ordinary mice, the animals learned better.

ISRIB activates a complex of proteins that, if mutated in people, can cause a rare and often fatal neurodegenerative disorder. At Calico, Sidrauski and her colleagues are conducting preclinical studies to explore whether it may be possible to prevent neurological deterioration in patients with this disorder by using ISRIB to revive activity in the flawed proteins.

Walter stresses that they did not begin by focusing on a particular disease. "We are trying to understand the basic ways by which cells operate," he says. That knowledge can then guide the research along paths that lead to an exploration of what goes wrong in disease and whether it's possible to intervene clinically.

The unpredictable nature of this journey led Walter, in a 2010 commentary, to describe the path to discovery as "serendipity." It's thus no surprise that when he and his labmates began discussing names for their unicorn mascot, Serendipity was Walter's own suggestion. After all, "she represents the mystical things we discover," he has pointed out. Just as many scientific questions remain unanswered, the unicorn's name was still unsettled. But she's due to be christened at the lab's annual retreat this fall. ■

Problem Solvers

BY NICOLE KRESGE

HHMI's 26 new investigators will have the freedom to pursue the questions that fascinate them the most.

BRITT GLAUNSINGER

JOSHUA MENDELL

REUBEN HARRIS

SQUIRE BOOKER

HENING LIN

JOSEPH MOUGOUS

JOHN MACMICKING

DORIS TSAO

TOBIAS WALTHER

JARED RUTTER

KIM ORTH

XINZHONG DONG

YIFAN CHENG

JENNIFER ZALLEN

PORTRAITS BY
BARRY FALLS

KRISHNA SHENOY

J. PAUL TAYLOR

LOREN FRANK

MICHAEL LAUB

JAY SHENDURE

PARDIS SABETI

JOB DEKKER

JOANNA WYSOCKA

ANDREAS MARTIN

OLGA BOUDKER

LEVI GARRAWAY

SUE BIGGINS

To learn more about the newest cohort of HHMI investigators, go to hhmi.org/bulletin/fall-2015.

Six Golden Eggs

AS A TEENAGER, Doris Tsao picked up Immanuel Kant's *Critique of Pure Reason*, an investigation into the origin of human knowledge. The book is not an easy read. Tsao admits she made it through only the first 60 pages, but even that brief dip into Kant's writings made a huge impression on her. Already set on a career in science, Tsao had her eyes opened by the book to the mysteries of the brain and spatial perception. While still in high school, she settled on the scientific problem she would devote her life to: How does the brain translate photons of light into recognizable objects?

Science is filled with questions like Tsao's. How does the brain generate consciousness? How did life begin? How does a protein's sequence determine its shape? Some scientists, like Tsao, find their questions at a young age. Others stumble upon them later in life. Regardless of their genesis, such questions are the force that pushes scientific exploration forward. Discovery doesn't happen without inquiry, and every experiment starts with a question.

This past May, HHMI announced that Tsao and 25 other talented scientists would be given an initial five years of freedom to pursue the scientific questions that keep them up at night. The Institute has committed $153 million to support this newest cohort of HHMI investigators. Chosen from among 894 candidates, the researchers hail from 19 institutions and represent a variety of disciplines, ranging from computational biology to biochemistry to neuroscience. And with them, they bring a diverse array of problems they hope to solve.

Doris Tsao, now at the California Institute of Technology, is still trying to get to the bottom of how the brain represents visual objects. Her dream, she says, is to understand the visual system with the same mathematical clarity that physicists use to understand the universe.

"One reason I'm so interested in object perception is that objects are essentially information folders," she explains. "The contents of these folders are read in dozens and dozens of visual areas in the brain, and I'm trying to understand exactly how this is organized."

Tsao made a major step toward cracking the brain's filing system in 2006, when she was a postdoctoral fellow at Harvard Medical School. She and Harvard electrophysiologist Winrich Freiwald combined two of the most important tools in neuroscience – brain imaging and single neuron recordings – to reveal areas of the monkey brain whose sole purpose is recognizing faces. First, the pair used functional magnetic resonance imaging to get a bird's-eye view of the brain and pinpoint the areas – six in all – that saw increased blood flow as monkeys viewed pictures of faces. Then, during what Tsao calls one of the most exciting days of her life, they probed one of those areas of the brain with electrodes and discovered that almost every single neuron in the patch fired only in response to faces. The same was true for the other five areas. These "face patches," as Tsao named them, were the first concrete evidence that the primate brain operates something like a face-processing machine.

"These patches are like a half-dozen golden eggs, and we're trying to understand how each one is processing faces in detail," says Tsao. She's only just scratched the surface, but it's clear that the patches are working together to recognize and discriminate among faces. Each face patch has its own task; some respond to certain characteristics like amount of hair or iris size, while others are in charge of recognizing faces from specific views, such as the front or side.

Next, Tsao wants to figure out how the brain takes bits of information – like facial features – and integrates them into a perception of a whole object. To this end, she has recently embarked on a collaborative project with her mathematician father, Thomas Tsao. They're working on a mathematical theory to solve one of the greatest problems in vision – the invariance problem, or how objects can be recognized despite changes in appearance due to perspective.

Radical Research

Squire Booker's passion lies at the opposite end of the spectrum from Tsao's. While Tsao is after the big picture of brain function, Booker is fascinated by the atomic details of chemical reactions. The origins of his research were not quite as deliberate as Tsao's, either.

"When I was in college, I liked a lot of different areas of science, and I wanted to be able to do a little bit of everything," he explains. "But one of my professors at Austin College told me, 'If you want to do research, you're going to have to choose. You're going to have to decide what you want to be.'" Booker chose enzymology, a discipline that incorporates everything from analytical chemistry to bioinformatics. "I'm sort of a jack-of-all-trades," he says. "Not necessarily a master of anything, but able to blend a lot of scientific disciplines into one."

This cross-disciplinary approach, combined with a nose for important research problems and a knack for clever experimental design, has allowed Booker to decipher the chemistry behind dozens of novel reactions in biology. In his lab at Pennsylvania State University, Booker studies a large family of proteins called radical S-adenosylmethionine (SAM) enzymes. The enzymes, which are found predominantly in anaerobic bacteria, harness the energy from an unstable form of S-adenosylmethionine to drive reluctant chemical reactions forward.

In true polymath fashion, Booker combines a variety of biochemical, enzymological, and structural tools with small-scale organic synthesis and fast-reaction kinetic methods to figure out what makes these radical reactions go.

One of those reactions is catalyzed lipoyl synthase, a radical SAM enzyme that adds sulfur atoms to octanoic acid inside cells. The resulting product, lipoic acid, is an important cofactor involved in energy metabolism and the breakdown of a number of different amino acids. "If you don't have lipoic acid, you die," Booker explains. In 2004, and most recently in 2014, he worked with Carsten Krebs, one of his colleagues at Penn State, to show that lipoyl synthase uses an unstable SAM molecule to remove two of its own sulfur atoms to donate to octanoic acid. Interestingly, this action renders lipoyl synthase unable to catalyze any further reactions. "In other words, the enzyme kills itself after it does a turnover," Booker says. "It's completely novel, and a lot of people didn't want to believe this mechanism at the time."

Another radical SAM enzyme called Cfr confers antibiotic resistance, most notably to some strains of *Staphylococcus* bacteria. Cfr adds a methyl group to the bacteria's ribosomal RNA, which blocks antibiotic binding to the ribosome. Booker and his colleagues solved the three-dimensional structure of the related enzyme, RlmN, and elucidated the mechanism that Cfr and RlmN use to add that methyl group. Because the atom that receives the methyl group is inert and can't easily accept new chemical groups, Cfr has to take a methyl group from a SAM molecule, strip it down, and then rebuild the methyl on the target RNA, rather than just transferring it whole. Now that he knows how Cfr works, Booker is looking at ways to stop the reaction and prevent antibiotic resistance.

Discovery doesn't happen without inquiry, and every experiment starts with a question.

Booker's latest endeavor is a big one. He's partnered with several other labs to assign functions to radical SAM enzymes. Of the protein family's almost 115,000 members, the vast majority catalyze unknown reactions, so Booker and his team have their work cut out for them.

Granular Investigation

J. Paul Taylor is also interested in unknowns, only his relate to neurodegenerative diseases. In 2004, Taylor was just starting his lab at the University of Pennsylvania School of Medicine. A trained clinical neurologist with a love of research, he was interested in the genetic basis of motor neuron diseases but didn't have a set research program. "I basically started my lab with no projects and just followed what came in the door at the clinic," he recalls.

What came through the door were patients with odd versions of common neurodegenerative and muscle diseases: families with inherited diseases that didn't fit neatly into a standard diagnosis, or patients with genetic mutations who developed something other than the expected syndrome. Neurologists call these patients outliers – cases that can't be explained by known disease-causing genes. "Those are the ones I went after, and we began to find a whole series of new genes that have given us complete insight into the basis of such diseases," says Taylor.

By sequencing the outlier patients' exomes, or expressed DNA, Taylor and his collaborators have been able to pinpoint the genes responsible for their symptoms. Surprisingly, he found evidence that many seemingly unrelated degenerative brain diseases are caused by mutations in RNA-binding proteins associated with so-called stress granules. These clumps of RNA and protein assemble when a cell encounters unexpected stress, such as extreme heat, and needs to quickly switch up the genes it's expressing. By sponging up loose RNA, the cell

can prevent the nucleic acid from being translated into protein until the stress is over. Taylor and his colleagues discovered that disease-causing RNA-binding proteins fall into two classes: those that are part of the granules themselves, and those that assist in granule assembly or disassembly.

Taylor has moved his lab to St. Jude Children's Research Hospital in Memphis and is now focusing on how these mutant RNA-binding proteins produce disease. He learned that the mutations can cause hyper-assembly of granules or impair granule disassembly. But the mutant proteins are also very prone to forming amyloid-like fibrils, such as the ones found in patients with amyotrophic lateral sclerosis or certain illnesses causing dementia. "We don't know if the bad thing is the accumulation of these fibrils, or the fact that you are holding the granule together too long and the RNAs are not liberated to be used – or both," he says.

Another puzzle Taylor wants to solve is why these ubiquitously expressed RNA-binding proteins cause disease only in neurons and muscles, and why mutations that exist throughout life don't cause disease until a person is 40 or 50 years old. "These questions have been there since I was born, and for all I know, they may still exist when I'm long gone," he explains. "But they're always in the back of my mind every time we make an advance."

Chromosome Segregation

In the late 1990s, **Sue Biggins** had mutants on her mind as well. She was a postdoctoral fellow in the lab of geneticist Andrew Murray, who was then at the University of California, San Francisco, and is now an HHMI professor at Harvard University, using a new technique to track yeast chromosomes. Looking through a microscope, Biggins noticed a group of mutant cells that couldn't seem to segregate their chromosomes correctly during cell division. When she examined those mutants more closely, she saw that a chromosomal structure called the kinetochore was affected. "So I started digging deep in the literature to learn more about kinetochores, and that's when I realized how little was known," she recalls. When it came time to start her own lab at the Fred Hutchinson Cancer Research Center in Seattle, Biggins wrote a research proposal on the kinetochore – what she wanted to learn about its components and how they function.

Kinetochores are complex molecular machines made of hundreds of proteins. They connect chromosomes to the long, thin microtubules that tug them to opposite ends of a dividing cell. But this is no easy task. Microtubules are constantly in flux, growing and shrinking at a rapid pace, and kinetochores need to keep their grip on them while simultaneously bearing the load of the chromosome. This interaction is so crucial to cell division that a surveillance mechanism called the spindle checkpoint immediately halts the cell cycle if a single kinetochore is not properly attached to its microtubule.

"These questions have been there since I was born, and they may still exist when I'm long gone. But they're always in the back of my mind."

—J. PAUL TAYLOR

In 2000, just after opening her lab, Biggins decided that her best shot at understanding the kinetochore was to remove it from its complicated cellular milieu. She chose to isolate a relatively simple kinetochore, a complex of about 250 proteins, from budding yeast. "It was very much trial and error and brute force, but my grad student figured it out," says Biggins.

Her research quickly took off from there. With pure kinetochores in hand, Biggins made several discoveries about the molecular machines. When she and her University of Washington collaborator Charles Asbury added microtubules to the mix, they made the surprising finding that tension directly stabilizes kinetochore attachments to microtubules. As with Chinese finger traps, the harder the microtubules pull on the kinetochores, the stronger their grip on chromosomes. Her team has also identified many of the molecular events that regulate kinetochore assembly and the spindle checkpoint pathway.

In 2012, Biggins and Tamir Gonen, a group leader at Janelia Research Campus, published the first-ever three-dimensional structure of an isolated kinetochore attached to a microtubule. Their images revealed a key factor in the molecular machine's ability to maintain its grip on those dynamic microtubules: multiple attachment points. "It's like you're climbing a rope and someone's always pulling the rope out from under you," says Biggins. "One way to stay attached is to have multiple contacts so that if one releases, the other one is still there."

Ultimately, Biggins wants to understand what's gone awry in cancer and other diseases, such as birth defects, involving the wrong number of chromosomes. "Aneuploidy is one of the biggest hallmarks of cancer cells," she explains. "Whether and how often it arises due to altered kinetochore function, no one knows." To figure that out, she'll have to isolate the human kinetochore. So far, no one has done it, but Biggins and her team are already working on the challenge.

A 3C Concept

Job Dekker has been trying to answer a different question involving chromosomes for almost 20 years. As a postdoctoral fellow at Harvard University, he started thinking about how genomes and chromosomes work from a different point of view. "Most people see chromosomes as long molecules full of information," Dekker explains. "But I've always been driven by the idea that if we want to understand how cells work with that information, we have to understand how chromosomes are organizing, how they live inside cells. What does the living genome – the real chromosome – actually look like?"

What we do know is that the chromosome is extremely long and very dynamic. During mitosis, it needs to fold its six feet of DNA into an improbably compressed form. At other times, the very same chromosome must reorganize itself in a completely different, less compact, fashion to make its genes accessible for transcription. Both forms of DNA are physically distinct and extremely customized for the tasks at hand.

To determine what a chromosome looks like in three dimensions, Dekker developed a technique for detecting physical interactions between DNA segments. The result is comparable to a molecular microscope. "I remember when I proposed this in a lab meeting, I just had a rough scheme of how this would work. Almost everybody said it would never work," Dekker recalls. But it did. In spades. Today, hundreds of scientists around the world are using Dekker's chromosome conformation capture, or 3C, method to find connections between far-flung regions of DNA.

The concept behind 3C is surprisingly simple. Because DNA is folded, genes that are otherwise far apart along the linear molecule can end up extremely close together in three-dimensional space. By cross-linking neighboring areas of DNA and then cutting those regions into small pieces for sequencing, Dekker was able to decipher which parts of the chromosome interact with each other. The more interactions between segments, the more closely the segments are associated in space.

Since opening his own lab at the University of Massachusetts Medical School in 2003, Dekker has refined 3C to visualize entire genomes. In 2009, he published the first three-dimensional map of the human genome. The map revealed a lot about chromosomes, including the fact that loops of chromatin are used to activate the right genes at the right times, and that DNA is compartmentalized into "neighborhoods" of active and inactive genes. The map also provided physical evidence for how some genes can be regulated by distant bits of DNA called enhancers.

Although Dekker has finally created the map he dreamed of back in 1998, he is nowhere near ready to move on to a new problem. "I thought that if we solved the structure, we would get all the answers," he admits. "We did get some answers, but it also raised a lot of questions that we didn't even think of asking earlier." Answers that he intends to pursue during the next five years, as an HHMI investigator. ■

2015 HHMI Investigator Competition Winners

Sue Biggins, PhD
Fred Hutchinson Cancer Research Center

Squire Booker, PhD
Pennsylvania State University, University Park

Olga Boudker, PhD
Cornell University

Yifan Cheng, PhD
University of California, San Francisco

Job Dekker, PhD
University of Massachusetts Medical School

Xinzhong Dong, PhD
Johns Hopkins University

Loren Frank, PhD
University of California, San Francisco

Levi Garraway, MD, PhD
Dana-Farber Cancer Institute

Britt Glaunsinger, PhD
University of California, Berkeley

Reuben Harris, PhD
University of Minnesota, Twin Cities

Michael Laub, PhD
Massachusetts Institute of Technology

Hening Lin, PhD
Cornell University

John MacMicking, PhD
Yale University

Andreas Martin, PhD
University of California, Berkeley

Joshua Mendell, MD, PhD
University of Texas Southwestern Medical Center

Joseph Mougous, PhD
University of Washington

Kim Orth, PhD
University of Texas Southwestern Medical Center

Jared Rutter, PhD
University of Utah

Pardis Sabeti, DPhil, MD
Harvard University

Jay Shendure, MD, PhD
University of Washington

Krishna Shenoy, PhD
Stanford University

J. Paul Taylor, MD, PhD
St. Jude Children's Research Hospital

Doris Tsao, PhD
California Institute of Technology

Tobias Walther, PhD
Harvard University

Joanna Wysocka, PhD
Stanford University

Jennifer Zallen, PhD
Memorial Sloan Kettering Cancer Center

Perspectives & Opinions

Catalysis

A new HHMI science education initiative reflects some of the same qualities – and rules – as a catalytic reaction, says David Asai, senior director of the Institute's undergraduate and graduate programs.

A COUPLE OF generations ago, students majoring in what we now call the STEM fields – science, technology, engineering, and math – fit a homogeneous profile: most were single, white, and male; they entered college at 18 with solid academic preparation; and they generally graduated in four years.

Today's STEM students stand in stark contrast to that homogeneity. As noted in the 2012 report from the President's Council of Advisors on Science and Technology, they instead "come from diverse backgrounds, have widely divergent levels of preparation, may be returning to school after years in the workforce or serving in the U.S. military, and often are employed while in college to support themselves and families." Many STEM students nowadays – 50 percent of those earning bachelor's degrees and 20 percent of those earning PhDs – have taken at least one course at a community college, and about 30 percent of undergraduates depend on community colleges for their introductory coursework. Nearly 25 percent of undergraduates are first-generation college students – meaning their parents don't hold a college degree. Racial and ethnic "minorities" (who soon will be a majority of the nation's population, according to U.S. Census projections) and individuals from economically disadvantaged backgrounds are disproportionately overrepresented among transfer and first-generation students, but significantly underrepresented among those students who complete the baccalaureate degree.

David Asai

—

David J. Asai is senior director of undergraduate and graduate programs in science education at HHMI.

These "new majority" students – a term coined by Carol Geary Schneider – are vital for the future of science. They are a large and growing part of the pool that will supply the nation's future scientific talent. And they bring to science the diversity of perspectives needed for creative problem solving. Unfortunately, today's educational system fails to enable these students to realize their potential. The baccalaureate completion rate is nearly six-fold better for students who begin college at a four-year institution compared to those who begin in community college.[1] And, in a study of a large cohort of students from 1992 to 2000, the baccalaureate degree completion rate for students whose parents had a bachelor's degree was nearly three-fold greater than for first-generation students.[2]

A new HHMI initiative, dubbed Inclusive Excellence, challenges colleges and universities to do a better job at providing effective science education for *all* students, especially those who come to college along nontraditional pathways. Our goal is to catalyze change that will result in lasting institutional capacity for inclusion, reaping benefits well beyond the lifetime of the HHMI grant.

What do we mean by "catalyze change"? In my previous life as a faculty member, I began my introductory biology course every semester by discussing a simple biological reaction – the phosphorylation of glucose in the first step of glycolysis, the cellular process that breaks down sugar to yield useful energy. In this example, the reaction substrates (S) are glucose and ATP, the product (P) is glucose-6-phosphate, and the catalyst (E) is the enzyme hexokinase, as indicated in this simplified equation:

$$\mathbf{S + E} \rightleftharpoons \left| \mathbf{S \cdot E} \right| \rightarrow \mathbf{P + E}$$

This metaphor reminds us of three rules relevant to the HHMI initiative:

Rule 1: The enzyme is not consumed; it is recycled, available to catalyze the same reaction again and again. The HHMI grant should be a catalyst and not a substrate for campus change. As a catalyst, the grant should enable the institution to change the way it does business, continuing its forward trajectory by implementing inclusive practices that persist.

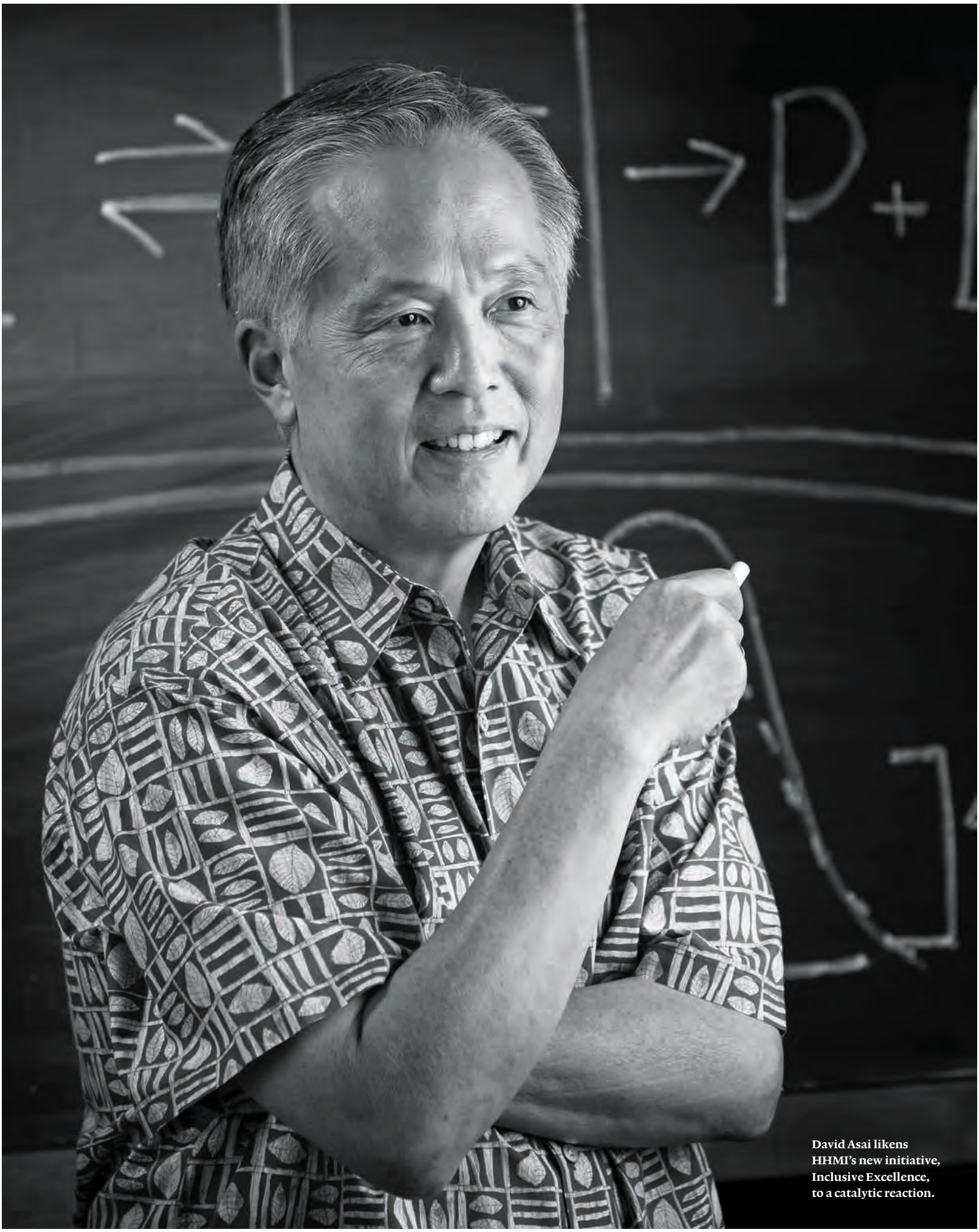
Rule 2: The enzyme makes the reaction go faster, but only if the reaction is energetically spontaneous. Translating that concept to the Inclusive Excellence initiative, the institution must be ready for change. This means a successful idea cannot depend on one lonely champion; it has to be owned by the institution and engage a large number of faculty and administrators.

Rule 3: Wanting something and achieving it are not the same. The enzyme accelerates the spontaneous reaction by forming, with the substrate, the transition state, during which the reactants are twisted and contorted under enormous strain. The transition state is so unstable that it can't be readily isolated and so is denoted within brackets. Nevertheless, for the reaction to go all the way to the right, it has to go through the transition state. Therein lies a third important lesson for the Inclusive Excellence initiative. Because the goal is to change the way an institution thinks and behaves, getting there will require the institution to go through transition states, times of strain and difficulty. Indeed, if the institution does *not* go through difficult transition states, it will likely not achieve the cultural changes we seek.

Especially during such times, institutional leadership and collective focus are critically important. The good done by colleges and universities depends on people – faculty and administrators – working with all students. Our goal is that, through the HHMI Inclusive Excellence initiative, colleges and universities will undergo these difficult but necessary transitions.

1. Skomsvold et al., 2011. National Center for Education Statistics.
2. Chen and Carroll, 2005. National Center for Education Statistics.

Paul Fetters



David Asai likens HHMI's new initiative, Inclusive Excellence, to a catalytic reaction.

Perspectives & Opinions

Q&A

What career lessons do you pass on to young scientists?

Advice can be beneficial, especially when it comes from someone who has been in your shoes. Here, four HHMI scientists offer words of wisdom that are equally applicable inside or outside the lab.

–Edited by Nicole Kresge

Erol Fikrig
HHMI Investigator
Yale University

I encourage young scientists to enjoy the process of scientific inquiry for as long as they can. It might be for a summer, a year, a decade, or, in some cases, a lifetime. As careers develop, there are competing challenges that demand attention. If a scientist gets to the point where less than two or three hours of each day are devoted to considering scientific questions and designing experiments, then it's time to reflect and, hopefully, reorganize.

Vivian Cheung
HHMI Investigator
University of Michigan

Find what you love to do. To quote Steve Jobs, "Keep looking; don't settle." Passion gives you strength to persevere and reasons to care. Invest time and be genuine in the search. Life is full of unexpected things – some good, some bad – though it is never clear in the moment what may be good or bad in the end.

If you love what you do, you will dive in and accomplish what is needed, and you will do it well. This is particularly challenging today, when the emphasis seems to be on speed rather than perfection. To achieve excellence, you have to care deeply. The results will be rewarding.

Tanya Paull
HHMI Investigator
University of Texas at Austin

Choose your research questions carefully. What are the most important questions that need to be answered in your field? What are the critical experiments that could revolutionize your area of research? Is it possible to answer any of these questions, and are any of them uniquely answered with the skills, information, and reagents that you have?

Vivek Jayaraman
Group Leader
Janelia Research Campus

My own tortuous career path took me from aerospace engineering to insect neurobiology. I tell people who are uncertain of what they want to do to take their time figuring it out – a career isn't a race. If you're going to spend most of your life working on something, it had better be something you really care about and enjoy doing. Once you know what "it" is, I think it's important to acquire the confidence to do things your own way. Listen to expert advice, but, ultimately, hone and trust your own scientific instincts.

Fikrig: Brian Ach, Paull: Kevin Wolf, Cheung: Peter Wodarczyk, Vivek: James Kegley

Chronicle

This 40,000-year-old human jawbone was found in a cave in Romania. That places its origin at a critical time in Europe's history, when modern humans were supplanting Neanderthals. Scientists have been wondering how this transition happened – archaeological evidence suggests that the two groups interacted, but few skeletal remains exist to back up the evidence. A team of scientists analyzed the tiny bit of human DNA extracted from this jawbone and discovered that 6 to 9 percent of it was Neanderthal, providing the first genetic evidence that humans interbred with Neanderthals in Europe. *Read more about the research in "Jawbone Reveals Neanderthal Origins" on page 39.*

Svante Pääbo, Max Planck Institute for Evolutionary Anthropology

Chronicle / *Science Education*

Powered by Students

Two HHMI-supported scientists involve undergraduates by the hundreds and thousands in real, published research.

EVEN AFTER CENTURIES of scientific discovery, there's a lot of mystery left in our universe. In the last six years, astronomers have found more than 1,000 previously unrecognized planets. Here on Earth, biologists identify over 15,000 new species each year. And today's biomedical scientists seek clues about human health and disease in genetic data so vast that even computers are having trouble parsing it.

How to make sense of all that? By using technology, of course, but meaningful progress also requires scientists' discriminating eyes and creative minds.

Educators working to inspire the next generation of scientists are learning that engaging students in research – not one by one, but by the hundreds or thousands on a single project – can drive discovery forward, propelling research in ways that would be impossible without a massive group effort.

This spring, two separate, unusually large teams reported findings on microbial diversity and fruit fly genomics in the journals *eLife* and *G3*. The publications represent the work of hundreds of faculty and more than 3,500 students who conducted research through an HHMI program called the Science Education Alliance – Phage Hunters Advancing Genomics and Evolutionary Science (SEA-PHAGES) and the Genomics Education Partnership (GEP). Both involve undergraduates in real research as part of their coursework at institutions around the country.

Delving into genuine research, where outcomes are uncertain and false starts are inevitable, can be both daunting and empowering for students and faculty alike. SEA-PHAGES and GEP faculty say their students gain confidence as the courses progress, and both programs have data demonstrating that the experience boosts undergrads' academic performance as well as their interest in science. But the students aren't the only ones who benefit. The young scientists make lasting contributions to the research community – collecting and analyzing data, sharing their findings, and establishing a base of knowledge upon which other scientists can build.

Connecting the Dots

HHMI Professor Sarah Elgin, director of GEP, studies the dot chromosome, a small genetic element in fruit flies, in her lab at Washington University in St. Louis. DNA in the dot chromosome appears to be tightly packaged into heterochromatin, a format that usually restricts the activity of genes, but genes on the dot chromosome work just fine. Understanding how those genes have evolved could help illuminate the relationship between DNA packaging and gene function.

GEP students at over 110 schools have been learning about the power of genomics as they piece together genomic evidence for how the dot chromosome has evolved. Each student or pair of students is responsible for a small chunk of raw sequence data from a fruit fly genome. Their first task is to find and correct errors in the sequence, after which they evaluate several lines of evidence to determine whether genes are present and, if so, how they're organized.

That divide-and-conquer strategy has enabled Elgin and her colleagues to compare high-quality sequences from the dot chromosome with a second, more loosely packaged piece of DNA across four species of fruit flies. They found most of the dot chromosome's distinctive characteristics in all species and uncovered evidence that genes on the dot chromosome have been less affected by natural selection than genes in the more loosely packaged DNA. Those findings were reported May 1, 2015, in *G3*, in a paper coauthored by 1,014 researchers, including 940 undergraduates from 63 institutions who worked on the problem between 2007 and 2012.

"This is not a lightning-like way to do research," Elgin acknowledges. But without GEP, it might *never* get done. "When you think about the man-hours that go into careful annotation, there's just no other way to do it," she says. "The computer programs are getting better, but they're not as good as the human mind."

Breaking Ground

Students in the SEA-PHAGES course are involved in a similar large-scale effort. They are analyzing genomes they isolate from bacteria-infecting viruses that they find in local soils. These viruses, called bacteriophages, thrive just about everywhere, outnumbering all other life forms on the planet. Their impact on ecosystems and the environment is likely profound, but little is known about their astounding diversity.

To read more about the SEA-PHAGES program, go to hhmi.org/bulletin/fall-2015.

Monica Ramos

In fact, relatively few phages have been isolated at all, let alone had their genomes sequenced and made available for comparative analysis. But now SEA-PHAGES students are filling in the missing information, phage by phage. Since SEA-PHAGES was launched in 2008, thousands of undergraduates have sequenced and analyzed bacteriophage genomes and shared their results through a custom-built online database. Pooling that data has allowed a team of scientists led by HHMI Professor Graham Hatfull at the University of Pittsburgh to compare the genomes of 627 different bacteriophages, all of which students had isolated using the soil-dwelling bacterium *Mycobacterium smegmatis*.

Researchers had wondered how much genetic diversity exists among bacteriophages that infect a single host. Based on more limited analyses, such phages had been sorted into several clusters with shared genetic features – but with few genomes represented, it was impossible to know whether the clusters were truly distinct.

"This is all part and parcel of a whole classroom-based research movement."
—SARAH ELGIN

"You need a sufficiently large collection of sequenced genomes to give you the resolution you need to address the question," says Hatfull, who is lead scientist for the SEA-PHAGES program, now running on 95 campuses. When he and his colleagues analyzed the vast new dataset, what emerged was a continuum of genetic diversity.

Hatfull's team found that phages that infect *M. smegmatis* are related to one another in complex ways that cannot be explained with discrete genetic groups. "We couldn't have gotten that perspective without getting the data the way we did, as a collective consortium," he says. The group reported the findings April 28, 2015, in the journal *eLife*, in a paper authored by 199 faculty and 2,664 students at 81 institutions in the United States and South Africa.

After participating in real research, students sometimes wonder why all science classes don't use that approach. But for educators, implementing a shift from traditional lab courses to true discovery requires planning, flexibility, and new resources. SEA-PHAGES and GEP support that effort with training for faculty, as well as by fostering communities where students and faculty can exchange ideas across institutions; both programs continue to seek new schools to join their ventures.

Other efforts to integrate research into undergraduate courses are yielding results, too.

For example, students at the University of California, Los Angeles, have helped identify genes that drive fruit fly development through the Undergraduate Research Consortium in Functional Genomics, run by HHMI Professor Utpal Banerjee. And thousands of students have contributed to the field of synthetic biology, designing new biological circuits and devices, through the Genome Consortium for Active Teaching (GCAT), organized by biology professor Malcolm Campbell at Davidson College in North Carolina.

Meanwhile, Elgin hopes to make it easier for interested faculty to launch their own bioinformatics-based courses, creating opportunities to tie student activities more closely to their own research questions, by driving the development of a new, user-friendly genome browser.

"This is all part and parcel of a whole classroom-based research movement, and I'm hoping that's a movement that's really going to grow," Elgin says. "It's the ultimate active-learning strategy." – *Jennifer Michalowski*

Chronicle / *Up Close*

For more about the Bamfield stickleback aquarium, go to hhmi.org/bulletin/fall-2015.

Wild Immunology

Collecting data in the great outdoors brings a fresh perspective to work in the lab.

DAN BOLNICK HAS a summer ritual. Almost every year for the past decade, he's made the 2,400-mile trek from his home in Austin, Texas, to a campsite on Vancouver Island. It's no secret that British Columbia's majestic snow-capped mountains, pristine lakes, and mossy old-growth rainforests are perfect for off-the-grid getaways. But the HHMI early career scientist isn't after a little R&R. He's more interested in a little thumb-sized fish that makes its home in the island's remote lakes and streams.

In his lab at the University of Texas at Austin, Bolnick uses a unique combination of ecology, evolutionary biology, genetics, and immunology to understand how the three-spined stickleback fish, also known as *Gasterosteus aculeatus*, interacts with parasites. His goal is to uncover the genes and immune processes the fish uses to protect itself against helminths – parasitic tapeworms that are acquired by eating infected zooplankton. And, thanks to the last ice age, the myriad lakes and streams that dot Vancouver Island provide the perfect site for Bolnick's summertime field studies.

"If you want to understand how vertebrates get rid of tapeworms, what you really need to do is find vertebrate populations that don't have tapeworms and vertebrate populations that have a lot of tapeworms, and then ask what the difference is," Bolnick explains.

Twelve thousand years ago, retreating glaciers created countless lakes and streams on Vancouver Island – a gulf island about the size of Belgium that lies just northwest of Seattle. These bodies of water were eventually colonized by the stickleback's marine ancestors, who proved remarkably successful in adapting to niche environments in their new freshwater dwellings. Across these different habitats, sticklebacks today exhibit incredible variation in size, behavior, skeletal morphology, feeding ecology, and breeding color.

"Every watershed, every river system, every lake represents a replicate of an unparalleled evolutionary experiment," says Bolnick.

The parasitic populations also differ, to the extent that adjoining lakes and streams often have distinct parasite communities. As a result, some stickleback populations have only a few parasites, while others are heavily infested. These variations provide Bolnick's team with the opportunity to see how individual stickleback populations have evolved different immunological responses to their unique parasite loads.

Out and About

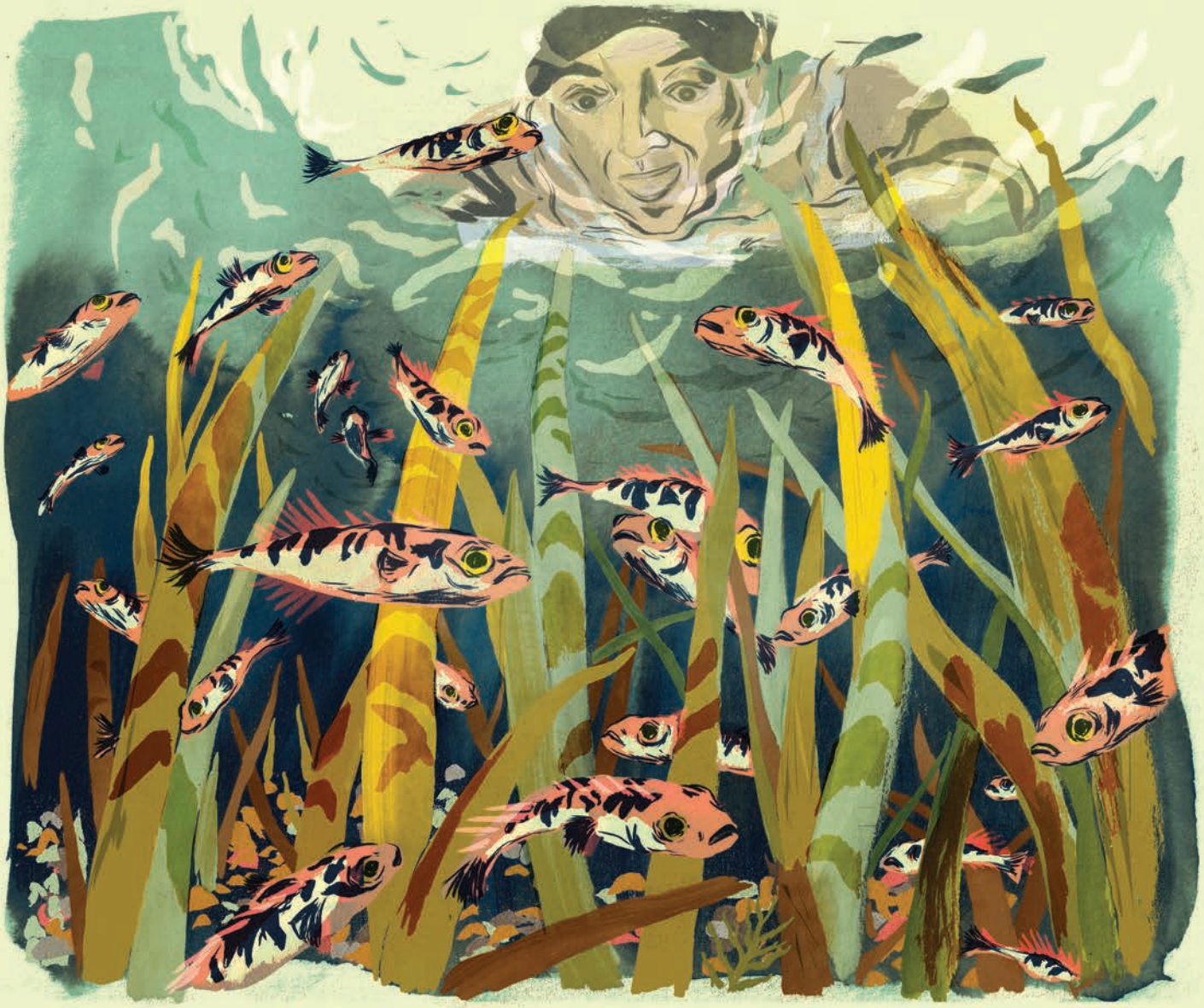
Bolnick estimates he's visited nearly 100 different lakes, streams, and estuaries on Vancouver Island since he started studying the stickleback 15 years ago. His field trips range from six weeks to two months and can involve as few as one or two scientists or as many as 25. The days are full and long – in the summertime, island daylight can last up to 16 hours, and the team takes full advantage of it.

"One drawback of living in Texas and doing field research in British Columbia is the limited time that we get to spend up there," says Bolnick. "We try and make the most of it, which means a lot of early mornings." Each summer, Bolnick's goal is to collect enough fish, and data, to sustain his group until the next year's trip.

Most days in the field start with stickleback collection. "The terrain up there is really physical in certain places," explains Jesse Weber, a postdoc in Bolnick's lab. "Sometimes you have to hike an hour just to get to the lake that you're hoping to sample from, and then you have to be able to transfer all those fish back out." The fate of those captured sticklebacks depends on the experiment du jour.

If the fish are destined for genetic mapping studies, their tail fins are placed in ethanol for DNA extractions, while their bodies (including any parasites on board) are preserved in formaldehyde; everything is shipped back to Texas for analysis. Bolnick's team uses the data from these specimens to compare the resistance genes and parasites found in different populations of sticklebacks.

Other sticklebacks are taken to neighboring lakes, where they are placed in



Juliana Wang

"Every watershed, every river system, every lake represents a replicate of an unparalleled evolutionary experiment."
—DAN BOLNICK

enclosures; the idea with this cohort is to see how they fare in a different ecological niche. Bolnick wants to know if the transplants are more resistant to their native parasites than to unfamiliar parasites.

Still other fish are placed in coolers and taken to a field station. There, they are mated with sticklebacks from other lakes and streams. The eggs produced from these encounters then go by car to the Bamfield Marine Sciences Centre (see Web-Extra sidebar, "Opportunity Knocks") – a drive as long as eight hours – where they are raised to adulthood and then bred to create second-generation hybrids. A year and a half later, the Bamfield fish retrace the road trip, returning to cages in their grandparents' native environments. These experiments will help the scientists identify genes that confer parasite resistance.

Although creating a research program around a field site that takes four days of driving to reach seems impractical, the data Bolnick and his colleagues are collecting might one day help combat parasite-borne diseases in humans. The time away from Austin also gives the scientists a fresh perspective on their research. "Vancouver Island is where some of our best thinking happens," says Weber. "After sitting there all day long, looking at the fish, we start to view our discipline in a whole different way. I think that almost every evolutionary biologist will say that the field is where some of their best ideas happen, because that's where inspiration comes from."
–*Nicole Kresge*

Chronicle / *Lab Book*

Hangry? Here's Why

Scientists unravel why feeling hungry can also mean feeling angry.

LET'S BE HONEST; dieting is rough. Hunger can deflate a dieter's spirit and render friends and co-workers unbearable.

Still, hunger is evolutionarily beneficial, as it signals when our bodies need food. Eating activates reward systems in the brain, but scientists have puzzled for decades over why our mood turns bleak when hunger hits.

Scott Sternson, a group leader at Janelia Research Campus, decided to tackle that question in mice. His team started by looking at the brain's agouti-related peptide (AGRP) neurons, which, when activated in mice optogenetically, elicit voracious eating.

The researchers presented well-fed mice with two flavored gels; the mice showed no preference for one over the other, and neither had nutritional value. Whenever the mice nibbled at one of the gels, scientists activated their AGRP neurons. Surprisingly, the mice began avoiding that gel.

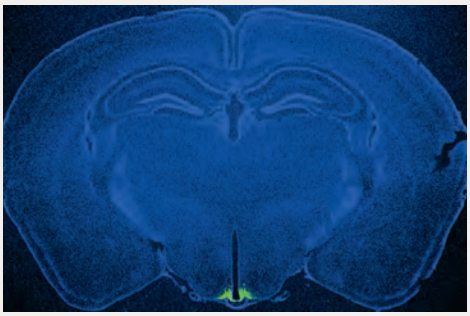
To further test the link, Sternson's team activated the AGRP neurons every time the mice went to a certain part of their cage. Sure enough, the mice began avoiding that area.

When the scientists peered into the rodents' brains, they observed that AGRP neurons are indeed active when the animals are hungry. But the neurons showed low activity during eating. In fact, they're inhibited as soon as food is sensed.

Thus, it appears that AGRP neurons encourage us to pursue food to avoid a state of physiological need for nutrients. Based on his team's findings, published April 27, 2015, in *Nature*, Sternson thinks the unpleasant feeling associated with AGRP activation prompts the drive to find food. This is important evolutionarily, as animals often face risks in seeking food. If hunger is unpleasant, animals are more likely to take that risk, ensuring their survival.

While that works for animals, it's tough on dieters. "When people try a weight-loss diet and find it to be unpleasant … it's pretty likely that the elevated activity of the AGRP neurons has something to do with it," Sternson says.

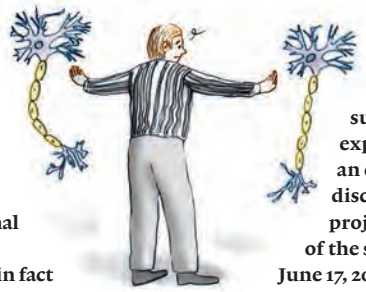
With that in mind, scientists are looking at how they might interfere with AGRP neuron activity. If the neurons behave similarly in humans, help in dropping those extra pounds may not be far off. *–Anzar Abbas*



The brain's hunger-sensitive AGRP neurons (green) are responsible for the unpleasant feeling that drives us to snack.

IN BRIEF

TEASING OUT NEURONAL FUNCTION



The brain holds a host of different kinds of neurons, each with its own job. Though you might think neuronal cells are highly organized, they are in fact intertwined in a colossal tangle. For scientists who want to study particular neuron types individually, teasing them apart is a major challenge.

Now, a team of researchers – led by HHMI Investigators Jeremy Nathans and Joseph Ecker, and Janelia Group Leader Sean Eddy – has devised a way to study individual cell types without getting mired in the tangle. Rather than trying to separate cells of a certain type from their neighbors, they've developed a way to isolate their nuclei. From there, they can study the cells' DNA, which provides information about the cells' activity and history.

"We weren't sure what to expect. This was an exploratory, discovery-level project," says Ecker of the study, published June 17, 2015, in *Neuron*.

But already, the method has revealed astonishing differences in cell types previously thought to be similar in function. "That means there's a lot of additional information here," says Ecker. Using the new technology, scientists will not only be able to delve even deeper into the secrets of the brain, but they might also gain greater understanding of other systems in the body as well.

RADICAL VACCINE HAMPERS HERPES

The herpes simplex virus infects millions of people worldwide, yet the pathogen has for decades thwarted attempts to develop a vaccine.

Most efforts by scientists to create a herpes vaccine have focused on glycoprotein D (gD), a protein that triggers the production of protective antibodies. However, attempts to exploit gD in a vaccine have been futile.

"It was necessary to shake the field up and go another route," says virologist and infectious disease physician Betsy Herold. So she and HHMI Investigator William Jacobs, both at the Albert Einstein College of Medicine, joined forces to take a radically different approach.

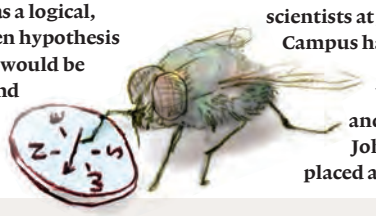
Instead of using gD, the researchers used a mutant strain of the virus lacking gD. "Once we had this mutant in our hands," says Herold, "it was a logical, scientifically driven hypothesis to say, 'This strain would be 100-percent safe and might elicit a very different immune response than the gD subunit vaccines that have been tried.'"

The study, published March 10, 2015, in *eLife*, tested the hypothesis in mice. The new vaccine completely protected the mice from the most common herpes infections, without any adverse effects.

If the vaccine works in humans as well as it does in mice, it could have a profound impact on the global prevalence of herpes.

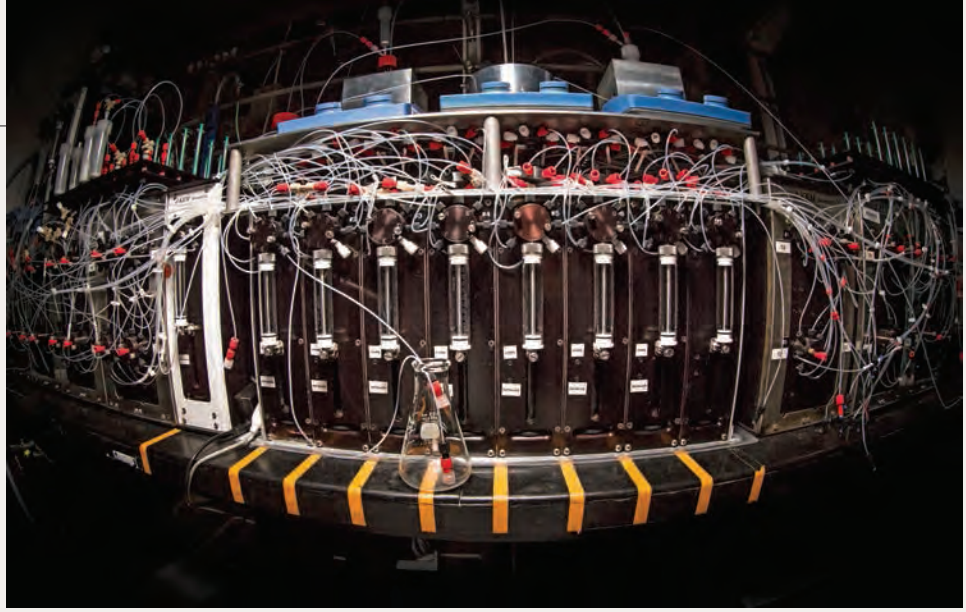
A COMPASS FOR FLIES

If you've ever made your way through a dark room, you've relied on neurons to help maintain your balance and bearings without vision. A fly's brain is much less complex than a human's, yet flies, too, can keep a sense of direction in the dark, scientists at Janelia Research Campus have found.



Group Leader Vivek Jayaraman and postdoc Johannes Seelig placed a tethered fly

Photo: Christopher Magnus, Illustration: Leif Parsons



Taking cues from nature, this molecule-making machine couples chemical building blocks to create small molecules.

Made-to-order Molecules

A new invention acts as a molecular 3-D printer.

WHEN CHEMIST FRIEDRICH WÖHLER accidently made synthetic urea about 200 years ago, he stumbled upon a feat that has occupied scientists ever since: the synthesis of small molecules.

Today, we use small molecules everywhere. You can find them in most medicines, foods, scientific research – even coffee sweeteners and light bulbs. Yet when it comes to the vast possibilities arising from small molecule production, we've barely scratched the surface.

"The bottleneck is synthesis," says Martin Burke, an HHMI early career scientist at the University of Illinois at Urbana-Champaign. To date, making small molecules has required a customized approach achievable only by highly trained specialists.

But now, Burke and his team have developed an invention that extends that ability from a select few to anyone with a computer. "We've created a machine that can do on-demand small molecule synthesis – kind of like a 3-D printer for small molecules."

Burke says the machine, described in *Science* on March 13, 2015, was inspired by living organisms. "Nature makes most small molecule natural products through very simple building-block chemistry. ... So in a sense, nature is already telling us the answer."

The machine takes basic chemical modules and stitches them together to create small molecules. When mixed and matched in different combinations, these building blocks can generate a plethora of new small molecules – made automatically and using relatively little effort.

"History speaks strongly to the major impact that can be achieved when you take a powerful technology like molecule making and put it into the hands of everyone," says Burke, whose long-term vision is to have a website where anyone in the world – a chemist, biologist, engineer, or high school student – can order small molecules to be made and shipped directly to themselves. For now, the machine is already enabling a new biotech company to enhance its drug development efforts; it has the broader potential to expand possibilities in many fields of scientific research. *– Anzar Abbas*

in a virtual reality arena to observe the insect's neurons as it walks. The study, published May 14, 2015, in *Nature*, focused on a part of the fly brain called the ellipsoid body, a donut-shaped structure suspected to be involved in directional movement.

The researchers saw a strong relationship between the fly's orientation relative to its visual surroundings and the neurons activated in the ellipsoid body. When the fly changed direction, even in total darkness, neuronal activity shifted from one part of the ellipsoid body to another, much like the needle of a compass.

"We think we have a window into the fly's internal model of its world," says Vivek, who believes ellipsoid body neurons may share characteristics with human head direction cells. "We're starting to see increasing evidence that the fly may have a lot to tell us about how our own brains work, even when it comes to more complex aspects of cognition."

RARE MUTATION MAKES FLU FATAL

While catching the flu might be an inconsequential annoyance for many of us, the flu virus can prove life threatening in some people. Research led by HHMI Investigator Jean-Laurent Casanova at Rockefeller University tackled the question of why some patients respond differently to the virus than others.

The study, published April 24, 2015, in *Science*, describes a two-year-old girl who had been treated for a severe case of the flu at the Necker Hospital for Sick Children in France. The researchers sequenced her exome to hunt down the reason for her immune system's weakened response to the virus.

What they found was a rare mutation in her *IRF7* gene, known to be responsible for the production of antiviral molecules called interferons. Without the functional protein, a patient would have an inadequate response to the flu virus.

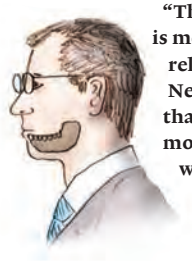
"Now we have proof that life-threatening flu, an infectious disease, can also be a genetic disease," says Casanova, whose past work has identified other mutations that make patients more vulnerable to a variety of infectious diseases.

Understanding *IRF7*'s role in fighting the flu virus may allow doctors to consider other treatment options, such as administering interferons, when faced with severe unexplained flu.

JAWBONE REVEALS NEANDERTHAL ORIGINS

Scientists have successfully retrieved and examined DNA from a 40,000-year-old bone.

And not just any old bone. This human jawbone, found in 2002 in a Romanian cave called Peştera cu Oase, dates back to a critical period of Europe's history when modern humans were replacing Neanderthals. Scientists have always wondered how this transition happened. Now, the bone's DNA indicates that it belonged to a modern human whose recent ancestors included Neanderthals.



On average, humans today living outside Sub-Saharan Africa owe about 2 percent of their genes to Neanderthal ancestors. The study, published August 13, 2015, in *Nature*, shows that 6 to 9 percent of the Oase bone's DNA came from Neanderthals.

"The sample is more closely related to Neanderthals than any other modern human we've ever looked at before," says David

Photo: L. Brian Stauffer, Illustration: Leif Parsons

Chronicle / *Lab Book*

A Test Tells the Tale

One drop of blood reveals a history of viral infection.

STEPHEN ELLEDGE AND his research team at Brigham and Women's Hospital in Boston have developed a technique that will allow doctors to learn about a patient's entire viral infection history from just a single drop of his or her blood.

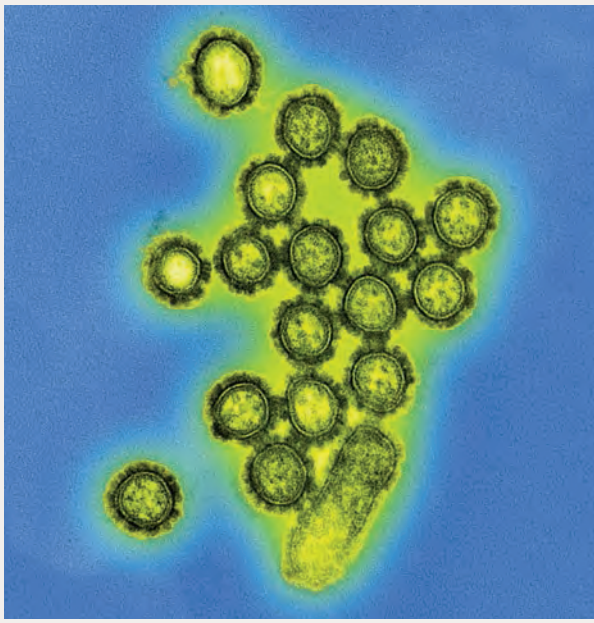
The technique, called VirScan, is a giant leap forward from current tests designed to hunt for individual viruses. VirScan, which costs only $25, searches for all 206 species of viruses known to infect humans. Evaluated in more than 500 people on four continents, the test is proving beneficial in both health care and medical research.

With a more thorough patient clinical history, a doctor can make better treatment decisions. "You could go to the doctor once a year and get all your viruses checked," says Elledge, an HHMI investigator. "It's cheap to do it, it's routine, and your doctor might pick up on new infections … before they do a lot of damage."

Knowing patient viral infection histories can also help scientists studying diseases understand associations previously unknown to them. "We have an ability to now ask, 'Okay, what about autoimmune diseases like type 1 diabetes,'" says Elledge. "Is there an association between that disease and a particular type of viral infection?"

VirScan works by exploiting the fact that we have memories of past viral infections floating in our blood – immune particles that will attack a given virus if it decides to return. The test introduces a host of virus-mimicking molecules into a patient's blood sample to see which ones elicit a response. If a particular virus molecule is attacked, it is likely the person was exposed to that virus in the past. The team published details of the test on June 5, 2015, in *Science*.

Elledge thinks VirScan might see its greatest potential in developing countries, where doctors could use the test to track the extent of new viral epidemics in entire populations. *–Anzar Abbas*



Using a single drop of blood, a new test can detect antibodies against more than 200 species of virus, including this influenza virus.

Photo: National Institute of Allergy and Infectious Diseases, Illustration: Leif Parsons

IN BRIEF

Reich, an HHMI investigator at Harvard Medical School, who co-led the study with Svante Pääbo at the Max Planck Institute in Germany.

The data suggest that the Oase individual had a Neanderthal ancestor as recently as four to six generations back. "It's an incredibly unexpected thing," Reich says. "In the last few years, we've documented interbreeding between Neanderthals and modern humans. But we never thought we'd be so lucky to find someone so close to the event."

LESSONS FROM PARROTS

If you've wondered how parrots can imitate humans so well, you're in good company – many scientists have marveled at the behavior. Among them is HHMI Investigator Erich Jarvis of Duke University, who studies how certain birds mimic humans.

Scientists have known that the brains of certain vocal-learning bird species have specialized neurons involved in learning to produce sounds, but they did not know why parrots are better at imitating compared to other rare vocal-learning bird groups. In a study published June 24, 2015, in *PLOS ONE*, Jarvis and his postdoc Mukta Chakraborty found that parrots have a "shell system" of vocal-learning neurons not found in other species. This shell surrounds a "core system" found in songbirds and hummingbirds.

By comparing nine different parrot species, the team learned that the larger this shell was in a particular species' brain, the better those birds were at imitating spoken language. This suggested the shell might play a role in the skill.

Jarvis hypothesizes that the shell emerged from a duplication of the core language region millions of years ago, developing a more complex function as it evolved. "Maybe in the human brain we have multiple duplications of an ancient pathway that's controlling our complex speech abilities."

COMPLEX SENSORY CIRCUITS

We rarely use just one sense at a time. Even when we eat, our experience is affected by a food's look, feel, and smell, as well as its taste. Other creatures' brains appear to be wired similarly.

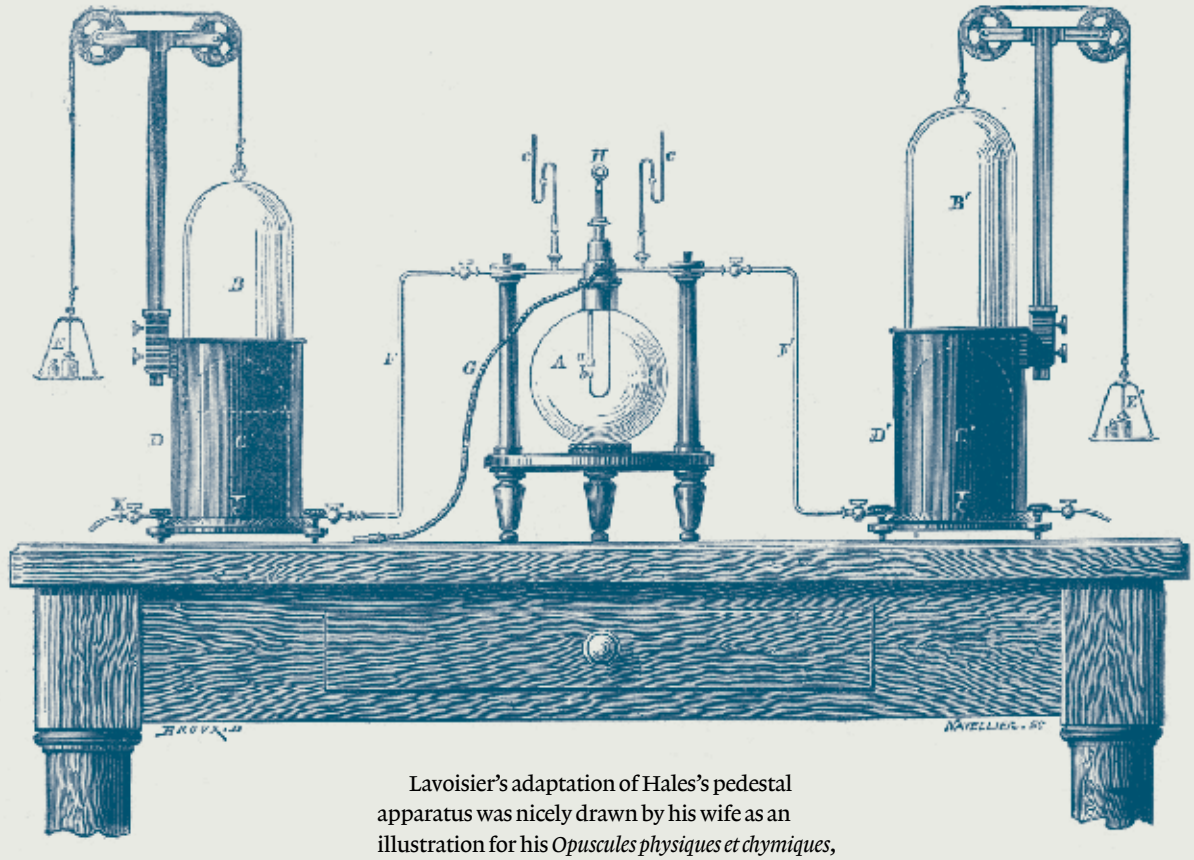
Fruit fly larvae seem to integrate cues from multiple senses, too. For example, a larva is more likely to roll over to defend itself from a predator if it's sensing a noxious stimulus – stinging, for example – and physical cues at the same time, according to findings from scientists at Janelia Research Campus.

Janelia Group Leaders Marta Zlatic and Albert Cardona led a team that mapped the neurons involved in this behavior. In a study published April 20, 2015, in *Nature*, the researchers mechanically stimulated fruit fly larvae while activating their nociceptor, or injury-sensing, neurons to understand the circuits involved from the point of stimulation to when the larva rolls over.

Surprisingly, they found that the circuits for nociceptive and mechanical stimulation were integrated on multiple levels, resulting in a very sophisticated structure. "Initially, I would have thought this circuit would be simpler, but the complex network could really allow the animal to do a complex computation and react to very particular combinations of cues," says Zlatic.

The team has made its electron micrograph information freely available, with the hope that it will help in mapping the insect's entire nervous system.

Observations



HIP / Art Resource

In the Crucible

A true Renaissance man, Antoine Lavoisier spent the years leading up to the French Revolution consumed with civic and scientific activity while immersed in the political crucible of the times. In 1788 alone, he held five important public posts at once, including the directorship of the Gunpowder and Saltpeter Administration and a seat on the board of the government's central bank. At the same time, he was an active scientist, having built with his considerable fortune a state-of-the-art laboratory. There, he and his wife, Marie-Anne, a noted scientist in her own right, conducted robust research and participated in the race to identify the processes behind combustion. His theory on chemical reactions – published in a treatise in 1789, just four months before the fall of the Bastille – dispelled the last traces of medieval alchemic thinking and established the modern science of chemistry.

Lavoisier's adaptation of Hales's pedestal apparatus was nicely drawn by his wife as an illustration for his *Opuscules physiques et chymiques*, in which the results of these experiments were recorded. In his version, he set a porcelain crucible on a crystal pedestal, covered it with a bell jar, and controlled the water level with a siphon. A layer of oil on the surface of the water under the jar prevented any gases released from dissolving. In October of 1772, he put a lead oxide called *minium* [Pb_3O_4] into his crucible with a small amount of charcoal and heated it through the bell jar with the burning glass, whose beam was narrowly focused on the contents of the crucible. This method, common for smelting metals from oxide ores, produced a significant release of gas of some description, or elastic fluid. Although (uncharacteristically) Lavoisier did not make an exact measurement of the gas, he recorded "a volume at least a thousand times greater" than that of the lead oxide used.

What actually happened in this experiment, though Lavoisier did not yet know it, was that the oxygen released in the reduction of lead oxide combined with carbon in the charcoal to form a large volume of carbon dioxide (fixed air). For his immediate purposes, the minium experiment demonstrated and confirmed an already known fact: the reduction of lead oxide released a gas. It also complemented the syntheses he had performed by combining air, phosphorus, and sulfur with an analysis where air was subtracted from a calx. Lavoisier's notion that air was fixed in the process of calcination (and released in the reduction of calces) was now supported at both ends.

Lavoisier was satisfied (or at least willing to claim) that these results had "Completely Confirmed my Conjectures." The experiments on phosphorus, sulfur, and minium became the basis for the sealed note he deposited at the academy on November 1, 1772. The truth was that even though Lavoisier was convinced his discovery was "one of the most interesting that has been made since Stahl," he still could not say precisely what had been discovered – nor did the discovery yet fit comfortably into his evolving theory. Not until February of the following year would he feel confident enough to declare, in that famous lab notebook entry, that he was going to bring about "a revolution in physics and chemistry."

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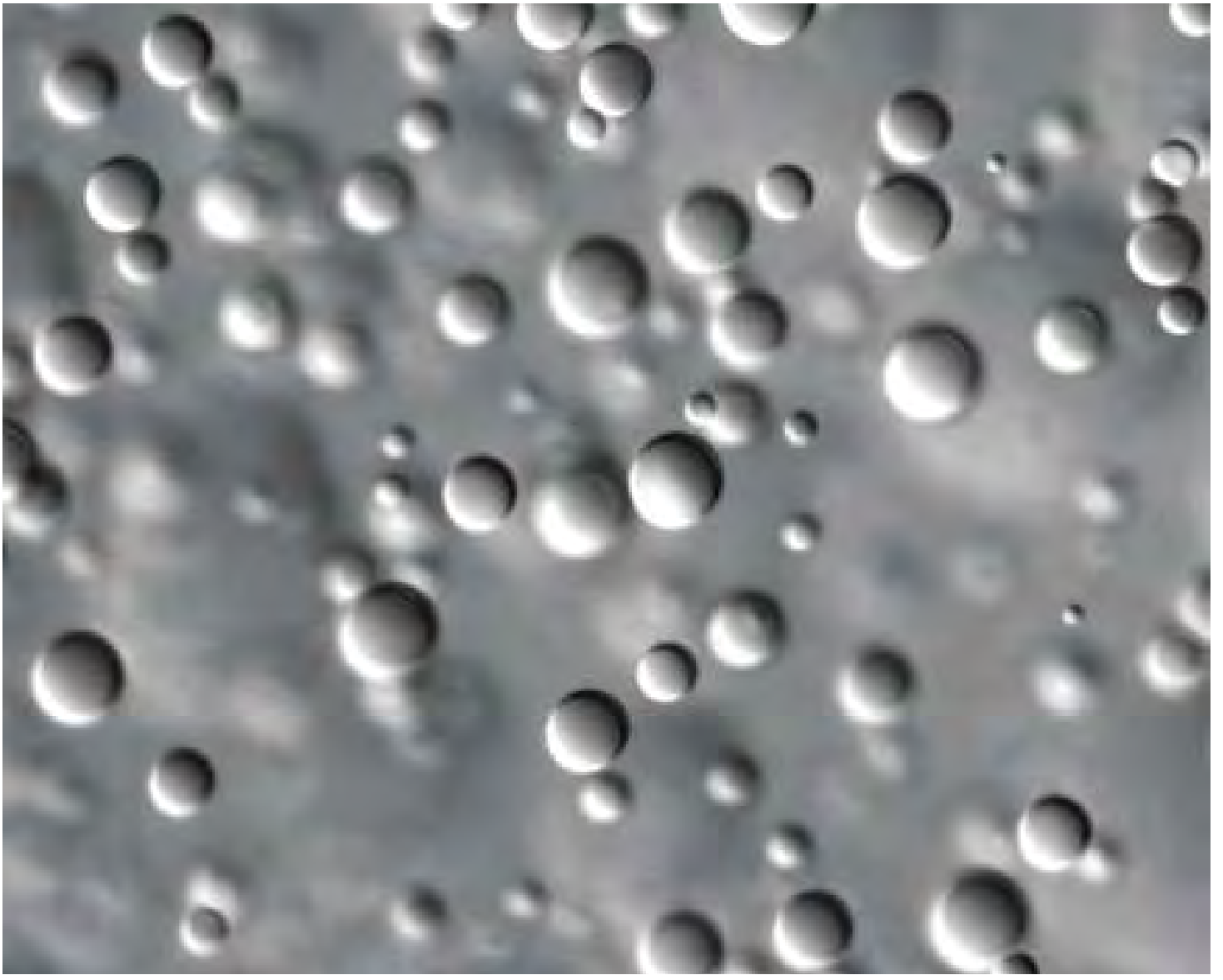
To Bead or Not To Bead

These droplets may look like rain beading on a freshly waxed car, but they are actually a super-concentrated form of an RNA-binding protein called hnRNPA1. Newly minted HHMI Investigator J. Paul Taylor discovered that hnRNPA1's liquid-like properties help stress granules – membrane-free clumps of RNA and protein – form rapidly, and reversibly, when a cell encounters unexpected stress, such as extreme heat. This quicksilver response allows the cell to temporarily switch up the genes it's expressing. Learn more about these granules and their surprising role in neurodegenerative and muscle diseases in "Problem Solvers," page 24.
Go online to watch a video of these droplets assembling and disassembling at hhmi.org/bulletin/fall-2015.



Amandine Molliex