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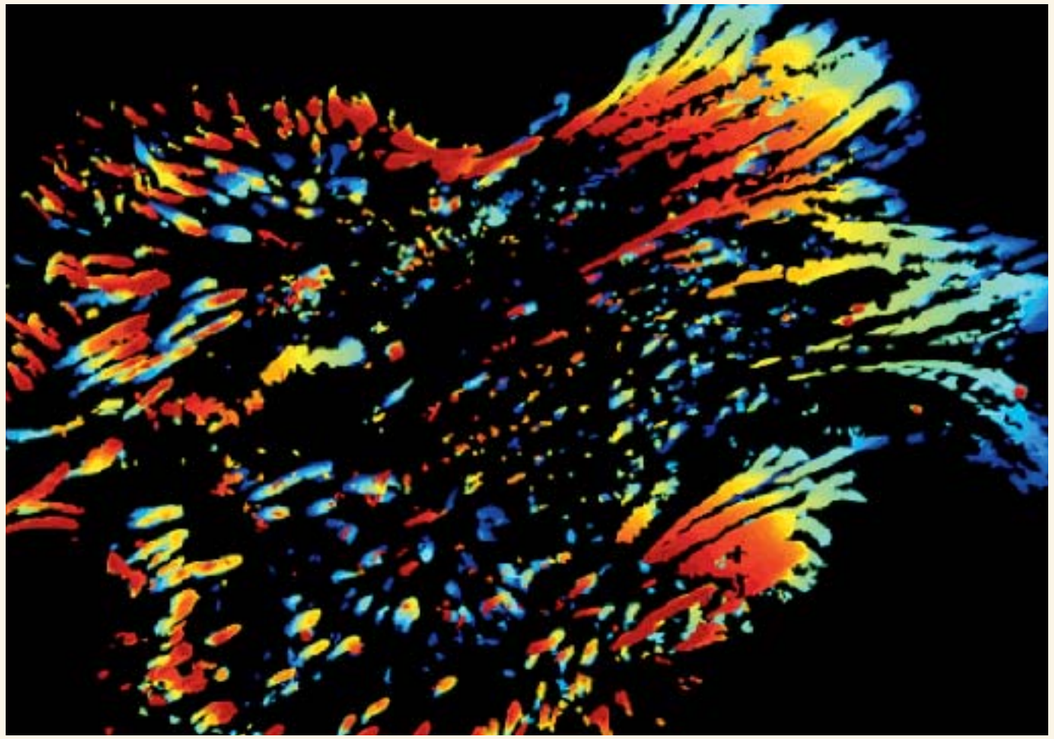
Grab and Go

Though the pace isn't Formula One fast, cells of various kinds speed through our bodies daily. To launch themselves forward, some cells, such as this fibroblast, get a toehold by using dynamic protein complexes that work with the cytoskeleton to grab the surface they crawl along. Here, the structures are color-coded to show time of formation, with red being the most recent. Fibroblasts—the most common connective tissue cells, which play a critical role in wound-healing—also require a blended fuel of cytoskeletal and signaling proteins to propel them forward. Using genetic engineering, HHMI investigator James Bear is tinkering with the fibroblast "engine" to understand how it all works. Read about his research in "Cells on the Move," page 12.



Emma Wu and Matt Berginski / Bear lab

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Built to Move

A mix of scaffolding and signaling combine to power cell movement.

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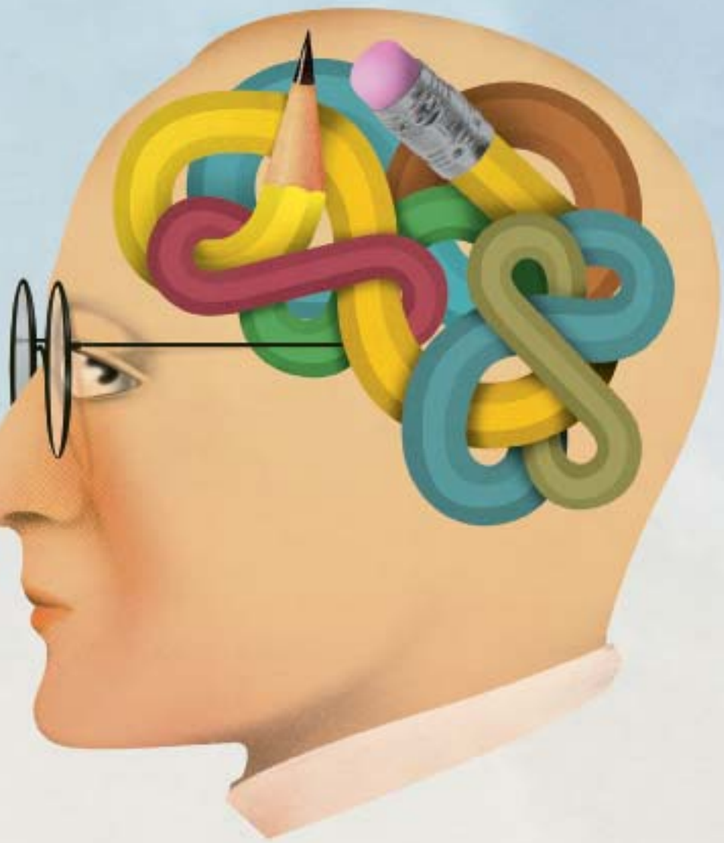
Like an inchworm, pushing its head forward then bringing up its rear, a metastatic cancer cell can move. Here, human breast cancer cells (green) have begun to work their way through a capillary wall (red) into brain tissue. The front of the cells have broken through, (bright green) while the rear ends are still trapped inside the blood vessels. The proteins that help the cells push forward may be good targets for drugs.

Manuel Valiente, Massagué lab



Brett Ryder

DRAWING ON THE BRAIN

It's been studied for centuries, yet the brain remains in large part an enigma. Every day we remember the past, process the present, and imagine the future. How do we accomplish these remarkable feats? In his new book, HHMI investigator Sebastian Seung says the answer—and our uniqueness—lies in the connectome, the wiring of all the neurons in our nervous system.

Perhaps the brain's ability to remember depends on the persistence of its material structure. What else could account for the indelibility of memories that last an entire lifetime? Then again, we sometimes forget or misremember, and we add new memories every day. That's why Plato compared memory to another kind of material, one more flexible than the pyramid's stone blocks:

There exists in the mind of man a block of wax .... Let us say that this tablet is a gift of Memory, the mother of the Muses: and that when we wish to remember anything ... we hold the wax to the perceptions and thoughts, and in that material receive the impression of them as from the seal of a ring.

In the ancient world, wooden boards coated with wax were a common sight, functioning much like our modern-day notepads. A sharp stylus was used to write text or draw diagrams in the wax. Afterward, a straight-edged instrument smoothed the wax, erasing the tablet for its next use. As an artificial memory device the wax tablet served as a natural metaphor for human memory.

Plato did not mean, of course, that your skull is literally filled with wax. He imagined some analogue—a material that could hold its shape and could also be reshaped. Artisans and engineers mold "plastic" materials and hammer or press "malleable" ones. Likewise, we say that parents and teachers mold young minds. Could that be more than metaphor? What if education and other experiences literally reshape the material structure of the brain? People often say that the brain is plastic or malleable, but what exactly does this mean?

Neuroscientists have long hypothesized that the connectome is the analogue of Plato's wax tablet. Neural connections are material structures, as we've seen from electron microscope images. Like wax, they are stable enough to remain the same for long periods of time, but they are also plastic enough to change.

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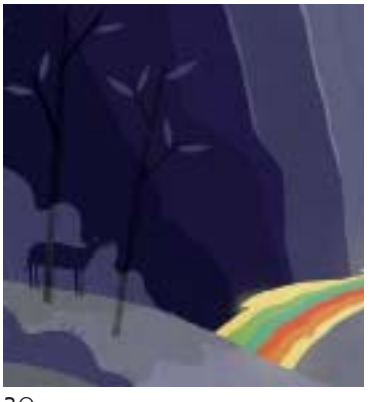

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Web-Only Content

- Is it dangerous or harmless? Watch Jeremy Weaver demo his Texas snake ID app.
- Hear Brandeis University's first science posse talk about their experiences and their plans after graduation.
- Learn about the worm straitjacket that holds a squiggler still for a photo op.
- Listen to three scientists explain what it means to be an HHMI investigator.
- Join us at www.hhmi.org/bulletin/may2012.

GO GREEN

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Features

Departments

JAMIE CULLEN (cover and "Cells on the Move," page 12) is an English illustrator who cites Pop Art and M.C. Escher's impossible constructions among his many influences. His illustrations often involve layers of visual discovery, with hidden elements emerging from intricate drawings. Cullen has worked with a range of clients, including Nike, Coca-Cola, Virgin Mobile, VW, and Reebok. (1)

Nashville-based **ELISE LAMAR** ("Cells on the Move," page 12) is a freelance science writer and editor. After working in labs for 15 years, she earned a midlife Ph.D. at the University of California, San Diego, where she studied neurogenesis at the Salk Institute. She writes primarily about molecular biology, but a three-year stint in Los Angeles left her obsessed with extreme commuting, a health hazard she is looking for a fellow writer to help her explore. (2)

ERIN PETERSON ("Making Bigger Better," page 24), a Minneapolis-based freelancer, writes about higher education issues for *USA TODAY* publications, *Minnesota Monthly*, and numerous colleges and universities. She learned to appreciate science from her dad, who once helped her try to fry an egg on a sidewalk. In addition to writing, her favorite activities include running and cheering for the Minnesota Twins. (3)

California-born, Brooklyn-based, **DUSTIN AKSLAND** ("Enter the Samurai," page 18) exhibits his photographs regularly and has collaborated with clients such as *Monocle, Esquire, Details*, and *Dwell*. When he's not traveling or retouching images in his dark, windowless studio, he can be found roaming the streets of New York City in search of a good taco. (4)


(1)


(3)


(2)


(4)

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Jamie Cullen, Elise Lamar, Erin Peterson, Dustin Aksland

Critical Thinking

IN THE PH.D. PROGRAM AT THE UNIVERSITY OF CALIFORNIA, Berkeley, we have a course in which students read published papers and analyze the quality of the science. It is one of the most valuable parts of their training. We intentionally pick really great papers and really bad papers. Sometimes the students can't tell the difference, because the bad paper might be flashy and seemingly interesting. They learn that it takes a lot of probing before you can see the flaws. Developing deep analytical skills and a healthy skepticism—for careers in and out of the lab—is good training.

There's an ongoing discussion in this country about whether we're training too many Ph.D.s. The general assumption is that there aren't enough scientific jobs for them. In academia, that's been true for a while, and in industry, job growth seems to be plateauing as pharmaceutical and biotech companies consolidate and contract.

Last year the journal *Nature* published a series of articles on the subject, citing some surprising statistics about doctoral education in the United States. From 1973 to 2006, for example, the number of Ph.D. recipients in the biological sciences who held a tenure-track position six years after completing their degree dropped from 55 percent to 15 percent. That rate continues to fall.

Some critics compare the situation to a pyramid scheme: graduate schools take on too many students, and then principal investigators take on too many postdocs—an inexpensive and effective way to advance their research—knowing full well that there won't be jobs for the trainees once they finish. I have a different view and would argue that the training behind a master's or Ph.D. degree is a rigorous, critical-thinking process that is good for the world. It's a worthy investment.

I've seen many of my most brilliant students, who were very talented in the lab, decide to do something other than science. They've taken what they learned and made contributions in law, venture capital, finance, and other fields. I don't see that as a negative. I see a broader positive impact for society.

How to balance the resource commitment necessary for this kind of training with what comes out of it is another question. From the country's economic standpoint, we must train more students in STEM fields—that is, science, technology, engineering, and math. Manufacturing, which used to power the U.S. economy, has been surpassed by the health care industry. According to projections released in February by the Bureau of Labor Statistics, health care jobs will add more than 5.6 million employees by 2020, by far the largest area of job gains. And it's safe to say there will also be high-tech job growth in areas such as alternative energy and information technology.

To remain globally competitive, this country must be better educated in science and math. President Obama has voiced his concerns, calling for 100,000 new STEM teachers for our schools over the next decade. And as HHMI professor Jo Handelsman describes in a Perspective piece in this issue of the *Bulletin*, the President's Council of Advisors on Science and Technology recently laid out recommendations to dramatically alter the way science and math are taught in our colleges and universities.

James Kegley

> "The world needs more smart, well-educated, curious, critical thinkers."
>
> ROBERT TJIAN

Making these changes in a way that is economically feasible and sustainable won't be easy. At HHMI, we give a lot of thought to how we can help advance the cause. Programs that start small can grow to have a much larger influence. Consider the efforts by some forward-thinking individuals to create research-based courses at large universities, described in this *Bulletin*. An early experience contributing to an actual research project can help cement a student's interest in science. Finding the funds and resources to support such courses will no doubt be a challenge for universities, but we believe that initial experiments will lead to efficiencies over time.

Though HHMI's efforts to improve the training of STEM teachers and students are modest in the big picture, we hope the work becomes an amplifying mechanism. And with new initiatives coming out of our science education group, we plan to have an even bigger influence on STEM education in this country.

The world needs more smart, well-educated, curious, critical thinkers. Some of the great inventions and advances we enjoy came from esoteric, unpredictable small beginnings. That's what was going on at Bell Labs from the 1920s through the 1980s. They didn't necessarily know what their research and investment would produce. But they brought together inquisitive folks who were willing to try some creative, unconventional things, and out of this mix and freedom to explore came amazing discoveries that we're still benefitting from today. There aren't too many organizations like that left and we hope that in our own way we are one of them.

Snakes in Cyberspace

Jeremy Weaver likes to spend warm summer nights wandering through Texas deserts and pastures armed with a headlamp, three-foot-long tongs, and a pillowcase. He roams the state's nature conservancy land and wildlife reserves—places like Oasis Ranch on Independence Creek Preserve—to capture, collect data on, photograph, and then release poisonous and non-venomous snakes.

Weaver's love of reptiles was sparked through the HHMI undergraduate research program at Texas Tech University, directed by herpetologist Lou Densmore. Now a grad student at Texas Tech with Densmore as his mentor, Weaver specializes in American and Cuban crocodiles, but snakes still captivate him.

Weaver's wife, Mary Ann, a fourth-year medical student, sometimes joins him on snake-hunting jaunts. "She's more comfortable with snakes than she used to be, but she's not a fan of holding them," he says. Still, last year she suggested that he combine his computer skills with his snake smarts and, just for the fun of it, develop reference apps.

Weaver's first app, called TX Snakes, has a regional focus, unlike other snake identification apps. It provides detailed, descriptive information, by county, on all 72 recognized species in Texas, including probable ranges of each species within the state's 254 counties.

So, for example, when Weaver's friend stumbled across a snake while playing Disc Golf, he entered the snake's county location and banding pattern in the app. "He was able to identify it as a Southern Copperhead, a common venomous snake in Texas," says Weaver. "Using a long stick, he encouraged the snake off the golf course so other players would not accidentally step on it or get bitten."

Weaver usually photographs snakes at night when they're hunting for food, careful to stay out of striking distance of the venomous ones. "I like to have someone with snake tongs close by so they can wrangle the snake while I take pictures," he says. "My wife will hold a flashlight, but that's about as close as she gets to the snakes." In January, he updated the software with 400 photos of Texas species and subspecies.

Similar apps cost around $10, but Weaver prices his at $1.99 to encourage snake appreciation and respect—and to alleviate fear, especially among parents of young children. "Many people discover they've come across a non-venomous snake they don't have to kill," says Weaver, who has a five-month-old son.

Available through iTunes, TX Snakes generates especially brisk sales in the spring and summer months before snakes enter winter hibernation. Downloads the first three months totaled 4,000, for instance, and during the first winter, 1,000. "That's pretty good for a first app," he says, adding that plans for a student digital field notebook are on his "to-do" list. But Weaver regards himself as more a hobbyist than an entrepreneur. "I do one computer task each day," he says, "and this gives me a sense of accomplishment." Occasionally, buyers grumble that they prefer different common names for certain snakes, but the feedback—"that app saved my life"—is mainly positive.

Weaver is creating other state apps. Thanks to his computer language experience, he produced OK Snakes for Oklahoma and KS Snakes for Kansas in just a few days, but he says, "California will be difficult—it has a ton of snakes."

—Janice Arenofsky

WEB EXTRA: For a video demonstration of the app by Jeremy Weaver, visit www.hhmi.org/bulletin/may2012.

Ping Zhu

An Artist's Eye

Cody Pickens

Tirin Moore sits with a notepad on his knee, hesitantly putting a ballpoint pen to paper. A few quick strokes, and an old childhood friend—with a peanut-shaped head, wild flagella-like hair, and striped shirt—skips onto the page. It's Silly Willy, a cartoon character that Moore invented when he was around nine years old. "Wow, I haven't drawn this in decades," says Moore, a neurobiologist and HHMI early career scientist at Stanford University.

While many scientists grew up obsessed with microscope kits or bug collections, Moore stretched his mind in a different way—pouring himself into cartooning and filmmaking. Raised in Oakland and Vallejo, California, he sketched "Peanuts"-style comic strips about Silly Willy, who was a TV addict, and his pals. Moore also teamed up with his best friend, Brett, to create a satirical strip called "Underworld Incorporated," which featured two assassins who were drawn like muscle-bound superheroes but "were complete morons," he says, laughing. "They would bungle every job they had." Some of Moore's cartoon work was published in his high school newspaper.

Back then, "if you asked my parents, they would say, 'Oh yeah, he's going to be a cartoonist,'" Moore recalls. Actually, young Tirin had other dreams. "I wanted to be a filmmaker." His artistic leanings were inspired by his father, a well-read, self-taught enthusiast of far-flung interests—from photography and making home movies to electronics, hieroglyphics, and black history.

One year, Moore's parents gave him a Super 8 camera as a Christmas present. He and Brett filmed stop-motion animations and "adventure-fantasy rip-offs of *Indiana Jones* and *Star Wars*," Moore says. They begged and borrowed funny hats and makeshift costumes, whips, and treasures and staged chase scenes at the park and nearby swimming pool. "We loved to choreograph fight scenes."

Moore put away his camera and cartooning pen at California State University in Chico, where he studied another subject that had always intrigued him—biology. He had had many discussions with his father pondering mysteries such as memory, awareness, and déjà vu. Those sorts of fascinating subjective phenomena, he realized, could be understood by studying the brain. He majored in biological psychology and earned a neuroscience Ph.D. from Princeton University.

At Stanford, Moore explores the neural circuitry that controls visual perception, a natural move, he says, from visual art. For instance, cartoons are simplistic line drawings that efficiently convey surprise in a face or a sense of movement. How do such simple cues capture the viewer's eye? Why can we perceive motion or depth in a static, two-dimensional image? These are important scientific questions to explore, says Moore.

Today, his only artwork is drawing the occasional cartoon monkey to illustrate his experiments in scientific papers. But while most academics see art and science as separate, Moore has a different view. Art sounds antithetical to science because "it's not precise and serious," he says. "But if you ask most scientists what is the most valuable trait to a scientist, it's creativity."
—Ingfei Chen

WEB EXTRA: For a glimpse of Silly Willy, go to www.hhmi.org/bulletin/may2012.

Accidental Weatherman

When Raúl Padrón notices tiny crackles of electricity dancing on the telephone lines, he smiles. By then, the midday sky has darkened ominously over El Alto de Pipe, a 5,700-foot-high mountain near Caracas, Venezuela, where Padrón's structural biology lab is located. Pelting rain and startling thunderclaps will follow, and he knows chances are good he'll be plunged into darkness when lightning knocks out power to the entire plateau.

The quiet panic Padrón once felt as these massive storms descended—threatening $500,000 of fragile research instruments inside his lab—has given way to a satisfying sense of control. Previously at the mercy of his own senses to predict the weather, the former HHMI international research scholar has become the accidental instigator of a network of weather stations and lightning detectors in Venezuela that have saved his own equipment (and sanity) and effectively, if unofficially, filled in the gaps of existing forecasting systems in the region.

Now that they have advance warning of impending storms, Padrón's collaborators have time to cut power to their cryoelectron microscope at the Center of Structural Biology at the Venezuelan Institute for Scientific Research (IVIC). Its million-times-magnified images help him delve into the molecular basis of muscle relaxation and activation. The equipment is high maintenance: the microscope and related accessories—the size of a small car—are housed in a 30 × 30-foot room located on the ground floor to minimize vibrations.

Because power surges can damage the microscope's electronic circuits, lightning strikes can be financially painful. Repairs to the instrument's electronic motherboard after one incident cost $8,000, a headache compounded by Venezuelan customs laws that can tie up equipment returns for many months.

After Padrón read up on meteorology, it took him surprisingly little time and effort—only a few days—to devise two homemade weather stations and lightning detectors from easily obtained items. Set up at IVIC and Padrón's nearby home, the detectors anticipate oncoming lightning, while the stations measure temperature, air pressure, wind direction, and rainfall. When word spread of the ability of his $1,000 assemblages to predict heavy weather, volunteers lined up to buy equipment and install other stations across Venezuela. Today, more than a dozen exist, with a companion website that automatically posts hourly meteorological data.

Padrón couldn't have predicted how interest in his venture would snowball. He's gone on to build a lightning detector network south of IVIC near Los Altos Mirandinos, has been a speaker at meteorological society meetings, and is teaming up with a local engineer to establish a computer server offering longer-term forecasts around Venezuela, the Caribbean, and the northern coast of South America.

"It became like a second career," says Padrón. "There were many times I said to myself, 'This wasn't the science I wanted to do!' But it's very pleasing because wow, this came from something I started." Several students at IVIC, which created a Unit of Meteorology based on Padrón's efforts, now maintain the weather stations, and one is in New York City studying for his Ph.D. in meteorology.

"This was necessary for my passion, a requirement to do my work," he says. "You work on it alone, and then it grows and takes on a life of its own. It doesn't need me now—it belongs to everybody."

—Maureen Salamon

FOR MORE INFORMATION: Visit the Virtual Center of Meteorology at http://met.ivic.gob.ve/cvm and the Interactive Mesomap of Venezuela and the Caribbean at http://met.ivic.gob.ve/sammeti/meteomapa.

Ping Zhu

upfront

WEB ONLY CONTENT

STICKY-FINGERED CULPRIT
Researchers are discovering how the blood's wound-healing platelets have a hand in metastasis as well. Read about it at *www.hhmi.org/bulletin/may2012*.

So many leads to follow in science. One result sparks 10 questions. Some are pursued, others dropped—until maybe a postdoc or grad student joins the lab and picks up an unexplored vein. A trainee produces a fascinating time-lapse movie of asymmetric plant cell division or describes how growth factors in platelets encourage metastasis. Another finds a way to manipulate the reward value of food. New scientists, valuable findings, fresh questions. And the beat goes on.

Hungry for Pleasure, Hungry for Food

Our drive to eat can be based on physical hunger or desire. The two aren't as separate as once thought.

IMAGINE YOU HAVEN'T EATEN IN DAYS. THEN, SOMEONE PLACES TWO plates in front of you. One holds a chocolate truffle, the other, a large turkey sandwich. No matter how much you adore chocolate, you will likely opt for the more filling sandwich. But given the choice in a different situation—after a big dinner, for example—the chocolate might look vastly more appealing. Are these choices due to pure reasoning or an innate desire mediated by chemicals in your brain?

New research suggests the latter. Your level of hunger affects how much pleasure you'll get out of eating chocolate or a turkey sandwich. In a recent experiment, mice placed a higher reward value on a calorie-rich drink than on an artificially sweetened drink after they'd been deprived of food. It's the first experiment to show that hunger levels affect the reward value of food.

The choice to eat something is influenced by a mélange of messages: how good something tastes and smells, the time since your last meal, your mood, what emotions or memories you associate with a food.

"Our new findings provide an experimental approach for studying how feeding pathways, including those that sense hunger and pleasure, are wired together into one grand circuit," says HHMI investigator Jeffrey Friedman, who led the study.

Friedman, at the Rockefeller University, studies the complex chemical signaling in the brain that controls hunger, appetite, and eating behaviors. In 1994, he published results describing his discovery of leptin, a hormone that controls appetite. When a mouse loses weight or hasn't eaten recently, the leptin levels in its blood fall, making it hungry and likely causing it to eat. After a large meal or weight gain, leptin levels rise, and the mouse loses its appetite and eats less.

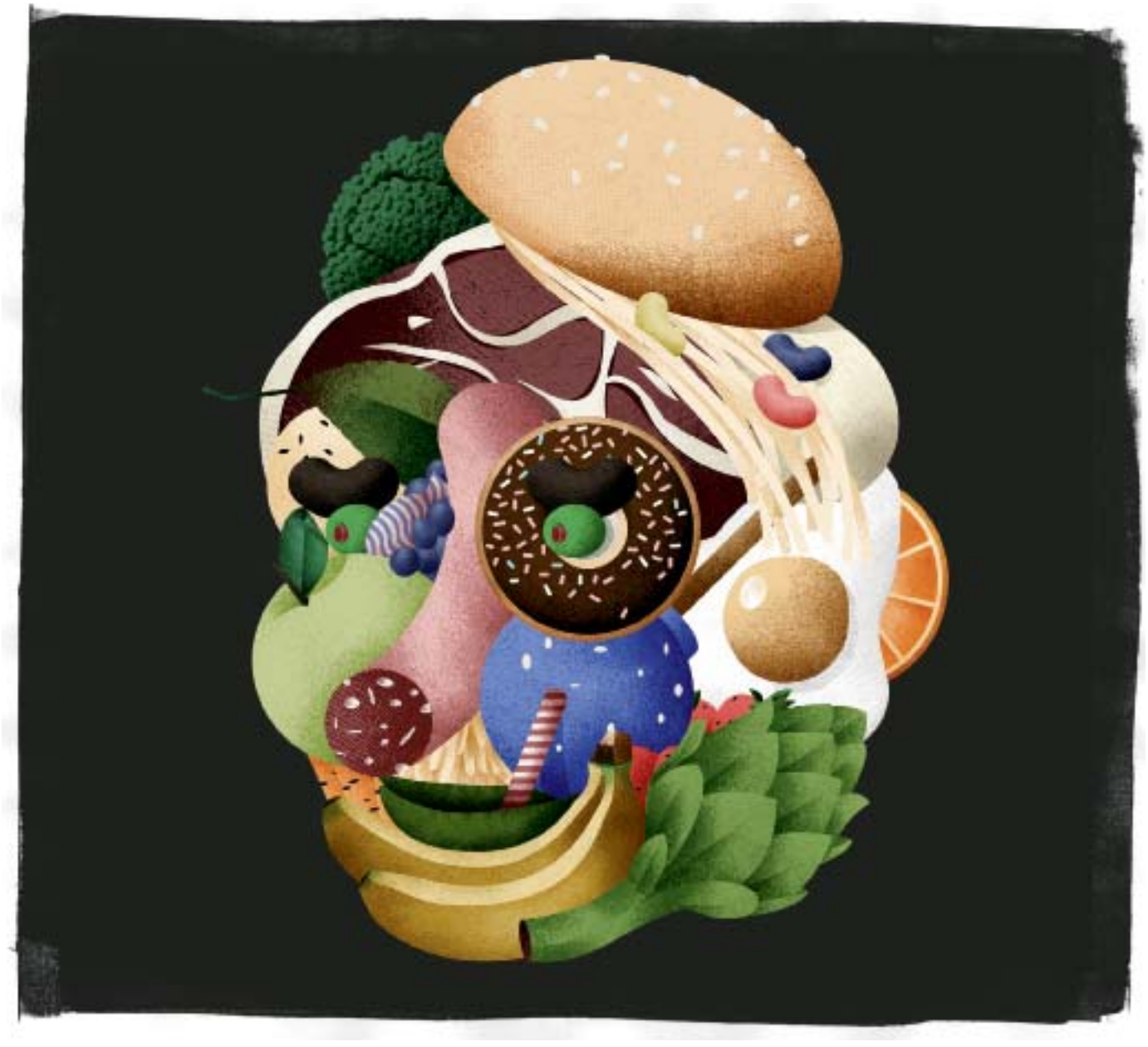
There is a separate aspect of appetite, however: the desire to eat based on pleasure. When someone consumes food that tastes good, neurons fire in the brain's reward center, the same area that's activated by sex and nicotine. This process explains how food can be addictive, and why people get so much joy out of eating good food.

Friedman and research associate Ana Domingos turned to mice to test the interactions between the hunger and pleasure pathways. They wanted to see whether leptin—and therefore starvation or obesity—could change the pleasure associated with food.

To control the activity of dopamine neurons associated with pleasure, Friedman and Domingos used a technique called optogenetics that was developed by HHMI early career scientist Karl Deisseroth at Stanford University. It allows researchers to use tiny lasers to selectively boost firing of specific neurons in the brain.

Friedman's team offered mice different combinations of choices between three drinks: water; liquid sweetened with natural, calorie-rich sucrose; and liquid sweetened with the calorie-free, artificial sweetener sucralose. They measured how long the mice drank each liquid.

Normally, if mice can choose between water, sucrose, and sucralose, they consume more of the drink with sucrose than of the one with sucralose. And they take more sips of either sweet beverage than of the water. But by using optogenetics to



Martin Nicolausson

turn up the activity of dopamine neurons, Friedman and his colleagues could change how much pleasure the mice experienced from each drink.

When the researchers activated dopamine neurons every time the animals lapped up sucralose, the mice began to prefer the artificial sweetener to natural sugar. In other words, the enhanced pleasure changed their normal preferences. Next, to test whether hunger made a difference, Friedman and Domingos repeated the experiment with mice that hadn't eaten in 24 hours. This time, activation of dopamine neurons to encourage sucralose preference didn't work; the mice drank more of the sucrose drink. When the scientists injected leptin into the hungry animals, however, mimicking a state of satiety, the sucralose once again became more appealing.

"This experiment suggests that the leptin is actually changing the hedonic value, the reward value, of the food," says Friedman. Since the dopamine neurons were being activated with the same intensity during each experiment, the scientists could rank the pleasure the mice got from each drink. And hunger, they concluded, changes these pleasure ratings.

"We can also use this method to test preferences for other nutrients, like fat or protein," says Friedman, "because it allows us to separate taste from reward. We can deliver pure taste through the sucralose or pure reward through the laser. Neither of these alone is more appealing to a mouse than sucrose, but together they are."

For humans, the results shed light on the interplay between metabolic signals that convey hunger and sensory inputs that convey pleasure. But further experiments are needed to show exactly how this system plays out in patients with obesity, which is associated with insensitivity to leptin.

One thing is for sure: if a food tastes better when you eat it after a period of undereating, it's not just your imagination. ■ – SARAH C.P. WILLIAMS

Tiny Breathing Plant Mouths

Keiko Torii is piecing together how stomata control plant respiration.

Jose Mandojana

Keiko Torii was drawn from an interest in cancer research to a career in plant biology, but keeps her eyes open for relevance in both arenas.

WHEN KEIKO TORII GAZED THROUGH THE MICROSCOPE AT A MUTANT *Arabidopsis thaliana* leaf covered in specialized cells called meristemoids, she saw more than a beautiful anatomic anomaly—she saw a new way to probe a fundamental system in developmental biology. ¶ Meristemoids are stem-cell-like precursors that give rise to a pair of guard cells, which form stomata—tiny pores on the skin of almost all land plants that are crucial for the exchange of water vapor and gas during photosynthesis. Close study of meristemoids has largely eluded scientists because the cells, by nature, are transient and few and far between.

"When I looked at this," Torii says, pointing to a poster-size image of the mutant leaf with a tightly packed honeycomb of DayGlo blue meristemoids hanging on her office wall at the University of Washington, "I thought maybe this could be an economical tool to study what makes a meristemoid a meristemoid."

To do so, she compared the readout of activated genes, known as a transcriptome, from the meristemoid-covered *Arabidopsis* mutant with the transcriptomes of two other mutants: one covered in only waxy pavement cells that shield plants from the elements, and one with stomata only. The study, published in the September 2011 issue of *Plant Cell*, revealed a novel protein that dramatically relocates during stem-cell divisions of a meristemoid.

Manipulating Genes

As a biology student in Japan, Torii was set on a career in medical research. "I wanted to study cancer," she says. But when she graduated from the University of Tsukuba in 1987, a buzz from the world of plant science turned her head. Researchers had successfully transferred specific genes from the microbe *Agrobacterium* into *Arabidopsis thaliana*, a tiny mustard plant commonly studied in labs.

"I thought, 'Wait a minute, that's kind of interesting. Now we can study plants by manipulating their genes in a much more sophisticated way,'" says Torii, a leafy-green cardigan draped over her shoulders.

Torii joined a plant lab for her graduate studies and today is a Howard Hughes Medical Institute–Gordon and Betty Moore Foundation (HHMI-GBMF) investigator and a world authority on *Arabidopsis* genetics. Her lab focuses on the development of stomata, which she calls the "tiny breathing mouths" of plants. These pores take up carbon dioxide from the atmosphere, which plants use to build biomass, and exchange it with oxygen and water brought up through the root system.

For nearly a decade, Torii's lab group has published a suite of papers that describe the proteins that act together to control stomatal development. The team zeros in on the function of each protein through experiments that manipulate how they are expressed.

POLAR Opposite

Their most recent transcriptome comparison revealed a protein that appears to help regulate how meristemoids divide asymmetrically, producing two cells with different fates. Intrigued, a graduate student in Torii's lab, Kylee Peterson, labeled the protein in a wild-type *Arabidopsis* embryo with a fluorescent tag and captured microscopic images of the plant's paired embryonic leaves, called cotyledons, every 30 minutes as they developed.

A time-lapse movie made from the images shows the expressed proteins grouping together on the polar opposite side of the cell from where a division will occur. After the meristemoid divides, the proteins typically increase in only one of the cells—the one that will continue on the direct path of stomatal development.

Once the meristemoid differentiates into a guard cell, the protein disappears. "It is very specific to this asymmetric dividing state and has this interesting behavior," Torii says. The team named the protein POLAR.

The group found that the behavior of the POLAR protein depends on a gene identified by Dominique Bergmann, an HHMI-GBMF investigator at Stanford University. The gene, *breaking of asymmetry in the stomatal lineage*, or *BASL*, stays in the nucleus of meristemoids but also relocates before asymmetric cell division and marks the cells that will eventually divide to become guard cells.

When *BASL* function is lost, the POLAR proteins "look very confused," Torii says, pointing at a time-lapse movie of the developing mutant plant. "They don't show this clean localization."

She hopes to learn what makes POLAR unique, which may help point to the differences and similarities between plants and animals. Although plant and animal cell divisions are fundamentally different, her other studies in stomatal development revealed remarkable similarities between transcription factors controlling development of stomatal lineage cells and of animal cell types, such as neurons and muscle fibers. In the future, Torii says, her studies may "provide unexpected molecular tools to manipulate cell proliferation and differentiation in animals for organ regeneration or to cure disease, maybe even cancers." ■ –JOHN ROACH

FOR MORE INFORMATION: To learn more about Torii's research on how plants establish a pattern for the placement of their stomata, see www.hhmi.org/news/torii20120111.html.

WEB EXTRA: See a video of POLAR at www.hhmi.org/bulletin/may2012.

Cells on the Move

Exploring the building blocks of cell movement, researchers are revealing delightful dances—and changing dogma.

by Elise Lamar • illustration by Jamie Cullen

Multicellular organisms harbor armies of cells on the move. Most are on goodwill missions—immune cells chase bacteria, and wound-healing fibroblasts rush in to fill gaps after injuries. Others, such as metastatic cancer cells, travel with deadly intent. The biochemical signals that set cells on a journey are as diverse as the tissues they move through, but the engine is driven by constant remodeling of a protein network built from a box of cellular Legos.

The cytoskeletal network of a cell is somewhat similar to an animal skeleton: it provides a scaffolding and a means for stepping forward. But unlike a bony skeleton, the cytoskeleton works only when it is unstable. Most locomoting cells move not by discrete steps but through continuous scaffold extension on the front end and destruction at the rear—a process sometimes likened to a treadmill.

The primary constituent of the scaffold is the protein actin—a molecule that never sits still. As the cytoskeleton extends, cells spin single actin molecules into long chains, or polymers, aided by a stew of molecular bundlers, cross-linkers, and branchers. The actin scaffold supports whatever protrusion a cell needs to crawl or pry its way through tissue. Disrupt the balance of construction and demolition and the cellular healers are going nowhere. Neither are metastasizing cells.

Given its importance, the cytoskeleton seems an obvious target for drug discovery. But the very ubiquity of cytoskeletal proteins has raised doubts about whether actin or any of its handlers could serve as pharmaceutical targets. "One prejudice has been that because cytoskeletal proteins are inside cells and abundant, they are undruggable," says Joan Massagué, cancer researcher and HHMI investigator at Memorial Sloan-Kettering Cancer Center.

But recent findings by HHMI scientists and others reveal that the cytoskeletal architecture differs significantly from cell to cell. "Immune cells and neurons put their Legos together in completely different patterns," says HHMI investigator Julie Theriot, who studies cell motility at Stanford University. If cells display specialized cytoskeletal structures, researchers have options for speeding the rescuers or blocking the invaders in a targeted way. In other words, the "undruggable" dogma is crumbling.

MOVING FORWARD

Topping the "Greatest Hits" page of Theriot's lab website is a video of disease-causing *Listeria monocytogenes* whirling around inside canine kidney cells. The cells are engineered to express fluorescent actin, and the bacteria inside them appear to stream a glowing "comet tail." But the tail actually represents dissolving actin filaments constructed by the host cell, whose cytoskeleton has been coopted by the bacteria to propel themselves through infected tissue.

"The comet tail video shows that the cytoskeleton is a powerful machine constantly running, poised to push things around," says Theriot. "All a bacterium needed was to figure how to tap into it." Her group discovered that a single surface protein expressed by *Listeria* was sufficient for "tapping into" the dynamic actin cytoskeleton and could generate comet tails when inserted in unrelated bacteria, or even plastic beads. The bacterial protein works by latching onto a host cell actin-binding protein complex called Arp 2/3, an actin "brancher." Once that happens, the Arp 2/3 complex stimulates growth of a new actin filament from the side of an existing filament, generating a branched structure that first pushes *Listeria* forward and then disintegrates in its wake.

Rather than conspire with bacteria, the primary purpose of the actin engine in a human cell is to move that cell to a specific location where it is needed. HHMI early career scientist James Bear at the University of North Carolina at Chapel Hill is trying to figure out what controls the migration by studying connective tissue cells called fibroblasts.

After an injury, chemical cues emanating from a wound lure reparative fibroblasts in a process called chemotaxis. Cells migrate toward the wound guided by a flat, foot-like structure known as the lamellipodium, from "lamella" (thin sheet) plus "podium" (foot). Lamellipodia constantly probe forward, advancing a cell by means of the persistent cytoskeletal engine as it assembles and dismantles actin branches. Until recently, many investigators believed that lamellipodia might also interpret chemical signals released from wounded tissue. But a study from the Bear lab published March 2, 2012, in *Cell* shows it's not that simple.

Bear genetically engineered fibroblasts without lamellipodia by depleting cells of the Arp 2/3 complex, blocking their ability to make highly branched actin. He then exposed the cells to traces

of a growth factor "lure" normally secreted from wounds. Even though their primary means of locomotion had been cut out from under them, the cells were able to move toward the growth factor using less efficient protrusions.

"This was a surprise—everybody in the field assumed Arp 2/3 was essential for chemotaxis," says Bear. On the other hand, the researchers reported, the loss of Arp 2/3 did adversely affect the ability of the cells to sense and respond to the surface they crawled over.

The take-home message is that coordinating external signals with cytoskeletal rearrangement is astonishingly complex, which could be good news: the more complex the process, the more opportunities for intervention. Take cancer cells, for example. Bear points out that in terms of motility, metastasizing cancer cells, though frighteningly effective, may just be generalists. "Metastatic cells are like the winners of the decathlon," he says. "They have to win 10 different events but only passably well." Tripping over a hurdle may be sufficient to put them out of the game.

THE SPECIALISTS

Actin and its brancher, the Arp 2/3 complex, are the nuts and bolts of the cytoskeleton and therefore may not be good starting points for designing drugs to perturb motility in a targeted way. Better candidates may be found in specialized actin bundlers or cross-linkers, which mold the scaffolding underlying specialized "feet" and other protrusions.

Among the bundlers is a group of proteins called coronins. In successive *Cell* articles, published in 2007 and 2008, Bear reported that an actin-binding protein called coronin 1B controlled the extent of actin branching by putting the brakes on the Arp 2/3 complex. Without coronin 1B, the cytoskeletal network was elaborate but rigid, causing fibroblasts to move more slowly—a big liability for a wound healer.

A different coronin, subtype 1A, appears critical for avoiding catastrophic immobilization of immune cells. Collaborating with Bear, HHMI investigator Jason Cyster reported in a 2008 *Nature Immunology* paper that in mice with a mutation in the gene encoding coronin 1A, T lymphocytes could not exit their birthplace, the thymus, to activate an immune response in peripheral tissues.

"These mutant mice have no peripheral T cells and were highly immune compromised," says Cyster, of the University of California, San Francisco (UCSF). The researchers also reported that a patient with severe combined immunodeficiency, or SCID, had coronin 1A mutations, suggesting that perturbing actin branching in a way that paralyzes cells is not insignificant but rather promotes a deadly disease.

Metastasizing cancer cells show protrusions reminiscent of lamellipodia but they are likely specialized for specific cellular environments. Some cancer cells express high levels of yet another coronin, coronin 1C, suggesting that changes in actin branching may enhance tumor cell invasion. Bear's lab is examining cultured cells and animal models to determine whether upregulation of coronin 1C stimulates actin cycling in a way that enhances motility in human melanoma cells.

For most of his career, cancer researcher Massagué has investigated signals that fire up the cytoskeletal engine; he is also

Leah Fasten

Jason Cyster studies the molecular cues that guide immune cells as they mature within lymph nodes and then move out into the body.

evaluating the effect of actin-interacting proteins on metastasis. In 2005, his lab group identified 18 "signature" genes associated with lung metastasis of human breast cancer. Most of them encoded factors that cells use for communication, like cytokines and their receptors. But one, called *fascin*, encoded a protein that bundles actin filaments into rods supporting spiky protrusions called invadopodia (picture lean lamellipodia armed with pickaxes). Blood and muscle cells occasionally use invadopodia to grasp a surface, but they are most common in tumor cells.

"Cells use fascin protrusions to pry through layers of cells—for example, those lining lung capillaries," says Massagué. "It makes complete sense that breast cancer cells would find a way through the bloodstream into the lungs by augmenting invadopodia power."

Japanese scientists seeking tumor inhibitors based on natural products have identified an anti-fascin molecule called migrastatin from *Streptomyces platensis* bacteria. Massagué and chemist Samuel Danishefsky, of Columbia University and Memorial Sloan-Kettering Cancer Center, have teamed up to create and test potent migrastatin analogs to slow movement of metastatic cells; in work published September 13, 2011, in the *Proceedings of the National Academy of Sciences*, Danishefsky reported that some of those analogs effectively block metastasis to several sites, including liver, heart, kidneys, and spleen, in a mouse model of human lung cancer.

A direct link between coronins and metastasis has not been confirmed, nor have migrastatin-type drugs been tested in a clinical setting. But two exciting concepts emerge from these studies: One is that actin accessory proteins modulate cytoskeletal rearrangements related to the motility of either healers or invaders. More significantly, these factors are diverse in the way they bind to and mold actin filaments, suggesting it may be possible to tinker with one interaction without perturbing another.

James Bear studies wound healing to learn how external signals are coordinated with cytoskeletal rearrangement in migrating fibroblasts. Julie Theriot focuses on fish scale keratocytes—highly motile cells that rapidly repair skin lesions.

THE DIRECTORS

Targeting actin accessory proteins such as coronins might be a viable strategy in some immune disorders. In their coronin 1A mouse mutants, Cyster's team showed that the signaling apparatus that lymphocytes use to find their way out of the thymus, a receptor called S1PR1, was intact. Yet cells remained paralyzed, as they couldn't move their lamellipodia because of coronin defects, a situation analogous to the crippled chemotaxis displayed by Bear's lamellipodia-less fibroblasts. These experiments suggest that the converse may also be true—the motility of cells with a perfectly normal cytoskeleton could be halted if the signals regulating it are blocked.

The signal detected by the S1PR1 receptor is a lipid called sphingosine-1-phosphate (S1P), present in blood and lymph. Cyster's group has shown that when mature immune cells are ready to leave lymph nodes to travel to target sites, they move toward node exit doors by detecting faint traces of S1P in the circulation via the S1PR1 receptor. In work published September 30, 2011, in *Science*, his lab demonstrated the converse: that the receptor temporarily shuts down when immature cells need to get back in to the node.

In 2010, the FDA approved use of a fungal derivative drug called fingolimod (FTY720) to treat multiple sclerosis, a condition characterized by an autoimmune response against cells of the patient's own nervous system. Chemically, fingolimod resembles S1P and likely works by acting as a decoy and binding to S1PR1, jamming its deployment signals to the cytoskeleton. "The current hypothesis is that FTY720 acts as an immunosuppressant by inhibiting lymphocyte egress from lymph nodes," Cyster says. But he cautions that other mechanisms are also possible.

MOVING BACKWARD

Yale University cell biologist Tom Pollard is a pioneer in cytoskeletal research. Not only did his lab group discover the Arp 2/3 complex, his team was also the first to image fluorescently labeled actin filaments forming in real time. He remembers his fascination with amoebas in high school in the 1950s. "Back then I wanted to be a gremlin inside cells to see how these things happen."

Four decades later, just such a gremlin would testify that crawling cells first advance some kind of protrusion, lean forward to extend it (often by actin branching), simultaneously demolish the rear scaffolding, and then let go and scrunch forward.

Lavish attention has been paid to step one, in part because protrusions exhibited by motile cells from amoebas to white blood cells called neutrophils are often big, easy to image, and highly photogenic. But Theriot is addressing the equally critical but much less documented "anti-event"—namely, how the back end of the cell lets go. To do so she studies keratocytes, highly motile cells that are found in the basal layer of the epidermis. As a model, Theriot uses fish scale keratocytes, which rapidly repair skin lesions.

Like fibroblasts, keratocytes project a lamellipodium filled with branched actin. But in 2010, Theriot reported in *Nature* that deconstruction of that meshwork, a process necessary to keep the

Bear: Paul Fetters Theriot: George Nikitin / AP, ©HHMI

"It was a big surprise that we could look through a fly pupae and see R8 cells developing in synchrony. When I saw that, I knew we had something unique."

Larry Zipursky

treadmill moving, required recruitment of a form of myosin—a motor protein filament common in muscle—to the actin cytoskeleton at the rear of the cell, which literally ripped the actin fragments apart. Without that destruction, cells couldn't move because their cytoskeleton was too stable, analogous to how coronin loss slows cells by making the cytoskeleton overly stiff.

How rapidly the cytoskeleton undergoes cycles of construction and demolition directly determines cell speed, which in keratocytes is roughly a fraction of a micron per second. Factoring into that equation is tissue adhesiveness. "If adhesion is too low, myosin activity keeps a cell running in place," explains Theriot. "But on a surface that is too sticky, keratocytes have difficulty pulling up their backside to glide along."

In a 2011 follow-up *PLoS Biology* study, Theriot quantified every move a keratocyte makes on "sticky" versus smoother surfaces—how fast actin filaments form and dissolve, how much traction the cell gets, how its shape changes—so she could calculate cell speed in various microenvironments. "Cells of the immune system may travel through the bloodstream, inflammatory environments, or layers of epithelial cells where things could get stickier," she says. Knowing how to calculate speed through different tissues could come in handy when devising ways to speed up cells or stop them in their tracks.

MARCH OF THE GROWTH CONES

Orkun Akin started his career playing soccer with the actin cytoskeleton. As a UCSF graduate student working with R. Dyche Mullins, Akin used a cell-free system to analyze motility by tweaking concentrations of actin, Arp 2/3 complex, and other actin-binding proteins. Without the boundaries of a cell, he measured "motility" based on how well the "motility mixture" kicked around a polystyrene bead in a dish, similar to propulsion of *Listeria*. His observations, published in *Cell* in 2008, suggest another mechanism of actin branching.

Now a postdoctoral fellow in the lab of HHMI investigator Larry Zipursky at the University of California, Los Angeles (UCLA), Akin is imaging the cytoskeletal machines guiding nerve cell axons, to form synapses—neural connections—between R8 photoreceptors in the *Drosophila* eye and the fly's brain. During synapse formation those machines, called growth cones, creep forward, seeking the right target.

Zipursky's group and others are making headway in understanding the cell surface receptors, signaling molecules, and cytoskeletal proteins that regulate growth cone movement in the fruit fly. Much of the work on the developing visual system has drawn on the power of the fly model, which allows scientists to genetically manipulate specific neuronal cell types. A major limitation to linking gene function to growth cone motility, however, has been the lack of a robust system for visualizing growth cone movement in live animals.

To address this challenge, Akin teamed with UCLA neurobiologist Joshua Trachtenberg to build two-photon microscopy to follow development of R8 growth cones in flies. The work led to the creation of a remarkable video of R8 growth cones forming connections in the intact animal. First, some 750 amorphous R8 photoreceptor growth cones glowing green with actin filaments hover like a fleet of *Close Encounters* spacecraft over the optic lobe landing pad. Some hours later, each R8 growth cone extends a spiky, fluorescent finger-like extension, a filopodium, into the region of the optic lobe where it will make synapses. This action is followed by extension of the rest of the axon to the same region.

"It was a big surprise that we could look through a fly pupa and see R8 cells developing in synchrony," says Zipursky. "When I saw that, I knew we had something unique."

Akin will now determine how that choreography is disrupted in flies with mutations in various signaling proteins. "Growth cones go from a stalled morphology abruptly to a moving state and then stop again," says Akin. "We know the signal that activates the movement and its receptor, and now we want to know what role actin dynamics plays in this transition and how signaling factors regulate that process."

Clinical applications of the photoreceptor work are far off, but Zipursky sees obvious relevance to stem cell–based replacement therapies aimed at regeneration. "Knowing how to wire neurons up properly will require knowing what's going on biochemically inside a growth cone," he says.

And the success of the multiple sclerosis drug fingolimod, which alters cell motility, suggests that this goal is not unrealistic. The factors that drive the cytoskeletal engine are not, in fact, undruggable. Engine components themselves, like coronins and fascins, could be next on the list.

Akin, buoyed by the youthful optimism that drove him to build a microscope, agrees. "The more we focus on specific cell types, the more insight we may gain about whether cells in any disease model have a cytoskeletal Achilles heel." ■

WEB EXTRA: To see the cells described in this story in motion, visit www.hhmi.org/bulletin/may2012.

ENTER THE SAMURAI

Loren Looger likes to solve other people's problems—at least their technical ones. That's working out well for his Janelia Farm colleagues.

by Jennifer Michalowski
photography by Dustin Aksland

IN THE CORNER

of Loren Looger's office, a jumble of colored leather and shoelaces lies in a heap: black and red soccer cleats for games on the nearby field; a pair of sleek, red soccer shoes for when the weather forces games indoors; high-top basketball shoes; bright-green running shoes; and some weathered Tevas for mucking around in the creek. Glancing at the pile, Looger says he's had to trim back his activities since coming to the Janelia Farm Research Campus six years ago.

Cutting back has been tough for a man who admits to being "interested in everything," but he's given up most of his hobbies to focus on his research program and, in off hours, indulge in silliness with his four-year-old son, Hampton. The kayak commute he envisioned when he moved to the riverside campus never had a chance.

The long workdays have done nothing to squelch his far-flung curiosity, however. Fortunately, he has found a way to let his scientific pursuits embrace diversity as much as his athletic ones. As his pile of footwear attests, Looger—sporting moss-colored velvet slip-ons—believes in having the right tool for the job, and his lab is dedicated to making that possible. His mission at Janelia Farm, he says, is simple: "do whatever needs to be done."

Unlike many scientists, Looger doesn't frame his work around a central question. Instead, by building molecular tools that let his collaborators explore their own questions in new ways, he has constructed a research program that branches into a broad range of biological investigations. At Janelia, where a central goal is learning how circuits in the brain process information, doing what needs to be done means improving researchers' abilities to visualize neurons, monitor their activity, and manipulate their behavior.

With his knowledge of protein structure and function, Looger can build tools that allow researchers to explore all kinds of biology. He says such tools can be truly transformative for the field of neuroscience, where so much remains unknown. "A little insight can go a long way when applied to questions that are wide open," he says.

With the success he's had so far, Looger is coming up with strategies—some rather unconventional—to maximize the impact of his work. He's not often in the lab, but that doesn't mean he's not doing science. He spends most of his day in front of a computer—scouring DNA sequences in search of molecular tricks he can borrow from evolution, using them to alter proteins' properties in predictable ways, and planning assays to screen for useful tools. He is also likely to be found sifting through articles about research for which his tools might be useful or proposing a new collaboration while he fetches a cup of tea from the campus pub. He calls himself a protein engineer. His Janelia Farm colleague Karel Svoboda calls him a samurai.

WHAT'S CALCIUM GOT TO DO WITH IT?

"Loren is the consummate collaborator. He has a very unique skill set, and he is looking for damsels in distress," Svoboda says. "He's the kind of person who loves getting involved in other people's problems, in the very best sense."

For Svoboda, who investigates the neural circuits that link sensory information to behavior, the most urgent problem is a lack of adequate tools to watch nerve cells signal one another in the brains of active animals. He approached Looger during Janelia Farm's earliest days, asking the biochemist when they met in 2005 if he could build a protein that signaled the presence of calcium inside cells.

Looger—fresh from a postdoctoral stint in a plant biology lab—couldn't imagine what calcium had to do with the brain. Svoboda explained that soon after a nerve cell fires, calcium surges inside the cell. By watching the ion's concentration grow, neuroscientists can monitor neural activity. Protein sensors that emit a fluorescent light to signal the presence of calcium had been used in animals since the late 1990s, but the signals were too weak to reveal much meaningful activity.

By solving the structure of a recent calcium indicator and tweaking its sequence to swap four of the protein's amino acids for different ones, Looger's team created an indicator that bound calcium more tightly and fluoresced at least three times as brightly.

The most in demand of any of the tools he has developed, that indicator, GCaMP3, has been distributed to hundreds of labs

where it illuminates neural activity that went unnoticed with earlier sensors. Still, neuroscientists are demanding a suite of similar tools that excel at different aspects of calcium sensing, so the overall effort to build better genetically encoded calcium indicators has, like GCaMP3, spread beyond Looger's lab. Thanks to a large-scale push to generate and evaluate new versions of the protein, GCaMP3 has been mostly superseded by GCaMP5, which produces even less background fluorescence, gives a greater signal in the presence of calcium, and picks up more activity in the brains of living animals. Looger remains integral to that effort, but with a team of Janelia colleagues now sustaining its momentum, he has diverted most of his attention to new projects—lots of them (see Web Extra, "A Kaleidoscope of Projects").

Each project has its own quirks, but the modular nature of proteins makes the job easier, Looger says. If nature has evolved a protein that lets an ocean coral glow red far beneath the sea, the relevant parts of that protein can be borrowed and adapted to bring the same fluorescent hue inside the lab. Likewise, a brittle star whose predator-dazzling luminescence triggers fluorescence that lingers for days offers clues to a longer-lasting "integrator" that could record a history of neural activity. By changing the genetic sequence that encodes any protein, Looger, using "intuition and a relatively easy bag of tricks," can alter the molecule in predictable ways, shifting its shape so it becomes more stable or binds more tightly to its target, for example.

Marveling at the opportunities he has to affect science by solving biochemical puzzles, Looger says he can imagine few careers that could be as invigorating, satisfying, and just plain fun. "Science," he says, "is an absolute scream." Yet he insists that his path to Janelia Farm has been almost entirely haphazard. "If any one of 10 different things hadn't happened, I wouldn't be here."

WANTED: TOOL BUILDERS

For much of his life, Looger assumed his future was in mathematics. But when he realized as a graduate student that a career in the field would be less about the puzzle-solving camaraderie of youth math camps and more about a solitary pursuit of knowledge, he altered his course. He fled to biology, he says, selecting a biochemistry program at Duke University largely because his girlfriend, Covington Brown (now his wife), was working nearby. Four years later, he left Duke with a Ph.D. in biochemistry and no plan for the future. An unexpected phone call determined his next step: Wolf Frommer, a plant scientist at Stanford University, about 45 minutes south of San Francisco, had read about the protein biosensors Looger designed as a graduate student. He wanted a reagent to detect glucose inside living plants. Looger, who happened to be traveling on a train outside San Francisco, told Frommer he would come to his lab to discuss the matter straight away. By the end of the day, he had accepted a postdoctoral position.

In Frommer's lab, Looger grappled for the first time with the challenges of creating sensors that function inside living cells, helping to engineer not just sugar sensors (the main task) but also a protein that would detect a different plant metabolite,

Loren Looger, who calls science "an absolute scream," considers himself lucky to devise tools for neural imaging plus studies of tuberculosis, malaria, diabetes, and cancer.

glutamate. As a side project, Looger helped test the glutamate sensor in neurons, which use the molecule as a key signal transmitter. Soon after that first dabbling in neuroscience, he set out to land a job at HHMI's nascent Janelia Farm Research Campus.

As Janelia Farm began recruiting its very first lab heads, HHMI leaders had made clear that they wanted tool builders to be an integral part of the scientific community, where they would contribute to an anticipated synergy between technology development and biological research. When Looger stood before the selection committee in red bell bottoms and a flowered shirt to convince its members he had the skills and creativity they needed, he unabashedly announced that he knew nothing about neuroscience that he hadn't read in the past two weeks. The roomful of accomplished neuroscientists listened with undisguised skepticism to his proposed plan to "reengineer the brain," and Looger began to regret not applying for other jobs.

That's when Svoboda approached him to consider developing new calcium sensors. And Janelia group leader Scott Sternson, who was also applying for a job at Janelia, asked Looger if he could help design ion channels that would respond to novel drugs so biologists could manipulate brain activity (see February 2012 *HHMI Bulletin* Web Extra, "Cowboy Chemistry"). Looger was game. So when Janelia Farm director Gerry Rubin, impressed by Looger's bravado and open mind, surprised him with a job offer—as long as he promised not to work on the project he had proposed in his seminar—Looger didn't hesitate.

bacterial DNA is manipulated and three-dimensional protein structures are examined, feels industrious but calm. Step into a smaller windowless back room, however, and it becomes immediately apparent that Looger's team is churning out high-volume science. Plastic plates, each sectioned to contain 96 populations of bacteria, are stacked high on counters and incubators. Looger says the system is set up to isolate as many as 10,000 different proteins from bacterial colonies and crudely characterize their biophysical properties—fluorescence, stability, and light absorption, for example—in a day. Yet there is no bustle inside this room. Robotic instruments handle the more tedious tasks of protein design with quiet precision.

All that effort, Looger emphasizes, is ultimately about getting working tools into people's hands. New tools are thoroughly tested, not just in living cells but in living organisms, and adjusted as necessary to make them more practical. "Loren is not out to prove anything, he just wants to get the right tool to the right person so they can learn something new about biology," says Luke Lavis, a chemist with whom Looger recently designed a system to target chemicals to specific cells by masking them with chemical shields that can be removed only by a corresponding enzyme. The two tool builders share a friendly rivalry as to whose technique will yield the best results, but ultimately they are working toward common goals. That's what being a tool builder is all about, Looger says. "If I find a tool in the gutter and it works … we're done here."

"LOREN IS NOT OUT TO PROVE ANYTHING, HE JUST WANTS TO GET THE RIGHT TOOL TO THE RIGHT PERSON SO THEY CAN LEARN SOMETHING NEW ABOUT BIOLOGY." **LUKE LAVIS**

Six years of immersion in the Janelia Farm community have given Looger a new perspective on the complexity of the brain. "My naïve idea, until I actually got here, was that a bunch of neurons hook together to make a brain, and they all basically do nothing until they decide to signal something. That turns out to be absolutely not the case." Working alongside neuroscientists—huddling in a tiny room searching for glimmers of activity in a zebrafish brain, or witnessing unexpected behavior in a worm expressing a slightly toxic protein sensor—has given him an understanding that textbooks and journal articles could not. "In the beginning, I was clueless about what people wanted tools to really do, but now I get it."

To generate and evaluate their tools, biologists and chemists work side by side in Looger's lab. Graduate students, technicians, and senior scientists pursue their own projects with considerable autonomy and independence—an advantage, they say, of the lab's diverse portfolio. Their airy, glass-walled workspace, where

HYPER TO COLLABORATE

Despite his accumulating successes, Looger acknowledges there's little glory in designing and optimizing reagents for other people's experiments. "Being a toolmaker can be a bit thankless," he says. No matter how much it advances science, "the BBC is never going to call you up to talk about the calcium sensor that you made a few percent better."

He didn't come to Janelia Farm seeking fame, but it's an issue he thinks about a lot. To maximize the impact of his work, Looger knows he has to overcome a problem that stymies many toolmakers. Sensors that bind more tightly or shine more brightly than their predecessors tend to be reported in chemistry and engineering journals, which are not widely read by biologists. Subsequent publications, in which the sensors reveal something new about biology, might catch potential collaborators' attention—but at that point, the toolmaker's contributions have often been relegated to the fine print.

Looger doesn't wait for collaborators to come to him. He takes every opportunity—hallway run-ins at Janelia Farm or emails to unfamiliar researchers—if he thinks he can help.

He has a solution—or at least a strategy. "We are going to hyper-collaborate," he declares. "We'll send tools to 1,000 people, and even if just 200 of those acknowledge us, we'll be hooked into new fields. I have faith that it's going to work out."

Discovering ways he can contribute to projects he doesn't yet know he should care about—that's what energizes Looger most. Though his tools are born out of needs within the neuroscience community, those needs are often mirrored in other fields; in the brain, calcium is a sign of neural activity, but in red blood cells it can signal the presence of a malaria parasite, for example. And Looger's intuition and "bag of tricks" can be even more broadly applied. A conversation with him can careen from fluorescing starfish arms to the genetics of sex determination in no time, and when he talks about how fortunate he feels to be a protein engineer at Janelia Farm, he ticks off the fields he's involved with as evidence of his unbelievable luck: "We're not just working on neural imaging," he says. "Our tools are being used to study tuberculosis, malaria, diabetes, and cancer, to name a few. I've also been dabbling in lupus on the side."

Committed to his model of hyper-collaboration, Looger says he has 120 projects catalogued on his computer. A few are "someday" ambitions, but most merit Looger's active attention at least some of the time. A handwritten list of in-progress manuscripts runs two columns in Looger's notebook and helps keep things on track: circles and stars and sweeps of color compete for urgency, while a handful of completed items are emphatically stricken from the list.

Colleagues at Janelia Farm and elsewhere seek Looger out for his protein-modeling expertise, but he doesn't wait for people to come to him. "I definitely spam a lot of people," he laughs, meaning he never hesitates to stop by a colleague's lab or dash off an email to a stranger saying, in essence, "What if you had a reagent that did *this*? Would that be useful?" Usually the answer is yes. Sometimes, the answer is "yes, but that's not possible," but Looger doesn't seem to hear the last part.

That willingness to dive in and find out what works strikes colleagues as part of Looger's inherent optimism, but he says it comes largely from his outsider perspective. Because he's not entrenched in the dogma of his collaborators' disciplines, he says, the assumed limits of those fields rarely restrict his imagination. "I don't know what's impossible," he declares. "So we try a lot of things that people say will never work … and a lot of it has been successful." ■

WEB EXTRA: Learn about some of Looger's research projects at www.hhmi.org/bulletin/may2012.

bigger

Making Bigger Better

Scaling up research opportunities in introductory science courses requires a new way of thinking and working.

by Erin Peterson illustration by Robert Frank Hunter

Holli Duhon arrived at the University of Texas at Austin as an honors science student—who didn't really understand the process of science. "In high school, science was straightforward," she says. "The Nobel Prize was yours to claim if you just followed logical steps."

In a traditional program, Duhon could have maintained that assumption for years as she worked her way through textbooks and lectures. But instead, she—along with more than 500 other first-year students—joined the three-semester Freshman Research Initiative (FRI), a large-scale program started in 2005 that teaches through experimental research.

After spending her first semester learning basic research methods, she chose a project from 20-plus research "streams," ranging from biofuels to nanomaterials. Duhon decided on the nucleic acids aptamer stream aimed at examining the interactions of certain nucleic acids with an eye toward drug development. She spent two semesters searching for short DNA sequences called oligonucleotides that could bind a target protein from the bacterium *Burkholderia pseudomallei*, a pathogen that causes an infectious disease common in Southeast Asia called melioidosis.

The search was like looking for a needle in a haystack, but that needle had the potential to be very valuable. A tightly binding oligonucleotide could lead to a diagnostic test for melioidosis. Meanwhile, Duhon's fellow aptamer stream students looked for oligonucleotide sequences to bind target proteins linked to Parkinson's disease, diabetes, and Alzheimer's—all before wrapping up their sophomore year.

Duhon soon realized that real-world research didn't look much like the clean, streamlined labs she'd experienced in high school. "There are so many times you try out a protocol thinking it will work out brilliantly, only to find out that something fails on the first step. Or the last step. Or anywhere in between," she says. "I was not aware that science involved such creativity."

Duhon didn't find the oligonucleotide magic bullet, but she developed critical thinking skills, tenacity, and an appreciation for the challenges and joys of science in a way that more traditional courses don't often allow. More important, she wasn't one of a privileged few having this type of powerful experience; she was one of hundreds.

The University of Texas (UT) is one of many major research universities—along with dozens of smaller colleges—experimenting with classroom-based research opportunities for undergraduates. Sarah Simmons, director of UT's FRI, which is partially funded by HHMI, acknowledges that there are challenges to upending the traditional "lecture and lab" model for introductory science courses. Moving toward a research-based approach requires creating appropriate projects, for example, as well as staffing labs for longer hours.

Those issues get even trickier as student numbers climb from dozens to hundreds. But compared with a group of similar UT students, FRI students have better graduation rates—67 percent compared with 53 percent—and a higher likelihood of pursuing advanced degrees in science—32 percent compared with 9 percent.

For Simmons, those numbers indicate that making difficult changes will have a meaningful impact. "The status quo doesn't reach students early enough," Simmons says. "We need to invent a new paradigm."

Think Big

There's a growing drumbeat to increase research opportunities for undergrads, including pressing recommendations in recent reports released by the American Association for the Advancement of Science and the President's Council of Advisors on Science and Technology (see Perspectives & Opinions, "Engage to Excel"). Some major organizations already have a jump on these goals: the National Science Foundation supports thousands of students each summer through its Research Experiences for Undergraduates program. HHMI also provides funding for some 4,000 students to do life science research each summer and supports efforts to scale up research opportunities in the classroom.

Graham Hatfull, an early promoter of large-scale classroom research, created—and now helps oversee—a project that has grown from a few high school classrooms to 70 colleges and more than 2,000 students. A decade or so ago, Hatfull, an HHMI professor at the University of Pittsburgh, developed a course for high school and undergraduate students to discover, sequence, and annotate the genomes of bacteriophages, viruses that infect bacteria linked to human diseases such as tuberculosis. It was a small course that was perfectly designed to grow. The processes and tools were simple enough even for novice scientists to understand. The vast, unexplored territory gave students ownership of their projects, and the results were often notable enough to warrant publication. Even better, the work provided rich data for Hatfull's own bacteriophage research.

Hatfull worked with HHMI to tweak the model for the undergraduate classroom and then introduce it into college curricula around the country through the Institute's Science Education

Alliance (SEA). Since it was first introduced to college classes nationwide in 2008, SEA has had major successes, including two research papers in *PLoS One* and a paper announcing the genomic sequences of 138 bacteriophages. One of the *PLoS One* papers had nearly 200 student coauthors, and the genome announcement represented the contributions of more than a thousand students. Hatfull is convinced that the model can be applied to a wide range of projects. "[Faculty] who can identify a research-based platform that can be implemented on the freshman level while advancing their research programs will see a great impact," he says.

At the University of California, Santa Barbara (UCSB), biology professors Joel Rothman and Rolf Christoffersen, along with academic coordinator Douglas Bush, saw an opportunity for students to gain research experience working on a piece of a larger study by Rothman on the roundworm *Caenorhabditis elegans*. With HHMI funding, they developed a 3-week module as part of a 10-week sophomore biology course. Students learn to knock down certain genes in the worms using RNA interference, perform a chemotaxis assay to learn what odors the worms are attracted to (or repelled by), and then compare their results with other experimental findings. The research is designed to help identify genes involved in the worm's chemosensory signaling pathway.

After testing the concept with about 50 honor students last year and making some modest changes, they expanded it to a much larger audience: this year, some 800 students will participate in the *C. elegans* module. To accommodate all 30 sections that meet each week, the school opened two adjacent lab classrooms with three-hour lab sessions running from morning through evening, five days a week. The labs are taught by TAs, with help from two staff members and part-time undergraduate lab assistants. "We still have bugs to work out," says Rothman. "Nonetheless, we've already made several original research discoveries, and we're really excited about this. The results are something we plan to publish, not just in educational literature but also in the primary scientific literature."

Not all—or even most—students who are part of a large-scale research project will pursue science careers, but that's not the point, says David Asai, director of precollege and undergraduate science education at HHMI. "It's not just about adding scientists,"

Jay Sauceda

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Holli Duhon was one of hundreds of freshmen at University of Texas who did original research. She learned science involves creativity—and a tolerance for failure. Early exposure to research, says Sarah Simmons, is a powerful way to move beyond the status quo.

At the University of California, Santa Barbara, Rolf Christoffersen (left) and Joel Rothman revamped their teaching module to suit the pace and skills of novice student researchers.

he says. "We also need a lot more people who understand science—teachers, lawyers, journalists, and parents."

Simplify and Succeed

A significant stumbling block to creating a research experience in the classroom is finding projects that are small enough and straightforward enough for novices—but that also move a project ahead in a meaningful way. If a research project is a marathon, the collective work of students may move it forward only a single step or simply show researchers which roads are not worth traveling. But these results can be valuable.

Andy Ellington, a UT biochemistry professor who heads the aptamer stream, chiseled away at the larger scope of his aptamer-based research to find small but critical pieces where students could contribute. While each student's project is unique, the processes are similar enough that students learn the basic procedures together and go off to do research on their own. "We're not reinventing the wheel," he says. "In some ways, they can work together as a group and use one another's successes and failures to hone their technique for their individual ends."

About 10 percent of the students in each group produce something that Ellington describes as "interesting" and worth pursuing. Those who don't might team up with students who have had success, and the best—those who are sharp, enthusiastic, and have the "good hands" that are essential for lab work—often end up working in Ellington's lab a year or two later. Many of them go on to publish papers on their work. But it all starts with a very simple project.

At UCSB, Rothman, Christoffersen, and Bush learned quickly that they couldn't work with novice students the way they could with postdocs, who are typically much more proficient at the physical manipulations required for research. A procedure that a postdoc could perform on *C. elegans* in two minutes might take an undergrad just learning the process 20 times longer. That kind of time lag can confound findings.

Instead of trying to get students to do more, Rothman and his colleagues redesigned the experiments so students were less likely to introduce errors—or injure the animals they were studying. "It's like asking a student who has never been on a bicycle to enter a race," says Rothman. "We've had to build a bicycle that students can stay on without falling over and killing themselves." Adapting the teaching module required time and creativity, but students were better able to complete their research successfully.

For classroom-based experiences, researchers and instructors must navigate one of the most difficult parts of the research process—frequent failure. Most traditional labs are designed so that students who do everything correctly will succeed; in individual research projects, a positive outcome is never guaranteed. Instructors have learned to offer students early research experiences that give them the taste of success before they delve into unknown territory.

At the University of California, Los Angeles (UCLA), for example, classes of 20 to 25 students work in the lab of HHMI professor Utpal Banerjee on a range of projects studying the fruit fly, *Drosophila melanogaster*. In one project, students learn a clever genetic trick called "lineage tracing." They fluorescently label a group of cells in early *Drosophila* development and watch to see what tissues those cells eventually become part of.

The lab work is difficult, says Ira Clark, the academic administrator for the UCLA minor in biomedical research, and while failure is common, he, Banerjee, and instructor John Olson did their best to make sure it wasn't inevitable. Instead of designing projects in which only a tiny portion of *Drosophila* lines would

Lou Mora

yield a positive result, they were able to design one in which positive results were more common. "It is the nature of the project that if you do the experiments on 10 random lines, you are likely to get at least one—and in many cases several—positive results," he says. While some students may still see all negative lines, it's quite rare. "We wanted to give every student that discovery moment," he says.

As students move forward, however, there is no guarantee of success. Instead, they must find different ways of feeling accomplishment, whether it's creating new approaches to solving a problem or discovering something unexpected in a failed experiment. Duhon realized early on that she might be well-suited for research. "In most lab classes, you pursue an A and put the experience second," she says. "But in [the research course] the priority was not the grade. We needed to engage in the experiments and learn what it feels like to personally contribute to legitimate academic discoveries. I learned that I was willing to fail 99 times for one successful moment."

University of Georgia biochemistry professor Erin Dolan is taking an even broader approach. She is heading up a fledgling national network, called CUREnet, aimed at creating and sharing course-based undergraduate research experiences in biology. Started in 2011, the National Science Foundation–funded network is being initiated through a collaboration of about 25 programs across the nation that are already sharing best practices in teaching through course-based research.

Dolan expects to find common ground among programs. "There will be annual meetings, but we'll also have a website and social networking functions so that people can discuss what they've tried in their classrooms or share software that undergraduates might find useful, for example," she says.

Research and evaluation of these experiences are providing important data for professors to use to further develop and expand their courses. One of the most comprehensive surveys of broad-based classroom research is the Classroom Undergraduate Research Experience survey (CURE; unrelated to CUREnet). Over several years, Grinnell College psychology professor David Lopatto and colleagues have collected thousands of data points about classroom research and how it compares to more in-depth summer programs and traditional courses. Last year alone, 51 institutions participated in the CURE survey.

"We needed to engage in the experiments and learn what it feels like to personally contribute to legitimate academic discoveries. I learned that I was willing to fail 99 times for one successful moment." Holli Duhon

An Infrastructure for Growth

Many large-scale research programs, including Banerjee's *Drosophila* projects and Hatfull's bacteriophage work, are showing significant progress, but translating those successes to other schools—different sizes, different cultures, different goals—is a tall order. Faculty from successful institutions are sharing individual successes and best practices to create a framework that others can use to adapt existing programs and build their own.

Sarah Elgin, an HHMI professor at Washington University in St. Louis who runs the successful Genomics Education Partnership (GEP) that now includes more than 70 schools, has been refining this process for years. The GEP, which focuses on the "dot chromosome" of *Drosophila*, so-called because of its small size and condensed genetic material, is designed to help students work with large data sets to transform the genome's raw data into a more polished sequence through universally accepted annotation and finishing standards.

As the program grows, Elgin has found ways to share lessons learned to help others get their courses off the ground. She has run one- to five-day workshops, for example, and has set up a website (http://gep.wustl.edu) where faculty can share curricula and details of their approach. "It's got entries from different members about their class sizes, how the course was organized, and the hours they scheduled for the research and guiding their students in critical thinking," she says. "It's a place for people to look for help when they begin to think about bringing [research] into the curriculum."

The surveys showed where otherwise strong programs needed work, says Lopatto. "When we first started doing surveys, one of the lowest-scoring learning gains [overall] was in learning ethical conduct in the field," he says. "Program directors told us that they hadn't been formally teaching ethics or the proper conduct of research and that they would start doing so." Some individual programs found gaps in writing or discussion and changed their programs to strengthen those components.

But perhaps more important, the surveys showcased some of the powerful benefits of a research-based approach. In the self-reported surveys, students participating in classroom-based research experienced, to a somewhat lesser degree, an almost identical list of benefits as those in summer programs. From understanding the scientific process to the ability to analyze data, students in research-based courses tended to come out far ahead of their peers in traditional classes.

Looking Ahead

Opening up the scientific process to large numbers of undergraduates has shown early success. In a variety of measurable ways—from

(continued on page 48)

OPENING THE FLOOD GATES

To speed the hunt for disease-related genes, researchers are delving into the exome, the fraction of the genome responsible for encoding proteins.

by Sarah C.P. Williams
illustration by Dadu Shin

FOR 10 years, scientists knew that a severe form of microcephaly, an inherited brain malformation, was due to a mutation on chromosome 19. Christopher A. Walsh and other researchers had even narrowed the search for the mutation to a particular stretch of the chromosome. But the section was long and dense, spanning almost 148 genes. The task of identifying a single mutation among those genes was daunting.

"It was staring us in the face for a decade," says Walsh, an HHMI investigator at Children's Hospital Boston, "but it was in such a packed area of the genome that no one wanted to go after it."

Scientists had no way to quickly sequence many genes at once. They could painstakingly sequence the genes one by one, or they could sequence an entire human genome—far more expensive and just as time-consuming.

Finally, in 2009, a new automated method opened the floodgates. Called exome sequencing, it allows researchers to quickly piece together the sequence of the exome, the 1 percent of the genome that encodes proteins. Focusing on this small portion, where many disease-related genes had already been found, made sense.

Researchers admit, however, that exome sequencing ignores mutations in the other 99 percent of the genome—the regulatory sequences that influence whether a protein is made or how much is produced plus the stretches of nucleotides with unknown functions. And there's no shortcut for interpreting the data that come from exome sequencing. So, when the cost of whole genome sequencing drops, exome sequencing will likely become obsolete. But, for now, it's giving scientists a head start on studying the human genome.

In October 2010, barely a year after the first reports of exome sequencing being used to locate disease genes, Walsh published the gene mutations responsible for one form of microcephaly. He used exome sequencing to burrow into the 148 genes on chromosome 19 and found that mutations in *WDR62*, a gene expressed in developing neurons, are involved. Within months, before and after Walsh's discovery, two other labs used exome sequencing to do the same thing—and replicated Walsh's results.

"It was a mountain that no one could climb and then as soon as the tools were developed to make it easier, everybody could do it," says Walsh. Today, for many labs, exome sequencing is the go-to method to pin down genetic mutations responsible for rare diseases. And researchers who study more common afflictions—like heart disease and autism—are using it to make inroads as well.

> "The goal of my lab used to be to identify one disease gene per year; now, we're identifying one or two per week. It's like a dam opening up." JOSEPH G. GLEESON

For some researchers, exome sequencing is allowing findings that never would have been possible without the method. For others, it's speeding the pace of discovery.

"The goal of my lab used to be to identify one disease gene per year," says HHMI investigator Joseph G. Gleeson, who studies the genetics of pediatric brain disorders at the University of California, San Diego. "Now, we're identifying one or two per week. It's like a dam opening up."

SAVING TIME

Before 2009, Gleeson, Walsh, and others who wanted to find the gene mutations responsible for an inherited disorder had to build extensive pedigrees of families with the disease. The more family members they could find, the better the odds of uncovering the relevant mutations. Then, they used genetic linkage studies—a classic technique based on observations made in the late 1800s—to narrow down the location of the mutation.

When egg and sperm cells form, genetic material is shuffled between matching chromosomes to form unique combinations. The idea behind genetic linkage is that genes closest to each other are likely to stick together and be inherited as a bundle after this shuffle. So by finding known genes shared by family members with a disorder—and lacking in those without the disorder—scientists can deduce that the disease-causing mutation is nearby. But linkage studies are tedious—researchers must test dozens of family members for genetic markers. Even once they crunch the numbers, they are often left with a large swath of chromosome that may or may not contain the mutation they're looking for.

Each exome segment within this area must then be individually isolated and sequenced using a series of reactions. "In a typical project, there might be 200 genes in your candidate sequence and you were faced with running thousands of reactions to test for potential mutations," Gleeson recalls.

A handful of labs expanded this technique to isolate and manually sequence all the exons in a genome, a massive undertaking. Their success in using this method to identify genes, however, suggested that if it were made quicker and cheaper, it could be useful on a broad scale. During a six-month period in 2009, several research teams came up with an idea that made the technology more feasible, and labs across the country picked it up.

HHMI investigator Richard P. Lifton at Yale School of Medicine was among the first to realize there was a quicker way to sequence exomes. He proposed that by using a microarray to capture exomes from the genome, sequencing of the exome could be streamlined. At the same time, biologist Jay Shendure at the University of Washington, Seattle, was pursuing a similar idea.

"This was a natural next step to what else had been going on in the field of next-generation sequencing," says Shendure. In 2008 and 2009, he adds, it cost close to $250,000 to sequence a full genome, depending on the methods used. By comparison, the first exomes were sequenced for about $10,000, plus the initial cost of the sequencing equipment.

"Close to 3,000 disease genes had been mapped at that point and the obvious fact to us was that very few of these had fallen outside the exome," says Lifton. "So at a time when the cost of sequencing was still relatively high, it occurred to us that we could get a huge advantage if we could fish out the exomes and just sequence them."

Lifton worked with postdoc Murim Choi and NimbleGen, a private company, to develop an exome-sequencing platform. DNA that's been cut up into manageable sizes is screened using a microarray made with probes specific for markers throughout the exome. Then the captured DNA bits, which ideally make up the whole exome, can be sequenced.

As a proof of concept that the method could be used to discover disease-related genes, Lifton's lab used exome sequencing to take a close look at the DNA of a five-month-old Turkish boy diagnosed with Bartter syndrome, a rare disease characterized by low levels of potassium in the blood. Exome sequencing changed the child's diagnosis, showing that he had a mutation in a chloride channel protein involved in a different disease: congenital chloride diarrhea. Lifton's team got the result from the DNA of a single affected patient, with no need for dozens of affected individuals. Within a month, Shendure's team published its own proof of concept.

The power of exome sequencing was immediately clear to geneticists who had spent years toiling on linkage studies. The family pedigrees they'd built for particular diseases could be tackled in mere weeks rather than languishing on seemingly endless waiting lists.

Most recently, Lifton, in January 2012, identified two genes responsible for an inherited form of hypertension in 41 families. The genes encode components of a ubiquitin ligase complex never before linked to blood pressure; that work has advanced understanding of normal blood pressure control. Both Gleeson and HHMI investigator Christine E. Seidman at Brigham and Women's Hospital have used exome sequencing to diagnose hard-to-pin-down diseases (see Web Extra sidebar, "Exomes in the Clinic").

Brian Park

Richard Lifton helped make exome sequencing viable and has used it to make discoveries in blood pressure control and cancer.

SEQUENCING TUMORS

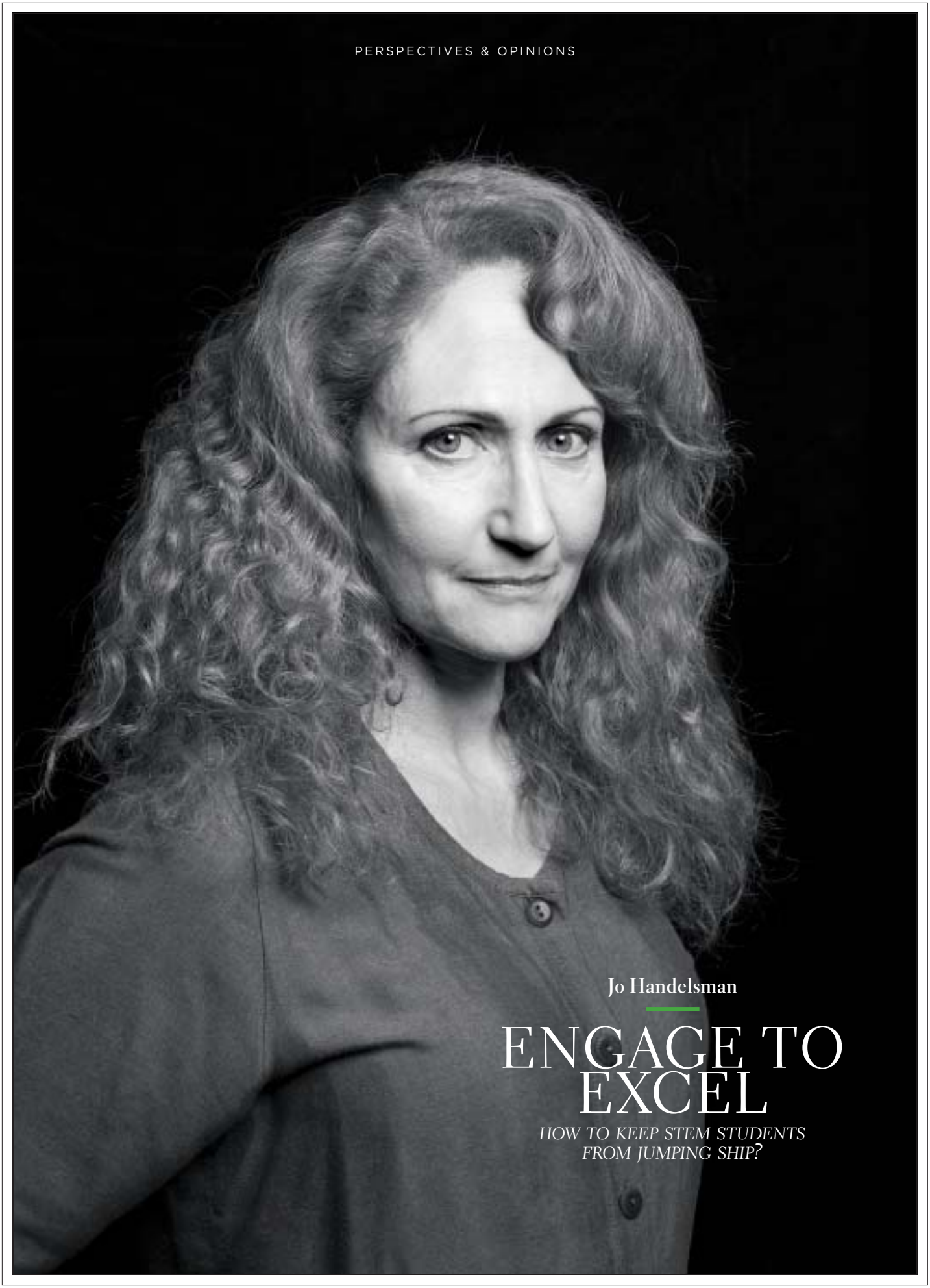
Exome sequencing is proving useful for studying tumors as well. Researchers sequence the exomes from a cancer patient's cheek swab or blood sample in addition to the patient's tumor tissue. They can compare the sequences to see how tumor cells have accumulated genetic mutations distinct from the patient's healthy cells.

Analyses of all the protein-encoding genes in a tumor have revealed mutations in genes that never would have been implicated in cancer, says HHMI investigator Bert Vogelstein of the Johns Hopkins University School of Medicine. In 2009, Vogelstein and his colleagues used exome sequencing to discover a mutation in a gene called *IDH1* in brain tumors.

"This was a gene that was thought to be involved in basic metabolism and no one would have thought to check whether it was mutated in cancer," says Vogelstein. Since then, scientists have found the same mutation in other cancers including leukemia. The discovery has led to a new area of research, he says, to understand how cancer cells alter their metabolism to survive.

Today, more than 25 cancer types have been subjected to exome sequencing, in many cases revealing surprises (see *Bulletin* May 2011, A Crowd in the Kitchen)—or at least newfound genes. In July 2011, Vogelstein and HHMI investigator Todd R. Golub of the Dana-Farber Cancer Institute separately published data online in *Science* on the exomes of head and neck cancers. They revealed a handful of mutations that could help drive the development of new therapeutics for the cancers.

(continued on page 48)



Jo Handelsman

ENGAGE TO EXCEL

HOW TO KEEP STEM STUDENTS FROM JUMPING SHIP?

Peter Ross

Of the students who enter college intending to major in science, technology, engineering, or math—the STEM fields—fewer than 40 percent complete a STEM degree. A 10 percentage point increase in retention would boost the ranks of STEM graduates by almost three-quarters of a million in the next decade. That's close to the goal of 1 million, according to a February report released by the President's Council of Advisors on Science and Technology (PCAST). Jo Handelsman, who co-wrote the report, explains why it will make a difference.

Why are we losing so many college students from science?
Students tell us that they leave science for three major reasons: introductory courses are uninspiring, their math skills are not strong enough, and many students from groups underrepresented in STEM fields cite an unwelcoming atmosphere from faculty who teach the courses.

PCAST says that keeping students interested in science is the way to go. What changes do you want to see?
Why not start with the audience already interested who are turning away for completely legitimate reasons that have nothing to do with what science is? College students who engage early in research are more likely to remain STEM majors and to perform well in STEM classes. We need to stop regarding research as only a culmination of an undergraduate education. Let's capture students with the thrill of discovery and inquiry in their first two years. And we need to address the math gap. If students aren't prepared for quantitative aspects of STEM studies, they won't be successful.

What needs to happen in math?
We have to accept that students are coming out of high school weak in math: 60 percent don't have the math skills to do college science. That's not a small group. Part of the problem is that math is typically not taught well in college. The PCAST working group couldn't find enough evidence to define a solution, so we proposed launching a national experiment in postsecondary math education to remove the math bottleneck. We want to see new players get involved. The people who use calculus are in math-intensive science and engineering fields. If we can get *them* to teach calculus, students will see the relevance of math to science.

Do college faculty want training in how to teach?
It varies. Some are extremely excited and are demanding it. We have a full house every year at the National Academies Summer Institute on Undergraduate Education in Biology, a one-week immersion course in the science behind successful teaching and student learning. With HHMI support, we've launched seven new summer institutes around the country. That said, there's a large segment, especially at research universities, who don't feel they can spend any more time on teaching than they already do, and they don't see any need for change. Many scientists think that, since they came through the system and are successful, the system works. We need to change that self-referential, nonscientific thinking because current faculty are not a model for all students.

How is this report different from others on U.S. science education?
I think the biggest difference is that this report went directly to the President, it recommends specific policy changes, and he's already started to take action. His budget includes more than $100 million in investments by the National Science Foundation (NSF) to improve undergraduate STEM education practices and a joint initiative by NSF and the Department of Education to study how to improve math education. We focused on mechanisms and levers to make change happen. The report recommends a multifaceted approach from government, academia, and industry at many kinds of universities and colleges.

Do you think you're at a tipping point?
Not quite, but we are on a very rapid upward slope. What's not there yet is getting university faculty on board. Changing a culture is hard. In the report, we discuss that challenge and cite successful efforts that have generated sweeping, cultural change.

INTERVIEW BY CORI VANCHIERI. *Jo Handelsman is an HHMI professor at Yale University. The PCAST report is available at: www.whitehouse.gov/ostp/pcast.*

Q&A

If you could invent an app for the iPhone, iPad, or any other mobile device, what would it do?

Tablet computers and smart phones are becoming ubiquitous, with apps for just about everything. Here, we asked four scientists to imagine the app of their dreams.

—EDITED BY NICOLE KRESGE

Miguel Godinho Ferreira

HHMI INTERNATIONAL EARLY CAREER SCIENTIST
GULBENKIAN SCIENCE INSTITUTE, OEIRAS, PORTUGAL

"My all-time desirable app would have to be for teleportation. A true 'Beam me up, Scotty.' Can you imagine? No more hustle of airports and cramped airplane seats … just think of a place, and you're there! Unfortunately, this is not likely to happen during my lifetime. Then again, one should never stop hoping! A more realistic idea would be a speech recognition app that actually works. This would finally take computers to the next level. No more fumbling with big fingers on little keyboards. You say it, and the machine writes it down. And no need to correct every word one by one. That's what folks at Apple are aiming at with Siri, I am sure. But she is not there yet."

Tzumin Lee

JFRC GROUP LEADER
JANELIA FARM RESEARCH CAMPUS

"Oftentimes, the greatest obstacle I encounter in my career as a scientist is effectively communicating my ideas to the public with my accented English. I would therefore like to invent an app—let's call it 'DeAx'—which would essentially 'deaccent' a non-native speaker's lecture in English. DeAx wouldn't take the speaker's words and reiterate them in an artificially contrived voice. Instead, it would tweak the little accents and discrepancies in the speaker's words, thus preserving the original tone and, most importantly, the speaker's enthusiasm about science."

Dianne K. Newman

HHMI INVESTIGATOR
CALIFORNIA INSTITUTE OF TECHNOLOGY

"I'd invent the 'Email Liberator.' This app would handle everything—it would politely decline all uninteresting invitations and unessential administrative requests; accept only a limited number of things that it would automatically sync with my calendar and forward to my administrative assistant; and reply to all collegial, postdoctoral, and student inquiries. At the end of the day, it would give me the low-down on the things that I needed to know about and sign off with the happy salutation: 'Free at last, free at last, thank the email liberator you are free at last!'"

Michael B. Eisen

HHMI INVESTIGATOR
UNIVERSITY OF CALIFORNIA, BERKELEY

"There are so many! One simple iPhone app would track the spread of viral infections. The app would record your movements. Then, any time you get sick, you would enter the details. Or, even better, you could use the phone to sense when you're sick—I bet the accelerometer could tell when you sneeze, and a simple thermal sensor could detect a fever. If enough people used the app, you could then track back to when you came in contact with someone with similar symptoms and figure out how you likely got infected. It would bring much higher resolution to our study of disease transmission and might suggest ways to prevent it. It could even warn you when someone who has a nasty cold is getting too close!"

Ferreira: Kevin Wolf / AP, ©HHMI Lee: Matt Staley Newman: Robert E. Klein / AP, ©HHMI Eisen: Noah Berger / AP, ©HHMI

chronicle

Exercise is clearly beneficial, and now there's scientific evidence that explains why time in the gym can help fend off one form of diabetes—and potentially other diseases. HHMI investigator Beth Levine has shown that exercise causes healthy muscle cells, like the ones seen here, to break down cellular junk, yielding raw materials for producing new proteins or energy for the cell. This process, called autophagy, may be the reason exercise protects against type 2 diabetes and other metabolic disorders.

Learn more about autophagy and exercise in Lab Book, page 42.

Congcong He / Levine lab

Bob O'Connor

A Posse on the Loose

TEN EXTRAORDINARY NEW YORKERS WHO WERE GIVEN A CHANCE will clasp their diplomas, flip their tassels, and make history on May 20, 2012, at the Gosman Sports and Convocation Center at Brandeis University outside Boston. The students are the science posse, a collection of urban-schooled, best in class who entered Brandeis four years ago as an innovative experiment in science education.

Would it be possible to group some really sharp, overlooked students and, with a combination of boot camps, mentoring, counseling, workshops, and peer support, coach them through the rigors of university-level academics to pursue scientific careers?

"It seems like we can," says Kim Godsoe, Dean of Academic Services at Brandeis. "We have. We've got this formula now. And it's really exciting, really transformative."

The program, proposed to the Posse Foundation in 2005 by Brandeis faculty member Irv Epstein and piloted with his grant as an HHMI professor, can boast tangible success. All 10 of the first science posse members are graduating, and seven will complete majors in science—chemistry, biology, and neuroscience. Six will pursue either an M.D. or Ph.D. degree. And one of them, Nana Owusu-Sarpong, was accepted to Tufts University School of Medicine through an early admissions program as a Brandeis sophomore. He will begin a joint M.D. and M.B.A. program this summer.

Meanwhile, the science posse concept has spread. Brandeis has launched another four groups of 10. The Brandeis science posse program—and a student in the most recent group, Steven Colon—were acknowledged recently by President Obama at the second White House Science Fair. Two other schools—the University of Wisconsin–Madison and Franklin & Marshall College, in Lancaster, Pennsylvania—have begun their own science posse programs, the latter based on the Brandeis model. Texas A&M University and Bryn Mawr College in Pennsylvania have committed to launch science posses in September 2013.

These successes, however, belie a deeper story—of struggle and setbacks, soul searching and salvation. Some of the first science posse members faltered academically, especially after their first year. Others struggled with personal problems, including the need to tend to sick parents at home. Still others grappled

with what many 18-year-olds at college face: questions of identity, career aspirations, and whether the initial interest in science could hold through four years of labs and long nights at the library. But all persevered and stayed connected to science in some way.

"I have changed my career course, like 50 billion times," says Yvonne Perez, one of the science posse members who'll graduate in May.

The child of Mexican immigrants, Perez grew up believing that becoming a doctor was the pinnacle of success. Venturing off the science track was therefore unacceptable. Yet, as she entered Brandeis and struggled through courses such as general chemistry, she questioned her own fitness for science—and almost gave it up. But the posse stepped in with academic help, moral support, and their highly visible status.

"They are the greatest source of motivation for me," she says, "the most brilliant people I have ever met."

As Perez realized that she was "part of this prestigious group," chosen for some of the same reasons as the others, she gained confidence—and a reason to keep from "slacking off."

Keeping science as her base, Perez branched off into a major called Health: Science, Society, and Policy. She plans, eventually, to obtain a Ph.D. in health or community policy. But she is still searching. "If you ask me again come May, I will tell you that I will be doing something completely different," she adds.

A similar search for a fit befell Usman Hameedi, who felt torn between his interest in medicine and a love of poetry. "There's science and there is humanity," he muses, "and they are seen as a dichotomy. Ah, but to combine them both—that would be the beauty."

And he is trying for that combination, considering a career as a science writer, or the new field of narrative medicine, in which patients tell or write stories as a way to heal.

Gliding into the Future

Four years may not have been enough exploration time for most posse scholars. A surprising six of 10 in this high-achieving group say they plan to take a year or two off after they graduate, the so-called "glide year(s)." While that was not exactly what Epstein envisioned when he proposed the posse as a means to retain diversity in the sciences, gliding is now a common practice between bachelor's and graduate degrees, and he is not worried that his posse students are gliding into the sunset.

"It actually makes a great deal of educational sense to do something different for a year or two after college instead of plunging right into further education," he says. "It shows great maturity."

Gliding is becoming more popular for students who want time to figure out what they want to do or to boost their résumés with job skills, community service, research, or clinical hours, says Godsoe.

For science posse members, there is something more. Many, when younger, did not have the exposure or resources to hunt for alternatives to a medical career. And once that door to exploration opened at Brandeis, posse members wanted to keep it open longer in preparation for doing something big.

But for those for whom a medical or science degree is certain, the science training itself may open the door to success.

"A person is very fortunate to be good at science because science can be applied to so many things," says posse member Gloriya Nedler. "It doesn't always work the other way around. So having the science background is like starting at the top."

With a strong interest in neuroscience, Nedler will apply to medical schools this June. In the meantime, she's been offered a full-time position at Harvard Medical School for the coming year to lead a study of observed disparities in the advancement of women of color in academic medicine.

"All of them have the potential to make some big impact on whatever they do," says biophysicist Susannah Gordon-Messer, who mentored the science posse for two years. "Because they are very strong, and very thoughtful, and very, very determined.

> "All of them have the potential to make some big impact on whatever they do because they are very strong, and very thoughtful, and very, very determined."
>
> SUSANNAH GORDON-MESSER

Hameedi, for example, plans to take a year or two off, possibly to travel. He learned in a class that schizophrenia affects Japanese differently than Americans, which prompted his curiosity to understand how culture can affect the course of mental disorders. He hopes to bring that knowledge of diversity and disease to his work in medical school—and transform medical care for people overlooked by the American medical system.

While no one can guarantee that he or the other five gliders will actually follow through with their plans for a higher degree in science—and more—everyone is betting on them.

As other posses follow suit, says Hameedi, the group is proud of what they accomplished. "We set the bar really high." ■ –TRISHA GURA

FOR MORE INFORMATION: See "Three's a Crowd, Ten's a Posse," in the May 2009 *HHMI Bulletin* (www.hhmi.org/bulletin/may2009/features/posse.html).

2012 Gilliam Fellows Announced

HHMI HAS SELECTED NINE STUDENTS TO receive the 2012 Gilliam Fellowships for Advanced Study.

Established in 2004, the fellowship program is designed to promote excellence and diversity in science and education. The Gilliam fellows, who are from groups underrepresented in the sciences or from disadvantaged backgrounds, will receive financial support for up to five years of study toward a doctoral degree.

"These students share a passion and aptitude for research that has been shaped by their unique backgrounds and experience. That diversity of perspectives is crucial for the growth of the scientific community," says Sean B. Carroll, HHMI's vice president for science education.

Gilliam fellows are selected from among students who have participated in HHMI's Exceptional Research Opportunities Program, which places undergraduates from underrepresented groups in the labs of HHMI investigators and professors. Eight of this year's Gilliam fellows are applying to Ph.D. or M.D., Ph.D. programs, and one student is in his first year of a Ph.D. program at Baylor College of Medicine. Each fellow will receive $46,500 a year to apply toward graduate studies.

FOR MORE INFORMATION: To learn more about the Gilliam Fellowship program, visit www.hhmi.org/grants/individuals/gilliam.html.

2012 GILLIAM FELLOWS

ROBERT AMEZQUITA
University of California, San Diego

DANIEL GARCIA
Harvey Mudd College

DERIC GRIFFIN
Louisiana State University & A&M College; Graduate School, Baylor College of Medicine

TIEN-PHAT HUYNH
University of California, Los Angeles

LAUREN RODRIGUEZ
University of California, Santa Cruz

KAILAN SIERRA-DAVIDSON
Harvard University

HUGO VEGA-RAMIREZ
University of California, Davis

ROBERT WARDLOW
University of Maryland Baltimore County

MARTHA ZEPEDA RIVERA
University of Washington

eLife Announces Editors, Launches Website

THE EDITORIAL BOARD OF *eLIFE*, THE NEW journal for life and biomedical science launched with the support of HHMI, the Max Planck Society, and the Wellcome Trust, announced the names of the more than 150 reviewing editors who will help deliver on the initiative's commitment to change peer review. Expediting the review process is one of the fundamental ways *eLife* will drive change in research communication.

Like the senior editors, who were announced in November, the scientists who make up the international Board of Reviewing Editors (BRE) represent the wide array of disciplines targeted for the *eLife* journal—from human genetics and molecular neuroscience to oncology and epidemiology.

A key goal for *eLife* is to improve the peer review process by offering rapid initial decisions, constructive peer review, limited requests for revision, and clear guidance to authors. Once the journal receives a manuscript, the senior editors will work quickly to determine whether it is appropriate for in-depth peer review. Suitable papers will be assigned to a member of the BRE who will review the article along with one or two additional reviewers. The BRE and reviewers will discuss their recommendations and make a final decision. Their decision letter, plus the authors' responses, will be published with the accepted version of the article.

The names of the BRE members are listed on the *eLife* website at elifesciences.org. The launch of the organization's website also marks the unveiling of the *eLife* logo, which represents life, growth, change, and diversity. The design symbolizes the journal's breadth of topics, inclusive approach, and commitment to changing the way things are done.

"Everyone wants to know if *eLife* will deliver on our commitment to sit in the top tier of science publishing," says Randy Schekman, the journal's editor-in-chief. "We believe the involvement of scientists of this caliber as senior and reviewing editors is another clear sign of that commitment. Prepare your papers now."

The journal will open for manuscript submissions in the coming weeks. ■

FOR MORE INFORMATION: The names of the new editors and information about manuscript submission can be found on the *eLife* website at elifesciences.org.

WEB EXTRA: Go to www.hhmi.org/bulletin/may2012 to hear the journal's editors and leaders from HHMI, the Max Planck Society, and the Wellcome Trust, talk about *eLife*.

Wyszynski Joins HHMI as Vice President for Human Resources

THIS PAST JANUARY, KATHY A. WYSZYNSKI joined HHMI as an officer in the recently created position of vice president for human resources. In her new role, Wyszynski oversees all aspects of human resources for the Institute, including human resources strategy, recruitment, benefits and compensation, visa administration, performance management, training and development, and employee relations.

Wyszynski is focused on creating a human resources culture that drives exceptional service in innovative ways, enabling the Institute to continue to attract, sustain, and inspire excellence in its employees. She plans to initiate strategic human resources programs designed to advance scientific excellence, foster engagement, and provide collaborative learning opportunities.

"It is important that we share a common set of values characterized by trust, collaboration, communication, and partnership and that we all take pride in our contributions big or small," says Wyszynski. "We want our people to feel really good about being a part of HHMI's successes."

Before coming to HHMI, Wyszynski spent 10 years in human resources leadership roles in the office of the Chief Administrative Officer of the U.S. House of Representatives. During her tenure at the House, she developed a Human Capital Strategic Plan, a competency-based performance management system, and a professional development program for staff.

Before joining the House, Wyszynski served in multiple roles, including head of human resources at the Henry M. Jackson Foundation (HJF) for the Advancement of Military Medicine.

"Kathy's combination of strategic human resources leadership experience and time spent working in a laboratory environment make her an ideal addition to the management team," says Cheryl Moore, HHMI's executive vice president and chief operating officer. "I'm very pleased to have her join us as we embark on new initiatives to support HHMI employees."

Looking back on her time spent with HJF and in public service, says Wyszynksi, it became clear that one of her key motivators

was doing work that matters. "Joining HHMI as vice president for human resources is an opportunity to leverage my previous experience and apply my skills and talents in new ways," she says. "To help drive the Institute's extraordinary mission of empowering and supporting the world's finest scientists and educators is an exciting prospect for me. Coming to HHMI was an easy decision." ■

Institute Launches New Investigator Competition

HHMI INITIATED AN OPEN COMPETITION in March aimed at appointing 20 to 30 new investigators. These appointments will enable the Institute to strengthen its community of researchers and bring innovative approaches to the study of biological problems.

"HHMI has a very simple mission," says HHMI President Robert Tjian. "We find the best original-thinking scientists and give them the resources to follow their instincts in discovering basic biological processes that will lead to better biomedical outcomes."

The initiative represents an investment of approximately $200 million by HHMI over the next five years. The competition is open to scientists at more than 200 institutions who are involved in basic biomedical research and related areas, from evolutionary biology to patient-oriented research. Eligible researchers must hold a tenured or tenure-track position and have between five and 15 years of experience since appointment as an assistant professor or equivalent position. The deadline for applications is June 13.

A panel of distinguished biomedical researchers will evaluate the candidates' applications, and all semifinalists will present their research at a scientific symposium at HHMI in April 2013. Finalists will be selected shortly after the symposium. Each new investigator will receive a five-year renewable appointment, worth about $1 million a year.

The HHMI Investigator Program currently supports approximately 340 scientists at more than 70 host institutions in the United States. Seventy-nine, or 23 percent, of these investigators are women. By appointing scientists as HHMI investigators—funding people rather than projects—the Institute provides long-term, flexible support that enables its researchers to pursue their scientific interests wherever they lead.

"We're betting on the individual, not necessarily on the specific research that they're conducting today," says Jack E. Dixon, HHMI's vice president and chief scientific officer. ■

FOR MORE INFORMATION: To learn more about the competition, visit www.hhmi.org/inv2013.

WEB EXTRA: Hear three HHMI investigators talk about their research and how HHMI advances science. Go to www.hhmi.org/bulletin/may2012.

James Kegley

Reduce and Recycle

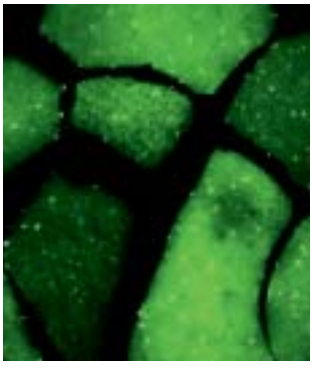
EXERCISE PROMPTS CELLS TO TURN UNWANTED PROTEINS AND CELLULAR JUNK INTO ENERGY.

Exercise is clearly beneficial, and now there's scientific evidence that explains why time in the gym can help fend off diabetes—and potentially other diseases. According to HHMI investigator Beth Levine, cells break down cellular junk to get extra energy, thereby cleaning house while you exercise.

Cells use a process called autophagy to recycle unwanted proteins and cellular structures. During this process, a double membrane forms around the cellular garbage. An organelle called a lysosome then fuses with the membrane and its enzymes rush in to break up the unwanted cargo, yielding raw materials for producing new proteins or energy for the cell.

Scientists have long known that stress can trigger a boost in autophagy, as the process helps cells adapt to changing nutritional and energy demands. Levine, a physician at the University of Texas Southwestern Medical Center, suspected that exercise might have a similar effect because it also increases cells' energy demands. To test this idea, she and her colleagues used transgenic mice whose cells produce a green glowing signal when autophagy occurs. After 30 minutes of running on treadmills, the mice showed increased autophagy in their heart and skeletal muscle cells as well as in their liver and pancreatic cells.

Next, the scientists created mice that could experience autophagy under normal conditions but were unable to ramp it up during exercise or starvation. In a paper published January 18, 2012, in *Nature*, the researchers report that these mice were unable to increase their muscle glucose uptake and had decreased endurance. And, unlike normal mice, exercise did not protect them against diabetes induced by a high-fat diet. During exertion in normal mice, an enzyme called AMP kinase helps cells take in more sugar from the bloodstream. However, this enzyme wasn't activated in Levine's mice. Several oral drugs used to treat type 2 diabetes work by activating AMP kinase, and it appears that autophagy induced by exercise does the same thing.



Muscle cells experience increased autophagy (signified by glowing green dots) during exercise.

These findings suggest that increased autophagy may be the reason exercise protects against type 2 diabetes and other metabolic disorders. Levine also thinks it's possible that activation of autophagy may contribute to other health benefits of exercise, including protection against cancer, neurodegenerative diseases, and aging.

■ –NICOLE KRESGE

IN BRIEF

WHY YOU CAN'T CLONE A HUMAN

HHMI scientists recently discovered why a cloning technique called somatic cell nuclear transfer works in animals but not in humans. The study, done at the Harvard Stem Cell Institute, brings scientists closer to using stem cells to study disease and create healthy tissue.

Somatic cell nuclear transfer is a form of cloning in which the nucleus of an adult cell is transferred into another cell—usually an unfertilized egg—whose nucleus has been removed. When the recipient cell divides, it creates daughter cells that are genetically identical to the donor. To date, the technique has not successfully been used in human cells.

HHMI early career scientist Kevin Eggan and HHMI investigator Doug Melton attempted to tackle this problem using single-celled embryos donated by couples undergoing fertility treatment, rather than unfertilized eggs. When they transferred DNA into the embryos, development continued though its early stages but came to a halt after four days. The same technique in mouse embryos produced stem cells within hours. The reason for this difference, the scientists report in the October 4, 2011, issue of *Nature Communications*, is that the human cells failed to turn on the genes in the transferred nucleus.

It's not clear what prevents this essential activity from occurring in the human cells, but Eggan says his team's finding could eventually help make nuclear transfer a viable option.

PATTERNING FLIGHT FOR FOOD

When a fruit fly gets a whiff of a rotting banana, it abandons its normal random flight pattern and assumes a more directed trajectory toward the food. According to HHMI early career scientist Mark Frye, this switch is coordinated by a particular area of the brain that integrates smell and visual information.

Frye and his colleagues at the University of California, Los Angeles, showed that a fly normally has some variability in its flight path, ignoring the visual world to an extent. When it smells food, however, the fly switches to a visual path that will quickly take it to its next meal. But, as they report in the October 19, 2011, issue of the *Journal of Neuroscience*, when a region in the brain called the mushroom body is blocked, the flies no longer change their visual flight patterns in response to food odors.

The mushroom body has been implicated in smell processing in other organisms. But it's most commonly been associated with learning and remembering smells. Flies, which don't return to where they were born or to a home base, have less need for this type of learning. So it's not surprising, Frye says, that the mushroom body has more diverse functions in flies.

ACTIVATING EMBRYONIC DEVELOPMENT

In nearly all animals, the newly fertilized egg initially relies on proteins and RNA from its mother to get through the first stages of development. Within a few hours, however, the embryo's own genome kicks in and the process of development begins in earnest. New research by HHMI investigator Michael Eisen and colleagues suggests that a single protein called Zelda is largely responsible for driving this maternal-to-zygotic transition in the fruit fly.

Eisen and his colleagues at the University of California, Berkeley, knew that Zelda controlled the activation of a few genes expressed just before the maternal-

Congcong He / University of Texas Southwestern Medical Center

Locating a Genetic Glitch

INTERNATIONAL TEAM FINDS GENE RESPONSIBLE FOR RARE MOVEMENT DISORDER.

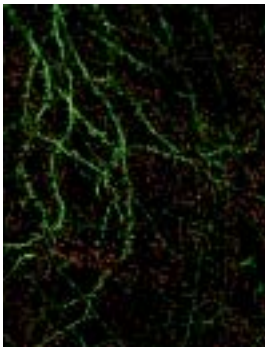
A team of 41 scientists led by HHMI investigator Louis Ptáček has pinpointed the gene responsible for a rare disease that causes sudden, uncontrollable movements. The culprit is a little known protein that may be responsible for communication between neurons.

Paroxysmal kinesigenic dyskinesia with infantile convulsions, or PKD/IC, is characterized by attacks of involuntary movements triggered when a person switches between voluntary movements—for example, a transition from sitting to standing or walking to running.

Ptáček, a researcher at the University of California, San Francisco, and collaborators from two dozen institutions in 10 countries sequenced the entire genomes of one member from each of six families with PKD/IC. All the individuals carried mutations in a gene called *proline-rich transmembrane protein* 2 or *PRRT2*. In a second analysis, the researchers found the same *PRRT2* mutations in 24 of 25 families with PKD/IC. The vast majority of these mutations were truncating, meaning they shortened the PRRT2 protein they encode.

PRRT2 is normally found in the axons of nerve cells, but cells expressing mutant PRRT2 had almost no protein in their axons. As a result, the researchers theorize that individuals with PKD/IC have hyperexcitable nerve cells that cause the sudden movements. They published their findings January 26, 2012, in the inaugural issue of *Cell Reports*.

The scientists also found that PRRT2 interacts with a protein called SNAP25, which is involved in signaling between nerve cells. SNAP25 plays a role in helping synaptic vesicles dock to the cell membrane and empty their contents into the junction between nerve cells. This finding suggested to the researchers that people with PKD/IC may have defects in signaling between their brain cells. Ptáček found further support for this idea when he discovered that a protein that causes a related disease called paroxysmal nonkinesigenic dyskinesia, or PNKD, regulates neuronal signaling. He plans to test this hypothesis by engineering mice that lack the PRRT2 protein.



Defects in the interaction between the PRRT2 protein (green) and a protein called synapsin (red) have been linked to infantile convulsions.

New treatments aren't necessary for PKD/IC can easily be controlled with existing drugs, but Ptáček's findings could pave the way for new therapies for more common forms of movement disorders, such as those in Huntington's and Parkinson's diseases.

■ –NICOLE KRESGE

IN BRIEF

to-zygotic transition, but they had a hunch that was just the tip of the iceberg. The scientists gathered fruit fly embryos at various stages of development and isolated bits of embryonic DNA to which Zelda was bound. They discovered that after only eight cycles of cell division—approximately an hour before the maternal-to-zygotic transition—Zelda was bound to most of the genomic regions active during the transition. Their findings were published October 20, 2011, in *PLoS Genetics*.

"Zelda appears to be acting as a kind of gatekeeper," says Eisen. "While most of the genome remains dormant at the maternal-to-zygotic transition, places where Zelda binds are poised for activation." Eisen's analysis of other insect genomes reveals that they a have proteins similar to Zelda, highlighting its importance to insect development.

ORIGINS OF THE MOLECULAR MACHINE

Many cellular processes are carried out by molecular machines composed of multiple proteins with specific functions. This begs the question of how the gradual processes of evolution built up these elaborate complexes. HHMI early career scientist Joseph Thornton of the University of Oregon may have found an answer.

Thornton and his colleagues focused on part of an enzyme called vacuolar proton-ATPase, or V-ATPase. In plants and animals, the enzyme's transmembrane ring is assembled from copies of two different kinds of proteins, but three distinct proteins form the ring in fungi. Thornton's lab, working with biochemist Tom Stevens at the University of Oregon, wanted to know how the fungal ring became more elaborate.

To answer this question, they resurrected the ancient ring proteins as they existed just before and just after the increase in complexity and assayed their functions in yeast. They found that a gene duplication of one of the components of the two-subunit ring produced the third subunit, and this ancestral protein could carry out all the functions that were later divided among its two daughter copies.

As the team reports in *Nature* on January 9, 2012, the explanation for the proteins' specialization lies in the structure of the complex. The ancestral protein was able to occupy almost any position in the complex because it could interact with any ring component on either side; each daughter protein, however, lost the capacity to interact with certain neighbors on one side or the other.

Thornton believes that this kind of process—elaborate complexes evolving when generalist proteins duplicate and lose ancestral functions in a complementary fashion—is likely to be widespread in the evolution of molecular machines.

INITIATING A CALL TO ARMS IN PLANTS

When a plant is attacked by pathogens, it changes its focus from growth to defense. According to HHMI-GBMF investigator Xinnian Dong, a single protein acts as the master switch to coordinate all the genes involved in this call to arms.

Fifteen years ago Dong, at Duke University, discovered that a protein called NPR1 helps turn on genes for antipathogen proteins in plants. Now, she and her colleagues have shown that NPR1, in turn, is activated by a protein called TL1-binding factor 1 (TBF1). In fact, TBF1 turns out to be a key genetic manager that orchestrates the growth-to-defense transition by activating or silencing around 3,000 genes.

James Maas

Fighting Fluoride

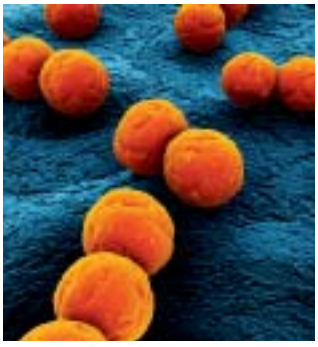
RIBOSWITCH HELPS BACTERIA TOSS OUT TOXIC FLUORIDE.

Since the early 1950s, fluoride has been added to toothpaste, mouthwash, and water to strengthen tooth enamel and prevent tooth decay by killing bacteria. Now, research by HHMI investigator Ronald R. Breaker shows how bacteria that live inside the mouth respond to this toxic ion.

Breaker's lab group at Yale University studies a type of noncoding RNA, called a riboswitch, that helps turn genes on and off. Riboswitches are attached to the genes they regulate; if a gene is involved in the production of a certain compound, the riboswitch usually is sensitive to that compound. If the level of the compound gets too high or too low, the riboswitch can cause more or less of it to be made.

Recently, Breaker and his colleagues discovered a riboswitch attached to several genes with a diverse set of functions. Curious about the riboswitch's job, the scientists put the RNA in a test tube and added different compounds, observing whether the substances bound to the riboswitch. They worked through a long list of chemicals before accidentally stumbling upon fluoride—the ion was a contaminant in one sample they were testing.

Once the team learned their riboswitch interacted with fluoride, they determined that some of the genes controlled by the RNA are involved in removing fluoride from a cell. Breaker explains that when fluoride builds up to toxic levels in a cell, a riboswitch binds to fluoride and turns on genes that can overcome its effects by transporting it out of the cell.



Bacteria, such as streptococcus, use an RNA switch to turn on genes that fight off toxic fluoride.

Because genes associated with fluoride-sensitive riboswitches are found in many types of bacteria, fungi, and plants, the research team concluded that these RNAs and the genes they control may represent components of an ancient system that cells have evolved to deal with toxic levels of this ion. The researchers published their findings January 13, 2012, in *Science*.

"Our data not only help explain how cells fight the toxicity of fluoride, the results also give us a sense of how we might enhance the antimicrobial properties of fluoride," says Breaker. For example, the researchers showed that deleting the fluoride channel makes cells 200 times more sensitive to fluoride. ■ –NICOLE KRESGE

IN BRIEF

That figure, Dong notes, amounts to about 10 percent of the genes in *Arabidopsis thaliana*, a member of the mustard family that she studies. The team reported its findings January 24, 2012, in *Current Biology*.

TBF1's widespread effects raise a question—how do plants turn it on and off? "TBF1 controls so many genes you don't want it around when it's not necessary," Dong says. The mechanism is surprisingly intricate. One factor is NPR1, which has a reciprocal relationship with TBF1—each protein regulates the other's gene. Sequences in the TBF1 mRNA can also sense the metabolic changes that occur during pathogen invasion and trigger TBF1 production.

NEW WEAPON AGAINST PROSTATE CANCER

Patients with advanced forms of prostate cancer undergo treatment with drugs that suppress the growth of cancer cells by targeting the androgen receptor. Unfortunately, many patients develop resistance to the drugs, and their cancer returns. Now, a compound developed by HHMI investigator Charles Sawyers of Memorial Sloan-Kettering Cancer Center may give these patients a fighting chance.

Sawyers and his team discovered that a compound called RU59063 binds to the androgen receptor about 100 times more strongly than bicalutamide, a current drug for prostate cancer. The scientists made a series of tweaks to RU59063 and created a compound—MDV3100—that was able to shrink drug-resistant tumors in mice. In a phase III clinical trial, men treated with MDV3100 had a median survival about 5 months longer than men treated with a placebo. On the basis of the trial results, which were reported in February at the American Society of Clinical Oncology Genitourinary Cancers meeting, it is anticipated that a drug application will be filed with the FDA later this year.

Sawyers, meanwhile, is continuing his research on MDV3100. "One of the key questions we're trying to pin down is how does MDV3100 change the structure of the androgen receptor once it is bound to it," he says. "We also want to know how tumors might escape from MDV3100, so we can be ready with the next drug."

DELAYING ALZHEIMER'S MEMORY LOSS

New research from an HHMI investigator shows that blocking a molecule called HDAC2 might delay the memory loss associated with Alzheimer's disease.

HDAC2 is an enzyme that turns off genes by removing chemical groups from histones—the protein spools around which DNA is wrapped. Li-Huei Tsai of the Massachusetts Institute of Technology showed that in mice with neurodegeneration and in patients with Alzheimer's disease, HDAC2 levels are increased in certain areas of the brain. In these regions, HDAC2 binds to a host of memory genes and dampens their expression. As Tsai and her team report in *Nature* on February 29, 2012, blocking the expression of HDAC2 in the brain increases the number of functioning neurons, thereby improving memory. The scientists also showed that amyloid beta and oxidative stress—key features of Alzheimer's disease—can activate a protein called glucocorticoid receptor 1, which, in turn, can switch on the expression of HDAC2.

"The striking thing is that amyloid beta has a very, very acute effect in elevating HDAC2 expression, but then the consequences can be very long term," says Tsai. This mechanism could explain why clinical trials of drugs that clear out amyloid beta in people with Alzheimer's haven't worked very well, she adds.

Thinkstock

Q A

How does the skin detect solutions with a strong pH? Some burns are not apparent until a day later, so is there a difference between the physical discomfort and physical harm from chemicals?

Asked by Abhishek, a high school student from California

This is a really interesting question. Since you mention burns, I assume that by "strong pH" you mean solutions of a pH that can burn the skin. These solutions can be either very acidic (low pH) or very alkaline (high pH).

The skin does not actually detect anything—detection and perception occur in the brain. However, there are receptors in the skin whose job is to respond to chemicals. The nerve cells that are most sensitive to pH are termed nociceptors (or pain receptors). They contain a family of receptors that includes those sensitive to capsaicin, the burning ingredient in hot peppers.

When a strongly acidic or alkaline solution touches the skin, these receptors are activated and send electrical signals (action potentials) to the brain via specific nociceptive or pain pathways. These signals then lead to the detection or perception of pain. The pathways conveying signals from nociceptors to the brain do not conduct information very rapidly—perhaps at only a meter per second or so. Thus, there is a significant delay between the time a solution hits the skin and the time the brain perceives pain.

You also ask if there is a difference between the physical discomfort and physical harm from chemicals. The simple answer is yes. If a chemical is damaging enough to cause pain, then that pain is usually perceived in a matter of seconds. If a chemical does not cause an immediate burn, but a burn appears later, then the initial exposure has activated an inflammation cascade that requires time for you to notice.

Inflammatory cascades involve a variety of mechanisms that depend on specific signals and chemicals that damaged tissues release as a result of injury. Inflammation makes the receptors more sensitive, which is why it hurts to touch skin that's been burned. The burned area becomes red and warm due to blood vessel dilation and increased blood circulation. Blood vessels also become more permeable, so fluid leaves them, causing swelling or even a blister. After a few days, the skin under the blister begins to heal while the skin on top of the blister dries up and eventually peels off. These responses are quite distinct from the initial painful experience.

All toxic and potentially harmful chemicals should be handled with great care and your skin should be protected while using them. In the laboratory, we use personal safety equipment, including lab coats, gloves, face shields, safety glasses, and fume hoods with exhaust circulation, to protect people who handle damaging chemicals.

ANSWERED BY JEREMY B. TUTTLE,
a professor at the University of Virginia School of Medicine.

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

SPOTLIGHT

Bustamante Awarded Vilcek Prize

CARLOS J. BUSTAMANTE

KONRAD HOCHEDLINGER

HHMI investigator **Carlos J. Bustamante** of the University of California, Berkeley, is the 2012 recipient of the Vilcek Prize in Biomedical Science. The annual award, given by the Vilcek Foundation, honors outstanding creative achievement by immigrants to the United States. Bustamante, a native of Peru, is developing methods of single-molecule manipulation, such as optical and magnetic tweezers, to investigate DNA, RNA, and molecular motors. HHMI early career scientist **Konrad Hochedlinger** of Massachusetts General Hospital was one of four finalists for the Vilcek Prize for Creative Promise.

CHRISTOPHER J. CHANG, an HHMI investigator at the University of California, Berkeley, received the American Chemical Society's 2012 Eli Lilly Award in Biological Chemistry. Chang was selected for developing probes that enable visualization of the production and trafficking of reactive oxygen species and metal ions in living cells.

HHMI investigator ZHIJIAN "JAMES" CHEN of the University of Texas Southwestern Medical Center received the National Academy of Sciences 2012 Award in Molecular Biology. The prize recognizes Chen's research on mitochondria's contribution to the immune response and the role of ubiquitin in activating proteins.

The World Technology Network presented JAMES J. COLLINS, an HHMI investigator at Boston University, with its 2011 World Technology Award for Biotechnology. Collins was recognized for developing innovative ways to design and reprogram gene networks within bacteria and other organisms to attack tumors and direct stem cell development. HHMI investigators H. ROBERT HORVITZ of the Massachusetts Institute of Technology and YI ZHANG of the University of North Carolina at Chapel Hill were among the four other finalists for the award.

The American Association of Immunologists (AAI) recently honored two HHMI investigators. PETER CRESSWELL of Yale School of Medicine was presented with the 2012 AAI–Life Technologies Meritorious Career Award for his research on proteins involved in the immune response, and ARTHUR WEISS of the University of California, San Francisco, received an AAI Lifetime Achievement Award for his work on biochemical signal transduction.

HHMI investigator ROGER J. DAVIS of the University of Massachusetts Medical School was one of 80 scientists elected to a fellowship in the American Academy of Microbiology. Davis studies the mechanisms that cells use to respond to extracellular stimulation.

The Biophysical Society gave its Sir Bernard Katz Award for Excellence in Research on Exocytosis and Endocytosis to PIETRO DE CAMILLI, an HHMI investigator at Yale School of Medicine. De Camilli studies the molecular mechanisms that operate in neuronal synapses.

Two HHMI investigators were honored by the March of Dimes. HARRY C. DIETZ of the Johns Hopkins University School of Medicine won the 2012 March of Dimes/Colonel Harland Sanders Award for lifetime achievement in the field of human genetics. ELAINE FUCHS of the Rockefeller University shared the 2012 March of Dimes Prize in Developmental Biology with Howard Green of Harvard Medical School.

HHMI investigator BRIAN DRUKER of Oregon Health and Science University was honored with the 2012 Japan Prize, one of the world's most prestigious awards in science and technology. He shares the award with Janet Rowley of the University of Chicago and Nicholas Lydon of Blueprint Medicines for their contributions to the "development of a new therapeutic drug targeting cancer-specific molecules."

BARRY HONIG, an HHMI investigator at Columbia University College of Physicians and Surgeons, received the 2012 Christian B. Anfinsen award from the Protein Society. Honig was honored for his work on elucidating the electrostatic properties of proteins and

SPOTLIGHT

Vale Receives Wiley Prize

RONALD VALE

Ronald Vale, an HHMI investigator at the University of California, San Francisco, is one of three recipients of the 2012 Wiley Prize in Biomedical Sciences. The annual award recognizes contributions that have opened new fields of research or have advanced novel concepts and applications in biomedical disciplines. Vale shares the prize with Michael Sheetz of Columbia University and James Spudich of Stanford University for determining how kinesin and myosin move cargo along microtubules and actin filaments.

Bustamante: Andrew Nagata Hochedlinger: Massachusetts General Hospital Vale: Anne Hamensky

HHMI Investigators Win Gairdner Awards

THOMAS M. JESSELL

MICHAEL ROSBASH

HHMI investigators **Thomas M. Jessell** and **Michael Rosbash** are recipients of 2012 Canada Gairdner International Awards. Presented to scientists worldwide whose work is expected to significantly improve quality of life, the Gairdner Award is one of the most esteemed awards in medical research. Jessell, who is at Columbia University, was honored for discovering basic principles of communication within the nervous system. Rosbash, of Brandeis University, was chosen for discoveries that revealed the genetic underpinnings of the circadian clock.

the development of DelPhi and GRASP—two of the most widely used computer programs in structural biology.

ARTHUR L. HORWICH, an HHMI investigator at Yale School of Medicine, was awarded the 2011 Massry Prize. Horwich shares the honor with F. Ulrich Hartl of the Max Planck Institute of Biochemistry for their elucidation of how proteins fold.

HHMI investigator WILLIAM G. KAELIN, JR. of the Dana-Farber Cancer Institute won the 2012 Stanley J. Korsmeyer Award. He shares the honor with Gregg L. Semenza of the Johns Hopkins University for their contributions to the molecular understanding of cellular oxygen sensing and cellular adaptation to hypoxia.

ERIC R. KANDEL, an HHMI investigator at the Columbia University College of Physicians and Surgeons, received the Child Mind Institute's 2012 Distinguished Scientist Award. Kandel was given the prize, which recognizes outstanding contributions to child and adolescent psychiatry, psychology, or developmental neuroscience, for his research on the molecular mechanisms of memory storage in sea slugs and mice.

JUDITH KIMBLE, an HHMI investigator at the University of Wisconsin–Madison, was selected to serve on the President's National Medal of Science committee. As a member of the 13-person committee, Kimble will help choose the next winners of the National Medal of Science, the most prestigious science award in the country.

The American Society for Pharmacology and Experimental Therapeutics honored HHMI investigator ROBERT J. LEFKOWITZ of Duke University with its 2012 Robert R. Ruffolo Career Achievement Award in Pharmacology. Lefkowitz studies receptor biology and signal transduction and has characterized the sequences, structures, and functions of many β-adrenergic receptors.

The International Union of Biochemistry and Molecular Biology (IUBMB) recently presented two HHMI investigators with awards. SCOTT W. LOWE of the Memorial Sloan-Kettering Cancer Center received the 2011 Kunio Yagi Medal for his identification of tumor suppressor and tumor maintenance genes. RICHARD A. FLAVELL of Yale School of Medicine received the 2011 IUBMB Lecture and Medal for his work on inflammasomes and homeostasis.

HHMI investigator DAVID J. MANGELSDORF of the University of Texas Southwestern Medical Center was presented with the Karolinska Institutet's 2012 Rolf Luft Award. The prize recognizes Mangelsdorf's work on nuclear receptors.

The *Proceedings of the National Academy of Sciences* editorial board selected a paper published by DIANNE K. NEWMAN, an HHMI investigator at the California Institute of Technology, for a 2011 Cozzarelli Prize. The paper, titled "Microaerobic steroid biosynthesis and the molecular fossil record of Archean life," was authored by Newman, Jacob R. Waldbauer of the University of Chicago, and Roger E. Summons of the Massachusetts Institute of Technology.

KERRY J. RESSLER, an HHMI investigator at Emory University School of Medicine, was presented with the inaugural Eva King Killam Research Award for outstanding translational research. The award was given to Ressler by the American College of Neuropsychopharmacology for his work on understanding and treating fear- and stress-related disorders.

HHMI EXROP student SAID SAAB was awarded two doctoral training program scholarships to study at the University of Cambridge. He received the Gates Cambridge Scholarship from the Gates Cambridge Trust as well as a scholarship from the National Institutes of Health Oxford–Cambridge Scholars Program.

JOSEPH S. TAKAHASHI, an HHMI investigator at the University of Texas Southwestern Medical Center, won the 2012 Sleep Research Society Outstanding Scientific Achievement Award. Takahashi was recognized for his discovery of genes regulating circadian and sleep/wake behaviors.

HHMI investigator PETER WALTER of the University of California, San Francisco, received the Paul Ehrlich and Ludwig Darmstaedter Prize for his discovery of the signals used by proteins to ensure they are shuttled to their proper destinations in the cell. Walter also shared the 2012 Ernst Jung Prize for Medicine with Elisa Izaurralde of the Max Planck Institute for Developmental Biology in Tübingen.

Jessell: Paul Fetters Rosbash: Paul Fetters

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(MAKING BIGGER BETTER)

CURE survey reported skill improvements to FRI student graduation and subsequent graduate school enrollment rates—it has helped boost students' performance while encouraging a larger percentage of students to pursue science classes and careers.

But it's time to think even bigger. Grants have helped some schools open up a class or two to research, but that might not be enough, says Asai. "We could challenge big schools to take on [research-based courses] not just for one section, but for 40 sections," he says. "We could bring this approach to big schools that produce lots of science teachers. There are a lot of exciting ways to think about using these courses."

The courses don't just shape semesters or college experiences—they can also shape careers. Holli Duhon had planned to be a doctor, but now she'll add research to her plans. "I am on my way to completing a B.S. in medical laboratory science, and it's my goal to incorporate research into my career," she says. "The aptamer stream provided me with the insight to critically evaluate what my next steps should be." ■

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(OPENING THE FLOODGATES)

FOCUS ON THE DRIVERS

Hearing the way researchers praise exome sequencing for expediting their work, you'd think it was the solve-all technique. But it has its limits. After all, it provides only what it advertises: the sequences of exomes. For scientists, interpreting those sequences still requires old-fashioned elbow grease.

"In cancer sequences it's often difficult to distinguish the wheat from the chaff," says Vogelstein. The wheat, in cancer genetics, includes those mutations that drive cells to become cancerous or encourage a tumor's growth. The chaff is the mutations that just happen to also be present—called passenger mutations.

And it's not just a problem in cancer genomics. Every researcher who uses exome sequencing is faced with a pile of data to sort through. Sequencing is the easy part; you prepare a sample of DNA and feed it into a lab machine. "The interpretation is the hard part," says Walsh. "If you have a big family to study, it will be easier. But interpreting the hard cases is still hard."

Then there's that other 99 percent of the genome. If researchers can't find a disease-causing gene in the exome, is it because that gene is in the regulatory part of the genome, or because they just haven't pinpointed the right mutation in the exome?

"It's one of the really pressing questions," says Golub. "How much are we missing? We're beginning to see cancer types that appear to have particularly low mutation rates, based on the exome. It could be that you don't need many mutations [to cause the cancer]. But it also could be that you need mutations in the other 99 percent of the genome."

Eventually, researchers will use whole genome sequencing the way they use exome sequencing today. It's a matter of waiting for the cost to drop, they all say. Today, sequencing a whole genome costs five to 10 times more than sequencing an exome. And the costs of storing and processing whole genome data are as much as a hundred times higher—and dropping more slowly—than whole genome sequencing costs, which are now below $5,000 per genome, and quickly approaching $1,000 per genome. But the initial costs of sequencers, which can be used for either exome or whole genome sequencing, are also part of the equation.

"Exome sequencing, while it's amazing, is really just a bridge until the price drops further and we can do whole genome sequencing," says Gleeson.

"If you were told you could sequence 1 percent of the genome and you asked yourself what's the most important 1 percent of the genome to sequence, you'd say it's probably the 1 percent that makes proteins," says Golub. "Which isn't to say that nothing else is important. But it's a good place to start." ■

Correction:
In a February 2012 Nota Bene brief, the *Bulletin* incorrectly stated that Xinnian Dong is an HHMI early career scientist at the Johns Hopkins University School of Medicine. Dong is actually an HHMI-GBMF investigator at Duke University. The *Bulletin* regrets the error.