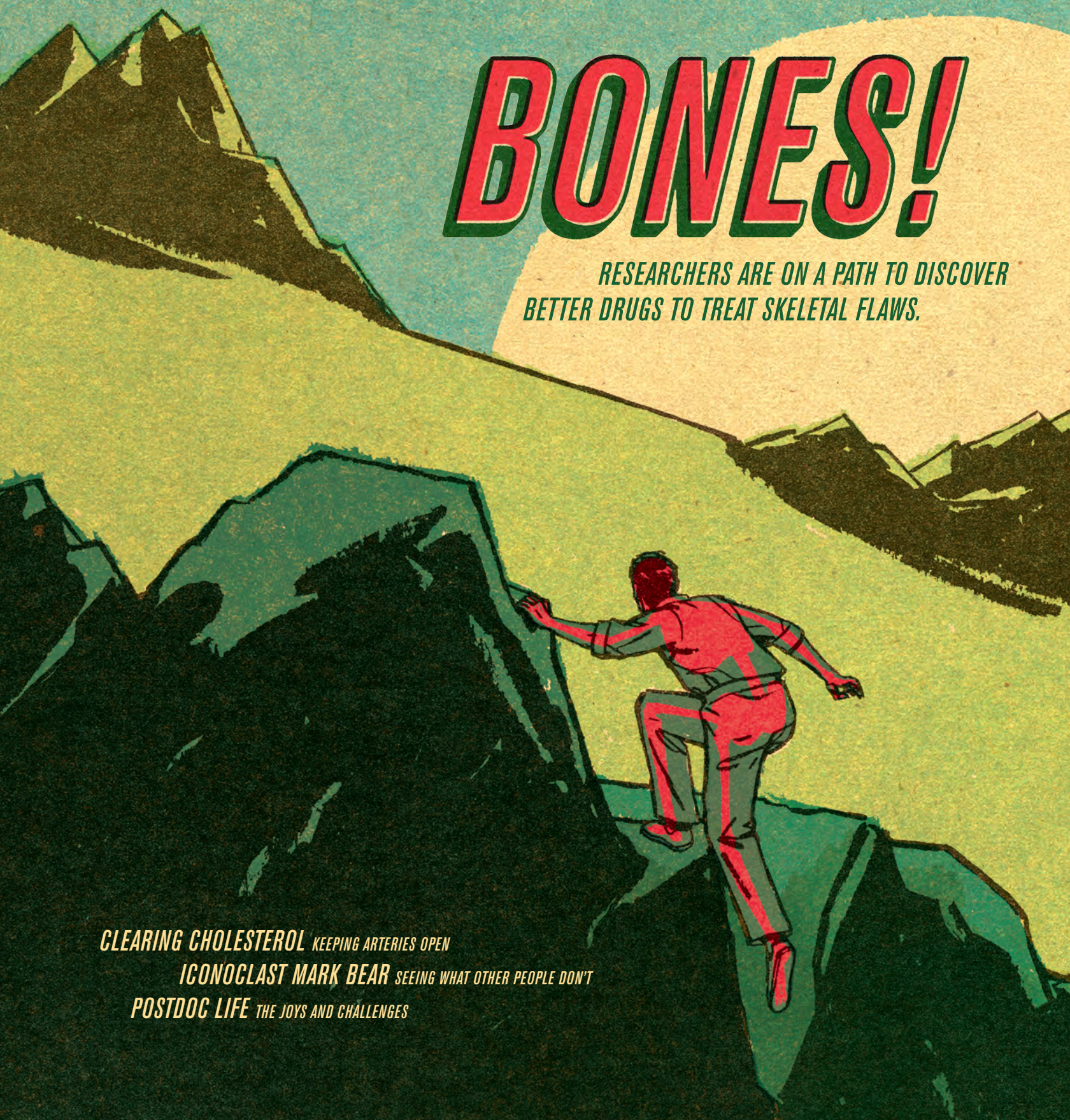
May '11 | Vol. 24 • No. 02

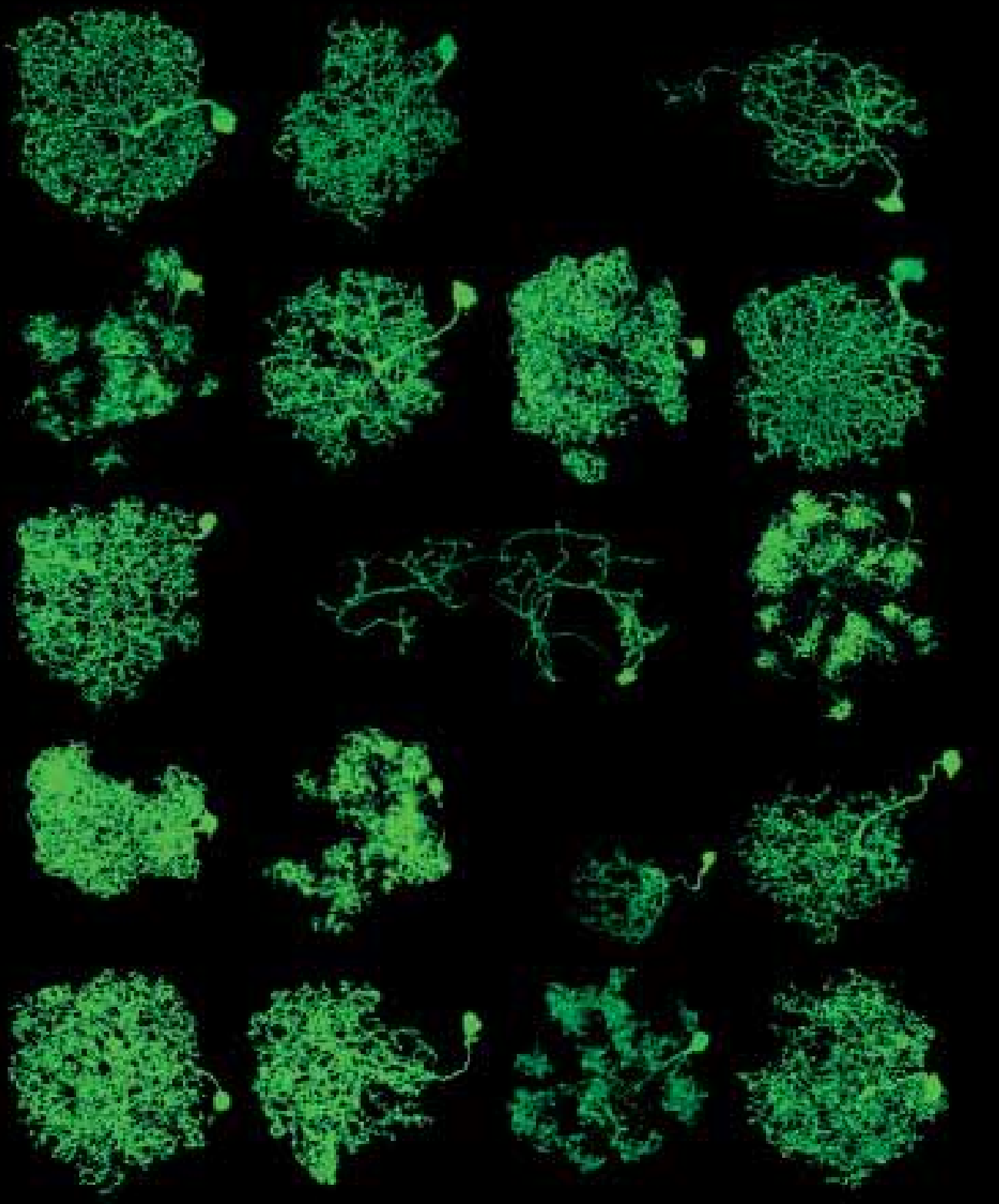
HHMI BULLETIN

Howard Hughes Medical Institute www.hhmi.org



BONES!

RESEARCHERS ARE ON A PATH TO DISCOVER BETTER DRUGS TO TREAT SKELETAL FLAWS.



Web Only Content

In the antennal lobe of a fly, environmental smells are processed and sent to the rest of the brain so the fly can react—Eat! Follow! Fly away! The lobe is a mishmash of olfactory neurons normally hard to distinguish, but visualize them one at a time (as above) and it's clear that each group of related neurons forms a unique structure. Understanding how these neuron groups interact to send messages is the next challenge. Read more in "Wired for Smell" at www.hhmi.org/bulletin/may2011.

Liqun Luo lab

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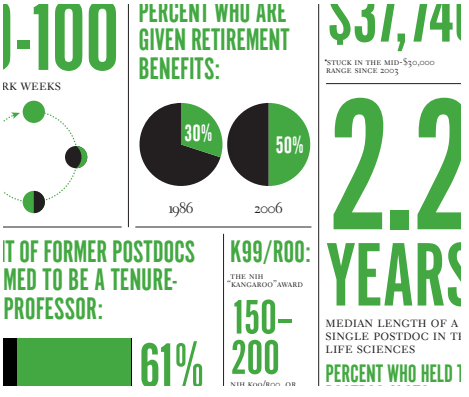

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Web Only Content

- Explore the scientific images behind a mosaic portrait of Gregor Mendel.
- Learn how researchers can follow real-time neuron growth in a mouse brain.
- See the stunning variety of dragonflies that Hal White has photographed.
- Join us at www.hhmi.org/bulletin/may2011.

Features

Departments

When my brother was small, he jumped off the back of our living room sofa, in some superhero-inspired game, and fractured his leg. Broken bones are a right of passage for many kids, but he stands out in the history of our family—the only one of four siblings to ever wear a cast. His junior by three years, I was so impressed by the event that I have always steered clear of ski slopes. The thrill of shushing downhill never outweighed the prospect of hobbling on crutches.

Most of the time, we take our bones for granted—until something goes wrong. Our cover story highlights the work of researchers trying to understand the mechanisms behind normal bone buildup and breakdown and what happens when that process goes awry. What they are learning about bone repair, genetic bone disease, and cancers of the bone tells us that the pathways involved are much more complicated than once thought.

These days my family is keenly aware of the effects of aging on bones. My mother, now 89, was diagnosed with osteoporosis several years ago. Initial treatment with the drug Fosamax proved disappointing, due to side effects. After careful assessment of other available options by her doctor and my sister, a bone genetics researcher, my mother is now facing her second treatment with the once-a-year drug Reclast. Time—and her next bone density test—will tell if the drug is doing its intended job of slowing bone loss.

My father is not exempt. At 92, he's dealing with weakening and compression of his spinal vertebrae. Two of his sisters have experienced the same fates, both of them developing noticeable "dowager's humps"—a forward curvature of the upper back due to osteoporosis—in their later years.

Genetic odds say that I will face a similar destiny. My first bone density test, which I had last year, showed mild bone loss. Ever since, with almost religious zeal, I've taken a calcium plus vitamin D supplement at breakfast, chased by a bowl of yogurt. I'm hoping this daily routine will at least postpone further bone loss. Like missing out on the thrill of skiing, it's a small concession I'm happy to make for the health of my bones.

Meanwhile, I will count on researchers like my sister and the ones described in this issue to continue making headway in understanding bone biology, which will no doubt lead to better treatments for all types of skeletal flaws. I hope you find the work as fascinating as I do. And for those of you with iPads, be sure to download the free *Bulletin* app for a deeper dive into the topic as well as a fun twist on the story's design.

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Paul Vetters

Learn, Show, and Tell

James Keglev

MORE THAN TWO DECADES AGO, AS THE HOWARD HUGHES MEDICAL Institute reorganized itself and entered a period of exponential growth in scientific research, the Institute also made a commitment to supporting programs in science education. It stemmed from a settlement with the Internal Revenue Service and resolved tax issues that had dogged the Institute during the life of its founder, Howard R. Hughes. HHMI agreed to spend an extra $100 million over a 10-year period on an activity related to its research mission but went beyond that commitment many years ago. Today, with total investments of more than $1 billion, programs in science education have become an integral part of our mission and culture.

As an avid tennis player who's always seeking that elusive sweet spot on the tennis court, I can tell you that HHMI has found its educational "sweet spot" in programs aimed at undergraduate faculty and students. This spring, we announced our eighth undergraduate education competition—this one targeting colleges and universities that focus on undergraduates—and plan to award $60 million in new grants about a year from now. We are setting the bar high, asking our potential collaborators to think big and be creative. We have asked schools to unify their proposals around a single education objective, made it clear that we'll reward those who partner with other institutions to create comprehensive programs, and set new expectations for schools that we've supported for many years.

This is good, important work. But it's clear that HHMI's educational commitment needs to extend beyond the classroom and laboratory to reach in new directions. Under the leadership of Sean Carroll, who has been an HHMI investigator for many years and now heads our Department of Science Education, the Institute will launch a science documentary initiative. We will create high-quality programming and disseminate it internationally through television, classrooms, and other media. This initiative, still in the early stages of development, is important for science in America and around the world.

Science has gotten so complicated that many people have given up trying to make sense of the flood of information that comes their way. Conflicting claims, new information, and misuse of facts combine to create confusion among individuals who try to follow the public conversation about science. Has human activity contributed to climate change and what does that mean? Is mammography good or bad? How can we know that today's miracle drug will be safe? How do living organisms evolve? These are big questions and worth understanding for nonscientists and scientists alike.

As scientists, we haven't done a particularly good job of explaining what we do, how we do it, and why. We talk openly among ourselves about how discovery is an ongoing exercise in assessing and revising our understanding of the physical world. It also makes sense to us that our colleagues can reach certain conclusions about the world sometimes based on partial or fragmentary knowledge. We recognize that the weight of accumulated evidence has significance, even if a specific model, finding, or assumption is later found to be only partially correct. Yet keeping this sort of productive conversation inside the scientific community doesn't have much of an impact—particularly because it can create the impression that we are smug about our own "superior" knowledge and erect unintended barriers that can often alienate nonscientists and further widen the gulf of trust.

> "It's clear that HHMI's educational commitment needs to extend beyond the classroom and laboratory to reach in new directions."
>
> ROBERT TJIAN

HHMI has had some limited experience with television programming. We have helped fund the public broadcasting series *NOVA scienceNOW* and provided modest support for the new science reporting unit on the *PBS NewsHour*. And we have long used video as a tool for expanding knowledge through our popular Holiday Lectures on Science, which provide in-depth information on topics important to high school teachers and students. This year, we'll tackle human evolution with Holiday Lectures from a trio of experts on October 6 and 7.

We expect that the new documentary initiative will significantly extend our science education outreach on a larger scale—certainly on more screens—and at a level of quality on par with HHMI's program in scientific research. Carroll and his colleagues aim to create television programming built around compelling stories of scientists' lives and discoveries, stories with the power to inspire and nourish curiosity. As an accomplished author of popular science books and a columnist for *The New York Times*, Carroll knows how to spin a lively tale that's scientifically accurate and opens a window into the essence of the scientific process. But we hope these documentaries and related educational materials will do something more: Show how science is done, how experiments test ideas about the natural world, how accumulated data can lead us to insights that make it possible to distinguish observable truth from opinion or belief. That's an investment we feel an obligation to make.

Ode to Dragonflies

In his small, quiet book about large, charismatic insects, Hal White sounds a persuasive alarm about our vanishing connections with the natural world.

"As people forget their sense of the outdoors, it's being destroyed," he says. "And nobody will even see it go." His book is *Natural History of Delmarva Dragonflies and Damselflies: Essays of a Lifelong Observer*, published this spring by the University of Delaware Press with the Delaware Nature Society.

It's a leisurely ramble through a rich patch of natural history, featuring almost 200 razor-sharp portraits of the spiketails, emeralds, darners, and other aquatic insects that have fascinated him since he was a teenager in the 1950s. He rounds out his reminiscences, field notes, and observations with sketches of dragonfly hunters he has known—and the occasional haiku.

White is a University of Delaware biochemist who spends weekends and holidays with net and camera prowling the wet places of the Delmarva Peninsula between the Chesapeake Bay and the Atlantic Ocean. "I'd rather be up to my knees in a swamp than cooped up in an office," he says.

A self-described "enthusiastic amateur," he's published a swarm of articles on dragonflies and damselflies and was proud to coauthor descriptions of the rare ringed boghaunter and pygmy snaketail larvae, which he tracked down (and dredged up) in Massachusetts and Virginia.

White's university duties include directing an HHMI-supported program that makes calculus more accessible to biology students by substituting biological examples for physics and engineering problems. "It's surprising how often kids who love biology are taken aback by math requirements. If they can understand how math relates to their field—if math anxiety doesn't stifle their attitude of inquiry—I call it a great success," he says.

He traces his own attitude of inquiry to a childhood lived with educators as parents and the Pennsylvania woods for a playground. "I got to roam unsupervised, catching animals, damming streams, harvesting berries, climbing mountains." Later, in his formal education, "those experiences were real to me, not abstractions."

"But today, students are no longer interested in a walk in the woods," he says. "They've been conditioned to be afraid of poison ivy, mosquitoes, those sorts of things."

White's office is decked with dragonfly-themed artifacts, among them a door knocker, an oversize kite, and a Tiffany-style lamp. Here he opens up about the concerns that sparked his book: "Science comes from field observation; field biologists like Darwin make observations that lead to experiments that otherwise would never happen."

Everyday people lack boots-in-the mud experience, too, he says, and the consequences are dire: The jewel-like creatures lyrically depicted in his book stand for all of "our fellow earthlings whose survival we threaten—not through deliberate actions … but through our relentless destruction and disruption of fragile and unique habitats."

He writes, "Our seemingly innocent routine activities of building houses, fertilizing lawns and crops, salting roads in the winter, cutting down stream-side vegetation, tapping ground water … contribute far more to the demise of certain species than most people realize."

"This book is a plea to humankind," White says, to return to the wonder of the woods, the mountains, and the marshes—to experience biodiversity directly, and to appreciate just how vulnerable and precious it is.

—George Heidekat

WEB EXTRA: To see a slideshow of photos from White's book, visit www.hhmi.org/bulletin/may2011.

"I'd rather be up to my knees in a swamp than cooped up in an office."

HAL WHITE

Ping Zhu

Andrew Cutraro

Science History as Art

For neurobiologist Julie Simpson, beauty is microscopic. In her second-floor office at HHMI's Janelia Farm Research Campus, circuit diagrams of fly brains are neatly framed. Simpson's favorite t-shirt is an Andy Warhol-style shot of fly images, in four squares. "I'm not tempted to buy a Monet," she remarks, "but I do like a good Golgi stain."

Now, Simpson can get the best of big portraits *and* tiny science. She and her partner Frank Midgley, a scientific computing expert at Janelia Farm, have created a one-of-a-kind art exhibit, "MacOSaiX Scientific Heroes." They generated mosaic portraits of 35 scientists—from Gregor Mendel to E.O. Wilson—assembled from Google search images of key research terms.

Midgley wrote a software program, using the Macintosh operating system, that cranks out the portraits. To remix the classic portrait of Mendel, for instance, the program performed a Google search for images chosen to describe Mendel's work: "genetics," "peas," "heredity," "law of segregation," and "law of independent assortment." The program then compared the resulting image tiles against his portrait, numerically ranking and sorting the tiles into a logical layout to fill up the picture. Tile by tile, the new portrait emerged, composed of about 5,000 images that convey Mendel's work.

At a distance, the mosaic Mendel thoughtfully gazes, same as always, from a simple background. Draw closer, however, and you see that his eyes dance with a motley mix of tiled images of peas, the DNA double helix, a butterfly, chromosomes, garden images, monk robes, and thousands of other illustrations, pieced together like a giant crossword puzzle.

"What's cool is that these portraits are driven by the real work the scientists did," Midgley says. Equally satisfying, Simpson adds, is learning the history behind that work. The couple wrote short biographies to accompany each portrait.

Simpson and Midgley got the idea for their MacOSaiX project in the spring of 2010 as they stopped in Janelia's art gallery and began thinking of ideas to dress the walls in art with a scientific twist. Soon, they were spending weekend hours on the project, with Simpson researching scientists and Midgley writing code. The collection grew as colleagues at Janelia lobbied for must-haves, like Freeman Dyson and Maria Goepfert, and voted down others (sorry, B.F. Skinner).

"It was a huge hit. Our scientists loved it," says Kim Ripley, special projects manager at Janelia Farm, who coordinates exhibits. "In fact, we've decided to make the images a permanent collection," just outside Janelia's popular dining room.

Back on the second floor, Simpson is identifying brain cells that control fly behaviors, such as grooming. Midgley is developing computer tools to allow Simpson and other scientists to make sense of huge data sets on those behaviors.

You can try out Midgley's free MacOSaiX program at http://web.me.com/knarf. Midgley notes that your creation will be your own: image search results constantly change. No two portraits are ever the same. *—Kathryn Brown*

WEB EXTRA: To see how Gregor Mendel's portrait came together, visit www.hhmi.org/bulletin/may2011.

From Bench to Brahms

At least one evening a week, doctors and scientists from Boston's biomedical community escape the laboratory or bedside to unleash their musical creativity with the Longwood Symphony Orchestra (LSO).

In this acclaimed amateur orchestra they've found an outlet for a lifelong passion that ended up playing second fiddle to their demanding careers.

"A lot of scientists and physicians use music to enrich their lives, to recharge after a long day of work, and to pursue another avenue that is artistic yet just as fulfilling," says Sherman Jia, a violinist and LSO concertmaster. Jia is an HHMI medical research fellow in the lab of HHMI investigator Bruce Walker, an HIV-AIDS researcher at Massachusetts General Hospital.

The orchestra's 120 musicians represent nearly every major biomedical institution in Massachusetts, says violinist and LSO president Lisa Wong. Architects, teachers, dentists, software engineers, and biotech workers also sprinkle the ranks.

For the LSO, music is more than entertainment; through performances, it raises awareness and funds for nonprofit medical organizations that support research on amyotrophic lateral sclerosis, Alzheimer's disease, and genetic disorders. Also, through "LSO on Call" it brings music to patients in hospitals, hospices, and rehabilitation centers.

The weekly rehearsals plus extra practices for five major concerts a year strain the schedules of busy doctors and scientists. For many, though, the LSO, founded in 1982, is a high priority.

Several years ago, for instance, HHMI investigator and LSO principal trumpet Leonard Zon rushed in late to a rehearsal. Zon, head of stem cell research at Children's Hospital Boston, was trying to squeeze in the rehearsal before flying to Washington to brief legislators on stem cell research.

"I do everything I can to get there," says Zon. "The orchestra is a great venue for relaxing amid the pace of everyday life as a physician-scientist, and it has a wonderful mission to help people in need." On that day, however, the conductor sent him off: "'Go to Congress and educate them on stem cells,'" Zon recalls.

For many, as with science, classical music is a family tradition.

"My grandfather was a doctor and a violinist—he would play every time I visited as a child," recalls Mark Emerson, a postdoc in the Harvard laboratory of HHMI investigator Connie Cepko. "I started playing in fifth grade, and my grandfather gave me his violin. I think about him every time I play in a concert."

At one point, Emerson thought about playing violin professionally. But he's happy he became a scientist and joined the LSO to maintain his affair with music. Emerson says Zon's example "was what made me think I could balance the two."

For Maria Lehtinen, something had to give. She is a violinist, a pianist, and a postdoc in the lab of HHMI investigator Christopher Walsh at Children's Hospital Boston. She was thrilled to join the LSO in 1999. "There aren't many opportunities to play in an orchestra unless you're a very serious professional," Lehtinen says. However, her career has intensified and she now has a family, forcing her to resign. "I'd really like to come back," she says. "I've thought about it a lot. But for now, I'm just too busy."

Comings and goings are a fact of life for LSO members. So far, Emerson is successfully juggling his research, family life, and the orchestra.

"One of the main reasons is the community outreach work," Emerson says. Another motivation is the family tradition; like his grandfather, he is handing down the gift of music to his children.

"My son, who's four, has a little violin," says Emerson. "When I'm practicing, he likes to stand up and conduct me." *—Richard Saltus*

WEB EXTRA: To learn more about Leonard Zon, who plays shofar as well as trumpet, visit www.pbs.org/wgbh/nova/secretlife/scientists/len-zon/.

Ping Zhu

upfront

WEB ONLY CONTENT

WIRED FOR SMELL
Complex circuits of excitation and inhibition help the brain interpret odors. Read the story at *www.hhmi.org/bulletin/may2011*.

The human body is full of fine-tuned sensors and circuits that respond to changes in the environment. Some are self-explanatory: in the cold, the body shivers to warm up. Others take probing to understand. Scientists scrutinizing how cells react to low oxygen found a complicated response pathway linked to aging and heart disease. And researchers have discovered that a mutation in an ion channel triggers cells to proliferate out of control, causing a rare type of tumor—and high blood pressure. When it comes to biology, the tiniest imbalances can have surprising implications.

A Crowd in the Kitchen

A global team of researchers showed that potassium channel mutations promote tumor formation and hypertension.

WHOEVER SAID TOO MANY COOKS SPOIL THE BROTH MUST NOT HAVE been a geneticist. ¶ According to HHMI investigator Richard Lifton, a kitchen full of cooks—plus some very high-end cookware—was exactly what was needed to define the molecular defects underlying a severe form of hypertension, and a specific type of tumor.

Lifton, a human geneticist at Yale School of Medicine, has long been interested in a type of adrenal gland tumor that causes high blood pressure. Normally, the adrenal gland, located atop the kidney, secretes the steroid hormone aldosterone into the blood. The hormone instructs the kidney to retain water and salt (and hence elevate blood pressure) in times of acute physiological stress, such as blood loss or salt imbalance.

Some 5 to 10 percent of patients with extreme hypertension, however, have tumors of the adrenal gland. These benign, sometimes massive tumors pump out unregulated levels of aldosterone into the bloodstream. Unrestrained aldosterone production causes the kidney to retain sodium, keeping blood pressure high. The condition is curable only by surgical removal of the adrenal gland.

Lifton lab postdoctoral fellows Murim Choi and Ute Scholl and a team of collaborators recently discovered the surprising cause of a subset of those adrenal tumors: mutations in a gene encoding an ion channel protein. Normally that channel, known as KCNJ5, allows potassium ions to pass in and out of cells. But in the tumor cells, the channel also allows sodium ions to leak through, which activates signaling pathways that stimulate tumor cell growth and unregulated aldosterone production.

"It seemed so obvious that these tumors were caused by somatic mutations," says Lifton, referring to mutations that are acquired rather than inherited. "But it wasn't until we could sequence all the DNA in a tumor that we could identify what those mutations were."

That's where all the cooks come in, starting with physicians at Uppsala University in Sweden, who diagnosed hypertensive patients with adrenal tumors, surgically removed the tumors, and then meticulously stored tumor specimens to preserve their DNA.

Lifton then did a high-tech search through the 23,000 or so genes in the patients' tumor cell DNA to find culprit mutations. That analysis, called whole exome sequencing, was a two-step process. First, the team used gene microchips to "capture" the approximately 1 percent of a cell's 3 billion DNA letters that contains genes (the exome). Second, they sequenced that relatively small portion of the genome using next-generation machinery at the Yale Center for Genome Analysis.

Choi took on the daunting task of devising computer programs (see Web Extra, "Dedication Personified") to make sense of all that DNA data—including whole exome analysis of four patients and partial analysis of 18 more. In the end, his analysis identified eight patients harboring mutations in the KCNJ5 channel gene. According to Lifton, the odds of that happening by chance are 10^{-30}.

Pietari Posti

But was it structural damage that made the mutant KCNJ5 channels leaky? Collaborating with Wenhui Wang at New York Medical College in Valhalla, Scholl answered the question experimentally. When she studied the mutant channels in cultured cell lines, she found that they allowed sodium ions to flow abnormally into the cells. The work was reported February 11, 2011, in *Science*.

Particularly notable to Lifton was how beautifully this story meshed with predictions made in the 1990s by fellow HHMI investigator Rod MacKinnon of Rockefeller University.

MacKinnon had shown that channel proteins allow only certain ions to pass through due to the configuration of protein building blocks that form a gate—a so-called "selectivity filter." For that work, he was awarded the Nobel Prize in Chemistry in 2003.

"One mutation we found in KCNJ5 in tumors was in a residue that MacKinnon had defined as critical for potassium selectivity for similar channels," says Lifton. MacKinnon's work offers a satisfying architectural explanation for why sodium ions slip through the mutant channel, he adds.

The KCNJ5 story is the first report of an ion channel playing a role in the unbridled cell proliferation characteristic of tumors. Whether this knowledge will lead to less invasive treatment for adrenal tumors remains to be seen. In the meantime, Lifton envisions a simple blood test to detect KCNJ5 mutations to help diagnose this type of adrenal tumor.

Now, almost two decades after Lifton began his effort to discover the genetic basis of hypertension, his lab has identified 10 or so genes that when mutated increase blood pressure. All, including *KCNJ5*, control regulation of salt balance. He's hoping these investigations will lead to better treatment strategies for the approximately 1 billion patients worldwide who have hypertension, a major risk factor for heart disease and stroke.

"To treat hypertensive disease, we often use three or more drugs per patient, and about two-thirds of those patients don't improve under that kind of control," says Lifton. "We must figure out a better way to treat these patients." ■ –ELISE LAMAR

WEB EXTRA: For more on the exome analysis by postdoc Murim Choi, visit www.hhmi.org/bulletin/may2011.

NEURO$_2$GENESIS

An ancient cellular program to protect cells when oxygen is low seems crucial for the production of new brain cells.

Nick Antony

Celeste Simon has shown that some cells need low oxygen to function well. In the brain, that finding offers clues on depression.

FOR MORE THAN TWO BILLION YEARS ON THIS PLANET, O_2 HAS BEEN the go-to gas for generating efficient cellular energy. But life on Earth never takes oxygen for granted. "When it runs low, cells swiftly adapt," says cell biologist Celeste Simon. ¶ This ancient adaptive reaction, known as the low-oxygen, or hypoxia, response, typically involves a cascade of protective changes in cells: protein synthesis drops and cells switch to a less efficient process of energy production that doesn't require oxygen. But organisms have evolved uses for the hypoxia response that are not merely protective.

Simon, an HHMI investigator at the University of Pennsylvania, recently found evidence that the response is crucial for maintaining the health of stem cells in the hippocampus, a key memory region of the brain. The discovery could alter our understanding of a host of stem cell-related brain conditions.

"It's a seemingly puzzling finding, but the normal functioning of neural stem cells in the hippocampus does appear to require low oxygen levels and consequent hypoxia responses," says Simon.

The neural stem cells in question are meant to keep the population of hippocampal neurons replenished. A certain level of this replenishment, or "neurogenesis," is increasingly thought to be important for a healthy mood and memory. Interruption of neurogenesis causes depression-like behavior in mice, while in humans antidepressant medications appear to work largely by boosting neurogenesis. Alzheimer's disease, as well as ordinary aging, features a decline in this replenishment process.

In an October 2010 *Nature Cell Biology* paper, Simon and her colleagues reported that neurogenesis markedly declined in mice when their brain cells were genetically altered to knock out their ability to produce the hypoxia response. "We saw fewer stem cells, fewer of the immature daughter cells that stem cells produce, and fewer connections coming from these daughter cells," says Simon.

Why would the hypoxia response even matter to brain cells, which are known for their voracious intake of oxygen? Simon and her team found that the usual habitat for stem cells in the mouse hippocampus is riddled with low-oxygen zones, where the signs of stem cell activity are particularly evident. "It seems that these lower-oxygen zones are essential for maintaining neural stem cells' healthy activity," she says. "In fact, these stem cells appear to be spread out, in and near these zones, with different activities depending on the oxygen level, suggesting that the stem cells' activities are being regulated by the local oxygen levels." The hypoxia response may be acting as a growth signal for the stem cells.

> "It seems that these lower-oxygen zones are essential for maintaining neural stem cells' healthy activity."
>
> CELESTE SIMON

Preliminary tests on the engineered no-hypoxia-response mice suggest that they do have behavioral defects consistent with those seen in other mouse models of depression. Simon and her colleagues now are trying to determine whether inadequate hypoxia responses in the hippocampus might be at least partly to blame for depression in humans.

Some activities are known to *promote* neurogenesis—such as physical exercise—and here again Simon wants to know whether hypoxia signaling is a factor. "One of the things on our to-do list is to determine how exercise affects oxygen distribution in these stem-cell-rich regions of the hippocampus," she says.

The clinical possibilities don't end there, given the links between decreased neurogenesis and both Alzheimer's and aging. "We haven't yet had a chance to investigate in this area, but naturally we're intrigued by the possibility that age-related declines in the hypoxia response help to drive the age-related functional declines we see in the brain and other organs," says Simon.

It might seem odd that a protective response to low oxygen has ended up being adopted by some cells so that they actually need a bit of hypoxia to function normally. But most of Simon's prior research in the field has aimed at understanding such adaptations. "Embryonic cells, for example, can grow so quickly that they create a hypoxic zone around themselves," she says. "This switches on their hypoxia response, which among other things promotes the sprouting of new blood vessels toward them, so that they can continue to grow." Her work has helped to show, too, how the hypoxia response is used in some cancer cells and also directly regulates stem cells in the developing bone marrow and heart.

"It's been clear for some time now that hypoxia signaling is relevant in many areas of biology," she says. "But it could turn out to have more importance for health and disease than we'd ever imagined." ■ –JIM SCHNABEL

WEB EXTRA: For other work related to hypoxia and the heart, see the sidebar "Hearts and HIFs" at www.hhmi.org/bulletin/may2011.

BONE'S BALANCING ACT

Searching for cures, scientists are revealing the biological complexity of bones.

ILLUSTRATION BY PATRICK LEGER

BY DAN FERBER

ones are the body's framework and support, our strongest tissues. Unlike the scaffold of a building, however, bones are anything but inert. They pulse with life and their maintenance requires a surprisingly delicate balancing act.

Throughout our adult lives, the body works day and night to clear away patches of weak bone and build up new and stronger bone. When that balance falters in either direction, it spells trouble. Osteoporosis, which literally means porous bones, occurs when bone breakdown outpaces bone buildup. Just bending or coughing can cause a fracture. Too much bone, on the other hand, can lead to rare bone diseases or even bone cancer.

A small army of bone researchers, including several HHMI investigators, is exploring the cellular pathways that strengthen weak bones and support healing in broken bones. Their efforts are yielding new drugs to treat osteoporosis, heal severe fractures, and treat rare hereditary bone diseases. They're working on new precision therapies to stop bone cancer, as well.

The work is essential. By 2020, half of all Americans over age 50 will have weak bones and the low bone mass of osteoporosis, according to a 2004 Surgeon General's Report. Roughly 4 in 10 white women age 50 or older in the United States will experience a hip, spine, or wrist fracture, most likely due to osteoporosis. And the problem isn't limited to women. Up to one in four men over age 50 will break a bone due to the disease. The consequences are profound: one in four patients over 50 with a hip fracture will die within a year.

"Skeletal diseases are incredibly common," says developmental biologist David Kingsley, an HHMI investigator at Stanford University School of Medicine, noting that patients with less common but devastating bone diseases desperately need effective treatments too.

Studying bone also sheds light on fascinating and fundamental biological questions, Kingsley adds. The development of bone reveals how "just a few cell types can be organized into highly specific shapes and sizes that underlie the things that animals do." The forms of animal skeletons, past and present, offer clues about how their owners flew, ran, swam, and ate. Bone can do all that—but only if it stays in balance.

THE MAGIC IN BONE

Early in embryonic development, our bones are mostly cartilage, and it's the cartilage-filled ends of bones that lengthen as we grow. As we mature and growth slows, bone gradually replaces that cartilage. The thick, hard outer layer of bone resembles reinforced concrete in its structure, deriving strength from fibrous proteins called collagen encrusted with crystals of a calcium-containing mineral. Even hard bone is plumbed with blood vessels and wired with nerves. And inside the outer layer sits marrow, a softer tissue packed with immature cells that can form blood, bone, and cartilage cells.

In 1992, Kingsley reported a pivotal discovery about how the body constructs bones. He examined a mutant line of mice with very short ears, a wide skull, and a reduced ability to heal fractured ribs in search of something that had been hinted at two decades earlier. An orthopedic surgeon named Marshall Urist had made an extract of rabbit bone and implanted it under the skin of a living rabbit. It produced an intact, marrow-filled bone under the rabbit's skin. The discovery meant, Kingsley says, "that there is some magic in bone that could induce formation of new bone."

He found that the short-eared mice had a mutation in a gene that produced that magic ingredient, called bone morphogenetic protein (BMP). Today 20 related BMPs are known, many of which induce the body to make bone or cartilage. BMP-2 is the active ingredient of a drug that grows new bone after spinal fusion surgery. Surgeons implant a biodegradable sponge soaked with the drug, called INFUSE Bone Graft by Medtronic. The procedure replaces an older, painful, and infection-prone method in which surgeons transplanted bone from the patient's hip.

The same drug is used for other dental and orthopedic problems: to bolster bone that anchors crowns or teeth, to heal foot and ankle injuries, and to repair gunshot wounds to the jaw. It can help knit shin bones shattered in motorcycle accidents, for example, or replace sections of cancerous bone that have been removed in children, according to bone cell biologist Hari Reddi, of University of California, Davis, who purified the first BMPs in the 1980s.

However, the drug must be implanted with the sponge, rather than given as a pill or injected into the bloodstream, because it doesn't easily circulate to where it's needed, according to Reddi.

THE DISCOVERY MEANT, KINGSLEY SAYS, "THAT THERE IS SOME MAGIC IN BONE THAT COULD INDUCE FORMATION OF NEW BONE."

Clinicians would like better alternatives, and they need treatments that preserve and repair bone when it gradually deteriorates throughout the body, as it does in osteoporosis.

BUILDING BONE BULK

Even when bone is healthy, it's always growing, dying, changing. To build and maintain healthy bone, we need weight-bearing exercise such as tennis, hiking, and walking; a healthy diet with calcium-rich food such as milk, cheese, and certain vegetables; and vitamin D, from dairy products and sunlight, or a supplement. This is true during childhood and adolescence when the body builds 85 percent of adult bone mass, and it's true during adulthood to prevent bones from thinning and weakening.

The only reliable detection method for osteoporosis before a fracture is a bone density scan. Such tests have shown that a full 44 million Americans have low bone mass and 10 million, most of them women, have osteoporosis. In men, the disease is linked to low testosterone levels, smoking and alcohol use, and lack of physical activity. In women, it is linked closely to menopause, when estrogen levels in the body drop. In the 1980s and 1990s, doctors recommended that postmenopausal women prevent osteoporosis and fractures by taking estrogen supplements, which jam two cellular pathways used for bone resorption—one pathway involves compounds called cytokines and a second is called the Rank ligand pathway. But in 2002, researchers running a long-term trial called the Women's Health Initiative reported that estrogen plus progestin supplements raised the risk for breast cancer and stroke; two years later, estrogen alone was found to also increase the risk for stroke. Estrogen use plummeted.

Fortunately, by then researchers had begun uncovering cellular signaling pathways that maintain bone's thickness and strength. Three types of bone cells balance breakdown and repair: osteoclasts, which clear away patches of weak or defective bone; osteoblasts, which build it; and osteocytes, which are entombed in solid bone, sensing and directing the others. For all these cells, "the quest is to find out how signaling works and start designing therapies around that," says bone biologist Alex Robling of Indiana University School of Medicine.

Today, several targeted therapies are available to prevent and treat osteoporosis by blocking bone breakdown. They include four members of a class of drugs called bisphosphonates—Fosamax, Actonel, Boniva, and Reclast—and Denosumab, which blocks the Rank ligand pathway. These bone-preserving drugs are also used to treat osteogenesis imperfecta, which causes children to produce weak, defective bone.

But while bisphosphonates and Denosumab are effective at preventing bone resorption, they also cripple the bone-degrading cells that are supposed to clean out weak or damaged bone. Over time this can make bones even more brittle, increasing the risk of fractures and, rarely, cause the jawbone to decay. Researchers are now investigating ways to get around this dangerous side effect, such as giving patients drug holidays after a few years.

Bone endocrinologist and geneticist Gerard Karsenty of Columbia University Medical Center likens osteoporosis to a house fire and antiresorptive drugs to water. "If you come with water you are going to stop the destruction, but you still need to rebuild," he says. Just one drug exists to rebuild lost bone—Forteo (teriparatide), a synthetic form of human parathyroid hormone. Although the drug looks safe in humans so far, long-term treatment with high doses of it caused bone cancer in rats; as a result, doctors stop giving it to patients after two years. New drugs that build bone would be helpful. "That's where the need is," says endocrinologist and bone expert Sundeep Khosla of the Mayo Clinic in Rochester, Minnesota.

LEARNING FROM OVERGROWTH

Researchers have identified at least three ways to build bone. Two involve a cellular signaling pathway called Wnt. In 2001,

an international consortium led by HHMI investigator Matthew Warman, a pediatrician and geneticist at Children's Hospital in Boston, showed that a Wnt pathway gene called *LRP5* is mutated in a disease called osteoporosis-pseudoglioma syndrome, which causes people to develop brittle bones.

A year later, HHMI investigator Richard Lifton of Yale University School of Medicine reported a different *LRP5* mutation that makes the LRP5 protein overactive, leading patients to make too much bone. His team showed that the mutation causes high bone mass by preventing the natural antagonist Dkk and, by inference, the related protein sclerostin from inhibiting LRP5 function. Warman and Lifton later found other *LRP5* mutations in patients with syndromes characterized by high bone density.

Since loss of LRP5 causes brittle bones and people with overactive LRP5 build extra bone, drugs that boost LRP5 activity could boost bone growth without keeping damaged bone from being recycled. This is why Warman says that "LRP pathways in bone are very exciting targets."

Warman has studied bone building in patients who make too much bone to better understand—and ultimately enhance—bone building. What happens in these patients resembles an extreme version of what happens during weight-bearing exercise like hiking or weight lifting, which spurs the body to bolster bone where it's needed. (In a famous 1977 study, the upper arm bones of professional tennis players were 30 percent thicker in the arm they used to hit the ball than in their other arm.)

Recently, Warman's team engineered mice to produce the overactive version of *Lrp5* but only in mature osteocytes in hard bone. Osteocytes are believed to sense mechanical stress and release compounds that recruit osteoblasts to lay down more bone. Warman's collaborator, Robling, at Indiana University, anesthetized the mice and then mimicked the effects of weight-bearing exercise by repeatedly bending their forelimbs. Mice with overactive *Lrp5* in their osteocytes produced three times more bone than normal mice put through the same exercises.

"That tells us that the high bone mass mutation works in very mature bone cells," Warman says. "And, if we can think of a way to make an LRP5 receptor in mature bone cells think that it has a high bone mass mutation, then you and I can have more bone." At least three companies have looked for and found a compound that tricks the LRP5 receptor in just this way. For example, Amgen is running phase 2 clinical trials on its version of an antibody to sclerostin. Eli Lilly and Company has developed a chemical compound that keeps sclerostin from blocking LRP5.

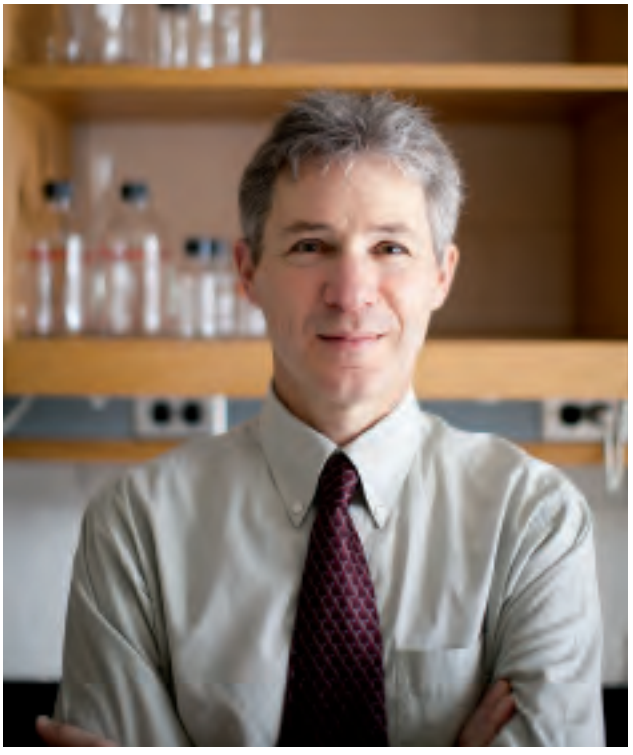
Warman is eager to develop bone-building drugs to help some of his youngest patients—children with osteogenesis imperfecta. This hereditary disease can kill before birth or make children so susceptible to fractures that they must spend their lives in a wheelchair, Warman says.

As Warman's team tries to build bone by targeting LRP5 in bone cells, Karsenty's team is trying to build it by blocking production of a compound called serotonin in the gut. In 2008, his team found to their surprise that LRP5 blocks gut cells from producing serotonin, which normally signals bone-building cells to stop multiplying. Last year, they reported in *Nature Medicine* that a drug that blocks serotonin synthesis in the gut builds bone in mice. The results seem to conflict with Warman's, but "it's possible that both groups are in part correct, and more needs to be done to sort out that whole story," Khosla says.

While most researchers seeking bone-building drugs have targeted Wnt signaling, including LRP5, HHMI investigator Gerald Crabtree, at Stanford University, has discovered a second pathway that seems to help the body build bone. A few years ago, Monte Winslow, an HHMI predoctoral fellow in Crabtree's lab, was investigating why the anti-rejection drug cyclosporine causes bone loss. They knew that cyclosporine indirectly changes the shape of a protein called NFATc that typically sits in the cell's cytoplasm but moves into the nucleus to activate genes.

When they engineered mice with a mutant version of NFATc that stays in the nucleus just 10 percent longer, the result was "the boniest mouse anyone ever produced," Crabtree says. Unlike a normal mouse, which feels "soft and cuddly," Crabtree says, these mice "felt like a bag of bones." Now, he and biochemist and HHMI investigator Stuart Schreiber of Harvard University are hunting for chemical compounds that tweak normal NFATc to act like the nucleus-loving version. Such compounds will shed

"WE'RE VERY EXCITED BECAUSE WE'VE GOT WHAT WE THINK IS A MORE AUTHENTIC MODEL OF OSTEOSARCOMA," LEE SAYS.



Clockwise from left: Matt Warman targets LRP5 to build bone, Brendan Lee linked Notch signaling to bone cancer, and David Kingsley placed BMPs in the center of early bone-building efforts.

Warman: Matt Kalinowski Lee: Pam Francis Kingsley: Davis Tower Kingsley

light on how the NFATc pathway leads to bone growth and, with luck, may lead to drugs that boost bone growth in a new way.

IMMATURE BONE AND CANCER

Sometimes bones lose their balance by overgrowing and becoming cancerous. Brendan Lee, a pediatric geneticist and HHMI investigator at Baylor College of Medicine in Houston, pursues therapies for osteosarcoma, the most common type of cancer that originates in the bones, from which about 60 percent of patients recover. To do so, he draws on insights gained by treating patients with hereditary bone, cartilage, and joint diseases at the Skeletal Dysplasia Clinic at Texas Children's Hospital.

Among them are children with spondylocostal dysostosis, a rare disease in which babies are born with fused and misshapen vertebrae and a rib cage several sizes too small. Children who survive often can't breathe without a ventilator and sometimes need a hole inserted in their trachea, or major rib and chest surgery, just to breathe. "It tugs at your heartstrings," Lee says. "Their brain is okay, but they're kind of trapped in a body."

Lee noticed that many patients with spondylocostal dysostosis weren't growing. What's more, their bones were "washed-out" or darker on x-rays, which suggested they had low bone mass—an observation that Lee corroborated with bone density scans. Lee knew that genes in a signaling pathway known as Notch were mutated in this disease and that Notch signaling helped immature stem cells in the bone marrow decide which of two types of blood cells to become. He suspected that Notch might help another type of bone marrow stem cell decide whether to become a bone- or cartilage-forming cell.

Sure enough, his lab group discovered, it did. Mice with overactive Notch in their bone marrow stem cells developed far too much bone in their skull, ribs, and leg bones, the team reported in *Nature Medicine* in 2008. But it was immature bone, not the strong, layered bone that supports the healthy adult skeleton. Lots of immature bone forms in human osteosarcoma, too. That "helped us make the leap to bone cancer," Lee says.

To see if Notch signaling was also altered in bone cancer, Lee's group tested lab-grown human bone cancer cells, including tissue cultured directly from patients' bone tumors. As anticipated, Notch signaling was overactive, suggesting that the pathway contributed to human osteosarcoma. And compounds that block

(continued on page 48)

CHARTING NEW WATERS

The same daring spirit drives Mark Bear to win sailboat races and to craft treatments for fragile X syndrome.

BY MADELINE DREXLER

The Laser is not built for leisurely sailing. With a sleek hull just under 14 feet long, a tall mast, simple sail, and minimal controls, this craft has one purpose: to race. The singular helmsman—almost always a "he" because of the physical demands—must scramble, in a race on high seas, from one side of the craft to the other, suspend himself outboard straight-legged against a stiff wind, and torque his body in response to every wave. Since all Lasers are structurally identical, winning or losing lies entirely in his hands.

Mark Bear—a champion helmsman and neuroscientist at the Massachusetts Institute of Technology—says he applies the same principles to racing and research.

"You begin with probabilities. You don't know a priori whether heading off to the left side of the racecourse or the right is the way to go. So you collect information, make observations, test hypotheses. You do a few pilot experiments, sailing upwind a little in either direction, to see what looks promising. You make a plan, and take measurements of whether or not the plan is working. If you made a wrong guess, you make on-course corrections.

"But what really separates great sailors from less great sailors," adds the HHMI investigator, "is that they see things that other people don't."

He should know. On the water, in a boat inaptly named "Fat Bastard," Bear has won the U.S. Masters National Championship and the New England Championship. In the lab, he's challenged reigning dogmas in neuroscience.

Over a quarter century, Bear has tacked toward elusive problems in his field. His main obsession has been brain plasticity: the process by which neurons change in response to experience. Early on, he explored neural connections in the hippocampus, which plays a key role in long-term memory and spatial navigation. Controversially, he used these findings as a model for a very different part of the brain, the visual cortex.

More recently, Bear has applied his discoveries in brain plasticity to understanding fragile X syndrome, an inherited form of mental impairment. He has described surprising mechanisms underlying fragile X and has shepherded a promising treatment through phase 2

PHOTOGRAPHS BY JEFF BARNETT-WINSBY

clinical trials testing for efficacy in patients. The course he has charted may yield the first neurobehavioral targeted pharmaceutical treatment that grew from the bottom up: from gene discovery to an understanding of pathophysiology to a targeted drug.

Early Inspiration

On November 22, 1963, the day President John F. Kennedy was assassinated, six-year-old Mark Bear was glued to the television. What transfixed him, even then, were the early conjectures from newscasters about what Kennedy's life would be like if he survived the gunshots to his head and neck. "I remember being astounded: so much resides in the brain," Bear says. The next Christmas, he asked his parents for a human brain modeling kit.

Now 53, Bear has the look of an ageless East Coast postdoc: neat but decidedly casual—khakis, crew neck sweater, hiking boots. He is tall and fine-featured, with a slightly receding hairline and an early morning hint of a five-o'clock shadow. His eyes often have an abstracted and amused expression, as if he's formulating a joke.

Across the street from where he works on the MIT campus, dominating the view through his lab's plate glass windows, is Frank Gehry's Stata Center: big and boxy, with defiantly jangled angles. It's an odd panorama. In his unassuming office, Bear—sometimes slouched, sometimes leaning forward to explain a fine point of science—is soft-spoken but plainly passionate about the mysteries of the brain.

In the decades since JFK's death, neuroscience came of age, and Bear caught the wave. Researchers learned that the brain's adaptive plasticity extends into adulthood. And this plasticity is centered in the synapse—the junction across which a nerve impulse passes from one neuron to another. At the synapses, axons—the long, slender projections of nerve cells that conduct electrical impulses to target cells—connect to dendrites, the short-branched extensions of nerve cells that ferry impulses toward the cell body. The terminus of the sending cell contains neurotransmitters, chemicals that diffuse across the gap and activate sites on the target cell, called receptors. Synaptic plasticity is the ability of the connection between two neurons to change in strength.

Figuring out the basis of this plasticity has been Bear's mission from the start. To convey how he has gone about that quest, he switches metaphors from the sea to the casino. "Imagine nature as a deck of cards," he says. "The first experiment you do should not be one where you peel off a card from the top. It should be the deck-splitting experiment. The most incisive experiment. The experiment that most narrows the range of possibilities and will define your subsequent course."

Bear launched his career as a doctoral student at Brown University, followed by a postdoctoral fellowship with Wolf Singer at the Max Planck Institute for Brain Research, in Frankfurt, and a return to Brown with his own lab. His research spun off from a well-studied phenomenon known as long-term potentiation, or LTP. When a rapid train of strong nerve impulses hurtles down an axon, the synapses that connect the axon to the dendrites of other neurons are strengthened, or "potentiated." LTP is one of the cellular processes underlying learning and memory.

In his research on brain plasticity, Mark Bear asks questions and designs experiments that challenge conventional views.

What piqued Bear's interest was the opposite process: synaptic weakening, a phenomenon known as long-term depression, or LTD. He was inspired by classic experiments performed in the early 1960s by Harvard University's David Hubel and Torsten Wiesel that won them the 1981 Nobel Prize in Physiology or Medicine. They temporarily sealed one eye in infant kittens. When the eye was reopened weeks later, neurons in each animal's visual cortex no longer responded to stimulation, while brain cells compensated by responding more strongly to inputs from the open eye. In effect, the kittens' brains had rewired themselves under visual deprivation—enough to cause permanent blindness.

The kitten experiment "was the most exciting demonstration of experience-dependent brain plasticity ever," says Bear. "I wanted to understand the mechanisms at the synaptic level and ultimately at the molecular level." He focused on a group of receptors known as metabotropic glutamate receptors, or mGluRs, which are especially active during periods of high plasticity.

But he took an unconventional route to the answer. He employed a formula in computational biology known as the BCM theory—for Bienenstock, Cooper, and Munro—a model of how synapses change and respond selectively to stimulation. This theory suggested that LTD is a consequence of synaptic activity that fails to strongly activate the target neuron. Using stimulating and recording electrodes, Bear and his graduate student Serena Dudek looked for LTD in the hippocampus, an easy site to study synaptic physiology. They eventually were able to reliably trigger LTD in hippocampal slices freshly prepared from mice and rats, with both electrical stimulation of synapses and with chemicals that stimulate glutamate receptors. Further experiments showed that LTD was widespread in slices from different brain regions—including the visual cortex.

Next, he temporarily deprived young kittens of sight in one eye in two different ways, either by anesthetizing the retina or by closing the eyelid, which allowed the retinal cells to continue firing nerve impulses randomly. A few days later, after the anesthesia wore off and the closed eyes were reopened, the scientists displayed visual patterns to each eye and measured brain activity.

In animals whose eye had been closed temporarily, synapses had predictably weakened. But in animals whose retinas had been anesthetized—and therefore sent *no* signals to the brain—the cortex responded about equally to stimuli from both eyes. This suggested it wasn't the absence of visual stimulation that caused blindness—"use it or lose it"—but a mismatch of activity between the signals the brain was getting from the open and closed eyes. Synaptic strength declined through the active process of LTD. Bear had illuminated the mechanisms of the famous Hubel and Wiesel experiments decades earlier.

"He was willing to stick his neck out," says Richard Huganir, an HHMI investigator and neuroscientist at Johns Hopkins University, coauthor on several of Bear's papers and a longtime friend. Bear had used discoveries about how LTD takes place in the hippocampus—where it wasn't even clear what effects that plasticity had—and applied it to the visual cortex, where the end results were obvious: blindness. The conceptual leap drew flak from fellow scientists. As Bear drily recalls, "I can still remember someone saying, 'The visual cortex is not a hippocampal slice with eyes.'"

Yet his findings were later replicated. Indeed, Bear's lab is still working on the problem, publishing important papers in 2009 and 2010 that explore molecular mechanisms for perceptual learning and the mechanisms of visual cortex plasticity. "We half-joke about 'the curing blindness experiment,'" he says. "We haven't quite succeeded yet, but we're going to, I hope."

"He's one of the few neuroscientists who pays any attention to theoretical arguments," notes Leon Cooper, director of Brown University's Institute for Brain and Neural Systems and Bear's mentor at Brown. (Cooper—the "C" in the BCM theory—shared the 1972 Nobel Prize in Physics for studies on the theory of superconductivity.) "Mark developed a rather deep understanding of theories of synaptic modification and realized that they depended on assumptions about cell behavior that hadn't been checked. He set out to check them—and in the process, discovered some remarkable new phenomena, including LTD."

Cooper says this approach to discovery sets Bear apart from many scientists. "They say seeing is believing, but Mark had to believe in order to see."

Daring Experimentalist

Fragile X syndrome is the most common inherited form of intellectual impairment and the most common known genetic cause of autism. Though its symptoms vary among individuals, they are profound and devastating: low IQ, seizures, autistic behavior, anxiety, attention deficit, and sometimes an abnormal

"WHAT REALLY SEPARATES GREAT SAILORS FROM LESS GREAT SAILORS IS THAT THEY SEE THINGS THAT OTHER PEOPLE DON'T." *Mark Bear*

SCIENTIST & MENTOR

"Professor Bear's Patented Fundamental Brain Tonic & Cure All," proclaims the Victorian-lettered notice on a bulletin board in Mark Bear's suite of labs. "For the immediate relief of Scientific Thought, Enlightened Ideas, Secular Reasoning, Humanist Morality, and the General Confusion of having to think for yourself."

The occasion was a graduate student presentation at the lab—poking fun at Bear's enthusiasm for mGluR5 as a broad therapeutic target. Among his grad students and postdocs, Bear is known as an encouraging, enthusiastic, and joyful mentor.

Hey-Kyoung Lee was impressed by this side of him even as an undergrad at Brown University. In an "Introduction to Neuroscience" class, Bear began one lecture by wheeling in a cart on which a hospital sheet was draped over large, round objects. A hush of anticipation swept over the students. Bear donned a lab coat and surgical gloves. In a solemn voice, he reminded the students that they were lucky to have materials to demonstrate the brain's structures, and that it was important to respect the sanctity of the donors.

He then pulled away the sheet. Underneath were honeydew melons adorned with Mr. Potato Head accessories.

"He's a great lecturer," says Lee, now associate professor of biology at the University of Maryland. "And he changed my career direction. He turned me on to how interesting it is to study the molecular basis for memory formation. I decided that this is what I want to do for the rest of my life."

As a graduate student with Bear, Lee worked for two arduous years to figure out a chemical way to depress synapses. "I spent two years getting no data, running experiment after experiment." Every time she brought her dismal findings to Bear, he showed her promising new directions. "I was finally able to debug the protocol and make it work. It turned out to be a robust protocol, and simple, too. Nowadays, people use it widely, which makes me very happy. It's all because Mark was inspirational, getting me through the hardships of the project."

Kim Huber, now associate professor of neuroscience at the University of Texas Southwestern Medical Center, as a postdoc performed the decisive laboratory experiments proving the mGluR connection to synaptic weakening. "Even now when I see Mark—and I've been out of his lab for 10 years—I still want to tell him about findings in my lab, because he was always so enthusiastic."

"Science is fun," Bear says. "If you're not having fun, then maybe you shouldn't be doing science." —*M.D.*

physical appearance. It strikes 1 in 4,000 boys and 1 in 8,000 girls. There is no cure—only treatments for problems such as anxiety and impulsive behavior.

Fragile X is caused by a mutation in the *FMR1* gene, discovered in 1991, which leads to loss of a protein, the fragile X mental retardation protein, or FMRP. Under a microscope, the defective X chromosome looks broken—fragile—where the *FMR1* gene is disrupted and mutated. In 1994, researchers created an *Fmr1* knockout mouse.

At an HHMI science meeting in 2000, Bear unexpectedly crossed paths with fragile X. In a prepared lecture, he explained the link between protein synthesis and memory. When he returned to his seat, the stranger next to him leaned over, complimented him on the talk, and offered to send him some fragile X knockout mice, which lack the *Fmr1* gene. The stranger was then-HHMI investigator Stephen Warren, the geneticist at Emory University who had discovered the mutation for fragile X.

Bear enthusiastically accepted. The conventional wisdom was that LTD's synaptic weakening was a result of protein synthesis and that one of those LTD proteins was FMRP. That meant that Warren's *Fmr1* knockout mice would presumably show fewer signs of LTD. In Bear's lab, postdoc Kimberly Huber, a gifted physiologist, performed experiments comparing hippocampal LTD in the knockouts with that in wild–type mice. The experiments were blinded—that is, she didn't know at the outset which animals were the knockouts and which were wild type.

When the experiment was completed and the scientists finally genotyped the animals, Bear and Huber were dumbfounded. Contrary to expectations, it was the knockout mice that showed high levels of LTD, not the wild type. "I swear to God, I thought somebody had mixed up the code," says Bear. They repeated the experiment: same incongruous result.

"If you're doing an experiment, and you've worked very hard at it, and you get a bizarre result, chances are 99 out of 100 that the bizarre result is just some kind of fluke," explains Cooper. "But 1 time in 100 it's not a fluke. That's up to the taste, the discretion, the daring of the experimentalist. And Mark is a daring experimentalist."

After pondering the results for several months, Bear came up with an explanation that turned the conventional wisdom on its head. Simply put, it states that mGluR5 drives protein synthesis to keep up with the demands of the cell. FMRP acts as a brake on protein translation. Without FMRP, mGluR5-triggered protein synthesis goes unchecked, eventually disrupting synaptic function.

In 2002, Bear presented the idea at a conference on fragile X at Cold Spring Harbor Laboratory. "I was the last speaker of the meeting. I laid out this idea. And there was a sort of stunned silence. I felt relieved that I hadn't been laughed at."

In 2004, based on this single experiment and an exhaustive literature search on the downstream effects of mGluR5, he published a paper in *Trends in Neurosciences* boldly titled "The mGluR theory of fragile X mental retardation." It suggested that a vast array of fragile X symptoms—epilepsy, cognitive impairments, developmental delays, loss of motor coordination, anxiety, autistic behavior, habit formation, sensitivity to touch, even changes in gastrointestinal motility—could be accounted for by runaway effects of mGluR5. Fragile X, Bear wrote, was a disease of excess: excessive sensitivity to environmental change,

excessive neural connectivity, excessive protein synthesis, excessive excitability, excessive body growth. Was it possible to undo this cellular chain of events?

Bear and his colleagues at MIT later performed a genetic rescue experiment in mice—"rescuing" normal behavior through DNA manipulation. They crossed mice that were heterozygous for the gene that encodes mGluR5 with *Fmr1* knockout mice, which lacked the gene for FMRP that restrains protein synthesis. The offspring had only half of the normal mGluR5 receptors and so produced only half the normal amount of mGluR5 protein. Reducing mGluR5 compensated for the lack of FMRP and eliminated many of the symptoms of fragile X. It was as if the genetic manipulation had compensated for lack of a protein synthesis brake by taking the foot off the gas pedal.

In the genetically engineered mice, seven of eight fragile X phenotypes similar to those in humans were corrected or prevented. (The only phenotype not corrected was abnormally large testes.) The animals didn't have exaggerated LTD, they didn't suffer seizures when exposed to a loud noise, they didn't gain abnormal weight, and their neurons didn't show the abnormal dendrites seen in the *Fmr1* knockout mice.

While the results are encouraging—suggesting global effects of a single medication—"the behavioral manifestations of fragile X are different in a mouse than in a human," Bear says. "It is hard to know a priori which aspects will be helped and which will not."

The experiment did demonstrate that mGluR5 was a valid target for drug therapy. Other investigators have found that the interaction between FMRP and mGluRs is highly conserved in evolution, showing up in fruit flies and zebrafish in addition to mammals. This evolutionary conservation boosts confidence that pharmacologic approaches successful in animals may fare well in humans.

Trial Treatments

In 2005, Bear cofounded Seaside Therapeutics, Inc., a Cambridge, Massachusetts-based company dedicated to creating treatments to correct or improve the course of fragile X syndrome, autism, and other disorders of brain development. In July 2010, Seaside announced positive data from a randomized, placebo-controlled phase 2 study of pediatric patients with fragile X syndrome. Seaside used an experimental drug dubbed STX209, or arbaclofen, which inhibits glutamate signaling.

The trial showed that the drug reduced outbursts and tantrums and boosted sociability and communication. In September 2010, the company announced promising results from an "open label" phase 2 study of the drug in young patients with autism spectrum disorders, where the participants knew what drug they were receiving. These patients likewise were less irritable and less socially withdrawn.

> "BEING BORN WITH A DEVELOPMENTAL BRAIN DISORDER MAY NOT BE AN IRREVOCABLE SENTENCE." *Mark Bear*

The company has received federal regulatory approval to undertake larger trials of children with fragile X and autism. Meanwhile, another Seaside drug—STX107, which selectively blocks mGluR5—is in the pipeline. Other companies, including Novartis and Roche, are also working on glutamate inhibitors for fragile X.

How would a treatment that could ease the symptoms of fragile X change people's lives? "It's like asking: What would it be like to have the best dream you could ever have come true?" says Katie Clapp, parent of a 21-year-old son with the disease. Clapp cofounded the FRAXA Research Foundation, which is dedicated to finding treatments and a cure for fragile X syndrome and has funded some of Bear's work.

But Bear cautions that there may be limits to the mGluR theory. Most neurodevelopmental disorders are not diagnosed until well after symptoms begin, suggesting that doctors may not be able to give drug treatments early enough to stave off the worst effects of the disease, such as severe cognitive impairments. As Bear conceded in a 2008 paper in *Neuropsychopharmacology*, "derailment in brain development might be difficult to reverse retrospectively." Some drugs may also carry intolerable side effects. In early clinical trials of glutamate inhibitors, a small proportion of patients suffered adverse events such as upper respiratory infections, sedation, and headache.

Despite these cautions, the recent clinical trials represent a dramatic shift in thinking. Scientists had long assumed that genetically based developmental disorders of the brain were permanent. But Bear has shown that treating the functional deficits with small molecule therapies may alter one's fate in life, even if the gene remains unchanged. "Being born with a developmental brain disorder," he says, "may not be an irrevocable sentence."

And fragile X may just be the start. "The big splitting-the-deck question now," he says, "is whether other rare, single-gene causes of autism—such as Rett syndrome and tuberous sclerosis complex—share similar characteristics with fragile X syndrome." Even autism without a known cause may respond to the treatment. If so, mGluR5 blockers (or, with some disorders, enhancers) could have wide applications. Returning to a familiar metaphor, Bear calls this new line of thinking—and of hope—"a sea change." ■

THE BEST OF TIMES AND THE WORST OF TIMES

BY AMBER DANCE

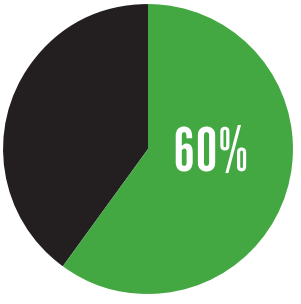
POSTDOCS BALANCE THE JOYS OF PURE RESEARCH WITH TOUGH WORKING CONDITIONS.

POST-DOCS

A DOCTORATE HOLDER IN A TEMPORARY RESEARCH JOB, RECEIVING MENTORING AND TRAINING NEEDED FOR THE NEXT CAREER STAGE.

43,000–89,000

U.S. TRAINED POSTDOCS



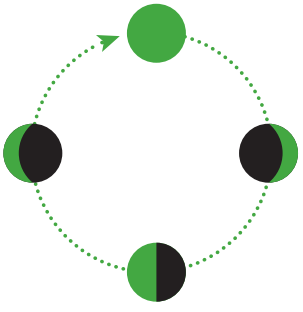
UP TO SIXTY PERCENT OF U.S. POSTDOCS ARE FOREIGN CITIZENS

42

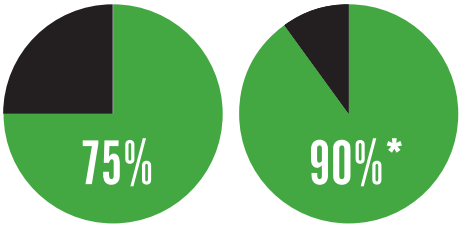
AVERAGE AGE THAT SCIENTISTS GET A FIRST RESEARCH GRANT

80-100

HOUR WORK WEEKS



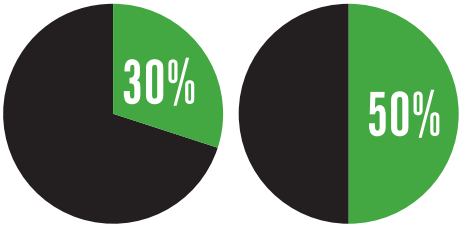
PERCENT WHO HAVE HEALTH INSURANCE:



1986 2006

*POSTDOCS OFTEN PAY THE TAB THEMSELVES

HOW MANY GET RETIREMENT BENEFITS?



1986 2006

NIH'S NATIONAL RESEARCH SERVICE AWARD STIPEND FOR STARTING POSTDOCS, WHICH MANY INSTITUTIONS USE AS A GUIDELINE, HAS RISEN.

POSTDOC STIPEND:

(BASED ON NIH)

2000

$26,916

2010

$37,740*

*STUCK IN THE MID-$30,000 RANGE SINCE 2003

2.2 YEARS

MEDIAN LENGTH OF A SINGLE POSTDOC IN THE LIFE SCIENCES

FORMER POSTDOCS WHO AIMED TO BE A TENURE-TRACK PROFESSOR:

61%

PERCENT WHO ACTUALLY ACHIEVED THAT GOAL:

37%

K99/R00:

THE NIH "KANGAROO" AWARD

150–200

NIH K99/R00, OR "KANGAROO" AWARDS PER YEAR

NIH DIRECTOR'S EARLY INDEPENDENCE AWARDS:

10 SUPERSTAR PH.D. RECIPIENTS ARE CHOSEN TO SKIP THE POSTDOC AND GO STRAIGHT TO PI

PERCENT WHO HELD TWO POSTDOC SLOTS:

29%

PERCENT WHO HELD THREE OR MORE:

11%

PART 2 OF 2: IN PART 1 OF THIS SERIES, READERS LEARNED HOW PRINCIPAL INVESTIGATORS FIND AND TRAIN THE MOST PROMISING POSTDOCS. (SEE *HHMI BULLETIN*, FEBRUARY 2011)

Fresh from a Ph.D. in virology, Nancy Van Prooyen is carving her own scientific niche. She's taking on the little-known fungal pathogen, *Histoplasma capsulatum*, as a postdoctoral fellow at the University of California, San Francisco.

Her graduate work on human T cell leukemia virus—supported by an HHMI Gilliam Fellowship at Johns Hopkins University—was interesting, but the virology field is saturated with seasoned researchers. As a young scientist, Van Prooyen wanted to do something new. Far fewer researchers study *Histoplasma*, which causes an infection called histoplasmosis.

The fungus also appeals to Van Prooyen because it is a real challenge to work with. No one has built genetic libraries or developed the standard tools that other scientists can rely on. Sifting through hundreds of *Histoplasma* to find interesting mutants is a puzzle Van Prooyen relishes.

Like many postdocs, she's thrilled to focus her time on science alone—no classroom teaching or lab management to distract her. It's an opportunity many professors would envy.

But Van Prooyen is also realistic about her position and she has no intention of being a postdoc—with the typical 80- to 100-hour workweek—for any longer than a few years. Her wages are paltry, as well, even with her recent postdoctoral fellowship from the A.P. Giannini Foundation.

Low wages are the norm. The National Institutes of Health (NIH) National Research Service Award stipend for starting postdocs, which many institutions use as a guideline, has been stuck in the mid-$30,000s since 2003. "We're all in our 30s, we have a lot of education, and we're still scraping by," Van Prooyen says. Add to that the constant stress of the publish-or-perish lifestyle on what is usually a year-to-year contract. "It's a sacrifice, I think, to do a postdoc."

Once an optional pit stop on the road to professorship, a postdoc position like Van Prooyen's has become a required apprenticeship. Because their positions are temporary, it's easy for postdocs to go unappreciated, and some simply don't receive the training they deserve. With these positions stretching four years or much longer, some enthusiastic young scientists molder in a kind of postdoctoral purgatory, hoping for a career that seems further away with each passing experiment.

Even so, a postdoc that doesn't drag on is well worth it for the opportunity to untangle biology's mysteries and a shot at the professor's chair, Van Prooyen says.

Postdocs have won some victories lately, asking for and getting employee benefits and other perks with help from national associations and unions (see Web Extra, "Who Speaks for the Postdocs?"). But a big worry still looms large: what comes next? At the end of that long, hard slog, the desired reward may turn out to be just a mirage.

"Getting out of the gate continues to get harder," says Sean B. Carroll, HHMI's vice president for science education. With intense competition for grant monies, moving from a postdoc to a faculty position can take a few cycles to achieve funding and get a new lab going. He's seen some talented young scientists faced with these frustrating facts forgo academic research for other options.

THE POSTDOC: DEFINED AND COUNTED

"POSTDOCS ARE AN INVISIBLE WORK FORCE for a university," says Elizabeth Johnson, president of the Postdoc Association at Duke University in Durham, North Carolina, from 2004 to 2008. Today Johnson is associate director of the Duke Institute for Brain Sciences.

"They do science, write grants, mentor grad students," Johnson says. "And yet they don't have full status as core members of any institution." Instead, postdocs inhabit a sort of career limbo—a vague midpoint between student and independent professional.

In 2004, Duke started working on its own postdoc policy. The first task was to figure out who the postdocs were. Johnson asked around for numbers and heard estimates as low as 70 and as high as 2,500. With postdocs often hired by a handshake and just as easily cut loose, no one knew. Once the committee defined who was and wasn't a postdoc, and performed a head count, the actual number was between 600 and 700.

No one has a solid figure of the number of postdocs in the United States. A 2008 National Science Foundation (NSF) survey counted more than 54,000 postdocs, up 6.5 percent from 2007, but included only those at degree-granting institutions. The National Postdoctoral Association (NPA) cites a range of

43,000 to 89,000 postdocs. That includes scientists who got their degrees outside the United States; NSF data show 55 percent to 60 percent of U.S. postdocs are foreign citizens.

One key advance, says NPA executive director Cathee Johnson Phillips, was defining what a postdoc is. In 2007, the NPA, NSF, and NIH agreed that a postdoc is a doctorate holder in a temporary research job, receiving mentoring and training needed for the next career stage.

SPOTTY PROGRESS

IN 2005, THEN-HHMI PRESIDENT THOMAS CECH and others examined the needs of postdocs in the National Research Council report "Bridges to Independence." The goal was to identify ways NIH and other funding agencies could help postdocs—who work under an advisor—transition to an independent position. The authors recommended, for example, that NIH allocate funds to support postdocs as individuals rather than as simply part of an advisor's grant.

They also recommended that research institutions provide postdocs with more than a lab bench: they need mentoring and career advice. And with fellowships lasting longer, the authors suggested that there should be a time limit. To find out whether postdocs' needs are met, the committee recommended that NIH collect data on the postdocs it funds, including whether they continue in research.

Since the Bridges report, change has been spotty, says Cech, an HHMI investigator at the University of Colorado at Boulder. Some universities have implemented postdoc policies and support postdoc offices and clubs; the NPA reports that 160 institutions have acted on at least some of its policy recommendations. In 2010, NIH began requiring grantees to identify their postdocs by name, so it could track their appearance on subsequent grants.

Duke is ahead of the curve; the administration took seriously its postdocs' plight and spearheaded the policy effort, Johnson says. Still, it took from 2004 to 2008 to craft a policy, which undergoes regular revisions. Now, all Duke postdoc slots are paid positions; no postdoc is a volunteer. They get vacation, sick leave, and parental leave, just like regular employees. They receive annual progress reviews. As recommended by the Bridges report, they won't be postdocs forever; after five years, they cannot continue as postdocs but may be hired as regular employees. And while they're postdocs, they get health care benefits and retirement savings.

Similar policies are coming together at institutions across the country. For example, according to the NSF's 2006 Survey of Doctorate Recipients, 90 percent of postdocs received health insurance in 2006, up from 75 percent in 1986 (these data do not indicate how many postdocs must pay for their own insurance). The number receiving retirement benefits has risen from 30 percent in 1986 to 50 percent in 2006.

For the more than 700 postdocs that HHMI supports in the laboratories of HHMI investigators and HHMI early career scientists, pay is scaled to NIH and other postdoctoral fellowships, says Pamela Phillips, HHMI's director of research operations. Starting HHMI postdocs make between $37,500 and $50,000, at their advisor's discretion. They also receive health insurance and retirement benefits. Vacation time is at the advisor's discretion, but Phillips notes that postdocs so rarely take time off that it usually isn't an issue.

FINANCIAL HELP TOWARD INDEPENDENCE

SATINDER SINGH, A FORMER HHMI PREDOCTORAL FELLOW, put in her time as a postdoc at Oregon Health and Science University in Portland, working on the bacterial version of a neurotransmitter transporter. She divided her time between experimenting with cells and lipid vesicles, exploring the protein's structure, mentoring students in the lab, and writing papers.

In 2007, Singh applied for the Pathways to Independence Award, one of the initiatives NIH launched in the wake of the Bridges report. Announced in 2006, the award, a K99/R00, is affectionately referred to as the "kangaroo" award. It provides five years of funding designed to bridge the end of a postdoc and the beginning of a faculty position. The idea, Cech says, is to wean postdocs from mentored to independent research. Each year, NIH offers between 150 and 200 of these grants, with various dollar amounts.

Just writing the application was a useful process, Singh says, because she had to organize her thoughts for an independent program. Her plan to study the human version of the transporter she worked on as a postdoc earned her a kangaroo award. And Singh suspects the award helped during her final interviews for faculty positions in early 2008; she already had evidence that her ideas were grant-worthy.

Singh got a job offer from Yale University, but she still wanted to finish up some papers in her postdoctoral lab and take a couple of neurobiology courses. With the kangaroo funding, she was able to work mostly independently in her postdoc lab, and Yale waited until she was ready to start. She used the extra time to collect preliminary data before starting the Yale tenure clock—with all its associated responsibilities in the classroom and on committees. Since July 2010, Singh has been living the postdoc's dream at Yale: a lab of her own, with two of her own postdocs to train.

"THEY DO SCIENCE, WRITE GRANTS, MENTOR GRAD STUDENTS," JOHNSON SAYS. "AND YET THEY DON'T HAVE FULL STATUS AS CORE MEMBERS OF ANY INSTITUTION."

A handful of current graduate students may realize that dream much faster. In 2010, NIH director Francis Collins announced the new Director's Early Independence Awards. They allow superstar Ph.D. recipients to skip the postdoc and move straight to the principal investigator level. NIH plans to make 10 awards, each with a budget of $250,000 a year for five years.

MEANINGFUL MENTORING

NEAL SWEENEY WAS A POSTDOC AT YALE for three years. He had a good relationship with his advisor, but the advisor was always busy, juggling a lab with more than 20 people plus teaching and grant writing. "I didn't really feel like I was getting enough mentorship that my research could move forward at the pace I wanted it to," he says.

In 2009, to be closer to an ailing family member, Sweeney took a second postdoc at the University of California (UC), Santa Cruz. He's now studying how stem cells morph into the neurons required for vision. He's in a smaller lab, with fewer of the high-tech facilities Yale offered. But he's been able to learn new techniques, achieve more responsibility, and practice grant writing in the cozier environment.

At first he felt like he was starting over, Sweeney says, but he's now excited about his new projects. He spends his days fiddling with DNA strands, growing cells in dishes, or sitting at the microscope. And he's gotten involved as a leader in the UC union, the UAW Local 5810.

Finding a mentor is a big concern among postdocs and was one of the issues noted in the Bridges report. One of the UC union's key interests in negotiating its new contract, Sweeney says, was to make sure postdocs get the mentoring they need for both their current research and their future career. "This is one of the things that came up again and again," he says.

Some advisors don't take their role as mentors seriously, treating their trainees as cheap hands in the lab. "Some fraction of postdocs do not get much career advice," Cech says. "They're mostly being employed for the purpose of doing a certain set of experiments."

And that lack of training shows when postdocs apply for jobs, says HHMI investigator Celeste Simon of the University of Pennsylvania School of Medicine. When she interviews applicants for faculty positions, she can tell when postdocs from big labs didn't get all the help they needed in preparing their application and job talk. "Sometimes postdoctoral fellows can fall through the cracks," Simon says.

UC postdocs and their mentors are now expected to design an individual development plan (IDP), with short- and long-term goals, and hold regular meetings to assess progress. Making an IDP is the greatest factor in postdoc satisfaction, according to a 2005 survey by the scientific research honor society Sigma Xi. For example, postdocs need to know what part of their projects they can take to a new job.

Postdocs who become professors also need to learn how to manage a lab. "You're going from pure science to running a small business," says Maryrose Franko, senior program officer for HHMI's department of science education.

With its successful weeklong training course of new lab heads, HHMI—in collaboration with the Burroughs Wellcome Fund—turned the information into a highly popular book, "Making the Right Moves." HHMI now works with partner institutions to support similar training on their campuses.

WHERE ARE THE JOBS?

NONE OF THOSE EFFORTS, however, solves the most crucial issue: not enough academic jobs for the academically trained scientists

LEFT TO RIGHT: SATINDER SINGH AIMED HIGH FOR AN NIH KANGAROO AWARD, AND LANDED AT YALE; NANCY VAN PROOYEN VOWS NOT TO LET HER POSTDOC GO TOO LONG; ELIZABETH JOHNSON HELPED USHER IN DUKE'S PROGRESSIVE POSTDOC POLICY.

Singh: Chris Jones Van Prooyen: Tom Kochel Johnson: Jeff McCullough

"AT FIRST, IT'S REALLY FUN," ROHN SAYS. "ONCE YOU GET INTO YOUR FIFTH OR SIXTH YEAR OF THE POSTDOC, ONE STARTS TO GET A BIT ANXIOUS."

out there. "I was not warned about this," says Jennifer Rohn, a postdoc at University College London, who wrote a March 2 column in *Nature News* on the subject. She spends her days sorting through images of cells, looking for conditions that change their shape.

"We may be overproducing biomedical scientists," agrees Shirley Tilghman, president of Princeton University and an HHMI alumna.

There's no quick fix. "Science would grind to a halt without all these people working," Rohn says. She suggests that universities hire more permanent, nonfaculty scientists. These researchers—sometimes nicknamed "perma-postdocs"—offer huge value to a lab because, unlike trainees who come and go, they are always up to speed and able to assist newcomers, Rohn says. But they're a bit different from a postdoc in that they have a decent salary and often work normal hours. "Once you hire a permanent scientist, you can't treat them like a slave," Rohn says.

The tight job market also means that postdoctoral periods can stretch for years. "It's very, very rare for the postdoc training period to run shorter than four years these days," says HHMI president Robert Tjian, who has seen postdocs stick around for six or seven years. It doesn't help that publishing in top journals requires more data than ever before, he adds. "There's a lot of pressure to knock something out of the park … to do something that will be the beginning of a whole career."

The median length of a single postdoc in the life sciences is 2.2 years, according to the NSF's 2006 Survey of Doctorate Recipients. But many postdocs string together multiple positions; 29 percent of postdocs who responded to a 2010 survey by Science Careers had held two postdoc slots and 11 percent had already done at least three.

"At first, it's really fun," Rohn says. "Once you get into your fifth or sixth year of the postdoc, one starts to get a bit anxious." Plus, this extended training period comes just as researchers are reaching the age when they'd like to settle down, perhaps start a family. Yet they bounce from position to position, and who can afford day care on a postdoc's salary?

The conflict between postdoc-ing and parenting is "just unacceptable," says Tom Rapoport, an HHMI investigator at Harvard Medical School in Boston. Given the stark choice between science and family, many female postdocs leave the lab, Rapoport says. He suggests that subsidized day care would be the best way to keep talented women in science.

With the expanding postdoc timeline, Tilghman says, a scientist's most creative years are spent toiling on someone else's project. In 2009, the average age at which scientists got a first research grant was 42. On the flip side, science-loving undergraduates who observe graying postdocs look to other careers, such as medicine. "I was finding it harder and harder to convince the brightest young Princeton students to go into biomedical science," Tilghman says.

In December 2010, NIH's Collins proposed a working group to address the lopsided science workforce. He enlisted Tilghman to run the project. She plans to come up with a workforce model that better matches the nation's science needs and uses financial incentives to alter the science landscape (see Perspective, page 34). The group has yet to assemble, however, so recommendations are still to come.

LOOKING BEYOND THE BENCH

RICHARD TING IS IN THE THIRD YEAR of his postdoc in the UC San Diego laboratory of HHMI investigator Roger Tsien. He came to Tsien's lab because it was a multidisciplinary group with plenty of good ideas. Even then, Ting was thinking about his post-postdoc career. Tsien is a Nobel laureate, and as Ting notes, "It definitely helps to have some name recognition on your reference letters."

Ting spends most of his time synthesizing new molecules that might be useful in positron emission tomography (PET) medical imaging. "The synthesis, by itself, is pretty boring," he admits. "But being able to personally test the impact of these new molecules on a PET scanner makes the job worthwhile."

Right now, things are going well—but the future is a big question mark. "That's the stressful part," he says. "You don't really know what you're going to do."

Ting has applied for the kangaroo award. However, he's realistic about his chances. If he doesn't receive the funding he's after, he'll likely consider a career in the biotechnology industry as well.

In his hopes, Ting is like many of his compatriots. According to the 2010 Science Careers survey, 61 percent of former postdocs went into the apprenticeship aiming for a tenure-track professor job. Only 37 percent achieved that goal.

With the tough job market, many postdocs are considering more than one career. "We have to get away from thinking that we are only training postdocs to be professors," Cech says. "That's just a false premise." Postdocs today have lots of options: journal editor, policymaker, patent attorney, and more. Van Prooyen, for example, is considering science writing. Ph.D.s would make great science teachers, Carroll adds.

Given the challenges of making it in academia, is it worth signing on for a postdoc? "I don't want them to get discouraged by the fact that the slope is very steep," Tjian says. "I still think that doing science is one of the most rewarding careers you can have." ■

WEB EXTRA: To read about who's speaking for postdocs and explore some atypical fellowships, visit www.hhmi.org/bulletin/may2011.

the Next Statin

Could new findings on how the human body regulates cholesterol lead to a better drug?

BY SARAH C.P. WILLIAMS
ILLUSTRATION BY GAVIN POTENZA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Chances

are, you know someone with high cholesterol. A parent, a friend, yourself. Too many fatty molecules pulsing through the bloodstream, sticking to the sides of blood vessels, and doubling—or more—the chances of a heart attack. In the United States, one in six adults has cholesterol levels considered too high and doctors write more than 200 million prescriptions a year for cholesterol-lowering drugs.

Statins, the most widely prescribed cholesterol medications, have been successful in curbing cholesterol levels for many people. But in some, statins lead to severe joint and muscle pain or liver inflammation. In others—perhaps due to genetic quirks—statins don't lower cholesterol levels enough. And when one statin was compared with sugar pills in a clinical trial, the drug lowered the risk of heart attack by only one-third.

Although clinicians have firmly established the link between cholesterol levels and heart disease, there are still more questions than answers when it comes to the nitty-gritty molecular details of this connection. Unraveling the genetics and biochemistry of the body's natural cholesterol-control mechanisms would do more than satisfy scientists' curiosity: It could provide targets for better cholesterol drugs and fresh ways to predict earlier in life who is at risk for high cholesterol and related heart disease.

"This is one of the most tightly regulated systems in biology," says Joe Goldstein of the University of Texas (UT) Southwestern Medical Center at Dallas. Goldstein, an HHMI Trustee, shared the 1985 Nobel Prize in Physiology or Medicine with Michael Brown for their discoveries about cholesterol metabolism. "It's regulated at so many levels, in so many ways that there's no shortage of questions about how it works," he says. That means no shortage of potential drug targets.

Goldstein, Brown, and a handful of other HHMI scientists are still piecing together the full picture of how the human body manages cholesterol. In the process, they're revealing new ways to stop atherosclerosis and heart attacks: by controlling cholesterol production, absorption, and the immune system's response.

Finding Balance

Despite its bad rap, cholesterol isn't harmful in moderation. "It's absolutely required," says cholesterol researcher Russell DeBose-Boyd, an HHMI early career scientist at UT Southwestern who was a postdoc in the Brown–Goldstein lab. The human body needs cholesterol to function properly—it's integrated into cellular membranes, in bile it aids digestion, and it plays a key role in the connections between neurons in the brain. But too much cholesterol is toxic for a cell and for the body as a whole. So cells have a complex feedback system to regulate cholesterol levels. The body can make cholesterol, absorb it from food digested in the gut, move it around, and excrete it as bile.

At any given point, each of these processes can be turned up or down depending on a cell's needs. "If the cell is deprived of cholesterol, you turn on uptake, and you turn on synthesis," says DeBose-Boyd. "When the demands are met, synthesis and uptake are both turned off." But when cholesterol levels from the diet get too high, the body's system to deal with it becomes overloaded, and molecules idle dangerously in the arteries.

Statins work by halting cholesterol production in cells. They do it by blocking hydroxymethylglutaryl-CoA (HMG-CoA) reductase, an enzyme that carries out an early step of cholesterol synthesis. But the cell reacts to those falling cholesterol levels by making more reductase in an attempt to revive cholesterol synthesis.

"Statins are basically inducing accumulation of the very protein they're targeting," says DeBose-Boyd. "We could improve their effectiveness if we can stop that accumulation." That's his lab's goal.

When they are replete with cholesterol, cells not only stop producing HMG-CoA reductase, they also speed up the enzyme's degradation. In cells deprived of cholesterol and other sterols, reductase molecules stick around, churning out cholesterol, for an average of 10 or 11 hours, says De-Bose Boyd. But with lots of cholesterol around, reductase survives only about an hour.

DeBose-Boyd wants to coax cells to turn on this degradation process even in the low-cholesterol state induced by statins. This would prevent the reductase buildup that limits the drugs' effectiveness.

"It looks like there is a switch for this whole cholesterol system where it's either on or it's off," says Goldstein, just down the hall from DeBose-Boyd's lab. "Understanding this switch is really fundamental to understanding the system." HMG-CoA reductase is normally located on the outer membrane of a cell's endoplasmic reticulum (ER), a packaging center that directs newly made proteins to their destinations in the rest of the cell.

DeBose-Boyd discovered that in times of high cholesterol, a protein called Insig binds to reductase and removes it from the ER, according to work published June 2010 in the *Journal of Biological Chemistry*. From there, the reductase ends up in lipid droplets. "They're basically little balls of fat in the cell," he says. Exactly how this happens, he's not sure, but somewhere in the lipid droplet or the cell's watery cytosol, the reductase is broken into pieces, no longer functional.

DeBose-Boyd's lab has also revealed that it's not cholesterol that triggers Insig to bind to reductase and ship it out of the ER. It's a molecule related to cholesterol, called dihydrolanosterol (DHL). Because it's not identical to cholesterol, DHL can

potentially turn on HMG-CoA reductase degradation without the risk associated with increasing cholesterol levels.

"If we were to get a drug from this work, it'd have to be designed after DHL," says DeBose-Boyd. But such a drug is still hypothetical. No pharmaceutical company will pursue it until DeBose-Boyd or others reveal the full picture of how reductase degradation works—the role of the lipid droplets, how DHL mediates Insig, and how the final degradation happens.

Genetic Targets

Other researchers are aiming new drugs at the part of the system that imports cholesterol. When it travels in blood, cholesterol is packaged inside lipoproteins—either low-density lipoproteins (LDL), considered the bad guys for their accumulation in arteries, or high-density lipoproteins (HDL), the "good" lipoproteins that carry cholesterol to the liver for excretion. People with low levels of LDL and high levels of HDL have the lowest chance of atherosclerosis and heart disease. These days, cholesterol reduction is measured by tracking LDL; the role of HDL is not as clear-cut.

For more than three decades, HHMI investigator Helen Hobbs has been tracking down individuals with extreme LDL and HDL levels—either low or high—and analyzing their genetics. Hobbs, a physician and researcher at UT Southwestern, got her start in research with a postdoctoral fellowship in the Brown–Goldstein lab. She hopes to uncover genetic mutations that hint at new drug targets for managing cholesterol. She's already revealed one promising candidate—a protein that sweeps the bloodstream clear of LDL—and it's in the pharmaceutical pipeline.

In 2003, a research group in France identified a gene called *PCSK9* that helps control LDL levels. Hobbs had already been following the genetics and cholesterol levels of almost 3,500 people as part of the Dallas Heart Study, her large-scale attempt to find genetic causes of heart disease. So her team tested a handful of participants for mutations in the *PCSK9* gene. They found them—in 2 percent of their African-American participants. They repeated the work in a larger population and showed that *PCSK9* mutations were associated with a 28 percent reduction in LDL and an 88 percent decrease in coronary heart disease.

"Studies like the Dallas Heart Study are absolutely key to this field," says Joe Goldstein. "The way to find interesting mutations is to find a population and look at those extremes."

The research team led by Hobbs then relied on basic biochemistry to piece together *PCSK9*'s function. They discovered that the protein encoded by *PCSK9* is required to degrade the LDL receptor—the protein that pulls LDL from the bloodstream into a cell's interior. Removal of functioning PCSK9 protein is an ideal recipe for treating high cholesterol: LDL receptors increase, LDL in the bloodstream decreases, and atherosclerosis risk drops.

"This is the single biggest story in the translational medicine side of cholesterol research right now," says Goldstein. "Hobbs has taken PCSK9 all the way from a finding in a population to learn the real importance of the protein to medicine. And now we have a really good drug target."

Hobbs identified a person in the Dallas Heart Study who has no PCSK9 and appears to be completely healthy, which has reassured pharmaceutical companies about the safety of the protein as a drug target. A PCSK9 inhibitor is now in early phase human studies with the pharmaceutical company Regeneron. It blocks PCSK9 from binding to and degrading the LDL receptor and results in a dramatic reduction in LDL levels.

(continued on page 48)

DeBose-Boyd: UT Southwestern Medical Center at Dallas Hobbs: UT Southwestern Medical Center at Dallas Tontonoz: Paul Fetters

Research by Russell DeBose-Boyd, Helen Hobbs, and Peter Tontonoz (l-r) on how the body manages cholesterol is revealing new targets for cholesterol-lowering drugs.

Shirley Tilghman

THE FUTURE OF SCIENCE

GETTING REALISTIC ABOUT BIOMEDICAL TRAINEES

Jesse Winter

Shirley Tilghman is an outspoken advocate for young scientists. She was an HHMI investigator at Princeton University from 1988 until 2001, when she was named university president—the first woman and first scientist to hold the position. Tilghman will have a hand in modernizing the prospects for scientists as the recently appointed chair of a National Institutes of Health (NIH) study on the future of the biomedical workforce in the United States.

What are your goals for the NIH biomedical workforce panel?
Ultimately, we want to create a biomedical enterprise that produces the best science and brings out the best in the people engaged in it. Today the training path has become too long. The average age of a biomedical scientist receiving a first NIH grant is 42. I don't know a single person who thinks that's optimal for generating good science. So the question is, why does the path take so long? And are there things that could be done to speed it up?

Do other people agree this is a problem?
Definitely. There has been welcome recognition that business as usual is not acceptable, and changes must be made if we are to sustain the vibrancy of the U.S. biomedical research enterprise. Many feel that significant changes in how NIH supports the biomedical workforce must be on the table, including reducing the number of trainees and changing the way they are supported.

Could you elaborate on the solutions you have in mind?
At the root of the problem is the fact that we are overproducing Ph.D.s. As a consequence, there are too many people chasing too few jobs and too few grant dollars. This problem will only get worse in the next decade, given the current federal budget.

I believe there could be changes made to the structure of the typical biomedical research laboratory. The typical lab consists of about 10 trainees, a technician, and a principal investigator. The majority of those trainees will not become principal investigators, because those jobs are not multiplying. And at the moment, there aren't enough career alternatives to capitalize on the time investment of these trainees. So I think we need to change the scenario.

From years of being a mentor, I know that not all students want a career running their own lab and raising money. Instead, they want to do what they love: research. Perhaps more members of a lab could be permanent employees, and fewer could be trainees. We need to explore such options.

With tighter budgets, should graduate students still focus on unapplied research?
Absolutely. There will be no jobs in applied science in 20 years if we are not doing fundamental research. Basic science feeds the applied science pipeline. They are deeply complementary to one another. Everyone knows the applied work is important, but frankly, you can't do it without the basic stuff.

Speaking of tighter budgets, how do you feel about cuts to the research and development budget pushed by many in Congress?
There are many aspects of the budget cuts proposed by the House of Representatives that give me great concern. At the highest level, the cuts have the potential of undermining the future prosperity of the United States, by consuming our "seed corn"—the innovation that has been the basis for the staggering vitality of the U.S. economy. The cuts to the Department of Energy and the Environmental Protection Agency certainly fall into that category; green technology is likely to be one of the biggest growth industries in the future, and it would behoove the United States to be in the forefront of that economic wave. On a deeper level, investing in green technology is so important because the future of the globe depends on our finding economically viable alternatives to fossil fuels. I don't know a single serious research university today that is not making major investments in research and education in these areas.

Are policy makers open to hearing from young investigators?
Yes, in fact, I think the public discourse on science is better now than any time in my memory. Under this administration, we have highly distinguished scientists in important positions, who speak effectively about science. We have an administration that is pro-science and makes a clear distinction between what is scientifically knowable and what can be known only through religious faith. I welcome the disappearance of politics from science that many of us found disturbing in the past.

How has research prepared you for being a university president?
For a long period university presidents were economists, but I think a scientific background is actually beneficial. Science taught me how to ask questions, collect data, and analyze information. In that way, what I do now is not so different than what I did before.

INTERVIEW BY AMY MAXMEN. *Shirley Tilghman is a member of HHMI's Science Education Advisory Board.*

Q&A

What do you wish you had known before you started your lab?

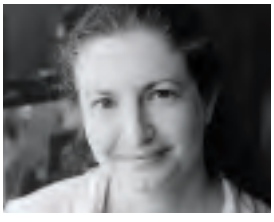
Managing the day-to-day details of an active lab takes a different skill set than experimental know-how. For many scientists, the first years of running their own labs bring a realization that science is about more than bench work. Here, a few describe what they've learned about keeping a lab going.

—EDITED BY SARAH C.P. WILLIAMS

James E. Bear

HHMI EARLY CAREER SCIENTIST
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

"I wish I had realized how many jobs I was actually applying for when I responded to the ad for assistant professor. Perhaps the ad should have read something like: Assistant professor sought to lead research team and do a bit of graduate teaching. Duties include, but are in no way limited to, clinical psychology (with a specialty in emotional crises of 20- and 30-year-olds), mopping skills (for late night lab emergencies involving plumbing), graphic arts (with a focus on designing graphs and charts), bureaucratic street fighting, computer hard-drive recovery, and microscope repair. I would still have applied."



Rachel I. Wilson

HHMI EARLY CAREER SCIENTIST
HARVARD MEDICAL SCHOOL

"A colleague once remarked to me that it's useful to determine the current rate-limiting factor in your research program. Is it space? People? Money? Creativity? Your time? A specific reagent? Once you have determined that, you can be more rational in setting your day-to-day priorities. In the end, we're all driven by the same enduring motivations (e.g., curiosity), but day-to-day priorities may be very specific to each person and they may change over time. I found this to be good advice, and I wish I had known it from the start."

Phillip D. Zamore

HHMI INVESTIGATOR
UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL

"Nothing. The process of discovery has made having my own lab so rewarding. I've discovered strengths I didn't know I had as well as weaknesses that required hard work to improve. I discovered—much to my shock—that pink sheets aren't pink, that the collective wisdom of a lab is often wiser than the opinions of a lone PI, and that managing a successful research team requires both teamwork and promoting individual talent. Had someone told me in advance the secrets to building and running a lab, I'd have struggled a bit less in the beginning. But I'd have also undervalued the pleasure of the struggle itself, and I would have missed out on so many wonderful surprises."

Nancy M. Bonini

HHMI INVESTIGATOR
UNIVERSITY OF PENNSYLVANIA

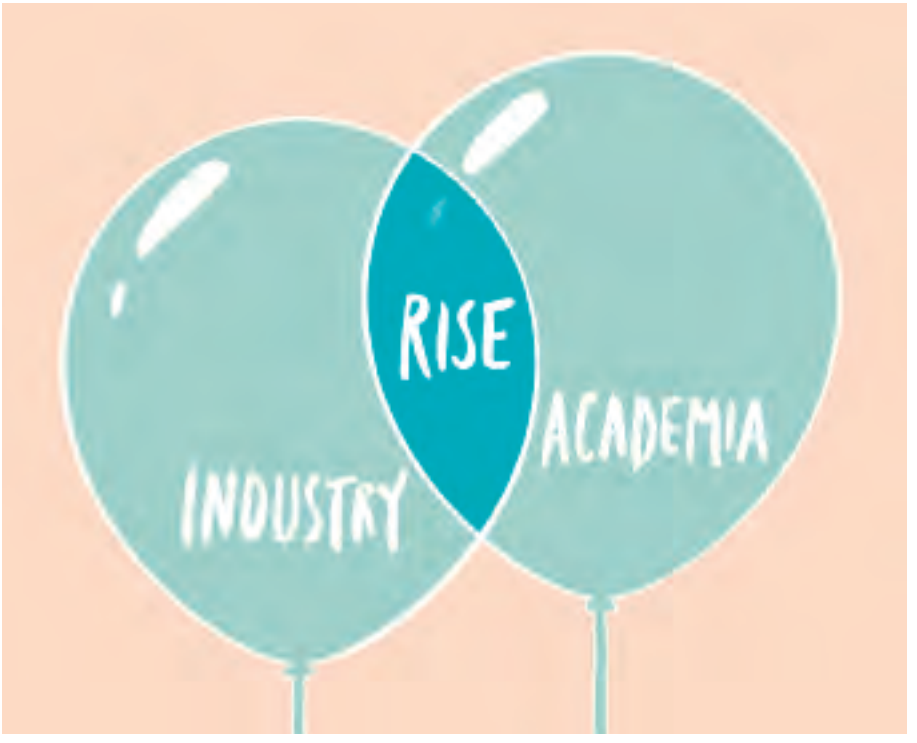
"I wish I had known the importance of filing disclosures and patenting scientific findings. I do studies of value to treating human diseases, and part of my motivation is to make a difference—to provide the foundation for biotech companies to make therapeutics. However, for biotechs to be interested in pursuing therapeutics, the approach or assay typically needs to be patented—something I didn't know when I started my lab. Now I know that it is critical to file disclosures—the most important part of a patent application—and to be at an institution with a strong technology transfer office to help do this in the most effective and efficient manner."

Bear: Paul Fetters Wilson: Graham Ramsey Zamore: Robert E. Klein / AP, ©HHMI Bonini: Paul Fetters

chronicle

Deep in the brain, neurons grow, form branches, and then shrink as memories are created and forgotten. The surrounding blood vessels change in concert with the neurons. For the first time, scientists have been able to watch these long-term changes in the brains of living mice. This snapshot of what they saw in one mouse illustrates the complexity of the branching: blood vessels in red and pyramidal neurons—critical for long-term memory—in green. To read more about the new method and what the scientists saw, visit www.hhmi.org/bulletin/may2011.

Yaniv Ziv and the Schnitzer Lab



Industrial-Strength Training

RETIRED INDUSTRIAL SCIENTISTS SET UP SHOP AT A UNIVERSITY TO TRAIN TOMORROW'S RESEARCHERS.

AS A FRESHMAN BIOLOGY MAJOR AT DREW UNIVERSITY, YANG YANG was interested in both biochemistry and neuroscience. She couldn't decide where to focus her efforts.

Early that year, Yang attended a seminar by a small group of industry veterans who were part of a special program at Drew: The Charles A. Dana Research Institute for Scientists Emeriti (RISE) program. RISE fellows are retired scientists from pharmaceutical and telecommunications companies across New Jersey who receive lab space and equipment at Drew so they can continue doing research while introducing undergraduate students to life in the lab.

The RISE program, which has eight fellows and trains about 10 students a year, has been partially supported by HHMI since 2008. The scientists have mentored about 250 students since the program's inception in 1980.

Yang saw new possibilities when she heard RISE fellow Barbara Petrack talk about Alzheimer's disease. Petrack, a retired biochemist, worked for Ciba-Geigy (now Novartis) for 35 years before joining RISE. "In the RISE program at Drew, our primary interest is to get students excited to do research," she explains. "Most of the students have gone on to medical or graduate school. I consider the RISE program a success."

When Yang approached Petrack after her presentation, Petrack explained that she collaborates with Drew neuroscientist Roger Knowles to study the neurobiology of Alzheimer's disease. Intrigued by the merging of the two fields, Yang immediately joined them to do her research; now, as a senior, she is writing her undergraduate dissertation. "Working with the RISE fellows gives us knowledge that goes beyond the textbook and beyond the classroom, knowledge that we could not get anywhere else." Students get specific tips, for example, on how to effectively design and analyze experiments specific to pharmaceutical research.

"The RISE fellows spent years working at places like Merck and Novartis and are used to working in industrial settings where the research is focused on the development of new pharmaceuticals," says Knowles, director of the HHMI program at Drew. They bring that industrial perspective to Drew where, at the end stages of their careers, they are able to continue their research and share their passion for science with the students. They also open some industry doors. For example, an entourage of 12 Drew students toured research labs at Merck (Kenilworth, NJ), and one student did her research on the premises at Novartis, incorporating the results into her honor's thesis.

Vincent Gullo became a RISE fellow after a 30-year career at Merck and Schering-Plough. He and his RISE students are trying to identify novel antibiotics against resistant organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), a deadly bacterial infection. Gullo says he tries to give his students a "real research experience with all its trials and tribulations." His aim is to better prepare them for graduate school and medical school, he says.

Christian Maggio, a senior studying in Gullo's lab, entered college with plans to attend medical school. Since his freshman year, however, he's done research with several RISE fellows and now plans to pursue a Ph.D. in microbiology and immunology. Maggio believes his work with RISE fellows will give him a head start in graduate school.

"The RISE fellows expect us to write up our own scientific work, which is great preparation for writing papers and theses in graduate school," he says. "Also, because of my experience in the RISE program, I feel that I am very well versed in a lot of different areas, including microbiology and synthetic chemistry."

The RISE program is also helpful to students who don't plan on a basic science career. For example, Yang's roommate was a student in the RISE program and is now attending dental school. "The critical thinking skills we are taught in the RISE program are applicable to any science field," Yang says. ■ –JAMES NETTERWALD

VSA Partners

HHMI Selects Nine Students for Gilliam Fellowships

AFTER FLEEING ZAIRE AS A REFUGEE, IN 1996, ESPOIR KYUBWA struggled to learn English at his new elementary school in California. Many subjects were difficult, but he found comfort in science class because it relied on a language he already knew: math.

Now 24, Kyubwa still has the love of science he discovered as a child. He will be using his HHMI graduate student research fellowship to study how the body repair's itself, as part of an M.D./Ph.D. program at the University of California, San Diego.

Kyubwa is one of nine students chosen this year to receive HHMI's Gilliam Fellowships for Advanced Study. The fellowships are aimed at increasing the diversity of college and university faculty by supporting Ph.D. research by students from groups traditionally underrepresented in the sciences. "Our goal is to train tomorrow's leaders in science and education," says William Galey, director of HHMI's graduate and medical education program.

This year, HHMI doubled the number of the Gilliam fellowships available after realizing that they had more top applicants than they could fund. "The talent pool is amazingly deep. We've seen spectacular students who go on to great schools and are very promising," says Sean B. Carroll, HHMI's vice president for science education. "We think it is really important to support these outstanding students."

NICOLAS ALTEMOSE
DUKE UNIVERSITY

ANDRIA ASHMORE
UNIVERSITY OF CALIFORNIA, LOS ANGELES

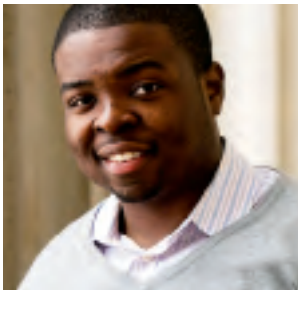
NADIA HERRERA
UNIVERSITY OF TEXAS AT EL PASO

JESSICA CABRAL JIMENEZ
UNIVERSITY OF CALIFORNIA, LOS ANGELES

SANDRA JONES
SPELMAN COLLEGE

BENYAM KINDE
HARVARD MEDICAL SCHOOL

ESPOIR KYUBWA
UNIVERSITY OF CALIFORNIA, SAN DIEGO



CHINWEIKE OKEGBE
COLUMBIA UNIVERSITY

GLORIA TAVERA
UNIVERSITY OF FLORIDA

Gilliam fellows are chosen from among students who have participated in HHMI's Exceptional Research Opportunities Program (EXROP), which places undergraduate students from minority or other groups traditionally underrepresented in the sciences in the labs of HHMI investigators and professors. The expansion of the program will allow up to 10 students each year to become Gilliam Fellows, an increase from five in previous years.

That means more support for doctoral students like Gloria Tavera, who is starting an M.D./Ph.D. program this fall to study infectious diseases after spending a year doing research on dengue fever on a Fulbright fellowship in Mexico. And for students like Sandra Jones, who was inspired to study neuroscience after hearing a seminar on the science of anesthesia.

Among the new Gilliam fellows, five have graduated from college or will graduate this year and are applying to graduate school. The remaining four awardees are in their first year of Ph.D. or M.D./Ph.D. programs.

As for Kyubwa, he hopes to eventually go back to his native country, now called the Democratic Republic of Congo, where he can use his doctoral research on medical trauma and injury to help heal the strife-torn country.

"I have a lot of aspirations to develop something, maybe a teaching hospital or something along those lines," he says. "I'm really interested in helping." ■

Altemose: Jim Bounds for HHMI Ashmore: Rene Macura for HHMI Herrera: Victor Calzada for HHMI Jimenez: Rene Macura for HHMI Jones: John Amis for HHMI Kinde: Jeff Barnett-Winsby Kyubwa: Denis Poroy for HHMI Okegbe: Charles Sykes for HHMI Tavera: Nick Wass for HHMI

Kotak Elected HHMI Vice President and Chief Financial Officer

THE HHMI BOARD OF TRUSTEES HAS ELECTED NITIN KOTAK AS THE Institute's next vice president of finance and chief financial officer. Kotak, 53, joins HHMI from Technest Holdings, Inc., where he was chief financial officer and treasurer. He succeeds Edward J. Palmerino, who had held the post since 2006.

"Nitin comes to us with great enthusiasm for our mission and significant experience in financial analysis, reporting, and compliance," says Cheryl Moore, HHMI's executive vice president and chief operating officer. "He is a strong addition to our management team and we're pleased to welcome him to the Institute."

A native of India, Kotak received a bachelor of commerce degree from the University of Calcutta, where he graduated with first class honors in accounting and auditing. He spent more than 17 years working in a variety of finance-related positions at ITC Limited, the Indian associate of the Fortune 500 company British American Tobacco. He has also worked at India-based Mattel Toys, a subsidiary of Mattel, Inc., and Able Laboratories, Inc., a developer and manufacturer of generic pharmaceuticals.

In 2005, Kotak joined Technest, located in Bethesda, Maryland, as vice president for finance and operations and became chief financial officer and treasurer in 2008. Technest provides advanced sensor technologies and services to the National Institutes of Health as well as national defense, homeland security, military, and intelligence agencies.

At HHMI, Kotak will oversee budget and financial analysis, the controller's office, treasury, internal audit, and procurement. "I am very excited at this opportunity to be a part of this outstanding organization and work in a spirit of giving back to the community," says Kotak. "I feel honored to be selected for this great responsibility."

Kotak also serves as president of the Maryland-based Washington Kali Temple, an Indian religious and cultural center. He and his wife, Dipti, live in Silver Spring and have two sons. Kotak remains a senior member of three major professional institutes in India—the Institute of Chartered Accountants, the Institute of Company Secretaries, and the Institute of Cost and Works Accountants. ■

Summer Institute Expands with HHMI Support

MICHELLE WITHERS' FIRST YEARS OF TEACHING WERE FRUSTRATING. "I had been trying to learn how to teach better, but I didn't know what to do," says Withers, now a biology professor at West Virginia University.

Then she went to the National Academies Summer Institute for Undergraduate Education in Biology, a week-long course that shows faculty better ways to teach. It changed her life. Withers was so excited by what she learned that she started her own local version of the training program. "I really drank the Kool-Aid," she says.

Now the Summer Institute is expanding to allow more educators to learn the techniques behind successful teaching. What started as a single site in Wisconsin will include up to nine regional training centers across the country over the next five years, with the help of $3 million provided by HHMI. Four new training sites will start up this summer in New Haven, Seattle, Boulder, and Minneapolis.

"The Summer Institute is very successful, but at the rate it was going it would never reach enough faculty," says Sean B. Carroll, HHMI's vice president for science education. "With this expansion, we hope to greatly increase the number of faculty members who participate and bring what they learn back to their campuses. The scale of this effort is aimed at changing biology teaching across the country."

The expanded Summer Institute will continue to use the National Academy of Sciences' Bio2010 report as a touchstone. The report concluded that biology faculty needed to learn the science behind successful teaching. "People have a strong tendency to teach the way they were taught," says Jo Handelsman at Yale University, who co-leads the Summer Institute with Bill Wood at the University of Colorado, Boulder. "But we know that lectures are the worst way to teach if you care about student learning."

At the Summer Institute, faculty learn how to incorporate active-learning techniques, including interactive projects and discussion groups with constant assessment. They also learn how to make it work in a large lecture-style classroom. Since 2004, 304 faculty and instructional staff members from 94 institutions have gone through the Summer Institute. Its graduates teach approximately 100,000 undergraduates each year. ■

James Kegley

Institute Launches Documentary Film Unit

AT A MEETING IN FEBRUARY THAT BROUGHT TOGETHER SCIENTISTS, educators, and entertainment industry professionals, HHMI announced the launch of a $60 million documentary film initiative that aims to bring engaging science features to television.

"Film is the most powerful medium for bringing ideas, knowledge, and stories to life and communicating them to any audience," says Sean B. Carroll, HHMI's vice president for science education, who spoke at the meeting. "HHMI can harness that power by producing high-quality, compelling documentary films on scientific topics."

HHMI has funded television projects on a more modest scale in the past—including support for the public broadcasting series *NOVA scienceNOW* and science reporting on *PBS NewsHour*—but this is its first foray into the documentary film arena. The HHMI film division's priority will be to tell intriguing science stories that grab the viewer, Carroll says. They will cover all areas of science, especially biology and medicine, and will go beyond the work of HHMI's own researchers.

The institute will collaborate with broadcasters and other partners to develop, produce, and disseminate programs and specials internationally. The documentary film initiative also includes a major educational component. Subjects will be chosen based on their potential for powerful narrative, but HHMI's staff—primarily its Educational Resources Group—will work hand-in-hand with the executive producer and filmmakers to repackage the film footage into materials that can be used by teachers and students at both the high school and college levels.

"Compelling films have the power to inspire people and nourish curiosity—which also happen to be central goals of our science education program," says HHMI President Robert Tjian.

Carroll, who took over as HHMI's vice president for science education in 2010, has a longstanding interest in public science education. In addition to writing several popular books on science and a regular column for *The New York Times*, he has participated in numerous television documentaries.

Although Carroll has not identified specific film topics, he says that most scientists and science educators agree that the public would benefit from access to engaging materials that provide better insight into how science works, how evidence is weighed and tested, and how conclusions are reached. "We want the public to understand the process of science and gain an appreciation for it so they can trust its results and use them in their daily lives," he says. ■

Measuring Quality: HHMI Announces $60 Million Competition for Colleges

CHALLENGING COLLEGES AND UNIVERSITIES TO THINK CREATIVELY about how they teach science, HHMI has invited 215 undergraduate-focused institutions across the country to apply for a total of $60 million in science education grants.

The new round of grants differs from previous HHMI education grants in that they include a focus on collecting better information about which programs succeed in developing the talent and leadership skills of students. Institutions will be asked to identify an overarching educational objective for their program, and schools will be encouraged to create joint programs with other institutions to build on shared science education interests. In addition, colleges and universities that have previously received four or more education grants from HHMI will be asked to share the cost of their ongoing programs to demonstrate their commitment.

"The question is not whether we can produce more scientists and science teachers, but whether we can produce better ones," says David J. Asai, director of HHMI's precollege and undergraduate program. "That is our goal with these changes."

In the past, HHMI's grants have allowed applicants to submit projects in four categories: student research, faculty development, curriculum and laboratory development, and outreach. Although schools were not expected to put forward a program in every category, Asai notes that the modular design of the grant competition often led schools to "check the boxes" rather than encouraging them to think strategically about a more global objective.

Under the new guidelines, the grant proposal must support the institution's larger science education goal. Asai hopes this new, focused design will make it easier for grantees to measure and understand which components of a program are successful.

"We want to get away from just counting the numbers of students who do research. We want to find out what schools are doing that is preparing undergraduates to be successful as future scientists, teachers, or members of a scientifically literate public," he says. "It is a harder question, but it is an important question."

The grants will range from $800,000 to $1.6 million over four years for individual institutions and up to $4.8 million over four years for programs run jointly by multiple institutions.

"Grants of this size can have a big impact at small schools," says Sean B. Carroll, HHMI's vice president for science education. "A small number of faculty working together can quickly make changes that will have an immediate impact on the quality of science education for their students."

Applications are due October 4, 2011, and grants will be announced in the spring of 2012. ■

FOR MORE INFORMATION: To learn more about the competition and how to apply, visit www.hhmi.org.

The Pace of Evolution

A CLOSE LOOK AT THE HUMAN GENOME SHOWS THE SLOW AND STEADY BEAT OF ADAPTATION.

Here's how scientists have typically explained the emergence of a new genetic trait: A genetic mutation randomly occurs that gives its carrier an advantage in reproducing. Over a handful of generations, the mutation becomes more prevalent in the population, quickly becoming ubiquitous. It's called a "selective sweep" and has been the predominant explanation for how most new human genes have surfaced. Now here's Molly Przeworski's take: evolution is slow and complex and few human traits have ever emerged through such a speedy takeover.

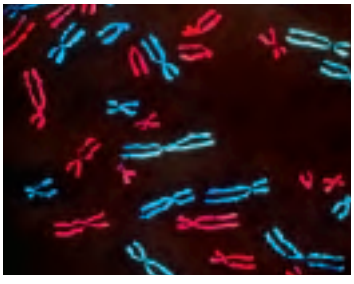
Przeworski, an HHMI early career scientist at the University of Chicago, relied on the fact that if a gene mutation moved that quickly across the human population, most everyone would have inherited the identical genetic material bordering the mutation. If a mutation spread slowly, on the other hand, or arose more than once, it would gradually pick up other mutations in surrounding genes as it broadened throughout the population.

Using this reasoning, Przeworski and her team analyzed 179 human genomes collected through the 1000 Genomes Project. They looked at 40,000 genetic changes that set humans apart from their primate ancestors—some that might change a protein's function, others that are essentially silent. If the "selective sweep" model had dominated throughout human history, Przeworski's team would see more highly conserved regions around mutations that had functional effects. Yet they saw no differences between the variability surrounding functional mutations compared with the rest of the genome, they reported on February 18, 2011, in *Science*.

This finding must mean that "not many adaptations in our history have proceeded through sweeps," says Przeworski. "Selective sweeps must be really rare."

She suggests two alternatives that could explain how adaptations might spread more often. Preexisting mutations across the population can face a new selective pressure from a change in the environment—this process is called "selection on standing variation." Or, a trait can rely on many gene changes rather than one change with a large effect. "Height, for example, is controlled by thousands of loci," says Przeworki. "If the environment is selecting for height, that will happen through hundreds of gene locations." ■

–SARAH C.P. WILLIAMS



Scientists looked at 40,000 genetic changes to determine the pace of human evolution.

IN BRIEF

CELLULAR STRESS PATHWAY LINKED TO TRAUMATIC STRESS DISORDER

Researchers have discovered a genetic marker for post-traumatic stress disorder (PTSD) in women. They found that the gene's effect relies on the hormone estrogen and therefore is not linked to the disorder in men, who have very low levels of estrogen. Led by HHMI investigator Kerry Ressler at Emory University, the multi-institutional study could lead to the first blood test for PTSD susceptibility.

Ressler and his collaborators began with blood samples from 64 men and women in a highly traumatized population. Levels of a protein called pituitary adenylate cyclase activating polypeptide (PACAP) were higher in women who had been diagnosed with PTSD than in women without the diagnosis. A study in a larger group of women yielded the same results.

To understand PACAP's role in PTSD, the team looked for variations of the gene encoding the protein in more than 1,200 women at high risk for PTSD. They found that a mutation in the gene is associated with the presence of PTSD. The researchers then compared PACAP levels in female rats lacking ovaries, and thus estrogen, and in such mice receiving estrogen replacement. The mice with estrogen had higher levels of *PACAP* gene activity in regions of the brain associated with stress and fear, suggesting that estrogen controls this activity, the team reports in the February 24, 2011, issue of *Nature*.

This result provides the first evidence linking the PACAP pathway to PTSD. The pathway is normally linked to cellular response to stress.

MATING TRUMPS FIGHTING

In a tiny area deep in the mouse brain, a set of neurons ensures that mice don't mate and fight at the same time. Crude experiments from the 1920s had hinted that both behaviors were controlled by neurons in the brain's hypothalamus region. Now, HHMI investigator David Anderson has used modern techniques to resolve the details.

In his lab at the California Institute of Technology, Anderson and colleagues began by inserting electrodes into an area of the hypothalamus called VMHv1. Then they recorded the behavior—and firing patterns of 104 neurons in the region—of the male mice over the next several months.

When one male mouse encountered another male mouse and began to fight, a group of neurons in VMHv1 began firing. When a male mouse encountered a female mouse, however, a separate group of neurons switched on—and the aggression-linked neurons appeared to be actively suppressed.

Next the researchers engineered the male mice so that they could control the aggression neurons with bursts of light coming through an optic cable into the brain. When the light came on, the mice immediately fought—with a male, a female, or a nearby object. When researchers blocked the neurons from firing, the mice refused to fight, even around another male. Moreover, when researchers allowed a mouse to mount a female and then shined the light, the mouse did not engage in attacks. The results, published February 10, 2011, in *Nature*, suggest that the VMHv1 neurons activated during mating might inhibit fight behavior.

FLASH-FREEZING CELLS REVEALS BACKWARD TRANSCRIPTION

A new technique of freezing cells in liquid nitrogen allows scientists to view how a cell accesses information encoded in genes. The technique has allowed HHMI scientists to make fundamental discoveries about transcription—the process a cell uses to copy strands of DNA to single-stranded RNA.

Omikron / Photo Researchers, Inc.

The Very Hungry Mouse

ACTIVATING ONE SET OF NEURONS MAKES A MOUSE EAT, AND EAT, AND EAT.

Within minutes of the activation of specific neurons in a mouse's brain, the animal heads straight for its food dish. Despite the fact that the mouse is well fed and it's not mealtime, it eats voraciously, as if starved. The mouse continues overeating until scientists turn off the neurons.

For Scott Sternson, a group leader at HHMI's Janelia Farm Research Campus, this display is proof that a single group of neurons can modulate a complex behavior. Previous research suggested that feeding habits might be strongly affected by one neuron type, called agouti-related peptide (AGRP) neurons. When AGRP or a related molecule is injected into the brain of a mouse, it eats more. But the neurons had never been activated directly.

Sternson and his team relied on optogenetics, the use of light to activate neurons. They engineered AGRP neurons in mice to fire when illuminated by blue light from an optical fiber. When researchers switched on the light, the mice ate—more than 20 times the usual meal. The more neurons that were activated, the more the mice ate. When the light was quenched, the mice stopped eating.

It was thought that activating another neuron type, called POMC neurons, would have the opposite effect—that is, activating them would cause mice to eat less. Indeed, when Sternson's team activated POMC neurons optogenetically, mice ate 40 percent less and lost 7 percent of their body weight in one day. This effect was abolished in mice with blocked melanocortin receptors, a key target of POMC neurons.

When certain neurons are turned on, mice eat ravenously.

The researchers decided to tease apart the effects of POMC and AGRP neurons. "We wanted to know if the AGRP neurons were activating feeding by suppressing melanocortin receptor signaling," says Sternson. So his team blocked this output of POMC neurons and then activated the AGRP neurons. The mice still raced to their food, the researchers reported in *Nature Neuroscience* in March 2011, showing that AGRP neurons are not acting through melanocortin receptors.

Sternson's next goal is to identify the downstream neuron populations that AGRP neurons work through and construct a full circuit in the brain that controls eating behavior. ■ –SARAH C.P. WILLIAMS

IN BRIEF

Transcription begins when double-stranded DNA unwinds to expose its strands. Then the RNA polymerase (RNAP) enzyme attaches to the DNA and works its way along a gene sequence, producing a complementary strand of RNA as it moves. When it reaches the end of a gene, RNAP removes itself and releases the new RNA strand.

This process doesn't always go smoothly, according to recent research: the RNAP can pause, restart, and even launch in the wrong direction. A research team led by HHMI investigator Jonathan S. Weissman of the University of California, San Francisco, found a way to study these bumps in transcription using a technique they call native elongating transcript sequencing (NET-seq). Once they've frozen the cell, stopping all activity, researchers can purify RNA strands mid-transcription. The sequences of the "frozen" strands tell them how transcription is progressing.

The team found instances of transcription happening in the wrong direction, but the process appeared to be actively discouraged by the cell. They also found specific places on the DNA where RNAP is most likely to stop and restart. The researchers are confident that their technique, described January 20, 2011, in *Nature* will reveal more about transcription and other cellular activities.

WHAT SETS CANCER CELLS APART

Research by an HHMI-funded medical student has revealed that cancer cells display two important proteins recognized by the immune system. One tells the immune system to not attack and the other gives it a go-ahead. If scientists turn off the first protein, the immune system's macrophages will destroy the cancer cells.

Mark Chao did the work at Stanford University while participating in HHMI's Medical Research Fellows Program. In earlier research, Stanford's Irving Weissman and Ravindea Majeti showed that macrophages attack cancer cells only if a surface protein called CD47 is blocked. CD47 is also present in normal cells, but blocking CD47 in those cells isn't enough to get macrophages to attack. So researchers thought cancer cells must possess an additional protein that lets the body know they're invaders. They suspected a protein called calreticulin.

Chao worked with Weissman and Majeti to show that calreticulin is expressed on the surface of many types of human cancer cells but not on the surface of normal cells. Furthermore, calreticulin was required for macrophages to recognize cancer cells and eliminate them. When calreticulin and CD47 are blocked, cancer cells are no longer destroyed.

Reporting their findings in the December 22, 2011, issue of *Science Translational Medicine*, the researchers also note that calreticulin is expressed more highly in cancers with worse clinical outcomes. The higher level of protein, unfortunately, isn't enough to overcome the block that CD47 puts in place. But a therapeutic aimed at CD47 could get the job done.

A POSITIVE FINDING FOR TRIPLE-NEGATIVE CANCER

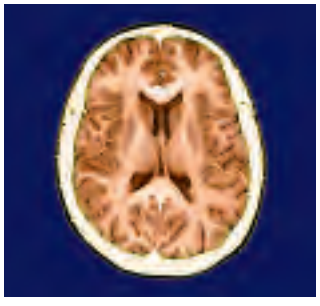
New research reveals the genetic underpinnings of some cases of aggressive breast cancer. Triple-negative tumors are so named because they fail to test positive for any of the three traits that can be targeted by current drugs. HHMI investigator Steve Elledge has shown that in many of these cases a molecule called a tyrosine phosphatase is mutated.

Elledge's team at Harvard Medical School used a genetic screen of triple-negative tumor cells to zero in on the phosphatase. An enzyme called PTPN12 is responsible for impeding the activity of a class of tumor-causing tyrosine kinases.

BSIP / Photo Researchers, Inc.

Nourishing Neural Stem Cells

CEREBROSPINAL FLUID DOES MORE THAN PROTECT THE BRAIN.



Cerebrospinal fluid surrounds the brain and fills its central cavities, like those shown here in the darkest brown.

Inside your skull, your brain is floating in a clear liquid. This *liquor cerebrospinalis*, or cerebrospinal fluid (CSF), until recently was considered simply cushioning for the brain. It maintains a constant pressure in the skull, keeps the brain protected when it's jolted, and carries waste away from the vital organ. Now, HHMI investigator Christopher A. Walsh has revealed that CSF does much more—it holds proteins that play irreplaceable roles in controlling brain development, growth, and health.

Walsh and his colleagues at Children's Hospital Boston suspected that CSF has such important roles when they identified, in 2007, hundreds of proteins suspended in the fluid. In their latest work, they looked at how these proteins might affect the brain's neural stem cells—the precursors to brain cells. They took bits of brain tissue from embryonic rats and bathed them in CSF from old and young rats. When exposed to the CSF from young animals, neural stem cells divided quickly. When soaked in older CSF, stem cells divided more slowly, and they more often differentiated into adult brain cells rather than renewing the population of stem cells.

"What we showed for the first time is that CSF's role changes with time," says Walsh.

The research team went on to determine that one particular CSF protein—called insulin-like growth factor 2 (Igf2)—largely controls neural stem cells. Knowing this, the scientists suspected that Igf2 could play a role in glioblastoma, a type of brain tumor in which neural stem cells are misdirected. So, in collaboration with another group, they analyzed a collection of CSF samples taken from glioblastoma patients. Indeed, they reported in *Neuron* on March 10, 2011, that more advanced cases of the cancer are associated with higher levels of Igf2 in the CSF. Whether this is a cause or an effect, they can't yet conclude, but it ushers in a new mindset about CSF.

"This really changes how we think about a lot of things," says Walsh. "The CSF clearly carries many different proteins that have active, and changing, roles in modulating the brain. There may be many other processes—potentially learning or behavioral states—that are modulated by CSF." ■ –SARAH C.P. WILLIAMS

IN BRIEF

Elledge and his colleagues found that when PTPN12 is mutated, deleted, or turned off, the kinases initiate tumor growth.

The good news, says Elledge, is that existing drugs inhibit the activity of many of these kinases, which have also been implicated in some head, lung, pancreatic, and colorectal cancers. The researchers reported in *Cell* on March 4, 2011, that a combination of two of these kinase inhibitors slowed and reversed tumor growth in mice with triple-negative breast cancers. The scientists are working to identify all the kinases affected by changes in PTPN12 and are investigating whether different phosphatases may explain other cases of triple-negative breast cancer.

THE NATURE OF ASYMMETRY

Most of the time when cells divide, their goal is to divide evenly, producing two equal daughter cells. But sometimes, a dividing cell needs to send daughters down different paths. In developing mammalian skin, for example, asymmetric cell divisions of skin stem cells are required to turn a single layer of skin into the many layers that protect an organism. In this process, known as stratification, asymmetric divisions leave one daughter cell in the innermost layer of skin and push the other to an outer layer.

HHMI investigator Elaine Fuchs and her colleagues at the Rockefeller University knew of a regulatory pathway that regulates asymmetric cell divisions in flies and wondered whether this pathway also operates in mice. After they found mouse versions of three proteins in the pathway—LGN, NuMA, and DCTN1—they blocked the RNAs that code for them by using a new technique that allows them to turn off genes when the skin is only a single layer. The skin cells failed to orient correctly and the skin failed to stratify.

Moreover, by blocking the three proteins, the team reported in *Nature* on February 17, 2011, they inhibited part of another developmental pathway, called Notch. Next, the researchers hope to work out the rest of the biochemical pathway involved in asymmetrical cell division and skin stratification.

SHUTTING OFF ANXIETY

Anxiety isn't a hard-wired state of the brain but a continuously adapting condition that can be altered instantaneously, according to new research. The flip of a neural switch can make an anxious mouse more apt to explore its cage, the latest study by HHMI early career scientist Karl Deisseroth shows.

Over the past six years, Deisseroth and his colleagues at Stanford University have pioneered the field of "optogenetics," the use of light to manipulate neuron behavior in the brain. Now, they've used their optogenetic techniques to explore an area of the brain called the basolateral amygdala. But rather than activate all the neurons in this area—which has a broad, and hard to tease apart, effect—the researchers activated only a subset of the neural projections.

They focused on the neurons that connect the basolateral amygdala to a neighboring area called the central amygdala and found that when these neurons are turned on, mice showed fewer signs of anxiety. When the same neurons are shut off, the mice become more nervous. Activating all the cells in the basolateral amygdala, rather than just those leading to the central amygdala, had little effect on anxiety, presumably because the light switch activated pathways that both trigger and stifle anxiety, canceling one another out, says Deisseroth. The results appear in the March 17, 2011, issue of *Nature*.

"Most thinking [in the field] had suggested that anxiety was a very stable state in the brain," he adds. "What we found is that it's really something that's under real-time, continuous control."

Medical Body Scans / Photo Researchers, Inc.

Q A

How did viruses evolve from a universal common ancestor?

Asked by a science-curious lifelong learner

Fossil records can help us understand how complex organisms evolved, but, unfortunately, viruses are too small and fragile to withstand the processes required for extremely long-term preservation. As a result, we are left to infer their origins by studying how present viruses evolve. The genetics of today's viruses and their hosts can give us hints about their evolution: viruses often contain bits of genes that they have picked up from a previous host, and there is evidence that host cell genomes can likewise be changed by a viral infection. But modern-day viruses vary dramatically from species to species, and no single gene is shared by all viruses. So genetic relatedness can only teach us so much.

There are three main theories that attempt to explain how viruses originated. The time frame for them probably would have been between two and three billion years ago, after life arose and cells developed the ability to duplicate and metabolize. Since viruses depend on other cells for replication, they likely appeared shortly after the first cells, though this cannot be proven.

The first hypothesis, known as the *regressive hypothesis*, proposes that viruses evolved from small cells that acted as parasites—relying on larger cells. Over time, these parasitic cells would have lost genes they no longer required. Eventually, they would become a cell-dependent virus. *Chlamydia* bacteria—which cannot reproduce outside their host cell—may have evolved similarly. But unlike a bacterium such as *Chlamydia*, viruses never encode for ribosomes—the cellular organelles that produce proteins. And some viruses have RNA genomes, which is difficult to explain by the regressive theory.

The *cellular origin hypothesis* suggests that viruses began from rogue molecules of DNA or RNA that jumped ship and left the host cell's genome. Circular DNA molecules called plasmids are known to churn out RNA even though they are not part of a genome and can move between cells. And scientists have discovered transposons, sequences of jumping DNA that can copy and paste themselves within a cell's genome. These examples lend validity to the idea that a section of DNA or RNA could leave a cell's genome and continue to function, which may explain how a virus could first emerge.

Finally, the *coevolution hypothesis* proposes that the first viruses originated from self-replicating molecules, such as ribozymes, some of which can store genetic information but also possess the ability to copy themselves. They would have appeared on earth at the same time as the first cells. Over time, these pre-virus molecules could have hijacked the machinery of emerging cellular life and transitioned to parasitic viruses. Viroids, small RNA molecules that can infect plants, may be examples of this phenomenon.

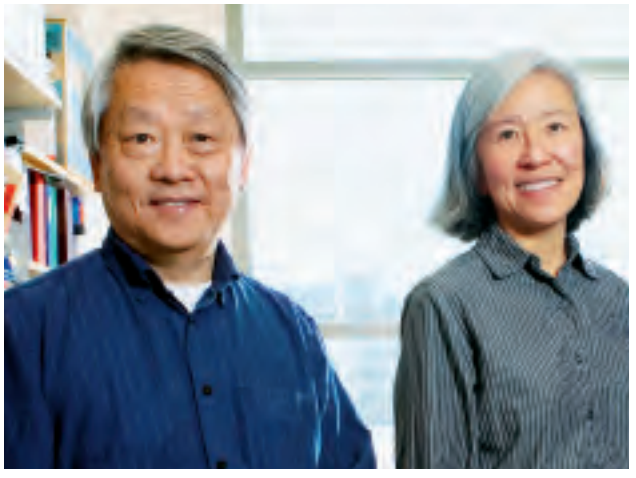
Most likely, viruses have arisen numerous times (and may even continue to arise!) by one or more mechanisms and, as a result, may not possess a common universal ancestor in the same sense as cellular life.

ANSWER RESEARCHED BY NATHAN YOZWIAK, *a graduate student in the lab of HHMI investigator Joseph DeRisi.*

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

Wiley Prize Goes to Lily Jan and Yuh Nung Jan



YUH NUNG JAN AND LILY Y. JAN

The 2011 Wiley Prize in Biomedical Sciences was awarded to HHMI investigators **Lily Y. Jan** and **Yuh Nung Jan**, a wife and husband team who share a lab at the University of California, San Francisco. The pair received the annual prize, given by the Wiley Foundation, for their research on potassium ion channels that control neuron activity. In 1987, the Jans were the first to determine the DNA sequence of a potassium channel. Since then, scientists have linked mutations of potassium channels to epilepsy, heart arrhythmias, deafness, and other diseases.

JAMES P. ALLISON, an HHMI investigator at Memorial Sloan-Kettering Cancer Center, won the 2011 Lifetime Achievement Award from the American Association of Immunologists. Allison was chosen for his research on the interplay between the immune system and cancers. His findings have led to the development of a drug—ipilimumab—for treating some types of melanomas.

MARK BATES, a former graduate student in the lab of HHMI investigator Xiaowei Zhuang, won the 2010 GE & *Science* Prize for Young Life Scientists for work he did while in the Zhuang lab. The GE Prize—sponsored jointly by GE Healthcare and *Science* magazine—goes to one grand prize winner and three finalists each year to recognize promising young molecular biologists around the world. Bates, the 2010 grand prize winner, developed new methods of using fluorescence to visualize cellular processes. He's now doing a postdoctoral fellowship at the Max Planck Institute for Biophysical Chemistry.

JAMES J. COLLINS, an HHMI investigator at Boston University, won the 2010 Lagrange-CRT Foundation Prize. Given annually, the award honors a scientist under 45 years of age for achievement in research on complex systems. Collins uses his background in engineering to understand how various biological networks function. Collins was also elected a member of the National Academy of Engineering, along with HHMI investigator TERRENCE J. SEJNOWSKI, of the Salk Institute for Biological Studies.

HHMI investigators BRIAN J. DRUKER, of Oregon Health & Science University, and CHARLES L. SAWYERS, of Memorial Sloan-Kettering Cancer Center, share the 2011 Stanley J. Korsmeyer Award from the American Society for Clinical Investigation. The award recognizes the work by both scientists that led to imatinib, a treatment for chronic myeloid leukemia (CML), as well as further research into imatinib-resistant CML.

HHMI investigator ELAINE FUCHS, of the Rockefeller University, has been named the 2011 Passano Laureate by the Passano Foundation. Each year, the foundation presents this award to a scientist who has made outstanding contributions to medical science. Fuchs was chosen for her research on how skin stem cells decide whether to become a skin cell or a hair follicle. She has discovered key pathways that affect this cellular decision.

In a ceremony at the White House, President Obama presented HHMI professor JO HANDELSMAN, of Yale University, with a 2011 Presidential Award for Excellence in Science, Mathematics and Engineering Mentoring (PAESMEM). Handelsman is a co-organizer of the Summer Institute on Undergraduate Education in Biology, sponsored by the National Academy of Sciences and HHMI. Also receiving a PAESMEM award was JULIO RAMIREZ, director of an HHMI-funded program at Davidson College that supports minority students and mentors in neuroscience.

HHMI investigator WILLIAM G. KAELIN, of the Dana-Farber Cancer Institute, won the National Cancer Institute's 15th Annual Alfred G. Knudson Award in Cancer Genetics. Kaelin, who studies tumor-suppressor proteins and their role in cancers, has shown how cells in the body monitor and respond to oxygen levels—a process that's affected by some tumors.

Gabriela Hasbun

RUTH LEHMANN, an HHMI investigator at New York University, is the 2011 recipient of the Edwin Grant Conklin Medal from the Society for Developmental Biology. Lehmann studies germ cell development in *Drosophila*, investigating how germ cells are specified in an embryo and how they become stem cells that continue to produce egg and sperm throughout adulthood.

DOUGLAS A. MELTON, an HHMI investigator at Harvard University, received the 2010 David Rumbough Award for Scientific Excellence from the Juvenile Diabetes Research Foundation. Melton's research has helped advance understanding of how embryonic stem cells give rise to the pancreatic cells that are destroyed in patients with type 1 diabetes. Coaxing stem cells to become pancreas cells could lead to a treatment for diabetes.

HHMI investigator **MELISSA J. MOORE**, of the University of Massachusetts Medical School, won the 2011 William C. Rose Award from the American Society for Biochemistry and Molecular Biology. The annual award recognizes outstanding contributions to biochemistry and molecular biology research as well as a commitment to training younger scientists. Moore studies the spliceosome, part of the molecular machinery that processes newly transcribed RNA strands.

HHMI investigator **BRENDA A. SCHULMAN**, of St. Jude Children's Research Hospital, is the 2011 recipient of the Dorothy Crowfoot Hodgkin Award from the Protein Society. She shares the award with Wei Yang of the National Institutes of Health. Schulman's research has revealed how a class of molecules called ubiquitin-like proteins (UBLs) control the functioning of other proteins in a cell. Different UBLs can affect their target proteins in different ways, including changing the target's half-life, conformation, localization, enzymatic activity, and intermolecular interactions.

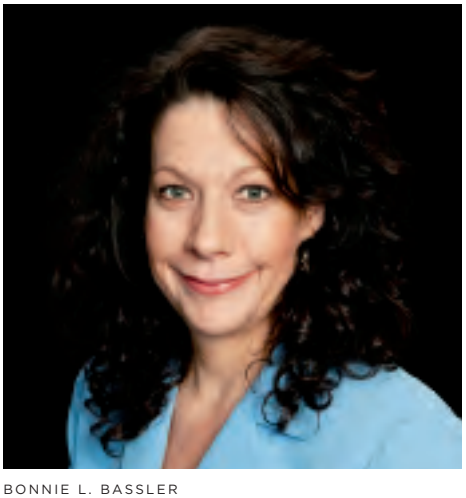
MICHAEL F. SUMMERS, an HHMI investigator at the University of Maryland, Baltimore County, won the 2011 Carl Brändén Award from the Protein Society. The award is given annually to a protein scientist who has also made exceptional contributions to science education or service. Summers studies the molecular structures of proteins related to HIV and is passionate about training undergraduate students in science.

The Society for Neuroscience named HHMI early career scientist **RACHEL I. WILSON**, of Harvard Medical School, recipient of its 2010 Young Investigator Award. The award is given annually to a researcher in the field of neuroscience who completed a Ph.D. within the past 10 years. Wilson studies how the fruit fly brain processes information about odors.

HHMI investigator **BERT VOGELSTEIN**, of the Johns Hopkins University School of Medicine, is a recipient of the 2011 Charles Rodolphe Brupbacher Prize for Cancer Research. The biennial award is given by the Charles Rodolphe Brupbacher Foundation for outstanding contributions to basic oncological research. Vogelstein has characterized numerous genes involved in the development of cancers, including colorectal, pancreatic, and brain cancers.

SPOTLIGHT

Bassler Wins Lounsbery Award



BONNIE L. BASSLER

Paul Fetters

The National Academy of Sciences honored HHMI investigator **Bonnie L. Bassler**, of Princeton University, with the 2011 Richard Lounsbery Award. The prize is given in alternate years to American and French scientists in recognition of achievement in biological and medical research. Bassler studies how individual bacteria communicate with each other and how bacteria behave as a group. She discovered that when a group of bacteria have reached a critical mass, they change their behavior to carry our processes that require cells to act together. Her research has important implications in fighting pathogenic bacteria.

CONTINUED FROM PAGE 17
(BONE'S BALANCING ACT)

Notch signaling dramatically slowed the growth of human tumors implanted in immune-deficient mice, the group reported in *Human Molecular Genetics* in 2009.

Since then, the researchers have engineered a line of mice with an intact immune system that would be better than immune-deficient mice at predicting how potential drug compounds might affect tumors in people, Lee says. Notch is activated continually in these mice, and the animals develop bone cancer, Lee's team reported last October at the American Society for Bone and Mineral Research. "We're very excited because we've got what we think is a more authentic model of osteosarcoma," Lee says.

Now they're testing whether blocking Notch genetically in mice will prevent bone cancer. If so, then compounds that block Notch signaling could also stop the disease. And if that works in mice, Lee plans to test them on osteosarcoma patients.

As with other bone diseases, treating bone cancer is also a matter of regaining balance. Lee thinks it's possible: "If we could inhibit Notch in osteosarcoma, that would be spectacular." New drugs for bone cancers, childhood skeletal diseases, fracture healing, and a major disease of aging may all come from these pathway explorations. ■

CONTINUED FROM PAGE 33
(THE NEXT STATIN)

A Role for Inflammation

Cholesterol build-up causes inflammation too, which is a risk factor for atherosclerosis. That inflammation pathway offers another target for drug developers.

When cholesterol accumulates along artery walls, macrophages—immune cells that recognize foreign material—are the first cells to encounter the clumps. The reaction of the macrophage to the cholesterol can either help clear the artery or make problems worse.

"A macrophage is a scavenger for extracellular garbage," says HHMI investigator Peter Tontonoz of the University of California, Los Angeles. "And when there are cholesterol deposits, they're recognized by the macrophage as junk that it wants to clear." Normally, this is a good thing—macrophages help remove LDL from the artery wall. But when a macrophage is overwhelmed with too much cholesterol to process, it turns into a foam cell—so named because the LDL in its interior looks like foamy bubbles.

Foam cells are the first sign of an atherosclerotic plaque. The foamy macrophage produces inflammatory molecules and recruits other immune cells to the site, setting up an inflammatory response, a hallmark of coronary artery disease. "The reason the plaque eventually gets so big and complicated is that the macrophage talks to and recruits other cell types," says Tontonoz.

But what scientists have struggled to understand is why the macrophage recruits inflammatory molecules when it fills with cholesterol. When the macrophage eats other foreign material, it clears them with no inflammation.

Tontonoz has an answer: a protein called LXR. Originally identified by HHMI investigator David Mangelsdorf, of UT Southwestern, LXR switches between an inactive form, in the presence of low cholesterol, and an active form, in the presence of high cholesterol. In its active form, LXR causes the cell to pump cholesterol out and stop taking cholesterol in.

There are different versions of LXR in different cell types, including macrophages. Mangelsdorf and Tontonoz published a 2003 paper showing that LXR also has anti-inflammatory effects. Tontonoz has since discovered that mice without LXR are more susceptible to a host of diseases, including listeria and tuberculosis. Other studies have shown that drugs increasing the activity of LXR in macrophages have the potential to stop the formation of a foam cell—by pumping cholesterol out—and to decrease arterial inflammation. The combination could stop atherosclerosis.

As Tontonoz has explored the pathway of LXR, he's also discovered how it arrests cholesterol input, and it's a familiar mechanism: degradation. In a July 2009 paper in *Science*, Tontonoz reported that one of the proteins that LXR turns on is a protein called Idol. Idol in macrophages has the same job as Hobbs's PCSK9 in the liver—degradation of LDL receptors. So Idol, like PCSK9, could be a target for new pharmaceuticals. Already, compounds activating LXR are in the pharmaceutical pipeline.

Pieces of the Puzzle

For every 10 milligrams per deciliter of blood that you decrease your LDL, you have a 10 percent decrease in coronary heart disease risk, says Hobbs. Statins have been an effective way to achieve this LDL reduction, but for some patients, they're not effective enough to stop heart disease. The network of proteins and genes that regulate cholesterol in the body is complex and far-reaching. Statins affect only one part of this system.

The next cholesterol drug—be it a compound that blocks PCSK9, degrades HMG-CoA reductase, or turns on LXR—will likely be used in concert with statins to come at the problem from two angles.

You can't predict which aspect of the field will lead to the next breakthrough, says Goldstein. "You have to wait and see. But the important thing is to keep looking at this from new angles."

As scientists forge ahead in probing those new angles and revealing each part of the cholesterol puzzle, they get closer to that next breakthrough, and the promises of the next drug come into focus. ■

WEB EXTRA: To learn more about cholesterol research and cholesterol-related diseases, visit www.hhmi.org/bulletin/may2011.

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Brett Ryder

STRONG FLIERS

Biochemist Hal White is a dragonfly enthusiast, spending much of his free time observing and documenting the insects in their natural habitat. In his new book, White weaves observational anecdotes with substantial knowledge of dragonfly biology and natural history, creating vignettes of darners, clubtails, and petaltails that entertain and inform. Through the book, White says, he hopes to illuminate biological principles that apply to all living things, including humans.

Although present throughout the summer, the Shadow Darner seems to attract attention most in the fall when it sometimes flies in open windows on warm days. When this happens in a classroom or busy office, the effect can be dramatic. Being strong fliers and almost three inches long, the Shadow Darner can move swiftly about a room, inadvertently frightening humans who may think it is a giant wasp and with a corresponding sting.

Normally, however, Shadow Darners prefer small woodland streams, where males patrolling for females fly low and follow the shoreline. They leave this habitat to feed on midges and other small insects that often fly in clearings or at the edges of fields protected from the wind. Sometimes, if the conditions are right, hundreds of feeding dragonflies slice back and forth through clouds of small insects—like sharks attacking and terrorizing a school of fish.

Excerpted from *Natural History of Delmarva Dragonflies and Damselflies: Essays of a Lifelong Observer*, by Hal White. Published by the University of Delaware Press, © 2011.

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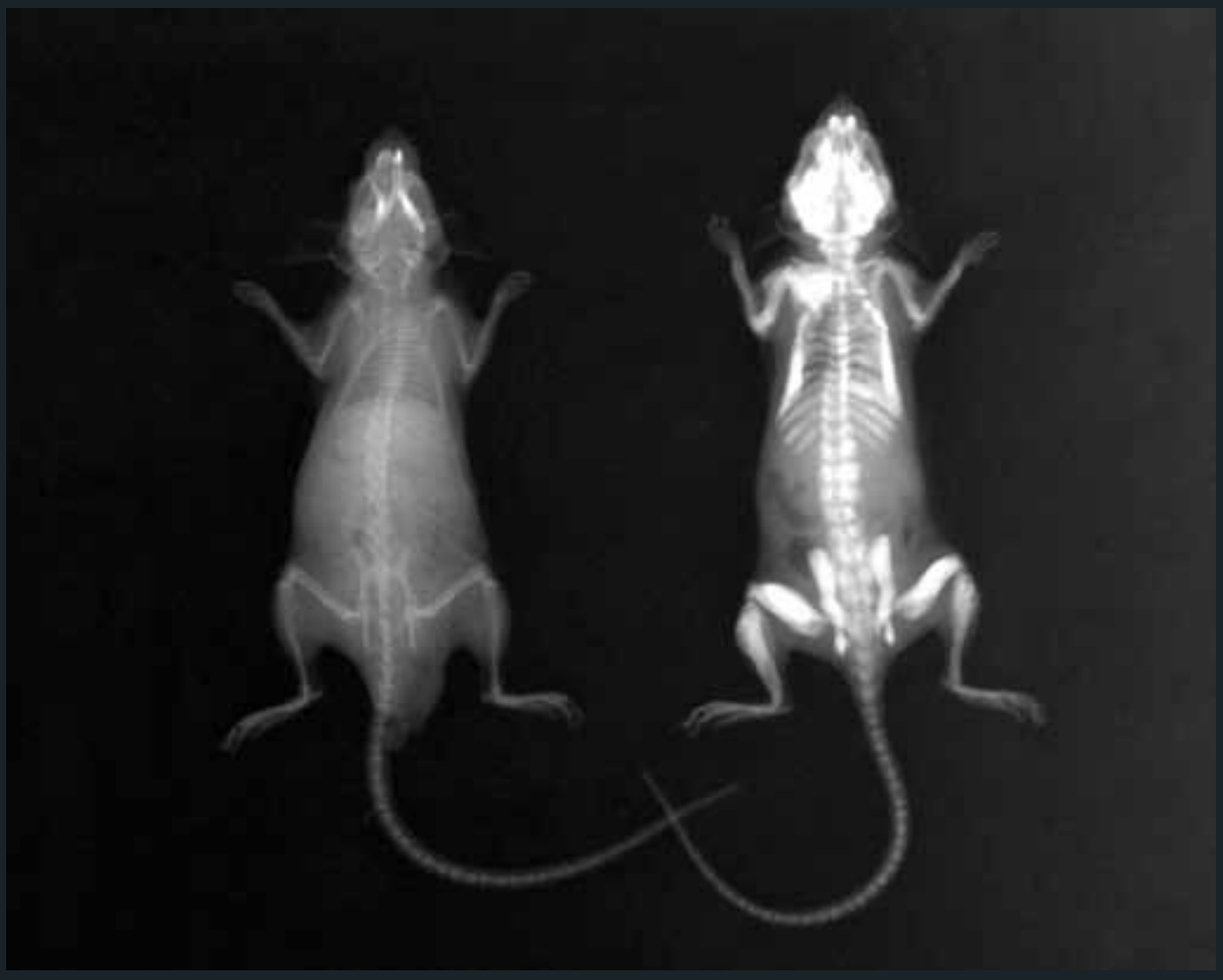
Dem Bones

On the outside, these two mice have the same sleek fur, dainty whiskers, and thin tails. Look inside, however, and the resemblance ends. A CT scan reveals drastically different skeletons and the reason lies with a single gene. The protein product of the gene called *NFATc1* normally enters a cell's nucleus only occasionally to turn on genes that encourage bone growth. But in the mouse on the right, NFATc1 was engineered to stay in the nucleus longer, and the result is ultrastrong bones. Every bone, from the mouse's skull and spine to its toe bones, is thicker than normal. For researchers, it's a hint at how osteoporosis may one day be treated (see "Bone's Balancing Act," page 12).



Gerald Crabtree lab