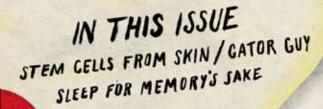
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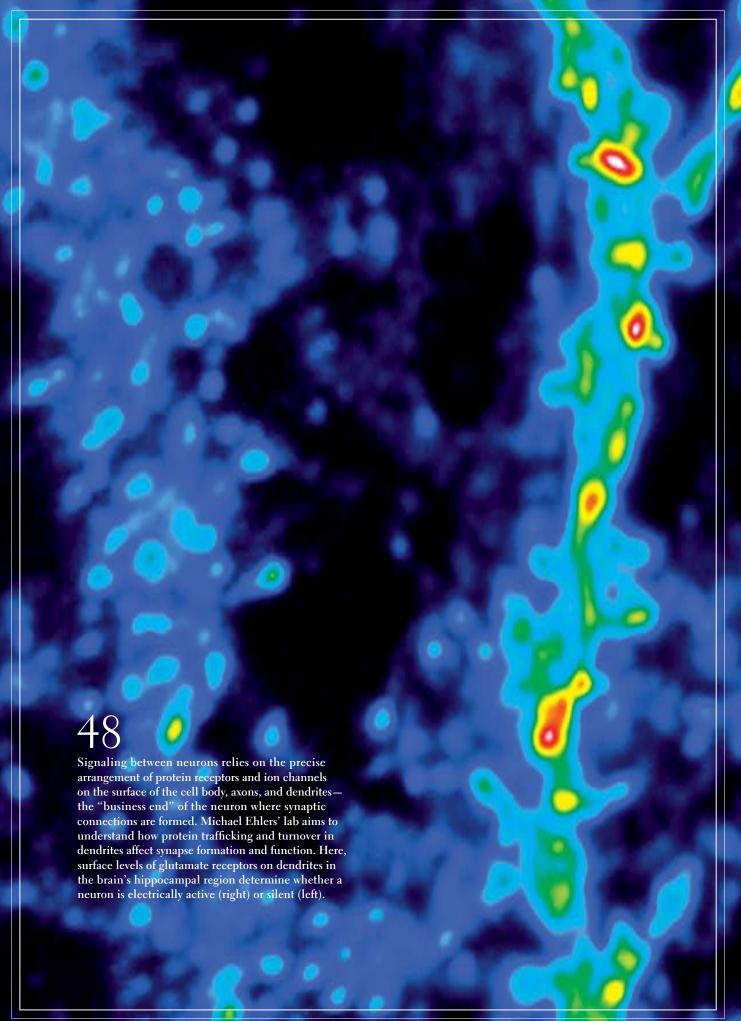
A Prescription

For Endurante

Can a pill be the solution ?

Can a pill be the epidemic ?

to the diabesity epidemic ?



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Exercise In A Pill?

Not quite. But toying with metabolism's machinery might lead to obesity-fighting drugs that bolster the effects of a workout.

[COVER STORY]



Memories Are Made Like This

Researchers believe they are deciphering some of the mysteries of sleep, particularly its role in forging new memories. 26



For the Good of Gators—and Humankind

The thrill of the chase and the challenge of the classroom keep alligator expert and HHMI professor Louis Guillette's instincts and insights sharp.



Modern Relics

Bits of possibly ancient RNA are turning up in modern bacteria and other organisms. Their capacity to monitor the environment and regulate gene expression makes them a welcome target for new antibiotics that confuse bacteria into starving to death.

JULIA BRECKENREID is an illustrator and educator living in Toronto, Canada. Her work has been recognized by 3 x 3 magazine, American Illustration 25, and Society of Illustrators of Los Angeles. She teaches "conceptual process" in the illustration program at Canada's Sheridan Institute of Technology and Advanced Learning and is working on picture books for publishers Henry Holt and Simply Read Books. (2)

As a boy, GEORGE HEIDEKAT passed many a happy evening under the covers with a flashlight and a copy of *Scientific American*. Since then, he's written for the Pittsburgh Supercomputing Center and the Software Engineering Institute. Heidekat lives in Pittsburgh with his fountain pen collection, his cat, and his screenwriter wife, Lorraine. (3)

CHRISTOPHER NEAL, an illustrator, designer, and artist born in Texas and raised in Florida and Colorado, has published in a variety of magazines and books, and is a regular contributor to *The New York Times*. His work has been recognized by Communication Arts, *American Illustration*, Society of Illustrators, Society of Publication Designers, Art Directors Club, *PRINT*, and Society of News Designers. Neal lives and works in Brooklyn. (4)









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A Standard for Openness

AS ANY ARCHITECT OR GARDENER CAN ATTEST, THE DESIGN and construction of a proper glass house requires ingenuity and creativity; maintaining one requires a more prosaic investment of time, attention, and resources. It's not the stark beauty of the glass-walled Janelia Farm Research Campus—or even the fact that an icon of modernism, Philip Johnson's glass house, is about to turn 50—that prompts these reflections. Rather, I am inspired by Nobelist Max Perutz, who famously remarked, "True science thrives best in glass houses, where everyone can look in."

That quotation summarizes the conclusions of a National Research Council committee, which I chaired, that was charged with taking a fresh look at the responsibilities of scientists to share the data and materials referenced in original research articles. Our 2003 report articulated a concept that we dubbed UPSIDE—the Uniform Principle for Sharing Integral Data and Materials Expeditiously.

Scientists publish to disclose their discoveries and get credit for making them. In exchange, authors are expected to demonstrate good behavior in the scientific playground—that is, to share research materials in a timely and useful fashion—because that's what enables their colleagues to validate the research and to use the knowledge as a foundation for new discoveries.

We have long required Howard Hughes Medical Institute investigators to share their published research materials to the extent possible. In 2003, we instituted a formal policy that sets out our expectations for adherence to UPSIDE in the clearest possible terms. The policy, which now extends to scientists at Janelia Farm, reflects the value we place on full participation in the scientific community and the discovery of knowledge.

Sharing may be essential, but ensuring that it occurs is no simple matter when academic and commercial interests collide or when colleagues simply decline to supply research materials because they lack the time, resources, or interest. We recognize that HHMI investigators experience many frustrations in living up to this policy. They tell us that preparing mice and other reagents is time-consuming, that many researchers don't reciprocate, that it can be difficult to gain access to a computer program's source code, and that many barriers limit the sharing of derivatives created from someone else's material. We have a number of initiatives under way aimed at alleviating the burden on HHMI investigators and facilitating sharing.

One example is a collaborative agreement with the Jackson Laboratory that ultimately should streamline the process of sharing mouse strains developed by HHMI scientists with other laboratories. Although we have no ready-made solutions for encouraging greater acceptance of the upside of UPSIDE outside HHMI, we are giving thought to the ways in which intellectual property policies writ large may impede the ability of scientists to share reagents, tools, and data. Stay tuned.

True science—to borrow once again from Max Perutz—also benefits when research articles are freely available after publication. As an extension of our commitment to the free distribution of research materials, the Institute is actively considering a policy that would require our scientists



"I am inspired by Nobelist Max Perutz, who famously remarked, "True science thrives best in glass houses, where everyone can look in."

THOMAS CECH

to publish original research articles only in those journals that make the articles freely available within six months through PubMed Central, the repository maintained by the National Library of Medicine. Toward that end, we have spent the past several months consulting with HHMI investigators, journal publishers and editors, scientific societies, and international colleagues. The conversations have been lively, energetic, and always instructive. Recently, we reached an agreement with Elsevier under which we will pay to have manuscripts by HHMI scientists in Elsevier and Cell Press publications deposited directly into PubMed Central after six months. We expect other agreements to follow.

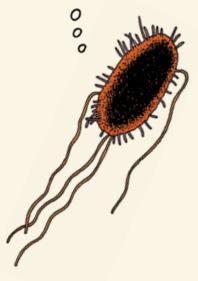
Currently, only the Wellcome Trust in the United Kingdom requires its grantees to publish in journals that make content freely available within six months. Although the National Institutes of Health has established a voluntary policy for its grantees, the number of papers deposited in PubMed Central has fallen short of what many had envisioned. We hope that HHMI's policy will enable public access without sacrificing the important principles that underlie scholarly freedom. This matters not only because our scientists produce more than 1,000 original research articles a year and collaborate with colleagues from around the world but also because our approach may contribute to a new uniform standard for public access to scientific publications. After all, if the scientific community requires UPSIDE for published materials, databases, and software, there is certainly an additional upside to making the publications themselves readily available.

Thomas R Cech

FOR MORE INFORMATION: The NRC report, Sharing Publication-Related Data and Materials: Responsibilities of Authorship in the Life Sciences, can be found at www.nap.edu. For HHMI's policy on sharing research tools, visit www.hhmi.org/about/ogc/policies.html.



Judges Flip for Bacterial Computer



So, you've whipped up a big stack of pancakes, but you burned them on one side—too busy turning out pancakes to notice. Your folly is a pile of flapjacks in random order of size, burnt side up or down. Being a scientific type, you decide to make a cool puzzle out of figuring how to flip them into a neat stack, in order by size, with all the embarrassingly burnt sides down.

This pancake puzzle was actually tackled by a "bacterial computer" engineered by a predominantly student team of gene tinkerers at Davidson College (Davidson, North Carolina). Their synthetic-biology solution to the breakfast blunder won them a sweet stack of awards at the 2006

took second prize in three categories, as well as third prize for Best Conquest of Adversity.

The students' conceptual equivalent of a stack of pancakes was a set of gene segments that they inserted into the DNA of the bacterium Escherichia coli. When those pieces are all correctly oriented in a piece of carrier DNA called a plasmid, the gene works normally, but if any functional piece is inserted backward, the gene sits inactive. Thus, an active gene is the equivalent of a properly ordered stack of burnt-sidedown pancakes.

As an indication that their "pancakes" were all flipped into the right orientation, the students chose a gene that, when activated, confers antibiotic resistance to the E. coli. Therefore, they could treat the cultures with an antibiotic to winnow out those that "failed."

A daunting engineering challenge, however, was how to get the inserted gene segments to flip like pancakes in the first place. The students' solution was to engineer gene-inverting machinery, borrowed from Salmonella bacteria, into E. coli. Wily Salmonella ordinarily uses such "flipping" as part of its infectious process-which

A Brew of Bitter

If you mix lab skills, nostalgia, and a hankering for diversion, what do you get? For HHMI professor Graham F. Hatfull, the answer is The Plowman's Lunch: bread, cheese, and beer.

Hatfull is a professor of biotechnology at the University of Pittsburgh. His day job is studying mycobacteriophages—viruses that infect mycobacteria, like the kind that cause tuberculosis. Outside the lab, he likes to plumb the mysteries of bread, cheese, and beer. Especially beer.

"Maybe this is coincidence," he says, "but the things I really like to eat and drink are, fundamentally, experiments in microbiology."

His quest: "the perfect pint of British bitter." For beer drinkers in this country, a bitter is a pale ale, with what Hatfull calls an "artisanal" touch. He cultivated that touch during a 1980s flirtation with kitchen-sink brewing, while earning his Ph.D. in molecular biology at the University of Edinburgh. By 2006, an established researcher plagued by bureaucratic chores, he thought, "I really need something to take my mind away from the administrative details." So he blew the dust off his British-made equipment, sorted out voltage differences, located a Pittsburgh source of hops and grain, and was soon happily brewing away in his garage. Five gallons at a time, no two batches exactly alike.

With afternoon sunlight glancing off his John Lennon glasses, Hatfull elaborates in his campus office. "Both brewing and what we do in the lab require appreciation and respect for the power of microorganisms. They can make you very ill, but you can view them as essential pieces of civilization." He bakes bread as well another traditional mainstay that uses yeasts. "And I just started getting into cheese, which is microbiology of yet another sort."



Each new brew is a mild surprise, and Hatfull relishes the impact of tiny, random variations in taste, aroma, and color. "I like the sense of being an artisan. It depends, from batch to batch, on you, and on the microorganisms, and what their particular behaviors are.'

At the same time (here he slips into a mock-professorial tone), "There are clearly a lot of scientific elements: You have a hypothesis as to how a particular brew is going to be made. You devise a recipe that you hypothesize will give you that kind of brew. You go in and do the experiment-right?-and at the end, you get to drink the experiment." - George Heidekat

enables it to evade immune detection during an infection.

Inserting the Salmonella machinery into E. coli was no piece of cake, says Karmella Haynes, an HHMI researchteaching fellow in biology and one of the team's faculty leaders. The students had to engineer the inserted gene segments so that they were flanked by short DNA sequences that the geneflipping machinery would target. This allowed them to persuade the Salmonella snipping-and-flipping enzyme, called an invertase, to flip DNA fragments that it does not normally flip.

"What I admire about the group is their gutsiness," says Haynes. "They went ahead and said 'Let's reconstitute this thing in E. coli. Let's strip out the bare minimal components and adapt it so that we can flip any segment of DNA we want." Besides Haynes, two of the students-Sabriya Rosemond from Hampton University (Hampton, Virginia) and Lance Harden from Davidson-were supported by an HHMI undergraduate science education grant to Davidson. Collaborators

included other Davidson students and students from Missouri Western State University (St. Joseph, Missouri).

"Besides learning a good deal about synthetic biology," says Harden, "we also learned a lot about communication between people in different disciplines, in this case, biologists and mathematical modelers. Our weekly lab meetings really served a dual role of educating each other and teaching us technical public speaking."

Haynes is excited about the geneflipping bacteria's potential to help solve huge mathematical problems. "This system has tremendous parallelprocessing capacity. Just one liter of cell culture has about a hundred million bacteria, all working on the problem at the same time."

The students' name for their system? "E.HOP," of course! -Dennis Meredith



"What I admire about this group is their gutsiness. They went ahead and said 'Let's reconstitute this thing in E. coli. Let's strip out the bare minimal components and adapt it so that we can flip any type of DNA we want."

KARMELLA HAYNES



Tumblers and Fantails

As a 10-year-old Japanese-American boy living in Pakistan in the early 1960s, Joseph Takahashi spent a great deal of time on the long flat roof of his parents' Karachi home tending his flocks of pigeons. He raised "tumblers," birds that perform dramatic backward somersaults in the air, and "fantails," with upright tails like turkeys.

"I had 50 pigeons, and it was fascinating that they could fly free but stayed 'home,'" says Takahashi. "I got firsthand experience with genetics by breeding the pigeons, and I learned much about their courtship, maternal behavior, and development."

Now an HHMI investigator and a neuroscientist studying circadian clocks at Northwestern University in Evanston, Illinois, Takahashi's memories are filled with interactions with animals large and small. The 55-year-old scientist says, "When I was a kid, I loved nature and animals. It really was the love of animals, how interesting and diverse they are, that first sparked my interest in biology."

Joseph Takahashi was born in 1951 at a U.S. Army hospital in Tokyo to Shigeharu Takahashi, a Japanese-American economist who worked for Gen. Douglas MacArthur on the reconstruction of Japan after World War II, and Hiroko Hara, an Englishspeaking native Japanese from an aristocratic family.

Soon after his father was discharged from the army, he moved the family to Burma (now called Myanmar), where Takahashi remembers being surrounded by a collection of pets, including a dog (Lhasa Apso), cats, rabbits, ducks, and fish. He remembers regular fishing trips with his father. "We went on field trips to the Irrawaddy River. You'd see all these really strange fish. There was one with a snakelike head, a really big mouth, and a round tail with an eyespot on it." And he fondly recalls riding on elephants.

When his family moved on to Pakistan, in addition to his pigeons,



Takahashi focused on the marine life along the Arabian Sea beaches. "Pakistan had beautiful coastline beaches. I was fascinated with the crabs that lived on the rocks and the unusual fish in the tide pools." There, he rode camels.

When the family moved back to the United States, Takahashi attended junior high and high school in the Maryland suburbs. While he had to leave his pigeons behind in the care of friends, he managed to maintain his interest in exotic animals, raising tropical fish, mainly from the Amazon, and even selling some to pet stores.

At Swarthmore College he majored in biology and got an early look into his future: "I did a senior research thesis on circadian rhythms in electric fish," he says.

Years later, Takahashi is still studying circadian cycles, uncovering genes—in golden hamsters and mice—that act as clocks to control the beat of life. They regulate energy use, metabolism of drugs and food, cholesterol synthesis, breakdown of fatty acids, and other essential functions.

Takahashi and his wife Barbara have two children—Erika, 15, and Matthew, 12. Both share their father's interest in animals. The result is a household menagerie lacking pigeons, but including a golden retriever, gerbils, mice, degus (small rodents native to Chile), Syrian hamsters, Roborovski dwarf hamsters, a corn snake, and a ball python. —Howard Wolinsky



"When I was a kid, I loved nature and animals. It really was the love of animals, how interesting and diverse they are, that first sparked my interest in biology.

JOSEPH TAKAHASHI



- New research findings may ultimately broaden the beneficial uses of botulinum toxin and help protect people from its threat as an instrument of terrorism.
- Adult skin stem cells can be used to produce embryonic stem cells, and thus any other tissue of the body.
- Big Lessons from Small Brains If a mouse brain can self-repair under certain conditions, can a new stem-cell approach for diseases such as Alzheimer's be far behind?

When spring comes around, everything seems new again. HHMI scientists are encouraging spring-like regeneration with adult stem cells from the brain and the skin. In mice lacking two crucial genes, stem cells in the brain repaired what was thought to be irreparable damage. The mice scampered like healthy youngsters. The restorative potential of these stem cells is now being tested in a mouse model of brain injury. Even more dramatic, skin stem cells made possible the first successful cloning of healthy mice from adult stem cells. Possibilities bloom like a field of daffodils.

Toward a Kinder, Gentler Toxin

New research findings may ultimately broaden the beneficial uses of botulinum toxin and help protect people from its threat as an instrument of terrorism.

THE POISON PRODUCED BY CLOSTRIDIUM BOTULINUM HAS UNDERGONE A reputation makeover—from feared to favored. In the 1950s, foodborne botulism killed one in four of its victims; half a century later, more than 3 million Americans paid for commercial Botox injections to smooth their wrinkles and frown lines. ¶ Botulinum could have far greater impacts at both ends of this spectrum.



"These are among the most potent toxins on earth."
Once we've figured out how they do what they have evolved to do, we can begin working on getting them to do what we want them to do.

EDWIN CHAPMAN

Its potential as a vehicle for innovative medical therapies, or as a devastating weapon of mass destruction, imparts a special urgency to the work of two HHMI scientists.

HHMI investigator Edwin R. Chapman, a physiology professor at the University of Wisconsin–Madison, and biophysicist Axel T. Brunger, an HHMI investigator at Stanford University, are broadly interested in neurotransmission—the passage of signals from one nerve cell to another. Both have been looking specifically at how botulinum neurotoxins (BoNTs) impair the release of chemical neurotransmitters at junctions between nerves and muscles, resulting in paralysis that ranges from therapeutic to lethal.

"These are among the most potent toxins on earth," says Chapman. "Once we've figured out how they do what they have evolved to do, we can begin working on getting them to do what we want them to do." Applications might include antitoxins that combat botulism poisoning, vaccines that prevent it, and a range of disease therapies derived from a better understanding of botulinum's efficiency in targeting and shutting down neurons.

The latest findings by Chapman and Brunger build on earlier research indicating that BoNTs attach to their target neurons in a high-affinity bind involving proteins and gangliosides (sugar-containing lipids). In 2003, Chapman's group singled out a protein called synaptotagmin II as a cell entry mediator for BoNT/B, one of the seven types of BoNT. Brunger, in 2004, showed how BoNT/A recognizes and ensnares its target protein on the nerve cell; in 2006, Chapman's group published its discovery of the protein receptor for BoNT/A.

This past December, Brunger and Chapman both presented crystal structures of BoNT/B binding in papers published simultaneously in *Nature*. The groups

The Good, the Bad, and the Ugly

AS THE FIRST BIOLOGICAL TOXIN approved for the treatment of human disease, botulinum has already addressed an impressive array of conditions. It is licensed as a therapy for involuntary neck-muscle spasms and eyelid contractions, crossed eyes, and abnormally heavy perspiration. Experimental uses—some with promising results—include treatment of migraine headaches, chronic low back pain, stroke, and cerebral palsy. National Public Radio talk show host Diane Rehm has spoken extensively about the botulinum treatment she receives for spasmodic dysphonia, a larynx-muscle disorder that nearly ended her career. >> MEANWHILE, HISTORY SUGGESTS that the potential use of botulinum toxin as a biological weapon should be a continuing concern. The Journal of the American Medical Association published a report months before the 9/11 attacks that summarized the threat in a short history—from Japan's testing of botulinum toxins on prisoners in Manchuria in the 1930s to Iraq's 1991 revelation to United Nations inspectors that it had created enough botulinum to kill the world's population three times over. —T.T.

Photo: Stephen Gladfelter, Stanford School of Medicine Visual Arts Services Illustration: Julia Breckenreid

used different approaches to crystallize the complex between BoNT/B and synaptotagmin II. Brunger's group collaborated with researchers from Germany's Medizinische Hochschule, Hannover (Hannover Medical School); Chapman worked with Ray Stevens of The Scripps Research Institute.

With resulting crystal structures that were very similar, both teams found that synaptotagmin II forms a short helix that binds to a water-repellent groove within BoNT/B. And both found that just a slight change, or mutation, of the synaptotagmin receptor disrupts the binding.

Brunger's team altered the protein by single amino acids, which they selected based on their crystal structure, and then tested the effect on the nerve that causes the diaphragm to contract in mice. "We found that just single mutations can lower the toxicity of BoNT/B a thousand-fold," he says. Their work suggests that a small-molecule inhibitor could be designed to interfere with the binding of botulinum toxin and avert lethal paralysis of the diaphragm.

Both researchers are energized by the broader prospects of the research. Chapman's inspiration is to see the creation of a mutant toxin that would not affect regular cells but would bind to an engineered mutant receptor for targeted use in the body. "By persuading the toxins to act only on cells that have been sensitized to them, we hope to further harness their usefulness as medicines and as research tools," he says.

Meanwhile, given the threat posed by botulinum as a biological weapon, U.S. military and security officials are very interested in the development of inhibitors or vaccines. The current state of the art is limited to two problematic options: an equine antitoxin that

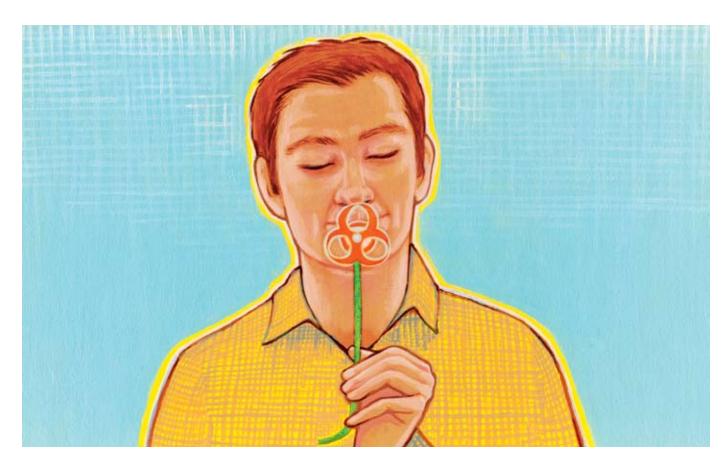


"We found that just single mutations can lower the toxicity of BoNT/B a thousand-fold.

AXEL BRUNGER

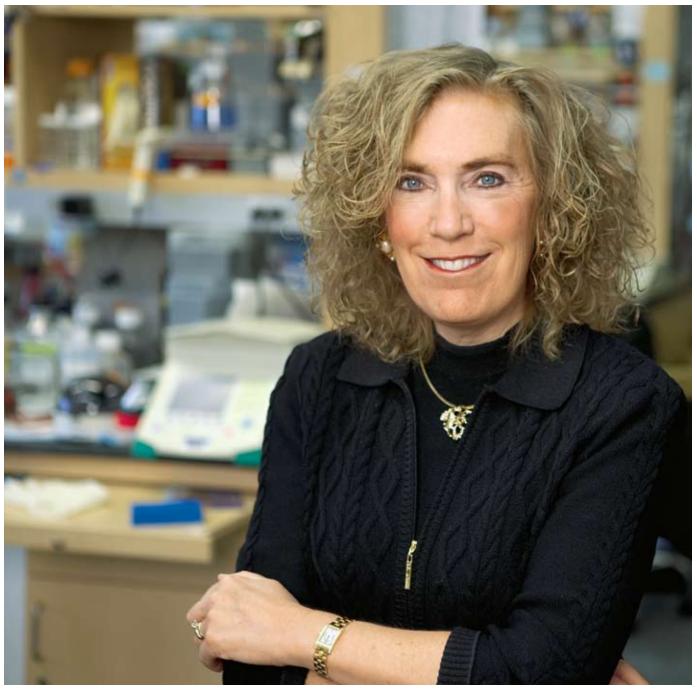
carries a significant risk of adverse reaction in humans, and an investigational detoxified botulism toxin that prevents botulism poisoning but also renders Botox and other botulinum treatments ineffective.

■ -TRACIE THOMPSON



More than Skin Deep

Adult skin stem cells can be used to produce embryonic stem cells, and thus any other tissue of the body.



Elaine Fuchs explores the mechanisms governing skin stem cells and their remarkable ability to both self-renew and to commit to a particular tissue, such as sebaceous glands. She turned that journey into the first mouse successfully cloned from adult skin stem cells.

ELAINE FUCHS USED TO DO CROSSWORD PUZZLES AS A DIVERSION FROM HER

undergraduate studies. With crosswords, every solved clue creates new hints to help solve neighboring clues. Fuchs, an HHMI investigator at The Rockefeller University, has followed a similar approach throughout her professional life. By honing each experimental finding into a new set of tools, she has probed deeper into the question that first piqued her curiosity three decades ago: How does mammalian skin grow and produce complex tissues such as hair follicles and sebaceous glands?

Fuchs' recent work focuses on the stem cells, sprinkled throughout adult skin, from which all new skin tissues arise, and her latest findings are considerably more than skin deep. With a technique known as "nuclear transfer," she and Rockefeller colleague Peter Mombaerts have demonstrated that adult skin stem cells can be used to produce a complete cloned organism.

Early in her career, Fuchs set out to understand how cell growth and differentiation influence human disease. Using cultured cells as her experimental model, she learned all she could about key skin proteins, their genes, and the developmental pathways they control. "I felt that if you want to understand the basis of human diseases, you need to understand what's normal before you can attempt to understand what's abnormal." Shifting between cultured cells and transgenic mice as model systems, Fuchs' team discovered the genetic bases of two key classes of skin blistering diseases, epidermolysis bullosa simplex and epidermolytic hyperkeratosis, and their various subtypes. Fuchs extended this work to elucidate the gene responsible for a related muscle degenerative disorder and set the paradigm for more than a dozen disorders involving a cytoskeletal structure called the intermediate filament.

Three years ago, researchers in Fuchs' lab learned how to fluorescently mark stem cells in skin, a technique she says "helps us monitor different types of stem cells, including those of skin, within the living mouse." The researchers purified the glowing cells and used gene-chip technology to determine their

gene-expression profiles. After identifying genes preferentially expressed in skin stem cells, they turned to mouse genetics to reveal some of the genes' functions. In a series of three papers published last year, Fuchs' team reported on three different transcription factors that they learned have profound roles in the respective differentiation of stem cells into hair follicles, sebaceous glands, or epidermis. The findings, she says, revealed that the developmental pathways adult skin stem cells use to build tissues are strikingly similar to those used by embryonic skin stem cells.

That realization led Fuchs and Mombaerts to wonder whether the skin stem cells they studied could be reprogrammed to generate other tissues. In the February 20, 2007, issue of the Proceedings of the National Academy of Sciences, the scientists reported the first successful cloning of healthy mice from adult stem cells. They achieved that goal by using the technique of nuclear transfer: replacing the nucleus of an unfertilized oocyte with the nucleus of an adult skin stem cell (see "A Visual Primer on Cloning," page 56). After transfer to a mouse's uterus, such hybrid cells were capable of developing into healthy adult

mice, showing that the adult skin stem-cell nuclei could be reprogrammed to produce all tissues in the adult mouse.

Mouse cloning from other somatic stem cells has been attempted before, but the few cloned mice that resulted were not normal and almost always died soon after birth. Fuchs' and Mombaerts' cloning experiments had success rates as high as 5.4 percent, and half of their cloned mice lived out normal life spans.

Instead of introducing a mouse hybrid embryo into a mother to produce a cloned offspring, Fuchs points out, the embryo could be grown in a culture dish with the goal of producing embryonic stem cells. If scientists are able to adapt this strategy to human skin stem cells, she says, this technology might prove to be clinically important in the future. "You might then be able to tailor-make embryonic stem cells to a particular patient and thereby avoid rejection by the immune system," she says. "Additionally, you might be able to study a patient's neurodegenerative disease by creating neurons from the embryonic stem cells generated from a skin biopsy."

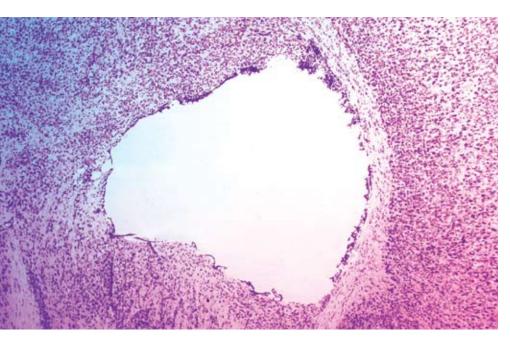
Does Fuchs still do crossword puzzles as a diversion? She says they no longer interest her. "What I used to like about crossword puzzles is that you knew when you had solved the problem. In biology, you can never solve the problem. But that's what I now find fascinating. With the results of each new experiment comes the next question to address." ■ - PAUL MUHLRAD

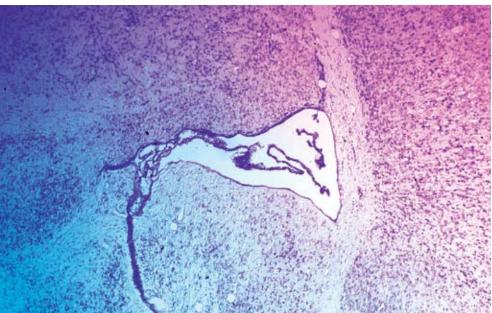
"I felt that if you want to understand the basis of human diseases, you need to understand what's normal before you can attempt to understand what's abnormal.

ELAINE FUCHS

Big Lessons from Small Brains

If a mouse brain can self-repair under certain conditions, can a new stem-cell approach for diseases such as Alzheimer's be far behind?





Top: Stained slice from the brain of a 2-week-old mutant mouse showing a dramatically enlarged lateral ventricle, due to deletions of Numb and Numblike. **Bottom:** Another mutant mouse, 6 weeks old, reveals substantial self-repair of the lateral ventricle, which is now close to normal size.

black mouse pup, No. 4302, scurried around its cage. The mouse and its siblings were born with an abnormally large cavity in the brain as a result of a genetic experiment in the joint neuroscience laboratory of Yuh Nung Jan and Lily Y. Jan.

Postdoctoral researcher Chay Kuo had low expectations for the animals' survival, but when he noticed that 4302 was still alive at 4 weeks of age, he investigated further. Kuo made the startling discovery that the neural damage had healed, implying that "the brain has an innate ability to repair that defect," he says.

More specifically, with the help of their collaborators, Kuo and the Jans, both HHMI investigators at the University of California, San Francisco, found that adult stem cells in the brain had responded to the damage by helping to regenerate much of the missing tissue. This finding raises the hope that, if a similar healing mechanism exists in humans, physicians may one day be able to rev it up to treat people with brain disorders such as head trauma, stroke, and neurodegenerative diseases.

The research team's results, reported in the December 15, 2006, issue of *Cell*, are rooted in years of research on the fruit fly, beginning in 1989 when the Jan lab identified a strain of flies without sensory neurons. These insects lack a gene, called *Numb*, that instructs a progenitor cell to divide and produce a variety of specialized sensory cells such as a neuron and a body-hair cell.

In recent years, the Jan group decided to see whether Numb also plays a role in the development of the mammalian brain, particularly in a special niche known to house neural progenitors-stem cellsduring embryo growth, after birth, and even into adulthood. This stem cell niche borders a fluid-filled gap called the lateral ventricle and matures into the subventricular zone (SVZ). The biologists identified two equivalent genes, Numb and Numblike, in mice, and showed in 2002 and 2003 that selectively deleting, or "knocking out," the pair from the stem cell niche during embryo development caused "a very messed up" brain cortex, says Yuh Nung Jan. Mouse embryos with the mutation had lateral ventricles that were larger than normal.

Kuo joined the Jan lab in the fall of 2002. A newly minted M.D.-Ph.D. from the University of Chicago, he was eager to explore how the brain responds to changes from injury or disease. He particularly wanted to see whether turning off *Numb* and *Numblike* after birth—after the mouse brain has fully formed—might affect subsequent production of neural stem cells. Kuo's work was largely funded with an HHMI postdoctoral fellowship, along with a grant from the California Institute for Regenerative Medicine.

He set out to create a strain of mice in which he could control *when* the genes were inactivated in the SVZ's stem cells. After 3 years' work, Kuo bred the colony that made possible the experiments that led to the brain-repair discovery.

Sitting at his office computer, Yuh Nung Jan pulls up slides of magnified purple-stained slices of mouse brain from Kuo's mutants. One image, from a 2-week-old pup, shows a triangular hole—a grossly enlarged lateral ventricle. But in another slide, from

a 6-week-old, the gap has shrunk to near normal. Moreover, these mutants, which start out smaller than control mice, catch up in growth and seem to be just fine.

Numb and Numblike do more than control neural stem-cell specialization, Jan says. The mouse analyses indicate that these genes also act to maintain junctions between epithelial cells that line the ventricle wall. In mutants without the genes, he says, "the wall sort of disintegrates."

Then, because some SVZ stem cells escape the gene knockout treatment, says Kuo, those cells are able to trigger the

rebuilding of the wall—although it is not the same as the original—and save the animals.

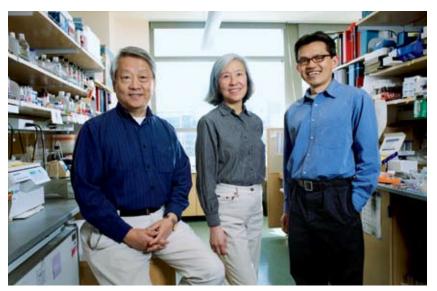
The investigators are now exploring the cellular underpinnings of the lateral-ventricle repair; they are also studying the same stem cells in a mouse model of brain injury. Their aim is to provide an alternative to the scientific community's current attempts to coax blank-slate embryonic stem cells in the Petri dish to grow into neurons for treatment of conditions like Alzheimer's disease.

The Jan lab's work suggests a more direct route: If scientists understood the mechanisms that prompt the body's existing stem cells to regenerate specific tissue, they might be able to design drugs that enhance that process. "We may be able to coach these cells to do a better job of repairing," says Kuo.

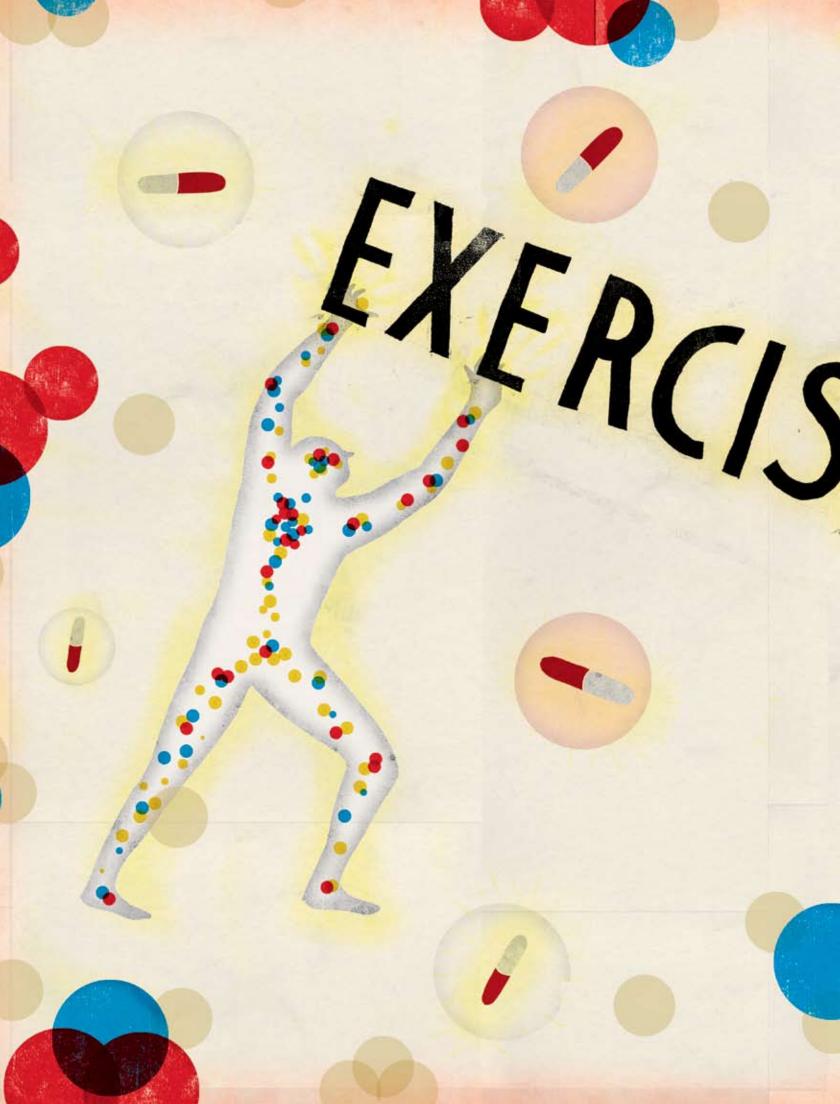
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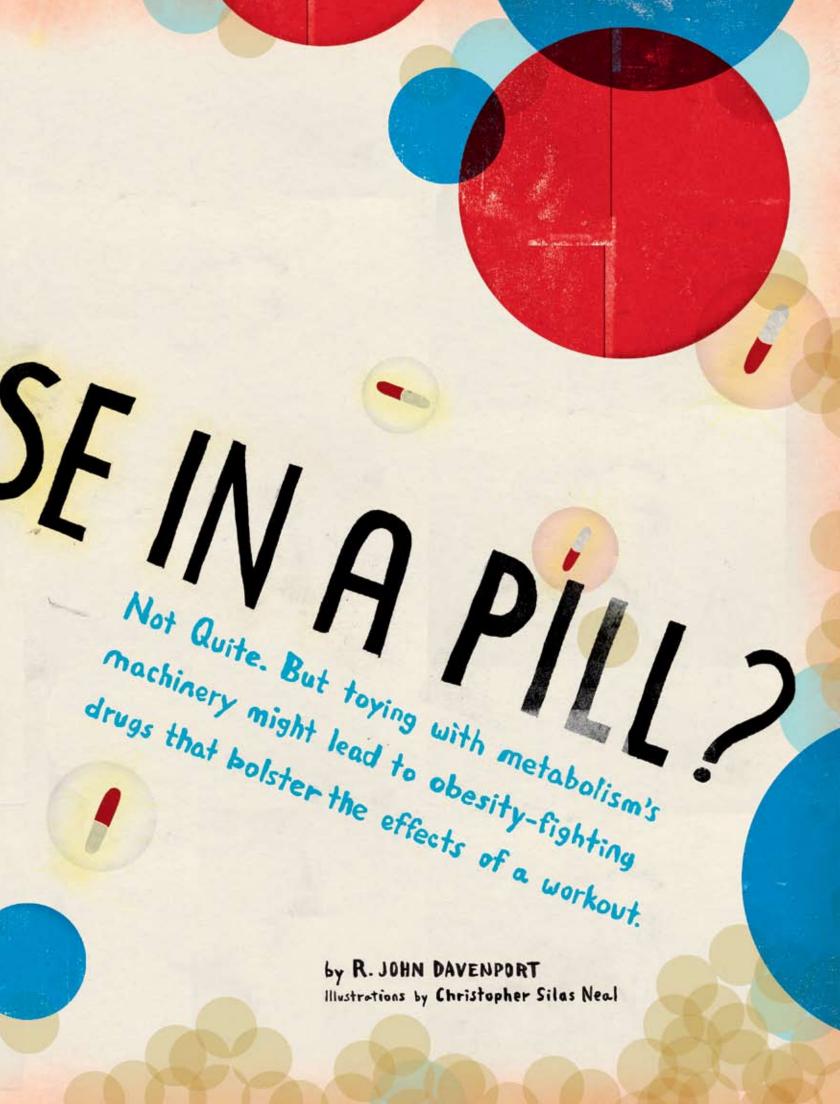
"We may be able to coach [these cells] to do a better job of repairing.

CHAY KUO



Yuh Nung Jan, Lily Jan, and postdoc Chay Kuo hope that a tissue repair mechanism they found in mice exists in humans.





In today's typical family, the whirl of work, school, extracurricular activities, and driving, driving, driving leaves little time for sitting down to a healthy meal—and even less time for serious exercise. It's no wonder that obesity and diabetes have reached epidemic proportions.

IN RESPONSE, SCIENTISTS ARE DELVING into the genes and proteins that control the flow of energy in our bodies, and they're making surprising connections to exercise. Their findings could lead to drugs that fight diabetes and obesity by mimicking a vigorous workout.

Just as the government stockpiles and releases gasoline reserves according to demand, our bodies store and mobilize energy to meet our needs—making it available to muscles when we're active and hoarding it when food is scarce. Normally, we control metabolism exquisitely, maintaining a constant body weight even as our pace of life ebbs and flows. But when we eat far more than we burn, obesity results.

Weight-loss strategies typically focus on reducing the number of calories a person consumes. But this strategy doesn't work for most people, says Ronald M. Evans, an HHMI investigator at the Salk Institute for Biological Studies in La Jolla, California. "Few people can make a lifestyle change and eat less," he says.

In 2004, Evans announced he had engineered, by genetically altering the animal's muscle, a "marathon mouse" that, with no prior training, could run longer than the average mouse. Now, he is trying to create superfit mice by using drugs rather than genetic manipulation—a more practical real-world treatment. One such promising drug is already being tested in the hopes it might speed people's efforts to get in shape and help steady a fluctuating metabolism that can lead to diabetes.

Slow Twitch or Fast Twitch?

WHILE GENETIC ENGINEERING "PREPROGRAMS" the young muscle of his marathon mouse, Evans says, a drug faces the more daunting challenge of "reprogramming" normal adult muscle. To begin to tackle this problem, he decided to work with exploratory drugs under development by the pharmaceutical industry. Previously, Evans showed that a new class of experimental drugs can improve the ability of mice to burn fat. He reasoned that one way to improve athletic performance might be by redirecting a similar set of molecular circuits to maximize fuel consumption in muscle.

For years, Evans and his colleagues have focused on a team of proteins, known as PPARs, that call the shots in metabolism; they direct groups of genes involved in burning and storing energy. PPARgamma, for instance, prods fat cells to grab and store fat from the blood, whereas PPARdelta stokes muscles to burn fat. "One is like charging a battery and the other is like freeing up all that stored energy," says Evans.

POTENTIAL FOR ABUSE

Drugs that enhance exercise could be a boon for fighting obesity and diabetes, but they could also give athletes an unfair advantage over their competition. Like some existing doping practices—such as injecting red blood cells and taking erythropoietin (EPO), both of which increase the oxygen-carrying capacity of the blood—a PPARdelta stimulator could help athletes run, ski, or pedal farther by helping them use more oxygen. PPARdelta wouldn't alter the blood composition directly, but it would enable muscles to consume more oxygen.

"There are two concerns," says Evans. "Using the gene as the doping agent and using the drug as the doping agent." Genes injected into the tails of mice can get into cells and become active, suggesting that athletes could use the PPARdelta gene directly. Gene doping isn't widely practiced, but since 2003 the World Anti-Doping Agency (WADA) has included gene doping among its banned substances and practices, and Evans is working with WADA to develop a test for both the PPARdelta drug and the gene. (The International Olympic Committee founded WADA in 1999 to coordinate anti-doping efforts across all sports; many sports federations and national Olympic committees have adopted WADA's anti-doping code.)

Drugs that target PPARdelta aren't commercially available, but several pharmaceutical companies are pursuing such pills for lipid-related diseases. Once on the market, they would undoubtedly hold appeal for reprobate athletes looking for a shortcut to the winner's podium.

Because no one has tested PPARdelta drugs in human performance, Evans isn't sure how they would stack up against other doping methods. But eventually someone will make the comparisons—or even test for synergisms. Says Evans: "Lots of people ask me what would happen if you take this drug with EPO." —R.J.D.

Could toying with these molecules, he wondered, tip the balance of metabolism in favor of burning fat and help people lose weight? Some results produced intriguing hints of success: mice without PPARdelta grew portly when they ate a high-fat diet, whereas mice with boosted PPARdelta activity stayed slim even when they chowed down on fat.

PPARdelta is more prevalent in so-called slow-twitch muscles (the ones that power marathoners) than in fast-twitch muscles (which provide explosive power for sprinters). Slow-twitch muscles devour oxygen—an efficient way to fuel muscles without fatigue—because they are replete with mitochondria, the cellular power plants that burn fat to produce a steady stream of energy for cells. Not surprisingly, obese people tend to carry fewer slow-twitch muscle fibers than normal and are known to fatigue easily.

Evans and his team used a genetic trick to flip the PPARdelta switch to a permanently "on" position by affixing it to another gene-prodding protein; then they bred mice that produced this modified PPARdelta in muscle. As the team reported in October 2004 in *Public Library of Science (PLoS) Biology*, these animals looked like they'd done some serious distance training, even though they weren't on an exercise regime. The mice possessed an abnormally high percentage of slow-twitch fibers; they had more mitochondria and more of a protein that triggers contractions in slow-twitch muscles.

Next, the researchers subjected the animals to a stress test. They put them on a treadmill, gradually cranked up the speed, and timed how long it took the rodents to poop out. Control animals exhausted themselves in about 90 minutes, but the marathon mice with juiced-up PPARdelta scrambled for an extra hour and nearly twice the distance. They showed other signs of exercise benefit as well: they dined on a high-fat diet without gaining nearly as much weight as the control animals did, and they demonstrated increased blood flow. "Exercise causes a whole-body change, increasing metabolism, lowering blood sugar, improving response to insulin, and protecting against weight gain," says Evans. "These animals enjoy all those benefits."

More than One Way to Hustle a Mouse

OTHER FINDINGS SUPPORT the idea that genetic changes can produce high-performance animals. Harvard Medical School's Bruce M. Spiegelman, a member of HHMI's Scientific Review Board who has collaborated with Evans on other projects, generated his own team of endurance athletes as part of his studies of







Studies by RONALD EVANS at the SALK INSTITUTE (top), BRUCE SPIEGELMAN AT HARVARD UNIVERSITY (middle), and GERALD SHULMAN AT YALE UNIVERSITY (bottom) shed light on how muscle and metabolism contribute to fitness.

PGC-lalpha and PGC-lbeta. These so-called coactivator proteins link up with proteins similar to PPARs and help them turn on genes.

The PGC-1s prod cells to make more mitochondria and turn on oxygen-utilizing metabolism. Muscles forced to produce PGC-1alpha turn into slow-twitch muscles, Spiegelman's team found. They also found that turning on PGC-1beta in muscles alters muscle complement—but in a different way. Animals with PGC-1beta harbored more of an unusual, in-between muscle type: fast-twitch but, like slow-twitch, with lots of mitochondria and active oxidative metabolism.

Because these animals had a greater capacity to burn oxygen in their muscles, Spiegelman wondered if they would perform better on a treadmill. They did: PGC-1beta mice outran normal animals by 25 percent. It's not clear yet which mice to bet on—Spiegelman's rodents didn't run as long as Evans's PPARdelta mice, but Spiegelman's mice ran faster than those in Evans's experiments.

Spiegelman is investigating whether boosting PGC-1 pathways helps fight conditions in which people lose muscle, such as muscular dystrophy and muscle wasting. In addition, PGC-1s might protect against diabetes.

No Free Ride

EVANS'S GROUP HAS DELVED into a more practical way of toying with PPARdelta. In earlier studies, the animals' muscles luxuriated in activated PPARdelta their whole lives because they had been genetically altered from birth. Could the same feat be reproduced in normal mice not carrying the long-distance-running gene? Would tinkering with PPARdelta in adulthood boost performance in the absence of exercise? Evans and his team have probed these questions in new work.

Instead of altering the genome of mice, they gave the mice a drug that switches on PPARdelta. (The drug is currently being tested as a cholesterol-lowering drug in human studies.) Unexpectedly, when the researchers put the animals on the treadmill after a steady diet of the PPARdelta-activating drug, they ran no farther than normal mice. "By itself, in an adult it's not an exercise pill," concludes Evans. "Obviously, changing adult muscle with a drug is a very different undertaking than creating a permanent change in its genes."

Still, Evans remains hopeful. To better understand why the pill didn't work on its own, he and his team determined which genes cranked up in animals that took the drug and in animals that exercised. While half the genes overlapped, exercise triggered a set of genes that the pill did not. Evans thinks that, even

"You can't get away with doing nothing. Our idea is that the pill could make exercise more beneficial by revving up metabolism."

- RONALD EVANS

though the drug apparently missed some key elements along the way, the pill clearly shows promise.

Given the gene overlap, Evans now wonders whether the pill might *augment* exercise, if not replace it. To address this question, he and his colleagues are putting two groups of mouse runners in a head-to-head training program. One group will run several days a week at a steady but not all-out effort—the equivalent of a brisk middistance run. The other group will get the same training but will also receive the PPARdelta pill. "With the exact same training, we hope the mice with the drug will run longer," says Evans. Indeed, preliminary studies look very promising.

Even if it works, the pill shouldn't put any gyms out of business. "You can't get away with doing nothing," says Evans. "Our idea is that the pill could make exercise more beneficial by revving up metabolism." It might also give overweight people a much needed endurance boost to get through those painful first workouts.

By contrast, "a lot of the drugs being developed try to alter appetite, but it is very difficult to change appetite," Evans adds. Plus a side effect of changing appetite can sabotage the weightloss strategy. "Your metabolism slows down during a diet, which makes it even harder to lose weight and easier to gain weight." A PPARdelta drug "does not require the willful reduction in eating," he points out, although exercise is still a must.

Fighting Diabetes

MAKING EXERCISE EASIER might do more than just slim corpulent bodies. Faulty fat-burning pathways portend diabetes, says HHMI investigator Gerald I. Shulman at Yale University, so activating those circuits could stave off the metabolic disease. He has studied sedentary people in their 20s whose parents have diabetes. The young people aren't yet diabetic, but they're already showing insulin resistance despite having a relatively normal body mass index, and Shulman wants to understand why. His team used nuclear magnetic resonance spectroscopy to noninvasively probe the molecular basis of insulin resistance—the first sign of diabetes. They found that the muscle cells of young people with insulin resistance accumulate lipids, which in turn dampen insulin's signal, preventing cells from taking up glucose.

People with insulin resistance have 30 percent fewer mitochondria than normal, and 30 percent less capacity to metabolize lipids. They hang on to energy, says Shulman, which is useful when food is scarce but deadly in modern societies where food is abundant. Accruing lipids might prime young people for diabetes later on.

Shulman aims to prevent this fate, and exercise can help. Vigorous activity activates fatty acid oxidation in mitochondria, restores the insulin response, and boosts numbers of mitochondria. But as much as doctors prescribe physical activity, only a small percentage of patients comply, says Shulman. "If we know mechanistically what's causing diabetes, we can come up with novel agents that mimic exercise and reduce diabetes and even obesity." He's focused on altering specific biochemical pathways to prevent them from making nefarious lipids such as diacylglycerol, which Shulman posits is the main trigger of insulin resistance in liver and muscle cells.

Drugs that activate PPARdelta might help, too. Evans's group reported in the February 28, 2006, issue of the *Proceedings of the National Academy of Sciences* that fat-fed animals treated with the PPARdelta drug controlled their blood sugar better than untreated animals. Evans is now working with Salk colleague and HHMI investigator Joseph P. Noel to capture three-dimensional pictures of PPARdelta and its partner proteins to devise new and improved PPARdelta drugs. The drug they've been using is a useful lab tool, but Evans sees room for improvement. He and Noel are aiming for second-generation compounds that might, for instance, be more easily absorbed and safer or that might target specific tissues: for instance, liver for metabolic diseases in the liver, muscle for endurance, and fat for weight loss.

Such new and improved drugs won't likely permit would-be couch potatoes to avoid exercise altogether, but they might someday make people's workouts easier or more effective.

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memories are made likothic

By Tom Siegfried Photograph by Fredrik Brodén

Researchers

believe they are deciphering some of the mysteries of sleep, particularly its role in forging new memories.

Perhaps, \

as Homer wrote in The Iliad, sleep is "the twin of death." But to many modern neurobiologists, sleep is more like the mother of memory.

Sleep provides downtime for processing the previous day's events. Free from the rush of messages bombarding the waking senses, the brain can converse with itself. Just as your computer warns you to close all running programs before installing a new one, the brain closes your eyes each night to install memories from the day before, numerous researchers believe.

In fact, its role in making memories may explain why sleep is so popular—a necessity really—throughout the animal kingdom. Nearly all creatures great and small sleep to some extent, suggesting that evolution found it valuable for survival—despite the apparent risk of spending so much time in a defenseless and vulnerable condition.

But that doesn't mean memory was sleep's original purpose, says HHMI investigator Terrence J. Sejnowski.

"Asking what sleep is for is a little bit like asking what blood is for," he says. "Maybe blood originally was there to get oxygen to different parts of the body, but once you have this big conduit running through your body you can put all kinds of things in it." From delivering drugs to disposing of waste, blood performs dozens of valuable tasks.

"Same thing with sleep," Sejnowski says. "It may be that it started out as some sort of way to recharge your energy supplies." But during the time that nerve cells don't have to worry about their day job, they can engage in other interesting biochemistry, free from the interference of wakeful activity.

Pursuing the secrets of that nighttime biochemistry has led Sejnowski and other

scientists to a new and deeper understanding of sleep, which ultimately could benefit the many victims of sleep-related disorders.

A New View of Sleep

More than 50 million Americans suffer from conditions ranging from insomnia to restless legs syndrome to narcolepsy. In some people, sleep apnea interrupts breathing and deprives the body of oxygen, fueling metabolic problems that contribute to obesity and diabetes.

"That translates into an enormous impact on quality of life," Sejnowski says.

Work in his lab, at the Salk Institute for Biological Studies in La Jolla, California, has produced a computer-based system for analyzing sleeptime electrical activity in the cerebral cortex, the brain's wrinkled outer layer. That activity is recorded via a single pair of electrodes attached to the scalp to produce electroencephalogram (EEG) readouts.

Similar analyses for assessing sleep problems are performed at sleep clinics, where patients snooze while wearing a cap covered by a dozen or more electrodes. Human experts then study the EEG graphs to identify how long the sleeper has spent in sleep's various stages. But these analysts typically take hours or days to decipher the EEG recordings. By contrast, Sejnowski's computer system can report on sleep state in real time, with an accuracy rate that is as good as or better than the humans' analyses. (Sejnowski is on the scientific advisory board of a new company, NeuroVigil, that

will use the system to offer sleep EEG analysis over the Internet to the nation's 2,000 or so sleep clinics.)

Furthermore, the computer can tease out other details from the data, identifying previously undetected features in the electrical activity underlying sleep's stages. "Some of the work we're doing in my lab has actually overturned a lot of the beliefs in the textbooks about the different sleep states," Sejnowski says.

For one thing, his computer analysis shows that the rapid eye movement (or REM) sleep associated with dreaming does not, in fact, show basically the same electrical activity as an awake brain, as textbooks assert.

Besides REM, sleepers cycle through several other phases, including an intermediate state of sleep (with a mix of slow and fast electrical activity) and deeper, "slow-wave" sleep. Some studies have identified slow-wave sleep as important for firming up memories, but Sejnowski's work suggests that intermediate sleep may play a more significant role in memory formation. His analyses have detected new patterns of activity within that state.

At times during intermediate sleep, the research indicates, cortex electrical activity rapidly alternates between high frequencies and low frequencies every few seconds. "We think that's going to be the best place to look for the biochemical changes that are occurring [during sleep]. In some cases you can spend half your sleeping hours in intermediate sleep," says Sejnowski, "and I think that's where the key to understanding the true function of sleep is going to be found."

Intermediate sleep is marked by brief bursts, or "spindles," of electrical signaling produced by the thalamus, an important relay station for transmitting information between the cortex and various other parts of the brain. Those spindles recur every few seconds, setting up synchronized electrical oscillations throughout the cortex. Sejnowski hypothesizes that the spindle activity puts the brain into a state conducive to storing new memories without interference from other activity.

Nighttime Replay

New details about sleep's role in memory also come from HHMI's Janelia Farm Research Campus in Ashburn, Virginia, where Jeffrey C. Magee and his team seek help from rats to decipher sleep's mysterious methods. Magee and collaborators perform experiments impossible in live animals by extracting slices of living neurons from a rat brain and recording their electrical activity.

Memory storage is believed to involve the strengthening of synapses, the junctions connecting neurons. To build stronger synapses, the neuron must be studded with abundant quantities of protein molecules that sense the neural messenger molecule glutamate. When deprived of sleep, the neurons display fewer of those sensor proteins, and the ability to make permanent memories diminishes, Magee's research shows.

"If you don't get enough sleep, you mess up this whole process of keeping the right amounts of membrane proteins at their right locations inside the cell," he says.

Magee and his colleagues study slices of rat neurons taken from the hippocampus, the brain region that plays a prominent role in forming long-term memories. Those neurons retain their connections and signaling patterns, responding to the stimulus of messenger molecules just as neurons in a living animal do. Magee and colleagues have developed techniques to deliver those messenger chemicals to specific neurons, thereby stimulating the slices into states similar to those found in either the awake or sleeping animal. In the "awake" neurons, input from other cells flows in haphazardly, and a neuron fires its electrical signals based on the summed-up influences of all those inputs.

"In the sleep state, we see a very different kind of output pattern," says Magee, who reported on his work in the February 2006 issue of *The Journal of Neuroscience*. The same information is processed, but much more rapidly and precisely. The signaling speed is accelerated to 20 times the original rate. So it seems that during sleep, the cells from the hippocampus may be replaying the day's activity.

"In fact, the networks that are involved in the replay are the exact same sets of cells that actually process that information to begin with," he says.

This work supports the developing view that memory formation depends on cross talk between hippocampus and cortex, where memories are ultimately stored. The hypothesis is that daytime memories held temporarily in the hippocampus are rebroadcast during sleep from the hippo-



Ramped up information processing in the hippocampus during sleep suggests to Jeff Magee that the brain uses this "downtime" to replay the day's events.



There are dozens of different memory systems, says Terry Sejnowski, that use different mechanisms and different parts of the brain.

campus to the cortex, which then replays the signals itself, strengthening the synapses to imprint the new memories. "The hippocampus can learn very, very rapidly, but it doesn't have a very high capacity," says Sejnowski. "The big knowledge storage is in the cortex."

Knowledge in the cortex changes more slowly, though. It has to rehearse many times to learn a new memory. "Through the replaying of the hippocampus, the cortex will gradually figure out which of the new items coming in are the most important ones and how to fit them into existing knowledge," says Sejnowski. "That's the story that's emerging from all the electrical recordings."

Still, many issues about sleep and memory remain to be resolved, such as the relative importance of slow-wave sleep and

WHEN THE CLOCK RUNS FAST

Some of us may decide to live by an "early to bed and early to rise" routine, but certain people-those with a particular genetic mutation—have no choice. Individuals with familial advanced sleep-phase syndrome (FASPS) are the ultimate early birds, awakening in the wee hours of the morning (by 4 a.m. or so), then turning desperately tired just as prime-time TV is about to begin. ¶ FASPS occurs in people with a rare variant in a gene implicated in regulating the body's internal clock. That gene, called human Period 2 (Per2), is one of a small number of genes that influence the length of the circadian rhythm cycle governing sleep. Ordinarily, the body's clock runs on a timetable that nearly matches the 24-hour day, sounding a biochemical alarm in the morning that calls the slumbering brain to action. But a variant in the Per2 gene can shorten and displace the ordinary circadian cycle, causing

those possessing it to wake up extra early, according to HHMI investigator Louis J. Ptáček of the University of California, San Francisco. ¶ Per2's machinations have recently been rendered less mysterious by work in Ptáček's lab, in collaboration with the UCSF lab of Ying-Hui Fu, using mice implanted with human versions of the gene. Their insights are helping to explain the genetics and biochemistry of sleep in normal people as well. Ultimately, the research could lead to new drugs for sleeping disorders or for coping with jet lag and shift work. ¶ In a normal sleep cycle, Per2 codes for a protein that builds up during sleep time until it surpasses a threshold level, thereby triggering biochemical signals to inactivate the gene. The PER2 protein then gradually decomposes until its levels drop so low that the gene is reactivated, restarting the wake-sleep cycle. ¶ A key chemical governing production and destruction of this protein is the enzyme casein kinase I (CKI), which attaches

Asking what sleep is for is a little bit like asking what blood is for. —Terrence Sejnowski

intermediate sleep. And questions linger about which types of memory are actually stored during sleep. Evidence is strong that memory for procedures and skills is improved by sleep, Sejnowski says. But whether factual (declarative) memories are consolidated by sleep as well has been more controversial.

"Memory is not a monolithic single thing," says Sejnowski. "One of the major discoveries we've made is that there are dozens of different memory systems . . . that use different mechanisms and different parts of our brain."

Unquestioned Importance

Other researchers point out that much of this story, while plausible, awaits rigorous confirmation. For one thing, whether the information in the sleeping brain really flows from hippocampus to cortex needs to be established more definitively, says Giulio Tononi, winner of an NIH Director's Pioneer Award in 2005 for his studies of sleep and consciousness.

"I don't suspect that the hippocampus cannot talk back to the cortex, it just needs to be proven better," says Tononi, a neuroscientist at the University of Wisconsin –Madison who is studying other synapse mechanisms during sleep. He suggests that more work is needed to show whether the replay activity is faithful enough to the original input for strengthening long-term memories effectively.

Tononi also notes that some studies find similar replay signaling during quiet wakefulness, suggesting that sleep itself may not really be needed for memory storage. If that is so, the mystery of why evolution has made sleep so ubiquitous resurfaces.

There is no disagreement, though, about sleep's importance and the need to understand it better. This is a message that today's society seems to be neglecting, according to Magee, and we are paying a price in the reduced productivity and degraded learning capacity that come from sleep deprivation.

Sleep is not simply a time for storing memories, he points out. It's also a time for tune-up and repair to keep the brain in peak operating order. "There is a housekeeping function going on," he says. If you don't get enough sleep tonight, it's not just today's memories that will be less likely to be permanently stored. Your brain won't be working so well tomorrow, either.

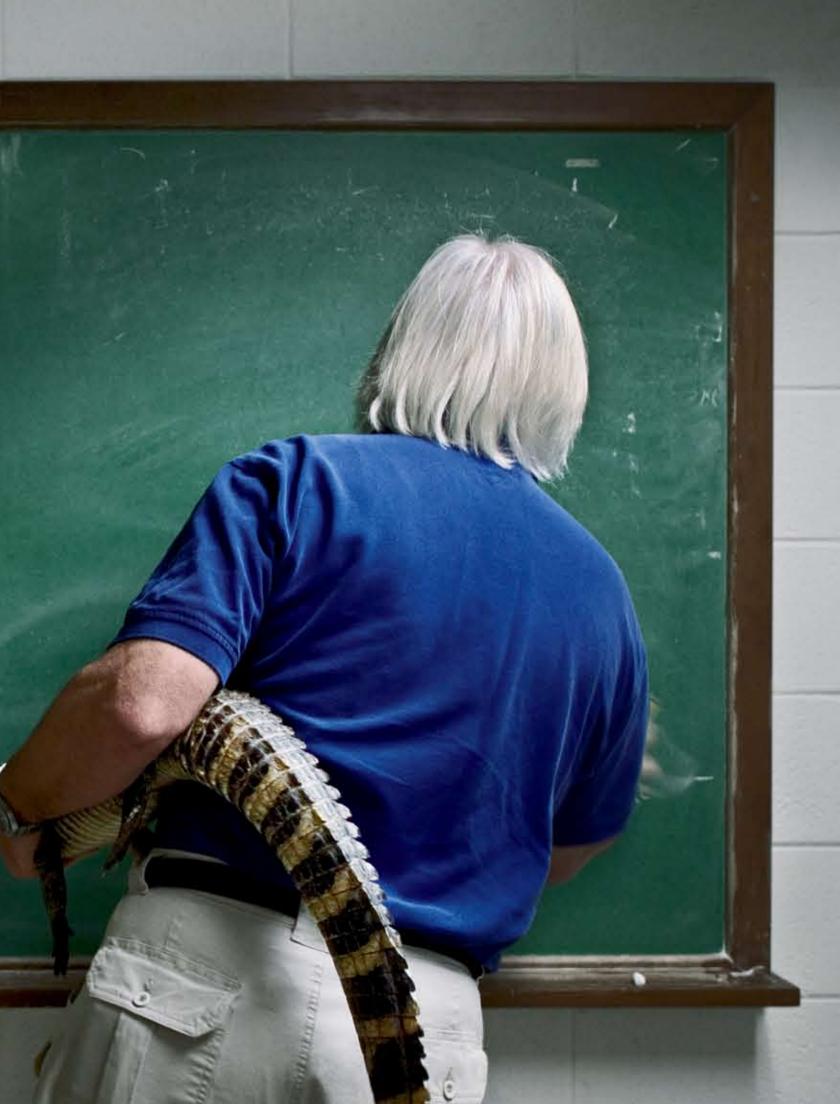
phosphate groups to it. Depending on where the phosphate is attached, the result is either increased production or faster destruction of the protein. "We believe this is a way the clock is really fine-tuning the system," says Ptáček. ¶ CKI cannot enhance PER2 protein production, though, unless a phosphate has already been attached at link 662 in the protein's chain of amino acids. That phosphate is installed with the help of an as-yet-unidentified "priming" enzyme. ¶ In a normal PER2 protein, position 662 is occupied by the amino acid serine, which is happy to accept the phosphate provided by the mystery enzyme. But in people with FASPS, position 662 is occupied by glycine, an amino acid that refuses to have anything to do with phosphate. Thus, the mystery enzyme is powerless to attach the phosphate, which in turn means that CKI can no longer stimulate PER2-protein production. But CKI continues to facilitate protein destruction, the transgenic mouse studies show. Thus, protein levels fall faster,

making the circadian period shorter and causing early awakening, just as in humans with FASPS. ¶ The latest work, published in the January 12, 2007, issue of Cell by Ptáček and Fu with collaborators from China, Singapore, and the University of Utah, has gone a long way toward teasing out the molecular intricacies underlying Per2's function. Now someone needs to identify the mystery priming enzyme. "I think it will be an outstanding candidate for drugs to modulate the circadian period," Ptáček says. ¶ That will be good news to some people with FASPS, at least those bothered by their condition. "I don't call this a disease," he says. "It's a behavioral trait, a behavioral variant. Some people do not like it—they think it's a disease and would do anything possible to fix it if we could do that." Yet others, he says, find early rising an advantage that actually does pave the way to health, wealth, and wisdom. ¶ "Whether it's a good or bad thing," says Ptáček, "really depends on the person's perspective." -T.S.

FOR THE GOOD OF GATORS -AND HUMANKIND

The thrill of the chase and the challenge of the classroom keep alligator expert and HHMI professor Louis Guillette's instincts and insights sharp.

BY JOSEPH KAYS photographs by Minnich Photo



STUDYING ALLIGATORS IS NOT FOR THE FAINT OF HEART.

Even the smallest of these prehistoric reptiles are powerful bundles of muscle and teeth, and catching them involves cruising Florida's mosquito-infested lakes in the middle of the night, ever alert for the critters' 800-pound brethren lurking nearby.

So why has University of Florida (UF) zoologist Louis J. Guillette made hundreds of these expeditions and handled more than half a million alligators, from eggs to adults, over the last two decades?

"You're on an airboat, in a swamp, at night, hunting an alligator," Guillette says. "That's why you go on thrill rides. That's why we watch *Shark Week* on TV."

The adrenaline rush isn't his only motivation, however. Dedicated to the welfare of *Alligator mississippiensis*, Guillette has become the patron saint of alligators, so to speak, working to ensure their reproductive health and preserve their rightful place in the ecology of Florida's waterways. And now he's beginning to extend his studies on the impact of pollutants on alligator reproduction to mammals, whose hormonal systems are remarkably similar to those of reptiles. In the process, he's also introducing a host of students to the rewards of practicing hands-on science.

Through an HHMI professorship awarded in April 2006, Guillette is developing a mentoring program that promotes collaboration among graduate students, undergraduates, and area high schoolers (see sidebar, page 30). And the mentoring isn't limited to the classroom and lab; Guillette regularly takes crews of students on his collecting trips.

Guillette first started plucking alligators out of Florida's lakes in the mid-1980s. State game officials wanted to understand the reptiles' reproduction so they could better manage permits for alligator farmers to harvest eggs and animals, and at the time Guillette was UF's resident expert on alligator reproduction.

Over the next few years, Guillette's team gathered data from lakes all over Florida.

"We started out doing some basic reproductive biology, partly because the alligator farmers wanted data," Guillette says. "As we went along, we realized things didn't add up. It was like we were trying to put a square peg in a round hole, and it just didn't fit."

FAILURE TO THRIVE

This was especially true for Lake Apopka, near Orlando, one of Florida's largest freshwater lakes and one of its most polluted. In some years, as few as 5 percent of its alligator eggs hatched, compared with 70 to 80 percent of eggs from a nearby lake. In the lab, half the animals that did hatch died within weeks, a mortality rate many times the norm.

Much of alligator development depends on nest variables such as temperature and moisture. But after Guillette and his team eliminated those variables as sources of the reproductive problems, they refocused on the lake water and soil. The researchers suspected that pollutant toxins, possibly stemming in part from a large pesticide spill at Lake Apopka in 1980, might be affecting the newborn alligators' hormone levels and contributing to their failure to thrive.

When the scientists analyzed blood from young alligators, they found estrogen and testosterone levels that were totally out of balance. "When you see males with hormone levels that look like those of females, that's not normal and that's what we were seeing in Lake Apopka," says Guillette. These imbalances persisted as the alligators matured. Juveniles, male and female, looked like "superfemales," and when they reached adolescence, the males were still demasculinized and the females had become defeminized.

Given the abnormal hormone levels, the researchers needed to look for physical manifestations, such as effects on the animals' genitalia. Sure enough, they found that male alligators in Lake Apopka had penises that were 25 to 30 percent smaller than those of their counterparts in other lakes.

"Penis measurements have always been a tool; if this one marker is disrupted, I'm assuming others are disrupted," he says.

Alligators are a charismatic species that people care about. Plus, if you know that alligators are having problems in the lake, you can assume that all the other species there, many of which people really don't care about, are also having problems.

-LOUIS GUILLETTE



HORMONAL IMPOSTERS

Although the data kept pointing to hormonal imbalances, Guillette says he didn't put all the pieces together until his "academic grandfather"—zoologist Howard Bern of the University of California, Berkeley—visited his lab and made a presentation about the impact of the synthetic estrogen called DES (diethylstilbestrol) on the ovaries of mice and women. "During his talk, a slide came up that showed the pathology of an ovary with multi-oocytic follicles," Guillette says, referring to follicles, or sacs, with more than one egg in them. "When I realized that the alligators I was working on had the same weird follicles, it was an 'Aha!' moment."

As Guillette later said in "Fooling with Nature," a 1998 Frontline documentary, "It was one of these incredible experiences when suddenly everything adds up. I realized, 'I have hormonal abnormalities. I have a contaminated lake. I have a top predator that accumulates contaminants.' It all just kind of came together as a hypothesis."

Once Guillette realized that he might be dealing with endocrine disrupters, he focused his research accordingly. "We had been taught, and had taught our students, that in the endocrine system the receptor was so specific it could be described as a lock, with the hormone being the key," says Guillette. "Now we realize, after an

GIVING STUDENTS RESPONSIBILITY

Lou Guillette vividly remembers the first time his undergraduate mentor gave him the keys to the lab and asked him to prepare some growth medium for an experiment the next day. >> "That was a telling moment in my professional career," says Guillette. "Not only was he trusting me with thousands of dollars of equipment, he was also trusting me to mix this stuff up correctly. Otherwise, the whole experiment would be blown. >> "I can remember working in the lab that night, thinking 'I'm a scientist. This is the real thing.' It was like I'd psychologically jumped some monster hurdle. Not only did I want to do it. I could do it." >> That experience has inspired Guillette to provide as many similar opportunities to UF undergraduates as possible. His teaching mantra is "Scholarship, not studentship," and he practices what he preaches. Over the last decade, more than 150 undergraduates have benefited from Guillette's hands-on, directed-research mentoring. Now, through a \$1 million, four-year grant from HHMI, Guillette has created the Group Advantaged Training of Research, or G.A.T.O.R., program to fine-tune that approach for a larger audience. >> "Everyone has to be a student for a certain period of time, but at some point you have to transition to the pursuit of knowledge yourself," he

says. "The undergraduate students in my laboratory are exposed to our research in a way few students experience. They help capture alligators, turtles, frogs, and fish. In the lab, they assist in all aspects of sample analysis." Guillette manages as many as 15 undergraduates at a time through a system that relies heavily on his graduate students. "If each graduate student is responsible for several undergraduates, I can accommodate a lot more undergraduates in my lab and the graduate students can gain valuable experience in mentoring," Guillette says.

>> Postdoctoral researcher Thea Edwards, who oversees the G.A.T.O.R. program, is clearly proud of the students she mentored while pursuing her Ph.D. with Guillette. "These students were amazing and I would not have been able to complete my research without them," she says. "Of the 20, five went on to graduate school and five to medical or dental school." >> Although he easily delegates authority, Guillette's door is always open. Ed Orlando, now an assistant professor at Florida Atlantic University, says that he and other of Guillette's UF graduate students knew they could call on him any time. "He was available almost seven days a week, 24 hours a day to answer questions and offer advice," says Orlando. "He never said no and I expect that 25 years from

now he will be doing the same." >> One of Guillette's goals with the G.A.T.O.R. program is to make his teaching philosophy and strategy "exportable." >> "Does it work effectively only in my lab under my research conditions, or can other labs in other disciplines run this way also? We want to optimize this mentoring for any given research setting," he says. >> Guillette also puts a high premium on scientific communication, especially with graduate students. "Some of our students have a tough time explaining what they do, even to their parents." >> He has developed a new class, "Communicating Complexity in Science," which focuses on everything from creating effective scientific posters to dealing with the media to making science come alive for high schoolers. During the semester, he brings in prominent scientists, journalists, and policymakers to meet with students. "I think one of the reasons we're having such intense debates in our society about scientific questions like stem cells, global warming, and evolution is that we in the scientific community are expecting somebody else to interpret all of our data." In other words, it's as if the scientistseven though they understand the phenomena best-are unable or unwilling to do the interpreting themselves. -JK

awful lot of science, that yes, the estrogen receptor is exquisitely able to recognize estrogens, but really what it was designed to do was to distinguish between estrogens and androgens, like testosterone. It wasn't necessarily designed to preclude all other keys."

In 1999, Guillette began collaborating with Taisen Iguchi of Japan's Okazaki National Research Institutes to sequence hundreds of alligator genes related to reproduction, particularly those related to estrogen receptors. "This allowed us to start talking about the genetic basis of the alligator, which not only gave us a powerful toolbox for understanding alligators but also for doing comparisons with mice and humans. The genetic mechanisms that turn reproductive development on and off are almost identical whether you're studying a mouse, a human, or an alligator."

The researchers also learned that even trace amounts of hormonal imposters could have an impact. "Hormones work at incredibly small concentrations," says Guillette.

While he is careful not to draw parallels between alligators and humans, Guillette says it would be naïve to dismiss the implications, considering that reproductive hormones in both species are very similar. In fact, the similarities are so great that, in 2006, the National Institute of Environmental Health Sciences (NIEHS) awarded a grant to Guillette to study ovarian development in alligators.

"At NIEHS we are not interested in alligator health, but Lou shows how understanding that can inform studies on animal models and humans," says Jerry Heindel, scientific program administrator for the NIEHS Cellular, Organ and Systems Pathobiology Branch. "That is why we fund him. He sees the big picture and helps people connect the dots."

AN OBJECT LESSON

Although the alligator is important as an animal model for human disease, Guillette is also interested in alligator health per se. And he is committed to protecting the species.

"I want to conserve and preserve these animals and the environment they live in," Guillette says. "Alligators are a charismatic species that people care about. Plus, if you know that alligators are having problems in the lake, you can assume that all the other species there, many of which people really don't care about, are also having problems."

He points out that, because of the alligator's high profile, Florida and the federal government have purchased thousands of acres of farmland around Lake Okeechobee, a massive lake in south-central Florida where Guillette also found alligator reproductive problems, and are restoring it to a wild state. Preserving alligator habitat is also a core goal of the federally funded Everglades restoration project.

Guillette acknowledges that some may wonder why all the effort. "I've heard people say we're up to our armpits in alligators, but what we're really up to our armpits in is people," he says. "It's not that there are so many alligators. It's just that people are pushing them into smaller and smaller spaces."

HELPING HUMAN POPULATIONS

As the father of four grown children, Guillette was always concerned about the implications of endocrine disrupters for children. But as a zoologist he just couldn't envision studying actual human effects by himself. >> In this case, a suitable collaborator was already close at hand. Guillette's wife, Elizabeth, a medical anthropologist at UF, was able to identify a perfect natural laboratory in and around the Yaqui Valley of northwestern Mexico. There she found two groups of people, located about 50 miles apart, who were demographically near-identical except for their exposure to pesticides. >> The Sonoran Mayan people of the valley split philosophi-

cally over the use of pesticides and other modern agricultural techniques during the country's Green Revolution of the 1940s and '50s. Residents who remained in the valley embraced pesticides, herbicides, and other agricultural chemicals, while the other group moved to the foothills and stuck to organic farming. >> Aside from that one difference, says Elizabeth Guillette, "these groups were the same in every respectculturally, genetically, and socioeconomically. They had the same diet, the same child-rearing practices, and the same school system." >> But when she asked children from the two communities to perform simple

play activities, like catching a ball or drawing stick figures, "the kids who had been exposed to pesticides lagged far behind." >> Follow-up studies that Elizabeth Guillette published with her husband and several other collaborators in Environmental Health Perspectives in 2006 showed that daughters born to women who were exposed to pesticides had significantly less mammary tissue than their counterparts in the foothills. >>Lou Guillette says that private agencies have translated the research results into Spanish and have done extensive outreach in the area to encourage residents to limit their exposure to chemicals. -JK

MODERN RELICS

by Lisa Seachrist Chiu

Bits of possibly ancient RNA are turning up in bacteria and other modern organisms. Their capacity to monitor the environment and regulate gene expression makes them a welcome target for new antibiotics that could confuse bacteria into starving to death.

illustration by Christian Northeast



onald R. Breaker is a man comfortably caught between two worlds. His training as both a biologist and a chemist enables him to apply those disciplines to the search for relics of an ancient world within modern organisms.

In this so-called RNA World—where RNA reigned supreme—the molecule known for its role as a messenger and intermediary would have needed to accomplish a much broader array of activities. Breaker has zeroed in on RNA's need to monitor the available nutrients in its environment. Survival for all organisms requires them to conserve nutrients and shut down cellular activities that are not needed—otherwise they starve, says Breaker, an HHMI investigator at Yale University. "To do that," he adds, "RNA would have had to sense its own surroundings."

Research spearheaded by Breaker has opened a window back in time, offering a tantalizing glimpse at just how RNA organisms may have achieved such complex environmental surveillance. He has found sequences of RNA that control gene expression by binding vital nutrients and switching on or off genes involved in producing or transporting those nutrients.

Following a tradition that molecules involving RNA begin with the word ribo—as in ribosome—Breaker dubbed these RNA sequences riboswitches. "The name didn't impress one of the reviewers of our first paper," Breaker laughs. "He

said it sounded like something that came from the back of a cereal box." But the name stuck and these snippets of antiquity have proven useful to scientists exploring evolution.

Breaker, however, is most recently interested in targeting certain riboswitches in the modern world to develop new types of antibiotics against bacterial scourges like salmonella and anthrax.

A Technology That Time Did Not Forget

o hear Breaker tell it, the entire field of riboswitches began with an intellectual exercise. He decided to engineer RNA sensors in the lab to demonstrate that components of the RNA World could monitor RNA's environment. As a chemist, he wanted to understand the chemical limitations of RNA, figuring it must be capable of doing more than simply folding and catalyzing the cleavage reactions that Yale University's Sidney Altman and University of Colorado researcher (and now HHMI president) Thomas R. Cech described in winning the 1989 Nobel Prize in Chemistry.

"I wanted to test the RNA World hypothesis in a small way," Breaker says. "If we had failed to create RNA sensors, that would have struck a significant blow against the RNA World hypothesis."

He built on the work of HHMI investigator Jack W. Szostak, at the Massachusetts General Hospital, and Larry Gold, at the University of Colorado, who independently discovered that short RNAs could form structures capable of binding molecules such as vitamins and amino acids. Szostak dubbed these RNAs "aptamers," and he and others subjected them to evolution in a test tube by selecting only those RNAs that were exceptionally good at binding a target molecule.

Breaker engineered his RNA sensors to include an aptamer that bound a target molecule, like a vitamin or drug, followed by sequences of RNA that folded into a structure capable of cleaving the RNA strand at a specific location. The cleavage structure formed only if the aptamer section bound the target molecule. Once the metabolite was bound, Breaker could watch the RNA cut itself in two: the RNA truly sensed its environment and took action as a result.

"We were engineering riboswitches long before we discovered them in nature," Breaker says. "There was no evidence at the time that these switches were still in existence. But, it was so easy to build them that we thought there was no way that nature had forgotten this technology."

With that thought, Breaker decided to search for ancient RNA switches in modern bacteria.

An Early Glimpse with Riboflavin

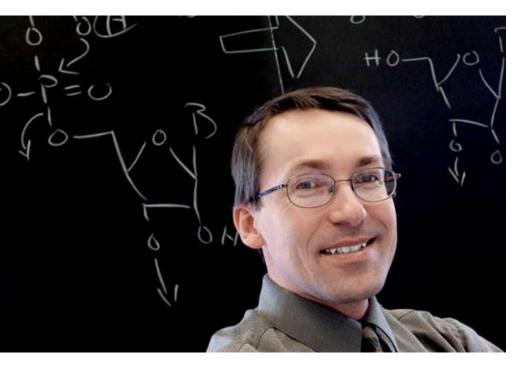
hile Breaker's group was building RNA sensors, Mikhail S. Gelfand, then at the Research Institute of Genetics and Selection of Industrial Microorganisms in Moscow, his student Alexey Vitreschak, and biologist Yuri Kozlov were probing how bacteria regulate production of riboflavin, one of the B vitamins the body uses to metabolize fats, carbohydrates, and proteins.

They knew the vitamin derivative flavin mononucleotide (FMN) stopped expression of certain genes involved in riboflavin biosynthesis. "But, the biologists were saying that there wasn't a protein involved. It was about that same time that people started writing about RNA

messenger RNA (mRNA) called the 5 prime untranslated region (5' UTR). "These very different species had a region of similarity in the 5' UTR that was completely unexpected," Gelfand says.

Their computational work revealed that the 5' UTR of the RNA could fold into a

Back in Connecticut, Breaker began looking for examples of genes that are sensitive to the amount of a vital nutrient, but for which scientists had been unable to find a regulatory protein that orchestrates response to the level of that nutrient. If there was no protein, maybe there was a riboswitch.



Ronald Breaker says riboswitches are strong proof of the RNA World hypothesis—and they make great targets for new antibiotics.

aptamers," says Gelfand, now an HHMI international research scholar at the A.A. Kharkevich Institute for Information Transmission Problems in Moscow.

By examining the genomes of diverse bacterial species, the group found an unusual similarity in a section of the cloverleaf structure that was highly conserved among species. He speculated that this structure bound FMN. What's more, Vitreschak and Gelfand discovered that the RNA could form another structure that would stop the transcription of mRNA dead in its tracks and suggested that the RNA was regulating gene expression.

Normally, when a cell needs to shut down production of a protein from an mRNA, regulatory proteins jump onto the 5' UTR—the real estate on the mRNA in front of the section coding for protein. That gums up the works, stopping the ribosome from making the protein.

To Modern Cells

reaker's biologist side was taking over. "As a biologist, I want to study something that is actually in a cell," Breaker says. "Evolution isn't kind to inefficient molecules, and the biologist in me argued that if RNA was so good at sensing metabolites, there were probably still riboswitches in modern cells." His group was studying a gene whose product helps transport vitamin B12 into the cell. By identifying parts of the mRNA that formed new structures in the presence of B12, Breaker's group discovered a structure that bound a B12 derivative and prevented ribosomes from reading the mRNA.

Nature hadn't forgotten the RNA sensor technology at all, as Breaker and his team detailed in the September 2002 issue of *Chemistry & Biology*. Soon thereafter, Breaker's team documented riboswitches at work in the biosynthesis of riboflavin and another B vitamin, thiamine.

Since their discovery in 2002, dozens of natural riboswitches, which bind vitamin derivatives, amino acids, nucleic acids, and other metabolites, have been discovered. The constant among them is that they consist of an aptamer sequence that senses

NA ON PATROL FOR MAGNESIUM

Eduardo A. Groisman knows the frustration of searching for a protein that isn't there. Ever since he was a postdoctoral fellow, Groisman, an HHMI investigator at Washington University School of Medicine in St. Louis, has been studying how Salmonella typhimurium bacteria regulate magnesium via the PhoP/PhoQ system—a twocomponent regulatory system that controls two of three magnesium-transporter genes. > MAGNESIUM REGULA-TION IS VITAL for cell survival. The metal exists as a positively charged ion in biological systems, where it stabilizes DNA and RNA and is critical to certain enzymatic reactions as well as membrane and ribosome stability. In Salmonella, the PhoQ protein monitors magnesium and responds to changes in concentration by riding herd on the PhoP protein. When magnesium concentrations are low, PhoQ keeps PhoP in a form that turns on expression of the genes encoding magnesium transporters, which pump the metal ion into the cell. When magnesium is abundant, PhoQ changes PhoP into a form that shuts down expression of the three genes. "AT ONE POINT, we decided to make a PhoP mutant that works independently of PhoQ," Groisman says.

Presumably, genes regulated by PhoP should then be blind to the magnesium concentration. And that was true for all the genes they looked at except mgtA. This gene still turned on when magnesium was scarce and turned off when it was plentiful. VNABLE TO IDENTIFY THE PROTEIN regulating mgtA, Groisman's team examined the unusually large section of the mRNA transcript preceding the sequence that actually encodes the protein. When they mutated the 5' UTR, the gene wasn't repressed in the presence of high levels of magnesium. COMPUTATIONAL STRUCTURAL ANALYSIS suggested that a riboswitch may be involved in the gene's expression, and the group then proved that the 5' UTR could bind magnesium and alter the RNA's structure to halt transcription. In work published in the April 7, 2006, issue of Cell, Groisman and his colleagues announced that they had found a magnesium-binding riboswitch, the first example of a riboswitch that responds to a metal. ▶ HE BELIEVES THE 5' UTR of mgtA may offer some surprises—the RNA fragment can be detected in the cell after it is cleaved, indicating it may still have some unidentified function. "My fantasy," says Groisman, "is that the 5' untranslated region has a life of its own in

addition to that of a riboswitch." - L.C.

metabolites and a sequence that turns gene expression on or off in response to that environmental monitoring. It's an elegant model that allows the riboswitch to control its gene expression by binding a metabolite and either preventing or inducing termination of mRNA synthesis, protein synthesis, or RNA self-destruction through self-cleavage.

Riboswitches demonstrate striking complexity. For example, the glycine riboswitch in *Bacillus subtilis* employs two glycine-binding domains to control a set of genes whose products allow the bacteria to live off of glycine, an essential amino acid. The two-aptamer regions cooperate with each other to allow the

bacteria to sense small changes in available glycine, says Breaker.

Another riboswitch has proven itself as sophisticated as certain proteins, findings that Breaker's team reported in the October 13, 2006, issue of Science. The bacteria Escherichia coli and Bacillus clausii both have two different enzymatic proteins that turn the amino acid homocysteine into methionine. One pathway is more efficient but needs vitamin B12 to help. The other is less efficient, and bacteria use it only when B12 and another nutrient, S-adenosylmethionine (SAM), are in short supply. E. coli uses proteins to monitor the concentrations of these nutrients and regulate the expression of these enzymes. B. clausii, on the other hand, uses a riboswitch to control expression of the less efficient enzyme. What's interesting is that the riboswitch harbors two different aptamer binding sites—one for SAM and one for B12. If either nutrient

binds the riboswitch, the gene for the less efficient enzyme is switched off.

Although metabolite-binding riboswitches are relatively common among bacteria, only one riboswitch has been found in a higher organism: the TPP riboswitch, which exists in bacteria, is also found in fungi and the flowering plant *Arabidopsis*. In bacteria, this riboswitch regulates thiamine production and transport by binding thiamine pyrophosphate. In fungi, it's involved in a process called RNA splicing, which removes nonsensical bits from mRNA transcripts.

"As bioinformatics search strategies improve, we might still find some riboswitches in common between bacteria and humans," Breaker suggests. "If humans do have riboswitches, they likely form different shapes and sense different compounds than those found in bacteria."

For Humanity's Benefit

he application of riboswitches to human health does not necessarily depend on whether humans have them. More than a dozen bacteria that are dangerous to humans rely on riboswitches, which offers "a real opportunity to specifically target bacterial processes," Breaker says.

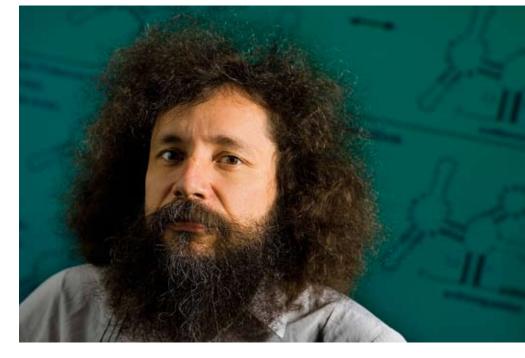
He believes the capacity of riboswitches to control gene expression by monitoring nutrient availability could provide desperately needed targets for developing antibiotics. Although bacteria have a prodigious talent for replicating themselves, they still struggle to survive in a nutrient-poor environment. Drugs that mimic vital metabolites could take advantage of that fact. Breaker has cofounded a company called BioRelix to pursue this technology.

"Drugs targeted at unique and essential riboswitches could trick microorganisms into believing that they are swimming in nutrients when they are actually starving for them," says Breaker, who described in the January 2007 issue of *Nature Chemical Biology* that several antibacterial compounds, which never became drugs for humans, appear to target lysine riboswitches in anthrax and other bacteria. He also believes that designing metabolite mimics that target only riboswitches presents an opportunity to ameliorate adverse drug interactions.

Breaker speculates that, if bacteria were to develop resistance to the metabolite mimics, they wouldn't have much of a survival advantage because they would continue to produce unnecessary proteins, exhausting resources. For example, Tina Henkin at Ohio State University discovered a mutation that deregulates the riboswitch-regulated SAM synthetase gene, leaving *Bacillus subtilis* struggling to grow in laboratory growth media.

Still unclear is whether riboswitches are actual relics of the RNA World. To date, the closest living descendant of that world is the ribosome—a protein-enrobed RNA machine that translates mRNA into

Gelfand, who is using riboswitches to study evolution, agrees noting that "the riboswitches that are present in diverse bacteria are likely very old." That's not to say that all riboswitches are ancient. Gelfand and Breaker posit that a number of riboswitches may have emerged much later than the RNA World. "This doesn't contradict the hypothesis of ancient origin of some riboswitches," Gelfand says. "Rather it demonstrates that the process of their creation continues."

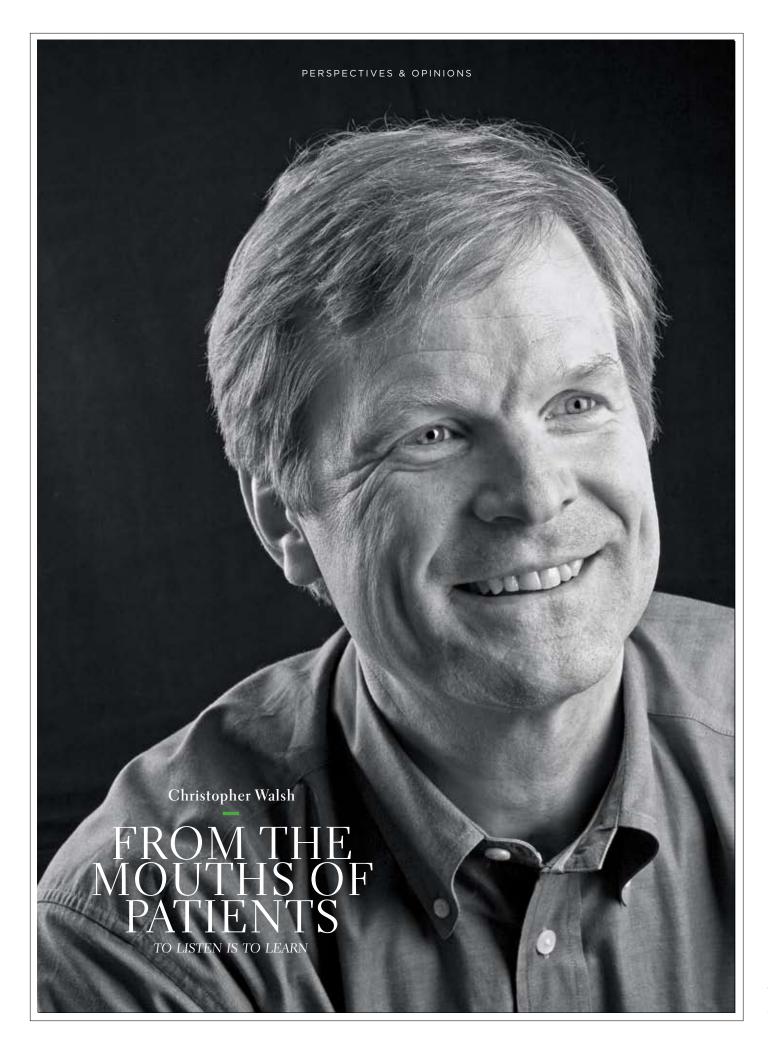


After his computational studies suggested that RNA regulates gene expression in riboflavin biosynthesis, Mikhail Gelfand began using riboswitches to study evolution.

protein. Scientists speculate that the ribosome marks the place where RNA ceded its supremacy to more stable and efficient molecules. Riboswitches could be one step further back in evolution.

"It is very tempting to speculate that at least some riboswitches are ancient relics from the RNA World," Breaker says. "Some riboswitch classes sense metabolites that certainly were present in the last common ancestor of all modern cells, and these riboswitches are preserved with very little variation in most bacteria." From his vantage point in the modern world, Breaker sees riboswitches as good proof of the RNA World hypothesis. Even though a self-replicating RNA would offer ultimate proof of the RNA World, Breaker notes, "All you have to do is crack open a modern cell and see how common these RNA elements are and everything screams RNA World."





How do genes guide brain development and, in turn, our behavior? This question fascinates HHMI investigator and physician-scientist Christopher A. Walsh, whose Harvard lab studies the cerebral cortex, the thin layer of gray matter that controls complex thoughts and motor functions. Despite his active research program, Walsh makes time to spend with patients and their families. These interactions often guide his research—and increase his drive to do all he can to help.

What types of patients do you see?

In our pediatric and adult clinics, we see patients with brain abnormalities and their families. Many of these conditions are genetic. For example, in periventricular heterotopia (PH), clusters of brain cells remain near the ventricles (the fluid-filled spaces deep in the brain) instead of migrating out to the cerebral cortex. Another condition is lissencephaly, which means "smooth brain." Instead of having a normal folding pattern, the cortex is smoother and thicker.

You collaborate with physicians in Turkey and Arabic countries of the Persian Gulf. Why those countries in particular?

These are rare genetic neurological diseases. Prevalence varies from about 1 in 10,000 to 1 in 100,000 people worldwide. Based on referrals from their local doctors—often, in Canada, England, and France—we usually see here in Boston only about a half-dozen patients per month. So we also visit pediatric clinics in Turkey, Dubai, and nearby countries because in these regions, people tend to have large families and about half of the marriages are between first cousins. Together, these two factors make recessive genetic disorders easier to study.

How has talking with patients informed your research? The best example is in people with PH, most of whom have normal intelligence and can function well, except that many have a seizure disorder. In our clinic, one after another of these patients have told us that they suffer from dyslexia. Ten of 12 PH patients we've tested have reading scores remarkably lower than their general IQ scores would indicate.

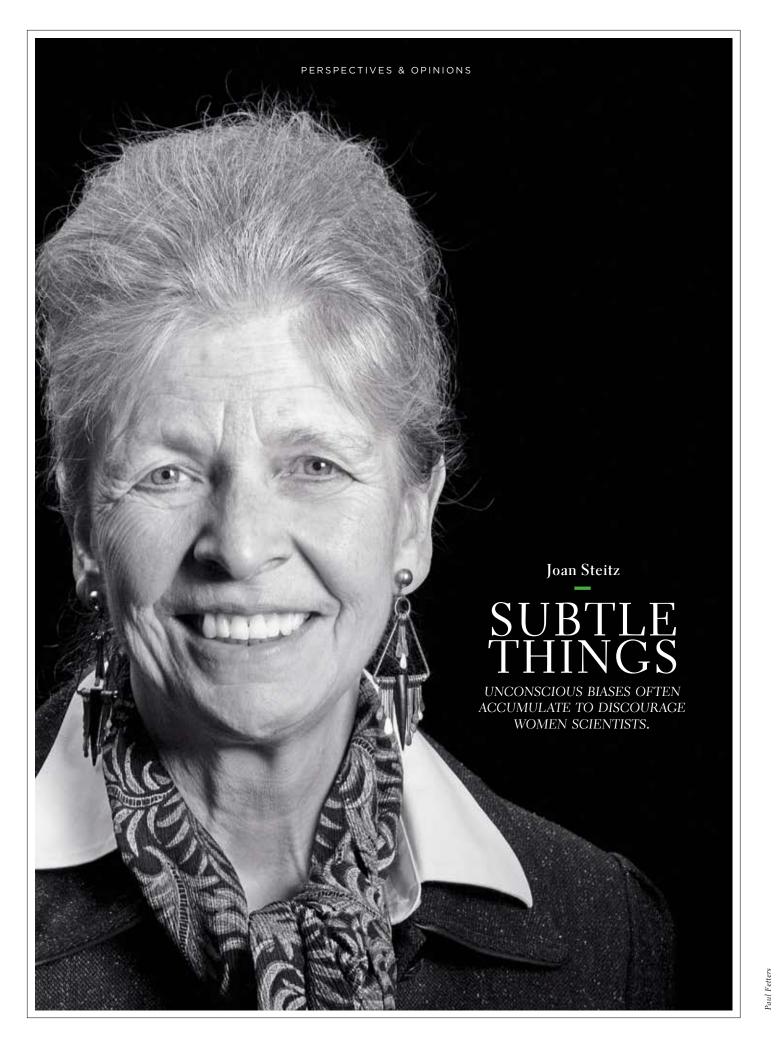
Interestingly, further study has shown that they have a distinctive subtype of dyslexia. People with typical dyslexia have trouble deciphering sounds into syllables. By contrast, those with PH have a general defect that reduces the speed at which they can process information. Reading is the hardest thing the human brain does—it is the last developmental milestone that kids reach—and this probably explains why these patients will have specific reading difficulties. Now the question is, how does this form of dyslexia relate to the functional architecture of the cerebral cortex?

Another example is schizencephaly, which is a cleft or slit in the brain. Through a study of about 50 kids with this disorder, we found that a huge number of them either had very young mothers or were adopted. It's a fact that adopted children tend to have young birth mothers too. So we think this condition is probably not genetic, because the frequency of genetic disorders increases with the age of the mother. Instead, schizencephaly may result from a blood-flow problem during pregnancy, possibly caused by exposure to infections, drugs, or toxins.

Sitting down and taking a history helps you recognize things more readily than if you just read about [a disorder]. And what we learn gives us ideas for scientific studies.

Has working with these families affected you in other ways? Although some patients are almost completely normal, we also see families with severely handicapped children. Having a child with a serious brain disorder becomes the defining event for that family; it completely envelops them. As a parent with two healthy kids, I feel incredibly fortunate and blessed. It never ceases to impress me how resilient these families are, which inspires me to do everything I can to help them.

INTERVIEW BY JULIE CORLISS. Christopher Walsh is an HHMI investigator at Harvard Medical School, Beth Israel Deaconess Medical Center, and Children's Hospital Boston.



Joan A. Steitz has been a principal investigator, a department chair, a teacher of undergraduates—and a role model for women in science. As a member of a National Academy of Sciences committee on the barriers women face in academic science, she became much more aware of the sometimes-subtle reasons why the ranks of women at high levels are so sparse.

When we think of a scientist, 99.9 percent of us picture a male. It's one of the many unconscious biases—on the part of men and women—that impedes women's desire to move forward in science. It is these unintended biases, much more than any overt offenses, that hold women back.

We women scientists have been agitated since Larry Summers made comments about women and science early in 2005 that eventually cost him his job as president of Harvard University. He listed three reasons why women couldn't succeed in science. Loosely put: Their brains aren't very good at math, they don't want to work hard enough to be scientists, and maybe a small bit of adverse cultural influence plays a role.

Data from our 2006 National Academy of Sciences report Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering convincingly show that women have both the ability and the drive to be high-level scientists. So that leaves us with the (not-so-small) cultural influence. It's quite amazing how extensive this is—a large number of small disadvantages that add up to the proverbial 800-pound gorilla.

One of the most fascinating studies I read was from Wayne State University, where researchers evaluated some 300 letters of recommendation for people who successfully applied for faculty positions within a medical school. Multiple statistically significant differences emerged between letters written about women and those about men—regardless of whether the letter writer was male or female!

One stunning finding: Family situation was mentioned six times more frequently in letters for women than for men. When I first read that result, I thought, "Have I unintentionally fallen into this trap?"

The most important thing that all of us can do is recognize such unconscious biases and help bring them into the light of day. Unless people are willing to look at the data and say, "this doesn't look right," we can't begin to fix the problem. But I see encouraging signs that people, including many men, are beginning to accept the challenge.

At a recent forum on women in science at Yale, nearly 20 percent of the audience was male. One of the men, a graduate student in computer science, asked, "What can I do to help?" Meg Urry [a professor of physics and astronomy at Yale], who often has just the right answer ready, responded

with one concrete suggestion: "Have you ever been in a group discussion when a woman expresses an idea, then a man makes the same point later and gets credit for it?" The grad student nodded. "You, as a man, could point out that the woman made the suggestion just moments ago."

Women, on the other hand, also need to overcome their own biases. For example, though it is undeniable that many women are paid less than men who do comparable work, women are less inclined to be confrontational on issues like salary. Women's traditionally collegial style—often, a good thing—can work against them. When a submitted paper is rejected by a scientific journal, is a woman lab head as likely as a man to fight back and somehow get the manuscript published? I have talked to several editors who say those data are available and could be examined if someone had the time and inclination to do so.

Somebody should do that study. More important, women need to be willing to confront adverse situations when they arise. The principal investigator is *supposed* to fight. How hard you fight, whether over an inappropriately rejected paper or some other injustice, and whether gender-related or not, can make a huge difference.

Much would be gained if universities reassessed their own policies. They haven't changed much since the 1930s, when virtually all faculty were men with wives at home supporting their needs. Times have changed, however, for men and women alike, and universities need to change as well. They must review their procedures, major and minor, on such things as promotion criteria, the nature of people's jobs, and even the time of day that meetings are held. If the academic system indeed becomes more family friendly, both sexes will benefit.

I am very encouraged by the February selection of Drew Gilpin Faust as the next Harvard president. When I started as a faculty member in 1970, women were barely represented on the faculties of research universities. The appointment of a woman to such a position was unthinkable. But today, according to the search committee, she was simply the best-qualified candidate for the job.

INTERVIEW BY CORI VANCHIERI. Joan Steitz is an HHMI investigator at Yale University School of Medicine. For more on the report, see "Blinding Bias" (inside back cover).

Chklovskii: Paul Fetters Kimble: Michael Forster Rothbart MacKinnon: Matthew Septimus Taylor: Nina Haste

Q&A

Where do you do your best thinking?

There is no standard time or place for finding one's muse. Some see a new angle or answer a puzzling problem when they are alone, others in teamwork, and some when confronted. Vive la différence! Four HHMI researchers shared with the Bulletin where and when their own creativity flows most freely. — EDITED BY JACQUELINE RUTTIMANN



Dmitri B. Chklovskii GROUP LEADER, JANELIA FARM RESEARCH CAMPUS "When I am debating with

someone. Some of my best ideas have come to me when I was challenged to defend my point of view. Scottish philosopher David Hume said that "Truth springs from argument amongst friends." Although I don't know what argument led him to say this, I have found it

true on many occasions."



Judith Kimble
PROFESSOR OF
BIOCHEMISTRY, UNIVERSITY
OF WISCONSIN-MADISON

"I regularly walk alone on a wooded path that runs along the shore of Lake Mendota right here in Madison, only a few blocks from my home. This is where I do my best freeform thinking. But for more focused thinking, my office is the place—there I can easily connect with people in the lab, search the Web for relevant facts, and scribble down thoughts as they emerge."



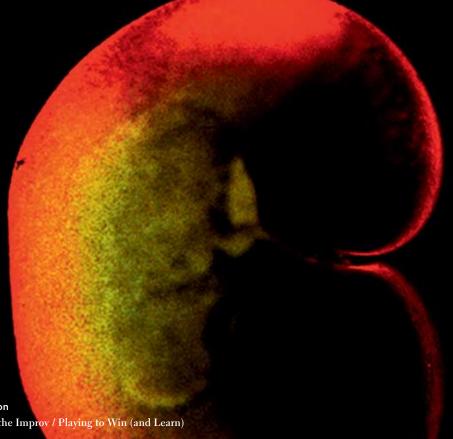
Roderick MacKinnon 2003 NOBEL LAUREATE IN CHEMISTRY, THE ROCKEFELLER UNIVERSITY

"In the shower—I do not know why this is so but it is. Getting away from work once in a while is also real important for clearing my head; otherwise, my thinking gets bogged down and I lose sight of what the important questions are. By itself, getting away does not really qualify as 'best thinking,' but without it I wouldn't be able to find the right question, the answer to which may come to me in the shower!"



Susan S. Taylor PROFESSOR OF CHEMISTRY AND BIOCHEMISTRY, UNIVERSITY OF CALIFORNIA, SAN DIEGO

"When I am jogging, on a cross-country flight, or in the middle of the night when I wake up with an idea."



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National Academy of Sciences Honors Six HHMI Researchers / Molecular Movie Goes Mainstream

Known for its role in development, the Wnt/B-catenin family of signaling proteins—highlighted in red in this zebrafish embryo—has recently been shown to play a part in restoring damaged tailfins in adult zebrafish (see page 49).



Science Night at the Improv

COMEDY HELPS WHEN YOU HAVE THREE MINUTES TO EXPLAIN YOUR SCIENCE.

AS A GRADUATE STUDENT PRESENTING HIS research at a national science meeting, Ben Dubin-Thaler was a little nervous. After all, more than 300 people were spilling out the door and into the hallway to hear about his work on cell migration.

Dubin-Thaler had a brief three minutes to give his talk without slides or laser pointer. Instead, he had to rely on his wit and the power of spoken words:

You see, we take a balled up cell and then we drop the ball,

Onto a sticky lawn of matrix whatchamacall.

It could be fibronectin, or laminin, Or it could be collagen, like the lips of Pam Anderson.

But the cells, you know, they aren't really that picky,

They start kissing those lips, integrin binding makes 'em sticky.

The crowd was amused and the 28-year-old won third place in the first-ever CellSlam event, a contest that drew eight scientist communicators and took place at the American Society for Cell Biology (ASCB) meeting in San Diego, California, December 9–13, 2006.

The event gave scientists a chance to use humor, rhythm, song, or skit to communicate a scientific concept. University of California, San Diego (UCSD), geneticist Amy Kiger proposed the idea after she attended a similar contest in the United Kingdom called FameLab.

"We really need to be training the troops to think outward about how to communicate science to the public," says Kiger, a former HHMI predoctoral fellow who judged the contestants with colleagues including Elias A. Zerhouni, director of the National Institutes of Health.

Zerhouni says he enjoyed CellSlam and thinks it should be held every year. "Never take yourself too seriously in science," he advises practitioners. "Humor, wit, and simplicity in explaining your work is a common attribute of the very best scientists."

A fan of poetry slams, Dubin-Thaler says he drew inspiration from one of his classes at Columbia University with neurobiologist and HHMI professor Darcy Kelley, who belts out mating calls of the South African clawed frog to make her point during lectures. He says her "willingness to be bizarre gives people that little nudge that says, 'Hey, this is cool and exciting and worth your time to stop daydreaming!" He and other slammers say that, while it may be hard to teach a complete science lesson to any audience in three minutes, it is enough to spark a desire to learn more.

Kirsty Roach, a doctoral student at the University of Manchester in England, won CellSlam (whose official prize was "glory and an ASCB T-shirt") with her engaging skit about how cells repair wounds. The audience roared as she instructed her blindfolded friend Mark, playing the role of a disoriented cell, to "protrude" and "detach at the rear."

Kiger says Roach won because she used humor, props, and audience participation, all squeezed into three minutes, to convey a tiny bit of her own research. Blindfolding her assistant, Roach explained, was like knocking out a cellular receptor called syndecan-4, which the cell needs to find its way along the extracellular matrix. Roach explains her research to schoolchildren much the same way, by letting them act out the different cells and molecules needed for tissue repair.

"Every scientist has a responsibility to convey research to the public," says Roach. She notes, however, that many scientists fear looking silly or simplistic in front of their peers if they engage in less-than-serious educational efforts.

So as role models, several top scientists let down their guard and joined the fun



'You can't be creative unless you are relaxed and having fun.

SANDRA SCHMID

at their own expense. Randy Hampton, a professor of cell and developmental biology at UCSD, exhibited his "street cred" as the night's emcee. A stand-up comedian in a previous life, Hampton loosened up the crowd with political gags, some off-color humor, and jokes only a scientist

could love: "Everyone take a deep breath," he instructed. "Now, just breathe out the nitrogen. [Laughter] I love collecting data, and this is a huge amount of proof that scientists are desperate for entertainment."

Sandra Schmid, chair of cell biology at The Scripps Research Institute in La Jolla, California, had the audience clapping and singing along to her entry, "Ode to NIH"—a shameless plug for more grant money sung to the tune of "Let It Snow."

Schmid, who has taught HHMI workshops, says that part of giving any scientific talk is "putting on a good show." She knows that students often feel stressed out by the competitive nature of research and believes events like CellSlam can help lighten up the pressures of scientific discovery. "You can't be creative unless you are relaxed and having fun."

- KENDALL POWELL

Playing to Win (and Learn)

INSPIRED BY HHMI'S HOLIDAY LECTURES
ON SCIENCE DVDS, A HIGH SCHOOL TEACHER
CONJURES UP AN ENGAGING WAY FOR
STUDENTS TO LEARN THE SUBJECT MATTER.

YOU'RE ON THE BACKBONE OF A DNA MOLECULE, TRYING TO get down the spiraling staircase structure as fast as possible. You could take the steps (composed of purines and pyrimidines) or race along the railing (made up of phosphates and sugars). The only impediments to your speedy descent are the questions you must stop and answer along the way. Answer correctly and you're free to continue. An incorrect response means your opponents may pass you by.

Sounds like a fun board game, right? It's that, plus a science lesson.

Julie Breeden, a high school teacher at Hampton Roads Academy in Newport News, Virginia, wanted to make her genetics class more engaging. Inspired by HHMI's Holiday Lectures on Science, specifically the 2002 series "Scanning Life's Matrix," she asked her students to design board games to complement those lectures.

Through this exercise, Breeden expected the students to learn a number of important lessons: how to organize information, how to acquire knowledge on their own, how to ask good questions, and how to use their imaginations.

She also had a grander purpose: "I wanted to help ensure that, when the students encounter large and expansive amounts of information in college, they won't be put off by it and will feel comfortable attacking it." She instructed her students to watch the DVD of the lectures several times—making notes on broad topics the first time and adding detailed notes on subsequent viewings. She then asked them to team up in groups of three to brainstorm and build a game.

They surpassed her wildest expectations—and often, their own. Tyler Branscome, for one, was initially apprehensive. "When I first saw the DVD I got a little scared," she says. "There was a lot of



Collective ingenuity was behind this Holiday Lectures on Scienceinspired board game assigned by Hampton Roads Academy genetics teacher Julie Breeden (right) and created by her former students (left to right) Alexandra Aloba, Tyler Branscome, and Dasha Afanaseva.

vocabulary that I didn't understand." But eventually she saw it as a valuable exercise that made good use of her creativity.

Branscome and her teammates devised "Journey Through the Human Genome," which features a three-dimensional, DNA model made of doll heads (just for the fun of it) held together by magnetized paint and wires. Using metal pieces, contestants race down the molecule as fast as they can, trying to earn the most points by correctly answering questions that reflect the lectures' content. Simpler questions along the DNA bases award five points and critical-thinking questions along the railing are worth 10 points.

Branscome's methods for finding and choosing her unconventional materials portend a career as a budding scientist.

"When I think of things to do, they are usually a little off base and people don't think they are going to work," she says. "But somehow I research and find the way."

She found magnetic paint online and decided, "well, if you paint something that's round and put it all together with metal wiring then the magnets [game pieces] will stick to the game board and then you

CONTINUED ON THE NEXT PAGE

CONTINUED FROM SCIENCE EDUCATION

PLAYING TO WIN (AND LEARN)

can play on it." As for the team's curious choice of doll heads: "It just came to me, but I think it works," she says.

The team's efforts paid off with a finished assignment and better comprehension of the material.

"The way that the game, the DVD, and the questions all come together have made it a lot easier for me to understand the human genome and DNA," she says.

Branscome's classmates were equally successful in coming up with creative board games. One team invented "The Building Blocks of Life," a wooden puzzle that yields a picture of a DNA molecule when pieced together. To complete the picture, players read questions from the lectures found on the bottom of each wooden block and match them to the appropriate answers

printed inside the shallow game box. Another team invented a game called "Jumbo Genetics around the World," in which players answer rhyming questions and work their way around a world map printed on a shower curtain. A fourth group designed a flat board game called "Saved at the Centromere," in which contestants vie to be the first to reach the center of a chromosome by coursing down the chromosome's four arms, answering lecture questions as they go.

The project was such a hit, Breeden may ask next year's classes to develop new games, based on the Holiday Lectures DVDs on evolution (2005) and stem cells (2006).

As to whether any of these games could be marketed by companies such as Parker Brothers or Milton Bradley, Breeden doesn't dismiss the notion.

"There's certainly potential," she says. ■ - JACQUELINE RUTTIMANN

HHMI Invites Colleges to Compete for Grants

THE INSTITUTE AIMS TO BOLSTER RESEARCH AND TEACHING IN COLLEGE SCIENCE DEPARTMENTS AND GIVE A BOOST TO INTERDISCIPLINARY PROGRAMS.

colleges and master's-level universities face enormous challenges in finding funds to support undergraduate and faculty research in the sciences. A 2006 National Science Board report on science and engineering indicators, for example, showed that, although colleges produce almost half the bachelor's degrees in the physical, biological, and agricultural sciences and educate substantial numbers of minorities underrepresented in the sciences, they receive less than 5 percent of all federal research dollars.

Now, HHMI has invited more than 200 baccalaureate colleges and master's-level universities to compete for \$60 million in grant funding to support science education. The Institute expects to award approximately 50 grants ranging from \$800,000 to \$1.6 million to support innovative programs that strengthen undergraduate research, mentoring, interdisciplinary

research, and the computational skills of students and faculty.

"Because they get very little federal research support, colleges struggle to create the infrastructure to conduct cutting-edge research," says Peter J. Bruns, HHMI vice president for grants and special programs. "And to do good teaching, you need to be doing good research."

Through this competition, HHMI seeks to buttress the research capacity of college science departments as it relates to teaching and to integrate the life sciences with disciplines such as mathematics and computer science in a way that reflects the increasingly quantitative nature of modern biological research.

"We hope that these grants will enable the colleges to engage more students in inquiry-based science earlier in their undergraduate years. We also hope to help science departments broaden their expertise in emerging

disciplines and to support and disseminate innovative approaches to science teaching," says HHMI president Thomas R. Cech.

In the past, the top 200 colleges, based on proven records of preparing students for graduate education and careers in science and medicine, were invited to apply. This year, to increase the applicant pool, the Institute invited the 226 colleges with the highest percentages of graduates, including underrepresented minorities, who go on to graduate or medical school. For the first time, the pool includes a Native American tribal college.

A panel of leading scientists and educators will review the applications, due May 16, 2007, and make recommendations to HHMI. The awards will be announced in May 2008.

FOR MORE INFORMATION about this competition as well as a list of the invited institutions and descriptions of previously funded programs, go to www.hhmi.org/colleges.

Gilliam Fellowships Pave the Way for Five Future Scientists

after proving their mettle as undergraduates doing summer research in HHMI-supported laboratories, five young, promising scientists have been granted HHMI's 2007 Gilliam Fellowships for Advanced Studies. The competitive awards provide funding to disadvantaged students, including minorities underrepresented in the sciences, for up to five years of study toward a doctoral degree in the life sciences. The fellowships are named for the late James H. Gilliam Jr., a charter Trustee of HHMI

who spent his life fostering excellence and diversity in education and science. ¶ Gilliam Fellows are selected from a pool of undergraduate students who participated in HHMI's Exceptional Research Opportunities Program (EXROP). Over the past four summers, 188 EXROP students have conducted research in the labs of HHMI investigators and HHMI professors. In addition to their graduate studies, Gilliam Fellows take on mentoring and leadership roles at EXROP meetings.



Irene C. Blat UNDERGRADUATE DUKE UNIVERSITY (GRADUATE SCHOOL UNDECIDED) Of Venezuelan descent and fluent in Spanish, Blat has volunteered as a translator at free medical clinics in immigrant communities in Charlotte, North Carolina. While a 2004 EXROP student, she worked with HHMI investigator Tania Baker (MIT) to understand how the viral protein MuB facilitates infection Blat wants to become an academic biomedical researcher and stay involved in helping her community.



Nisha M. Broodie UNDERGRADUATE UNIVERSITY OF MIAMI (GRADUATE SCHOOL UNDECIDED) Losing her mother to breast cancer contributed to Broodie's determination to pursue a career in biomedical science. As an EXROP student, her work in the MIT lab of HHMI investigator Li-Huei Tsai helped implicate DNA damage in the progression of neurodegenerative disorders such as Alzheimer's disease.



Veder J. Garcia GRADUATE STUDENT UNIVERSITY OF CALIFORNIA, BERKELEY Garcia's interest in plant biology took root during childhood visits to his grandparents' farm in El Salvador. The first in his family to go to college, Garcia graduated with honors and was designated as the Botanical Society of America's 2006 Young Botanist of the Year. He hopes to work with Salvadoran biology professors to improve environmental education.



Eunha Kim GRADUATE STUDENT UNIVERSITY OF CALIFORNIA, LOS ANGELES (MEDICAL SCHOOL UNDECIDED) Kim escaped a certain future of factory work by leaving her family behind in South Korea to bursue an education in the United States. She earned a bachelor's and master's degree in molecular, cell, and developmental biology and now envisions one day running her own lab and curing diseases such as the one she suffers from - fibromyalgia, a disorder that causes chronic muscle pain and fatigue.



Jose A. Rodriguez UNDERGRADUATE UNIVERSITY OF CALIFORNIA. LOS ANGELES (GRADUATE SCHOOL UNDECIDED) Arriving in the United States from Ialisco, Mexico, with his family at the age of five, Rodriguez knew no English. In high school, he was taking advanced placement science and math classes while working as a busboy 20 hours a week. Now a biophysics major, Rodriguez hopes "to channel the current explosion of technological innovation into the field of biomedical research."

Lummis Retires from HHMI Board of Trustees

ONE OF EIGHT CHARTER TRUSTEES, LUMMIS STEPS DOWN AFTER NEARLY 23 YEARS OF SERVICE.

the retirement of William R. Lummis, a Houston attorney, in March 2007. Lummis played a pivotal role in establishing HHMI as a leader in biomedical research and helped ensure the Institute's successful reorganization after the death of his cousin and its founder, Howard R. Hughes. He was one of eight charter Trustees appointed in

1984 by the Delaware Court of Chancery to oversee the Institute.

"It is owing in large part to Will Lummis that the Institute has developed into the distinguished leader it has now become in the world of the biomedical sciences," says Hanna H. Gray, chair of the Trustees and president emeritus of the University of Chicago.

A graduate of Rice University and the University of Texas Law School, Lummis practiced law in Houston for 23 years with the firm now known as Andrews & Kurth. In 1976, Lummis became administrator of the Hughes estate and left Houston for Las Vegas, Nevada, where he assumed the leadership of a variety of Hughes businesses. After achieving considerable success with these enterprises, Lummis retired as chief executive officer of the Hughes Corporation and the Summa Corporation in 1990.

Throughout his varied career Lummis maintained his home in Houston where he has been a civic leader and where he and his wife Doris continue to live.

Sculpting Brain Connections

A SIMPLE AND ELEGANT WAY TO ENABLE THE PROCESS OF LEARNING

Unlike your computer's memory chips, whose circuits are etched into a solid slab of silicon, real brain circuits change shape as they learn. HHMI investigator Michael D. Ehlers and his colleagues at Duke University are themselves learning how neurons remold their connections, and they may have identified the brain's favored sculpting tool.

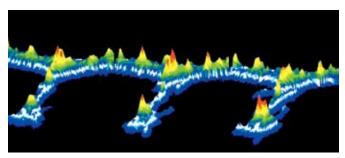
Ehlers' team focuses on dendrites—the neuronal branches that support the nerve cell's connections to other neurons—and in particular on the tiny spines that sprout on dendrites and act as the receiving stations for incoming signals. These dendritic spines, Ehlers explains, are the centers of neuronal rewiring—i.e., learning.

The spines contain receptors for neurotransmitters, notably the AMPA receptor proteins that accumulate in the surrounding membranes. Several years ago, Ehlers' group discovered that these receptors migrate to the membrane by way of tiny vesicles called recycling endosomes. "The way you functionally enhance the synapse (the connection between neighboring neurons) is to get more AMPA receptors there," says Ehlers.

In a paper published in the December 7, 2006, issue of *Neuron*, Ehlers and colleagues extended those earlier findings. Using advanced light- and electron-microscopy techniques, they found that recycling endosomes provide not only the AMPA receptors but also the membrane components neurons need to shape their connections. This discovery, he says, emerged from

no small amount of free thinking. "No one had ever asked 'Where does the membrane come from?""

The findings are already simplifying the way neuroscientists think about learning and brain circuitry, says Ehlers. "You don't need a hundred different mechanisms to mobilize a hundred different molecules. Maybe you just need one core transport mechanism that delivers a prepackaged set of molecules and membranes to the synapse." He hopes the discovery may lead to new avenues for restoring or augmenting the brain's plasticity—its ability to mobilize healthy nerve cells to compensate for damage caused by disease or injury. ■ -PAUL MUHLRAD



As it develops and stores information, the brain undergoes physical changes in microcircuitry. These three-dimensional profiles show intensity of recycling endosome cargo in a single dendritic spine, with a scale from low (purple) to high (red), as well as long term potentiation of synaptic strength over time (left to right).

IN BRIEF

GENES LARGE OR SMALL, P[ACMAN] PLACES THEM ALL

To determine a gene's function, scientists often alter the gene and insert it into the genome of a model organism; larger genes. however, have proven more difficult to insert. Now, HHMI investigator Hugo J. Bellen at the Baylor College of Medicine and colleagues have developed a technique that enables both large and small genes to be inserted into mammalian and fruit fly chromosomes. By applying a method called "recombineering," they retrieved large DNA fragments from fruit flies and inserted them into modified bacterial artificial chromosomes (BACs). They then used an enzyme called phiC31 integrase to integrate the BACcarried gene fragment into specific docking sites in the fruit fly chromosome, giving rise to the technique's name, "P/phiC31 artificial chromosome for manipulation," or P[acman] for short. Their findings were published November 30, 2006, in Science Express.

GLEEVEC'S GOOD NEWS

In a study of patients with chronic myeloid leukemia (CML), some 95 percent survived the cancer after five years due to treatment with Gleevec, according to results published

in the December 7, 2006, issue of *The New England Journal of Medicine*.

"The lesson from Gleevec for cancer treatment is simple: if you understand what's driving the growth of the cancer and develop a specific drug to target that cause, you can obtain remarkable results," says HHMI investigator Brian J. Druker at the Oregon Health & Science University Cancer Institute, who led the original clinical development of Gleevec (imatinib) as well as this follow-up study.

Gleevec inhibits a biological switch called a tyrosine kinase that is abnormally activated in CML. This activation, triggered by an abnormal breakage and rearrangement of a chromosome, drives uncontrolled proliferation of white blood cells.

The study followed 553 patients who were receiving Gleevec as their primary therapy. Aside from the high survival rate, the report shows that the drug produced few significant side effects, which is important because CML patients need to remain on Gleevec long term.

The researchers are now working on eradicating the reservoir of aberrant cells that cause the disease to reappear if therapy is stopped.

SEEING THE PATTERN IN HAIR FOLLICLE DEVELOPMENT

Studying the unruly fur that swaddles certain mutant mice has provided HHMI investigator Jeremy Nathans at the Johns Hopkins University School of Medicine and his colleagues with a glimpse of how hair follicles communicate their position and orientation to neighboring follicles.

The team studied mice carrying a knockout mutation in the gene called *Frizzled6*. In contrast to the well-organized hair follicles of normal mice, the mutant mice show a complex disruption of hair follicle patterns much like the whorls and waves in fingerprints.

The researchers created mice in which normal hairs were intermingled with mutant hairs and then they created small wounds in the skin of the mice to study how follicle orientation was affected. Using microscopy techniques, they showed that the follicles are mobile in their orientation and that they transmit both global and local signals that can alter that orientation. The normal follicles seem to influence orientation of the mutant follicles, but not vice versa.

"Finding that kind of mobility was quite remarkable, because until now most

Hints from Wnts

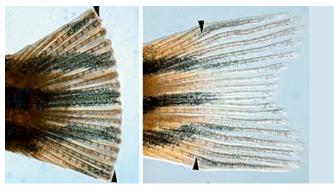
THE SECRET TO REBUILDING BODY PARTS MIGHT BE FOUND IN A FISH FIN.

When it comes to replenishing lost body parts, some of our distant cousins can teach humans a thing or two. Zebrafish, for example, have no problem regenerating perfect tailfins after being nipped by an aquarium mate—or snipped by an inquisitive doctoral student, like the University of Washington's Cristi Stoick-Cooper.

She and her colleagues in the laboratory of HHMI investigator Randall T. Moon recently coaxed a few secrets from zebrafish on how they regrow their tails. Specifically, the researchers discovered a critical ingredient in the creatures' regeneration potion—a group of signaling molecules called Wnt proteins (pronounced "wint"). Although Wnts are well-known regulators of many cellular processes, their role in organ regeneration had never been examined.

Wnt proteins typically respond to extracellular signals by prompting another protein, called \(\beta\)-catenin, to enter the nucleus and activate specific genes. In particular, Stoick-Cooper, University of Washington postdoc Gilbert Weidinger (now at the Technical University of Dresden), and colleagues found that Wnt/\(\beta\)-catenin activity rises in zebrafish undergoing tailfin regeneration, but the fish were unable to regrow snipped tailfins when researchers disabled the Wnt/\(\beta\)-catenin pathway. Zebrafish engineered with elevated Wnt signaling levels regenerated their tailfins with added haste.

Surprisingly, zebrafish that overproduced a different Wnt—Wnt5b—failed to regenerate tailfins altogether, but mutant fish lacking a functional *Wnt5b* gene replaced their tailfins at an



One day after trimming the edges of a zebrafish tail fin (left), things look a little too neat. Never fear: by ten days post amputation, the tail fin has regenerated.

accelerated pace, indicating that this Wnt protein normally inhibits regeneration.

These experiments, reported in the February 1, 2007, issue of *Development*, reveal that Wnts are central to the regeneration process in zebrafish, says Moon. Moreover, he cites his team's observation that Wnt activity in mice increases during liver regeneration, suggesting that the same pathways may be at work—and potentially extendable—in mammals. "Manipulating Wnt signaling could hold the key to regenerating damaged organs or limbs in humans," says Stoick-Cooper. "It's just a dream right now, but we're getting closer to understanding how this might be possible."
—PAUL MUHLRAD

IN BRIEF

people working on skin biology described hair follicles in the dermis as basically like telephone poles stuck in cement," Nathans says. The studies were published December 15, 2006, in the online early edition of the *Proceedings of the National Academy of Sciences*.

ANCIENT DNA-REPAIR MECHANISM AIDS IN ANTIBODY SELECTION

New research by HHMI investigator Frederick Alt of Harvard University and colleagues shows how the immune system slices and dices genes so that B cells can program antibodies to seek out and destroy invaders. Their work, published December 14, 2006, in *Science Express*, suggests that an ancient DNA-repair mechanism designed to repair broken chromosomes may have evolved to play this role.

B cells are the immune system's armories, where antibodies that attack viruses, bacteria, and other invaders are produced. To take on specific pathogens, B cells first tailor antibodies to recognize the invaders. Called class switch recombination, the process entails cutting and joining two widely separated switch regions on the

genomic immunoglobulin heavy chain (IgH) locus so that one type of antibody constant region gene is cut out and replaced with another.

The team replaced very large switch regions with short DNA sequences that would be recognized not by the usual DNA-altering enzyme, activation-induced cytidine deaminase, but by endonuclease, a yeast DNA-cutting enzyme. The IgH class switching still functioned, albeit at a lower-than-normal frequency.

The findings also have implications for understanding the types of chromosomal rearrangements that underlie some cancers. "This mechanism might act as a sort of 'glue' to hold chromosomes together so that breaks are not allowed to migrate and be joined to other chromosomes," Alt says.

SCIENTISTS DISCOVER A NEW RISK FACTOR FOR ALZHEIMER'S

Researchers have identified a gene called *SORL1* that is implicated in late-onset Alzheimer's disease.

In a January 14, 2007, advance online publication of *Nature Genetics*, HHMI international research scholar Peter St George-Hyslop at the University of Toronto and colleagues connected the gene to the disease in six groups of people by using a database that listed single nucleotide polymorphisms (SNPs), or single-letter changes in a gene's sequence. The researchers looked at more than 6,800 people, including groups of Caucasians, one group of African Americans, one group of Hispanics from the Dominican Republic, and a group of Israeli Arabs. The team used the SNP databases to track the *SORL1* gene in the populations studied but did not actually pinpoint the precise changes in the gene that contribute to disease.

After linking *SORL1* to late-onset Alzheimer's, the team investigated the gene's function. Using cell culture studies, they discovered that decreasing the amount of *SORL1* increased cells' production of amyloid-beta, a toxic protein fragment that is a key event in the progression of Alzheimer's disease.

A new player has been found among the mechanisms causing Alzheimer's disease, St George-Hyslop says. "This will lead to the real endgame, which is to see how to exploit the findings as a new diagnostic or therapeutic target."

Molecular Relay Team

RESEARCHERS DISCOVER HOW CRITICAL INFORMATION IS PASSED FROM ONE PROTEIN TO ANOTHER.

Like athletes passing batons in a relay race, protein "teams" inside cells transfer smaller proteins, called ubiquitin-like proteins, to certain other proteins to set them on track to their final destiny.

HHMI investigator Brenda A. Schulman and her colleagues at St. Jude Children's Research Hospital have discovered new details about this process. The relay team is made up of three enzymes—E1, E2, and E3—that work in tandem to attach ubiquitin or ubiquitin-like tags to cellular proteins. The tags determine the modified proteins' ultimate fate, such as destruction in the cell's garbage disposal, the proteasome. Such degradation in turn can cause activation of a specific event like cell division.

The E1 enzyme selects the correct tag and forms a high-energy bond with it. Next, the activated tag is transferred to E2, which then works with E3 to ultimately hand the tag to the targeted protein. If the system gets out of sync, diseases—such as cancer and neurodegenerative disorders—may occur.

To dissect the transfer process, Schulman's group studied the enzymatic line-up associated with the ubiquitin-like protein NEDD8, which has a relatively simple E1-E2-E3 cascade. They genetically altered the E2 enzyme to stop action, in mid-handoff, during its receipt of NEDD8 from E1. The researchers then crystallized the structures and exposed them to x-ray beams to determine their three-dimensional shapes.



To get where they need to go, certain proteins receive ubiquitin or ubiquitin-like guiding proteins from enzymatic "relay teams."

Previous studies could not explain how the relay worked because available models showed E1 and E2 positioned with E1's baton-carrying hand far away from E2's baton accepting hand. Instead, says Schulman, a switch occurs as if between two novice relayers: the second turns around to face the first for the handoff.

The ubiquitin-like protein (and probably ubiquitin) not only serves as a baton, she adds, but also as a coach. "When bound to E1, it says bind to E2; when bound to E2 it says run away from E1," says Schulman.

The group reported its results in the January 25, 2007, issue of *Nature*. They are now considering how an anchor enzyme, E3, completes the relay and adds ubiquitin or NEDD8 to the final target protein.

- JACQUELINE RUTTIMANN

IN BRIEF

SINGLE GENETIC DEFECT CAUSES EARLY HEART DISEASE

Researchers have identified a genetic mutation that causes early-onset coronary artery disease. Although the genetic defect is rare, it may offer clues about what causes the body's metabolic machinery to malfunction in the more "garden variety" forms of heart disease.

HHMI investigator Richard P. Lifton at Yale University School of Medicine and colleagues discovered members of an Iranian family who carried a genetic mutation that caused them to die in their early fifties from coronary artery disease that resulted in heart attacks and heart failure. They also had osteoporosis. The results were published in the March 2, 2007, issue of *Science*.

Medical records and blood samples from surviving family members showed that the family members had a characteristic cluster of symptoms called metabolic syndrome. People with this syndrome have hypertension, high blood lipid levels, and diabetes, and they are at much higher risk of developing heart disease.

Detailed genetic comparison of all family members found a culprit gene called *LDL receptor-related protein 6 (LRP6)*. This

gene was previously implicated in bone development; mutation of the gene also causes problems in the Wnt signaling pathway, a key metabolic signaling pathway that is important in embryonic development and contributes to an array of normal physiological processes in adults.

The possible linkage to the Wnt pathway may become an important research target for understanding coronary heart disease, says Lifton, who added that the discovery of the *LRP6* mutation causing osteoporosis may link this disease with coronary artery disease.

FRUIT FLY MODEL MIMICS HUMAN NEURODEGENERATIVE DISEASES

Researchers have developed a fruit fly model that replicates the genetic instability seen in a variety of neurodegenerative diseases, including spinocerebellar ataxia type 3 (SCA3) and Huntington's disease.

In some neurodegenerative diseases, certain gene mutations cause the production of an abnormally long number of repeats of three nucleotides called triplet repeats, which encode an amino acid called glutamine, and thus leads to a protein with an abnormally long glutamine string that is toxic to cells.

The length of this glutamine string can grow or shrink as it is passed from one generation to the next—a feature called repeat instability. Expansion of repeats causes the disease to arise earlier and with greater severity in successive generations of people who carry the mutation.

Researchers have had difficulty reproducing the genetic instability of the disorders. Now, a team of scientists led by HHMI investigator Nancy Bonini at the University of Pennsylvania reported in the March 1, 2007, publication of *Science Express* that they see repeat instability in the fruit fly model of SCA3. They directed expression of the SCA-associated gene in germline cells—those associated with eggs and sperm—and saw dramatic instability from generation to generation.

They also found that a gene called *CBP*, which is involved in DNA repair pathways and has been implicated in this class of diseases, affects repeat instability. A drug that counteracts this protein in similar disease models sharply reduced repeat instability in the fruit flies. Drugs of this type are already being investigated as potential treatments for these disorders, says Bonini.





The scientific process starts with a question. When a scientific inquiry piques the interest of a high school or college student and answers can't be found in class or in a textbook, students can turn to HHM's Ask a Scientist Website. There, working scientists field a wide range of biomedical questions.

FOR MORE INFORMATION
on friction skin growth
and development, visit
www.ridgesandfurrows.homestead.
com/friction_skin.html.

Do identical twins have identical fingerprints?

We've all heard stories of identical twins taking tests for each other and playing tricks on their teachers because they look so similar. They couldn't fool those trained scientists on *CSI*, though—their fingerprints would quickly reveal their true identity.

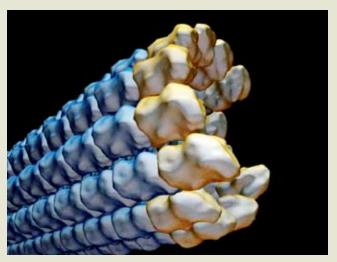
Our DNA provides the blueprint for forming most of our anatomy. However, every detail of every structural feature on our body is not encoded in that DNA instruction set. The environment in which we live—even within the womb—provides additional information that plays a role in our development. Identical twins develop from the same fertilized egg, and thus inherit the same DNA blueprint. Each twin embryo, however, develops in a unique microenvironment in the uterus. This location may affect the types of materials available, provide different sensory input and stimuli, and so forth, which creates variation in the final morphological structures of the body. It's similar to building two houses from the same general blueprint. If you follow the same set of instructions to build both houses, the two buildings may look the same at first glance, but the finer details (e.g., exact widths of boards used or patterns in the wood grains of the boards) may differ.

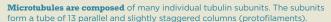
To determine if two people have identical fingerprints, you must analyze the patterns in close detail. Fingerprints are very complex patterns on the outer layer of our skin, called the epidermis. In general, fingerprints are grouped into a few major classes, including whorls, loops, and arches, depending on the macroscopic pattern formed by ridges in the epidermis. The ridges that create the whorls and loops may vary in their spacing or arrangement, and entire ridge systems may merge with one another (termed triradii), adding to the variation in fingerprint pattern. Even the properties of ridges themselves provide more detailed information as ridges can split or end, resulting in pattern alterations known as minutiae. In addition, ridges have numerous sweat pores scattered across them and their locations provide another level of complexity and variation to the overall fingerprint pattern.

Scientists hypothesize that ridge pattern formation results from changes in the number and positioning of cells in the dermis or lower layer of our skin. As dermal cell proliferation increases tension within this cell layer, cells begin to move away from the direction of the stress and create the perpendicular ridges seen in fingerprints. Additionally, the amnion in which a fetus develops contains various salts, waste products, and other useful nutrients and proteins. This fluid environment is constantly changing, and particles may not be uniformly present at all times and locations during development. All of this variation may alter cell growth or proliferation, which could then change tension within the dermis, and result in different ridge characteristics. Although the general pattern is coded in the DNA, these slight environmental changes may alter the finer details of ridge formation, like splits or ends in ridges.

Identical twins are likely to have similar fingerprints at some levels, but their prints are unique when examined in greater detail. Twins and other siblings are more likely to share the same finger-print class than two random people. Identical twins may even share some ridge characteristics such as width or number. However, some of the finer details like sweat pore location and breaks in epidermal ridges may differ. Though microscopic, these differences provide enough information for automatic fingerprint scanners to decipher between identical twins.

RESEARCHED BY DANIELLE LIUBICICH, a Ph.D. candidate in the laboratory of HHMI investigator Nipam H. Patel, Department of Integrative Biology, University of California, Berkeley.







When the microtubule breaks down, columns splay apart and peel backwards. The peels then snap off from the disassembling microtubule, break down into smaller pieces, and eventually into individual subunits.

Molecules in Motion Animation shows the complex lyricism of chromosome movement in a dividing cell.

LIKE THE STRANGE, DREAMLIKE UNDERWATER WORLD of Jacques Cousteau, particles flow freely, but with purpose, through a liquid atmosphere. Tranquil music further sets the marine-like scene. Eva Nogales's movie uses captivating animation and real molecular structures to offer an eye-opening view of how microtubules—the long protein polymers that help cells divide their genetic material—assemble and disassemble.

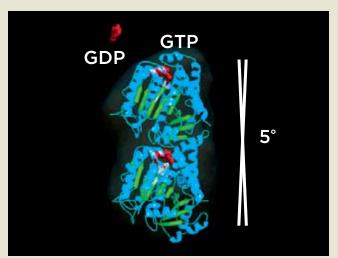
Although most biologists are familiar with microtubules, Nogales, an HHMI investigator at the University of California, Berkeley, found that when she described her work to colleagues they had a hard time *seeing* what she was talking about. Especially when she described how individual protein subunits, called tubulin, add onto a growing microtubule filament or fall away from it.

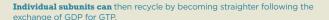
Then Nogales attended a lecture by one of her Berkeley colleagues in which he played a video of a parasite's life cycle. The movie allowed the audience to observe, and then understand, what her colleague had discovered. She decided to make a movie of her own to convey some of the details that she and her team had discovered through their use of electron microscopy.

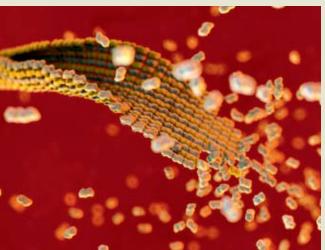
In the animation, the Zen-like music underlies Nogales's guiding narration. The viewer is transported along the three-

dimensional microtubule polymer, swooping in for close-up views of the building-block tubulin subunits, then panning wide to watch them join the growing end of the microtubule. Three subunits add on to the microtubule, like individual railroad cars joining a waiting train, and the video settles on the mature polymer—a tube of 13 full-length columns.

The researchers believe a tubulin subunit must undergo a subtle change in shape before it can join in the process. They propose that in solution tubulin can have at least two shapes: curved with a kink at the midpoint or straighter. To show how this might work, the filmmakers overlay a colorful crystal structure of the protein backbone on the animated image of a tubulin subunit. As a small nucleotide with two phosphates (guanosine diphosphate, or GDP) drifts off the subunit and one with three phosphates (guanosine triphosphate, or GTP) slides in to replace it, the subunit straightens. Only when it takes on the straighter conformation can it add onto a growing polymer. Once the sheet reaches a critical length, the edges seal together like a zipper closing up a jacket, resulting in a long, tube-shaped microtubule polymer. [Here's where the moving pictures come in handy. See link at end.]







The newly activated subunits form a sheet that will soon zip up to form the tubular polymer.

Nogales's insight into microtubule *dis*assembly, also called depolymerization, has shed new light on a long-standing puzzle in cell biology: How do microtubules manage to pull chromosomes to the poles in a dividing cell, even though the chromosomes attach to the end of the microtubule that is falling apart? As Nogales puts it, "the kinetochore [a large complex of proteins that acts like a dock for the chromosome to connect with the microtubule] is grabbing onto the microtubule, but the microtubule starts breaking down. So it's like grabbing onto a rope that is burning. Yet somehow the chromosomes are being pulled instead of falling off."

Her revelation came from two key pieces of data. First, her group characterized how the microtubules break down, defining how the columns of the polymer peel back, a bit like the peels of a banana. Second, by studying a key kinetochore complex in budding yeast, they observed that about 16 copies of the complex snap into a ring *around* the microtubule. When microtubules start fraying apart, with their ends curling backward, the fraying action pushes the ring, which then slides along the intact portion of the microtubule, toward the edge of the cell, taking the chromosome with it.

Nogales made her film before she and her collaborators discovered the kinetochore ring. Even so, she says, having the movie makes it easier for people to understand how the system might work. "When you see something moving, you get a feeling of motion in your brain that you don't get from seeing a picture," she says. "Now the only thing we have to do is tell them to imagine a ring around the microtubules, and they see what will happen."

With audiences following her work more completely, Nogales says the value of the movie far exceeds what she paid for it. The company that made it was still testing its product, and so charged her only \$5,000. The real cost for the time-intensive project (it took about 2 months of twice-weekly meetings with the filmmakers) would have been \$50,000. At that rate the company couldn't find any takers and closed its doors. Although she's not sure if NIH or HHMI would agree, Nogales says even that fee might not be too much. She expects her movie to be useful for several years to come, adding, "It was the best \$5,000 I've ever spent."

— RABIYA S. TUMA

FOR MORE INFORMATION: See Eva Nogales's video at www.hhmi.org/bulletin/may2007.









National Academy of Sciences Honors Six HHMI Researchers

TOP ROW: XIAODONG WANG, GREGORY J. HANNON, RANDY L. BUCKNER BOTTOM ROW: JEFFREY M. FRIEDMAN, BARRY H. HONIG, RICHARD M. LOSICK

Five HHMI investigators and one HHMI professor were honored by the National Academy of Sciences (NAS) for outstanding scientific achievements. HHMI investigator Xiaodong Wang, University of Texas Southwestern Medical Center at Dallas, received the 2007 Richard Lounsbery Award for "pioneering biochemical studies on apoptosis, which have elucidated a molecular pathway leading into and out of the mitochondrion and to the nucleus." HHMI investigator Gregory J. Hannon, Cold Spring Harbor Laboratory, won the 2007 NAS Award in Molecular Biology for "elucidation of the enzymatic engine for RNA interference." HHMI investigator Randy L. Buckner, Harvard University, received the 2007 Troland Research Award for "substantive contributions to understandings of the neural mechanisms of memory formation and retrieval." HHMI investigator Jeffrey M. Friedman, The Rockefeller University, was given the 2007 Jessie Stevenson Kovalenko Medal for "the discovery of leptin and its role in the regulation of appetite, energy expenditure, and the molecular mechanisms underlying obesity." HHMI investigator Barry H. Honig, Columbia University, received the 2007 Alexander Hollaender Award in Biophysics for "pioneering theoretical and computational studies of electrostatic interactions in biological macromolecules and of the energetics of protein folding." HHMI professor Richard M. Losick, Harvard University, received the 2007 Selman A. Waksman Award in Microbiology for "discovering alternative bacterial sigma factors and his fundamental contributions to understanding the mechanism of bacterial sporulation."

FREDERICK W. ALT, an HHMI investigator at Children's Hospital, Boston, will receive the 2007 American Association of Immunologists—Huang Foundation Meritorious Career Award for his lifelong work on immune receptor gene assembly and expression. His work has had a major impact in the fields of immunology, cancer biology, and DNA recombination and repair.

ATUL BUTTE, recipient of a 2006 HHMI Physician-Scientist Early Career Award, has been named one of "Tomorrow's PIs" by *Genome Technology* magazine. Butte is an assistant professor of medicine and pediatrics

at the Stanford School of Medicine who works in the field of bioinformatics.

THOMAS R. CECH, president of HHMI, will receive the 2007 Othmer Gold Medal from the Chemical Heritage Foundation. The medal honors individuals who have made significant contributions to chemical and scientific heritage through areas such as innovation, entrepreneurship, research, education, public understanding, legislation, and philanthropy.

Janelia Farm group leader SEAN R. EDDY will receive the 2007 Benjamin Franklin Award for Open Access in the Life Sciences

from the Bioinformatics Organization. The humanitarian and bioethics award recognizes individuals who have "promoted free and open access to the materials and methods used in the life sciences." Eddy is an open-source author of the computer software program HMMER, which allows researchers to search protein sequence databases with statistical descriptions of the conserved sequences in a given protein domain query. He also created the protein domain family Pfam, which has greatly advanced the field of protein classification.

HHMI investigator MICHAEL D. EHLERS, a neurobiologist at the Duke University

Kris Snibbe, Harvard News Office

Medical Center, received the 2007 John J. Abel Award from the American Society for Pharmacology and Experimental Therapeutics. The award is given to a young investigator for "outstanding research contributions in the field of pharmacology and/or experimental therapeutics." Ehlers studies the mechanisms and organelles underlying protein trafficking and turnover in dendrites and their relation to neural synapse formation and function.

HHMI investigator RICHARD A. FLAVELL, an immunologist at the Yale University School of Medicine, was elected in 2007 to the Henry G. Kunkel Society, an international society of distinguished investigative immunologists.

HHMI international research scholar MIKHAIL S. GELFAND at the Research Institute for the Genetics and Selection of Industrial Microorganisms in Moscow, Russia, was awarded the 2007 A.A. Baev Prize from the Russian Academy of Sciences. The award recognizes his work on computational comparative genomics.

ELIZABETH W. JONES, an HHMI professor at Carnegie Mellon University, received the Genetics Society of America's first Excellence in Education Award. This honor recognizes "individuals or groups who have had a significant impact on genetics education from the kindergarten to post-graduate level." Jones is working on an interactive computer software program or "cognitive tutor" to assist undergraduate students in solving genetics problems.

Harvard undergraduate KEVIN KOO was named to the 2007 USA Today ALL-USA College Academic First Team. Koo is a student of HHMI professor RICHARD M. LOSICK in Harvard University's undergraduate experimental biology program.

HHMI investigator RICHARD P. LIFTON, a geneticist at the Yale University School of Medicine, received the 2007 Alfred Newton Richards Award from the International Society of Nephrology for "outstanding basic research in fields relevant to nephrology." Lifton uses genetic approaches to identify

genes and pathways that contribute to common human diseases including renal and cardiovascular diseases.

BALDOMERO OLIVERA, an HHMI professor at the University of Utah, was named 2007 Scientist of the Year by the Harvard Foundation for "his contributions to the study of the molecular mechanisms that underlie nervous system function." Olivera is known for his groundbreaking research with neurotoxins produced by venomous cone snails found in the Philippines. The toxins his lab has identified are widely used in neuroscience research. One such toxin led to the development of Prialt, a drug approved by the U.S. Food and Drug Administration to treat chronic pain.

FELICIA WALTON, an HHMI-supported undergraduate at Duke University, was awarded a 2007 Marshall Scholarship from the British government to study and conduct research in the United Kingdom for up to 3 years. Walton plans to study mammalian cell division at the University of Cambridge.

SPOTLIGHT



ROBERT LUE

Molecular Movie Goes Mainstream

Robert Lue, an HHMI undergraduate program director at Harvard University, received cinematic accolades for his three-dimensional science animation film "The Inner Life of a Cell." Similar to the National Aeronautics and Space Administration's imagined "flights" over distant planets, the film journeys through the microscopic world of the cell. Lue's film was presented alongside Hollywood's best at the Association for Computing Machinery's Special Interest Group on Computer Graphics and Interactive Techniques 2006 Computer Animation Festival. It also won the 2006 Telly Award, a premier award honoring outstanding local, regional, and cable TV commercials and programs as well as video and film productions. ¶ Originally conceived to educate biology undergraduates at Harvard, the film is part of Lue's integrated computer-learning system called Biovisions, a project that bridges the gap between multimedia and science education by using computer animations as supplemental classroom material. Lue's research suggests that, compared with textbook studies alone, animation can boost comprehension by 30 percent. To view the film, go to www.xvivo.net.

A VISUAL PRIMER ON CLONING

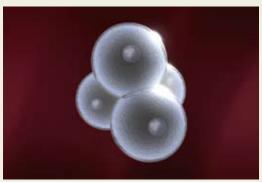
Curious about how Elaine Fuchs was able to create mice from adult stem cells (see "More than Skin Deep," page 10)? You can watch the technique she used, called somatic cell nuclear transfer (SCNT), demonstrated in a video clip and depicted as an animation on HHMI's BioInteractive Website (www.hhmi.org/biointeractive/animations/index.html). The images below, captured from the animation, provide a glimpse of the procedure.



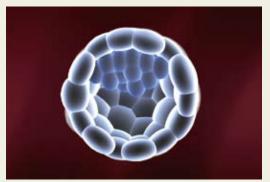
1) In SCNT, the nucleus of an adult body cell—in Fuchs' case, a skin stem cell—is plucked out and injected into an unfertilized egg that has had its own nucleus removed.



2) A reprogramming phenomenon occurs in which the egg cell with the transferred nucleus initiates development.



3) The cell begins to divide, eventually forming a clustered ball of cells known as a blastocyst.



4) Embryonic stem cells harvested from the inner cell mass (dark blue) of the blastocyst can be coaxed to generate a variety of cells that are a genetic match to the nucleus donor (therapeutic cloning). Alternatively, the blastocyst can be implanted into a surrogate mother to create a cloned individual, such as with Fuchs' mice (reproductive cloning).

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Blinding Bias

Almost all English-language scientific and medical journals use anonymous review, in which authors do not learn the names of reviewers, but fewer than 20 percent use blinded review, in which reviewers do not learn the names of authors. Journal editors who use blinded review have argued that blinding serves to decrease bias in the review process. Indeed, several studies have examined the effect of blinding and found that it reduced reviewer bias with regard to personal characteristics of the authors, including nationality, institutional affiliation, sex, friendship with the reviewer, race or ethnicity, and intellectual conformity with the reviewer.

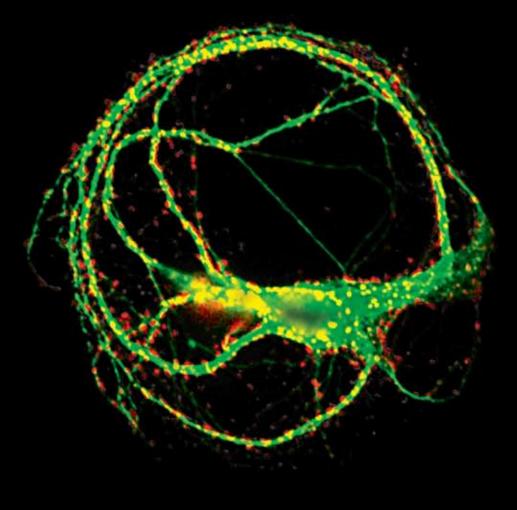
This phenomenon was demonstrated with alarming clarity in a study examining the effects of blinding auditions for symphony orchestras, where, similar to universities, the training period is long, there are many more candidates than slots available, and in which number of positions is highly fixed and turnover is slow. The practice of "blind" auditions (placing a screen between the player and the judge) increased by 50 percent the probability that women would advance out of preliminary rounds, and

explained between 30 to 55 percent of the increase in the proportion of women among new hires and between 25 to 46 percent of the increase in the percentage of women in the orchestras from 1970 to 1996.

From Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering, a prepublished report by the Committee on Maximizing the Potential of Women in Academic Science and Engineering, National Academy of Sciences, National Academy of Engineering, and Institute of Medicine. © 2006 National Academy of Sciences. Reprinted with permission of the publisher, The National Academies Press.

For related comments by Joan A. Steitz, an HHMI investigator at Yale University who served on the committee submitting this report, see "Subtle Things," page 40.





min Dean / Chahman

Island Bound

EDWIN CHAPMAN GROWS NEURONS ON BEADLIKE "MICROISLANDS" TO STIMULATE AND RECORD ELECTRICAL RESPONSES FROM A SINGLE NEURON. AS IT GROWS AROUND THE SPHERICAL ISLAND, THE NEURON IS FORCED TO FORM SYNAPSES—CONNECTIONS FOR COMMUNICATION—WITH ITSELF, SINCE NO OTHER NEURONS ARE AROUND TO "TALK WITH." CHAPMAN USES THE TECHNIQUE TO STUDY THE EFFECTS OF NEUROTOXINS ON VARIOUS NERVE CELLS (SEE PAGE 8). IN THIS CULTURED MOUSE HIPPOCAMPAL NEURON, THE YELLOW SPOTS ARE PRESYNAPTIC NERVE TERMINALS WHERE BOTULINUM NEUROTOXINS ARE TAKEN INTO THE NEURON.

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