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One Lump or Two?

Once again, those fast-growing yeast find a way to turn a long-held theory on its head. This time, it's about prions, which aren't as universally nasty as once suspected. Some may actually help organisms evolve. The yeast colony shown here contains a protein in its prion form. Because the prion, known as PSI+, is self-replicating and forms fibrous amyloids, the yeast look lumpy and bumpy—strikingly different from normally smooth yeast. Susan Lindquist's group has found 19 yeast proteins that can switch back and forth between a normal and a prion version. The prions are thought to help the yeast adapt to changing conditions (see "A Silver Lining," page 22).

Heather True / Lindquist lab

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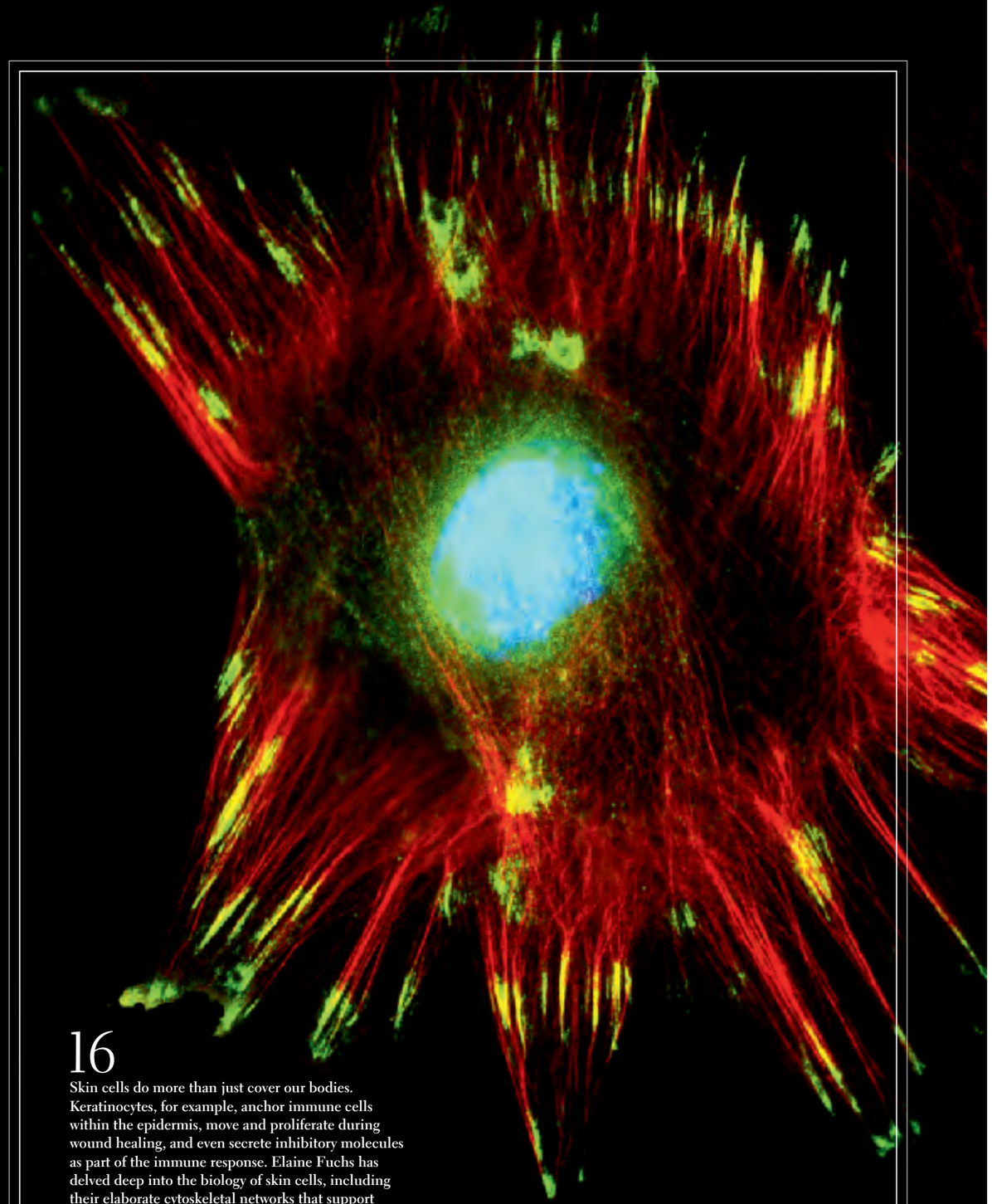
LIGHT MOVES

Light is becoming the tool of choice for researchers who want to precisely manipulate neurons and other cells.



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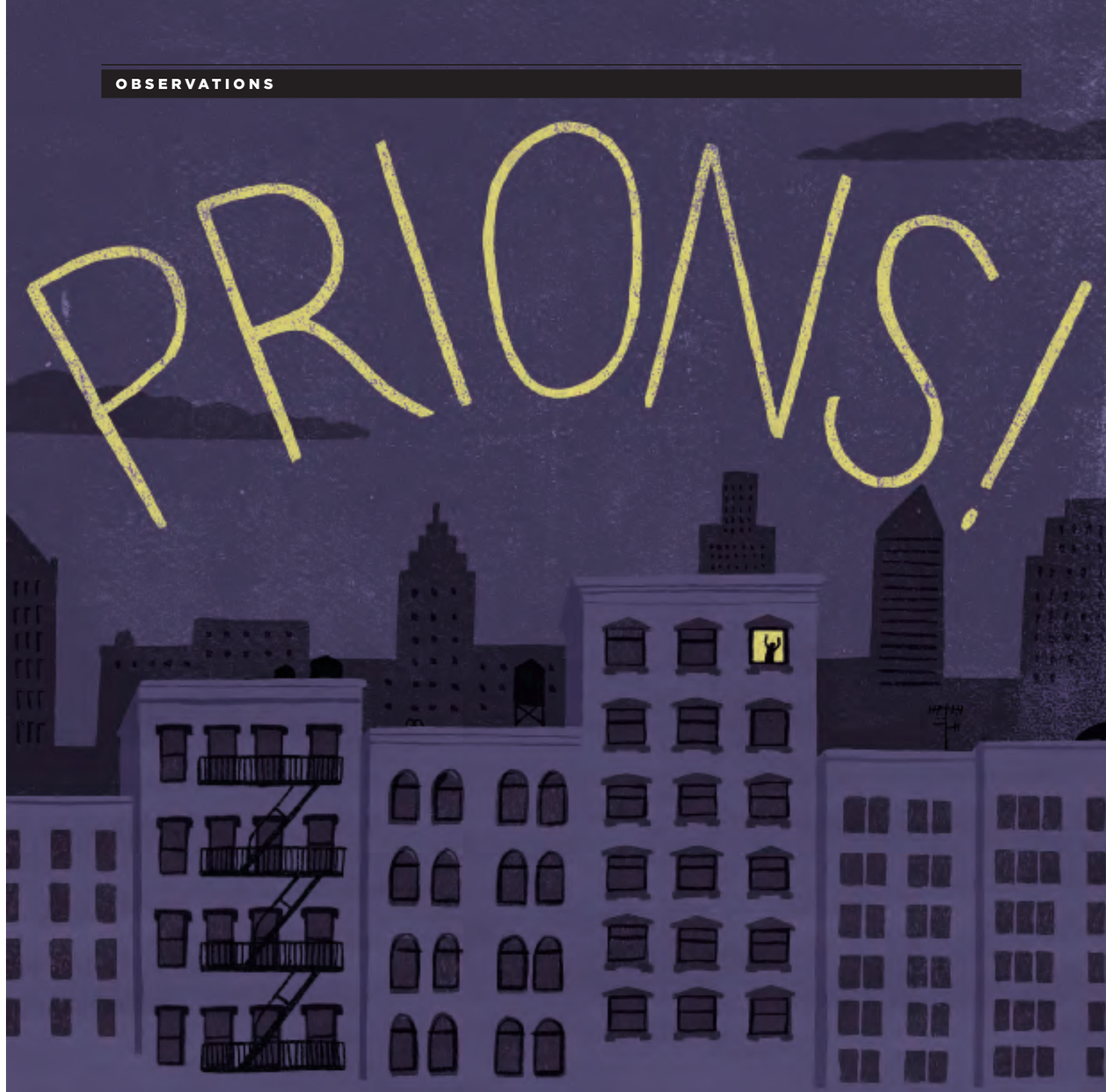
Skin cells do more than just cover our bodies. Keratinocytes, for example, anchor immune cells within the epidermis, move and proliferate during wound healing, and even secrete inhibitory molecules as part of the immune response. Elaine Fuchs has delved deep into the biology of skin cells, including their elaborate cytoskeletal networks that support movement. In the keratinocyte shown here, the blue-stained nucleus is surrounded by microtubules (red) crosslinked by the protein ACF7 (yellow), which plays a critical role in cell migration.

Xiaoyang Wu / Fuchs lab



Dan Haskett

SECRET AGENT MAN

As a neurology resident, Stanley Prusiner saw Creutzfeldt–Jakob disease kill a patient in a matter of months. Researchers knew the rare neurodegenerative disease and scrapie, a similar disease in sheep, were infectious but not as a result of a typical virus. At the University of California, San Francisco, Prusiner set out to determine the molecular structure of the elusive infectious agent. Hypotheses about the nature of the agent ranged from DNA viruses to membrane fragments to proteins. Prusiner published the surprising answer in 1982 and set off a firestorm of skepticism. He turned out to be right, which earned him the 1997 Nobel Prize in Physiology or Medicine.

As reproducible data began to accumulate indicating that scrapie infectivity could be reduced by procedures that hydrolyze or modify proteins but was resistant to procedures that alter nucleic acids, a family of hypotheses about the molecular architecture of the scrapie agent began to emerge. These data established, for the first time, that a particular macromolecule was required for infectivity and that this macromolecule was a protein ....

Once the requirement of protein for infectivity was established, I thought that it was appropriate to give the infectious pathogen of scrapie a provisional name that would distinguish it both from viruses and viroids. After some contemplation, I suggested the term "prion" derived from proteinaceous and infectious. At that time, I defined prions as proteinaceous infectious particles that resist inactivation by procedures that modify nucleic acids. I never imagined the irate reaction of some scientists to the word prion—it was truly remarkable!

From Stanley Prusiner's Nobel Prize Lecture. ©The Nobel Foundation 1997

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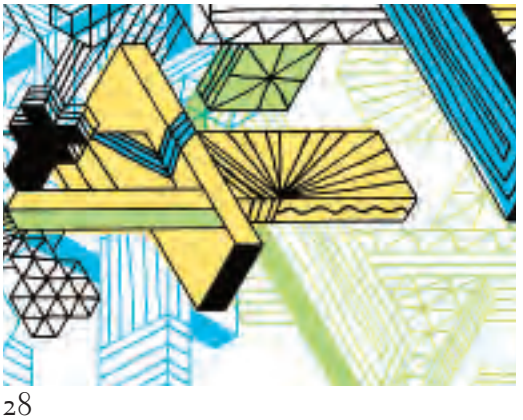

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WEB ONLY CONTENT

Hear Pat Brown discuss our society's dependence on animal agriculture. Watch fossil hunter Jason Osborne in action on Maryland's coast. Read how Dan Goldberg and Alan Cowman, on two different continents, zeroed in on an enzyme critical to the malaria parasite's infectivity.

Join us at www.hhmi.org/bulletin/may2010.

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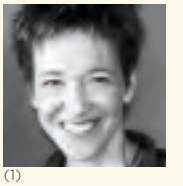
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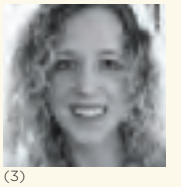
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After raising two daughters in Takoma Park, Maryland, **ROBIN MARANTZ HENIG** ("A Kaleidoscopic View," page 16) and her husband pulled up roots in 2002 and moved to Manhattan, where she indulges her love of theatre, art museums, and take-out Thai food. Since that time, she's written her eighth book (*Pandora's Baby*) and become a contributing writer at *The New York Times Magazine*, writing about big topics like God, death, anxiety, and whether hunky humanoid robots make the best husbands. (1)

Although **IVAN AMATO** ("A Silver Lining," page 22) thrives on writing about science and technology, he sometimes laments that, in learning more about the world to do his work, he becomes ever more aware of how much he does not know about the world. He has written hundreds of articles and several books. His latest book, *Super Vision: A New View of Nature*, is a celebration of the way science imagery makes the invisible visible. (2)

A fallen biologist, **SARAH GOFORTH** ("Scratching the Surface," page 8) traded the pipette for the pen in 2000. Since then, her work has appeared in *The Scientist*, *Popular Science*, and *The Dallas Morning News*, and online at *The Why Files* and Discovery.com. As manager of print and electronic publications at HHMI, she now works at the bustling intersection of science and digital media. Sarah lives in Annapolis, Maryland, with her husband and two dogs. (3)

PETER ROSS ("A Kaleidoscopic View," page 16) works as a portrait photographer in New York City, making portraits for magazines, websites, and corporations, among others. He recently photographed the possessions of the late author William Burroughs: typewriter, handgun, shoes, quilt. This led him to ponder what personal possessions he would most like to be remembered for: his chainsaw, a collection of Odd Fellows pottery, and the world's best coffee maker, the Chemex. His current project is photographing the 18 people who now live in apartments and homes where he once lived. (4)

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Robin Henig, Ivan Amato, Sarah Goforth, Chuck Gonzales

Biomolecular Crowdsourcing

A GENERATION OF WEB-SAVVY ENTREPRENEURS HAS FOUND A relatively cheap and effective approach to solving complex problems and soliciting ideas: toss out a challenge into a vibrant digital community and watch what happens. Professionals and amateurs compete on an equal footing to provide often surprising solutions. HHMI investigator David Baker sees it on a daily basis with Rosetta@home, a distributed network dedicated to solving big questions in protein folding.

This phenomenon of crowdsourcing—a term that journalist Jeff Howe lays claim to coining—has some interesting parallels with old-fashioned bucket biochemistry (my kind of science). Each requires a vast input and powerful filters to yield a pure nugget of information. In biochemistry—which often requires real buckets of biological material, such as liters of HeLa cells—the nugget is a few nanograms of scarce proteins that researchers need to begin the real work of understanding the machinery of life.

Fishing is one of my passions, but some of my most successful fishing expeditions have been scientific. Starting during my years as a postdoc with Jim Watson at the Cold Spring Harbor Laboratory and subsequently at the University of California, Berkeley, my colleagues and I went fishing for a very specific molecular target: transcription factors—key regulatory proteins that control the flow of biological information in cells. We used short segments of DNA as bait, hunting for a match among the tens of thousands of proteins in cells. We started with viruses and then found the first transcription factor in human cells, something we called specificity protein 1, or Sp1.

We've learned that transcription factors work by interacting with short regions of DNA once denigrated as "junk" that in fact control the activity of all our genes. You can think of transcription factors as specialized proteins that recognize DNA sequence "punctuation marks"—start and stop signals recognized by the enzymes that read and transcribe genes. The transcribed "messenger" RNAs go on to generate important products like hemoglobin, the iron-rich protein that carries oxygen in red blood cells. Not surprisingly, when gene regulation goes wrong, disease occurs: diabetes, cancer, inflammation, and heart disease among them.

Like collaborations in cyberspace that rely on many anonymous contributors, bucket biochemistry has inherent limits. For example, by measuring transcriptional events in extracts derived from mixtures of cell types, we can detect only average events, not the reactions taking place in individual cells or at a single gene locus. In short, biochemists like me have been missing the rapid, dynamic, and mysterious real-time events taking place in individual cells at specific genes. But now developments in fluorescence microscopy make it possible to witness transcription as it unfolds in real time, molecule by molecule, and in some cases even in living cells.

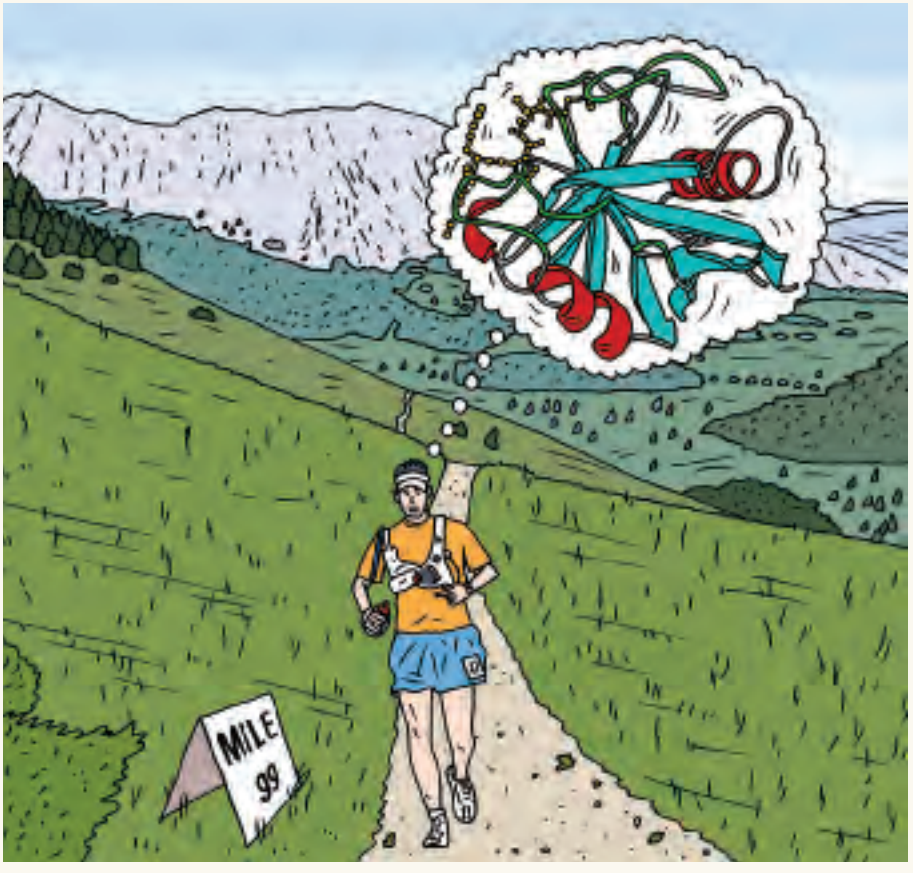
A convergence of serendipity—involving a sabbatical detour in Paris in 2005, a collaborative project with a Berkeley colleague, and a subsequent stint as a visiting scientist at HHMI's Janelia Farm Research Campus—has led my research in unexpected and illuminating new directions.

Barbara Ries

> "A convergence of serendipity has led my research in unexpected and illuminating new directions."
>
> ROBERT TJIAN

Imaging tools have long played an important role in cell biology, but the fuzzy world glimpsed through the lens of a microscope always seemed too qualitative for my taste. Then, during a sabbatical at the École Normale Supérieure in Paris, I had the good fortune to occupy a lab bench next to Xavier Darzacq, a new faculty member who had just completed postdoctoral training in Robert Singer's laboratory at the Albert Einstein College of Medicine. The two scientists and their colleagues have contributed to major advances in our capacity to visualize actively transcribing RNA in live cells and to track the movements of RNA polymerase—the enzyme responsible for producing RNA during transcription—through the development of new molecular techniques, high-resolution microscopes, and sophisticated computational tools.

Back at Berkeley, physicist Steve Chu and I brought our labs together to build a new kind of microscope—one that uses multiple-color lasers to observe and measure complex events at the single molecule level. These collaborations developed into an international consortium that includes Singer, Darzacq, Chu, and many other scientists working at the frontiers of molecular and cell biology, biophysics, and mathematics. Our small collaborative project team also benefits mightily from interactions with Janelians Eric Betzig, Harald Hess, and Mats Gustafsson, who have done so much to advance light microscopy that we're now able to peer into cells with exquisite precision. It's been a literal eye opener for me. I'd describe it as biomolecular crowdsourcing—of a very different type—in a venue that allows us to cross national, disciplinary, and subject-matter boundaries to think about big interesting questions.



Peter Arkle

For the Long Haul

If you're trying to find Chris Garcia on a Saturday morning, focus your search dozens of miles deep in the Santa Cruz Mountains or halfway up nearby Mount Diablo. He'll be on foot, but if you want to catch him you'll have to move fast.

Garcia, an HHMI investigator at Stanford School of Medicine, reserves his Saturday mornings to train for ultramarathons, grueling tests of endurance that stretch between 30 and 100 miles. On an average Saturday, he runs 25 to 30 miles—on narrow, winding, mountainous trails—with a handful of training partners. During the peak of his training season he follows up with another 20-miler on Sunday and shorter runs throughout the week, for a total of 70 to 80 miles.

Garcia wasn't always a runner: in high school he was on the tennis team, and during graduate school he rowed a single scull with the Baltimore Rowing Club. Then a postdoctoral fellowship took him to San Diego, where he competed in triathlons and marathons.

"Then one day, I'm flipping through the channels on my TV and see this story on ultramarathons," says Garcia. "I just remember being totally transfixed. When you hear about people running 100 miles, you have one of two reactions: you either think it's completely crazy, or you think 'Hey, I should go do that.' For me, it made complete sense."

In the past decade, Garcia has run more than 75 ultramarathons, including nine 100-milers, all over the United States. Races usually start around 4:00 a.m. to take advantage of cool morning temperatures. The 100-milers take Garcia between 20 and 30 hours to finish, depending on the elevation and how mountainous the terrain is. He wears a headlamp and runs through the following night, pausing only at food and water stops offered every 10 or so miles.

"My favorite times during these races are actually at dusk, right before the sun sets, and then at sunrise in the morning," he says. "When you just start to see the flicker of sun come up you know that you're on the downhill slope of the race, you're getting close."

Ultramarathoning, with its physical and mental challenges, isn't for everyone. "You have to not mind spending hours and hours on the trail by yourself," says Garcia. "In fact, you have to look forward to it."

The trails offer him breathtaking views, an occasional mountain lion encounter, and precious solitary time to process information and solve problems in his research—a break from life's chaos. At the finish line of a 100-mile race, Garcia says he is more himself than at any other time. "It just puts life in perspective," he says.

Garcia says his 40-something body is starting to feel the stress of a decade of these races. "My body is definitely getting pretty beat up," he says. He's not bothered by the puking, shivering, fuzzy thinking, and sore muscles that come in the latter stages of an ultramarathon. Experience has taught him that he can push through those temporary discomforts. But chronically sore hips may eventually send Garcia back to shorter races—marathons and triathlons. Not yet, though. He's got three 100-milers on his summer calendar.

—Sarah C.P. Williams

Fossil Hunter

Cold waves lapping at his rubber-booted feet, Jason Osborne fishes into his pocket and pulls out a flathead screwdriver. Kneeling, he pushes it gently into a craggy, waist-high rock and carefully scrapes away millions of years of embedded sand to reveal the distinctive curves of an *Ecphora*—an extinct marine snail that inhabited Maryland's coastal waters in prehistoric times.

A screwdriver might not be the first tool that comes to mind for a paleontological dig. But for this fossil hunter, it's the tool of choice.

"It fits in my pocket and does just what I need it to," he says.

Considering Osborne's day job, it's no wonder the screwdriver feels natural in his hand. The mechanical engineer is part of the instrument design and fabrication team at HHMI's Janelia Farm Research Campus, where he helps build imaging and electrophysiology tools for studying the brain.

A self-taught aficionado of fossilized marine life, Osborne spends most weekends on the beaches flanking Maryland's hundreds of miles of inland waterways. The Calvert Formation—cliffs that line the western coast of the Chesapeake Bay from mid-Maryland to southern Virginia—is a favorite spot for Osborne and other avid fossil hunters, amateur and professional.

Those cliffs contain Miocene deposits, composed of sediment laid down when the area was covered by ocean, some 10 to 23 million years ago. The cliffs periodically disgorge the remains of sea creatures preserved in sand and rock onto the beaches below. Fossils are so abundant that any beachcomber with a sharp eye can spot ancient shark teeth, mollusks, and bone fragments from marine mammals, such as sea cows and porpoises.

"Everything tells a story," Osborne says. "You look at a rib fragment and you see the serrations and lacerations from a shark attack. It's absolutely amazing to imagine what the seas were like back then."

James Kegley

Some of those shark teeth can be big—really big. In his personal collection—Osborne also donates some of his finds to museums—he has one specimen from a megatooth shark that measures 5 3/4 inches from top to bottom. He's also made larger fossil finds, including the skull and vertebrae of a baleen whale, a rare partial association of sea snake vertebrae from the Eocene epoch that he uncovered along the Potomac River last New Year's Day, and the skull of a yet-to-be-identified porpoise species that he found while diving in southern Virginia.

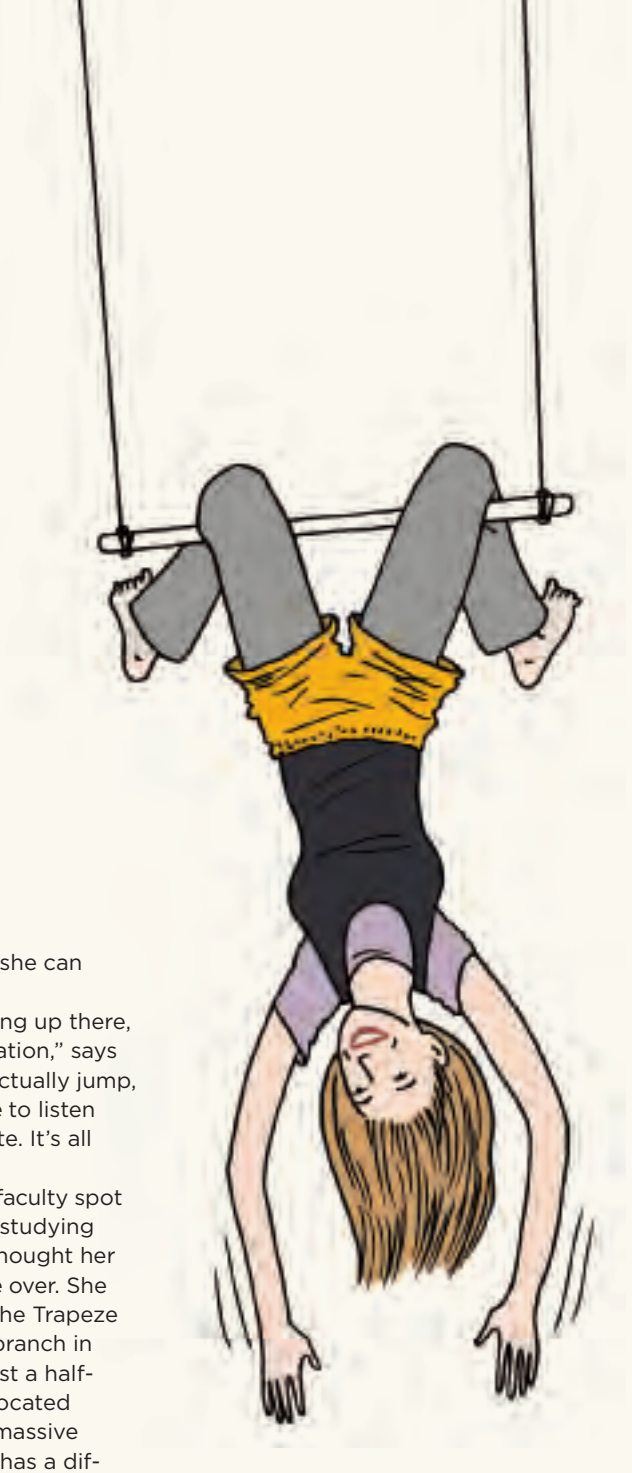
"There's nothing like it when you're crawling around on the bottom and you find something like that just lying on the riverbed, and you're the first person to see it and touch it," he says. "It's a heck of a feeling."

On this brisk midwinter day, Osborne scours the tideline for tiny tiger shark teeth and other fossil remnants. After a time, he turns his trained eye upward, to the steep cliffs rising above the beach. A glint of white catches his eye. "That might be something," he says and reaches for his binoculars. With the powerful glasses, he can make out a flat, chalky circle with what appear to be white extensions coming out of the side. Though state laws prohibit him from climbing the unstable cliff to investigate, he plans to report the find to his friends at the Calvert Marine Museum.

"It could be a big radius [bone] but I can't imagine one that big," he says, grinning as he lowers the binoculars. "That's cool. That's definitely cool."

—Mary Beth Gardiner

WEB EXTRA: To see and hear Osborne on a collection trip to the Calvert Formation, and to take a virtual tour of an exhibit of some of his fossil finds, visit www.hhmi.org/bulletin/may2010.



She Floats Through the Air

For Amy Wagers, the adrenaline rush of getting a paper accepted for publication is nothing compared to what comes next: a 10,000-foot fall from an airplane. Wagers, an HHMI early career scientist at Harvard Medical School, has a tradition of skydiving with the first author of each of her lab's major research articles. For most who agree to join her, plummeting through the sky is a once in a lifetime experience.

Wagers, however, is no stranger to soaring through midair. She took up the flying trapeze when she was a postdoc at Stanford University.

She wanted a hobby to take her mind off science after a particularly grueling week of lab work, and a friend mentioned the San Francisco School of Circus Arts. "I thought that sounded pretty fun," says Wagers. "I went to a trapeze class and absolutely loved it." She became a regular at the school.

"It's really pretty thrilling," she says. When it's her turn to jump, Wagers climbs to a 23-foot-high platform and reaches for the trapeze bar dangling in front of her. With her toes on the very edge of the platform, she can glimpse the net below.

"At that moment, standing up there, there's that rush of intimidation," says Wagers. "Then when you actually jump, it's very focusing. You have to listen and you have to not hesitate. It's all about timing."

When Wagers landed a faculty spot at Harvard Medical School studying stem cells and aging, she thought her days of flying trapeze were over. She discovered, however, that the Trapeze School of New York has a branch in Reading, Massachusetts, just a half-hour drive from Harvard. Located above the food court of a massive Jordan's Furniture store, it has a different feel from the circus school in San Francisco.

"There are families sitting there, eating ice cream and watching you," says Wagers. "If you miss a catch everyone goes 'Aaah' and if you make it everyone claps."

Wagers had always loved heights, but her spontaneous foray into trapeze made her curious to try other sky-high stunts. When she and another junior faculty member at Harvard collaborated on their first paper and got positive comments from *Nature*, Wagers came up with a plan: "If this very first paper for both of us gets in," she told her collaborator, "we're going skydiving." The paper was accepted, and Wagers booked a sky dive in Newport, Rhode Island. Though her collaborator conveniently forgot the date of the booking, Wagers went ahead and jumped. "Then I decided whenever my lab had an important paper published, I would go skydiving."

On the trapeze, Wagers has learned several basic maneuvers, including the knee hang, in which she suspends herself upside down from the bar by only her knees. She says her love of flying trapeze is going to stay a hobby, though—a way to clear her mind of science for just those few terrifying seconds up on the platform. "I'm still very much a novice," she says. "I'm definitely not leaving science for the circus." —*Sarah C.P. Williams*

FOR MORE INFORMATION: To learn more about Amy Wagers' research, see "Young Again" on page 42.

Peter Arkle

upfront

WEB ONLY CONTENT

With different approaches and on different continents, Dan Goldberg and Alan Cowman land on an enzyme critical to the malaria parasite's destructive ways. Read the story at *www.hhmi.org/bulletin/may2010*.

Why bother trying to extend life if those added years aren't healthy ones? Disease and disability ruin countless retirement plans. For some people, the discomfort from a skin disease or an allergic reaction can make life miserable. For others, a life-saving medication becomes impossible to take because it causes an unbearable itch. Researchers are thinking hard about quality of life. Some are trying to figure out how to add years while bypassing the neurological diseases of aging. Others are dissecting the pathways involved in itch—which can spill over into pain—so it no longer drives people to distraction.

Scratching the Surface

There's nothing funny about an itch that drives you mad.

IF THE SUBJECT OF ITCH SEEMS FRIVOLOUS COMPARED TO OTHER medical matters, consider this: in regions where the drug chloroquine is used to treat malaria, patients often discontinue treatment rather than endure the excruciating itch that comes as a side effect. And case studies tell of itch sufferers who injure themselves in search of relief; in one well-documented case, a woman scratched through her skull and into her brain tissue in her sleep. ¶ Still, the subject of itch was ignored in favor of pain studies for decades, says HHMI early career scientist Xinzhong Dong, a neuroscientist at the Johns Hopkins University School of Medicine. Attention to the field is increasing now, thanks in part to Dong's work unraveling the puzzling pathways that carry certain itch sensations from the skin to the brain.

In collaboration with HHMI investigator David Anderson, a neuroscientist at the California Institute of Technology, Dong identified a protein that functions as an itch receptor in a small subset of nerve cells. The scientists reported the research in the December 25, 2009, issue of *Cell*.

Allergic itch happens when cells in the immune system release the chemical histamine. It is easily treated with antihistamines, which lessen itch by binding to histamine receptors on the surface of sensory neurons. But allergic itch accounts for only one-third of all types of itch.

Other forms of itch—including the kind caused by chloroquine—don't work through histamine receptors, so antihistamines are ineffective. Lacking a better option, physicians usually treat nonallergic itch with steroids, which, if used for long, can have dangerous side effects, including eye disease, osteoporosis, and gastrointestinal illness. The search for alternative treatments has been complicated by the absence of a known receptor.

Nearly a decade ago, when Dong was a postdoc in Anderson's lab, he stumbled on a class of receptors called Mrgprs. A subset of these receptors was found almost exclusively on a class of sensory neurons thought to be involved in the sensing of pain.

Dong and Anderson first presumed that the Mrgprs, too, were related to pain. "At the time, we had no inkling of itch," he says.

To determine the role of the receptors, the scientists engineered a line of what Anderson calls "super-knockout" mice lacking 12 genes coding for receptors in the Mrgpr family.

They expected the mice to be less sensitive to pain than normal mice, but the mice lacking the *Mrgpr* genes appeared suspiciously normal. "What was striking was that there was very little wrong with these mice," recalls Anderson. They showed virtually no difference in their response to pain, compared with normal mice.

Years later, Dong was inspired by studies conducted by Zhou-Feng Chen, another former postdoc from Anderson's lab who is now at the Washington University School of Medicine, on how neurons deliver itch

VSA Partners

sensations to the brain. Dong returned to the *Mrgpr*-knockout mice with a new question: would they show any deficits in their itch responses?

The researchers first injected itch-inducing histamine into the mice. Both the normal and knockout mice behaved similarly, scratching furiously. But when the researchers injected chloroquine, the mice lacking *Mrgpr* genes scratched less—nearly three times less often than normal mice.

"Now, we think these receptors function as novel itch receptors, like the histamine receptor," says Dong.

It can't be said yet whether the receptors respond to other forms of nonallergic itch, like that associated with psoriasis or poison ivy; Dong's lab is testing that question. But the discovery helps get to the root of a sensation about which there's heated debate, says Dong.

"Some people propose that itch is the little brother to pain," explains Dong. "If you get a little bit of the sensation, you get the itch, if you get a lot, you feel pain." Another possibility is that there are distinct nerve cells—those dedicated to itch, different ones for pain, and others for ordinary touch.

Dong proposes a third view. "We think that these two circuitries are not really separate, but the pain circuitry is much larger. If you activate a large population of pain-sensing neurons, you get pain. The itch-sensing neurons reside within a subset of pain-sensing neurons, and if you activate them specifically you get itch sensation," he says.

"The big prize here would be to find the population of neurons that respond to multiple nonhistaminergic, itch-inducing compounds and find a drug that shuts those cells down," says Anderson.

And he has a daily reminder of the relief that such a drug could bring: his cat. "She has a chronic itch problem; she just tears acres of fur off her head and her neck," he says. The only treatment is steroids, and Anderson's veterinarian has warned that continued steroid exposure could create its own health issues for the animal. "People have underestimated the importance of itch because it's not a life-threatening condition like cancer or Alzheimer's disease. But it has a huge impact on the quality of life." ■

–SARAH GOFORTH

Live Long and Prosper

Mix amyloid plaques with longevity and you get mice that not only live longer, but healthier too.

Andrew Dillin has found a way to manipulate the IGF pathway to sequester misfolded proteins.

Lou Mora

ANDREW DILLIN WANTS TO INCREASE THE HUMAN HEALTH SPAN — NOT just years, but healthy years. He believes the secret to preventing many age-related neurotoxic diseases—including Alzheimer's, Parkinson's, and Lou Gehrig's diseases—lies in the body's ability to recognize and sequester improperly folded proteins. ¶ Dillin, an HHMI investigator at the Salk Institute for Biological Studies, has been building a strong case for his misfolded-protein theory. A few years ago, he showed that there are mechanisms in immature worms that can inactivate misfolded, toxic proteins; as the animals age, however, that surveillance system degrades until the aggregation of those proteins leads to disease. Now, he and his colleagues have linked that finding to mice engineered to exhibit Alzheimer's disease. [Prions are a different set of proteins that misfold with different results—see "A Silver Lining," page 22.]

Amyloid beta, or Aβ, is a misfolded protein that accumulates in the brains of Alzheimer's patients and creates dense plaques that are a hallmark of the disease. When Dillin genetically reprograms mice to have a longer lifespan, they seem to retain the youthful ability to isolate, compartmentalize, and pack away Aβ proteins. The result: plaques that appear similar to those of Alzheimer's but are denser and seemingly benign. Somehow, the surveillance mechanism identifies and secludes the dangerous proteins in a way that older brains cannot.

He began to take a hard look at aging during his postdoc at the University of California, San Francisco. From 1999 to 2002, he studied the genetics of aging in the lab of Cynthia Kenyon, who in 1993 discovered that changing a single gene could double a roundworm's lifespan. Changing the gene, called *daf*-2, downregulated the insulin/insulin growth factor (IGF) pathway, which is found in organisms from the tiny worm to the largest mammals.

The IGF pathway is one of three genetic pathways known to affect aging. Dillin had a hand in discovering the other two. One, involved in mitochondrial signaling, he discovered in 2002 during his time in Kenyon's lab. "If you reduce mitochondrial function you can increase lifespan," he says. "If you go down too far, it kills the animal, but at a certain level you get a positive response." In his own lab, Dillin discovered the genetic determinant responsible for longevity induced by caloric restriction—another long-known but little-understood cause of increased lifespan—and found that a different signaling pathway, acting on the roundworm gene *pha-4* (*FoxA* in mammals), was responsible.

Dillin contends these three distinct pathways have at least one thing in common: "We think that all these pathways, when they are downregulated, trick the system to turn on the protein surveillance machinery much more highly, to really take care of the proteome," he says.

Using Kenyon's discovery of the IGF pathway as his springboard, Dillin has begun investigating whether downregulating the IGF pathway can keep an animal healthy as it lives longer. A postdoc in his lab, Ehud Cohen, combined a worm model of Alzheimer's—in which Aβ proteins accumulate in the roundworm's body wall—with the long-lived, IGF-downregulated worms. The onset of toxicity was delayed in the worms. "I thought the protected worms would actually have fewer plaques than the unprotected worms. That's what any neurologist would tell you," Dillin says. "But they actually had more."

The longer-lived worms accumulated plaques, but the plaques seemed far less toxic than those in the regular IGF worms. "It was a really striking result, because it was so clear that it wasn't just time—there was something inherent about remaining youthful," Dillin says.

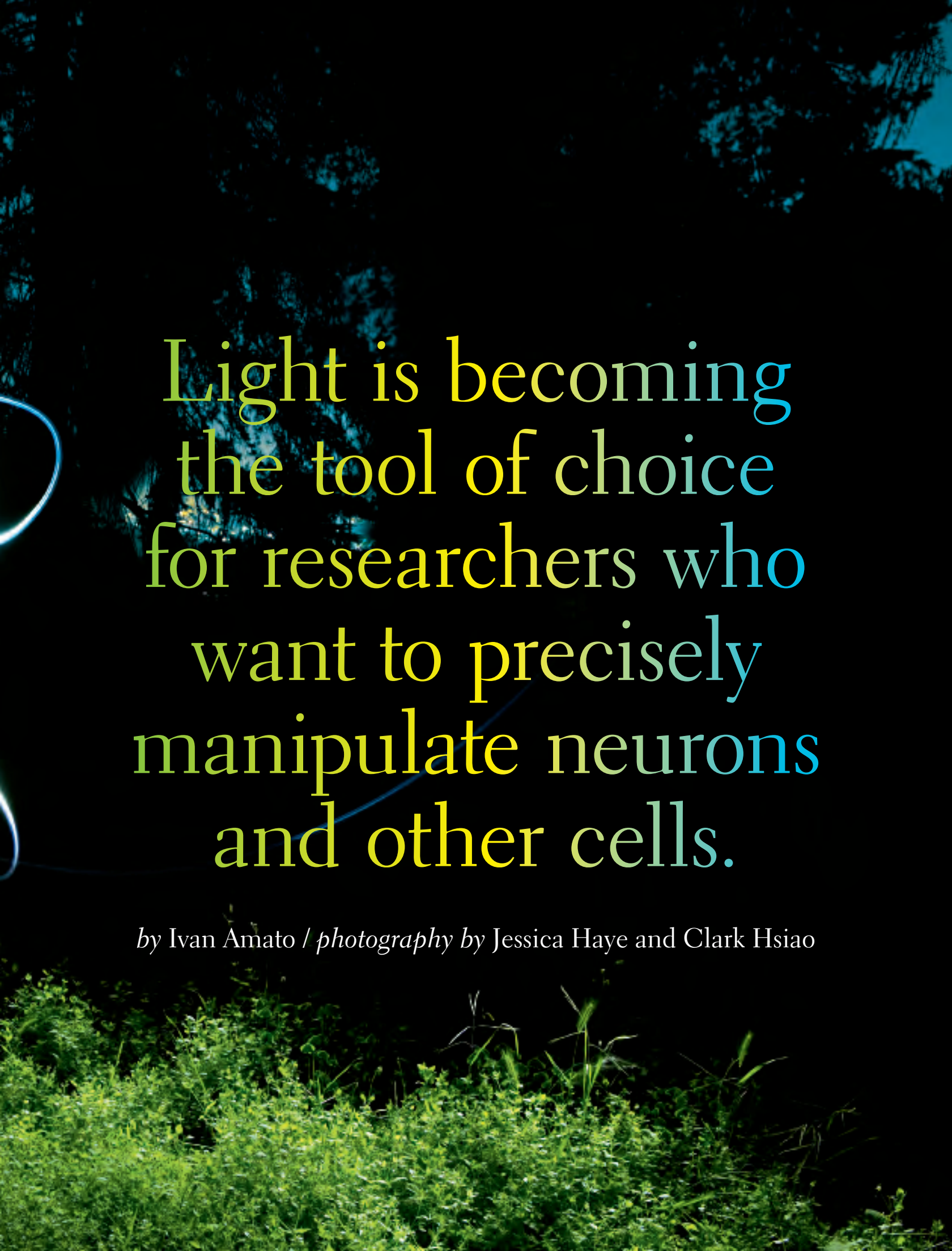
When they moved the Alzheimer's research to mice, Dillin and Cohen, now at the Hebrew University Medical School in Jerusalem, found even more striking results. In research published in *Cell* on December 11, 2009, they created an Alzheimer's mouse model with downregulated IGF signaling and compared those animals with mice engineered to have Alzheimer's with a normal lifespan. Just like the worms, mice with downregulated IGF still had Aβ aggregating in their brains—with as many plaques as their Alzheimer's addled counterparts—but they were almost completely asymptomatic.

The results confounded the group for the better part of a year. But they eventually found that the longer-lived mice had plaques that were far denser and in a conformation that likely eliminated much of the misfolded proteins' toxicity. Rather than destructive, the plaques in these mice were actually protective, amassing the dangerous protein in such a way as to inactivate it. Something about muting the IGF pathway, Dillin believes, allows for continued protein surveillance and protection from mechanisms that have gone awry.

> "This is the first study to show that you've not only extended an animal's lifespan but also actually improved its quality of life."
>
> ANDREW DILLIN

"This is the first study to show that you've not only extended an animal's lifespan but also actually improved its quality of life," Dillin says. The transgenic mice were living longer, and they were eluding a disease they had been genetically programmed to develop. Dillin is investigating the mechanisms involved and is looking at other neural conditions as well, including Parkinson's and Lou Gehrig's diseases. ■ –LAUREN GRAVITZ


Light
Moves



Light is becoming the tool of choice for researchers who want to precisely manipulate neurons and other cells.

by Ivan Amato / *photography by* Jessica Haye and Clark Hsiao

There's a reason neuroscientist and bioengineer Karl Deisseroth shows the same video at most of his talks. The movements of the gray mouse with the long tail offer a striking illustration of the power of light to manipulate specific cells.

Barely visible in the overhead view of the mouse is a hair-thin optical fiber that feeds through the animal's skull into the right motor cortex of its brain. As the mouse casually sniffs around and explores its white basin, a cool blue glow appears at the fiber's point of entry. At that instant, the mouse starts circling leftward around the basin, swiftly and deliberately, as though it just received marching orders. A few moments later in the video, the blue glow disappears. The mouse suddenly stops marching and reverts to its lazy meandering, eventually sitting on its haunches.

Deisseroth, an HHMI early career scientist at Stanford University, is part of a growing community of researchers, including several HHMI investigators, who draw upon genomics, genetic engineering, biochemistry, molecular biology, microbiology, biophysics, bioengineering, and optics to tease out the complexities of brain circuitry and to manipulate researcher-specified cells (such as the motor cortex cells of the marching mouse) among thickets of diverse cell types.

Patients with optical fibers inserted into their brains are not on the agenda, says Deisseroth, a psychiatrist who sees patients one day a week. But the laboratory approaches he and others have been developing could reveal telling details about healthy and dysfunctional brains that point the way to improved treatments for people. Today's therapies—drugs, electroshock, surgery—sometimes work. But "they are crude and have side effects," he says, because they are not very selective about the cells and tissues they affect. "My patients have motivated me to find elegant tools that speak the language of the brain."

Edward Boyden, a former postdoctoral fellow of Deisseroth who now runs the Synthetic Neurobiology Group at the Massachusetts Institute of Technology, has taken early steps in the direction of human applications. In April 2009, he and colleagues published a paper in *Neuron* reporting that the same kind of protocol underlying the marching mouse can work, apparently safely, in macaque monkeys. And in 2008, he and two colleagues launched the start-up Eos Neuroscience in San Francisco, whose mission, according to its website, is to "develop treatments for chronic neurological disorders."

Fixing brains is quite an ambition for a field that commandeered its core technology from single-celled organisms.

Borrowing from Nature

Bacteria, fungi, plants, and other organisms use a repertoire of molecular switches that respond to light. Spanning the membranes of many of these microbial species are light-activated gates and pumps that control the passage of positively charged sodium, potassium, calcium, and hydrogen ions or negatively charged chloride ions.

Those ancient, light-activated membrane gates and pumps can be transferred into other cells of the living kingdom, including mammalian brain and muscle cells, with genetic engineering techniques. Once transferred, those mobile modules become controllable with light. "If you can do that," says synthetic biologist and HHMI investigator Wendell Lim at the University of California, San Francisco (UCSF), "you have an extraordinarily powerful tool. You can use light to perturb systems and modify them. We can get a kind of systematic control that we have not had before."

The handiest light-activated molecule so far is channelrhodopsin-2 (ChR2), which was originally found in the light-sensitive "eye spot" of *Chlamydomonas reinhardtii*, a type of green algae. In *Chlamydomonas*, upon exposure to blue light, ChR2 opens and allows positively charged ions into the cell. That triggers a sequence of changes that influence the cell's cilia-based propulsion and, thereby, its motion and feeding behavior. When transferred into neurons, ChR2 becomes a light-activated trigger that makes the modified neurons fire more easily. Deisseroth's group used motor neurons that they genetically modified to bear ChR2 receptors to make the mouse march in response to light.

If ChR2 is a blue activator, halorhodopsin (NpHR) is a yellow silencer. It was discovered in *Natronobacterium pharaonis*, a bacterium isolated from a high-alkaline, high-salt lake in Egypt. In the bacterium, the light-driven NpHR channels pump chloride ions into the cell, a flow that ultimately helps drive the synthesis of ATP, the cell's biochemical fuel. Transferred into neurons, however, these channels respond to yellow light by hyperpolarizing the cells, effectively silencing them.

ChR2 and NpHR make for a powerful duo. They enable researchers to rig neurons and other cell types, including muscle cells and perhaps even insulin-making pancreas cells and immune system cells (see Web Extra, "No Neuron Left

Unturned," www.hhmi.org/bulletin/may2010), with light-controlled on and off switches. From a third light-activated gate, VChR1, Deisseroth's group developed a tool that responds to light on the red side of the spectrum. VChR1, a channelrhodopsin in *Volvox* algae, is a cell excitor like ChR2.

For neuroscientists like HHMI investigator Massimo Scanziani of the University of California, San Diego, the real experimental power of these switches becomes clear when they are inserted into specific types of neurons.

To achieve this, Scanziani appends the gene for, say, ChR2 or NpHR, to stretches of DNA known as "cell selective promoters," each of which becomes operative in only one neuron type. So, even though the gene-insertion step might occur in all neuron types, only one of those types will actually express the ChR2 or NpHR switches.

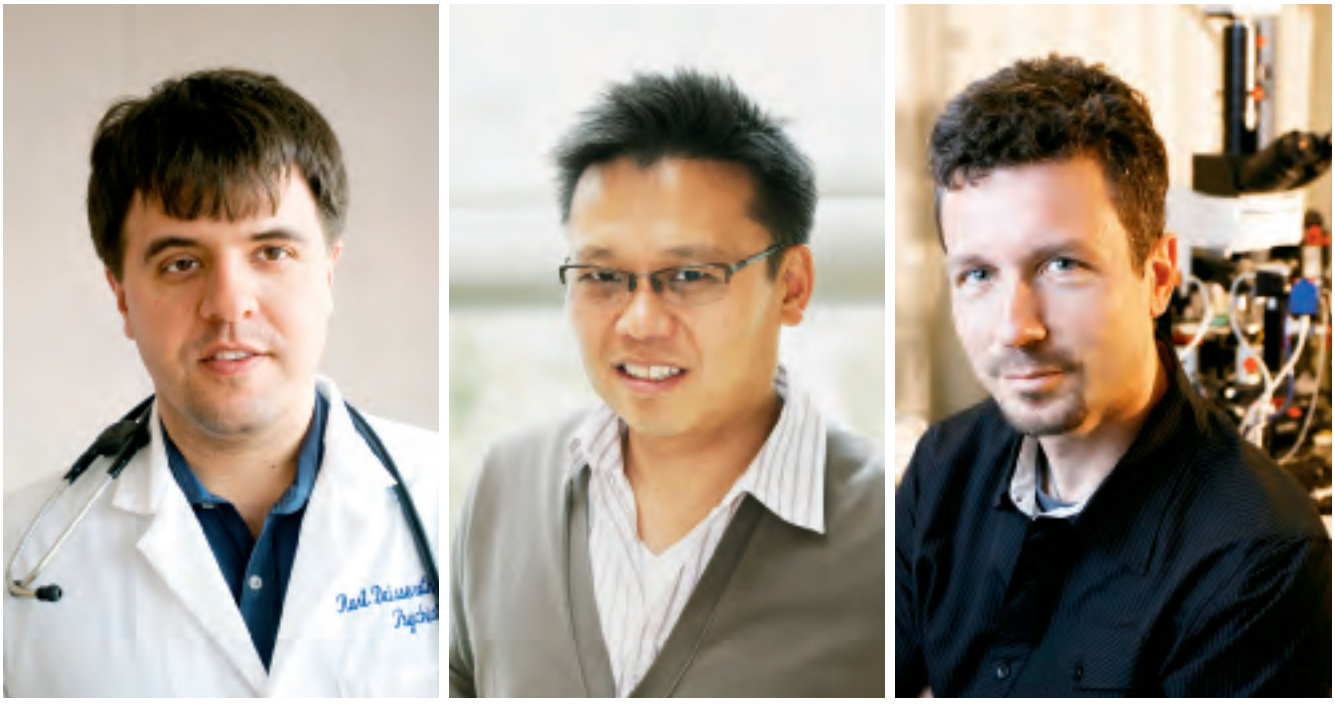
"This gives you immense sensitivity," says Scanziani, who uses the technique to probe the function of specific cells in the cortex of animal brains, the region associated with sensation and thought. In mice and rats, for example, Scanziani studies how sensory inputs, such as the contrast between different elements of a visual scene, are processed by neuronal circuitry in the visual cortex. "You now can manipulate a circuit and understand what the heck it does in the brain," Scanziani says.

The repertoire of light-switchable modules available for optogenetics studies is growing. "There's a Home Depot of different kinds of switches out there," says Michael Ehlers, an HHMI investigator at Duke University Medical Center, where he studies the structure and dynamics of the synapses through which neurons communicate with one another. Deisseroth's group, for one, continues to stock the shelves with more and more optogenetic switches.

Their newest category of switches, the optoXRs, enable researchers to modify cells to respond to light as though they were being stimulated by neurotransmitters, such as adrenaline and dopamine. These switches combine a light-sensing rhodopsin component with the internal parts of a G protein-coupled receptor. That's a large family of receptors that trigger internal cellular responses to sensory, hormonal, neurochemical, and other stimuli arriving at the outside of the cell. For neuroscientists, optoXRs open entirely new research approaches for studying Parkinson's disease, schizophrenia, addiction, and other severe neurological problems, Deisseroth says.

Boyden and his colleagues are trolling the ever-enlarging library of genomic databases to diversify the optogenetic tool set. That's how he and his coworkers found Arch and Mac, two light-driven proton pumps (the first from a bacterium, the second from a fungus) that silence cells into which the researchers insert them when the switches are exposed to yellow and blue light, respectively. The scientists reported their initial work with them in a *Nature* paper on January 7, 2010.

(continued on page 48)



Karl Deisseroth, Wendell Lim, and Massimo Scanziani are using light as a type of remote control to manipulate cells and tease out the daunting complexity of muscle, heart tissue, and particularly brain tissue.

Deisseroth: Darcy Padilla Lim: George Nikitin / AP, ©HHMI Scanziani: Denis Poroy / AP, ©HHMI

A KALEIDOSCOPIC VIEW

Elaine Fuchs brings an eye for the creative to the many-colored facets of her life and work.

by ROBIN MARANTZ HENIG | *photography by* PETER ROSS

WALKING THROUGH THE MUSEUM OF MODERN ART

arm-in-arm, Elaine Fuchs and her husband, David Hansen, look like any other New York couple: slim, elegant, dressed in black. But listen in on their conversation as they pause before a Picasso, as I was able to do one afternoon last winter, and you can hear something more: two fiercely intellectual people who look for inspiration for their creative work in almost everything they do, including museum-going.

This trait might be one reason that Fuchs, head of the Laboratory of Mammalian Cell Biology and Development at Rockefeller University in New York, has managed, in her nearly 30-year career, to pioneer new ways of studying skin and hair and to manipulate stem cell differentiation so deftly that she was able to turn a skin stem cell into a cloned adult mouse.

"I look immediately at the central figure," Fuchs says to her husband as they gaze at Picasso's *Three Women at the Spring*, "and I follow her hair." Eventually, she tells him, she follows the folds of the woman's robe and the stream of water she directs into a brown pitcher. "I get a sense of the river here, with the river as a part of the flow of life." And over on the left side of the canvas, she says, "the exposed features of the women are tantalizing, in a way that suggests fertility." Much of what Fuchs sees in the paintings that inspire her carries back to biology.

Hansen, a professor of philosophy and education at Columbia University's Teachers College, has a different interpretation, focusing instead on geometry, on the flatness of Picasso's figures.

Trailing the couple on this museum outing is a film crew making a documentary on women in science. The crew is supported by L'Oréal, the French cosmetics company that partners with the UNESCO Foundation to fund the prestigious L'Oréal-UNESCO Awards in the Life Sciences, given every other year to five outstanding women scientists, one from each continent. Vignettes from this documentary will be presented at a ceremony in Paris in early March, celebrating Fuchs and the four other 2010 award recipients. It is the latest in a string of accolades for Fuchs, an HHMI investigator since 1988. She also received the National Medal of Science from President Barack Obama in a 2009 White House ceremony.

Fuchs's stem cell work is among the discoveries that led to these honors. In the late 1990s, she and her students and postdocs generated mice with thick fur coats, suggesting that they might have stumbled on a clue about how hair follicle stem cells work. Several years later, her team devised a method to test the hypothesis. They attached green fluorescent markers to infrequently dividing cells from adult mouse tissue, which they thought might be stem cells, and then purified, cultured, and grafted the cells onto hairless mice. When the mice grew green fluorescent hair and skin, the scientists knew the tagged cells were in fact stem cells.

With her colleague Peter Mombaerts, Fuchs later cloned healthy mice from these stem cells using a technique known as nuclear transfer. They removed the nucleus of a mouse oocyte and replaced it with the nucleus of a hair follicle stem cell. They then grew the hybrid cell *in vitro* to the blastocyst stage and implanted those cells into the uterus of a mouse. While only a few percent of the clones survived to become healthy mice, the experiment demonstrated that skin stem cells can be successfully reprogrammed to a pluripotent state with the capacity to generate all 220 different cell types in the body.

The reports of these experiments—published in 2007 in *Cell*, *Science*, and the *Proceedings of the National Academy of Sciences*—led to a flurry of media attention. Such attention, however, is not really what Fuchs is interested in. To her, the real questions about stem cells are much more basic than creating hair or cloned animals.

"What I really want to know is why embryonic stem cells can choose any tissue pathway, while adult stem cells are much more restricted in their options," she says. Yes, she has shown that skin stem cells can be reprogrammed to generate a whole mouse. But more important is what happens in nature, when skin stem cells turn into skin, hair, or sebaceous glands, but never—without laboratory manipulation—a neuron or a kidney cell.

SEEING OPPORTUNITY

This kind of lifelong questioning began, in a way, with a butterfly net in a field behind Fuchs's childhood home in Illinois.

"Early on, my mother made a butterfly net for my sister and me," recalls Fuchs. Her sister Jannon is four years older, and the two girls spent long after-

ELAINE FUCHS'S STUDIES OF SKIN AND HAIR CELLS MAY EVENTUALLY LEAD TO A CURE FOR BALDNESS, BUT SHE MANIPULATES STEM CELLS TO ADDRESS LARGER HEALTH QUESTIONS.

noons in the fields behind their house in Downers Grove. Soon they were catching butterflies, insects, pollywogs, and the occasional crayfish from a nearby swamp. "We had butterfly nets and strainers and old kitchen utensils, and we started to ask for science books for Christmas," she says.

When she was about eight years old, Fuchs read about using thyroid hormone to accelerate metamorphosis in pollywogs. She pleaded with her father, a geochemist at Argonne National Laboratory, to get her some so she could try it for herself. "I had no concept of nanomolar concentration," she says with a smile. "I just wanted to speed things up. So I dumped the entire contents into the water—and killed all of my tadpoles. That was my first real science experiment"—pretty much a complete failure.

It was Jannon who seemed destined to be a scientist, she says; Jannon was "the smart one" and Elaine was "the fun one." Elaine admired her big sister, but Jannon Fuchs remembers it from a slightly different vantage point. "If given the choice," Jannon told me by phone from her home in Denton, Texas, where she is a professor of neuroscience at the University of North Texas, "I would have preferred to be the social one!"

Fuchs's father assumed Elaine would become a teacher—it was Jannon whom he urged to go into science—and so Elaine headed down that path. When she entered the University of Illinois in 1968, she enrolled in chemistry, physics, and mathematics classes, but she still didn't think of herself as an especially good student—until she looked around her.

In her science classes, Fuchs was one of just three women of some 200 students. She knew that meant a particular kind of scrutiny.

"I remember being in the physics class thinking, 'If I were to get an A, the professor would think I cheated. But if I get the best grade in the class, the professor couldn't think I cheated, since I would be doing better than everyone else.' Boy, that really motivated me." She made straight As in college, often at the top of her class.

But Fuchs wasn't a total grind. She joked around with the science geeks, hung out with the graduate students, and in one class asked the TA to teach her how to juggle tennis balls. She intended to join the Peace Corps after graduation—a plan that changed when she was assigned to work in Uganda, then under the bloody rule of Idi Amin. She chose graduate school at Princeton University instead.

At Princeton, in 1972, Fuchs again felt the sting of being a woman in a man's world. Fuchs recalls her advisor, Charles Gilvarg, saying on more than one occasion that he didn't think there was a place for women in science. Fuchs took his dismissive attitude as a challenge. She worked hard, often staying in the lab until 10 p.m., studying spore formation in bacteria as she sought to acquire the skills of a bench scientist. But she also played hard, beginning what would become a lifelong love affair with travel. Even on a paltry $3,000 a year stipend, Fuchs managed to travel to India, Nepal, Guatemala, Mexico, Peru, Bolivia, Ecuador, Turkey, Greece, and Egypt during her five years at Princeton.

Eager to tackle human biological problems, Fuchs pursued a postdoc in the Massachusetts Institute of Technology (MIT) lab of Howard Green, a pioneer in culturing human cells—specifically, skin cells derived from newborn foreskins. "I learned cell culture from a master," she says. "Howard really paid attention to the kind of detail that, even now, very few people have the capacity to do." He recognized, for instance, that to grow human epidermal cells, you have to co-culture them with fibroblast cells from the dermis, located just beneath the epidermis, thus reproducing the "cross talk" between cell types that occurs in nature.

At MIT, Fuchs started wearing makeup and nice clothes, partly to annoy a female colleague who said women scientists should avoid looking too feminine. Today she still dresses carefully and elegantly, and her long blonde hair is always permed. With bright blue eyes, a long oval-shaped face, and a dazzling smile, she has skin so wrinkle-free that it makes you wonder whether studying skin cells is its own fountain of youth.

CREATING NEW DYNAMICS

In 1980, Fuchs became an assistant professor of biochemistry at the University of Chicago and once again found herself in a man's world. As she was setting up equipment on the first day in her lab, the department chairman's lab technician dropped by. "Are you Dr. Fuchs's new lab technician?" he asked.

"Umm … I *am* Dr. Fuchs," she replied.

Things got better a few years later when a departmental reorganization brought a cohort of three strong female biologists together into the new Department of Molecular Genetics and Cell Biology: Fuchs; Janet Rowley, already a member of the National Academy of Sciences; and another assistant professor, Susan Lindquist, now a lifelong friend and fellow HHMI investigator. Fuchs and Lindquist designed and co-taught a course called Gene Expression in Cell Biology, which they continued until Lindquist left for MIT and the Whitehead Institute for Biomedical Research. And their friendship went beyond the classroom. They were neighbors in Hyde Park, and their husbands were also good friends—in fact, Lindquist introduced Fuchs and Hansen—so the two couples got together often for dinner and conversation.

"Every New Year's Eve we would go out together to a restaurant, and then to a dance party sponsored by the Chicago Symphony," says Lindquist. Getting to know her professionally and socially, Lindquist says, showed her that Fuchs is "both a phenomenally good scientist and a phenomenally good human being."

One of Fuchs's goals when she got to Chicago was to make a cDNA library (a collection of DNA fragments used to help identify genes and the proteins they produce) of the major structural proteins she'd been characterizing at MIT. In those early days of recombinant DNA technology, such a goal was ambitious. Eventually, Fuchs and her colleagues not only determined the DNA sequences encoding these proteins but also defined the two basic subunits required for the most important structural protein, keratin,

WE CAN STAND IN FRONT OF A PAINTING FOR AN HOUR. AND EVEN THOUGH WE'VE SEEN IT DOZENS OF TIMES BEFORE, WE SEE SOMETHING NEW IN IT. –DAVID HANSEN

to self-assemble into filaments. And they discovered that the filaments, in turn, were essential for the skin's protective and hydrating functions, forming an elaborate cytoskeletal network that provides mechanical integrity to the cells at the skin surface.

By the mid-1980s, Fuchs moved on to investigate what happens when the genes involved in making keratin proteins are damaged. At the time, geneticists approached such a question using a technique known as positional cloning. An investigator would choose a disease of interest and then find a large family with affected members. Then the scientist would collect DNA samples from everyone in the family and study the differences in DNA sequences between the affected and the unaffected, hoping to find the relevant mutation.

"This strategy did not divulge how or why the defect in the protein caused the tissue abnormality, which was what I was interested in," Fuchs says. "So we started at the reverse end and worked our way back." This process involved a relatively new kind of laboratory model, developed in the early 1980s: the transgenic mouse. It was a backward approach, since the idea was first to create a mouse with a specific mutation of interest, then analyze the pathology of the tissue defects, and finally find a resemblance to a human genetic disorder.

Not many scientists were making transgenic mice in 1986. Fuchs contacted one of the few in the Midwest—Susan Ross at the University of Illinois—and asked about sending a graduate student, Robert Vassar, to train in the Ross lab.

With this training, Vassar created a transgenic mouse expressing a mutation in the *K14* gene, which is responsible for building a keratin network in the innermost layer of the epidermis. But the transgenic mouse with the *K14* mutation seemed to be normal in appearance, health, and behavior—in other words, the mutation showed no distinct phenotype. "We were very disappointed," Fuchs recalls. "We thought it was a complete failure, a good idea but bad luck."

After a few litters of *K14* mutants were born with no apparent defects, Fuchs's lab manager, Linda Degenstein, noticed a mother mouse eating a newborn pup with an apparent skin defect. Might Degenstein have stumbled on nature's way of taking care of deformed offspring—and also an explanation for why all the transgenic pups in the litter appeared normal? Clearly, they thought, close observation of the mice in the immediate hours after delivery was needed.

"We essentially had a stakeout all night long," recalls Vassar, now a professor of cell and molecular biology at Northwestern University in Chicago. "We would bring the mice into the lab, and then camp out the entire evening waiting for them to give birth." The stakeout revealed that some of the *K14* mutations were so severe that the very act of birthing stripped the epidermis off the newborn. The mouse pups were unlikely to survive in this way, so the mother was instinctively cutting her losses, eating the doomed mutants so she didn't have to waste energy caring for them. A less attentive team would have missed it altogether.

Vassar and a postdoc, Pierre Coulombe, now chairman of biochemistry and molecular biology at the Bloomberg School of Public Health at Johns Hopkins University in Baltimore, managed to remove the mutant newborns from the cage in time to assess the damage. "The severe blistering was due to mechanical fragility in these mice," Vassar says. Without a proper keratin network, the skin cells were as fragile as eggshells, ready to break under the mildest strain.

After a trip to the medical library, Fuchs and Vassar uncovered two rare human diseases that looked much like the mouse disease: epidermolysis bullosa simplex (EBS), which involves blistering of the inner epidermal layer, and epidermolytic hyperkeratosis (EH), which manifests in the outer layers. Within a year, they had worked out the genetic basis for both EBS and EH, building on a discovery Fuchs had made as a postdoc, that as epidermal stem cells differentiate, they switch off two keratin genes, *K5* and *K14*, and switch on two others, *K1* and *K10*.

These studies established a paradigm for what are now 89 distinct genetic disorders of intermediate filament proteins. This work also led to a greater understanding of normal skin. When Fuchs moved her lab to Rockefeller in 2002, she continued to focus on skin stem cell differentiation.

Fuchs's research today looks at the signaling pathways that help a skin stem cell decide whether to become an epidermal cell or a hair follicle. For a stem cell to become a hair follicle, at the right moment, the pathway known as Wnt must be turned on, and another, known as BMP, must be switched off. In the absence of these opposing signals, the stem cell becomes skin. While such research at some point could lead to the elusive cure for baldness, Fuchs is focused on its less commercial, more profound implications for human health. She and her colleagues are now investigating the relationship between the process of stem cell activation and defects that cause cell proliferation and cancer.

MAINTAINING FOCUS

Fuchs and Hansen spend most weekends exploring New York, often ending up at one of the city's many art museums, standing for long stretches at a time in front of their favorite paintings. A few in particular at the Metropolitan Museum of Art—*Virgin and Child* by Murillo, Vermeer's *Young Woman with a Water Pitcher*—really hold their attention, as well as several Picassos at the Museum of Modern Art. "We can stand in front of a painting for an hour," Hansen told me, "and even though we've seen it dozens of times before, we see something new in it."

The same is true, it seems, of the way Fuchs looks at a skin cell—like a work of art that reveals new insights every time she studies it, no matter how many times she's looked at it before. Like Picasso in his cubist period, she continues to focus her kaleidoscopic view on familiar questions in search of surprising answers. ■

A SILVER LINING

Sure, some prions can cause diseases, but others are turning out to be beneficial.

by Richard Saltus
illustration by Deth P. Sun

EVEN THE WORST gang of rogues may reveal surprising qualities that cast them in a more favorable light. In fact, evidence is mounting that a class of proteins called prions—despite the fact that their best-known member causes a rare, deadly brain-wasting scourge in humans—can also be good citizens in the life of a cell.

In 1982, Stanley Prusiner, a biochemist at the University of California, San Francisco (UCSF), isolated the first prion as the cause of lethal scrapie in sheep. In 1997, he won a Nobel Prize for the achievement and for characterizing a mechanism for protein aggregation and self-perpetuation, or as the Nobel committee wrote, "for his discovery of prions, a new biological principle of infection."

In the intervening years, a variety of proteins with primitive self-sustaining properties have been found in yeast, fungi and bacteria, snails, flies, turtles, frogs, birds, mice, and other mammals, including cattle, sheep, deer, elk, and people. The functions of these prions are far more diverse and complex than anyone imagined.

Prions are proteins that have converted from a normal configuration to a "misfolded," self-perpetuating form that reproduces even though it lacks a genetic blueprint like DNA or RNA. Like one bad apple spoiling the barrel, the prion sets off a cascade, converting other proteins of the same kind from which it was formed into prions as well.

To be sure, some prions are nothing but bad news. That first one, termed PrPSc by Prusiner, forms toxic amyloids, abnormal proteins that aggregate to form tough, fibrous deposits in cells. Amyloids spread through the brain and spinal cord, decimating nerve cells in animals and humans.

A string of recent findings, however, shows that some prions can serve beneficial functions—among them: helping maintain long-term memories in snails, mice, and fruit flies; fast-forwarding evolution in yeast to equip them with survival traits; aiding synthesis of the pigment melanin in mammals; forming biofilms that give adhesive properties to bacteria; and storing hormones inside endocrine cells.

"The disease prions are just a minor idiosyncrasy," says HHMI investigator Susan Lindquist, a leading researcher on protein folding and prions at the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology. "Prions are a really deeply rooted part of normal biology."

She developed this silver-lining view of prions back when most scientists saw nothing but their destructive side. In a review written in 1997, Lindquist wrote: "My contention is that yeast and mammalian prions are not oddities in a biological freak show, but actors in a larger production now playing in a theater near you."

That prediction is being borne out by a stream of discoveries from her Whitehead laboratory and others in the United States and abroad. "The real excitement now is to determine how widespread this biology is," Lindquist says.

THE GOOD GUYS

The first hint that prions might be advantageous in multicellular organisms came in 2003 in a series of studies in the giant marine snail *Aplysia californica*. A major question in brain research is how memories are stored. Research in *Aplysia* had shown that memories are stored at specific nerve synapses that undergo long-term strengthening that lasts as long as the memory lasts. In the first of two papers published in *Cell* in 2003, HHMI investigator and neuroscientist Eric Kandel at Columbia University, and his former postdoc, Kausik Si, now at the Stowers Institute for Medical Research, found that the long-term maintenance of this process at nerve synapses requires continuous production of proteins, which is regulated by a protein called CPEB.

But how did CPEB keep this process going? Si noticed that one end of CPEB resembles the prion domain found in yeast prions. He suggested that the protein could convert to a self-perpetuating form that was distinctively prion-like. He and Kandel wondered if, when stimulated repeatedly (as in learning), the CPEB in synapses could become a self-sustaining protein that spurs the ongoing translation of messenger RNA (mRNA) into memory.

"In principle, this could be how you remember things for the rest of your life," says Kandel.

To test this idea Kandel and Si joined forces with Lindquist. In the second 2003 *Cell* paper, they observed that CPEB proteins from the *Aplysia*, when inserted into yeast, formed self-perpetuating units. In a follow-up paper in *Cell* in February 2010, Si and Kandel showed the same in *Aplysia*'s own sensory neurons:

Evidence that prions have been conserved over long periods of time suggests to Jonathan Weissman that some proteins can form beneficial prions.

CPEB acts like a self-sustaining prion and the prion form is essential for maintaining the synaptic strengthening that forms a memory.

Si is working on the *Aplysia* CPEB homolog in the fruit fly and is using the model system to probe the role of prion-like features in learning and memory. Kandel's lab group has found a homolog of *Aplysia* and fly CPEB in mice. A homolog of CPEB also exists in humans.

Most prion studies have been in the fast-growing yeast *Saccharomyces cerevisiae*, which yielded the first clues to the potential benefits of some prions. In 1994, Reed Wickner of the National Institutes of Health reported that certain yeast proteins could exist in a normal form and a misfolded prion form. A case in point, the protein known as Sup35p can switch back and forth between a normal and a prion version—PSI+ and psi–. The PSI+ form is self-replicating and forms fibrous amyloids, just as in mammals.

Lindquist entered the field around the time that Wickner published his landmark observations. She was working on a "heat-shock" protein, Hsp104, which, she showed in a 1998 paper, helps yeast adapt to changes in temperature by dissolving aggregated proteins. She and others observed that Hsp104 plays an essential role in the maintenance of yeast prions.

"Later, my lab reported that PSI+ was an 'evolvability factor' that had a beneficial effect in allowing cells to try out genetic variation hidden in their genome," Lindquist says.

"When the proteins switch into the prion state, their function is switched," Lindquist explains. "They change the pattern of gene expression in the cell, and we think that this provides immediate new biological states that are potentially beneficial and could help the organism to evolve more quickly."

When the yeast is suddenly confronted with changing conditions, says Lindquist, the organism doesn't switch the whole colony to prions. Just a small number of cells make the conversion—turning on previously silent genes to test the waters, so to speak. "We think of this as a 'bet-hedging' strategy," she explains. The more stress the yeast is under, the more likely its proteins will misfold and become prions—"like gamblers who put money on more numbers on a roulette wheel."

For example, Lindquist explains, if a grape dusted with yeast falls from the vine and into a puddle, the yeast is now in a drastically different environment. Various prions in the waterlogged yeast cells will switch from inactive to active, or active to inactive, to ensure that some of the cells survive underwater. Some of those activation switches help the yeast, but some do not.

Jonathan Weissman, an HHMI investigator at UCSF, has studied survival functions of the PSI+ prion independently and also in collaboration with Lindquist. He agrees that, while the PrPSc is almost certainly toxic, "that doesn't mean that other proteins can't form prions that are beneficial,"—especially because, as he has shown, they have been conserved in microorganisms for hundreds of thousands of years.

Lindquist and colleagues reported in *Cell* in 2009 that they had surveyed the yeast genome and uncovered 19 proteins that have prion states. The collection of new phenotypes that can be selected by prion switching potentially helps the yeast adapt to environmental variables such as salt concentration, oxidative stress, and changes in carbon sources.

The results reinforce Lindquist's suggestion that prions may have evolved through the selective pressure of stress.

"I think the prion principle is a wonderful way to distribute information in a non-genetic way," says Adriano Aguzzi, a prion expert at the University Hospital of Zurich in Switzerland, who credits Lindquist with building a convincing argument that the prion phenomenon is an alternate evolutionary pathway.

Lenny Gonzalez

Susan Lindquist, Eric Kandel, and colleagues have collaborated to show that proteins involved in normal cell processes can convert to a self-perpetuating, prion-like form to maintain memory, for example.

Lindquist: Cheryl Senter / AP, ©HHMI Kandel: Matthew Septimus

A KILLER INTRODUCTION

The 1982 discovery of prions by Stanley Prusiner, a biochemist at UCSF, was a stunning answer to a longstanding and stubborn problem: what was the mysterious agent responsible for transmissible spongiform encephalopathies (TSEs)—progressive, incurable, and lethal diseases that destroy nerve cells and leave a sponge-like trail of destruction?

The earliest known TSE was scrapie, an affliction of sheep. Other TSEs now known to be prion diseases are bovine spongiform encephalopathy (BSE, or mad cow disease) and some very rare but lethal neurodegenerative diseases in humans, including Creutzfeldt–Jakob disease (CJD), variant CJD, kuru, and familial fatal insomnia. These diseases have incubation periods measured in years.

The BSE epidemic of the 1980s and early 1990s killed 170,000 head of cattle and led to the slaughter of more than 4 million cows, mostly in England, before it subsided. During this epidemic, a form of BSE called variant CJD spread to humans who ate meat products from the infected herds. Mad cow disease killed about 200 people.

Scientists had determined that the agent carrying scrapie was very small and extremely hardy: it couldn't be inactivated by heat, ultraviolet radiation, or denaturing, which would destroy any genetic material used in reproduction.

Prusiner reported that the cause of scrapie was a novel infectious particle, which he dubbed a "prion," consisting solely of misfolded proteins, devoid of genetic material. This was hard to swallow for many scientists, since even the smallest bacteria and viruses have some genetically encoded instructions for replication.

For years afterward, some skeptics rejected the "protein-only" model of prions, arguing that they must contain *some* genetic material that had escaped detection. A strong refutation of that view came in 2000 when Weissman at UCSF reported that he had created synthetic prions in a test tube directly from a pure yeast protein, Sup35.

To understand what makes a prion, recall that cells manufacture proteins by assembling chains of amino acids according to a "recipe" contained in a specific gene. Then the protein folds into a three-dimensional configuration like a complex piece of origami. If for any reason the protein fails to fold correctly, it may not work at all, or its function may be different from what was specified.

PrPSc, the scrapie prion isolated by Prusiner, is a misfolded form of a naturally occurring cell-membrane protein, PrP, which is expressed in nerve tissue and elsewhere in healthy people and many animals.

REASON FOR BEING

Researchers have spent many years in a frustrating hunt for the function of the normal PrP protein. Surely this protein must have some other reason for being than to form lethal prions. Studies showed that mice in which the PrP protein was "knocked out" were resistant to infection with the misfolded PrPSc prions. Otherwise, lacking the PrP protein seemed to have little effect.

A piece of the puzzle seems to have fallen into place. Aguzzi and other scientists reported in January 2010 in *Nature Neuroscience* that the protein helps maintain the myelin sheaths that surround and protect neurons in the peripheral nervous system. In mice engineered to lack PrP, peripheral nerves suffered progressive damage as a result of demyelination. Aguzzi said in an interview in the journal that he suspects PrP plays a similar role in higher mammals.

The finding may also bear on another longstanding enigma: are prion diseases caused by a "gain-of-function" process—the misfolded protein itself damages nerve cells—or a "loss-of-function"

change, in which conversion of the normal protein to prions robs the nerves of something they need to stay healthy?

Outside the nervous system, another hint of PrP's normal function came in a 2006 report from the Lindquist lab. The scientists found that expression of the protein in stem cells is necessary for the self-renewal of blood-manufacturing tissues in bone marrow. The study showed that all long-term hematopoietic stem cells express PrP on their surfaces and that blood-forming tissues lacking PrP in stem cells exhibited increased sensitivity to cell depletion.

STRUCTURE AS BLUEPRINT

HHMI scientists have begun to decipher another prion riddle—the existence of distinct "strains" of prions that produce different phenotypes. For example, the PrPSc prion causes several distinct neurological diseases in animals and humans. Each disease is slightly different in the length of its incubation period, the typical symptoms, and the areas of the brain that are damaged.

"This was one of the most intriguing and challenging questions," explains Weissman. In viruses or bacteria, strain differences are specified by instructions in their genetic code. If prions lacked any genetic material at all, where were the blueprints that determine strains?

Weissman carried out a series of experiments demonstrating that prions could propagate as distinct strains, each specified by different arrangements of atoms in the protein's structure. The structural configuration of a prion strain *was* the blueprint for making more copies—no DNA required.

Using the powerful yeast system, Weissman and colleagues created synthetic prions with different configurations that generated phenotypically diverse strains. In another experiment, they analyzed two distinct strains of the yeast protein Sup35, one of which was strongly infectious and the other weakly infectious.

The analysis required a special application of nuclear magnetic resonance spectroscopy, which enabled him to identify structural differences at the atomic level underlying these different phenotypes. The results, published in *Nature* in 2007, confirmed that the same protein can misfold into dramatically different prion conformations—which is why the phenotypes they produce can vary so significantly.

Some of the newest prion work takes a deeper look at multiple strains. The goal is to figure out how the amino acid sequence of a prion determines its configuration and how the resulting structures differ at the atomic level.

HHMI investigator David Eisenberg, a protein structure specialist at the University of California, Los Angeles, uses various types of x-ray crystallography techniques to study the structure of the amyloid proteins produced by prions.

In 2005, Eisenberg showed that when a protein converts to a prion, it polymerizes into an aggregate made up of tightly packed layers known as beta sheets (as opposed to the coiled alpha helices that dominate in the normal protein structure). The firmly bound beta sheets, held together by an interlocking of their side chains that Eisenberg has termed a "steric zipper," give the prion its stable, tough properties. In fact, the sheets are so closely packed that they exclude water, making prions insoluble.

In a 2009 paper in *Nature Structural & Molecular Biology*, Eisenberg proposed an explanation of how a single protein gives rise to varying shapes of amyloids that specify different strains. Instead of DNA alterations, as in living organisms, prion strains are specified by structural changes that are sufficiently stable to perpetuate the strain identity in successive prions—and when they jump from cell to cell and animal to animal.

In one type of strain-determining mechanism, the same segment of a protein's amino acid sequence can specify different "packing" arrangements of the beta sheets. In an alternative mechanism, distinctive beta sheets are produced by different segments of the protein.

"Our hypothesis is that the differences in packing produce diverse amyloid fibrils, and these fibers cause different disease types," says Eisenberg.

In fact, these variations that Eisenberg is finding at the most fundamental, atomic level may come full circle to explain the array of functions—some harmful, some helpful—found in prions ranging from yeast to humans.

Meanwhile, he and other scientists, including Si, Kandel, and Lindquist, are searching for evidence of the positive side of prions.

If that search is fruitful, Si has a radical proposal: "Prions have been so tightly linked to the diseases that if we find more of these positive functions, I think eventually we might have to come up with a new name for them." ■

BY RANDY BARRETT
ILLUSTRATION BY MIKE PERRY

THE LICON RAVEL

THE NEW JANELIA COMPUTING CLUSTER PUTS A PREMIUM ON EXPANDABILITY AND SPEED.

Computational biologists have a need for speed. The computing cluster at HHMI's Janelia Farm Research Campus delivers the performance they require—at a mind-boggling 36 trillion operations per second.

In the course of their work, Janelia researchers generate millions of digitized images and gigabytes of data files, and they run algorithms daily that demand robust computational horsepower. Geneticists, molecular biologists, biophysicists, physiologists, and even electrical engineers pursue some of the most challenging problems in neuroscience, chief among them how individual neuronal circuits process information. Their discoveries depend, now more than ever, on the seamless interplay of scientists and computers.

Humming nonstop in Janelia's compact computing center are 4,000 processors, 500 servers, and storage machines holding half a petabyte of data—about 50 Libraries of Congress worth of information.

Though there are many larger clusters around the world, this particular one is just right for Janelia Farm. "Beautifully conceived, ruthlessly efficient, and extraordinarily well run by the high-performance computing team," according to Janelia researcher Sean Eddy, the system is designed to make digital images available lightning fast while muscling through the monster calculations required to help investigators conduct genome searches and catalog the inner workings and structures of the brain.

FASTER ANSWERS

A group leader at Janelia Farm, Eddy deals in the realm of millions of computations daily as he compares sequences of DNA. He is a rare breed, both biologist and code jockey. "I'm asking biological questions, and designing technologies for other people to ask biological questions," he says.

Eddy writes algorithms to help researchers extract information from DNA sequences. It's a gargantuan matching game where a biological sequence—DNA, RNA, or protein—is treated as a string of letters and compared with other sequences. "From a computer science standpoint, it's similar to voice recognition and data mining," he says. "You're comparing one piece against another. We look for a signal in what looks like random noise."

Eddy looks for the hand of evolution in DNA by comparing different organisms' genomes. He's searching for strings of DNA sequences that match—more than random chance would dictate.

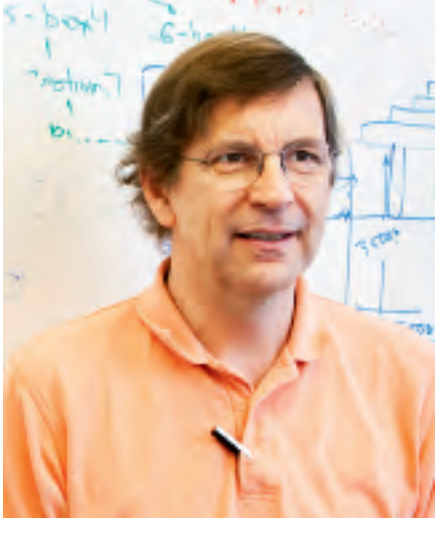
"It's a lot like recognizing words from different languages that have a common ancestry, thus probably the same meaning," he explains. "In two closely related languages—Italian and Spanish, for example—it's pretty obvious to anyone which words are basically the same. That would be like two genes from humans and apes."

But in organisms that are more divergent, Eddy needs to understand how DNA sequences tend to change over time. "And it becomes a difficult specialty, with serious statistical analysis," he says.

From a computational standpoint, that means churning through a lot of operations. Comparing two typical-sized protein sequences, to take a simple example, would require a whopping 10^{200} operations. Classic algorithms, available since the 1960s, can trim that search to 160,000 computations—a task that would take only a millisecond or so on any modern processor. But in the genome business, people routinely do enormous numbers of these sequence comparisons—trillions and trillions of them. These "routine" calculations could take years if they had to be done on a single computer.

That's where the Janelia cluster comes in. Because a different part of the workload can easily be doled out to each of its 4,000 processors, researchers can get their answers 4,000 times faster—in hours instead of years. The solutions don't tend to lead to eureka moments; rather, they provide reference data for genome researchers as they delve into the complexities of different organisms. "These computational tools are infrastructural, a foundation for many things," Eddy says.

While that may not sound dramatic, Eddy's protein-matching algorithms are an industry standard, used by researchers as the search tool for a reference library called the Protein Families database, or Pfam. There are roughly 10 million proteins in the database. Luckily about 80 percent of those sequences fall into a much smaller set of families and Eddy has designed the analysis software to query for matches in this data set. "When a new



Paul Vetters

sequence comes in, [Pfam] is like a dictionary—it's always being added to," he says. The database currently identifies 12,000 protein families.

There is also an RNA database called Rfam for which Eddy and his Janelia team have software design and upkeep responsibilities. Eddy has to keep one step ahead of his users, which means stressing his analysis tools to the failure point so he can improve them.

"We set up experiments and try to break the software and push the envelope," he says.

A MOSAIC OF FLY NEURONS

The Janelia computing system is referred to as a "cluster" of processors by both its overseers and its users. The cluster serves 350 researchers and support staff and can scale up to serve many more if requirements demand it. Its design puts a premium on expandability, flexibility, and fast response, particularly since the scientific needs may change and evolve rapidly.

The computer cluster was recently upgraded as part of a regular four-year technology refresh. Made up of commercially available hardware components built by Intel, Dell, and Arista Networks, Eddy calls the system a "working class supercomputer." Janelia is the first customer for this particular design—in fact, some of the components have serial number 1 or 2 and are signed by the engineers who built them. The new system is up to 10 times faster than the old one and has six times more memory.

"Janelia's new computing cluster provides a platform that is an order of magnitude more responsive than the previous system and can be grown easily to accom-

TOP: Roian Egnor
MIDDLE: Sean Eddy
BOTTOM: Elena Rivas, Lou Sheffer

modate changing requirements," says Vijay Samalam, Janelia's director of information technology and scientific computing.

That expanded capacity is a big help to Janelia fellow Louis Scheffer, an electrical engineer and chip designer by training. He uses the cluster to help researchers map the brain wiring of the common fruit fly *Drosophila melanogaster*. Essentially, it's a massive three-dimensional image-manipulation challenge. First, slices of brain 1/1,000th the thickness of a human hair are digitally photographed with an electron microscope and stored. In each layer, the computer assigns colors to the neurons so researchers can trace their path. As an example, the medulla of the fly, part of the brain responsible for vision, requires more than 150,000 individual images to create the full mosaic, which is 1,700 layers (slices) deep.

But all these pictures must be knitted together so scientists can follow neural paths and see where they lead. Think Google Earth. As you pan across the globe, data are fed onto the screen so you can "fly" from one location to another, and more images are required as you drill down to examine surface topography. Making the transitions smooth in between images requires fine-tuned alignment. "It's not completely simple—there are a whole bunch of distortions to deal with," says Scheffer. Some are caused by the electron microscope itself as it dries out the target specimen during imaging.

To align one image to its neighbor takes about one minute of computer time. But once matched, the resulting checkerboard must be stacked and aligned with the mosaic of images above and below. "You need to make about one million comparisons," Scheffer says. "It would take [a personal] computer four years." With Janelia's parallel processors on the task, the job is done in a few hours.

But Scheffer's matching is just the first step in the image-manipulation process. Janelia software engineer Philip Winston takes the processed pictures and does the unthinkable—he chops them up again. He creates smaller "tiles" of the photos, which can be more easily added and subtracted from a computer screen as a researcher pans across an image. "To open a single image would take five minutes if you didn't tile them," says Winston. Only 20 tiles are required on the screen at any one time. Currently, Winston is working with four million tiles as part of the Janelia Fly Electron Microscope project to map the entire brain of the fruit fly.

Humans proofread the final fly-brain image for accuracy, to trace the neural paths and make sure the computer has identified structures correctly. "[People] are an important step," says Winston. "Without them, the computer segmentation would be 95 percent right and we wouldn't know about the other 5 percent."

Scheffer and Winston's ultimate goal is to completely automate the mapping process and to teach the computer to identify the inner structures of the fruit fly brain, in particular the different types of neurons, and the axons and dendrites branching out from them. "To do the whole fly brain we have to improve the automated segmentation," says Winston. Scheffer hopes to achieve the computer-generated—and accurate—mapping of the brain within the next five years as more pieces are imaged and processed.

EASIER COMMUNICATIONS

The increased speed of the new computing system will make that effort easier going forward. The cluster is faster than its predecessor for two reasons: it has more than four times as many individual processors, and it's using a networking technology that speeds up the communication between processors. Those familiar with office networks know it well: Ethernet, the popular standard for moving electronic data from point A to B. While it has been a long-standing protocol for slower connections, 10-gigabit Ethernet has not traditionally been the choice of makers and engineers of top supercomputers who until recently, when best performance was a must, used specialized networking technology called InfiniBand.

"Now Ethernet switches are as efficient as, or very close to, InfiniBand and you don't need a different [networking] skill set," says Spartaco Cicerchia, manager of network infrastructure at Janelia Farm. The bottom-line advantage is that Ethernet is easier to work with, familiar to more networking engineers, and tends to be cheaper to use.

Lower latency—the time it takes to move data across a network connection—is now possible via Ethernet due to a relatively new networking standard called iWarp. Traditionally, computers' processors must manage the flow of information packets as they pass between them. In the new systems, those packets are handled by a separate piece of hardware made by the chip manufacturer Intel.

"Traditionally, [central processing units handle] network packets. However, when network interface speeds went from 1 to 10 gigabits per second, the load on CPUs increased by an order of magnitude," says Goran Ceric, Janelia's manager of scientific computing systems.

The creation of iWarp helped alleviate this issue and reduce latency and overhead. iWarp helps in three ways, according to Ceric: by processing network packets using specialized hardware instead of CPUs; by placing data directly into application buffers, thus eliminating intermediate packet copies; and by reducing a need for "context switching,"

Janelia's IT team—Vijay Samalam, Spartaco Cicerchia, and Goran Ceric—recently updated its computing cluster, building it from commercially available hardware components by Intel, Dell, and Arista Networks, and using popular and now faster Ethernet networking.

Paul Fetters

in which a processor must pass commands back and forth between an application and an operating system. "For many parallel applications," he says, "if you can lower communications time between processors in different systems over the network, the better your performance is."

The new network infrastructure has dropped the communications lag inside the Janelia cluster from 60 to 10 microseconds—a sixfold improvement.

MOUSE TALK

Janelia Farm fellow Roian Egnor isn't a computer scientist or network engineer, but her research on the vocalizations of mice (and the neural pathways required) depends partly on heavy computation power. Though famed for their quiet ways, it turns out mice are chatterboxes. All their communications, unfortunately, happen at frequencies between 30 and 100 kilohertz, far above the range of human hearing.

"There's a secret world up there," says Egnor, who records hours of mouse talk daily. "If you take those vocalizations and computationally lower frequencies, they sound remarkably like bird songs."

Egnor is trying to better understand the elements of these mouse whispers. "When you look at mouse vocalizations, there appears to be some acoustic structure to them. What is it for?" she says.

To find out, she is collaborating with another Janelia fellow, Elena Rivas, who is starting to process the communications using a statistical analysis tool called a hidden Markov model. The software is similar to that which Sean Eddy uses to compare millions of DNA strands.

"The cool thing about hidden Markov models is, you can tell them 'Look, here's what I think are good examples of what I want you to characterize. Learn them, and then I'm going to give you unlabeled vocalizations and I want you to see which match and which don't,'" Egnor says.

Rivas has reworked a standard protein analysis program called HMMER3 to handle Egnor's data, which comes in one-terabyte chunks. "The core of the programs is identical," Rivas says. "We're going to try to determine the types of [mouse] vocalizations and try to model each one."

Once those models, or "families," are delineated, researchers can then test new mouse vocalizations against these templates. "Then we'll try to catalog everything the mouse says," Rivas explains. The analysis takes the computing cluster only a few moments to run.

"The beautiful thing about Janelia is that I stream that [information] to the data share, and Elena picks it up and starts working on it," Egnor says.

Making that transfer possible is another hidden attribute of the Janelia research complex—its internal network. It's the pipeline that carries huge image or auditory files without clogging or slowing down the system. In the startup phase, that meant overbuilding the fiber infrastructure as much as possible and designing it to handle unpredictable loads through 10-gigabit ports. Janelia's network is fully

(continued on page 48)

Joseph P. Noel

PEERING BACK IN TIME

John Dole

Joseph P. Noel wants to use paleontology to learn how plants endured history's harsh climates—and how to ready crops to face severe conditions in the future. Protecting the world's food supply by borrowing from plants of the past is a natural solution that should appeal to the public, says the HHMI investigator at the Salk Institute for Biological Studies.

Most people are familiar with biodiversity. But "chemodiversity"—the tapestry of natural chemicals found in plants—is just as important for life, the appearance of new species, and the survival of many different ecosystems. More than any other organism, plants produce hundreds of thousands of different kinds of chemicals. They use unique chemical cocktails to protect themselves from the elements, battle infections, and attract pollinators, among many other things.

People have long exploited plant chemicals—as medicines, for example. With modern tools to compare genes and enzymes from diverse organisms, we are now in a position to understand the natural history of plant chemical systems—much like a paleontologist but at a molecular level. Evolution teaches us how plants responded to threats such as climate change in the past and how we can speed up their adaptation today.

The importance of plant chemicals to animals, and ultimately people, goes all the way back to the Cambrian explosion. Approximately 500 million years ago, animal life underwent a large evolutionary expansion. That event was very likely predated by plants moving from water to land. Plants provided food for the newly arriving animals. If plants hadn't migrated onto land, you and I wouldn't be here.

These early land plants needed protection from the sun's damaging UV rays. When ancestors of these early plants lived in water, the water absorbed most of the UV rays. To live on dry land, however, plants needed sunscreens. The sunscreen molecules they likely used looked much like modern plant chemicals called flavonoids. In today's plants, flavonoids play a number of roles: they are very effective at absorbing UV radiation, and they are responsible for the colors of flowers.

Different species of plants make unique, but similar, chemicals using similar enzymes. By comparing the few genetic differences between closely related enzymes, we can envision the "ancestor enzyme" that these cousins evolved from. Studying this "old" enzyme in the lab, we learn what chemicals it likely made. In essence, we reanimate these molecular fossils to peer back in time.

In my lab, we have used this technique to discover that the enzymes that make flavonoids are very similar to the enzymes that make fatty acids in all organisms. Modern plant ancestors, by a fluke of evolution, coopted the enzymes that make fatty acids, changed them incrementally, and began making sunscreens.

Some plants have evolved those enzymes further to make a flavonoid-like molecule called resveratrol. This molecule, found in red wine, has received plenty of positive publicity over its anti-aging and cholesterol-lowering properties in animals. The grapevine makes resveratrol to defend against fungal infections. After generations of breeding for grape quality, however, some modern grapevines have lost the ability to make resveratrol as efficiently as their ancestors. To get the same level of protection that resveratrol could provide, wineries have to use artificial fungicides, which can damage the environment.

To make the grapevines naturally fungus resistant again, growers could try to restore resveratrol biosynthesis through breeding, a slow process. I suggest, instead, that scientists could use genetic engineering to quickly and precisely return the right enzyme to the grapevine. This kind of pinpoint engineering, based on what nature has already explored, would allow scientists to take a shortcut to engineer crop plants.

We could also use this technique to engineer plants to withstand climate change. History repeats itself: in past eras, carbon dioxide concentrations on Earth were 10 times higher than they are now, and most of the planet was a hot, wet environment. With collaborators, I hope to re-create ancestor enzymes from these time periods and discover what kinds of chemicals helped them thrive in high temperatures. We can apply the same genetic changes to speed up plant adaptation to climate change today.

Genetic manipulation of plants remains controversial; people worry about unintended consequences of moving a gene from one organism into another. But that's not what we're doing here. We want to restore an ability—thriving in a warmer, carbon-dioxide-rich climate—that the ancestors of modern plants once had. While the plants would be transgenic, we would use the plants' own genes, not genes borrowed from other organisms. I think the public will likely approve of this more natural approach.

INTERVIEW BY AMBER DANCE. *Joe Noel is the director of the Jack H. Skirball Center for Chemical Biology and Proteomics at the Salk Institute.*

Q&A

If you were to take a year off to "change the world," what would you aim to do?

Great scientists possess creativity and analytic skills that can be applied to problems outside their laboratories. In the online edition of this Bulletin, *Patrick O. Brown explains why he's trimming back his academic responsibilities for a year so he can make a difference for the planet. Here, other scientists ponder what they might do with a free year.*

—EDITED BY SARAH C.P. WILLIAMS

Richard H. Ebright

HHMI INVESTIGATOR
RUTGERS, THE STATE UNIVERSITY OF NEW JERSEY

"I would run for the United States Senate. Our country faces educational, economic, and environmental crises that threaten its preeminence and possibly even its survival. There is a dearth of persons in the Senate with the ability to process and interpret the quantitative information needed to recognize and address these crises.

Alternatively, I would restore coral reefs by transplanting artificially propagated corals. Over a one-year period, I would be able to plant 5,000–10,000 coral plugs and cover an acre of seabed. This would be a small part of the world, but it would be a start."

Maria Spies

HHMI EARLY CAREER SCIENTIST
UNIVERSITY OF ILLINOIS AT URBANA–CHAMPAIGN

"I would most certainly pass up this opportunity—a year is too short to 'change the world' for better, even if the offer comes with a superhero cape. People in my line of work are already in a privileged position to make a positive impact. With every scientific mystery we solve, with every young researcher trained, with every student taking something away from our lectures, we make the world, if not a better place, at least a more enlightened one. I believe I am in exactly the right place to make incremental but lasting contributions to the world."

L. René García

HHMI INVESTIGATOR
TEXAS A&M UNIVERSITY

"I would spend the year traveling areas of the world that are experiencing social and educational problems, both to share my own expertise with the people there and to learn from them. I would coordinate the trip with a traveling hands-on science exhibition, so people could play with simple microscopes, telescopes, and other scientific tools to explore their environment. Through my travels, my goal would be to observe the differences and similarities between the various regions' troubles. At the end, I would contemplate what I had learned and then decide future activities to promote more lasting changes."

Susana López

HHMI INTERNATIONAL RESEARCH SCHOLAR
INSTITUTE OF BIOTECHNOLOGY, NATIONAL AUTONOMOUS UNIVERSITY OF MEXICO

"I would invest that year in convincing people who make enormous amounts of money (TV and movie stars, singers, athletes, etc.) to donate just a small part of their earnings to make a well-administered foundation, with the sole purpose of ensuring that every child in underdeveloped countries has access to all available vaccines, independent of their cost, and to guarantee that these children are nourished properly during the first five years of their lives. This would help give a fair start in life to the people born in underdeveloped nations."

Ebright: Jennifer Altman Spies: L. Brian Stauffer / UIUC News Bureau García: Michael Stravato / AP, ©HHMI López: David Rolls

chronicle

Specific areas of a mouse brain are visible with a new molecular tool developed by HHMI scientists. Here, fluorescence reveals which neurons in a mouse's brain are involved in whisker movement and tactile sensation. Visit www.hhmi.org/bulletin/may2010 to read about the brain-illuminating tool.

Longer Lab

The Heart of a Snake

AN UNUSUAL MODEL ORGANISM IS OFFERING INSIGHT INTO CARDIAC PHYSIOLOGY—AND ATTRACTING STUDENTS TO RESEARCH.

YOU WANT TO STUDY EXTREME BIOLOGY? CHECK OUT THE PYTHON. These snakes can go a full year without food, and, once they do score a meal, their heart and liver nearly double in size. HHMI professor Leslie Leinwand's animal model of choice has turned out to be a great way to lure upper class students into hands-on biology.

Because python organs undergo such a dramatic response to feeding, they make an ideal study organism for Leinwand, who is interested in understanding how the genetic landscape of the mammalian heart shifts during feeding, exercise, pregnancy, and disease.

Leinwand, at the University of Colorado, Boulder, had been studying heart biology in mammals, including humans, for 15 years when her research took an unexpected turn. In 2006, she came across an article by reptile physiologist Jared Diamond exhorting researchers to think beyond typical model organisms and study animals with more "extreme" physiology.

Diamond was studying Burmese pythons, which can survive in the wild through these year-long fasts. Their heart and liver balloon after a long-awaited meal; then, within a few days, the organs revert to fasting size. Leinwand was intrigued that pythons thrive under physiological conditions that would be toxic to humans.

"Not only are they not sick [during fasting], they don't even lose muscle by virtue of not taking in nutrition," Leinwand says. "I read this article and said to myself, 'this is the coolest thing. I'm going to work on this.'"

So four years ago, Leinwand placed an order for Burmese pythons. Soon, a gaggle of baby pythons arrived, writhing and tangled inside a pillowcase and packed in a Styrofoam box. "People in my lab thought I had lost my mind," Leinwand remembers.

But she had a hunch her undergrads would think it was as cool as she did. With an HHMI grant, Leinwand developed a course that included a lecture program—"From Bench to Bedside: The Role of Science in Medicine"—and a lab-based class called the "Python Project." The course gives students a chance to learn fundamental molecular biology techniques and make discoveries about python biology.

Brett Ryder

Because of the novelty of working with snakes, and the fact that almost nothing is known about the genetics and molecular biology of pythons, she thought it would create an ideal learning opportunity.

The snakes are housed in a balmy room in the basement of the psychology department. Leinwand's laboratory assistant, Chris Wall, reaches into one of the bins with a gloved hand and deftly retrieves a dappled chocolate brown and tan Burmese python and drops it onto a scale. This 210-gram snake is nowhere near as intimidating as the 20-foot-long, 200-pound specimens that grow in the wild. Burmese pythons are really quite docile, Wall explains, though they can be testy when hungry.

Back in the classroom laboratory, 16 students look on as Wall makes a smooth incision along the length of the euthanized snake's glossy, muscular underbelly, explaining that snake organs are quite similar to humans', only greatly elongated. The young snake hasn't eaten in a month, so the tissues the class collects today will yield genetic information about its fasting condition. "So, pythons have no venom sac?" one student asks. "Nope, they just kill by constriction," says Wall. "They're actually really strong, and you'll see that the entire body, outside of the internal cavity here, is solid muscle."

Wall took Leinwand's course in the spring of 2008 and joined her research group immediately afterward. He has been accepted into a Ph.D. program in biomedical sciences at the University of California, San Diego, and says that Leinwand's course cemented his interest in becoming a researcher.

This semester, the students in Leinwand's lab are analyzing gene expression in a set of python genes that control liver proliferation. They huddle in small groups around their lab benches, painstakingly inspecting agarose gels containing amplified DNA samples from polymerase chain reactions they performed earlier that week. The gels separate DNA fragments by size, allowing the students to compare their amplified product against a standard of known size and identity. Next they will work with RNA derived directly from the python's liver tissue.

Several groups exclaim that they have successfully obtained the DNA product they were after. Kaisa Wallace-Moyer, a junior majoring in chemical and biological engineering, says she enjoys the ownership that comes with running experiments that don't have a predictable outcome. "It's just really cool knowing I get to come in here and do my own experiment," she says.

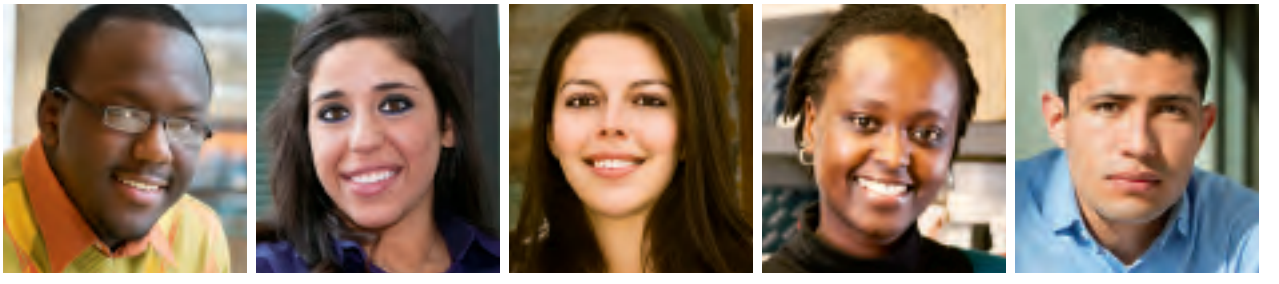
Senior Ashley Crary agrees that the hands-on experience is critical to learning the techniques. "It's scary but also exciting that we're actually practicing what we say we want to grow up and do."

Leinwand compares the python's dramatic heart enlargement after a meal to the beneficial heart enlargement that occurs in highly trained athletes. "If we can understand how the python does this over and over again throughout its life, it could lead to therapeutics that could promote improved cardiovascular health," she says.

She hopes the students' work will help paint a complete picture of the expression patterns of these python genes during the extreme metabolic shifts before and after feeding. But it's not just the experimental results that Leinwand is after. "My main goal is not the outcomes from the students' experiments," she says. "If they learn to be excited about research and to think scientifically, that would be a success. If great results are a by-product, all the better." ■

–AMANDA MASCARELLI

2010 GILLIAM FELLOWS



After his grandmother died of liver cancer, Flavian D. Brown decided to devote his career to cancer research. Rachel A. Johnston's childhood obsession with breeding guppies started her down the path to becoming a population geneticist. They are just two of the five exceptional students who received HHMI's 2010 Gilliam Fellowships for Advanced Study. Since 2005, Gilliam fellowships have helped 30 students go to graduate school. Gilliam fellows come from groups traditionally underrepresented in the sciences and are former participants in the Institute's Exceptional Research Opportunities Program. Each fellow receives $44,000 in graduate school support annually for up to five years. The 2010 fellows are (from left) Brown, Mariam El-Ashmawy, Johnston, Silvia N. Kariuki, and Lisandro Maya-Ramos.

Brown: Tom Roster El-Ashmawy: Amy Gutierrez Johnston: Ken Stinnett Kariuki: Mark Segal Maya-Ramos: Mark Harmel

Lummis Elected HHMI Trustee

FRED R. LUMMIS, A HOUSTON BUSINESSMAN AND ENTREPRENEUR, has been elected a Trustee of HHMI. He becomes one of 11 Trustees of the Institute.

Lummis, 56, is Chairman and Chief Executive Officer of Platform Partners LLC, a Houston, Texas-based investment company that he cofounded in 2006. Before founding Platform Partners, he managed private equity investments for two successor firms, The CapStreet Group and Summit Capital.

Lummis began his business career at Texas Commerce Bank in 1978 and ultimately managed a venture capital portfolio for the bank before becoming senior vice president of the private investment firm of Duncan, Cook & Co. in 1986. From 1994 to 1998, Lummis served as Chairman, President, Chief Executive Officer, and a director, until 2008, for American Tower Corporation—today the largest independent operator and owner of telecommunications towers in the world. In 1998, he took over Advantage Outdoor Co. and managed its operations until it merged with Lamar Advertising Co. in 2000.

A trustee of Baylor College of Medicine in Houston since 1996, Lummis also serves as Chairman of Cardtronics and a director of Landmark FBO, TRE Financial Services, Avalon Advisors, and Amegy Bancorporation. He is a cum laude graduate of Vanderbilt University, in Nashville, Tennessee, where he captained the men's tennis team. He received his M.B.A. from the University of Texas at Austin. He and Claudia, his wife of 33 years, have three grown sons.

Lummis and his family have a long association with HHMI. His father, William R. Lummis, served as a charter Trustee of the Institute for more than two decades, until he retired in 2007. The elder Lummis played a critical role in reorganizing the Institute following the death of Howard R. Hughes, Jr., the Institute's founder and Lummis's cousin. ■

Jibrell Selected as Vice President of Information Technology

MOHAMOUD JIBRELL, AN expert in global information technology (IT), has been named HHMI's next Vice President of Information Technology. Jibrell joined the Institute in March 2010, after a seven-year tenure at the Ford Foundation.

"Mohamoud brings a wealth of experience to HHMI as a leader in information technology within the nonprofit sector," says Robert Tjian, president of HHMI. "He brings vision, as well as a demonstrated ability to collaborate effectively across a distributed organization."

At the Ford Foundation in New York, Jibrell served as chief technology officer, overseeing IT operations in 13 locations. He led major initiatives to streamline the foundation's IT operations and was involved in developing and implementing new enterprise-wide systems to support its worldwide grant-making activities. These efforts included implementing a strategic plan, integrating global IT infrastructure, and consolidating application systems into a single facility.

As chief information officer and director of information technology for the Washington, D.C.-based American Psychiatric Association (APA) from 2001 to 2002, Jibrell led a major realignment of the systems that support the APA's publishing and other activities. He also has extensive experience in the manufacturing sector and held positions in IT and product management with the Thermo King Corp., a division of the Ingersoll-Rand Co. that manufactures heating and cooling systems, from 1992 to 2001. From 1998 to 2001, he was a global product manager responsible for a line of bus air conditioning systems manufactured in the United States, the Czech Republic, China, and Brazil.

Trained as a mechanical engineer, Jibrell received his bachelor's degree from Trinity College in Hartford, Connecticut, and began his career as an engineer with the Otis Elevator Co., a subsidiary of United Technologies Corp. in Farmington, Connecticut. He was born in Somalia and moved to the United States as a teenager. He lives in Vienna, Virginia, with his wife Teha and their three children.

Jibrell serves on the board of Samasource, a nonprofit organization that leverages the power of the Internet to provide paying work to marginalized people, including refugees and disadvantaged women around the world. He is also a board member of XBRL US, Inc., a nonprofit consortium that supports business reporting standards in the United States through the adoption of XBRL (extensible business reporting language). ■

Jibrell: Paul Fetters Lummis: Courtesy of Fred Lummis

HHMI Investigator Sean Carroll Named Vice President for Science Education

HHMI ANNOUNCED IN APRIL THAT SEAN CARROLL, AN AWARD-winning scientist, author, and educator, will become the Institute's vice president for science education.

Carroll will be responsible for directing HHMI's portfolio of science education activities when he succeeds Peter J. Bruns in September. Bruns, a geneticist and former Cornell University faculty member, announced his retirement last year after nine years in the post.

"Sean is a gifted scientist who also displays an extraordinary talent for translating complicated scientific ideas in compelling, understandable ways to members of the public of all ages," says HHMI president Robert Tjian. "He is in a unique position to connect our scientific and educational programs."

Carroll, an HHMI investigator at the University of Wisconsin–Madison since 1990, studies the development and evolution of animal form. He is considered a leader in the field of evolutionary developmental biology, or evo-devo. Carroll and his colleagues have used the tools of modern molecular biology and genetics to reveal how genetic changes during an organism's development shape the evolution of body parts and body patterns.

The 49-year-old Carroll is also widely known as a speaker and writer about science for the general public. He is the author of six books, including *Remarkable Creatures: Epic Adventures in the Origins of Species*, a finalist for the 2009 National Book Award in nonfiction. He writes a monthly column (also called "Remarkable Creatures") for the science section of *The New York Times* and has served as a consulting producer for the public television program NOVA distributed by WGBH in Boston. In March, Carroll received the 2010 Stephen Jay Gould Prize in recognition of his efforts to advance public understanding of evolutionary science.

"HHMI has had a big impact in shaping how science is taught, particularly at the undergraduate level. Colleges and universities are shaking up what they teach and HHMI has been a catalyst for that change. That's a great legacy to join," says Carroll.

HHMI is the nation's largest private supporter of science education. It has invested more than $1.6 billion in grants to reinvigorate life science education at research universities, liberal arts colleges, and undergraduate-focused institutions as well as to engage the nation's leading scientists in teaching through the HHMI Professors program. Other notable initiatives include the Science Education Alliance, launched in 2007 as a national resource for the development and distribution of innovative science education materials and methods, and the Exceptional Research Opportunities Program (EXROP), which offers mentored research experiences to select undergraduates.

"I want to help other people have as much fun as I have," says Carroll in describing his decision to take on the new role at HHMI. "That requires thinking about how to foster creativity and innovation on a larger scale. We all need inspiration, but how do we nourish curiosity and inspire an interest in science, particularly among young people? These are crucial challenges and I hope to promote the very positive role that science can play in our culture."

Jeff Miller

Carroll traces his own fascination with science to a childhood interest in collecting snakes, noting in an interview with the journal *Nature* that they inspired both his first experiments (their choice of food) and sense of beauty (the patterns of their skin). Today, Carroll's laboratory uses fruit flies—*Drosophila melanogaster* and its relatives—as models for understanding how new body patterns evolve over time.

In a series of studies published over the last several years, Carroll and his colleagues have traced the origins of complex body-color patterns. They've pinpointed mutations in gene regulatory elements responsible for when and where in the body those genes are used. "We are now able to trace the genetic steps of evolution in unprecedented detail. What our work has revealed is that, in general, body parts and body patterns evolve through 'teaching old genes new tricks'—that is, using very old genes in new ways," he says.

Carroll is recognized as an exemplary teacher and last year received the Viktor Hamburger Outstanding Educator Prize from the Society for Developmental Biology. The prize, established in 2002 in honor of a major figure in embryology, honored Carroll's contributions to the field and singled out his leadership as a mentor and educator. He is also a recipient of the Distinguished Service Award from the National Association of Biology Teachers. Along with David Kingsley, a fellow HHMI investigator, Carroll delivered the Institute's 2005 Holiday Lectures on Science, "Evolution: Constant Change and Common Threads."

A member of both the National Academy of Sciences and the American Academy of Arts and Sciences, Carroll graduated summa cum laude from the Washington University in St. Louis, Missouri, and received a Ph.D. in immunology from Tufts University, where he worked in David Stollar's laboratory. Carroll did his postdoctoral research at the University of Colorado, Boulder, in the laboratory of Matt Scott (now an HHMI investigator at the Stanford University School of Medicine), where he began his explorations in embryology and the study of genes that control body organization in the developing fruit fly.

Carroll joined the faculty of the University of Wisconsin in 1987 and became a full professor in 1995. He is the Allan Wilson Professor of Molecular Biology, Genetics, and Medical Genetics. Carroll plans to maintain his laboratory at the University of Wisconsin. ■

Young Again

NICHE CELLS CAN REVERSE THE AGING OF STEM CELLS.

Stem cells don't get wrinkles, but when they're old, it shows. Precursors to blood cells—called hematopoietic stem cells (HSCs)—become sloppy at their job as they age. The result is poorer immune function, increased risk of blood cancers, and an imbalance among the types of blood cells produced. Research has suggested that some of this aging is due to HSCs' intrinsic factors, such as DNA damage that accumulates over time. But HHMI early career scientist Amy Wagers suspected that external factors might also cause the cells to grow old, coordinating aging among organs.

"Different types of stem cells throughout the body all age together, so there could be some kind of global aging signal," says Wagers. "Since blood has access to all organs, it made sense to look there first."

To test whether blood could turn back the clock on stem cell function, Wagers' lab group at Harvard Medical School turned to mice. The researchers joined the circulations of old and young mice and observed the effects on HSCs. The results were dramatic: after 4 weeks of having young blood coursing through their veins, the older mice had HSCs that numbered—and functioned—much more like their younger counterparts. By using markers that distinguished old HSCs from young ones, the researchers verified that the older cells had recovered youthful characteristics (rather than young HSCs migrating from young mice to older animals). The stem cells in the younger mice appeared unchanged.

Wagers hypothesized that osteoblastic niche cells (ONCs), found at the interface of the bone and bone marrow where blood cells are formed, send aging signals to stem cells. So the researchers exposed stem cells in culture dishes to isolated old and young ONCs. The outcome, published January 28, 2010, in *Nature*, matched that of the first experiment: whereas old ONCs induced signs of age in young HSCs, old ONCs exposed to young blood regained their youthful characteristics.

Stem cells found in bone marrow change as they age, researchers have discovered.

While the scientists haven't yet pinpointed what ages the ONCs, and thereby the HSCs, Wagers suspects that more than one molecule is involved in regulation. She next plans to study the genes that are upregulated and downregulated in the blood and in ONCs as they age. ■ –SARAH C.P. WILLIAMS

IN BRIEF

DNA CRASH TEST

A DNA strand is a busy runway for proteins. A large complex called the replisome separates strands of the double helix and moves in one direction, whereas RNA polymerases—proteins that transcribe the DNA sequence into lengths of RNA—zip back and forth in both directions. HHMI investigator Michael E. O'Donnell wondered what happened when the two inevitably collide.

To find out, O'Donnell's lab group at the Rockefeller University set up crash tests between the complexes. They attached an RNA polymerase to a fragment of DNA and allowed it to move partway down the strand before they stalled it. Then they assembled a replisome at the other end of the DNA and set it into motion toward the polymerase.

They found that the replisome made it all the way down the DNA strand, pushing the stalled polymerase off its tracks and producing a full copy of the genetic material. Moreover, the team showed that another protein, Mfd, helped the replisome sidetrack the polymerase even more efficiently, allowing the complex to make additional copies of the DNA.

The results, which appear in the January 29, 2010, issue of *Science*, provide evidence that replisomes are more stable than some scientists suspected. O'Donnell is now searching for other factors that help the replisome push through blocks in the bacterium *Escherichia coli* and is studying whether replisomes in other organisms behave similarly.

VESSEL CUES

Turning human embryonic stem cells into cells that build blood vessels, or into any other specific cell type, takes just the right mix of molecular signals. Now HHMI investigator Shahin Rafii, at Weill Cornell Medical College, has identified the most robust signal yet for coaxing stem cells to become blood vessel-forming cells. The finding helps move scientists closer to developing stem cell-based treatments for heart disease and stroke.

Previously, for every five stem cells that researchers treated with particular molecules, one would become a vascular endothelial cell—the cell type that lines blood vessels. To identify new signals that could increase this efficiency, Rafii's lab group engineered a line of embryonic stem cells that glow green when they become vascular endothelial cells. This allowed the scientists to easily screen large numbers of molecules for their ability to help morph stem cells into vascular endothelial cells. One molecule, a compound that blocks growth factor TGF-beta, caused the most cells to light up.

When the researchers applied this finding to a new batch of stem cells, blocking TGF-beta and inducing the expression of a transcription factor at just the right time, they produced 40 endothelial cells for every five stem cells—a dramatic increase from previous yields. More importantly, a raft of tests showed that the endothelial cells behaved as they should in blood vessels, assimilating into mice circulatory systems and attracting the right types of molecules to their surfaces. The results were published in the February issue of *Nature Biotechnology*.

STOP THAT PROTEIN

Despite their diminutive size, small RNA molecules play a large role when it comes to regulating genes. How certain small RNAs (miRNAs) turn off gene expression, however, has remained poorly understood by scientists. One thing that *was* known: a family of proteins called Argonautes is required for miRNAs to block production of a protein from a gene. Now, HHMI inves-

Eye of Science / Photo Researchers, Inc.

Lab-Grown Liver

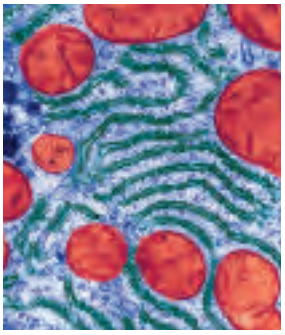
NEW CELL CULTURE SYSTEM SOLVES PROBLEM OF GROWING LIVER CELLS.

To study the molecular underpinnings of a disease, scientists often rely on an animal model of the disease or cells grown in a Petri dish. But neither of these methods has shed much light on hepatitis C virus (HCV), which affects the liver. It's exclusively a human disease, so animal models are limited. And liver cells don't survive in typical cell cultures, confounding scientists who want to grow them in the lab.

Now, HHMI investigator Sangeeta Bhatia has designed a workaround: a system that allows liver cells to thrive in the lab. Bhatia, a tissue engineer at the Massachusetts Institute of Technology, creates what she calls "micro-livers" by using computer engineering tools to dot microscopic patterns of liver cells on glass slides.

"Cultured liver cells are very finicky," says Bhatia. "They're dependent on interactions with other liver cells, and interactions with stromal cells of the liver's connective tissue." The tools Bhatia developed allow scientists to create an organized environment that lets the cells flourish outside the body.

To test whether HCV could fully infect these liver cultures, Bhatia's lab collaborated with Charles Rice, an HCV expert at Rockefeller University. The team designed an assay in which cells infected with an HCV-like retrovirus were made to fluoresce green when the virus entered. Cells with actively replicating copies of the virus secreted a different light-emitting protein. The researchers showed that liver cells grown in their micro-liver system could be infected with HCV for up to two weeks—enough time to potentially screen drugs or test how the virus behaves inside the cells. The results appeared in the February 16, 2010, issue of the *Proceedings of the National Academy of Sciences*.



The complicated organization of the liver's interior is tricky to reproduce in culture.

Bhatia's technique for applying organization to liver cell cultures may work for studying other cell types outside the human body—many stem cells, for example, rely on organized systems of multiple cell types to thrive.

"People usually think about tissue engineering for delivering cell therapies to patients," says Bhatia. "But there's also a benefit to using tissue engineering to develop better in vitro models for drug discovery, ultimately impacting patients with better drugs, not just the delivery of living cells." ■ –SARAH C.P. WILLIAMS

IN BRIEF

tigator Rachel Green at the Johns Hopkins University School of Medicine has learned something new about how this interaction plays out.

Based on some interesting bioinformatic predictions, Green and her colleagues studied the MID domain of Argonaute proteins from a variety of organisms and found that this domain exhibited some unusual behaviors. The researchers eventually realized that the Argonaute proteins have two binding sites for RNA—one for the miRNA and the other for mRNA, the intermediate genetic molecule between a DNA sequence and a protein.

The researchers revealed that communication between the two binding sites is important in allowing the miRNA to stop the gene expression of the associated mRNA. The work is described in the February 2010 issue of *Nature Structural & Molecular Biology*.

RARE EYE DISORDER EXPLAINED

A study involving 37 clinicians around the world has revealed the underlying genetics of a rare eye movement disorder. Led by HHMI investigator Elizabeth Engle at Children's Hospital Boston, the researchers analyzed the genes of 29 families and found that they all share a mutation in a gene called *TUBB3*.

Engle has previously identified genes underlying other eye disorders, linking them to defects in the development of motor neurons connecting the eye muscles to the brain. In the latest study, she and her colleagues turned their attention to a disorder called congenital fibrosis of the extraocular muscles type 3 (CFEOM3). Children born with the disorder have droopy eyelids and are unable to move their eyes fully. In addition, some children show signs of social, behavioral, or intellectual impairment and, as indicated by brain MRI, have abnormal white matter development, and some later develop nerve degeneration in their arms or legs.

With the help of collaborators across the United States, Europe, Turkey, Venezuela, and Australia, Engle identified 29 families with the disease and pinpointed the culprit mutations to one gene—*TUBB3*. Moreover, unrelated families with the same phenotype were found to have the identical mutation: a specific amino acid substitution in the TUBB3 protein.

To understand why the mutations lead to CFEOM3, the researchers engineered mice with the most common mutated version of *TUBB3*. They found that neurons did a poor job of projecting axons from the brainstem to the eye muscles and that their microtubules functioned abnormally. The findings, which appear in the January 8, 2010, issue of *Cell*, could lead to improvements in genetic testing for affected families and, eventually, to treatments for the disorder.

ANTHRAX ATTACK

Before it takes over a cell, the anthrax toxin hovers on the cell's surface, preparing for battle. HHMI scientists have now explained the delay and have discovered how the toxin gets inside. Led by HHMI international research scholar Gisou van der Goot, the team found that the toxin must assemble a seven-molecule structure to make its attack.

Van der Goot and her colleagues at the Global Health Institute of the École Polytechnique Fédérale de Lausanne in Switzerland revealed that the toxin assembles its seven parts after it attaches to one of two receptors on the cell's outer membrane. This attachment activates an enzyme inside the cell, signaling to the cell that the receptor needs to be internalized. The receptor—and the attached anthrax

Don W. Fawcett / Photo Researchers, Inc.

Going Solo

RESEARCH REVEALS HOW SOME LIZARDS REPRODUCE ASEXUALLY.

For decades, biologists thought the reason they captured only females of some whiptail lizard species was because the males were better at hiding. It wasn't until the 1960s that they realized the males didn't exist: female whiptails—a cross between the male of one lizard species and the female of another related species—carried on the lineage without sexual reproduction. Fifty years later, HHMI early career scientist Peter Baumann has now revealed the molecular basis for whiptail reproduction.

There are various ways that other organisms reproduce without the mixing of genes from two distinct sexes, but they often lose their genetic diversity after a number of generations—only one version of each gene eventually is present. But the asexual types of whiptail lizards, over several thousand generations, have maintained the mix of genes from the two species that spawned them. Baumann hypothesized they must have a different strategy.

Some species of whiptail lizards, like the one shown here, reproduce asexually.

"I went looking in the literature to find out what was known about this and found very little," says Baumann. "So I turned to classic cell biology." Baumann and his colleagues at the Stowers Institute for Medical Research, in Kansas City, isolated nuclei from whiptail eggs and examined the contents.

The eggs of sexually reproducing lizards contain 23 chromosomes each, so when they fuse with sperm, the resulting offspring have the correct number of chromosomes—46—in their nonreproducing, or somatic, cells. In the asexual whiptails, Baumann's lab group found, meiosis (the cell division process that produces eggs and halves the normal number of chromosomes) begins with cells containing twice the normal number of chromosomes: 92. The final egg, therefore, contains 46 chromosomes—double the number in sexually reproducing lizards—to compensate for the fact that it won't be fertilized.

Moreover, during the stage of cell division in which parts of matching chromosomes, originally derived from each parent, usually recombine, the asexual whiptail eggs have only identical chromosomes to pair up—those duplicated an extra time before meiosis. No matter how much they mix, these matching chromosomes maintain their identity. During the formation of eggs for sexual reproduction, however, a different approach is taken—the matching, though nonidentical, chromosomes pair up to shuffle genes around purposefully. The study results appeared online in *Nature* on February 21, 2010. ■ –SARAH C.P. WILLIAMS

IN BRIEF

toxin—are then pulled inside the cell. Once the toxin is inside, molecules burst out from inside a membrane-covered bubble and slice up proteins vital to the cell.

If the toxin enters the cell before assembly of the protein complex is completed, the researchers showed, the slicing molecules are left outside the cell and the toxin isn't able to kill it. The results appear in the January 26, 2010, issue of the *Proceedings of the National Academy of Sciences*.

HOW FRUIT FLIES GET THEIR COLORS

In the high mountains of Africa, fruit flies have dark black stripes across their abdomens. Elsewhere in the world, the flies are yellower, with fainter stripes. HHMI investigator Sean B. Carroll saw the difference as a perfect chance for some digging into the flies' evolutionary past.

Carroll knew that a gene called *ebony* was responsible for the difference, so he and his colleagues at the University of Wisconsin—Madison started there. After breeding flies with different versions of *ebony*, however, the researchers realized that the difference in stripe color wasn't due to a change in the protein-coding region of *ebony* itself but, instead, must be a result of influences from regulatory regions outside the gene. They searched a large region of what was once considered "junk DNA" and discovered various enhancers of *ebony*—bits of DNA that turn the gene on and off in different parts of the body.

By linking different enhancers to *ebony*, the team tracked down the enhancer regions that control the color of abdomen stripes and found two mutations that occurred only in the black-striped flies. The scientists were also able to estimate that the mutations had first appeared in the black-striped flies about 9,000 generations ago. The findings, which appear in the December 18, 2009, issue of *Science*, highlight the importance of enhancer regions in driving evolutionary change in organisms. This study marks the first time that researchers have determined the age of a mutation in a regulatory region.

TRACKING A MISSING PROTEIN

Scientists have known since the 1990s that deletion of a gene called *SMN1* leads to spinal muscular atrophy, a neurodegenerative disease that is the leading genetic cause of childhood mortality. But it's been a mystery as to why an almost identical gene, *SMN2*, can't produce enough SMN protein to make up for the dysfunction of *SMN1*. Now, a research group led by HHMI investigator Gideon Dreyfuss at the University of Pennsylvania School of Medicine has discovered why.

The DNA sequence of *SMN2* differs from that of *SMN1* by only one nucleotide, but when the gene is translated into protein, this single change leads to a chunk of missing protein. And moreover, Dreyfuss found that this shorter version of SMN protein, dubbed SMNΔ7, is quickly degraded by the cell.

Dreyfuss and Sungchan Cho, a postdoctoral researcher in his lab, found that the sections of SMN that had been improperly joined together in SMNΔ7 created a signal that sent the protein straight into degradation. By either changing this signal or shutting down the cell's degradation machinery, the researchers could restore SMNΔ7 to normal stability. The results appear in the March 1, 2010, issue of *Genes & Development*.

The researchers hope that, with the understanding of this mechanism, therapies stabilizing SMNΔ7, which apparently retains SMN functionality, can be developed for treatment of spinal muscular atrophy. If patients with deletion of *SMN1* had enough stable SMNΔ7, the symptoms of the disease might be alleviated.

Peter Baumann

Q A

How do scientists learn about plants that are extinct?

asked by Latrice, an elementary school student from Maryland

The fossil record is the primary way that scientists learn about extinct plants. Scientists in the field of paleobotany (*paleo* means ancient, *botany* is the study of plants) study fossils to learn about the evolution of plants that are alive today and to discover clues about what the Earth was like in the past.

Unfortunately for researchers, not all plants leave fossils behind. For a plant to become fossilized, mud or sediment has to bury it quickly but gently, so it doesn't fall apart. As the sediment around the plant gradually forms rock over time, the shape of the plant is preserved. Depending on the speed of the process and the surrounding environment, different types of fossils can form. In some fossils, called impressions or compressions, a flattened section of the plant is pressed into sediment. In fossils like this, scientists can use high-powered microscopes to observe details of the plant's overall shape and the organization of its parts, but they can't usually identify individual cells.

Other times, a three-dimensional plant is fossilized. This happens when undamaged plant material is surrounded by minerals as it decays. As with an impression fossil, scientists can usually observe only the external structure, but they can learn more than if the plant had been flattened. In rare cases, minerals penetrate the plant tissue and preserve the cells in great detail. This process, called permineralization, is also how petrified wood is formed. Scientists study petrified wood to learn about extinct trees.

Using the physical characteristics they observe in all these types of fossils, paleobotanists can gain information about how plants in the past survived. By matching fossils to living species, they can hypothesize about the climates in which extinct plants lived. For example, if the fossil shows a leaf with a thick, waxy structure, the plant probably lived in a dry environment where it had to conserve water, similar to many modern-day cactuses. By comparing fossilized plants with related plants of today, scientists can also identify when different traits first appeared, telling us how plants have evolved over time.

With the advent of DNA technology, paleobotanists have also been able to study plants and their evolution using genetic techniques. Although fossils preserved in rocks don't contain DNA, researchers sometimes luck out and discover actual plant material—such as spores, pollen, leaves, or pine cones—that's been preserved in very cold or dry climates or inside hardened tree resin (called amber once it's fossilized). Analyzing these preserved plant bits and the DNA inside them is one more way that scientists can learn about ancient plants.

ANSWER BY JAYATRI DAS, *a senior exhibit & program developer at The Franklin Institute in Philadelphia and a former HHMI predoctoral fellow.*

FURTHER READING

Museum Victoria in Australia
http://museumvictoria.com.au/prehistoric/time/plant.html

The Paleobotany Project at the Denver Museum of Nature & Science www.paleobotanyproject.org/

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

Lee Wins National Academy Award

JEANNIE LEE

Jeannie T. Lee, an HHMI investigator at Massachusetts General Hospital, won the 2010 National Academy of Sciences Award in Molecular Biology. The annual award recognizes a recent notable discovery in molecular biology by a young scientist. Lee was chosen for her research using X-chromosome inactivation as a system to study epigenetic regulation on a broader scale. Lee has discovered that the genes responsible for inactivation of one copy of a female's X chromosome can also inactivate other genes and has implicated noncoding RNAs in the mechanism.

The 2010 Elizabeth W. Jones Award for Excellence in Education, named for the late HHMI professor and given by the Genetics Society of America, went to **UTPAL BANERJEE**, an HHMI professor at the University of California, Los Angeles.

MICHAEL J. BEVAN, an HHMI investigator at the University of Washington School of Medicine, is the 2010 recipient of the American Transplant Congress Distinguished Career Award. Bevan was chosen by the American Society of Transplant Surgeons and the American Society of Transplantation for his research on how T cells distinguish the body's own cells from pathogens, which has implications in transplant rejection.

HHMI investigator **PATRICK O. BROWN** at the Stanford University School of Medicine won the 2010 Association of Biomolecular Resource Facilities Award in recognition of his pioneering work in the development of microarrays.

ATUL J. BUTTE of Stanford University School of Medicine, recipient of an HHMI Physician-Scientist Early Career Award, won the 2010 Young Investigator Award from the Society for Pediatric Research. Butte is a practicing pediatric oncologist and his research revolves around developing bioinformatics to study obesity and type 2 diabetes in children.

GEORGE CARLSON, HHMI program director at McLaughlin Research Institute, was selected to receive a 2010 First Lady's Math and Science Award from the State of Montana. The award recognizes the McLaughlin Institute's math and science education programs, which are supported by HHMI.

The American Federation for Aging Research awarded **ANDREW DILLIN**, an HHMI investigator at the Salk Institute for Biological Studies, with the 2010 Vincent Cristofalo Rising Star in Aging Research Award. Dillin studies how protein folding and misfolding play a role in aging and how diet affects that link.

HHMI investigator **BRIAN J. DRUKER** of the Oregon Health & Science University won the 2010 Robert J. and Claire Pasarow Foundation Annual Medical Research Award. Druker studies the molecular basis of cancers and has made great strides in understanding and treating chronic myeloid leukemia.

HHMI investigator **ELAINE FUCHS** of Rockefeller University was chosen by the American Association for Cancer Research (AACR) to receive the AACR-Women in Cancer Research Charlotte Friend Memorial Lectureship, an annual award given to a cancer researcher who has furthered the advancement of women in science. Fuchs also received the 2010 Distinguished Scientist Award from the Emerson Foundation.

The HHMI-supported **GENETIC SCIENCE LEARNING CENTER** at the University of Utah won the 2009 *Science* Prize for Online Resources in Education from *Science* magazine and the American Association for the Advancement of Science. The center was chosen for its Learn.Genetics (learn.genetics.utah.edu) and Teach.Genetics (teach.genetics.utah.edu) websites, which provide free educational materials on genetics to the public.

KATHERINE A. HIGH, an HHMI investigator at the Children's Hospital of Philadelphia, was named to the Board of Scientific Counselors of the National Heart, Lung, and Blood Institute. High studies hemophilia and other blood clotting disorders.

The North American Vascular Biology Organization awarded the 2010 Earl P. Benditt Award to HHMI investigator **RICHARD O. HYNES** at the Massachusetts Institute of Technology. Hynes studies how cells bind to one another, a phenomenon known as cell adhesion.

LILY Y. JAN and **YUH-NUNG JAN**, HHMI investigators at the University of California, San Francisco, were named joint winners of the 2010 Edward M. Scolnick Prize in Neuroscience. This award is given annually by the Massachusetts Institute of Technology McGovern Institute for Brain Research. The Jans husband-and-wife team studies potassium channels and their role in the brain.

The BBVA Foundation selected **ROBERT J. LEFKOWITZ**, an HHMI investigator at Duke University, to receive the Frontiers of Knowledge Award in Biomedicine. Lefkowitz was honored for his discoveries of G protein-

Lee: Courtesy of Jeannie T. Lee

HHMI Early Career Scientists Named Vilcek Finalists

HARMIT MALIK

IANNIS AIFANTIS

HHMI early career scientist **Harmit S. Malik** at the Fred Hutchinson Cancer Research Center won the 2010 Vilcek Prize for Creative Promise in Biomedical Science for his research on the coevolution of humans and diseases. The Vilcek Prizes for Creative Promise are given annually by the Vilcek Foundation to recognize the accomplishments of young immigrant scientists. HHMI early career scientist **Iannis Aifantis** of the New York University School of Medicine was one of four finalists for the prize. Malik was also honored at the White House in January with a Presidential Early Career Award for Scientists and Engineers.

coupled receptors, the largest family of cell receptors.

DAN R. LITTMAN, an HHMI investigator at New York University, is the recipient of the 2010 American Association of Immunologists-Invitrogen Meritorious Career Award. This award recognizes a midcareer scientist for outstanding contributions to immunology. Littman studies the interplay between the immune system and HIV.

At the Miami Winter Symposium sponsored by *Nature Biotechnology*, HHMI investigator JOAN MASSAGUÉ of Memorial Sloan-Kettering Cancer Center was awarded the 2010 Feodor Lynen Medal for his research on cancer metastasis.

HHMI investigator PHILIPPA MARRACK of National Jewish Health in Denver, Colorado, was among six women inducted into the Colorado Women's Hall of Fame. Marrack studies the role T cells play in the immune system.

HHMI investigator RUSLAN M. MEDZHITOV of the Yale School of Medicine received the 2010 Lewis S. Rosenstiel Award for Distinguished Work in Basic Medical Science. Brandeis University chose Medzhitov for the annual award for his research on the innate immune system.

HHMI early career scientist JOSHUA T. MENDELL at the Johns Hopkins University School of Medicine was named the 2010 winner of the Outstanding Achievement in Cancer Research Award from the American Association of Cancer Research. Mendell studies the roles that microRNAs play in cancer.

SHULAMIT MICHAELI, an HHMI international research scholar at Bar-Ilan University in Israel, was elected to head Life Science and Medicine at the Israel Science Foundation. The foundation is the predominant source of funding and support for basic research in Israel.

WILLIAM T. NEWSOME, an HHMI investigator at the Stanford University School of Medicine, won the 2010 Karl Spencer Lashley Award from the American Philosophical Society. The annual award is in recognition of work on the neural basis of behavior. Newsome studies the neural mechanisms underlying visual perception and visually based decision making.

HHMI investigator MARK J. SCHNITZER at Stanford University won the 2010 Michael and Kate Bárány Young Investigator Award from the Biophysical Society. Schnitzer's lab focuses on developing methods to image the nervous system, with the goal of watching living neurons at work to deepen our understanding of neurological diseases.

THOMAS TUSCHL, an HHMI investigator at Rockefeller University, was elected to the German Academy of Sciences Leopoldina. The Leopoldina is the world's oldest continuously existing academy for medicine and natural sciences. Tuschl studies the regulatory functions of RNA.

THE VIRTUAL TRANSGENIC FLY LAB, an interactive learning module on HHMI's BioInteractive website, was selected by the Multimedia Educational Resource for Learning and Online Teaching (MERLOT) Biology Editorial Board as a 2010 winner of the MERLOT Award for Exemplary Online Learning Resources. The online lab walks visitors through the steps of creating a transgenic fly.

BERT VOGELSTEIN, an HHMI investigator at the Johns Hopkins University School of Medicine, was named the 2011 recipient of the Charles Rodolphe Brupbacher Prize for Cancer Research. Awarded by the Charles Rodolphe Brupbacher Foundation, the biennial prize goes to a scientist who has made extraordinary contributions to basic oncological research. Vogelstein was chosen for his research on the molecular basis of colon cancer.

Malik: Susie Fitzhugh. Aifantis: Thomas Semkow

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(LIGHT MOVES)

Cell Sculpting

Lim, at UCSF, is applying optogenetic methods to illuminate the localized, protein–protein interactions that underlie everything from turning genes on and off, to making cells more or less sensitive to stimuli, to cytoskeletal remodeling that alters a cell's shape or influences its movements.

Phytochrome B is a light-sensitive receptor in the mustard plant *Arabidopsis thaliana* that Lim is developing as a versatile molecular tool. In its normal role, the phytochrome enables the plants to respond to shade. When bathed in red light, for example, the phytochrome undergoes a shape change that leads to the alteration of gene expression in ways that cause the plant to grow toward sunnier patches of space.

In one audacious show of experimental control, Lim and his colleagues combine the phytochrome with an enzymatic component into modules so they can use light to trigger the polymerization of actin protein molecules in a cell. This results in localized changes in the cell's cytoskeletal framework, which determines the cell's shape. Using precision optics, the researchers can induce localized shape changes with enough finesse that Lim refers to the process as cell sculpting.

Lim can imagine using light to orchestrate new organizations of cells, perhaps even for making neuron-based logic components for biological computers or to help reconstruct damaged nerve tissue.

To demonstrate the utility of the approach in fine cell sculpting, Lim's group used a digital micromirror array device to project a minuscule "game of life" movie onto mammalian cells containing the phytochrome module. Each movie frame displays a pattern of dark and light boxes. The pattern evolves in a systematic way from frame to frame—dark boxes become light and vice versa, according to simple mathematical rules. By projecting these changing patterns of light and dark boxes (pixels) onto a cell, the researchers induced the cell surface to embody the same morphing patterns.

In a paper in the September 13, 2009, issue of *Nature*, Lim and several UCSF colleagues at the Cell Propulsion Lab say they should be able to link the phytochrome light switch to many other cell signaling pathways that involve the recruitment of protein players. Lim refers to the system as a "universal remote control" for experimentally dictating when and where in a cell to activate a pathway of interest. He can also imagine expanding the toolkit (see Web Extra, "Beyond Light," www.hhmi.org/bulletin/may2010).

"We are learning how to dissect biological systems the way electronics engineers dissect circuits," Lim says. Elegant, precise interventions in neural circuitry, the kind that optogenetics researchers are exploring, stand a chance of eventually taking the place of blunt instruments like surgery, electrodes, and the present generation of pharmaceuticals. ■

WEB EXTRA: To learn about specific studies using optogenetics and how researchers are looking beyond light to manipulate neurons, go to www.hhmi.org/bulletin/may2010.

WEB EXTRA: Listen to Karl Deisseroth talk about the clinical potential of optogenetics. www.hhmi.org/bulletin/may2010

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(THE SILICON MARVEL)

meshed and runs at "line rate"—meaning that the 40-gigabit/second data-center backbone is available to every user at all times, rather than being designed to serve only a small percentage of researchers as they need it while the rest ponder their research or go to lunch.

The computing cluster communicates with the rest of the campus through 450 miles of fiber optic cable, operating at 1 gigabit/second to users' desktops.

The updated cluster also runs at an impressive 84 percent efficiency, based on the global standard, called the Linpack Benchmark, traditionally used to measure performance and rank top supercomputers. Right now, the Janelia system would rank roughly in the top 200 of existing computing clusters, says Ceric. Janelia plans to enter its cluster in the next edition of the Linpack ranking system this summer.

The installation's increased efficiency is also better for the planet, since it gobbles less electricity. The old cluster ran at 25 million operations per second per watt. Now it can produce 200 million operations per second on the same amount of power. And it throws off less heat that ultimately must be air conditioned away. "It takes less power and we produce fewer BTUs," says Cicerchia.

As Janelia researchers go about their day thinking up novel ways to explore neural networks, few contemplate the silicon marvel that quietly makes much of their work possible. But ask any of them to consider their research without the cluster and you quickly enter the realm of the unthinkable.

"In a single day at Janelia we can do something that would take 11 years on a single-processor workstation," says Eddy. "We breathe CPU cycles like air." ■