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HHMI BULLETIN

Howard Hughes Medical Institute www.hhmi.org

Reaching Rural Schools

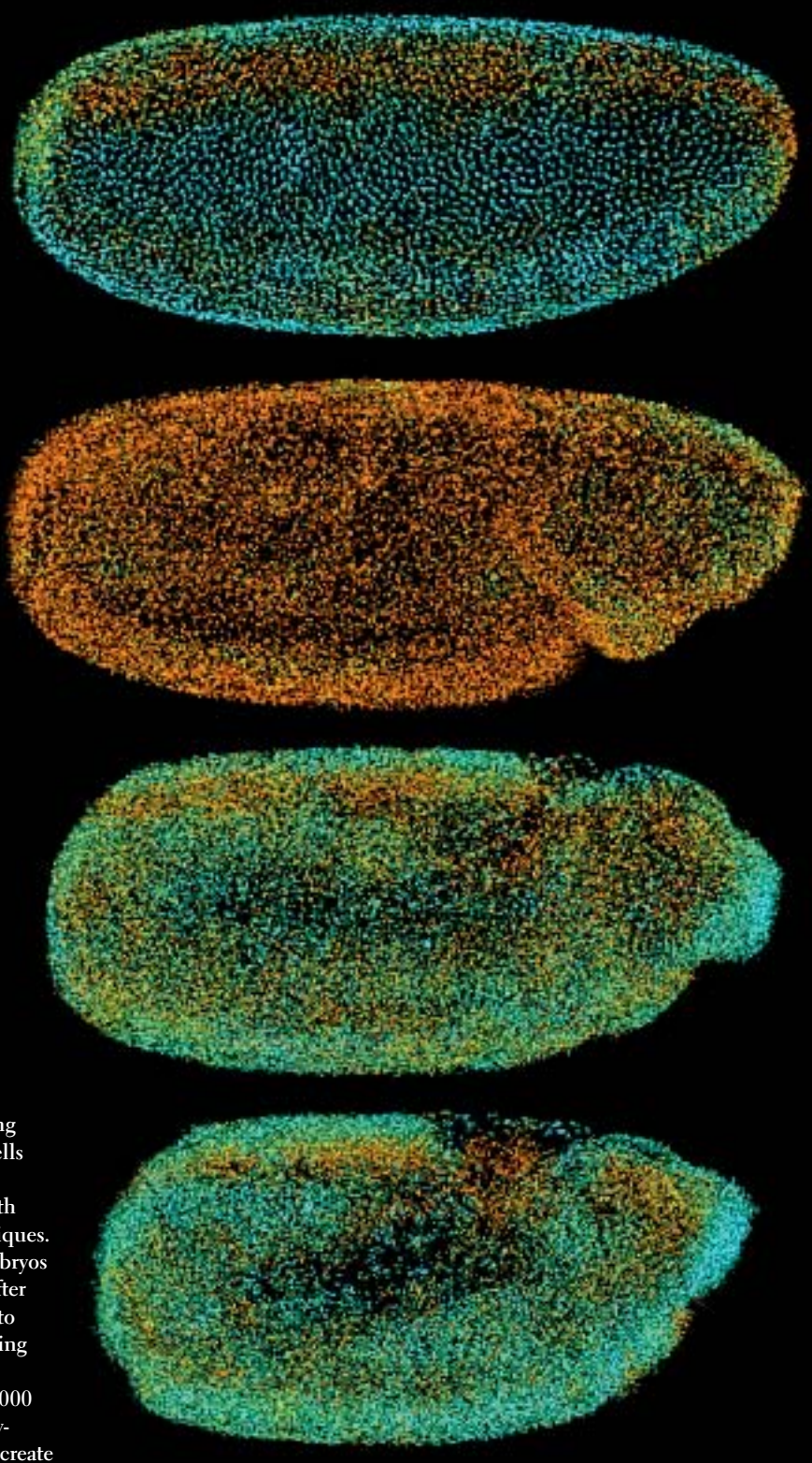
Students far from urban areas need extra support to learn science. And educators are bringing it to them.

IN THIS ISSUE

EXPOSING CANCER'S SOFT SPOT

PIERCING THE MULTIFACETED COAT

MOVIE MAGIC



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These dazzling, dancing arrays of fluorescent cells are developing fruit fly embryos, visualized with new microscopy techniques. Snapshots of living embryos 3, 5, 8, and 11 hours after fertilization (from top to bottom) show the shifting positions of every cell. It took more than 130,000 of these images of early-stage embryogenesis to create the digital fly embryos. The time-lapse series gives scientists a wealth of developmental biology data previously unavailable.

P.J. Keller, A.D. Schmidt, A. Santella, K. Khairy, Z. Bao, J. Wittbrodt, & E.H.K. Stelzer, Nature Methods, *2010*

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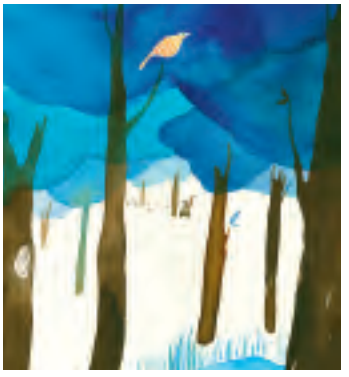

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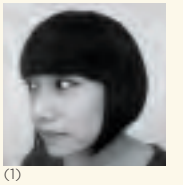
Join us at www.hhmi.org/bulletin/nov2010.

NOMOCO (cover and "In Their Own Backyard," page 12) was born in Fukuoka, Japan, and currently lives in London, England. Nature and sounds are her inspiration, and she enjoys playing with ink and its organic movement. She has exhibited her work in solo and group exhibitions in London, Milan, Tokyo, Singapore, and New York. She also produces work under the name Kazuko Nomoto. (1)

In 2009, only four years after receiving her BFA in photography from the California College of the Arts, **MELISSA KASEMAN** ("She's No Lightweight," page 5, and "Plant Matters," page 34) was named one of PDN30: Photo District News Top 30 Emerging Photographers. Her work can be found in numerous publications, including *T: The New York Times Style Magazine*, *Dwell*, *Readymade*, and *Wired*. She lives and works in Oakland, California. (2)

A freelance illustrator living in Sigtuna, Sweden, **MATTIAS ADOLFSSON** ("Piercing the Multifaceted Coat," page 18) tries to keep his ink from smudging while drawing (he refuses to follow the trends and go digital) but seldom succeeds. Apart from that, he is moderately clean and enjoys following online courses from American universities. (3)

DAN FERBER ("Exposing Cancer's Soft Spot," page 24) is a contributing correspondent for *Science*, a contributor to many magazines, and coauthor, with Paul Epstein, M.D., of the upcoming book *Changing Planet, Changing Health: How Climate Change Threatens Our Health and What We Can Do About It*. A resident of Indianapolis, he's a longtime enthusiast of the ancient Chinese art of t'ai chi. (4)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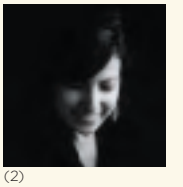
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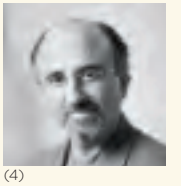
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Nomoco, Melissa Kaseman, Mattias Adolfsson, Dan Ferber

Seeding Plant Science

Barbara Ries

FOUR YEARS AGO JOANNE CHORY MADE A BOLD STATEMENT WITHIN the pages of the *HHMI Bulletin* that "the study of plant genomes might contribute more to human health and well-being than the study of any animal genome." As one of a handful of plant scientists within the HHMI community, the investigator at the Salk Institute for Biological Studies has spent many an hour explaining to quizzical colleagues how much they could learn from the mouse ear cress (*Arabidopsis thaliana*)—as distinct from the mammalian mouse (*Mus musculus*).

Chory's carefully cultivated seeds have now borne fruit. Earlier this fall, HHMI and the California-based Gordon and Betty Moore Foundation announced that we would hold a joint competition to identify up to 15 of this nation's most creative and talented plant scientists. When selected in 2011, they will join the Institute as investigators and also receive substantial grant support from the Moore Foundation over a five-year period. We think the creation of our joint program underscores the importance of investing in fundamental plant science and will encourage others in the United States to make analogous commitments. We also believe this core group will have an outsized impact on their fields, particularly in attracting a new generation of graduate students and postdoctoral researchers.

Why now? Plant research proved its value long ago—after all, study of the humble pea helped found the modern field of genetics—but one could argue there has never been a more important time in our history. Plant scientists have tremendous potential to help us understand—and possibly find solutions to—some of the most pressing concerns that face society: food production, human health, protection of the environment, identification of renewable energy sources. The 2009 National Research Council Report, "A New Biology for the 21st Century," provides a much-needed framework for discussing these important issues among policy makers and academic leaders. Other positive developments are on the horizon, including a plan for developing a competitive grants program within the National Institute of Food and Agriculture, part of the U.S. Department of Agriculture.

For too long, fundamental plant science has been something of an afterthought in the U.S.—where substantial resources are dedicated to applied agricultural research—and represents about 2 percent of overall life sciences spending by the federal government. A highly respected scientist like Chory may succeed in receiving grants through the National Institutes of Health (NIH), but she is an exception. At the turn of the millennium, for example, of some 24,000 scientists working with *Arabidopsis* as their model organism, fewer than five dozen received NIH research project grants.

The interagency National Plant Genome Initiative—funded through NIH, the National Science Foundation (NSF), the departments of Agriculture and Energy, and others—has generated useful tools and knowledge over the past decade. But the NSF, which supports many plant scientists, has had few dedicated programs in fundamental plant science. Elsewhere in this issue, Vicki L. Chandler, chief program officer for the Moore Foundation's science initiatives and a noted plant researcher in her own right, describes the challenges and opportunities that face her colleagues in the field.

> "Plant scientists have tremendous potential to help us understand—and possibly find solutions to—some of the most pressing concerns that face society."
>
> ROBERT TJIAN

The collaboration between HHMI and the Moore Foundation illustrates the extraordinary potential for targeted investment in plant science research because our organizations would not appear, at first glance, to be obvious partners. The Moore Foundation, which has long been committed to environmental conservation, has focused on supporting fundamental research in physical, life, and information sciences. Given HHMI's primary focus on biomedical research with the potential to improve human health, the Institute has historically viewed much of plant science research as outside its traditional scope. Just as the Moore Foundation sought to connect its environmental and scientific interests, HHMI began exploring potential new directions in plant science in a 2008 workshop that Chory helped organize. As a member of the Moore Foundation's scientific advisory board, I have seen first hand that our organizations share a commitment to supporting excellent science.

The result is something that ecologists might recognize: an example of facultative symbiosis that benefits both organizations and gives the scientists we support a greater chance to survive—if not flourish.

The Sound of Science

The melodies stick in Kevin Ahern's head, sometimes for days. They're songs everybody knows, like "A Few of My Favorite Things," "Santa Claus is Coming to Town," and "Downtown." The inspiration for his lyrics comes in an instant.

"It's always a phrase that will resonate with something in a melody," says Ahern, a senior instructor in biochemistry at Oregon State University. "The best example was when I was teaching a class and I had the music from "Supercalifragilisticexpialidocious" in my head. All of a sudden I thought, 'gluconeogenesis is really quite atrocious.'"

Bang. The rest just flows. And the result is Metabolic Melodies, more than 50 songs devoted to processes like glycolysis and the urea cycle. Ahern, also the university's HHMI summer undergraduate research coordinator, may break into any one of his songs at unexpected times to lighten up lectures. The response from his students, he says—even the ones who anticipate the Melodies—is priceless. "The look sweeps across the crowd, 'look, he's gone nuts.'"

During his first year of teaching in the mid-1990s Ahern heard about something called *The Biochemists' Songbook*, by Harold Baum, a professor emeritus at King's College London. Ahern decided to treat his students at the end of the term with songs of his own.

"I wrote two songs that very first time and sang them to the class," he says. "I'll always remember their reaction. It kept me going, and each new term I wrote a new song."

His students love them; they tell him in their evaluations of his class. By now, Ahern has earned a reputation on campus for his Melodies, even though he admits to singing off-key. Some students are inspired to write their own Melodies. Some choreograph them. Some post their renditions to YouTube. His wife, Indira Rajagopal, a senior instructor in biology, co-writes some of the songs.

It's not just a campus thing, either. Ahern hears from students as far away as Newfoundland and Ukraine about the Melodies. He's received his most flattering feedback from a group of Croatian students, who recorded two of his songs—"We All Need Just a Little ATP" (to the tune of "Yellow Submarine") and "B-DNA" (to the tune of "YMCA") and posted them to YouTube. "It felt really good," he says.

Ahern has received media attention for the Melodies as well, including BBC radio, *Nature Podcast*, and Geek Pop.

Although his Melodies cover the concepts that students learn in his class, Ahern doesn't necessarily see them as a teaching tool. Rather, he sees them as a way to diminish students' fear about a challenging subject.

"They see that biochemistry is not so daunting and scary, and the people who teach it aren't scary either. So if you cut through that barrier, they can laugh at something, relax, and learn more easily," he says.

Ahern makes his recorded Metabolic Melodies available to download for free at www.davincipress.com/metabmelodies.html. "I like getting the word out on the songs," he says. "Anything that furthers the cause is good."
—Celene Carillo

WEB EXTRA: To see video performances of some of Ahern's Metabolic Melodies, visit www.hhmi.org/bulletin/nov2010.

Peter Arkle

She's No Lightweight

Meet Anita Sil, M.D./Ph.D., mother of two young children, scientist, and resident of the West Coast's most relaxed city, San Francisco. She stands just 5′2″, an immaterial detail until you hear her say: "I remember the first time I kicked a man over six feet tall in the head."

Meet Anita Sil, *black belt*.

If it seems surprising for a warm, soft-spoken molecular biologist to take on taekwondo (loosely translated: "the way of the foot and the fist"), Sil doesn't see it that way. After all, both disciplines require patient dedication; both take unexpected turns; both can reach frustrating plateaus. In the lab and in the ring, she says, "the real goal is to try sincerely with everything you've got."

That she might someday achieve taekwondo's highest rank was not always obvious to Sil, an HHMI early career scientist at the University of California, San Francisco (UCSF). "I'm actually pretty uncoordinated," she laughs, remembering her decision 15 years ago to mix up her exercise routine. Then a student at the UCSF School of Medicine, Sil joined a taekwondo club near the lab where she spent most of her time.

"I still remember walking in that first day, very nervous," she recalls. "The first thing the instructor said was there would be *no* girl push-ups. Once you get to know him, he's a really compassionate and kind person, but he was scary that day."

After those first-day jitters, Sil quickly took to the sport. She enjoyed the physical and mental challenges and the sense of community with her instructors and sparring partners. A typical class included calisthenics, drills, and sparring—kicks, punches, strikes—with a partner.

Sil excelled in her science, receiving a UCSF fellowship that allowed her to establish a lab and circumvent the traditional postdoc stage. At the same time, she was switching fields to work on the fungal pathogen *Histoplasma*. It was exciting, but Sil says she felt insecure about everything.

Everything but taekwondo, that is. She was preparing to test for the black belt. From October 1998 to June 1999, she trained at least 25 hours a week, spending the rest of her time in the lab. She was lucky to get four or five hours of sleep a night.

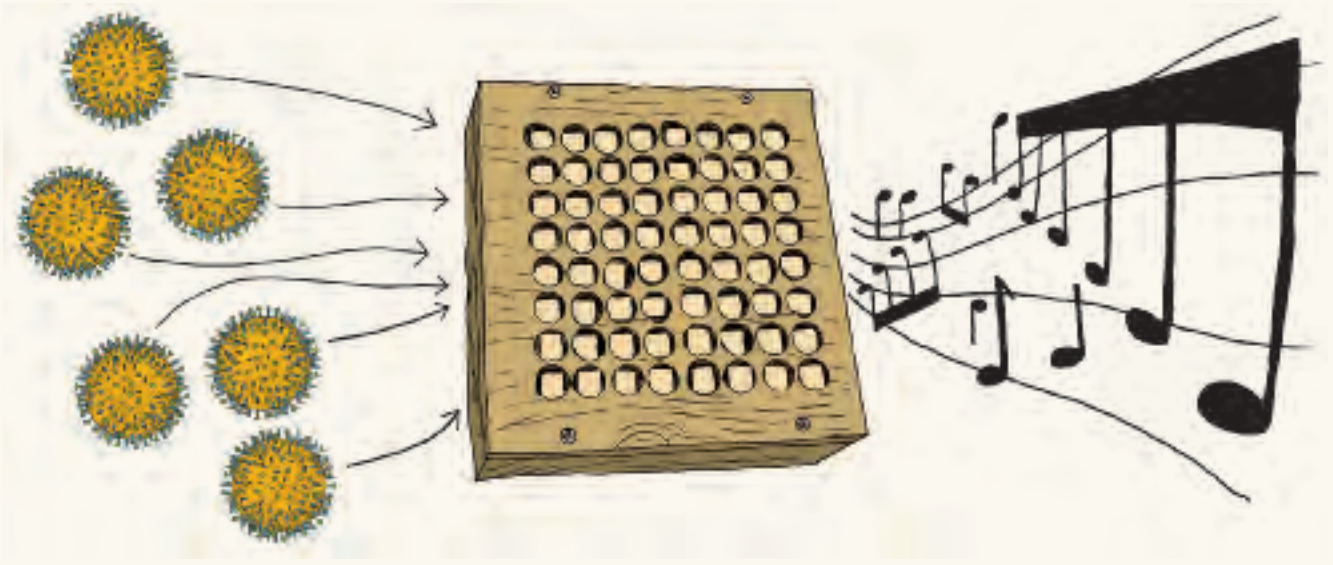
The test was a two-day series of challenges that included running, vigorous sessions on a rowing machine, rolling, and sparring. The point, she says, "is to get you physically and mentally exhausted first." During the test, "you can be asked to do anything, even if you've never seen or done it before. It's generating a mental structure to deal with the unexpected."

She passed and became an instructor. Sil says she aspires to motivate rather than intimidate her students—in science and taekwondo. "I'm going to ask people to do a lot, but I wouldn't ask them to do something I wouldn't do myself."

Sil continued to teach until 2008, after her second child was born, and she still trains when time permits. In the lab, when they need to focus and get work done, she fights the occasional urge to have her graduate students drop and give her 30. Despite her invitations, none of her lab members has joined her in the taekwondo studio. She laughs: "Maybe that's a good thing."

—*Sarah Goforth*

Melissa Kaseman



Melodious Genes

In the corner of a small art gallery in Queens, a white plaster pedestal supports a square wooden sculpture containing 64 silicon buttons. With the help of a willing gallery visitor, the piece can convert genetic code from the influenza virus into music.

The interactive artwork is the creation of Jeff Kim, a scientist who uses the basic biology he studies to make art in his spare time. Taking that mental leap out of the lab and into a gallery gives him a fresh perspective on his research. Usually, his artwork drives ideas for experiments. "It's kind of a guilty pleasure," he says.

Kim is a doctoral student in the Rockefeller University lab of HHMI early career scientist Sean Brady, who mines vast quantities of environmentally derived DNA—for example, from soil-dwelling bacteria—looking for genes that could lead to bioactive natural products, such as antibiotics and anticancer agents.

One of Kim's recent tasks in the lab was developing an easy way to visualize lots of genetic information in an intuitive manner. As a proof of principle, he focused initially on a protein involved in influenza virulence. There are nine versions of the viral enzyme, each with a slightly different genetic code.

It's hard to get a snapshot of all nine versions at once. Usually that information comes in a series of charts, graphs, and sequences of letters. Kim was stumped on how to proceed until he brought the problem to his artist friends. They suggested layering the information—somehow.

So Kim plotted the DNA base pairs—A, T, C, and G—as a grid of translucent, colored squares. The squares changed in color intensity based on whether the base pair existed in that particular version of the enzyme.

By layering the nine different grids, Kim created a simple map that revealed mutations: Squares with more intense colors meant the base pairs stayed the same for all nine types. Faded or discolored squares meant a change in the base pair. Suddenly, Kim could see interesting information about several versions of the enzyme at once, in an aesthetic way.

The grid became a central part of Kim's art. Which is where the sculpture comes in.

The piece is modeled after a section of his grid: inside a wooden frame are 64 keys, each connecting to a chip that communicates with a computer program. Each key corresponds to a colored square on the grid, which in turn corresponds to a different section of a piece of music Kim composed.

People can play the instrument by pressing different keys. The computer program registers the pattern and, from a desktop computer, strings together tracks of Kim playing the cello, based on the order in which the keys are pressed.

The grid is useful for intuitively visualizing complex genetic information, but the sculpture lets people interact with that information in an unexpected way, Kim says.

When he came to New York, seven years ago, Kim tried focusing on music, his first love. At Rockefeller, he learned that science could be a creative outlet and that both fields could complement one another.

"The music thing was fun but it was hard to survive solely on musical pursuits," he says.

Now, science keeps him fed, but his mind still sees genes and hears notes. *—Shelley DuBois*

WEB EXTRA: To see and hear Kim interact with his grid sculpture, visit www.hhmi.org/bulletin/nov2010.

Peter Arkle

upfront

08 OBSESSION'S UNLIKELY ORIGINS
A shortage of certain immune cells might prompt obsessive-compulsive disorder.

10 REALITY CHECK
David Stern wants to know how the fly genome behaves in the real world.

WEB ONLY CONTENT

MESSAGE TO IMMUNE CELLS: SIC 'EM!
Researcher's longtime efforts to drive T cells to attack tumors hits pay dirt. Read the story at *www.hhmi.org/bulletin/nov2010*.

The immune system is made to shield the body from disease and invaders. Sometimes the system fails: a pathogen's attack is too quick or a cancer's capacity to self-protect is too strong. Sometimes the system doesn't respond because of its own checks and balances. One researcher figured out how to free the immune system from the handcuffs that keep it from attacking cancerous cells; a resulting drug is showing promise in clinical trials. And it turns out that certain immune cells influence brain development. Their absence may play a role in obsessive-compulsive disorder, opening new avenues for treatment. More reasons to be in awe of human biology.

Obsession's Unlikely Origins

A shortage of certain immune cells might prompt obsessive-compulsive disorder.

A BONE MARROW TRANSPLANT SEEMS AN UNLIKELY PRESCRIPTION FOR obsessive-compulsive disorder (OCD), an anxiety condition that drives people to repetitively wash their hands, for example, or continually check door locks. Surprisingly, a transplant stopped obsessive grooming in mice with a disorder that resembles OCD, according to HHMI investigator Mario Capecchi of the University of Utah and colleagues.

The researchers don't recommend the procedure for OCD patients. Bone marrow transplant is usually reserved for people whose bone marrow doesn't work properly or has been destroyed by chemotherapy or radiation treatment. But they do think the discovery could spark new treatments for a disorder that affects more than 2 million adults in the United States alone.

The most recent study isn't the first to implicate a faulty gene in obsessive behavior (see Web Extra, "Is OCD in the Blood?"). But it provides the first experimental evidence that defects in the immune system help trigger OCD, Capecchi says. Researchers had long suspected a connection, but the data remained circumstantial.

It's not surprising that grooming and immune defenses are tightly linked, he adds. Both have the same goal—protecting against diseases.

Capecchi and his colleagues didn't set out to find an OCD-immune link. Capecchi helped develop gene targeting, a technique that allows researchers to rewrite the DNA instructions of any gene—work for which he shared the 2007 Nobel Prize in Physiology or Medicine. For more than a decade, his team has used gene targeting to tease out the functions of *Hox* genes, a family of 39 genes that help shape the developing embryo and perform other jobs in the body. They disabled, or knocked out, the genes one by one in mice and documented the impact on the animals' health.

When Capecchi and his then graduate student Joy Greer got around to the gene *Hoxb8*, however, they found that the knockout mice showed no obvious physical flaws. So the pair put the nocturnal rodents under surveillance with infrared cameras. "We were looking for behaviors because we weren't seeing anything else that was wrong," says Capecchi. By tallying how the rodents spent their time, the researchers found that the animals devoted an hour each day to washing themselves, twice that of normal mice.

The mice weren't just getting squeaky clean. They groomed so intently that they ripped out clumps of fur, leaving large bald patches, and often licked their skin raw, the researchers reported in 2002. Capecchi and Greer likened the behavior to a disorder that's similar to OCD called trichotillomania, in which patients repeatedly pull or twist their hair until it falls out.

Capecchi's group decided to trace the source of the abnormal grooming by determining which brain cells made Hoxb8 protein. Nerve cells that control behavior were the likely candidates. However, the only brain cells cranking out Hoxb8 were

microglia, immune cells that scoop up and destroy cellular rubbish and invading pathogens. "That was a complete surprise," says Capecchi.

When the researchers returned to their knockout mice, they found that animals lacking *Hoxb8* carried 15 percent fewer microglia in their brains, suggesting that the cells are somehow necessary for normal neural wiring.

Capecchi and colleagues tested the idea by giving the mice bone marrow transplants. The brain harbors two kinds of microglia. About 60 percent of the cells are present in the brain from early in life. But the others descend from cells that originate in the bone marrow and then migrate into position. A bone marrow transplant can replace these cells.

When mice missing *Hoxb8* received bone marrow from normal animals, most of them groomed less. Their fur filled in, and their skin sores healed. And when Capecchi and colleagues introduced bone marrow from mice lacking *Hoxb8* into normal animals, the recipients began cleaning themselves excessively. The team reported its findings May 28, 2010, in *Cell*.

"People thought of microglia as scavengers," Capecchi says. "But we say they are monitoring what's going on in the brain and having an influence on the output." In other words, they change behavior. The cells could modify how the brain works in several ways, he notes. They could release chemical messengers called cytokines that trigger brain cells to fire more or less often. Microglia also send out tendrils that cozy up to synapses, the junctions between nerve cells, and thus they might be able to alter the activity between neurons.

Capecchi and colleagues are extending the work to patients, testing people with trichotillomania to determine whether they carry defects in their *Hoxb8* genes. He'd also like to study bone marrow recipients—around 300,000 of the procedures have been performed—to determine whether their behavior changed after the transplant.

Current OCD treatments include psychotherapy and drugs like Prozac (fluoxetine). But focusing on microglia could lead to alternatives that might work better than tricky therapies that try to fine-tune the nervous system, says Capecchi. "Treating the immune system, which we know more about, might have an influence on the disease." ■ –MITCH LESLIE

WEB EXTRA: To read about Shahin Rafii's work in the sidebar, "Is OCD in the Blood?" go to www.hhmi.org/bulletin/nov2010.

VSA Partners

Reality Check

David Stern wants to know how the fly genome behaves in the real world.

The tiniest hairs on fruit fly larvae have complex genetic controls that David Stern almost missed—until he took the fruit flies out of their cozy incubators.

Mark Mahaney

THE AVERAGE FRUIT FLY DOESN'T LIVE IN A CLIMATE-CONTROLLED lab. Most must fend for themselves, seeking food, evading predators, and enduring chilly nights and hot days. These are the real-world conditions under which the insects have evolved, says HHMI investigator David Stern, and many of the marks that evolution has left on the fly's genome will be difficult to decipher unless researchers consider those factors as they design their experiments.

It's a lesson that Stern's lab group underscored with its latest discovery about the genetic components that control the production of tiny hairs that poke from the surface of newly hatched fly larvae. The hairs, called trichomes, show up in roughly the same spot in most species of fruit flies, and Stern's lab has solid evidence that evolution has made a point of keeping them around.

"It's very clear from the evolutionary pattern that the flies care very much [about their trichomes]," he says. Biologists, on the other hand, have yet to figure out why they're there. "We have a lot of stories about what the trichomes are for," Stern says, "but they're all just tall tales."

Trichomes captured Stern's attention with their deceptive simplicity: researchers had long known that when a gene called *shavenbaby* is missing in flies, they don't make the trichomes; instead, they hatch out bald. Stern found that *shavenbaby* was more active in some species than in others, and the level of activity correlated with species-specific variations in trichome patterns. He set out to identify nearby DNA sequences that contributed to these variations.

"We started bashing away at it very naively, imagining that all we had to do was go one or two kilobases upstream from the promoter, find the single nucleotide change, and we'd be home by Christmas," he remembers.

Ten years later, many of the microscopes in Stern's lab are still focused on the larval trichomes. His group's methodical search for regulators of *shavenbaby* has taken them far from the gene itself, and the story keeps getting more complicated. They've analyzed the DNA within 93,000 base pairs of *shavenbaby* and found six separate sections of DNA that promote the gene's activity. Five of these enhancers have acquired sufficient mutations during evolution to produce new trichome patterns in various species.

"This is for a gene whose job is to put these silly little hairs on the cuticle," Stern says. "But even this very, very simple little piece of morphology is built by a gene with a very complex architecture—and that complex architecture evolves through lots and lots of tiny little changes."

Curiously, the three enhancers farthest from the gene at first appeared to be unnecessary. Although the sequences could turn on a nearby gene when they were spliced into an artificial system, when Stern's team eliminated the enhancers in living flies, larvae emerged from the lab incubator with the usual carpet of trichomes.

> "We have a lot of stories about what the trichomes are for, but they're all just tall tales."
>
> DAVID STERN

That result was discouraging, Stern says, until he and postdoctoral researcher Nicolás Frankel realized that the comfortably warm incubator where they kept their flies was a poor imitation of the conditions under which the insects evolved. "Flies in nature probably experience a dramatic range of temperatures," Stern says, from hot sunny fields to chilly orchard nights. Protein production and developmental networks are strongly influenced by temperature, and Frankel and Stern wondered whether the enhancers they had found might be important for ensuring that the Shavenbaby protein was manufactured under suboptimal conditions.

When they grew flies at temperatures well above and below their usual laboratory conditions, but still within the range of temperatures flies might experience in nature, Stern's team saw what they had suspected all along: larvae produced far fewer trichomes when the three most distant enhancers were missing. The "extra" enhancers contributed to the fly's ability to produce trichomes, but they were called on only when temperatures fluctuated outside the ideal range. "We took that as our first evidence that these enhancers are there to provide a function for flies that live in the real world," Stern says.

Stern's group published their findings in *Nature* on July 22, 2010. He says he suspects that these types of regulatory regions—known as shadow enhancers—are quite common and that they probably protect organisms from many kinds of environmental and genetic variability. "One of the messages we're really trying to get across is that a lot of the genome may be encoding functions that you won't detect in laboratory conditions, because they provide a function in the real world, where temperatures are variable, where food resources are variable, where the genetic background of individuals changes each generation," he says.

Stern is eager to continue digging into the *shavenbaby* gene, because he's convinced that it still has big secrets to reveal. By way of example, he points out that the DNA flanking the *shavenbaby* enhancers is more evolutionarily conserved than the enhancer DNA itself. "That's basically 95 percent of the DNA surrounding the gene," he says. "And I have no idea what that 95 percent is doing. None. That's a lot of DNA to explain, and it's a lot of evolutionary conservation to explain. Those sorts of observations make me feel like we're missing something big." ■ –JENNIFER MICHALOWSKI


In Their Own Back Yard

Students in rural schools need extra support to learn science. And educators are bringing it to them.

BY ANDREA WIDENER ∂ ILLUSTRATION BY NOMOCO

During her first year teaching at Lake City High School in rural South Carolina, Patsy Williamson was approached by a student in her environmental and marine science class. He was writing about the local beaches and couldn't figure out when visitors should go. Williamson suggested he draw on his own experience. "I said, 'You've been to the beach and seen all the jellyfish, haven't you?'" The boy looked back blankly. "He said, 'No, ma'am. I've never been to the beach.'"

"I was dumbstruck," says Williamson, a long-time teacher who was a newcomer to rural schools. "He lives 50 miles from the Atlantic Ocean.... That's poverty. It's not lack of motivation. It's just poverty."

Students in rural areas are often separated from their urban and suburban counterparts by more than just distance. Many live in communities that have faced decades of decline in the agricultural and manufacturing industries, and they grow up without money or opportunities. It can put them at a disadvantage in school—about half the children in rural schools fail to meet federal reading and math proficiency goals—and later, when they are choosing a college or a career.

That's why many of HHMI's science education grantees are focusing their outreach efforts on teachers and students from rural schools. Because long-distance travel is often out of the question, they are sending curricula and materials to rural teachers and finding research experiences within the rural communities.

"We recognize that it doesn't do any good to tell rural teachers to take their kids to a great museum or somewhere else that would only be accessible in a city. There are special needs in a rural community," says Robin Fuchs-Young, who directs an educational program at the University of Texas MD Anderson Cancer Center campus in Smithville, Texas, that focuses, in part, on rural schools. "We realized we could not only help provide resources for our rural community but also work on building a model that better meets the needs of rural school systems."

Keeping Field Trips Local

More than 10 million students nationwide attend rural schools, according to a 2009 report by the Rural School and Community Trust, a nonprofit advocacy group. Getting to college is a long road for many of them because more than 40 percent of rural students live in poverty, and only 69 percent graduate from high school.

Rural school districts want to help their students overcome these barriers, but most just can't afford it. Science is a special problem because of the expense. Districts often don't have a tax base to support even the most basic science class supplies, like prisms and beakers, much less the expensive equipment needed for modern biology and chemistry labs. While some urban and suburban schools face similar budget problems, teachers in rural schools have fewer places to go for help: fewer local businesses to ask for donations of money or equipment, fewer scientists nearby to share their expertise, fewer universities and museums to illustrate why science matters.

"One of our biggest issues is showing kids how science can benefit them in the real world," says Keith Starr, a science teacher at a charter high school built in a former peanut field in Gaston, North Carolina. Starr, who has worked with the Trust, doesn't have many opportunities to invite scientists into his classes, but he has found the occasional scientist from outside who is willing to visit, including Howard University physics professor Walter Lowe who grew up in the area and NASA astrophysicist Harvey Moseley who Starr met through a member of his school's board of directors.

Field trips are a great way to spark student interest, many teachers say. They offer a real-world view of science, but distance, time, and money make trips especially difficult for rural schools. That's why Sara Swearingen and two dozen of her fellow teachers in rural Texas visited a hydroelectric power plant on the Guadalupe River between Austin and San Antonio, straining to hear over the rushing water and the loud buzz of the power equipment. On a sticky July afternoon, these central Texas teachers visited three sites for field trips that they may be able to re-create in many rural areas: a power plant, a cave, and an organic farm.

The visits are part of the Rural Schools Initiative run by Fuchs-Young at MD Anderson in Smithville, itself a rural community. "It was a response to the needs expressed to us by teachers, who are concerned about their students who want to stay in their rural community [after graduation]. They have very bright students who don't have the kinds of scientific career opportunities that those in more urban and suburban districts might have," Fuchs-Young explains. She and her colleague Heather Reddick started looking around their own rural town. "We found all kinds of resources and places that are in and around rural communities that provide rich learning environments and also show off scientific or health-related career opportunities."

Every small town has a wastewater treatment plant, a farm, or a local hospital, for example. The Rural Schools Initiative trains

teachers to create local field trips at these kinds of nearby, low-cost venues. Field trips give students a chance to meet people who work in science, like Scott Kolbe, the technician who explains how water turns into electricity at the hydroelectric power plant, or Malcolm Beck, the organic farmer who wowed the teachers by showing them how garden waste feeds the fish he farms; and the fish waste provides organic fertilizer for the garden.

Swearingen, who teaches fourth grade in Smithville, says field trips have been canceled in her district because of budget cuts. No more trips to the state capitol or the Blue Bell ice cream factory 60 miles away. But field trips closer to home might be an option. "There are things out there," she says, "we just don't know what is available." Reddick, Fuchs-Young, and the rest of the team help them find these resources.

Science in a Box

In far eastern Oregon, Rachel Aazzerah is the only science teacher for the tiny K–12 school in Monument, Oregon. She teaches the required science classes for all of the school's 60 students starting in seventh grade until they graduate.

Aazzerah is lucky enough to have a great science lab with hoods and a prep room; many of her fellow rural teachers work out of aging classrooms with carpeting and no access to water, which can be both dangerous and discouraging for a teacher who wants to tackle hands-on activities. And she's been successful in getting grants to help pay for equipment, like spectrometers and DNA gel electrophoresis machines, in part because with a master's degree in biochemistry, she knew where to look.

Aazzerah's biggest problem is time. Because she teaches so many different subjects, she has to prepare lessons and grade tests for up to five different classes daily (to save money, the school is on a four-day week). When she chooses to do hands-on labs, which is fairly often, Aazzerah spends her nights and weekends getting ready.

"Guts In A Box" and other science education kits offered by Oregon Health & Science University (OHSU) are a big help. The school has created six "In A Box" science kits specifically for rural teachers. They are funded by HHMI and distributed statewide through Oregon's Area Health Education Centers (AHEC), which do educational outreach to rural communities

Matt Rainwaters

With a grass-covered dam in front of him and the fish-filled Guadalupe River behind, technician Scott Kolbe tells two dozen rural Texas teachers how a hydroelectric power plant operates and what training he needed to do his job.

and schools. (All 50 states have their own rural health centers.) Around 3,700 students used the boxes during the 2009–2010 school year.

OHSU's Shera Felde, who helped design the kits, explains that they aim to give students a series of connected lessons on the same topic and, perhaps most important for cash-strapped rural teachers, the equipment needed to make the lessons fun. For the "Ear In A Box" kit, which Aazzerah has used in her classes, the lessons include ear anatomy using a plastic model ear; the science of hearing loss using a sound meter; pitch and volume, complete with a rollout piano and hearing aids; plus a lesson on how sound travels from the ear to the brain. Students also learn about science careers in audiology and hearing research.

Aazzerah says her students learned a lot from the lessons, especially the focus on hearing loss. As a teacher, she appreciated the guidance about what activities fit the state standards for different grade levels—and that it's free. "It's great especially when you don't have that kind of equipment in your room. You are able to use it and send it back," says Aazzerah, whose small budget barely covers textbooks. "[OHSU and AHEC] even pay for the shipping."

The original idea was for OHSU to train teachers in person on how to use the "In A Box" kits, but the distances proved too difficult to overcome. Now the boxes come with written instructions and a teacher training video. Like Aazzerah, who lives more than three hours from the nearest community college or university, many rural teachers don't have regular access to teacher training. "It's hard for working teachers in a non-city environment to get their science courses," says Barbara Speziale, who directs HHMI's science education program at South Carolina's Clemson University.

Speziale and her colleagues learned that rural teachers can't take classes that meet once a week at a college hours away. So they designed intensive graduate-level summer classes to help rural teachers learn new skills or incorporate more hands-on science in their classes. The Clemson team created short classes—one to two weeks on campus—based on the teachers' interests and state standards. The eclectic mix that resulted includes focused lab science courses like "Welcome to the Gene Age" and "What is Bioinformatics?" as well as ecology and natural science courses like "Ethnobotany and Ethnoecology of South Carolina" and "Teaching Your Watershed."

Deb Whittington, a science specialist at J. Paul Truluck Middle School in Lake City, South Carolina, has taken several Clemson classes, both the intensive summer courses and newer online offerings. "I probably wouldn't be able to do it if these were traditional courses offered only during the normal school year," she says. What's more, Clemson often provides materials—microscopes, electronic sensors, stains, or cellular growth media—that the schools wouldn't be able to fund otherwise. "They make it so you're comfortable that you can go back and use it in your classroom," Whittington says.

Do and Learn

Seventeen-year-old Severin Gilbert lives just outside Ulm, Montana, population 750, and goes to a kindergarten through 12th grade school in the slightly larger town of Cascade. Because the school is so small—about 30 students per grade—most classes are offered only during one class period each year, and scheduling conflicts can often mean that science classes take a back seat

Exposure to the Possibilities

In bad financial times, field trips are often the first cut that rural school districts make. But if someone else is paying the bills, taking students to visit a university can be immensely valuable. ¶ *Every year,* Patsy Williamson takes a few of her students more than 200 miles from Lake City, South Carolina, to Clemson University, where students from nine rural, largely minority high schools and middle schools tour the campus, meet scientists, visit labs, and talk to college students. The trip involves a four-hour bus ride each way and a biology achievement test once they get there, but Williamson's students fight for the chance to visit a college campus, most for the first time. ¶ *"They find out a lot* about possibilities, about opportunities, what kind of jobs you might be able to get. And when they see [Lake City graduates] there they realize 'I can get there too,'" Williamson says. "These kids are really poor, but they are good kids. This is the best teaching experience I've had." ¶ *Barbara Speziale,* who directs HHMI's science education program at Clemson, was inspired to help rural students and teachers by the grim reality facing South Carolina: only 14 percent of South Carolina-born state residents have bachelor's degrees, and the state ranks 48th in the percentage of ninth graders who graduate from high school within five years and go on to college. As the tobacco farming and textile manufacturing industries have declined, the problems in the state have gotten worse. "I have visited many of these rural communities," Speziale says. "In some, there is no opportunity as far as the eye can see." ¶ *A visit to Clemson* during high school changed Satoya Murray's path. She grew up in Clio, South Carolina, a former textile town with a population of less than 1,000. "It definitely got me more interested in science, seeing all of the opportunities that they had to offer," says Murray, now a junior majoring in biological and health science at Clemson and the first in her family to go to college. After her visit, she thought, "Man, this is like a whole new world. A world you definitely want to be a part of." —A.W.


Heather Reddick (left) from University of Texas MD Anderson Cancer Center campus in rural Smithville, Texas, identifies field trips that can be done in almost any small town. Sara Swearingen (right), a fourth grade teacher from Smithville, plans to encourage her cash-strapped district to organize local field trips, to sites like farms, recycling centers, or power plants.

Matt Rainwaters

to math, English, and other required courses. Severin, a senior this fall, hasn't been able to fit in chemistry yet; she took biology though a correspondence course. Still, she thought she might want to be a bioengineer. "It sounded like sort of what I wanted to do," she says. "But I hadn't done much lab work. There were really simple things I didn't know how to do."

Cascade's only full-time science teacher, Billie Perry, knew Severin was interested in science and suggested she apply for a summer research program for local students at the McLaughlin Research Institute, a mere 17 miles from her home. Severin's lack of lab experience was not a concern. The staff at McLaughlin recognizes that rural schools can't provide all the opportunities of a large urban or suburban school district, says George Carlson, HHMI's program director at McLaughlin, the only research center within a three-hour drive. Severin is just the type of student they were trying to attract to the program: someone who is interested in science but might not get to work in a research lab otherwise.

Severin was selected for the program and, during the summer of 2010, she worked with a teacher from a Great Falls high school on a research project in a lab studying Parkinson's disease. "It's been incredible, Severin says. "I thought I would be doing a lot less interesting things. I thought it would be more of a 'watch and learn' situation rather than 'do and learn.'" The experience cemented her desire to become a bioengineer—now that she knows what one is.

Having a research institution nearby is a rarity for most rural students, so sometimes a pond will have to do. For the last eight years, teachers and students from five high schools in four North Carolina counties have used a historic mill pond in Chowan County as a place to do hands-on research. The idea came from Colleen Karl, the northeastern outreach coordinator for The Science House, a North Carolina State University outreach program for teachers and students that is funded in part by HHMI. She stumbled across Bennett's Mill pond one day and thought it would be the perfect place to teach students the frustrations and rewards of real research.

Farmers brought corn to the mill pond for grinding for hundreds of years. Today, the mill is gone, but Karl and the teachers take students onto the 100-acre pond in canoes and help them decide what would make a good research topic. The young researchers then spend the next two years at this local site collecting and analyzing their data, with the help of their teachers as well as state biologists and extension workers. "It is an experience they can't get in a regular classroom," Karl says. "The biggest value to the students is that they are empowered when they work on a project like this. They have total ownership of it."

Student Joel Moreland spent his childhood fishing on the mill pond, Karl says. He wondered whether a drought in 2007 had harmed the black crappie population, so he designed an experiment with local fish and wildlife scientists to determine the age of the remaining black crappies by looking at their length, weight, and a bone in the fish's heads. Joel, currently a senior, is still collecting data, but so far the fish that would have been born in 2007 are missing from the lineup. "This is Joel's learning laboratory," Karl says. "He's really excited about this work and knows what he's doing is making a difference." Of the 74 students who have participated in the project, 86 percent are attending a four-year college and 70 percent are majoring in science.

Research centered on local resources is a model that is applicable anywhere, says Karl. "Not every county has a mill pond, but they have other resources. Projects like this work really well in our rural communities," she adds. "We do have great resources. We just need to learn how to use them." ■

WEB EXTRA: To see an audio slideshow of this summer's field trips sponsored by the Texas-based Rural Schools Initiative, visit www.hhmi.org/bulletin/nov2010.

by Robert Koenig
illustration by Mattias Adolfsson

Scientists are targeting pathogens' surface proteins to battle disease.

PIERCING THE MULTI-FACETED COAT

IMAGINE

battle armor that is so effective it continually transforms itself—adapting to protect its wearer from fast-changing assaults. In the microbial realm, the wearer is a pathogen that uses its responsive armor—consisting of the varying protein coats on its surface—to fend off the host's immune-system defenses.

"These pathogens keep changing their coats, fooling whatever the immune system sends after them," says HHMI international research scholar Hugo D. Luján, who studies surface-protein regulation in the intestinal parasite *Giardia lamblia* at his laboratory at the Catholic University of Cordoba in Argentina. Whether the pathogen defenses are compared to beasts with ever-changing scales or bandits with different disguises, the surface-protein variation poses major challenges to medicine.

Now that genomic analyses have identified the genes that express surface proteins, scientists are focusing on how pathogens detect attacks from the human immune system and quickly change their coats. That process, called antigenic variation, allows the microbe to evade the host's immune response and extend the length of infection. And by making it difficult for the host to identify the microbial invader, it opens the door to reinfection and increases the odds that the disease will be transmitted to more human hosts.

A handful of HHMI researchers are bringing determination and creativity to the fore. A bit like high-tech tailors examining and testing surface-protein garments, they are pushing a parasite to overload its coat and reveal all its defenses, investigating how the cloak is manufactured, and studying the role of the insect vectors that transfer the parasite to the human host. Their aim is to help develop treatments or vaccines for a wide range of masters-of-disguise microbes, including those that cause African sleeping sickness, diarrheal disease, and Lyme disease (see sidebar, "Another Shot at Lyme Disease").

The challenge is not new. A century ago, researchers experimenting with *Trypanosoma brucei*-infected monkeys in the laboratory of Nobel Prize winning biochemist Paul Ehrlich first uncovered evidence of antigenic variation, reporting that the trypanosomes "have acquired other biological properties … that rendered them resistant to the defensive substances." It took another seven decades before molecular parasitologist George A.M. Cross of the Rockefeller University in New York identified the molecular basis for antigenic variation in the African trypanosome. Since then, such variation has been studied in numerous parasites as well as bacterial and viral pathogens.

Many molecular details of antigenic variation remain inscrutable, says Cross, in part because of the complex cellular mechanisms involved. Even so, he is optimistic that scientists may find ways to slow down the rate of surface-protein switching and give the human immune response more leverage to control infections.

GIARDIA IN ARGENTINA

At his lab in Argentina, Luján has found a way to force the *Giardia* parasite to reveal nearly all its surface-protein defenses at once. In doing so, he has made progress in developing a vaccine to prevent the diarrheal infection caused by the parasite and created a model for attacking other pathogens with similar antigenic talents.

Giardia—which can evade the human immune response and survive as a cyst in adverse conditions—is a common cause of parasitic gastrointestinal disease, leading to as many as 2.5 million cases of giardiasis each year in the United States.

It is estimated that nearly one-fifth of the world's population is chronically infected.

Luján became interested in *Giardia*'s antigenic variation while he was a postdoc in the lab of Theodore E. Nash, head of the gastrointestinal parasites section of the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland. Nash, who first reported antigenic variation in *Giardia*, says the Argentinian was "a real star in my lab." Later, Luján helped reveal that, from a repertoire of about 200 genes that encode surface proteins in the *Giardia* genome, only one is expressed at any one time on the surface of the parasite. By the time the human immune system identifies and tries to knock out one set of surface armor, the parasite—with a wardrobe of a couple of hundred different protein armor sets to choose from—has shifted to another set.

In a December 2008 *Nature* paper, Luján and colleagues showed that antigenic variation in *Giardia* is regulated by RNA interference, a mechanism that eliminates all but one of the surface proteins at any given time. Then, in a paper in *Nature Medicine* in May 2010, Luján's group reported evidence that parasites engineered to express nearly all of their surface proteins at once could be used to rally an infected host's immune system.

His group purified all the antigens expressed by those engineered parasites and used them to create a vaccine. They administered it orally to gerbils—first making sure the vaccine's proteins could withstand the harsh environment of the gastrointestinal tract. It worked, successfully protecting the animals from future infections. "We were the first to demonstrate that, since the parasites continuously change their surface proteins, we must use all of the possible variants to confer full protection to subsequent infection."

His lab has since shown that its vaccine approach works in dogs as well, and Luján is seeking a partner to try the approach on humans. In addition, he says, other researchers are now using the strategy, including a scientist at the Pasteur Institute in Paris who is investigating several candidate drugs that would promote the expression of all surface variants of the malaria parasite.

TRYPANOSOMES IN SPAIN

Unfortunately, the full protein exposure model is not likely to work with every pathogen. The trypanosome parasite that

ANOTHER SHOT AT LYME DISEASE

The first vaccine that Erol Fikrig helped develop against Lyme disease targeted a surface protein of the *Borrelia burgdorferei* bacterium. That approach was good, but it didn't guarantee protection against the disease. Now he's taking a different approach: targeting a protein in tick saliva that helps the pathogen infect the host. » ***That tick protein*** is an extra "slicker" on top of the usual surface-protein coat that protects *Borrelia*. "We aren't targeting the pathogen's own armor, but the extra cloak provided by the tick vector," says Fikrig, an HHMI investigator at Yale University School of Medicine. » ***Fikrig's research team*** has made progress in battling *Borrelia* and has answered broader questions about how bacterial pathogens interact with their vectors and environments. » ***Named for a cluster of cases*** in the Connecticut towns of Old Lyme and Lyme in 1975, Lyme disease infects at least 10,000 to 20,000 Americans each year. Left untreated, it can cause serious damage to the heart, joints, and central nervous system. » ***Fikrig and fellow HHMI investigator Richard Flavell*** developed the first Lyme vaccine in mice in 1990, and Fikrig was part of the team that performed the human studies for the vaccine, which was first marketed in 1998. It focused on outer surface protein A (OspA), a dominant protein on *Borrelia*'s surface. The vaccine was 80 percent effective—good but not great—and, citing concerns about profitability, the manufacturer stopped production in 2002. » ***Looking for a new approach*** to blocking Lyme transmission, Fikrig shifted his focus to the tick. Unlike mosquitoes and tsetse flies, ticks must stay attached to the host for two or three days to transmit the *Borrelia* infection. » "***My question was:*** Is the microbe's interaction with tick saliva essential to *Borrelia*'s ability to infect humans?" Fikrig says. In a round of experiments with mouse models, his group found that the pathogen causes the tick to overproduce salivary protein 15 (Salp-15), which acts as a shield from the host's immune system. » ***Fikrig and colleagues*** developed an antiserum against Salp-15 and injected it into several mice. They treated the same number of mice with an inactive serum and then exposed all the rodents to *Borrelia* coated with Salp-15. A week later, every control mouse—but only half of the mice treated with the Salp-15 antiserum—showed signs of Lyme disease, with the bacterial burden significantly less in the mice treated with antiserum. At three weeks, 40 percent of the mice injected with the antiserum were free of symptoms, with lower levels of *Borrelia* in key tissues. » ***Since the Salp-15 antibodies*** made *Borrelia* less infective in the host, Fikrig decided to combine the Salp-15 antiserum with the older vaccine. His team injected different groups of mice with a low dose of either an OspA antibody or a Salp-15 antiserum and another group with a low-dose combination of the two. All the mice, including an untreated control group, were then exposed to *Borrelia*-infected ticks. The researchers used a lower-than-therapeutic OspA dose to get a clearer sense of the impact of the Salp-15 antigen, Fikrig says. » ***The scientists reported*** in 2009 in *Cell Host and Microbe* that the mice treated with the combined dose fared the best, with only about a quarter showing symptoms of Lyme. Those mice also had the lowest burden of bacterial infection. In contrast, 90 percent of the mice injected only with the low-dose OspA vaccine (and 100 percent of the untreated mice) showed symptoms of *Borrelia* infection. » ***If a pharmaceutical firm*** eventually conducts human studies on the combination vaccine, Fikrig says a higher-dose OspA vaccine would likely be combined with the Salp-15 antiserum to achieve greater effectiveness. In the meantime, his team is exploring the molecular biology of the tick–parasite interaction. » "***We're now investigating*** the molecular mechanism of how the antibodies provide the protection," he says, "and we are trying to determine the exact function of Salp-15 in both the tick and the host." —*R.K.*

causes African sleeping sickness, for example, devotes a tenth of its genome—as many as 1,500 genes—to antigenic variation. NIAID's Nash also points out that the relatively streamlined *Giardia* has "an extremely different mechanism" for shifting its surface proteins than the more complex trypanosome.

In the crossroads city of Granada, Spain, HHMI international research scholar Miguel Navarro is well down the path to explaining the molecular mechanisms and intricate nuclear architecture of *Trypanosoma brucei*, including how the parasite's bloodstream stage expresses only one surface-protein gene at a time, the variant surface glycoprotein (VSG).

The key appears to be the dynamic association of chromosomes with structures in the parasite's nucleus. Navarro's laboratory at the Spanish National Research Council's Institute of Parasitology and Biomedicine investigates "which molecules are involved in the [surface-protein] transcription switching that allows the parasite to elude the host immune response," he says.

Adopting techniques of both molecular and cell biology, Navarro uses three-dimensional microscopy and green fluorescent protein tagging to visualize the position of chromosomes in the nucleus and to investigate the position and dynamics of the telomeres—chromosome ends—that are active in antigenic variation.

The team has discovered that the African trypanosome mechanism for achieving its astounding surface variation is complex. Navarro's recent research has focused on a protein complex—called the cohesion complex—that is essential for gluing together replicated chromosomes, or chromatids, when a cell divides. When Navarro's group knocked out the protein complex in the trypanosome, it led to premature separation of the chromatids that contain genes for variable surface proteins. That interruption, in turn, caused a change in the antigenic switching of those proteins. These and previous findings have deepened the understanding of the trypanosome's nuclear architecture and are helping researchers find ways to target the parasites.

Navarro first worked on antigenic variation in Cross's laboratory from 1994 to 1998 and then moved to the University of Manchester in the U.K., where he published an influential 2001 paper in *Nature*. The paper reported that transcription of surface-protein genes is located in a specific area in the nucleus—called

There must be a way to topple a pathogen's defenses. Hugo Luján, Miguel Navarro, and Isabel Roditi are finding ways to give the human immune system a chance against fast-changing infectious agents.

Luján and Navarro: David Rolls Roditi: Dirk Dobbelaere

"THESE PATHOGENS KEEP CHANGING THEIR COATS, FOOLING WHATEVER THE IMMUNE SYSTEM SENDS AFTER THEM." —*Hugo D. Luján*

the expression site body—in such a way that only one surface gene is expressed at a time.

After returning to Spain, Navarro continued to explore the role of nuclear chromatin dynamics in antigenic variation. Cross says that Navarro's research and related investigations are "starting to identify several genetic factors and structural attributes" of variant surface proteins that affect their switching.

TSETSE FLIES IN THE ALPS

While Navarro's work has focused on the trypanosome's bloodstream-stage surface proteins, Isabel Roditi studies how the parasite regulates the expression of those proteins inside the gut and salivary glands of its vector, the tsetse fly. Of special interest is the parasite's ability to sense its outside environment and respond with the appropriate adjustment of its surface coat.

"There is a complex interaction between the trypanosome and the fly as the parasites differentiate, reproduce, and migrate through different tsetse tissues," says Roditi, an HHMI international research scholar at the University of Berne.

Using methods to genetically manipulate trypanosomes, Roditi's team was surprised to discover that many of the large number of surface molecules on trypanosomes were not needed to grow the parasites in cultures. In addition, the researchers found that the function of the proteins became clear only when studied within the flies.

Further research led to an overhaul of the prevailing notion that abundant surface proteins, known as procyclins, were present in invariant form in every major stage of the parasite in the fly. Roditi's lab found that procyclins are expressed only at certain times during the parasite's progression through the fly's gut—and not in the salivary glands.

Gloria Rudenko, a trypanosome expert at Imperial College London, says Roditi "has given us insight into the biology of the procyclin proteins that shield the trypanosome when it is in the gut of the tsetse fly insect vector."

PENETRATING THE ARMOR

But what do those discoveries mean to the effort to treat or prevent African sleeping sickness, a devastating disease that Roditi became aware of as a child growing up in southern Africa?

She says there is great potential to "exploit the discoveries to control trypanosome infection," either by blocking the parasite's reproduction in the tsetse fly or by altering the surface coat in a way that would spur an effective defense by the human host's immune system.

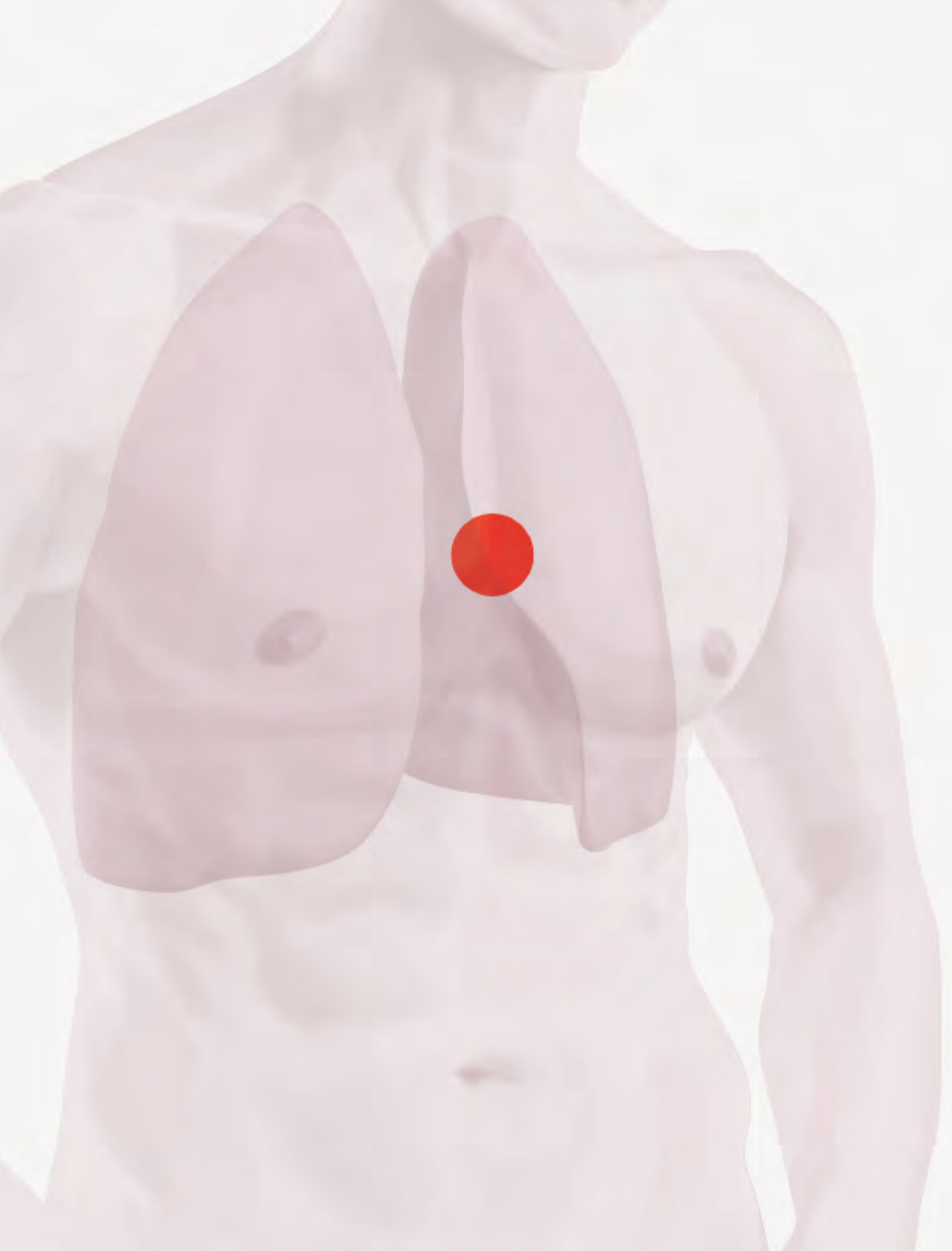
Because not all surface proteins are involved directly in antigenic variation—some are transporters that acquire nutrients or enzymes that break them down, others appear to be environmental sensors—such proteins might represent potential drug targets. For example, a drug might disrupt the growth of the parasite by interfering with its ability to bind host factors; alternatively, small molecules might bind the pathogen directly and deliver spurious signals. Other approaches include hijacking nutrient transporters to introduce harmful drugs into a parasite or inhibiting the activity of certain enzymes.

Working with researcher Reto Brun of the Swiss Tropical and Public Health Institute, Roditi's lab is now trying to develop a technique to trick trypanosomes into prematurely moving on to the next stage of their life cycle—that is, to become insect forms in their mammalian host. If parasites were to shed their VSG coat and cover themselves with a procyclin coat, the thinking goes, they would be vulnerable to destruction in the human bloodstream.

Despite the promise of finding new drugs to attack the African trypanosome, there is far less potential for developing an effective vaccine, Navarro says, because it would be so difficult to cover all 1,500 possible surface variants of the pathogen. But researchers are optimistic that they will find more effective ways to target trypanosomes and ease the burden of African sleeping sickness, which infects more than 50,000 people a year in sub-Saharan Africa and is fatal if not treated.

If scientists can make more progress in slowing the parasite's surface-protein switching, Cross believes, "the immune response can control a trypanosome infection." Reflecting similar optimism, Navarro hopes that "we may be able to block the mechanism that allows the parasite to escape the host immune response."

By weakening the surface-protein armor of trypanosomes, researchers are making them vulnerable and giving hope that the age-old African threat of sleeping sickness eventually will become a bad dream of the past. ■



Bill Schuette was in the best shape of his life. After retiring at 51 from his job as a high school principal, he'd set out to "get healthy and stay healthy," says the Versailles, Ohio, father of three.

After intensive training, he'd walked the 2,175-mile Appalachian Trail, from Springer Mountain, Georgia, to Mount Katahdin, Maine. He led weeks-long bicycle tours around Ireland and the Greek Islands. He ran triathlons. He competed in the Senior Olympics. But 6 years into his health makeover, in 2006, his chest began to hurt when he was breathing hard.

EXPOSING CANCER'S SOFT SPOT

Fusion genes that drive solid tumors are a new target for precision therapies.

by Dan Ferber *// illustration by Julien Roure*

IN April 2007, Schuette, then 58, gathered his wife, Connie, his two adult sons, and daughter for a meeting with his oncologist. The doctor explained that Schuette had a form of lung cancer called adenocarcinoma. Thousands of tiny tumors peppered each lung. Surgery was impossible. Radiation couldn't reach them all. And at best chemotherapy could contain them—for a while.

Over the next two years, Schuette took seven chemotherapy drugs. None stopped the cancer, and the side effects were hard to take. Schuette could no longer hike, bike, or swim. He couldn't keep food down. "There were times I could hardly get out of bed," he says. Early in 2009, his doctor told him he wouldn't see another Christmas.

Then, on June 2, 2009, he saw a television news report. A woman in her 50s, a nonsmoker with adenocarcinoma like Schuette, said chemotherapy hadn't worked for her, so she'd taken an experimental drug called crizotinib that targeted a rare mutation in her tumor. "My cancer is melting away," she told the reporter.

"You've got to be kidding me," Schuette said, looking at his wife. Within weeks he was in a phase I clinical trial taking the drug himself, seeking a new lease on life.

The hope is that crizotinib is the first of a new class of drugs that will do for solid tumors what Gleevec did for the blood cancer, chronic myeloid leukemia (CML).

Crizotinib opens the door for a class of diagnostics, prognostics, and therapies that target cancer-driving mutated genes in common solid tumors. They specifically block a fusion protein—produced by an abnormal fusing of two genes in cancer cells. The new diagnostic and prognostic tests would assess a patient's cancer by looking for these fusion genes. And new drugs, like crizotinib, would target the resulting fusion proteins.

The first fusion gene-targeted drug, called imatinib or Gleevec, was developed in the 1990s to arrest CML. "It changed a disease that was a death sentence within three to five years to a disease that's now a manageable condition" with a five-year survival rate of 90 percent, says medical oncologist and HHMI investigator Brian Druker of Oregon Health & Science University, who helped develop the drug.

Researchers have since found several fusion genes in other blood cancers but for years had less luck in common solid tumors of the breast, prostate, colon, lung, and pancreas, which account for 80 percent of U.S. cancer deaths.

Their luck is beginning to change. Arul Chinnaiyan, an HHMI investigator at the University of Michigan Medical School, and other scientists have uncovered a variety of gene fusions in prostate, breast, thyroid, kidney, brain, and salivary gland cancers.

These discoveries, along with Gleevec's success and promising results with crizotinib, have fueled "a gold rush" among cancer researchers to find new gene fusions in solid tumors, says oncologist and HHMI investigator Charles Sawyers of Memorial Sloan-Kettering Cancer Center. "How many exist? And, let's find out as fast as possible because the implications are just enormous."

A REAL PUZZLE

The groundwork for the current gold rush was laid more than a decade ago when Druker and Sawyers helped develop Gleevec.

Through a series of discoveries in the 1960s and 1970s, scientists learned that in patients with CML, chromosomes 9 and 22 invariably swapped segments—what has come to be called a genetic "translocation." By the 1980s, researchers had sequenced DNA at the break point in the CML translocation and discovered a hybrid between two genes. The gene fusion produced a protein called BCR-ABL that drove white blood cells to divide incessantly.

Druker worked with colleagues at the pharmaceutical company Ciba-Geigy (now Novartis) to find a compound—imatinib—that specifically blocked BCR-ABL in leukemia cells. Druker then joined forces with Sawyers to direct the clinical trials that demonstrated the compound's remarkable ability to stop leukemia. Marketed under the name Gleevec, the cancer therapeutic was approved by the Food and Drug Administration in 2001.

Since then researchers have learned that Gleevec and drugs like it are no panacea, as the aberrant target gene in many patients' cancer eventually mutates again to confer resistance. Sawyers and colleagues at Bristol-Myers Squibb have developed a drug called dasatinib that targets Gleevec-resistant BCR-ABL, and researchers are developing similar backup therapeutics for other Gleevec-like drugs.

The success of Gleevec and related drugs has inspired researchers to step up their hunt for the molecular defects underlying other cancers. By the mid-2000s, fusion genes akin to *BCR-ABL* had been found in various types of leukemia and lymphoma as well as in rare bone and soft-tissue cancers. But none had turned up in common solid tumors.

"It was a real puzzle why people weren't finding these things," says cancer biologist Jonathan Pollack of Stanford University School of Medicine. Some researchers argued that cancer-driving fusion genes were difficult to detect among the many abnormal chromosomes in solid tumors. Others argued that they simply didn't exist. Researchers hunted instead for cancer-causing genes that were mutated, copied excessively (amplified), or deleted.

In 2005, Chinnaiyan was busy hunting for such defective genes in prostate cancer when his graduate students showed him a surprising DNA sequence. His team had sifted through 20,000 candidate human genes and focused on two that were overexpressed in prostate tumors. Mutated versions of each were known to alter cell growth in other cancers. The DNA sequence revealed that the front end of each gene was replaced by part of a third gene, called *TMPRSS2*, which is activated by the male hormone testosterone.

Chinnaiyan's team had discovered what myriad cancer researchers had missed: the first recurrent gene fusions in a common solid tumor. The two mutated genes, called *ERG* and *ETV1*, were overexpressed in 50 percent and 10 percent, respectively, of prostate tumors examined. Their ubiquity suggested that they might drive prostate cancer, the researchers reported in *Science* in 2005.

The work kicked off a whirlwind of new research on prostate cancer, raising hopes of better prognostics and targeted therapies. In a 2007 *Nature* paper, Chinnaiyan's team reported four previously unknown types of gene fusions in prostate tumors. This diversity suggested for the first time that gene fusions played a major role in driving common solid tumors.

Chinnaiyan has since found recurring gene fusions in breast and stomach cancer and in melanoma. And because the driving genetic lesions of many cancers are unknown, the hunt is now on for gene fusions in other solid tumors. Chinnaiyan's results "energized and reinvigorated a whole new field of study," Pollack says.

LUNG CANCER PILL

Exciting news came in August 2007, just a few months after Bill Schuette received his diagnosis. Hiroyuki Mano's team at the Japan Science and Technology Agency in Saitama, Japan, reported in *Nature* that they'd discovered a gene fusion that drives tumor formation in about 5 percent of patients with non-small-cell lung cancer.

The fused lung cancer gene, known as *EML4-ALK*, encodes a cellular signaling enzyme called a tyrosine kinase. Both Gleevec and crizotinib block tyrosine kinases. Pfizer had produced crizotinib to treat cancers that had genetic alterations in ALK or another tyrosine kinase gene, including lymphoma, brain, and rare stomach and esophageal cancers. In 2006, oncologists at Massachusetts General Hospital in Boston and elsewhere had begun testing crizotinib's safety as part of a clinical trial. The *Nature* paper was big news, says thoracic oncologist Alice Shaw,

"He could barely breathe and was wheelchair bound," Shaw recalls. "Within a week or two he completely turned around."

who treats lung cancer patients and develops new therapies at Massachusetts General. "We got very excited because it suggested a new therapeutic target," Shaw recalls.

Within months, molecular pathologists at the hospital had developed a way to identify the *EML4-ALK* gene fusion in tissue biopsies from lung cancer patients. The Massachusetts General team treated its first EML4-ALK-positive lung cancer patient with crizotinib in December 2007. "He could barely breathe and was wheelchair bound," Shaw recalls. "Within a week or two he completely turned around."

Inspired, Shaw and her colleagues began screening more lung cancer patients for the *EML4-ALK* gene fusion and treating those patients having the fusion with crizotinib as part of the phase I clinical trial. At the June 2009 American Society of Clinical Oncology (ASCO) meeting in Florida, Eunice Kwak of the Massachusetts General team reported that crizotinib stabilized the disease in 15 of 19 of these patients and significantly reduced the total mass of tumor tissue in 10 of them. ABC World News picked up on that report, and on Shaw's experience treating her first patients, and beamed it into Bill Schuette's living room in Ohio.

Schuette, at that point, was very sick. "I was totally out of energy. I had lost weight and was in tremendous pain. Anytime I would cough it would bring me to my knees."

The news sent him to the computer. Schuette e-mailed Shaw, who returned the call quickly. She asked a few medical questions and requested a sample of biopsied lung tissue, which revealed that his tumors had the *EML4-ALK* fusion. Two weeks later, on August 12, 2009, Schuette sat in a hospital room at Massachusetts General, where he took his first dose of crizotinib.

A TRAIL OF BREADCRUMBS

When a fusion gene is seen repeatedly in a particular type of tumor, it suggests, but doesn't prove, that the resulting fusion protein alone can drive tumor growth. It's good news if it does, though, because Gleevec-like drugs that block the activity of a driving fusion gene, such as tyrosine kinase, often stop the tumor.

But each fusion gene must be tested to see whether it drives cancer on its own or whether it needs backup. For example, cells engineered to express *BCR-ABL* or *EML4-ALK* become cancerous, and mice engineered to express the two fusion genes develop leukemia or lung cancer, respectively. But mice engineered to produce the most common prostate cancer fusion gene, *TMPRSS2-ERG*, do not develop prostate cancer, Sawyers says.

To discover what else might be needed to drive prostate cancer, Sawyers obtained 218 prostate tumors, about half of which harbored the *TMPRSS2-ERG* fusion gene and sequenced 157 genes from each that have been linked to prostate cancer. One short stretch of chromosome 3 was deleted in almost all the tumors with the *TMPRSS2-ERG* fusion. Three of the eight genes in that deleted segment have hallmarks of genes that suppress tumor formation, and the three may turn out to collaborate with ERG to cause prostate cancer. "It's a trail of breadcrumbs, so we'll see," he says.

To stop gene fusions from causing cancer, it's also important to understand how these hybrid genes form in the first place, says molecular immunologist Fred Alt, an HHMI investigator at Children's Hospital Boston. First, DNA must break cleanly at two chromosome locations inside a single cell. Second, the ends of the broken DNA must be brought together and attached to create a chromosomal translocation. Third, cells with this translocation must outgrow normal cells. In 2007, Alt's team reported in *Nature* that they'd found a cellular pathway that can perform the second step, attaching broken ends of unrelated genes on different chromosomes. In 2009, they reported, again in *Nature*, that this pathway generates recurrent translocations that correlate with lymphoma. The pathway may also promote cancer-causing translocations in other tissues, he says.

Two HHMI investigators, Chinnaiyan and Michael G. Rosenfeld, of the University of California, San Diego School of Medicine, have recently shown that testosterone signaling actually spurs translocations in the prostate. This hormone binds to a gene-activating protein called the androgen receptor, and the resulting complex helps regulate thousands of prostate genes, including *TMPRSS2*. Chinnaiyan suspected that, when it binds testosterone, the receptor brings the *TMPRSS2* and *ERG* into proximity within the cell's nucleus, creating an opportunity for them to trade segments.

Chinnaiyan's team confirmed this hypothesis by adding testosterone to cultured prostate cells, then fragmenting their DNA with ionizing radiation. The *TMPRSS2-ERG* fusion was created only if testosterone was present, the researchers reported in *Science* in November 2009. The results could explain why the *TMPRSS2-ERG* fusions occur only in the prostate, the sole organ where testosterone plays a dominant role in coordinating cellular physiology, Chinnaiyan says. Rosenfeld's team reported similar results in *Cell* in December 2009. They also detailed how

By studying gene fusions—in blood cancers and solid tumors—Brian Druker, Charles Sawyers, and Arul Chinnaiyan have revealed vulnerabilities in tumors that can be targeted and successfully treated.



Druker: John Valls Sawyers: Liz Baylen / PR Newswire. ©HHMI Chinnaiyan: Liz Walker / University of Michigan

the androgen receptor recruits two enzymes that help to cut and rejoin the DNA. By studying how translocations occur, "we want to understand and screen for drugs or approaches to mitigate and abrogate the events," Rosenfeld explains.

TOWARD PERSONALIZED MEDICINE

As researchers elucidate how fusions form, Chinnaiyan and others are pushing to use what's already known to help cancer patients. By 2010, Chinnaiyan had found 23 different types of recurring gene fusions in patients with prostate tumors, and he's seeking new prognostics that use the presence of a specific fusion gene as a genetic fingerprint. By correlating patients' genetic fingerprints with their clinical outcome, he hopes to develop a knowledge base to help doctors distinguish fast-growing and invasive prostate tumors that require aggressive treatment from slow-growing tumors that do not.

Knowing that a patient has a cancer-driving fusion gene is not enough, however; scientists must find a way to block it. In July 2010, Chinnaiyan reported in *Nature Medicine* that 2 percent of prostate cancer patients—and a similar fraction of patients with gastric cancer and melanoma—have a gene fusion that encodes a tyrosine kinase. Chinnaiyan suspects that patients will be treatable with a kinase inhibitor. Although they're a small fraction of all prostate cancer patients, they still represent several thousand cases a year in the United States alone.

Other gene fusions will be tougher to target. Most of the gene fusions found so far in prostate cancer encode gene-activating proteins, called transcription factors, rather than kinases. Drug companies have struggled for years to produce compounds that block specific transcription factors. Chinnaiyan, however, has recently identified a workaround. By blocking an enzyme required by the transcription factors, his team was able to block their activity, he reported in September 2010 at the annual scientific retreat of the Prostate Cancer Foundation. Even better, drug companies have already developed compounds that block that enzyme, he says.

Down the road, Chinnaiyan and others envision personalized cancer treatment. With such treatment, physicians would classify every cancer by its driving mutation or mutations; characterize it by its aggressiveness; and treat it with one of an armamentarium of Gleevec-like drugs that target each tumor's Achilles heel.

In the meantime, doctors are helping whomever they can. In June 2010, Shaw and her colleagues returned to the annual ASCO conference to report the results of their expanded phase I trial on crizotinib. The drug stopped cancer from advancing in 87 percent of the 82 *EML4-ALK*-positive, late-stage lung cancer patients treated and shrank tumors in 57 percent of them. Results were so encouraging that investigators launched an international randomized phase III trial of *EML4-ALK*-positive non-small-cell lung cancer patients whose cancer withstood one earlier chemotherapy regimen. "It's a great story," says Sawyers.

One of the patients in the phase I trial is Schuette. From the first day he was treated, his pain disappeared and his energy returned, he says. A CT scan two months later showed that most of his tumors were gone. Since then Schuette and his wife have visited their far-flung children and grandchildren in Virginia, New York, and California. He's back to swimming—up to a mile at a time. "I cherish the opportunity to be able to get back into the pool and do that," he says.

Bill Schuette knows that his tumors, like leukemias treated with Gleevec, will eventually develop resistance to crizotinib. He may benefit from one of the backup therapies that Shaw says are under development. But for now, Schuette says, "I'll take every day." ■

MOVIE MAGIC

Live action microscopy is giving scientists an unprecedented view into the first days of a fish embryo's development.

BY CHRISTINE SUH · ILLUSTRATION BY JOSH COCHRAN

SCATTERED AGAINST A BLACK BACKGROUND, VIVID BLUE, BEIGE, AND ORANGE DOTS—

32 of them to start—commence an amazing dance. They quickly double in number, shrink, and double again. They fill one pole of a slowly spinning, invisible globe. As they continue to multiply, becoming hundreds, then thousands, of little points, they swarm, covering the globe evenly in brilliant blue with specks of orange flashing in and out of existence. The dots then crowd the equator and meld into the shape of a fish embryo.

The video is like computer-animated pointillism. But rather than a piece of digital art, it represents a scientific feat—a stunning series of images that reveals the development of a live zebrafish embryo over 24 hours. Each cell in the embryo is represented by a single dot, colored blue when still or moving slowly and shifting to beige and then orange when migrating more quickly.

This detailed way of watching development in action is the result of the latest version of the light-sheet microscope, developed by a team of scientists at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany. The new tool has the potential, says team member Philipp Keller, now a fellow at HHMI's Janelia Farm Research Campus, to achieve a goal coveted by developmental biologists: the generation of comprehensive computer models of embryogenesis in complex vertebrates.

Before this innovation, Keller notes that scientists had been able to reconstruct, in a comprehensive way, the development of only simple animals such as *Caenorhabditis elegans*—a tiny worm that hatches when it reaches just 500 to 600 cells, within 12 hours after fertilization.

Scientists studying the zebrafish, which grows to tens of thousands of cells on day one of its three-day embryonic development, had captured images of the embryo's transformation into a juvenile. But they could describe the stages of development only in broad strokes. They had no tool to explore in detail the mysteries of gene expression, morphogenesis, and cell movement and division patterns. Existing microscopes often damaged embryos.

In addition, the strategy of patching together multiple images from different specimens left sizable holes in the resulting information. Part of the problem is that every embryo develops slightly differently. "If you stitch together data from different animals," says Keller, "you don't get the same coherent data set that you'd get by looking at one animal and observing it over time. Live microscopy was the only option."

But in the early 2000s, microscopes fell short of the task.

"Neither confocal nor two-photon microscopes were fast enough," says Keller. "The limitations in imaging speed do not allow following cell behavior for the entire organism, and, in the confocal microscope, the fluorescent markers would bleach very quickly and the embryo would be alive only for a short time."

JOINING TEAM EMBL

By 2005, Keller was working on his doctorate, becoming interested in studying life at its inception, and had already joined a team of scientists at EMBL led by Ernst Stelzer. The group had developed a new type of microscope for observing the previously invisible processes of embryonic development.

The scientists used a relatively simple trick from 100 years back. In 1903, chemist Richard Zsigmondy had invented the "ultramicroscope," which illuminated a sample through a slit at a right angle to the viewing angle. Using the same principle, the EMBL researchers engineered a more sophisticated version for the 21st century, taking full advantage of the modern computing power needed to process and analyze massive amounts of data. They published the innovation in 2004 in *Science*, calling it selective plane illumination microscopy, or SPIM.

"Instead of collecting data point by point, using the same objective for illumination and fluorescence detection as the confocal microscope, we illuminate an entire plane [of the specimen] from the side," Keller says. The only thing you have to do is collect the fluorescence emitted at a right angle from this plane using a camera with a conventional detection system. It's relatively simple."

The inaugural version of the microscope yielded the first video of an embryo's beating heart—that of a Medaka, or Japanese rice fish. After refining the instrument for version 2.0—dubbed "digital scanned laser light-sheet fluorescence microscopy," or DSLM—Keller and his EMBL colleagues captured the first 24 hours of a zebrafish embryo's development with unprecedented resolution and speed. They published their results in *Science* in 2008.

Progressing beyond day one of development became the challenge. As the embryo grew more complex, images blurred. The increasingly complicated and numerous structures in the rapidly developing fish scattered the light from the scope. To maintain high resolution of these complex images, Keller and his colleagues tweaked the scope so they had rapid electronic control

over the pattern of light passing through the specimen. Increased control meant the instrument could accommodate the denser embryos of other lab animals, such as fruit flies and mice.

The scientists took nearly one million images over three days to follow neural development of a zebrafish embryo into its juvenile stage. They also created a "digital fly embryo," a three-dimensional reconstruction of early *Drosophila* development with single-cell resolution. The group published their results in the August 2010 issue of *Nature Methods*.

THE NEXT GENERATION

Since moving to Janelia in May 2010, Keller has been constructing the next generation of the light-sheet microscope. Using the new design and latest technology, he expects this iteration of the microscope to perform 40 times faster than the previous version. This faster speed and many additional capabilities will give scientists even more detailed information about the physical and chemical choreography that occurs during development.

Keller plans to use the revamped instrument to continue his embryology research, with a special focus on neural development in *Drosophila*. He also hopes to expand the technology's reach to studying early development in other model organisms, including mice, the gold standard lab model for early investigations into human disorders.

In addition to the lab's core research projects, Keller will have ample opportunities for collaboration. His work dovetails with that of his new Janelia Farm colleagues, including Hanchuan Peng and Gene Myers as well as Julie Simpson and Jim Truman. It was precisely for this kind of interaction that Keller came to Janelia, where integrated teams with very diverse backgrounds aim to break through existing barriers and solve problems.

Keller is working with Peng, a senior computer scientist at Janelia Farm, and Myers, a Janelia group leader, to implement computational solutions to managing the enormous amount of data the microscope will collect. Peng has created a three-dimensional digital map of the fruit fly brain, and his lab is developing a "smart" image acquisition method that can zero in on specific areas of the brain for analysis.

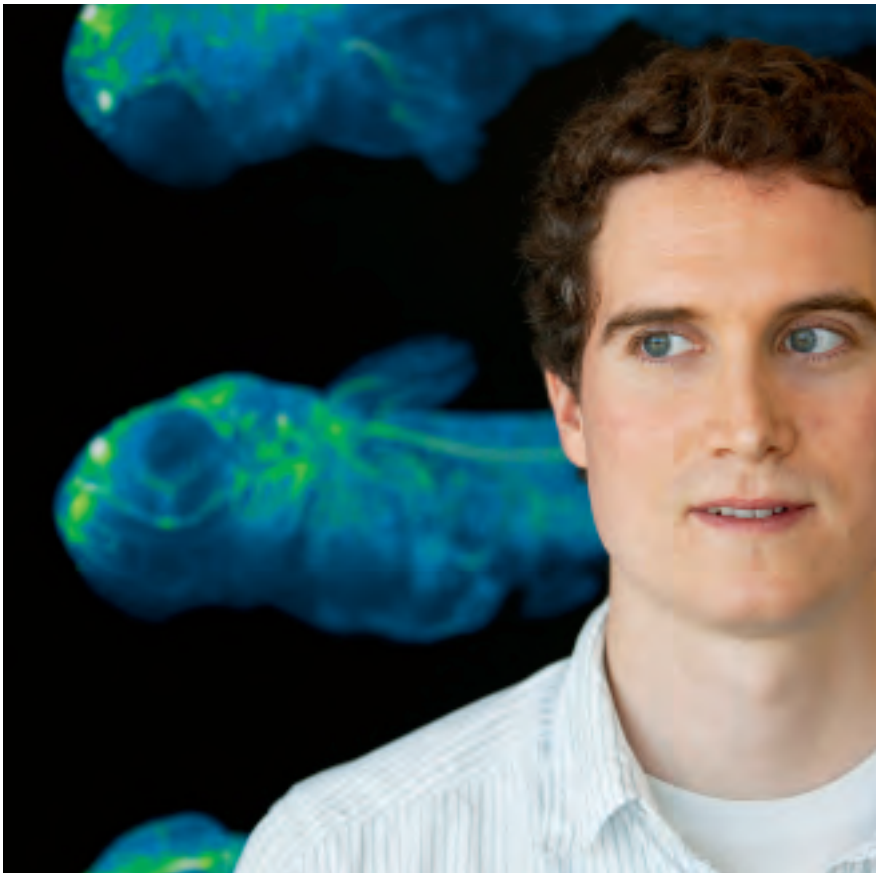
"These techniques," Peng says, "may well fit with Philipp's imaging pipeline—to reduce the data volume and produce quantitative analysis at the moment of [image] acquisition."

Keller is looking to Janelia group leaders Simpson and Truman for their expertise in fly neuroscience, genetics, and novel labeling strategies. Simpson is investigating how genes, neurons, and neural circuits affect fruit fly behavior. "My optical microscopy expertise is limited to commercial confocals," she says, "so I am eager to see what Philipp's microscope can do with our specimens."

The promise of live embryo imaging is unquestionable. Light-sheet microscopy will allow scientists for the first time to describe in detail the processes of development in complex vertebrates; to map the fates of cells as they become specialized; to track the effects of genetic mutations in a living embryo as it develops; and, of most interest to nonscientists, to witness and come to understand how developmental disorders arise.

"There is so much to be done, such an enormous potential," Keller says. He's not the only one to say so. In a review published in the same issue of *Nature Methods* as Keller's paper, one imaging expert describes light-sheet microscopy and several other new imaging methods as part of a new frontier.

For the moment, using live imaging to answer developmental biology's numerous lingering questions remains a sluggish endeavor. Keller says only a few dozen labs around the world have built versions of the microscope. But with a commercial version of the light-sheet microscope in the works, Keller hopes he'll soon have plenty of company within developmental biology to help fulfill its potential. ■



Paul Fetters

The microscopy developed by Philipp Keller and colleagues has the potential to give scientists a systems-level understanding of how cells behave and interact during development.

WEB EXTRA: To see videos of embryo development produced by the light-sheet microscope, visit www.hhmi.org/bulletin/nov2010.

Vicki Chandler

PLANT SCIENCE MATTERS

Melissa Kaseman

Vicki Chandler's research on how plants regulate their genes may ultimately inform studies of human diseases. She's leading the Gordon and Betty Moore Foundation's partnership with HHMI to support more of this kind of fundamental plant science.

I often say that because plants don't bleed red or run, they get overlooked. Most people don't realize that plants like corn (maize) and thale cress (*Arabidopsis thaliana*) are excellent model organisms for key areas of biomedical science. Through studies in plants, we've determined how small noncoding RNA can ratchet up or dial down genes, for instance, and how gene regulation responds differently in distinct environments.

But tight plant science funding consistently limits our ability to turn early theoretical gains into on-the-ground advances. Scientists doing absolutely core work in plant genetics, cell biology, biochemistry, and other areas have to vie for scant federal support—and, frankly, it holds us back.

That's about to change. HHMI and the Gordon and Betty Moore Foundation, which supports basic (nonmedical) research, have teamed up to kick-start fundamental plant science research with 5-year, potentially renewable grants to 15 plant scientists (see "Going Green: New Program Provides Vital Support for Plant Sciences," page 40). This is the first time the two organizations have collaborated, and I have high hopes for the outcome.

First, I hope the scientists who are selected are empowered to be more innovative and creative because they will have resources to work with. The funding is roughly equivalent to having two R01 grants from the National Institutes of Health (NIH). Five years of support is enough time to tackle higher risk yet very important questions. If that's all we did with this program—make this research possible for 15 scientists—it would be enough to impact a field and I'd sleep well at night.

But I also have a broader hope for more systemic change. The fact that HHMI and the Moore Foundation are contributing a total of $75 million to advance a key model system will put a spotlight on the huge research gap—and the opportunities. I hope our investment, and the research it generates, becomes a tool that federal agencies—including NIH, the National Science Foundation (NSF), the U.S. Department of Agriculture (USDA), and the Department of Energy (DOE)—can use to secure more support from Congress for fundamental plant science. We are sending a signal: plant science matters.

In my own research, I realized the relevance of plant science as a biochemistry graduate student. I was studying gene regulation at the University of California, San Francisco, in the late 1970s, working with mammalian systems. While looking for postdoc opportunities, I realized that maize is an ideal system for studying gene expression—in particular, a remarkable phenomenon in gene silencing called paramutation.

In paramutation, one parental copy (allele) of a gene silences, or turns off, the other parental copy of that gene. This silencing sticks: generations of progeny "remember" this change, dutifully expressing the gene according to the new pattern. And, this happens with no changes in the DNA sequence.

Over the course of 20 years, first at the University of Oregon and later at the University of Arizona, my lab has uncovered some of the underlying mechanisms. They involve RNA-mediated silencing, which occurs in multiple systems. We suspect similar biochemistry works in animals and humans. If so, our paramutation work may ultimately help us better understand certain diseases.

Basic plant research—even top-notch research—falls between the funding cracks. Because NIH focuses on humans and animal model systems, it has not traditionally supported plant science. USDA leans heavily toward applied science, while DOE focuses on bioenergy. At NSF, basic plant science competes with other biology fields for funds. Even at HHMI—with its track record of supporting innovative, interdisciplinary research across model systems—the number of researchers specializing in plant science can be counted on one hand.

We all want to make progress. My role leading the science program at the Gordon and Betty Moore Foundation is to identify fundamental research areas in which a foundation can make a difference. We support varied research, from marine microbiology to the largest land-based telescope. Part of our culture is to take smart risks because major leaps forward in science won't happen without them.

With HHMI, we're thrilled to strategically grow plant science. By funding top people at various career stages, we're poised to make a real—and lasting—difference.

INTERVIEW BY KATHRYN BROWN. *Vicki Chandler is the chief program officer for the Gordon and Betty Moore Foundation's Science Program.*

Q&A

What is your favorite example of a humorous, ironic, or spot-on gene name?

It's hard to slip humor into grant applications and scientific papers, but when it comes to naming genes, scientists' wit shines through. From tiggywinkle hedgehog *to* cheapdate *and* Van Gogh, *amusing gene names abound in biology. Here, four scientists share their favorites.*

—EDITED BY SARAH C.P. WILLIAMS

Hugo J. Bellen

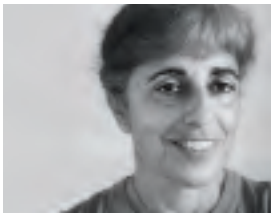
HHMI INVESTIGATOR
BAYLOR COLLEGE OF MEDICINE

"In the *Drosophila* field, the tradition has been to name a gene based on the phenotype caused by its absence or loss of function. Of course, we follow suit today, but there is somewhat of an underlying competition to find a memorable name, especially one that would be a snapshot of modern trends in our culture. Some of my favorites from my own lab are *couch potato* and *benchwarmer* (the mutant flies appear lazy), and *tweek* (flies quiver like a nervous South Park cartoon character)."

Jeannie T. Lee

HHMI INVESTIGATOR
MASSACHUSETTS GENERAL HOSPITAL

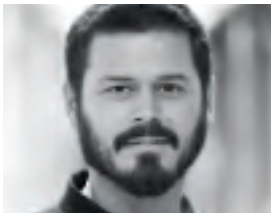
"With gene names like *Xist*, *Xite*, *Tsix*, *Tsx*, my field of X-inactivation has yet to utilize the complete alphabet. But I credit fly geneticists for a long history of creative gene names. My favorite: *Piwi*, a class of fly mutations causing testes of "pee-wee" stature—originally, *P-element induced wimpy testis*. *Piwi* has spawned whole families of related gene names in plants and mammals. Some roll off the tongue, like "piRNA" (piwi-interacting RNAs). Others are less imaginative, like *Hiwi* and *Miwi*, for human and mouse *Piwi* (mammalian geneticists are not known for creative nomenclature)."



Isabel Roditi

HHMI INTERNATIONAL RESEARCH SCHOLAR
UNIVERSITY OF BERNE

"When it comes to gene names, *Drosophila* wins hands down. My favorite for a long time was "*schnurri*," which I thought was a Swiss lab's ironic use of dialect (it means boaster or bragger, and I wondered who it referred to!). But before writing this I thought I had better check with someone who actually worked on it. I found that its origins lie in "aufgeschnurrt"—like a piece of wool that curls up on itself when it is pulled—because embryos with a defective gene look a bit like that. So it is an apt name, but not what I thought."



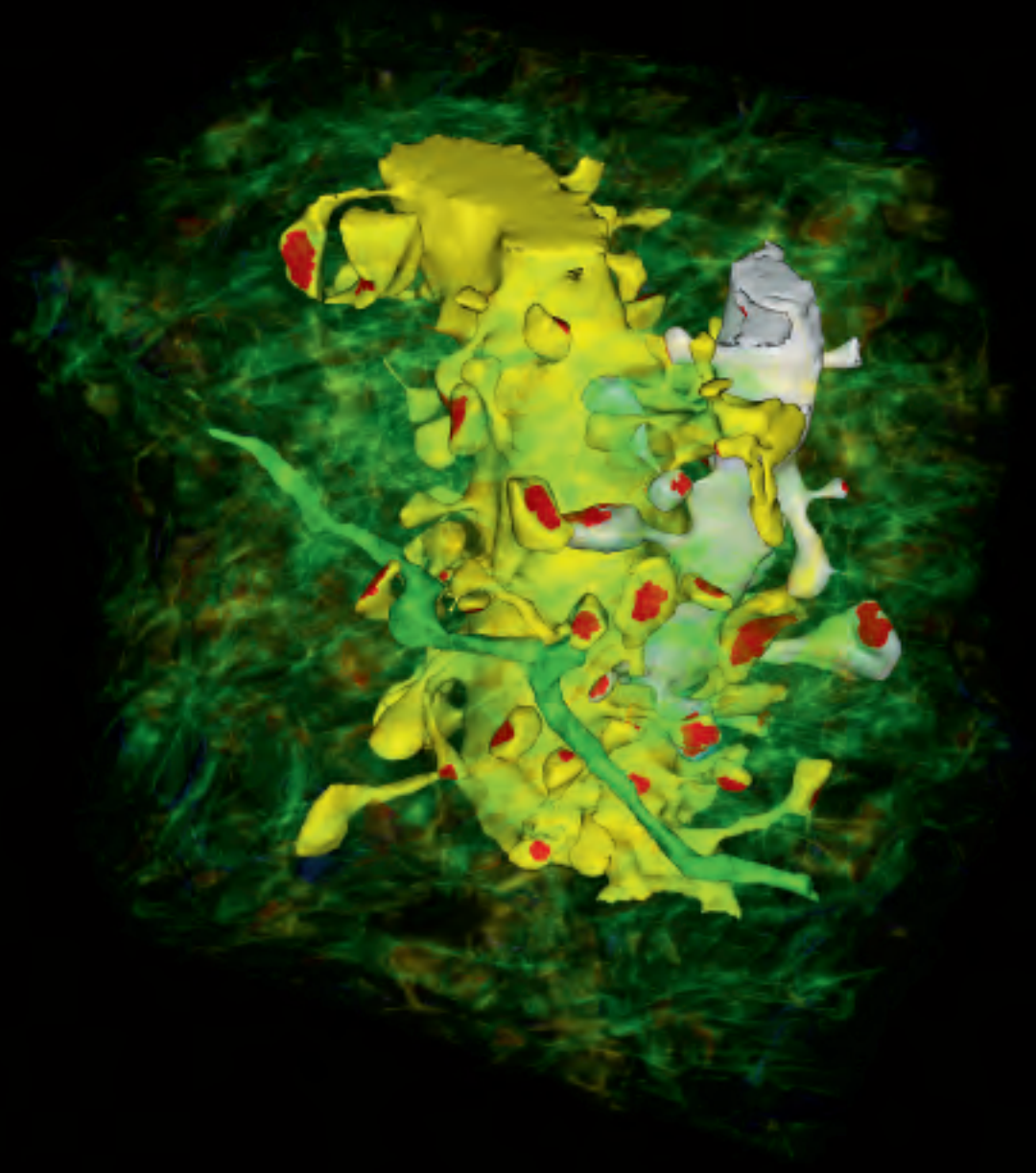
Marc R. Freeman

HHMI EARLY CAREER SCIENTIST
UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL

"There are so many great names it's hard to pick just one. One of the most hilarious has to be the *Drosophila* mutant that fails to develop recognizable external genitalia, *ken* and *barbie*. Who hasn't been disturbed when they saw their first naked Ken or Barbie doll? But my all time favorite may be the mutant that doesn't grow sensory hairs and is therefore bald—you guessed it, *kojak*. These silly names are important—they add some fun, help us remember gene functions and phenotypes, and demonstrate that bench scientists are susceptible to extremely poor humor, just like other groups."

Bellen: Paul Fetters Lee: Courtesy of Jeannie T. Lee Roditi: Dirk Dobbeluere Freeman: Courtesy of UMass Medical School

chronicle



Kristen Harris (UT at Austin), Mary Kennedy (Caltech), and the Sejnowski Lab (Salk Institute)

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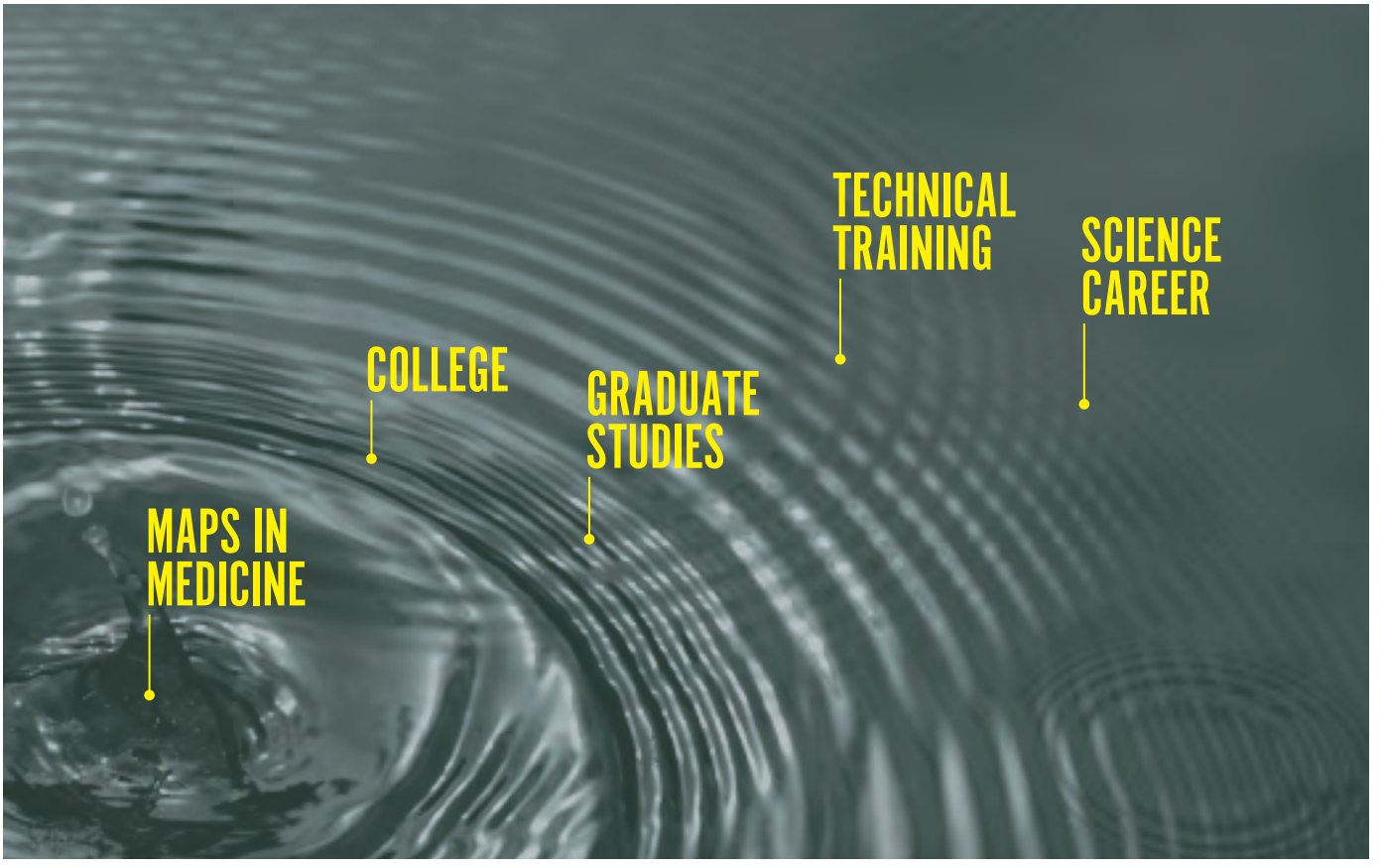
Friedman Wins Lasker Award / Champalimaud Vision Award Goes to Newsome

Thought and memory take shape where the axon from one neuron contacts the dendrite of another at a junction called the synapse, as depicted here. There are an estimated quadrillion synapses in the brain, creating a complex and mysterious network called the neuropil. Thanks to a new computer-generated 3-D model—encompassing 450 synapses, 69 axons, and 77 dendritic spines—scientists might get a clearer picture of how that web works. Visit www.hhmi.org/bulletin/nov2010 *to read about the virtual neuropil and see it in action.*



Mapping out a Future in Science

HELPING STUDENTS SEE COLLEGE—AND SCIENCE—IN THEIR FUTURES.

A 28-YEAR-OLD WOMAN WITH NIGHT SWEATS AND WEIGHT LOSS HAS a fist-sized mass in her chest and an elevated white blood count. "Tell me why lymphoma is your diagnosis," says the instructor.

Students sift through their papers to find the patient's medical history. Finally locating the laboratory results, Becky Maier reads aloud, comparing the patient's results with normal values.

Maier and the others are not in medical school or even college. They're high school students participating in the weeklong Maps in Medicine Program (MiM) at the University of Missouri, Columbia. Over the next few days they will use the Internet, pore over x-rays and CT scans, and learn how doctors diagnose illnesses by facing a problem one well-researched step at a time. They'll learn to map the path a cell takes, from stem cell to fully developed cell, and then switch gears and chart the spread of an infectious disease.

During an afternoon visit to the University of Missouri medical simulation lab, students began to experience being a doctor. They donned stethoscopes, secured airways, and started intravenous lines on lifelike mannequins. When long needles were first pulled from protective sheaths, more than one student looked woozy. Before long, all were jostling for their turn, pulling out cameras and cell phones, shouting, "Take a picture of me doing this!"

In MiM's first two years, only teachers attended the Summer Institute, a program to provide them with the tools and support to make science education exciting (see sidebar, "Zebrafish to Go"). In 2010, 23 students were invited to attend a parallel program, called the Student Summer Academy.

MiM organizers—a network of University of Missouri faculty, staff, and students, plus high school teachers and students from St. Louis, Kansas City, and rural Missouri—aim to spark an interest in science among high school students who have taken few or no introductory science classes. Some may be part of the first generation in their families considering college, while others view higher education as an impossible goal. The program staff deliberately recruited such students. "If they were already committed to science, then they wouldn't need us," says program director William R. Folk.

The teens will be followed through high school to monitor their college choices. Their mentors will also assess their interest in science classes and membership in science clubs.

To make that lymphoma diagnosis, students went through a problem-based learning exercise, similar to the type of puzzle medical students solve each week. "The experience made them realize they can learn anything put before them and solve any problem presented to them," says Susan Ailor, associate professor of dermatology

VSA Partners

ZEBRAFISH TO GO

TEACHER JONI BRAILSFORD HAS FOUR BREEDING pairs of zebrafish in her AP biology classroom at Blue Springs South High School. Her students watch each pair, noting mating behavior and eagerly awaiting the outcome. If all goes well, the students will capture the eggs and then watch the transparent embryos develop through the lens of a microscope. ¶ "Kids love to watch real life happen," says Brailsford, who prefers this method of teaching versus lectures alone. ¶ Teachers like to watch real life happen as well. Brailsford was introduced to her first batch of zebrafish embryos during the 2010 Maps in Medicine (MiM) Summer Institute at the University of Missouri. ¶ During the week-long session, 20 high school teachers peered at zebrafish embryos through a microscope and used Play-Doh to build embryo models. They amplified DNA and infected bacterial cultures with the "blue flu," a model of influenza virus. The exercises introduced teachers to the main themes of MiM: mapping cell fate and mapping the spread and transmission of influenza. Teachers spent the week becoming familiar with each of the theme's multiple elements. They also met teachers already skilled in teaching the themes. MiM provides resources, equipment, and reagents that the teachers take back to their classrooms. ¶ "The curriculum can be used at varying levels. Teachers can use the entry-level sections or they can add layers for an AP course," says Susan Ailor, a program leader in the HHMI-supported program. And it doesn't have to be limited to science classes. Teachers can use the materials to discuss the economic impact of flu, she adds. ¶ Ninfa Matiase, a biology teacher at Normandy High School, has helped develop and revise the MiM curriculum, and she uses the units in her classroom. The 2010 Institute inspired her to design a lesson on how disease spreads. Matiase will tell students that a dead bird was found near the school. Students will then use Google Maps to look at their own community to see how avian influenza could spread across town. ¶ Matiase has already used the blue flu unit to teach how viruses work. In that lesson, students infect bacterial cultures with the harmless virus. Then, they do a protein assay to see if the bacteria are infected. Next, they amplify DNA and examine the results for particular genetic patterns. The exercise gives her students a taste of bench science. "This is what I like best," she says. "Giving students an experience they would otherwise not have in high school." —*J.E.*

and a leader in the HHMI-supported program. "I had hoped for a really good experience. I think they had a really *great* experience."

Jack Short, one of four second-year medical students who served as program counselors, used the same lymphoma scenario to demonstrate the variety of career choices available in medicine. He started with the medical receptionist, who is the first person a patient contacts, and covered everyone from medical technologists to specialized nurses, physicians, and phlebotomists. Students learned about the relationship between years of education and potential salary as well as the importance of every member of the health care team, says Ailor.

During a session on college preparation, students were asked to close their eyes and make successive folds in a pink piece of paper, following deliberately vague instructions given by the moderator. No questions allowed. The students then snipped off one corner of their folded paper. Giggles bounced around the room as the teens unfolded their handiwork and discovered very different results from paper to paper. The task drove home that working in the dark without proper information is a bad way to prepare for college.

That evening, students attended a college fair where they met college advisors from institutions ranging from small private colleges to large public universities. "We wanted them to feel recruited," says Ailor.

On the last day of camp, Ailor reflected on the students' experiences. "It was amazing to me that they found their strengths and used them in different ways during the week. We'd love to turn them all on to science," she says. "If we can get them thinking about science, it's huge." ■ –JEANNE ERDMANN

2010 HOLIDAY LECTURES ON SCIENCE

VIRAL OUTBREAK: THE SCIENCE OF EMERGING DISEASE

Today, people can travel from country to country with ease. The result is a more global community. But all that international travel coupled with the planet's warming trends means more outbreaks of infectious diseases. Learn how viruses are thriving—and how scientists are working to fight them—at HHMI's 2010 Holiday Lectures on Science. Joe DeRisi and Eva Harris will talk about their virus research and the technologies they are using to detect and classify new viruses. DeRisi, an HHMI investigator at the University of California, San Francisco, will describe how he has used microarray technology to identify a number of new viruses, including some that are killing parrots and bees and infecting people in Nicaragua. Harris, a University of California, Berkeley, professor of public health, will talk about her research and community outreach in Central America, where she is studying the rapid spread of dengue fever. The Holiday Lectures will be available live by webcast December 2–3 at www.holidaylectures.org.

Moore Named HHMI's First Chief Operating Officer

CHERYL MOORE, WHO PLAYED A PIVOTAL ROLE IN DEVELOPMENT of the Janelia Farm Research Campus as its chief operating officer (COO), has been named executive vice president and COO for the Institute. Moore, 44, is the first person to hold the position and assumed her new responsibilities in September. She will lead collaborative strategic efforts for HHMI and oversee operational functions of the organization.

"This is a new position, one well suited to Cheryl's extraordinary record of achievement and dedication to HHMI," says HHMI President Robert Tjian. "She will be a superb partner for me and a great asset to HHMI's executive team, particularly as we identify strategic directions and implement best practices in our operations that will advance the Institute's work as a science-driven organization that supports research and education at the highest levels."

Moore joined HHMI in 2004 as COO of Janelia Farm. She was responsible for all operational aspects of the campus and its $100 million annual budget.

"Cheryl literally took Janelia Farm from an empty building to a fully operational campus. She recruited a team who worked tirelessly to create every bit of the infrastructure from scratch," says Gerald M. Rubin, director of the Janelia Farm campus.

Before becoming COO of Janelia Farm, Moore served as senior vice president and COO of what is now known as the Sanford-Burnham Institute for Medical Research in La Jolla, California. A native of Illinois, Moore spent much of her professional career in the San Diego area, where she also held top management positions with an international financial services firm and both start-up and public health care companies. She is a graduate of the University of San Diego.

Moore serves on the board of the Association of Independent Research Institutes and until recently served on advisory boards for a number of other organizations, including the Krasnow Institute for Advanced Study at George Mason University, the Virginia campus of George Washington University, and the Virginia Biotechnology Association. She has also been a member of the Economic Development Commission of Loudoun County, Virginia. She was named one of the top 25 "Women Who Mean Business" for 2007 by the *Washington Business Journal* and was nominated for the 2008 Athena Pinnacle Award, honoring women leaders in San Diego. ■

Going Green: New Program Provides Vital Support for Plant Scientists

HHMI AND THE GORDON AND BETTY MOORE FOUNDATION (GBMF) announced in September a new research program that will provide critical support to some of the nation's most innovative plant scientists. The institutions, which are collaborating for the first time, will invest a combined total of $75 million in the program over the next five years.

HHMI and GBMF will select as many as 15 investigators working in a range of scientific disciplines relevant to plant sciences. The national competition, which runs until November 9, 2010, is open to researchers who have managed their own lab for at least four years. The scientists will receive an initial five-year appointment to HHMI and the support necessary to move their research in creative, new directions. Appointments may be renewed for additional five-year terms, contingent on a successful scientific review.

Despite the central role plants play in maintaining human health and in healthcare, basic research in the plant sciences historically has been underfunded. The bulk of the United States Department of Agriculture funding has not gone to competitive basic research and the Biology Directorate program at the National Science Foundation is relatively small, with few dedicated programs in fundamental plant biology. Furthermore, plant science researchers receive a small percentage of funding from the National Institutes of Health.

"There is no question that plant scientists have a tremendous potential to help address—and possibly alleviate—some of society's most pressing concerns, such as food production, human health, protection of the environment, and renewable energy," says HHMI President Robert Tjian. "We are very fortunate to have found in the Gordon and Betty Moore Foundation an institution that believes, as we do, that we must act now to do more to nurture and support the bold ideas of the best plant scientists."

Since its creation in 2000, GBMF, headquartered in Palo Alto, California, has focused on supporting environmental conservation, non-biomedical science, and the San Francisco Bay Area. The path that led to the HHMI–GBMF collaboration began in 2008, when the scientific leadership of HHMI met with the Institute's medical advisory board to brainstorm ideas for new research initiatives. A plant science research program emerged as a top contender.

(continued on page 48)

Robert Merhaut

DIADEM Contest Moves Neuromapping in the Right Direction

CREATING A DETAILED MAP OF EVERY NEURAL CONNECTION IN the brain takes patience—and lots of time. Scientists have typically worked at the goal of a complete brain diagram by painstakingly tracing the structure of nerve cells by hand. But this is tedious, and it would take many lifetimes of this work to finish a full map.

To spur computer-driven algorithms for mapping the complex, branching shapes of neurons, HHMI, the Allen Institute for Brain Science, and the Krasnow Institute for Advanced Study at George Mason University launched, in April 2009, an international scientific contest. To win the grand prize, a team had to develop a method to trace neuronal morphology that is at least 20 times faster than mapping by hand.

In September, DIADEM—short for Digital Reconstruction of Axonal and Dendritic Morphology—came to a close, with a tournament-style conclusion between five final teams taking place at HHMI's Janelia Farm Research Campus. While no team hit the 20-fold goal, their computational tools could trace neurons 10 times faster than a human hand. The judges commended the teams for developing original and creative ideas that would help solve the difficult problem of automated image reconstruction, and $75,000 in prize money was distributed among four teams.

Georgio Ascoli, a neuroscientist at George Mason University who proposed the idea for the competition, acknowledges that the 20-fold increase was a demanding challenge. At the same time, he says, it is important to recognize that "this is only the first step towards the actual goal. If we're serious about automation at the brain level, we need a 20,000-fold speed up." Thus, he says, the DIADEM challenge was intended to set the necessary developmental efforts in motion. "Once the first brick comes down, the whole building might follow soon."

More than 100 teams, from both the private sector and academic laboratories, registered to participate in the DIADEM challenge. Competitors had one year to develop an algorithm and test it against manual reconstruction. An international panel of experts then selected five finalists. During the final tournament, these developers teamed with neuroscientists, whose real data were used to test the algorithms. In six editing sessions, each competitor worked with the data owners to solve six imaging problems.

Even with the advent of computer technology that enables mapping in three dimensions, full reconstruction of a single neuron may still take months. The vast majority of branching nerve projections must be traced manually, using fluorescent labeling to highlight the neurons and microscopes to view them. Many scientists who attended the DIADEM challenge, either as participants or as judges, openly commiserated about the inefficiency of manual reconstruction techniques.

The strategies presented by each of the finalist teams will help bring neuroscientists closer to eliminating this tedious task—allowing them to conduct larger studies and collect more data or to focus on less technical aspects of their research.

"We hope that we are seeing the light at the end of the tunnel in terms of the beginning of the end of manual reconstruction of neurons," says Ascoli. ■

WEB EXTRA: For a sense of what the competition was like, watch the audio slideshow found at www.hhmi.org/bulletin/nov2010. To learn more about the competing teams and their prizes, visit www.hhmi.org/news/20100902.html.

James Kegley

Five teams made it to the final DIADEM tournament at Janelia Farm. They were from: Rensselaer Polytechnic Institute (pictured right), École Polytechnique Fédérale de Lausanne, Janelia Farm Research Campus, and two from Northeastern University.

Bacteria Helping Bacteria

A STUDY ON ANTIBIOTIC RESISTANCE SHOWS THAT BACTERIA AREN'T JUST OUT TO HELP THEMSELVES.

When faced with an oncoming dose of antibiotics, bacteria work together in a neighborly way. Microbes that are resistant to the drug protect their weaker kin in the colony, HHMI researchers have found. The discovery upends traditional notions of antibiotic resistance and offers a target for new drugs against bacterial infections.

James J. Collins, an HHMI investigator at Boston University, set out to study how bacteria acquire resistance over time. His lab group designed a bioreactor to precisely control the growth of a bacterial colony and allow sample taking or the addition of antibiotics at various times. When they collected data from the bioreactor, they found something unexpected.

"The usual thinking about resistance is that a mutation arises in one bacterium, and then that bacterium has a survival advantage and thrives, growing and dividing, while the others die off," Collins says. But the team found that the bacterial population as a whole showed far more antibiotic resistance than did small samples of bacteria. And only a few bacteria had resistance-causing genetic mutations.

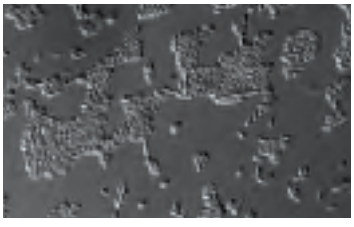
The scientists found that the few truly antibiotic-resistant bacteria emit a compound called indole that signals the rest of the bacteria to ramp up their defenses. When the nonresistant pathogens sense indole, they turn on a pump that expels antibiotic from the cell, and they turn on chemical pathways that protect them from the toxic molecules antibiotics normally induce inside bacteria.

"Bacteria, although they are unicellular organisms, can behave as a multicellular organism from a population standpoint," says Collins.

The findings, published September 2, 2010, in *Nature*, suggest that researchers might combat antibiotic resistance by blocking indole, Collins says. He also says the discovery could change the way resistance is measured in a clinical setting—a single sample from a patient might underestimate the real resistance of a bacterial strain inside the body.

Collins and his colleagues are now returning to some of their original questions, with the new viewpoint in mind. How do antibiotic-resistant supermutants arise? Do weaker bacteria protected by indole eventually develop their own resistance mutations, or eventually die off? The scientists are headed back to the bioreactor for the answers. ■

–SARAH C.P. WILLIAMS



E. coli *are more resistant to antibiotics as a group than as individual cells.*

IN BRIEF

MALARIA'S STICKY STRATEGY

When malaria parasites invade human red blood cells, they churn out a sticky protein that makes the blood cells clump together. This keeps the cells from reaching the spleen, where the immune system would destroy them, and gives the malaria parasite—*Plasmodium falciparum*—a safe haven inside the cells to replicate.

Research from HHMI international research scholar Anja T.R. Jensen has shown that producing more than one variation of the sticky protein at a time makes infected red blood cells become even stickier.

There are more than 60 versions of the sticky protein, called *Plasmodium falciparum* erythrocyte membrane protein 1, or PfEMP1, and Jensen wanted to know if any of them were associated with more severe cases of malaria. Scientists had presumed that a given malaria parasite produced only one type of PfEMP1. But when Jensen and her colleagues started isolating the RNA of PfEMP1 from malaria-infected blood cells, they were in for a surprise. Some infected cells had RNA for two forms of PfEMP1.

The researchers confirmed their observations by tagging the genes for two forms of PfEMP1, each with a different fluorescent color. Under the microscope, cells appeared to possess a combination of the two colors. The team then tested the stickiness of the red blood cells and found that cells with a combination of PfEMP1 proteins could attach to two different receptors on endothelial cells instead of just one. Jensen hypothesizes this could relate to the severity of different malaria infections. The results were published in the September 2010 issue of *PLoS Pathogens*.

DELIVERY METHOD AFFECTS NEWBORN'S MICROBIOME

The complex ecosystem of bacteria throughout a person's body, called the microbiome, isn't just affected by what that person touches, eats, and breathes. It has its roots in how the person was born, according to new research.

Rob Knight, an HHMI early career scientist at the University of Colorado at Boulder, previously developed DNA sequencing analysis techniques that determine the relatedness of assorted mixes of bacteria. He has used the technique to show how varied the collections of bacteria are in different body parts—as well as in different individuals.

In his most recent work, he teamed up with scientists in Venezuela and Puerto Rico to collect samples of bacteria from the skin and vaginas of nine mothers one hour before giving birth as well as from their newborns immediately after birth. Four of the babies were delivered vaginally and five by Cesarean section. The babies delivered vaginally harbored bacteria most similar to the bacteria found in their mothers' vaginas. Bacteria collected from the C-section babies were types typically found on the skin, the team reports in the June 29, 2010, issue of *Proceedings of the National Academy of Sciences*.

Knight thinks the differences in the microbiomes between the groups of newborns could account for certain health differences: C-section babies are at higher risk for skin infections and for allergies and asthma later in life.

PRION PROTEIN FUNCTION ILLUMINATED

When one prion protein in the brain folds up incorrectly, it starts a cascade of misfolding that takes over the brain—the cause of "mad cow" disease and other rare brain diseases. The normal function of the prion protein (PrPC) had been mysterious until recent reports indicated its importance in maintaining the nervous system. Now, a team of scientists at the Ludwig Institute for Cancer Research in Brazil, including HHMI international

Henry Lee, Collins Lab

Capture the Exon, Narrow the Hunt

TODAY'S GENETIC TECHNIQUES MAKE IT POSSIBLE TO TRACK DOWN DISEASE MUTATIONS FASTER THAN EVER.

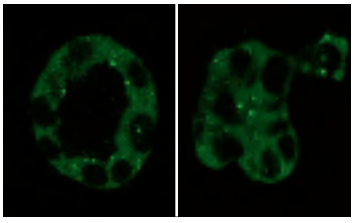
Scanning the human genome for a single disease-causing mutation is like taking a copy of *War and Peace* in a foreign language and searching for one misspelled word—a daunting and time-consuming task. But by narrowing the search in the right way, says one HHMI scientist, finding a mutation for even the rarest of diseases doesn't have to be difficult.

HHMI investigator Friedhelm Hildebrandt, of the University of Michigan, used an innovative combination of genetic techniques to find a mutation that causes kidney failure and blindness in affected children. The mutation is known to exist in only 10 families worldwide.

For years Hildebrandt's team has been collecting genetic samples from families with Senior-Loken syndrome, for which no treatment is available. They have more than 600 families in their database and have linked nine different genes to the disease. But there were still unexplained cases.

Rather than scrutinizing the entire genomes of affected individuals for mutations, the researchers narrowed their search. First, they sequenced only exons—stretches of DNA that code for proteins—which make up only 1 percent of the genome. Then, the team focused on 828 genes known to contribute to the function of cilia, cellular structures affected by the nine previously identified genes. Finally, they searched their database for matching DNA regions in two siblings affected by Senior-Loken syndrome.

The techniques made the search much more efficient than traditional methods, and it paid off: the team found mutations in a gene called *SDCCAG8* in 10 families affected by the syndrome. The group had been unable to find this gene despite a 6-year search, because of the syndrome's rarity. So-called "exon capture" allowed its identification in a single family within 6 months.



Grown in a gel, kidney cells lacking SDCCAG8 (right) don't form the perfect spheroids shown by normal kidney cells (left).

The exact role of the SDCCAG8 protein in the syndrome isn't known, but it is involved in the function of cilia—sensory extensions of a cell—in the kidneys and eyes, the scientists reported online September 12, 2010, in *Nature Genetics*. Furthermore, normal kidney cells form hollow, symmetrical spheroid structures when grown in a gel, but cells lacking SDCCAG8 form irregularly shaped spheres. Hildebrandt hopes they can use this trait to test compounds that might restore SDCCAG8's function. ■ –SARAH C.P. WILLIAMS

IN BRIEF

research scholar Vilma Martins, have added evidence to that case.

Martins and her colleagues showed that PrPC stimulates protein synthesis in neurons, possibly at their synapses—the junctions where electrical and chemical signals pass between neurons. By binding to a protein called stress-inducible protein 1 (STI1), PrPC turns on two signaling pathways known to be involved in neuroprotection, learning, and memory consolidation.

The scientists found that infecting cells with the abnormal prion protein blocked the ability of PrPC to turn on the STI1-dependent signaling pathways. This explains, in part, the detrimental effects of misfolded prion proteins in diseases. Not only are the abnormal proteins toxic, they also prevent the cell from responding to STI1. This could lead to neurodegeneration, the researchers hypothesize in the July 20, 2010, issue of *Proceedings of the National Academy of Sciences*.

PROTEIN LINKED TO MEMORY AND LEARNING

A protein that's been implicated in extending the lives of laboratory animals by preventing obesity and maintaining a healthy metabolism is now shown to be involved in keeping the brain healthy too. Drugs that boost the protein, called SIRT1, are already in human trials related to extending life spans.

In 2007, a team led by HHMI investigator Li-Huei Tsai first investigated SIRT1's role in the brain. Tsai's group at the Massachusetts Institute of Technology showed that it helped protect neurons in a mouse model of Alzheimer's disease.

To understand more about the protein, the researchers developed mice that could not make functioning SIRT1. The mice had severe learning and memory impairments, and also fewer neurons and neuronal connections in their brains, compared with normal mice. Because of the gene's widespread effects on the body, Tsai suspected that SIRT1 wasn't acting directly in the brain but was controlling other genes important for neuronal health. As she studied the expression of various genes in the brain, she found that mice lacking SIRT1 had a low level of CREB, a protein known to be important in synapse function.

Tsai and her colleagues revealed that SIRT1 affects CREB through the regulation of a microRNA molecule called mir134. Mice with too much mir134 in their brains had the same learning and memory deficits as mice lacking SIRT1. Furthermore, removing mir134 from the SIRT1-deficient mice reversed the cognitive effects. The study, published August 26, 2010, in *Nature*, suggests that SIRT1-boosting drugs may work to treat neuronal diseases.

STEM CELLS RECALL THEIR ORIGINS

Four years ago, researchers discovered how to reprogram adult cells—including skin, muscle, and blood cells—into seemingly blank slates that could develop into any cell type. The so-called induced pluripotent stem cells (iPS cells) were hailed as an alternative to embryonic stem cells. Now, two groups of HHMI researchers have shown that iPS cells don't have such a blank slate after all. But all is not lost—they've also discovered new ways to erase the cells' memories of their origins.

HHMI investigator George Q. Daley, of Children's Hospital Boston, was working to coax iPS cells into becoming blood cells to treat thalassemia, a blood disease. His team found that iPS cells originally derived from blood cells did a much better job than those that started out as skin cells. To figure out why, the scientists analyzed the patterns of methylation—a chemical signature of gene silencing—in each type of iPS cell. A similar analysis was done independently by HHMI early career scientist Konrad Hochedlinger, at Harvard University.

Hildebrandt Lab

Unequal Parenting

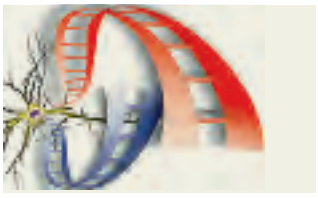
MATERNAL AND PATERNAL GENES DON'T ALWAYS HAVE THE SAME EFFECT ON OFFSPRING.

The genes you inherited from your mom and those passed along from your dad don't have equal footing when it comes to how they influence your biology. Research from a team of HHMI-supported scientists suggests that, throughout an individual's lifetime, the effect of maternal and paternal genes ebbs and flows in an intricate way.

The interdisciplinary team of scientists—led by HHMI investigator Catherine Dulac of Harvard University, and funded by an HHMI Collaborative Innovation Award—set out to find genes in the mouse brain that had only one activated copy. While mammals have two copies of almost all genes, chemical marks on one of the copies can result in only one being activated.

To find out the frequency of this phenomenon, called imprinting, the researchers bred two genetically distinct species of mice, making it easy to distinguish maternal and paternal genes in the offspring. Then they sampled various sections of the brains of 15-day-old embryos and adults. By sequencing RNA gene products, the scientists could determine whether both copies of that gene were making RNA or whether one copy was muted.

They discovered a whopping 1,308 imprinted genes. What's more, different genes were imprinted in different regions of the brain, and the patterns of imprinting varied between female and male offspring as well as between embryos and adult mice. About 60 percent of imprinted genes in the mouse embryo brains had the maternal copy turned on and the paternal version stifled. In adult mouse brains, however, about 70 percent of the imprinted genes favored the paternal copy. Almost 350 genes were imprinted in only males or only females. The results appear in two papers published August 6, 2010, in *Science*.



Paternal and maternal genes play a complicated balancing act in neurons.

"It's exciting because it suggests that the maternal and paternal genomes are not providing the same information in the brains of mammals," says Dulac. "And it affects many, many genes."

Her team plans to look into whether the imprinting patterns are linked to any diseases. One of the genes that was imprinted only in female mice has been linked to multiple sclerosis, which predominantly affects women. Further research could reveal whether these facts are connected. ■ –SARAH C.P. WILLIAMS

IN BRIEF

Both research teams found that patterns of gene silencing and activation differed between types of iPS cells depending on their origins. In cells that originated from skin cells, for example, genes for blood cell formation were silenced. And iPS cells derived from blood cells had silenced genes needed to make bone cells.

Daley's group found that drugs modifying DNA methylation could reset the iPS cells into a more embryonic state, they reported September 16, 2010, in *Nature*. Hochedlinger's lab group took a different approach to giving the iPS cells a blank slate: they found that growing iPS cells in dishes for a longer period, 3 weeks, cleared the methylation pattern. Those results appeared in the August 2010 issue of *Nature Biotechnology*.

GETTING TO THE BOTTOM OF CONFETTI SKIN SPOTS

The hallmark appearance of the skin disease "ichthyosis with confetti" (IWC) is bright red skin covering the body, widely speckled with pale, confetti-like spots. The skin disease is rare and doesn't affect multiple family members, making it hard to track down its genetic cause. But when HHMI investigator Richard Lifton, of Yale University, learned that the pale spots appeared to be normal skin, he had an idea.

Lifton hypothesized that whatever mutation was causing the disease was spontaneously lost in the speckles. So his lab group took 32 biopsies of the confetti spots from different patients and compared them to see if they were missing a similar area of DNA. They were: the same stretch of chromosome 17 was lost in each case.

That made it easier to find the problem in the red, inflamed skin. The researchers went right to chromosome 17 in the inflamed skin cells and found a mutation in the gene *keratin 10*. The mutations varied among individuals, but in all cases they caused the protein product of *keratin 10* to localize to the nucleolus of the cell instead of floating free in the cytoplasm. The results of the genetic study appeared online on August 26, 2010, in *Science*.

Next, Lifton's team hopes to understand why the mutation is lost in so many cells—each patient with the disease has hundreds to thousands of spots of normal skin, and each spot has thousands of healthy cells.

NEW CLASS OF CANCER-CAUSING MUTATION

A team of researchers studying one type of aggressive ovarian tumor has found that most cases are caused by a gene mutation that broadly regulates DNA activation patterns, linking two fields of research in a novel way.

HHMI investigator Bert Vogelstein and his colleagues at the Johns Hopkins University School of Medicine set out to find genes linked to clear cell ovarian carcinomas, the most treatment-resistant form of ovarian cancer. Their hunt revealed that the majority of these cancers had nearly two dozen mutated genes in each patient. The genes that were mutated varied from tumor to tumor, but four stood out as commonly occurring.

The most commonly mutated gene, *ARID1A*, was altered in 57 percent of the tumors they studied. *ARID1A* caught the researchers' attention because of its role in defining how cells are epigenetically regulated. Epigenetics refers to the pattern of chemical tags on DNA and histone proteins that regulate which genes are activated and which genes are silenced. Epigenetic attributes can affect the expression of genes but are not part of the DNA sequence itself.

Epigenetic mutations have been found in lung and kidney tumors but only in very rare cases. The *ARID1A* mutations are the first epigenetic mutations to predominate within a class of tumors. The research was published online in *Science Express* on September 8, 2010. Vogelstein hopes the finding will inspire other researchers to look for links between cancer genetics and epigenetics.

Catherine Dulac and Chris Gregg

Q A

Would it be possible to take a species and subject it to conditions from the past to produce its original ancestor?

Asked by Bryan, a college student from Georgia

This is a very interesting question and not so simple to answer. Let's start with an idea called convergent evolution. Often you see species that have evolved very similar features even though they are not closely related. For instance, bats, birds, and insects have all evolved wings to fly, although they are not close relatives. We say they have "converged" on these features in response to similar environmental circumstances. The converged features even share some things—some genes to make wings, for example, are shared across the species. But most of the parts are different. Bat wings have hair, bird wings have feathers, and insect wings are outgrowths of exoskeleton. Different designs with different components achieve the same solution—namely, flying.

Now take two closely related species that are placed in the same environment. Again, they might evolve the same new feature in response to their environment, like wings. However, since they are closely related, the parts that evolution can work with are very similar. So there is a good chance that the ways these two species evolve in the same environment will be very similar as well, not only in the final outcome but also in the design and parts that make up that final outcome.

If a population of penguins were placed in an environment where flying was favored, and survived many generations, for example, the population might eventually evolve into a bird that could fly. In that case, the penguin wings would almost certainly have feathers like those of other birds rather than hair like bat wings. The flight muscles and wing components would likely be more similar to those in other flying birds than to those in insects.

Taking a species that is well adapted to one environment and moving it back to an environment that its recent ancestors were well adapted to is similar to putting two closely related species in the same environment. Moved to the old environment, the species is likely to end up with the same features, and same design, its ancestors had.

But the farther back you go, the more it becomes like putting two unrelated species in an environment. As the current population becomes more and more different from its ancestors, it is more and more likely that evolution will use different parts, and even different solutions, to adapt to those previous environments. This is because the populations would have a different set of traits to begin with.

In general, going backward in biology is not the same as going forward. There are many branching paths in each direction. If a species takes one path going forward, there is no reason to expect that species would take the same path back. But you might nevertheless see some convergent evolution if there is one really good way of existing in an environment.

ANSWER RESEARCHED BY ELI MEIR, *a former HHMI predoctoral fellow and now president of SimBiotic Software (simbio.com), the developers of the EvoBeaker and SimUText biology education programs.*

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

Friedman Wins Lasker Award

JEFFREY FRIEDMAN

The 2010 Lasker Award for Basic Medical Research has been presented to HHMI investigator **Jeffrey M. Friedman**, of The Rockefeller University, and Douglas Coleman, an emeritus scientist at The Jackson Laboratory. The Lasker is the nation's most prestigious award in basic and clinical research. Friedman and Coleman were chosen for their work on the biological mechanisms of appetite regulation and how it goes wrong in some diseases. Friedman discovered the hormone leptin and its role in weight control, and Coleman made the link between leptin and diabetes.

MICHAEL J. BEVAN, an HHMI investigator at the University of Washington, was presented the 2010 Novartis Prize in Basic Immunology at the International Congress of Immunology. Bevan studies T lymphocytes and their role in the immune system.

HHMI investigator SANGEETA N. BHATIA, of the Massachusetts Institute of Technology, won the 2010 Young Investigator Award from the American College of Clinical Pharmacology for her research on tissue engineering.

AXEL T. BRUNGER, an HHMI investigator at Stanford University, was chosen as the inaugural recipient of the DeLano Award for Computational Biosciences from the American Society for Biochemistry and Molecular Biology. Brunger develops tools for interpreting x-ray crystallography diffraction data.

MARTIN D. BURKE, an HHMI early career scientist at the University of Illinois at Urbana-Champaign, won the 2011 Arthur C. Cope Scholar Award from the American Chemical Society. The annual prize is given in the field of organic chemistry. Burke uses organic chemistry to develop small molecules for treating diseases.

HHMI investigator KEVIN P. CAMPBELL, of the University of Iowa Roy J. and Lucille A. Carver College of Medicine, received the A. Ross McIntyre Award from the University of Nebraska Medical Center. This annual award honors contributions to the study of medicine or medical education and recognizes Campbell's research on muscular dystrophy.

HHMI early career scientist HOWARD Y. CHANG, of Stanford University School of Medicine, won the 2010 CE.R.I.E.S. Research Award, given annually by the Epidermal and Sensory Research and Investigation Center of CHANEL for research in dermatology. Chang is a practicing dermatologist who studies how cells, including skin cells, situate themselves in the body.

VIVIAN G. CHEUNG, an HHMI investigator at The Children's Hospital of Philadelphia, is the 2010 recipient of the Curt Stern Award from the American Society of Human Genetics. This award is presented yearly for outstanding scientific achievements in human genetics that occurred in the last 10 years. Cheung was chosen for her work on gene regulation and expression.

HHMI investigator JASON G. CYSTER, of the University of California, San Francisco, was chosen as the 2010 recipient of the Frederick W. Alt Award for New Discoveries in Immunology, an annual award given by the Cancer Research Institute and named after a current HHMI investigator. Cyster studies the immune system, particularly lymph nodes.

GRACE ECKHOFF, an HHMI-supported undergraduate at the University of Texas (UT) at Austin, won a Marshall Scholarship to pursue a master of science in public health in developing countries degree at the London School of Hygiene & Tropical Medicine. A native of Haiti, Eckhoff spent eight months in Afghanistan as a teacher's aide after graduating from high school. As an undergraduate at UT Austin, she returned to Afghanistan to study antibiotic-resistant tuberculosis. Also winning a Marshall Scholarship was JAMES LUCARELLI, an undergraduate in the Yale-HHMI Future Scientists Program. Lucarelli will pursue a degree in chemistry at Oxford.

HHMI professor SARAH C.R. ELGIN, of Washington University in St. Louis, won the 2010 Janet Andersen Lecture Award from the Midstates Consortium for Math and Science for her mentoring of undergraduates.

The 2010 Dickson Prize in Medicine was awarded to STEPHEN J. ELLEDGE, an HHMI investigator at Brigham and Women's Hospital. The prize is given annually by the University of Pittsburgh School of Medicine to a leading American scientist. Elledge

Courtesy of The Rockefeller University

was chosen for his pioneering work in cell cycle regulation and cellular response to DNA damage.

The American Heart Association named CHARLES T. ESMON, an HHMI investigator at Oklahoma Medical Research Foundation, the 2010 recipient of the AHA Basic Research Prize for his work on the biochemistry of blood clotting.

SARAH FORTUNE, a grantee of the HHMI-supported KwaZulu-Natal Research Institute for Tuberculosis and HIV, and H. SEBASTIAN SEUNG, an HHMI investigator at the Massachusetts Institute of Technology, were named PopTech Science and Public Leadership Fellows. The Fellows are supported in part by PopTech, a nonprofit organization; Microsoft Research; the Doris Duke Charitable Foundation; and the Rita Allen Foundation. The fellowship program aims to give scientists the tools they need to be socially engaged public communicators.

The HEALTH SCIENCES AND TECHNOLOGY ACADEMY at West Virginia University, an HHMI-funded partnership between educators, health professionals, and community leaders, was awarded the 2010 Outreach Scholarship W.K. Kellogg Foundation Engagement Award. This award recognizes outreach and engagement partnership efforts of four-year public universities.

HHMI investigator A. JAMES HUDSPETH, of The Rockefeller University, won the 2010 John and Samuel Bard Award in Medicine and Science from Bard College for his research on the biomolecular details of hearing and equilibrium through inner ear hair cells.

The Association of American Physicians named HHMI investigator ROBERT J. LEFKOWITZ, of Duke University, winner of the 2011 George M. Kober Medal. The annual award goes to Lefkowitz for his work on G-protein coupled receptors, cell receptors now linked to numerous physiological processes.

HHMI international research scholar HUGO D. LUJÁN, of the Catholic University of Córdoba, won a 2010 Guggenheim Latin American fellowship for his research on *Giardia*.

HHMI investigator TOM A. RAPOPORT, of Harvard Medical School, is the 2010 recipient of the van Deenen Medal, awarded by the Institute of Biomembranes to a scientist for accomplishments in the membrane field. Rapoport studies how proteins are transported across membranes and how the membranes inside cells maintain their shapes.

HHMI investigator LI-HUEI TSAI, of the Massachusetts Institute of Technology, received a 2010 Glenn Foundation Award for her research in the biological mechanisms of aging. Tsai studies neurodegenerative diseases, such as Alzheimer's disease, as well as the biology of memory.

RONALD D. VALE, an HHMI investigator at the University of California, San Francisco, was elected the 2012 president of the American Society for Cell Biology for a one-year term.

CHRISTOPHER A. WALSH, an HHMI investigator at Children's Hospital Boston, won the 2010 Krieg Cortical Discoverer Award from the Cajal Club, an international organization of neuroscientists. The annual award is given for outstanding research on the structure and connections of the cerebral cortex.

LEONARD I. ZON, an HHMI investigator at Children's Hospital Boston, was awarded the 2010 E. Donnall Thomas Lecture and Prize from the American Society of Hematology. The annual prize recognizes outstanding work in the study of blood. Zon's research focuses on blood stem cells.

SPOTLIGHT

Champalimaud Vision Award Goes to Newsome

WILLIAM NEWSOME

Brie Linkenhoker

HHMI investigator **William T. Newsome**, of Stanford University School of Medicine, won the 2010 Champalimaud Vision Award from the Champalimaud Foundation for his research on the brain mechanisms underlying vision. Newsome shares the award with J. Anthony Movshon of New York University, with whom he has collaborated to show the importance of brain neurons in perceiving moving objects. The annual Champalimaud Vision Award is the largest monetary award in the field of visual research and one of the largest scientific and humanitarian prizes in the world.

CONTINUED FROM PAGE 40
(GOING GREEN)

When Robert Tjian became president of HHMI in 2009, a plant sciences initiative rose to the top of his list of priority items. Furthermore, Tjian, who formerly served as chairman of the scientific advisory board at GBMF, suggested that HHMI and GBMF explore a partnership to invest jointly in plant sciences research.

"We are thrilled to be partnering with HHMI to support current and emerging leaders in the plant sciences field," says Steven J. McCormick, President of GBMF. "Our increasingly interconnected world, and the challenges and opportunities it faces, oblige us to seek shared approaches with both grantees and other funders. Through collaboration and alignment of resources with an exceptional partner like HHMI, we will have a far greater impact in the fields where we engage."

HHMI and GBMF believe the establishment of this joint program will underscore the importance of enhanced support for plant sciences research and can be leveraged to increase others' interest in this field.

"Plants play a critical role in sustaining the health of the planet," says Vicki L. Chandler, chief program officer for science at GBMF. "We believe that generating fundamental new knowledge about how plants function and relate to Earth's ecology, biodiversity, and climate—and to human health and well-being—will 'move the needle' in the plant sciences and will cross disciplinary lines, impacting other fields as well."

Detailed information about the competition—including a list of eligible institutions and access to the secure application site—may be found at the HHMI website (www.hhmi.org). ■

FOR MORE INFORMATION: See "Plant Sciences Matters," a perspective piece by Vicki Chandler, on page 34.

Ben Weeks

COMMAND PERFORMANCE

Even today, child psychiatrist Judith Rapoport's 1989 book on obsessive-compulsive disorder (OCD), *The Boy Who Couldn't Stop Washing*, is widely considered a classic. Her insights into the confounding disorder continue to lend comfort to the tormented and understanding to the family members and health care providers who care for them. Chief of the child psychiatry branch of the National Institute of Mental Health since 1984, Rapoport has said that of the many psychiatric studies she has carried out, and of the many unusual cases she has treated, none compares with the fascination and drama of OCD.

[Obsessive-Compulsive Disorder] has also been called obsessional neurosis. Psychiatrists have been fascinated by this disorder for over a hundred years. Priests have described the overly scrupulous for much longer than that. Children suffer from Obsessive-Compulsive Disorder with exactly the same symptoms as adults. To a child psychiatrist like myself, an early start in a mental disorder is unusual. Other mental illnesses, such as depression or schizophrenia, often appear in a different form in young children and, in any case, are much more rare in children than in adults.

But with OCD it is the same at any age. I have seen a two-year-old start to walk in circles around manhole covers; ten years later he couldn't go to school because of his bizarre compulsion to draw O's! How these complex behaviors spring up in childhood is mysterious but suggests that some innate program of behavior is running wild in this disease. That each young patient has the same habits, even though they have never seen or heard of one another, is eerie. At Swarthmore, I studied how parrots build nests, how cranes dance, how squirrels hoard. None have teachers, yet each species builds the same nest, hoards food in the same way, and so forth. I think of these creatures as I meet new young patients with their bewildering tales of new patterns of behaviors that intruded from nowhere. I introduce them to each other and they are astonished that this has happened to someone else, that they are so much alike! But I am not describing a new avian courtship dance, or the rituals of an isolated primitive tribe. These are frightened, lonely people and the cruel script erupts from somewhere inside their brains.

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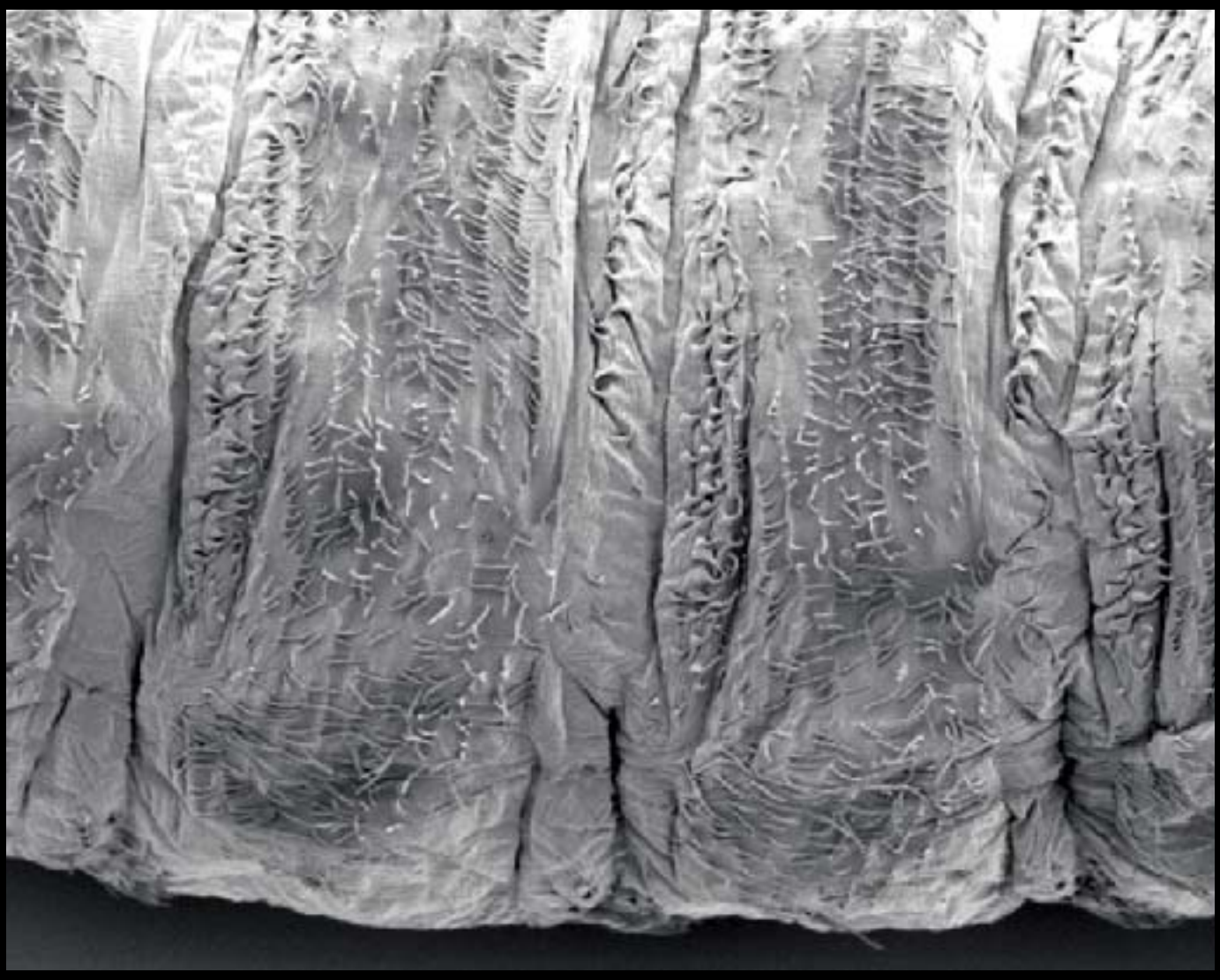
Hairy Details

To the casual observer, all fruit flies look the same. But evolutionary biologist David Stern knows better. He studies the physical differences among fruit fly species—down to the tiny hairs that cover the surface of newly hatched larvae, shown magnified in this electron micrograph. It may sound trivial, crazy even, but there is method to Stern's madness: he's looking for body parts that have evolved, trying to understand why the changes have occurred. Ten years into his study of the microscopic hairs—called trichomes—Stern is still uncovering details of their complex genetic architecture. Read about it in "Reality Check" on page 10.



David Stern