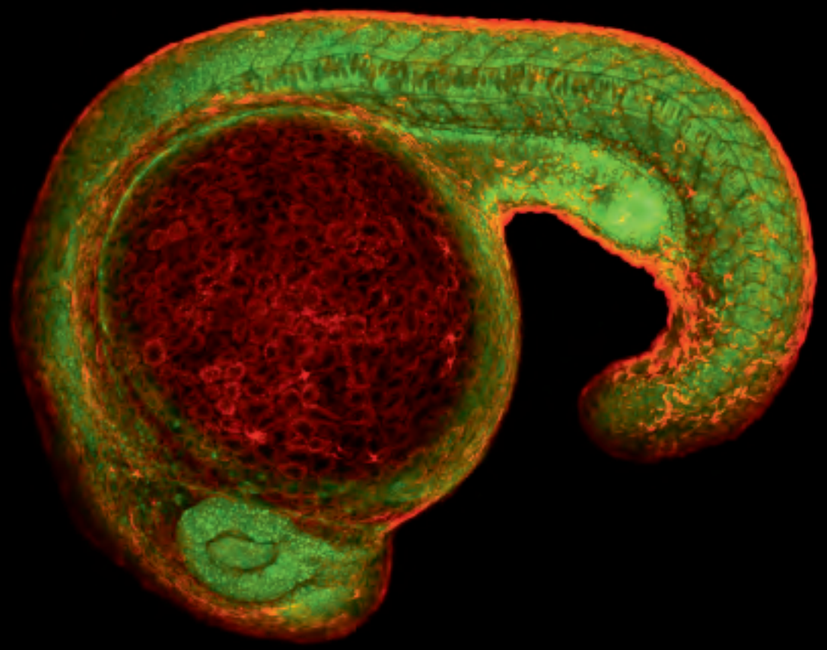
HHMI
HOWARD HUGHES MEDICAL INSTITUTE

4000 Jones Bridge Road
Chevy Chase, Maryland 20815-6789
www.hhmi.org

Address Service Requested

Sugar Coated

Sugar has become notorious, with countless claims of its ill effects on health. But not all sugars are bad for you. Consider fucose, an essential sugar the body needs. Without it, neurons can't communicate, kidneys can't filter blood, and skin can't stay hydrated. Chemical biologist Carolyn Bertozzi and her group are trying to learn more about the role of fucose in development. To do this, they injected modified versions of fucose into live, single-celled zebrafish embryos. As the embryos developed, the altered fucose molecules were incorporated into the sugars that coat cell surfaces. Using a simple chemical reaction, the team attached a labeled probe molecule to the altered fucose so they could visualize its location in the developing embryo. In this image of a 19-hour-old zebrafish embryo, labeled fucose (red) glows in the peripheral cells. Just one of many ways chemistry is helping answer biological questions (see "Living Chemistry," page 12).



Karen Dehnert and Scott Laughlin / Bertozzi lab

HHMI BULLETIN • Howard Hughes Medical Institute • www.hhmi.org

vol. 24 / no. 04

Nov. '11 | Vol. 24 • No. 04

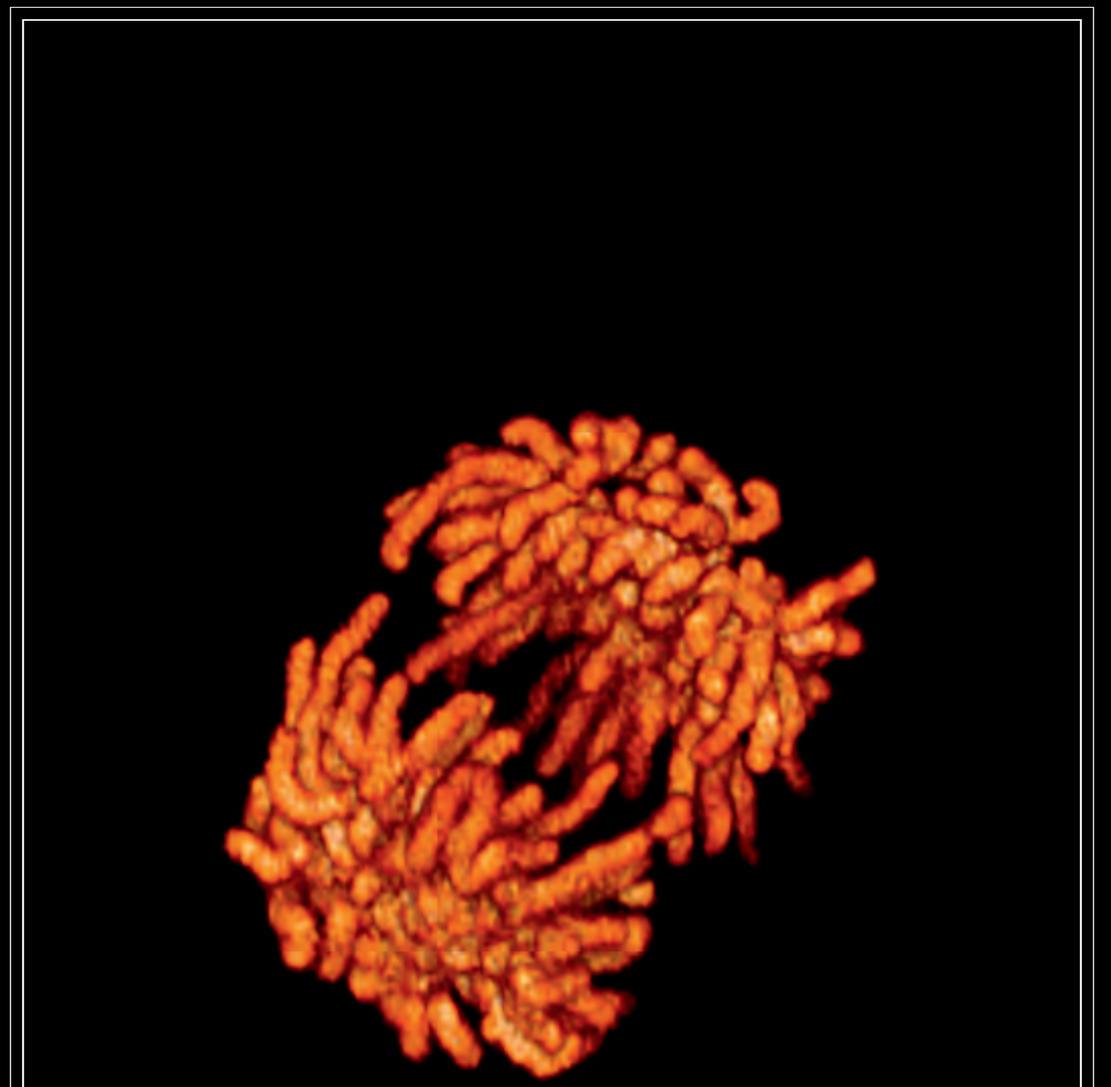
HHMI BULLETIN

Howard Hughes Medical Institute www.hhmi.org

YEAR OF CHEMISTRY

Chemists fascinated by the complexity of biology are solving problems in neuroscience, immunology, and cell signaling.

In This Issue: Traveling Microscope / Lemur vs Mouse / Spotlight on Science Teacher Training



24

Catching chromosomes in the act, this still frame of a dividing human cancer cell, an osteosarcoma cell, comes from video recorded by Bessel beam plane illumination microscopy. Developed by Eric Betzig and his team at Janelia Farm, the microscope directs a narrow pencil of light to illuminate a single plane within a specimen and then repeats, plane by plane, until the entire volume is imaged. Combining 3-D spatial resolution with high speed and minimal light-induced damage, the approach is particularly suited for imaging activity within living cells—something that biologists have been eager to do.

Betzig lab

Emily Roberston

THE GIVING TREE

The history of science overflows with captivating stories of breakthroughs that led to innovative disease treatments. Chemical biologist Brent Stockwell chose his favorites—including the story of aspirin—in a new book on the science behind drug discoveries. In the telling, Stockwell reveals how curiosity, persistence, and scientific know-how combine in sometimes powerful and far-reaching ways.

In many cases, extraction and synthesis methods have been combined to make derivatives of molecules found in nature. An example of this type of combined approach is the discovery of fever-reducing drugs.

An active component of Willow tree extract is salicin. Raffaele Piria, an Italian chemist, prepared salicylic acid from salicin, which was advantageous because salicylic acid was easier to modify into other molecules compared to salicin. Salicylic acid, however, caused gut toxicity, and so was of limited value. Charles Frédéric Gerhardt, a French chemist, then synthesized a key derivative named acetylsalicylic acid in 1853. Refined methods for synthesizing acetylsalicylic acid were developed by two chemists, Johann Kraut in 1869 and Hermann Kolbe in 1874, but then, unfortunately, this molecule languished, with little interest in its medicinal properties.

At the end of the nineteenth century, many researchers began to pursue medicines that could reduce fever, with the rationale that fever could be damaging to the body. These so-called anti-pyretics (fever-reducing molecules) were aggressively sought. The nascent pharmaceutical company Bayer introduced acetylsalicylic acid as an anti-pyretic in 1899, coining the name "aspirin." This fever-reducing drug quickly became popular around the world. It was the first of the non-steroidal anti-inflammatory drugs (NSAIDs) used. Subsequently, other NSAIDs were introduced, such as ibuprofen (now sold as Advil). Such drugs represent a huge class of beneficial medicines that are widely used around the globe.

NOVEMBER '11 VOL. 24 · NO. 04

12

18

24

30

Web Only Content

- Hear Eric Betzig talk about taking his new microscope to Woods Hole and see how it dazzled summer students and faculty.
- Learn how Irv Epstein brings chemistry alive for students in the classroom.
- Travel with Mark Krasnow to the rainforests of Madagascar to spy the mouse lemur in its native habitat.
- Join us at www.hhmi.org/bulletin/nov2011.

Features

COVER STORY

LIVING CHEMISTRY

12 As engineers of the molecular world, chemists are making their mark in biology.

CALLING ALL TEACHERS

18 Everyone agrees that the U.S. needs to train a new generation of inspiring science teachers. But how?

HAVE MICROSCOPE, WILL TRAVEL

24 Biology students and faculty immersed in science courses at Woods Hole get their hands on a remarkably powerful imaging tool developed at Janelia Farm.

STAR SEARCH

30 Could the grey mouse lemur be the next best model for human disease?

Departments

PRESIDENT'S LETTER

03 Intellectual Ferment

CENTRIFUGE

04 Game Changer

05 Stirring Debate

06 The Peripatetic Postdoc

UPFRONT

08 Creating Internal Maps

10 Helping Preemies

PERSPECTIVES AND OPINIONS

34 Changed Expectations

36 Q&A—What was your first cool chemistry experiment—one that turned you on to research before you were a bona fide scientist?

CHRONICLE

SCIENCE EDUCATION

38 Room to Grow—and Learn

INSTITUTE NEWS

40 Experiment Seeks to Create Interdisciplinary Curricula

40 HHMI Offers International Student Research Fellowships

41 Getting Back to the Bench

LAB BOOK

42 Unlocking the Interferon Puzzle

43 When Membranes Merge

44 Bacterial-Viral Warfare

ASK A SCIENTIST

45 How fast would an object have to move to be invisible to the naked eye?

NOTA BENE

46 News of recent awards and other notable achievements

OBSERVATIONS

The Giving Tree

In the fifth grade, I won a blue ribbon at my school's science fair. Truth be told, it wasn't much of a project—I grew a "popcorn plant" from an unpopped corn kernel. But my teacher, Mrs. Barnes, saw something there.

I treasured that ribbon, and it could be that Mrs. Barnes's vote of confidence launched me toward my graduate degree in biology. Sadly, though, the rest of my elementary, middle-, and high school years were almost bereft of science, with few good science teachers. The one exception was my eleventh grade chemistry teacher, Mrs. Otwell—a woman with sharp intelligence and charismatic delivery who taught me the "bus seat rule," to illustrate the orderly manner in which electrons fill atomic shells, and the meaning of a quark.

I wasn't the only one in my family touched by Mrs. Otwell's teaching magic. One of my older brothers majored in chemistry in college, and my sister, who as a Star Student in high school named Mrs. Otwell her Star Teacher, is now an academic researcher studying bone genetics.

Who's to say what might have been had the early spark that Mrs. Barnes lit been fanned into a flame during my later school years? After switching my college major from English to biology, I eventually arrived at a career in science, first in the research lab and now as a science writer and editor. It was the right path for me, though I sometimes imagine how things might have been different.

Clearly, those formative K-12 school years are critical. In this issue of the *Bulletin*, we spotlight the need in this country for more, and better, science teachers in our schools. In other articles, we pay homage to the increasingly powerful role that chemists play in biological discovery—chemists who no doubt got their start being fascinated by the fundamentals with teachers like Mrs. Barnes and Mrs. Otwell.

Don't miss the multimedia slideshows and other extras in this issue, which can be found online and in our iPad app. The digital versions of the *Bulletin* are proving a great way to expand on the stories we offer in print—for example, find new details of Matt Warman's bone research, first covered in the May 2011 issue. The magazine's stories continue to have lives long after they land in your mailbox, and we'll use our website to update them as we go.

HHMI BULLETIN STAFF

Mary Beth Gardiner / *Editor*
Cori Vanchieri / *Story Editor*
Jim Keeley / *Science Editor*
Andrea Widener / *Science Education Editor*
Nicole Kresge / *Assistant Editor*
Maya Pines / *Contributing Editor*

ADDITIONAL CONTRIBUTORS

Cay Butler, Michelle Cissell, Sarah Crespi, Mark Farrell, Heather McDonald
VSA Partners, NYC / *Concept & Design*
Finlay Printing / *Printing & Binding*

HHMI
HOWARD HUGHES MEDICAL INSTITUTE

Telephone (301) 215.8855 • Fax (301) 215.8863 • www.hhmi.org

Courtesy of M.B. Gardiner

Intellectual Ferment

James Keglev

CHEMISTRY WAS THE FOCUS OF MY ACADEMIC INTERESTS WHEN I arrived as a freshman on the campus of the University of California, Berkeley. But unlike countless undergraduates everywhere, it wasn't synthetic organic chemistry that turned my thoughts in new directions. Instead, it was a fascination with biology and the chance to work in the lab of the legendary Daniel Koshland that drew me to biochemistry. Ever since, my research has been shaped by a single view: to attack major problems in biology, it is essential to understand what molecules are doing and how they interact with each other.

Every field has a different definition of what it takes to be a good scientist and these competing definitions can be vexing when you're interested in working at the interface of multiple disciplines. At the risk of oversimplification, I would say that for many years, biologists were focused on discovering how things work and less interested in the underlying processes. Chemists, on the other hand, skipped past the question of how something worked because they were focused on figuring out how to manipulate a process or make it better. I'm happy to say that these disciplinary and philosophical distinctions have become increasingly blurry: biologists are manipulating systems and chemists delight in discovering biological phenomena.

For me, it has always come down to something that my scientist colleagues can have a hard time talking about: intuition. Do you have an instinctive feel for a subject? Does it speak to you? That intuition or instinct—whatever word you use to describe it—is not so much about solving problems as it is about asking the right questions. If you have "biological intuition"—whether you are a chemist or physicist—you will have a sense of what makes a profoundly important question worthy of your time and energy. Figuring that out is the big challenge for all of us in biomedical research because we have an almost infinite number to address.

Labs that mix biochemists, engineers, physicists, and mathematicians together with biologists generate a kind of intellectual ferment that is productive and exciting. I see it in my UC Berkeley lab all the time, at the Janelia Farm Research Campus as it approaches the five-year mark, and with greater frequency at universities throughout the country.

This issue of the *HHMI Bulletin* takes special notice of the interactions between biology and chemistry—a fitting subject as we near the end of 2011 and the International Year of Chemistry. We're taking a look at the complex and exciting connections between chemistry and biology from both "sides" of the disciplinary divide as well as what's changed for chemists interested in biological questions and vice versa. As Kevan Shokat of the University of California, San Francisco, rightly observes, some problems can't be addressed unless you harness both the tools of biology and those of chemistry. Instead of "Better Living through Chemistry"—Dupont's famous 1960s advertising slogan—this new breed of scientists might propose something along the lines of "Better Biology with Chemistry." Or in a variation on the Robert Frost poem, "Lower Fences Make Better Neighbors."

> "If you really want to understand the function of complex biological systems that underpin disease, you want to use every imaginable tool at your disposal."
>
> ROBERT TJIAN

If you really want to understand the function of complex biological systems that underpin disease, you want to use every imaginable tool at your disposal—that means genetics, cell biology, chemical engineering, computer science, and biophysics, to name just a few—because you can't get there by being purely descriptive. In my own work, I am interested in the molecular mechanism of complex reactions that involve close to 100 polypeptides doing the right thing at the right time. The problem is, how do those 100 proteins talk to each other in a live cell in real time?

It's solving problems like this, at the level of the living cell, that makes the confluence of biology and chemistry so important. And we have no better illustration of it than the discoveries honored by this year's Lasker Award for Basic Medical Research. You can figure out how proteins fold from the standpoint of expected atomic interactions or you can understand what actually occurs in living cells amid the complex regulatory processes that need to happen along the way. That is what Arthur L. Horwich, an HHMI investigator at the Yale School of Medicine, and Franz-Ulrich Hartl of the Max Planck Institute of Biochemistry, succeeded in doing with such elegance.

Game Changer

On a humid Sunday morning on the tail of a Boston heat wave, the steady thwok....thwok....thwok of sharply hit tennis volleys echoes from a secluded court on the Harvard Medical School campus.

Bright yellow-green balls explode off the racquet of a dark-haired biology student and slice toward her rallying partner and summer lab mentor, HHMI investigator George Daley of Children's Hospital Boston.

It's the first time the two have faced off. "You hit hard—really hard," says Daley. "I like that!"

Alana Van Dervort, an HHMI-supported EXROP (Exceptional Research Opportunities Program) student, returns the compliment. "He's a player," she comments knowingly to a bystander.

After a long layoff, Van Dervort is knocking the rust off the powerful game she honed since early childhood. Between 2003 and 2006, she traveled by herself to places like China, South Korea, Mexico, and Dubai on the professional women's tennis circuit, earning enough prize money to cover her expenses.

Van Dervort's approach to tennis—and life—shows a gritty determination and a certain readiness—like a player bouncing on the balls of her feet—to change directions as needed.

"At 5-foot-5, I'm a smaller player, so I made up for it by becoming a meticulous technician," she says. She hits the ball early in its upward bounce and powers her shots with the weight of her entire body, not just her arm.

At age 22, in part because of injuries, Van Dervort shifted gears. She enrolled as a freshman at Florida International University, trading the court for the laboratory to train in biological sciences. Last June, she was selected to work in the lab of Daley, a renowned stem cell biologist, for the summer between her junior and senior years. Energetic and animated, Van Dervort credits her father, who did research on septic shock and critical care medicine at the National Institutes of Health, with guiding her toward science and tennis.

"He used to let me 'help' him put test tubes in the centrifuge," recalls Van Dervort. "The NIH was my playground."

Her father, who died when Alana was 10, started her on tennis when she was four or five, taking her to play in tournaments. She had early success and even won the American Tennis Association's Women's Open at age 17.

Van Dervort spent her high school years at the famed Nick Bollettieri Tennis Academy in Bradenton, Florida, an incubator of top tennis talent, including Maria Sharapova, Serena and Venus Williams, Andre Agassi, and Monica Seles. Van Dervort trained daily with elite players, including Sharapova, formerly ranked No. 1 in the world.

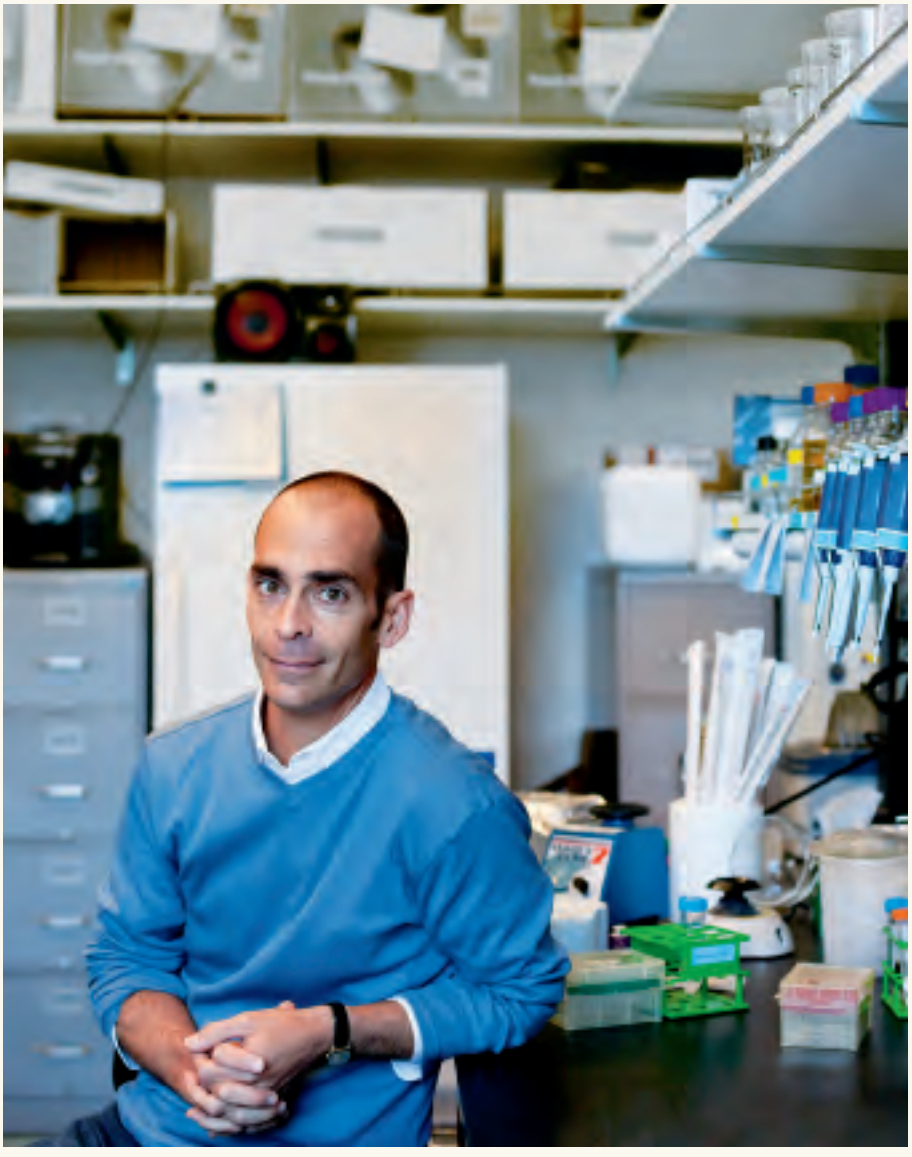
Van Dervort's father instilled in her a strong work ethic and taught her to be prepared for the unexpected. "In drills he would purposely distract me while I was serving, or make me play left-handed or use a foam racket. It gave me confidence that I could handle anything," she says.

Thus, Van Dervort could change her tennis tactics when needed and adjust to different cultures and locales in her travels. Today, she applies the same flexibility to her science.

"I find that the less I am attached to a specific notion—as long as I'm actively engaging the question—the faster a sounder notion evolves."

—Richard Saltus

Chris Silas Neal



Shawn Records

Stirring Debate

In his University of Oregon lab, Joe Thornton is a laser-focused scientist probing the molecular evolution of steroid hormones and their receptors.

When Thornton enters the classroom of "Biology and Politics," however, his focus broadens to embrace his background in the liberal arts and globe-trotting environmental activism. As director of the humanities-styled course, he leads discussions, sometimes heated, on topics as far ranging as toxic chemicals, intelligent design and evolution, and the use of science in the Bush and Obama administrations.

"Science is a form of culture. It's how we explain to ourselves the physical world and our place in it," says Thornton, an HHMI early career scientist. "That makes it an enormously potent social and political force."

Students in Thornton's course debate how science should inform politics in a democratic society. Along the way, they question their most basic assumptions about the nature of scientific knowledge, he says. "We explore readings in sociology, philosophy, and the history of science to articulate different views of the relationship between scientific expertise and authority in culture."

Thornton created the course after he received a 2006 Presidential Early Career Award for Scientists and Engineers.

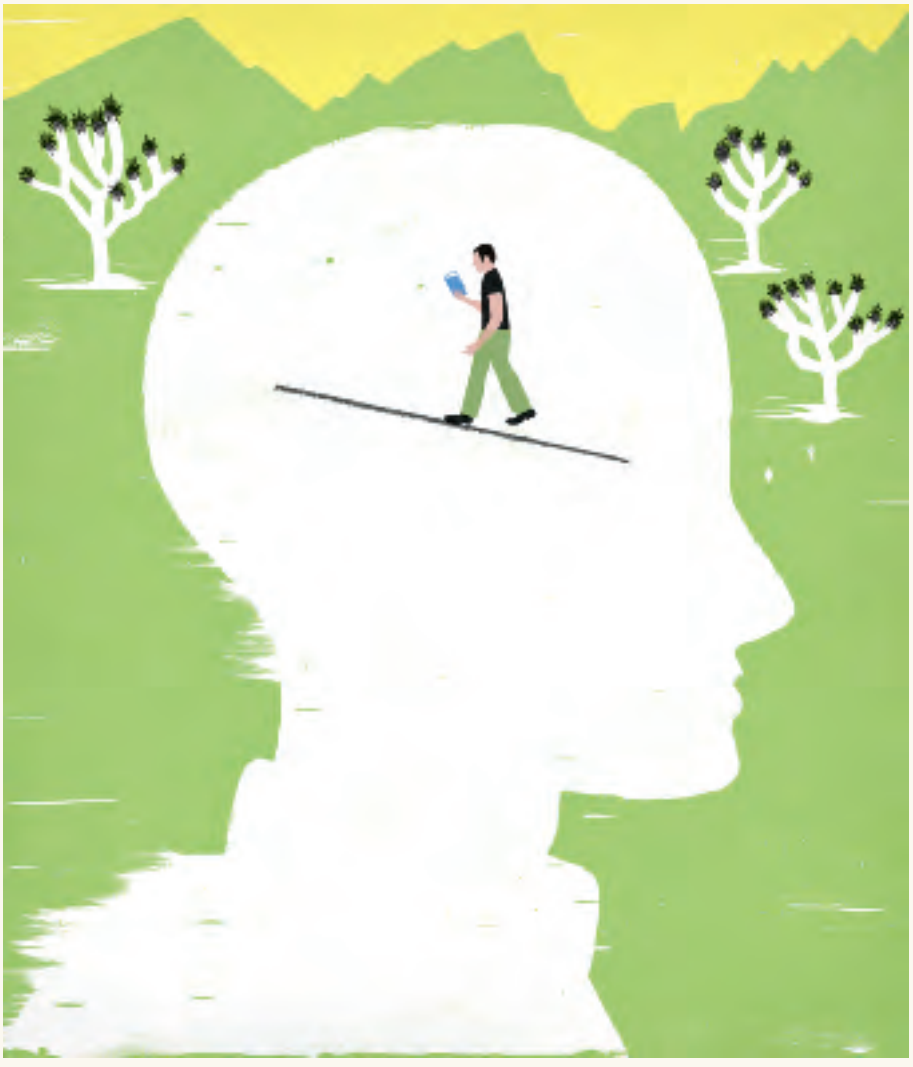
Thornton didn't plan on being a scientist. As an undergraduate in the 1980s at Yale University, he majored in English, with a focus on literary theory. "It was interesting and seductive, but it was divorced from any tangible reality," he says. Amid a growing national debate on the environment, he turned to political activism.

He worked as an activist for Greenpeace, where he spent nine years translating complex science to help improve public understanding of policies related to chemical pollution. Focusing on the emerging issue of endocrine disruptors and their effects on reproductive health in humans and wildlife, he worked with community groups around the world, testified before Congress, and authored hundreds of reports and articles, all without formal training. At age 30, he entered Columbia University to study molecular biology and evolution.

"During my time with Greenpeace, I became fascinated with the study of natural systems," he says. "That experience changed the way I look at science. I saw the enormous political authority that science carries in society. I also saw the ways in which politics and culture shape the scientific debate itself."

The debate on endocrine disruptors continues, he notes, making the issue a good opening case study for his Biology and Politics course. Recognition of the potential health dangers of these chemicals has grown over 20 years, with legislation aimed at addressing them introduced in Congress in each of the last three years. Senator John Kerry (D-Mass.) and Representative Jim Moran (D-Va.) introduced a new bill in July.

"Each time I teach the course, several students say that it fundamentally changed the way they think about science," Thornton says. "They come to see science as a rigorous but creative form of self-expression—a way of contributing to culture. That's extremely rewarding for me as a teacher and scientist." —*Jim Barlow*



Chris Silas Neal

The Peripatetic Postdoc

Morgan Beeby set out on a walk one Monday morning in June 2007 and didn't stop until a Tuesday afternoon in October—four months later. By then, he had traveled 2,590 of the 2,650 miles that constitute the Pacific Crest Trail, which meanders through the United States from the Mexican border to the edge of Canada. Beeby, however, never quite made it to the point where the U.S. meets its neighbor to the north. He came to a standstill just 60 miles south of the trail's end.

Why stop, so close to the finish line? "Because I was knee- and sometimes waist-deep in snow," Beeby laughs. "I'd gotten a late start; I'd had a little thing called my Ph.D. to finish up."

For this British-born microbiologist, now a postdoctoral scholar working with HHMI investigator Grant Jensen at the California Institute of Technology, walking is just a part of his native culture.

"The British are a nation of walkers," he says. "That's the case for a number of peoples—the English, the Japanese, the Koreans. I was brought up walking the hills near my home, in a town just south of Gloucester."

Perhaps that's why Beeby seems bemused by the interest shown in his ramblings, reacting as if he were being given a standing ovation for using a knife to cut his food into bite-sized pieces. To him, walking is neither vocation nor avocation, neither sport nor relaxation. It just is.

"Walking is a process," he says. "It's nice that it's incidentally exercise, and it's convenient that it's also transportation, but that's not the point of it. It's something to be enjoyed in and of itself, a fantastic way of getting perspective."

Although the time spent on the Pacific Coast Trail was by far Beeby's longest trek, it was by no means his only one. He and a friend trudged nearly 120 miles across some of Australia's least-hospitable terrain as part of an assignment for a magazine. He also hoofed 70 miles through Tasmania. And one summer he walked for five days from the university he attended in Birmingham, England, to his home in Gloucester. "I camped in fields wherever I could pitch a tent."

Don't count on Beeby for training tips or a discussion of the best walking shoes on the market, however. "I don't train, and I almost never get blisters," he says with a half-sheepish grin. "I think it's because I've always walked and spent a lot of my childhood barefoot."

These days, most of Beeby's trips are short weekend jaunts when his research permits. He studies flagellar motors, the molecular machines that power the whip-like appendages that allow bacteria to travel—or, more precisely, to glide or swim—through their environment.

The only link between his work and his pastime is the process. "It's not the surface similarity that I move and bacteria move," he says. "It's the pleasure and involvement I have with the process of research and development of an idea. Being able to get out and see the world is invaluable to me," he adds. "Who can think at a desk?"

—Lori Oliwenstein

upfront

08 CREATING INTERNAL MAPS
Combining complementary skills, a team of neuroscientists studies how flies navigate their surroundings.

10 HELPING PREEMIES
Treating myelin injuries and tracking brain cell development to rescue the littlest patients.

WEB ONLY CONTENT

A NEW TAKE ON RETINOBLASTOMA
Basic research findings upend old thoughts on this childhood tumor. Read the story at *www.hhmi.org/bulletin/nov2011*.

When inspired people come together, even briefly, great things can happen. A developmental biologist pulls together a team of pharmacologists, chemists, and genomics wizards to build a comprehensive picture of a rare childhood cancer—and they find a drug to attack it. A pediatric neurologist partners with a veteran stem cell biologist and a young neurosurgeon to study brain tissues and they discover a pathway for neurogenesis. A Janelia Farm researcher hits it off with a visiting scientist, they pull in a postdoc, and *voilá*, fly behavior is illuminated. Teamwork *par excellence*.

Creating Internal Maps

Combining complementary skills, a team of neuroscientists studies how flies navigate their surroundings.

SOME COLLABORATIONS CLICK FROM THE START. TAKE THE CHANCE meeting three years ago at Janelia Farm Research Campus between Michael Reiser, a group leader at Janelia, and Charles Zuker, an HHMI investigator then at the University of California, San Diego (UCSD). The two had never spoken before, but within a day or two, Reiser says, Zuker was suggesting his graduate student as a perfect fit for the project.

The partnership seemed so promising that Zuker arranged to work with Reiser through Janelia Farm's Visitor Program, where scientists from around the world conduct research of their own design for a few weeks or several years (see Web extra sidebar, "Visitors Welcome"). "We all hit it off beautifully," he says.

The researchers weren't just simpatico. They brought together complementary talents and knowledge that enabled them to explore an important question: do fruit flies commit details of their surroundings to memory? Humans and other vertebrates make spatial memories all the time. You can return to your car in a crowded parking lot, for example, by referencing landmarks stored in memory. So-called place neurons in the hippocampus, a brain structure crucial to memory, confer this ability. "In essence, the cells are creating an internal map of the outside world," says Zuker.

But how do neurons register this information? Reiser believes it might be possible to dissect mapping of spatial memory by analyzing the process in fruit flies, where brain cells can be precisely targeted for manipulation. "The fly presents a real sweet spot to try to answer this question," he says.

At the outset, Reiser brought his LED-based display that projects different background patterns, providing potential navigation landmarks for flies. Zuker brought small, hot and cool tiles that his lab had developed to study how the insects sense temperature.

The job of melding these technologies fell to the third member of the partnership, Tyler Ofstad—Zuker's graduate student and an M.D./Ph.D. candidate at UCSD. After a year of R&D in Reiser's lab, handled largely by Ofstad with what Zuker calls "devotion, drive, and maniacal commitment," the team had built a shallow, circular arena, about 20 centimeters across, with a clear glass lid. Most of the arena's floor was a warm-to-the-touch 36°C. One tile, however, was only 25°C, pleasantly cool for fruit flies. Each time the flies entered the arena, they typically wandered, but "once they found the cool spot, they stopped and stayed there," says Ofstad. The flies were allowed 10 five-minute trials to learn the location of the tile. To follow the flies' movements, the researchers were among the first to use software designed by Janelia Farm fellow Kristin Branson that Reiser describes as "the world's best fly tracking program."

The cool tile looked the same as the rest of the floor, so the only landmarks in the arena were patterns of bars projected on the wall. To determine whether the flies used this background to guide them to the cool tile, the researchers rotated the floor and walls of the arena after each trial so that the location of the cool floor tile changed, but its position relative to the wall patterns stayed the same.

The flies quickly learned to pinpoint the cool spot. After 10 attempts, the insects could find the tile in under 60 seconds, less than half the time of their first try, the group

Mike Lemanski

reported June 8, 2011, in *Nature*. Moreover, when the trained flies encountered an arena without a cool tile, they congregated where the tile should have been, based on the visual background.

Then the team tricked the flies, rotating the thermal pattern on the arena floor after each trial but leaving the wall stationary, so that the background pattern no longer corresponded to the location of the cool tile. The flies were baffled. When given the chance to find the cool tile in the dark, they also made no headway. Given this evidence, the researchers concluded that "flies can form memories about spatial locations," says Ofstad.

Next the researchers wanted to know which part of the fly brain remembers the location of the cool spot. They switched off certain brain cells in the flies, using genetic tools developed in the lab of Janelia Farm director Gerry Rubin that allow scientists to target small groups of identified neurons. When neurons in a structure called the ellipsoid body were shut down, the flies couldn't navigate the arena. Thus, this structure might be crucial for storing or retrieving spatial information in the insects. The role of the ellipsoid body isn't clear, but Zuker says it would be the first place to look for the fly equivalent of place neurons.

The researchers have gone their separate ways—Ofstad has returned to San Diego to finish clinical work for his M.D., and Zuker has moved his lab to the Columbia University College of Physicians and Surgeons in New York City. The team, however, is hatching a plan to use fruit fly vision and behavior to decipher another aspect of brain function. "When you find the unique synergy that helps some of the magic come out of exciting scientific problems, you want more of it," Zuker says. ■ –MITCH LESLIE

WEB EXTRA: To read more about the Visitor Program at Janelia Farm, visit www.hhmi.org/bulletin/nov2011.

Helping Preemies

Treating myelin injuries and tracking brain cell development to rescue the littlest patients.

BABIES BORN PREMATURELY—AS MUCH AS THREE MONTHS TOO soon—have a better chance of surviving than they did just a decade ago. But they face serious neurological problems that HHMI investigator David Rowitch sees too often in his clinical rounds at the University of California, San Francisco (UCSF). Using tissue from a new neonatal brain bank, he is gathering clues to devise treatments for brain-injured babies and perhaps also for adults with multiple sclerosis.

"We routinely take care of babies in the United States that are born at about six months of gestation, weighing about a pound," says Rowitch, a neonatologist. "About 10–20 percent will develop cerebral palsy—an inability to move and talk normally—and as many as 50 percent will develop learning, cognitive, or behavioral problems." At least some of those problems, Rowitch says, stem from damage to the protective myelin coating that insulates nerve cell axons in the "white matter" of the baby's brain.

"Therapies to limit the damage or enhance repair don't exist," Rowitch says. Answering even basic questions about the developing human brain has been tough because of the lack of autopsied tissue from young children available for study.

Last summer, however, Rowitch and colleagues published two studies, conducted using tissue from the neonatal and pediatric brain bank that he helped establish at UCSF in 2009 with HHMI support, that offer clues to nerve cell repair as well as human brain development.

In earlier work, Rowitch and postdoc Stephen Fancy had noticed that white matter injuries in some premature babies look similar to the damaged patches of myelin in multiple sclerosis. Closer study of brain bank specimens revealed why: In both cases, myelin-making cells known as oligodendrocytes and the progenitor cells that give rise to them (known as OPCs) rush in to repair the initial injury. Mysteriously, they don't complete their task.

"The obvious question is, why aren't these cells—which are all showing up at the right time in the right place—finishing the job they are almost hardwired to do?" Rowitch says. "We figured there had to be some inhibitor present, right there in the area of the lesion."

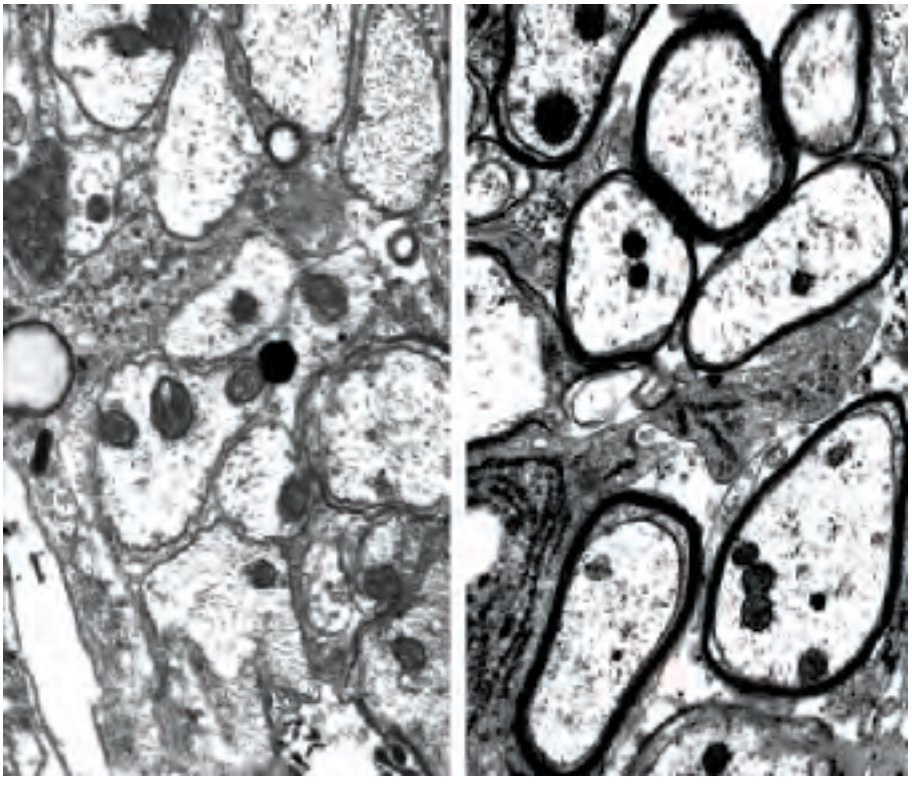
Reporting in *Nature Neuroscience* in June 2011, the team suggests one plausible reason for the blocked repair: overactivation of the Wnt pathway, as measured by expression of the gene *AXIN2*. Wnt is well known as an important, complex signaling pathway involved in the development of most organ systems throughout the body. When the scientists injected an experimental drug that slows degradation of the Axin2 protein directly into patches of damaged myelin in mice, it inhibited Wnt, and the OPCs lining the wound rapidly differentiated into healthy, myelin-making oligodendrocytes. The myelin injuries healed 30 percent faster than similar injuries in untreated mice.

Many questions remain. "We still don't know enough about this particular drug's toxicity—especially in young children," Rowitch says. "And, I think it would be simplistic to think this pathway is the only thing going on in the inhibition of myelin repair." Still, he says, the results suggest it might be possible to speed mending of tattered myelin with a drug soon after injury, before the underlying axon is permanently harmed.

Where and When Development Occurs

"Every baby's brain contains a variety of immature precursor cells that could, in theory, be enlisted to help mend injuries," says Rowitch. But first scientists need to

Stephen Fancy / Rowitch lab



David Rowitch's team improved remyelination repair in mouse models of demyelination using a small molecule Wnt inhibitor. An injection of lysolecithin removed oligodendrocytes and myelin, while sparing the axons. In the mice that received the Wnt inhibitor along with the lysolecithin, remyelination was more rapid than in mice that received no inhibitor with the injection. Note the thicker black myelin around the axons on the electron microscopy image on the right.

know more about how and what these cells do. To that end, he has been collaborating with UCSF neural stem cell biologist Arturo Alvarez-Buylla and neurosurgeon and postdoctoral fellow Nader Sanai, now at Barrow Neurological Institute in Phoenix, to map the trajectory of human stem cell activity emanating from a rich pocket of neurogenesis in the brain known as the subventricular zone (SVZ).

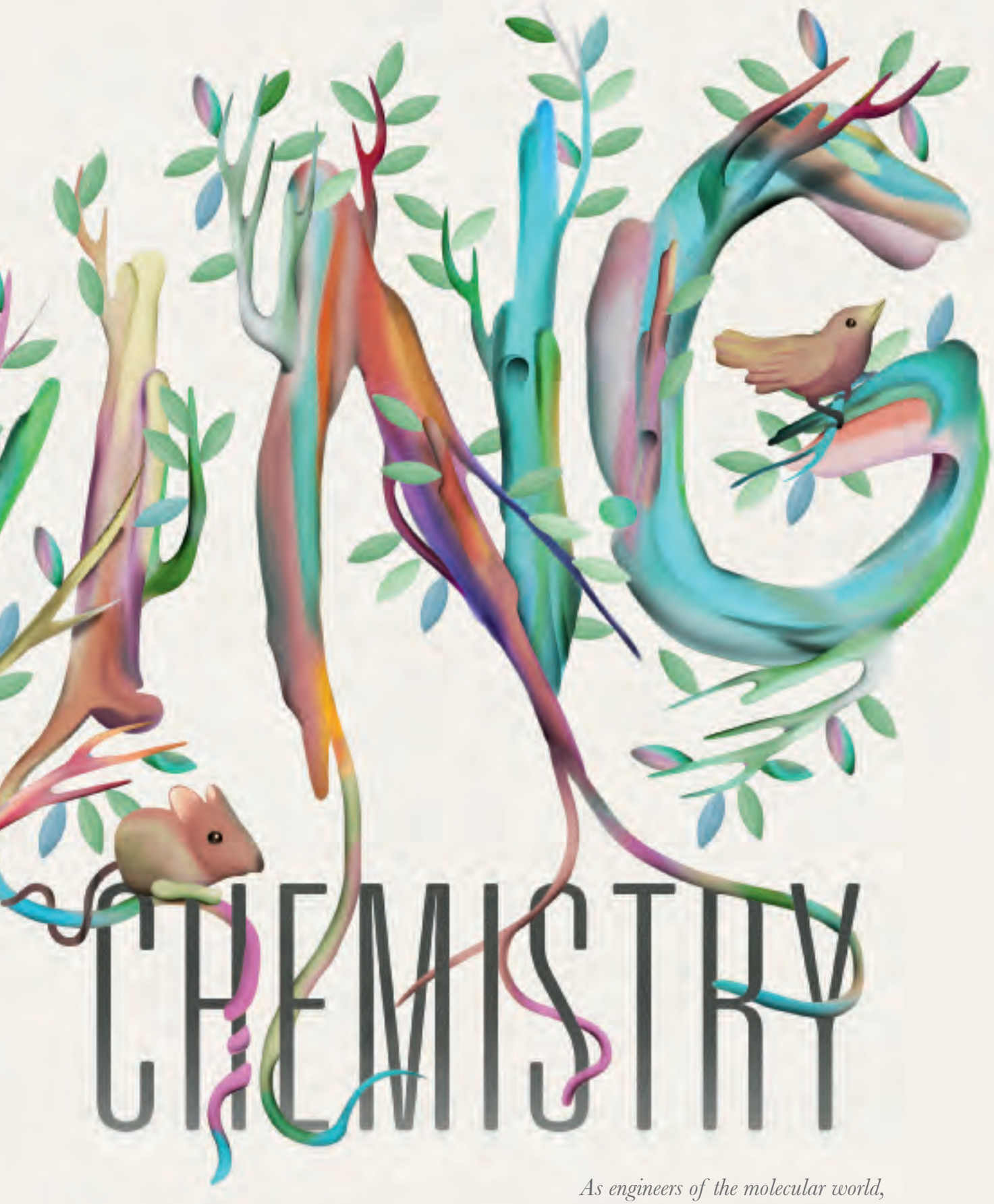
The SVZ has been well characterized in mice, in nonhuman primates, and, to a lesser extent, in human fetuses and older adults. But no one knew if or how activity in that region changed over the course of brain development in newborns and young children.

Now, by carefully comparing the cellular architecture of brain tissue from 54 infants, young children, and teens, Rowitch, Sanai, and Alvarez-Buylla have begun filling that information gap—and turning up surprises. For one thing, at least some of the stem cells arising from the SVZ travel to a different region in the human brain than in the mouse brain.

"In humans we're seeing streams of cells from the SVZ moving not just into the olfactory bulb but also toward the frontal cortex," says Sanai, who was an HHMI fellow during his medical school training at UCSF. "That newly discovered pathway raises questions about the mechanics of how the brain developed and evolved."

Another dramatic twist: after a period of robust neurogenesis in the first year of life, the human SVZ apparently slows down, sharply tapering production of brain cells by the time a child is 18 months old, and then slowing to almost zero by age two. The finding should help settle conflicting earlier reports, say Sanai and Rowitch, that suggested the SVZ might churn out new cells well into adulthood. The results were reported October 20, 2011, in *Nature*.

The first year of life is a window of particular vulnerability and opportunity for the brain, says Rowitch. It's a period of tremendous growth, organization, and flexibility, as fresh neural connections are created, broken, and remade. A better understanding of how things can go wrong in that critical period, he says, could ultimately improve the chances that things will go right. ■ –DEBORAH FRANKLIN



CHEMISTRY

As engineers of the molecular world, chemists are making their mark in biology.

by SARAH C.P. WILLIAMS *illustration by* MARIO HUGO

AT THIS VERY MOMENT,

your body is a living periodic table of elements. Chlorine atoms combine with hydrogen and churn through your stomach, breaking chemical bonds in the food you ate for lunch. Potassium pulses along your nerves, giving your fingers a sense of touch. Calcium makes up your bones and teeth; carbon is the backbone of your DNA; and oxygen seeps into your bloodstream with every breath you take.

If you are a chemist, you see the world in terms of these atoms. Not just humans, but plants, animals, bacteria, soil, computer chips, telephones, and light bulbs. Each is made of unique mixtures of the 118 elements posted on the wall of any high school chemistry classroom.

"Anything you see or touch or taste, it all comes down to these elements in different combinations," says HHMI investigator Chris Chang.

Both Chang's undergraduate degree and his Ph.D. are in chemistry. But now he studies the brain. His lab at the University of California, Berkeley, looks as much like a biology lab as a chemistry lab, with microscopes and mice and cell cultures. He's one of a handful of HHMI scientists—and a growing number of scientists around the country—who are applying their background in chemistry to biological problems.

These chemists are driven by a fascination with the complexity of biology and a desire to work in a fast-moving field. But the way they approach problems is distinct from biologists—they break organisms down to their most miniscule atomic parts to study how they work. And they build those biological systems back up using new chemicals they create from scratch.

"Chemists are able to not only study things at this molecular scale, but we can also reorganize things and build them from the ground up," says Chang. "It is this ability of chemists to create things that allows us to look at problems differently." Like structural engineers who design buildings and genetic engineers who create new genes from scratch, chemists are engineers of the molecular world.

Biology-interested chemists face no shortage of biological questions to answer. Chemical approaches are solving problems in neuroscience, immunology, cell signaling, and cancer biology.

"There are chemists now that are indistinguishable from biologists at the cutting edge of biological discovery," says Carolyn Bertozzi, another HHMI investigator whose research overlaps the two fields. "And then there are chemists who collaborate closely with biologists."

As biologists and chemists learn to bridge the gap between their fields, with training programs and increased appreciation for what the other has to offer, they are realizing just how complementary their skills can be.

Brain Chemistry

Choosing where to apply his chemistry knowledge wasn't hard for Chang. "There's nothing more complex or beautiful in biology than the brain," he says. Lucky for him, the brain is full of unique chemistry that's ripe for investigation. When Chang was launching his research career, he discovered that the brain has at least 20 times more copper than most of the body, and no one could explain why. As a chemist, he saw an opportunity—copper is a chemical element, the simplest building block of an organism. By studying copper in the brain, Chang could fulfill his desire to explore neuroscience and put his background in chemistry to use.

Biologists, however, had no way to visualize where the copper was in the brain. They couldn't track its movement or see where it was being integrated into larger molecules. So Chang created a new kind of copper—a copper atom attached to chemical probes that offer a way to watch copper's path in the brain. He engineered the copper so that the probes could light up under a fluorescence microscope or potentially be visualized in an MRI of the brain.

In an April 2011 paper published in the *Proceedings of the National Academy of Sciences*, Chang's team used the method to determine just how dynamic copper is in brain cells. They found that when a neuron receives a signal—in the form of calcium molecules—a wave of copper moves from one end of the neuron to the other.

"We showed that copper is not this static building block of brain cells like many believed. It's a dynamic, mobile signaling molecule," says Chang. "And this is the first time that someone

"Anything you see or touch or taste, it all comes down to these elements in different combinations."

CHRIS CHANG

can watch it flow through brain cells in real time." Next, the group aims to understand what this wave of copper movement triggers.

Copper is far from the only dynamic chemical in the brain. Linda C. Hsieh-Wilson, an HHMI investigator at the California Institute of Technology, has used her combined knowledge of organic chemistry and neuroscience to discover how a set of molecules—glycosaminoglycans, or GAGs—influences neuron growth. GAGs are long strings of carbohydrates that attach to proteins and influence their behaviors.

Each of the dozens of types of GAGs has a different function. At a molecular level, their distinction lies in the sulfate clusters—groups of sulfur atoms—that decorate the carbohydrate strings. For biologists trying to study each molecule's effect on the brain, the sulfate groups were frustratingly similar. There was no way to isolate only one type of GAG at a time. Moreover, biologists couldn't use genetics to study the sulfate clusters because DNA doesn't directly encode carbohydrates. And blocking the addition of all the sulfates at once caused such chaos that it was hard to tell what was what.

"And so here's where my chemistry background became very important," says Hsieh-Wilson. "We needed to be able to synthesize and study the different GAGs one at a time. So, we used organic chemistry to design and synthesize these very complex molecules from the ground up."

Hsieh-Wilson's group synthesized different GAG molecules and devised ways to block each one individually. Then, they added the synthetic molecules to cells to study the effect of specific sulfate clusters. By experimenting with blocking and unblocking different combinations of GAGs, the researchers began to decipher how the position of the sulfates offered molecular instructions, telling the GAGs what functions to perform in the cell.

"What I think is cool about being an organic chemist is that you can create molecules that are entirely new, that no one has ever dreamed of, or molecules that only exist in minute amounts in Nature," says Hsieh-Wilson. "And then you can use these molecules to discover something new and exciting about biology."

Although Hsieh-Wilson still has lots more to discover about GAGs, she's already found that the carbohydrates are involved in the growth and regeneration of nerve cells after injury. With this fundamental insight, she and her team are working to create a therapeutic approach to help treat spinal cord injuries.

Body Chemistry

Every organ in the human body functions through a constant interplay of chemicals. By modifying those chemicals—to block them, track them, or isolate them—chemists can add to the knowledge of how the body works.

Among the molecules constantly moving within cells is a large group of signaling molecules called protein kinases. There are more than 500 of them—and, like GAGs in the brain, they have widely varying functions but very similar chemical structures.

Schreiber: Jared Leeds Hsieh-Wilson: Darcy Hemley

Stuart Schreiber and Linda Hsieh-Wilson create new molecules to test pathways and circuits and, if they're lucky, discover exciting new things about biology.

To figure out which kinases do what, HHMI investigator Kevan Shokat developed a strategy similar to Hsieh-Wilson's approach to looking at GAGs.

Protein kinases work by binding ATP—a cellular source of energy—and then using it to add phosphates to proteins, a modification that changes the function of those proteins. Biologists know how to block kinases from binding to ATP, which shuts the enzymes down. But the action shuts down many different types of protein kinases in a cell at once.

"After six months of scrambling my brain on how I could tackle this problem through chemistry, I realized that I could chemically engineer the ATP pocket of one kinase at a time so that enzyme could be blocked specifically," says Shokat, at the University of California, San Francisco. First, the genes for kinases are removed from a human cell grown in a lab dish. Then, the newly engineered kinases can be added.

His method paid off: labs using his technique have discovered the function of more than 70 kinases. His own lab is now focusing on the role of some of these kinases in cancer development.

"I call the whole thing 'chemical genetics,'" says Shokat, "because neither chemistry nor genetics could have solved this problem on its own. You take the best of both worlds."

The combination of chemistry and genetics is one that other scientists have joined forces to explore. HHMI investigator Gerald Crabtree, a developmental biologist at the Stanford University School of Medicine, frequently collaborates with Stuart Schreiber, a chemist and HHMI investigator at Harvard University and the Broad Institute. Crabtree studies how signals from other cells or the surrounding environment are transmitted into a cell, eventually leading to changes in gene expression. Schreiber, with his organic chemistry training, can build molecules that block these signals at any step along the way.

Their first collaboration, in the 1990s, showed how an immunosuppressant drug blocks immune cell functioning. Schreiber altered different parts of the immunosuppressant at a time. After each chemical alteration, Crabtree tested whether the drug still blocked immune function.

"That collaboration allowed us to say which regions of the molecule were essential and to accurately order each of the steps of the pathway," says Crabtree.

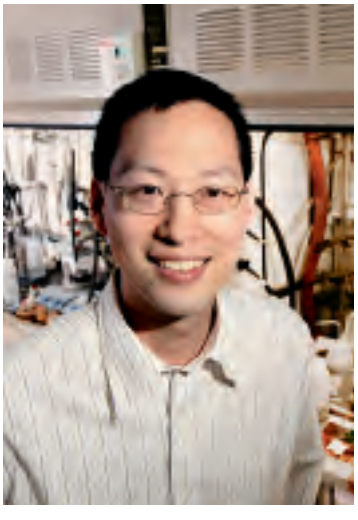
Despite being on opposite coasts of the country, the two continue to use small molecules designed by Schreiber to block chemical reactions within the cell. "Sometimes I'll have a question about how a biological process works, and I'll ask him how we can study this chemically," says Crabtree. "Other times he'll be interested in a particular molecule he's made and approach me about studying what it does in the cell. Such molecules allow biologists to order and test biological pathways and circuits. They also provide verification for mathematical models of how things work, an essential aspect of modern biology."

Schreiber is seeing more scientists embarking on this kind of collaboration. He says that now is a defining time in the intersection of chemistry and biology. He compares it, in fact, with the aftermath of Sputnik and the challenge by President Kennedy to send a spaceship to the moon.

"Kennedy didn't propose that a group of very smart physicists come together to calculate the thrust required of a rocket to escape our atmosphere. He brought many types of scientists—physicists, engineers, mathematicians, even biologists—together. And he didn't just have them calculate what would be needed to build a rocket. He had them actually do it. Fly a rocket to the moon."

Biology without chemistry, Schreiber says, is like "hypothesizing without testing things." Together, biologists and chemists might not be able to fly a rocket to the moon, but they can test biological hypotheses—and *do* things—using compounds created by chemists.

"The marriage of biology and chemistry has never been more important than today," he says. "We are in a position to use small molecules to test emerging concepts in human disease in physiologically relevant settings."



Chemists Chris Chang and Wilfred van der Donk say biologists and chemists have begun to understand what each can bring to the table to explore how the body works and to synthesize more efficient and cheaper drugs.

Learning from Biology

There are biological mysteries that chemistry can help solve, *and* there are also chemical phenomena that the biological world can help explain. The ultimate goal of the field of chemistry historically has been to be able to synthesize any molecule in the most efficient way possible. And Nature often is the best teacher when it comes to efficiency. The ways that cells produce chemicals—whether they're hormones, defensive molecules, or signals between cells—have been culled by billions of years of evolution.

"Natural enzymes are generally really efficient and good at their jobs," says Wilfred van der Donk, an HHMI investigator at the University of Illinois at Urbana–Champaign. Van der Donk, a chemist by

Chang: Noah Berger / AP, ©HHMI van der Donk: Darell Hoemann / AP, ©HHMI

"The marriage of biology and chemistry has never been more important than today." STUART SCHREIBER

training, takes apart reactions that occur in the natural world to learn how chemists can carry out the same reactions more efficiently in the lab.

Microbial cells naturally produce all sorts of antibiotics and antifungal chemicals, for example. His lab hopes to distinguish how cells do it and figure out which of these products have potential as human drugs. In a paper published July 19, 2011, in *Journal of the American Chemical Society*, van der Donk pieced apart how cells make one antibiotic that's currently in clinical development against cystic fibrosis. Understanding how the cell makes the chemical could help him design related molecules that also fight cystic fibrosis.

And then there's cellular chemistry that's like nothing chemists can do in the lab. He wants to understand that too.

"There are enzymes that do reactions where, as a chemist, you look at it and scratch your head and say 'How can we do that?'"

Van der Donk cites one example that's already made a difference. Many enzymes—proteins that carry out chemical reactions—do their job by breaking a few bonds and creating a few others. Energy is transferred from bond to bond to rearrange a compound. This means that to build a large compound from raw elements—either inside a cell or by industrial chemists in a lab—many chemical reactions are often needed. Each reaction shifts a few bonds, gradually building the desired molecule.

But some enzymes in cells are more efficient, carrying out many bond rearrangements at once. Chemists have used these enzymes as inspiration to design enzymes for industry. "This can make drug synthesis, or material synthesis, more efficient and cheaper," says van der Donk.

And sometimes it's not learning directly from cells but being inspired by a biological problem that drives chemistry forward. Schreiber calls it "next-generation synthesis." It's the idea that chemists faced with a difficult biological problem sometimes have to create new chemical methods to solve it. Schreiber, for example, developed a way to generate compounds with the ability to modulate biological processes not otherwise possible. His method, called diversity-oriented synthesis, allows scientists to discover chemicals that target, for example, proteins that cause human disease.

"In the same way that next-generation sequencing is transforming genetics, next-generation synthesis is transforming molecular biology," says Schreiber.

Learning to Cross Boundaries

While some chemists dive into postdocs or other training opportunities focused on biology to help round out their own lab's work, others stay specialized in chemistry and collaborate with biologists. Neither path is easy. But with the right navigation, both routes can lead to success.

For those who want to collaborate, the key is understanding what each field has to offer. Carolyn Bertozzi, an HHMI investigator at University of California, Berkeley, believes that biologists and chemists have different motivations. Bertozzi, whose lab has used chemical methods to track sugars within cells, has mentored both biology and chemistry students (see Perspectives & Opinions, "Changed Expectations").

"Biologists are very problem oriented," she says. "They often get frustrated if they can't solve the problem they want to solve. But chemists like developing new technologies, even if it doesn't get to the heart of a problem. It's still a success if it works." As a mentor, Bertozzi tries to help biology students see that their work can be successful as long as it leads to a discovery. For chemistry students, she pushes them to take greater responsibility when tackling an applied problem. "I want them to think about what biological questions cannot be answered using current methods and to focus their creative energies on technologies that really address that need," she says.

These days, even a chemistry student who wants to stay focused on chemistry often works in a biology lab to get a feel for how to work with biologists, according to Schreiber. "You'll join a project where next to you, elbow to elbow, may be a developmental biologist trying to differentiate a cell, and on the other side is a computer scientist trying to convert data to knowledge," he adds.

This won't necessarily teach chemists everything about developmental biology, or everything about computer science, but it will teach them how to work with those scientists. "The chemist simply needs to know what those fields are capable of achieving," says Schreiber, "and how it connects back to their own skill set and discipline."

Crabtree's biology lab frequently hosts chemistry postdocs. "Occasionally these students do actual chemical synthesis," says Crabtree. "But mostly they're there to learn biology. And I always hope they come away with an appreciation for what happens when you bring together the tremendous power of genetics with the tremendous power of chemistry."

Biologists too, are gaining an appreciation for how chemistry can help them, says Crabtree. "When you begin with a biological process that you want to understand," he says. "One of the first questions you can now ask is, 'Is there a chemical that prevents this process?' And if not, 'Can it be synthesized?'" Such a question

(continued on page 48)

CALLING *all* TEACHERS

Everyone agrees that the U.S. needs to train a new generation of inspiring science teachers. *But how?*

by Dan Ferber | *illustration by* Sanna Mander


#1
TEACHER

PART 1 OF 2: THIS ARTICLE FOCUSES ON PRESERVICE TRAINING—TRAINING COLLEGE STUDENTS AND GRADUATES TO BE STEM TEACHERS. PART 2 OF THE SERIES, ON TRAINING TEACHERS ONCE THEY'RE IN THE CLASSROOM—IN-SERVICE TRAINING—IS COMING IN FEBRUARY 2012.

Lauren Miller planned to teach high school biology as well as health and nutrition. She knew that having hands-on research experience would boost her resume. So the 21-year-old secondary education major at Western Michigan University (WMU) signed up to work in a biology laboratory. To be honest, Miller says, she was not looking forward to it.

"I came in thinking research was antisocial and I'd be sitting at a lab table by myself," she says. She expected a long, lonely 10 weeks.

But Miller got caught up in her summer research project, part of the university's HHMI-funded program to give science teachers-in-training, also called preservice teachers, some real-life research experience. Often working alongside her advisor, WMU biologist Chris Pearl, she prepared and stained slices of paraffin-embedded mouse testes to measure levels of a key estrogen-producing enzyme in normal and obese mice. And she learned a lot more.

"I found there's a lot of collaboration. You're going to conferences and talking to people in the lab next door. The people in your lab are very willing to help with anything," Miller says. "Now that I have a glimpse of what research is, I'm eager to show students that it's fun to do."

Innovative teacher-training efforts like Western Michigan's could be one solution to what experts consider a national crisis in science and mathematics education. In a 2009 study by the Organisation for Economic Co-operation and Development, for example, American students ranked 17th of 34 developed and emerging countries in science literacy, and 25th in math literacy. To bring U.S. students up to the top of the pack in science achievement and "enable our students to compete in the 21st century economy," President Barack Obama has called for 100,000 new high-quality STEM (science, technology, engineering, and math) teachers in the coming decade.

Education experts agree. Some schools succeed at teaching science and math, but too many of the nation's science teachers know too little about their subject, about effective teaching methods, or both, says Deb Felix, the senior program officer for HHMI's precollege science education initiatives. To be a great science teacher, she says, "You've got to know science and you've got to know effective teaching methods."

Science and math teaching methods and standards are undergoing a major overhaul to include more "inquiry-based" learning, in which students apply scientific thinking and experimentation to solve actual science problems (see Web extra sidebar, "A 21st Century Cookbook").

Educators are still figuring out how to train teachers to teach science and math this way. There's no one-size-fits-all approach to recruit teachers and get them up to speed on the latest science and pedagogy. So, funders of teacher-training programs—including HHMI, the largest private funder of science education in the nation—are experimenting. The particulars vary, but the goal remains the same: to train and put in place the talented science and math teachers that the nation desperately needs.

To ensure future teachers have the training they require to be comfortable and effective teaching science, HHMI is encouraging undergraduate institutions to focus on ways to promote high-quality science teacher training, says David Asai, director of HHMI's precollege and undergraduate programs. "Just as good pre-med programs provide a framework in which the student can demonstrate the competencies required for success in medicine," he says, "so too should science teacher training engage the undergraduate in intentional professional development."

Luring the Talent

In the midst of a national shortage of qualified science and math teachers, school districts don't always have the luxury of worrying about educational fine points. Sometimes they have slots that need to be filled now. To recruit good science and math teachers, school districts have offered signing bonuses, housing assistance, and tuition reimbursement. Policy makers have forgiven loans

and created initiatives to lure science and math teachers to districts that need them, especially high-need urban and rural school districts, where students are poor, academically struggling, or both, and teachers don't stay long.

A large supplier of STEM teachers nationwide is Teach For America (TFA). Education's version of the Peace Corps, TFA takes recent graduates of elite colleges, puts them through a five-week boot camp on how to teach, and places them in high-need districts for two years. During the 2010–11 school year, TFA's corps included 2,980 middle- and high school STEM teachers. And more than 2,300 of the organization's current corps of 9,300 teachers teach elementary school, which includes at least some science and math instruction, according to an overview of TFA's STEM initiative provided by spokesperson Carrie James.

TFA relies on selectivity to provide good teachers: the 2011 corps of teachers had an average undergraduate GPA of 3.6, and only 2,980 of 16,850 STEM applicants were accepted. But critics argue that their training is too short. Julian Vasquez Heilig of the University of Texas at Austin and Su Jin Jez of California State University, Sacramento, reviewed 11 outside studies on TFA and concluded that TFA teachers taught their students reading and math as well as or better than other uncertified beginning teachers but not as well as fully credentialed beginning teachers. The TFA teachers, like others, got better with experience. But after three years, 80 percent of them had left teaching. That's about twice the attrition rate of conventionally trained teachers, the authors wrote in a 2010 report from the Education and the Public Interest Center at University of Colorado and the Education Policy Research Unit at Arizona State University. To be fair, however, TFA teachers agree to teach for two years, and TFA's own research shows that 61 percent of its corps continues to teach the year after the two-year commitment ends.

Heightened teacher turnover does not serve students, says Francis Eberle, executive director of the National Science Teachers Association. "It generally takes several years for a person to get good at teaching. So students who keep getting new teachers are really disadvantaged."

The Noyce Scholarship Program at the National Science Foundation (NSF) takes a different approach. NSF provides funds for scholarships, stipends, and teacher training at colleges and universities that prepare undergraduate STEM majors and STEM professionals to teach. In exchange for each year of NSF support, Noyce recipients commit to teach two years (and receive a $10,000 salary supplement for each year) in a high-need school—one with high poverty, high teacher turnover, or many teachers teaching outside their field. As of fall 2010, Noyce had produced 4,148 new K–12 science or math teachers.

Noyce scholars have all majored in a STEM discipline and taken upper-level science courses, including laboratory courses, and many have conducted independent research. This gives them "the confidence to teach, the excitement, and the passion for the discipline that you might not find in a teacher who's taken just one or two courses" in their subject, says NSF's Joan Prival, who administers the Noyce program.

A University of Minnesota team surveyed 555 Noyce scholarship recipients from 2002 to 2006 and found that their GPAs were high and the proportion of Noyce scholars who were minorities was higher (33 percent) than the proportion of minorities working as STEM teachers nationwide (up to 14 percent). And 22 percent of Noyce scholars take on a leadership role in their first few years at a school, serving as a department chair, for example, or sitting on a committee that develops a new curriculum.

"Programs like Noyce have done a tremendous job in helping raise the level of the teaching profession in the eyes of undergraduates," says John Keller, a planetary scientist and director of the Center for Excellence in Science and Mathematics Education at California Polytechnic State University in San Luis Obispo.

Other preservice initiatives reach out to students with proven science or mathematics chops and train them to teach. Prospective master's degree students at the HHMI-funded Center for Science and Mathematics Education (CESAME) at Stony Brook University in New York need a bachelor's degree in science with a B+ average. Quite a few are health professionals or scientists—including, in recent years, four dentists, a medical doctor, and a research scientist.

Brian Park

At Stony Brook University, David Bynum trains top-level science students to teach and requires that they spend lots of time observing and teaching in classrooms.

"Right at the beginning, if you attract talent, it makes a lot of the problems go away," says David Bynum, CESAME's director. "The best districts lap up our graduates. That to me is a very powerful indicator of success," he says. And almost a third of CESAME's graduates teach in high-need districts.

Some programs focus on attracting that talent young. UTeach, launched in 1997 at the University of Texas at Austin, offers freshman science majors their first two education courses for free—a significant recruitment tool in this age of rising tuitions. Students also save thousands of dollars by completing their science and education training in four years with a bachelor's degree that qualifies them for certification to teach secondary school science or math in Texas, rather than the usual five or more years to get a bachelor's in science and a master's in teaching. UTeach has graduated 675 teachers, and 82 percent of its graduate hires are still teaching after five years, compared with about 50 percent of all teachers nationally. A nonprofit group called the National Math and Science Initiative is replicating UTeach at 28 universities in 13 states. Altogether about 4,700 more teachers-in-training are enrolled at these sites, according to UTeach. Both the National Research Council and the President's Council of Advisors on Science and Technology, or PCAST, have recommended further expansion.

At the new HHMI-funded program at Pennsylvania State University, molecular cell biologist Richard Cyr and his colleagues bring working teachers and education professors into freshman seminars to talk about teaching as a career and help interested students plan their coursework. They encourage academically successful biology majors to mentor their peers, watching them for traits like leadership, perseverance, and patience that predict a successful teaching career, Cyr says. Promising students are invited to help a graduate teaching assistant instruct a laboratory section of an undergraduate biology class; if they perform well, they are offered jobs as teaching assistants.

Many of the strongest programs, including UTeach, get undergraduates teaching early, which tends to get them hooked. Kristyn Moloney, a master's student at Penn State, says that after running an introductory biology laboratory section as a junior, she knew science teaching was for her. Year-end course evaluations from her students showed her how she had helped them. "That's what set it in stone for me, that this is what makes me happy," she says.

Back to Basics

When students go out to teach, they need up-to-date knowledge of their discipline. So even though the prospective science and math teachers enter the Stony Brook program with at least a bachelor's degree, half of their courses are still in their STEM discipline, be it mathematics, biology, chemistry, physics, or geology, Bynum says. And the science-trained Noyce scholars and UTeach students have the grounding they need to teach STEM classes.

But most science and math teachers still come through education schools, and their knowledge of the discipline they are teaching may be outdated or sketchy, especially in the lower and middle grades. For example, a Department of Education survey in 1999–2000 found that 29 percent of middle-school biology teachers and 41 percent of physical science teachers were not certified to teach their subject and did not major or even minor in it as an undergraduate. Certification requirements have tightened since then in many states, but the problem remains.

Maxine Singer, board president and founder of the Washington, D.C., branch of Math For America, a nonprofit dedicated to improving K–12 math education, recalls leading a training session for in-service elementary teachers at the Carnegie Institution for Science, where she is president emerita. According to Singer, many struggled when converting all but the most basic fractions and decimals. Jeff Nordine, assistant professor of science education at Trinity University, had a similarly disheartening experience meeting with some in-service elementary school teachers. "It was news to them that water expands when it freezes," he says. "I don't remember not knowing that."

Many future elementary school teachers are education majors who have taken a minimum of science during their undergraduate years, Nordine says. "They are uncomfortable with science, they don't like it, and they feel dumb. Then they have to teach it to students." Not surprisingly, the students lose interest in the subject.

THE CHALLENGE

TOTAL K–12 TEACHERS IN THE U.S.:

3.6 MILLION

TOTAL WHO ARE STEM TEACHERS:

477,000

ESTIMATED STEM TEACHERS WHO LEAVE PROFESSION EACH YEAR:

25,000

TOTAL NEW STEM TEACHERS REQUESTED BY PRESIDENT OBAMA:

100,000 in 10 YEARS

SOURCES:

National Center for Education Statistics (*nces.ed.gov/fastfacts/display.asp?id=28*)

President's Council of Advisors on Science and Technology, September 2010 (*www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-stemed-report.pdf*)

At Western Michigan University, Susan Stapleton (right) and colleagues require science teacher trainees to do a 10-week research project. The experience convinced Lauren Miller (left) that research is fun—enthusiasm she'll share with future students.

Lauren Miller: Peter Baker Susan Stapleton: Peter Baker

Learning by Doing

When Nordine teaches elementary science education to future teachers, he tells them, "Listen, it's OK to not know the answer; that's what science is all about." He helps them learn scientific content, as well as where to find journals and other science-teaching resources, from the National Science Teachers Association and elsewhere that can help them on the job.

Even more important, Nordine and other leading science educators also show future teachers how to create inquiry-based science units, in which students learn by solving real-world problems. For example, some preservice teachers in his elementary science education class have created a unit in which kids learn about density and buoyancy by investigating whether heavy objects sink and light objects float.

Such lessons build on two decades of work by cognitive scientists and education researchers on how students learn. In a landmark 1998 study, for example, Barbara White of the University of California, Berkeley, and John Frederiksen, now at the University of Washington, had students at an urban middle school learn physics by doing it—by formulating a question, generating predictions, carrying out and analyzing experiments, and checking the results with scientific models. Compared with grade 11 and 12 physics students who memorized facts and plugged through algebraic formulas, the middle school students learned more physics (averaging 68 percent on a short test of physics comprehension, versus 50 percent for the high school students) and were better at thinking scientifically. Researchers have since honed their understanding of inquiry-based learning by determining which types of classroom exercises promote real inquiry and which don't, says K. Ann Renninger, an HHMI-funded educator and education researcher at Swarthmore College.

Teachers can help students learn science by doing it, if the teachers have done the same. "Folks who want to teach need to know what it means to ask a good scientific question, to design experiments to answer it, and to interpret the results," says Susan Stapleton, a biochemist who helps run the HHMI-funded preservice program at Western Michigan University. WMU is the sixth largest U.S. preservice teacher training school. Most of its students go the traditional route: they major in education, including a slew of pedagogy courses, and minor in their teaching specialty (WMU produced 463 preservice teachers in 2010; 91 were science and math teachers).

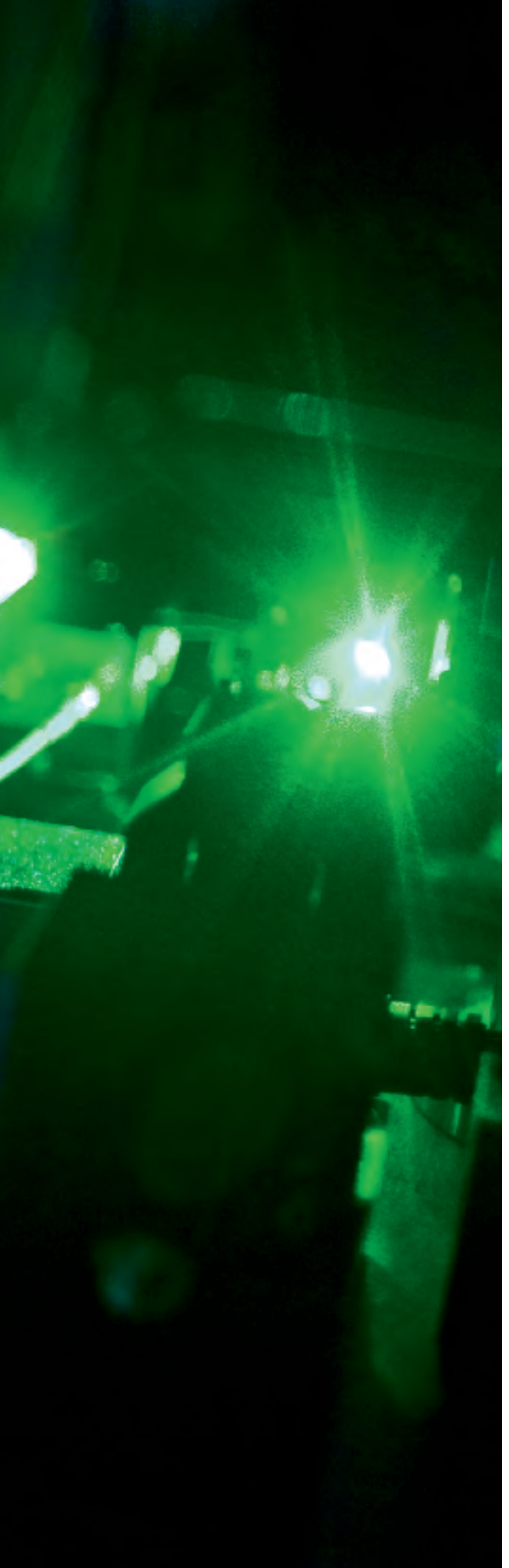
That's why she and one of the program's codirectors, science education professor Renee Schwartz, require science teachers-in-training like Lauren Miller to do a 10-week summer research project. But that's just part of the program. "It's one thing to give them research experience. It's another to translate that into teachable units they can take into the classroom," Stapleton says. So she and Schwartz will teach a class for preservice science teachers next spring on how to turn their research experiences into inquiry-based laboratory exercises. The trainees will then teach the exercises they've created to middle school students during a two-week science camp the following summer.

Giving preservice teachers tools like this helps them once they're on the job. Laura Gurick, a 2010 CESAME graduate of Stony Brook University, drew on her training last year for the 10th-grade chemistry class she taught at Herricks High School in New Hyde Park, New York. She could have taught paper chromatography, a method to separate and analyze component chemicals from a mixture, using a conventional laboratory in which the students were told exactly what to do. Instead she drew on a workshop she'd taken at Stony Brook on how to turn a conventional laboratory into one that's inquiry based.

Gurick told her students that there had been a kidnapping, that one of them was the kidnapper, and that a ransom note and a pen had been found at the scene of the crime. Several students

(continued on page 48)


CUBE



HAVE MICROSCOPE, WILL TRAVEL

Biology students and faculty immersed in summer courses at Woods Hole get their hands on a remarkably powerful imaging tool developed at Janelia Farm.

By Jennifer Michalowski
Photography by Jared Leeds

Bi-Chang Chen spent the fifth day of his postdoctoral fellowship in a rented van headed for Cape Cod. He'd barely had time to unpack in Virginia before he was enlisted to help take apart the very microscope he had come to Janelia Farm to work on. Its lenses, mirrors, lasers, and other components were now fastidiously packed and stowed in the back of the van, traveling north on I-95. Chen was about to undergo what his new boss, Janelia Farm group leader Eric Betzig, was calling "trial by fire."

Chen and his new colleague, Liang Gao, were transporting the Betzig lab's newest technology to the Marine Biological Laboratory (MBL) in Woods Hole, Massachusetts—a seaside hub of scientific activity with an educational program that draws hundreds of students and faculty from around the world each summer. It would take a full day to reassemble its components into what the Betzig group calls a Bessel beam plane illumination microscope—a high-speed, high-resolution, three-dimensional imaging technology that gives extraordinarily detailed views of cellular processes in action.

The plan was for Gao and Thomas Planchon—developers of the new microscope—to guide MBL students and faculty through the imaging process as they examined their specimens. Chen would have to learn quickly how to operate the microscope, because the team expected a steady stream of users, all demanding expert attention. In exchange, the Betzig team hoped to learn exactly what biologists need their microscope to do.

The Bessel beam plane illumination microscope, or "Bessel sheet," was a work in progress. Betzig's team had designed it to answer an obvious need of biologists—the ability to visually track movement of the tiniest structures inside living cells. In March 2011, they had described the new technology online in *Nature Methods*, including as evidence of its power startlingly vivid portrayals of chromosomes sorting themselves in preparation for cell division and a lively cell surface sending out long, thin projections that quickly retract and reappear elsewhere.

The short movies had generated considerable excitement among biologists: there was no doubt that the new microscope surpassed existing technologies in rapidly creating high-resolution, three-dimensional images without damaging living cells. But for Betzig's team, this acclaim was not the ultimate goal. "We're not developing technology for technology's sake," he says. "We want to create technologies that will have a broad and deep impact on biomedical research."

Maximizing the microscope's impact had been foremost in Betzig's mind from its earliest development. A physicist and engineer by training, Betzig listens carefully to biologists, and their top priorities have not changed since he began developing imaging technologies more than 30 years ago. Biologists want to see smaller structures. They want to see them with more detail, with more speed, and deeper inside a tissue. And they want to see them in healthy, living cells that are unperturbed by the tool they are using.

Betzig and his team had created the Bessel sheet microscope to answer those demands, and after three years of development, they were convinced the instrument could offer researchers unprecedented views of dynamic subcellular processes. But many of the biologists at Janelia Farm are neuroscientists interested in understanding how neurons work together in complete circuits in the brains of fruit flies or mice, and, Betzig says, Bessel beam technology is not ideal for the size and thickness of the samples they want to image. "Our mandate is to develop new imaging technologies for biology, not necessarily just for systems neuroscience. So if we want to find users for these techniques, we have to look outside."

Word was beginning to spread about the power of the Bessel sheet, but the cultural divide between microscopists and biologists still frustrated the Betzig team. "It takes a surprisingly long time to get new microscopes to biologists," Gao says. "So we decided to take our latest microscope to Woods Hole to introduce it to them."

RAPID-FIRE DAYS

The Marine Biological Laboratory is situated on a narrow, salt-swept piece of land in the far southwest corner of Cape Cod. Tourists unload bikes at the nearby ferry landing; fried clams, homemade ice cream, and other indulgences of a beach vacation are in ready supply. The tiny village of Woods Hole wakes up earlier than the usual beach town, however, and working scientists vastly outnumber vacationers.

Hundreds of scientists flock to Woods Hole in summer to immerse themselves in MBL's unique culture for a few weeks or months. Distanced from routine distractions, most visitors find the MBL experience gratifyingly intense. Between coursework, research, and discussions and debates, time in the lab routinely stretches until 2:00 a.m., for students and faculty alike. "We're not there to go to the beach," Gao stresses. "There's a vacationy feel here; it's nice outside," says Betzig, who set aside two weeks during June and July to work with Bessel sheet users at MBL. "But you're only here a short time, and everyone works really long days."

So when Chen, Gao, and their microscope parts reached Woods Hole at the end of June, they wasted no time. They were greeted by Jim and Cathy Galbraith, a husband and wife team who have taught in the neurobiology course for seven years, and a small crew ready to help maneuver an 800-pound optical table, on loan from Thorlabs, into a tiny, windowless room in the basement microscope facility. The top of the table went

in first, suspended on a scissor lift until its vibration-eliminating supports were positioned underneath. From there, the team followed Gao's lead. Modular segments of the microscope were unwrapped and bolted to threaded holes in the tabletop. A tower of electronic equipment—the control panel—was erected in the cramped room's remaining space. Cables were connected; alignment measured; blue, green, violet, and infrared lasers tested.

Gao knew what he was doing: he'd built this version of the microscope—a second-generation version, more compact and portable than the original built by Planchon at Janelia. And last summer, he and Planchon had accompanied the Bessel sheet on its first trip to Woods Hole, when it was so new Betzig was calling it "bleeding-edge." That visit had been grueling: two weeks of 18-hour days, imaging the very first living cells to be viewed with the microscope, save one quick run-through back at Janelia Farm with the Galbraiths. But the benefits were enormous. During the rapid-fire days, the team tested a panoply of samples and introduced the microscope to a range of users. The Bessel sheet's early successes at Woods Hole became the vivid movies the team published in its *Nature Methods* paper, which is coauthored by the Galbraiths, whose own labs are at the National Institutes of Health (NIH). And throughout the following year, the Betzig lab hosted collaborators at Janelia Farm to advance projects initiated during those fervent weeks.

So when Betzig suggested they repeat the experience this past summer, Gao's first thought was the challenge of transferring the delicate equipment to its temporary home. "It's almost like starting a new lab," he says. But he knew it would be worth the long drive and the long days that would follow, particularly if they extended their stay to work with a wider group of biologists.

They chose a four-week period during which their microscope could be integrated into two courses. Gao and Planchon made plans to helm the microscope in two-week shifts, while Chen would stay the entire four weeks to learn the intricacies of the Bessel sheet and become familiar with the language of its users. Betzig would join the team for the weeks in the middle.

During the first two weeks, the Bessel sheet would help physiology students working with Jennifer Lippincott-Schwartz from the NIH watch cells migrate or break down their unwanted parts; in the second half of the microscope's stay, neurobiology students working with the Galbraiths could use it to visualize the processes that drive nerve cell function. Spare moments

Jared Leeds

In what Eric Betzig calls a "trial by fire," postdoc Bi-Chang Chen spent a month at Woods Hole this summer, familiarizing himself with the Bessel sheet microscope while helping students and faculty analyze their samples.

would be tightly scheduled with MBL faculty curious to see what the Bessel sheet might reveal about their own samples.

THE PHOTON BUDGET

The Bessel sheet was the newest imaging technology at Loeb Laboratory, MBL's educational hub, but it was not the only one. The basement and first-floor hallways were crowded with bulky crates emptied of sophisticated microscopes on loan for the summer. Course directors had collected commercial instruments for super-resolution imaging (including Zeiss's ELYRA, based on the concept of photo-activated localization microscopy, or PALM, invented by Betzig and Janelia Farm colleague Harald Hess), microscopes designed to peer deep into tissue, and high-resolution methods for three-dimensional imaging of fixed tissue to offer their students new perspectives on biological complexity.

According to Cathy Galbraith, the two-week imaging section of the neurobiology course is designed not just to expose students to cutting-edge technology, but also to help them understand which tools are best suited for particular questions, as well as how the technologies are complementary. Likewise, physiology students experience firsthand how each tool has its strengths—but none can do it all.

It quickly becomes apparent how the Bessel sheet fits into the imaging landscape. Like other fluorescence microscopes, the Bessel sheet detects fluorescently tagged molecules within cells, letting biologists follow specific proteins and watch them interact with one another. The basic technique relies on fluorescent tags that absorb light—typically directed at a sample in a focused laser beam—and rerelease the energy as fluorescence, which the microscope captures to create an image. Up to a point, brighter fluorescence contributes to a clearer image, but there is a trade-off. Too much light exposure can make a cell sick, so living samples don't survive long under the laser's glare. What's more, light destroys fluorophores' ability to fluoresce, meaning even dead cells can be imaged only a brief time before their signal begins to fade. So, fluorescence microscopy often ends up being an exercise in compromise.

Capturing fluorescence becomes increasingly crucial as new technologies push the limits of both spatial resolution and speed. Higher-resolution microscopes must extract information faster, more frequently, and from ever-shrinking segments of a sample. Ideally, a microscope would glean information from each photon of fluorescence a sample emits. In practice, however, plenty of photons bounce off an illuminated sample and are lost forever.

Betzig and his team designed their new microscope to take better advantage of what they call the "photon budget." Most microscopes illuminate a sample from the same objective lens that collects light, directing a beam all the way through the sample even though only a single plane is in focus at a time. At high-resolution, where every photon counts, this is a problem because light in out-of-focus regions activates fluorescence and damages cells, with no imaging payoff.

An alternative is to direct a sheet of light through the side of a sample, via a lens that lies perpendicular to the objective that collects the returned light. This approach confines the excitation much closer to the portion of the sample in focus. It's an old idea—first proposed more than 100 years ago—that has recently been adapted to high-speed imaging of multicellular organisms. Ernst Stelzer, who was at the European Molecular Biology Laboratory in Heidelberg, Germany, and is now at the Frankfort Institute for Molecular Life Sciences, resurrected the technique, Betzig says, taking advantage of the reduction in light damage to image living samples repeatedly over prolonged periods.

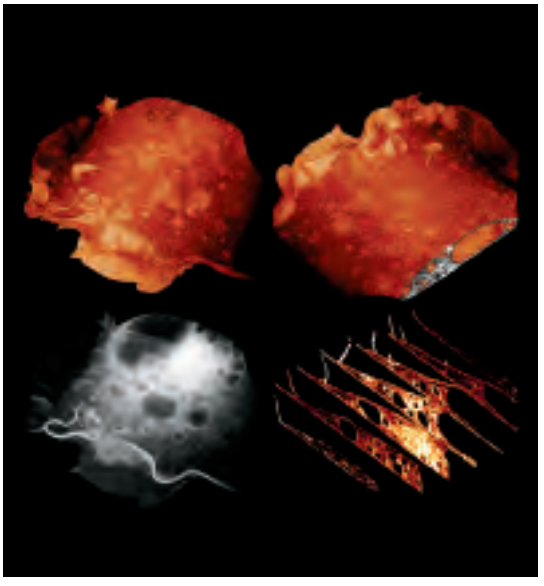
The thick sheets of light that have made Stelzer's technique a success, however, obscure the tiny structures inside cells—a problem that Betzig's team addressed with a Bessel beam. At its core, a Bessel beam is an extremely narrow beam of light that can be swept across a sample to create a thin sheet well suited for imaging subcellular structures. The Bessel's central beam is surrounded by concentric rings of weaker light, however, which cause the same problems as any unwanted light sources do. So Betzig, Planchon, and Gao devised a few tricks to minimize the contaminating light. Rather than sweeping the beam continuously, they pulse the beam rapidly to eliminate out-of-focus blur—a technique also used in super-resolution microscopy called structured illumination. They combined this pulsing with two-photon microscopy, a method in which weakly exposed regions generate very little fluorescence. Together, these tricks add up to a microscope that collects unusually detailed images without damaging living cells.

3-D CLARITY

Gao, Planchon, and Chen help students mount their samples so they can receive the sheet of light created by the Bessel beam at the appropriate angle, then tweak the microscope's parameters to accommodate variations in thickness, brightness, or background fluorescence. The Bessel beam sweeps quickly through each sample, collecting up to 200 images per second. As the microscope's computer compiles the two-dimensional images into three-dimensional stacks and the first pictures begin to appear on the monitor, what is astonishing is the extraordinary detail apparent in all three dimensions.

Clare Waterman, director of the MBL physiology course, says she was blown away when she saw the Bessel sheet's first images of her students' cells. "I've been looking at light microscopy images and 3-D reconstructions for 20 years," she says. "When you rotate a 3-D reconstruction, you always know what the z-axis is." That is, even when a microscope produces crisp, detailed images in two dimensions, resolution almost always declines significantly in the third dimension. But the Bessel sheet images were different. "I could not tell what the z-axis was," Waterman says. The cellular detail was clear from any angle.

The three-dimensional movies of migrating cells, which were grown in a collagen gel so they could move freely in any direction, settled for Waterman what she says had been an unresolved debate in her field. Waterman studies cell motility at the National Heart, Lung, and Blood Institute, and lately, she says, there's been a big push to find out whether structures thus far observed only in cells squashed flat between a microscope slide and a coverslip are



LEFT: *Interacting with biologists helps Eric Betzig (right) and Thomas Planchon improve design of their microscopes.* RIGHT: *Three-dimensional imaging of live cells by the Bessel sheet microscope reveals remarkable detail, such as a cell's ruffled edges and internal vacuoles.*

physiologically relevant. But, she acknowledges, "There's been a reason we've been doing stuff on a coverslip for so long: because that's where optics are good." Technologies that image in three dimensions lack the spatial resolution to determine, for example, whether migrating cells truly project the long, flat extensions thought to propel their motion. "Well, we could certainly see two-dimensional, flat lamellipods with this [Bessel sheet] system that we could measure the thickness of, in every dimension."

"It wasn't like I was pining away for this," Waterman says. "I had accepted the limits of optical microscopy and I'd learned to interpret my data within those limits." But once she saw what was possible, she says, "I was doing backflips for a week."

WATCHING EMBRYOS DEVELOP

The Bessel sheet gets little rest at Woods Hole. A grid on the wall blocks out time for faculty who want to squeeze into gaps between student projects, but unexpected visitors stream in at all hours. University of California, San Diego, developmental biologist Andrew Chisholm, who visits MBL as faculty in the neurobiology course, says so many people were in and out of the tiny room that the rising temperature sickened the *C. elegans* roundworm embryos whose developing skin he wanted to image. With the confocal microscopes Chisholm typically uses, he says, "you're constantly balancing imaging quality with viability of the embryos. With a conventional microscope you really have to settle for images that don't look very good." But since the Bessel sheet limits phototoxicity by using far less light, the dying worms were puzzling.

Chisholm and the Betzig team considered other factors, and discovered that if they imaged the developing embryos in the morning—after a few idle hours had let the room cool down—they had better success. Working with Planchon, Chisholm assembled a movie that shows skin cells forming, making junctions with one another, and then forming a sheet that spreads out to encase the growing embryo. Chisholm says the movie, which spans eight hours of early development, is "an order of magnitude better than what we can get away with using the last generation [of imaging technology]. It's just beautiful."

USER FEEDBACK

By the time the weary team of postdocs disassembles the microscope for the journey back to Virginia, they have imaged developing embryos, cells suspended in growth media, the nervous system of whole worms, cells embedded in collagen, dying cells, and dividing cells. Over the weeks, Chen says, they have taken every opportunity "to talk to biology people, to listen to what they are thinking. Because it's really, really different from us."

They have heard users' frustration about the microscope's unconventional sample holder, which requires a fussy assembly process to secure the sample in a vertical position—practical from an engineering perspective, but cumbersome for users. They know they need to adapt their optics to handle thicker samples, which introduce aberrations in the imaging process. And there is an unrelenting desire, biologists have told them, for even better spatial resolution, at even faster speeds.

None of these requests are a surprise, the microscopists agree. And they are prepared to address them. The group plans to build a third version of the Bessel sheet, so they can continue to tweak the instrument and test out improvements while the original setups collect data. Chen will begin work immediately to add additional Bessel beams to the microscope, which he says will increase imaging speed while reducing phototoxicity. A new postdoc in the Betzig lab, Kai Wang, will introduce adaptive optics into the system, and research scientist Lin Shao, who introduced the current methods of analyzing the data generated by the Bessel microscope, will continue to improve those algorithms. Thomas

(continued on page 48)

Betzig and Planchon: Jared Leeds Science image: Betzig lab

STAR SEARCH: COULD THE GREY MOUSE LEMUR BE THE NEXT BEST MODEL FOR HUMAN DISEASE?

BY ANDREA WIDENER

ILLUSTRATION BY PING ZHU

As he sat in a remote field station in Madagascar, surrounded by dense rainforests, Mark Krasnow realized that his journey halfway around the world was worth it. The handful of biologists gathered around him agreed that the mouse lemur could be the animal he was looking for.

The HHMI investigator from Stanford University School of Medicine was on a quest for a better animal model for human disease. The fruit flies and mice he'd been studying couldn't help him answer many basic research questions on lung diseases, and he knew that scientists studying other disorders had similar experiences. He wanted to find a better disease model.

After a year of research into species worldwide, Krasnow had brought an unlikely team of high school students, molecular biologists, mouse lemur experts, and a veterinarian to the East African country to search for an animal that might be a closer match to people than mice, the perennial lab favorite. Madagascar's early separation from the continental land masses, some 80–90 million years ago, created an evolutionarily eccentric collection of plants and animals, including lemurs. "It's like a biologist's dreamland," says team member Sarah Zohdy, a doctoral student at the University of Helsinki and one of a small number of scientists studying mouse lemurs.

The group spent several nights in the summer of 2010 scanning the tall trees for all types of lemurs, but they were most interested in the grey mouse lemur, *Microcebus murinus* (see Web extra, "Meet *Microcebus murinus*"). The big-eyed, bug-eating lemur from Madagascar's west coast is one of the world's smallest primates. And, more importantly for Krasnow's group, mouse lemurs' DNA has diverged from humans only half as much as the DNA of mice.

At the field station, in Ranomafana National Park, Krasnow talked with Malagasy biologists about the potential of mouse lemurs as a model for human disease. "They had grown up with lemurs but had never thought about model organisms," Krasnow says. They loved the idea that mouse lemurs could help cure diseases, he says, but they were concerned that the lemurs—and the country—not be exploited in the process.

MOVING BEYOND THE MOUSE

During the past half century, biomedical research has focused on a handful of model organisms, as research communities have developed tools that make in-depth studies possible. The most widely used models include the mouse, the roundworm, the fruit fly, and, more recently, the zebrafish. For disease research, mice have been the focus; introducing genetic changes, scientists have made great leaps in understanding disease and basic biology (see Web extra, "Model Redefined").

But mice can't do it all. A 2008 analysis by University of Michigan scientists showed that in 40 percent of genetic defects known to cause human disease, researchers either do not see symptoms in mice or cannot identify an equivalent gene. "The mouse has revolutionized medical research, but it is necessarily limited by its biology," Krasnow says.

Physician-scientist Michael Welsh had been studying cystic fibrosis (CF) for many years when it became clear that the field needed a new way to understand the disease. In humans, the single gene mutation that causes CF induces problems throughout the body, especially the lungs and gastrointestinal system. In mice, the mutations fail to produce typical CF disease.

"To understand the pathogenesis of a human disease, a model can be critical. If the model does not reproduce features seen in human disease, making progress can be a challenge. And if you want to develop new therapies, and the model does not manifest those key defects, you have nothing to correct," explains Welsh, an HHMI investigator at the University of Iowa. "It was frustration and the lack of an ability to make sufficient progress that led us to develop another model of cystic fibrosis."

Welsh's team settled on the pig, and their new CF model develops disease like that of humans. "It is a very exciting time," Welsh says. "We are able to answer questions and approach persistent problems that have been plaguing the field."

Failure to replicate human disease isn't the only problem with mouse models of disease. "There have been some very expensive long-term clinical trials based on mouse models that just didn't turn out the way they did in mice," says immunologist Mark Davis, an HHMI investigator at Stanford University. "The real test of a model is whether there is any predictive ability, and I think there is often a disconnect between mouse data and human disease."

Davis says scientists should make a more systematic attempt to understand disease in people, which is the direction he has taken his own research. For many diseases, he says, "We don't know enough about the human disease to know whether it is a good model or not." But he is enthusiastic about Krasnow's attempt to identify a better model. "We should rationally choose other models that are closer to humans and therefore more likely to translate."

FROM IDEA TO MADAGASCAR

Krasnow's path to Madagascar began in 2009 when several Palo Alto High School sophomores—Camille Ezran, Jason Willick, Krasnow's daughter Maya, and, later, Alex Scholz—pestered him to work in his lab. After fending them off several times, he realized he could apply their growing knowledge of biology to the mouse model problem.

"We spent the entire summer trying to understand what would make a good model, since we had never been exposed to genetic model organisms before," Ezran says. It had to be small and easy

"FOR DECADES MADAGASCAR HAS BEEN SEEN AS A HOTSPOT FOR BIODIVERSITY, AND RIGHTLY SO."

Alison Richard

to work with. Its brain, lungs, and other organs had to resemble those in humans. It had to reproduce fairly quickly. And it had to be more closely related to humans than mice were. Spending weeks in the library and on the Internet, the students constructed a spreadsheet of the world's smallest mammals, which they then narrowed to a dozen to examine in more detail.

The mouse lemur rose to the top. The idea gained traction when Krasnow starting discussing it with other scientists and colleagues. "They agreed with the need for a new genetic model organism and embraced the idea of the mouse lemur," he says.

Next, Krasnow turned to Stanford veterinarian and geneticist Megan Albertelli. At first, she thought the idea was farfetched, but then she heard Krasnow describe the biological argument for the mouse lemur as a model organism. After the group learned that several European research centers had decades-old colonies of mouse lemurs, Krasnow decided his team needed to visit one to talk to the scientists.

The group went to Europe, where they saw their first live mouse lemurs at a 40-year-old colony housed on the grounds of a small castle. "That convinced me that this was something we could do," Albertelli recalls. What excited Krasnow was that the scientists had been keeping detailed records and tissue samples for the colony's history, including the animals' tendency to get an Alzheimer's-like disease.

Their next stop was Madagascar, and more research paths emerged as they talked to field biologists there. Those experts could help study genetic links to behavior, the team realized. "Social groupings, behavior, and behavioral diseases, have been very hard to study in mice," Krasnow explains. "Those studies are already being done in mouse lemurs."

The visit made clear to Krasnow that, to help local scientists and conservation efforts, as much research as possible should be done in Madagascar. "We would like more researchers coming to Madagascar," says Benjamin Andriamihaja of the island's Institute for the Conservation of Tropical Environments, "but at the same time we would like to protect our forest to maintain its value."

This newfound interest in mouse lemur research offers a great opportunity for training, says lemur biologist Alison Richard, an HHMI Trustee and professor at Yale University who has worked on the island for decades. "Much of the work establishing mouse lemurs as a model organism could involve Malagasy students," she says.

CREATING A COLLABORATIVE LANDSCAPE

On their return, Krasnow and his team started planning how to move ahead. In June 2011, Krasnow and Albertelli hosted the first ever mouse lemur meeting, at HHMI's Janelia Farm Research Campus, bringing together field biologists from Madagascar, Europe, and the United States with geneticists, conservation biologists, and model organism experts. "I had not had the opportunity to be in the same workshop with so many other types of researchers," says Anne Yoder, who runs the Duke Lemur Center at Duke University, a sanctuary that studies lemur behavior and conservation. "It was neat to see what the collaborative landscape might look like."

One outcome is that Krasnow's group and others have committed to studying mouse lemurs without sacrificing them, instead turning to genetics, imaging, and other noninvasive techniques honed through the study of other model organisms. "There are huge opportunities in bringing to bear today's research tools on existing samples from lab colonies and field studies, for the benefit of humans and lemurs alike," Krasnow says.

The biggest area for immediate impact is genetics and genomics. The June meeting spurred a renewed effort to complete the mouse lemur genome, says Jeff Rogers of the Baylor College of Medicine's Human Genome Sequencing Center. That could help researchers analyze the thousands of existing tissue samples for genetic connections to disease, including the Alzheimer's-like syndrome found in these animals, and help to identify what DNA sequences are highly conserved between mouse lemurs and humans.

"It is so beneficial for us to have a community of investigators focused on doing research on mouse lemurs," Rogers says. "The opportunity to combine years

(continued on page 48)

Mark Krasnow thinks learning about the genetics and physiology of the mouse lemur could help humans as well as preserve the endangered animals.

Krasnow: Ramin Rahimian

Carolyn Bertozzi

CHANGED EXPECTATIONS

CHEMISTS TRAINED IN BIOLOGY WERE ONCE A RARITY— NOW THEY'RE BECOMING THE NORM.

Ramin Rahimian

After Carolyn Bertozzi finished her Ph.D. in organic chemistry in 1993, she did something risky. She accepted a postdoctoral fellowship in a cell biology lab, not a chemistry lab. In the two decades since, chemists have embraced the value of studying biology by total immersion. Bertozzi, an HHMI investigator at the University of California, Berkeley, who uses chemical approaches to tackle biological problems, reflects on this shift.

What was it like in the 1990s for chemists who wanted to tackle biological problems?

A handful of us were in the same boat. We had been trained broadly to design chemical tools for use in biology but didn't know enough biology to identify the problems in urgent need of such tools. We were contemplating doing postdocs in biology labs to gain such insights. But many of us received negative feedback from senior professors. It was considered maverick to leave your field and pursue total immersion in another.

If we left our circle of familiarity and went off into a strange land, the "chemistry establishment" would lose track of us and we'd have a hard time securing jobs. One advisor even went so far as to use the phrase "career suicide."

You went for a biology postdoc anyway. Did their predictions come true?

Not at all. When I applied for faculty jobs in chemistry departments, I'm sure some people wondered how to judge my postdoctoral work. Contrary to the earlier warnings, people valued that I had spent time in a pure biology laboratory. I was hardly an expert, but relative to other bioorganic chemists, I was in a much better position to identify important biological problems that chemistry could uniquely address.

Is it easier today for chemists to follow the path you took?

It wasn't too much later that it became fashionable for chemistry Ph.D.s to postdoc in a biology lab. By the early 2000s, when the first wave of students from my lab graduated, most went on to postdoc in labs that were even more biological than mine. Now, if students interested in working at the chemistry–biology interface do not take that route, they may find themselves at a disadvantage later on. Nonetheless, there are still many scientists who fear that cross-disciplinary training will produce neither the best chemists nor the best biologists. But this opinion is waning.

How are colleges and universities changing their curricula to meet this new expectation that chemists know more biology?

Some schools are doing a phenomenal job of creating programs tailored to training at the juncture of biology and chemistry. Several schools, including Berkeley, support programs that span the life sciences and chemistry departments, and graduate students rotate through labs in both departments. Many medical centers—for example, at the University of California, San Francisco—host chemical biology training programs. Stanford Medical School has renamed its Molecular Pharmacology Department "Chemical and Systems Biology." The basic coursework for a Ph.D. in chemistry hasn't changed much, but students are learning to integrate their chemistry skills with biology systems in research settings.

Is industry also embracing chemists who are trained in biology?

In a big way, but it's a fairly recent trend. Until about 5 years ago, to land a job as a chemist in a big pharma company, you had to do as much hardcore chemical synthesis as possible. I would even venture to say that if a chemist revealed more than a superficial understanding of biology during an interview, it might be considered a bad thing.

That has completely changed. These companies are under considerable pressure to find new and better drug targets. Hiring managers recognize that the people most likely to break out of the tired old mold are the ones with interdisciplinary training. I receive regular e-mails from pharma companies looking for chemical biologists—people who are comfortable engineering proteins, doing chemistry on large molecules in aqueous environments, designing systems far off the typical path of small molecule drug development. This is a very good sign, for the industry and for our trainees.

In what areas are biology-focused chemists making an impact?

Everything from drug development to materials science. A big one is medical diagnostics for developing countries—they need to be portable and cheap and still accurate. That problem will be solved by clever chemical engineering. The interface between physical chemistry and biology has led to all sorts of new ways to image molecules. There is a space for drug discovery—nanoparticles or big molecules—that pharmaceutical companies have been reluctant to pursue because of the difficulty of getting these drugs into the body. But as chemists find ways to engineer new delivery systems, that space is opening up.

INTERVIEW BY SARAH C.P. WILLIAMS. *Carolyn Bertozzi is a distinguished professor of chemistry and a professor of molecular and cell biology at UC Berkeley.*

Q&A

What was your first cool chemistry experiment—one that turned you on to research before you were a bona fide scientist?

Many scientists began experimenting well before their first paycheck. Here, a few describe the experiments that made them realize their calling.

—EDITED BY NICOLE KRESGE

Keiko Torii

HHMI-GBMF INVESTIGATOR
UNIVERSITY OF WASHINGTON

"My first chemistry experiment at home was growing large crystals of potash alum—potassium aluminum sulfate. It was very easy to purchase this chemical because Japanese people use it for food preparation. You make a highly saturated solution of potash alum, hang a small granule of potash alum in it, and then let it cool down. If you're lucky, you yield a few carats, or even larger, of beautiful octahedron crystal! I got into experimenting with the conditions—changing the initial temperature and speed of cooling, altering the size of the initial core granule and the way it hangs—to figure out how I could make bigger, prettier crystals."

Sinisa Urban

HHMI EARLY CAREER SCIENTIST
THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

"Just before starting grad school, I was studying DNA replication in hepatitis B virus, which synthesizes its DNA inside a viral core particle. I was looking at what happens to the byproduct of this reaction, pyrophosphate, in such a confined space, using a variety of radiolabeled reactants on different phosphates. I was amazed that, by putting the label on different atoms of the same basic molecules, I could follow all aspects of the reaction. To analyze my results, I ran thin-layer chromatograms, which was unbelievably cool, because I could use first-year undergrad chemistry techniques to tackle a state-of-the-art question. This experience taught me to never underestimate the importance of simple chemistry in solving complex problems!"

Roger Y. Tsien

HHMI INVESTIGATOR
UNIVERSITY OF CALIFORNIA, SAN DIEGO

"There are two experiments I remember best. First, 'silica gardens,' in which crystals of metal salts dropped into a solution of sodium silicate developed bright magenta, green, or blue gelatinous coatings from which vertical dendrites sprouted. The second involved a strongly alkaline aqueous solution of potassium permanganate, which colored the liquid an intense purple. As I passed this solution through a folded cone of filter paper, its color changed to a beautiful green, reflecting reduction of permanganate, presumably by the cellulose. Both experiments reflect an early and long-lasting obsession with pretty colors."

Loren L. Looger

JFRC GROUP LEADER
JANELIA FARM RESEARCH CAMPUS

"Like any little kid, I was really into making a big mess. Every child stumbles onto the baking soda and vinegar volcano. Word on the street was that this was a chemical reaction. This is true: covalent bonds are broken and formed. Another trick was adding a bunch of salt to a glass of Coke, resulting in a huge, bubbling mess capable of sliming nearby friends or enemies. This was also rumored to be chemistry, but that's not the case. No new compounds are made or destroyed—I was just accelerating a state change that was already proceeding. It's a nice example of things not always being what they seem."

Torii: Stephen Brashear / AP, ©HHMI Urban: Rosanna Baker Tsien: Paul Fetters Looger: James Kegley

chronicle

38 SCIENCE EDUCATION
Room to Grow—and Learn

40 INSTITUTE NEWS
Experiment Seeks to Create Interdisciplinary Curricula / HHMI Offers International Student Research Fellowships / Getting Back to the Bench

42 LAB BOOK
Unlocking the Interferon Puzzle / When Membranes Merge / Bacterial-Viral Warfare

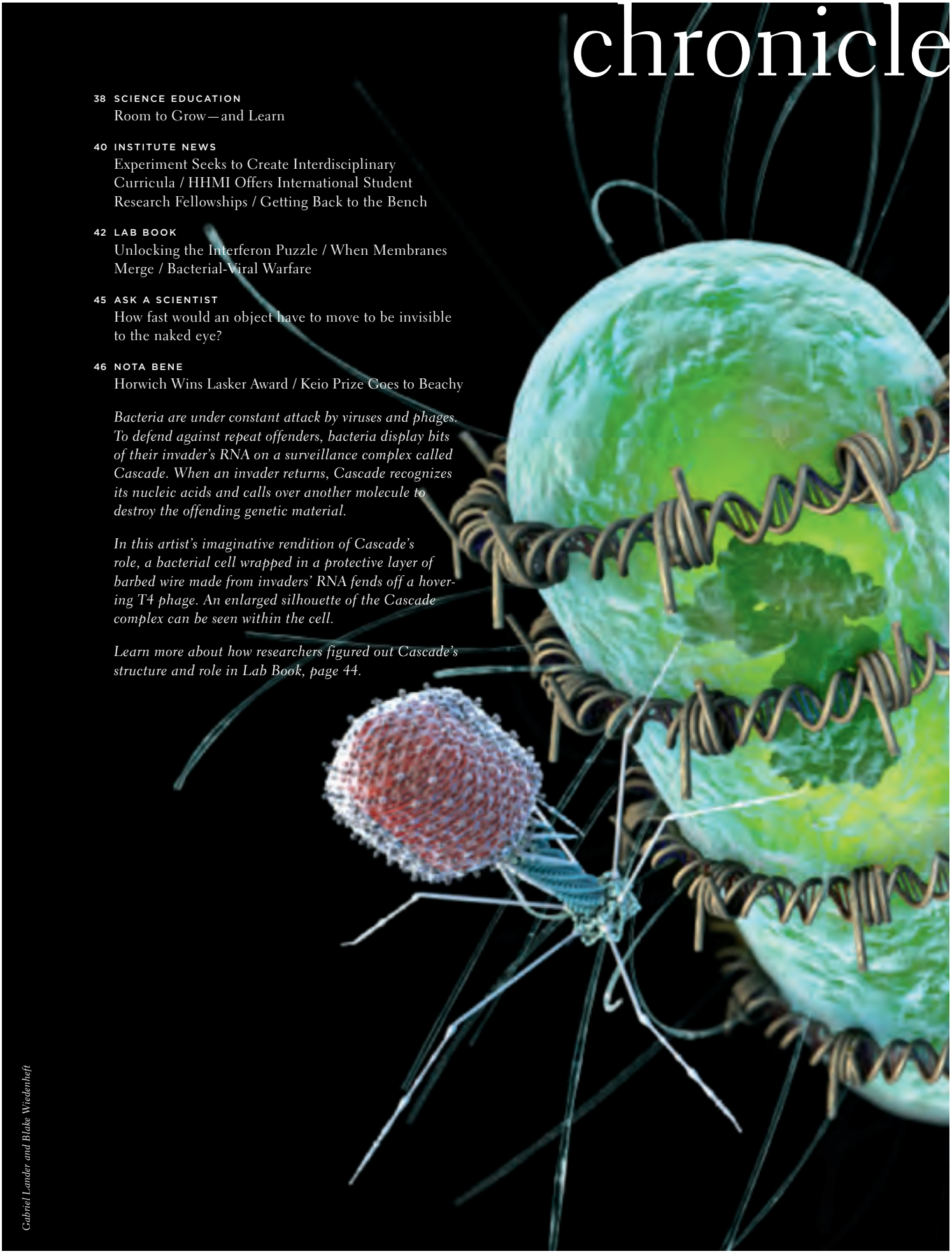
45 ASK A SCIENTIST
How fast would an object have to move to be invisible to the naked eye?

46 NOTA BENE
Horwich Wins Lasker Award / Keio Prize Goes to Beachy

Bacteria are under constant attack by viruses and phages. To defend against repeat offenders, bacteria display bits of their invader's RNA on a surveillance complex called Cascade. When an invader returns, Cascade recognizes its nucleic acids and calls over another molecule to destroy the offending genetic material.

In this artist's imaginative rendition of Cascade's role, a bacterial cell wrapped in a protective layer of barbed wire made from invaders' RNA fends off a hovering T4 phage. An enlarged silhouette of the Cascade complex can be seen within the cell.

Learn more about how researchers figured out Cascade's structure and role in Lab Book, page 44.



Gabriel Lander and Blake Wiedenheft

Room to Grow—and Learn

GIVEN DEDICATED SPACE FOR BOTH LECTURE AND LAB, STUDENTS CAN EXPERIENCE THE FULL ARC OF SCIENTIFIC RESEARCH.

Susan Wessler gazes around the brand-new science learning laboratory with a mixture of pride and anticipation.

On one side of the blue-and-white checkered hallway, there's a wet lab with most of the same equipment found in her plant genetics research lab one building away. Just across the hall is a discussion room and computer lab, with new Mac laptops for 25 students.

The Campbell Science Learning Laboratory, which opened at the University of California, Riverside, in early July, is designed to integrate teaching and hands-on experimental science. It aims to give incoming freshmen the experience of working in a real genetics laboratory, down to the radio playing music and the coffee machine. "For many students, this will be their first biology course—something very different from traditional, impersonal lecture courses," says Wessler.

Special spaces devoted to exploring science are beginning to appear on university campuses, changing the way science courses are organized and taught. "We were losing a lot of students who are interested in majoring in sciences because of big lecture courses," says Richard Losick, a professor of biology at Harvard University who has launched two HHMI-supported lab spaces.

When Wessler began teaching undergraduate biology courses at the University of Georgia more than two decades ago, the experience was not what she had hoped. "To be honest, it was disappointing," she says. She noticed something peculiar in the students when she saw them in lectures and when they worked on projects in her research lab: "I would walk out of the classroom and people wouldn't be particularly excited. But the undergraduates in the lab were bouncing off the walls." Seeing the instant engagement in the laboratory got her thinking about better ways to keep students engaged in science.

With support from an HHMI professor grant, awarded in 2006, Wessler developed a course that replicated her research program

Owen Gildersleeve

in an undergraduate classroom laboratory, allowing students to analyze transposable DNA—small pieces of DNA that can jump from one location to another inside a cell's genome. At the same time, she spearheaded the design of a special place to teach the unusual class—with all the elements of a working lab space. When Wessler made the move from Georgia to UC Riverside last year, bringing the lab and the class were part of the deal. The Riverside lab is named after the late Neil Campbell, an alum and coauthor of the biology textbook used in many high school and college introductory courses.

The crossover between discovery and practice in such learning spaces means that concepts get put to work immediately, and lab isn't just an add-on to lecture-based learning. "Rather than going to the lab the next day, we can do experiments at the same time we discuss concepts," says James Burnette, a researcher who coordinates Wessler's class laboratory. Even more importantly, students have the opportunity to repeat experiments if something doesn't work—just like a research lab—and they must master concepts before moving on to the next project.

The investment in infrastructure isn't small—Wessler says her space cost $700,000, with nearly three-quarters of that coming from Rochelle Campbell, Neil Campbell's widow. Now that the lab is paid for and in place, however, Burnette notes that it can be run with nearly the same student lab fees as a typical undergraduate science course.

For undergraduates who have the opportunity to do high-level research, the experience can be unforgettable. Paris Stowers, who took Wessler's course at the University of Georgia, says the class was one of the most influential of her college career. "We were guided through the process of designing an experiment, writing a grant proposal, and presenting the results." The class cemented her plans to pursue a career in medical research. Starting in September, Stowers will spend a year conducting research on neuroblastoma through Baylor College of Medicine's medical student research track program.

Ownership and Discovery

Rich Losick believes that labs and classrooms have the potential to work symbiotically for students—and professors. "For me, teaching and research go hand in hand, and I'd like to think I'm a better teacher for being a researcher and vice versa," he says. "It leads me to see the big picture and get to the heart of the matter."

Losick spearheaded the design of the new science learning spaces with help from HHMI professor grants, starting in 2002. His aim was to move away from formulaic science teaching where students go through the motions without really learning. "There are two features that make for a successful hands-on experiment: ownership and discovery," he says, adding that science is not just a series of facts but an active process.

Of course, designing courses so that every student can discover something novel is not easy. Losick has created two teaching spaces to take on the challenge. The Jeremy Knowles Teaching Lab, which opened at Harvard in December 2009, is a highly flexible space that can accommodate different science classes, from molecular biology to a new course on the science of cooking.

Around 120 students can simultaneously use the 7,000-square-foot laboratory for the research component of different lecture courses, thanks to engineering tricks like moveable benches and a false floor that serves different equipment. The space can be divided up with sound-proof walls, creating two or four smaller spaces. In this setting, rote-learning science labs are out and true experiments are in: small teams of undergrads tackle a semester-long project. One course, for example, trains students to work with a protein implicated in cancer and then has them look for other proteins involved.

The second space Losick designed is a 50-person, interdisciplinary laboratory used solely for research-based classes. In one project, students built their own confocal microscope and then used it to study neuronal firing in zebrafish. In another project, students studied samples of cheese from a gourmet store, identifying microbes in the cheese and rinds. "The projects are changing all the time, and the course is entirely devoted to research," says Losick. "It's like working in a real lab with a team of five or six students who are tackling some question of current research."

Back at Riverside, Susan Wessler would love to see the model of project-based science classes grow—for the students and for slightly more selfish reasons. "When we started, I thought that we'd be bringing ideas from my research lab to the classroom, to design and deconstruct complex projects to their fundamentals. But I've been surprised that the learning goes both ways—some of the user-friendly computer software we've developed in the classroom has moved back to my research lab," she says. "The lesson is: if you teach students what's out there in science and give them the right tools, they can do real experiments." And she's betting they're making discoveries for life. ■ –KATHARINE GAMMON

Experiment Seeks to Create Interdisciplinary Curricula

MOST PEOPLE ASSOCIATE EXPERIMENTS in science with test tubes and beakers. However, HHMI is trying a new type of science experiment—one that involves education. The Institute has brought together an expert in student evaluation with faculty members from four universities with one goal in mind: to create interdisciplinary science courses easily implemented in any undergraduate classroom.

The four-year, $1.8 million National Experiment in Undergraduate Science Education, or NEXUS, involves Purdue University; the University of Maryland, Baltimore County; the University of Maryland, College Park; and the University of Miami. Each is focusing on a specific topic, with the aim of creating undergraduate educational modules that integrate biology with physics, math, and chemistry (see box). The teams are pilot launching their modules this fall and hope to have them ready to share with other institutions in a few years.

"We really believe in the word 'experiment,' and here is an experiment that is being run on a larger scale than one discipline or one institution," says Sean B. Carroll, HHMI's vice president for science education.

The four schools are working together to ensure that the modules meet common goals and that the courses are designed and measured in a unified way. They are developing assessments that move beyond just testing students on factual knowledge to assess their ability to demonstrate scientific competencies and apply their knowledge to complex problems.

HHMI has hired David Hanauer, an evaluation specialist at Indiana University of Pennsylvania, to help coordinate the teams' assessment work and develop their capacity to tackle competency-based assessment approaches. This past summer, Hanauer led a two-day workshop, with representatives from the four institutions in attendance, to discuss strategy for assessment development.

The Institute has appointed a steering committee and an interdisciplinary advisory board of leaders in education reform. In the coming months, many steering committee members will present the NEXUS project at various educational conferences to expand its visibility and to solicit feedback.

"There are many conversations heading in the same direction, addressing how young people should be trained to participate in biomedicine and medical practice in the future," says Cynthia Bauerle, who oversees the NEXUS project and is a senior program officer in HHMI's precollege and undergraduate program. The hope is that NEXUS will be a hub for that broader national conversation. ■

FOR MORE INFORMATION: Learn more about this initiative at www.hhmi.org/news/nexus20110608.html.

THE NEXUS TEAM

PURDUE UNIVERSITY is revising its introductory chemistry curriculum to include more biological chemistry, with a focus on active learning approaches.

THE UNIVERSITY OF MARYLAND, BALTIMORE COUNTY, is infusing mathematical modeling into its introductory biology course, including quantitative reasoning skills and mathematical approaches to understand biological processes and living systems.

THE UNIVERSITY OF MARYLAND, COLLEGE PARK, is revising its introductory physics course for biology majors to present physics concepts in a biological context.

THE UNIVERSITY OF MIAMI is developing biomedical case studies that will challenge students to use scientific inquiry to analyze the biology, physics, chemistry, and math involved in human health and disease.

HHMI Offers International Student Research Fellowships

WHEN AMANDA VALETA CAME TO THE United States, she had trouble finding financial support for graduate school. "There are very limited sources of funding for non-U.S. citizens to train in the United States," says the Zimbabwe native. "This greatly limits the ability of foreign students like myself to bring back the education and expertise that are needed to address the complex health problems facing our native countries."

To encourage universities to take a chance on the best international graduate students, HHMI established a fellowship program to support science and engineering students during their third, fourth, and fifth years of graduate school.

Recently, the Institute selected Valeta and 47 other graduate students from 22 countries to be the inaugural recipients of the $43,000 a year International Student Research Fellowships. The support will allow them to devote their full attention to research at a critical time during their professional development.

"For my research project on cancer and the immune system, I need to carry out some very expensive studies," says Valeta, a graduate student at the New York University School of Medicine. Now, with her salary covered by the HHMI fellowship, she has more money for those experiments.

HHMI originally planned to give 35 fellowships in this pilot year but increased the number to 48 because the quality of the applicants was so high. "The applicant pool was spectacular," says Sean B. Carroll, HHMI's vice president for science education. "We hope, through these fellowships, to identify future scientific leaders."

Sixty research institutions with established relationships with HHMI were eligible to nominate between one and 10 graduate students for the fellowships, depending on the size of their graduate programs. A panel of top scientists and graduate educators reviewed applications from 385 students.

Institute leaders were particularly pleased with the broad distribution of countries represented by the awardees. Students from China and Canada received the most awards, but Turkey, Israel, Slovenia, and Colombia also are represented. The new fellows come from a wide variety of disciplines, including physics, chemistry, and engineering, in addition to the biomedical fields that HHMI has traditionally supported.

HHMI has committed to continue funding the program; planning for next year's competition is already under way. ■

FOR MORE INFORMATION: Visit http://www.hhmi.org/news/intlresearchfellows20110804.html to learn more about the International Student Research fellows.

Getting Back to the Bench

JANELIA FARM OFFERS RESEARCHERS THE TIME AND RESOURCES TO FOCUS ON SCIENCE.

AFTER SEVERAL YEARS AS AN INDEPENDENT researcher, David Stern says the demands of running a lab of 12 people, combined with teaching and administrative duties, simply became too much. In an effort to get back into the lab on a regular basis, last year the HHMI investigator took a "sabbatical" at his home institution, Princeton University.

During that one-year break, Stern threw himself into lab work—doing experiments and building hardware to study evolution and development of the nervous system in the fruit fly. "The most important things I realized during that time were that I missed doing research with my own hands and that my efforts in the lab could make a difference in advancing our work," he says.

So when the opportunity presented itself to make a fresh start at HHMI's Janelia Farm Research Campus in Ashburn, Virginia, Stern wasted no time in deciding to move south—even though that meant uprooting his family and giving up tenure at Princeton. He knew that at Janelia Farm, he'd spend less time on the administrative duties, teaching, and grant writing that had been consuming his days.

"At Janelia Farm, scientists have the time and resources to actually do their own research—not just manage it," says executive director Gerry Rubin. "One of the problems we see in academia is that scientists are forced to become full-time managers, instead of spending their time focusing on their science. Janelia Farm offers an alternative."

Stern and structural biologist Tamir Gonen, who was an HHMI early career scientist at the University of Washington, are Janelia Farm's newest group leaders, along with Michael Reiser, a Janelia Farm fellow who was promoted to group leader this year. Gonen and Stern will anchor two new research programs: structural biology (with a focus on cryoelectron microscopy), and the evolution and development of the nervous system. In the past 18 months, Janelia Farm has recruited two group leaders, four fellows, and four junior fellows (see box).

Stern says Janelia Farm appeals to him because he will be able to focus on the evolution of behavior, a relatively new area of inquiry for his lab. "I started this work about three years ago when I became an HHMI investigator," he says. "The work has been challenging and fascinating. I thought it would be wonderful if I could do this work close to other labs that are struggling with the same sort of challenges in studying behavior."

Gonen's decision to move to Janelia Farm was motivated by his realization that if he wanted to do his own experiments in the lab again, it was now or never. "I reached a stage where I thought, 'Either I get back to the lab now or I will never be able to get back,'" he says. "I don't really know yet what I'll be doing at Janelia—and I find that exhilarating."

All Janelia Farm group leaders, fellows, and junior fellows actively engage in research. They work in small interdisciplinary teams to address two broad scientific goals: discovering the basic rules and mechanisms of the brain's information-processing systems and developing biological and computational techniques for creating and interpreting biological images.

Group leaders direct research groups of two to six lab members and receive an initial appointment of six years. Fellows, who receive five-year appointments, are independent researchers who lead labs with up to two additional members. Junior fellows are postdoctoral fellows who develop their own research programs and are appointed for up to three years, with a possible two-year renewal.

Rubin notes that recruitment of new scientists continues, and researchers from a variety of disciplines—including biochemists, biologists, chemists, computer scientists, engineers, mathematicians, neurobiologists, and physicists—can apply for laboratory head positions through a competition that closes December 15, 2011. Applications in the competition for junior fellow positions (an independent postdoctoral position) close December 1. Further information is available at www.janelia.org/professional-opportunities/research-positions.

■ –JIM KEELEY

JANELIA'S NEW SCIENTISTS

GROUP LEADERS

TAMIR GONEN uses molecular electron microscopy to study structures of large protein complexes that function as molecular machines. His research addresses two fundamental questions in cell biology: How do cells interact with each other and with their environment? How do they obtain the nutrients essential for cell survival?

MICHAEL REISER studies sensory mechanisms that drive innate behaviors in the fruit fly, such as the ability to sense gravity and visual motion. He uses molecular genetics to uncover the functional organization of neural circuits that orchestrate behaviors.

DAVID STERN is trying to identify the genes—and ultimately the individual nucleotides—that generate phenotypic diversity in fruit flies. He believes that a thorough understanding of the molecular basis for diversity may lead to a revised view of how developmental mechanisms influence evolution.

FELLOWS

MENG CUI wants to develop robust, ready-to-use tools for biomedical imaging. He plans to use ultrasound as a virtual light source, allowing him to visualize deep tissues.

ADAM HANTMAN seeks to understand how the central nervous system uses sensory input called proprioception to inform and optimize circuits involved in motor control. He is using an approach that integrates genetics, physiology, optical-based circuit tracing, and behavioral assays.

VIREN JAIN is attempting to map the network of connections in the brain. He develops computational techniques for automating image analysis and applies them to studying neural circuits.

NA JI develops imaging tools capable of peering deep inside animals' brains to better comprehend the function of neural circuits. She is focused on improving the speed and resolution of in vivo brain imaging, and applying the resulting techniques to existing problems in neurobiology.

JUNIOR FELLOWS

PARVEZ AHAMMAD seeks to improve current methods and develop approaches to tackle a fundamental challenge in neuroscience: linking specific behaviors to specific neural activity in defined circuits.

STEPHEN HUSTON is a neuroscientist who has worked on the neural basis of flexible sensory-motor transformation in the fruit fly. He is continuing work on understanding how the outputs of the visual system are transformed into motor actions.

STEFAN PULVER wants to uncover fundamental operating principles behind the neural circuitry that controls locomotion in fruit fly larvae. He plans to study motor networks in the larva's locomotor system.

KOEN VERVAEKE has been exploring how networks of neurons can produce both synchronizing and desynchronizing behavior via electrical activity at the synapse. At Janelia Farm, he will study the roles of specific inhibitory neurons in attention.

Unlocking the Interferon Puzzle

SCIENTISTS SHOW THAT INTERFERON SIGNALING DEPENDS ON BOND STRENGTH.

How can different interferon molecules bind to the same receptor and elicit vastly different responses? This conundrum has long puzzled scientists who study these signaling proteins. A study led by HHMI investigator K. Chris Garcia suggests the key may lie in how tightly the interferons bind to that receptor.

Interferons are protective chemicals that cells produce to combat cancer, viruses, and infections. It takes the combined effort of many different interferon molecules to get the job done, and each one activates a particular component of the body's defense systems.

Garcia wanted to figure out how the 16 varieties of type I interferon trigger different cellular actions through just one cell surface receptor. He and his postdoctoral fellow Christoph Thomas at Stanford University School of Medicine used x-ray crystallography to deduce the three-dimensional structures of the receptor's two subunits, IFNAR1 and IFNAR2, bound to two kinds of type I interferons, IFNα2 and IFNω.

Surprisingly, both interferon varieties bound the subunits in a similar fashion. The finding countered the prevailing notion that each kind of type I interferon would bind in a unique way.

To dig deeper, Garcia teamed up with researchers from the Weizmann Institute of Science in Israel and the University of Osnabrück in Germany. Collectively, they mutated the interferon amino acids responsible for binding to the receptor and found that although the locations of most contact points are constant from one interferon to another, the strength of the bonds varies. Thus, the receptor differentiates between interferon molecules by how avidly they attach at certain positions. The punch line is that chemistry, rather than ultrastructure, appears to functionally differentiate interferons.

As Garcia reports in the August 19, 2011, issue of *Cell*, manipulating the chemistry of the binding surfaces can endow one interferon with the functional properties of another. For example, replacing a single amino acid in IFNω with the one found at the same position in IFNα2 boosts the mutant IFNω's cancer-fighting ability, making it more like IFNα2.

The interferon receptor (blue and green) can distinguish different interferons (brown) by how tightly they bind.

These findings provide an alternative to the long-standing "lock-and-key" model of receptor binding in which there's only one way a molecular key can bind to, and activate, its receptor lock. ■ – NICOLE KRESGE

IN BRIEF

DETECTING PROSTATE CANCER

The days of uncertainty in prostate cancer diagnosis may be numbered: HHMI scientists have developed a simple urine test to help determine the presence of the disease.

In 2005, HHMI investigator Arul M. Chinnaiyan and colleagues at the University of Michigan Medical School identified a fusion between two genes that occurs in approximately half of all prostate cancers. When *TMPRSS2* and *ERG* combine to form *TMPRSS2:ERG*, the new gene drives prostate cell growth out of control, leading to cancer.

In their latest work, published August 3, 2011, in *Science Translational Medicine*, the researchers recruited 1,312 men scheduled for a prostate needle biopsy. They collected the men's urine before the biopsy and compared *TMPRSS2:ERG* levels in samples from patients whose biopsy revealed cancer with levels in men whose biopsy was negative for cancer.

Around 50 percent of the men confirmed to have prostate cancer tested positive for *TMPRSS2:ERG* in their urine; fewer than 5 percent of men whose biopsy did not detect cancer had the gene. While lack of the fusion gene does not indicate the absence of prostate cancer, higher levels of the gene do suggest a larger and more invasive prostate tumor.

"We think of this as the first-generation version of this test," says Chinnaiyan. "We hope to add to it in the future by testing for additional gene fusions that we know about."

REBUILDING A FLATWORM

How do planarians regenerate themselves, cell by cell, when sliced into the tiniest of slivers? By exposing the flatworms to ionizing radiation that destroyed all but a few of the animals' neoblasts, researchers have come closer to answering that question.

HHMI early career scientist Peter Reddien and his colleagues at the Massachusetts Institute of Technology discovered that some of the surviving neoblasts seemed to possess all the qualities of a stem cell. So, they put these cells, called clonogenic neoblasts, to the ultimate test: they transplanted a single clonogenic neoblast into an irradiated worm lacking any other dividing cell.

"Tissues of the host were slowly but surely replaced with descendant cells from the transplanted donor cell," says Reddien. "All the various parts of the body—kidney, gut, eyes, brain, skin, muscle—were regenerated. It all came from one original starting cell."

Since most planarian genes have human counterparts, the findings, described May 13, 2011, in *Science*, could provide insight into human regenerative medicine.

GENETIC INSIGHT INTO HEAD AND NECK CANCERS

Two independent studies by teams of HHMI investigators have revealed genetic mutations often present in squamous cell carcinoma, the most common form of head and neck cancer.

Todd R. Golub of the Dana-Farber Cancer Institute looked at the genetics of 74 tumors diagnosed as head and neck squamous cell carcinoma (HNSCC). Bert Vogelstein of the Johns Hopkins University School of Medicine analyzed 32 HNSCC tumors and validated the results in an additional 88 tumors. The results of the studies appear in two separate papers published in *Science* on August 26, 2011.

Both studies compared the tumor exomes—the part of the genome that encodes proteins—with a noncancerous sample from the same patient to identify mutations unique to the tumors. A high

Garcia lab

When Membranes Merge

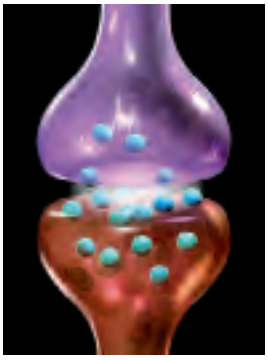
SCIENTISTS ARE UNCOVERING DETAILS OF SYNAPTIC SIGNALING BETWEEN NEURONS.

Neurons communicate by releasing the contents of vesicles full of neurotransmitters into the space between one neuron and the next. Details of this fraction-of-a-millisecond step are now clearer, thanks to a powerful tool developed by researchers led by HHMI investigator Axel T. Brunger.

As an electrical impulse travels through a nerve cell, channels in the cell membrane open, allowing calcium ions to rush in. Researchers knew this flash flood of calcium somehow signaled vesicles to fuse with the neuron's membrane and spill their contents into the synaptic cleft—the gap between neurons. But previous assays to illuminate the process told a misleading story. In those systems, membrane lipids were tagged with fluorescing dyes, and lipid mixing (from two distinct membranes) was used as an analog of fusion. The new assay, reported July 19, 2011, in the *Proceedings of the National Academy of Sciences*, demonstrates that while lipid mixing is necessary for fusion, it's far from the whole picture.

"Those assays showed only part of the process, and they kept the calcium concentration constant," says Brunger. "So they didn't show the process from start to finish."

To mimic fusion and neurotransmitter release, Brunger and colleagues at Stanford University and the University of California, Berkeley, tagged donor vesicle contents with green self-quenching dye and its membrane lipids with red self-quenching dye. Self-quenching dyes are more intense at lower concentrations; at higher concentrations, the fluorescence fades as the dye turns itself off.



A new assay sheds light on vesicular traffic at the synapse, depicted in this artistic rendition.

The researchers mixed these tagged donor vesicles with acceptor vesicles tethered to a glass surface and then exposed them to stepwise increases in calcium. Using microscopy, they were able to distinguish between the vesicles docking closely (red lipid mixing) versus merging completely (both green and red lipid mixing) by monitoring dye intensity. As the vesicles fused, the concentration of tagged content decreased, causing brighter fluorescence.

Using the new method, Brunger's team showed that a set of proteins called SNAREs initiates membrane fusion and that the protein synaptotagmin-1 lowers the barriers to fusion upon calcium influx while the protein complexin increases fusion efficiency. The team plans to continue to examine the roles of other proteins in the fusion process. ■ –JENNI LAIDMAN

IN BRIEF

percentage of the tumors had mutations in *NOTCH1*, a gene upregulated in several other cancer types. In HNSCC, however, *NOTCH1* was downregulated, meaning that in this case it acts as a tumor suppressor gene, keeping HNSCC tumors from forming when it's activated.

Many other mutations the researchers discovered were in genes involved in one molecular pathway: the differentiation of stem cells into specific types of squamous cells.

These results underscore the importance of understanding mutations specific to a tumor before developing therapeutics.

UNREGULATED TRANSLATION LINKED TO FRAGILE X AND AUTISM

Fragile X syndrome, the leading cause of inherited intellectual disability, results from mutations in the gene encoding the Fragile X mental retardation protein (FMRP). Researchers know that FMRP binds to messenger RNA (mRNA) in cells, but there is little consensus about the protein's specific RNA targets and mechanism of action.

In the July 22, 2011, issue of *Cell*, HHMI investigator Robert Darnell, together with his wife Jennifer Darnell and other colleagues at the Rockefeller University, propose that the cognitive dysfunction associated with Fragile X syndrome may be the consequence of FMRP's failure to do its job of blocking translation of certain mRNAs in the brain—a process that is critical for learning and memory.

Jennifer Darnell, a biochemist and leader of the group's Fragile X team, speculates that halting translation could allow the mRNA to be moved from the cell body to distant synapses, allowing the proteins to be rapidly manufactured "on site" as needed.

To pinpoint the specific mRNAs that interact with FMRP inside neurons, the group employed HITS-CLIP, a technique developed in Darnell's lab to identify RNAs that interact with particular proteins.

The team discovered that approximately 30 percent of the 842 mRNAs recognized by FMRP encode proteins found at neuronal synapses. Analysis revealed a striking overlap between these mRNAs and autism susceptibility genes or loci, illuminating a potential basis for shared symptoms in Fragile X syndrome and autism.

Further analysis revealed that FMRP is able to halt the ribosomes that catalyze protein synthesis as they move along mRNA strands, effectively stalling protein production. In the absence of functional FMRP, however, translation speeds along unimpeded.

PROTEIN AGGREGATES AMPLIFY IMMUNE RESPONSE

A cell needs to act quickly to ward off viral attack. According to a team led by HHMI investigator Zhijian J. Chen, this rapid response is made possible by a protein that behaves like a prion.

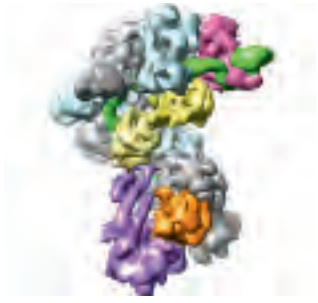
Previously, Chen's lab group at the University of Texas Southwestern Medical Center at Dallas discovered an immune system protein called MAVS (mitochondrial antiviral signaling) on the membranes of mitochondria—cellular organelles that generate energy. To study the role of MAVS in the antiviral immune response, Chen and his colleagues reconstituted the response pathway in a test tube, breaking open cells and combining their contents with viral RNA. The effect on MAVS was drastic and immediate: the normally solitary proteins aggregated by the hundreds on mitochondrial surfaces.

"This reminded us of prions," says Chen. "But the most important feature of prions is that they can cause the native protein

Laguna Design / Photo Researchers, Inc.

Bacterial–Viral Warfare

SEAHORSE-SHAPED COMPLEX HELPS BACTERIA DEFEND AGAINST PATHOGENS.



Bacteria ward off recurring attacks by displaying an invader's own RNA (green) on the surveillance molecule Cascade.

When bacteria survive a run-in with a virus or phage, they take some of the invader's DNA and integrate it into their own genome to help combat future attacks. HHMI investigators Eva Nogales and Jennifer Doudna have deduced molecular details of how bacteria use the RNA transcripts from these bits of DNA to target their intruder's genome without harming their own.

In *Escherichia coli*, the pieces of confiscated DNA, which are integrated into clustered regularly interspaced short palindromic repeats or CRISPRs, are transcribed as RNA and displayed on a multisubunit surveillance complex called Cascade. When Cascade encounters a piece of foreign DNA that is complementary to the CRISPR sequence it's carrying, the complex grabs hold and targets it for destruction by a nuclease.

Nogales, Doudna, and colleagues at the University of California, Berkeley, and Wageningen University in the Netherlands, used cryoelectron microscopy to look at the structure of the Cascade complex before and after it bound to bits of foreign RNA. The scientists discovered that Cascade is shaped like a seahorse and that it displays its CRISPR-derived RNA (crRNA) in a long groove that protects the crRNA from degradation while allowing it sufficient exposure to survey the environment.

When the complex encounters invading nucleic acids, the crRNA binds to them, forming several duplex regions. These short helical segments reduce the overall length of the crRNA, causing a conformational change in the Cascade molecule that may serve as a signal for a nuclease to destroy the invading nucleic acids.

The structure, which was reported in the September 22, 2011, issue of *Nature*, may provide a way for humans to combat harmful bacteria. "Anything that allows us to understand the mechanisms by which a bacterium is able to survive viral infection means that we have a potential way to control bacterial populations by reducing their defense capabilities," says Nogales. "The enemy of our enemy is a friend."

Next, Nogales and Doudna want to look at the interaction between Cascade and the nuclease to learn more about the events surrounding degradation of the foreign DNA. ■ –NICOLE KRESGE

IN BRIEF

to also form aggregates." To test for this, Chen's team added MAVS aggregates to mitochondria. Within minutes, every MAVS on the mitochondria had clumped into aggregates that were highly effective in activating immune reactions. The scientists also found that when they blocked MAVS aggregation in cells, no immune response was launched. The team reported its results on August 5, 2011, in *Cell*.

The prion-like behavior of MAVS allows the cell to launch a full-blown antiviral response, Chen says, even if it senses only a few copies of a virus.

AN UNUSUAL INFLUENZA ANTIBODY

Stephen C. Harrison, an HHMI investigator at Children's Hospital Boston and Harvard Medical School, was scanning antibodies from subjects who had received the influenza virus vaccine when he stumbled upon something unusual: an antibody that recognizes multiple strains of the flu virus.

Normally, an antibody recognizes a surface glycoprotein specific to one strain of flu virus. Unfortunately, these glycoproteins mutate rapidly, allowing the virus to evade the immune system. However, one part of the influenza virus doesn't mutate—the area that recognizes and binds to receptors on human cells.

"It has been assumed that because antibodies have a larger contact area than most virus receptors," says Harrison, "an antibody might target that receptor binding area, but it would also recognize surrounding, changeable areas." Thus, if that surrounding area mutated, the antibodies wouldn't bind.

The antibody that Harrison and his colleagues isolated, however, binds so tightly to the receptor pocket that it isn't affected by surrounding mutations. Collaborators tested the antibody—dubbed CH65—against 36 flu strains and found that it blocked 30 of them. The research was published August 23, 2011, in the *Proceedings of the National Academy of Sciences*.

This knowledge could, in principle, be used to develop a vaccine that stimulates production of CH65 antibody. Before embarking on such an endeavor, Harrison would like to use CH65 to learn more about how the immune system chooses which antibodies to produce.

SHEDDING LIGHT ON BLINDNESS

Retinitis pigmentosa (RP) is a group of genetic eye conditions that result in progressive vision loss. The disorder is thought to be caused by mutations in any one of more than 100 different genes, fewer than half of which have been identified. HHMI investigators Edwin M. Stone and Val C. Sheffield of the University of Iowa along with collaborators have added one more gene to this list and have devised a method for identifying many more.

Sequencing the exome—the portion of DNA that encodes proteins—of a patient with RP, the team found a mutation in both copies of the patient's *MAK* (male germ-cell associated kinase) gene. As reported August 23, 2011, in the *Proceedings of the National Academy of Sciences*, the mutation was also found in about 1 percent of unrelated individuals with RP. Although this gene previously had been studied predominantly in the testes, the scientists were able to find a unique version of the MAK protein in human retina cells as well.

The researchers then investigated the effects of the mutation on the eye by creating retina cells out of stem cells obtained from the RP patient's skin. These mutant cells were unable to make the full MAK protein at all.

Now, the group plans to apply the same combination of next-generation sequencing and induced pluripotent stem cell technology to identify as many new RP genes as they can.

Nogales lab

Q A

How fast would an object have to move to be invisible to the naked eye? Could Dash from "The Incredibles" really run so fast that we could not see him?

Asked by John, a high school student from Virginia.

The short answer is yes, Dash could run fast enough to be invisible. Exactly how fast he would have to run depends on many factors.

For an object to be visible, light particles (photons) must bounce off the object and into your eye. There must be enough light that specialized neurons in the eye—the rod and cone cells that form the photosensitive pixels of the retina—are activated to a level that triggers awareness. If Dash zipped through your field of view so quickly that too little light from him reached your retina, you would not see him.

What is the minimum amount of light required? In a classic experiment, people in complete darkness were exposed to flashes of light. Only the rod photoreceptors were sensitive enough to detect the light intensities used in this experiment. At the minimum flash brightness required to trigger visual awareness, only a handful of rods each absorbed just one photon. The implication is striking: single cells, capturing single particles of light, can trigger perception.

However, at best, the rods can provide only a low-resolution image. To see and recognize Dash requires cone photoreceptors. Cones allow high-resolution color vision in brighter light. Unlike rods, individual cones must absorb many photons to generate a sizeable response. And since each cone contributes a single pixel to the final image, many cones are required to "draw" Dash on the retina. If Dash were moving fast, photons bouncing off him would be scattered across many cones, and each of these cones might be insufficiently activated, so Dash would be invisible. If there were just a little more activation, he would appear as a blur.

The less light there is, the more Dash can afford to take it easy. At noon when there is a surplus of photons, he has to be at his speediest to be invisible.

Other factors are at play. One is eye movement. We never look steadily at a single point in space. We are not aware of it, but our eyes constantly dart from one location in the visual scene to another. They make small jumps that last about a fifth of a second. These jumps are called "saccades," during which our visual system is suppressed. If Dash shot past during a saccade, you would not see him. If he ran past a crowd, chances are that at least some people would be in midsaccade and would miss him.

The bottom line is, a complete answer to your question does not exist. How much light is required for a good cone signal, how activity across the array of cones is assembled into an image, how the visual system shuts down during a saccade, and other factors such as attention are active research areas.

ANSWERED BY MICHAEL TRI DO, *an assistant professor at Children's Hospital Boston, Harvard Medical School.*

FURTHER READING:
Webvision: webvision.med.utah.edu.

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

SPOTLIGHT

Horwich Wins Lasker Award

ARTHUR L. HORWICH

Arthur L. Horwich, an HHMI investigator at Yale School of Medicine, was awarded the 2011 Albert Lasker Basic Medical Research Award along with Franz-Ulrich Hartl of the Max Planck Institute of Biochemistry. Horwich and Hartl were honored for discovering that proteins cannot fold inside cells by themselves. They determined that a protein called chaperonin acts as a cage-like folding "machine" that provides a place for newly made proteins to be converted into their biologically active forms. The Lasker Awards—considered among the most respected science prizes in the world—are given annually for basic medical research, clinical medical research, and public service.

DAVID BAKER, an HHMI investigator at the University of Washington, received the Biochemical Society's 2012 Centenary Award. The international award recognizes scientists for their achievements and excellence in biochemistry. Baker uses computational methods to predict the structures of naturally occurring biomolecules and to design molecules with new and useful functions.

HHMI investigator SANGEETA N. BHATIA of the Massachusetts Institute of Technology was elected to the Biomedical Engineering Society's class of 2011 fellows. Fellow status is awarded to society members who demonstrate exceptional achievements in biomedical engineering and have a record of participating in the society. Bhatia's research focuses on the application of micro- and nanotechnology to tissue repair and regeneration.

SEAN B. CARROLL, vice president for science education at HHMI, has been awarded the 2012 Benjamin Franklin Medal in Life Sciences. The Franklin Institute Awards are among the oldest and most prestigious science awards in the world, and recipients are recognized for their formidable and ground-breaking contributions to science. Carroll, an HHMI investigator at the University of Wisconsin–Madison, studies how changes in the genes that control animal development shape the evolution of body parts and patterns.

HOWARD Y. CHANG, an HHMI early career scientist at the Stanford University School of Medicine, was awarded the 2011 Alfred Marchionini Research Prize for his contributions to dermatologic science. Chang looks at how the coordination of gene activity allows cells to know and remember their locations in the body.

The Human Frontier Science Program Organization awarded MICHAEL B. ELOWITZ, an HHMI investigator at the California Institute of Technology, the 2011 HFSP Nakasone award. The award, named for former Japanese Prime Minister Yasuhiro Nakasone, honors scientists who have made breakthroughs in life sciences. Elowitz was selected for his work that showed the importance of stochasticity, or "noise," in gene expression as a source of biological variation.

DAVID HAUSSLER, an HHMI investigator at the University of California, Santa Cruz, was selected to receive the 2011 Weldon Memorial Prize given by the University of Oxford. The annual prize is awarded for the development of mathematical or statistical methods that can be applied to problems in biology. Haussler develops statistical and algorithmic methods to explore the molecular evolution of human and other vertebrate genomes.

HHMI investigator BARRY HONIG of Columbia University received the 2012 American Society for Biochemistry and Molecular Biology DeLano Award for Computational Biosciences. The annual award is given to scientists who have created accessible and innovative computer technology that enhances research in the molecular life sciences. Honig was honored for his development of software tools used to analyze the role of electrostatics in macromolecular interactions.

HHMI investigator ERIC R. KANDEL of the Columbia University College of Physicians and Surgeons was awarded the 2011 National Leadership Award in Science and Education from the Merage Foundation for the American Dream. The annual award honors internationally respected American

Chris Jones

leaders who came to the United States as immigrants. Kandel looks at learning and memory in animals.

HHMI investigator **RANDALL T. MOON** of the University of Washington School of Medicine was elected to the Washington State Academy of Sciences. The academy provides scientific analysis on issues in areas such as health, energy, and science education. Moon studies the signal transduction pathways that are activated by the Wnt family of secreted ligands.

ARMANDO J. PARODI, an HHMI international research scholar at the Leloir Institute Foundation, was selected to receive the 2011 Karl Meyer Award by the Society for Glycobiology. The annual award is given to scientists who have made widely recognized contributions to glycobiology. Parodi was recognized for his research on protein folding in the endoplasmic reticulum.

HHMI investigators **STEPHEN R. QUAKE** of Stanford University and **XIAOWEI ZHUANG** of Harvard University shared the 2011 Raymond and Beverly Sackler International Prize in Biophysics from Tel Aviv University. Quake invents forms of biological automation and applies these tools to problems of biological and medical interest. Zhuang develops single-molecule and superresolution imaging methods to study the regulation of gene expression and virus–cell interactions. Quake was also recently honored with the 2011 Promega Biotechnology Research Award from the American Society for Microbiology.

HHMI investigator **TOM A. RAPOPORT** of Harvard Medical School won the 2011 Schleiden Medal from the German Academy of Sciences Leopoldina. The award is given every other year for outstanding discoveries in cell biology. Rapoport was honored for his research on how proteins are transported across membranes and how organelles form and maintain their shape.

The International Society for Traumatic Stress Studies honored **KERRY J. RESSLER**, an HHMI investigator at Emory University School of Medicine, with the 2011 Robert S. Laufer, Ph.D., Memorial Award for Outstanding Scientific Achievement. Ressler studies the molecular neurobiology of fear to develop therapies for anxiety and other fear-based disorders.

DAVID M. SABATINI, an HHMI investigator at the Massachusetts Institute of Technology, has been selected to receive the 2012 Earl and Thressa Stadtman Scholar Award from the American Society for Biochemistry and Molecular Biology. The award is given to scientists with 10 years or less of post-postdoctoral experience. Sabatini received the honor for his work on elucidating the mTOR signaling pathway, which regulates growth.

HHMI investigator **HUDA Y. ZOGHBI** of the Baylor College of Medicine was awarded the 2011 Gruber Neuroscience Prize. The prize is one of five annual international awards given by the Peter and Patricia Gruber Foundation for work that facilitates progress in knowledge and culture. Zoghbi was honored for her work elucidating the genetic and molecular mechanisms of several neurological disorders including Rett syndrome and spinocerebellar ataxia type 1.

SPOTLIGHT

Keio Prize Goes to Beachy

PHILIP A. BEACHY

Bill Denison

The 2011 Keio Medical Science Prize was awarded to HHMI investigator **Philip A. Beachy** of Stanford University School of Medicine and Keiji Tanaka of Tokyo Metropolitan Institute of Medical Science. The prize is given annually by Keio University in Japan to researchers who have made outstanding contributions to medicine or the life sciences. Beachy received the honor for identifying Hedgehog, a key molecule in development, and discovering its medical applications. Tanaka was selected for discovering the proteasome and elucidating its physiological functions.

CONTINUED FROM PAGE 17
(LIVING CHEMISTRY)

can launch career-changing collaborations, as Crabtree and Schreiber have learned.

"The important thing," says van der Donk, "is that biologists and chemists are really talking to one another more than we used to. As a result, biologists understand better what chemists can bring to the table. And chemists understand better the questions that biologists really care about." This, he says, has led to a bigger impact of chemists on biological problems. And they've only just begun. ■

FOR MORE INFORMATION: See other articles on researchers applying chemistry to biological questions throughout this issue, in print, online, and on the iPad.

CONTINUED FROM PAGE 23
(CALLING ALL TEACHERS)

were suspects, she added, and each suspect used a characteristic brand of pen. The students figured out how to use paper chromatography to distinguish the inks in Bic, RoseArt, and other pens. Most were able to finger the guilty suspect. "I wanted them to understand the concepts more deeply than they would if they had just been given the instructions," Gurick says.

Getting in Practice

Stony Brook's curriculum, like all good teaching programs, also requires preservice teachers to spend plenty of time in schools, watching and teaching. Before they're allowed to student-teach in the third and final semester of their master's course, preservice teachers at Stony Brook must spend 100 hours each observing teachers—in middle schools and high schools, in ordinary and high-need districts, and teaching different subjects. Many preservice teachers also help teach in the university's unique biotechnology, chemistry, physics, and earth science teaching laboratories. Science teachers from 80 percent of Long Island's school districts bring their students for half-day laboratories.

Establishing strong ties with local schools can pay off for much smaller teacher-training programs. At Trinity University, aspiring science teachers do a year-long internship at one of three "professional development schools"—elementary, middle, or high school—in San Antonio, where they are mentored by an experienced teacher. In exchange, the university appoints these mentors as clinical faculty for a year, complete with library and other privileges, and Trinity faculty lead professional development initiatives for the teachers at each school.

Back in Kalamazoo, Lauren Miller will do her student teaching next spring, and next summer she'll teach eighth graders the unit she develops on sex hormones and obesity. Beyond that, she plans to teach family consumer science, which includes personal nutrition, reproductive health, and parenting, to high schoolers. She'll take her newfound enthusiasm for science with her. "Science is asking questions—you ask one question and you've got 10 more after that," Miller says. "I want to take that to my students and get them excited about science." ■

FOR MORE INFORMATION: To learn about new science and math standards and to see a comparison of preservice programs, visit www.hhmi.org/bulletin/nov2011.

CONTINUED FROM PAGE 29
(HAVE MICROSCOPE, WILL TRAVEL)

Planchon, now an associate professor at Delaware State University, plans to develop similar microscopes to look at live multicellular organisms and continue working closely with biologists. Ultimately, Betzig's group would like to merge the Bessel sheet's capabilities with the super-resolution of PALM, a project that the Galbraiths—frequent collaborators at Janelia Farm who brought their own custom-built PALM with them to Woods Hole this summer—are urging forward.

The long days at MBL will transition into long days back at Janelia Farm, as the Betzig team continues to improve the Bessel sheet. Because what they really learned at Woods Hole, Gao says, is how urgently biologists await those improvements. ■

WEB EXTRA: Hear Eric Betzig talk about the microscope and see how it dazzled Woods Hole students and faculty in an audio slideshow. Go to www.hhmi.org/bulletin/nov2011.

CONTINUED FROM PAGE 33
(STAR SEARCH)

of background information concerning both wild and captive mouse lemurs with new genetic and genomic data is very exciting."

At Stanford, Krasnow and his group are pushing forward with mouse lemur research, starting with seeking out additional samples and setting up collaborations with Malagasy scientists and other lemur biologists around the world. They think that learning about the genetics and physiology of mouse lemurs could help preserve the endangered animals.

"For decades Madagascar has been seen as a hotspot for biodiversity, and rightly so," Richard says. "But it is welcome to see that recognition translating into a broader scientific interest in mouse lemurs—primates found nowhere else in the world." ■

WEB EXTRA: Travel with Mark Krasnow and his team as they explore the rainforests of Madagascar. See the slideshow at www.hhmi.org/bulletin/nov2011.