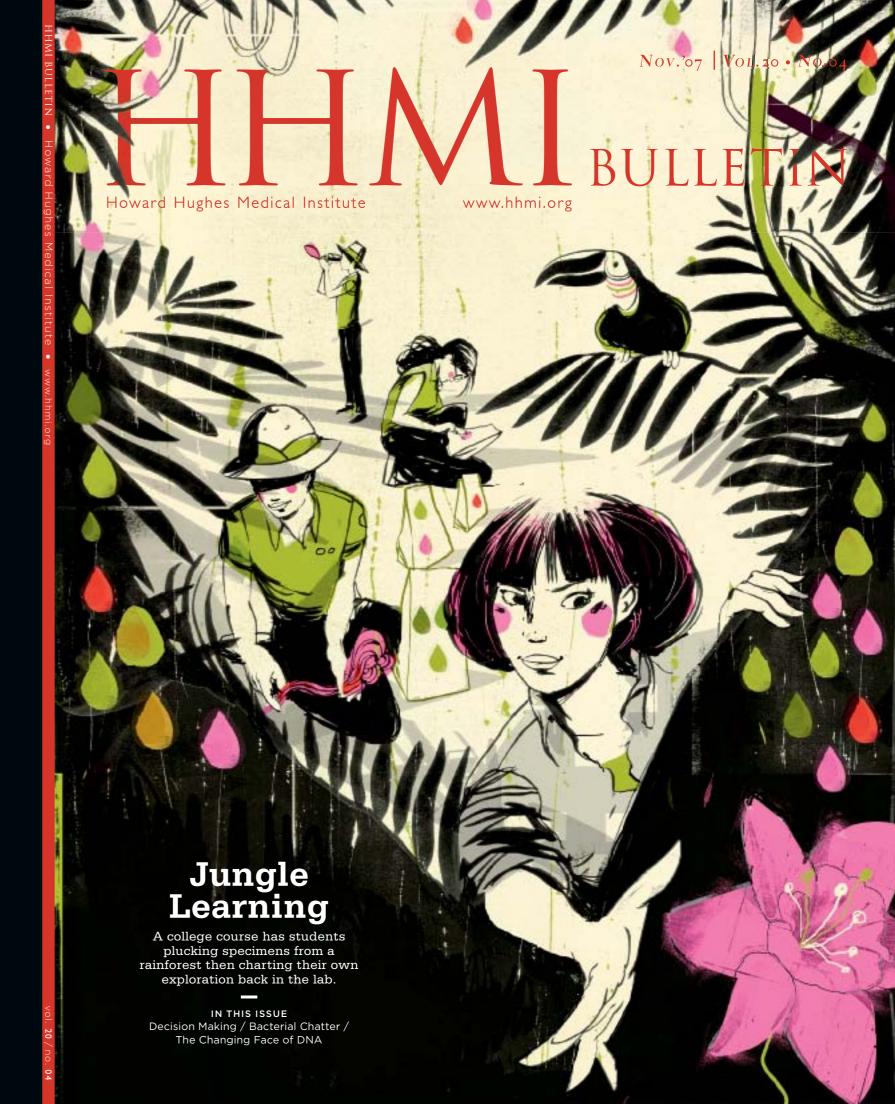


A Fungus Among Us

XYLARIA POLYMORPHA, ALSO KNOWN AS "DEAD MAN'S FINGERS," IS A FUNGUS COMMONLY FOUND ON DEAD WOOD. IN ITS PERFECT STAGE (MUSHROOM STAGE), IT LOOKS LIKE BLACK FINGERS CRAWLING FROM A FALLEN TREE TRUNK. AS PART OF AN EXPEDITION LED BY SCOTT STROBEL (SEE "GOING THE DISTANCE," PAGE 14), YALE UNDERGRADUATES COLLECTED THIS CULTURED ISOLATE OF THE IMPERFECT STAGE FROM A LIVING TREE IN PERU. IT IS ONE OF MORE THAN 500 SYMBIOTIC BACTERIA AND FUNGI THE STUDENTS ISOLATED FROM THE SAMPLES THEY COLLECTED.

HHMI HOWARD HUGHES MEDICAL INSTITUTE

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The Changing Face of DNA

Each individual's genome is its own unique landscape. And variations much larger than slight misspellings in our DNA base pairs may explain our looks as well as our susceptibility to disease.



Deciding Factors

Forage or mate? Stay or run? Innocent or guilty? Deal or no deal? Each is a job for the brain's "jury room."

PIETARI POSTI was born in Helsinki, Finland, in the late 1970s. When other kids asked him to come out and play, he preferred to stay in and draw. Eventually, they stopped asking. Nowadays he spends his days and nights illustrating in the traditional way and by computer, often using both. Posti has worked as a freelance illustrator in Barcelona since 2005. (2)

LINDSAY MORAN is a freelance writer whose memoir, *Blowing My Cover: My Life as a CIA Spy*, received critical acclaim and was a 2005 Washington-area bestseller. Her articles have appeared in *The New York Times, The Washington Post, USA Today*, and *Washingtonian* magazine, among other publications. Moran, who wrote about baby poop biology in this issue, has changed countless diapers as the mother of two young boys. (3)

A Canadian-born conceptual performance artist living and working in New York, CHARMAINE WHEATLEY began drawing obsessively in 1999. In 2003, her nonstop drawing took the form of comics. Never without pens, paper, and a mini-set of Schmincke brand watercolors, she is always ready to record a fleeting moment. Wheatley regularly exhibits in galleries throughout Canada, the United States, and Europe. Her next comic is "Brett's Ball," a true story about two Parks Canada employees on Prince Edward Island. (4)









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On Review

PEOPLE NOT PROJECTS - THAT'S A SHORTHAND DESCRIPTION

for HHMI's approach to supporting scientific research. We strive to identify creative scientists and set them free to explore challenging questions. They don't need anyone's permission if that search moves their work into unexpected directions and fields of inquiry. They have considerable latitude to decide how best to use their resources. They do not submit detailed research plans or annual progress reports.

Given our approach, we invest a considerable amount of time, thought, and energy in identifying promising scientists to join the HHMI investigator community. It is a task that has become more interesting and challenging since we switched to letting candidates submit applications directly to HHMI, rather than requesting nominations from invited institutions. We make a similar investment in the review of their work, which customarily occurs at the five-year mark.

The Institute's scientific leadership makes the final decisions about investigator appointment and renewal, but our decisions are guided and informed by the advice of dozens of scientists outside HHMI who serve on our review panels. They bring vigor and enthusiasm—as well as a high degree of thoughtfulness and fairness—to a process that is essential to the continued vitality of our effort. Like our investigator program, it is people intensive and we couldn't do it without them.

Each year, upward of 60 scientists participate in reviewing the work of our current investigators; this number increases when we hold a competition. Our reviewers include members of our Medical Advisory Board (MAB), who also advise me and my colleagues on everything from our undergraduate education programs to opportunities in international research. By participating in most reviews, even those outside their specific field, the MAB provides a consistent perspective. Scientific Review Board members are chosen for their more specialized expertise, and others may participate on an ad hoc basis to ensure that we fully understand an investigator's work in an emerging field.

Assembling a review panel is analogous to finding the ingredients for a batch of minestrone soup that takes a pinch of this and a spoonful of that to taste just right-complicated by the fact that some "ingredients" are off limits since investigators can't be reviewed by anyone who is a direct competitor or collaborator or from the same institution. HHMI's scientific staff is constantly foraging for fresh talent—scientists with the right mix of knowledge, skill, and temperament, who are comfortable in a collegial, interactive process, and who demonstrate an ability to hear what others have to say. We're also looking for diversity of expertise, geographical distribution, and gender.

You will be able to read more about the results of our competition for investigators engaged in patient-oriented research in the February 2008 issue of the HHMI Bulletin. Many of those who participated in the deliberations found the process electrifying. Why? To use lingo borrowed from the world of diplomacy, our 39 reviewers - brought to the Janelia Farm Research Campus for



"Assembling a review panel is analogous to finding the ingredients for a batch of minestrone soup that takes a pinch of this and a spoonful of that to taste just right.

THOMAS CECH

a two-day meeting-engaged in a full and frank discussion about what constitutes true patient-oriented research and the scientific merits of each candidate. The discussions focused on 40 finalists, selected from 242 applications through previous rounds of review. Fifteen will be named HHMI investigators.

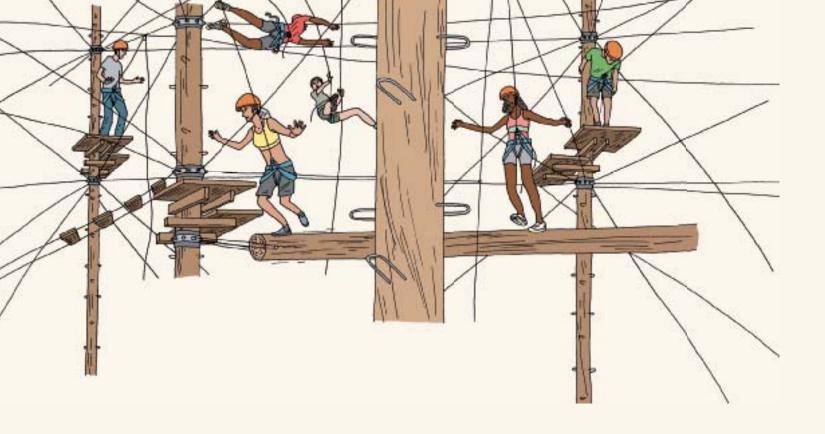
We meet individually with each of our investigators at the five-year mark for a highly focused discussion about their work to determine whether their HHMI appointment will be renewed. We ask that HHMI investigators demonstrate—at a superlative level one or more of the following attributes: that they identify and pursue significant biological questions in a deep and rigorous manner, push their chosen field in new directions, develop new tools and methods that enable creative experimental approaches to biological research, forge links between basic biology and medicine, and demonstrate great promise of innovative and original contributions.

The assessments are challenging all around and, once again, our reviewers play a vital role. Investigators submit materials in advance but also make a 35-minute presentation and have an opportunity to answer questions about their work. One size doesn't fit all, and our reviewers take a broad view of the variety of styles and approaches that contribute to scientific discovery.

We delight in giving our investigators the spotlight at HHMI. But that acclaim needs to be shared with those other scientists who, through their insight and judicious advice, help guide our choices.

Thomas R Cel





On the Ropes

Suspended 40 feet up, his foot stuck between two tightrope wires, graduate student Jay Chodaparambil is not quite sure how to proceed. "Get over it! C'mon, get a move on!" comes the joking encouragement of his research adviser, Karolin Luger. Chodaparambil eases forward as Luger cheers from below.

As a unique twist on the typical summer lab outing, Luger, an HHMI investigator at Colorado State University, has brought her 21 lab members to the school's ropes course for a scorching July day of challenging physical activities, team-building exercises, and outdoor fun—culminating with 40-foot-high tightropes, swaying rope ladders, and something called the Swinging Log of Terror.

After an ice-breaking foam noodle fight, the group gets down to business—two teams prepare to cross a low-ropes course of unsteady wire, rope, and wooden elements without touching the ground. At one end, a team mulls its first challenge: use two wooden "skis" with rope handles to get all members safely to a platform at the opposite end.

The first bunch starts out but soon freezes, unable to coordinate their feet

with their commands of "right" and "left." At one chaotic moment, two people yell "right" and "left" simultaneously. Finally, a loud baritone—undergraduate student researcher John Mecoli—takes control from the rear, and the group begins cross-country "skiing." "We have a natural leader!" says Luger triumphantly.

The Luger lab studies the structural biology and biochemistry of the nucleosome, a unit of DNA wrapped around eight histone proteins, which helps form chromatin. And while lab members certainly resemble tangled DNA wound around ropes, wires, and each other, there is little talk of science. Everyone enjoys cutting loose a bit outside of the lab. Postdoc Young-Jun Park, typically reserved, reveals his inner prankster on the course, rattling his team's wire balancing act.

During lunch, the group finds a shady spot to dig into giant deli sandwiches and gulp Gatorade. Between bites, Luger explains that the ropes course tradition started three years ago, initiated by lab manager Pam Dyer when the lab was smaller. "Everyone got addicted to it and it's really just plain fun," says Luger. "But I also learn who the leaders are and who likes to step back and see where the wind blows."

It helps her manage the lab's growing numbers as well. "In lots of large labs, things can get competitive, which I try to avoid," she says. "If two people are having a problem, I like to say, 'Go hash it out and I will try to facilitate'—

which is exactly what we do here at the ropes course."

She takes off suddenly, running gleefully with two students through the lawn sprinklers. Nearby, postdoc Andy Andrews observes, "I just can't imagine my old research adviser doing that."

—Kendall Powell



"Everyone got addicted to it and it's really just plain fun. But I also learn who the leaders are and who likes to step back and see where the wind blows.

KAROLIN LUGER

Stranger Than Fiction

Joan L. Slonczewski says the fast pace of scientific discovery makes her life as a biologist exciting, but as a science fiction novelist-it's tough.

"It's almost a kind of a shock wave, where the faster your imagination moves, the faster the world catches up," says Slonczewski, a biology professor and HHMI undergraduate program director at Kenyon College in Gambier, Ohio. "It becomes a real challenge to keep a step ahead."

For example, in the novel she is currently writing—her sixth—a space elevator runs from a college based on a space satellite to the planet below, a world disrupted by global warming. "Space elevators used to be a fantastical sciencefiction idea," she says, "yet now people are seriously planning to build them."

According to Slonczewski, her scientific knowledge, especially in her own research field, is her ace in the hole for helping her stay out in front. "Microbiology has undergone an explosion of discovery in the past decade into realms that are as bizarre as anything appearing so far in novels."

In A Door into Ocean, her best-known work (it won the 1987 John W. Campbell Memorial Award for the best sciencefiction novel of the year), human protagonists have purple bacteria living in their bodies that contribute to oxygen storage. "This was based on my research experience with purple bacteria that have unusual metabolic properties," she says.

Slonczewski started writing novels in graduate school, inspired by sci-fi authors Robert Heinlein (particularly his Have Space Suit—Will Travel) and Ursula Le Guin (The Left Hand of Darkness). The culture of the times also moved her. "I was deeply concerned about the nuclear arms race and global environmental change and wanted to write about a future where humans found a way to live with planet Earth."

Her writing has been colored as well by her beliefs as a member of the Religious Society of Friends, or Quakers, which she joined as a student. "The Friends have a unique 'experimental' view of truth that engages God and the natural world on equal terms," she says. "I have found this perspective inspirational in working with students struggling with questions that link faith and evolution, both of which are profoundly important principles to me."

Slonczewski says her experience with the Friends underlies the plot of A Door into Ocean, in which an advanced army invades an all-woman pacifist society, called Sharers, living in the ocean. This novel deals with evolution, ecology, and genetic engineering as well as the power of nonviolent action in social issues.

Now, Slonczewski is completing a book of a different sort: Microbiology: An Evolving Science, coauthored with John Foster, which is scheduled for publication by W.W. Norton & Company in January 2008. Seven years in the making,



In teaching the course "Biology in Science Fiction," Joan Slonczewski uses both a fossilized trilobite, extinct around 245 million years ago, and a furry tribble, an imaginary creature from Star Trek, to explain principles of evolution.

"Microbiology has undergone an explosion of discovery in the past decade into realms that are as bizarre as anything appearing so far in novels.

JOAN SLONCZEWSKI

the undergraduate-level textbook emphasizes genetics and fundamental chemistry, says Slonczewski, and is a "big improvement over the competition." And just as she includes science fact in her sci-fi, she has incorporated sci-fi into her text. "In the textbook I use science fiction examples to dramatize concepts, such as the Andromeda Strain as an example of thinking about an emerging pathogen."

After finishing the text, she plans to finish her novel. The working title? She prefers to keep that under wraps. -Howard Wolinsky





Baby Biology

What if someone told you the key to unlocking one of the mysteries of the human body might reside in your baby's poop? Would you be willing to save and store junior's fecal matter, in the family freezer no less, for the sake of important scientific research?

Luckily for HHMI investigator Patrick O. Brown at the Stanford University School of Medicine, several parents in the Silicon Valley area were willing to do just that, enabling Brown's team of researchers to make startling discoveries about the microbial ecosystem of the human intestine.

Chana Palmer, a former graduate student in Brown's lab, was the logistical mastermind behind what she and her colleagues referred to as the "poop project." She was also the lead author of the paper presenting their findings in *PLoS Biology* in July 2007.

The recruitment posters that Palmer distributed around the Stanford campus, she admits, "were a little vague about what was actually involved," focusing more on the end goal—an understanding of how bacteria colonize a newborn's digestive system—than on the actual dirty work involved.

Ultimately, Palmer was able to enlist 13 pregnant women—including one woman expecting twins—who were willing to collect their little ones' poop over a period of about a year. Palmer provided each mother with pre-labeled vials specifically designed for stool collection. "Like glass tubes you might find at a bead store," she explains, "but with a sterile spoon attached to the lid. We stressed that there was no need to scoop up the whole poop; just about one-fourth of a teaspoon. Sometimes the mothers gave us a bit too much."

Palmer also offered the families minifreezers if they didn't feel comfortable storing the goods among their frozen vegetables and pizzas. One mother admitted to hiding the samples at the back of the freezer when her motherin-law, sure to disapprove, came to visit.

Aside from some important discoveries that emerged from DNA microarray analyses of the stool samples (see "Baby's First Bacteria,"

page 48), Palmer enjoyed the human element of the research.

"We became close," she says of the mothers. "I wouldn't just pick up the poop and leave. I'd stay for a chat."

Indeed, Palmer participated in some of the families' most intimate moments. A few weeks before their due dates, the mothers were asked to provide vaginal swabs. "I met the moms immediately after their doctor's appointments," Palmer explains. "They'd hand off the swab and I'd walk across campus with it in a mini-ice-chest to the deep freezer." The mothers also called Palmer when they went into labor so she could bring to the hospital a small cooler for storing the baby's first poop. Called meconium, that first stool was, in Palmer's words, "a whole different beast." The thick, tarlike substance proved nearly impossible to work with, particularly on microscope slides.

Mothers provided samples of their own first postpartum stools, and also breast milk. Later, fathers were asked to make a contribution in the form of a stool sample. "Most, but not all, were cooperative," Palmer says of the fathers.

One of the more mundane eyeopeners for Palmer, who has no children and was just recently married, "I hadn't realized just how many diapers a newborn baby goes through every day!" —Lindsay Moran



"We became close.

I wouldn't just pick
up the poop and
leave. I'd stay for a
chat.

CHANA PALMER



After a 20-year wait, a team of scientists is building an atlas to map individual brain neurons the way astronomers identify stars in the sky.

10 Retrieving Lost Memories

Scientists have found that certain substances, at least in the lab, prevent neurodegeneration from Alzheimer's disease and restore what was seemingly forgotten.

Many of the brain's sophisticated functions may ultimately arise from the straightforward process of addition.

Our most complex of organs, the brain, takes center stage. HHMI scientists are mapping the signals that direct its development, revealing the logic of the surprisingly simple algorithms it uses to process information, and are even exploring ways to reverse the mind-robbing effects of Alzheimer's disease. One researcher kept a project on the back burner for 20 years until technology caught up with his dream to build a 3-D atlas of the developing nervous system. Never doubt the power of a doggedly curious mind.

Exploring 3-D Space

After a 20-year wait, a team of scientists is building an atlas to map individual brain neurons the way astronomers identify stars in the sky.

of stars. The idea was too far-fetched to tackle two decades ago, when Chris Q. Doe was a postdoctoral fellow. He wanted to build an atlas showing the three-dimensional location of transcription factors involved in generating the fruit fly's central nervous system (CNS). Other atlases, however, covered simpler one- and two-dimensional patterns.



"What we want to do would be like searching Google for the shape of a person's head.

CHRIS DOE

As proteins responsible for initiating gene expression, the many transcription factors in a fruit fly CNS correspond to different types of neurons. Making sense of these patterns could help scientists discover how brain cells develop and go on to form complex circuits.

Doe, now an HHMI investigator at the University of Oregon, gives credit for the idea of creating an atlas to his former postdoctoral adviser, HHMI investigator Matthew P. Scott, who is now at Stanford University. Scott had developed an atlas of *Hox* gene expression for *Drosophila*. He and his colleagues discovered that *Hox* genes, which determine where limbs and segments will form in the developing embryo, are expressed in a one-dimensional pattern. When Doe struggled to make sense of his three-dimensional data, he recalls Scott saying: "Just build an atlas."

Easier said than done. "I remember thinking it would be impossible—and that was with only a handful of CNS genes identified," says Doe. He dropped the idea as technologically unfeasible. The seed, however, was planted.

Now, 20 years and more than 200 transcription-factor genes later, Doe and his postdoc Michael Layden are on the verge of seeing such an atlas become a reality, thanks to a collaboration with computer scientist Eugene W. Myers, a group leader at HHMI's Janelia Farm Research Campus. Doe and Myers met at a neuroscience conference held at the Ashburn, Virginia, campus in March. "We've been working hard at this ever since," says Doe. "The methods of computational biology are now so advanced that it's conceivable to make a computer atlas of the nervous system and map the expression of hundreds of genes."

And if that atlas were searchable, he notes, it would potentially allow scientists to solve two important mysteries in neurobiology: how a stem cell becomes a particular type of neuron, and how neurons come together to



form circuits that allow for all the complex processes governed by the brain. "Our best hypothesis is that neurons that make up a circuit share a transcription-factor code," says Doe. "Many labs are looking to identify these circuits. We're hoping our atlas will help them determine which transcription factors those neurons have in common."

Then researchers could work backward to figure out which genes direct progenitor cells to differentiate into particular types of neurons, says Stephen Crews at the University of North Carolina at Chapel Hill. Crews has created a two-dimensional atlas of gene expression for more than a hundred genes involved in the development of Drosophila midline CNS. Because transcription factors are largely conserved throughout evolution, Crews expects the three-dimensional fly atlas will help in understanding development of the nervous systems of higher animals. "Having a searchable atlas of hundreds of genes that all labs could have access to would really be a huge step forward," he says.

To create the first draft of the atlas, Doe and Layden used fluorescent antibodies to label neuron-specific transcription factors in latedevelopmental *Drosophila* embryos. Then, using confocal microscopy, they produced twodimensional images—optical "slices"—of the resulting three-dimensional patterns of fluorescence. Doe and Layden are creating stacks of these slices for each of the more than 200 transcription-factor genes identified to date.

Myers and his team take these stacks and produce a computer-generated model for each gene that resembles a constellation—glowing points of color in a black three-dimensional space. The last step in building the atlas involves overlaying these patterns on one another. To do this, Myers' team is writing software that aids in the recognition of the patterns created by the glowing nuclei of each neuron. "We're learning to identify these nuclei the way astronomers identify stars in the sky," Myers says. "How do you find the North Star? You look for the pattern created by the stars that make up the Big Dipper. In the same way, we are looking for invariant patterns."

Making the atlas a searchable one will be the next challenge, as current search technology is limited to one dimension.



"We are creating stacks of these slices for each of the more than 200 transcription-factor genes we know.

MICHAEL LAYDEN

"We can easily do a Google search using the name of a person," says Doe. "What we want to do would be like searching Google for the shape of a person's head." According to Myers, no one has yet accomplished this next-level search technology. "We'll learn a lot of biology by doing this," he says, "but we will also learn a lot about exploring and understanding three-dimensional space."

- CAMILLE MOJICA REY



Retrieving Lost Memories

Scientists have found that certain substances, at least in the lab, prevent neurodegeneration from Alzheimer's disease and restore what was seemingly forgotten.

LI-HUEI TSAI RECALLS A LIFE-SHAPING EVENT WHEN SHE WAS A TODDLER living with her grandmother in Taiwan. "Every morning we took a short walk to the local market for groceries. One day, on the way back, there was a thunderstorm, so we took shelter in a little shed. After the rain, I said, 'Let's go home now.' I looked at my grandmother's face and it was completely without expression. 'Home?' she asked. 'Where is home?'"

Mystified and frightened at the time, Tsai came to understand that her grand-mother, then in her 50s, probably had early-onset Alzheimer's disease, a heritable form of the mind-robbing illness that strikes victims in the prime of life. Now an HHMI investigator at the Massachusetts Institute of Technology (MIT), Tsai's mission is to end Alzheimer's disease. "That memory and others like it," she says, "are a big source of my inspiration to carry out this line of research."

Four years ago, her research team created a powerful mouse model that, unlike most previous models, shows the hallmarks of human Alzheimer's disease: massive loss of neurons, the presence of neurofibrillary tangles, and accumulation of amyloid peptides in the brain, accompanied by severe memory loss. What's more, the extensive and rapid brain deterioration in the mice can be quickly turned on and off. "These two characteristics render the mice ideal for looking for potential therapeutics," Tsai says.

Her recent studies focus on a class of enzymes called histone deacetylases (HDACs), which perform many functions in cells and derive their name from their ability to remove small chemical tags, called acetyl groups, from histone proteins-key components of chromosomes. Because histone acetylation patterns can influence gene expression, HDACs have widespread physiological consequences, including in Alzheimer's disease, as Tsai's team first reported in the online version of *Nature* last April. They were investigating a well-described but poorly understood phenomenon called "fluctuating memory," in which even advanced-stage Alzheimer's patients suddenly regain, at least for a short while, seemingly long-gone remembrances. Caretakers have noted that immersing Alzheimer's patients in intellectually stimulating environments tends to evoke these lucid moments.

Remarkably, Tsai and her colleagues observed the same phenomenon in the lab. After inducing Alzheimer's disease in mice that had been taught a battery of learning and memory tasks, they found that those housed in cages with toys and other intellectual stimulation regained "lost" memories of their acquired skills, but the lessons learned by those kept in spartan cages remained forgotten.

When they examined the acetylation patterns of brain histones in these two groups of mice, researchers discovered that the patterns differed dramatically. With that finding, complemented by prior reports of the beneficial effect of HDAC inhibitors on learning and

"It seemed that the existing neurons were more active in communicating with each other and making more synapses.

LI-HUEI TSAI



Results from studies in the lab of Li-Huei Tsai suggest that "memory loss" may be an inaccurate description of certain mental deficits associated with neurodegnerative diseases.

memory, the Tsai team was motivated to test such agents on its mouse model. They discovered that administering an HDAC inhibitor—sodium butyrate or trichostatin A—to the mice instead of environmental enrichment was enough to restore lost memories.

"The brains of the treated mice didn't look any bigger and the number of cells in the brain didn't look significantly different from those of untreated mice," says Tsai. "But it seemed that the existing neurons were more active in communicating with each other and making more synapses."

Tsai cites recent studies on an HDAC called SIR2, which shows anti-aging properties in many organisms. "Alzheimer's disease is a typical product of aging," she says. "So to me, it's quite logical that the next question was whether SIR2 might also be beneficial in treating this illness." With her colleague David Sinclair's research team at Harvard Medical School, Tsai's group tested that notion using the MIT mice and then reported their findings last June in the online version of *The EMBO Journal*. The overexpression of SIRT1—the human version of SIR2—in the mice not only protected them from

neurodegeneration but preserved their cognitive and memory functions as well.

The scientists also tested the neuroprotective effects of resveratrol, the compound in red wine that has attracted considerable scientific and media attention for its possible anti-aging properties. They found that resveratrol, an activator of SIRT1, offered the mice substantial protection from neurodegeneration and preserved their learning ability. Just how SIRT1 protects the brain is unclear to Tsai, since the enzyme targets many other protein substrates besides histones, but her team is trying to pin down its biochemical role in the brain.

Given these experimental results, Tsai is "cautiously optimistic" that new drugs for preventing, even reversing, the effects of Alzheimer's disease may become realities in the not-too-distant future. "I can't tell you it's a year or two from now," she says, "but I don't think it will be as long as 10 years."
-PAUL MUHLRAD

The Sum of Its Parts

Many of the brain's sophisticated functions may ultimately arise from the straightforward process of addition.

Yuste likens the human brain to a computer, he is zeroing in on its breathtaking simplicity, a circuitry whose logic, he postulates, is the stuff of first-grade math. ¶ Yuste, an HHMI investigator at Columbia University, studies the cortex, the seat of perception, memory, and language. He and his colleagues treat the cortex in the same way engineering students are taught to treat a device of unknown function: "We take apart the box,

look at the wires and transistors, and try to identify the logic of its circuitry."

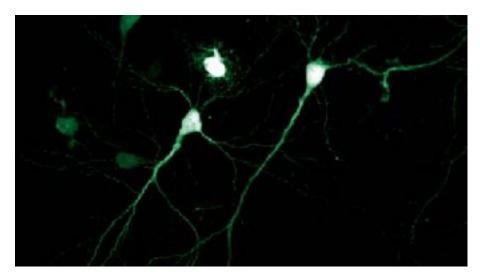
The potential of this reverse-engineering approach is evident in Yuste's recent investigation of an item in the cortical "parts list" called the dendritic spine.

In most cortical neurons, these tiny knob-like features are liberally scattered over the surface of dendrites—the projections emanating from neuronal cell bodies. When one neuron sends a signal to another, the impulse moves from its cell body, through its axon, to its axon terminals, across a gap, or synapse, to the head of a spine on the receiving dendrite and then to the cell body of the neuron.

The fact that most cortical neurons are covered with as many as 20,000 dendritic spines suggests the spines' importance in processing impulses. Yuste's postdoctoral

work revealed that spines are containers for calcium, which controls the strength of the neuron-to-neuron connection. But in a series of papers published over the last two years in *Proceedings of the National Academy of Sciences*, Yuste provides evidence, using slices of mouse brains, that spines also serve an electrical function, perhaps even more important in the neuron's processing of incoming nerve signals.

Working with Roberto Araya, a postdoctoral associate in Yuste's lab, and Kenneth Eisenthal from Columbia's chemistry department, Yuste started with evidence that nerve signals can be transmitted between neurons that *lack* spines. While such neurons are comparatively rare in the cortex, their ability to function without the help of spines—still able to marshal the calcium associated with nerve transmission—



These live dendrites in the brain are covered with slender-necked spines that help to accurately sum all incoming nerve signals.



"We take apart the box, look at the wires and transistors, and try to identify the logic of its circuitry.

RAFAEL YUSTE

suggested that "nature doesn't need spines to accomplish this."

Unable to believe that ubiquitous spines were superfluous, the researchers pursued a hunch that spines had an undiscovered electrical role. Using lasers, they "turned on" individual spines to mimic the arrival of an incoming nerve input. Then they measured the voltage generated in the cell body of the same nerve cell, finding that the amount of current delivered through the spine to the soma was inversely proportional to the length of the spine.

Now it was time to do some reverse engineering to find out why spines were "filtering," or impeding, incoming nerve signals. Why, after all, would evolution select an architecture that diminished incoming signals at the very point where they were received? It occurred to them that "maybe the logic of the design is to enable the nerve cell to add arithmetically, just as you would teach a child to do," Yuste explains. "The spine neck could serve to electrically isolate inputs, thus enabling the soma to add every input without interference."

They then found that, when two spines on the same dendrite were simultaneously stimulated, the voltage they conveyed to the soma was precisely the sum of their signals. At the same time, when two regions devoid of spines were stimulated, they interfered with each other, and the resulting voltage was much smaller than the sum of the two inputs. Thus, not only do spines compartmentalize calcium to regulate synaptic strength, but they also help the neuron accurately add inputs.

The implication, Yuste hypothesizes, is that dendritic spines enable cortical neurons

to work in a linear fashion and serve as adding machines. In a brain marked by a "distributed" circuitry, in which neurons sample incoming information over the widest possible area, a mechanism that accurately sums many signals would gather all possible information.

Yuste's speculation goes further. Perhaps, based on simple addition, nature found algorithms that could be used to build a diverse set of mental functions. Yuste aims to demonstrate this notion in human tissue. If he succeeds, linear summation would be shown to be the elegant operation that renders the cortex a kind of universal computer, able to mobilize elementary math to accomplish such complex (and, paradoxically, nonlinear) ends as thinking, remembering, and imagining.

-PETER TARR

NEURONS ON PATROL

HHMI INVESTIGATOR RAFAEL YUSTE is driven by more than a theoretical interest in the structure and function of the cerebral cortex. As a physician-scientist, he also wants to see what happens when cortical circuits malfunction and what clinicians can do about it. >> WHEN HE STARTED HIS LAB AT COLUMBIA. Yuste, took an interest in epilepsy, a major disease involving the cortex. The first to use calcium imaging to visualize a circuit, Yuste and graduate student Tudor Badea "were able to image the spread of an epileptic seizure, neuron by neuron, for the very first time," Yuste says. More recently, Yuste and postdoc Andrew Trevelyan (also a physician-scientist) carried out experiments aimed at discovering how epileptic seizures-or at least their analogs in mice—spread through cortical territory. Their findings, reported over the past year in the Journal of Neuroscience, showed that seizures advance in a series of small steps controlled by a specialized type of inhibitory neuron. >> "WHEN THEY ARE WORKING PROPERLY and firing, these inhibitory neurons prevent epilepsy from spreading," says Yuste. "You can think of them as policemen,

each responsible for a 'neighborhood' of cortical neurons." Three or four officers might patrol a beat encompassing some 1,000 neurons. When they detect an approaching epileptiform wave, the inhibitory neurons fire, discharging γ -aminobutyric acid (GABA), a neurotransmitter, directly into the cell bodies of neighborhood neurons. >> so LONG AS THEY HAVE A RESERVE of GABA, the neuronal police can stop the wave. A person with epilepsy might experience this as a seizure whose effects are localized. But if the GABAreleasing neurons exhaust their supply, the wave passes through, recruits nearby neurons, and prepares to invade the next territory leading to a full-blown seizure. >> while cautioning that the work to date involves mouse cells. Yuste believes it could eventually lead to new targets for better treatments in people. "Unfortunately, in 2007 the only 'cure' for severe epilepsy is still neurosurgery," he says. "But instead of cutting out a whole section of the cortex, we might find a way of stimulating this specific class of inhibitory cells so that they can stop progression of a seizure." -P.T.



HOW FAR WILL SCOTT STROBEL TAKE HIS STUDENTS TO FIRE THEIR INTEREST INSCIENCE? TO THE **AMAZON** AND BACK.

BY Marc Wortman

ILLUSTRATION BY Pietari Posti "Ain't no mountain high enough, ain't no valley low enough" could be Scott A. Strobel's theme when it comes to turning his students into scientists. There is almost no limit to how far he will go, even accompanying his undergraduates from New England to the heart of a South American jungle. But don't ask him to climb a tree.

A recent journey took Strobel, an HHMI professor at Yale University, and 15 undergraduates from a New York City airport to Lima, Peru, followed by a two-hour flight to Puerto Maldonado, a town in the Upper Amazon rainforest. Then they motored six hours by boat down the Madre de Dios River. A final two-mile slog through kneedeep mud, swarming insects, and pouring rain brought them to the base of an iboga tree (*Tabernanthe iboga*), an immense succulent whose upper branches disappeared in the dense canopy overhead.

Once there, student Daniel Vekhter, a wiry Yale junior from Buffalo, was near his prize. But it was up to him to do the climbing—more than 30 feet overhead and out on a limb stretching from the iboga's thick vine-draped trunk. He was after microorganisms that he planned to spend the coming summer and next school year studying, and that, he hoped, would form the beginnings of his career. With a wary Strobel and his classmates

watching, the 20-year-old slung his collection bag over his shoulders, took off his boots and socks, grabbed a dangling vine, and began his ascent.

Vekhter's and his fellow students' Amazon adventure was a bioprospecting trip, the first offering of an experimental discovery-based science education program Strobel created for Yale undergraduates. The concept for the course won Strobel an HHMI professor's award, which provides him and Yale with \$1 million in support over four years. Few undergraduates ever get the opportunity to learn by doing like Strobel's students. When they applied for the course, they knew they'd be trekking far from home, but they may not have realized just how far—as scientists—the experience would take them.

FIRING IMAGINATION

According to Strobel, most scientists can trace their professional start to a rewarding college research experience. But too many undergraduates who take on research projects abandon science after getting their diplomas. "Students grow discouraged

because they have not experienced enough of science's excitement or opportunities," Strobel says. He asserts that some of the blame rests with the types of projects offered to undergrads. "It's the problem of ownership," he says. "All too often, we give undergraduates too small or too technical a piece of the scientific question to figure out how it fits into the equation." Instead of firing the student's imagination, such experiences often extinguish the desire to pursue science as a career.

Strobel wanted to see what he could do to change that outcome at Yale. "The idea is to give students control of scientific decisions," he says. "That's critical to the success of any research experience, regardless of the student's academic level." He devised an experiment in undergraduate scientific research for which, as he explained in the course description, "There is no lab manual." Students choose plants and microbes that interest them, pluck small samples from an untouched part of nature, and then bring them back to a campus laboratory for analysis using a variety of available techniques-many of which Strobel uses in his own research program, which focuses on basic biological processes including how RNA catalyzes protein synthesis and RNA splicing in the genome.

He drew inspiration from a program launched in 2002 by HHMI professor Graham F. Hatfull at the University of

"THESE STUDENTS' PROJECTS
GIVE THEM A SENSE OF INTELLECTUAL OWNERSHIP

Pittsburgh. After collecting local soil samples, Hatfull's undergraduates and high school students isolate, sequence, and annotate mycobacteriophages—viruses that infect bacteria and are used by researchers to learn about the genetics of numerous diseases. "These students' projects give them a sense of intellectual ownership and project control," says Strobel. "It inspires them to see science as something they can do."

COMPLEMENTARY

STRENGTHS

Scott Strobel had an inspiring teacher from very early on—his own father, Gary Strobel, a renowned plant pathologist at Montana State University. From age 2, Scott would spend days with his father in the biology laboratory. After majoring in biochemistry at Brigham Young University, Scott earned his doctorate at the California Institute of Technology studying site-specific cleavage of genomic DNA. His current interest in the biochemistry of RNA gelled during post-doctoral work in the University of Colorado at Boulder laboratory of Thomas R. Cech, now president of HHMI.

Though their styles differ, his father continues to inspire. Now 69 years old, Gary Strobel is lean and weathered with close-cropped hair. Unlike Scott, 43, whose

experiments never require him to leave the laboratory, Gary's ventures into the biochemistry of natural products regularly take him to distant places. Several times each year, he travels to rainforests and other biologically diverse locations across the planet in search of endophytes—bacteria and fungi that live symbiotically on plants. The fascinating biology of these organisms led Scott to build his Yale course around them, and to persuade his father to lead the Amazon expedition.

Many endophytes produce natural chemicals that inhibit the growth of organisms potentially toxic to the plant host or provide it with some other evolutionary advantage. Endophytes' biological activity has also served human ends, providing a source of chemicals for pest control products, for example, and for many medicines. From cancer therapies to antibiotics, about 40 percent of all prescription drugs derive from natural compounds. Yet, very few endophytes on the Earth's 300,000 plant species have ever been characterized, even though nearly all plants serve as host to one or more bioactive microbes.

The senior Strobel has identified scores of previously unknown endophytes. Several have proven valuable, among them a fungus that produces the anti-cancer drug paclitaxel, more popularly known by its brand name Taxol, and a fungus that generates volatile chemicals that have proven useful for treating human waste.

Scott has accompanied his father on a few rainforest trips over the years, but those were nearly always family vacations, not bioprospecting trips. "That's my dad's type of science," he says. Sitting on a stool in a Yale laboratory sporting overalls and a wide grin, Gary looks like he would happily sleep in a tent in the wild. His son, wearing shirtsleeves, slacks, and a more serious demeanor, acknowledges, "I want to be in a comfortable bed at night." Yet for this HHMI research course, Scott says "trying to combine his brand of science with mine" made sense.

Cong Ma, now a Yale College senior from Williamsport, Pennsylvania, who participated in the HHMI research course, says that the two Strobels' different natures make them complementary, and highly effective, team leaders. "Gary is really encouraging and outgoing. Scott is a little

AND PROJECT CONTROL."

—SCOTT STROBEL

Scott Strobel (right) and his father, Gary Strobel, joined forces to bring their complementary styles and expertise to a discovery-based science course for undergraduates.



Tiny Plant, Grand Adventure

••••

Kaury Eisenman focused her hunt on carnivorous plants. She hypothesized they would be inhabited by more endophytes than other plants because they eat insects that have traveled from plant to plant. The only carnivorous plant the graduate teaching assistant could find during the Amazon expedition. however, was the tiny Drosera montana. Although the mature plant could fit on the face of a quarter, each leaf the size of a pencil tip, Eisenman's discovery is providing five students in the class a veritable fungal treasure chest to explore.

Her hypothesis seems to have been borne out as she isolated three fungi that killed every test organism she exposed to them. She found the colored compounds the fungi produced in culture media "striking and awe-inspiring." Two of the fungi release a dark red substance while a third fungus produces a very bright yellow compound, or mix of compounds.

Undergraduate students have now taken over her potent fungi. They developed two bioassays in which extracts from both red fungi continue to prove highly active. A student noticed that the nearly invisible tips of the Drosera montana's insect-catching appendages are red, possibly due to the presence of the red-producing fungi.

While Eisenman is returning to her graduate studies, she says, "I count myself very fortunate to have been a part of what has turned out to be a grand adventure start-to-finish." —M.W.

more reserved. But both are fun-loving and great characters. I wouldn't have picked anyone else to lead us."

All students participating in the program took a special spring-semester course, taught by Scott and visiting experts. It combined microbiology, pharmacology, plant science, ethnobotany (the study of plants in human culture), conservation, and intellectual-property law. After researching the indigenous plants and the culture of the Amazon, each student-and two graduate student teaching assistantsdefined a theme that would guide his or her plant collection during the expedition. One student collected plants native peoples use to treat tuberculosis infections; another opted for plants likely to produce antioxidants. One aspiring scientist targeted carnivorous plants, while another sought plants used to treat wounds. Vekhter's iboga-tree extracts appealed to him because of their reputed properties for battling opioid addiction. "From a societal point of view," he says, "it would be great if one of our plants had value. That's something everyone in the class cares about."

A DIFFERENT PLANET

While many of their friends headed for spring-break beaches or home, the Yale undergraduates left their world behind. They voyaged to a place in the upper Amazon basin still largely free from the developed world's intervention. "It was

one of the most remote places you can get to," says Ma. They hiked into an undisturbed, primeval forest with plenty to keep them on their toes: along with the biting bugs, he recalls walking past a small but potentially deadly pit viper, a venomous snake known as a fer-de-lance. He also witnessed a giant otter snagging and making a meal of a piranha. "It was amazing," he says.

Gary knows many of the world's rainforests intimately, yet even his knowledge counted as cursory within the overwhelming natural diversity and dense growth the group encountered. "It's not like going to a garden and picking flowers," he says. To scout out their plants within the seemingly impenetrable tangle, they relied on a guide, Percy Núñez, an Amazonbasin native and professional field biologist from Peru's National University of San Antonio Abad in Cusco with an encyclopedic knowledge of tropical botany.

Shouts of "I found my plant!" or calls over the walkie-talkie of "We found your plant!" came frequently as the students spied their prey, recalls Strobel. They used machetes and plastic bags to cut and collect small stems and leaves.

Most specimens had to be collected from upper portions of plants, where endophytes are more likely to be found in abundance and less likely to be contaminated by soil microbes. Hence, Vekhter's high climb up the iboga tree—where he did find the endophytes he was after. Other students collected samples from high branches using clippers attached to long poles. "The way Scott is making us get our scientific chops is really unique for undergraduates," Vekhter says of their adventures.

By the end of the two weeks, the students had found more than half the plants on their lists. For Gary Strobel, it was his most fruitful bioprospecting trip ever. The group returned to Yale with

SHOUTS OF "I FOUND MY PLANT!" OR CALLS OVER THE WALKIE-TALKIE OF "WE FOUND YOUR PLANT!" CAME FREQUENTLY AS THE STUDENTS SPIED THEIR PREY.

samples of around 300 plant species, many of which he had never seen before. All became reference species in the Yale University Herbarium, one of the nation's oldest and most extensive plant-specimen collections, and in Núñez's herbarium at the university in Cusco.

GETTING DOWN TO IT

Upon returning to Yale, the young researchers prepared their specimens for bioactivity screening. They dissected them, culturing minute bits in plates containing growth medium as well as test organisms placed a couple of inches away. The students then waited to see what activity might emerge when the endophytes and their bioactive products proliferated and encountered the test organisms, which included a variety of plant pathogens as well as human-infecting bacteria and fungi. Among them were Candida albicans (a cause of many fungal infections, some now resistant to treatment), Escherichia coli (responsible for many types of infection), and Bacillus subtilis (widely used by researchers as a model organism).

When an endophyte or its products showed visible activity, the students put them through a battery of tests to isolate the source of their bioactivity. DNA samples from several microbes were sent to a Yale laboratory for sequencing. In several cases, the resulting data revealed bacteria and fungi whose genomes differ significantly from any known organism in GenBank, the annotated online collection of all publicly available DNA sequences maintained by the National Institutes of Health. Michelle Schorn, a junior from San Diego, is one of the students who found a novel bacterium. As a result, she says she expects, "to write a paper identifying it and what compounds are in it. Having a publication would be really exciting."

The students probed their microbes further. They grew them in liquid culture and extracted metabolites to look for the biologically active components. The crude extracts were also screened using a variety of biochemical assays. Those steps might include separating out individual molecules using chromatography, studying structure through crystallography, and applying other laboratory techniques to look for interesting and potentially beneficial properties.

As the students dug into their projects, Scott challenged them, "Anything your mind can imagine, go for it. Figure out the taxonomy and what is known. Look beyond that and see what's new. Then you have to decide what you're going for."

Kathleen Fenn may have already discovered something truly new-and potentially medically beneficial—in the rainforest. She collected a stem sample from a Capirona decorticans tree. She hypothesized that it might prove useful after she learned that Amazonian native tribes apply capirona-based concoctions for a variety of medicinal purposes including treating fungal infections, diabetes, and wounds. Back in New Haven, Fenn isolated a strain of pink-colored bacteria from it, which when cultured formed pink crystals on top of the test colonies. A Yale crystallographer identified

those crystals as 2,4-diacetylphloroglucinol (DAPG), a broad-scale antibiotic produced by some strains of Pseudomonas fluorescens bacteria. Fenn's preliminary analysis shows that the bacterial strain she isolated produces DAPG on a scale several times greater than any previously reported. She plans to continue her research in hopes of demonstrating that this strain exhibits unprecedented efficiency in antibiotic production—and to learn more about its properties.

Fenn, like several other students in the class, intends to collaborate with various Yale laboratories to see if her molecules have any promising disease-modulating properties. In fact, a Yale School of Medicine scientist has already invited Schorn to screen the extracts she found using his cellular assay for potential Alzheimer's disease treatments. The undergraduates, most of whom expect to continue working on their projects during the current school year, are already thinking like advanced medical investigators, says Strobel.

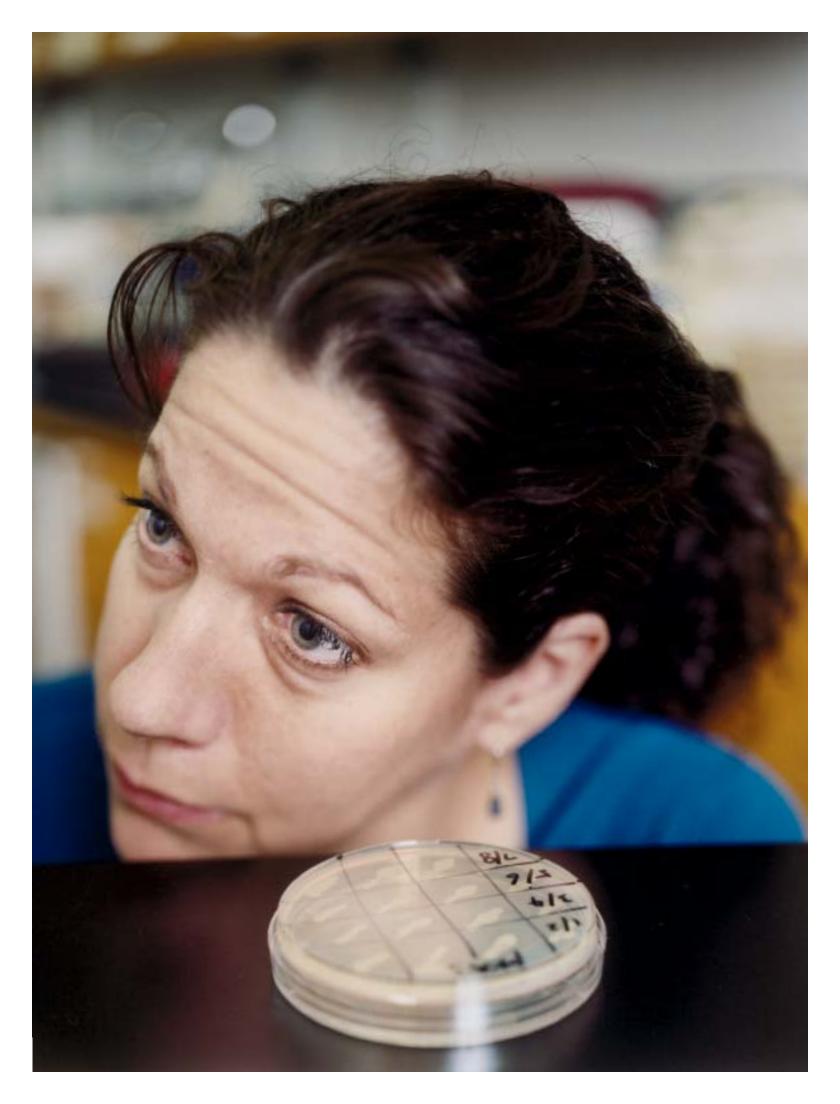
For him, the results prove something he was unsure of at the start. "We're seeing that undergraduate students can go from a jungle trail to complete chemical characterization of a natural product in less than four months," he says. "That's astounding." But much more important to him is the hope that the course has "inspired the scientific imagination" of his students, giving them a "feeling of empowerment to control the direction of an inquiry."

With the HHMI grant, Strobel will repeat the Yale course three times, taking his classes to new locations in search of endophytes. The final outcome of Strobel's experiment in science education may not be known for years to come. For Vekhter, who plans to study his iboga endophyte extracts through his senior year at Yale and intends to "stay in science," the results are already clear. As an undergraduate, he says, "Usually you get plugged in" on a professor's research project, "but here we get to do our own thing." ■



Studying how marine bacteria light up when ready, a scientist known for her communication skills revealed the purposeful chitchat used by these tiny organisms.

by Paul Raeburn photographs by Greg Miller



KNOWN FOR HER FULL-STEAM-AHEAD APPROACH TO LIFE AND WORK, HHMI INVESTIGATOR BONNIE L. BASSLER BEGAN HER CAREER PONDERING OCEAN-**DWELLING** BARNACLES THAT FOUL SHIPS AND SLOW THEM DOWN.

Her graduate adviser had funding from the U.S. Navy to study how certain bacteria provide footing for the barnacles, which cling to hulls and rudders with epoxy-like strength, causing an enormous drag on a ship's progress.

Bassler has picked up speed since then, becoming what one colleague calls a "rock star" of microbiology and earning a 2002 MacArthur Foundation Fellowship, popularly known as a "genius" award. "Bonnie stuck to her guns and knew what she was doing," says Richard M. Losick, an HHMI professor at Harvard University with whom Bassler has collaborated and published. "She is quite extraordinary in her energy and breadth of interests."

It comes as no surprise to people who've worked with her that Bassler's unglamorous experiments with barnacle-involved bacteria led to the puzzle of how and when a little-known ocean-dwelling bacterium becomes luminescent. And in solving that puzzle, she moved from an obscure area of research to a central unsolved problem in microbiology: How do bacteria communicate with each other?

The answers she found have transformed thinking about bacterial communities. She has shown that bacteria, far from being opportunistic loners, are highly social creatures that incessantly chatter among themselves, with the hosts they infect, and even with other species of bacteria by means of a common "language" that no one thought existed. That signaling system has been dubbed "quorum sensing" and Bassler is poised to devise a radically new

type of antibiotic based on interrupting bacterial communication—one that might work against all kinds of bacteria, not just one or a few species.

THE COMMUNICATOR



Bassler, often described as a force of nature, is known not only for her research achievements. She is a distinguished speaker, a gifted teacher, and having a conversation with her is like taking a drink of water from a fire hose. Ask her why she became a scientist, for example. "I had this wonderful experience in graduate school, where I loved doing experiments. I really liked being at the bench, and I really wanted to keep being in school, because Heaven forbid I should actually have to get a real job, I mean, I wasn't going to do that ... and so anyway ..."

Or ask her about teaching an introductory biology class to non-science majors. "We use the word 'evolution' in every lecture. We use it to explain how every protein folds to make its binding site, how the cell membrane and the proteins in it function. We don't use the word to imply anything about monkeys but, rather, to explain every single reaction in one's body that has been optimized to make us alive, or how things have gone wrong to, say, give you cancer. We try to convey to the students that evolution underpins every single, beautiful, magical biological thing that happens." Where she finds time to take a breath is itself a kind of magical biological thing.

Five days a week, Bassler begins her day with a 5:42 alarm, giving her just

enough time to get to the YMCA to teach a 6:15 a.m. aerobics class. She met her husband, actor/dancer Todd Reichart, shortly after she moved to Princeton, when she signed up for a swing dance class; he was the teacher. They still dance off and on. "We look really good at weddings, but that's it," she jokes. Her dual interests in dance and biology led to a friendship with choreographer Liz Lerman, who received a MacArthur Fellowship the same year that Bassler did. Bassler participated with other researchers in the development of a Lerman dance piece called *Ferocious Beauty: Genome*.

Bassler and Reichart (who refers to his wife as "hyperkinetic") also canoe and hike whenever they get the opportunity, often taking an extra week after one of Bassler's far-flung scientific meetings to climb the nearest 14,000-foot peak. "I don't do anything where I have to be attached to a rope and could fall off and die," she says. "But I will walk forever."

With all that exercise, Bassler is athlete trim. She curls her legs up under her on the chair when she talks, and when she wants to make an important point she leans in and whispers, as if confiding a secret. Or she stands up and shouts, if that's what it takes.

Her communication skills serve Bassler well in her teaching, something she considers an essential part of her work. She is director of graduate studies in the molecular biology department at Princeton and also teaches the molecular biology course for non-science majors.



Bonnie Bassler Sensed that a tiny, light-emitting organism could reveal big things about bacterial communications.

"For many of these kids, it's the first class they've taken that isn't subjective," she says. Unlike literature classes or creative writing workshops, in science—she teaches them—"there's a right answer and a wrong answer." Without a class like hers, she says, many of them may graduate from college without understanding that or anything about science. And that, in turn, will make it more difficult for them to address scientific debates as adults, and as citizens.



FOLLOW THE LIGHT

Back when Bassler was working on barnacles, while at Johns Hopkins University, she attended a meeting of Navy-sponsored researchers where Mike Silverman, a geneticist at the Agouron Institute, a nonprofit research organization in La Jolla, California, presented his research.

Silverman's focus was a marine bacterium called *Vibrio fischeri*, which has the ability to light up, or bioluminesce. It is found, among other places, in the "light organ" on the underside of the bobtail squid, with which the bacteria live symbiotically. The squid hunts at night in shallow water, and when moonlight threatens to make it visible to predators by virtue of its shadow on the sand below, the bacteria bioluminesce and the light organ glows. Goodbye shadow.

This clever masquerade depends on an unusual property of *V. fischeri*, discovered in the 1970s. When grown in the laboratory,

A Different Approach for Cholera

Most bacteria want to get into the body, reproduce, and stay forever. They multiply until they have reached sufficient numbers to attack, and then, sensing that they have a quorum, launch the attack. O But Vibrio cholerae, the cause of the devastating infection known as cholera, is different. It lives in contaminated drinking water, which is how it typically enters the body. Once there, it attaches itself to the intestine and begins to manufacture the toxins that cause the illness, even before its numbers have significantly risen. It is virulent from the start. And when it reaches a particular population threshold-which it measures through quorum sensing-it switches off its virulence genes. O Then V. cholerae produces an enzyme that clips many of its number off the intestinal walls. By that time, enough toxin has been produced to cause diarrhea, which washes the newly freed bacteria out of the body. Some of them wind up in puddles and rivers, and eventually in drinking water. V. cholerae's behavior clearly differs from that of most other pathogenic bacteria. It wants to stay in the body for only a short time-to reproduce far faster and more efficiently than it could in a pool of standing water—and then escape in large numbers to infect more hosts. O Although with other infections the idea is to develop a drug that disrupts quorum sensing—so that the bacteria don't initiate virulence—with V. cholerae the opposite strategy applies, says Bassler. "Here, the drug is the autoinducer itself, or a similar molecule that would hasten quorum sensing—and terminate virulence prematurely. We want the Vibrio cholerae to let go before they've increased their numbers and produced a lot of toxin." O In some of their most recent research efforts, Bassler and her colleagues have purified, identified, and synthesized the V. cholerae autoinducer. And they've shown that if they add the synthetic molecule to V. cholerae it turns off virulence. The next step is to try that experiment in mice. If the scientists can curtail virulence in mice, they could have the makings of a powerful new cholera drug. -P.R.

the bacteria don't glow until their population passes a critical threshold. Then they light up simultaneously.

But if bacteria are loners, seeking nothing more than nutrients and an opportunity to reproduce, how do they know their population has exceeded the threshold to light up and then do so in concert?

Silverman figured out that this lightemitting behavior represents an amazing feat of self-recognition on the part of the bacteria. He discovered the mechanism underlying how the bacteria produce and release a chemical signal that their fellows can detect. As the population grows, this chemical accumulates, and the bacteria detect it when it reaches a certain peak. When the level gets high enough, the lights go on.

The general reaction at that Navy research meeting, Bassler recalls, was "So what?" His findings were seen as an oddity in an odd organism, nothing more. But Bassler was fascinated. "I was a biochemist, Silverman was a geneticist. I didn't know any molecular biology or genetics. I didn't really know what a gene or a transcription factor was—nothing! But I knew I wanted to work on these *Vibrios*. I ran up to him—literally ran—after his talk, and said, 'You have to take me on as your postdoc.'" Despite her lack of experience, he did take her on. "I still don't understand that," she says, laughing.

DO WE HAVE A QUORUM?



Silverman, now retired in Jackson Hole, Wyoming, remembers it differently. "She came from a good lab, and I ran a small operation and I needed her," he says. "From the time she arrived, she worked hard. I would come into the lab at night, and there she was. And she would be there again in the morning." She soon asked for more responsibility, and he gave it to her. "In Wyoming, they say give a horse its head—let it run," he says.

In Silverman's lab, she began working on *Vibrio harveyi*, a species closely related to *V. fischeri* and also bioluminescent—again, as long as its population is large enough. Bassler's job was to learn how the bacteria produce and monitor the population-indicating chemical signal.

She started making mutants of the bacteria—to try to knock out the signal so that they wouldn't illuminate. But she couldn't get them to go dark. Sometimes they were dim, but they always lit up. That led to the first of a series of discoveries that, she says, were then difficult to imagine—but seem perfectly obvious in hindsight. V. harveyi, it turned out, has not one chemical signal but two. "You knock one out and the other one works, and they still light up," she says.

Another surprise was that the two *Vibrio* species use different molecules for signaling and different mechanisms for detecting those signals. Because they are so closely related, Bassler and everyone else had guessed they would use the same signaling



machinery. It was interesting work but still considered at that time to be an anomaly of these two bizarre bacteria.

"Everybody kept asking me 'Why do you want to study bioluminescence?' and I kept trying to explain that I wasn't studying bioluminescence," says Bassler. "I was trying to study cell-to-cell communication. Bioluminescence was the thing we could see in the lab—a remarkably easy way to detect when cells 'talked to each other' with the aid of these chemical words."

In the early 1990s, other scientists began to investigate chemical signaling in terrestrial bacteria as well, finding that it was not limited to marine oddities. "Now we understand that probably *all* bacteria use chemical

communication, likely with multiple signals," Bassler says. "They have incredibly complicated chemical lives, of which we so far understand almost nothing."

Bacterial chemical communication is now referred to as "quorum sensing." That is, the bacteria determine when their population has attained a quorum, so to speak, and that tells them they can go into action in unison—doing whatever they need to do. Not only do they converse with one another and then act simultaneously, they also divide up chores and specialize.

"They're recognizing that if they have the right number—and they synchronize their behavior—they can carry out tasks that they could never accomplish if they acted as individuals," explains Bassler. Thus, long before the appearance of multicellular organisms, bacteria had devised a way to act together, as if they were a multicellular organism.

Bassler's work gave bacteria a central role in the development of higher forms of life on earth. They have survived for billions of years not only because they are tough but also because they are far more sophisticated than anyone had realized.

These big-picture observations attracted other scientists' attention. Princeton professor Thomas J. Silhavy, who helped bring Bassler to Princeton, says he saw that her work on Vibrio "could lead to some

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BY STEVE OLSON

Each individual's genome is its own unique landscape. And variations much larger than slight misspellings in our DNA base pairs may explain our looks as well as our susceptibility to disease.

n the basement of the Foege Building on the campus of the University of Washington, the DNA of a woman known only as G248 lies in thousands of tiny wells inside a freezer cooled to –84°C. Five floors above, HHMI investigator Evan E. Eichler points to her DNA as the harbinger of a new way of thinking about human genetics.

"The human genome" is a misnomer, according to Eichler. G248 has big sections of DNA that other people don't have, and she's missing DNA that most people do have. "In the last few years, it's been shown that big changes in DNA—insertions and duplications and deletions and inversions—are extremely common in the population," Eichler says. "That's the first important point. The second important point is that these changes play a role in human disease—everything from HIV susceptibility to autism to mental retardation to epilepsy."

A few years ago, most human geneticists would have been very skeptical about such a statement. At that time, geneticists focused almost exclusively on spelling differences in the human genome—places where the chemical bases that make up DNA, represented by the letters A, T, C, and G, differ from one person to another. According to the thinking of the day, these individual changes in DNA codes largely accounted for differences in our genetic susceptibility to disease and in our physical appearance.

But in the first half of this decade, a handful of geneticists, working independently at laboratories scattered across the United States and Canada, began to notice something strange. As they looked more carefully at human DNA, they found that some people had multiple copies of big sections of DNA, hundreds or thousands of base pairs long. Sometimes these structural variants, as they came to be known, were in DNA regions that didn't seem to be doing anything. But sometimes they were in

regions rich with genes, so that some people had more copies of particular genes than other people.

"We were finding a huge amount of copy number variation—that was the message," says another pioneer in the study of structural variation, Stephen W. Scherer, a former HHMI international research scholar who directs the Centre for Applied Genomics at the Hospital for Sick Children in Toronto, Canada.

The discovery has been a revelation for many geneticists. "A lot of the more complex disorders are not explained by coding variation, which is what people were looking for," says HHMI investigator Val C. Sheffield, who for years has suspected that structural variation might play a prominent role in the eye diseases he studies in his University of Iowa lab. "But until recently we haven't had the technologies to look at variation on a genome-wide scale."

The new picture that Eichler, Scherer, and a handful of other geneticists have been painting differs radically from the traditional view of our genome. Instead of the book of life, DNA is more like the scrapbook of life. Sentences, paragraphs, or entire chapters are copied and haphazardly inserted into various parts of our genome. In some people, the same page repeats over and over, while other people don't have that page at all. And geneticists have been tying this structural variation to an increasing number of diseases. "It's amazing," says Scherer. "At human genetics meetings, 30 to 40 percent of the talks have a direct focus on copy number variation."

"WE'RE FIND_NG
NEW PARTS OF THE
HUMAN GENOME,
AND THAT'S A
POWERFUL THING."

EVAN EICHLER

The discovery of structural variation was partly a consequence of better technologies and new data. But it was also a case, says Eichler, of "good luck favoring the prepared mind."

DUA CHUЯNING

"I KNEW THAT I WANTED TO DO GENETICS when I was in grade 9, and by grade 10 I knew that I wanted to do human genetics," says Eichler. He grew up on a farm in far northern Canada, where winter locks the landscape in icy splendor. His father grew wheat and canola in summer and taught French in a nearby town the rest of the year. His mother raised Angora rabbits, whose wool she would spin into yarn for sweaters. "My mother was one of those people who didn't like dyes, so she decided that she

wanted a natural variation of colors," Eichler says. "She said to me, 'Can you figure out how to get these other colors, these creams and buffs and so on?' That's where I learned the basic genetic coat color system. I got a book, drew my first Punnett squares, and within about a year I was producing true lines of different colors. I knew at that point that this was probably the coolest field ever."

After receiving a baccalaureate from the University of Saskatchewan and working in a molecular virology laboratory in Munich for a year, Eichler enrolled in 1991 in the genetics program at Baylor University. Though he and his Canadian wife struggled with the climate and culture shock of living in Houston, it was the perfect place for Eichler scientifically. He began investigating the genetic disorder fragile X syndrome and "absolutely fell in love with research." His faculty adviser, David Nelson, was "a brilliant scientist and mentor who encouraged a lot of free thinking," Eichler says. "He didn't lord over me at all but let me hang myself with my own proposals."

Fragile X introduced Eichler to the instability of the genome. It occurs when mutations make a particular part of the X chromosome much longer than usual, inactivating a gene critical to development of the brain and other parts of the body. "The idea that an unstable region of the genome could increase the

A TRUE INDIVIDUAL

To be completely accurate, the Human Genome Project should have been called the "Half-of-a-Composite-Human Genome Project" because the DNA sequenced came from a single set of chromosomes drawn from several donors. Our cells contain two copies of every chromosome, with one copy coming from our mothers and one from our fathers. Therefore, the structural variation carried in our parents' chromosomes is passed down to us—making for a lot of variation in our own cells.

Recently, a team of researchers that included J. Craig Venter and Stephen Scherer compared the chromosome pairs in Venter's DNA. They found much more structural variation between his chromosomes than most geneticists expected. Forty-four percent of the genes on Venter's chromosomes differ from the corresponding genes on the other member of the chromosome pair. And three-fourths of the total variable DNA content between chromosome pairs arises from structural variants, with one-fourth coming from changes in individual DNA letters. —S.O.

probability of a disease a hundredfold or a thousandfold—that's the idea I fell in love with," Eichler says. "I haven't strayed far from those roots."

While at Baylor, Eichler also began working on a study associated with the Human Genome Project, which was just then getting under way. He was attaching short DNA probes to portions of the X chromosome when he noticed that the probes also were binding to parts of chromosomes 2, 12, 16, and 22. "That was odd," Eichler recalls. It was as if portions of human DNA had been copied and scattered across the genome. "I began to think, 'How widespread is this?""

In 1997 Eichler moved to Case Western Reserve University, where he continued investigating the genome's structure. During those years, duplications in the human genome were becoming a big problem for the Human Genome Project. When DNA is broken into pieces for sequencing, duplications make it hard to put the pieces back together, because one copy can be mistaken for another. Eichler and his coworkers took on the computer-intensive job of calculating the frequency of duplications from data being generated by both the public and the private sequencing efforts. Using PCs from CompUSA and fans from K-Mart to keep the computers cool, they found "there was a lot more duplication than anyone had thought," Eichler says.





Geneticists like Evan Eichler (top) and Stephen Scherer are tying structural variation seen in our genomes to an increasing number of diseases.

His team continued to study duplications after the release of the draft human genome in 2000, and they discovered that many were occurring in particular "bad neighborhoods" of the genome. There, multiple copies of DNA sequences made the genome susceptible to further rearrangements through a process known as nonallelic homologous recombination (see sidebar, page 31). The DNA in those regions seemed to be "churning," continually rearranging itself from one generation to the next. Eichler was sure those rearrangements had consequences for human evolution and health. But what were they?

HTJAEH NO TCAMI BHT

ABOUT THIS SAME TIME, AT TORONTO'S HOSPITAL FOR Sick Children, Scherer was equally puzzled by what he was seeing in the genome. He and his colleagues were searching chromosome 7 to uncover genes involved in disease. In the process, they were uncovering massive and unexpected differences in the chromosomes of different people. "Most geneticists thought that if you had a large genetic change, it would be associated with

disease all the time," says Scherer. But he and his team were finding big differences that didn't seem to have an obvious effect on health—including million-base-pair insertions or deletions, "which was really unbelievable."

Many geneticists were skeptical. At that time, the technologies they were using were so new that the differences might have come from experimental design or malfunctioning equipment. "We were criticized a lot," Scherer says. "My first grant application [to study structural variation] was rejected, because people said it couldn't possibly be true."

But as analytic techniques improved, so did the evidence for substantial structural variation. Charles Lee of Brigham and Women's Hospital in Boston had found similar DNA differences, as had a group at Cold Spring Harbor Laboratory led by Michael H. Wigler. By about 2003, the case for widespread structural variation in the human genome was becoming unassailable.

Furthermore, evidence was accumulating that some of these variants influence health. The human genome regulates itself through a

process still largely unknown. But variable numbers of a gene can produce a greater or smaller amount of a protein important to the body, and a duplicated section of DNA can disrupt the function of an important gene.

As Scherer and others investigated the genomes of people with genetic disorders, they found that structural variation often seemed a more likely contributor to the disorder than DNA spelling differences. Schizophrenia, Alzheimer's, Parkinson's, autism, kidney disease, and many other diseases were linked to structural variation. "We've been shocked to see how quickly the idea has been adopted and how many diseases are being associated with large structural variants," Scherer says.

In the past couple of years, Scherer has focused on structural variants in patients with birth defects and neurological disorders. For example, at the Hospital for Sick Children screens of children with unexplained genetic disorders have shown that some 20 percent have structural changes in their DNA that may contribute to their conditions. He also has been participating in studies to identify and characterize structural variation in the

genome, including differences between chromosomes in the same cell (see sidebar, page 29). "It's incredible how many people are using these data, from commercial companies to clinical geneticists to everyone in between," he says.

WHY VASIATION?

AT THE UNIVERSITY OF WASHINGTON, WHERE HE MOVED in 2004, Eichler and his colleagues also have been delving into the link between structural variation and disease. In one particularly intriguing study, they examined the DNA of 290 British children with neurological disabilities. "We were looking for recurrent deletions in regions of the genome that are highly dynamic," says Andrew Sharp, the postdoctoral fellow in Eichler's lab who headed the project.

Of the 290 children, 16 had deletions or duplications that are "likely to be pathogenic," according to the group's September 2006 paper in *Nature Genetics*. Remarkably, four had very similar but not identical deletions on the long arm of chromosome 17. All four, though unrelated, had very similar features, including silvery hair, blue eyes, and a bulbous nose—"they could be brothers and sisters," says Sharp—but their shared characteristics hadn't been noticed before. And the region of their deletions included several genes implicated previously in neurological and behavioral conditions.

Building on that success, Eichler's group has begun examining the connection between structural variation and a range of more common diseases. "The million dollar question is: What is the genetic basis of diseases like diabetes, hypertension, and high cholesterol levels?" he says. "We know there is a genetic factor, but what is the role of single base pair changes versus structural changes?"

To answer that question, Eichler and a group of colleagues known as the Human Genome Structural Variation Working Group have decided to get a better fix on where the structural variation in our genome occurs. The freezer in the basement of Eichler's laboratory containing the DNA of G248 is one of 62 freezers scattered around the United States, each containing the DNA of a single individual. The working group will compare each donor's DNA with the reference sequence from the Human Genome Project, looking for locations where the DNA doesn't line up. Wherever they find a discrepancy, they'll sequence the DNA to identify the differences.

Understanding human disease is the main objective, but Eichler wants to know something else. Why did variable regions of our genome evolve, and what purpose do they serve?

Eichler's hypothesis is that structural variation is a way for our genomes to remain fluid and adaptable. As our ancestors encountered new environments and new circumstances, continual rearrangement of their DNA would have generated lots of evolutionary experiments. In fact, initial comparisons have shown that humans and other primates have much more structural variation than do other mammals. Eichler speculates that the unique abilities of primates—our elaborate social structures and communication abilities—may be related to the amount of structural variation in our genomes. "Maybe the cost of having

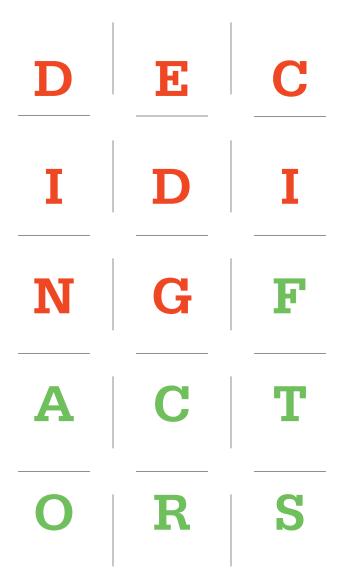
these new abilities is the possibility of disease caused by genes that allow us to adapt to the right environments at the right time," he says.

The discovery of structural variation has shattered the image of the human genome as an inert and largely stable object. Instead, there are as many human genomes as there are humans, and each unique assemblage of DNA has its own strengths and weaknesses. "My wife and I had a baby just two months ago, and I joke with her that it's amazing that any of us ever comes out normal, knowing what we know now," Eichler says. "But I think the right answer is that none of us is normal. And that's an enlightening feeling, to realize that no one has the perfect genome."

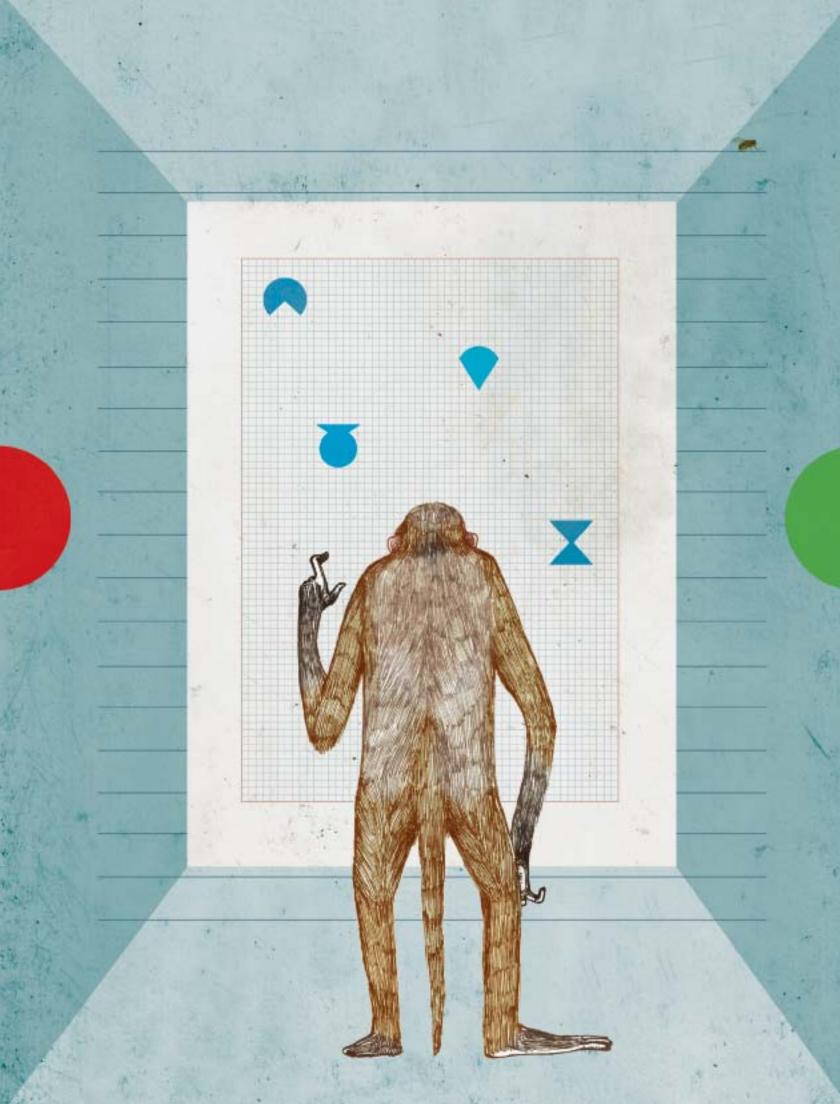
SWAPPING SEGMENTS

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Many structural variants in the numan genome arise when the male and female sex cells (egg and sperm) are preparing chromosomes to pass on to the next generation. During this process, the two members of each chromosome pair line up next to each other and swap segments through a mechanism known as recombination. But sometimes the chromosomes misalign. Duplications in the genome cause the wrong parts of chromosomes to line up next to each other, so that when the chromosomes swap parts, genes are added to one chromosome and deleted from another. The result is a new structural variant—an evolutionary experiment ready to be tested against nature. —S.O.



Forage or mate? Stay or run? Innocent or guilty? Deal or no deal? Each is a job for the brain's "jury room."



Whether

you're a

FRUIT

F L Y

or a

FINANCIER,

life is an

endless series

of decisions.

The world is an uncertain and changing place, to which humans and animals respond by considering the potential reward and cost of different options and estimating the odds of success before committing to a choice.

Neuroscientists have set their sights on identifying the network of cells, circuits, and chemicals—the brain's "jury room," so to speak—where the evidence is weighed and verdicts decided. "There are extremely few examples where we really know what the nervous system is doing from sensory input to a behavior," says Cornelia Bargmann, an HHMI investigator at Rockefeller University. "We can map them out in simple reflexes, like an animal's escape response, but what we'd really like to understand is the steps by which information is transformed and integrated all the way through."

Researchers, including HHMI scientists, have already done prodigious work over several decades to piece together how animal and human nervous systems detect sensory information—especially sights, odors, and tastes—and encode it in electrical signals in the brain. For example, HHMI investigator William Newsome, at Stanford University, identified specific neurons in monkeys that detect the direction in which an object is moving. On the output side, Newsome and others have mapped circuits that direct motor activity, such as a monkey's eye movements in response to a stimulus.

Bargmann and HHMI investigator Michael Shadlen, among others, want to uncover the critical cells and circuits that complete the chain from input to output—the bridge between sensation and action. Exploring this arena provides "a window on higher brain function," says Shadlen, a neurobiologist at the University of Washington. He's especially interested in "how humans and other complex animals take a bit of evidence from the world and hold onto it for later use, or combine it with other information."

With new tools and experimental designs that range from straightforward to elaborate, HHMI researchers are devising the means to observe and map decision making in simple organisms and complex primates. They are observing risk assessment and survival choices made by worms and flies—for themselves as well as for their offspring. Studies of monkeys are revealing circuitry involved in more sophisticated learning and keeping track, or playing the odds. Ultimately, they hope to understand higher cognitive abilities such as reasoning and deliberation. One thing made clear by these early studies: "thinking" like a statistician is not exclusive to humans.

Single-Neuron D E T A I L S

Human studies in psychology explain human choice behavior in economic, medical, ethical, and crisis situations, among others. Peering into the brain itself, functional MRI devices can locate activity in the cortex as people perform decision-related tasks. Such experiments have identified particular brain areas and structures that appear to be crucial, but the methods do not have sufficient resolution to tease out the exact neural wiring involved. For this reason, among others, experimental animals of several types offer numerous advantages.

Scientists like Shadlen want the details. He is seeking answers "at the level where single neurons are discharging and making decisions," he says. "You can't study that with functional imaging."

As monkeys play visual discrimination games that require a correct choice to win a reward, Shadlen records activity in groups

of single brain neurons. He varies the rules of the games to test different components of the decision process and determine how they are represented in the ebb and flow of neural activity.

When Shadlen was a postdoc in William Newsome's lab, the two researchers identified nerve circuits in the cerebral cortex of monkeys that became more active when the animals made a decision about visual information with which they were presented. These neurons were located in the lateral intraparietal (LIP) area of the cortex.

More recently, Shadlen designed a set of experiments to test the monkeys' ability to make a correct choice when they had to sum up statistical clues presented in a short series. People do this all the time: think of a poker player calculating the changing odds of winning a pot as she draws additional cards into her hand.

The research, published by Shadlen and Tianming Yang in the June 28, 2007, issue of *Nature*, found that the monkeys became quite adept at the task, showing that they were capable of probabilistic reasoning.

"No one had ever tried to train a monkey to do this kind of thing," says Shadlen. "We had no idea if the monkey could."

He and his colleagues trained two monkeys to stare at a point on a screen for several seconds, then shift their gaze to either a red spot or a green spot; if they picked the better target, they improved the chances of getting a reward. Sometimes the red spot brought the reward and sometimes the green, but even the better choice did not always pay off—it's a matter of playing the odds.

In each trial, the monkeys were shown four different shapes on the screen, one after another, every half-second. Each shape signified a different probability value of success, alone and in combination with the other shapes. If the monkey correctly combined the probabilities, he was likely to move his eyes to the correct target and improve the odds of winning a reward.

While the monkeys were playing this game, the researchers recorded electrical activity from 64 individual nerve cells in the LIP areas. The rate of firing in the nerve cells increased or decreased whenever the animals saw a new shape on the screen that altered the probability of a particular target being the correct choice. As the subject became more convinced of the right choice, the LIP neurons increased their firing rates. Shadlen and Yang showed that the quantity computed by the monkey's neurons could be described by a mathematical term, the "log likelihood ratio"; in other words, the logarithm of probabilities.

"It was enormously satisfying to watch a monkey add and subtract in his head and to keep a running tally of the state of odds in favor of one proposition and against another," Shadlen says. "To see these operations carried out by neurons in the brain was breathtaking."





Michael Shadlen (top) and Cornelia Bargmann study decisions in animals to gain insights into higher cognition.





Postdoc Rebecca Yang (right) and mentors Yuh Nung and Lily Jan observed fruit flies making choices for their offsprings' survival.

Tracking from T O U C H

Neurobiologist Ranulfo Romo has developed techniques to locate decision-making neurons involved with the monkey's sense of touch—the somatosensory system. Through many years of painstaking work, Romo, an HHMI international research scholar at the National Autonomous University of Mexico, has succeeded in recording neuronal activity simultaneously in several areas of the monkey cortex. His goal is to track sensory signals created by stimulating the animal's finger, following them from one cortical area to another as the monkey forms a response.

In Romo's experiments, a monkey receives a gentle stimulus to a finger and then another one a split-second later. The monkey's task is to compare them and press a button indicating which stimulus it perceives as stronger. To accomplish this, the monkey has to retain a sensation of the first poke in very short-term "working memory" while it takes note of the second stimulus and compares the two. So far, Romo has shown that the touch signals are initially received and encoded in electrical activity patterns in the primary somatosensory cortex. These patterns are sent on to the secondary somatosensory cortex, and then to the prefrontal cortex of the brain's frontal lobes. It's here that the second wave of touch signals are combined with memories of the initial stimulus (which came less than a half-second later).

"This comparison creates a decision signal that determines which stimulus the monkey is going to report as stronger," comments Romo. "We are seeing how neurons are interacting with each other to shape behavior." His next challenge is to determine whether the signals are processed by one brain area after another, or whether they somehow all work on the information simultaneously, controlled by some "master" controller.

Worms Make C H O I C E S

Although monkeys do not approach the sophisticated brain function of humans, they can be trained in tasks that illuminate different aspects of human decision making. Other animal models have other advantages: they are inexpensive, reproduce quickly, and large numbers of them can be used in studies. Decision behavior has been identified, for example, in the roundworm Caenorhabditis elegans and the common fruit fly Drosophila, which also lend themselves to genetic manipulation as a means of singling out nerve circuits of interest.

Rockefeller University's Bargmann has devised minuscule mazes, coaxing *C. elegans* through them with food rewards (and deterrents). Because every single gene and nerve cell in this worm has been mapped—its nervous system, for example, contains just 302 neurons—Bargmann can trace decision-making functions, if any, to specific nerve cells.

She and her colleagues have looked for such behavior, asking whether the worms can learn to associate a particular choice with a pleasant or disagreeable sensation. The researchers designed their miniature mazes using technology from the microfluidics field, with small channels projecting out like the arms of a starfish: the end of each arm contained tasty bacteria to lure the worms in their direction.

Then came the switch: the scientists infected the worms with disease-causing bacteria that made them sick. As a result, their previously preferred maze channels were now associated with an unpleasant feeling and the worms avoided them. "So, signals from nerves that make serotonin [a chemical messenger that triggered the sick feeling] converged with signals from the olfactory neurons [which sensed the bacteria to which they were initially attracted]," says Bargmann, "and the worms associated one with the other."

If not a full-fledged decision, this avoidance was at least a choice, Bargmann notes. In new research, she is studying how changing conditions influence the foraging behavior of roundworms. In their hunt for food, the worms search a region more thoroughly when food is expected nearby than when they think food is unlikely; it's as if the roundworms are doing the numbers and playing the odds.

Tiny Mothers' D E C I S I O N S

Rebecca Yang has been attempting to learn more about the decisionmaking capacities in fruit flies by using little more than some *Drosophila* food, a video camera, and her own ingenuity. "No one had ever tried to train a **M O N K E Y** to do this kind of thing. We had no idea

MICHAEL SHADLEN

could."

if the monkey

Yang, a postdoc in the laboratory of HHMI investigators Lily and Yuh Nung Jan at the University of California, San Francisco, studies the genetic basis of choice behaviors. While observing pregnant fruit flies in miniature plastic chambers she designed, Yang noticed that the females spent considerable time searching their environment for a suitable spot to lay their eggs.

She concluded that the *Drosophila* females considered both the consistency and taste of the medium on which they walked before committing their future offspring to a specific site. "After all, selecting an appropriate site to lay its eggs is presumably the ultimate decision a fly mother has to make, as the consequences of such decisions are likely to have a significant impact on the reproductive success of the species," says Yang.

In one experiment, she placed pregnant fruit flies in a small plastic chamber with a sweet substance on one half of the floor and a bitter compound on the other. Would the flies choose one side over the other for egg laying? Surprisingly, the mothers-to-be shunned the good-tasting medium and favored the bad-tasting side to deposit their eggs.

"Initially, I assumed that maybe I had accidentally switched the flavors," recalls Yang. "So I checked by licking them!"

After further trials, Yang concluded that a pregnant fly will lay eggs on a sugary medium if that's the only choice, but if there is a non-sweet alternative, it will opt for that side. Why? Yang can't say for sure, but she speculates that perhaps the bitter location is less likely to attract predators that could jeopardize the offspring. "The fly's response to the sucrose medium isn't automatic," the researcher notes. "Its decision to accept or reject the sweet medium as an egg-laying site appears to depend on the availability of 'better' options." Yang has identified some of the nerve pathways that control egg laying, and she plans to use genetic tools to further analyze simple decision making in animals.

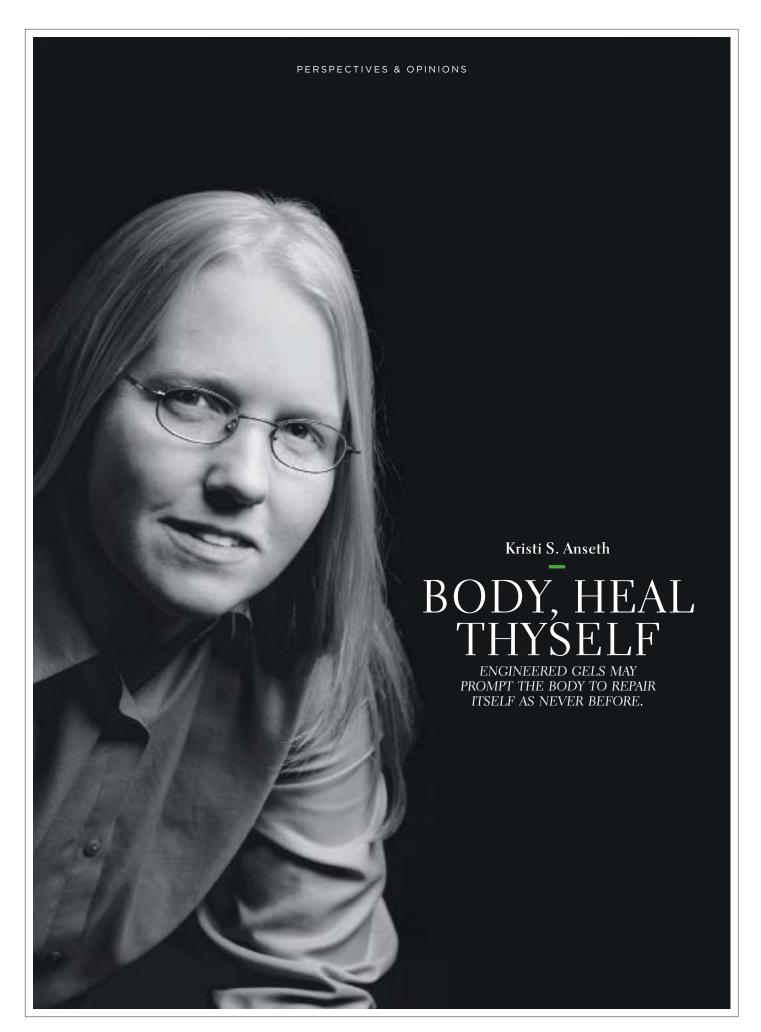
FLY ACROBATICS

Daunting feats of miniaturization stand between Vivek Jayaraman and the contraption he is building to read the minds of *Drosophila* in real time. + "Our goal is to understand the neural computations underlying decision making in response to sensory input," says Jayaraman, a Janelia Farm fellow. "We use the fly because its nervous system is simpler and we can use genetic tools to study circuit computation at a level of detail not possible in larger systems." + Using microsurgical tools and steady hands-Jayaraman says he has sworn off coffee to do this work—the researchers can expose the brain of the fly while its body and head are tethered in place with wax or glue, leaving its legs free to move. Hairlike microelectrodes are inserted into the brain of the one-eighth-inch-long insect to record activity in individual neurons, while a two-photon microscope obtains visual imagery of larger brain regions and populations of neurons. + Jayaraman and his postdocs, Eugenia Chiappe and Johannes Seelig, are next planning a center-stage juggling act: they are developing a system in which a tiny ball, less than one-quarter inch in diameter, is supported on an air column, like a ping-pong ball over a stream of air from a mini leaf-blower. The fly, tethered to its recording device, will be lowered until its feet touch the ball. "As the fly moves its legs in response to visual inputs," says Jayaraman, "we'll record the movements of the ball and infer what the fly wants to do. We hope this setup will allow us to link neural processing to decision-making behavior." -R.S.

"Her work really opens up a whole area," comments Yuh Nung Jan, Yang's mentor. "Because once we know there is this robust behavior for decision making, we can bring in all our techniques, already developed as well as new, to follow up and get at what might be components of the circuit."

Behavioral choices are the nitty-gritty of sheer animal survival as well as the engine of advanced human culture. HHMI scientists are betting that understanding these decision-making circuits in relatively simple settings will ultimately expose the brain mechanisms responsible for higher cognitive capacities in humans. As Shadlen argues, "even human consciousness is mediated by relatively simple, unconscious decisions to engage the environment."

FOR MORE INFORMATION and to see reproductions of experimental trials from Michael Shadlen's study, visit www.shadlen.org/mike/movies/ProbClass/Abstract.html.



Kristi S. Anseth, the first engineer to become an HHMI investigator, has invented new classes of hydrogels—synthetic bioinspired microenvironments that support and interact with living cells. Working with clinicians, chemists, and biologists, the University of Colorado at Boulder researcher and her colleagues are developing a form of tissue engineering to coax the body to heal itself.

Imagine that a soldier could quickly regrow the bones of his shattered leg, that a skier could donate a bit of her own cartilage to rebuild the protective cushion in her damaged knee, or that an implant of tailor-made brain cells could cure the shaking of Parkinson's disease.

That is the promise of tissue engineering, a field often called regeneration medicine. Clinicians, engineers, biologists, chemists, and materials scientists are joining forces to marshal the body's developmental and repair mechanisms to heal wounds, rebuild damaged tissues, and replace essential cells.

In my laboratory, our challenge is to design customized biomimetic gels, also called hydrogels, that imitate some aspects of the extracellular matrix—the natural three-dimensional microenvironment that encourages cell growth during development and wound healing and during normal tissue homeostasis. These artificial matrices already are being tested as structural supports for cell-built treatments such as joint repair. The next generation of gels will support cells' metabolic functions, such as insulin regulation for diabetes, and encourage cell-to-cell connections, as with neurons in the brain.

A second challenge is to learn the biomimetic cues that cells require to perform a desired repair. We may discover that our task is less to control natural processes than to trigger the right conditions so that the cells themselves can take on the job of building and organizing tissue.

A treatment now in clinical trials to repair the cartilage worn away from a skier's painfully damaged knee offers a simple example of the way a biomimetic gel works. Injected into the space within the joint, the hydrogel—which combines water with large macromolecules—is activated by beams of light to form a molecular mesh. This mesh forms a firm but flexible scaffold, rather like organized Jell-O, built in the presence of the patient's own cartilage-forming cells, which secrete tissue components that decorate the lattices of macromolecules like vines on a trellis. Stimulated by cues from the three-dimensional scaffolding, the cartilage-built structure gains strength

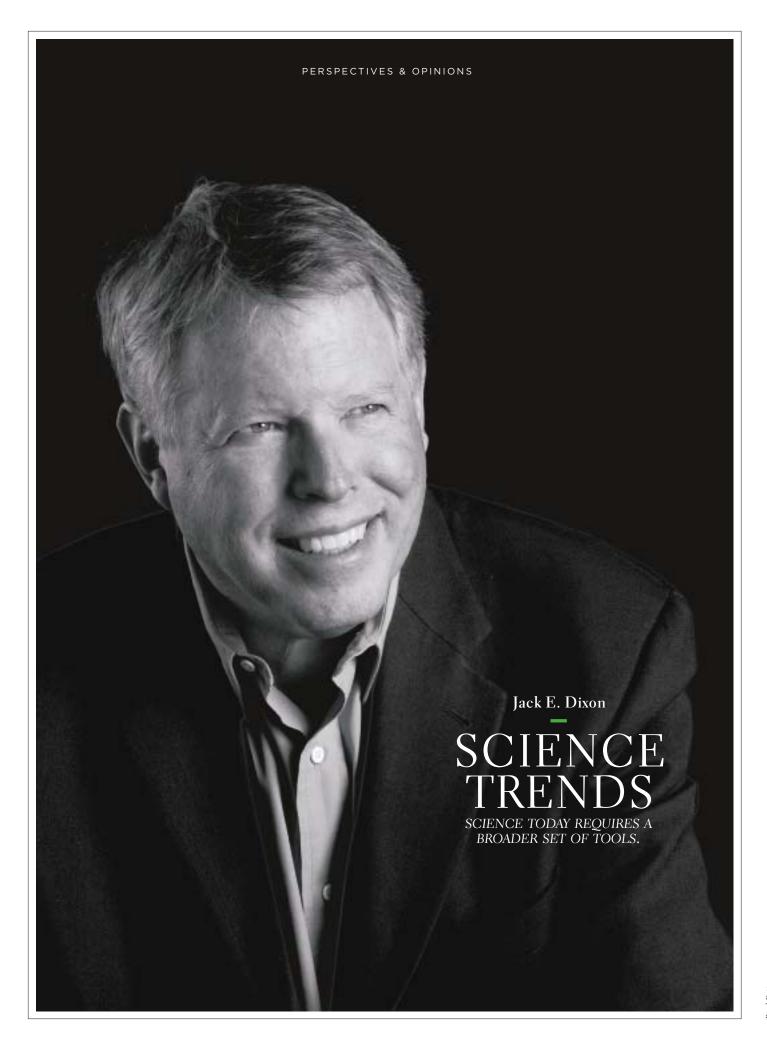
and the artificial scaffolding begins to dissolve. Meanwhile, the skier exercises her knee, and mechanical forces refine the shape. Instead of a titanium joint replacement, she has regrown a natural cushion of her own cartilage to support her knee.

In nature, the extracellular matrix provides not only support but also a location for molecular signals that are traded back and forth as the cells build a specific structure or organ. Taking advantage of this cell-gel crosstalk, Jeffrey A. Hubbell and his group at the École Polytechnique Fédérale de Lausanne (Switzerland) have shown in animal studies that a synthetic gel can provide a matrix that stimulates the animal's bone marrow to fill the gaps between fragments with strong bone cells. The matrix is laced with encapsulated doses of a growth-promoting protein that are only released, dose by dose, when growing bone-marrow cells send an activating signal to a cache of the protein within the gel.

With further advances, artificial gels may also be tailored to support stem cells—an important requirement for any cell-based treatments of Parkinson's disease or type 1 diabetes, which so far do not provide lasting benefits in the body. A customized gel could guide the process of coaxing precursors to become the desired cell type. The gel would then protect the therapeutic cells with molecular barriers. And it would be embedded with further instructions for cell therapy—signals to be activated once the cells were implanted in the body. Brain cells, for example, could be encouraged to send out axons and perhaps be guided to connect with specific types of neurons.

The technical advances needed to take advantage of these opportunities will require synergistic efforts across disciplines. Scientists and engineers working together will advance gel niches from their infancy to mature, sophisticated environments, illuminating the possibilities for cell-based strategies to repair tissues.

INTERVIEW BY JANET BASU. Kristi Anseth does research and teaches at the University of Colorado at Boulder.



Paul Fetter

The life of a researcher is not what it used to be, according to Jack E. Dixon. HHMI's vice president and chief scientific officer thinks scientists today face a more complex, more interesting venture than when he first set up his laboratory 30 years ago. At the same time, he says, young investigators must contend with a funding system that rewards "safe science" and saps creativity.

How has science changed?

When I first started in science it was possible to be at the top of your game by focusing intently on one narrow area. Today, we have new fields of study—molecular biology, genomics, stem cell biology—that pull so many scientific specialties together. Now scientists have to be willing to move into areas where they are less knowledgeable. Science today requires a broader range of skills than in the past, which is what makes it more complex and also more interesting.

This new complexity requires scientists to collaborate and be much more interactive to address scientific questions. The very best people must be better at communicating not only with researchers in their fields, but also with scientists in a broad range of fields. That is exciting because it means you are constantly challenging yourself. Research also appears to be moving at a faster pace.

Is anything important lost when scientists do less themselves and do more with reagent kits and other prepackaged tools?

Sure. I don't know of any lab director or principal investigator who is not concerned about this. Those who use kits know how to mix things together to get results, but they often don't know the biochemistry or the molecular biology that went into putting that kit together. If the experiment doesn't work, they don't really understand why. The kits are a blessing and a curse. However, it's a genie that's out of the bottle and it's clearly not going back in—kits are here to stay.

What is the short-term—and long-term—impact of the slowdown in federal funding for biomedical research? Scientists spend a lot of time writing and rewriting grant applications—time better spent working in their labs or

thinking creatively about solving biological problems. Without reliable funding, that lab is unstable. We have people with a tremendous amount of training—undergraduate, graduate, and postdoctoral training—who have become faculty members and they can't get a shot at using that training because they spend a large chunk of time applying for funding or having their grants turned down by funding agencies.

I would argue that isn't a good use of time for people to repeatedly rewrite a grant rather than conduct the research proposed in it, especially when one considers that extraordinary breakthroughs are often reported by younger scientists.

Are you seeing a different impact on young investigators and seasoned investigators?

The grant situation affects both groups. When I was chair of the biological chemistry department at the University of Michigan Medical School, I used to say there were two times in a scientist's career when he or she needed special attention: at the beginning and near the end. Young scientists are full of energy and ideas they want to try out. Yet, the percentage of grants going to investigators under age 40 has dropped from 27 percent in 1995 to 17 percent in 2005. This bleak funding outlook has a devastating effect on a young person's morale, confidence, and productivity.

Looked at another way, the average age for a scientist with a Ph.D. to get a first research project grant from the National Institutes of Health (the RO1 grant) is 42. To put that into perspective, HHMI President Tom Cech would have been awarded his Nobel Prize before he received his first RO1. My mother had a saying: pennywise and pound foolish. I think that applies to this situation where you effectively take away the 10 most productive years in a scientist's career.

INTERVIEW BY LISA SEACHRIST CHIU. Jack Dixon, a chemist by training, maintains an active research program at the University of California, San Diego.

Fanning: Daniel Dubois / Vanderbilt University Gouaux: Paul Fetters Boone: David Rolls Bear: Betsy Cullen

Q&A

What was your very first job?

As with many of life's firsts — first bike ride, first kiss, first car—one's first job is hard to forget (and sometimes hard to believe).

Four HHMI researchers reminisce with the Bulletin on their earliest working days. — edited by Jacqueline ruttimann



Ellen Fanning SOCIETY OF HHMI PROFESSORS, VANDERBILT UNIVERSITY

"As a freshman at UW-Madison, I set bowling pins at the college bowling alley. Behind the pins there was a pit with a platform high enough for me to stay out of the way of speeding bowling balls and flying pins. After each player's turn, I would jump down into the pit, roll the ball back to the player, retrieve the pins, place them in the triangular pin-setting cage, and hop back up on the platform. I can't remember how many lanes I took care of, but it was strenuous."



Eric Gouaux hhmi investigator, oregon health & science university

"The summer after my freshman year in college I hitch-hiked to a salmon processing plant in Kenai, Alaska, every morning and spent the day loading cleaned salmon onto huge stainless carts and wheeling the carts into cavernous cold boxes for flash-freezing. I later quit the salmon plant to join a small mining group that would helicopter into a claim west of Denali National Park and had to carry a .44 to protect myself from brown bears. I only encountered one bear-I looked at him, he at me, and, after a few moments, I turned and walked back to camp."



Charles Boone
HHMI INTERNATIONAL
RESEARCH SCHOLAR,
UNIVERSITY OF TORONTO,
TORONTO, CANADA

"My first summer job, at the prime age of 15, was as the right-hand-man for a dairy farmer. Waking up to milk cows at 5 a.m. while the stars twinkled and the summer dew was heavy on the grass, delivering calves, stacking thousands of bales of hay, and working in the barn became a normal way of life. The sheer volume of manure was memorable. I spent days moving vast amounts of excrement from the barn back to the field."



Mark F. Bear HHMI INVESTIGATOR, MASSACHUSETTS INSTITUTE OF TECHNOLOGY

"My first job was to wash sailboats for \$1 an hour at a local boat dealer. My friend and I were the dealer's first two employees; I think we were 12 years old."



An Even Broader Reach

THE JACKSON LAB'S SUMMER PROGRAM IS SERVING MORE HIGH SCHOOL AND COLLEGE STUDENTS THAN EVER.



Built by a Princeton University professor in 1912, Highseas mansion is a short walk from Jackson Laboratory and temporary home for students in the lab's Summer Student Program.

LYNN M. RIDDIFORD CREDITS SEVENTEEN MAGAZINE—AND THE Jackson Laboratory—for launching her career in science. The then-16-year-old found an article about the summer research program at the venerable institution in Bar Harbor, Maine, tucked amid pages of 1950s fashion layouts and dating advice. Intrigued, she wrote to the laboratory, requested an application, and set about convincing her parents to let her spend her summer 1,500 miles away from the family farm in Illinois.

"It would have been the first year that I could have worked in the summer and it was going to cost them \$15 a week," Riddiford remembers. Her parents agreed to let her go, and her experiences at The Jackson Lab sparked a lifelong love of science. Riddiford, recently appointed a senior fellow at the Janelia Farm Research Campus after 34 years on the faculty at the University of Washington, studies the hormonal control of insect growth, molting, and metamorphosis.

Since 1929, The Jackson Lab, known for its genetics research, has nurtured the scientific imaginations of thousands of students—many of whom have made names for themselves in the world of science.

Earlier this year, The Jackson Lab was one of 20 research institutions that received HHMI grants to reach out to their local communities

to stimulate interest in science, particularly among young students. The Jax, as scientists worldwide call it, received \$749,000 from HHMI, which will be distributed over five years. Some of that money will support the Summer Student Program for high school and undergraduate students, where students come from around the country to conduct original research as part of a team.

According to Jon R. Geiger, who directs the Summer Student Program, HHMI's investment in

the program has already paid handsome dividends, attracting more women and minority students to the program each year. Since 2003—the year the lab began receiving HHMI support for the program—the program has enrolled about 72 percent women and 29 percent minority students annually.

And the number of high school students applying has increased dramatically. From 1989 to 2003, an average of 56 high school students applied each year. From 2004 to 2007, that number jumped to an average of 131 high school applicants. Geiger recruits through former students as well as a national network of contacts among scientists

and high school and college teachers. "My recruiting is aimed at attracting applications from underrepresented students—minorities, first-generation college or college-bound, those from working class backgrounds, and inner-city students," he says. "I want to be sure that more kids from those backgrounds hear about us."

One of Geiger's pupils this summer was high school senior Seanna Pieper-Jordan, who is of Native Hawaiian and Native American descent. Just like Lynn Riddiford, Pieper-Jordan traveled thousands of miles—in this case, from Honolulu to Bar Harbor—to pursue her dream of becoming a scientist. She spent her summer doing research on muscular dystrophy in Gregory Cox's lab at The Jackson Laboratory.

A student at the Kamehameha Schools in Honolulu, Pieper-Jordan credits two teachers "who cared and encouraged me to look further into science," she says. "I applied to The Jackson Laboratory Summer Student Program with a small hope that I would be given the chance to show the abilities of a student from an often overlooked minority." Clearly inspired by her summer in the lab, Pieper-Jordan says she is now setting her sights on college and a career in the biological sciences.

— JIM KEELEY



'It would have been the first year that I could have worked in the summer and it was going to cost them \$15 a week.

LYNN RIDDIFORD

Paul Fetter

Smart Young Minds

A SUMMER TRAINING PROGRAM, INITIATED BY A HANDFUL OF MOTIVATED UNDERGRADUATES, IS MAKING A HOME AT JANELIA FARM.

NINETEEN-YEAR-OLD JONATHAN YOKE, SURROUNDED BY PLIERS, resistors, and small vials teeming with flies, proudly showed off the machine he was building to determine how flies respond to gravity. The device encloses them in a tube mounted on a wheel that will turn—effectively changing which way is "up"—according to a computer's instructions. A camera will spin with the wheel to record the flies' reactions.

Yoke's creation is the brainchild of Janelia Farm fellow Michael Reiser, who studies how fruit flies gather multisensory information and make choices as they interpret the world. Yoke is one of four undergraduates who conducted research at HHMI's northern Virginia research campus during summer 2007, finding their way to Janelia Farm on their own initiative. Each contacted Janelia's associate director for science and training to inquire about opportunities.

Reiser says he appreciates the contributions of undergraduates like Yoke because, "many of them possess impressive courage—a certain fearlessness—that allows them to tackle a challenging project." A computer-engineering major at the University of Virginia, Yoke has more experience in building robots than in biology. But his technical skills combined with his interest in neuroscience make him a good fit for Janelia, where interdisciplinary approaches are especially valued in addressing difficult questions about the brain.

Yoke became interested in signals in the brain as a Boy Scout participating in an annual wheel-chair walk with paralyzed veterans. "Their brains worked fine, but they couldn't control their limbs," he recalls. "It seemed like there should be some way to fix that."

On the same floor as Yoke and his machine-in-progress, University of Toronto student Arjun Bharioke worked in the lab of Janelia group leader Karel Svoboda. Though only 20 years old, Bharioke speaks about neuroscience like an old pro. His project aimed to understand how the brain gets rewired during learning. He used a new technique for activating specific neurons: injecting a light-sensitive protein into the brains of mice, followed by a pulse of light. First, he trained the mice to push a lever in response to a puff of air on their whiskers in exchange for a drink of water. Then, he aimed the light pulse at neurons believed to be involved in whisker movement. If the mice went for the water—even though the whiskers were not

actually deflected by a puff of air—that would confirm an important role for the targeted neural circuitry.

Bharioke says one of the best aspects of working at Janelia was access to the scientists. Livia Zarnescu, a math major at the University of Arizona, agrees. "Everybody is so smart and enthusiastic about what they do. Most hours of the day, you'll find someone here working. You can go in and ask someone about their work and they'll be happy to show you." She worked with group leaders Julie Simpson and Eugene Myers, who have taken on the ambitious task of mapping the fruit fly's neural circuitry for motor activity.



University of Colorado student Chelsea Trengrove worked with Loren Looger to improve imaging of neural activity in the brain.

Zarnescu's work covered a wide scope—from dissection and staining with fluorescent antibodies to programming the computer algorithm needed to overlay images from thousands of samples. Simpson was glad to have Zarnescu there for the summer. "She could speak computer [with the programmers] and then come back and speak English to us."

Chelsea Trengrove switched majors several times in her first year at University of Colorado at Boulder, yet her pull toward neuroscience remains strong. "When I was five years old, I would read about the brain. All I want to do is research the brain," she says. "Since being at Janelia, I've thought that maybe I should get my Ph.D."

CONTINUED ON THE NEXT PAGE

CONTINUED FROM SCIENCE EDUCATION (SMART YOUNG MINDS)

She plowed through textbooks to prepare for her work with group leader Loren Looger, a mathematician and chemist by training who has devoted himself to building better tools to study the brain. Trengrove's project focused on improving imaging of glutamate, the brain's primary excitatory neurotransmitter and a chemical that is useful for tracing neural activity.

The four undergrads stayed in a four-bedroom townhouse on campus, just a short walk from the laboratory building. The proximity helped them integrate into the larger community—including pick-up games of soccer and ultimate Frisbee after work. Trengrove was impressed by the sense of community. At lunchtime, for instance, there were empty tables in the cafeteria, but if people were sitting at any given table, every chair was taken.

The place was often abuzz with new hypotheses, setbacks, and results. "Everybody was talking about what they were doing," she says. "I just tried to listen and understand."

Based on the success of this fledgling effort, HHMI has formalized the Janelia Undergraduate Scholars program for 2008 and will be accepting online applications from students.

Simpson says that providing a positive research experience for young people at the college level is a good way to inspire future scientists. After all, Simpson's summer research while enrolled at Princeton University is what sold *her* on science. She believes the summer undergraduate training program at Janelia will help to "convert smart young minds to neuroscience."

-LINDSEY PUJANAUSKI

FOR MORE INFORMATION on applying for the 2008 Undergraduate Scholars program, visit www.hhmi.org/janelia/undergrad.

HHMI Expands Support of New Physician-Scientists

INSTITUTE INCREASES NUMBER, SIZE, AND DURATION OF PHYSICIAN-SCIENTIST EARLY CAREER AWARD PROGRAM.

only a small fraction of the physicians who graduate from U.S. medical schools each year pursue a career in academic research. The reasons vary, but graduates often cite two in particular: insufficient time for research and lack of financial support.

To minimize those hurdles for a small cadre of physicians, HHMI has named 20 new recipients of its Physician-Scientist Early Career Award. Now entering its second year, the awards program is part of the Institute's commitment to help promising physician-scientists launch their careers in academic research.

"It's not easy to go back and do science once you've started down the clinical path, so it's really important to get a good solid footing early in your career," says William Galey, program director for HHMI's graduate education and medical research training programs.

When the awards were created last year, 13 grantees received \$150,000 over a three-year period. This year, the 20 awardees will receive \$375,000 over five years.

Each year, HHMI invites alumni of the HHMI-National Institutes of Health Research Scholars Program and the HHMI Research Training Fellowships for Medical Students who are starting up their labs with full-time, tenure-track positions to apply. The funding must be used for direct research expenses, and the awardees' institutions must allow them to spend at least 70 percent of their time conducting research.



"It's not easy to go back and do science once you've started down the clinical path, so it's really important to get a good solid footing early in your career.

WILLIAM GALEY

Connecting Research Institutionswith Local Communities

HHMI INITIATIVE SUPPORTS OUTREACH PROGRAMS TO ADVANCE PUBLIC UNDERSTANDING OF SCIENCE.

TO BRIDGE RESEARCH INSTITUTIONS WITH their local communities and to spark the public's interest in science, particularly among young students, HHMI has awarded \$22.5 million for educational programs at 31 institutions around the country. The grants are going to medical schools, hospitals, research institutions, a school of dentistry, and a school of veterinary medicine. Ranging from \$529,308 to \$750,000 to be distributed over a fiveyear period, the grants will support new outreach programs or ongoing activities with a demonstrated record of success in broadening access to science across diverse populations.

"Many of these institutions are reaching out to traditionally underserved populations," says Jill Conley, director of HHMI's precollege science education program. "They are also engaging girls in science at a particularly critical time in their educational development."

A number of the grantees aim to improve science education by enhancing teachers' knowledge of scientific concepts and how science is done. Their programs will help teachers develop hands-on, inquiry-based activities for the classroom. Other projects will target students directly, teaching them how to think like scientists. And some will strengthen parents' and other community members' understanding of scientific concepts, thereby enriching the network available for fostering children's interest in science.

HIGHLIGHTS OF SELECTED PROGRAMS

❖ Virginia Commonwealth University in Richmond, Virginia, will use its \$750,000 grant to educate K-12 science teachers about systems biology, an approach in which a cell or organism is studied as a whole. Workshops will bring together science teachers with systems biology graduate students and postdoctoral fellows. This training will help teachers create activities that encourage students to design and conduct their own scientific inquiries. The school also plans to create downloadable videos, teacher lesson plans, and activities.

♦ Baylor College of Medicine in Houston, Texas, will use its \$749,627 grant to bolster its SELF (Science Education Leadership Fellows) program, in which experienced science teachers—many from schools in economically disadvantaged areas—pair up with Baylor postdoctoral researchers and graduate students to form science education improvement teams. The teachers and scientists learn from one another by trading places: teachers work in a lab for three weeks and scientists briefly teach in a classroom. SELF teachers make the knowledge they've gained available to all Houston teachers via online virtual workshops, and dozens of program alumni are now leading teacher professional development across the nation. The program has demonstrated remarkable success. For example, one SELF school saw its students' success on the science portion of the Texas Assessment of Knowledge and Skills rise from 28 percent to 82 percent after participating in the program for just one year.

▶ Purdue University School of Veterinary Medicine in Lafayette, Indiana, will use its \$749,755 grant to create computer-based "field" trips to give middle school students in rural Indiana schools with limited resources the opportunity to learn about the laboratory environment. Purdue is targeting students in grades 6 through 8 because middle school is considered an especially crucial time to nurture children's interest in science. Students will be able to view online animations, live demonstrations, and experiments as well as interact with working scientists.

The Queen's Medical Center in Honolulu, Hawaii, will use its \$747,644 grant to create a series of health science evening programs aimed at improving health literacy and increasing the enrollment of Native Hawaiian and Pacific Islander students in the biomedical sciences. Scientists at the center suspect that parents working more than one job in addition to struggling against a language barrier may need help supporting their children in school. The programs will bring students, their families, and their teachers together with biomedical professionals with diverse ethnic and cultural backgrounds. A typical evening might include hands-on research activities and discussions of biomedical careers and resources available to help students prepare for such careers. To increase family involvement, onsite child care will be provided and transportation costs reimbursed.

Baby's First Bacteria

RESEARCHERS DELVE INTO DIAPERS TO DISCOVER WHAT TYPES OF BACTERIA ESTABLISH A HOME IN THE HUMAN GUT.

A baby may get her eyes from mom and her hair from dad, but where does the bacteria in her gut come from? To answer this question, HHMI investigator Patrick O. Brown at Stanford University School of Medicine and colleagues found themselves up to their ears in diapers—about a year's worth—to analyze the microbial contents of newborns' bowels.

Babies are born with a sterile intestinal tract, but within a matter of days bacterial colonies establish themselves in the gut, eventually (by adulthood) outnumbering human cells 10 to 1. These multiplying microbes serve numerous purposes, including protecting against harmful pathogens and aiding digestion.

"The tricky thing is that we don't really know what the ideal population looks like," says Chana Palmer, Brown's former graduate student and first author of their July 2007 *PLoS Biology* report.

To get a view of the bacteria found in the gut, Palmer collected stool samples from 14 babies and their parents at several intervals over each baby's first year (see "Baby Biology," page 6). She spread fluorescently labeled DNA from the samples on a microarray glass chip dotted with known bacterial DNA. Samples whose DNA sequence matched any bacterial sequence on the chip latched onto those spots and were tallied by a computer.

Hundreds of different species of bacteria were found to inhabit an infant's gastrointestinal tract, and each baby had a different mix. The fraternal twins in the study showed the most similarity, suggesting that genetics and environment work together to shape



Scientists have found that the mix of bacteria in a baby's gut is shaped over time.

the gut population in a reproducible way. By year one, all the infants had a generalized profile close to that of an adult.

"It almost doesn't matter where you start off because we all end up in the same place," says Palmer. "There are some bacteria that are really well suited for your gut and they're going to win no matter what."

Whether bacterial flora are a function of genetics or the environment or both remains to be tested, says Brown, who likens the process to gardening. "What comes up depends both on what seeds were sown and which are best suited to the particular soil and climate."
— JACQUELINE RUTTIMANN

IN BRIEF

LITHIUM EASES SYMPTOMS OF NEUROLOGICAL DISORDER IN MICE

HHMI investigator Huda Y. Zoghbi at the Baylor College of Medicine and others have shown in mice that lithium, a psychiatric drug used to stabilize mood shifts, eases the symptoms of spinocerebellar ataxia type 1, an inherited neurodegenerative disorder. Their article was published May 29, 2007, in *PLoS Medicine*.

The findings suggest it may be possible to use the drug to alleviate deterioration in motor coordination, learning, and memory manifested by spinocerebellar ataxia type 1. Present treatments for the condition are limited. Patients, usually diagnosed in their thirties or forties, gradually lose motor and memory function and die within a few years of onset of the disease.

Zoghbi's group explored the effects of lithium on mice engineered to carry a mutant gene that causes a condition analogous to the human disease. Afflicted mice treated with lithium showed improved coordination, learning, and memory, even if therapy started after the symptoms began. The researchers also documented improvement in the morphology of the specialized cells that conduct nerve impulses in the hippocampus, a region of the brain important for learning and memory.

Exploring lithium as a potential salve for neurodegenerative disorders makes sense, according to Zoghbi, because in past studies lithium has been shown to provide some protection for the brain in a variety of conditions.

NEW GENES ASSOCIATED WITH HYPERTROPHIC CARDIOMYOPATHY

A sequencing technique developed by a team led by HHMI investigator Christine E. Seidman, at Brigham and Women's Hospital, and her husband Jonathan G. Seidman, at Harvard Medical School, has identified hundreds of genes with altered expression in the heart condition known as preclinical hypertrophic cardiomyopathy (HCM). In people with HCM, the heart muscle thickens and fails to relax normally after contraction. It is the most common cause of sudden death in athletes.

The technique, known as polony multiplex analysis of gene expression, or PMAGE, attaches short sequences cut from mRNAs (called tags) to tiny beads. These tags are amplified, so that each bead contains millions of copies of the same mRNA tag projecting from it like a minuscule Koosh ball. The beads—called polonies (short for polymerase chain reaction of colonies)—are layered onto

glass, then all the tags are sequenced simultaneously. A computer program matches the tags to known genes: the more tags associated with a gene, the higher the expression of that gene.

Using PMAGE, the researchers compared a group of healthy mice with a group that had a genetic mutation that causes HCM after about 25 weeks of age. Seidman's group found 706 genes that were overactive or underactive in HCM mice compared with normal mice. Some of these genes are newly linked with the disease.

The study, published June 8, 2007, in *Science* could help scientists define the pathways that lead to the disease and ultimately to targets for prevention and treatment.

MICRORNAS CAN TURN OFF CANCER CELL GROWTH

Research by HHMI investigators Gregory J. Hannon and Scott W. Lowe at Cold Spring Harbor Laboratory and colleagues suggests that bits of genetic material known as microRNAs can also shut down the proliferation of cancer cells.

Their experiments, reported June 28, 2007, in *Nature*, show that microRNAs are part of a network governed by the gene *p53*. This gene, mutated in nearly half of all human cancers, regulates the expression

Gender Switch?

MICE THAT CAN NO LONGER DETECT PHEROMONES BECAUSE OF A SINGLE GENE DELETION CROSS THE BOUNDARIES OF TYPICAL GENDER BEHAVIOR.

Female mice do not usually initiate sex or mount their partners. Yet a subset of mutant females, studied by HHMI investigator Catherine Dulac and her Harvard research team, has upended the world of lab mouse intercourse.

Dulac's study suggests that sexual behavior in mice is not exclusively connected to inherent differences in the male and female brain. Instead, she found that gender roles become strikingly fluid when the mice are unable to detect pheromones.

Mice detect pheromones through a chemosensory organ called the vomeronasal organ (VNO), located in the nasal cavity. The VNO requires a specific ion channel called TRPC2 to function. When Dulac and colleagues Dr. Tali Kimchi and Jennings Xu bred TRPC2 knockout male and female mice, the mutant mice ignored chemical cues that generally produce gendered behavior. Male knockouts showed a lack of aggression toward other males, and mounted male and female mice indiscriminately. Female knockouts exhibited typical male behavior, such as attacking intruding males, pelvic thrusting, and soliciting sex by using their noses to poke other mice in the rear.

"There's a major finding here," says Dulac. "Sex-specific behaviors were assumed to be controlled by sex-specific neurons. We found that the brains of animals in a given species may have male and female components controlled by a switch. That switch is sexually dimorphic and modulated by pheromones."

Dulac is careful to clarify that olfactory cues impact sexual behavior in mice much more than in humans. Like other primates, people lack vomeronasal organs and perceive the world mostly through vision. But Dulac insists that focusing on the fact that her study pertains to olfaction is missing the point. It is the *switch mechanism*, independent of the sensory modality, that could apply to several other species, she says. "We are shattering the dogma on the male and female brain and the major importance of testosterone."

Dulac hopes that her findings will provide a fresh outlook for everybody in her field. Next, she plans to focus on whether the

male knockout mice demonstrate typically female behavior. "There are some species of rodents in which the father exhibits parental behavior," she explains. "Maybe there's something there."

- SHELLEY DUBOIS



A female mouse shows surprising behavior by pursuing another female.

IN BRIEF

of other genes and triggers cell suicide, called apoptosis, in damaged cells.

MicroRNAs, no more than a couple of dozen nucleotides long, regulate a broad array of physiological and developmental processes. Researchers knew that microRNA levels decrease in human cancers, but they knew little about the significance of that decrease, says Hannon.

The team, working with mouse models, compared gene activity between cancerous p53 knockout cells and normal cells. Their studies revealed that p53 directly targets and switches on the genes for the miR-34 microRNA family. When these genes were turned on in cells, researchers saw an increase in apoptosis as well as cell senescence, a kind of "genetic death" in which cells lose the ability to replicate. The miR-34 genes also regulate many target genes involved in the cell division cycle.

"There has always been a hole in the p53 pathway, and people have been looking for genes that code for regulatory proteins to fill that hole," says Hannon. "That hole may well be filled by microRNAs."

NEW CLUE INTO HOW DIET AND EXERCISE ENHANCE LONGEVITY

The traditional prescriptions for a healthy life—sensible diet, exercise, and weight

control—extend life by reducing signaling through a specific pathway in the brain, according to HHMI researchers who discovered the connection while studying long-lived mice.

HHMI investigator Morris F. White at Children's Hospital Boston and his colleagues published their findings July 20, 2007, in *Science*.

The researchers sought to understand the role of the "insulin-like" signaling pathway in extending life span. This pathway governs growth and metabolic processes in cells throughout the body. Insulin and insulin-like growth factor-1 activate the pathway when they switch on proteins inside the cell called insulin receptor substrates (Irs).

When scientists knocked out one copy of the *Irs2* gene in mice, the animals lived 18 percent longer than control mice. When they removed both copies of the gene, the mice were more active as they aged, and their glucose metabolism resembled that of younger mice.

White speculates that the insulin-like signaling pathway in the brain might also promote age-related brain diseases such as Alzheimer's disease, Huntington's disease, and general dementias. "It might be that, in people who are genetically

predisposed to these diseases, too much insulin overactivates Irs2 in the brain and accelerates disease progression," he says.

PROTEIN SUPPRESSES PROSTATE CANCER METASTASIS

HHMI researcher Richard O. Hynes at the Massachusetts Institute of Technology and others have shown in mice that a protein whose function is lost in a broad array of cancers normally suppresses prostate cancer metastasis. Testing for loss of the protein, called Protein 4.1B, could help clinicians predict which cancers are likely to spread.

The team published their findings in the July 31, 2007, issue of the *Proceedings* of the National Academy of Sciences.

To test how loss of Protein 4.1B affected tumors in living animals, the researchers implanted clumps of human prostate cancer tumors into the prostates of mice. From these mice, the researchers isolated variants of prostate cancer cells with different metastatic potential. A genetic comparison of the cells revealed that the highly metastatic cells had lost Protein 4.1B gene activity. Furthermore, when the researchers suppressed the Protein 4.1B gene in poorly metastatic cells, those cells became highly metastatic.

A Noisy Brain Is a Normal Brain

BACKGROUND ACTIVITY IN THE BRAIN MAY BE MORE PREVALENT—AND MORE IMPORTANT—THAN PREVIOUSLY THOUGHT.



Neural activity in the brain changes gradually, even when nothing new is being learned.

New research from H. Sebastian Seung's laboratory at the Massachusetts Institute of Technology (MIT) suggests that scientists still have quite a bit to learn about learning.

The researchers were following up on intriguing observations made by MIT collabo-

rator Emilio Bizzi while studying behavioral tasks of macaques in 2003. Bizzi's group saw slow changes in neural activity even while the macaques were performing familiar tasks, during which no learning was going on. Previously, scientists had assumed that slow changes in neural firing corresponded to learning of motor activities, but these changes in neuron firing rates produced no corresponding changes in motor behavior.

It was Uri Rokni, a postdoc in Seung's lab, who realized that these slow changes in the macaque brain, dubbed background noise, were distributed randomly. The changes were seen during the learning tasks as well and could represent the existence of an unstable neural network in the motor cortex. For decades, scientists have thought that the process of learning can be detected as changes in a stable neural network: when there is no learning, there are no changes in firing rates. According to Seung, the background noise was surprising. "Then the question became how to interpret [it]," he says.

One idea is that there are two components in the brain—a teacher and a tinkerer. The tinkerer is constantly adjusting things, which produces the background noise; the teacher goes back and fixes or optimizes the changes. According to Seung, "if you get rid of the noise, which is made by the tinkerer, you get rid of any ability to learn."

Rokni developed a simple mathematical model to represent how changes in neural activity during the familiar tasks could be irrelevant to behavioral performance. His hypothesis is rooted in the notion that the motor cortex is a redundant network, meaning that it uses more neurons than it needs. As a result, changes that produce background noise can affect the wiring of the brain without affecting motor behavior. ■ -LINDSEY PUJANAUSKI

IN BRIEF

The findings in mice are likely relevant to human prostate cancers, says Hynes, because other researchers had found Protein 4.1B to be reduced in metastatic prostate cancers compared with normal prostate tissue.

HANDICAPPING TUBERCULOSIS

HHMI investigator William R. Jacobs Jr. and colleagues at the Albert Einstein College of Medicine have produced a genetically altered strain of tuberculosiscausing bacteria that elicits a stronger immune reaction than the current vaccine, bacillus Calmette-Guérin (BCG).

Approximately 2 billion people world-wide are infected with tuberculosis (TB) and more than 1.6 million die each year from the disease. The bacteria that cause TB are becoming increasingly resistant to current treatments.

Mycobacterium tuberculosis, the bacterium responsible for tuberculosis, lives in immune cells in the lungs called macrophages. The pathogen uses an enzyme called superoxide dismutase A (sodA) to hide infection from the macrophage.

Jacob's team disabled sodA activity by deleting the gene responsible for shuttling the enzyme out of the bacteria. The mutant bacterial strain caused increased cell death, or apoptosis, in macrophages

grown in culture. In general, increased apoptosis activates cytotoxic T lymphocytes, which attack the pathogen.

When scientists infected mice with the two strains of bacteria, they observed that cytotoxic T lymphocytes proliferated much more in mice infected with the apoptosis-inducing strain. This means that the immune system was better able to detect and respond to infection by the mutant strain than by the normal bacteria. In addition, when mice were injected with either the mutant strain or BCG and then exposed to the TB pathogen, the mutant strain appeared to be more effective at preventing manifestation of the disease.

The team published their findings in the August 2007 *Journal of Clinical Investigation*.

CULTURE MATTERS TO EMBRYONIC CELL LINES

When it comes to generating neurons, researchers have found that not all embryonic stem (ES) cell lines are equal. In comparing neurons generated from two embryonic stem cell lines approved by the National Institutes of Health, scientists uncovered significant differences in the mature, functioning neurons. The discovery implies that culture conditions—which have yet to be identified—during human ES cell generation can

influence the developmental properties of the cells.

HHMI investigator Thomas C. Südhof at the University of Texas Southwestern Medical Center at Dallas and colleagues published their findings in the August 21, 2007, issue of the *Proceedings of the National Academy of Sciences*.

ES cells are developmentally immature cells capable of self-renewal and of differentiating into any type of bodily tissue. Researchers believe they can generate neural, cardiac, and other cells that can be implanted to restore damaged tissue.

The researchers developed a culture technique that induced newly produced neurons to establish synapses, or communicating junctions, with one another. Electrophysiological studies showed that the neurons derived from the two cell lines differed in the type of synapses that formed and when, and the neurons used different chemicals (neurotransmitters) to communicate with one another. The researchers also found differences in gene expression of microRNAs—snippets of genetic material believed to regulate stem cell differentiation.

The findings present a strong argument for developing more ES cell lines, the researchers say, since the causes for the functional differences they found remain unknown.





inflammation of a nerve cause inflammation of the tissue it serves?

Philip, a curious adult from Virginia

Inflammation is caused by the body's response to a perceived threat. When the body senses a disturbance, such as an insect bite, wound, infection, or allergen, immune system cells swarm to the affected area. The physical presence of the immune cells and the chemicals they release for communication and action, known as cytokines, cause the four classic signs of inflammation: redness, swelling, heat, and pain.

In at least one instance, inflammation of a nerve causes inflammation in the tissue it innervates, albeit indirectly. This case involves reactivation of the varicella zoster virus (VZV), the virus responsible for chickenpox, which many people contract as children. A vaccine is now available that protects against VZV. Initial VZV infection, characterized by an extensive itchy rash, rarely results in anything that cannot be taken care of by an oatmeal bath. However, even after symptoms disappear, the virus remains in the body, traveling up the spinal cord to nest in the dorsal root ganglia (clusters of sensory neurons that lie along the spine), where it becomes dormant and just quietly inhabits nerve cells.

For about 1 million Americans each year, that dormancy ends and VZV reactivates and causes shingles. Reactivation usually occurs when the immune system becomes suppressed and can no longer keep the virus at bay. VZV actively replicates and travels down the infected nerve, causing havoc along the way. Inflammation and necrosis—the death

of cells due to injury or infection—are found even in neighboring cells.

The resulting symptoms are quite different from chickenpox. Shingles starts with sensations of pain or tingling of the skin that the infected nerve serves. A few days later, painful lesions appear on the skin. While chickenpox appears all over the body, shingles is restricted to a dermatome, an area of skin served by a specific nerve, producing a localized rash, usually on one side of the face or trunk. The immune system responds accordingly and the area becomes inflamed. During the next five weeks, the rash turns into blisters that break open, crust over, and then disappear.

Most patients feel relief from pain when the rash disappears, but some experience pain for weeks, months, or even years. This condition, known as post-herpetic neuralgia, is the most common serious complication from VZV reactivation. It results from damage to pain-sensing neurons, causing them to misinterpret harmless signals as painful ones. Problems may also arise depending on which nerves are infected. Infected facial nerves can cause facial weakness, such as in Ramsay Hunt syndrome and Bell's palsy; infected nerves serving the eye or ear can cause disabling pain and loss of vision or hearing.

ANSWER RESEARCHED BY LINDSEY
PUJANAUSKI, a graduate student in
immunology at the University of Colorado
Health Sciences Center.

FOR MORE INFORMATION on shingles, visit www.cdc.gov/vaccines/vpd-vac/shingles/dis-faqs.htm.

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 HHMI's Ask a Scientist Website. There, working scientists field a wide range of biomedical questions.

Hackathon It takes a dedicated chunk of time to agree on a system for making sense of everybody's fruit fly brain images.

Mark Longair

University of Edinburgh, Scotland

A neuroinformaticist, Longair develops tools to extract neural connectivity information from stacks of three-dimensional images of the fly brain produced by confocal microscopy.

Stephan Saalfeld

Max Planck Institute, Dresden, Germany

A computer science student with expertise in image processing, visualization, and the creation of Web applications, Saalfeld is currently interested in aligning consecutive microscopy slices in three dimensions.

Stephan Preibisch

Max Planck Institute, Dresden, Germany

Preibisch is a computer scientist focused on image processing, statistics, and pattern recognition. He says a personal highlight from the workshop was "the completion of my fast 2-D and 3-D stitching algorithm."

Arnim Jenett

Janelia Farm Research Campus, Ashburn, Virginia

Jenett is a neuro-biologist interested in understanding "where functions are located in the *Drosophila* brain" and how it processes information. He is constructing an atlas of the fly brain correlating function and anatomy.



LOCK THEM IN A ROOM, GIVE THEM PLENTY OF CAFFEINE, and let them have at it. Well, it wasn't that draconian, but an international group of "hackers"—so named for their ability to find their way through a morass of code—did put in an energetic two weeks this summer at Janelia Farm Research Campus to hash out a way to compare anatomic images of the *Drosophila* brain. It sounds simple enough, but considering the variety of microscopes in use, each run by its own particular software,

and the variety of scientific approaches, each covering different degrees of detail, the prospect was fairly daunting. Yet, the group devised the basis for a file-sharing system for importing and exporting digital images across microscope platforms. Ultimately, the goal is a "brain morphing" software program that lets researchers orient themselves within the fly brain and reliably compare measurements. Plans for Hackathon II are in the works.

Benjamin Schmid

Wuerzburg, Germany A bioinformatician interested in all fields that bring together mathematics, computers, and

computers, and biology, Schmid currently focuses on three-dimensional visualization and alignment of *Drosophila* neuro-

anatomy.

Albert Cardona

University of California, Los Angeles

Cardona is a biologist studying how the brain works. Most recently, he is focused on the microarchitecture of the *Drosophila* brain.

Yuriy Mishchenko

Janelia Farm Research Campus, Ashburn, Virginia

Mishchenko is a computation biologist with an interest in image processing. He is an associate in the lab of Janelia group leader Dmitri Chklovskii, where the goal is to understand brain function at the level of neuronal circuits.

Participants not pictured:
Julie Simpson, Janelia Farm;
Wayne Rasband, National
Institutes of Health, Bethesda;
Greg Jefferis, Cambridge
University, England; Torsten
Rohlfing, Stanford University;
Hanchuan Peng, Janelia Farm;
Johannes Schindelin, University
of St Andrews, Scotland.



Celebrating 60 Years of Cech Inspirations











Friends, family, and colleagues of HHMI President **Thomas R. Cech** gathered in Boulder, Colorado, July 12-13 for a symposium in Cech's honor. The event commemorated several milestones: the 25th anniversary of Cech's Nobel Prize-winning discovery of catalytic RNA, the 10 years since his lab's discovery of telomerase reverse transcriptase, or TERT, and 60 years of Tom, whose official birthday will be December 8.

More than 250 Cech lab fans and offspring (aka Cechies and Cechlets) from around the globe participated, many presenting their latest research findings on the amazing properties of RNA, and how telomeres and telomerase preserve chromosome ends. The talks were peppered with flashback tales of Cech's adventures in home cooking and his scientific discourse on the ski slopes.

Even as Cech gathered accolades and rose through the scientific ranks, colleagues say he never lost touch with his Midwestern humility, encyclopedic knowledge of biochemistry, and infectious enthusiasm for the pursuit of basic scientific questions. "It's really about the students and postdocs who join the lab, struggle, grow, succeed, and then leave to succeed elsewhere," says Cech. Keynote speaker Olke Uhlenbeck, of Northwestern University in Evanston, Illinois, cautioned Cech not to rest on his laurels: "I expect to be celebrating something else in another 10 years or so."

SCENES FROM THE CECH "ROAST" (CLOCKWISE FROM TOP LEFT) TOM CECH; HIS WIFE CAROL CECH; A GROUP CELEBRATION, CIRCA 1979, SOON AFTER CECH JOINED THE UNIVERSITY OF COLORADO FACULTY, INCLUDING (CLOCKWISE FROM LOWER LEFT) CAROL CECH, TOM CECH, AND FELLOW SCIENTISTS JENNIE CARUTHERS AND RAY FALL; (FROM LEFT) CHRYSA LATRICK, A CURRENT CECH LAB GRAD STUDENT; TOM CECH; ANNE GOODING, CECH LAB RESEARCH SPECIALIST; AND ELSEBET LUND, UNIVERSITY OF WISCONSIN-MADISON; JOHN HEARST, PROFESSOR EMERITUS U.C. BERKELEY AND TOM CECH'S PH.D. ADVISER.

HHMI investigator FREDERICK W. ALT at Children's Hospital Boston received the 2007 Novartis Basic Immunology Prize for his discovery of the mechanisms of antigen receptor rearrangement in B lymphocytes.

HHMI international research scholar PASCALE F. COSSART, of the Pasteur Institute of Paris, France, received the 2007 Robert Koch Award for her work on the food-borne disease listeriosis.

Three HHMI investigators and one HHMI professor will be honored in 2008

by the American Chemical Society (ACS) for outstanding scientific achievements. HHMI investigator DAVID EISENBERG, University of California, Los Angeles, and his former graduate student REBECCA ANNE NELSON, will receive the 2008 Nobel Laureate Signature Award for Graduate Education in Chemistry; HHMI investigator LINDA C. HSIEH-WILSON, California Institute of Technology, will receive the 2008 Arthur C. Cope Scholar Award for "excellence in organic chemistry"; and HHMI investigator J. ANDREW MCCAMMON, University of California, San Diego, will receive the 2008 ACS

Award for Computers in Chemical and Pharmaceutical Research. HHMI professor RICHARD N. ZARE, Stanford University, will receive the 2008 George C. Pimentel Award in Chemical Education.

STANLEY FIELDS, an HHMI investigator at University of Washington School of Medicine, received the 2007 Vollum Award for Distinguished Accomplishment in Science and Technology from Reed College. Fields developed the yeast two-hybrid system, a method for detecting protein-protein interactions in living cells.

DAVID GINSBURG, an HHMI investigator at University of Michigan Medical School, received the 2007 Distinguished Career Award from the International Society on Thrombosis and Haemostasis for his work on elucidating components of the blood-clotting system.

HHMI investigator ARTHUR L. HORWICH at the Yale University School of Medicine was awarded the 2007 Wiley Prize in Biomedical Sciences from the Wiley Foundation for his work contributing to the understanding of protein folding.

WILLIAM G. KAELIN JR., an HHMI investigator at the Dana-Farber Cancer Institute, received a 2007 Distinguished Alumni Award from Duke University School of Medicine.

Two HHMI investigators and one HHMI professor will be honored in 2008 by the American Society for Biochemistry and

SPOTLIGHT

Druker Wins Keio Medical Science Prize



BRIAN DRUKER

HHMI investigator **Brian J. Druker** of Oregon Health & Science University won the 2007 Keio Medical Science Prize from Keio University in Tokyo, Japan. Typically given to one Japanese and one non-Japanese researcher, the award honors outstanding achievements in the fields of medical or life sciences. Druker was recognized for his development of Gleevec, a molecular-targeted drug used in the treatment of chronic myelogenous leukemia.

Molecular Biology (ASBMB) for their significant scientific contributions. HHMI investigator JOHN D. SCOTT, Oregon Health & Science University, will receive the 2008 William C. Rose Award for his research and his "demonstrated commitment to the training of younger scientists."

HHMI investigator MICHAEL F. SUMMERS, University of Maryland, Baltimore County, will receive the 2008 ASBMB Award for Exemplary Contributions to Education. HHMI professor SCOTT A. STROBEL, of Yale University, will receive the ASBMB–Schering-Plough Research Institute Award, an honor given to researchers within 15 years of receiving a doctorate, for "outstanding research contributions to biochemistry and molecular biology."

TERRENCE J. SEJNOWSKI, an HHMI investigator at the Salk Institute for Biological Studies, was honored with a surprise symposium in recognition of his 60th birthday and his work on the biophysical properties of neuronal synapses.

ISIAH M. WARNER, an HHMI professor at Louisiana State University, received the 2007 Anachem Award from the Federation of Analytical Chemistry and Spectroscopy Societies for "his fundamental contributions to luminescence spectroscopy and separations in organized media."

HHMI professor RICHARD N. ZARE at Stanford University was a recipient of the first Dudley R. Herschbach Award for Excellence in Research at the XXI Dynamics of Molecular Collisions Meeting. The 2007 meeting also included, as part of its proceedings, a symposium highlighting Zare's work in nanotechnology.

SPOTLIGHT

HHMI Researchers Receive Paul Marks Prize



ANGELIKA AMON



TODD GOLUB



GREGORY HANNON

Three HHMI investigators have been honored with the 2007 Paul Marks Prize for Cancer Research. Named for Paul A. Marks, president emeritus of Memorial Sloan-Kettering Cancer Center, the biennial prize recognizes significant contributions to the field of cancer research made by young investigators.

The winners are **Angelika Amon**, of the Massachusetts Institute of Technology, who studies the effects of chromosome segregation in cancer cell growth; **Todd R. Golub**, of the Dana-Farber Cancer Institute, who employs microarrays in order to better classify subtypes of cancer; and **Gregory J. Hannon**, of Cold Spring Harbor Laboratory, who studies the role of RNA interference in cancer initiation and progression.

CONTINUED FROM PAGE 25

(SMALL TALK)

very interesting biology." His instinct was right. "She is the leader in quorum sensing," he says. "Which is a pretty big deal." Yet again it wasn't just Bassler's research that attracted the attention. "We were very, very impressed with her obvious enthusiasm," Silhavy says.

A Universal Language

That second chemical signal she had discovered in *V. harveyi* revealed what Bassler calls a bacterial Esperanto—a universal language that bacteria use to talk to other species. The first signal, called AI-1 (AI stands for autoinducer, because it induces the bacteria to act), was unique to *V. harveyi*; it didn't exist in any other species of bacteria. But Bassler found that all kinds of bacteria produced the second molecule, AI-2, suggesting that it had an entirely different role. While the bacteria used AI-1 to talk among themselves, AI-2 was a common language among different species. And, critically, it helps them distinguish between like and unlike bacteria—self and other.

"This is the basis for cells specializing," Bassler explains. "If you have a mix of species, different groups can do different things." Bacteria, in other words, not only invented multicellularity, they also invented the kind of division of labor seen in multicellular organisms.

For example, biofilms—like the sticky glaze that collects on teeth overnight—are composed of hundreds of species of bacteria, each performing a specialized job to keep the "organism" alive. "You brush them off, and

then the next morning they come back and they're in exactly the same organization," Bassler says. "Only a couple of species are the primary colonizers, then the next guys depend on them to stick." Others provide nutrients, and so on. All in all, it's a mutually advantageous architecture that allows all the species to flourish.

This level of complexity is another example, Bassler says, of something she and her colleagues could not have imagined a decade ago. "How could I have been so slow?" she says. "Now it seems obvious to me that it had to work like this."

Bassler decoded the structure of the AI-2 molecule and has shown what happens inside bacteria when they detect these chemical signals—how their communication changes the bacteria's behavior. "She's shown that bacteria have much more sophisticated information-processing systems than we imagined," says Harvard's Losick.

Researchers elsewhere have now found Bassler's second signal in hundreds of other bacterial species. But there is an unsolved problem regarding the determination of "other." The molecules they've been studying identify an organism as self or other but do not tell who that other organism is or whether it's an ally or a threat. Bacteria must have additional signals—other molecules—to distinguish between species. "There are probably a lot of them," says Bassler. Nobody yet knows how many.

Better Than Poison

One potential application of Bassler's work is an entirely new kind of antibiotic. At

present, most antibiotics are poisons of one sort or another—they kill bacteria. But here, she says, "the idea is that instead of killing bacteria, you make molecules that lead to behavior modification."

When infectious bacteria invade human beings, they generally do not start to make toxins right away. That would only draw the attention of the immune system, which would blast them out of existence. They wait until their numbers have increased, and, using quorum sensing, when they detect the appropriate threshold population, they act together to launch a major attack, making it far more likely they can overpower the immune system's defenses. An anti-quorum-sensing drug, by preventing this process from occurring, should avert or even cure infections. It might also be possible to make molecules that enhance quorum sensing in the commensal bacteria, described by Bassler as "those harmless gobs of everyday bacteria that live in and on us," thereby allowing them to keep out invading infectious microbes.

And then comes the next leap, as Bassler sees it. Over billions of years of evolution, bacteria have undoubtedly learned to modify quorum sensing in competing bacteria. Therefore, the drugs that researchers seek probably already exist in nature. It's just a question of finding them. She's interested in basic research—not drug development—but her work could point drug makers to these naturally occurring medicines.

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