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Up in Arms

Even the smallest of Earth's creatures can bring a little swagger when threatened. A native of western Africa, this male giant mantis—*Plistospilota guineensis*—rears up and spreads his colorful wings to ward off potential predators. Measuring 9 centimeters in length, adults of this species can overwhelm bigger, stronger prey as well. It didn't take much provocation for photographer Igor Siwanowicz to elicit this dramatic pose. When not in the lab, Siwanowicz becomes a kind of insect and small animal whisperer to pursue his second love—capturing nature through a camera lens. Read more about his pastime in "Beautiful Beasts" on page 4, and visit the online *Bulletin* to see a video about the magic behind his photography.

Igor Siwanowicz

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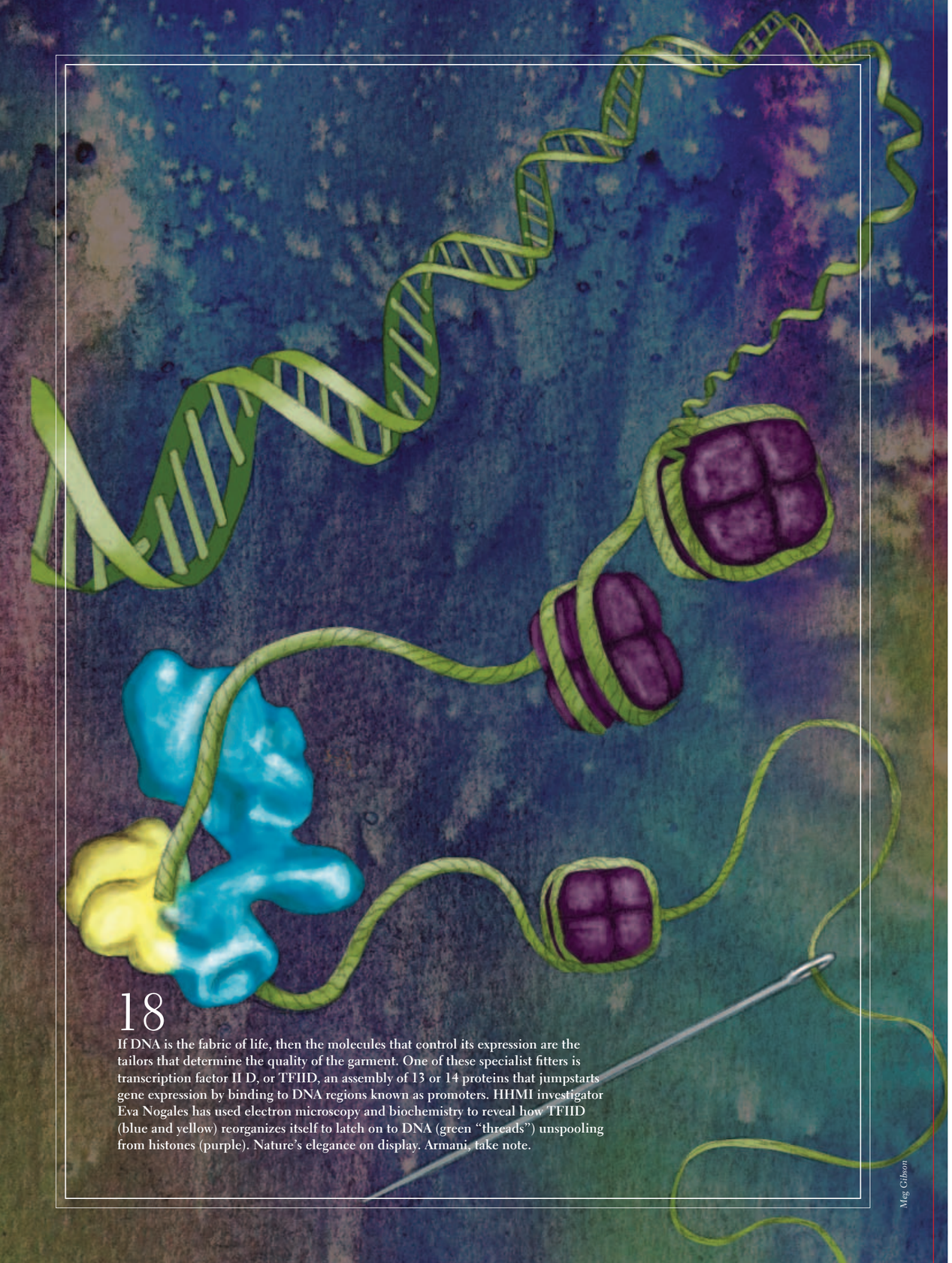
10 YEARS OF EXROP

Underrepresented minorities embrace life in the lab



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If DNA is the fabric of life, then the molecules that control its expression are the tailors that determine the quality of the garment. One of these specialist fitters is transcription factor II D, or TFIID, an assembly of 13 or 14 proteins that jumpstarts gene expression by binding to DNA regions known as promoters. HHMI investigator Eva Nogales has used electron microscopy and biochemistry to reveal how TFIID (blue and yellow) reorganizes itself to latch on to DNA (green "threads") unspooling from histones (purple). Nature's elegance on display. Armani, take note.

Meg Gibson

OBSERVATIONS

A. R. Wallace Memorial Fund

ADMIRING DARWIN

At the time Alfred Russel Wallace died in 1913, he was arguably the world's most famous scientist. An intellectual with wide-ranging interests, he is best known today for his work with Charles Darwin to conceive the theory of evolution by natural selection. Less appreciated are his bounteous contributions to other realms of science, from glaciology to astrobiology. In this centennial anniversary of his death, his correspondence with colleagues is still illuminating. In 1860, he wrote to Henry Walter Bates, a fellow explorer and naturalist who had accompanied him on expeditions to the rainforests of the Amazon. Even then, biologists knew the power of collaboration.

I know not how or to whom to express fully my admiration of Darwin's book. To him it would seem flattery [and] to others self-praise; but I do honestly believe that with however much patience I had worked up and experimented on the subject I could never have approached the completeness of his book—its vast accumulation of evidence, its overwhelming argument, and its admirable tone and spirit. I really feel thankful that it has not been left to me to give the theory to the public.

Mr. Darwin has created a new science and a new Philosophy, and I believe that never has such a complete illustration of a new branch of human knowledge been due to the labours and researches of a single man. Never have such vast masses of widely scattered and hitherto utterly disconnected facts been combined in to a system, and brought to bear upon the establishment of such a grand and new and simple philosophy! ...

I am now convinced that insects on the whole do not give such true indications in Zoological Geog[raphy] as Birds and Mammals because they have, 1st. such immensely greater chances of distribution, and 2nd. because they are so much more affected by local circumstances. Also 3rd. because the sp[ecies] seem to change quicker and therefore disguise a comparatively recent identity. Thus the insects of two originally distinct regions very rapidly become amalgamated— a portion of the same region may come to be inhabited by very distinct insect faunas owing to differences of soil, climate, etc. etc. This is strikingly shown here, where the insect fauna from Malacca to N[ew] Guinea has a very large amount of characteristic uniformity; while Australia from its distinct climate and vegetation shows a wide difference. I am inclined to think, therefore, that a preliminary study of first the Mammals and then the Birds are indispensable to a correct understanding of the Geographical and physical changes on which the present insect distribution depends.

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Web-Only Content

- Travel in a 40-foot bus equipped with 12 lab workstations as it journeys to a rural high school near the Mexican border.
- Meet two HHMI investigators who share a love of biology—and the same parents.
- Watch transcription factors assemble into the tiny machinery that reads DNA, one gene at a time.
- Get up close and personal with insects and spiders in some extreme photos.
- Listen to undergraduate students reflect on their experiences in HHMI's Exceptional Research Opportunities Program.

GO GREEN

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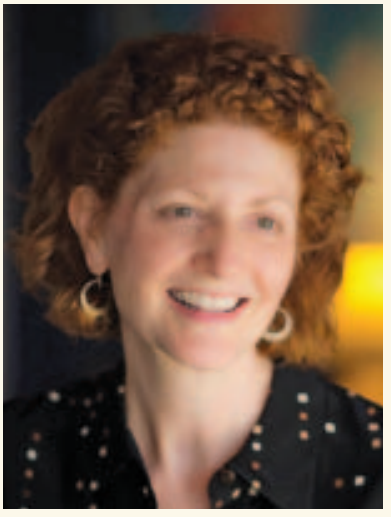

Spring Forward

Spring came late this year to HHMI headquarters in Maryland. But once here, it was glorious: the redbuds and azaleas zinged with pinks and purples, and the robins arrived in legions. At least 45 dotted the ground in my neighborhood park one recent morning. Quite a sight—even my dog took notice.

Not to rush us through this gentle season, but as summer edges near I want to take a moment to remind you that the next issue of the *HHMI Bulletin* will arrive in the fall. That's right, the *Bulletin* is on a new publication schedule, coming out three times a year—fall, winter, and spring.

This doesn't mean the *Bulletin* will be idle, however. We'll be updating the website with fresh content over the summer. Look for additions to our structural biology feature, for example, reporting late-breaking technological advances—including a new kind of camera that could change views on crystallizing proteins. You'll find other stories from our researchers as well. After all, scientific discovery doesn't take a vacation!

Join us online this summer, and we'll see you again in print—and on the Web and iPad—come September.

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Paul Vetters

Ripple Effect

James Kegley

THE SMALL NEW JERSEY TOWN WHERE I GREW UP, OUTSIDE Philadelphia, was wonderful, but its schools were lacking. Academically speaking, they were behind the curve. Two fantastic teachers are the reason I began demonstrating ability in math and science in junior high and high school. My math teacher, Mr. Adams, and my chemistry teacher, Mr. Curry, saw my potential.

After I completed his classes, Mr. Adams, recognizing that I could handle more, sent me to the Franklin Institute in Philly for after-school instruction in advanced math. And in science, I studied molecular biology and paired up with another student to carry out a research project, looking at chromosome aberrations—something I would not have attempted without encouragement from Mr. Curry. These two teachers really pushed me, and for that I am grateful.

My tale is not unusual. Most scientists can name one or two standout teachers who were early influences. But in the United States today, there's a shortage of good science and math teachers in classrooms. We must take steps toward change to replenish this country's star teachers, teachers who can move students to explore and love math and science. That's why it's especially exciting to me that HHMI is awarding a $22.5 million, 5-year grant to the National Math and Science Initiative to expand UTeach, an established training program aimed at preparing science and math majors to become teachers.

> "We must take steps toward change to replenish this country's star teachers, teachers who can move students to explore and love math and science."
>
> ROBERT TJIAN

Started at the University of Texas, Austin (UT), in 1997, UTeach is now in place at 34 universities. Its record of success—80 percent of students who came out of UT's program are still teaching after five years, for example—speaks to its effectiveness. The HHMI grant will extend UTeach's reach to 10 additional major research universities. Those universities are expected to produce more than 1,700 math and science teachers during the next decade, increasing the number of UTeach graduates in U.S. classrooms to more than 14,000 by 2022.

Lending support to a model that's working, rather than trying to reinvent the wheel, just makes sense, and it's something we are eager to do. Such efforts complement the Institute's other long-standing initiatives in science education, including the Exceptional Research Opportunities Program, or EXROP, whose 10th anniversary is highlighted in the cover story of this issue of the *HHMI Bulletin*. Created to attract outstanding students from underrepresented minorities to the sciences, the program provides mentored summer research experiences in the labs of HHMI investigators. Being immersed in a top-notch research lab can give students the confidence to see themselves as scientists and the skills to get there.

I've hosted a number of EXROP students in my University of California, Berkeley, lab, and I can attest that it's an extremely rewarding experience for all involved. Nothing pleases me more than to see a student from California's Central Valley farmlands be the first in her family not only to attend college but to pursue a graduate degree in the sciences.

This summer, a group of 77 EXROP students will be conducting research in HHMI labs across the country. We believe these students will go on to inspire others, as exemplified by Kelley Harris-Johnson, one of EXROP's first graduates whom you'll meet in our *Bulletin* feature article. Much more needs to be done, without a doubt, so we do not miss out on the raw talent we know exists among this country's underrepresented minorities. But we hope that our small efforts, just as Mr. Adams and Mr. Curry realized back when I was in school, will ripple, like raindrops on water, to carry far and wide.

Igor Siwanowicz

Beautiful Beasts

Two green orbs glow, separated by arcs of shimmering flecks in blue, purple, magenta, and chartreuse, on a black background. The image resembles a faraway galaxy or magical realm. In truth, it's a fluorescence microscopy image of the eyes of a daddy longlegs spider.

Igor Siwanowicz is a scientist and photographer who captures his subjects in extreme close-up with a digital camera and creates haunting, fluorescent images of others with a confocal microscope. He aims to reveal the beauty of nature's tiniest beasts. "People have been socialized to be afraid of and revolted by insects and spiders. But that isn't what I see."

A gallery at the Janelia Farm Research Campus offers a sampling of Siwanowicz's view of the world, including the daddy longlegs image, which won the 2010 Olympus BioScapes Digital Imaging Competition. Other striking photographs include one that captures red-eyed tree frogs twirling around a twig, a colorful sequence of kelly-green backs, blue and yellow legs, orange toes, and white bellies. Nearby, a pair of praying mantis rear up on their hind legs, flashing red "defensive colors" and displaying the "peacock eye" on their striated wings.

The praying mantis, with its fluid movements and stunning colors, is Siwanowicz's favorite model. "Jumping spiders are pretty endearing, too," he notes of the arachnids with prominent eyes. "They are the kittens of the spider world—fuzzy and very aware."

Siwanowicz took up photography 10 years ago as a means to keep the winter blues at bay. It provided an outlet for his "quirky" sense of humor. "I wanted to show insects as celebrities," he laughs. He treated them like miniature supermodels, employing the lighting and background techniques of fashion photography.

As his image library grew, Siwanowicz began posting them on a photo.net site. Soon, Olympus invited him to enter its BioScapes contest (five of his images—a record— earned recognition in 2012). The attention was gratifying, but Siwanowicz really knew he was onto something when people started asking permission to tattoo his images—like a devil's flower mantis, front legs lifted high—on their bodies. "That's a pretty big reward: seeing a full sleeve or back with your images," he says. "I wouldn't do it!"

As a member of Anthony Leonardo's Janelia lab group since 2011, Siwanowicz studies the intricacies of dragonfly behavior as it hunts for prey. Specifically, he's trying to suss out how a fruit fly's position is communicated from the dragonfly's brain to its flight muscles.

His science informs his art without question, but the converse has happened as well. Intrigued by the challenge of creating a three-dimensional microscopic image of a tick's mouth, Siwanowicz used the same technique to explore the architecture of the joints between a dragonfly's neck and wings.

"I've found the perfect marriage of art and science," he says. "So many people think the beauty of nature is wasted on scientists. But, it's all so beautiful at any scale."

—Lisa Chiu

WEB EXTRA: To see more of Siwanowicz's beautiful beasts, visit www.hhmi.org/bulletin/spring2013.

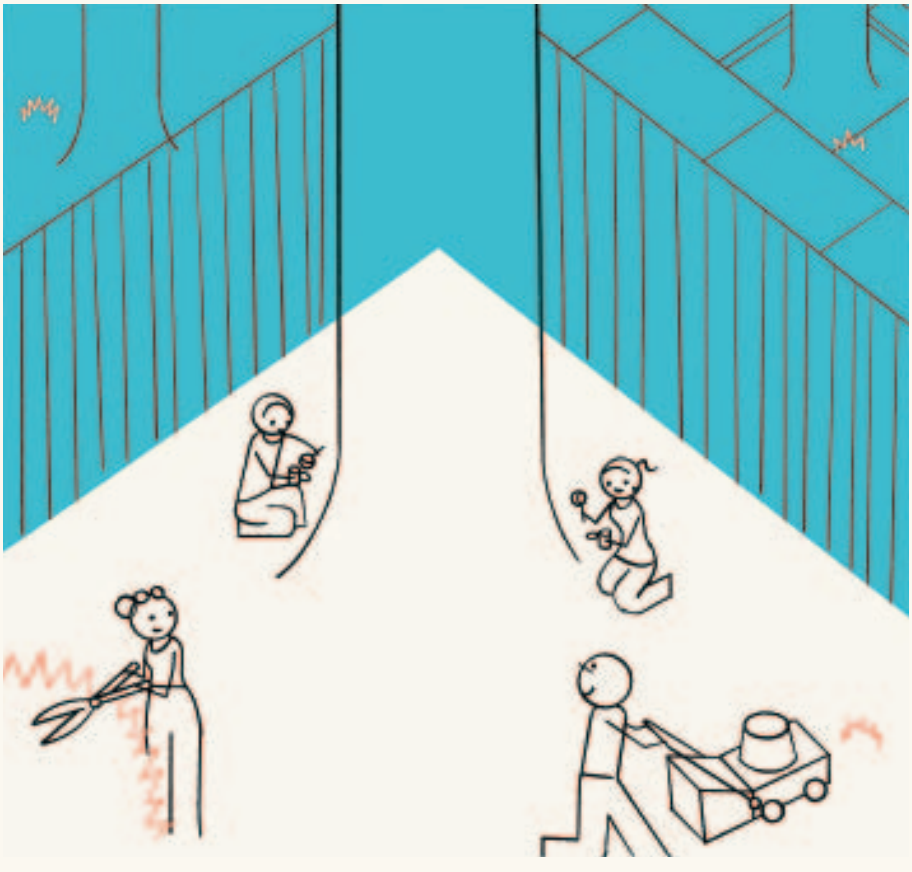
Backyard Science

Albert and Talar Kiladjian had no idea what was living in their Massachusetts backyard. To their surprise, the siblings discovered their soil is home to tiny viruses that invade and multiply inside bacteria.

As part of their college coursework, the brother and sister isolated and studied two of the strange-looking soil dwellers, known as bacteriophages, with their long tails and bulky heads. Albert named his Winchester, for their hometown, and Talar called hers Lahmajoon, after the style of pizza that is a popular part of the family's Armenian culture.

Bacteriophages (or phages, for short) flourish anywhere bacteria thrive, which is pretty much everywhere. They are so widespread and diverse, there's a good chance that phage hunters like Albert and Talar might turn up a never-before-seen specimen.

When Talar arrived at Bucknell University in Lewisburg, Pennsylvania, for her second year, she wasn't quite prepared. "I actually didn't realize that I had to bring a soil sample to school," she confesses. "I had to call my mom and ask her to send one." Although not the typical care package, a triple-ziplocked, still-moist handful of soil arrived at Bucknell soon after. Mrs. Kiladjian knew what to do because Albert, still at home, had dug up soil of his own just a few days earlier in preparation for his freshman year at Trinity College in Hartford, Connecticut. That's when the family realized the two would be taking the same year-long research course at their separate schools.



Laurent Cilluffo

Along with students at the 78 colleges and universities that make up HHMI's Science Education Alliance, Talar and Albert examined their phages using electron microscopes, tested the effects of the phages on bacterial growth, and compared the genetic makeup with that of phages found by other students. The siblings soon discovered that, although they had started their searches using soil collected beneath the same spruce tree, the phages they isolated were far from identical.

Both students filtered, extracted, and purified their starting material until they had a single type of phage. When they chatted on weekends, the two compared what they had learned. Talar's class was always a few weeks ahead, so big sis offered the younger Albert previews of experiments to come as both classes grew their phages in the lab, isolated them, and extracted DNA. They also commiserated about the inevitable frustrations they encountered during their research.

Albert and Talar added Winchester and Lahmajoon to the online Mycobacteriophage Database (phagesdb.org), which contains information on more than 450 phages. For now, they've set aside their personal phages to focus, along with their classmates, on detailed genetic analysis of a single phage. But they have a new appreciation for the hidden world beneath their childhood tree house.

—Jennifer Michalowski

Pressure to See Clearly

Mouse models of a blinding disease paired with tiny devices lead to big ideas for treatments.

CONSIDER THE EYE OF A MOUSE, A SPHERE ROUGHLY THE SIZE of a peppercorn. The anterior chamber, a small space in the very front of the eye, between the iris and cornea, holds just a fraction of a drop of fluid. Now, imagine a device that is so tiny, it fits inside the anterior chamber. ¶ HHMI investigator Simon John is partnering with engineers to develop just such a tool, for good reason.

Too much pressure in the eye is a red flag for glaucoma, a leading cause of blindness worldwide. But understanding the link between high intraocular pressure (IOP) and destruction of the optic nerve—the hallmark of glaucoma—has long bedeviled researchers who study this complex disease.

At the Jackson Laboratory in Bar Harbor, Maine, John has spent nearly two decades honing tools to illuminate glaucoma's shadowy corners. His lab group pioneered the development of genetic mouse models of glaucoma to study early nerve-damaging changes in the disease. And with support from a 2008 Hughes Collaborative Innovation Award, they are creating the ultra-miniature device to continuously monitor IOP inside a mouse eye.

His team recently revealed the role of inflammation and the immune system in causing damage to the optic nerve. In response to early tissue stresses, a class of immune cells known as monocytes seep into the optic nerve at the earliest stage of the disease, before any damage can be detected. The discovery supports a growing belief that neuroinflammation—an inflammatory response to stress or injury in neural tissues—is a primary cause of glaucoma, John says.

Another key finding, described April 2, 2012, in the *Journal of Clinical Investigation*, offers clues to a potential treatment for glaucoma. A single, targeted x-ray treatment to the eye of a glaucoma-prone mouse provided long-term protection against the disease in that eye.

The idea to test radiation arose from an earlier study that used whole-body radiation when replacing the bone marrow in glaucoma-prone mice. Normally, about 80 percent of these mice develop glaucoma. But in John's study, 96 percent of the irradiated mice had no evidence of it. "The magnitude of the effect was so large, it was almost unbelievable, so we did the experiment three more times to make sure it was correct," John says.

The radiation, they found, changes the expression of genes in the endothelium, the thin layer of cells lining blood vessels. The endothelium controls monocyte movement into the optic nerve, so blocking that route may be one explanation for the protection, though other, as-yet-unidentified factors may be involved as well. Radiation per se might not prove a practical treatment, John says, but the finding may aid in creating other neuroprotective therapies.

A Wireless Sensor

Importantly, the radiation treatment does not alter IOP. Clarifying the role of this key risk factor remains a challenge. As John explains, current methods for measuring eye pressure are inadequate; they cannot provide around-the-clock data, and pressure can vary considerably during a day. A snapshot measurement taken just once a day, for example, is not enough to accurately relate pressure effects to neural damage. Additionally, repeatedly disturbing a mouse to measure pressure may alter the disease process. That's where the tiny IOP sensor may help.

Purdue University engineers Pedro P. Irazoqui and William J. Chappell created the device, which incorporates a silicon chip, a pressure sensor, and an antenna.

"I challenged Pedro and Bill, and they came up with some remarkable innovations

Michael C. York / AP, ©HHMI

to allow miniaturization of the devices," John says. For example, the engineers developed special glue embedded with gold-coated nickel beads that conduct electricity, but only in the desired direction. The glue binds the components together. No need for wires.

The silicon chip processes data from the sensor, and both are powered by radiofrequency waves sent via an external transmitter to the antenna. The device then automatically sends the information to a receiver outside the cage. The team is close to having a fully functional prototype, John says. Once that happens, they hope to move the hand-built device to a commercial developer to produce it for research laboratories worldwide.

By providing more detailed information on how IOP changes over time, the device will enable researchers to relate those changes to optic nerve damage, John says. "That, in turn, will allow us to identify new mouse models for glaucoma far more easily and accurately, which will have a revolutionary effect on our ability to understand the genetics and molecular mechanism of glaucoma."

John also envisions the monitor helping develop treatments. "For example, a sensor could measure pressure and then wirelessly send that data to a miniature pump, which would then deliver a drug as needed, based on biofeedback. These are the types of things we're thinking about and hope to test in the future."

■ – JULIE CORLISS

Sounding the Alarm

Details on how cells detect and respond to foreign DNA may provide clues to autoimmune diseases.

THE SURVEILLANCE SYSTEM OF A CELL RIVALS THAT OF ANY bank vault: a complicated configuration of sensors, tripwires, and alarms. Molecular guards patrol the periphery and interior of cells to lock out, inactivate, or destroy harmful particles. It takes a cunning invader to cross the physical barriers and elude second- and third-line sensors. ¶ Cell biologists have long understood some components of the security system while others remained hidden in a tangle of cellular wiring. Now, HHMI investigator Zhijian "James" Chen of the University of Texas Southwestern Medical Center has uncovered a mechanism the cell uses to detect and react to signs of invading organisms—specifically, loose pieces of DNA inside the cell. The discovery helps explain a basic cellular function and sheds light on how the biological surveillance system is poorly wired in some autoimmune diseases.

Even before scientists knew the role of DNA and RNA in transmitting genetic information, they knew that these molecules could trigger immune responses in humans. More recently, scientists learned that if DNA or RNA of microbial pathogens, such as viruses and parasites, entered the watery interior cytosol of a cell, the immune system would be called into action to fight the invaders. In some cases, however, a cell's own DNA is found loose in the cytosol rather than contained in a central nucleus or organelle, and this loose DNA can trigger autoimmune reactions that cause diseases such as lupus.

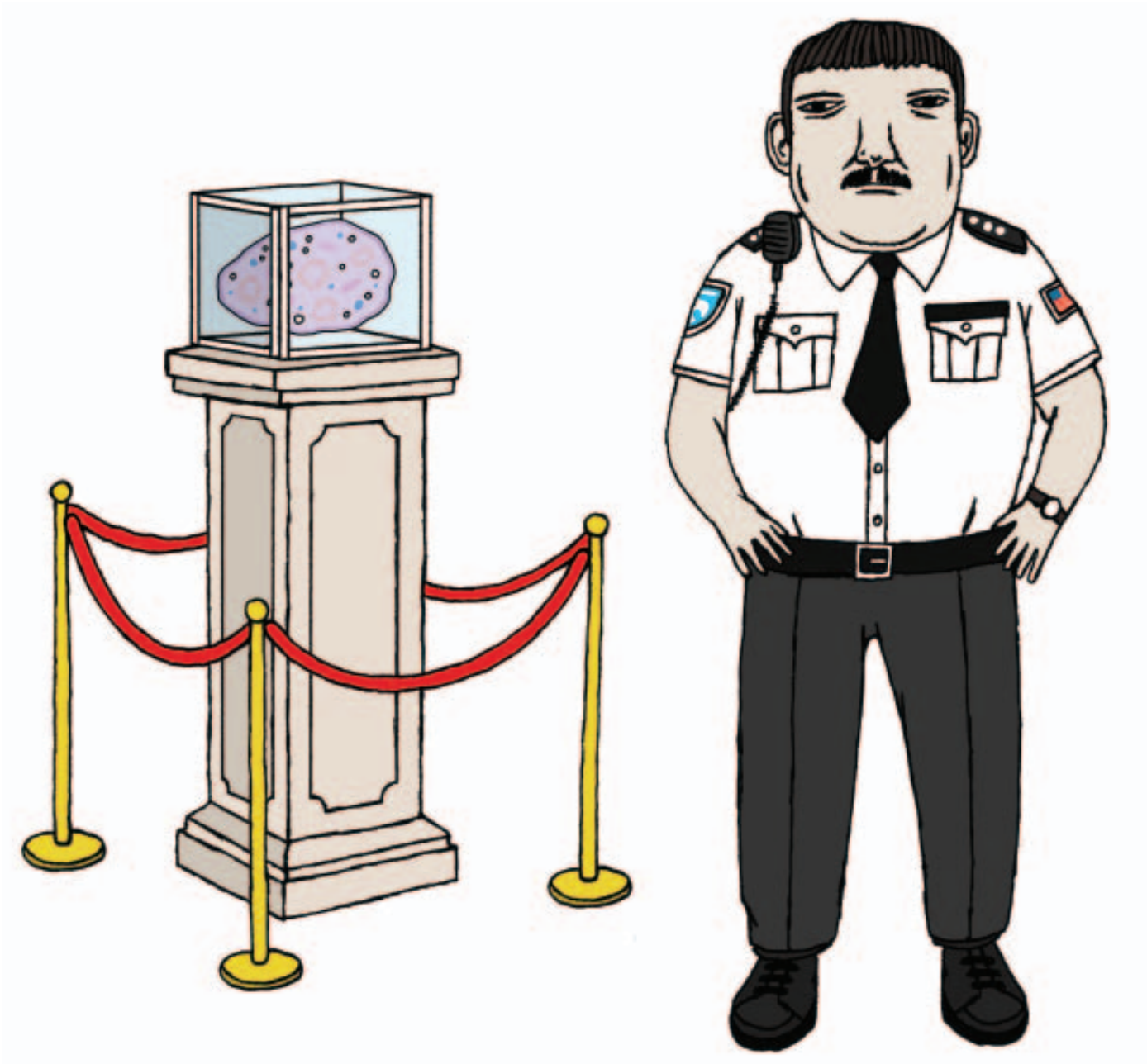
"The cytosol has to be very clean," says Chen. "If DNA gets in, that is actually a danger signal to cells."

After discovering how molecules patrol the cytosol for loose RNA, Chen and his colleagues wanted to know how cells detect rogue DNA. So they added bits of DNA to cytosol that had been removed from cells and then fractionated, or divided, the liquid mixture into different components. By inserting each component into fresh cells and running gene expression assays, the scientists could determine which fraction turned on immune system activation genes—in other words, which one contained the molecules responsible for sensing the loose DNA.

"Using this method, we could repeatedly fractionate the samples to narrow down our search for the active components of the system," says Chen. "This assay was really the key to our discovery."

Through repeated narrowing down of the fractions, followed by analytical chemistry, Chen's lab group revealed that two molecules are critical to detecting loose DNA. Further biochemical experiments helped them understand the roles of the molecules in sensing DNA and setting off an immune response.

An enzyme called cyclic GMP-AMP synthase (cGAS), they discovered, binds directly to any DNA that's free-floating in the cytosol—it's the initial sensor of free DNA. "The cGAS enzyme recognizes all double-stranded DNA without any apparent sequence specificity," says Chen.



Bob London

"Which makes sense because an organism wants to recognize all sorts of DNA from different sources."

Once cGAS is bound to DNA, it becomes active as an enzyme, a protein that can carry out chemical reactions. In this case, when cGAS is activated it synthesizes a chemical messenger called cyclic GMP-AMP (cGAMP). The newly made cGAMP binds to a protein called STING, which turns on a cascade of immune reactions.

The scientists' findings, reported in two papers published online in *Science* on December 20, 2012, could also launch a new generation of treatments for some autoimmune disorders. In diseases such as lupus and Sjögren's syndrome, the immune system is in a state of constant activation—as if a bank vault's alarms ring incessantly even when all is clear. One trigger of the constant immune reaction in these diseases may be the loose DNA in cells. So it's likely that cGAMP and cGAS are abnormally active, Chen says, in people with these diseases. More research is needed to fully understand the roles the molecules may play in disease, but it's possible that blocking their activity could block the constant immune response, Chen says.

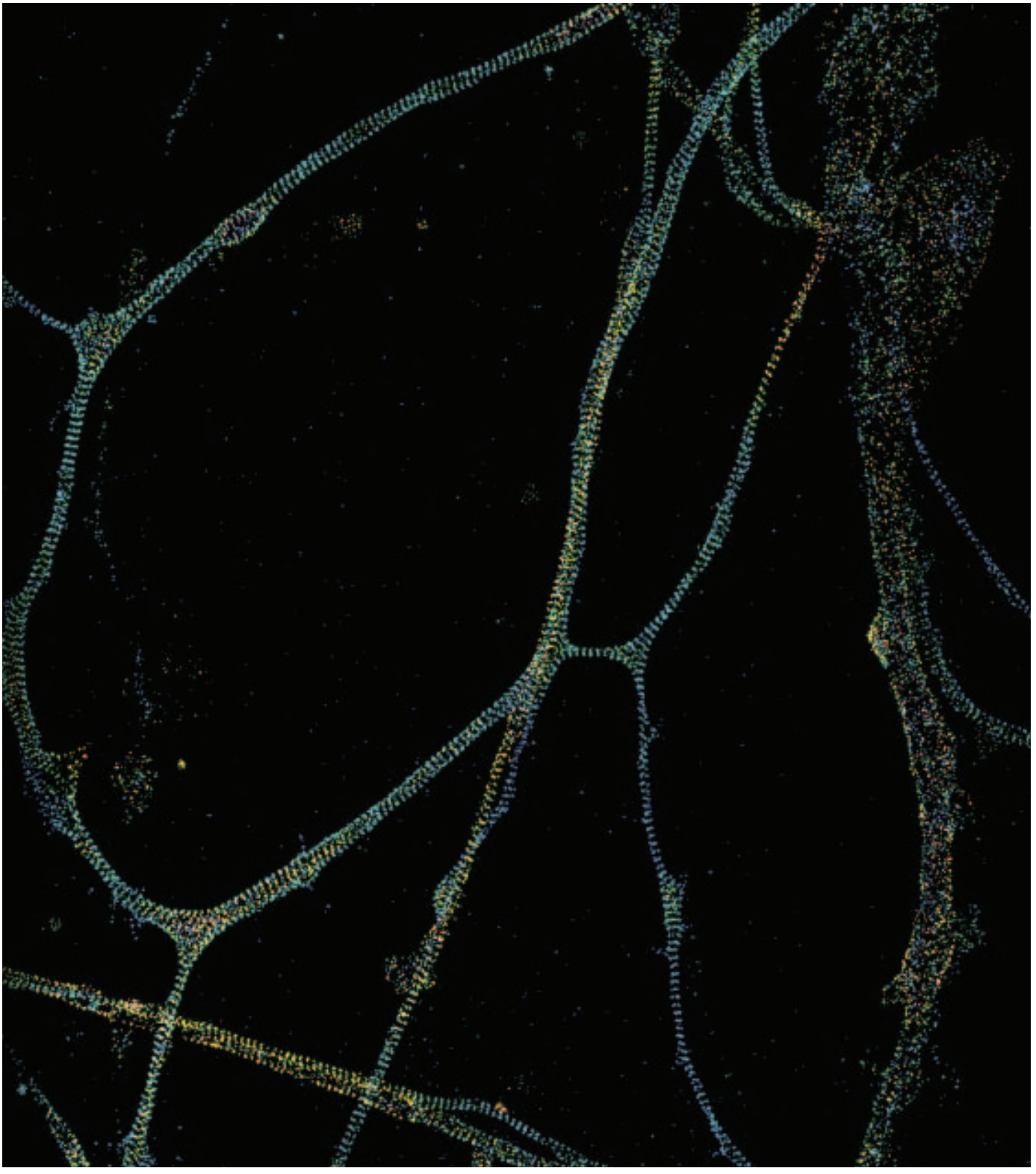
"We hope we can go on to identify chemical inhibitors of this enzyme," says Chen. "Such inhibitors could be developed into therapies for autoimmune diseases."

For now, Chen wants to work out more of the molecular details of the loose DNA alert system and test its role in animal model systems. He hopes to learn ways to hack the molecular alarms, to coax the cell to let down its guard in some cases, and to help cells strengthen their defenses against intruders in others.

■ – SARAH C.P. WILLIAMS

Ring Around the Axon

Cytoskeletal proteins form a unique structure in nerve cells.



Xiaowei Zhuang and her team used a microscopy technique called STORM to show that actin protein forms evenly-spaced rings around the axons of nerve cells.

Zhuang lab

IN ALL BUT THE SIMPLEST CELLS, A PROTEIN CALLED ACTIN organizes to support the cell's shape. It typically does so in linear or branched formations. Turns out, actin can come together in a completely different way as well, according to work by HHMI investigator Xiaowei Zhuang and her lab team.

In the thin, extending part of a nerve cell, called the axon, actin forms rings, encircling the length of the fiber at regular intervals. Zhuang suggests that these repeated rings lend flexible yet robust support to axons. She also proposes that the pattern may affect how electric signals are transmitted along axons.

"No one has ever seen periodic rings like this formed by actin," says Zhuang, a biophysicist at Harvard University whose team published the findings on January 25, 2013, in *Science*. The discovery comes as a surprise to neuroscientists, who have pondered the structure of actin within brain cells—in particular, within axons and the threadlike extensions of the nerve cell body known as dendrites.

At less than a ten-millionth of a millimeter (10 nanometers) in diameter, the protein was too small for most light microscopes to visualize in detail. Early last year, Zhuang's postdoc Ke Xu improved a microscopic technique developed in Zhuang's lab called STORM (stochastic optical reconstruction microscopy) and captured high-resolution images of individual filaments of actin in fibroblasts and epithelial cells—work published January 8, 2012, in *Nature Methods*. Soon after, Zhuang challenged Xu and another postdoc in the lab, Guisheng Zhong, to image actin within brain cells, where its structural organization is thought to influence brain cell communication and other neurologic processes.

Zhuang suggested that Xu and Zhong focus on actin in the synapses—specialized cell–cell junctions responsible for communication—because neuroscientists predicted that the protein's structure at these junctions would influence chemical signaling. Instead, the two became preoccupied with fluorescent dots that aligned along the neurons' axonal fibers. Over the following months, Xu and Zhong perfected their methods of labeling and imaging neurons until they could image actin clearly in three dimensions. The images revealed that the dots were in fact individual rings of actin periodically encircling the axonal fibers just beneath the membrane.

In addition, they found that one of actin's binding partners, a protein called spectrin, was also part of the pattern. Zhong and Xu fluorescently labeled spectrin and saw that a long stretch of the protein—180 to 190 nanometers—bridged each actin ring.

The team revealed that sodium ion channels embedded in the axonal membrane follow a periodic pattern as well. Ions passing through these channels create electric charges that rise and fall rapidly, sending signals throughout the brain as they travel along axons. This electric movement is detailed in a mathematical model called the cable equation. As a result of the team's findings, "The outcome of the equation that describes how electrical signals propagate along axons may now need to be modified," says Zhuang's colleague, Harvard chemical biologist Xiaoliang "Sunney" Xie.

> "These talented guys were so persistent in overcoming one difficulty after another to optimize the experimental conditions and generate these convincing images."
>
> XIAOWEI ZHUANG

Zhuang credits her postdocs for having the intuition to pursue whether the "dots" they saw in STORM's first image were more than an artifact and for having the endurance to enrich and perfect the results until they could construct a model of this molecular lattice. "When they first noticed the seemingly periodic pattern, it was not so obvious at all, but they did not let it go," recalls Zhuang. "These talented guys were so persistent in overcoming one difficulty after another to optimize the experimental conditions and generate these convincing images."

Zhuang would like to capture even finer images of actin–spectrin interaction within the lattice and to better understand the functional role it serves. She plans to improve STORM so that it can delve down from 10 nanometers to just a few nanometers. A STORM microscope snaps only a subset of glowing fluorescent molecules in a sample at a time and then iterates this process until a high-resolution image is reconstructed. In contrast, conventional microscopes image all glowing molecules at once, creating a blur that limits resolution. To increase STORM's power, Zhuang needs to find brighter fluorescent tags that label molecules of interest in the sample more densely and hone the microscope to determine the positions of the molecules more precisely.

Xie attributes Zhuang's unexpected finding to her focus on perfecting techniques and exploring biologically important topics. She had the foresight to focus on actin in the brain, he says, with one of the only tools capable of doing it.

Unveiling the structure of the actin–spectrin rings speaks to the worth of super-resolution microscopes like STORM, Zhuang says. "Making a scientific discovery is extremely rewarding for people like us who develop new methods. It is the ultimate validation of a method."

■ – AMY MAXMEN

WEB EXTRA: To learn more about STORM, visit www.hhmi.org/bulletin/spring2013.

I AM A SCIENTIST

THE EXROP PROGRAM HAS HELPED HUNDREDS OF UNDERREPRESENTED MINORITIES IDENTIFY AS RESEARCHERS, A KEY STEP TOWARD A SCIENCE CAREER.

BY ERIN PETERSON
ILLUSTRATION BY LARA HARWOOD

Snow is falling steadily on an early February afternoon, but Kelley Harris-Johnson isn't admiring the scene from her office windows at the University of Wisconsin–Madison. She's deep in conversation with a student.

They chat about his athletic accomplishments, his volunteer work with a local hospital, and his family. They discuss his challenging course load and strong GPA. And when he expresses an interest in doing summer research, she launches into a mini master class on finding faculty members conducting research, writing targeted emails, and doing extensive interview preparation. By the time he pulls on his coat to leave, another half-inch of snow blankets the campus, and he is armed with knowledge that can propel him to graduation and beyond.

Harris-Johnson, an assistant faculty associate in Wisconsin's biochemistry department, believes in the importance of getting to know students as people and taking the time to guide them when they ask for help. "Mentorship from key people in my life helped me reach the goals I set for myself," she says. "It influenced me in my career and it changed my life. Any opportunity I have to give that sort of mentoring to a student, I feel obligated to do." The shelves in her office display dozens of bright thank-you cards from students she's worked with over the years.

A decade ago, Harris-Johnson was not unlike the young man who came for help on that snowy day: bright, motivated, and in search of the right opportunity. In early 2003, just months before graduating from Xavier University of Louisiana, a historically black college, she learned about a new program offered by the Howard Hughes Medical Institute. It was called the Exceptional Research Opportunities Program (EXROP), and her biology professor, Michelle Boissiere, thought it was the perfect fit for Harris-Johnson, a biology major and chemistry minor. Created to provide talented underrepresented minority undergraduates the opportunity to do mentored summer research with HHMI-funded scientists, the program was designed to attract outstanding students and give them the skills and confidence to succeed in graduate school.

Celebrating its 10th anniversary, EXROP has built a trove of success stories that move beyond the singular anecdote to statistical significance. HHMI has sponsored 578 students from more than 100 colleges and universities. Of the 370 EXROP alumni who have completed their baccalaureate degrees, 362 are in science careers. A full 50 percent have pursued graduate degrees (see chart on page 17). To further support the development of EXROP students, the program recently added an ambitious component called the "capstone experience."

Harris-Johnson, a member of the first cohort of EXROP students, credits the program with cementing her love of research. It also gave her the chance to add to her resume, which already listed two other college research experiences. For her EXROP summer, she worked in the lab of the University of Wisconsin's Paul Ahlquist, an HHMI investigator. She studied yeast as a model to understand how viruses get help from host cells during infection. The tough project taught her to handle failures, appreciate even small successes, and experience life as a researcher. "I learned an entirely new vocabulary, a new system, and a new skill set," she says. "And that gave me a lot of confidence."

The next fall, she enrolled at the University of Wisconsin to obtain a graduate degree in genetics. In 2008, she graduated with a Ph.D. Today, she teaches a freshman seminar course and a large introductory biochemistry course and works closely with students. Though she no longer does her own research, she draws on her lab experience when giving advice to students and when she

One of the first EXROP students, Kelley Harris-Johnson teaches university-level science and takes time to mentor.

Kevin Miyazaki

"FINDING SOLUTIONS TO HARD SCIENTIFIC PROBLEMS OFTEN DEPENDS ON THE DIVERSITY OF THE PROBLEM SOLVERS WHO BRING TO THE CHALLENGE DIFFERENT PERSPECTIVES, TOOLS, AND WAYS OF THINKING." –DAVID ASAI

wants to add context to a classroom discussion.

There were many steps along Harris-Johnson's path to success, but she says her experience with EXROP helped her stick to the difficult but rewarding path she chose.

A New Approach

Science benefits from diversity, says David Asai, senior director of HHMI's precollege and undergraduate science education programs. "Finding solutions to hard [scientific] problems often depends on the diversity of the problem solvers who bring to the challenge different perspectives, tools, and ways of thinking."

The lack of diversity in science was glaring as this century began: just 7.3 percent of Ph.D. recipients in a science, technology, engineering, or math (STEM) field in 2001 self-identified as black, Native American, or Hispanic. The numbers did not reflect the growth in U.S. minority populations.

To tackle the problem, many organizations have tried an array of approaches. HHMI, for example, offered a full slate of high school and museum outreach programs for underrepresented minorities in the sciences. Tom Cech, HHMI's president from 2000 to 2009, says the Institute was proud to have brought 50,000 students through such programs over the years.

Because of that record, Cech invited Freeman Hrabowski, a longtime proponent of minority participation in the sciences and president of the University of Maryland, Baltimore County (UMBC), to discuss programming back in the early 2000s. To Cech's surprise, Hrabowski delivered a challenging message. "We expected that he would give us a giant pat on the back," Cech recalls. "Instead, he looked at the data and said, 'You haven't done anything.'" Though HHMI could point to vast numbers of students going through the programs, the organization didn't know how many students more seriously pursued a career in the sciences as a result.

After Hrabowski's harsh appraisal, HHMI looked at other approaches. Summer research looked promising. Undergraduates who participate in hands-on research are more likely to pursue advanced degrees and careers in science, according to dozens of studies. At the time, UMBC had a decade's worth of success with the Meyerhoff Scholars Program, which was designed to provide support to African American students committed to earning a Ph.D. in math, science, or engineering.

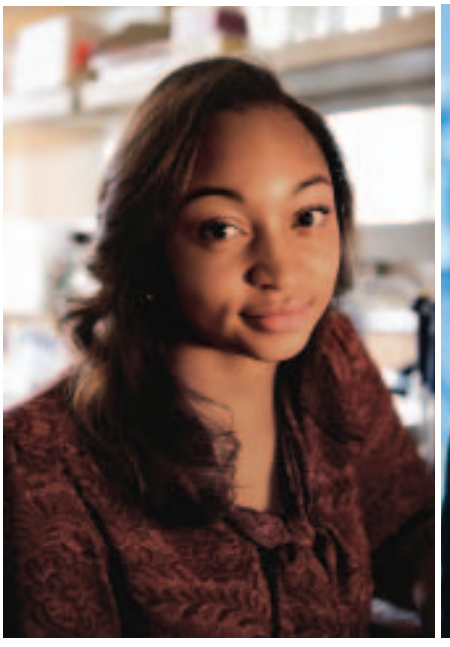
A summer research approach could help HHMI encourage students to consider careers as researchers. Hrabowski also suggested to Cech that this kind of work might boost the number of underrepresented minorities who choose careers as professors, where they would be at the front of the classroom and could influence future generations of students. And HHMI could track results to stay laser focused on the program's efficacy.

To be sure, other organizations were using summer research as a tool to get students excited about science careers. The Amgen Foundation, for example, offers hundreds of undergraduate students the opportunity to do hands-on research each summer, though it does not focus on underrepresented minorities. The National Science Foundation, meanwhile, provides colleges and universities with funding for hundreds of students through its Research Experiences for Undergraduates program. The schools themselves select the students for lab work.

HHMI needed to do something valuable and distinctive. Peter Bruns, then vice president for grants and special programs at HHMI, realized that the ingredients for such a program could already be found within HHMI. The organization had long supported top research scientists across the country. It was also giving grants to colleges to develop and run innovative science education programs for undergraduates.

"With EXROP, we could join both sides of the house," Bruns says. Faculty at the colleges and universities could serve as "talent scouts," nominating promising students to participate and serving as advocates for them throughout the process. And HHMI investigators could give students experience in top-notch labs. HHMI investigator Mike Summers, who helps lead the UMBC Meyerhoff Scholars Program, assisted in designing the EXROP program.

In 2003, HHMI launched the program with 32 students. In its 10 years, the number of participants has increased; the 2013 class includes 77 students. This year's budget is $1.2 million. The total budget for the 10 years climbs to about $6.4 million. And the diversity of the students who have participated over the program's history is significant: 42 percent are African American, 34 percent are Hispanic, 10 percent are Asian, and 1 percent is Native American. Women make up 58 percent of EXROP participants.



EXROP graduates Kayla Lee and Cornelius Taabazuing are both pursuing a Ph.D.; Lee won a Gilliam Fellowship for advanced studies.

Building Confidence

EXROP is designed to give students challenging and meaningful research experiences with exceptional researchers. But the program is also designed to provide emotional and career support to students through mentoring, networking, and other opportunities. In addition to the 10 weeks of summer research, EXROP students spend time at HHMI headquarters meeting other EXROP students and hearing from scientists who were in their shoes just a few years earlier.

The reason behind these extra program components is that it's often not enough for students to "know" that they can do research. They must also internalize that idea, "to believe it with their hearts as well as their minds," according to Asai. A significant obstacle for underrepresented minorities isn't necessarily the process of research but the mental barriers that undermine their confidence.

Harris-Johnson, for example, says that her fantastic grades and previous research experience at Xavier weren't enough to convince her she could be successful. "At Xavier, most of my instructors looked like me, and I was grateful for that," she says. "But I didn't know if I could cut the mustard at a majority school." It didn't help that family members encouraged her to settle into a more traditional lifestyle—husband and kids—instead of pursuing a research career.

These cultural pressures could have limited her, but her experience with EXROP helped change her mind. Support from Ahlquist and the postdocs in his lab—combined with significant progress throughout the summer—convinced her that she had the skills and tenacity to do research. "At one point, after making a mistake, I remember talking to a postdoc about research and saying, 'I'm not ready to do this.' And he looked at me and said, 'Kelley, you're more than ready to do this.' I will never forget that as long as I live."

Kayla Lee, a senior at Hampton University, a small, historically black institution in Virginia, says that her 2011 EXROP experience under the guidance of HHMI investigator Ron Breaker at Yale University was eye-opening way beyond the research experience; it made her rethink her job options. "I am convinced there is an unwritten blueprint somewhere that says that students—especially minority students—who enjoy science have to grow up to be doctors," she says. "[Research] is not a well advertised career path. Luckily, through a series of my own questions and amazing professors, research found me."

Lee adds that her EXROP faculty sponsor at Hampton, biology professor Edison Fowlks, supported her throughout the process. "His mentorship is one of the main reasons that academia is a very important part of my future career," she says. "Without him, it would have taken me a lot longer to [reach] my goals." Lee, who received a 2013 Gilliam Fellowship from HHMI that will fund four more years of advanced study, will begin a Ph.D. program at Harvard this fall.

For Cornelius Taabazuing, the EXROP-funded research that he did in 2009 with Cech at the University of Colorado, Boulder, led to a coauthored study published in *Cell* in 2012, a validation unlike any other. "After the program, I had the self-confidence to know that I can perform research at the highest level and be successful in a career as a scientist," he says. Today, he is studying for a Ph.D. in chemistry at the University of Massachusetts at Amherst.

HHMI investigator and Nobel Prize winner Eric Kandel, who has mentored 14 EXROP students at Columbia University, says that while he's happy to reassure students who may feel insecure about their abilities, success is its own confidence builder. "If you do well in the lab, that's very satisfying," he says. "Sometimes, that's all the certification you need." It's a sentiment borne out by outcomes data: undergraduate researchers from HHMI-funded summer research programs routinely say that self-confidence is one of the many benefits they gain from their experience. These markers of achievement—praise from a top researcher, success with an experiment, and even publication in a journal—can provide the reinforcement that continues to motivate students to take science seriously.

To help underrepresented students stay in the sciences, HHMI offers an array of options to EXROP alumni. For example, some

Lee: Mark Edward Atkinson Taabazuing: Jason Grow

alumni visit Woods Hole for a few days to encourage them to participate in a summer course at the Marine Biological Laboratory. And the HHMI Gilliam fellowships provide extended support to EXROP alumni who attend graduate school. These options help students maintain their momentum after their EXROP summer is over.

Thanks to the efforts of HHMI and other organizations, more underrepresented minority students are receiving Ph.D.s. While the number of doctorates in STEM fields climbed from 11,823 to 15,910 between 2001 and 2011, the proportion of Native American, black, and Hispanic recipients has grown even faster, from 858 (7.3 percent) to 1,641 (10.3 percent). There remains a great deal of work to bring the number of minority Ph.D.s to reflect the talent pool (currently, about 31 percent of undergraduates interested in STEM are minorities), but the nation appears to be headed in the right direction.

From Capstone to Career

The EXROP outcomes data demonstrate the power of a summer research experience, but they raise a question: If one summer of research is good, would two be better?

Logically, it makes sense. Students who return to their host lab for a second summer don't have to devote precious time learning to use the equipment and getting up to speed on the research. Other benefits recommend the practice as well. In a 2012 study published in the journal *CBE–Life Sciences Education*, for example, students with multiyear research experiences were more likely to develop higher-order scientific thinking skills, including the ability to analyze and interpret data, solve problems, and identify the next steps of an experiment. They developed greater confidence, intellectual independence, and a larger sense of ownership of their work.

In 2012, armed with those ideas and data, HHMI began offering a capstone summer research experience for students who want to do research for a second summer in the same lab. Last year, 31 of the 81 EXROP students from 2011 took advantage of the capstone experience. This summer, 34 of 60 will participate.

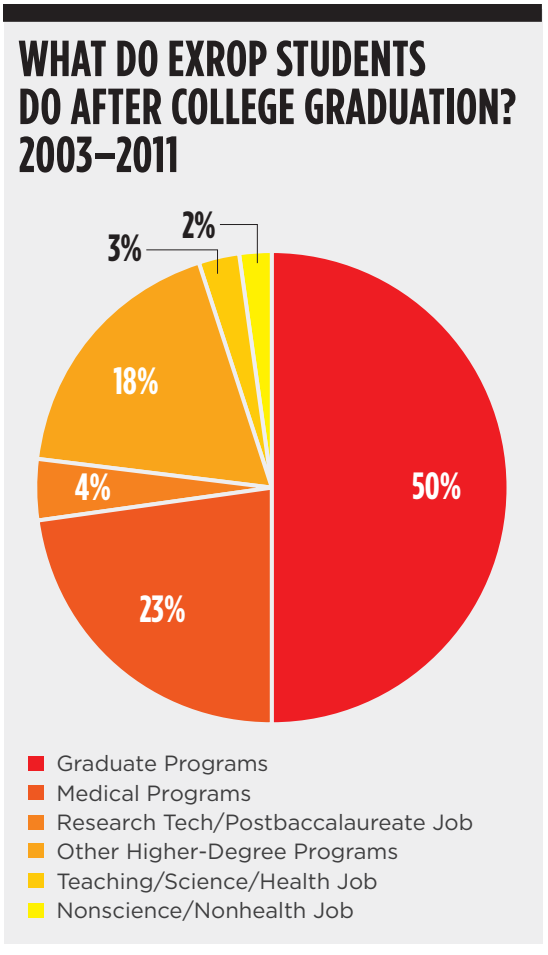
According to Asai, early results are encouraging. "We launched the capstone experience on the premise that a second experience will reinforce students' identities as scientists," he says. "Comments from last year's 'capstoners' support this rationale: they speak of already feeling that they belonged to the lab and that they were able to make more significant contributions, rather than feeling like a temporary guest."

Izzy Cerullo, a senior at Columbia University, first participated in EXROP in 2011, when she worked in the lab of HHMI investigator Michael Rosbash at Brandeis University. She studied certain groups of neurons and how firing those groups can control circadian rhythms and affect periodic behavior in fruit flies.

Cerullo loved the work and was eager to return; when HHMI offered the capstone experience, she signed on. "I didn't have to be taught the basics," she says. "[The second summer] was really productive."

While she plans to take some time off from school after she graduates this spring, she's already applied for research-related positions in several labs so that she can stay sharp for the next steps in her career.

Buoyed by this kind of enthusiasm and compelling data, Asai hopes to see other institutions, both public and private, find ways to replicate HHMI's efforts by connecting top scientists with top students from underrepresented groups. He also hopes other organizations can find more ways to reinforce scientific identities in these students. In the coming years, he'd like to see EXROP come full circle. "My greatest hope for EXROP is that the students who have come through the program will continue to grow, thrive, and excel so that one day some of our EXROP alumni will themselves be HHMI investigators and professors." ■

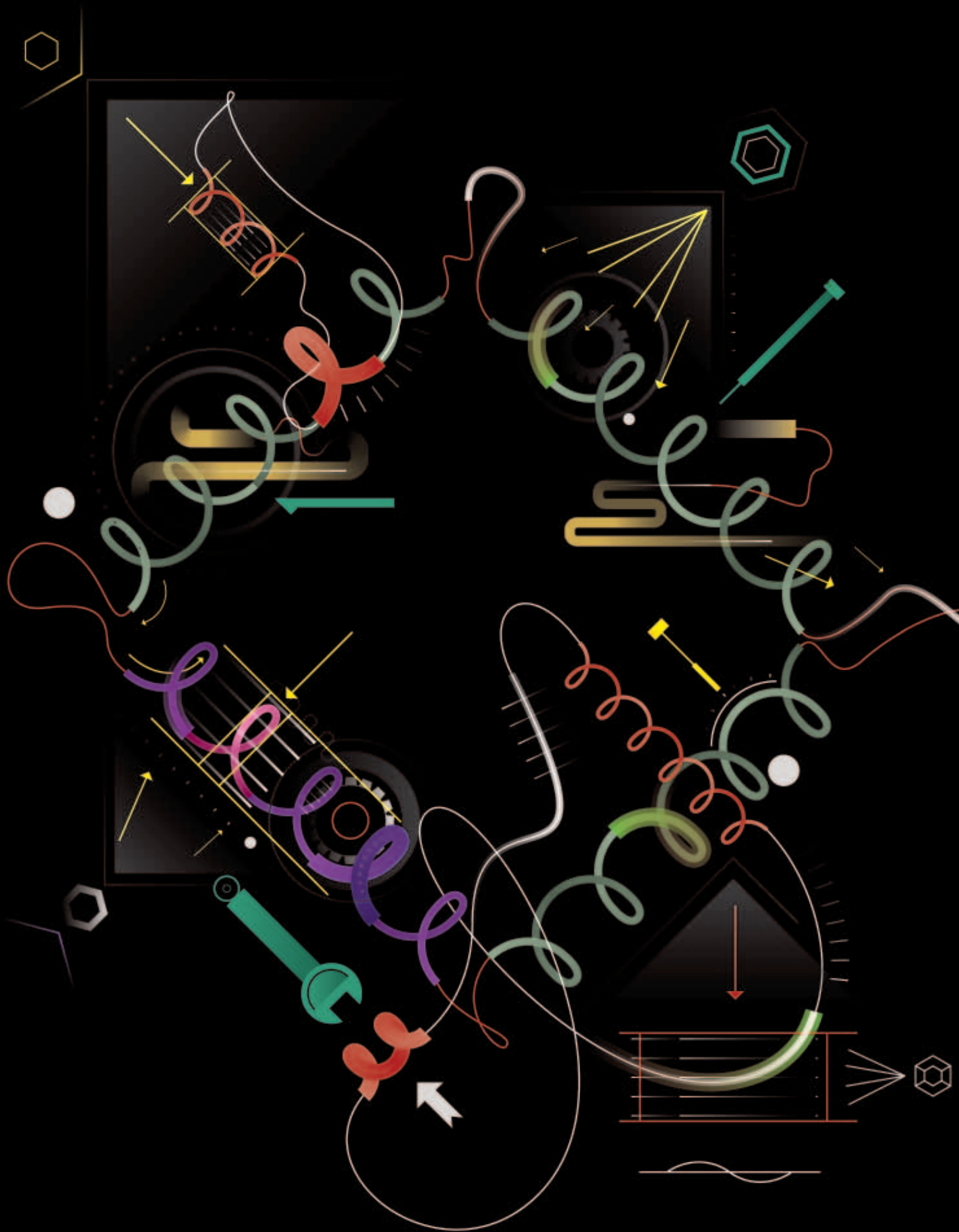


WEB EXTRA: See video and slideshows of EXROP students reflecting on their experiences at www.hhmi.org/bulletin/spring2013.

A STRUCTURAL TOOLBOX

No longer content with static snapshots, biologists are using a medley of techniques to get a global view of molecules at work.

By Nicole Kresge
Illustration by Leandro Castelao



Part 2 of 2: This is the second in a series of articles that commemorates the 25th anniversary of HHMI's structural biology program. Part 1 explored the program's genesis and its first investigators.

Natalie Strynadka wants to design a better antibiotic. Her strategy: learn about the molecules bacteria use to invade cells. Her tool: structural biology.

Easier said than done. Some structural biology techniques can't handle the big, membrane-embedded complexes bacteria use to overtake their hosts. Others don't give the level of detail Strynadka wants. And still others can't show her exactly how individual molecules interact.

So, she's combining multiple techniques—electron microscopy (EM), nuclear magnetic resonance (NMR), and x-ray crystallography—to visualize her molecular subjects. "When you're tackling these larger assemblies you really need to have a multidisciplinary approach," says Strynadka, an HHMI senior international research scholar at the University of British Columbia. "You aren't going to capture the whole picture in just one image. You have to piece together the information."

Strynadka is one of a handful of HHMI scientists who have been molding the tools of structural biology to fit their interests (see box on page 23 for a description of these tools). Twenty-five years ago when the Institute started its structural biology program, the goal was basic: to discover how molecules looked. Researchers spent years using a single method to solve a single structure.

"In the early days, we tried to choose interesting proteins for which the structures could be determined, but they also had to be proteins that were sufficiently well behaved and were easy to purify," recalls Brian Matthews, a biophysicist and HHMI investigator alumnus at the University of Oregon. "Now the progress is really driven by the biology."

Today, researchers want more than a simple structure. They want to watch molecules in action. They want to learn how proteins work together in molecular assemblies. They want to understand why cellular membrane pores let some things inside but deter others.

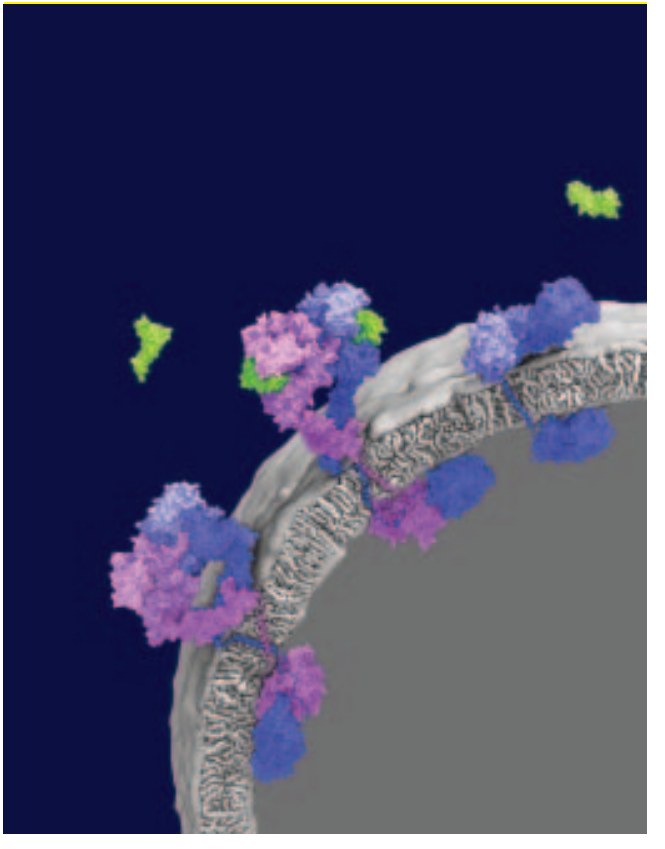
To do so, they routinely tweak and merge structural techniques or combine them with approaches from other fields—cell biology, genetics, and biochemistry—to create tools that can make their wishes come true. They are assembling multidisciplinary teams in their labs, mixing experts in x-ray crystallography, EM, and NMR with biologists, physicists, and computational biologists. They are going across the halls and across the country to initiate collaborations to address a dizzying number of questions—from watching enzymes remodel themselves to matching proteins with their undiscovered binding partners.

A COLLABORATIVE APPROACH

In her lab at Brandeis University, HHMI investigator Dorothee Kern studies the dynamics of enzymes as they catalyze, or speed, chemical reactions along. She then uses the data to create real-time movies of enzymes in action. The perfect technique for following these tiny movements is NMR, which allows molecules to perform their biological functions while they're being visualized at atomic resolution.

One of her more unexpected findings came from human cyclophilin A—the cellular target for the immunosuppressive drug cyclosporin A and the enzyme that is hijacked by HIV. After characterizing cyclophilin's motion during catalysis, Kern discovered that the enzyme has a "dynamic personality." Even when it's not bound to its substrate, cyclophilin A goes through the entire range of motions it uses during catalysis.

To learn more, Kern turned to x-ray crystallography—a tool usually called on to look at static structures—and modified it to also get a sense of structural change. Kern had a hunch that x-ray crystallography data contained overlooked information about a molecule's motions. When a protein forms a crystal, each molecule in the crystal is frozen in a slightly different conformation.



John Kuriyan and his collaborators used a combination of molecular biology, nuclear magnetic resonance, x-ray crystallography, and computational analysis to explore the membrane-bound epidermal growth factor receptor (EGFR). They learned that two molecules of EGFR (purple and pink) come together to form an active receptor.

D. E. Shaw Research

"NOWADAYS, NO ONE WHO DOES STRUCTURAL BIOLOGY STUDIES JUST THE STRUCTURE. IT IS VERY IMPORTANT THAT WE PUT OUR STRUCTURES IN BIOLOGICAL CONTEXT."
→ EVA NOGALES

A scientist's map of the protein's atoms is the average of all the different arrangements. Kern believed one could tease out these minute movements from the data.

She called on a close friend—x-ray crystallographer Tom Alber at the University of California, Berkeley (UC Berkeley)—who developed an algorithm to look more closely at the data. When they used the new program on cyclophilin A, Alber and Kern saw several of the molecule's alternative structures in the electron density data, previously written off as noise. The molecular movements were the same ones she'd seen in solution with NMR, but x-ray crystallography provided high-resolution images. NMR delivered information on the speed of these conformational changes.

Alber and Kern published their results in *Nature* in 2009 and the algorithm has caught on. "I think the whole field has really changed in the last few years," says Kern. "Now we're all talking about conformational ensembles. We can ask how proteins work rather than just look at a molecule's shape."

HHMI investigator Eva Nogales, whose specialty is EM, agrees. "Nowadays no one who does structural biology studies just the structure," she says. "It is very important that we put our structures in biological context."

Much like Alber and Kern, Nogales joined forces with another scientist to learn more about a molecular assembly. Shortly after she arrived at UC Berkeley in 1998, Robert Tjian, then an HHMI investigator at UC Berkeley and now president of HHMI, approached Nogales about collaborating. He had been trying to get a look at the transcription factor II D (TFIID) complex—a sizable assembly of 13 or 14 proteins that jumpstarts gene expression by binding to regions on DNA known as promoters. The complex was proving to be a difficult target for x-ray crystallography. Because TFIID had to be isolated from human cells, it was hard to get enough protein to grow crystals. And the flexible nature of the complex, so essential to its function, was making it difficult to crystallize.

Tjian was hoping that EM would succeed where x-ray crystallography had failed. It did.

Within a year, Nogales and Tjian had published in *Science* the structure of human TFIID in complex with two other transcription factors, TFIIA and TFIIB. Next, Nogales decided to try cryo-EM.

The cryo-EM data, published in *Cell* in January 2013, revealed that the hulking TFIID can reorganize itself. This property is likely essential for its regulation by activators and cofactors. One-third of the multiprotein complex shifts across a large central channel, creating a very different looking structure. With Jim Kadonaga at the University of California, San Diego, Nogales's team combined the cryo-EM data with biochemical analysis to reveal that one conformation of TFIID binds DNA much more tightly than the other.

"Cryo-EM was absolutely essential to visualize this conformational flexibility," says Nogales. "My collaboration with [Tjian] made me realize that my set of experimental tools is ideally suited to study this system."

In March 2013, Nogales published a paper in *Nature* that took the work even further. She created the EM equivalent of a stop-motion movie (see Web Extra animation). The short film shows several transcription factors assembling into what's known as the preinitiation complex—a massive structure that helps position RNA polymerase II on DNA to start gene transcription. Nogales did this by adding the transcription factors sequentially, taking pictures of the growing complex after each addition.

IN-HOUSE EXPERTISE

Instead of collaborating with other lab groups, some HHMI scientists have gathered the structural techniques they need right under their own roof. An x-ray crystallographer by training, Strynadka has added EM, cryo-EM, NMR, and customized mass spectrometry approaches to her own lab. She needs them all to study the membrane protein assemblies she is targeting for antibacterial and vaccine development.

Strynadka is building a detailed picture of the type III secretion apparatus, an impressive needle-like complex bacteria use to inject host cells with a dose of proteins so they can infect the cells. The entire complex consists of more than two dozen different proteins and spans three membranes—two bacterial membranes and the host membrane. She uses cryo-EM to get an outline of the complex's general features. X-ray crystallography and NMR give her the structures of the individual proteins that make up the assembly. Mass spectrometry allows her to see how the structures interact. And computational approaches, such as those developed by HHMI investigator David Baker at the University of Washington, are ultimately used to fit the structures and supporting data into EM-generated silhouettes—like solving a big jigsaw puzzle.

So far, her group has characterized several of the major structural components of the type III secretion system, including a series of rings that act as a molecular lock to support the extracellular needle components—details published in *PLoS Pathogens* in April 2013. She's using her collection of techniques to look at a cluster of a half-dozen membrane-spanning proteins known as the export apparatus, which binds, sorts, and secretes type III specific virulence toxins.

Many of the molecules Strynadka studies are dynamic, multidomain protein complexes that span multiple membranes. These

"I THINK THE WHOLE FIELD HAS REALLY CHANGED IN THE LAST FEW YEARS. WE CAN ASK HOW PROTEINS WORK RATHER THAN JUST LOOK AT A MOLECULE'S SHAPE."
→ DOROTHEE KERN

unwieldy research subjects typically lack stability when out of the membrane, are very flexible, and have water-averse hydrophobic surfaces—all characteristics that make crystallization challenging.

Strynadka tries to circumvent this problem by extracting the proteins in a solution of detergents and lipids that mimic the native membrane environment. "It comes down to trying to understand, by a variety of analyses, what mixture of conditions, including potential binding partners, may make a protein amenable to crystallization."

That mixture can be elusive, however. Especially when it comes to certain membrane-bound receptor tyrosine kinases—enzymes that add phosphate atoms to proteins. Attempts to crystallize these molecules by surrounding them with detergents have met with little success.

HHMI investigator John Kuriyan is a structural biologist who has managed to tackle the problem. In his lab at UC Berkeley, he uses molecular biology to slice proteins into specific regions, or "domains"—an extracellular domain, an intracellular domain, and a transmembrane domain. Then he determines the shapes of the extra- and intracellular domains with x-ray crystallography and visualizes the transmembrane domains with NMR, with the help of his Berkeley colleague David Wemmer.

"Then the problem becomes stitching them together and seeing how they work," says Kuriyan. For this, he collaborates with HHMI investigator Jay Groves, also at Berkeley. By creating mutant versions of the kinases and measuring the effects of these changes on receptor activity in mammalian cells, Kuriyan and Groves have been able to get a grasp of the protein's function.

Kuriyan has used the same approach to learn about a kinase called the epidermal growth factor receptor (EGFR), an enzyme important to cell division that is overactive in many cancers. By analyzing crystal structures of EGFR and carrying out experiments using artificial membranes, he discovered that the receptor is activated by coupling with another EGFR molecule. Recently, he teamed up with computational biochemist David E. Shaw to do computer simulations of EGFR in the membrane. In two papers published January 2013 in *Cell*, they detailed how one EGRF molecule interacts with another to turn it on.

METHOD MASH-UPS

In his lab at Janelia Farm Research Campus, Tamir Gonen applies a powerful but little-used method called electron crystallography to get at the structures of membrane proteins. His results have helped account for observations that other structural biology techniques couldn't make sense of.

Gonen coaxes membrane-embedded proteins to form two-dimensional crystals, which he then exposes to intense electron beams produced by powerful microscopes at Janelia. The result: a protein structure in an actual membrane rather than in detergent.

Using electron crystallography, Gonen produced an exquisitely detailed portrait of aquaporin-0 while working as a postdoc in the lab of HHMI investigator Thomas Walz at Harvard Medical School. The channel protein allows water molecules to pass, one at a time, through the cell membrane. Since then, Gonen, in collaboration with HHMI investigator Stephen Harrison, has visualized the entire membrane around aquaporin-0 and learned about the interactions that occur between lipids and proteins.

Membrane biologists had known that channel proteins

Natalie Strynadka is studying bacterial structure to design better antibiotics and Tamir Gonen is making sense of membrane proteins that allow water or sugar molecules into cells.

Strynadka: Kent Kallberg Gonen: Paul Fetters

interact with their environments in certain ways, such as pairing positively and negatively charged atoms, but they had never seen this process in action. "Once we had the structure of a complete bilayer around a protein, we actually saw these things for the first time," says Gonen. As his next step, he's combining biochemistry, x-ray crystallography, EM, NMR, and computer simulations to learn how the channel is regulated.

Gonen is also using electron crystallography to explore a bacterial membrane protein, galactose permease, that transports sugar into cells. Malfunctions in a human version of the protein have been linked to diabetes, heart disease, and hyper- and hypoglycemia. Gonen and his team have managed to grow two-dimensional crystals of galactose permease embedded in membranes. Next, they aim to produce a detailed structure, which they hope will shed light on the mechanism of how sugar enters a cell.

Christopher Garcia, an HHMI investigator at Stanford University School of Medicine, is also interested in things people haven't seen before. He is combining x-ray crystallography and proteomics—the study of an organism's entire set of proteins—to uncover hidden interactions between receptors and their ligands. He calls the effort his "deorphanization project."

"The vast majority of receptors in any genome are orphans," explains Garcia. "We don't know what their ligands are. And the same is true for secreted proteins. We don't know what their receptors are. So I thought, 'what can I do as a biochemist and a structural biologist to address this problem in a way that others can't?'"

Garcia is taking a pairwise approach to the problem. He and his team are using proteomics to find orphan receptors and orphan-secreted proteins in the fruit fly *Drosophila* and then matching them up to find naturally occurring interactions to explore with x-ray crystallography. So far, they've discovered more than 63 pairs.

Garcia hopes to embark on a genome-wide receptor deorphanization program. While his project is one of the more ambitious structure-based HHMI efforts, the trend is undeniable. Today, very few scientists are pure structural biologists. Instead, they are researchers who use all the tools and expertise at their disposal to find out about biology.

"About 25 years ago when HHMI started the program, the emphasis in all of our labs was determining structures," says Kuriyan. "Now, increasingly the structure determination endeavor is carried out within a larger biological framework. If I had my way, I'd just remove the label 'structural biology.' I would call myself a biologist or a molecular biologist—I prefer to use the broadest label." ■

WEB EXTRA: To read about how HHMI is ensuring its investigators have access to a very powerful x-ray crystallography tool, go to www.hhmi.org/bulletin/spring2013.

COMING THIS SUMMER: Look for a special Web-only article on the future of structural biology in July.

TOOLS OF THE TRADE

X-ray crystallography
In x-ray crystallography, molecules are coaxed to form crystals, which are bombarded with intense beams of x-rays. Each atom in the crystal scatters the x-rays, producing what's called a diffraction pattern. Scientists gather diffraction data from many angles by rotating the crystal in the beam. With help from a high-powered computer, the data are combined with a known protein sequence to produce a three-dimensional map of the molecule.

Electron microscopy
Electron microscopes illuminate samples with electrons, producing high-magnification images. The technology requires only small amounts of sample and is well suited to visualizing larger molecular assemblies. Because the molecules aren't locked into a crystal, it's possible to capture the dynamics of very flexible proteins.

Electron crystallography
In this mash-up of electron microscopy and x-ray crystallography, two-dimensional protein crystals are exposed to an intense beam of electrons from an electron microscope. The resulting diffraction patterns are similar to those produced in x-ray crystallography. The technique is ideal for membrane proteins that cannot easily form large three-dimensional crystals.

Nuclear magnetic resonance
This method exposes molecules to a giant magnet that causes their nuclei to absorb and re-emit electromagnetic radiation. This emitted energy gives clues about each atom's orientation and location in the protein. Because the molecules are free to move about, the technique is useful for watching molecules move and interact.

Cryoelectron microscopy
In this method, samples are plunged into liquid nitrogen and flash frozen before going into the microscope. The freezing preserves a layer of water around the protein, capturing it in a more natural environment than that created by the harsh stains required in regular electron microscopy.

Mass spectrometry
In mass spectrometry, a molecule is sliced into pieces that are then ionized—electrons are added or removed to create charged particles. The fragments are sorted by their mass and charge, and then the fragmentation pattern is compared with predicted patterns for the protein to get an idea of which parts of a molecule are near each other. The technique can also be used to learn how two molecules interact with each other by cross-linking the proteins—permanently binding the molecules together—and studying the resulting fragmentation pattern.

THE O'SHEA WAY

HHMI's new chief scientific officer Erin O'Shea applies an uncommon intensity to her research and training—of students and German shepherds.

By Sarah Goforth
Photography by Kathleen Dooher

Erin O'Shea does not waste time. She finished a Ph.D. in two and a half years, rose from novice to world champion dog trainer in under three, and, at age 47, is moving into an executive leadership role at HHMI.

The eldest of five children, O'Shea is just six years older than her youngest sibling Meggan. Both women describe their middle class upbringing in western New York as happy and ordinary. Their father ran a residential contracting business, and their mother left a career in physical therapy to run the household. All the O'Shea kids performed well in school and excelled as athletes.

But there was something different about Erin. "She was intensely focused, much more so than the rest of us," says Meggan O'Shea. "With Erin it's always been, she's going to do what she wants to do, she'll do it very, very well, and she'll do it fast."

Andrew Murray, a longtime colleague of O'Shea's, puts it another way: "Soon after people meet Erin, if you were to ask them how fast this woman could gnaw through a quarter-inch bar of steel, they'd be like, 'oh, probably 90 seconds.'" After hearing O'Shea present her research as a graduate student, Murray was so impressed he helped recruit her to the University of California, San Francisco (UCSF), and later to Harvard University, where she's been since 2005.

O'Shea, an HHMI investigator since 2000, maintains a prolific research lab focused on understanding how cells sense and respond to their environment. Her contributions range from discovering how single cells adapt at the molecular level to changing levels of light and stress to analyzing randomness in gene expression patterns. Her work has advanced the broad understanding of basic biological mechanisms and helped scientists studying cell growth patterns in cancer and other diseases.

In July, O'Shea will become vice president and chief scientific officer at HHMI, moving with her husband Douglas Jeffery to Chevy Chase, Maryland, where HHMI is headquartered. She views the job as both an opportunity to do something new and as a natural extension of her past work—as a scientist, administrator, mentor, and educator.

Influencing Undergrads

By the time O'Shea joined Harvard, she felt an obligation to give back to the scientific community by training and educating the next generation of researchers. As director of Harvard's Faculty of Arts and Sciences (FAS) Center for Systems Biology, O'Shea has recruited and mentored many junior faculty. With a tight-knit group of colleagues, she created an innovative undergraduate science course.

"A lot of people with her level of accomplishment are not great listeners, but she's interested in people and makes time for them," says Dan Kahne, a Harvard chemistry professor who created the course Life Sciences 1A with O'Shea and four other faculty members. "With students, that's very important. It doesn't have to be all about her."

The enormously popular course is a matter of pride for Kahne, O'Shea, and the others on the faculty team. They present science as a detective story at the intersection of chemistry and biology—the two disciplines that drive progress in the life sciences today. Students explore a handful of experimental case studies rather than a body of facts and prefabricated lab exercises. The course draws more than 500 students a year, and O'Shea reports that the number of life science majors at Harvard has grown by 40 percent since its inception.

"We choose topics that capture students' interest and motivate them to learn the underlying detail," she says. "We tell them like mystery novels with a thread that hooks them all together." O'Shea keeps regular office hours for her undergraduate students, meeting with them one on one and often helping them find research positions in labs.

"I came to Harvard in part because I wanted to teach undergraduates, because the people who taught me at that stage of my education had a big influence on my career," she says.

Sparks of Interest

As a high school student in Leroy, New York, O'Shea enjoyed learning about science but envisioned herself as a veterinarian or doctor. It wasn't until her sophomore year at Smith College in Northampton, Massachusetts, that she learned what it meant to *do* science. She began conducting research on catalysts in an inorganic chemistry lab and was allured by firsthand discovery.

"I was excited to be doing something where, unlike the science course labs I'd had before, we didn't know the answer. We were actually *finding* the answer," she says.

Her famous focus kicked in. "There was a pretty marked change in her," says her sister Meggan. "She had found something that she loved and put all her energy into it. By the second

"I WANTED TO TEACH UNDERGRADUATES BECAUSE THE PEOPLE WHO TAUGHT ME AT THAT STAGE OF MY EDUCATION HAD A BIG INFLUENCE ON MY CAREER." – ERIN O'SHEA

part of her sophomore year, she was around a lot less. We all noticed it, that she was really dedicated to what she was doing."

By the time Meggan entered Smith in 1989, her sister had published a groundbreaking paper as a graduate student in Peter Kim's lab at the Massachusetts Institute of Technology (MIT). It had people talking. "My bio professor said to me, 'Are you one of *the* O'Shea's?' and I knew she was taking off," recalls Meggan.

Driven by Questions

Erin O'Shea distinctly remembers the moment that fueled her running start. In the latter part of her senior year at Smith she began working at MIT's Whitehead Institute for Biomedical Research. One afternoon the following summer, she was reading the journal *Science* at a picnic table outside the Whitehead, where she had taken on a short-term research project on nucleic acids in Kim's lab. A paper by Steve McKnight, a biochemist now at the University of Texas Southwestern Medical Center, described a protein motif called the leucine zipper—a key part of many transcription factors that guide cells to turn genes on and off.

"I had this idea that McKnight's model was basically correct but wrong in detail," she remembers. O'Shea had taken a course at Smith that focused on a class of structural proteins called coiled coils, and she thought she recognized their hallmarks in McKnight's protein motif.

So she went to Kim, who had worked on protein folding, and he let her try to make the peptide and see if it was a coiled coil. "And it was. It was a big result in the field of protein folding, and it was an idea I had come up with. It was very exciting." O'Shea's work changed the way the scientific community understood the leucine zipper and, by extension, how transcription factors interact with genes.

To her parents' dismay, O'Shea decided not to enter the M.D., Ph.D. program at Yale. She had no alternative long-term plan. Instead, she stayed at MIT to follow the leucine zipper trail in Kim's lab. "It wasn't some big vision I had about how it would help my career. It was more, I want to do these experiments, and I have to stay here if I want to do them." The following January, she was admitted to MIT's Ph.D. program, funded by an HHMI predoctoral fellowship.

She solved the crystal structure of a leucine zipper in fine detail two years later, a paper that caught the attention of Francis Crick, famed for his discovery with James Watson of the DNA double helix. Crick had proposed the structure of a coiled coil in the 1950s. He wrote the young O'Shea a letter, congratulating her on the high-resolution structure. Her confidence boosted, O'Shea presented her work in a seminar at UCSF the following year.

Andrew Murray was a junior faculty member at UCSF at the time. "I went home and told my wife I'd seen the best seminar I'd ever heard, and it was given by a graduate student who looks like she's fresh out of college," he recalls. "It was a combination of the quality of the work, the way she framed it conceptually, and the confidence and panache with which it was presented."

UCSF offered O'Shea a faculty position—a rare opportunity

Erin O'Shea and her world champion Zambo run the paces of Schutzhund, a test of agility and obedience among German shepherds.

Carole Schultz

for a scientist just out of graduate school—and gave her two years to do whatever she wanted. She split the time working with HHMI President Robert Tjian, who at the time was a Hughes investigator at the University California, Berkeley, and with Ira Herskowitz at UCSF.

In Tjian's laboratory, O'Shea became interested in how gene expression is regulated by chromatin—the tight packages of DNA and proteins inside the nuclei of cells. It was a divergence from her protein structure work. "Tjian was incredibly supportive, even though I was heading in this new direction," she says. "He wanted my curiosity to guide what I did, rather than telling me what approach to take."

At that time, much of the transcription field was focused on studying transcription in test tubes, says O'Shea. She wanted to examine the system in a physiological context, inside the chromatin.

That decision led her to the Herskowitz lab, where researchers were studying transcription factors in yeast. Herskowitz had determined the genetic pathways that allow yeast to reproduce, and he supported O'Shea's decision to refocus on biology. "I was used to doing physical chemistry, so it was another big change in my career track," she says.

Expert Timekeeping

That change stuck. At Harvard, O'Shea's lab of 15 students and postdocs, which occupies a modest space on the second floor of the FAS Center for Systems Biology, is surprisingly diverse for its size. Lab members represent half a dozen countries and just as many disciplines, and they study biology at the cellular level in mice, yeast, and bacteria. No question is off-limits as long as it is both interesting and important, says O'Shea, but the lab's primary areas are still gene expression and regulation—how cells turn genes on and off or dial them up and down. In recent years O'Shea has also taken an interest in the molecular clocks that govern circadian rhythms—the 24-hour patterns of activity that help organisms predict the availability of and respond to warmth, light, and nutrients.

"There's something special about the clock in the cyanobacterium," says O'Shea, referring to the blue-green algae that are responsible for 70 percent of all photosynthesis on Earth. The molecular clocks inside cyanobacteria anticipate daylight and then drive the production of proteins needed for photosynthesis. "There was this remarkable paper where a Japanese team [led by Takao Kondo] showed they could take the three proteins that make up the clock, mix them together in a test tube, and reconstitute oscillations with 24-hour periodicity," O'Shea says. In other words, the clock proteins appeared to be sufficient to keep time, independent of any other processes of the cell. This was contrary to conventional wisdom, which held that circadian clocks are governed by cycles of transcription and translation in a cell—in which a gene produces a protein that performs a task and then eventually halts its own production. When O'Shea read the paper, she couldn't resist asking: how do these proteins function absent those cellular cues?

"People thought the clocks in all organisms had a common architecture that relied on this transcription–translation feedback," she explains. Instead, the clock appeared to rely on biochemical interactions of the three proteins. To stay synchronized for weeks at a time, it needed only to be supplied with the energy-storing molecule adenosine triphosphate (ATP).

Kondo's team had wowed the biochemistry community with this news, but the mechanism by which these three proteins kept ticking remained a mystery. Intrigued, O'Shea tested the proteins in different conditions and eventually described the process by which it happened—phosphate groups from the ATP being the key ingredient—in a detailed mathematical model.

O'Shea described the process by which three proteins in cyanobacteria, like the ones shown here, synchronize the organisms' circadian clocks so that photosynthesis occurs during daylight hours.

Photo Researchers, Inc.

The Meaning of Mentorship

The cyanobacterial circadian clock is a small but illustrative piece of O'Shea's research portfolio. She encourages the researchers in her group to follow their interests and develop questions independently, even if they diverge somewhat from her own. Two of her postdocs, for example, are testing drug-screening platforms, projects that are more clinical than O'Shea might choose out of a more fundamental

SHE ENCOURAGES RESEARCHERS IN HER GROUP TO FOLLOW THEIR INTERESTS AND DEVELOP QUESTIONS INDEPENDENTLY, EVEN IF THEY DIVERGE SOMEWHAT FROM HER OWN.

curiosity about the way things work. Team members view her as a decisive but relatively hands-off leader who invests her energy and attention where it will have the most impact.

"Erin manages her time very well," says Xu Zhou, who just completed a Ph.D. in O'Shea's lab and will soon begin a postdoc in the lab of HHMI investigator Ruslan Medzhitov, an immunologist at Yale University. "She will tell you when she's available to review your paper or grant, and if you send it on time, she is there waiting. You know when she sleeps, because the emails stop around 11:00 at night and start again at 5:30 in the morning."

As Zhou became more confident in his research, O'Shea stepped back, giving him freedom to follow his instincts and troubleshoot his own problems. But when it came time for him to apply for postdoctoral positions, she became an everyday presence again, making herself available to speak with the researchers Zhou interviewed with. In the end, he received offers from each one.

"She says few words, so when she does, it's kind of like it's pronounced from the heavens," adds Tim Peterson, a gregarious postdoc who is working to develop drug screens for a class of bone diseases. "When I wrote my first grant, I sent it to Erin when the deadline was a couple of weeks away. She had some suggestions, so I revised it. Then every day or two for the next few weeks, she'd send me a few more questions or changes," he says. She kept coming back until it was better than solid. "It was this really interesting refinement process, not entirely painless, but the end product was excellent."

Enter Zambo

All evidence suggests that is the O'Shea way. In 2007, O'Shea and her husband were at the Denver airport when a working German shepherd caught her eye. O'Shea's family had kept German shepherds as pets, and she loved the energetic breed—though she knew they required more time and attention than the mellow bulldog she had at home.

"Right then I told my husband we should get one, and he's like, sure, okay. That's what he's always like," O'Shea remembers with a laugh. They found a breeder and bought a four-month-old puppy named Zambo, a "gorgeous, red and black little thing." Soon, dog and owner were immersed in the training sport called Schutzhund, in which judges rate dogs on anatomy, obedience, and agility.

"Schutzhund is like a religion in Germany, but I had barely heard of it. I just figured I had to get some obedience training anyway, so why not try it," she says. Zambo was a natural at the sport. Soon he was winning local competitions and placing in the top 10 nationally, with O'Shea as his handler.

"One day I was Googling the word 'Schutzhund,' and the next thing I knew I was spending three months in Germany with Zambo, preparing for the world championship," she says. It paid off. Zambo earned the world championship title in 2011. At age 3, he was the youngest winner ever, an early achiever like his owner. Rumors of a fluke victory circulated, but Zambo won again the following year. After that high point, O'Shea decided it was time for him to retire: "Like Michael Jordan, you gotta go out on top," she laughs.

"That's just what Erin does," says HHMI professor Richard Losick, another Harvard colleague. "She picks something up, because it's important or because it interests her, and before you know it, in the blink of an eye, she's the best in the world."

The Leadership Stamp

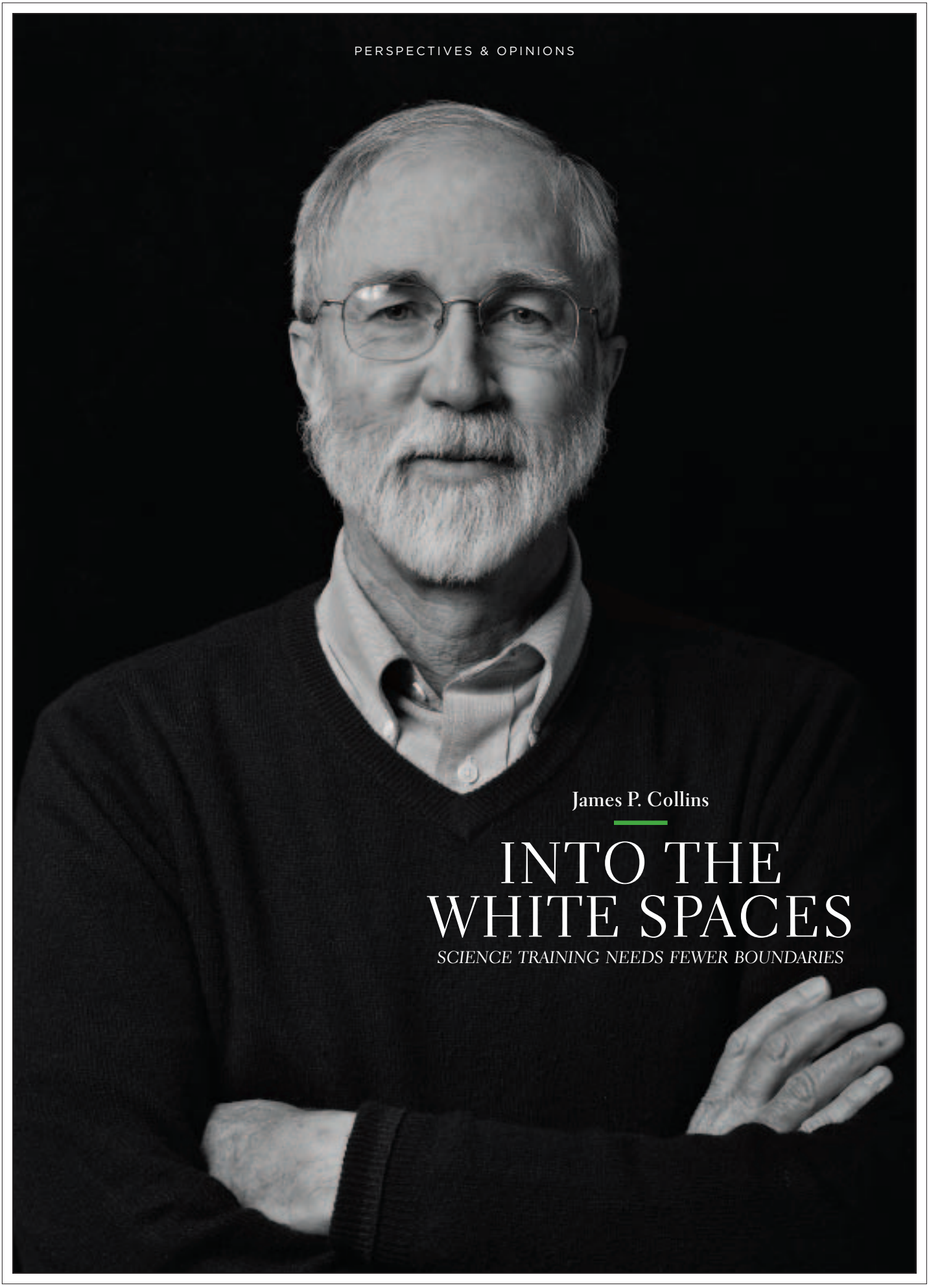
"Erin is one of those people who have leadership stamped on their foreheads," says her friend and colleague Andrew Murray. "Sometimes when she's running at full intensity, it is easy to mistake her for one of those people who is occasionally wrong but never in doubt. But she has the intelligence, courage, and grace to go back and reflect, and if necessary, rethink her position. She has great judgment as an administrator."

In her new role as vice president and chief scientific officer at HHMI, O'Shea will lead the Institute's flagship Investigator program and its many extensions. She will maintain her Harvard lab, Skyping in for lab meetings and returning in person every month.

As at Harvard, O'Shea sees her most important job at HHMI as finding, recruiting, and supporting the best people. "If you want people to succeed, you've got to pick the people well and do everything you can to support them," she says.

For O'Shea, offering support often means yielding control, says her colleague Dan Kahne, citing an analogy from a shared trip to the O'Shea family's lakeside cabin in New Hampshire. Kahne recalls: "My wife and I weren't sure about bringing our kids, but Erin said, 'Are you kidding? Pack up the water skis and bring everyone.' She was the only one who would let my son take the canoe out by himself. I told her that was a good way to lose a canoe. She said, 'But look how much fun he's having. It's the only way he'll learn.'"

Giving scientists freedom—to explore untested ideas; to pursue unexpected leads; to enter, and even forge, new disciplines—is a cornerstone of the HHMI model. As Kahne sees it, there is no one better suited to deliver on that promise than O'Shea. ■



James P. Collins

INTO THE WHITE SPACES

SCIENCE TRAINING NEEDS FEWER BOUNDARIES

Blair Bunting

Like other science graduates in the 1960s, James Collins accepted that research was largely a solitary pursuit with results taught as a collection of facts by the "sage on the stage." No more, says the ecologist and evolutionary biologist at Arizona State University (ASU). The balance is shifting from singular experts doing independent research to a mix of individual and team approaches.

Learning should not be confined by disciplinary boundaries. I realized this when I was investigating the role of infectious disease in declining amphibian populations. Through collaboration with a dozen scientists in immunology, mathematics, veterinary medicine, physiology, and molecular biology, we tested the conditions under which infectious disease might be the cause of extinction. The challenge to solve this theoretical and practical problem took me on a journey into the white spaces between traditional disciplines.

Knowing when to seek the aid of other experts is a vital skill for students to learn—just as an engineer must consult others to construct a safe bridge or electrical system, students cannot limit themselves to discrete silos.

This educational approach is so important that, in my 2011 fall semester ecology class at ASU, I challenged students with real-life, interdisciplinary-based problems. Each week a colleague and I posted a research paper on ASU's "Blackboard" website and the class discussed the complexities behind a global problem. During a class on evolutionary biology, for example, I integrated historical references to the black plague and HIV/AIDS and suggested students read multidisciplinary titles by scientists such as Jared Diamond, author of *Guns, Germs, and Steel*.

In discussing climate change, I directed the class to manage a hypothetical southern Arizona species that moves farther up a mountain as prevailing temperatures rise. Students see how personal values—determined in part by religion, ethics, philosophy, and literature—can have an impact on policy decisions that integrate scientific results.

I also use mentoring to advance an interdisciplinary approach. I remember encouraging Katy Richards-Hrdlicka, a biology major conducting research in my lab, to investigate fungal pathogens in lowland leopard frogs, a project that took her into microbial sequencing techniques. To design her experiments, she had to learn advanced statistics. Now, as she pursues her doctoral degree at Yale's School of Forestry and Environmental Studies, she has specialized in genomics. This lengthy scholarly jump into the white spaces has helped her see the link between ecology and genetics, sparking a career interest in conservation biology and policy making.

Of course, nurturing interdisciplinary research and education requires financial incentives for both students and faculty members. When I was chair of Biology at ASU, faculty members received support in areas such as urban ecology for an Integrative Graduate Education and Research Traineeship (IGERT) program that required collaboration between biologists, geologists, and social scientists. To encourage a more positive perception of coauthorship, graduate students cowrote a chapter of their dissertation with a peer from another department. In another case, fellow professor Jim Elser received funding from the National Science Foundation and National Institutes of Health to extend his interdisciplinary ecological stoichiometry theory (which posits the dynamic interactions between living organisms and chemical elements such as phosphorus and iron) to human cancer.

Research projects such as these take advantage of leading-edge communication techniques and networking. For example, in 2008 when researchers, including HHMI investigator David Baker and colleagues at the University of Washington, explored protein folding, they brought in computer scientists and biochemists to devise the online game Foldit. They opened it to a national and global audience, which succeeded in discovering new algorithms. An August 2010 *Nature* article credits Baker along with eight other scientists and Foldit players worldwide.

The Internet has made possible online classes, which have the potential to push the interdisciplinary envelope further. I remember when as a professor I wanted to advance my math skills, but these digital options did not exist. So, I attended a traditionally taught linear algebra class several times a week. Now students can enroll in online classes on a need-to-know basis and acquire the subject content to help them seek appropriate collaborations and solve important problems. As we move into the 21st century, the thoughtful, creative use of online resources will undoubtedly be a source of great change for scientific research and education.

INTERVIEW BY JANICE ARENOFSKY. *Collins is Virginia M. Ullman Professor of Natural History and the Environment at ASU.*

Q&A

If you had to create the ideal science course for first-year college students, what would it look like?

Science is changing. Boundaries between disciplines are fading. Shouldn't this be reflected in the way we train future scientists? Below, four educators describe their dream introductory science class.

–EDITED BY NICOLE KRESGE

Isiah Warner

HHMI PROFESSOR, LOUISIANA STATE UNIVERSITY

"I would structure my ideal class quite differently than today's average classes. I would teach physics, chemistry, and biology at the same time. Students would learn fundamental scientific principles and simultaneously explore them in an adaptable laboratory setting. The lab would be used to verify or enforce the lecture concepts and would allow experimentation and open discussion. Students who grasp the concepts could help students who don't understand them. Both sets of students would benefit from this approach."

Catherine Drennan

HHMI INVESTIGATOR AND HHMI PROFESSOR, MASSACHUSETTS INSTITUTE OF TECHNOLOGY

"As a chemist who works at the interface of chemistry, biology, and medicine, one of my personal missions is to help first-year college students appreciate the power and beauty of chemistry. Thus, my ideal course conveys the basic chemical principles in a way that helps students see the connection between chemistry and other disciplines. My ideal course is not a history lesson. Rather, it provides snapshots of how chemical principles are employed in modern-day research and how chemistry can be used to solve real-world problems in medicine and engineering."

Harold (Hal) B. White

DIRECTOR, HHMI UNDERGRADUATE SCIENCE EDUCATION GRANT, UNIVERSITY OF DELAWARE

"My ideal introductory science course would enroll fewer than 50 students. They would work in small groups on engaging projects and activities that focus on understanding one substantive interdisciplinary concept like randomness, equilibrium, or natural selection—ideas that fundamentally affect our world and how we perceive it. The course would not attempt to survey a discipline or fill students' heads with facts and definitions. Instead, the goal would be to stimulate attitudes of scientific inquiry that can enable learning beyond formal education and promote responsible citizenship."

Diane O'Dowd

HHMI PROFESSOR, UNIVERSITY OF CALIFORNIA, IRVINE

"All science courses should provide both students and instructors with the opportunity for intellectual discovery. My ideal first-year biology course would be concept driven, using real-world problems to motivate students. This process encourages the instructor to stay current with cutting-edge developments across a broad range of topics. I think it's also important to stimulate dialogue in class so that students learn from each other and can practice problem solving in a mentored setting. Classroom discourse also gives the instructor interesting, and often unexpected, insights into the learning process, which can guide course revisions to improve outcomes."

Warner: James Kegley Drennan: Robert Klein / AP ©HHMI White: Paul Fetters O'Dowd: James Kegley

CHRONICLE

Gluekit

Lab on the Move

WHEN THE CLASSROOM SETTING IS LACKING, ENTER THE MOBILE LAB.

"You might want to hold on to something," Lupe Medina tells me, steering his 40-foot bus onto a narrow bumpy road. We are 18 miles from the Mexican border in South Texas, headed to La Villa High School.

Equipped with 12 lab workstations for up to 24 students, and thousands of dollars worth of laboratory tools, the bus is a mobile lab from the University of Texas–Pan American (UTPA), in Edinburg, funded with HHMI grants in 2004 and 2008.

The lab has logged more than 10,000 miles traveling to hundreds of disadvantaged schools in the Rio Grande Valley—bringing real-world bioscience to more than 4,000 elementary, middle, and high school students each year as part of UTPA's community outreach program.

La Villa High School stands alone, surrounded by farms and empty fields. It's just 15 miles from the UTPA campus but a world away when it comes to educational resources. The school's 185 students are all first-generation Mexican Americans. As with most public schools in rural Texas, La Villa's science budget is very limited. Its students do not have access to high-tech lab facilities.

That's where Medina comes in—or drives in—with his lab on wheels.

Each week he visits a different high school, spending three days leading students and their teachers in hands-on experiments in DNA fingerprinting, replication, forensic analysis, and gene expression.

An entomology instructor at UTPA since 1999, Medina's been taking the mobile lab to schools along the Mexican border for the past five years. He's a teacher, a driver, and a self-taught mechanic. And he was a migrant, just like the students.

"I see myself in them when I was their age. I was curious, and our school didn't have the necessary means to pursue that education," he says. "Out there in the fields, I was more intrigued with all the cool insects that were around me." He took a real interest in studying insects in high school and pursued entomology at UTPA. "It showed me that science was a way out; I didn't have to be a migrant all my life," he says. "And I try to instill this in them."

He arrives at La Villa and begins to outfit each workstation on

the bus with micropipettes, solutions, spectrophotometers, centrifuges, thermocyclers, rubber gloves, and cheek swabs. A group of ninth graders approaches the bus and rummages through a box of white lab coats that Medina launders with bleach at his home.

These students may not think of themselves as budding scientists, but Medina tells them otherwise. "Once you put on your lab coats and step inside my lab, you are scientists."

This week the students are DNA detectives investigating genetic evidence left at a crime scene. They extract DNA from their own cheek cells, replicate it by means of a process called polymerase chain reaction (PCR) analysis, and separate the DNA fragments by using gel electrophoresis—all tools of the trade in today's crime labs.

"I was kind of nervous. It was my first time," says ninth grader Maria Martinez. Although her experiment didn't go well today, it still piqued her interest. "I'll need to get more cheek cells next time."

"I tell them it doesn't matter if your science experiment didn't work," Medina says. "That's science. I just hope that this helps them develop a passion for something that they want to do."

Maria says she might study criminology in college and is considering the field of forensic science. "From what I've seen on TV, they go to crime scenes and start looking at DNA. But it's actually a lot more detailed than what they show on TV."

To get young scientists like Maria into the pipeline requires engaging them early and often, says John Trant, dean of UTPA's College of Science and Mathematics and director of the university's current HHMI grant. "And the best way to get them engaged is to get their hands on the equipment, on the ideas," he says. "That's how we're going to get our physicians, our next layer of faculty, and our graduate students."

> "I tell them it doesn't matter if your science experiment didn't work. That's science. I just hope this helps them develop a passion for something they want to do."
>
> LUPE MEDINA

That Cool Factor

CityLab set up the first classroom-in-a-lab program in 1992. A centralized biotech learning lab for high school students and teachers at Boston University School of Medicine, CityLab was funded by HHMI from 1994 to 2003.

In 1998, CityLab created its first MobileLab to take the show on the road and reach more high school students. Soon mobile labs sprang up in Connecticut, Georgia, North Carolina, South Dakota, Maryland, and Missouri. An informal alliance of mobile labs called the Mobile Laboratory Coalition emerged in 2003 and now serves as the umbrella organization for about 26 mobile lab programs across the United States and in Chile, Hong Kong, and Switzerland.

The Rio Grande Valley's population growth outpaces almost every other corner of America. Yet, the UTPA mobile lab is the only one of its kind in Texas, and Medina cannot meet all the visit requests he receives from schools. Trant is trying to persuade other universities in Texas to start mobile lab programs, perhaps one day forming a consortium of mobile labs across the state. But for now, Medina is on his own.

The university will soon merge with its sister campus, the University of Texas at Brownsville, to become the second largest Hispanic-serving institution in the country. UTPA is already one of the top three producers of STEM (science, technology, engineering, and mathematics) degrees in Texas and plans to build its own medical school in two years. The new school will need highly skilled researchers, technicians, and investigators.

"I think of future scientists being born in that lab," says Paul Duke, head of the science department at La Villa. When he arrived at the school in 2006, the students had a 24 percent passing rate in science. Today, the rate is 88 percent. Duke brings what he learns in his graduate studies at UTPA, and he brought the mobile lab to the school, which visits two or three times a year. "They have some sophisticated equipment there that we couldn't possibly fund and keep in our labs here," he adds.

"Plus, the mobile lab has that cool factor," he adds. "It's something new, it's not the same everyday classroom setting."

How to Be Everywhere?

HHMI has funded mobile lab programs at UTPA, the University of North Carolina at Chapel Hill, Georgia State University, and Harvard University and is currently funding programs at University of Cincinnati, New Mexico State University (NMSU), and University of Pittsburgh. All the labs engage students in hands-on bioscience, covering topics such as genetic engineering, infectious disease, forensics, DNA, and human health.

The NMSU mobile lab, which travels vast expanses between remote communities, has visited nearly 3,500 students at 25 schools in the past two years. Sixty-six percent of the students were underrepresented minorities. "It's a chance to engage these students and open some doors, and eyes, to career paths that might not have been obvious to them," says Michèle Shuster, codirector

(Clockwise from top) La Villa High School juniors Delia Palomin and Yadira Colmenares become scientists for a day in UTPA's mobile lab. Instructor Lupe Medina holds up a giant crab-like sea creature known as *Bathynomas gianteus* for students Stephanie Guerra, Brandon Urena, Andrea Perez, Beatriz Deleon, Yadira Colmenares, and Juan Salazar. Handling a pipette is hands-on classwork for Connie Martinez.

Fritz Faenber

of the HHMI grant at NMSU.

Raena Cota, NMSU's Mobile Molecular Lab outreach scientist, has just returned from a two-and-a-half-week, 1,000-mile trip to three high schools. Instead of housing the labs in a bus, she packs the equipment into large crates, transports them in an SUV, and sets up the lab kits inside science classrooms for a week of hands-on experiments.

The students' most requested experiment, Cota says, involves genetics and the ability to taste a bitter flavor. "We give them a paper with a chemical on it, and the first time they put it into their mouths they completely freak out," she says. "A lot of them who claim they are strong tasters are actually weak tasters." Students use PCR and gel electrophoresis to determine their genotypes, the genetic make up of their cells.

Cota has traveled more than 8,000 miles in the past year and says the hardest part of her job is turning down requests for visits. "It feels disappointing because I want to be everywhere at all times."

To deal with this problem, NMSU created the Access to Science Center, which trains high school teachers to run their own mobile labs. "We're trying to expand the number of students we're reaching by helping teachers become less dependent on us," says Ralph Preszler, director of the HHMI grant at NMSU.

A high school teacher attends a series of training workshops at NMSU to become certified; then the university loans the teacher a mobile lab kit to take back to the classroom. Last year, eight teachers independently ran activities in 22 classes with 544 students, 73 percent of whom were underrepresented minorities.

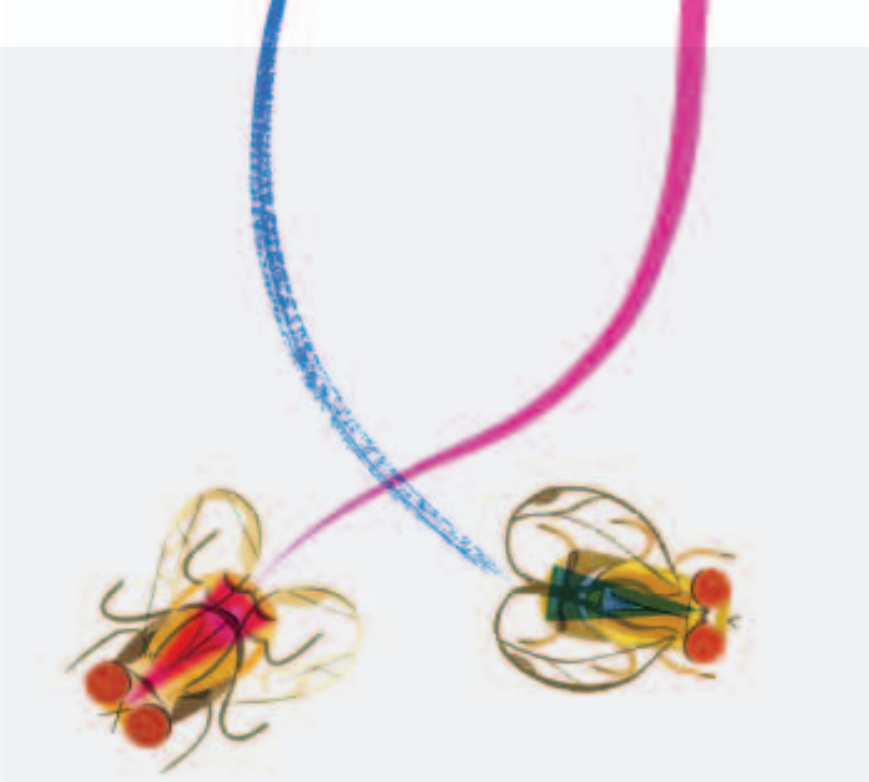
"They're expanding the reach beyond what the mobile lab can do," says Shuster. "Teachers get reenergized and reinvigorated."

And the mobile labs are catching on with the students. After going through the program, the majority of the students—62 percent—reported being interested in taking science classes in high school, and 39 percent reported an interest in majoring in science in college.

"The more you teach someone, the more they want to learn," Cota says. "I want to bring something to the students that they've never seen before."

Back in Texas, UTPA has decided to make the HHMI mobile lab its own. It began funding the program last semester and has budgeted $283,000 to run the lab over the next four years—including lab supplies, bus repairs, Medina's salary, and that special box of white lab coats. ■ – ROBERT GUTNIKOFF

WEB EXTRA: Go on a road trip with Lupe Medina and the UTPA mobile lab at www.hhmi.org/bulletin/spring2013.



JAABA: Automating the Human Observer

THIS SOFTWARE CAN LEARN TO ID ANIMAL BEHAVIOR.

Even the simplest experiments must be reproducible to be convincing. And as new variables are introduced—different genes, conditions, or time points to be tested—a study's size can become unwieldy. Automated technologies can take over some of lab work's more tedious tasks, but when it comes time to make sense of the data, a scientist's intuition is irreplaceable. Right?

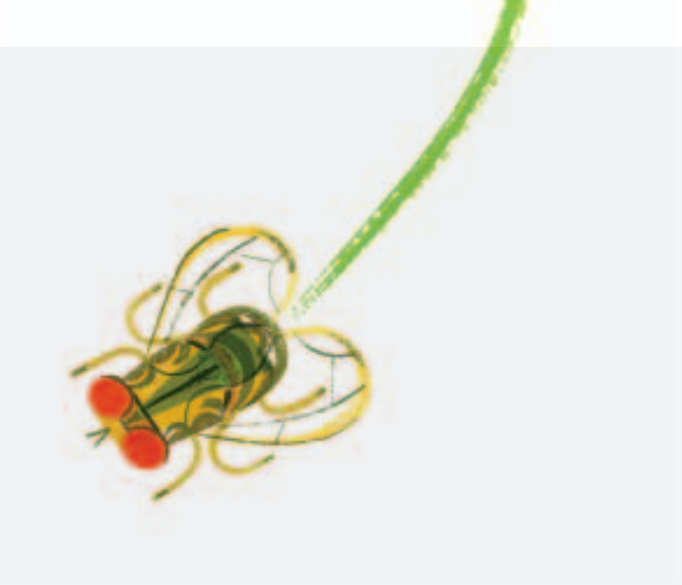
Not always, says computer scientist Kristin Branson, a lab head at HHMI's Janelia Farm Research Campus. Branson agrees that intuition will probably always be critical in the quest for scientific truth. But for certain tasks, she says, computers can be trained to re-create researchers' gut instincts. Her new machine learning software, which she calls JAABA for Janelia Automatic Animal Behavior Annotator, is a tool for identifying characteristic behaviors captured on video. Reviewing hours of recorded activity, the software can zero in on, for example, each instance of one fruit fly chasing another.

Biologists study behavior in model organisms to answer many questions—to help reveal, for example, how the brain works, how genes drive behavior, or how learning changes it. Behavioral studies can offer insights into developmental biology or clues about the evolutionary past. Analyzing animal behavior requires careful observation, and while many behavior patterns are well characterized and easy to recognize, the task can become daunting when a study involves hundreds or thousands of individuals. Searching for an organism that exhibits subtle changes in behavior—such as a fly that walks 20 percent slower than others because of a genetic mutation—increases the challenge.

Technology advances have made large-scale studies more common, and even in smaller labs behavioral scientists commonly collect video containing more data than they could ever hope to analyze, Branson says. "It's cheap and easy to collect a lot of video. It's not that easy to say anything quantitative about it," she points out.

When Branson moved to Janelia in 2010, she brought along the machine vision software she had developed as a postdoctoral researcher at the California Institute of Technology. That software identifies and tracks the movements of fruit flies on video, churning out data about animals' speed and position. Branson had planned to

Ping Zhu



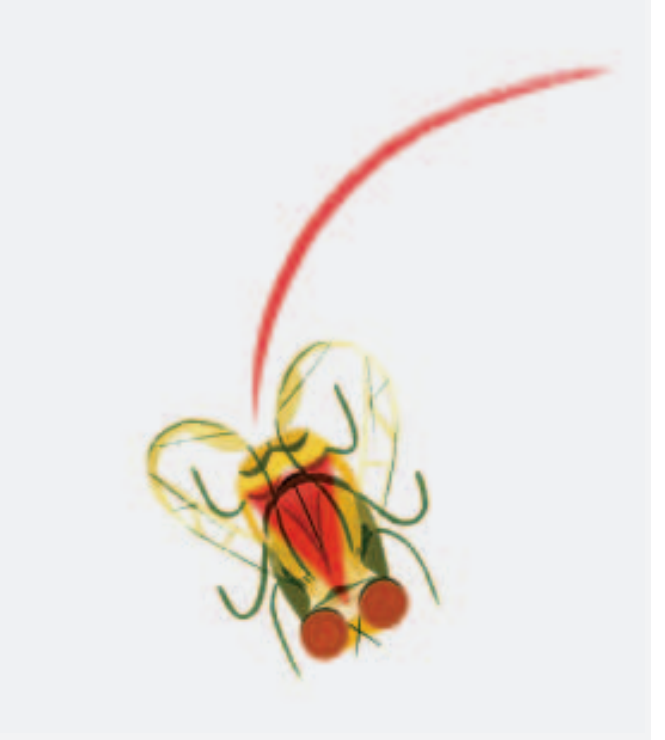
> "For certain tasks, computers can be trained to re-create researchers' gut instincts."
>
> KRISTIN BRANSON

work with Janelia biologists to refine the program and make it more useful for their studies. "But Janelia is a special place. People here love technology," she says. "When I got here, there were already four different tracking programs in use."

So Branson switched her focus. Instead of extracting the simple quantitative information that tracking programs derive from videos, her next program went further. With JAABA, she says, "our goal is to automate the human."

Even when experienced biologists can readily recognize a behavior, the precise qualities that define that behavior might be difficult to articulate. How fast does a fruit fly move when it gives chase? How close does it have to be to another fly for it to be considered chasing? At what point does walking transition to chasing? Biologists may not have explicit answers to these questions, but somehow, Branson says, experimenters know what they're looking for. To automate behavior identification, biologists must transfer that knowledge to the computer.

Scientists teach JAABA to recognize behaviors through short training sessions with rapid feedback. For each frame of a training video, the user tells the computer whether a particular behavior,



such as walking or wing grooming, is taking place. JAABA computes key features from the labeled frames—for example, an animal's speed and its distance from other animals—and combines that information with context from surrounding frames to develop its own criteria for detecting the behavior. The user can test JAABA's accuracy at any time during the training process.

That immediate feedback helps users understand how the software is performing and recognize areas in which JAABA requires additional training, Branson says. The software can be trained to recognize behaviors in several animals, including adult fruit flies, fruit fly larvae, and mice—even by a user with no background in computer science, according to a paper her team published in *Nature Methods* in January 2013. They've made JAABA freely available for download at jaaba.sourceforge.net, and she hopes researchers will use it to free themselves from manual analysis.

Eventually, Branson says, JAABA might do something more ambitious. As they train the software to recognize more behaviors, her team may be able to mine the data they collect to go beyond human capabilities and find measurable features of behavior that are not apparent to the human eye. ■ – JENNIFER MICHALOWSKI

WEB EXTRA: To see JAABA at work, go to www.hhmi.org/bulletin/spring2013.

When the Bee Stings

LARGE PROTEIN COMPLEX PLAYS KEY ROLE IN BODY'S RESPONSE TO VENOM.

The immune system is hailed for detecting and fighting bacterial and viral infections. But what of the system's equally important response to bee stings and snake bites? Spiders, bees, snakes, and scorpions inject their victims with a toxic cocktail of proteins that cause an inflammatory response—pain, swelling, redness—and severe tissue damage. Just how the immune system detects and responds to venom is a mystery. New studies by HHMI investigator Ruslan Medzhitov suggest that clues may lie in the actions of a protein complex called the inflammasome.

"Much of our understanding of the immune system is based on its reaction to microbial pathogens," Medzhitov says. "But venoms don't follow the same rules of immune recognition and response."

A protein complex called the inflammasome helps the body sense venom from bee stings.

Although the makeup of venom differs from species to species, one common denominator is a group of proteins that damage the cell membrane. Medzhitov and his Yale University postdoctoral fellow Noah Palm looked at inflammasomes, multiprotein immune complexes that react to membrane damage.

To study the inflammasome's role, the pair injected two groups of mice with bee venom. Half the mice were normal while the other half lacked caspase-1—an enzyme found in inflammasomes. In the normal mice, the toxin activated an inflammasome that turns on the inflammatory system, a protective response that promotes tissue repair. The caspase-1-deficient mice had less inflammation than the normal group, but they experienced far more tissue damage. This result points to a key role for inflammasomes in detecting venom, says Medzhitov, who published the findings January 29, 2013, in *Proceedings of the National Academy of Sciences*.

"We found that instead of inflammation passively following tissue damage, inflammation is actively engaged by a sensor and that sensor is the inflammasome," he says. "This also demonstrates very clearly the protective effect of inflammation."

Now that Medzhitov has identified the sensor involved in venom-induced inflammation, he wants to find the trigger in another venom response. Around 2 percent of Americans have severe, life-threatening allergic reactions to bee stings, a malady that kills about 100 people a year in the United States. Pinpointing the sensor involved in venom allergies would be a key first step in preventing those deaths. ■ – KELLI WHITLOCK BURTON

IN BRIEF

A MOTOR'S MECHANISM

Cells can control gene expression by winding their DNA around proteins to create disks called nucleosomes. The condensed DNA, known as repressed chromatin, can't be transcribed, so its genes are effectively turned off. HHMI investigator Bradley Cairns recently discovered how one of the molecular machines that assembles chromatin knows when to work.

Cairns and Cedric Clapier, at the University of Utah School of Medicine, focused on a complex called an assembly remodeler, which moves nucleosomes close together. The remodeler has an internal motor that winds DNA around the nucleosome, but scientists struggled to understand how this motor was turned on and regulated. Cairns and Clapier discovered that the nucleosome activates the motor by flipping a "switch" adjacent to it. As they reported December 13, 2012, in *Nature*, this mechanism ensures that the motor operates only when the remodeler is bound to the right nucleosome.

Cairns believes this switch is a universal toggle for remodelers. "I think we will find that all remodelers have motors flanked by specialized switches specific for that particular remodeler," he says. Cairns hopes to substantiate that idea by looking for switches on disassembly remodelers, protein complexes that eject nucleosomes from DNA to promote transcription.

BACTERIAL SEQUENCING SURPRISE

In 2011, a particular strain of *Escherichia coli* bacteria wreaked havoc in Germany. Known as *E. coli* O104:H4, the pathogen killed 53 people and landed hundreds in hospitals. The strain was clearly atypical, and findings by a team of scientists that includes HHMI investigator Matthew Waldor, of Boston's Brigham and Women's Hospital, suggest why.

In animals and plants, methylation—the addition of a chemical methyl group to DNA—can turn genes on and off. When the researchers compared DNA from *E. coli* O104:H4 to that of other strains, they noticed certain genes were methylated differently. Closer inspection showed a virus called a bacteriophage had infected the *E. coli*, bringing with it a methylating protein.

Using a technique called single-molecule real-time DNA sequencing, the researchers mapped the methylation patterns of *E. coli* O104:H4. They discovered that not only did the phage add thousands of methylation sites to the pathogen's genome, it also altered expression patterns of more than a third of its genes—including several essential for growth and mobility. The team published the work December 2012 in *Nature Biotechnology*.

Waldor says the findings will help researchers understand the role of methylation in the bacteria's life cycles, infectivity, and perhaps even drug resistance.

COORDINATING COPULATION

Worm sex and human sex are surprisingly similar—in some ways. HHMI investigator Cornelia Bargmann recently showed that worms and mammals use the same types of

Thinkstock

Use It or Lose It

A PROTEIN HELPS TUNE NERVES TO THE ENVIRONMENT BY KILLING OFF INACTIVE CELLS IN THE NOSE.

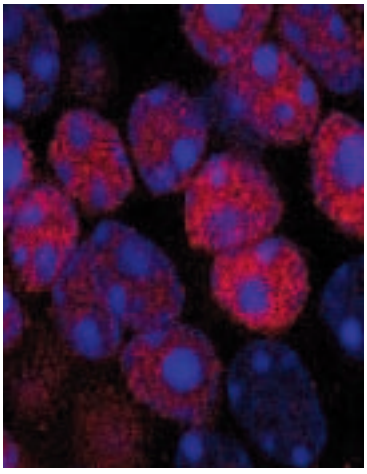
For a newborn mouse pup, some smells are critical to survival: milk, mom, bedding. As the pup grows older, the critical smells change to predator, food source, and mate. Over time, a mouse's olfactory system becomes more adept at detecting the odors that matter. HHMI investigator Catherine Dulac of Harvard University has uncovered a small molecule that plays a big role in this process.

Each odor-sensing nerve cell, or neuron, in a mammal's nose is specialized to detect a single type of smell. Because a typical mammal has about 1,000 odorant receptors, a fraction of which are needed at any one time, Dulac hypothesized that an animal might be able to "tune" its olfactory system to the environment by choosing which receptor to express at a given time.

Dulac and research associate Stephen Santoro found that olfactory neurons containing a protein called H2BE die sooner than neurons without the protein. H2BE is closely related to H2B, a so-called histone—a protein that helps organize DNA into compact forms that fit inside a cell's nucleus and participate in regulating gene expression. Furthermore, as the team reported in the journal *eLife* on December 13, 2012, H2BE levels are inversely related to how active a cell is. Neurons with receptors that are constantly stimulated by smells have lower H2BE levels and thus live longer.

H2BE, they discovered, was replacing H2B in inactive neurons. "Slowly but surely, the genomes of neurons that are not very active become populated by H2BE instead of H2B," Dulac explains. The presence of H2BE instead of H2B causes DNA transcription to change dramatically and to slow down, and the cell eventually dies.

This system provides a novel mechanism by which an animal adapts its selection of nasal neurons to the environment. When the animal is constantly surrounded by certain smells, the receptors corresponding to the various odorants are stimulated and the neurons expressing those receptors live longer. Neurons for rarely occurring smells—for example, mother's milk once a pup matures—have a limited lifespan.



The histone-like H2BE protein (red) can be found in the nuclei of olfactory neurons, where it controls the expression of odor-sensing receptors.

Steve Santoro

There are still many uncharacterized histone-like molecules in the brain, and Dulac believes that this novel system of regulation may be applicable to other brain functions. ■ –NICOLE KRESGE

IN BRIEF

brain chemicals, known as neuropeptides, to coordinate their reproductive behaviors.

Bargmann and her lab group at the Rockefeller University found a molecule in the worm *Caenorhabditis elegans* that is chemically similar to vasopressin and oxytocin—neuropeptides involved in mammalian reproductive behavior. Dubbed nematocin, the worm peptide binds to receptors in nerves and muscles and plays a role in coordinating complex behaviors. When Bargmann's team created male worms lacking nematocin, the worms spent less time looking for mates. And when they encountered a partner, only a fraction of the nematocin-deficient males were able to complete the mating process. The group published the findings October 26, 2012, in *Science*.

That worms and mammals use similar neuropeptides suggests that a nematocin-like molecule has been conserved in animal nervous systems since worms separated from vertebrates about 600 million years ago. Next, Bargmann plans to figure out how the neuropeptide regulates behavior and then trace the evolution of that regulation.

OPPOSING NUCLEOTIDES

Several years ago, scientists in the laboratory of HHMI investigator Nathaniel Heintz discovered high levels of an unusual molecule called 5-hydroxymethylcytosine, or 5hmC, in brain cells. Its function was unknown, but new research by Heintz and his colleagues hints that it may play a role in the neurological disorder Rett syndrome.

5hmC is a modified form of cytosine—one of the four DNA building blocks. Intrigued by its abundance in brain cells, Heintz's team at the Rockefeller University began mapping where the nucleotide occurred in the genome. They also identified locations of another modified version of cytosine, 5-methylcytosine, or 5mC. The resulting map revealed that 5hmC was most plentiful in active genes, while large amounts of 5mC appeared in inactive, or silent, genes.

A search for molecules that bind to 5hmC turned up only one candidate—MeCP2, a regulatory protein that is mutated in Rett syndrome. As the team reported December 21, 2012, in *Cell*, tests showed that MeCP2 binds 5hmC and 5mC with equal affinity and that binding to 5hmC is associated with active transcription.

Heintz hypothesizes that the two modified forms of cytosine are responsible for different aspects of the disease. He plans to investigate how the same MeCP2 protein can trigger these opposing effects, depending on which nucleotide it binds.

THE SECRET TO (WORM) LONGEVITY

Schistosomes are parasitic flatworms that burrow through human skin and lay eggs that eventually lodge in major organs. As if that isn't bad enough, the worms thrive in their hosts for decades. A discovery by HHMI investigator Phillip Newmark may help shorten this parasite's lifespan.

Newmark studies planarians, relatives of schistosomes, in his laboratory at the

Itching to Be Discovered

SKIN-DEEP RECEPTOR IN NERVE CELLS SENSES ITCH.

Humans do, and mice as well. Dogs and cats? Definitely. Itch is a near-universal experience. But, until recently, understanding how it works has remained a mystery. For decades, scientists have been trying to figure out if the nerve cells that detect itch and pain are one and the same. This winter, HHMI early career scientist Xinzhong Dong and his colleagues resolved the debate.

When the receptor for capsaicin—the chemical that gives heat to chili peppers—is added to itch-sensing neurons, exposure to the normally painful capsaicin causes itchiness.

In 2009, Dong, whose lab is at the Johns Hopkins University School of Medicine, discovered a family of proteins in sensory nerves that is activated by multiple itchy compounds. In follow-up experiments, he and his colleagues used a glowing protein to label cells that express one member of this family—MrgprA3. As they report in the February 2013 issue of *Nature Neuroscience*, they learned that these MrgprA3-expressing neurons extend only to the skin. "They don't go to deeper tissue like muscles, bones, or visceral organs," says Dong. "That really explains why we feel itch only from our skin and not from deeper tissue."

The glowing labels also enabled the team to see the MrgprA3-expressing neurons in live mice and stimulate those cells with irritating compounds. When the scientists destroyed the neurons with a toxin, the animals scratched less, but they still responded to pain.

"To prove that the neurons only sense itch and not pain, we did the ultimate test," explains Dong. He and his colleagues modified mice so that their MrgprA3-expressing neurons contained a receptor that binds to capsaicin, the chemical that gives heat to chili peppers. When the scientists rubbed capsaicin on rodents' skin, the animals didn't react as if they were in pain. Instead, they scratched.

Now that Dong and his team have pinpointed the nerve fibers responsible for itch, they are looking for small molecules that will block Mrg receptors to silence the itch-inducing nerves. If they succeed, there will be many fewer itches to scratch.

■ –NICOLE KRESGE

IN BRIEF

University of Illinois at Urbana–Champaign. Planarians have extraordinary regenerative powers—they can replace lost body parts by calling on a reserve of stem cells called neoblasts. Postdoctoral fellow Jim Collins and Newmark had a hunch that schistosomes might use similar cells to repair damaged tissues, allowing them to live longer lives.

They were right. The researchers found similar actively dividing cells. "The cells we found in schistosomes look remarkably like planarian neoblasts," explains Newmark. And they can give rise to multiple cell types. The scientists published their results February 28, 2013, in *Nature*.

Newmark says the schistosome stem cells aren't necessarily the sole reason the parasites survive for so many years. But their ability to replenish multiple cell types likely plays a role. With more work, scientists may be able to figure out how to target the schistosome stem cells and shorten the parasite's lifespan.

ANCIENT BALANCING ACT

In evolution, "survival of the fittest" refers to genetic selection of the single best adaptation. But what happens when more than one adaptation is advantageous? Research by Molly Przeworski, an HHMI early career scientist at the University of Chicago, has found some instances in which this scenario dates back several million years.

Although evolution usually works to select a single adaptive trait, sometimes it keeps all hereditary options open by not favoring a particular version, or allele, of a gene. This phenomenon, known as balancing selection, maintains genetic variation in a population. In an effort to find examples of ancient balancing selection, Przeworski and her team analyzed the genomes of 59 humans from sub-Saharan Africa and 10 chimpanzees from western Africa, looking for variation shared between the two species since they diverged from their common ancestor. They reported their results online in *Science* on March 29, 2013.

The researchers found strong evidence for long-lived balancing selection in six regions of the human genome and weaker evidence in another 119 regions. Unexpectedly, not one of these six areas occurred in DNA that coded for genes. That variants in these noncoding regions are preserved in humans and chimps suggests that regulatory variation dates back millions of years before the two species split. Przeworski plans to investigate the function of these regions, which appear to play a role in fending off disease.

BENEFICIAL BACTERIA

Just as there are beneficial bacteria that live in our digestive tracts, a good dose of microbes may also be essential for healthy lungs, according to research by HHMI investigator Stephen Quake.

Quake and his team at Stanford University compared microbes in patients with cystic fibrosis to those in healthy human lungs. Cystic fibrosis causes the lungs to produce sticky, thick mucus—a perfect breeding ground for bacteria. Surprisingly, the healthy lungs contained a wider variety of microbes than the diseased lungs. The team also discovered that patients with cystic fibrosis have a distinct microbial profile, with bacteria so unique they can be used to distinguish cystic fibrosis patients from individuals without the disease. The results were published September 2012 in *Science Translational Medicine*.

Quake doesn't know whether the differences in lung bacteria might be due to heavy use of antibiotics by cystic fibrosis patients, for example, or due to the lung disease itself. However, the results do suggest that certain microbes may benefit lung health. Next, the research team plans to see if the microbiomes can be correlated to lung function in cystic fibrosis patients.