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Locked and Loaded

This bullet-shaped structure serves as a changing room of sorts for bacterial proteins. Called GroEL, the molecular complex has a cap called GroES (blue) that pops open to allow an unfolded protein to move inside. With the protein sequestered, the top closes, sealing it off from the cellular environment. Once folded, the protein is released, free to move on to its job. Without the GroEL/GroES complex, proteins clump together before they have a chance to fold, and the cell dies. Over three years of painstaking work, HHMI investigator Art Horwich and colleagues determined the molecular structure of the complex by x-ray crystallography, an effort for which he shared the 2011 Lasker Award (see "An Intentional Life," page 18).

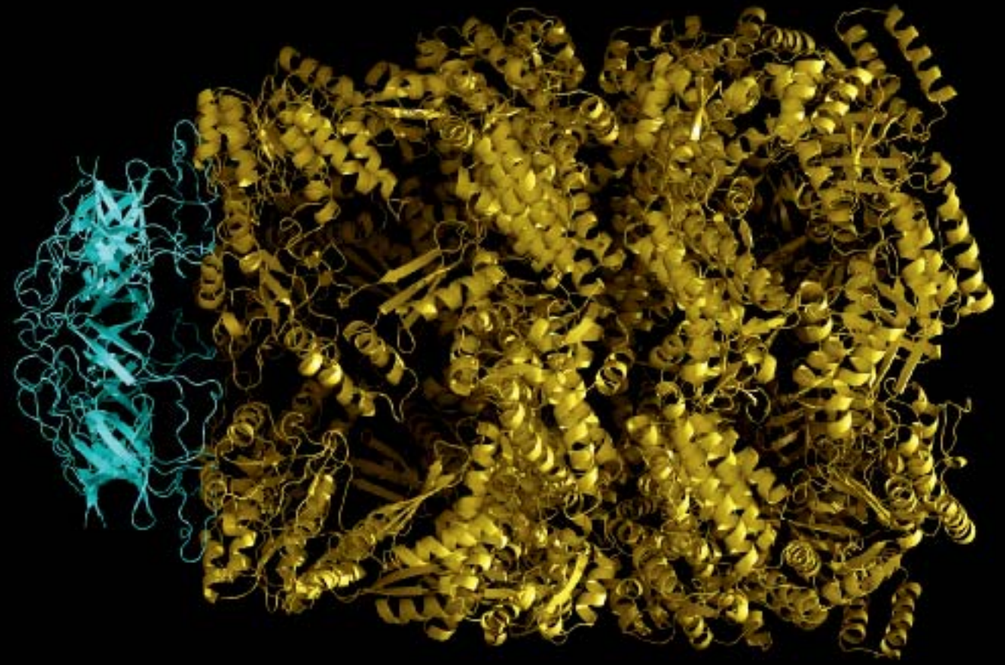

Illustration by Cassio Lynn (Lasker Awards 2011); adapted from Xu Z, Horwich AL, Sigler PB. Nature (1977) 388:741–750.

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HHMI BULLETIN

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IN THIS ISSUE:

FORCE

MARRYING PHYSICS WITH BIOLOGY TO STUDY THE PUSH AND PULL OF MOLECULAR MACHINES

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Optical trapping. Sounds like the latest vision-correction technique, but it's actually a clever way of using a tightly focused laser beam (red) to measure the force exerted by a molecule. This image shows a cellular enzyme called a helicase (yellow) as it unwinds double-stranded DNA, freeing two single strands to replicate. HHMI investigator Michelle Wang used optical trapping to show that the helicase is not a passive acceptor of the DNA strands but an active DNA-unwinding motor. Read about the work of her team and others in our cover story.

Chris Pelkie and Daniel Ripoll/Cornell Theory Center

illustration by Ciara Phelan, photography by Sam Hofman

FREE FALL

Putting physicist Walter Lewin in front of a classroom is a guaranteed recipe for instant fun. He made everyday physics understandable for students at the Massachusetts Institute of Technology for more than 30 years. When his lectures became available online, his theatrical antics made him a YouTube celebrity. Now retired, he still approaches physics with evangelical zeal, as evidenced in his new book *For the Love of Physics*. "I introduce people to their own world," he says. "The world they live in and are familiar with but don't approach like a physicist—yet."

The whole idea of changing weight is so fascinating that I really wanted to be able to demonstrate this phenomenon—even weightlessness—in class. What if I climbed up on a table, standing on a bathroom scale that was tied very securely to my feet? I thought then maybe I could somehow show my students—by rigging up a special camera—that for the half second or so that I was in free fall the bathroom scale would indicate zero. I might recommend that you try this yourself, but don't bother; trust me, I tried it many times and only broke many scales. The problem is that the scales you can buy commercially don't react nearly fast enough, since there is inertia in their springs. One of Newton's laws bedeviling another! If you could jump off a thirty-story building, you would probably have enough time (you would have about 4.5 seconds) to see the effect, but of course there would be other problems with that experiment.

So rather than breaking scales or jumping off buildings, here's something you can try in your backyard to experience weightlessness, if you have a picnic table and good knees. I do this from the lab table in front of my classroom. Climb up on the table and hold a gallon or half-gallon jug of water in your outstretched hands, just cradling it lightly on top of them, not holding the sides of the jug. It has to be just resting on your hands. Now jump off the table, and while you are in the air you will see the jug start floating above your hands. If you can get a friend to make a digital video of you taking the jump, and play it back in slow motion, you will very clearly see the jug of water start to float. Why? Because as you accelerate downward the force with which you have been pushing up on the jug, to keep it in your hands, has become zero. The jug will now be accelerated at 9.8 meters per second per second, just as you are. You and the jug are both in free fall.

From *FOR THE LOVE OF PHYSICS: From the End of the Rainbow to the Edge Of Time—A Journey Through the Wonders of Physics* by Walter Lewin with Warren Goldstein. Copyright © 2011 by Walter Lewin and Warren Goldstein. Reprinted by permission of Free Press, a Division of Simon & Schuster.

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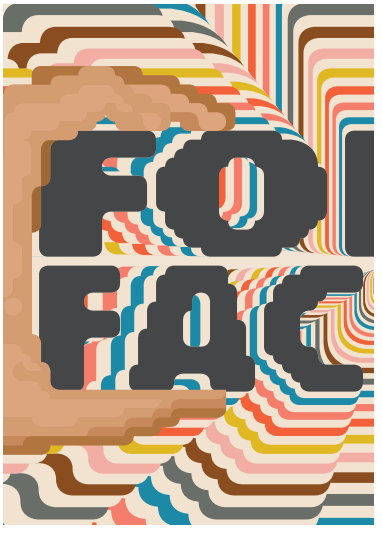

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Web-Only Content

- See students as flintknappers, turning stones into tools, at the Holiday Lectures.
- Learn how researchers discovered a safe way to shut down the tuberculosis bacterium.
- Watch a mouse sniff out a predator's presence in mere moments, thanks to special receptors in its nose.
- View an animation of how a compound from the venomous cone snail acts to dampen pain in mammals.
- Join us at www.hhmi.org/bulletin/feb2012.

GO GREEN

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Features

Departments

JOSH COCHRAN ("Raising Their Game," page 24) grew up in Taiwan but currently lives in Brooklyn, where he illustrates for a wide range of clients including the Dubai Metro, Facebook, IBM, Nike, and *TIME* magazine. He loves drawing weird, unique characters and had a great time working on this month's feature on education and teachers. (1)

After earning a Ph.D. in molecular biology, NICOLE KRESGE ("Bones, Stones, and Genes," page 38) spent five years as editor of *ASBMB Today* and is now assistant editor of the *HHMI Bulletin*. She lives in Washington, D.C., with her husband, two children, and a beautiful but neurotic pit bull terrier. As a result of growing up in Canada, she loves hockey and ketchup chips and thinks it's weird to spell the word "color" without a "u." (2)

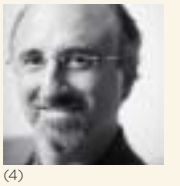
A resident of Brooklyn, photographer MARK MAHANEY ("An Intentional Life," page 18) works for clients ranging from *Dwell*, *Monocle*, *TIME*, *The New York Times*, and Nike. He and his wife, Jess, have a baby on the way and dream of moving their growing family to Northern California, where they can get back to the land. (3)

DAN FERBER ("Raising Their Game," page 24) learned science the old-fashioned way—by memorizing oodles of facts and plugging through cookbook laboratories—and he's glad educators now know a better way. A correspondent for *Science* and contributor to many magazines, Indianapolis-based Ferber is coauthor, with the late Paul Epstein, M.D., of *Changing Planet, Changing Health: How Climate Change Threatens Our Health and What We Can Do About It*. (4)


(1)


(3)


(2)


(4)

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Josh Cochran, Nicole Kresge, Mark Mahaney, Dan Ferber

Fundamentals for Uncertain Times

James Keglev

IT DOESN'T TAKE A PH.D. TO UNCOVER EVIDENCE OF UNEASE IN the scientific community. Peruse the news and commentary section of any scientific journal. View the daily back and forth on Twitter among scientists and journalists who follow the issues. Check out the headlines in national newspapers.

The challenges are numerous. Federal budgets are constrained, with government spending for science expected to remain flat or decline. Partisan gridlock—accompanied by the ongoing potential for government shutdowns—generates even more turmoil. The health of the overall economy is fragile, placing pressure on the ability of other entities—for example, nonprofit organizations, venture capitalists, and pharmaceutical companies—to make additional investments in research.

The value of science is questioned by significant segments of the American populace. They are not inclined to agree with what many scientists accept as settled fact—from the tenets of evolution to the evidence that human activity contributes to climate change and the value of vaccines in preventing disease. While opinion surveys consistently show that medical research is highly valued, the public also wants to see a return on investment of their tax dollars: effective drugs for cancer and other devastating diseases, answers about the apparent rise in the incidence of autism, and unambiguous guidance about what to eat, for starters.

No wonder many established scientists feel beleaguered and those at early stages in their careers—graduate students and postdocs among them—are left questioning their long-term career prospects. Indeed, the National Institutes of Health (NIH) generated passionate commentary from all sectors of the scientific community when it asked the provocative question, "How do you think we should manage science in fiscally challenging times?" The question is an important one and the range of potential responses will have a profound impact on the nation for many years to come.

As a federal agency accountable for the expenditure of taxpayer dollars, NIH is under pressure to demonstrate impact and value—at speed. That's clearly a driver behind the efforts of NIH Director Francis Collins to create the National Center for Advancing Translational Sciences as a means of giving the NIH a direct, substantial role in speeding drug development and other translational research activities. Whether this approach will successfully engage scientists from academia, industry, and regulatory entities such as the Food and Drug Administration, and result in more rapid translation of basic science discoveries into useful therapies, remains an open question.

My colleagues and I at the Howard Hughes Medical Institute have also been thinking deeply about how to manage our scientific portfolio during this time of economic uncertainty. We recognize that the performance of the endowment that fuels our research investments will likely fluctuate even as our scientists place greater reliance on the flexible support that funds some of their most creative work.

Two attributes distinguish HHMI from other organizations that are under stress in the current environment: independence and agility. Our commitment to basic research remains unwavering. Yet we also have the freedom to grow more slowly and deliberately in the coming years, to ensure that we are giving the very best people the level of support they need—for example, by managing the timing and size of future competitions. We also have the opportunity to experiment with smaller programs that extend the reach of HHMI's scientific community. A good example is the Hughes Collaborative Innovation Award program. Given the success of the first round of projects, we've announced a second competition. Our goal is to identify high-risk proposals that bring together a diverse group of collaborators focused on solving important scientific problems. The group assembled by Peter Walter at the University of California, San Francisco, for example, aims to identify clinically useful compounds that affect how cells manage unfolded proteins, specifically in the cancer multiple myeloma.

> "Two attributes distinguish HHMI from other organizations that are under stress in the current environment: independence and agility."
>
> ROBERT TJIAN

At the same time, we are making important changes to policies that govern the interactions of our scientists with start-up companies and venture capital firms—the policies have been streamlined, simplified, and made more flexible. These revisions balance our interest in preserving the integrity of HHMI research with our view that start-ups can play an important role in translating basic discoveries into effective therapies and diagnostics. I believe that basic research in the life sciences is a powerful engine of innovation that drives our economy and enhances our standard of living. It's another way to look at how HHMI's efforts to develop sophisticated tools for digging deeply into basic biological processes are on a critical path toward improving people's lives.

Mark Smith

Born to Tackle

From nine to five, Beth Kaleta manages HHMI investigator George Daley's research lab at Children's Hospital Boston, using good humor and approachability to keep the place running for 35 other employees.

After work, the five-foot-four 27-year-old is tough as nails: she powers it out on the gridiron as an offensive guard for the Boston Militia, a women's tackle football team—one of 63 teams in the nationwide Women's Football Alliance.

Kaleta has played in organized sports since she was 4: from soccer and softball to track and taekwondo. But no football. "Football was a *man's* sport," she says. She always loved it, though. "I've watched the NFL every Sunday with my dad for as long as I can remember and even tried to reenact some of my favorite plays against my male cousins after Thanksgiving dinners," says Kaleta. When she noticed a female player on the field at a high school football game, she told her parents she wanted to try out, but they nixed that idea. Too dangerous, they said.

Kaleta went on to play softball and soccer and to swim for Regis College in Weston, Massachusetts; she graduated with a degree in biology and quickly landed a job with Children's Hospital Boston. In 2009, she joined the Boston Women's Flag Football League. Some of her teammates also played tackle football, and they encouraged Kaleta to try out for the Boston Militia.

After a week of tryouts—sprinting, jogging through tires, and showing how she handles the pigskin—Kaleta made the first cut. After two months of preseason practice, she made the second cut and was chosen to play starting right guard on the offensive line—a huge accomplishment for her rookie year.

On the field, Kaleta sometimes faces off against women who stand a foot taller and outweigh her by 150 pounds. "It's pretty brutal," she says. In the team's third game, a large player landed on her, spraining Kaleta's shoulder so badly she needed help getting dressed for the next two weeks.

The Boston Militia won all but their first game last season and traveled to Dallas for the 2011 WFA National Championship against the San Diego Surge. In front of more than 1,000 fans, the two teams battled it out during a record-breaking Texas heat wave.

Despite the size disparity between Kaleta and her burly opponent on the defensive line—"one of the largest women I've had to go against the entire season"—the teams were fairly evenly matched. "We scored the first touchdown, so that set the pace, but it was a back and forth battle," Kaleta says. In the end, the Boston Militia won 34–19 to take the championship.

Kaleta continues to play flag football in the off-season and plans to keep fighting it out on the gridiron with the Boston Militia. "I'm so honored to be a member of the team," she says. "I get to have some fun and play a sport that I love." And, despite their initial misgivings, Kaleta's parents have become fans: they attend every home game they can, decked out in Militia shirts and hats.
—Linda Formichelli

High-Tech Reboot

Computer geek Ted Goldstein spent 30 years working in Silicon Valley, rising to prominence at Apple, the company famous for its mantra, "think different." He oversaw the building of software tools that let engineers create Mac and iPhone applications. In 2008, however, Goldstein traded in his industry success for the modest life of a graduate student.

Think different, indeed.

Today, the pale-bearded 50-year-old is back at his college alma mater, the University of California, Santa Cruz. He is earning a Ph.D. in the biomolecular engineering lab of HHMI investigator David Haussler. Goldstein focuses on using bioinformatics—the application of computer algorithms to dissect biological processes—to improve people's health. "I think it's just the most interesting thing there is," he says.

Haussler, whose group analyzes glitches across the human genome that fuel cancer, is thrilled to have the former Apple executive. "We don't usually get someone at that level who says, 'Okay, I'm an accomplished individual, but I want to learn a new field,'" Haussler says. It was no small sacrifice. Goldstein, a fundraising trustee for UC Santa Cruz, takes no salary, though he does have his own office with a door and a view of the redwoods.

Biology always fascinated Goldstein. As a computer science major in college, he wrote a program for a biology professor that aligned RNA sequences for comparison. It was his first bioinformatics work, he says, though "we didn't have that word yet." After graduating in 1983, he worked at Xerox's ParcPlace Systems, Sun Microsystems, and elsewhere before joining Apple as a vice president.

From 2002 to 2007, Goldstein led the team that created developer tools (including the Xcode software development system) for Apple's transition to Intel chips and helped engineer the iPhone's operating system, iOS. "Pretty much everyone in the Apple universe uses the tools he helped define," says Bertrand Serlet, a former senior vice president at the company.

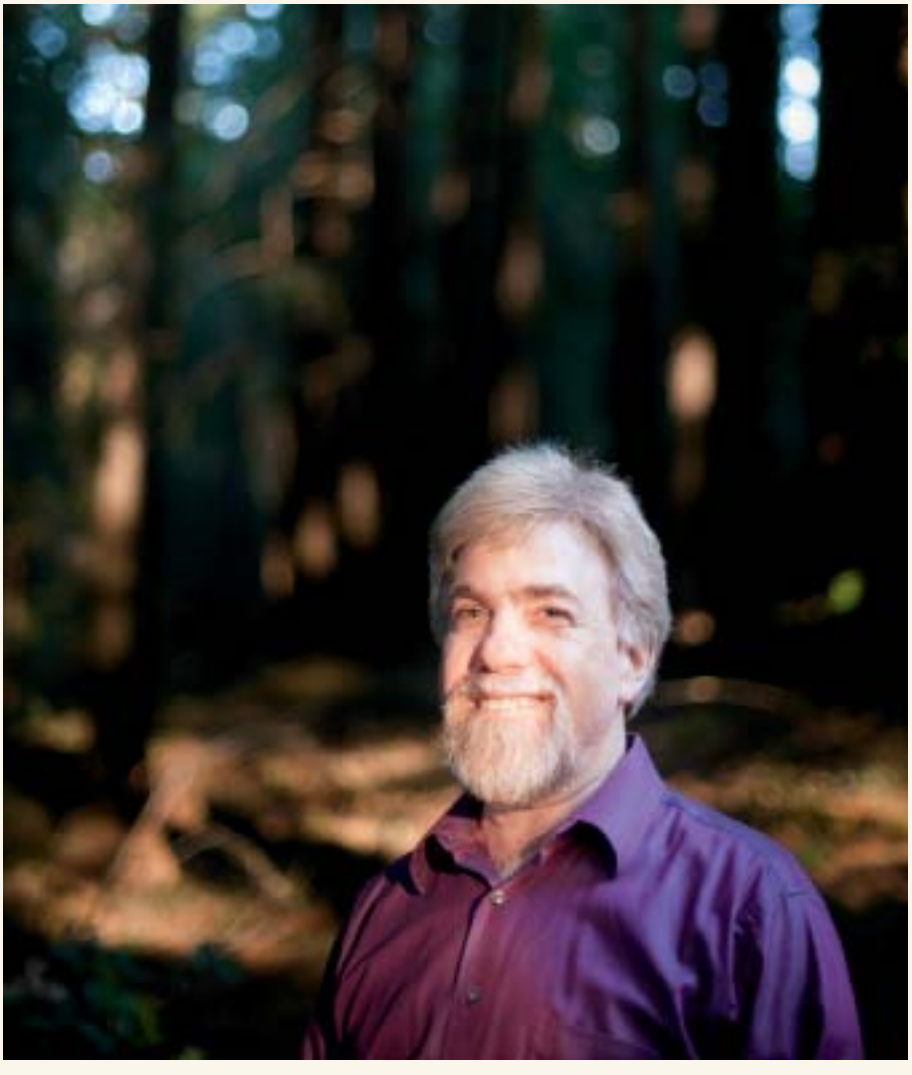
While Apple is a fabulous firm, Goldstein says, one downside is that "last year's insanely great product is this year's landfill." He wanted to build something that would last. He left in 2007 to work on bioinformatics at a medical diagnostic startup but quickly "realized I didn't know anything." So he went back to grad school, diving into all the required courses, relearning some material from the ground up. "I had to work much harder on my math skills," he says. But other things come easily. "I am used to getting up in front of a room of 4,000 people and making a presentation," he says with a laugh.

Haussler hopes other stars from the high-tech world will follow Goldstein's example. "He thinks much more broadly than the typical Ph.D. student." Given Goldstein's industry savvy, Haussler relies on him for strategic advice on matters such as building the group's sizeable computer infrastructure.

For his Ph.D. work, Goldstein's ambitious vision is to create a "Facebook for cancer." Called MedBook, its algorithms would analyze individual patients' cancer mutations so that they can receive tailored treatments where possible. The idea is to link patients, their doctors, clinical scientists, and bioinformatics researchers—and, Goldstein hopes, revolutionize the search for cancer cures.

The late Steve Jobs's battle with pancreatic cancer is a big inspiration for his focus on cancer genomics, Goldstein says. He can still hear the last words the Apple CEO said to him when he headed off into bioinformatics: "Good luck changing the world again."

—Ingfei Chen



Leah Fasten

True Grit

Mark Smith

When Jorge Martinez took a couple of days off work last summer, his colleagues in Janelia Farm's information technology department assumed he was celebrating his recent engagement. In fact, he did take a whirlwind trip to Europe—but without his fiancée, Jessica.

"She wanted to come, but we decided together that she shouldn't," says Martinez. The reason? He was on a single-minded mission that fewer than 1 percent of computer networking experts worldwide complete: becoming a Cisco Certified Internetwork Expert (CCIE).

Nearly everyone who seeks the certification—largely considered the highest and most prestigious networking certificate worldwide—takes the test multiple times before passing. Martinez had taken the exam recently in San Jose, California. The all-day test requires solving 10 trouble-shooting tickets on a fully-built Cisco network in just two hours as well as building a network from scratch in six hours.

Martinez, 32, was well prepared. Colleagues recall seeing him at his desk until 9 or 10 p.m., immersed in test preparation. Before coming to Janelia Farm in 2006, he'd logged thousands of hours working on computers and networks. While earning a bachelor's degree in computer science and a master's degree in telecommunications at George Mason University, he worked full time at the university to fund his education, first at the information technology help desk and then as a network engineer.

During the CCIE test in San Jose, Martinez cracked all the trouble-shooting tickets save one, which he suspected involved a "ghost" issue, meaning the problem appeared to be part of the exam but was actually due to a server malfunction. He complained to the proctor but got nowhere—and failed the exam because of that single ticket.

Frustrated but undaunted, he wanted to take the exam again as soon as possible. "It was now or never," says Martinez, who knew he was at the top of his game and that waiting too long would mean he'd have to learn more new technology. But the next opportunity in the U.S. was six months away. He searched worldwide and discovered only one site offering the test within the next month—in Brussels, Belgium.

Without telling anyone but Jessica, he signed up for the test and bought a plane ticket. He flew to Brussels on a Friday, staying in a hotel near the exam site to save money. "It was in an industrial area and had no restaurant. I had to walk about a mile to a gas station to buy sandwiches," recalls Martinez. He took the exam Monday and learned he'd passed before flying home on Tuesday. Anticipating disbelief from his colleagues, he took a photo of himself next to a local highway sign and e-mailed it to his Janelia coworkers along with his passing score.

"We were gobsmacked," says Vijay Samalam, senior director of scientific computing and information technology at Janelia. "First of all, we know how difficult it is to pass that exam. But taking that gamble and putting up his own money? That shows true grit and determination," he says.

To recognize Martinez and his achievement, Samalam nominated him for an Outstanding Janelian award, an honor that's granted on an ad hoc basis to employees in operations who go beyond the call of duty. Martinez received the award last fall, on November 16. Cisco came through as well: They acknowledged their error on the earlier exam and reimbursed the testing fee for the Brussels exam. Soon afterward, Martinez and Jessica took a real vacation together—a cruise to Mexico, Belize, and Costa Rica—and are planning their wedding next summer.

—Julie Corliss

upfront

WEB-ONLY CONTENT

A SAFER SHOT AT TB
While trying to understand tuberculosis bacteria genes, researchers discovered a safe way to shut down the pathogen. Read about it at *www.hhmi.org/bulletin/feb2012*.

Mysteries are irresistible, for scientists especially. Solving some biological puzzles can take years of persistence, with progress coming in arduous steps. Other times, answers arrive like a bolt from the sky. Whether it's delving into the drive behind hunger, or how antibody diversity is generated, or the best way to cripple the TB pathogen, the scientists trying to plumb these enigmatic problems get downright gleeful when big pieces of the puzzle fall into place. See for yourself.

Changing Channels

Appetite and other deep-seated desires could be modified by altering brain ion channels, according to new research at Janelia Farm.

SCOTT STERNSON HAS ALWAYS WONDERED WHAT DRIVES behavior, especially those fundamental motivations required for survival. Hunger, for example, is so crucial that it must be evolutionarily "hard-wired" deep within the brain. After all, as Sternson observes, "if the animal doesn't eat, it dies."

Melding the diverse disciplines of synthetic chemistry, structural biology, and computational modeling, Sternson and Loren Looger, both group leaders at HHMI's Janelia Farm Research Campus, have uncovered clues about the brain circuitry that controls deep-seated behaviors, like that irresistible urge to visit the dessert table.

The pair devised a noninvasive method to stimulate individual brain neurons or clusters of neurons in live, conscious animals—a remote control for the brain, of sorts. They demonstrated the technique by converting gluttonous mice into champion dieters. The researchers published their findings September 2, 2011, in *Science*.

You can blame those dessert cravings in part on ion channels, explains Sternson. Ion channels are molecular pores, donut-shaped proteins embedded in the surface of neurons that allow charged particles to enter and exit the cells. Like a subway system's turnstiles, ion channels have moving parts, opening and closing to ensure passage of only the proper type of ion, single file, by the millions every second. Like their mass transit counterparts, some ion channels, called ligand-gated ion channels, won't budge until presented with a ticket—in this case, a chemical neurotransmitter. The ensuing electrochemical impulses that race through neurons create thoughts, emotions, and, ultimately, behavior.

Sternson's scientific interest in hunger began when he was a postdoc in the laboratory of HHMI investigator Jeffrey Friedman at the Rockefeller University. In the mid-1990s, Friedman identified a hormone called leptin that exerts powerful control on appetite by acting on a region of the brain called the hypothalamus. Sternson's goal was to understand the neuronal wiring in the hypothalamus that controls appetite. He wanted to identify the different neurons and deduce the contribution of each toward evoking hunger. The problem was that no tools were available to systematically probe brain wiring with the precision he needed.

Neurons perform their assigned duties by firing or turning silent in response to chemical neurotransmitters, depending on what types of ion channels they contain. Neuroscientists can study how isolated neurons work in a lab dish. However, to connect neural circuitry to complex behaviors, Sternson wanted to probe the neuronal wiring in living mice. To do that, he needed a way to "re-ticket" individual ion channels within a neuron or small group of neurons by forcing them to respond to a unique, synthetic neurotransmitter—one not normally seen in nature.

Sternson began by collaborating with Looger, a protein chemist, to exploit the modular structure of ligand-gated ion channels. In these channels, the ion pore domain (IPD) is tethered to an independently functioning ligand-binding domain (LBD). Scientists had previously engineered "chimeric" ion channels by genetically splicing the LBD from one type of channel to the IPD from another. Such hybrid channels transport ions specified by the IPD but in response to the neurotransmitter recognized by the grafted LBD.

To create an ion channel that could respond to a novel neurotransmitter, Sternson and Looger needed to design a new LBD and synthesize a neurotransmitter that could bind and activate it—two tall orders, Sternson says. "The thinking was that it would be very difficult. It was an uncertain

Jing Wei

challenge for us whether or not we could even modify these complex ligand-binding domains." Nonetheless, they persevered.

Starting with the LBD that recognizes acetylcholine, the team applied a combination of protein structural chemistry and molecular modeling to predict which parts of the LBD were most likely to contact this natural neurotransmitter. They then created dozens of channels, each containing a mutation at one or more of the 19 positions on the LBD predicted to be important for acetylcholine binding.

Next, they designed a compound that would unlock their newfangled ion channels. Starting with a chemical analog of acetylcholine, the researchers synthesized a collection of 71 slightly modified versions of the compound. When they tested each one for its ability to selectively activate or silence each of the hybrid ion channels, they found many combinations that worked.

The ultimate test of the artificial ion channel system, the researchers knew, would be trying it out in a living organism. So Sternson inserted a neuron-silencing version of one of his designer ion channels into specific hypothalamus neurons, called AGRP neurons, in mice. His team had previously tailored these neurons to stimulate voracious appetites in the mice. When Sternson injected the animals with the appropriate synthetic neurotransmitter, their overindulging habits subsided dramatically.

With their toolbox of new ion channels and neurotransmitters in hand, the Janelia Farm researchers intend to examine the role of specific neurons in other complex behaviors. "To me, that's a real frontier for neuroscience and will ultimately allow us to demystify some of the processes that underlie why we do what we do," Sternson says.

■ –PAUL MUHLRAD

WEB EXTRA: For more detail about the collaborative effort by Janelia Farm scientists that went into this work, visit www.hhmi.org/bulletin/feb2012.

The Twists and Turns of Immunity

The diversity of the immune system's antibodies depends on the three-dimensional structure of DNA.

Fred Alt has built a career making sense of the immune system—specifically, the diverse antibodies that fight off invading molecules, from viruses to cancer cells to pollen.

Jared Leeds

IMAGINE THAT THE ONLY ROAD CONNECTING TWO CITIES HAD rollercoaster-inspired loops. Cars and trucks attempting to make the journey would plummet off the highway. It would surely discourage direct traffic between the towns. ¶ In the cell, where molecular machines constantly travel along strands of genetic material, such uninviting loops and curls are commonplace. They help keep proteins from accessing genes the cell doesn't need at the time. Later, when the cell needs the genes to be activated, the dizzying roundabouts can be straightened out to support molecular traffic.

In the late 1970s, when HHMI investigator Fred Alt at Children's Hospital Boston started studying the human immune system, he had no idea this higher-order structure of DNA even existed. Today, he's found that the way DNA is packaged into three-dimensional structures is crucial to every immune process he's looked at.

Alt studies how the immune system generates antibodies against any potential invader to the body—from a virus to a cancer cell or bit of pollen. When an antibody recognizes an invader, it signals the rest of the immune system to destroy it. This means millions of different antibodies are somehow encoded in the DNA of immune cells to recognize all types of invading molecules.

"It's important for a cell to make only one type of antibody at a time," says Alt. In immunology, that quality is called specificity. "But it's also important that different cells make different antibodies." This is diversity.

If the immune system had enough genes for every possible antibody the body might need, our genomes would be exponentially larger than they are. Instead, immune cells combine different bits of genes in different ways to make millions of unique combinations. Three gene segments—dubbed variable (or V, for short), diversity (D), and joining (J)—are the basis for these permutations.

In 1984, Alt discovered that immune cells always combine a D and J segment before adding a V. Cells early in their development, he found, contained partial antibody genes composed of only Ds and Js. When Alt grew those cells in the lab, the antibody genes added a V later in the cell's development. He has since worked out some of the proteins responsible for combining these gene segments in different ways. And he's pinpointed how the cell makes sure only one antibody is produced—by suppressing alternate antibody genes once a combination is successfully produced.

But Alt wanted to know how the cell ensured the order in which the genes were combined. The hint came when he was looking at the DNA between D and V gene segments. He noticed a stretch of DNA that's found elsewhere in the genome and is known to regulate DNA transcription. A protein called CTCF that attaches to certain DNA sequences to regulate gene expression can bind to the region. It folds the surrounding DNA into loops.

Alt wanted to know the role of the so-called CTCF-binding element in controlling the assembly of antibody genes. So he mutated the binding element, with drastic results.

"We saw a very unordered pattern of antibody gene generation," says Alt. Segments from the V genes joined with Ds before the Js were tacked on. And only a few of the possible V segments were used, leading to fewer unique antibody possibilities. Moreover, cells lost the ability to ensure production of only one antibody at a time. Both specificity and diversity were obliterated. His group, led by postdoctoral fellow Chunguang Guo, published the observations September 11, 2011, in *Nature*.

"This site impacts every regulatory process that we've been studying for 30 years," Alt says of the CTCF.

The CTCF protein is normally bound to the CTCF-binding site during development. Alt's team discovered that the antibody gene forms a number of loops that require the bound protein. Transcription proteins—which travel along DNA and use it as a blueprint for RNA strands—get stuck between the D and V segments because of these loops, Alt thinks. The arrangement allows developing cells to produce antibodies with only the D and J regions; the V segment is added later.

"Genes have incredibly complex three-dimensional organization," Alt says. "And we're learning that all of biology depends on that organization."

Alt's next task is to uncover the other proteins responsible for controlling the CTCF site. Now that he's found a master control site that keeps the V from being added to antibodies too early, he wants to know what signals the cell to finally add the V segment. Stay tuned. ■ –SARAH C.P. WILLIAMS


FORCE
FACTOR

BORROWING TRICKS FROM PHYSICS, BIOLOGISTS ARE GETTING A HANDLE ON THE MINIMACHINES THAT PROVIDE PUSH AND PULL INSIDE LIVING CELLS.

BY SARAH C.P. WILLIAMS

WHY MEASURE FORCE?

This is research at its purest, done to advance our understanding of the inner workings of the cell. But every molecule that generates or responds to force is one that, when it doesn't work properly, could lead to cellular malfunction and disease. Understanding the forces at work inside a cell helps scientists discover ways to strengthen or stifle those forces to cause broader changes in a cell.

SCI-EN-TISTS

in the early 1900s invented a relatively easy way to measure the force generated by a muscle. They would hang muscle fiber, biopsied from an animal, between two finely calibrated springs and then probe the muscle with an electric shock to make it contract. The stronger the muscle, the more it pulled the springs.

But physiologists soon learned that individual molecules in cells generate the collective force in muscles. And the crude spring experiments couldn't be applied to these tiny molecules. The challenge of how to measure molecular forces became even more vital as they discovered other molecular motors—molecules in a cell that convert energy to movement. Motors, scientists realized, help sperm swim, pull DNA apart so it can be copied, and carry molecules from one side of the cell to the other. Every directional, nonrandom movement that had been visible under microscopes for centuries was, at some level, due to molecular motors generating force inside cells.

Force is anything that makes an object change its speed, direction, or shape. In the context of cells, forces are required to move molecules. Quantifying these forces gives scientists a way to compare and contrast different molecular motors. Without measurements of force, they were missing a crucial entry in the equations of how cells use energy.

"The bottom line is that the cell is not just a little bag of concentrated reactants. The cell resembles a factory," says Carlos Bustamante, an HHMI investigator at the University of California, Berkeley. "There are different centers, each specialized in certain functions. Those centers are primarily made up of protein machines. And those machines work as motors that produce torque and movement and force."

Today, thanks to techniques that Bustamante helped bring from physics to biology, scientists can quantify the forces and movements generated by molecular motors. They can precisely measure the force it takes to unfold a protein or unwind a strand of DNA. The innovative methods not only provide fascinating insight into the magnitude of force being generated inside living cells, they also offer ways to change this force and study the consequences. Scientists can play tug of war with a strand of DNA or pull a protein backward along a track to see how the molecules behave under stress.

Shining a Light on Force

In the 1980s, Bustamante worked at the University of New Mexico studying how pieces of DNA moved through gels. When coaxed through the gel by an electric current, fluorescently stained DNA strands moved at different speeds depending on their sizes.

"As I was watching this separation, what became evident to me was how elastic these molecules appeared," he says. "Sometimes a little piece would get caught and the DNA would stretch out, and then it would snap back like a spring."

He became curious about the elasticity of DNA and how to measure it. How much force would he need to stretch out a strand like the gel was doing?

In his earliest calculations, Bustamante estimated that he needed a tenth of a piconewton to begin to stretch DNA. "A newton is about the weight of an apple on the surface of the earth," he says. A piconewton is a millionth of a millionth of that, around the weight of a red blood cell."

To generate this small amount of force, Bustamante attached one end of a DNA strand to a glass coverslip and the other end to a tiny magnetic bead. Then, he used a second magnet, with a known magnetic strength, to tug on the magnetized end of the

DNA strand. He could measure how strong the magnet had to be to stretch the DNA by different amounts. It was the first direct measurement of the elasticity of a strand of DNA and was reported in *Science* in 1992.

Over the next decade, Bustamante and his colleagues refined the method and brought cutting-edge physics to bear. Instead of using magnetism, their techniques relied on optics, or light. These methods allowed them to make more precise measurements and apply even smaller forces.

If a powerful laser shines through a plastic bead, the light beam is slightly deflected at the bead's surface. This change in direction of the light beam requires a tiny amount of force. And according to Newton's third law—for every action there is an equal and opposite reaction—this miniscule amount of force pulls the tiny bead toward the center of the beam. Change the intensity of light, and the amount of force exerted on the bead changes.

Physicist Steven Chu, now the U.S. Secretary of Energy, won the 1997 Nobel Prize in Physics for his quantum physics application of this technique, called optical trapping because it traps a particle in the beam of light. Bustamante was among a handful of scientists who pioneered its use in biology for single-molecule studies.

The small plastic bead used in optical trapping can be attached to a strand of DNA or a protein and pulled using the force generated by the laser beam. To stretch a piece of DNA, Bustamante could attach a plastic bead in place of the magnet, put it under the laser, and slowly move the laser in one direction.

"We knew we were doing experiments that hadn't been done before," says Bustamante. "But we came to realize that besides just learning what the elasticity of DNA was, these techniques offered the chance to learn about other interesting things in the cell."

Suddenly, Bustamante had a way to physically manipulate any molecule that he wanted. He imagined using optical traps to pull proteins apart or drag motors along pieces of DNA. Today, these experiments are reality, and optical trapping is the go-to way for biologists to push and pull on individual molecules to study their behavior.

Measuring Moving Parts

At Yale University, HHMI investigator Anna Pyle studies the shuffling movements of RNA helicases along strands of RNA, the genetic material that translates DNA codes into proteins. As they move, some RNA helicases push other molecules off the RNA. Other helicases are required to unwind double strands of RNA or to recognize foreign RNA brought into a cell by a virus.

Jason Grow

Tania Baker has used optical trapping techniques to measure the forces involved in protein folding. Next up: the force required for molecular machines to yank protein sections apart.

"At their core, all these proteins work by opening and closing, shuffling along an RNA strand," says Pyle. "But that behavior is coupled to all sorts of different functions in the cell."

Having studied the biochemistry and structure of helicases, Pyle wanted to quantify the force it took for the proteins to move along RNA. In collaboration with Bustamante, she used an optical trap to tug on a helicase as it moved along an RNA strand. As the helicase moved, the optical trap exerted an increasing amount of force on the bead attached to the helicase. The scientists could measure these forces through the laser beam holding the bead in place.

"Getting these numbers on force serves as a real window into basic thermodynamics of these motors," says Pyle. Biochemists like to think of chemical reactions in terms of equations, she says, and force has been a missing number in those equations. She can now use her initial results to compare the force used by different helicases or to see how a mutation changes the force a helicase can generate, and thus, its function.

Optical trapping experiments by Michelle Wang, an HHMI investigator at Cornell University, upended ideas on how one protein works. In the 1990s, Wang was part of a Princeton University team that used the technique to measure forces of a DNA-based motor protein for the first time. Today, Wang has turned her attention to T7 helicase, a molecular motor that separates double-stranded DNA into two single strands by pulling the DNA through the center of its donut-shaped structure. Other proteins then add nucleotides—the building blocks of DNA—to turn the single strands into two double strands.

T7 helicase can bind two forms of cellular energy. One, called ATP, is the most common currency of energy in cells. Breaking ATP's chemical bonds releases energy used in many molecular motors. The other form, called dTTP, is both an energy-storing molecule and a DNA nucleotide. Previous experiments with T7 helicase showed that when only ATP was present, the helicase didn't unwind DNA. But the studies looked at many strands of DNA and helicases at once, averaging how fast the motors moved. Wang wasn't convinced the collective results told the whole story, since she knew ATP could bind to the helicase.

"When you do an experiment like that, you don't know the behavior of each molecule and it's hard to interpret," says Wang. "It's like trying to analyze a whole bunch of runners going at different speeds. But instead of measuring the speed of each runner, you measure how long it takes until the last runner crosses the finish line."

Wang's team devised optical traps to hold two DNA strands in place, so they could track the unwinding progress of the T7 helicase one molecule at a time. In the presence of dTTP, their associated helicase unwound the DNA at a consistent rate. With only ATP present, the helicase unwound the strands at a faster rate but constantly slipped backward on the DNA, never getting to the end. The group published their work October 6, 2011, in *Nature*.

"In bulk studies, researchers didn't get an unwinding signal at all in the presence of ATP," says Wang. "So we didn't know this was happening." She thinks the slippage is an adaptation by the cell to slow unwinding of DNA when there aren't nucleotides around to quickly bind and pair with each single strand. Since dTTP is a nucleotide that can be incorporated into the strands, its binding to the helicase signals that there are plenty of nucleotides around and the single strands won't be left hanging.

Molecular Tug of War

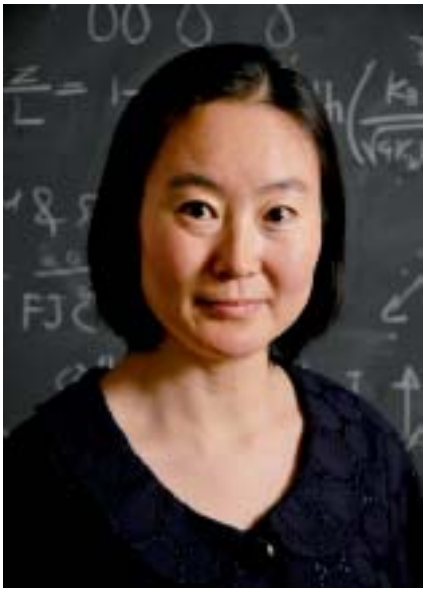
The first applications of optical trapping in biology revolved around DNA and RNA. Since Bustamante had already calculated the elasticity of the molecules, these measurements provided a starting point for other experiments on the forces exerted on or by the nucleic acids. But scientists soon wanted to manipulate proteins on their own—to study how they can alter their complex conformations, unfold, and interact with each other. Optical trapping offered a way to do this physical wrangling.

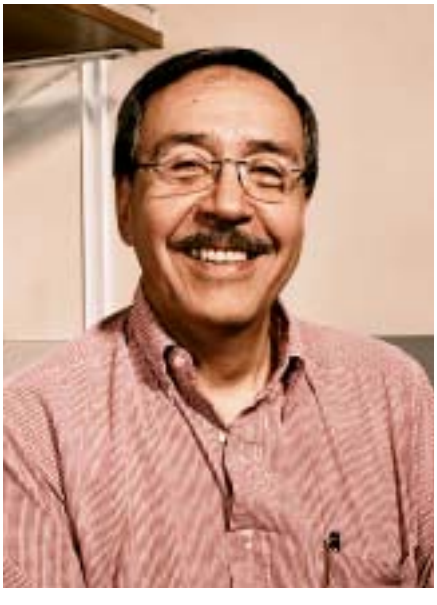
At the Massachusetts Institute of Technology (MIT), HHMI investigator Tania Baker, as part of a long-term collaboration with HHMI scientific review board member Bob Sauer, runs experiments that are similar to those Michelle Wang set up to study T7 helicase. But Baker studies how one molecular machine, ClpXP, unfolds entire proteins rather than DNA strands.

"Proteins are designed to be really stable in cells, but there are critical times when the cell needs to unfold them," says Baker. Unfolding a protein inactivates it if the protein is no longer needed, has to cross a membrane, or needs to be remodeled, she explains.

ClpXP, like helicase T7, is ring shaped, and pulls proteins through its center. But it doesn't always move at a steady rate—some proteins, or parts of proteins, are harder to unfold and cause ClpXP to stall, while other proteins or sections unravel easily, especially once a neighboring bit is unfolded. Baker wanted a way to study the range of speeds at which ClpXP moves as it unwinds different parts of a protein.

So she collaborated with biophysicist Matt Lang, then at MIT and now at Vanderbilt University, to devise an optical trap setup. Two traps held either end of a protein strand in place. As ClpXP unfolded the protein, the strand lengthened—measurable by determining the distance between the traps. So far, she's shown that the technique works, quantifying the stop–start motion of the unfolding process. Next, she'll use it to tackle the tougher question of what determines how hard it is for ClpXP to yank protein sections apart.





Carlos Bustamante devised optical trapping to physically manipulate molecules and study their behavior. Michelle Wang used the technique to watch DNA unwinding in the presence of two different energy sources—and saw distinctions that no one had picked up before.

Wang: Kevin Rivoli/AP, ©HHMI Bustamante: Andrew Nagata

"It's like trying to analyze a whole bunch of runners going at different speeds. But instead of measuring the speed of each runner, you measure how long it takes until the last runner crosses the finish line."
—Michelle Wang

"We do a lot of biochemistry and a lot of structural studies, and now this is another tool to study this family of enzymes," says Baker. "One of the things this protein does is create force, so it's important to study that aspect of it."

Not all motors in the cell are pulling molecules apart. Some are vehicles, carrying cellular supplies from one location to another. A neuron, for example, has a long process—the axon—that can extend up to one meter. Proteins, membranes, and chemicals must move rapidly from one end of the axon to the other, requiring a molecular motor.

In 1985, HHMI investigator Ron Vale of the University of California, San Francisco, discovered kinesin, the molecular motor that transports materials through neurons on filaments called microtubules. In his early experiments, Vale could watch kinesin moving a plastic bead along microtubules under a microscope and later could follow the movement of the motor by single-molecule fluorescence microscopy. But in their natural state, molecular motors of the neuron need to produce a reasonable amount of force to drag their cargos through the dense environment of the cytoplasm. Vale found optical traps to be a useful tool for studying this force.

"It's like learning how an engine works by studying how it performs under different loads," says Vale.

In his latest experiments, optical traps have allowed him to push and pull a single kinesin molecule along microtubules and observe how it responds. Unexpectedly, he found that simply pulling on the kinesin causes it to take regular steps along the microtubule, even in the absence of the chemical energy that it usually needs to produce movement. He also found that he could pull the molecule backward along microtubules, but it takes more force. The difference in the required force provides clues about how kinesin works and how it moves in the correct direction.

The Force of Innovation

While optical traps have answered some questions posed by biologists and given them a way to quantify force in their systems, the method has also led to more questions.

Vale, for instance, now wants to know how kinesin's structure changes while it's stepping along microtubules. The atomic details of protein structure can be obtained by x-ray crystallography but are not visible under a light microscope; thus optical traps alone do not provide data on structural changes.

"I'm fascinated by the idea of putting these two worlds of x-ray crystallography and light microscopy together," says Vale. "What are the real structural changes that are occurring during force generation?"

HHMI investigator Taekjip Ha, at the University of Illinois at Urbana–Champaign, has developed a technique that offers a way to pair structural data with the force control of optical trapping.

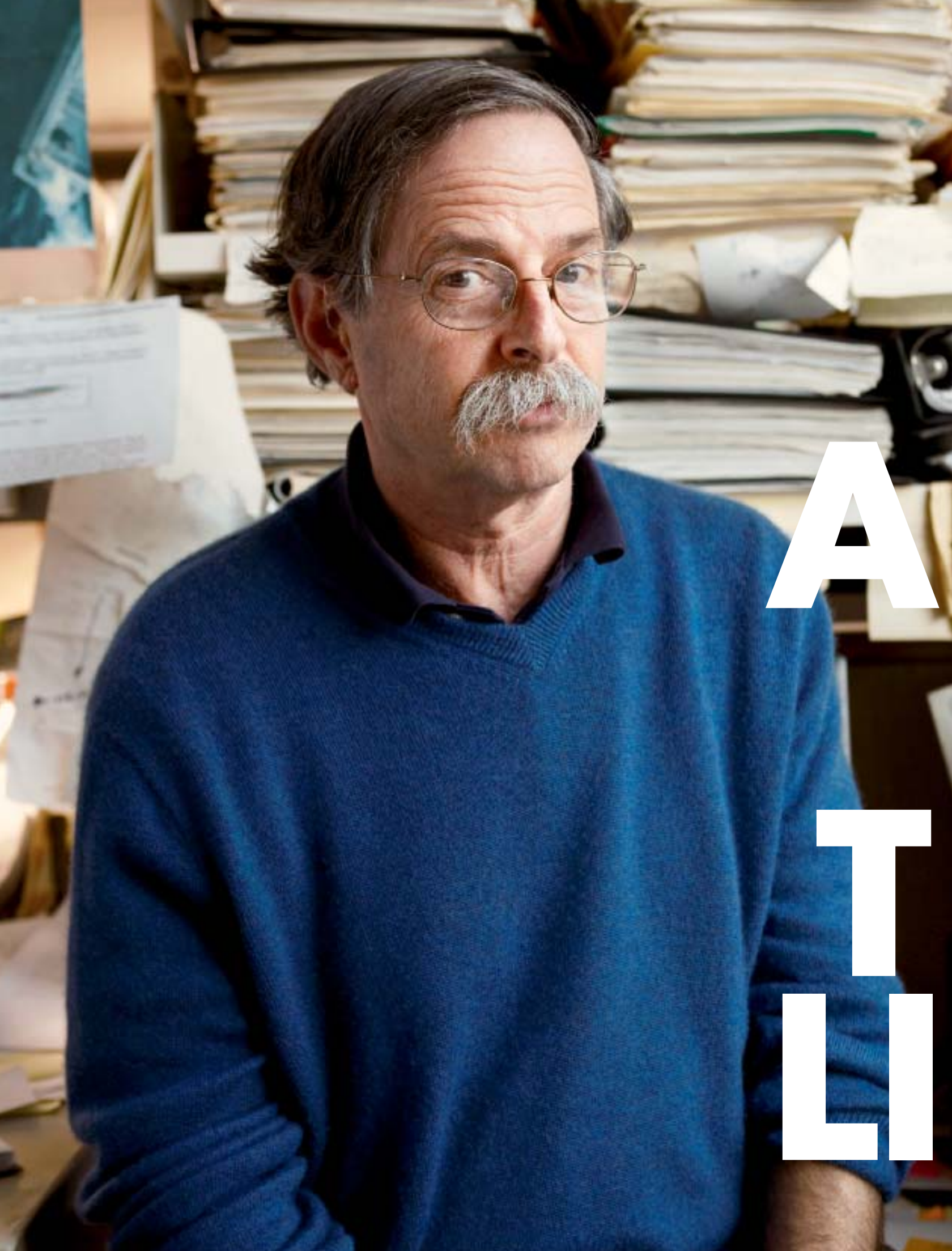
In 1996, Ha developed a method to determine the proximity of two fluorescent molecules based on the light they give off. The technique, called fluorescence resonance energy transfer (FRET), had been around for decades, but he showed that it could be used on two single molecules, rather than as an average. The fluorescent tags can be attached to two molecules or two parts of a molecule. As the two tags come closer together or move apart, the fluorescence changes. He uses FRET as a measure of distance, and therefore movement, between any molecules or parts of molecules.

In a test of the method, Ha collaborated with Pyle to uncover details of how one particular helicase—from the hepatitis C virus—unwinds DNA. Its DNA-unwinding function is vital for the virus to make new DNA and infect cells. The scientists attached fluorescent tags to two strands of DNA and attached the strands to optical traps. As the helicase moved along the double strand, separating it, the researchers could observe the unwinding of the DNA, base pair by base pair, as the fluorescent tags got farther apart.

The pair discovered that the helicase unwinds three base pairs at a time, then releases tension in the strand, letting it relax, before unwinding three more. The discovery could help them understand how to block the helicase from helping the virus replicate.

Next, they want to know how much force this unwinding takes. So Ha is combining FRET with experiments measuring force. By measuring how the distance between two parts of a protein changes as a result of force, scientists can get a fuller picture of how unfolding or conformational changes happen.

(continued on page 48)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A hands-on scientist with a clear vision, Art Horwich lets nothing stand in the way of his mission.

by Sarah Goforth
photography by Mark Mahaney

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FOLLOW ART HORWICH

into his first-floor laboratory at Yale's Boyer Center for Molecular Medicine, and you will quickly see where status ranks among his priorities. Dressed for comfort in khaki corduroys and a worn North Face fleece, the 61-year-old medical geneticist drops his bag on a cluttered corner desk and reaches for a tray of DNA samples left on the lab bench in an overnight experiment. He grins from behind round wire glasses and an Einsteinian moustache. "I'm a little stunted," he apologizes as he completes a task normally reserved for students and technicians. "I still function as a postdoc."

Loathe to distance himself from data, Horwich keeps four microscopes (three dissecting, one confocal) in his small office down the hall. Chin-high piles of manuscripts are stacked against the far wall; he is on the editorial boards of three scientific journals. Photos of his wife, three grown children, and lab members, along with a former patient's yellowed thank-you letter, decorate his bulletin board. What's missing is any evidence of the many honors he's received—including the prestigious Albert Lasker Basic Medical Research Award, which he shared in 2011 with Franz-Ulrich Hartl of the Max Planck Institute of Biochemistry—for his game-changing contributions to our understanding of protein folding.

"In science, it's not what did you do for me 20 years ago, it's what have you done for me today," says a cheerful Horwich, who has been an HHMI investigator since 1990. Today his full attention is on a mystery of biology gone wrong that has eluded scientists for decades and a disease that takes thousands of human lives every year. His goal, pursued with relentless open-mindedness, is nothing short of a cure.

THE VIEW FROM THE BENCH

On a chilly Sunday afternoon in April 1939, New York Yankees' first baseman Lou Gehrig went to bat in the Bronx for the last time. Having played a record-setting 2,130 consecutive games, Gehrig's power and once uncanny aim were fading visibly. He struck out. Inside his body, clumps of misfolded proteins wrecked the nerve cells that for 35 years had faithfully sent messages from his brain to the muscles operating his arms, legs, and lungs. Just a couple of months after that game, Gehrig was diagnosed with the neurodegenerative disease that would thereafter be linked with his name; he lived just over two more years.

These days, the prognosis for a patient diagnosed with amyotrophic lateral sclerosis (ALS) remains grim. For Horwich, a sad reminder of that fact came in 2003 when his children's beloved tennis coach began limping on the court and struggled to communicate. Like Gehrig at the time of his diagnosis, this man was in his 30s and otherwise healthy; he died a year after his ALS diagnosis.

"It really affected me," says Horwich, whose career has straddled clinical medicine and basic science. Having spent decades studying cellular machines called chaperones that help proteins fold properly into their useful forms, Horwich turned his attention to a scientific problem with a human face: "Why, in ALS and other neurodegenerative diseases, are chaperones failing to do their jobs?" he asked.

And so five years ago, Horwich transformed a laboratory dedicated to the biology and kinetics of protein folding—a field in which he is widely recognized as a pioneer—to a multidisciplinary combat zone against a brutal human disease. "I felt a deep obligation to go in this direction," he says.

REVISITING A CLASSIC

Although that decision required Horwich to become expert in disciplines in which he had little experience—mouse genetics,

stem cell biology, neuroscience—it was also a natural extension of his past work.

Proteins are made from chains of amino acids that fold in intricate, specific ways into three-dimensional structures. The physical shape of a protein, once folded, governs its behavior. The process sometimes goes awry, however, and misfolded proteins are associated with a number of neurodegenerative and other diseases. In the 1950s, American biochemist Christian Anfinsen unfolded a protein—a common mammalian enzyme—in a test tube and found that it spontaneously refolded into its useful conformation. His conclusion, and that of most scientists who conducted protein research in the following three decades, was that proteins don't need help from the cell to get into shape.

Horwich was just a boy, growing up in a western suburb of Chicago, when Anfinsen conducted his famous experiment. But he remembers the day he learned about it, the day Anfinsen received the Nobel Prize in 1972. Horwich was an undergraduate at Brown University, having joined the first class of students in a program that combined an undergraduate degree with a medical degree. That evening, he says, "we went to the lab and looked for every protein we could find to duplicate Anfinsen's experiment, it was so astonishing." Taken as he was by Anfinsen's discovery, Horwich could not have predicted that decades later his own work would forever amend it.

Horwich completed medical school, graduating first in his class at Brown, followed by a residency in pediatrics at Yale School of Medicine. He loved the human contact that came with clinical medicine but knew the life of a physician wouldn't satisfy his curiosity. Lured by the California climate and a chance to study a particular virus, polyoma, with Walter Eckhart and Tony Hunter, he took a postdoctoral research position at the Salk Institute before returning to Yale in 1981. There, in the lab of Leon Rosenberg, Horwich began his work on a human enzyme—ornithine transcarbamylase (OTC)—that would prove key to overturning the dogma, grounded in Anfinsen's work, that proteins fold on their own.

OTC facilitates the conversion of ammonia to urea in human cells, neutralizing waste. In newborns with a rare, X-linked genetic mutation, OTC deficiency can cause ammonia to accumulate. Seemingly normal at birth, the infants can fall into a coma within days. Rosenberg, Horwich, and colleagues cloned and sequenced the gene responsible for OTC, ultimately developing a genetic test that allowed patients with a family history of the disease to determine whether a fetus carries the often lethal mutation.

CAPTURING A COMPLEX PICTURE

Horwich established his own lab at Yale and was soon joined by Krystyna Furtak, his technical "right hand" to this day, and graduate student Ming Cheng. They had learned that to do its job, OTC must first be delivered to the mitochondria, the oval organelles that supply energy to cells. Curious about how this happens, the group inserted the human OTC gene into yeast. They then created mutant forms of the yeast, looking for failures in the OTC pathway that might help them decipher the steps involved.

By then it was known that proteins generally can't enter mitochondria in their bulky three-dimensional forms. To pass through tiny entryways in the mitochondrial membranes, they must first unfold. Once inside, before they can do their jobs, they must fold up again. One evening in 1987, after a day of examining mutant yeast for variations, Horwich and Cheng, looked across the lab bench at each other and asked a question no one else had: might the OTC protein need help folding after it has entered the mitochondrial chamber?

Anfinsen's experiment, after all, had been conducted in the protected isolation of a test tube; the environment inside a cell is a cacophony of enzymes, chemicals, and tiny protein machines. Some of these machines were known to help refold proteins under stressful conditions that disrupt their shape, such as heat. What if such machines were also required for a protein to fold under normal conditions? Horwich and Cheng decided to look for a mutant yeast strain in which OTC made it into the mitochondria but didn't fold properly once there. That, they guessed, would signal the absence of any such protein-folding machine if it existed.

Within days, Cheng had identified such a mutant, which seemed to confirm their hypothesis. Hartl, an expert on how proteins are imported into the mitochondria, then at the University of Munich, heard about these experiments and called Horwich to see if he needed assistance on the biochemistry side of the problem. "And of course we did," laughs Horwich. "We were three people in a new lab who had little or no experience with yeast biochemistry and were stumbling our way around."

Horwich shared the mutant strain, called mif4, and heard back from an excited Hartl two weeks later. "He said, 'you're absolutely right,'" remembers Horwich. "His work suggested that whatever

was going wrong with this mutant, it had something to do with polypeptide chain folding inside the mitochondrial matrix."

The mutation carried by this strain, it turned out, was in a gene that encodes a mitochondrial protein whose production is amped up when cells overheat—one of the class of protein machines thought to help refold proteins under stressful conditions. For that reason it had been dubbed heat shock protein 60, or Hsp60. Versions of this protein are found in nearly every cell of every organism in the world. The surprising thing was that Hsp60, in Horwich's mutant yeast, appeared necessary for protein folding under normal conditions.

The notion that Hsp60 could be necessary for protein folding provided "enormous focus" for the group, according to Wayne Fenton, a senior member of Horwich's lab. The researchers probed a related protein found in bacteria, called GroEL, from every angle possible to understand how it worked. "If we didn't have the tools or the skills to answer the question we needed to answer, then we figured someone else did and we found a collaborator," says Fenton. "Usually they would teach us a thing or two, and we'd say, 'hey, this isn't so hard,' and then start doing it ourselves. Art and I share that point of view."

cell dies. The scientists named the complex a chaperonin and placed it in a class of proteins—called chaperones—believed to assist other proteins in their tasks.

"From the time of Anfinsen we thought that proteins fold and that's all there is to it," says Richard Lifton, an HHMI investigator and Horwich's department head at Yale. "Art's work completely overturned that paradigm because actually, no, if you didn't have these chaperonin machines, the proteins would come crashing down."

Anfinsen's principles, Horwich hastens to point out, were alive and well throughout these experiments. Horwich's belief has always been that chaperonins facilitate a process that happens quite naturally by creating a sheltered "changing room" for proteins much like Anfinsen's test tube.

AN OBLIGATION TO EVOLVE

Horwich and his collaborators still study GroEL—most recently using electron microscopy with Saibil and collaborators in California to capture images of proteins moving through the machine—but with the larger mystery of its structure and function solved, the ALS work now occupies most of his time.

"In whatever direction the project needs him to go to become expert, he does that. It's one of the hallmarks of a great scientist, following the trail wherever it leads." **RICHARD LIFTON**

A biochemist by training, Fenton was a research scientist in the Rosenberg lab at Yale when Horwich joined as a postdoc. He ran his own lab for a time but lacked patience for the administrative duties that came along with being a principal investigator. When Horwich established his own lab, sights set on OTC, Fenton joined up and has been working at Horwich's side ever since. Both avid sailors, the two men are friends as well as colleagues.

In the 1980s and early '90s, Horwich, Fenton, Cheng, and a growing group of collaborators focused their attention on GroEL. In a painstaking three-year effort with Yale crystallographer Paul Sigler, who died in 2000, the group elucidated GroEL's molecular structure by x-ray crystallography. Working with Helen Saibil at Birkbeck College in London, the team captured further details of the machine in various states via electron microscopy.

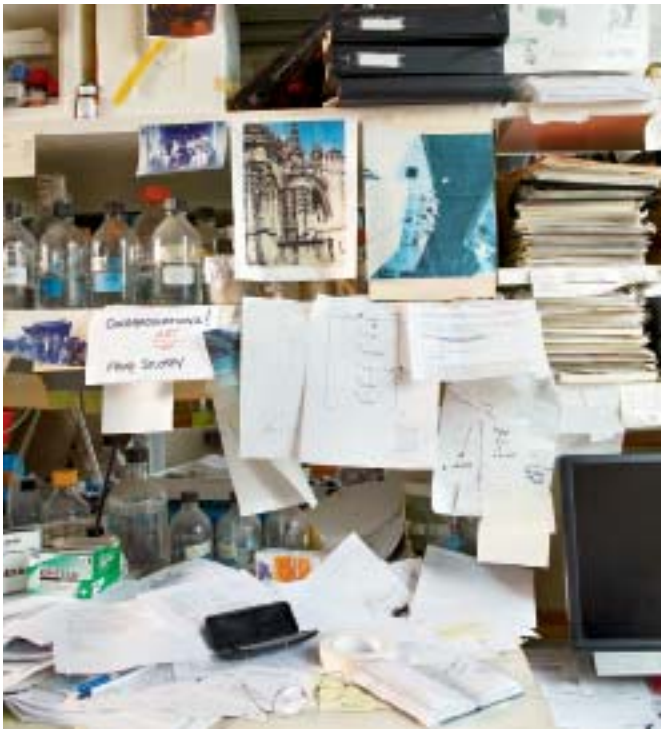
Snapped together in the cell with a protein cap called GroES, the GroEL complex is shaped like a hollow bullet whose tip pops on and off to chauffeur in unfolded proteins and close them off from the cellular environment. Safely inside, the proteins fold on their own, as Anfinsen predicted. But without GroEL, the proteins clump together before they have a chance to fold, and the

"While we were busy trying to understand the mechanism of chaperones," Horwich says, "a whole industrious group of people was learning that many common neurodegenerative diseases are associated with protein misfolding and aggregation. It was shocking to see that a number of these aggregates are occurring in the cytosol—the cell's watery interior—where there should be a good supply of chaperones."

In ALS, the aggregates form almost exclusively in the spindly motor neurons that extend down the body's limbs and operate the muscles. Despite years of study, no one knows why this happens or whether the aggregates are a cause or a symptom of the disease. Tackling those questions requires the kind of experimental openness Horwich is known for. "We just have to look at it at all levels," he says. "Electron microscopy, light microscopy, whole animal, embryonic stem cells if they'll work, genomics."

On a given day, you might find Fenton bent over a microscope, his long white beard dangling as he examines fledgling motor neurons cultured from stem cells. In the next room, postdoctoral researcher Urmi Bandyopadhyay might be examining a spinal cord cross-section from a mouse in the last stages of the murine equivalent of ALS. She guides a fine laser to cut out and capture, for further study, the protein clumps associated with the disease.

Though Art Horwich has a full schedule—he's on the editorial boards of three scientific journals—he still makes time to keep his hands in the work at the lab bench.



Mark Mahaney

MAKING THE ROUNDS

If it's early in the morning, Horwich can be found in the basement of the building next door, making his daily rounds.

Most ALS cases in people are sporadic, meaning that the family of the affected person has no history of the disease. But roughly 10 percent of cases are familial, inherited from one generation to the next. Scientists have identified a number of genes associated with familial forms of ALS, and Horwich has homed in on one of them, called *SOD1*, to study a mouse model for the disease. He begins every day by checking in on his mouse colony, many members of which have been bred to express mutations in *SOD1*.

The *SOD1* gene codes for an abundant protein—it accounts for roughly 1 percent of the proteins in a cell's cytosol—whose precise role in ALS is unknown. Horwich bred mice with a mutant form of the SOD1 protein, called G85R, that cannot fold properly and causes features of disease like those associated with ALS in humans, including partial paralysis and clumped proteins inside motor neurons. The mutation appears to cause a gain of function, not the loss of one: delete the gene entirely, and the animals survive.

How an animal could survive without a protein normally so abundant is one of the many questions in the overall ALS puzzle that Horwich's lab is pursuing. Pinpointing the function gained as a result of the mutation associated with the disease is another. With Lifton, Horwich is also sequencing the protein-coding portions of genomes of ALS patients. In doing so, the scientists hope to explain the role of genetics in sporadic forms of the disease.

"There hasn't been a lot of ambiguity in Art's lab as to what the mission has been," says Lifton. "In whatever direction the project needs him to go to become expert, he does that. It's one of the hallmarks of a great scientist, following the trail wherever it leads."

But beyond elucidating the basic biology of ALS, Horwich is not shy about his ultimate goal. "If, when my children's tennis coach first started limping we had known what to do to arrest the process associated with aggregation of these proteins, he would still be alive," he says. "That would be the dream."

To that end, Horwich has treated some of his mutant mice with experimental therapies; in others, he is investigating how variations in the *SOD1* gene affect the progression of disease. He is also exploring whether it's possible to get cells to ramp up their production of chaperone proteins, amplifying their ability to capture free-floating unfolded proteins that might otherwise clump together.

It's too soon to say whether any of these approaches will yield a viable treatment. For Horwich, who in the GroEL days grew accustomed to experiments that could be conceived and completed in a single day, the work is maddeningly slow. Still, his characteristic optimism is on full display.

"I keep going in the mouse room and hoping that we will be able to see an animal whose disease improves because of something we can track," he says. But "whether we're successful at trying this huge thing that we're trying to tackle or not, I'm still going to come to work. I'm still going to tinker side by side with my group." ■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RAISING THEIR GAME

by Dan Ferber
illustration by Josh Cochran

Science and math teachers need to be *relentless learners* to keep up with the science and effective teaching principles.

PART 2 OF 2: This article focuses on in-service training—professional development for teachers once they are in the classroom. Part 1 of the series, on preservice training for college students and graduates who intend to be STEM teachers, appeared in the November 2011 *Bulletin*.

AFTER A DECADE

teaching high school and middle school science, Wendy Bramlett had taught every topic in the book. No joke.

"I used to think you had to cover every concept in the textbook," says Bramlett, a science teacher at Tuscaloosa Magnet Middle School in Tuscaloosa, Alabama. Her students would dutifully regurgitate the information on tests.

Laboratories, when she could afford them, were low-tech affairs. She taught mitosis by giving her students pipe cleaners to model chromosomes in a dividing cell. Often she just did what she calls "pencil and paper" labs, in which students plodded through problems in a workbook. "For the students it was boring. Science wasn't one of their favorite subjects," Bramlett says.

"It really wasn't fun for me either," she adds.

Then Bramlett got some training. She enrolled in the Alabama Math, Science, and Technology Initiative, an extensive, state-run teacher training program for science and math teachers aimed at boosting student performance. Bramlett took advantage of every aspect of the program: She completed a two-week workshop two summers in a row, connected with a science-teaching mentor, and began borrowing modern laboratory equipment and teaching her students how to use it. Her teaching—and her students' learning—turned around.

Today only about one-third of eighth graders in the United States show proficiency in math and science. Several standard-setting groups have taken action to boost U.S. performance in science and math. Last summer the National Research Council outlined new science teaching standards that lean heavily on inquiry-based learning. The College Board has overhauled the Advanced Placement Biology curriculum to emphasize scientific inquiry and reduce the emphasis on rote memorization. And 45 states have adopted the Common Core State Standards for Mathematics, a state-led initiative that raises the bar for K–12 mathematics education. These efforts are built on an education research base that says students understand science better by doing it and they learn math best by applying it to real-world problems.

Educators and funders are revamping preparation of prospective teachers (called preservice training) to help them learn how to teach in these new and more effective ways (see "Calling All Teachers," November 2011 *HHMI Bulletin*). But what about the nation's 250,000 middle and high school science and math teachers already in classrooms, and the 1.5 million elementary school teachers who teach some science and math? They're going to have to raise their game.

For that they'll need good professional development. It's no easy task, however, for trainers to change teachers' practices enough to improve student learning, says Deb Felix, senior program officer for HHMI's precollege science education initiatives. Good programs help teachers acquire a firm grasp of modern scientific techniques and the teaching methods they need to enable their students to learn through inquiry. They also create opportunities for teachers to test and refine new lessons and carve out ample time for training, mentoring, and peer support—often despite tight and shrinking training budgets (see sidebar, "STEM Teaching 2.0"). A mix of large nonprofit agencies, universities, states, and school districts are incorporating these tested approaches. The work they're doing is beginning to pay off.

LOTS OF OPTIONS, NOT ENOUGH TIME

U.S. schools invest 1 to 12 percent of their budgets on staff professional development, according to Learning Forward, a trade group for teacher trainers. This spending creates a huge market for teacher professional development, and there is no shortage of organizations that offer it. School districts often develop and run their own programs, sometimes with advice from companies and independent consultants. Universities, colleges, medical schools, and museums hold summer workshops and develop teaching modules. Some companies sponsor programs for teachers, such as Intel's Thinking with Technology course. Nonprofit organizations, such as WestEd and the National Science Teachers Association (NSTA), offer workshops and online programs for teachers, some of them supported by federal funds. "Anybody can get into this mix who can sell it," says Julie Luft, a science education researcher at the University of Georgia and former director of research at NSTA.

Still, most teachers receive far less training than they need, and not by choice. More than half of U.S. teachers are offered at most two days of paid professional development per year from their districts, according to a large 2003–2004 survey by the U.S. Department of Education. More than half of science teachers surveyed by NSTA in 2009 said they wanted more. In many school districts, professional development is limited to a single

workshop. "They get a day right before the school year begins," Felix points out. These workshops are too short to be of much use, yet districts keep doing them, she says.

SEEING STUDENTS BENEFIT

When done right, however, professional development can make a real difference for students. Carla C. Johnson, of the University of Cincinnati, and two colleagues tracked students at a middle school where all science and math teachers received comprehensive professional development, including monthly in-school sessions in which trainers modeled effective instruction and let teachers practice it. Their students were compared with students at a middle school in the same district with no such program. After two years of instruction by these newly trained science teachers, Johnson's team gave the seventh-graders a 29-point test to gauge scientific knowledge and reasoning. They scored 50 percent better than students of untrained teachers, Johnson and colleagues reported in 2007 in the *Journal of Research in Science Teaching*. What's more, the effects lasted. In 10th grade, 88 percent of the students who had learned from the specially trained middle school teachers passed the Ohio Graduation Test on their first try, compared with a 34 percent pass rate among students of the control teachers, Johnson's team reported in 2010 in *School Science and Mathematics*.

Two summers of training in an inquiry-based neuroscience curriculum was a big help for middle school science teachers in Minnesota. When science educator Gillian Roehrig and neuroscientist Jan Dubinsky of the University of Minnesota tested the impact of the curriculum, called BrainU, they found that the teachers adopted the methods immediately after the first year, Dubinsky reported at the 2011 conference of the Association for Science Teacher Education. However, "after the second year it's really transformative in terms of how they're using inquiry in the classroom," Roehrig says.

That was Rachelle Haroldson's experience. A year after she completed BrainU's partner program for high school science teachers, her students were dissecting a sheep brain, exploring how it compared structurally with a human brain. And after her students assembled model neurons from beads and string as they studied neural signaling, she had them investigate questions like: What is a drug? If you take a drug, what does it do to your body? The students learned how alcohol affects decision making in the frontal lobes and how marijuana mimics endogenous cannabinoids. "When they thought about their brain as a muscle and that they were weakening it [with drugs], that seemed to have a profound impact on them," Haroldson recalls.

HONING SCIENCE SKILLS

To help students learn science through inquiry, teachers must first understand how scientific inquiry works. But many are simply not up to speed. They may lack research experience or—especially in middle schools—they may be teaching a subject for which they weren't trained, says developmental biologist Barbara Wakimoto of the University of Washington in Seattle.

Scientists, like Wakimoto, can play an important role offering the research experience and inquiry-focused approach. K–12 science education requires a multifaceted strategy that should involve scientists as well as preservice and in-service training, says David Asai, HHMI's undergraduate science education program director. "The community of scientists, in particular, can provide excellent ways for in-service teachers to build more inquiry into their teaching. In-service teachers can be the principal partners with scientists, who can help develop those tools, and they can be a huge resource for future teachers."

Wakimoto and two colleagues run an intensive four-week summer life sciences teaching institute for 20 Washington State K–8 teachers. They focus on upper elementary and middle school teachers because, unlike high school teachers who see their students for one period a day, these teachers "are with students long enough to get them excited about science," Wakimoto says.

Wakimoto and program manager Helen Buttemer show teachers how to create simple inquiry-based lessons with readily available materials—for example, testing the adhesive powers of slug slime, studying lentil seed germination, or observing fruit fly mating rituals. They train teachers to walk students through a scientific investigation using a tool called an inquiry board. The teacher records ideas on an eight-section poster board as the class brainstorms a question, the variables to test, the controls, the experimental setup, and the predicted outcome. After the study is completed, the class tabulates results, looking for patterns, and answers the original question.

Wakimoto's colleagues follow up by visiting each participating teacher's home school, often bringing equipment to lend. "When we go back to the classrooms, we find these inquiry boards all over the state," she says.

Rob Culpepper

Spurred by workshops, mentoring, and access to equipment, Alabama teacher Wendy Bramlett shifted from lectures to hands-on lessons—and her students' science scores soared.

High school teachers need the hands-on experience as well. In Louisiana, for example, many teachers are certified to teach high school biology or chemistry with just a smattering of college courses in the subject. They "have a working knowledge of the discipline, but they have no lab skills and no research experience as an undergraduate with respect to how science is really done," says Ann Findley, a biology professor at the University of Louisiana at Monroe (ULM).

To build their laboratory skills and confidence, each summer Findley and her colleagues invite eight Louisiana high school teachers and up to 60 of their students for an HHMI-sponsored month-long summer science workshop. The teachers and students work together through four successive one-week investigations, each in a different field of biology. "You might be tagging DNA with fluorescent dyes this week, and next week you may be out seining in the bayou to get the biomass of life in an aquatic environment," says Brenda Grover, science chair at Richwood High School in Monroe and a workshop veteran. "Then you might move to geography, looking at satellite views of our area."

Teachers learn best how to lead inquiry-based lessons by working through them, according to research on professional development. Findley and her colleagues advise teachers privately about how to turn workshop exercises into lessons that will benefit their students. They also challenge teachers to prepare supplies and solutions for an exercise and discuss how to troubleshoot it.

During the school year, the ULM team lends financially strapped high schools trunks with PCR machines, microscopes, centrifuges, and other equipment and supplies. Findley and her students act as science ambassadors to the 20 participating schools, modeling a culture of science for teachers and their students. Undergraduate biology majors help less-experienced teachers run lab investigations. Findley and biology graduate students assist with school science days, encourage kids to enter science fairs, and help students envision getting a science, technology, engineering, and mathematics (STEM) degree, even if no one in their family has gone to college.

The ULM workshop "gets teachers excited about teaching science," Grover says. Students, too. The program has trained more than 500 students since it launched in 2000. Ninety-five percent of them go to college, according to years of follow-up surveys, and many major in science—no small accomplishment in an area with many schools like Richwood High School, where fewer than half of the students' parents attended college and about 90 percent of students qualify for a free or reduced-price lunch. "You look at the poverty rate, and the area surrounding the school, and there's nothing in the community [for the kids] to look forward to," Grover says. "So if you find something to light their fire, man you just want to keep that fire going."

PEER SUPPORT

Peer coaching helps teachers shift their focus from what teachers are teaching to what students are learning. An HHMI-funded program run by Occidental College in Los Angeles uses peer coaching in a method called Lesson Study. The college runs summer workshops in biology, chemistry, and physics for middle and high school teachers in the area, and they employ two science educators who visit schools and coach teachers throughout the school year.

Robert de Groot is one of those science educators. He supervises Lesson Study at Jerry D. Holland Middle School in Baldwin Park, California, where six science teachers take turns teaching one of three inquiry-based science lessons. While one teaches, the other teachers and de Groot observe the students' reactions. They note how well kids follow lab procedures, collect and report data, grasp scientific concepts, and use scientific vocabulary. Afterward, the teachers meet, discuss how the lesson can be improved, and offer tips to their colleague. Then the teachers switch roles; another teacher in the group teaches the revised lesson, and his or her classroom becomes the teaching laboratory.

Chris Craney, a professor of chemistry at Occidental who supervises their science outreach program, reported in the *Journal of Chemical Education* in 1996 that the program increases student interest in science as well as chemistry and biology teachers' knowledge of scientific topics. And inquiry-based laboratories taught by the newly trained teachers significantly improved students' understanding of chemistry, biology, and physics concepts, according to the Occidental team's unpublished assessments of 3,000 students before and after the labs.

Although Lesson Study keeps the focus on student learning, where it belongs, it's expensive because substitutes must cover for the teachers who are observing, says Roehrig. As co-director of Minnesota's Math and Science Teacher Partnership, a statewide professional development program for K–12 science and math teachers, Roehrig instead fosters what educators call "professional learning communities." Science and math teachers are allowed paid time to meet at the school after hours to discuss what worked in the classroom and how they can improve next time.

STEM TEACHING 2.0

Education researchers say they have enough data to know what makes for good professional development.

- MODEL EFFECTIVE TEACHING
- BE IN-DEPTH AND SUSTAINED
- LET TEACHERS HELP TEACHERS
- DEVELOP TEACHER LEADERS
- GET SYSTEM SUPPORT
- DON'T FORGET ESTABLISHED TEACHERS

To learn a little more about each of these ideas, visit WWW.HHMI.ORG/BULLETIN/FEB2012.

Louisiana biology professor Ann Findley trains high school teachers and offers on-site support to build a culture of science at their schools.

Misty Keasler

Teams of science teachers can also help develop an inquiry-based curriculum. Ninety-six middle school science teachers from Loudoun County Public Schools in Northern Virginia collaborated with faculty at Penn State College of Medicine in Hershey, Pennsylvania, over five years to develop an inquiry-based middle school science curriculum. When that HHMI-funded program ended in 2008, about a dozen of the teachers began meeting each summer to update and expand the curriculum, which now underlies middle school science instruction countywide, and to design HHMI-funded training programs for their colleagues around the district. Now "the teachers own the program," says Odette Scovel, the district's K–12 science supervisor.

HELP FOR ROOKIES

Peer support is particularly important for new teachers, who struggle to get the hang of content and lesson plans as well as issues that more experienced teachers have mastered, such as how to manage their classrooms and deal with student misbehavior, says Francis Eberle, president of NSTA. In the past, fledgling teachers were often tossed into the classroom to sink or swim. That still happens, but today more school districts try to ease their transition into the job, a process educators call "induction."

It's important that induction for new science teachers focus on teaching science, and not simply teaching, according to research by Luft and Roehrig. Teachers in science-specific induction programs use more inquiry-based lessons than those in general induction programs or those who've had no induction at all, the two reported in 2003 in the *Journal of Research in Science Teaching*. And teaching habits acquired early often last. Those first years are "when teachers are really forming who they're going to be as teachers," Roehrig says.

And beginning science teachers still need strong support during their second year, according to Luft. Otherwise they're apt to revert to the easier but less effective methods that rely on lectures and textbooks, her group reported in 2011 in the *Journal of Research in Science Teaching*.

One common strategy is to appoint as a mentor a more experienced teacher who covers the same subject and grade level. NSTA and the National Council of Teachers of Mathematics have called for more intensive induction programs in which competent, experienced science and math teachers mentor novices. But "there are actually very few" good induction programs, says NSTA's Eberle.

Roehrig runs one of them, an induction program for middle and high school STEM teachers in Minnesota. Mentors and new teachers in the Teacher Induction Network can hold video chats using Skype-like technology, share lesson plans via Google Docs, or take part in virtual classroom observation. Rookies videotape themselves teaching, post the video, and then peers and mentors use video annotation technology to comment on the teacher's interactions with the students. "It's as good as, if not better than, being in a classroom," Roehrig says. And it makes effective mentoring possible even when the beginning science teachers work in northern Minnesota, hundreds of miles from her university's Minneapolis campus.

SCALING UP

With budgets tight everywhere, district training programs have to do more with less. Anita O'Neill supervises professional development programs in science, technology, and engineering for Montgomery County Public Schools in Maryland, a district with 200 schools and about 600 teachers at each grade level. In 2006, she and project manager Mary Doran Brown began building a district-wide cadre of teacher leaders to help train their elementary school peers to teach science better—and they are moving it online.

They recruited prospective teacher leaders from 90 of the district's 131 elementary schools—not all of them, as they had hoped. Then, with HHMI support, they trained those teachers to help colleagues at their respective schools teach inquiry-based science lessons. At some elementary schools, the teacher leaders got their colleagues to take students to annual "inquiry conferences" at a local college. There, the students presented a science project to their peers and fielded questions from them, just as practicing scientists do at a scientific conference. The program lasted four years until the district's budget tightened in 2010.

To affordably reach the district's throng of elementary school teachers, O'Neill's team enlisted its teacher leaders to help move the training online. At a summer workshop, teacher leaders from elementary and middle schools learned to videotape a lesson, edit the video, and then post it as an example of effective teaching. Ultimately, O'Neill's team wants an interactive website for all K–12 teachers that allows them to review the district's science, technology, and engineering curriculum and plan lessons or learn inquiry-based teaching in line with national standards. "Our vision is a professional learning community," O'Neill says.

To change science and math teaching nationwide, though, there's really no substitute for investment. And no state has invested as much as Alabama. Thanks to an enthusiastic state superintendent and a powerful booster group that included leaders of the state's high-tech businesses, Alabama has invested up to $46 million per year in the Alabama Math, Science and Technology Initiative (AMSTI), says Steve Ricks, who directs the program at the state's education department. AMSTI employs 850 teacher

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WHERE DOES IT HURT?

Researchers are getting to the molecular details of pain's circuitry to answer the question with real specificity.

BY MARC WORTMAN | ILLUSTRATION BY SAM GREEN

THE

SHELVES IN DAVID JULIUS'S LAB AT THE University of California, San Francisco, could be confused with those in a traditional herbal medicine shop. They hold bottles labeled "menthol extract" and "capsaicin," the substance that gives heat to hot peppers. The eye-watering scents of Szechuan peppers, wasabi, and herbs waft through the air. They might seem unlikely tools for one of the world's most advanced neurobiology pain research centers, but Julius uses this trove of natural ingredients to probe the molecular world of pain.

Neurologists and pain specialists long struggled to prove that controlling pain can speed a patient's recovery after surgery or an injury and that people with chronic pain have a genuine malady that's not "all in their head." Today the biomedical world recognizes that pain is a real and pressing health care issue that needs improved diagnosis and more effective treatments. Until about 15 years ago, though, researchers could study pain based only on patient behavior and subjective responses to questions about "where" and "how much" it hurts. As a result of emerging molecular findings, new pain medications and diagnostic tools are being developed.

Neuroscientists often use natural ingredients—like menthol, capsaicin, and wasabi extracts—that stimulate nerve cells to react just as they would in response to painful cold and heat, for example, or to inflammation and chemical irritants. Drawing on electrical recordings, imaging, molecular techniques, mouse models, and genetic studies, scientists can explore the nervous system as it reacts to "pain" at the subcellular level. Their studies have revealed many molecular pathways that regulate pain perception, including specialized ion channels that open and close to send pain signals along nerves to the spinal cord and brain. They have also begun to explain the systemic changes in response to pain sensation that can cause chronic disorders.

HHMI scientific officer Ed McCleskey, who spent much of his research career studying pain, believes such progress will translate into health care benefits. "We have been using more or less the same aspirin and morphine variants for centuries now. But a wave of recent basic science discoveries has begun to transform the pain field, and they are already yielding insights for finding new ways to treat pain."

THE MANY TYPES OF PAIN

Aspirin and opiates work just fine for most of us most of the time. But plenty of people don't benefit from either drug or can't handle their serious drawbacks, which range from stomach irritation and excessive bleeding to addiction and respiratory suppression. The devastating daily reality of uncontrolled chronic pain far exceeds the ability of today's medicines to help. Every year, at least 116 million adult Americans experience severe chronic pain—more than the number affected by heart disease, diabetes, and cancer combined—at a cost of $560 billion annually in direct medical expenses and $635 billion in lost productivity, according to a June 2011 report from the Institute of Medicine.

Researchers today recognize several pain subtypes, which develop via electrical signals running along a complex, interconnected neural perception system genetically encoded to detect and respond to painful stimuli.

The body detects and converts pain stimuli into electrical signals at the fine nerve endings of "nociceptors," sensory neurons specialized to respond to pain. Their axons, which conduct electrical signals, are only a millionth of a meter in diameter but can be more than a meter long, with one end located where a stimulus is detected—at a fingertip, for example—and the other end in the spinal cord, where it forms a synapse, or communication junction, with a second cell that sends the signal to the brain. The nociceptor's spinal synapse is highly sensitive to opiates and other agents that can alter pain perception. The cell bodies of nociceptors and other sensory neurons sit just outside the spinal cord in clumps called dorsal root ganglia; action potentials—short-term changes in electrical charge—pass through the ganglia on the way to the spinal cord.

To convey signals from a peripheral organ to the spinal cord, the axon depends on a variety of molecules. Some convert a physical or chemical event into a small electrical signal at the peripheral nerve ending; others amplify the signal and send it along the length of the axon. Molecules at the synapse convert the electrical signal into a chemical signal, triggering release of a neurotransmitter that activates the postsynaptic neuron. Other molecules tune transmission of pain signals. Various types of ion channels—proteins that create pores in cell membranes—serve as detectors, amplifiers, and electrical-to-chemical translators, while receptors for hormone-like molecules modulate the activity of the channels.

When everything works, the pain system triggers behaviors that lead us to flee danger or to rest and recover from an injury. But it doesn't always work right. In chronic pain, for instance, signaling can become hyperactive so that even the

lightest touch hurts or, in extreme cases, electrical signals fire for no apparent reason. Researchers have recently begun to describe how this malfunction, known as central sensitization, makes nociceptor synapses dangerously hyperactive, as occurs in some mysterious and hard-to-treat pain disorders, such as neuropathy, chronic inflammatory pain, and fibromyalgia.

CHANNELING PAIN

Nerve cell ion channels selectively allow the passage of four types of charged atoms: positive ions of sodium, potassium, and calcium, and a negative ion, chloride. The movement of these ions across a membrane creates an electric current that transiently alters the cell's membrane voltage. The past two decades have seen an avalanche of discoveries of ion channels related to pain sensation.

In the 1990s, Gail Mandel, now an HHMI investigator at the Oregon Health and Science University, and her colleagues Simon Halegoua and Paul Brehm at New York's Stony Brook University were exploring the variety of sodium-selective channels in mammals. Sodium channels act as molecular amplifiers, turning small electrical signals into action potentials that can conduct for long distances along an axon. In 1997, Mandel discovered a sodium channel, now called Nav1.7, which is abundant on sensory neurons. From the channel's location and density, the researchers theorized that it plays a role in pain perception.

Xinzhong Dong, an HHMI early career scientist, is testing compounds that target an Mrg receptor that appears to dull pain.

Paul Fetters

"WE HAVE BEEN USING MORE OR LESS THE SAME ASPIRIN AND MORPHINE VARIANTS FOR CENTURIES NOW. BUT A WAVE OF RECENT BASIC SCIENCE DISCOVERIES HAS BEGUN TO TRANSFORM THE PAIN FIELD, AND THEY ARE ALREADY YIELDING INSIGHTS FOR FINDING NEW WAYS TO TREAT PAIN." ED MCCLESKEY

Human genetic studies strongly support the idea. Erythromelalgia, a rare disease in which patients periodically feel severe burning pain without any sensory stimulus, is caused by a mutation that increases Nav1.7 activity, rendering nociceptors hyperexcitable. Another mutation that diminishes Nav1.7 activity causes a rare disease in which patients are profoundly insensitive to burns and some other kinds of tissue damage. A few pharmaceutical companies are testing compounds to control Nav1.7 as a way to suppress pain (see Web Extra, "Pain Medicines From Under the Sea").

The same year that Mandel's group found the sodium channel, Julius and colleagues published findings about pain perception emanating from one among a subfamily of ion channels called transient receptor-potential vanilloid (TRPV, called "trip-vee") channels. Julius used capsaicin to demonstrate that burning heat specifically activates the TRPV channel in peripheral nociceptors. That discovery also provided a model for future pain studies using natural ingredients to simulate painful stimuli, opening the door to a host of other findings.

Since then, Julius and others have characterized several TRP channels and their interconnected roles in sensory perception. HHMI investigator David Clapham, an ion channel expert at Children's Hospital Boston and Harvard Medical School, also studies the channels, looking at their roles in a variety of sensations. He characterized a member of the human vanilloid TRP subfamily, TRPV3, found in the skin and other major organs, and showed its involvement in controlling some aspects of temperature sensitivity. His lab also identified common plant compounds used as spices and insecticides that activate TRPV3, TRPV1, TRPA1, and other TRP channels, leading to irritations and allergies.

RECEPTORS TO DULL PAIN

A major new direction in pain research began with the discovery of the family of Mas-related gene (Mrg) receptors by HHMI investigator David Anderson and his colleagues, including Xinzhong Dong, at the California Institute of Technology. Mrg receptors are found exclusively in sensory neurons. Dong, now an HHMI early career scientist at Johns Hopkins School of Medicine, has shown that while certain Mrg receptors function in itch sensation, one appears to function like the body's naturally occurring opioid receptors, which help to dull pain. Dong is testing compounds that target this Mrg

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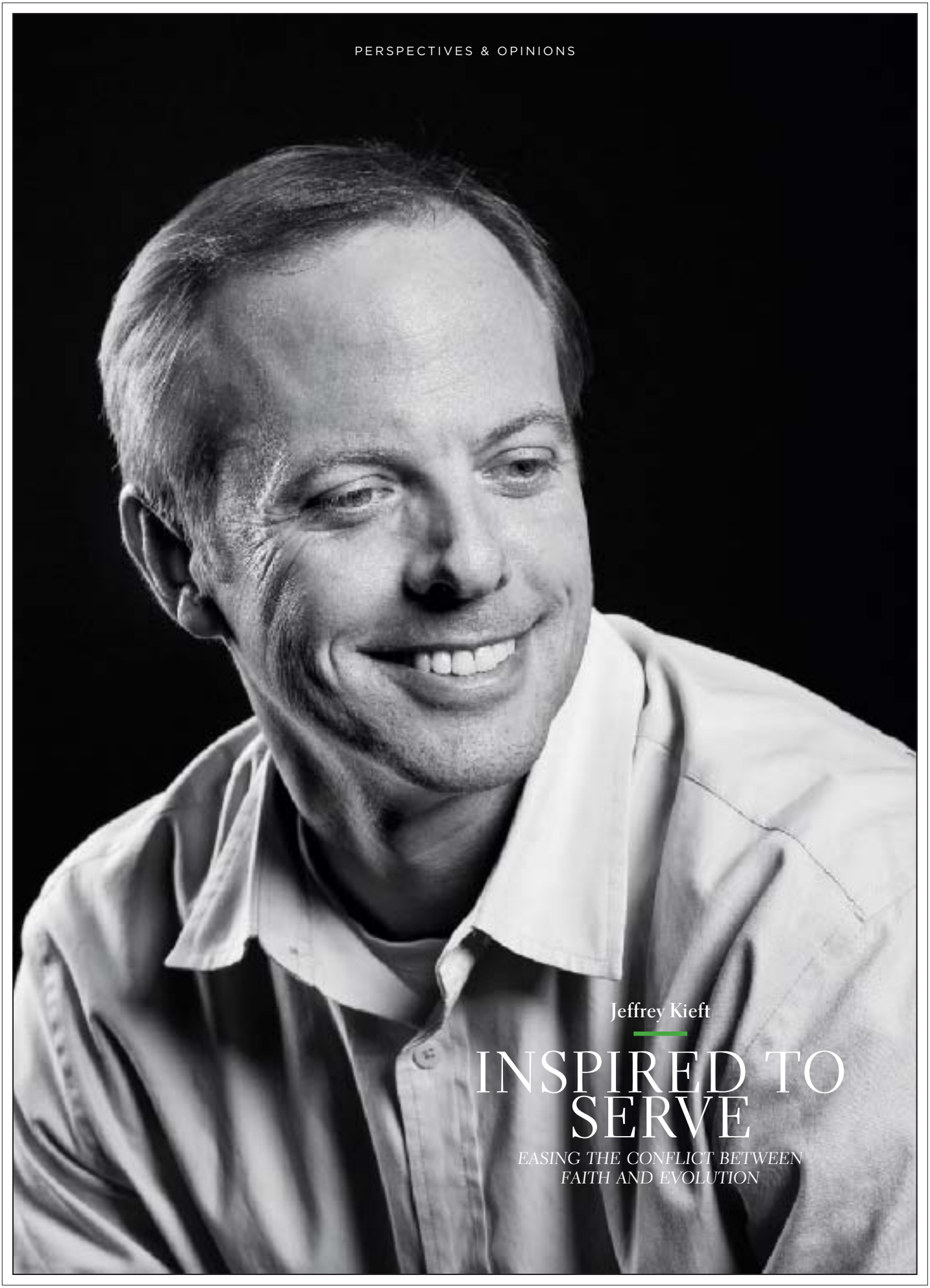


Jeffrey Kieft

INSPIRED TO SERVE

EASING THE CONFLICT BETWEEN FAITH AND EVOLUTION

Matt Nager

Jeffrey Kieft has always been willing to step out of his comfort zone to make a difference. The HHMI early career scientist attended West Point and served as an army tank platoon leader in Mannheim, Germany. Then he worked as a policy fellow at the White House. Now, in addition to running his University of Colorado lab, he engages church groups on the theory of evolution. He's driven to advocate for science.

I think the scientific community has to be careful that we don't adopt the attitude that science belongs to scientists. We need the public to see some connection to their lives. The discoveries that we make really do belong to everyone and should be communicated. I don't see this as service outside of my job but rather integral to the job.

When I started as an army officer, I naively thought my goals matched those of all of my subordinates. I learned that everyone is motivated by different things. Motivating diverse people became a challenge I enjoy—in the lab and when I speak with the public.

During a AAAS policy fellowship in the White House Office of Science and Technology Policy, I got a bird's eye view of science. I saw that the public and policymakers don't necessarily understand how science works. Many don't see it as an investment in the future. That experience made me eager to speak at places such as church forums, Cafe Scientifiques, and community colleges. For me, talking to the public satisfies that itch to get science's voice out there. When I read something in the newspaper or hear something that is an obvious misunderstanding or misstatement about science, I can't *not* do something about it.

But I don't get confrontational. When speaking to a church group, for example, I don't gear myself up for a debate. My goal is to find some common ground and move the discussion forward. I say, let's examine evolution and see if it really must conflict with religion. I cover the basic tenets of evolutionary theory and, even more importantly, what evolution is not. I've been asked, "Isn't the first rule of evolution that there is no God?" I reply, "Well, no actually, that isn't in any science textbook." Just teaching these basic concepts puts people more at ease because they've never learned what evolution means.

To explain a concept like natural selection, I start with a story that everyone can understand. Imagine a valley where rabbits live with few predators. Then wolves move in and that pressure selects for survival and reproductive success of rabbits with certain genes, such as those that make them faster. Over time the rabbit population adapts to become better at evading wolves. If you understand that, then you understand a key part of what Darwin proposed.

People also love hearing about vestigial structures—for instance, the fact that when you get scared, your hair stands on end. That's a vestige of our ability to puff up and look bigger—that is, if we still had fur. We are still carrying in our bodies evidence of our lineage.

I never serve up a watered-down version of evolution, and I am clear that intelligent design is not science and is logically flawed. But I show people than none of this requires them to give up their faith. Evolution is a 'How did it happen?' story, not a 'Who dunnit?'

I respect the view of a friend who is a pastor in Iowa. He says his faith is enhanced by a God clever enough to think up evolution. Some people are not placated, but if they go home and think about it or talk about it around the dinner table, then I've had a positive influence.

And sometimes people ask questions that send me home thinking. Once, a woman asked, "If we are all evolved from common ancestors, us and gorillas and fruit flies, and I believe that humans have a soul, then when did the soul evolve?" I gave her the standard answer that science could not answer that. She replied, "But if my faith says I have a soul and the fruit fly doesn't, and if we both came from the same thing biologically, how is that not in conflict?" That made me realize that, for some people, it is really hard to separate evolutionary theory from their faith.

But, even with this challenge, if we as scientists don't step out and say something—even in little bits and pieces and in small forums—then we're shooting ourselves in the foot because the misinformation and antiscience voices win by default.

INTERVIEW BY KENDALL POWELL. *Jeffrey Kieft studies RNA structural biology at the University of Colorado Denver School of Medicine.*

Q&A

The portrayal of science in films often gets mixed reviews. What's your favorite science-themed film and why does it appeal to you?

From Jurassic Park *to* Contagion, *a film's scientific accuracy is often a hot-button topic. Here, four scientists share their top picks and, unlike movie critics, almost come to a consensus on an all-time favorite.*

—EDITED BY NICOLE KRESGE

Simon W.-L. Chan

HHMI-GBMF INVESTIGATOR
UNIVERSITY OF CALIFORNIA, DAVIS

"I like the movie *Gattaca*. Although it came out in 1997, it seems prescient now that we are sequencing many human genomes. It's an entertaining way to introduce ethical issues about personal genetic information. Plus, it was directed by a fellow Kiwi."

Eugene W. Myers

JFRC GROUP LEADER
JANELIA FARM RESEARCH CAMPUS

"I'm a sci-fi junkie—I'll watch the worst stuff as long as it's even remotely plausible. But there are many great films too, so it's hard to pick a favorite. *Blade Runner. Alien. Star Wars. Jurassic Park. Brazil.* It's mostly about the visuals and the mood created—the special effects, the technology, and the feeling of being transported to another world. But the film that intrigued me the most was *Gattaca*. While it was a dud in terms of special effects and acting (sorry Ethan and Uma), it hit incredibly close to home. Not only was the movie's thesis plausible, but I think it's just around the corner. I wonder if the audience realized it!"

Lora V. Hooper

HHMI INVESTIGATOR
UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER AT DALLAS

"One of my favorite science-themed films is the 1997 movie *Contact*. Jodie Foster did an excellent job portraying a heroic radio scientist on a lonely search for extraterrestrial intelligence. This is a rare example of a film in which the lead character is a sympathetically portrayed female scientist, and for that reason this remains one of my favorites."

Konrad Hochedlinger

HHMI EARLY CAREER SCIENTIST
MASSACHUSETTS GENERAL HOSPITAL

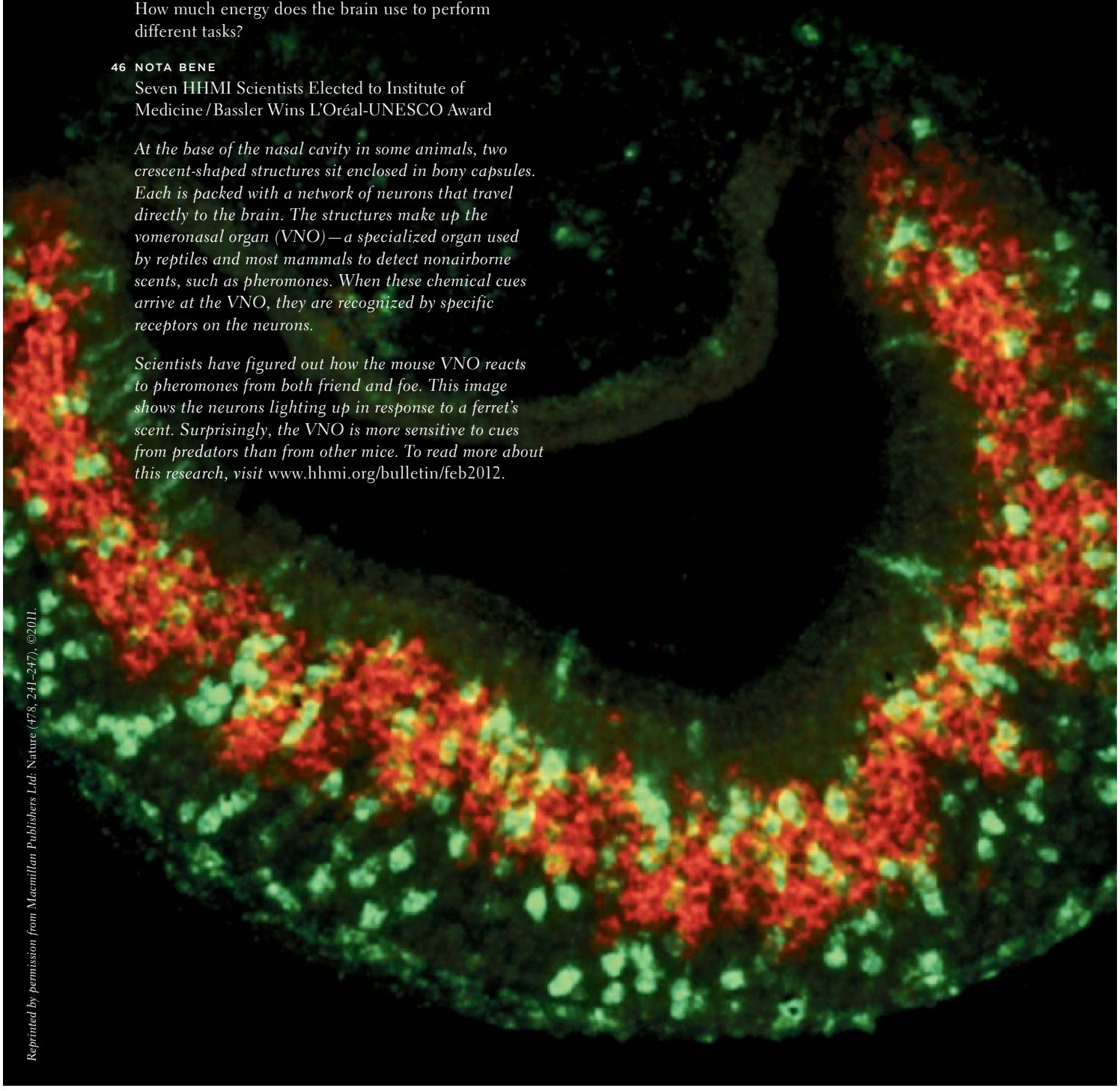
"I would pick *Gattaca* as my favorite science [fiction] movie because it is based on a real scientific discovery—preimplantation genetic diagnosis (PGD)—which is widely used to screen embryos for potential genetic defects. Given that this method is abused by some people to prescreen embryos for a desired gender, the possibility of misusing PGD to select for other traits unrelated to disease raises interesting ethical, legal, and societal questions. That made me think a lot while I watched this movie."

Chan: Steve Yeater/AP, ©HHMI Hochedlinger: MGH Photography Hooper: Amy Gutierrez/AP, ©HHMI Myers: Paul Fetters

chronicle

At the base of the nasal cavity in some animals, two crescent-shaped structures sit enclosed in bony capsules. Each is packed with a network of neurons that travel directly to the brain. The structures make up the vomeronasal organ (VNO)—a specialized organ used by reptiles and most mammals to detect nonairborne scents, such as pheromones. When these chemical cues arrive at the VNO, they are recognized by specific receptors on the neurons.

Scientists have figured out how the mouse VNO reacts to pheromones from both friend and foe. This image shows the neurons lighting up in response to a ferret's scent. Surprisingly, the VNO is more sensitive to cues from predators than from other mice. To read more about this research, visit www.hhmi.org/bulletin/feb2012.



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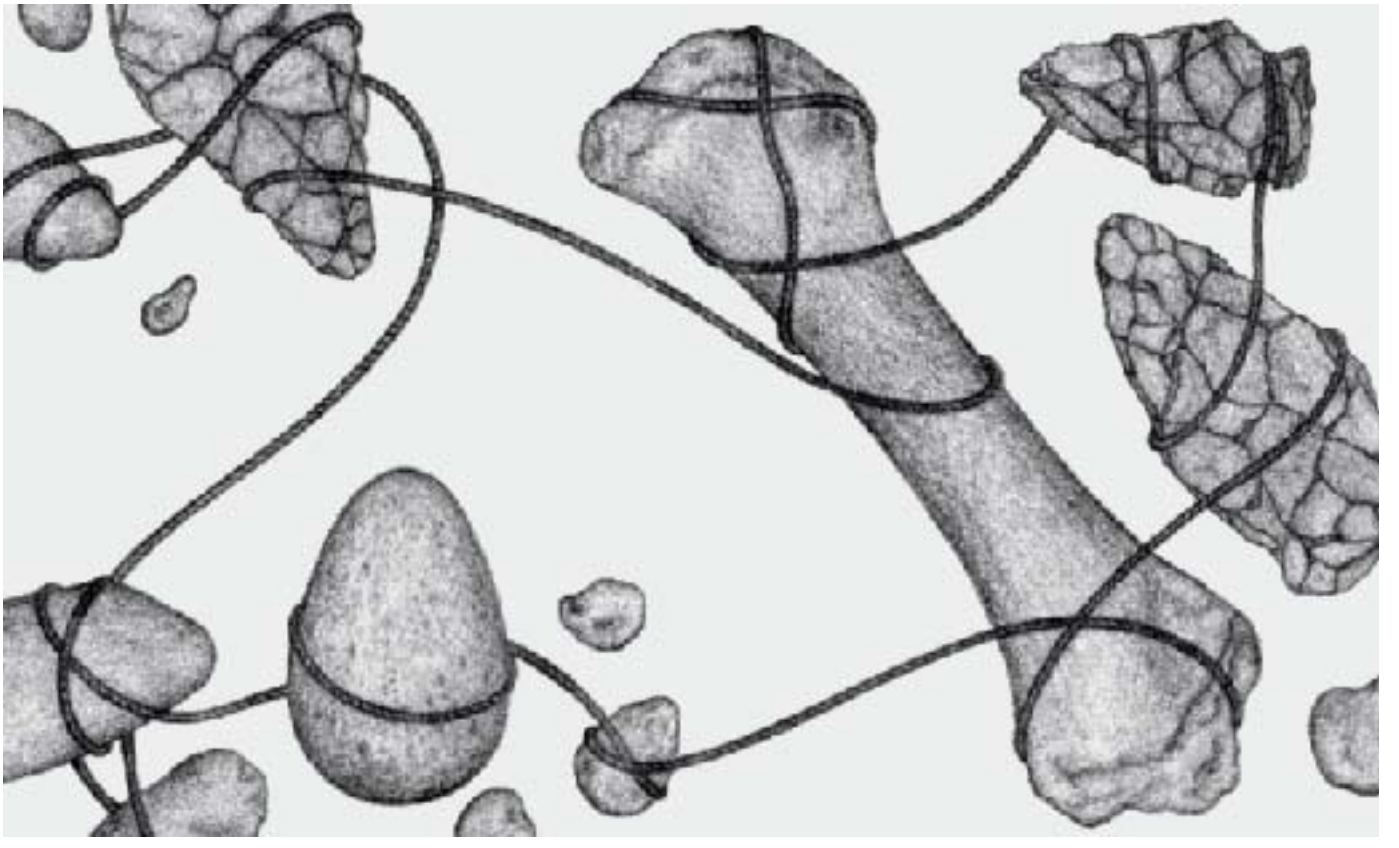


Bones, Stones, and Genes

THE 2011 HOLIDAY LECTURES SERIES DELVES INTO WHERE WE CAME FROM AND HOW WE GOT HERE.

Teaching human evolution is not always straightforward, even when you have an advanced degree in the subject. Take biology teacher Keri Shingleton. She has a Ph.D. in evolutionary biology and teaches biology courses that cover human evolution at Holland Hall, a private Episcopal-affiliated grade school in Tulsa, Oklahoma. Yet even she has shied away from the topic, admitting, "Perhaps I had a bit of a misconception that there were still too many unknowns."

Although Tulsa is a very conservative city, the administrators at Holland Hall stand by Shingleton's decision to teach human evolution. "But that doesn't mean I don't have students in my classroom who are opposed to what we teach," says Shingleton.

Shingleton is one of 14 teachers from around the U.S. who were invited to attend the 2011 HHMI Holiday Lectures on Science this past October. The teachers joined about 200 Washington, D.C., area students to learn answers to questions about human evolution such as: Where and when did humans arise? What distinguishes us from other species? Did our distant ancestors look and behave like us? More than 10,000 other students and teachers watched a live webcast of the lectures, titled "Bones, Stones, and Genes: The Origin of Modern Humans."

"We chose to focus on the origin of modern humans this year because understanding where we come from and how we got here is one of the most fundamental questions that humans have asked for ages," says Sean B. Carroll, vice president for science education at HHMI. "Due to local controversies about the teaching of evolution, many kids don't get exposure to good information on the topic. We want to equip teachers with the best information available from leading figures in this quest."

Recent advances in paleontology, archeology, and genetics prompted HHMI to invite three dynamic speakers from very different research fields to participate in this annual series that aims to bring the latest scientific developments into the classroom.

Tim D. White, a paleontologist at the University of California, Berkeley, took the audience through time, describing fossil evidence

Sasha Prood

for human evolution from Africa to Europe and explaining how the great apes fit in the tree of life.

The students and teachers learned about stone tools—the most durable evidence for human evolution—from John Shea of Stony Brook University. Shea, an archeologist and anthropologist, explained that these tools can give us clues to what life was like for humans who existed thousands, and even millions, of years ago. After the lecture, the audience joined five experts in what may have been the largest stone tool-making session in the history of human evolution. Donning safety goggles, lab coats, gloves, and protective booties, the students and teachers set to work on about 550 pounds of dacite rock with 80 hammerstones.

Although two emergency medical technicians were on hand to deal with injuries caused by flying rocks and wayward hammerstones, only a few Band-aids were needed. "I thought it was going to be difficult and that I would be hitting my fingers, but once I figured out the flip of the wrist, it worked pretty well," says Leslie Mark, a student at Dominion High School in Sterling, Virginia. "After I got the hang of it and I was actually getting a shape out of my stone, it was pretty cool."

"These are the skills that got our ancestors through the last ice age," explains Shea. "To get our species through the next one, it is important that these skills be passed along to our descendants. I think of teaching flintknapping as a kind of 'extinction insurance' for *Homo sapiens*."

Moving from the field to the lab, genetic anthropologist Sarah Tishkoff, of the University of Pennsylvania, explained how scientists are using genetic methods to analyze DNA variation among early humans and learn about their relationships to modern humans. Tishkoff studies the genetic variation in modern humans and nonhuman primates, such as chimpanzees, to learn more about the evolutionary forces that shape and maintain genetic variation in modern populations. Students got to explore their own genetic variation by analyzing their saliva for different versions of a gene that controls perception of one type of bitter taste.

After the lectures, the 14 teachers had one-on-one time with the scientists, then stuck around for a few days exchanging ideas on how to craft educational resources based on the lecture series and implement what they learned in the classroom. Many participants really appreciated this aspect of the lectures. "As a teacher you don't get a whole lot of time to talk to other educators and exchange ideas; you are kind of isolated in your classroom," says Randi Neff, a science teacher at Tuscola High School in Waynesville, North Carolina. "Being able to exchange ideas with other people who are in the same business as you is a rare occasion."

> "These are the skills that got our ancestors through the last ice age. To get our species through the next one, it is important that these skills be passed along to our descendants. I think of teaching flintknapping as a kind of 'extinction insurance' for *Homo sapiens*."
>
> JOHN SHEA

Shingleton left HHMI energized and ready to teach her students about human evolution. "There's a lot more information than I realized," she says. "I've never synthesized the ideas of archeology and paleontology. When you put all of that together it paints a bigger, more complete picture that I feel much more confident presenting in my classroom." ■ –NICOLE KRESGE

FOR MORE INFORMATION: Visit www.hhmi.org/biointeractive for a webcast of the lectures. The series will be available on DVD and as a podcast this spring.

WEB EXTRA: To see a slideshow of the flintknapping activity, go to www.hhmi.org/bulletin/feb2012.

Short Films Make Evolutionary Biology Memorable

The Antarctic icefish, which stars in a new short film by HHMI, has adapted to an icy environment by getting rid of its hemoglobin and red blood cells.

A COLDWATER FISH, A TINY MOUSE, AND A MUTANT GENE ARE THE unlikely stars of three short films produced by HHMI. The movies premiered at a red carpet event attended by 600 teachers at the National Association of Biology Teachers annual meeting last October. They are the first of a series of 10-minute science films that use storytelling to teach topics in evolutionary biology.

The stars were naturals for their parts. For example, the Antarctic icefish, whose blood is as clear as the ice water it lives in, provides a stunning illustration of an animal adapting to a hostile environment.

"Film is a powerful way to tell stories," says HHMI Vice President for Science Education Sean B. Carroll. "You can have moving images and animations. You can hear scientists talking in their own words and see the places where they do their own work. The right story, told well, can be engaging, informative, and memorable."

The idea for the series came to Carroll when he was a consulting producer for the public television program NOVA. He saw how much footage was left on the cutting-room floor and recognized the potential of this unused film.

The three movies were assembled by award-winning filmmakers Sarah Holt and Bill Anderson, using video already shot for NOVA specials as well as new interviews with scientists to tie the stories together.

HHMI's recently launched film production unit will begin making feature-length films soon, and the team plans to use footage from that effort to create additional short films. The goal is to have a library of dozens of short films, with companion resources such as online animations, videos, and lesson plans, to help teachers connect the movies to their curricula.

HHMI's education resource group is already talking to teachers to identify important topics for future films. "I think there's a really healthy dynamic, even a tension, between the way filmmakers want to tell a story—with pace and drama—and the way educators want to make sure certain points are hit upon and made clear," says Dennis W.C. Liu, who heads the group. "And so it's important to us that this is a collaboration, a constant back and forth, between those groups."

More importantly, Liu and Carroll want the films to show students the process of scientific discovery. "By telling these stories, we hope we will excite students and encourage them to look deeper into these topics," Liu says. ■

FOR MORE INFORMATION: Visit hhmi.org/biointeractive/shortfilms to download the movies and companion resources.

New Open Access Journal Gets Name and Editorial Team

HHMI, THE MAX PLANCK SOCIETY, AND THE WELLCOME TRUST are a step closer to launching a top-tier journal with the recent announcement of the publication's editorial team and name.

The open-access research journal will be called "*eLife*," reflecting its coverage of a full range of life and biomedical sciences, from the most fundamental science to translational, applied, and clinical research.

eLife will aim to develop an unparalleled editorial service for authors, designed and run by an outstanding team of active researchers, led by editor-in-chief and HHMI investigator Randy Schekman. Schekman is joined at the helm of *eLife* by managing executive editor Mark N. Patterson, most recently director of publishing at the Public Library of Science.

"Mark has enormous experience with online publications and in open-access publishing," says Schekman. "He played a fundamental role in helping to launch the Public Library of Science and in establishing it as a pioneer of open access and innovative scholarly publishing in the life sciences."

Two deputy editors have joined the leadership team—Fiona Watt, at the University of Cambridge, UK, and Detlef Weigel, from the Max Planck Institute for Developmental Biology, Tubingen, Germany.

The team has selected 17 active and prominent scientists to serve as senior editors, and up to five more will be added in the coming months. About 150 additional scientists will complete the roster as members of a board of reviewing editors.

eLife is expected to publish its first issue in late 2012. ■

FOR MORE INFORMATION: Go to www.hhmi.org/news/elife20111107.html to learn more about *eLife* and its editorial team.

The Birth and Death of Genes, ©2011 HHMI

International Early Career Awards Provide Connections and Funding

"BACK IN SCHOOL, I ALWAYS HEARD THAT IF YOU WANTED TO DO research you would probably have to go work in other parts of the world," says Miguel Godinho Ferreira, a researcher at the Gulbenkian Science Institute in Portugal. "Being able to prove that advice wrong gives me enormous pleasure."

Godinho Ferreira is one of 28 scientists from 12 countries who were selected to receive HHMI's inaugural International Early Career Scientist (IECS) awards. "These are the people who, 10 years from now, we expect will be the scientific leaders in their countries," says HHMI President Robert Tjian.

These researchers—who have all run their own labs for less than seven years—will be integrated into HHMI's scientific community, attending meetings and giving talks to the Institute's U.S.-based investigators and early career scientists.

"This program is about building connections internationally," says Edwin W. McCleskey, a scientific officer at HHMI who helps run the IECS program. "We have chosen talented people who we feel can build connections with our scientists."

The IECS program is the latest incarnation of HHMI's international grants to individual researchers. When it came time to rethink those grants, Tjian and Jack E. Dixon, HHMI's vice president and chief scientific officer, wanted to design a program that provided support for early career scientists who would benefit most from a financial boost and the connection with HHMI's scientific community. The research arena for early career scientists can be challenging internationally. For example, funding to help new scientists start up their labs can be quite variable, and often much less money is available than in the United States.

Scientists from 18 countries were eligible to apply for the awards and HHMI received 760 applications. A rigorous peer review process narrowed the field to 55 semifinalists from 14 countries.

As part of the review process, the semifinalists gave a 15-minute scientific presentation at a symposium in November at HHMI's Janelia Farm Research Campus, in Ashburn, Virginia.

"The major criterion was really scientific excellence: what have they accomplished in their young careers; what kind of potential did they have; could they explain their science in a clear way," Dixon says.

Most of the awardees come from China, Portugal, and Spain, but recipients are also based in nine other countries: Argentina, Brazil, Chile, Hungary, India, Italy, Poland, South Africa, and South Korea. Nine of the 28 (32 percent) are women. Each International Early Career Scientist will receive $650,000: $100,000 a year for five years, plus a $150,000 award in the first year for major equipment purchases.

Godinho Ferreira plans to use his award to gain insights into the mechanisms that cause and direct aging—insights that might lead to solutions for age-related ailments such as cancer and cardiovascular disease.

FOR MORE INFORMATION: To learn more about the scientists and their work, visit www.hhmi.org/iecs20120124.

NEW INTERNATIONAL SCIENTISTS

ANDRÉ BÁFICA
Federal University of Santa Catarina
Florianópolis, Brazil

MEGAN R. CAREY
The Champalimaud Center for the Unknown
Lisbon, Portugal

PEDRO CARVALHO
Center for Genomic Regulation
Barcelona, Spain

RUI M. COSTA
The Champalimaud Center for the Unknown
Lisbon, Portugal

LÁSZLÓ CSANÁDY
Semmelweis University of Medicine
Budapest, Hungary

ÓSCAR FERNÁNDEZ-CAPETILLO
Spanish National Cancer Research Center
Madrid, Spain

MIGUEL GODINHO FERREIRA
Gulbenkian Science Institute
Oeiras, Portugal

LUÍSA M. FIGUEIREDO
Institute of Molecular Medicine
Lisbon, Portugal

JOSÉ L. GARCÍA-PÉREZ
Pfizer—University of Granada—Junta de Andalucía Center for Genomics and Oncological Research
Granada, Spain

RODRIGO A. GUTIÉRREZ
Pontifical Catholic University of Chile
Santiago, Chile

JUNJIE HU
Nankai University
Tianjin, China

BAVESH D. KANA
University of the Witwatersrand
Johannesburg, South Africa

FYODOR KONDRASHOV
Center for Genomic Regulation
Barcelona, Spain

SANDHYA P. KOUSHIKA
National Center for Biological Sciences
Bangalore, India

SIMÓN MÉNDEZ-FERRER
National Center for Cardiovascular Research
Madrid, Spain

THUMBI NDUNG'U
University of KwaZulu-Natal
Durban, South Africa

MARCIN NOWOTNY
International Institute of Molecular and Cell Biology
Warsaw, Poland

DONG-CHAN OH
Seoul National University
Seoul, South Korea

GABRIELA C. PAGNUSSAT
National University of Mar Del Plata
Mar del Plata, Argentina

FENG SHAO
National Institute of Biological Sciences
Beijing, China

ROCÍO SOTILLO
European Molecular Biology Laboratory
Monterotondo, Italy

CHUN TANG
Wuhan Institute of Physics and Mathematics-Chinese Academy of Sciences
Wuhan, China

ROSELLA VISINTIN
European Institute Foundation of Oncology
Milan, Italy

XIAOCHEN WANG
National Institute of Biological Sciences
Beijing, China

KARINA B. XAVIER
Gulbenkian Science Institute
Oeiras, Portugal

NIENG YAN
Tsinghua University
Beijing, China

HONG ZHANG
National Institute of Biological Sciences
Beijing, China

BING ZHU
National Institute of Biological Sciences
Beijing, China

How Much Is Too Much?

STUDIES IN MICE SUGGEST LONG-TERM FOLIC ACID SUPPLEMENTATION MAY INCREASE THE INCIDENCE OF SOME BIRTH DEFECTS.

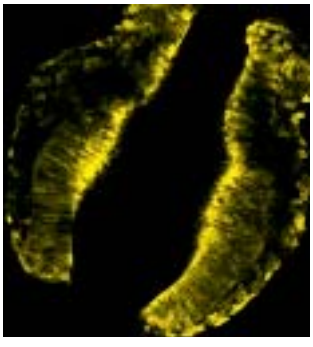
Since 1998, the federal government has required that most flour be fortified with folic acid to help prevent some neurological birth defects. However, research by HHMI investigator Lee Niswander indicates that, in some cases, folic acid may have the opposite effect.

During the third or fourth week after conception, tissue destined to become the nervous system rolls up to form the neural tube. But if gaps remain in the tube, birth defects such as spina bifida ensue. Studies have shown that folic acid fortification reduces the chance of neural tube defects by 30 to 40 percent, leading to the recommendation that pregnant women supplement their diets with the vitamin.

"It is still pretty much a mystery what folic acid does to help the neural tube close," Niswander says. "That's really where we started our studies."

Niswander and her colleagues at the University of Colorado School of Medicine focused on just a handful of the more than 240 genes involved in neural tube closure. They created mice with defects in five genes essential to different steps in the closure process. As reported September, 15, 2011, in *Human Molecular Genetics*, the mice were fed either a regular diet or a diet supplemented with folic acid. The supplemented diet increased mouse serum folic acid to levels similar to those of a human taking recommended amounts of supplements. To the researchers' surprise, three of the five mutant mice strains experienced more neural tube defects and embryo losses when fed a diet high in folic acid.

"Something else is going on there," says Niswander. "By giving folic acid to women, we see a decreased incidence of neural tube defects. That could be because the neural tube is closing. But it could also reflect that some embryos with a genetic defect don't survive to the stage of neural tube closure."



Birth defects such as spina bifida result when the neural tube (shown here) fails to close properly during development.

Niswander still believes that folic acid supplementation during pregnancy is a good idea, but she advises caution before increasing doses, as some groups have advocated.

"Our mouse studies indicate that at least some genetic mutations can respond detrimentally to more folic acid," says Niswander. "There may be a balance that needs to be struck [to accommodate all of our] different genetic make-ups." ■ – NICOLE KRESGE

IN BRIEF

NEW USES FOR OLD DRUGS

While it may be true that you can't teach an old dog new tricks, you can occasionally find new ways to use old drugs. HHMI early career physician scientist Atul Butte has created a computer program that does just that, by comparing gene expression patterns in diseased cells with patterns produced by healthy cells treated with various drugs. Butte's team at Stanford University School of Medicine reasoned that if a given disease drove expression of a set of genes in one direction and a drug drove their expression in the opposite direction, then the drug might be useful in treating the disease.

The project, described in two papers published August 17, 2011, in *Science Translational Medicine*, looked at the expression patterns of 100 diseases and 164 drugs. Butte and his colleagues discovered potential therapeutics for 53 diseases. They tested two leads and found evidence of success—an over-the-counter heartburn medicine slowed lung cancer growth in mice and an antiseizure drug controlled inflammatory bowel disease in rats.

Although the concept of repurposing existing drugs isn't new, until now there have been few strategies for testing large numbers of diseases and drugs simultaneously.

"Using molecular similarities in our new method gives us a leg up, compared with looking at patient responses," says Butte. "We have a higher level of resolution for both disease biology and drug effects, so we can match them better."

A CHINK IN MALARIA'S ARMOR

HHMI investigator Joseph L. DeRisi recently deduced the function of the apicoplast, an organelle vital to the survival of some parasites. In doing so, he may have found a way to combat malaria.

Apicoplasts are often referred to as malaria's Achilles' heel because they contain an ideal drug target: ancestral bacterial genes that have no counterpart in the human host. DeRisi and his colleagues at the University of California, San Francisco, used antibiotics to destroy apicoplasts in the malaria parasite *Plasmodium falciparum*. Normally, this would be fatal. However, as they report in the August 2011 issue of *PLoS Biology*, the parasites could be "rescued" by adding the essential metabolite isopentenyl pyrophosphate.

"This, in no uncertain terms, confirms that the only truly essential function of the apicoplast during the blood stage [of malaria infection] is the production of this one chemical," says DeRisi.

Not only does this discovery provide researchers with a validated target for drugs, it also potentially paves the way for a unique malaria vaccine. DeRisi's research showed that *Plasmodium* cells can survive only one generation without an apicoplast—long enough to expose a human immune system to the pathogen but not long enough to cause disease. A vaccine made from *Plasmodium* cells with the apicoplast removed could significantly alter the field of malaria research by providing a simple route to create an attenuated strain of malaria without the need for irradiation or other inactivating agents.

MAPPING TASTE IN THE BRAIN

When you bite into a lemon, a unique set of receptors on the tongue detects the sour taste. Salty potato chips arouse a different set of receptors. In fact, each of the five basic tastes—sour, sweet, bitter, salty, and "umami," or savory—is detected by a distinct set of receptor cells on the tongue. Now, an HHMI investigator at the Columbia University College of Physicians and Surgeons has created the first map showing

Christina Pyrgaki, Rockefeller University

Protein Precision in the Brain

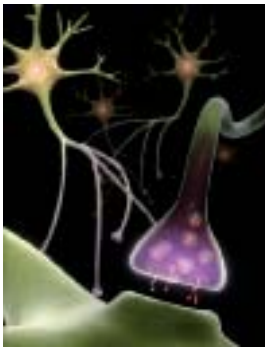
TWO CAUSES OF AUTISM ARISE FROM OPPOSITE CELLULAR MECHANISMS.

To function normally, the brain needs to maintain a precise level of synaptic protein synthesis—too much or too little can cause problems, according to research by HHMI investigator Mark F. Bear and his lab team. Their findings provide insight into two forms of autism with overlapping symptoms.

A decade ago, Bear and his colleagues at the Massachusetts Institute of Technology discovered that fragile X mental retardation protein (FMRP) counterbalances a neurotransmitter receptor called mGluR5. Normally, FMRP keeps mGluR5 from turning on protein synthesis at the synapse between neurons. But in fragile X syndrome, FMRP is missing so protein synthesis proceeds unchecked. This increase in protein synthesis in brain cells, Bear has shown, accounts for multiple symptoms in animal models of fragile X. Drugs that block mGluR5 are now in clinical trials to treat autism and intellectual disability in fragile X patients.

Bear wanted to see if the same drugs could be used to treat another disease—tuberous sclerosis complex—that causes autism and learning delays and is also linked to genes that regulate synaptic protein synthesis. The disease is caused by mutations in tuberous sclerosis complex protein 1 or 2 (Tsc1 or Tsc2). Inactivation of either of these proteins results in an increase in the activity of mTOR, a protein involved in RNA translation. Scientists hypothesized that a boost in mTOR levels might increase synaptic protein production via the same pathway as mGluR5.

Using a mouse model of tuberous sclerosis, Bear's team looked at how mutations in Tsc2 affect protein synthesis at the synapse. To their surprise, synthesis decreased in neurons with the Tsc2 mutations—the opposite of what happens in fragile X. Interestingly, mice engineered to carry mutations in both the *Tsc2* and *Fmr1* genes generate just the right amount of synaptic protein. The team published its findings online November 23, 2011, in *Nature*.



Too much or too little protein production at the synapse between neurons can cause autism and intellectual disability.

A drug that blocks mTOR—called rapamycin—is already in clinical trials to treat tuberous sclerosis, and Bear's new study offers an explanation of how the drug works to reverse some problems caused by the disease. Next, he hopes to more fully understand how the pathway controls synaptic protein synthesis. ■ –NICOLE KRESGE

IN BRIEF

which parts of the brain these taste receptors activate.

Charles S. Zuker and his colleagues injected neurons with a dye that made them light up when activated. Using high-powered microscopes, the scientists could watch hundreds of nerve cells in the brain at once. They discovered that when a mouse is given something bitter to taste, many neurons in a small, specific area light up. Salty foods activate a separate area a few millimeters away. As they reported in the September 2, 2011, issue of *Science*, each basic taste corresponded to a different hotspot in the brain.

Now, that he's created a "gustotopic map," Zuker is studying how taste combines with other sensory inputs, such as smell and texture, and the internal state—hunger and expectation, for example—to choreograph flavor, taste memories, and taste behaviors.

THE DEET DEFENSE AGAINST MOSQUITOES

Campers often find relief from mosquito attacks by dousing themselves in DEET-laden bug sprays. But until recently, no one knew how this bug-repelling compound worked. A new study suggests that DEET confuses insects by jamming their odor receptors.

Insects smell with their antennae, which contain neurons with odor receptors. Each receptor consists of two components: a protein called Orco and a variable protein that confers odor selectivity. HHMI investigator Leslie Vosshall, a neurobiologist at Rockefeller University, previously determined that DEET prevents some of these odor receptors from functioning properly.

In her latest work, published October 27, 2011, in *Nature*, Vosshall and her team reported that DEET alters the way different neurons respond to an odor. For example a compound called 1-octen-3-ol normally inhibits a neuron with a receptor containing the variable protein or59b and activates a neighboring neuron that contains or85a. In the presence of DEET, 1-octen-3-ol has the opposite effects on the same two neurons—it activates the or59b-containing neuron and suppresses the activity of the neurons containing or85a. A mutation in the or59b receptor makes the neuron insensitive to DEET, which shows that DEET is acting directly on the odor receptor protein.

"It completely scrambles the code," says Vosshall, explaining that her team's data indicate that insects do detect odors in the presence of DEET—they just can't figure out what they are.

TURNING ON FETAL HEMOGLOBIN

A single mutation in the adult hemoglobin gene can cause normally flexible, disk-like red blood cells to assume rigid, crescent shapes and clog the small blood vessels. The resulting condition, sickle cell anemia, is marked by fatigue, severe pain, and organ damage, including strokes. All the features of sickle cell disease can be alleviated by elevating levels of fetal hemoglobin, but finding an effective way to do this has eluded scientists, until now.

Several years ago, HHMI investigator Stuart H. Orkin of Children's Hospital Boston discovered that BCL11A, a transcription factor that binds to DNA and regulates gene expression, can halt fetal hemoglobin production. In the November 18, 2011, issue of *Science*, Orkin and his team revealed that suppressing BCL11A can reactivate fetal hemoglobin production in adult mice, effectively reversing sickle cell disease.

BCL11A is probably one of many molecules involved in controlling fetal hemoglobin production, but Orkin's results indicate that it's an essential player in the process.

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Now You See It, Now You Don't

A DISAPPEARING RECEPTOR COULD HOLD THE KEY TO BETA-CELL GROWTH AND INSULIN PRODUCTION.

For years, diabetes researchers have sought to understand what regulates the growth and death of insulin-producing beta cells. According to new research by HHMI investigator Seung K. Kim at Stanford University, the key may lie in a receptor that disappears as an organism ages.

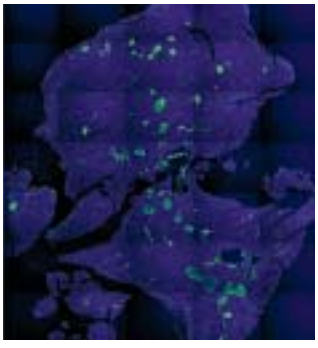
When mice, humans, and other species are developing, their beta cells multiply by replicating themselves. As organisms age through adolescence and then adulthood, their ability to produce beta cells decreases. Kim discovered that as mice grow older their beta cells produce fewer receptors for a protein called platelet-derived growth factor (PDGF).

"The loss of that receptor is an important feature that's programmed as you age and may underlie the decline of beta-cell proliferation that you normally see," Kim says.

To test whether loss of the receptor is the reason for decreasing beta-cell proliferation, Kim and his colleagues created mice with beta cells in which the *PDGF* gene could be inactivated. When the gene was inactivated in three-week-old mice, they developed mild diabetes, indicating a decrease in beta-cell levels.

Conversely, when the scientists turned on the receptor in older mice that had stopped producing beta cells, their beta cells began to grow again.

"This told us that activating the pathway might overcome normal restrictions imposed by aging," Kim says. More importantly, the new beta cells adjusted their function appropriately and didn't, for example, cause the mice to lose control of insulin regulation or become hypoglycemic.



Pancreatic beta cells can be coaxed to produce insulin (green) by activating the cells' PDGF receptor.

Kim then confirmed the link between the PDGF receptor and beta-cell growth. He discovered that when PDGF binds to its receptor, it activates production of a protein called Ezh2. This protein regulates the production of another protein, p16INK4a, that controls beta-cell proliferation. The team published its findings October 20, 2011, in *Nature*.

Kim is now looking at why PDGF receptors disappear as mice age, which could lead to therapies for diabetes. "You could imagine a one-two punch: if you can stimulate beta cells to reexpress the receptor in adults, then you could conceive of trying to stimulate those cells to grow," says Kim. ■ –NICOLE KRESGE

IN BRIEF

Now that this key switch has been identified, Orkin asserts, the chances of finding powerful new therapies for sickle cell disease and other hemoglobin disorders are more promising: "For the last 20 years we've been shooting arrows in the dark in hopes of hitting the target. Now we can see the target and it is a meaningful one."

BARRIER KEEPS GUT BACTERIA AT BAY

Approximately 100 trillion bacteria live in the mammalian gut, helping animals and humans digest food and produce energy. But how can we carry so many microorganisms and not get sick? HHMI investigator Lora V. Hooper of the University of Texas Southwestern Medical Center at Dallas suggests that molecules from the immune system patrol a mucus-covered "demilitarized zone" (DMZ) that keeps bacteria floating in the gut, away from the intestinal lining.

Hooper led a team that looked at mice lacking MyD88, a protein activated by the toll-like receptors that turn on the immune system in response to bacteria. As the scientists reported in the October 14, 2011, issue of *Science*, mice missing MyD88 have about 100 times more bacteria in their intestinal lining than normal mice. The team also discovered that the DMZ is effective at keeping bacteria away only when both MyD88 and an antibacterial protein called RegIII$_\gamma$ are present.

These findings suggest that toll-like receptors sense the presence of bacteria and then use MyD88 to spur the production of RegIII$_\gamma$, which eliminates the invading microorganisms. "It's like a burglar alarm that senses your home is being invaded and radios the police," says Hooper. "The toll-like receptor is the alarm and RegIII$_\gamma$ is the police."

The gut likely has several burglar alarms that work against different types of microorganisms. RegIII$_\gamma$ kills only Gram-positive bacteria, and Hooper is now searching for a similar alarm system that activates antibacterial proteins targeting Gram-negative bacteria.

A SIGNAL FOR LUNG REGENERATION

The lungs of the average person contain about 700 million alveoli—tiny air sacs—each surrounded by a spider web of capillaries. Alveoli, responsible for getting oxygen into the blood and carbon dioxide out of it, can easily be damaged or destroyed by smoking, infection, and toxic chemicals. Recently, scientists discovered a switch, initiated in the lung blood vessels of mice, that can activate regeneration of alveoli. This switch could supply relief when normal breathing is impaired.

The switch is a single molecule called MMP14, produced by specialized lung endothelial cells that line the capillaries surrounding the air sacs. When activated, MMP14 increases the availability of growth factors that stimulate alveolar regeneration.

A team led by HHMI investigator Shahin Rafii of the Weill Cornell Medical College created mice with endothelial cells that were unable to produce MMP14 and other growth factors. When they surgically removed the left lungs of the mice, the remaining right lungs had difficulty creating new alveoli. However, when the scientists administered MMP14 or transplanted normal endothelial cells into the mice, new alveoli were created in the right lungs of the mice and their breathing capacity was restored to near normal levels. The team published its findings October 28, 2011, in *Cell*.

"MMP14 is probably the tip of the iceberg," says Rafii. "Activated endothelial cells produce many other angiocrine growth factors to promote lung and organ regeneration as well as orchestrate tumor growth."

Hainan Chen, Stanford University School of Medicine

Q A

How much energy does the brain use to perform different tasks?

Asked by Tom, a graduate student from California

The brain consumes, on average, 20 percent of the body's total oxygen. This number is a good reflection of the amount of energy, in the form of glucose, the brain uses. However, it hides a more interesting story about the variation in energy use by the brain, including how much energy the brain uses for different functions.

We know the brain's use of glucose varies at different times of day, from 11 percent of the body's glucose in the morning to almost 20 percent in the evening. In addition, different parts of the brain use different amounts of glucose. We can use brain-imaging technology, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), to get an idea of this variation in energy use.

The medial and lateral parietal and prefrontal cortices use more glucose than other parts. These regions are involved in the brain's default (non-task-related) activity as well as cognitive control and working memory, which is used for temporarily storing and manipulating information. The cerebellum, used for motor control and learning, and medial temporal lobes, involved in long-term memory, use less glucose. Thus, different brain functions have different metabolic requirements.

But the story is not so simple: Several factors make it difficult to identify specific metabolic requirements. First, we know the brain is constantly active, even at rest, but we don't have a good estimate of how much energy it uses for this baseline activity. Second, the metabolic and blood flow changes associated with functional activation are fairly small—local changes in blood flow during cognitive tasks, for example, are less than 5 percent. And finally, the variation in glucose use in different regions of the brain accounts for only a small fraction of the total observed variation. So, the high level of constant activity throughout the brain makes it very hard to detect small changes associated with specific functions.

Another major challenge is determining which regions of the brain are involved in those tasks. Functional imaging of the brain is powerful but the technology has its limitations. Brain functions are complex, occur on a rapid timescale, and do not always occur in just one location; in addition, imaging may not capture the full scope of functional activation. The images produced by fMRI and PET studies look very definitive, but in fact they are the result of a lot of data processing that pulls a small signal out of a very noisy background.

As you can see, there are many reasons why we can't say how much energy it takes the brain to solve a calculus problem or recite a poem. This area of research is exciting, however, as it ties together the neurophysiology of the brain with our understanding of human behavior. With advances in brain imaging and cell monitoring technology, researchers hope to shed light on this problem in the near future.

ANSWERED BY JAYATRI DAS, *a senior exhibit and program developer at The Franklin Institute Science Museum.*

FURTHER READING:

Raichle ME, Gusnard DA. Appraising the brain's energy budget. *Proc Natl Acad Sci.* 2002;99:10237–9. Accessible at www.pnas.org/content/99/16/10237.full.pdf+html

Raichle ME. The brain's dark energy. *Sci Am.* March 2010;302:44–9. Accessible at www.braininnovations.nl/Dark-Energy.pdf

Brain Imaging Technologies: learn.genetics.utah.edu/content/addiction/drugs/brainimage.html

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

Seven HHMI Scientists Elected to Institute of Medicine

Seven HHMI investigators are among the 65 new members elected to the National Academy of Sciences' Institute of Medicine. The investigators are **Frederick W. Alt**, Children's Hospital Boston; **Carolyn R. Bertozzi**, University of California, Berkeley; **Vivian G. Cheung**, University of Pennsylvania, Perelman School of Medicine; **George Q. Daley**, Children's Hospital Boston; **Richard L. Huganir**, the Johns Hopkins University School of Medicine; **Jeremy Nathans**, the Johns Hopkins University School of Medicine; and **Li-Huei Tsai**, Massachusetts Institute of Technology.

Eleven HHMI investigators, two HHMI-GBMF investigators, and one HHMI early career scientist were elected to the American Association for the Advancement of Science. The HHMI investigators are NANCY M. BONINI, University of Pennsylvania; KATHLEEN L. GOULD, Vanderbilt University School of Medicine; LIQUN LUO, Stanford University; MIN HAN, University of Colorado at Boulder; WILLIAM R. JACOBS, JR., Albert Einstein College of Medicine; BETH LEVINE, University of Texas Southwestern Medical Center at Dallas; PHILIPPA MARRACK, National Jewish Health; RUSLAN M. MEDZHITOV, Yale School of Medicine; WILFRED A. VAN DER DONK, University of Illinois at Urbana—Champaign; MATTHEW K. WALDOR, Brigham and Women's Hospital; and TIAN XU, Yale School of Medicine. The HHMI-GBMF investigators are XUEMEI CHEN, University of California, Riverside, and SHENG YANG HE, Michigan State University. The HHMI early career scientist is XINNIAN DONG, the Johns Hopkins University School of Medicine.

JAMES P. ALLISON, an HHMI investigator at the Memorial Sloan-Kettering Cancer Center, won the 2011 Roche Award for Cancer Immunology and Immunotherapy as well as Brandeis University's Jacob Heskel Gabbay Award in Biotechnology and Medicine. Allison studies how T cells respond to antigens and how these responses can be used to fight tumors. Allison was also recently presented the Advancement of Cancer Research Award from Gilda's Club New York City.

HHMI professor WINSTON A. ANDERSON of Howard University was honored with a 2011 Presidential Award for Excellence in Science, Mathematics, and Engineering Mentoring. Anderson created a research-intensive, mentored curriculum for science and math majors to give them a competitive edge for pursuing graduate degrees. Two university programs that were funded by HHMI—THE STANFORD MEDICAL YOUTH SCIENCE PROGRAM and the UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, SCIENCE AND HEALTH EDUCATION PARTNERSHIP HIGH SCHOOL INTERN PROGRAM—also received mentoring awards.

Three HHMI investigators are among the 46 scientists awarded lifelong membership to the European Molecular Biology Organization. The investigators are CORNELIA I. BARGMANN of the Rockefeller Institute, SUSAN LINDQUIST of the Massachusetts Institute of Technology, and NORBERT PERRIMON of Harvard Medical School.

The FRAXA Research Foundation presented MARK F. BEAR, an HHMI investigator at the Massachusetts Institute of Technology, with a 2011 Pioneer Award for translational research. Bear studies the neurobiology of fragile X syndrome.

HHMI investigator GEORGE Q. DALEY of Children's Hospital Boston was awarded the 2011 E. Donnall Thomas Prize by the American Society of Hematology. Daley was honored for using human induced pluripotent stem cells to understand the mechanisms of disease initiation and progression.

KARL DEISSEROTH, an HHMI early career scientist at Stanford University, received the 2011 W. Alden Spencer Award given by the College of Physicians and Surgeons. Deisseroth develops optical neuroengineering technologies for real-time, noninvasive imaging and control of brain circuits.

The Genetics Society of America honored ABBY F. DERNBURG, an HHMI investigator at the University of California, Berkeley, with its 2011 Edward Novitski Prize, recognizing creativity and intellectual ingenuity in solving problems in genetics. Dernburg studies the mechanisms behind chromosome organization and dynamics during meiosis.

HHMI investigators CHRIS Q. DOE of the University of Oregon and GAIL MANDEL of Oregon Health & Science University were honored with 2011 Discovery Awards from the Medical Research Foundation of Oregon. Doe was recognized for his research

Alt: Jeff Barnett-Winsby Bertozzi: Christopher Jones Cheung: Peter Wodarczyk/PR Newswire Daley: Leah Fasten Huganir: Bill Denison Nathans: Paul Fetters Tsai: Matt Kalinowski

on cell fate patterning in the nervous system while Mandel received the award for her investigation of regulation of gene expression and function in the nervous system.

BRIAN J. DRUKER, an HHMI investigator at Oregon Health & Science University, was awarded the American Society of Hematology's 2011 Ernest Beutler Lecture and Prize. The annual award is presented to two individuals: a scientist who has enabled advances in basic science and a scientist who has facilitated achievements in clinical science or translational medicine. Druker shares the honor with Janet Rowley of the University of Chicago Medical Center for their contributions to the diagnosis and treatment of chronic myeloid leukemia.

HHMI-GBMF investigator JORGE DUBCOVSKY of the University of California, Davis, received a 2011 U.S. Department of Agriculture Secretary's Honor Award for exceptional leadership in science, public policy, and management. Dubcovsky and the members of his Barley, Wheat, Potato and Tomato Coordinated Agricultural Project team were selected for identifying genetic variations that enhance productivity of these food crops.

The National Institute of Neurological Disorders and Stroke appointed DAVID D. GINTY, an HHMI investigator at the Johns Hopkins University School of Medicine, to its National Advisory Neurological Disorders and Stroke Council. Ginty's laboratory looks at the assembly and function of nerves and circuits underlying the sense of touch.

ROBERT GRASSUCCI, a senior microscopist in HHMI investigator Joachim Frank's laboratory at the Columbia University College of Physicians and Surgeons, was presented with the Hildegard H. Crowley Outstanding Technologist Award in Biological Sciences. The prize, given by the Microscopy Society of America, honors technologists who make contributions that have advanced microscopy and microanalysis.

HHMI investigators TYLER JACKS of the Massachusetts Institute of Technology and OWEN N. WITTE of the University of California, Los Angeles, were appointed to key administration posts by President Barack Obama. Jacks became a member of the National Cancer Advisory Board, an advisory committee to the National Cancer Institute. He will serve for six years. Witte was selected to serve a two-year term on the President's Cancer Panel, which monitors the development and execution of the National Cancer Program.

The Society for Neuroscience presented STEPHEN G. LISBERGER, an HHMI investigator at Duke University, with the 2011 Bernice Grafstein Award for Outstanding Accomplishments in Mentoring. The annual award recognizes individuals who facilitate women's entry and retention in the field of neuroscience through mentoring.

PETER W. REDDIEN, an HHMI early career scientist at the Massachusetts Institute of Technology, won the 2012 Harland Winfield Mossman Award in Developmental Biology given by the American Association of Anatomists. The prize recognizes Reddien's work demonstrating the pluripotent stem cell-like nature of tissue in planaria and defining key pathways involved in regeneration.

MICHAEL ROSBASH, an HHMI investigator at Brandeis University, was awarded the 2011 Louisa Gross Horwitz Prize from Columbia University. Rosbash shares the award with Jeffrey C. Hall, also of Brandeis University, and Michael W. Young of the Rockefeller University for work on the molecular basis of circadian rhythms.

HHMI investigator JACK W. SZOSTAK of the Massachusetts General Hospital received the 2011 Harold C. Urey Medal from ISSOL, The International Astrobiology Society. Szostak's goal is to construct a simple, artificial cell that can grow, divide, and undergo Darwinian evolution to adapt to its changing environment.

The Linda and Jack Gill Center for Biomolecular Science at Indiana University presented LESLIE B. VOSSHALL, an HHMI investigator at the Rockefeller University, with the 2011 Gill Young Investigator Award. The award recognizes Vosshall's research on how complex behaviors such as odor detection are modulated by external cues and internal physiological states.

SPOTLIGHT

Bassler Wins L'Oréal-UNESCO Award

BONNIE L. BASSLER

Paul Fetters

HHMI investigator **Bonnie L. Bassler** of Princeton University is the North American recipient of the 2012 L'Oréal-UNESCO Award in the Life Sciences. Bassler was recognized for her contributions to understanding chemical communication among bacteria and for opening doors to treating infections. The annual award recognizes exceptional women scientists from five regions of the world and is the result of a partnership between cosmetic company L'Oréal and the United Nations Educational, Scientific and Cultural Organization. Bassler also was recently nominated by President Barack Obama to serve as a member of the National Science Board, which oversees the National Science Foundation.

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(FORCE FACTOR)

And Bustamante is now using similar techniques to probe the basics of numerous biological processes, including protein folding. He's using optical traps and fluorescent tags to see what happens when a protein strand is stretched and then released, allowing it to fold into its preferred conformation.

He's also applying the method to nucleosomes—clumps of proteins that control the structure of DNA within a chromosome and influence when genes are expressed. He's already looked at the interaction between polymerases—enzymes that move along DNA strands—and nucleotides. His team discovered that when polymerases encounter a nucleosome, they pause, not having enough force to unravel the DNA from the nucleosome. Instead, the protein waits for the clump to spontaneously unravel. If he can use optical traps to pull apart a fluorescent chromosome, Bustamante says, he can observe its higher-order structure and the forces that proteins within the nucleosomes exert on the nucleotides.

"It's natural that as optical trapping starts to mature, we now want to combine these techniques with others," says Bustamante. "I think in the future we will see even more hybrid experiments that combine optical trapping with other methods."

He's happy to see his technique mature and change, he says, if it means applying it to more biological questions.

"There are so many unknowns inside the cell," he says. Optical trapping lets researchers get a physical handle on those unknowns. While scientists can't reach inside cells and feel for themselves the forces at work, optical trapping has become their hands that work to sense and manipulate these forces. ■

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(RAISING THEIR GAME)

trainers to train up to 8,500 K–12 science and math teachers each year, offering them subject-specific, grade-specific mentoring. Since 1999 they've trained half the STEM teachers in the state, Ricks says. Teachers come for two-week workshops for two consecutive summers. AMSTI also employs 300 master science or master math teachers who advise and mentor teachers and even co-teach if the mentees need a hand. AMSTI operates 11 regional 35,000-square-foot warehouses, where workers run forklifts to help sort bins of laboratory materials and equipment designated for math and science teachers.

The state's investment is paying off in better student performance, according to eight years of external evaluations. For example, Alabama students improved more in math than those in all but one other state, as judged by an internationally recognized test called the National Assessment of Educational Progress. "The state has seen that if you really want students to compete, they need top-notch math and science skills," says Ricks.

Wendy Bramlett, who used AMSTI to raise her game, is a fan. "My whole way of teaching changed," she says. "I went from a lecture class to no lecture and all hands on," she says. Her students' performance has improved—92 percent scored at the top level on the state science exam last year. And she hears something else she never heard in her first years of teaching. "I have children tell me, 'Science is my favorite subject.'" ■

WEB EXTRA: Read more about STEM teacher training online. Go to www.hhmi.org/bulletin/feb2012.

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(WHERE DOES IT HURT?)

receptor, looking for ways to avoid narcotic and other side effects from opiates, which would benefit people with chronic pain (see Web Extra, "Boosting the Body's Natural Painkilling Power").

The initial discovery that abnormal central sensitization can lead to pain hypersensitivity came from Clifford Woolf at Children's Hospital Boston and Harvard Medical School. Woolf is now generating hypersensitive and normal human pain neurons in his laboratory from fibroblasts using stem cell techniques to characterize their differences and, perhaps, find ways to regulate their firing without harming other necessary physiological functions. He is also looking at ways to deliver pain relievers directly to hyperactive nociceptors while leaving normal ones untouched.

Undoubtedly, other molecules of normal and pathological pain signaling await discovery, thereby offering additional possibilities for improving pain treatment. "I tell my medical students," says Woolf, "that pain will be treated completely differently 10 years from now." Physicians may one day treat pain based on both the source of pain within the patient's nervous system and the individual's genetic predisposition for responding to a specific therapy. Perhaps the day isn't too far off when a physician will ask where it hurts and nearly all patients will respond, nowhere. ■

WEB EXTRA: For more of the latest research on understanding and controlling pain, go to www.hhmi.org/bulletin/feb2012.

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