

HHMI BULLETIN

Howard Hughes Medical Institute

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Tinkerers

Scientists with technical ingenuity are opening new vistas into the finer points of the cell.

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Wise Man of Janelia



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Planaria would make great magician's assistants. Cut these flatworms in two and each half quickly becomes a whole. Cut them to about 1/279th of their size and presto! Each piece still regrows into a complete worm. The secret behind planaria's regenerative wizardry lies in stem cells, called neoblasts (green), scattered throughout their bodies. Finding out what goes on in these cells could bring scientists closer to discovering how human tissues damaged from injury or disease might be repaired.

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A Different Mindset

To true tinkerers, the limits of the present are never permanent barriers, merely offers they can't refuse.

[COVER STORY]

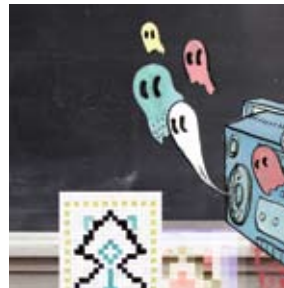
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The Wise Man of Janelia

Sydney Brenner's hopes for understanding the brain—put on hold 30 years ago—are now revived, courtesy of advanced techniques and new insights about a humble but invaluable worm.

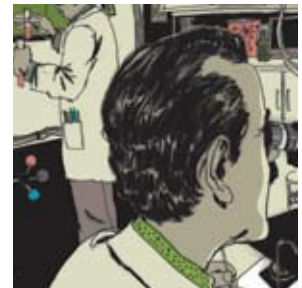
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Broken Symmetry

The fact that the two sides of many animals' brains are not mirror images—particularly in humans—may ultimately help to explain the differences in behavior between species and even among individuals.

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Regeneration for Repair's Sake

If a salamander can regrow a lost limb, why can't we? Or should we be aiming for a different goal?



The term “diabetes” on the cover of the last issue of the *HHMI Bulletin* struck a nerve in one of our readers. As someone with type 1 diabetes, the reader pointed out that her disease has nothing to do with obesity. She added, quite validly, that we neither explained the term within the cover story, “Exercise in a Pill?,” nor did we distinguish between type 1 and type 2 diabetes—which have notably different origins and mechanisms.

As there are likely others among our readers with similar reactions to that story, I want to clarify what we previously left oblique. HHMI did not coin “diabetes”—it’s a nonscientific term that has crept into use in popular media in the last few years in reaction to the enormous increase in type 2 diabetes in our country, which is believed to be related to obesity and lack of exercise. Some 90-95 percent of the 14.6 million Americans diagnosed with diabetes have type 2, according to the American Diabetes Association; 5-10 percent of those diagnosed have type 1.

Type 1 diabetes is an autoimmune disease in which the body’s immune system attacks the cells in the pancreas that produce the hormone insulin, which is essential for converting food into the energy our cells and organs need to function. In type 2 diabetes, in contrast, fat, muscle, and liver cells no longer use insulin properly and the body eventually can’t produce enough insulin in response to meals. Scientists are still working to fully understand what causes both types of the disease. However, we intended for the article to focus on type 2 diabetes and the role exercise might play in reducing the risk for obesity and, in turn, type 2 diabetes. We should have been clearer about that.

While the *Bulletin* editorial staff strives to make each story in the magazine accurate and complete, in this case, we fell short of our goal. Letters from astute readers, such as the one that prompted this response, remind us to be particularly scrupulous. Who better to keep us on our toes? Keep those letters coming.

Mary Beth Gardiner

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Summer's Rhythm

THE ARIA THAT OPENS *PORGY AND BESS* EVOKES THE SLOW, heat-induced tempo of August like nothing else: "Summertime and the living is easy/Fish are jumping and the cotton is high." Indeed, for anyone whose life and work follow the rhythm of an academic calendar, this can be a still, quiet time of year. Classrooms are empty of students, colleagues have fled to idyllic maritime laboratories to teach and think, and more leisurely pursuits beckon. Under normal circumstances, that might have been the case at the Howard Hughes Medical Institute, but this has been a summer unlike any other. Fish—of the metaphorical variety, that is—are jumping everywhere.

We are in the throes of two competitions for new investigators. For starters, we are preparing to select a group of physician-scientists from among more than 240 researchers who applied during our patient-oriented research competition—the first time faculty could apply directly, without institutional nominations, in HHMI's history. Our scientific officers and advisors are also hard at work reviewing the 1,072 applications we received in the general competition for new investigators, again based on applications rather than nominations. Final decisions about this group of candidates will not be made until 2008, yet we can already see the value of the open competition model. The field is strong and diverse: it reflects a wide array of disciplines and institutions and establishes a high bar for future competitions.

Despite all this activity, summer still offers an opportunity for reflection. My colleagues and I have thought a lot about the attributes of HHMI's investigator program that optimize its impact on biomedical science. Many of the core principles established in the 1980s remain intact, even as HHMI has evolved to encompass new areas of research, more open selection of investigators, and development of the Janelia Farm Research Campus. Future initiatives—and we're hoping to have news on that front over the next year—will be judged on the basis of their fidelity to those principles.

So what are our core values? Some readers of the *HHMI Bulletin* are probably familiar with the most basic principle: people, not projects. That's a shorthand way of saying that HHMI seeks highly creative and energetic scientists, trusting them to overcome the challenges that arise in their research and giving them the freedom to switch into new areas of opportunity. As a corollary principle, we respect diversity in research styles. We believe that smaller research groups generally provide the best mentoring and encourage collaboration; thus, HHMI supports between five and eight research staff in each of our laboratories. But we recognize that a robust science program must encompass a variety of approaches, so our investigators may seek funds from other agencies to support a larger laboratory.

Gaining expertise in a field takes time and onerous reporting requirements can sap valuable energy, so HHMI believes it is imperative to provide stable, flexible funding. The Institute intervenes only at critical points—for example, to review agreements for consulting or other industry interactions. With freedom and flexibility come high expectations for intellectual output. HHMI



"We recognize that a robust science program must encompass a variety of approaches."

THOMAS CECHE

demands creativity and innovation. We expect our investigators to work at the frontiers of their chosen field, to ask fundamental questions, and to take risks. HHMI prizes impact over publication volume in its merit-based renewal of investigator appointments and recognizes that some areas of research will proceed more slowly than others.

The core principles that guide HHMI's research program extend beyond the individual investigator and laboratory. As an organization, HHMI maintains a diversified research portfolio by taking a broad view of the fields that contribute to progress in the biomedical sciences. We are pleased that so many chemists, engineers, computer scientists, and physicists applied for the general competition. We strive to avoid incremental additions to research areas already well funded by the federal government—the opposite of "living easy." HHMI seeks a healthy dynamic equilibrium by supporting excellent scientists independent of their location while maintaining a presence at numerous geographically dispersed, outstanding research institutions. We hope to create a diverse community of research scientists who are fully engaged at their home institutions and with their HHMI colleagues as collaborators, teachers, and leaders.

With all the care and thought that goes into identifying 65 new HHMI investigators, my colleagues and I won't be slowing down any time soon. Yet these competitions—and the opportunity to reflect on how core beliefs about research might guide our future plans—make it possible for the Institute to "spread [its] wings and take to the sky."

Thomas R. Cech

The Magic of Ham

A little spark of wonder can persist for a lifetime.

As a boy in Montgomery, Alabama, Ed Stone was the kind of kid who disassembled radios and puzzled over music from faraway cities that came in only after sundown. He learned how the ionosphere bounces AM signals around the earth's curve more readily after dark. He advanced from tuning in Chicago rock stations to monitoring shortwave from ships at sea. By the time Stone entered grad school, he was on the air himself, after earning the most advanced amateur ("ham") license the FCC issues. Radio continues to delight him because, he says, "It's magic."

An HHMI investigator at the University of Iowa, Stone spends his days working to cure eye diseases through molecular genetics. In his off time, he relaxes by flipping the switch on one of his ham sets and conversing wirelessly (call sign: NV5K) with people beyond the horizon.

One dimension of the magic is the universal fraternity of people who believe in it, says Stone. "There's a certain sequence of things that you share: 'What radio are you using? How long have you been in amateur radio?' Then, maybe, 'What do you do for a living, where do you live, what's the weather?'"

"People who don't have the radio gene—the vast majority—say things like, 'You talk to people you don't know? Why not just pick up the telephone and dial 10 random digits and strike up a conversation with whoever answers?'"



"With this odd little assortment of stuff, you can talk with somebody hundreds of miles away!"

ED STONE

Stone responds with a story:

"When I was doing my residency, I had a radio in my car so I could talk to people while I drove to the hospital.

"One day I'm on the road, talking with some guy named 'Al.'" (Ham etiquette requires only first names.) "He asks where I'm headed, and I tell him—maybe a little pompously—I'm on my way to morning rounds. 'I'm an *ophthalmology resident*,' I say, half expecting him to ask, 'What's ophthalmology?' There's a pause, and he says, 'That conference room you're going to.'

"'Yeah?'"

"'The Braley Conference Room.'

"'Yeah?'"

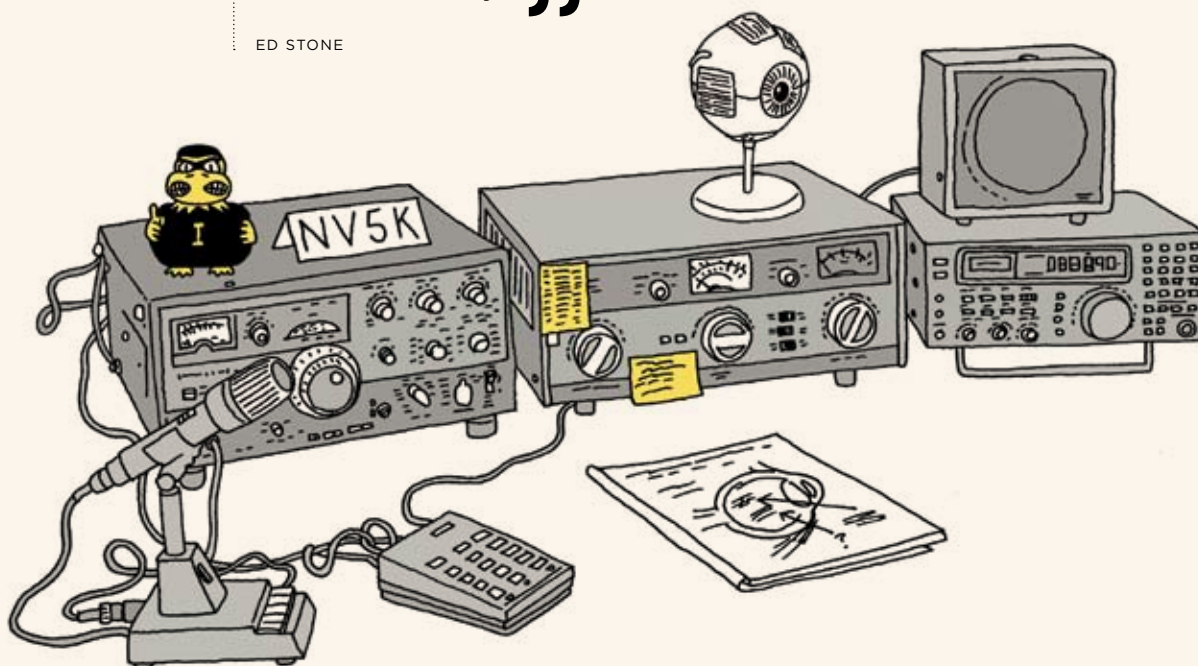
"'That place,' he says, 'is named after me.'

"And that's how I first met Alson E. Braley, the former head of the University of Iowa Department of Ophthalmology, and one of the first surgeons to perform corneal transplantation in this part of the world."

Another side of Stone's magic is closer to alchemy.

"Here we have the notion of a simple device—it might be as small as a tuna-fish can—built with your own hands. Buy a handful of little parts, get out your soldering iron, measure the wire precisely, wrap the correct number of turns around a little ferrite core, connect the right poles of the battery, fuss over it for a few hours' time. Then measure another length of wire, tie the end of it to a weight, and throw it up into a tree." Excitement shades his generally level tone. "With this odd little assortment of stuff, you can talk with somebody hundreds of miles away!"

"That," Stone says, "is *absolutely* magic—of the very best kind." —George Heidekat





“We don’t have time for art. We have to make the time.”

PETER WALTER

Walter’s home and garden are a testament to more than 20 years of his gratifying handiwork. He built the magnificent cherry wood floor-to-ceiling bookshelves in his home office, for example, complete with a sliding section that reveals a secret storage room. (For now, filled with books and extra equipment.) In his garden, water flows down an eight-foot-tall pane of glass, giving the lush green foliage behind it an impressionistic cast. Water also bubbles over the smooth surface of a 1,000-pound ball of polished black granite, the centerpiece of a second fountain.

Walter also creates quirky gifts for members of his lab, including one sculptural piece with a vise crushing a kitchen clock poised above a bottle marked “Time: Freshly Squeezed.” The sentiment is close to Walter’s heart. “We don’t have time for art. We have to make the time,” he says.

Creating art can inspire more creative science, Walter believes. Hoping to do just that, he provided acrylic paints and a stretched canvas to each member of his lab during their annual retreat, asking them to interpret their research project. “We are all so self-conscious as adults, so it was fun to see everyone’s childhood come back to them,” Walter says. The artistically diverse results adorn the lab today. “It worked wonderfully,” he says.
—Camille Mojica Rey

A Fountain of Creativity

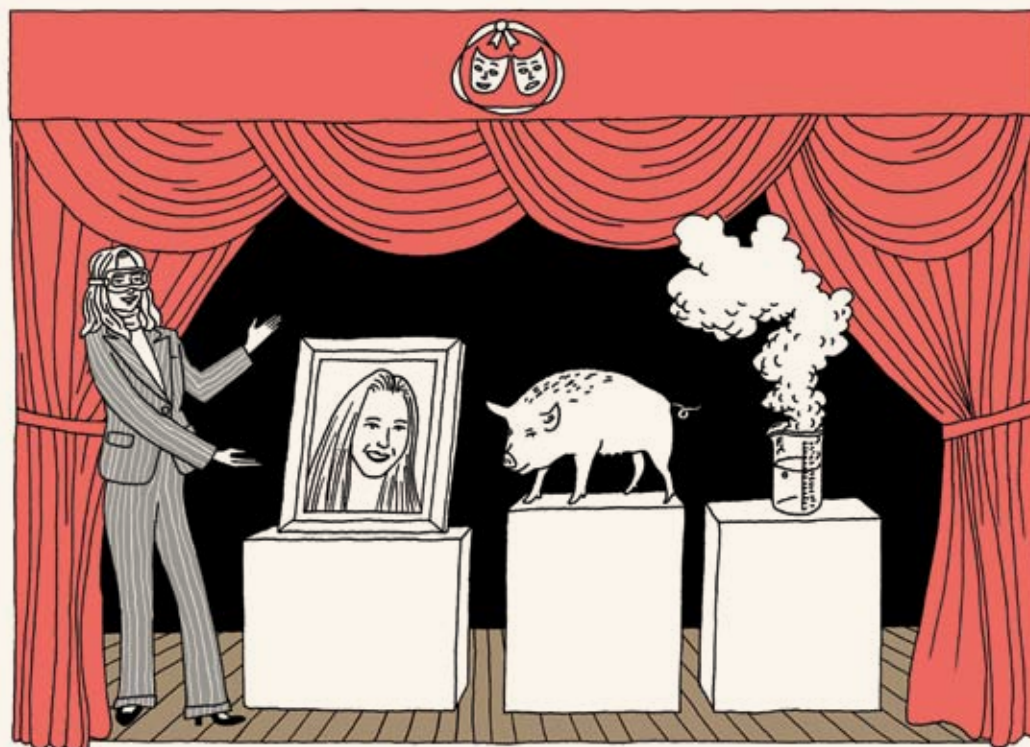
In a low-ceilinged San Francisco garage, a seven-foot work in progress named *La Monique* hangs in a sling of blue and green nylon ropes. The copper fountain resembles a square-edged column that has been twisted and bent over near the top, like a cane. The column’s end gapes to reveal a hollow interior that appears to be vascularized, its web of veins seemingly pulsing with life.

“I like how the geometry of the outside reveals an organic interior,” says *La Monique*’s creator, HHMI investigator Peter Walter. Though Walter admits to sometimes going weeks without working on *La Monique*, he credits his many artistic hobbies with providing balance in his busy life and enriching his

career as a cell biologist at the University of California, San Francisco.

The balance, Walter says, comes from working with his hands. “The funny thing about science is that as you move up and your lab grows, you spend most of your time in front of a computer and less time actually doing experiments.” He says his hobbies—which also include woodworking and photography—provide him with the immediate gratification not always found in his lab, where he studies protein sorting and folding as well as cellular quality control. “You can work on something in science for quite some time before making an exciting, new discovery,” he says.

All the World's a Stage



Lisa Kudrow and Catherine L. Drennan were classmates at Vassar College. Kudrow is the actress best known as the ditzzy blond on the TV show *Friends*; Drennan teaches Introduction to Chemistry at the Massachusetts Institute of Technology. Drennan opens her first lecture with a photo of herself, Kudrow, and the rest of their undergraduate class and talks about trading places.

"I make the students guess which one is me and which one is the famous actress," says Drennan, who shares a certain twinkle in the eye with Kudrow. Drennan, who is also an HHMI professor, then reveals that she went to Vassar intending to major in drama or biopsychology, while Kudrow studied biology.

"I think I actually took more drama classes than she did," says Drennan, who planned to take only one chemistry class. But she found herself drawn to the precision and logic of chemistry and how its core principles form the foundation of both biology and psychology—and she switched her major.

Still, her commitment to theater came in handy. While rehearsing a play directed by renowned Punjabi dramatist Balwant Gargi, who spent a year as a visiting professor at Vassar, she had to sit on stage cross-legged and silent for hours. Gargi insisted that the sitters attend every rehearsal, despite their lack of lines. So Drennan kept flash cards from her Analytic Chemistry class in her lap and read them over and over. "That's how drama helped me get the American Chemical Society Award for Analytical Chemistry," laughs Drennan.

After Vassar, Drennan taught at Scattergood Friends School, a Quaker boarding school in Iowa, which also serves as a working hog farm. As the resident science and drama teacher, her duties included detailing the nuances of hog reproduction and directing a production of *The Importance of Being Earnest*. The job was rewarding but unexpectedly challenging, as some of her students' lives were marred by drug abuse and related trauma. "For some

kids, you thought, 'What colleges could they get accepted to?' For others it was, 'How can I keep them sober and off drugs?'" says Drennan.

Some students had experiences that most of the faculty couldn't imagine, she says. One girl had witnessed a friend's fatal drug overdose at age 13 and lived with a terrible guilt that she'd been responsible. "I had lived such a sheltered life until then," says Drennan, who "matured decades" during her three years there. "Some of my students had been through years of therapy, so they confronted me on certain things. For example, if I got upset about something, they'd say, 'You should ask yourself *why* you're so upset.'"

Still, she has fond memories of the plays she did with them, especially those written by Monk Ferris, a playwright who specialized in "silly comedies full of characters with exaggerated personalities and mistaken identities—perfect for kids in high school."

Even today, her drama background comes in handy. "A big part of teaching is the performance aspect. If I am nervous about a seminar, I will buy a new 'costume'—the kind of thing that a very confident, successful professor would wear!" says Drennan. —Julie Corliss



"A big part of teaching is the performance aspect. "

CATHERINE DRENNAN

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Researchers use their large gene database to find an elusive enzyme.

10 An Elegant Molecular Dance

Images reveal how telomerase is created.

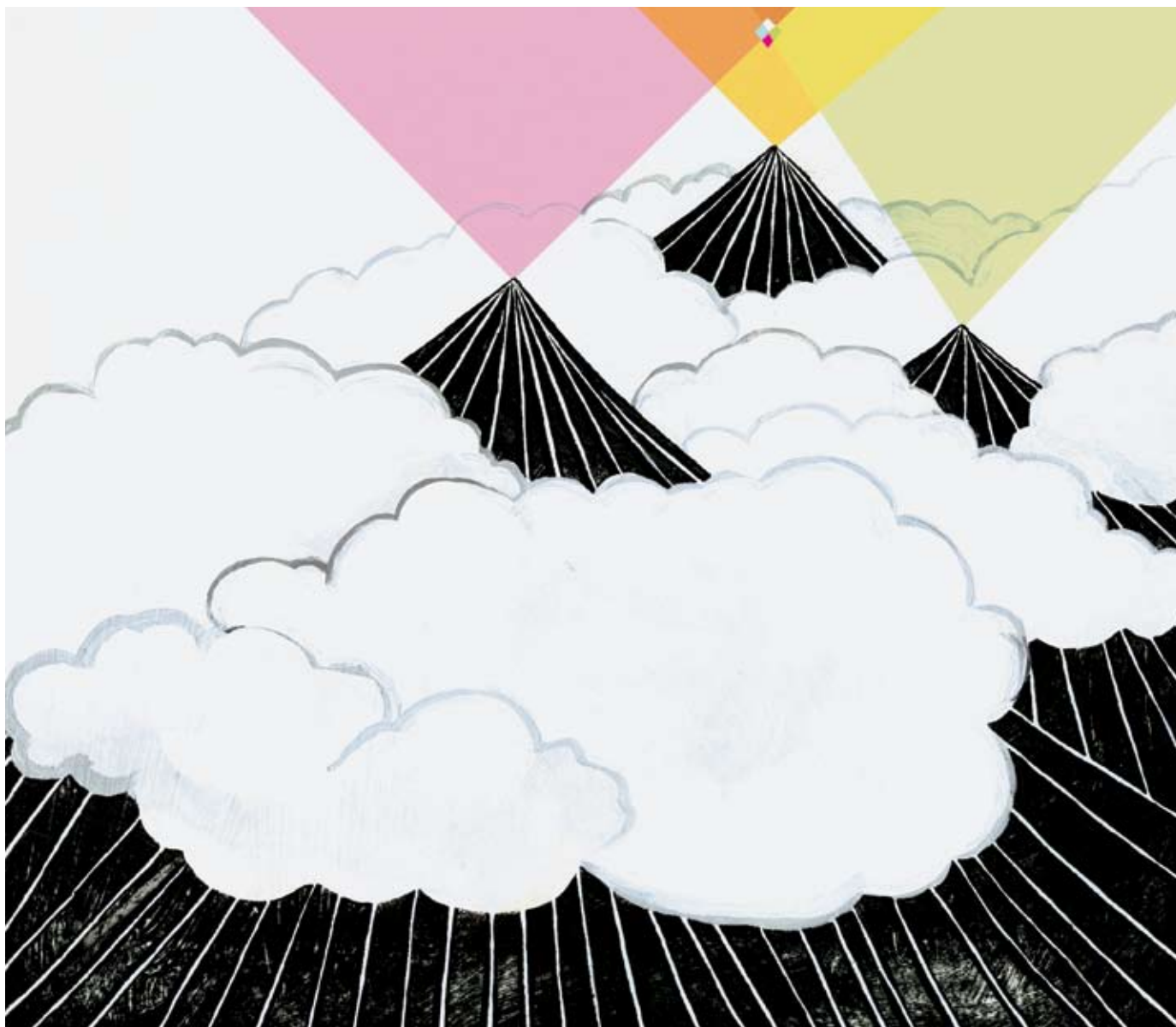
12 Outsmarting the Toughest Bacteria

Can an antibiotic that works in cows be modified to solve resistance in humans?

No cell is an island, no molecule works alone. Consider the one-celled yeast: around 6,000 interacting genes give it life. How to make sense of interplay on a single-cell scale? HHMI researchers devised a large gene-interaction database to shine light on cellular processes in yeast. Others used single-molecule imaging to detail the stepwise assembly of the human telomerase complex, which protects the ends of chromosomes. A third team used x-ray crystallography to catch an antibiotic in the act of grabbing its target in a microbe's cell wall. An inquisitive mind paired with the right tool can do wonders.

A No-Nonsense Approach to Gene Relationships

Researchers use their large gene database to find an elusive enzyme.



LIKE A CASSETTE IN A TAPE DECK, DNA IS ESPECIALLY VULNERABLE TO damage while it is being copied. A particular protein modification is known to protect cell integrity during replication, but despite efforts by several well-established laboratories, the trigger for this event has been a mystery. ¶ Using a technique they developed to assemble

large-scale gene-interaction databases, HHMI investigator Jonathan S. Weissman, HHMI postdoctoral fellow Sean Collins, and colleague Nevan Krogan—all at the University of California, San Francisco (UCSF)—discovered more quickly than other labs that the mystery protein is an

Rachel Salomon

enzyme called Rtt109 (see sidebar, “The Protective Trigger”).

Score one for E-MAP, a technique the scientists unveiled in 2005 to enhance studies of gene-gene, or epistatic, interactions. E-MAP stands for epistatic miniarray profiles. “It provides functional information that you just can’t get any other way,” notes Harvard Medical School biochemist Kevin Struhl. “It provides more detailed and comprehensive information than smaller studies can.”

Weissman explains its purpose: “E-MAP is an automated technique to rapidly and systematically catalog how individual genes work together in a cell.” Traditionally, biologists study gene interactions in yeast by eliminating or damaging an individual gene in a laboratory cell sample, pairing the resulting mutant with others, and observing whether the cells live or die. The drawback of this method is that it is slow and painstaking, and it requires subjective choices: which genes to select for study, which mutants to pair with which others.



“E-MAP is an automated technique to rapidly and systematically catalog how individual genes work together in a cell. ”

JONATHAN WEISSMAN

For example, the budding yeast, *Saccharomyces cerevisiae*, contains about 6,000 genes. To analyze every gene-gene interaction would mean testing a daunting 18 million gene pairs. Scientists have devoted years to scrutinizing a few gene relationships of interest, knowing that, as a practical matter, they are ignoring others. Not necessary with E-MAP.

Krogan compares E-MAP to finding the light switch after stumbling around with just a flashlight. “With a flashlight, you see things in bits and pieces. With the lights on, you see how everything is connected.”

To develop their most recent E-MAP, the UCSF group selected 743 genes in *S. cerevisiae* that code for a group of proteins involved in maintaining, replicating, and translating DNA to RNA. The team created double mutants from every possible combination of the genes—more

than 200,000 gene pairs. Using software they developed, they compared the double mutants’ growth rates with growth rates for single mutants. The result, detailed in an advance online publication in the journal *Nature* on February 21, 2007, was an atlas of how every gene they tested communicates with the others.

The scientists wanted to eliminate any preconceived biases in selecting the gene pairs to study, and they wanted a more nuanced picture of how particular combinations of genes affect cell function. “It’s one thing to say that a double mutant is dead—dead is very clear,” Weissman says. Harder to analyze but equally important are the subtler cases, where double mutations sicken a yeast colony, but less so than a single mutation would, or where they actually make a colony healthier.

Because the database currently covers only a small percentage of all yeast genes, says Harvard’s Struhl, its usefulness is limited to researchers who happen to be interested in those genes. “A whole-genome analysis would be a great boon,” he says.

Weissman and colleagues are working on expanding the method to the rest of the yeast genome—and then to other organisms, including humans. Meanwhile, the scientists have made the atlas freely available on the Web (<http://interactome-cmp.ucsf.edu>) so that other researchers can mine the database for gene-gene interactions. ■ —SIRI CARPENTER

THE PROTECTIVE TRIGGER

RESEARCHERS HAD NOT SUSPECTED Rtt109’s protective role because it bears no structural or chemical resemblance to the group of proteins believed to do that work, explains Jonathan Weissman. It turns out that the enzyme marks chromosomal components called histones to signal that a particular stretch of DNA has already been copied. This chemical cross-checking is essential to preventing DNA damage during replication. >> **ABOUT THE SAME** time Weissman and colleagues published their results in early 2007, three other groups, using more conventional approaches, also reported Rtt109’s role in protecting DNA. But to do so, Nevan Krogan observes, took laborious screening through the entire yeast genome. In contrast, the E-MAP database allowed the UCSF group to narrow the possibilities to just a handful of promising proteins. “We came to the same answer,” says Krogan, “but in their case, it took years of work. In ours, it took months.” — S.C.

An Elegant Molecular Dance

Images reveal how telomerase is created.

XIAOWEI ZHUANG ONCE SCORNE BIOLOGY FOR ITS LACK OF ELEGANCE.

She'd been drawn to physics for its ability to explain the world with fundamental concepts since before she'd entered grade school, when her father, a physicist, set a cup on a table and asked her to speculate about the forces that held it there. Gravity, supporting force from the table, air pressure—those things made sense. But she saw little, she says, simple or beautiful about biology. ¶ Zhuang has since changed

her mind. "I have no doubt now that biology is the discipline where I want to make my contributions." As she studied physics as an undergraduate in China and a graduate student at the University of California, Berkeley, she came to realize that much of its appeal lay in the fact that the physical world was, relatively speaking, fairly well understood. "That was attractive as a student," she notes, "but when it came time to be an independent researcher, it was more interesting to begin to think about things that were less explored." Today Zhuang, an HHMI investigator at Harvard University, relies on her lab team's collective expertise in the physical and life sciences to try to explain some of biology's seeming complexity.

Her team's strategy is to spy on biological machines in action, watching as individual molecules fold, interact with one another, and do their work. They use sensitive optical imaging techniques to collect extraordinarily detailed pictures of this activity—watching, for example, as a single molecule of RNA folds into its functional shape or a tiny polio virus invades a mammalian cell. Combining those images with findings from their experiments in molecular biology and biochemistry, the scientists are revealing how the structural dynamics and movements

of molecules drive biological processes. A related technique developed in Zhuang's lab, called stochastic optical reconstruction microscopy, or STORM, can generate images of cells and other biological specimens with molecular-scale resolution.

Zhuang focuses on biomolecules of obvious medical relevance, and part of the research in her lab investigates viral infection. It's a system for which the lab's ability to track individual molecules and particles is especially germane, Zhuang says, since as few as one in a hundred to a thousand of the viruses that swarm a potential host cell may lead to infection. Thus, the behavior of a single virus may be more pertinent than the behavior of the group. By following individual influenza and polio viruses on their journeys into cells, the group has already unveiled several pathways and molecules that enable infection.

One of the lab's most recent successes, however, is developing a precise portrait of the molecular dance that creates telomerase, a complex of molecules that protects the

ends of chromosomes during DNA replication. Michael Stone, a postdoctoral fellow in Zhuang's lab, led the study published in the March 22, 2007, issue of *Nature*. The enzyme is essential for rapidly dividing cells, such as those in a developing embryo, but is usually shut off in healthy adult human cells. Upregulating the enzyme's activity allows adult cells to achieve a dangerous immortality. The enzyme is inappropriately active in the vast majority of human cancers, making it a potential target for new cancer therapies.

To preserve the tips of chromosomes, telomerase uses a protein enzyme called telomerase reverse transcriptase, or TERT, and a short stretch of RNA that serves as the enzyme's instruction sheet. The two components, however, can't seem to interact properly with each other on their own; helper proteins are needed to promote their assembly into a functional complex.

To find out how one helper protein called p65 helps choreograph the movements that bring together TERT and telomerase RNA, Zhuang and her collaborator, Kathleen Collins, a telomerase biochemist at UC Berkeley, used a technique known as fluorescence resonance energy transfer (FRET). Researchers label the molecule at precise locations with two dyes that emit distinct colors of

"It's like a jigsaw puzzle. When you put in one piece, it helps another find its proper place."

XIAOWEI ZHUANG



Xiaowei Zhuang pairs sensitive optical imaging techniques with molecular biology experiments to reveal with precision how molecule movement drives biological processes.

light. One of these dyes can transfer energy to the other; how much is transferred depends on how close together the two dyes are.

Zhuang and her colleagues attached FRET labels to telomerase RNA and, by monitoring changes in the energy transfer between the labels, observed step-by-step changes in the assembling complex. Their data showed that p65 kicks off the process by binding to the RNA, flexing it so that its

TERT binding sites are close together. TERT can then latch on, snapping the RNA into its final, functional form. “It’s like a jigsaw puzzle,” Zhuang says. “When you put in one piece, it helps another find its proper place.”

With experiments like these, Zhuang says biophysicists and biologists are steadily moving their field toward the kind of fundamental and quantitative ways of explaining the world that first attracted her to science.

She acknowledges, however, that biology’s underlying elegance will differ from that found in physics. “We don’t necessarily want to strip away all the complexity of biology, to say ‘here are the bare bones and now it’s simple,’” she says. “But a different way of viewing that complexity may emerge, to allow us to understand the connections and interplay between biology’s many components.” ■ —JENNIFER MICHALOWSKI

Outsmarting the Toughest Bacteria

Can an antibiotic that works in cows be modified to solve resistance in humans?

SUPERBUGS, THE DISEASE-CAUSING BACTERIA THAT ARE RESISTANT TO EVEN the most high-powered antibiotics, are becoming more commonplace. One dangerous strain called methicillin-resistant *Staphylococcus aureus* (MRSA), once restricted to hospital wards, is turning up in soccer fields and gym lockers. Doctors are having a hard time keeping up. ¶ Although several new antibiotics to MRSA became available a few years ago, “we’re already starting to see resistance to those,” says



“You always need a couple more bullets in your arsenal to stay ahead of the game.”

NATALIE STRYNADKA

Natalie C. J. Strynadka, an HHMI international research scholar at the University of British Columbia in Canada. “You always need a couple more bullets in your arsenal to stay ahead of the game.”

In fact, what Strynadka and her Vancouver team would prefer to more bullets is a *better* bullet—an antibiotic not so readily foiled by bacteria. In their effort to develop one, the researchers focused on an antibiotic called moenomycin. “It’s been used in huge quantities in cattle feed,” Strynadka says, “and yet we’ve seen very little resistance.”

In fact, says Andrew Lovering, a postdoc in Strynadka’s lab, the drug appears to be “resistant” to resistance.

The problem, however, is that moenomycin doesn’t work in people. “It’s a really complex molecule and is not absorbed well in our bodies,” Lovering explains. “We wanted to see if we could change it to make it still effective but amenable to uptake in humans.” As a first step, he and his labmates set out to capture a precise atomic picture of moenomycin in midattack on its bacterial target, a membrane-anchored enzyme called penicillin binding protein 2 (PBP2).

As its name suggests, PBP2 is also the protein targeted by penicillin, methicillin, and a host of other conventional antibiotics. The dumbbell-shaped enzyme, tethered by one of its lobes to the bacterial cell membrane, is a molecular knitting machine. It stitches together the cell wall—a dense meshwork of polysaccharide and peptide threads that forms the bacterium’s protective outer shell.

Both ends of the enzyme contribute to get the job done. The part anchored to the membrane, called the GT domain, first stitches the sugars into chains that form the main fabric of the cell wall. The other end, called the TP domain, then crosslinks the sugar strands with short peptide chains. Penicillin-type drugs attack the TP domain. Moenomycin is the only well-characterized antibiotic that directly cripples the more mysterious GT domain. In either case, the sabotaged cell wall becomes so weak that the bacterium dies.

Lovering, Strynadka, and their colleagues sought to purify and crystallize moenomycin-bound PBP2 to determine the three-dimensional structure of the complex by x-ray crystallography. By understanding how moenomycin binds and interacts with PBP2, explains Strynadka, “we could ask what is really important in the moenomycin molecule for inhibition, and what can we get rid of to make this a smaller compound,

with better pharmacokinetic properties so it will work in humans?”

Proteins like PBP2 are notoriously difficult to extract from their membranes in a way that preserves their native structure. Lovering and research assistant Liza H. de Castro persevered for three years to find just the right conditions to purify and crystallize the protein, on top of an additional two years invested by Daniel Lim, a postdoc previously in the lab. The long-anticipated results, reported in the March 9, 2007, issue of *Science*, offer drug designers a wellspring

of information. “Our structure tells us exactly what the key components are that allow moenomycin to bind to the GT domain,” says Strynadka. It also enables them to define the smallest possible part of moenomycin that will react with PBP2, key to reducing the antibiotic’s size for use in humans.

The researchers also found that the bacterial membrane, which caused so much

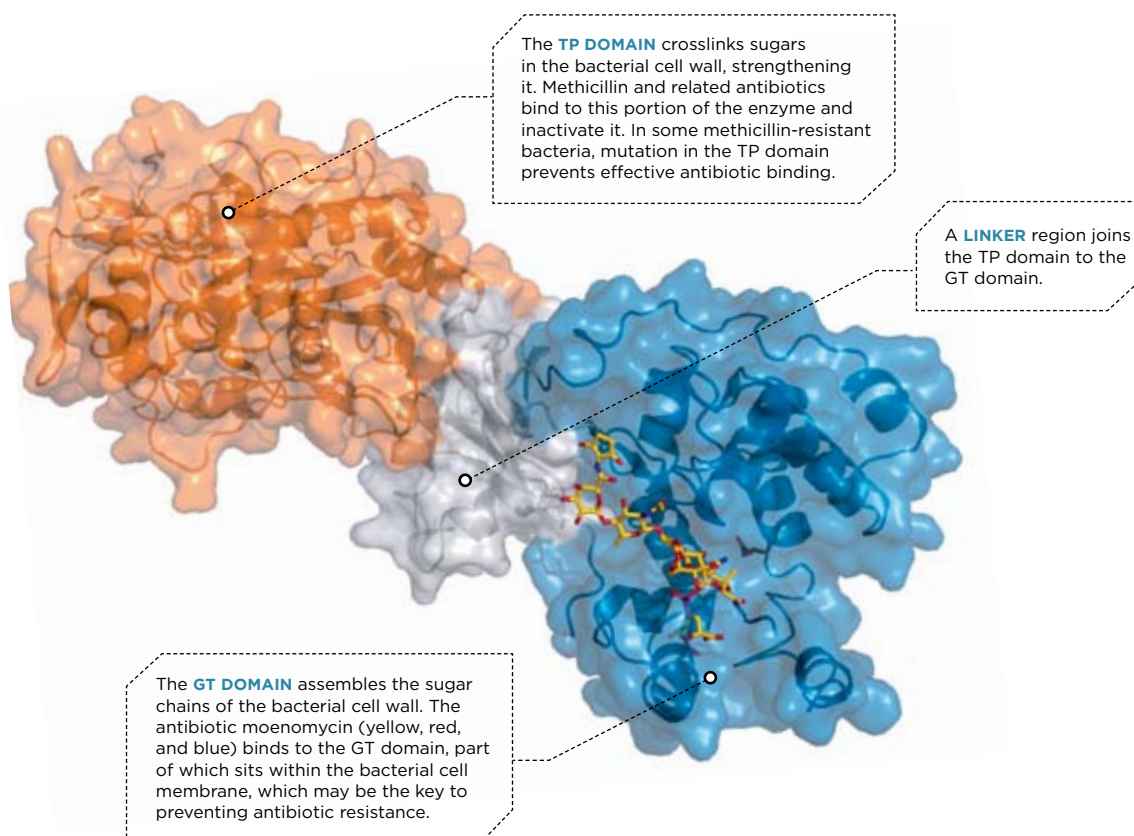
frustration, might be a large factor in helping the moenomycin-PBP2 reaction fend off resistance, Strynadka says. “From what our structure shows, the GT enzyme activity appears to work within the membrane. And perhaps that protects the enzyme from modifications that would normally be part of a resistance phenomenon.”

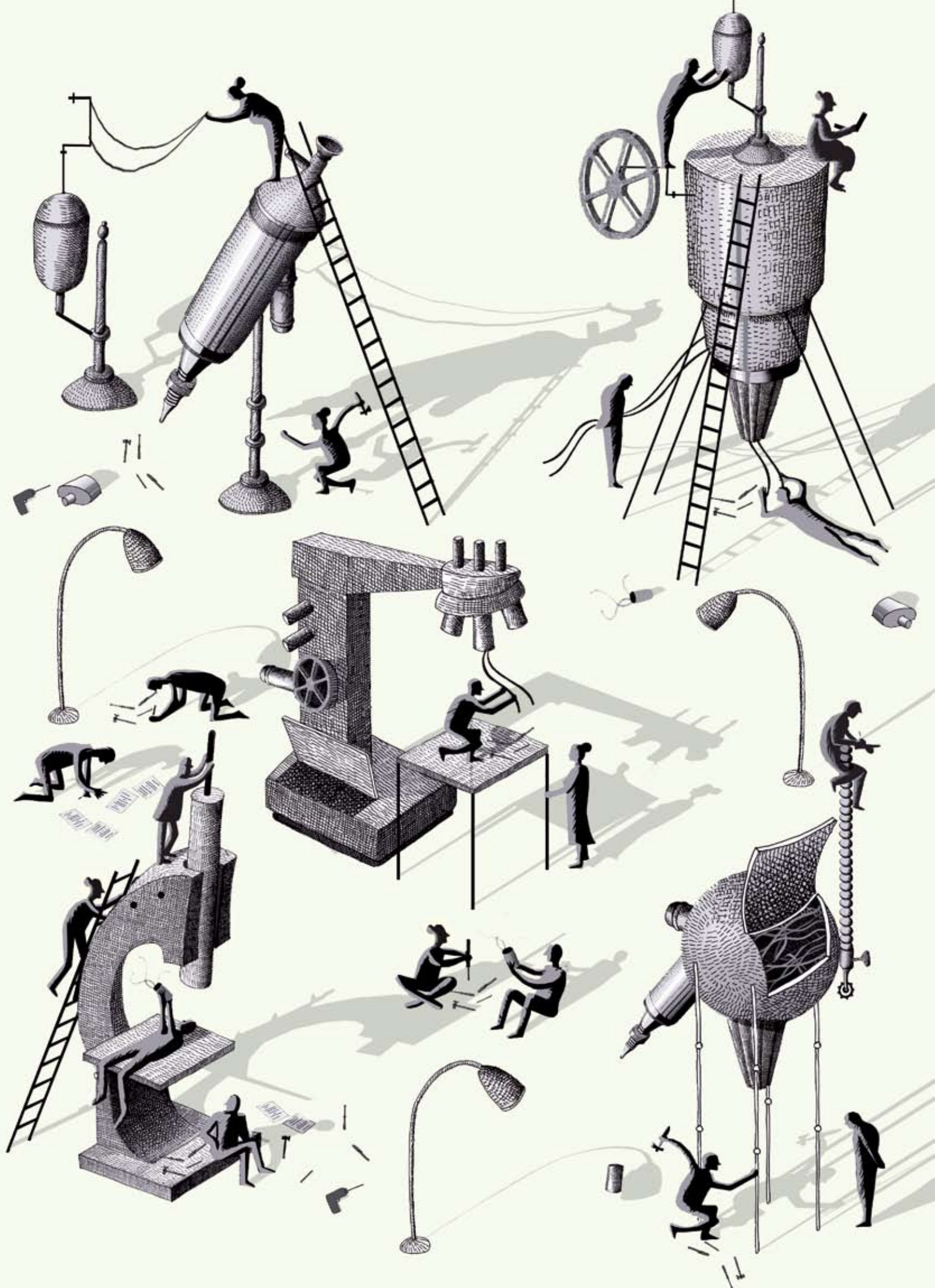
Sounds like the makings of a better bullet against the toughest germs. ■

—PAUL MUHLRAD

ENZYME FREEZE-FRAME

A structural model of the penicillin binding protein 2 (PBP2) engaged with the antibiotic moenomycin. The strands and helical ribbons represent the “backbone” of the PBP2 chain, while the surrounding shapes represent the entire protein structure.





A DIFFERENT MINDSET

TO TRUE TINKERERS, THE LIMITS OF THE PRESENT ARE NEVER PERMANENT BARRIERS, MERELY OFFERS THEY CAN'T REFUSE.

by **Tim Friend and Jennifer Michalowski**
illustration by Adam Simpson

To most people, a microscope is a microscope—a device for revealing structures too small to see with the naked eye. But to some, a microscope or any other tool is a collection of parts that might be reconfigured to do its designated task better, or perhaps accomplish something else entirely. Their world is a collage of potentially useful bits and pieces. By shuffling the pieces and fitting them together in inventive ways, they come up with new tools—many of which are redefining the limits of biological research. ¶ Tinkerers fiddle and adapt, look across disciplines, test and redesign, and ultimately devise methods to explore areas of research that once seemed unapproachable. For example, the semiconductor industry, which continues to find ways to cram more information onto a computer chip, has some lessons to teach the alert biologist interested in observing life at its smallest scale but stymied by the capabilities of modern microscopes. Similarly, bulky needles used to inject labeling molecules can damage cells, but scientists who dabble in nanotechnology are producing thinner and stronger materials that are less likely to disturb the sample. ¶ HHMI investigators Carlos Bustamante, Taekjip Ha, and Carolyn Bertozzi, and Janelia Farm scientist Herschel Marchman, are making such innovations. They craft tools to help explore the scientific mysteries that compel them personally, but their gadgets are enabling a far broader community of researchers to address diverse and intriguing biological questions. ¶

Start with a Need



CARLOS BUSTAMANTE GREW UP IN PERU, WHERE HIS KNACK for tinkering became apparent at a very young age. Playing with his toy cars meant taking them apart and putting them back together. As the space age dawned, his interests turned skyward. He built rockets and experimented with different types of fuels. But his world changed at about age 12 when his father, a physician, brought him a microscope from the United States.

“I thought it was the most marvelous thing. You could peer into this microscopic world, where all these exciting things were happening,” says Bustamante, now an HHMI investigator at the University of California, Berkeley, and head of the Advanced Microscopies Department at Lawrence Berkeley National Laboratory.

In the late 1980s at the University of New Mexico, he and his colleagues used fluorescence microscopy and wire electrodes to coax DNA to “inch along like a caterpillar,” enabling real-time study of DNA movement through a gel during electrophoresis. Then he added magnetic tweezers, figuring out how to anchor one end of a DNA molecule to a glass slide and attach magnetic beads to the other end to characterize the elastic response of the molecule—a first.

Bustamante is probably best known for tinkering with optical tweezers—a laser-based technique physicists invented in 1970 that uses the minute forces exerted by light waves to manipulate molecules. He adapted optical tweezers in the 1990s so that a molecule, trapped in a kind of Star Trek tractor beam, can be poked, prodded, and analyzed. This method has become a standard for measuring single molecules.

Because good can always be better, the upgrading in Bustamante’s lab continues—at smaller and smaller scales. He says his most exciting invention so far is an ultra-high-resolution optical tweezers machine. “Measuring changes down to the angstrom, it opens up a way of following the dynamics of biological systems,” says Bustamante. He is currently searching for nanoscale handles he can attach to molecules to obtain even more precise information. Those handles will likely be carbon nanotubes, he says—cylindrical carbon molecules 1–3

nanometers in diameter that are unusually strong and have unique electrical and heat-conducting properties.

Bustamante says he was deeply inspired in his youth, and adulthood, by two of humanity’s greatest scientists—and tinkerers *extraordinaire*. “Galileo, my all-time hero, was a professor of mathematics, but he was always building things. It is breathtaking the way he put reasoning into instruments that allowed him to arrive at such profound conclusions as the law of inertia.”

Louis Pasteur’s elegant logic similarly impressed Bustamante. Pasteur discovered stereochemistry when he precipitated tartaric acid crystals from a solution and, to his surprise, found two mirror-image shapes. Curiosity piqued, Pasteur used a small stick to separate the crystals into two bunches, using his microscope, and proceeded to dissolve them and study further. He found the solutions identical in all aspects, except that one rotated the plane of polarization of light clockwise and the other counterclockwise. “Pasteur arrived at the remarkable conclusion that molecules can exist in two different forms that are mirror images of one another. That’s tinkering for you, at its best.”

A scientist can accomplish remarkable results just by reflecting that same curiosity-driven spirit, according to Bustamante. “There is nothing written—no rule—that says scientists should work only with instruments that exist. You start with a need and develop the instrument to fit that need,” he says.

“Oftentimes, tinkering doesn’t involve sophisticated thinking,” he insists. “It involves simple logic, and the simpler a system is the better it will be.”



Andrew Nugata

Extreme Techniques

AS A YOUNG STUDENT IN KOREA, TAEKJIP HA WAS A SELF-described “test taker.” He didn’t discover his inventive side until he became a researcher with goals that were unattainable with existing technologies.

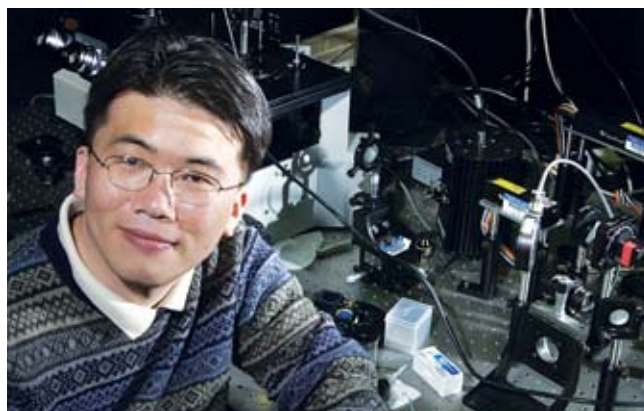
“I was just a very good student who did what I was told to do,” he recalls. “But once I began to work on my own projects, it was a whole new world. I began to think ‘How can I do measurements?’ That is when I became a tinkerer,” says Ha, a biophysicist and HHMI investigator at the University of Illinois at Urbana-Champaign. Since then, he has immersed himself in the role, even ordering off-the-shelf parts to build a microscope from scratch.

Ha’s overriding goal has been to observe single molecules in action. For example, his group recently devised the “nancontainer”—a nanoscale test tube with a diameter one-thousandth that of a human hair—to enable scientists to observe the behavior of single molecules of DNA, RNA, or proteins. In the June 11, 2007, online issue of the *Proceedings of the National Academy of Sciences*, the team described how they intentionally made the nanocontainers porous; the large subject molecules cannot escape, but smaller molecules such as ions and the cellular energy source ATP can be added to start reactions. Ha calls the technique “another cool addition to the tool set that is being made available by our research.”

That tool set got its start when Ha was challenged to improve fluorescence resonance energy transfer (FRET) as an optical measurement technique. At the time, FRET could measure the distance between only two points. The “donor” and “acceptor,” two different colors, are attached to two points on a molecule, or on two molecules. If the distance between them remains larger than 10 nanometers, their colors do not change. But if the dyes come into closer proximity, indicating the molecules are interacting, the ratio of the two colors—and thus the intensity—changes.

Unsatisfied, Ha continued to experiment, building an apparatus that combines single-molecule FRET with optical tweezers. Today he is performing FRET in three colors, allowing measurements of three different molecular distances at a time. “With complex molecules there is more than one moving part,” he explains.

“My ultimate goal is to reconstitute the entire DNA replication system,” says Ha. “When all these proteins are labeled with



different molecules and we have nanoscale handles to manipulate and study their coordination in great detail, we will see how molecules really work.”

Ha’s graduate advisor, Shimon Weiss, now at the University of California, Los Angeles, considers Ha exceptional. “Taekjip has the rare ability to identify the bottlenecks in any problem he attacks, and then come up with the most correct, simple way to overcome those bottlenecks. Never overdesigning to solve a problem, he optimizes his work investment and stops where the solution is just adequate.”

Ha says he has developed an instinct for choosing people with a similar bent to work in his lab—and he pushes them to use it. “I tell my students to find ways to reduce the setup time for their experiments by a factor of two to four. I encourage them to change the whole process of doing measurements to make things more reliable and efficient so they can do better science.” There’s no need for him to push them very hard, Ha adds. “We always have pressure to do more tinkering.”

“I was just a very good student who did what I was told to do. But once I began to work on my own projects, it was a whole new world.” — TAEKJIP HA

Fantastic Vision

CAROLYN BERTOZZI'S PENCHANT FOR TECHNICAL INGENUITY

showed itself when she was a youngster playing dolls with her sisters. “We had great fun taking dolls apart and reassembling them as alien creatures,” she recalls. The gadgets that her father, a physicist at the Massachusetts Institute of Technology, brought home were also an outlet. “A great favorite was a strong magnet. My sisters and I used it to build strange sculptures from nails, staples, nuts, and bolts.”

Now a chemist and an HHMI investigator at the University of California, Berkeley, Bertozzi exercises her creativity in the field of glycosylation—the cellular process by which sugars are added to proteins or other molecules. The resulting “glycans” govern a variety of cell-to-cell interactions. Scientists had known for decades that changes in glycosylation were associated with cancer, bacterial infections, and other illnesses, but they had no way of studying how molecules at the cell surface use sugars. Bertozzi’s lab devised a method of imaging glycosylation—something not thought possible.

Her group developed a chemical reporter, or label, that can be installed in the glycans of cells in culture or in living animals, such as worms, zebrafish, and mice. The reporter, linked to a simple sugar and introduced into the media of worms or fish, or injected into mice, is metabolized and incorporated into cell-surface glycans. After chemical reaction with a probe molecule, the reporter can be visualized by using an imaging technique such as fluorescence microscopy or positron emission tomography.

Bertozzi says her inspiration for building gadgets comes from “the demands of research at the interface of disciplines,” whereby members of one community express a need that can be met by another. As director of the Molecular Foundry at the Lawrence Berkeley National Laboratory—a user facility that supports research in nanoscience worldwide—she orchestrates that kind of interaction, and participates herself. “Of the many tools my group has worked on,” she says, “the coolest is probably the



carbon nanotube-based ‘nanoinjector,’ which we developed with Alex Zettl’s lab in the Physics Department here at Berkeley.”

In this case, carbon nanotubes served as new building blocks for injecting imaging agents, called quantum dots, into cells, and conducting surgery on single cells. Carbon nanotubes, being harder than steel and manipulable with angstrom-resolution precision, make ideal injectors for delicate cell membranes.

In collaboration with Zettl, Bertozzi’s lab mounted a single carbon nanotube to an atomic force microscope (AFM)—a widely used instrument that scans surfaces by manipulating a probe at subnanometer scales. The tip of this “nanomanipulator” can be moved in three dimensions—X, Y, and Z. After loading the carbon nanotube with quantum dots and other molecules, the device can be positioned just above a cell. The AFM can then push the carbon nanotube through the cell membrane and deliver the load of quantum dots, bright enough to track single particles, into the cell’s interior. The nanoinjector is described in detail in the May 15, 2007, issue of the *Proceedings of the National Academy of Sciences*.

For a devoted tinkerer like Bertozzi, life can imitate art: “In one of my favorite movies, *Fantastic Voyage* [1966], a group of scientists and physicians miniaturize a ship, and themselves, to navigate inside the human body in order to diagnose and treat disease. This fantasy may now essentially come true as nanoscale probes and manipulators revolutionize medicine. What was fiction a few decades ago may ultimately be realized in the hands of scientists, engineers, and physicians working together.”

HOW SMALL ARE WE TALKING?		
1 millimeter = 0.03937 INCH	1 nanometer = 0.000001 MILLIMETER	1 angstrom = 0.1 NANOMETER OR 1/250 MILLIONTH OF AN INCH

Barbara Ries

Inner Engineer

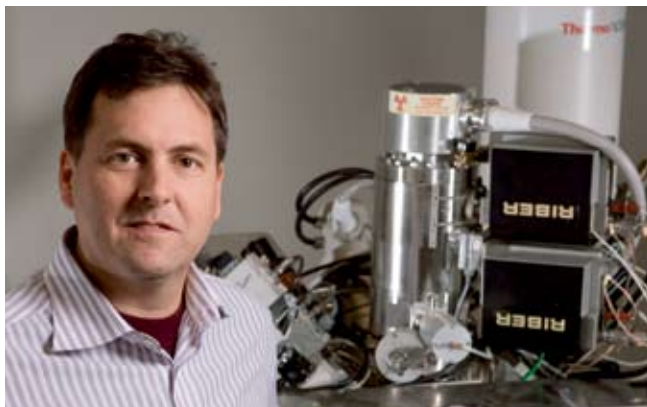


WHEN HERSCHEL MARCHMAN SAYS “WE NEED TO LOOK AT things in different ways,” he’s not just talking about the view through a microscope. Marchman is intent on expanding researchers’ options through creative variations on existing technology, and his unique perspective provides a wellspring of ideas for vexed scientists who think they have hit a wall in their research because of technological limitations.

Marchman, a senior scientist working in Harald Hess’s applied physics and instrumentation group at HHMI’s Janelia Farm Research Campus, approaches such issues as an engineer, often seeing parallels to problems the semiconductor industry—in which he spent some 15 years—has already solved. He readily borrows tools from that field, adapting them in ways he anticipates will dramatically affect biological discovery.

High on his priority list is reducing the need to stain biological samples, which enhances their contrast but also imposes constraints. In the case of scanning electron microscopy, for example, users are limited to imaging only those cellular structures that can be labeled with metal stains during sample preparation. “I’m sure there’s more information there that we’re missing,” Marchman says.

To begin with, he’d like to harness the power of deep-ultraviolet illumination (DUV), a favorite of computer-chip lithographers because its ultra-short wavelength allows them to print exceedingly tiny patterns. Though DUV has not been applied to biological samples for high-resolution imaging, Marchman thinks that, with some experimenting, it might allow researchers to detect contrast patterns in cells more naturally, without using stains.



Paul Fellers

“When we tinker we don’t want to build something completely from scratch. We want to add value to what you can buy by modifying it.” —HERSCHEL MARCHMAN

Meanwhile, he’s working with Hess to design a detector for a scanning electron microscope that will break from the current paradigm, in which electrons bounce off a sample’s surface. The modification should bring the instrument closer to the far superior resolution of transmission electron microscopy. It’s an example of Marchman’s way of improving on the status quo.

“When we tinker,” he says, “we don’t want to build something completely from scratch. We want to add value to what you can buy by modifying it.”

Marchman has some high-tech tools to enable his innovations. Many of his projects depend on a focused ion beam, which allows him to etch and deposit materials at the nanoscale level. Marchman sees an opportunity to make the standard focused ion beam he has purchased even more useful: he plans to add a photocell and a gas chamber to the instrument so that he can perform chemical reactions directly on the small-scale parts he produces.

This setup, Marchman believes, will help meet the needs of Janelia Farm researchers in a variety of ways. For example, he imagines using the gas chamber to fill fruit fly brains with a resin so they can be sliced thin for microscopy, eliminating the need for microsurgery, which is time-consuming and tends to destroy delicate brain tissue. Again borrowing from the semiconductor industry, he will take advantage of hydrocarbon gases mixed with metals. With a vacuum, the metals can be deposited onto a highly localized region of a computer chip. Marchman will use the technique to deposit a spot of gold onto a single cell, making the gold a simple, inert marker for navigating back to that cell under the microscope.

“If you really understand the technology,” he says, “you can modify it to your own problem.” ■

FOR MORE INFORMATION: To read about other HHMI tinkerers, visit the *Bulletin* online at www.hhmi.org/bulletin/aug2007.

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Sydney Brenner's hopes for understanding the brain — put on hold 30 years ago — are now revived, courtesy of advanced techniques and new insights about a humble but invaluable worm.

by Maya Pines

illustration by Aaron Smith

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The Wise Man of Janelia



As soon as Sydney Brenner walked into the hall, leaning on his cane, several young scientists rushed toward him like bees drawn to nectar. They wanted to talk to him about many things—his current activities, their own work, even a recently published article by someone else. Brenner, 80 years old, answered their questions with gusto. He made it clear that he disliked the new article. “The only thing that’s worse than ‘bad’ is ‘boring,’” he quipped. They laughed.

Brenner doesn’t do boring. A Nobel Prize winner and one of the founders of molecular biology, he keeps opening up new fields of research. After solving some initial problems and attracting clever collaborators, he then moves on to try something different. On this occasion, last March at HHMI’s Janelia Farm Research Campus in Ashburn, Virginia, he was attending a conference on the nervous system. A senior fellow at Janelia, Brenner was making one of many stops on an ever-full itinerary. He spends much of his time flying around the world, giving talks and advice, running research projects, launching new alliances, stirring things up.

“I’ve been a rebel, or as I was once called, an *enfant terrible*,” he said in a series of interviews later published as an autobiography, *My Life in Science*, by BioMed Central Ltd. “Being a rebel has always appealed to me, largely because I’m convinced that the standard parts of any activity are already petrified at the core.”

A Most Worthy Worm

In the late 1960s, for instance, “after cracking the genetic code, Sydney decided he wanted to understand how genes control the development and function of the nervous system,” says Paul W. Sternberg, an HHMI investigator at the California Institute of Technology. “So he chose to work with the worm”—specifically, a tiny transparent nematode called *Caenorhabditis elegans*, that he seemed to pick out of obscurity.

“People thought I was crazy,” Brenner recalls.

But these worms are only 1 millimeter long—a good size to study under an electron microscope—and easy to grow in bulk. Ten thousand can fit onto one petri dish, where they feed on *Escherichia coli* bacteria. And they take only three and a half days to grow from egg to sexual maturity, when they produce about 300 progeny apiece.

Brenner liked them for all these reasons and also because of what he called their “beautiful sex lives.” *C. elegans* is usually “a self-fertilizing hermaphrodite,” he notes, and “each animal is the result of a cross of itself with itself.” This means the worms have a uniform genetic constitution, as if they are clones. Occasionally, some smaller, male *C. elegans* worms crop up, which researchers can use to move genetic markers from one animal to another in experiments.

Brenner hoped his worms would enable scientists to study how genes affect behavior “because there is no simple mapping that connects the two,” he explains. “The link between genes and behavior resides in understanding the structure of the nervous system”—partic-



ularly, the brain. So, in the early 1970s, he began to find mutant worms with behavioral abnormalities and to map the sites of their genetic mutations. Brenner also started a program of cutting up the worms into serial slices and examining each slice with an electron microscope.

Ultimately, in 1986, he and his colleagues John White, Eileen Southgate, and J. Nichol Thomson published the structure of the nervous system of *C. elegans*. (Some ten thousand electron micrographs from these studies are now archived and accessible for scientific review at the Albert Einstein College of Medicine. For more information, visit www.hhmi.org/bulletin/may2006/features/archives.html.)

Other results flowed in. By 1977, after years of doggedly staring into microscopes, John Sulston—who had joined Brenner’s group at the Medical Research Council (MRC) in Cambridge, England—produced the complete lineage map of an adult worm, from a single fertilized egg cell to the 959 cells in the fully organized animal. H. Robert Horvitz, doing a post-doctoral fellowship in the same lab, teamed up with Sulston in the later stages of this work, tracing the fate of each cell

during the worm's growth from embryo to adult. Their research revealed that cell division produced 131 more cells than actually make up the mature worm. They learned that those extra cells died through an orderly process known as apoptosis, or programmed cell death, during which certain cells commit suicide for the benefit of the whole animal.

In a series of experiments that began in the 1970s, Horvitz, who is now an HHMI investigator at the Massachusetts Institute of Technology, identified a number of genes that regulate apoptosis in the worm. He also found that one of those genes had a similar counterpart in humans. Researchers subsequently found versions of other worm apoptosis genes in humans, where they play an essential role in normal development. Both Sulston and Horvitz eventually shared the Nobel Prize in Physiology or Medicine with Brenner in 2002 for their achievements.

Brenner, a short man with bushy eyebrows who has been known to wave his cane in the air during arguments with other scientists, has a low tolerance for delay. He became disappointed that the new findings did not make a dent in the much more complex problem he had started out with: how genes control the nervous system and behavior. Concluding that the right tools for this work were not yet available, he simply gave it up temporarily. "That's why I like to have a lot of things to do," he explains, "so that if one gets stuck, you can go on with the others."

Now Is the Time

Now, 30 years later, Brenner is once again eager to tackle one of biology's greatest challenges—"understanding how a complete brain works," as he puts it. That is also the stated goal of the Janelia Farm Research Campus, whose work so far has focused on the brains of flies and mice. But Brenner pins his hopes on the worm, which has the simplest and best-known nervous system. "We will fulfill the program of Janelia in *C. elegans*," he predicts.

Brenner helped organize the March conference at Janelia on "Neural Circuits and Behavior in *C. elegans*." It was prompted by the fact that researchers have now obtained three types of information that Brenner considers crucial for relating brain to behavior, and all three are available in the worm.

First, "we have the wiring diagram—we know exactly how many neurons are in the worm's nervous system and how they are connected," Brenner points out. Second, "we know the complete cell lineage of the worm"—how a single egg cell develops into all the other cells, and which cell comes from which progenitor. And third, researchers have established the complete DNA sequence of the worm's genome, which was published in 1998.

With all this information, "you can make models of how some circuits work and test them," says Brenner. But the key, he adds, is to use "the real structure of the worm's neural circuits." What needs to be done, he says, is "to think hard about how the worm solves a problem."



I like to have a lot of things to do so that if one gets stuck, you can go on with the others.

— Sydney Brenner

Exceeding All Expectations

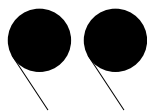
The 40 scientists who came to the Janelia Farm conference talked about their first efforts in this direction. Cornelia I. Bargmann, an HHMI investigator at The Rockefeller University in New York City (and co-organizer of the meeting), described her studies of how worms regulate their patterns of locomotion after they have been removed from food. She analyzed the hungry worms' search patterns, located the neurons involved in each pattern, and confirmed their activity by means of imaging. Jamie White, a postdoc in the University of Utah lab of HHMI investigator Erik M. Jorgensen, took a different approach: he analyzed the neuronal circuits that make male worms differ from hermaphrodites in their responses to pheromones, the chemical signals with which animals communicate. The males were attracted to pheromones released by hermaphrodites, while other hermaphrodites avoided them.

Other scientists used their expertise in imaging or computation to pave the

way for future experiments. Rex Kerr, a fellow at Janelia Farm, pointed out "there is no easy way to precisely monitor the activity of neurons, or to quantify behavior at the same time." To help solve this problem, Kerr is working with a new microscope that could provide three-dimensional views—even movies—of what goes on inside the worm's head, where half of the animal's 302 neurons are located.

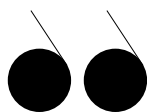
Brenner seemed thrilled by what he heard. "People are modeling all parts of the nervous system," he says. "This has exceeded all expectations. ... It will be seen as a turning point in our understanding of the nervous system.

"If we can simulate a behavior with a computer model of the nervous system," he adds, "then we have the capacity to predict how [the animal] will behave under circumstances that have not yet been tested. And if we can check it by experiment, then we have the basis for explaining the nervous system."



Being a rebel has always appealed to me,
largely because I'm convinced that
the standard parts of any activity are
already petrified at the core.

— Sydney Brenner



Scientist-Citizen of the World

Brenner himself has influenced these and other results, directly or indirectly, and his insights and advice continue to be sought the world over. He and his wife have a house in Ely, England, a small town near Cambridge renowned for its cathedral, but they live there only a few months a year. In the winter they move to the Salk Institute for Biological Studies in La Jolla, California, where he collaborates with HHMI investigator Terrence J. Sejnowski at the Crick-Jacobs Center for Theoretical and Computational Biology.

He travels frequently to Singapore, where he says he's "been helping to build a new biomedical research program that now has several thousand people and is going very well." While in Singapore, he guides the program, gives lectures, supervises students, and even runs some research projects. A decade ago Brenner started a study of *fugu*, a pufferfish that he chose because it is a vertebrate with a tiny genome. The Singapore team played a big role in the international consortium that sequenced and published the *fugu* genome in 2002. Last October, Brenner received Singapore's top science award, the National Science and Technology Medal, and an orchid there has been named after him.

In addition, Brenner heads a planned Okinawa Institute of Science and Technology in Japan. He works with the Molecular Sciences Institute in Berkeley, California, which he founded a decade ago, and holds a variety of other positions, some of which, he says, "are secret."

A Precious Asset to Janelia

Gerald M. Rubin, director of Janelia Farm, recruited Brenner during the earliest planning stages of the research campus. Rubin remembered the stimulating environment he had found at the Medical Research Council in Cambridge where he did his graduate studies with Brenner, beginning in 1971, and he wanted to reproduce some of its best features at Janelia—in particular, having people like Brenner to talk to.

“I could hardly think of a single person who could do more for the intellectual environment,” says Rubin. Just consider some of Brenner’s early work. He was a co-discoverer of messenger RNA and he collaborated with Francis Crick, the co-discoverer of DNA’s double helix, to show that the genetic code consists of nonoverlapping triplets of nucleotides, with each triplet specifying a particular amino acid. “He did work worthy of a Nobel Prize even before he got into *C. elegans*,” says Rubin.

“And Sydney has a combination of wit and insight that is very rare. He was so entertaining when he taught at Cambridge



Sydney Brenner (right) with Gerry Rubin at Janelia Farm.

that students would bring their nonscientist friends to his lectures just to listen to him. So for me,” says Rubin, “it would be enough if Sydney just came here and sat at a table in the pub and talked to all comers, happily giving advice on people’s experiments and careers.”

As Brenner describes it with a smile, “My function is to be decorative, ornamental ... to talk to the young people, tell them stories, and keep the conversation going—about science, its puzzles, and its problems.”

Such conversations have already produced results. During a recent talk

with Brenner, Janelia group leader Gene Myers, a computer scientist famous for developing the whole-genome shotgun technique that his team used in sequencing the human genome, became very interested in the problem of the brain. “It’s a little surprising to me,” he says, “but I started thinking about some experiments, which I described to Sydney, and he made some astute comments. We had a period of a day or so when the conversation was really intense.”

Myers finds Brenner’s attitude particularly impressive. “Very often, scientists look for reasons why something can’t be done,” he says. “But Sydney’s response is, ‘Let’s have a go!’ Especially since I’m not an experimental scientist, I’ve found that liberating. So we’ve now got a very interesting project going in which we’re literally watching the neurons firing in transgenic constructs. It’s fairly high risk, yet easy and inexpensive, and there’s a nice little computational problem involved. Sydney and I have got ourselves all worked up in a lather about it and we’ve infected everyone else at Janelia. We’re going to have a go!” ■

ALL IN THE FAMILY

The number of people in the “worm community,” as *C. elegans* researchers call themselves, is growing rapidly. Once regarded as a joke organism, the little worms have become a powerful experimental system, with more than 3,000 scientists working on them in some 400 labs. “Somebody told me a new nematode lab is opening every week—I believe that’s the same rate as McDonald’s!” says Sydney Brenner. ○ ○ ○ Actually, most members of this community can trace their scientific lineage to Brenner. They are either his direct professional offspring, such as Robert Horvitz, who was a postdoctoral fellow of his at the MRC, or they were trained by people whom Brenner

has trained. Paul Sternberg, who joined Horvitz’s lab as a graduate student, considers himself “second generation,” or F_2 in the jargon of genetic researchers. So does Cornelia Bargmann, who joined Horvitz’s lab as a postdoctoral fellow. Rex Kerr, an F_3 , was trained by William Schafer, an F_2 who was trained by Cynthia Kenyon, who was a postdoctoral fellow in Brenner’s lab. ○ ○ ○ They share a kind of family feeling for Brenner. When a new species of nematode, closely related to *C. elegans*, was officially named “*Caenorhabditis brenneri*” in April of this year, Sternberg and his “relatives” rejoiced. He says, “It made everyone in the field very happy.” — M.P.

BROKEN SYMMETRY

THE FACT THAT THE TWO SIDES OF MANY ANIMALS' BRAINS ARE NOT MIRROR IMAGES—PARTICULARLY IN HUMANS—MAY ULTIMATELY HELP TO EXPLAIN THE DIFFERENCES IN BEHAVIOR BETWEEN SPECIES AND EVEN AMONG INDIVIDUALS.

BY RICHARD SALTUS

ILLUSTRATION BY TED McGRATH

PROJECT DUE FRIDAY

$$A^2 + 2B + C = X$$

MASHA'S PARTY SATURDAY NIGHT

MOM'S BIRTHDAY
MAY 20

BAND PRACTICE
TUESDAY NIGHT





Human
beings
see order,
beauty, and
perfection in
symmetry—
witness
the
popularity
of the
balanced
geometric
patterns
of Amish
quilts and
oriental rugs.

Our eyes and brains are innately attuned to symmetry and deviations from it, even in other humans. “People will pick out the most perfectly symmetrical (computer-generated) faces as the most attractive,”

notes HHMI investigator Oliver Hobert, a neuroscientist at Columbia University.

In some important circumstances, however, asymmetry rules. Hobert, a fan of the intricate, repeating, and symmetrical geometries of Islamic art and architecture, focuses his research on the asymmetrical nature of the brain. Outwardly, it appears to be made up of a matched pair of gray, wrinkled hemispheres. But on closer inspection, certain brain regions have broken symmetry in terms of shape, structure, size, or function. The two sides of the human brain differ most radically in the way they process information. In effect, the two hemispheres “think” in contrasting ways. The left side controls speech and language processing, math, and logical thought, while the right hemisphere deals in spatial and face recognition, emotional control, and artistic abilities.

Fossil evidence suggests that left-brain, right-brain differences began showing up in the expanding brains of prehuman hominids around 2 million years ago. Present-day nonhuman primates also show brain asymmetries, though they are less pronounced than in humans. Asymmetric brain structures are probably widespread and have been discovered in creatures as varied as chickens, toads, fish, bees, and worms, including the roundworm *Caenorhabditis elegans*.

The first discoveries of functions localized in different hemispheres of the human brain came about 150 years ago, when speech and language were traced to left-hemisphere locations that weren’t duplicated in the right half. Since then,

many other specialized functions have been traced to one hemisphere or the other, and the field has lately been given fresh impetus with tools such as confocal microscopy, novel animal models, techniques for tagging cells with antibodies and fluorescent proteins, and large-scale gene-expression analyses.

Molecular Tug of War

Breaking symmetry involves some very complex biology in the course of embryonic development. Starting out as a ball of identical cells, the embryo divides along axes—head and tail, front and back, left and right sides. Initially, the cells on the two sides of the brain are identical, but they differentiate in response to genetic signals. The question is not only how they become different from each other, but what determines whether a cell is “left” or “right?”

Fortunately for neuroscientists, brain asymmetries have been identified in two of the simple, well-understood model organisms routinely used in developmental studies—the nematode *C. elegans* and the striped, minnow-like zebrafish. (The geneticist’s favorite model, the fruit fly, has not been of much use here as not many asymmetries have been found in its brain.)

“Our goal is to use zebrafish to look at asymmetries to see how they are generated, from genes through circuitry to behavior,” says Stephen Wilson, professor of developmental genetics at University College London. The zebrafish has a number of convenient qualities, including a small but “conspicuous” brain asymmetry and the fact that its embryos are transparent, says Miguel L. Concha, an



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OLIVER HOBERT

So how does this unbalanced brain affect the fish's behavior? Wilson, Concha, and others believe the neural asymmetry makes it possible for the animal's two eyes to have different, specialized functions. It was previously known that one eye scans the environment for novel stimuli such as predators, while the other pays attention to other zebrafish. Wilson's group found that when a zebrafish is trained to look into a mirror, it tends to use the same eye. Then they created mutants with reversed brain asymmetries—and the eye preferences were reversed as well. While this doesn't clinch the case, it is strong evidence supporting the structure–behavior connection. Moreover, it looks as if the lateral assignment of the functions is the same in all members of the species—a kind of organized behavioral specialization with survival implications.

Competing Sides

In a similar quest, Hobert has turned to an even simpler model—*C. elegans*, the roundworm with a primitive nervous system made up of just 302 cells. This little worm has evolved a slight asymmetry to sharpen its detection of food-related chemical cues in the environment. In the *C. elegans* embryo, certain chemosensory nerve cells, called ASE neurons, are initially identical. By the time the worm has hatched, however, cells on the left side (ASEL) of the head region have expressed receptors that are sensitive to certain chemicals, while the neurons on the right (ASER) are tuned to different compounds.

“What that means is that asymmetry is derived,” says Hobert, and it raises the question: how does “same” become “different?”

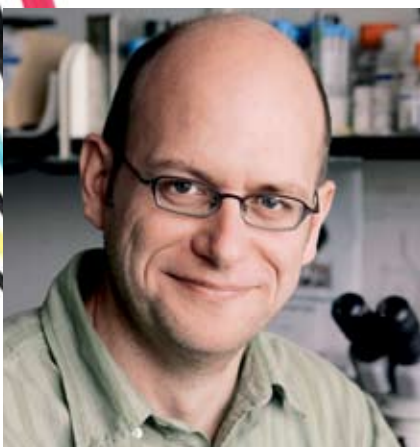
After generating hundreds of thousands of mutant *C. elegans*, Hobert and his colleagues discovered variants that lacked the asymmetry. These mutants had either left-sided neurons or right-sided neurons but not both, as in normal worms. These clues led the scientists to identify several molecular regulators that normally decide the fate of some ASE neurons to be “left” and others to be “right.” In principle, it's much like the competitive process that Concha found in the zebrafish.

One of the decisive molecules turned out to be a micro-RNA—a small, single-stranded RNA with a gene-silencing function similar to the one performed by RNA interference. This molecule, dubbed *lisy-6*, is expressed only in the left-sided ASE neurons. It represses “right-sided” gene activity, which ordinarily would be the default case, thereby allowing left-orientation gene programs to do their work. In certain *C. elegans* mutants, *lisy-6* is knocked out; as a result, right orientation is “de-repressed” so that all ASE neurons are right-sided.

As with the zebrafish research, Hobert can't quite follow the trail to identify the first signal in the embryo that triggers asymmetrical nerve-cell fates. But the worm findings have put on the table a mechanism that, like the processes being uncovered in the zebrafish, may be a general method adopted by higher animals.

“The discovery that there are asymmetries in invertebrate nervous systems is in itself exciting, and I predict that insights gained from these studies (i.e., of *C. elegans*) will be very relevant to the human story, although with some very major differences,” says David C. Van Essen, a brain researcher at Washington University and a member of the HHMI Scientific Review Board. Van Essen notes that his colleagues have used functional MRI to reveal previously unknown nerve networks in human brains that allow the two hemispheres to communicate with each other more closely than had been thought. These findings fit with previous

CHOOSING SIDES Through a clever use of asymmetry, the roundworm *C. elegans* makes an odor-sniffing nerve cell do double duty. The AWC neuron takes two slightly different forms—AWC-ON and AWC-OFF, tuned for different scents—randomly destined for opposite sides of the worm. ✱ But since the scent-sensors can end up on either side, how does nature ensure there will always be one of each type? HHMI investigator Cornelia Bargmann at The Rockefeller University has discovered that the developing AWC cells choose up sides in a brief “chat” via cellular channels called gap junctions that form in the embryo—then vanish when their job is done. — R.S.



Oliver Hobert, Columbia University; **Miguel Concha**, University of Chile; and **Christopher Walsh**, Harvard Medical School, are making early inroads into the origins of asymmetry in the brain.

observations that the opposite side of the brain can often compensate when an important, localized function like speech is lost through a stroke or disease.

Right-Left Genes in Human Brains

In the early 1860s, French physician Paul Broca found that a man who had become almost speechless after infection with syphilis had damage in a part of the left hemisphere now known as “Broca’s area.” Broca inferred, from this and other brain studies, that this left-brain structure controlled speech, as damage in the corresponding area of the right hemisphere did not affect speaking ability. This finding was the first strong evidence of lateralization of brain functions in human beings.

One hundred fifty years later, scientists are beginning to understand what genetic programs guide asymmetry and lateralization. It’s a logical assumption that some genes are expressed differently in the right and left brains—as in the zebrafish and *C. elegans*—though studies of the brains of

human adults haven’t turned up any significant differences, according to Christopher A. Walsh, an HHMI investigator at Harvard Medical School and Beth Israel Deaconess Medical Center in Boston.

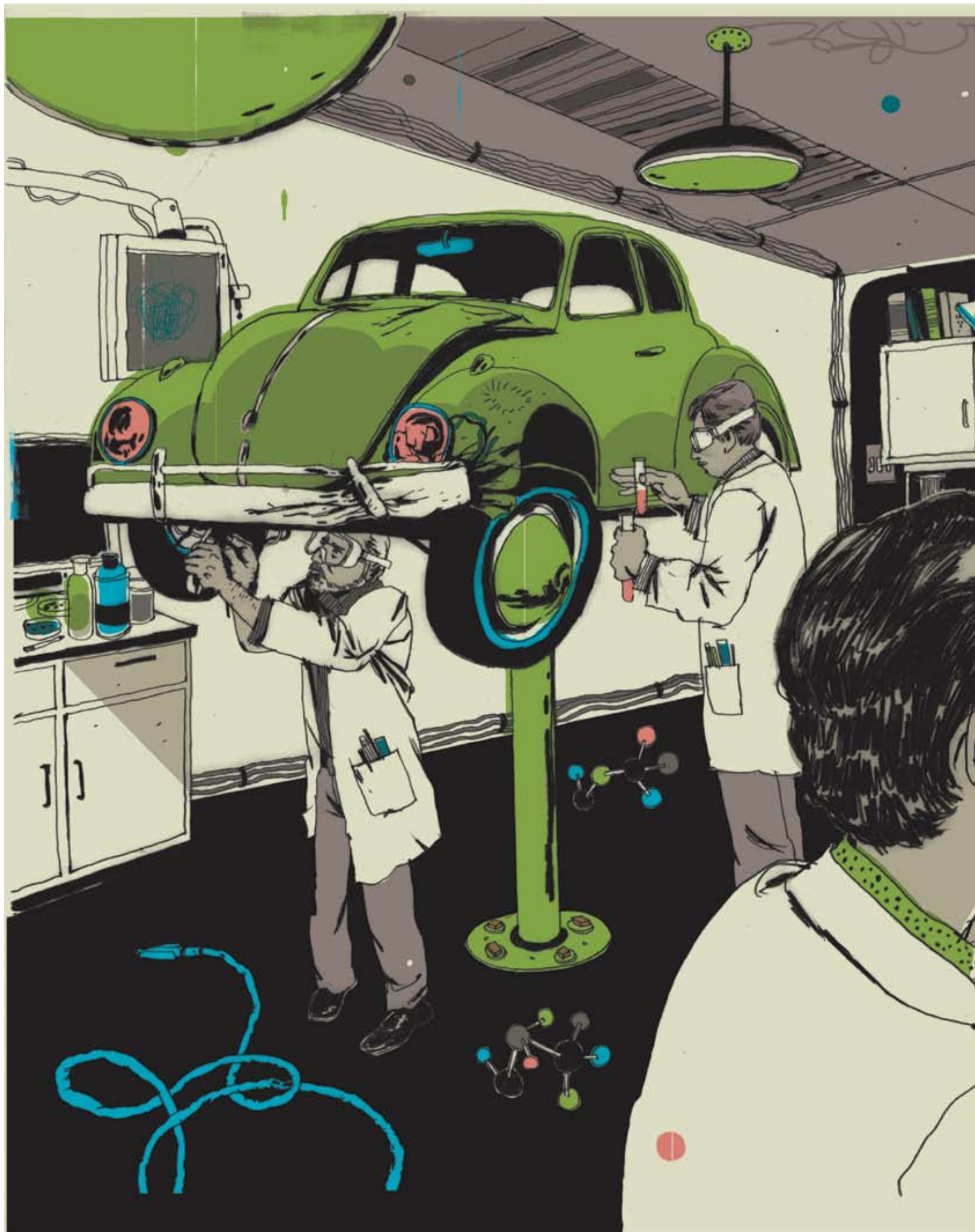
Reasoning that it might be more fruitful to hunt for differences in gene expression during development when asymmetries are being established, Walsh and his colleagues obtained fetal brain tissue from an NIH-funded repository. They analyzed and compared gene activity in tissue from the left hemisphere area where language centers form and tissue from the corresponding area of the right hemisphere.

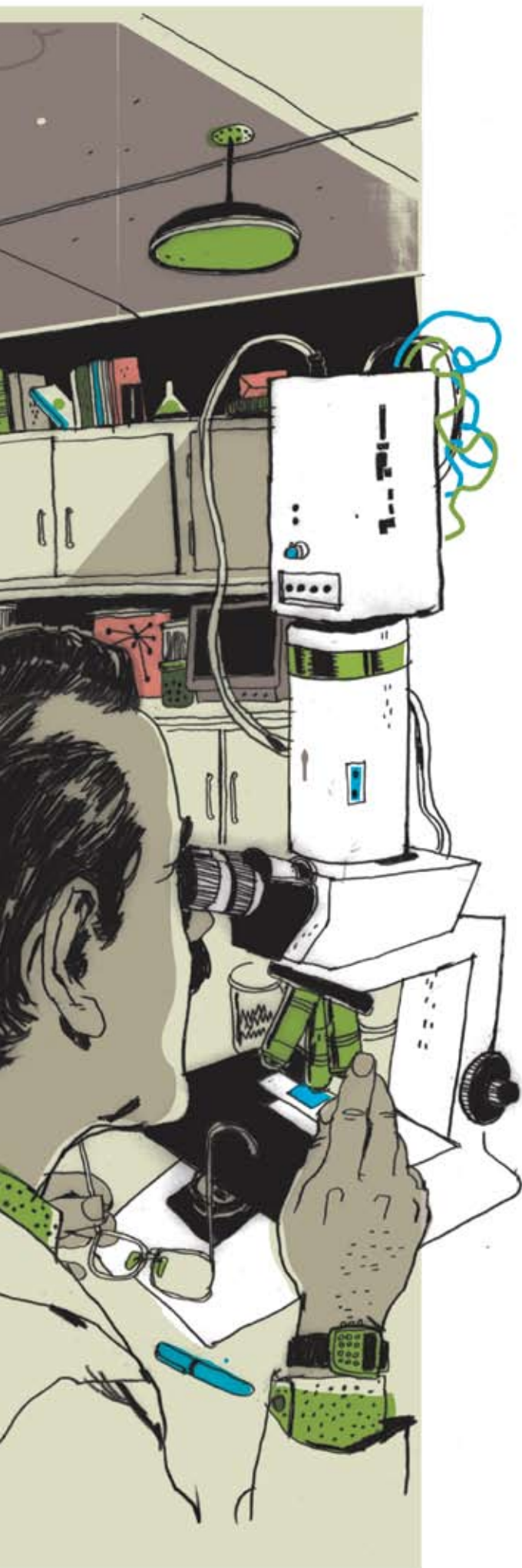
The researchers reported in *Science* in 2005 that 27 genes (the group has since found 13 more) were differentially expressed in the left and right hemispheres, particularly in the perisylvian regions—those around a landmark structure called the Sylvian fissure—that are specialized in the left hemisphere for language.

The activity of one gene in particular, *Lmo4*, was markedly reduced in the tissue from the left-brain region. In the corresponding tissue from the right side, which

isn’t destined to have language functions, *Lmo4* was expressed at normal levels. How this asymmetric gene activity is related to language functions remains unknown, but Walsh views these findings as an important clue to a still-obscure mechanism for generating asymmetry in the human brain. At the same time, it will send researchers on a search for even earlier molecular signals that, as in the roundworm and the zebrafish, regulate the necessary imbalance in gene expression to begin with.

Such painstaking research efforts in organisms of varying complexity could explain relationships between brain asymmetries and behavior. Walsh predicts that much will be learned about how the diverse specialization within our complex, asymmetric brains distinguishes humans from all other animals. Further, the true understanding of asymmetry may help illuminate brain function not just in relation to species but also on the individual level. There is, after all, a unique interplay of left- and right-brain skills that governs each person’s perceptual tendencies and his or her way of being in the world. ■





Regeneration for Repair's Sake

If a salamander can regrow a lost limb, why can't we? Or should we be aiming for a different goal?

by Kathryn Brown

illustration by Josh Cochran

The two-headed tadpoles were a shock.

When he unexpectedly bred a dish of the aberrant creatures 19 years ago, Randall T. Moon soon realized he was witnessing the power of regeneration—in the form of a protein that helps regulate development.

“We knew this protein, called Wnt, helped flies develop, but its role in vertebrate models was completely unknown,” says Moon, now an HHMI investigator at the University of Washington. The memorable tadpoles had higher than normal amounts of Wnt, loudly hinting that the protein’s signals regulate early embryo development.

“We basically shut down every other project in the lab, and we’ve been pursuing Wnt ever since,” says Moon, who heads the university’s Institute for Stem Cell and Regenerative Medicine. “We were eager to know how Wnt signaling normally works—and what happens when it doesn’t.”

Today, Moon’s long-term goal is to use Wnt signaling to coax stem cells into heart, brain, and other organs to replace, or regenerate, diseased cells. Rather than trying to grow whole limbs or sci-fi animals, Moon and a growing group of scientists focus on repairing existing tissue and organs.

“In the past, developmental biologists concentrated on the question of how you make an animal,” says Douglas A. Melton, an HHMI investigator at Harvard University, who began in developmental biology before shifting his energies to stem cell medicine. “Now, researchers are returning to a question asked decades earlier: how do you *maintain* that animal?” He compares this shift in focus to working at a car repair shop, as opposed to a car factory. “We’re beginning to appreciate the importance of maintenance, replenishment, and repair.”

Response to Injury

AN ECLECTIC RANGE OF ORGANISMS—including crustaceans, snakes, and salamanders—have evolved the ability to regrow lost tissues or limbs, whether from injury or natural biological cycles. Even humans share this talent to some degree: every day, the

human body replaces an estimated 10 billion cells, including those in the liver, skin, and blood. But why do some species regenerate body parts handily, while others do not? Why can humans regrow a liver but not a pancreas? Can we borrow from nature’s regeneration toolkit to treat human disease?

To address these questions, Moon and his colleagues have been documenting Wnt’s mechanisms. Their studies show that zebrafish, tadpoles, mice, and potentially many other organisms respond to injury by turning on Wnt, a major signaling molecule. Wnt activates a cellular pathway, Wnt/ β -catenin, which launches the biochemistry of regeneration. Conversely, Moon’s lab has found that another Wnt protein, Wnt5b, inhibits regeneration by launching a pathway that puts the brakes on regrowth signals.

In a study published online last December in *Development*, Moon’s team demonstrated Wnt proteins in action: first they amputated zebrafish fins, and then they turned on or blocked regeneration of those fins by altering the activity of different Wnt proteins. In a related study, the researchers showed that *Xenopus* (African clawed frog) tadpoles also require Wnt activity to fully regenerate amputated limbs.

“We suspect that Wnt signaling is one of the earliest responses to injury in any form and is essentially a universal component of regeneration in animals,” concludes Moon. “If we can fully determine the normal function of Wnt proteins, we might develop therapies for humans.” By revving up certain Wnt proteins, for instance, researchers might one day replace brain cells lost to neurodegenerative disorders. Alternatively, by shutting off other Wnt proteins, they might treat certain cancers.

Boosting the Immune System

THE FIRST REGENERATION-INSPIRED THERAPY COULD BE TESTED IN humans as early as 2008. The lab of HHMI investigator Leonard I. Zon, a hematologist/oncologist at Harvard University, hopes to clinically test a therapeutic compound that eventually could allow doctors to regenerate a patient’s immune system after damage by chemotherapy.

Zon’s team recently screened a library of 2,500 chemicals to find small molecules that spark the production of blood



HHMI investigators Douglas Melton, Harvard University, Leonard Zon, Harvard University, and Randall Moon, University of Washington.

stem cells, a prerequisite for developing immune systems. The researchers discovered that prostaglandins—which, like hormones, regulate diverse chemical reactions—help to boost these stem cells. In particular, Zon’s search identified a promising version of prostaglandin E2 (PGE2), made by drug manufacturer Upjohn in the 1980s.

To see how well the candidate PGE2 could help regenerate a damaged immune system, Zon’s lab first irradiated zebrafish, essentially wiping out their native immune systems. When the researchers injected the irradiated fish with PGE2, the animals readily produced new blood stem cells. In related experiments on mice, they extracted blood marrow, bathed it in PGE2 for two hours, and found that the treated marrow at least doubled its rate of blood stem cell production for several months.

“This PGE2 derivative is the first known small-molecule mediator of stem cells and regeneration,” says Zon. And that makes it a potential drug candidate. In a small but growing number of cases, doctors have successfully replenished a patient’s weakened immune system by providing blood transplants from umbilical cord blood, which contains blood stem cells. In the future, physicians might instead administer a drug such as the PGE2 derivative. Joining forces, Zon and Moon are now studying how Wnt and PGE2, as well as their respective signaling pathways, work together to regenerate tissue in zebrafish.

Why Not the Heart or the Pancreas?

CANCER PATIENTS AREN’T THE ONLY ONES WHO COULD BENEFIT from regenerative therapy. This year, more than 1 million Americans will have a heart attack, according to the American Heart Association. An injured human heart cannot regenerate; instead, it scars. Too much scarring limits the heart’s capacity to pump blood and can trigger abnormal heart rhythms, or arrhythmias.

While an HHMI investigator at Harvard Medical School, Mark T. Keating revealed, through a decade of studies in newts, mice, and zebrafish, that certain molecular signals enable specialized cells at the site of an injury to “dedifferentiate,” or revert to stem cells, and then respecialize into the types of tissue needed to replace the lost or damaged cells.

Keating and colleagues at Children's Hospital Boston later uncovered some key biochemistry that naturally inhibits heart regeneration. In a 2005 study in *Genes and Development*, Keating's team revealed that an enzyme known as p38 MAP kinase suppresses rat heart cells, or cardiomyocytes, so they cannot multiply. When the team chemically inhibited this enzyme, however, the cells replicated in a petri dish. "Our work laid out some of the basic molecular mechanisms needed for heart regeneration," explains Keating, now a vice president and head of ophthalmology at the Novartis Institute of Biomedical Research in Boston. "I think we accelerated the field."

Indeed, Keating's work inspired ongoing heart regeneration research. His collaborators at Children's Hospital reported last year that rats injected with two drugs, to inhibit p38 MAP kinase and grow blood vessels, regained heart function after damage. That preliminary work continues.

Meanwhile, one of Keating's former postdoctoral researchers, Kenneth D. Poss, now a cell biologist at Duke University, is continuing the heart studies in zebrafish. While tiny—only a millimeter across and a microliter in volume—the zebrafish heart offers big lessons in regeneration basics. The Poss lab has developed a technique to clip off a piece of one ventricle—about a quarter of the chamber—and document how one population of cells, known as "progenitor" cells, effectively rebuilds the lost cardiac muscle in two months. Now, the lab is attempting to characterize the progenitor cells that launch heart regrowth.

While scientists work toward one day regenerating the human heart, another organ already regrows naturally: the liver. Even

after surgeons remove almost two-thirds of the liver, remaining cells can rebuild a complete organ in three to six months. As they reported last January in *Nature*, Melton and his colleagues studied developing mice to compare, up close, the growth habits of the liver and its neighbor, the pancreas. Melton's long-term research aim is to learn how to generate pancreatic beta cells, which produce insulin, to cure type 1 diabetes.

His team applied two genetic techniques to alter the number of progenitor cells in the liver and pancreas of mouse embryos. In one set of experiments, they destroyed different numbers of pancreatic progenitor cells to challenge the pancreas. In a second set, they injected pancreatic progenitor cells into a strain of mice deficient in this cell type. Across all the experiments, the number of progenitor cells predicted the organ's final size: fewer cells, smaller pancreas; more cells, larger pancreas.

The liver, however, proved more adaptable. Its final size was normal, virtually regardless of the number of liver progenitor cells the researchers left in or injected into the embryos.

"Why the liver and not the pancreas?" asks Melton. The liver faces regular assault from the environment, in the form of alcohol and other blood toxins that the organ filters. Human skin also suffers damage, getting burned, scraped, and otherwise injured. Maybe, Melton speculates, these systems have evolved a way to endure frequent environmental insults by repairing themselves through regeneration.

Proceed with Caution

MEANWHILE, THERE MAY BE GOOD REASON WHY THE HUMAN BODY refuses to regenerate so many other tissues and organs, not to

"We're beginning to appreciate the importance of maintenance, replenishment, and repair."

Doug Melton

OUT ON A LIMB

In 1578, a British mathematician proposed an incredible boat called a submarine. Science fiction writer Jules Verne fantasized in 1865 that humans would fly to the moon. More recently, news reports have celebrated the idea that, with the application of some scientific knowledge, lost human limbs might grow back. Will this sensational idea, like others before it, come true?

Even regeneration enthusiasts hesitate. “It’s reasonable to think about regenerating specific cell types, like neurons,” says HHMI investigator Alejandro Sánchez Alvarado, a molecular biologist at the University of Utah. “But something as complex as a hand? Before we even embark on that in humans, we need to do so much more.”

Sánchez Alvarado has spent the past decade studying an invertebrate model of animal regeneration: a freshwater flatworm called *Schmidtea mediterranea*, or planaria. This flatworm can fully regenerate from a fragment as tiny as 1/279th of the original organism.

Sánchez Alvarado and his colleagues have begun to unveil the flatworm’s regenerative machinery in detail, using RNA interference—a technique that systematically silences targeted genes to determine their function. In 2005, his lab conducted the first large-scale gene inhibition study of planaria, as reported in *Developmental Cell*. Of 1,065 genes screened, the team identified 240 associated with specific developmental processes or defects. In particular, they identified cells that potentially regulate stem cells, regeneration, and homeostasis—a cell’s dynamic equilibrium.

Building on that work, the lab is now deconstructing seven major signaling pathways in planaria, all known to govern cell signals. “How do progenitor cells work?” asks Sánchez Alvarado. “When are they on and off? Which cells activate them—and in turn, what types of cells do progenitors activate?” The advantage of the fast-growing flatworm, he says, is that experiments to address these questions can be performed more quickly than in vertebrate models such as the zebrafish.

“Regeneration is more than just early development played out again in maturity,” Sánchez Alvarado adds. “The same basic protein players are at work, but their regulation is different. And that’s what makes it fascinating.” — K.B.

mention limbs. Unchecked regeneration resembles the runaway cell growth that characterizes cancer. In a study published May 18 in *Science*, Moon and collaborators reported evidence for concern.

Some proteins act as cellular brakes, regularly shutting down Wnt signaling and other cell-regeneration pathways. This “stop” mechanism keeps cell populations in check. For instance, scientists have documented that, in colorectal cancer and melanoma, mutations disrupt proteins that normally turn off Wnt.

Moon’s team explained how this biochemistry might play out in Wilms’ tumor, a form of pediatric kidney cancer. Through their investigations, the researchers discovered the potential involvement of WTX, a protein that normally acts as a tumor suppressor by degrading a protein network that activates the Wnt pathway. Working in zebrafish, frogs, and cultured cells, the team found that Wilms’ tumor mutates the gene that encodes WTX, thus disabling the protein. Without WTX as a brake, the Wnt pathway is activated more than usual, triggering harmful cell growth that becomes a tumor.

Thus, although regenerative medicine has great potential, researchers looking for dramatic outcomes in humans might well proceed with caution, lest they re-create, in one way or another, Moon’s surprise results long ago in tadpoles.

There may be a safer and more practical application of regeneration research—the familiar human condition of degeneration, which, according to Melton, is the flip side of regeneration. On that note, Moon and colleagues published a May study in the *Proceedings of the National Academy of Sciences* demonstrating that a single amino acid change in a protein that works with Wnt is associated with late-onset Alzheimer’s disease. Moon concludes that Wnt biochemistry is all about balance. Too much—or too little—Wnt affects both regeneration and degeneration.

“We increasingly suffer from diseases of degeneration,” Melton notes. “Diabetes, neurodegenerative disorders, cardiovascular disease. All have features in common: an unknown environmental stimulus, many genes, and a long time between cause and effect. If we’re interested in slowing degeneration, we should be focusing on how the body maintains and repairs itself.” ■

A black and white portrait of Mikhail S. Gelfand, a man with long, dark, curly hair and a full beard. He is looking slightly to the right with a thoughtful expression. His hands are visible in the foreground, gesturing as if in conversation. He is wearing a light-colored button-down shirt. The background is dark and out of focus.

PERSPECTIVES & OPINIONS

Mikhail S. Gelfand

RUSSIAN CHANGE AGENT

SPEAKING OUT FOR
TRANSPARENCY IN SCIENCE

Paul Feters

As a Russian scientist whose research in bioinformatics and comparative genomics has earned him several foreign-based grants, Mikhail S. Gelfand is in a unique position to advocate for modernization of the Russian Academy of Sciences, his country's main supporter of fundamental research. Notably, the HHMI international research scholar strongly favors the call by the Ministry of Education and Science for a much more transparent, merit-based, grant-focused system.

What is the quarrel between the ministry and the academy?

A year or two ago, the Russian government started pouring money into science and discovered that distribution mechanisms are extremely inefficient and nontransparent. For example, the same people who set strategic direction for the academy can then apply for those funds—a huge conflict of interest. If you have a pipe full of holes, you don't pour water into it. So the government started requesting more modern mechanisms.

The academy argues that this is part of the Russian government's effort to increase its control over society.

Of course, that possibility makes me uncomfortable. Still, the conflict is not between bureaucracy and society, but between two bureaucracies. The ministry, at least on the outside, looks progressive. The academy's leaders are dead set against change. They insist that everything at the academy is okay, that it just needs more money. Not true. Less than 8 percent of the budget for fundamental science is distributed through competitive grants. The ministry wants a much higher rate plus a shift in day-to-day management and decisions—on how money is spent and property is managed—to hired administrators. The ministry would leave strategic scientific planning to the academy.

What do you think needs to happen?

Reasonable intermediate steps would be salary increases based on merit, which to some extent has begun. Second, we need a much larger fraction of science spending channeled toward competitive grants for group projects, personal research, and purchasing large pieces of equipment. As it stands now, all decisions about buying equipment are made by people with political clout. There are outrageous examples of equipment never used properly, or at all.

We need something closer to the grant system that exists in Europe or the United States. Review could rely on the Russian diaspora for external expertise. Many of my collaborators are

Russians in the U.S. and Europe, and they are willing to review applications. They feel a moral obligation.

Now that the government is putting more money into science, are international grants less important?

They are still very important. But they have become less about money per se and more about providing people with some independence from local politics and showing an example of how the system should function.

In April, the academy voted to reject the ministry's suggested changes to academy operations. Now what?

I expected as much, although I'd hoped that some people within the academy would resist the herd mentality instilled by its leadership. The bad news is that the scientific community is bitterly opposed to all ministry moves, however reasonable (though not all are), and this community resolve has been strengthened by the symbolic unanimous vote. Also, there are signs that the ministry's resolve is failing.

Still, the episode could help force the academy toward a more reasonable position, as happens whenever there is a clash. But by consistently opposing any reform, the academy puts itself in a situation where even reasonable objections and opinions are not heard.

How do you stay optimistic that change will happen?

The choice is not between change and no change. Either change will occur or Russian science will disappear. This is something the academy leadership fails to comprehend.

You come from a family of accomplished mathematicians and scientists. Does that make it easier to be outspoken about these issues?

They all emigrated to America! Sometimes I feel like the one left behind to watch the shop. Having some degree of independence helps. I don't know how I would behave if my group was completely dependent on Russian money.

INTERVIEW BY CORI VANCHIERI. *Mikhail Gelfand is a mathematician and biologist at Moscow's A.A. Kharkevich Institute for Information Transmission Problems. Find more of his opinions on www.scientific.ru.*

PERSPECTIVES & OPINIONS

Sarah C.R. Elgin

GENOMICS FOR ALL

BROADER ACCESS TO
EDUCATION IS KEY TO AN
INFORMED CITIZENRY.

Scott Ferguson

Sarah C.R. Elgin likens modern gene sequencing to Henry Ford's revolutionary mass production of the automobile. Just as Ford made cars affordable, automation and high-throughput technologies have rapidly lowered the cost of gene sequencing. Now comes a new and critical responsibility, says Elgin, an HHMI professor: to train a generation of informed genomics consumers.

The next generation of consumers will be the true beneficiaries of the promise of genomics. But how will they make informed choices in a world resplendent with genomics products, including tools to predict disease and the engineered drugs to treat those diseases?

The answer is more genetics and genomics at every level of American education. When I first approached HHMI with this idea in 2002, I knew we needed to focus on the full educational continuum. Over the last five years, I and other HHMI professors have created prototypes and pilot programs for middle school, high school, and undergraduate students.

I am most excited, however, about a program we're developing at Washington University in St. Louis for undergraduates across the country, using the Internet. The Genomics Education Partnership (GEP) was born from the need to bring genomics into the curriculum, and from the realization that genomics provides a terrific vehicle for engaging undergraduates in research. Traditional research experiences for undergrads, typically offered in the summer, do not work for every student. Nor do we have the national resources to uniformly offer summer programs. Genomics provides a cost-effective way to reach out further.

GEP is a partnership between Wash U. and 17 primarily undergraduate institutions scattered across the United States. Wash U. and partner students participate in collaborative research using Web-based resources, and they ultimately go on to publish. Like their on-campus peers, GEP partner students analyze complex genomics problems while interacting with the Wash U. Biology Department and Genome Sequencing Center.

We piloted the concept with a dozen adventurous juniors and seniors at Wash U., comparing gene sequence organization on a single chromosome among various fruit fly species and drawing conclusions about the evolutionary implications. The students worked as a team, each taking on one piece of the task. Sequencing work was done with the Genome Sequencing Center, and gene annotation and analysis was completed with coaching from computer science faculty.

The course was a major success, capped by a peer-reviewed publication with 13 Wash U. undergraduate authors published in *Genome Biology* last year. Student surveys confirmed learning gains rooted in collaboration, analysis, interpretation, and pooled results. I am now convinced that collaborative

research courses work and can be offered on a widespread basis, not simply at the nation's largest or wealthiest universities.

GEP is actively looking for partner institutions; we have 17 and would like 100. We are looking for faculty members who want to bring genomics into their teaching of genetics, and for faculty members who have good DNA sequence annotation projects for the students to carry out.

In my opinion, and recent experience, students everywhere want to participate in the process of science. Research is how new knowledge is generated in our field, and where students can become engaged with science in the making. As research-based learning enters the curricula, we see a critical benefit: students understand how scientists work on real problems. Those who go on to non-science careers will be more discerning consumers of technology. Plus, we'll be inspiring more students to enter science and technology careers, and giving them the foundation to do so.

Of course, I'm not the only one who has noticed the educational opportunities created by online access to databases and genomics tools. Graham Hatfull, an HHMI professor at the University of Pittsburgh, has developed a program that enables students to isolate and sequence unique phages, and he and I are working with HHMI to develop a "national experiment," called the Science Education Alliance, to engage students in this sort of research (see *Chronicle*, page 46).

If we're to create a genomics-knowledgeable next generation, such innovations in education are vital. Our children need the tools to make informed choices about their world, and to help them do so we have to bring genomics into schools and colleges. Elementary students can gain a basic understanding of life cycles, and by the time kids reach middle school, they're ready to start talking about DNA as an information molecule.

In another decade, genomics will be so accessible and affordable that middle school and high school students everywhere will be plucking organisms from their back yards and sequencing them—provided they have the education and tools to do so. It was, after all, Henry Ford who said, "Before all else, preparation is the secret of success."

INTERVIEW BY RICHARD CURREY. Sarah Elgin is a biologist at Washington University in St. Louis. Information on the GEP is available at <http://gep.wustl.edu>.

Q&A

What discovery would you put your money on for a future Nobel Prize?

Scientists, rational beings that they are, don't usually put much stock in gambling. But each year a sweepstakes of sorts intrigues the science community all the way to the announcement, in October, of the Nobel Prizes. Below, four HHMI scientists ante up, so to speak, by revealing to the Bulletin what discovery they think should ultimately win that most coveted of honors. — EDITED BY JACQUELINE RUTTIMANN



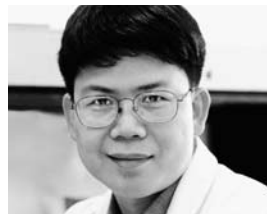
James C.A. Bardwell
PROFESSOR OF MOLECULAR,
CELLULAR, AND
DEVELOPMENTAL BIOLOGY,
UNIVERSITY OF MICHIGAN

"I think a Prize will come out of the field of aging. Studies of model organisms have made it clear that aging is a regulated process. When insulin and reproductive signaling are perturbed in worms, for example, animals live up to six times longer than normal. A clear understanding of how and why organisms age seems to be within reach, and achieving this goal should take the Prize—particularly if it results in effective pharmacological interventions."



Charles T. Esmon
LLOYD NOBLE CHAIR IN
CARDIOVASCULAR RESEARCH,
OKLAHOMA MEDICAL
RESEARCH FOUNDATION

"My best guess is that the Nobel Prize will go to someone who figures out how to selectively impair vascular growth in solid tumors. Success in this area would have broad implications for treatments that would produce few side effects."



Zhijian "James" Chen
PROFESSOR OF MOLECULAR
BIOLOGY, UNIVERSITY OF
TEXAS SOUTHWESTERN
MEDICAL CENTER AT DALLAS

"The Nobel should go to the discoveries of DNA topoisomerase and telomerase, which solve two of the most fundamental problems in biology: how to unravel the condensed spiral structure of DNA, and how to overcome the loss of DNA ends during the transmission of genetic information. Not only are these discoveries important for understanding all life forms, they are also directly relevant to human diseases. Inhibitors of topoisomerases are used in the clinic, and inhibitors of telomerases are in clinical trials, both for the treatment of cancer."



Melissa J. Moore
PROFESSOR OF
BIOCHEMISTRY, BRANDEIS
UNIVERSITY

"One of my top choices would be the determination of the ribosome crystal structures. It was a tour de force because ribosomes, the machines responsible for synthesizing practically all proteins in the cell, are some of the largest asymmetric particles to be visualized at atomic resolution. Plus, the structures revealed that ribosomes are ribozymes (RNA-based enzymes), supporting the RNA World hypothesis that RNA begets proteins."

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Neurons in the brain, like the ones seen in this image, get their messages across with the help of proteins such as synapsin (green) and clathrin adaptor AP2 (red). Scientists were recently surprised to find that another protein, dynamin 1, may not be as essential to this process as once thought (see page 49).



Lessons From the Field

REWARDS LARGE AND SMALL COME FROM GETTING OUT INTO THE WORLD AND DIGGING IN THE DIRT.

THE CHANCE TO LEARN FIRSTHAND ABOUT HUMAN EVOLUTION by joining their teacher, noted chemist Anne Skinner, on an archeological dig in India gave two adventurous Williams College students more than aching muscles. As they labored in the hot sun, they gained new skills and an appreciation of chemistry's contribution to explorations of the past.

Sergio Marte, age 20, and Daniel Jamorabo, age 21—both New Yorkers and community service-minded chemistry majors who plan to become doctors—spent two weeks in January with Skinner and an Indian team exploring several sites along the Narmada River Valley, 100 miles from Bhopal. An HHMI undergraduate education program grant supported their hands-on learning experience about human evolution via chemistry.

"It was a great opportunity to see that chemistry is not just about mixing chemicals and making explosions," says Marte. "It was a lot about going out into the field, collecting data, and working with people ... who can provide perspectives and insight into the work you are doing." Marte talked to local villagers who knew that companies had been excavating in the region—crucial information needed to evaluate whether artifacts were indigenous to the site or had been washed down from upriver.

Skinner earned a "very conventional physical chemistry Ph.D." but now regards increasing the understanding of human evolution as her main area of research, and she collaborates with archeologists and geologists from around the world to advance that work. Skinner is expert at dating the bones and teeth of mammal fossils with a relatively new technique, electron spin resonance (ESR),

which can determine the extent of damage caused by the radioisotopes that accumulate in the animals' dead tissue and in the surrounding soil. By dating animal fossils from a geologic layer that also contains stone tools or other evidence of human activity—with the understanding that more damage occurs the longer something is buried—Skinner can approximate when human life appeared in that area.

She used ESR to show that antelope bones discovered in a cave near Johannesburg, South Africa, had been burnt at tempera-

tures so high they had to be produced by campfires using wood and not grass fires. Her evidence indicated that hominids harvested fire from lightning 1.5 million years ago—about a million years earlier than previously believed. Skinner says her work reveals that the hominids, while not able to deliberately strike flint to make sparks, could "take advantage of natural occurrences. They displayed more intellectual ability, creativity, and cultural complexity than people would have thought."

The Indian sites—which were challenging because their acidic soil significantly decays whatever is buried in it—gave the students a chance to practice their newfound archeology skills. After rising early, loading their gear, and traveling an hour to a site, or prospecting for a new one, Marte and Jamorabo dug step trenches, or terraces, at outcrops exposed by erosion. The young men kept detailed field notebooks, and Skinner took pictures and soil samples.

Although the most important discovery—a hippopotamus's tooth—was made by the Indian team after Skinner and her young apprentices had returned home (it was later given to her for analysis), Skinner says the students' "main rewards were the experience of being in a different environment intellectually—out in the field, not in the library or lab—and seeing a different way of life."

Jamorabo, who loves traveling and learning for its own sake, says the trip gave him a chance to ponder the broad picture of human evolution as he examined stone tools and discussed their uses with the Indian archeology team. "Dr. Skinner gave us the context [in discussions before and during the trip], but it's not the same as seeing it and doing it yourself," he says. ■ —JUDITH SAKS

To Ph.D. or Not to Ph.D.?

SUMMER PROGRAM TRIES TO HOOK DISADVANTAGED STUDENTS, AND LARGELY SUCCEEDS, ON THE PLEASURES AND REWARDS OF BIOMEDICAL RESEARCH.

WITH EASELS LINING THE HALLWAY ON EITHER SIDE OF HIM, 22-year-old Miguel Edwards demonstrated to several eager young researchers how he spent the previous summer tugging on RNA held in place by a laser beam. Fingers pinched together, he mimicked how micropipettes gently yanked on the RNA molecules, allowing him to calculate the kinetics and thermodynamics involved in RNA binding.

The scientists participating in this exchange at HHMI headquarters in May were current and former students in the Institute's Exceptional Research Opportunities Program (EXROP), which provides a summer of research experience to talented disadvantaged undergraduates by pairing them with HHMI investigators and professors.

Edwards, a native of Dominica and a 2007 graduate of CUNY–Hunter College, did his RNA work in HHMI investigator Carlos Bustamante's lab at University of California, Berkeley. He says his time there solidified his career plan. "The EXROP experience helped me decide I want to continue with research."

As EXROP enters its fifth year, some 95 percent of the 128 students who have completed the program and graduated have chosen to stay in science and medicine. Moreover, most of the students are pursuing post-baccalaureate work, with the largest number planning on research careers. Fifty percent have entered graduate programs—to earn master's, Ph.D., or M.D./Ph.D. degrees—and 25 percent have chosen medical school. Another 20 percent of the students have opted to pursue research-related activities, such as becoming a laboratory research technician, while 2 percent are teaching and 3 percent are planning non-science-related activities.

The biggest career "problem" facing most of these students has not been whether biomedical professions are attainable but whether the best path is research, clinical medicine, or both.

At the event, HHMI President Thomas R. Cech spoke directly to the students' struggles, noting he had heard some of them say they "would prefer to get an M.D. because it's a simpler career track." With four years of medical school, followed by residency, becoming a physician offers some certainties in the way of training. By contrast, the time it takes to earn a Ph.D. depends on the program, the project, and research outcomes, leaving a student to count on anywhere from four to eight years for degree completion, followed by an open-ended postdoctoral fellowship. A combined M.D./Ph.D. path is even more complicated, as it involves interrupting medical school with a doctorate program.

Clearly hoping to motivate the students toward a Ph.D., Cech noted that "this country needs people like you standing in front of the classroom, and teaching is largely the activity of Ph.D.s." He

acknowledged that many M.D.s do outstanding research, but Cech stressed that "Ph.D.s get highly rigorous research training."

That kind of encouragement, combined with strong mentoring, is what Naira Rezende says helped her decide to pursue a Ph.D. While an undergraduate at CUNY–Hunter College, the Brazil native conducted summer research in the Massachusetts Institute of Technology lab of HHMI investigator Tania Baker, where she heard about EXROP. The following year, Rezende participated in the program, working in the laboratory of HHMI investigator David Schatz at Yale University. The year after that, she received a 2005 Gilliam fellowship (named after charter HHMI Trustee James H. Gilliam Jr.), which provides up to five years of financial support for graduate study; it is available only to the most competitive EXROP students.

Rezende credits all her mentors with demonstrating that science was a promising career path for her, but she found the example set by Baker as a successful woman in science particularly reassuring. Currently in a Ph.D. program at Weill Medical College of Cornell University, Rezende hopes one day to run her own academic research lab.



Keynote speaker Shirley A. Malcom (right), head of education and human resources at the American Association for the Advancement of Science, focused on increasing diversity and opportunities in the sciences.

Research experience gained through EXROP can sometimes tip the balance one way or the other for a student who is deliberating about the future.

For example, Jasmine Ellis spent this summer working in HHMI investigator Morris Birnbaum's lab at the University of Pennsylvania. A Princeton University sophomore, Ellis has her sights set on medical school but sees her EXROP summer as a terrific opportunity to test the research waters. Ethan Sanford, on the other hand, spent his summer working in David Ginsburg's University of Michigan laboratory. Surrounded by M.D.s and Ph.D.s in Ginsburg's lab, Sanford observed that M.D.s who truly wanted to conduct research could do so. That gave this University of Colorado, Boulder, graduate, who is eager to choose a path with plenty of patient interaction, the confidence to apply to medical schools. ■ —LISA SEACHRIST CHIU

FOR MORE INFORMATION on the work of Carlos Bustamante's lab, see "A Different Mindset," page 14.

HHMI Pilots a “SEA” Change

EXPERIMENTAL COURSE TO BRING GENOMICS TEACHING AND RESEARCH TO UNDERGRADUATES ACROSS THE NATION

STUDENTS AT THE UNIVERSITY OF Pittsburgh will participate in an important experiment during the upcoming academic year as they identify and characterize previously unknown bacteriophages, viruses that infect bacteria. Even as they engage in hands-on research themselves, these undergraduates will be helping HHMI pilot-test a course in genomics that ultimately will be made available to colleges and universities nationwide.

“Our goal is to leverage the knowledge and experience of educators supported by HHMI over the past two decades to create a national course that will make it possible for undergraduates to have an authentic research experience,” says Tuajuanda Jordan, a senior program officer who heads HHMI’s newly created Science Education Alliance (SEA).

The SEA aims to be a national resource for science education by developing and supplying materials and methods to the undergraduate education community, and by assembling and supporting educator networks working on common activities.

The genomics course builds on the work of two HHMI professors—Graham F. Hatfull at the University of Pittsburgh and Sarah C.R. Elgin at Washington University in St. Louis

(see “Genomics for All,” page 40)—and the efforts of several other grantees: Brad Goodner, HHMI undergraduate program director at Hiram College in Ohio, and A. Malcolm Campbell, director of the HHMI-supported Genome Consortium for Active Teaching at Davidson College in North Carolina.

“We’re making explicit connections between teaching and research,” says Jordan.

Students will isolate bacteriophages; progress through DNA isolation, cloning, and sequencing; and ultimately annotate, finish, and compare the genomic sequences using vetted, interactive computer programs and public databases. Bacteriophages are a proven starting point for student genome analysis since they are plentiful, highly diverse, easily isolated directly from nature, and have relatively simple and small genomes. HHMI will provide reagent kits and pay for all costs associated with genomic sequencing and annotation.



“We’re making explicit connections between teaching and research.”

TUAJUANDA JORDAN

Jordan says the long-term goal is to provide students with a rigorous research experience that results in the complete genomic characterization of at least 12 unique bacteriophages per year, leading to peer-review publications with student co-authors in mainstream scientific journals and science education-focused journals. Making the genetic data available through scientific literature and national databases has real-life value: researchers believe that gene recombinations between bacteriophage and host are responsible for the toxins of diseases such as cholera and diphtheria.

Based on the pilot-course experience, Jordan and her collaborators will develop a resource guide for the course and design a training workshop for faculty to be held next summer. Formal recruitment of the first 12 participating institutions to offer the course—six universities and six colleges—will begin this coming fall. By 2011, Jordan hopes that more than 700 students will be taking the course at 36 institutions. ■

Wellcome Trust, HHMI Establish International Postdoctoral Fellowships

Postdoctoral researchers in HHMI and Wellcome Trust laboratories wanting to do their research abroad may now have that opportunity, thanks to an overseas exchange program the two institutes recently established. Designed to promote scientific collaboration and research opportunities for scientists at the beginning stages of their careers, the program will enable postdocs to study and work for up to a year in any of the HHMI laboratories in the United States or in one of a number of the Wellcome Trust laboratories in the United Kingdom. Travel and living expenses for participants will be paid and assistance will be provided for obtaining visas and work authorization. For applications and further information, visit www.hhmi.org or www.wellcome.ac.uk.

HHMI Forges Partnerships to Support Postdoctoral Research

Over the next three years HHMI will contribute about \$9 million to fund postdoctoral scholarships provided by the Jane Coffin Childs Memorial Fund, the Helen Hay Whitney Foundation, the Damon Runyon Cancer Research Foundation, and the Life Sciences Research Foundation. Each organization will competitively select the fellows, who will conduct research in the labs of HHMI investigators. “By funding this program, HHMI anticipates that these organizations will be able to offer 16 additional fellowships each year to help advance the careers of promising young scientists,” says Jack E. Dixon, HHMI’s vice president and chief scientific officer. The fellowships will have three-year terms and fellows will be employed by HHMI.

In Memoriam

Frank William Gay

1921–2007

FRANK WILLIAM GAY, A BUSINESS EXECUTIVE AND CHARTER
HHMI TRUSTEE, DIED ON MAY 21. HE WAS 86 YEARS OLD.



Frank William Gay, whose association with the Howard Hughes Medical Institute extended over more than 30 years, died on May 21, 2007, in Kingwood, Texas. He was 86.

Gay, a business associate of the Institute's founder Howard R. Hughes Jr., was one of eight original Trustees appointed by the Delaware Court of Chancery to oversee HHMI. He served as a Trustee of the Institute from 1984 until his retirement in 2006, providing thoughtful guidance and counsel during a period of transformation and growth for the Institute. Before being appointed as a Trustee, Gay served on the Institute's executive committee from 1971 to 1984.

A successful business executive, Gay held a number of positions during his career and association with Howard Hughes. He was chairman of the board of directors of the Hughes Air Corporation, a senior vice president and member of the board of directors of the Hughes Tool Company, and president and chief executive officer of Summa Corporation. Gay was active on behalf of a number of organizations, including the Boy Scouts of America, for which he served as national treasurer in the 1980s.

A veteran of the U.S. Army and the Marine Corps, Gay was a graduate of Brigham Young University and was honored with its Distinguished Alumni Award in 1976. He is survived by his wife, Mary, and three children.

Institute Supports Public Access

After extensive consultation within the HHMI community, the Institute will require its scientists to publish original research articles in scientific journals that allow the articles and supplementary materials to be made freely accessible in a public repository within six months of publication. ¶ The policy applies to all manuscripts submitted on or after January 1, 2008, and is an extension of existing policies that require HHMI scientists to share published research materials, databases, and software in a timely and useful fashion. Collaborative research articles on which an HHMI scientist is not a major author are not subject to the policy, but HHMI strongly encourages its scientists and collaborators to meet its public access standards. ¶ PubMed Central, the free digital archive of biomedical and life sciences literature maintained by the National Institutes of Health, is the repository for journals in the biological sciences. Articles published in journals from other fields are expected to be deposited in comparable repositories and made publicly available within six months.

FOR MORE INFORMATION: The policy and related resources are available at www.hhmi.org/about/research/policies.html#papp.

HHMI Boosts Support for Advanced Education Programs

In recognition of the central roles the organizations play in educating the biomedical scientific community, for the next four years, HHMI will increase its financial support for the advanced education programs of Cold Spring Harbor Laboratory and the Marine Biological Laboratory and will offer new funding for The Jackson Laboratory. Currently, HHMI annually awards \$330,000 to Cold Spring Harbor Laboratory and \$550,000 to the Marine Biological Laboratory. In its next fiscal year, beginning August 2007, HHMI will increase annual funding for Cold Spring Harbor Laboratory to \$750,000 and for the Marine Biological Laboratory to \$1 million; The Jackson Laboratory will receive \$500,000 annually.

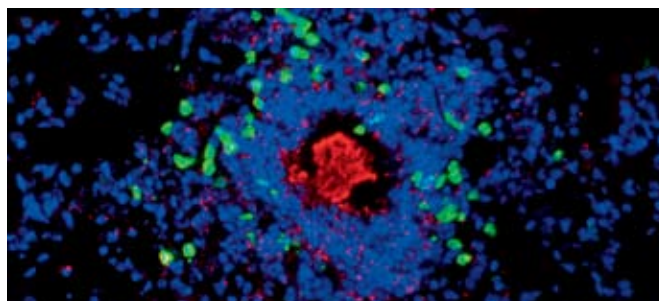
Ubiquitous Allergen

ONE OF THE MOST COMMON BIOPOLYMERS ON EARTH
MAY SOMETIMES CAUSE ASTHMA.

The culprit for some forms of asthma may not be blowing in the wind but rather swimming in the sea or pushing through the soil. HHMI investigator Richard M. Locksley of the University of California, San Francisco, and colleagues have identified it as chitin—nature's second-most-abundant biopolymer—which is found, for example, in the exoskeletons of shellfish, the powerful inner grinders of worms, and the cell walls of fungi and insects.

Many of these organisms, including cockroaches and dust mites, are associated with allergies. And a sizeable percentage of asthma—as high as 25 percent—has been detected in previously asymptomatic workers in shellfish-processing plants. While humans and other vertebrates do not produce chitin, our immune systems innately recognize and eliminate it from the body. When this response goes awry, the result could be inflammation of airways that sets off asthma.

To pinpoint the exact molecular mechanism, Locksley's team infected mice with common parasitic worms called helminths. These mice were genetically engineered with fluorescent probes in their immune systems that would light up when activated. The researchers then observed that the mice responded by producing interleukin-4 and interleukin-13, which are the immune-cell chemicals typically dispatched to attack an allergen invader.



Upon encountering the allergen chitin (red), immune cells release interleukin-4 (green) and interleukin-13, causing an allergic reaction. Host cells (blue) may release the enzyme chitinase to preempt the immune response.

Locksley and colleagues also increased the expression of a gene coding for the enzyme, acidic mammalian chitinase (AMCase), that normally breaks chitin down. When the mice expressed more AMCase than normal, the immune response to chitin was greatly reduced. Similarly, mice exposed to purified chitin that was pretreated with AMCase had attenuated allergic reactions. The team's results were published in the May 3, 2007, issue of *Nature*.

"It's been an intriguing finding that we're continuing to follow up on," says Locksley, who is now looking at human lung cells to see whether asthma patients have less of the enzyme or a weaker form. ■ —JACQUELINE RUTTIMANN

IN BRIEF

RESEARCHERS LEARN WHAT SPARKS PLANT GROWTH

How plants "decide" to grow, a secret long held by plants, has been revealed by HHMI investigator Joanne Chory and others at the Salk Institute for Biological Studies.

The findings, published March 8, 2007, in *Nature*, put to rest a century-old debate over how tissue systems in plants coordinate cell growth.

The scientists examined the three tissue layers that make up the shoots of the mustard plant *Arabidopsis*: the epidermis, which is the waxy, protective skin; the mesophyll tissue, which contains the plant's chloroplasts—cell organelles that conduct photosynthesis; and the vascular tissue through which water and nutrients are transported.

Chory's team looked at the expression of plant hormones called brassinosteroids in the outer and inner layers. Dwarf plants grew to full size when brassinosteroid was expressed and taken up by receptors in the epidermis, whereas the plant's growth was restricted when a gene was expressed in the epidermis that inactivated brassinosteroid. Thus, cell signaling began in the epidermis and followed into the inner

layers of tissue, directing those cells to grow or to restrict growth.

"This knowledge will ultimately lead to our ability to increase yield, while decreasing the need for fertilizer and pesticides," says Chory.

SLEEPING SICKNESS PARASITE CAN'T LIVE WITH STRESS

Research from HHMI international research scholar Shulamit Michaeli at Bar-Ilan University in Ramat-Gan, Israel, and colleagues, shows that the African sleeping sickness parasite's natural response to stress is enough to kill it, a weakness that researchers may be able to exploit.

African sleeping sickness is caused by the parasite *Trypanosoma brucei*, which lives in tsetse flies. After a person is bitten by an infected fly, the parasite crosses into the brain, where it disrupts neurological function and leads to death if not treated.

Understanding how proteins move across the parasite's internal membranes led to the discovery. Before they leave the ribosome where they are created, certain newly synthesized proteins are given a molecular tag, called a signal peptide, that allows them to cross the cell's membranes.

The tags are noted by the signal recognition particle (SRP) complex, which interacts with a membrane receptor and directs the proteins to unbind from the ribosome and go there.

When Michaeli's team knocked out the membrane receptor, the SRP complex had no place to dock, causing it to stick to ribosomes with the newly synthesized tagged protein. This "stress" causes the parasite cells' nuclei to shut down a small RNA molecule called the spliced leader RNA, which is responsible for all mRNA production in the cell. Protein production then stops and the organism dies. This novel stress-induced mechanism, described in the April 2007 issue of *EMBO Reports*, is termed spliced leader RNA silencing.

SHAKING UP HIV'S FAMILY TREE

In the battles that rage between the human immunodeficiency virus (HIV) and an infected patient's T cells, the rules of engagement are always changing. The T cells adapt continuously to recognize HIV proteins and alert the immune system to attack. But, with its exceptional capacity to mutate to forms that can escape immune surveillance, the virus perseveres.

The No-Brainer That Wasn't

A SURPRISING RESULT POSES NEW QUESTIONS ABOUT THE ROLE OF AN "ESSENTIAL" BRAIN PROTEIN.

Imagine your mechanic yanked the engine out of your car. You buckle up, turn the ignition, and off you drive, undoubtedly with a shattered notion of how automobiles work. That's essentially what researchers led by HHMI investigator Pietro De Camilli experienced earlier this year when they eliminated a brain protein from mice thought to be an engine for transmitting nerve impulses.

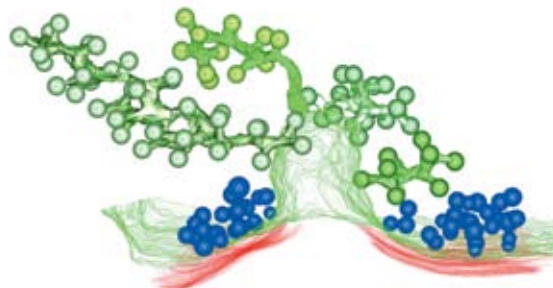
The Yale University School of Medicine team and their colleagues knocked out the *dynamin 1* gene, which encodes a protein implicated in pinching off budding synaptic vesicles from the plasma membrane of neurons—a process that recycles these vesicles once they have released their neurotransmitter content. Work in fruit flies and other species had led neurobiologists to presume dynamin 1 played an essential role.

But nobody had performed the definitive test—removing dynamin 1 from mice—to see what happened. “We thought it would be a no-brainer—no dynamin 1, no synaptic vesicles,” says De Camilli. Astoundingly, when his team created dynamin1 knockout mice, the newborns appeared normal and lived for up to two weeks, as reported in the April 27, 2007, issue of *Science*.

Microscopic examination revealed that the neurons of the knockout mice contained plenty of synaptic vesicles, though they tended to be larger and less uniform in size, and numerous budding vesicles stayed attached to the plasma membrane in grape-like

clusters. Electrophysiology and other biophysical tests showed that the neurons behaved almost perfectly under normal stimulation, failing only under strong electrical stimulation.

Because mammals have two additional dynamin genes, producing slightly different forms of the protein, De Camilli suspects that one or both of these variants may compensate for dynamin 1 in the knockout mice. But given that these variants together represent less than 10 percent of the total dynamin in the brain, he wonders whether dynamin in any form is truly essential for synaptic transmission. The De Camilli lab plans to delete the other two forms to find out. ■ —PAUL MUHLRAD



A lack of dynamin 1 (green) causes synaptic vesicles (blue) and endocytic buds to arrest at the pre-fission stage, as revealed here by electron tomography.

IN BRIEF

Researchers initially believed that analyzing a cross section of mutations in HIV could identify those that had arisen as a result of immune escape and pinpoint viral genome regions important for recognition by T cells.

HHMI investigator Bruce D. Walker at Harvard Medical School and others have now established that the accuracy of this type of analysis can falter because of the many HIV subtypes that circulate globally. Some of the mutations represent historical subtype or lineage differences rather than mutations that have arisen as a result of immune selection pressure.

The scientists found that identifying the presence of these multiple HIV lineages can greatly improve the accuracy of genetic analyses. Furthermore, statistical methods for elucidating such phylogenetic relationships among viral genome sequences will give virologists new insights into the evolution of viruses and how viruses mutate as they adapt to the immune system.

Their findings were published March 16, 2007, in *Science*.

GENETIC "GANG OF FOUR" LINKED TO BREAST CANCER

Research by HHMI investigator Joan

Massagué at the Memorial Sloan-Kettering Cancer Center and colleagues suggests that abnormal activation of four genes drives the spread of breast cancer to the lungs. Their work, published April 12, 2007, in *Nature*, reveals that the aberrant genes work together to promote the growth of primary breast tumors, enabling cancerous cells to escape into the bloodstream and penetrate through blood vessels into lung tissues.

The researchers focused on genes coding for proteins called epiregulin, COX2, and matrix metalloproteinases 1 and 2. Various combinations of the four genes in human breast cancer cells that had metastasized to the lung were silenced by a technique called RNA interference. The cells were then tested in mice.

Silencing all four genes greatly reduced the tangled blood vessel growth typically seen in tumors. The tumor blood vessels that did form allowed fewer cancer cells to escape into circulation. But when these cells reached the lung capillaries, they got stuck. From this, Massagué's team concluded that these genes act to loosen up capillaries, allowing the cells to penetrate the lung and grow there.

BEING BAD IS BEST FOR BACTERIA

Defying the old assumption that pathogens evolve to become less infectious, research by HHMI international research scholar B. Brett Finlay at the University of British Columbia, Vancouver, suggests that genes enhancing the virulence of bacteria are clearly favored for evolutionary survival.

Finlay's team created a model of natural selection that demonstrates how type III secretion system genes, a molecular complex that many virulent bacteria use to infect mammalian cells, contribute to an organism's fitness.

Using a strain of mouse that dies from infection by *Citrobacter rodentium* bacteria, the team exposed groups of mice either to the normal pathogen or to versions in which different type III secretion genes had been eliminated. The infected mice were exposed to uninfected mice, which in turn were exposed to more uninfected mice, thus producing various degrees of pathogenicity, ranging from mild to fatal. Bacterial strains with the greatest damage to their virulence genes were slowest at spreading from one host to another, suggesting that these swapped virulence genes are essential for spreading. The bacterial strain with all its virulence genes intact spread the fastest.

These Rodents See Red

JUST ONE EXTRA GENE IS ALL
MICE NEED TO SEE VIBRANT COLORS.

Some lab mice can see the world in a whole new light, thanks to HHMI investigator Jeremy Nathans and his colleague Gerald H. Jacobs. Their findings provide insight into the remarkable plasticity of mammalian brains, and shed light on a plausible means by which humans may have acquired the ability to see many colors.

Nathans, at Johns Hopkins University School of Medicine; Jacobs, of the University of California, Santa Barbara; and their colleagues introduced the gene for a human red-light-sensing pigment into mice, and showed that the new photopigment functioned correctly, allowing the mice to distinguish colors they previously could not detect.

Most mammals have only two types of photopigments in the color-sensitive cone cells of their retinas. In mice, one pigment detects ultraviolet light, while the other sees yellowish-green wavelengths. Many primates, including humans, have three color-sensing pigments, which gives us our rainbow palette of color vision.

The researchers wondered whether the gene alone would alter sensory perception, or if additional changes in the nervous system would be necessary. Nathans and Jacobs showed that just the addition of the new photopigment endowed the mice with broader color vision. Using electrophysiological tests, the researchers determined that the rodents' retinas responded to red



Colored lights help show that the brains of genetically-altered mice can process information from new photoreceptors in their eyes. Here, a mouse deciding that the third colored panel looks different from the other two is rewarded with a drop of soy milk.

light. Then they subjected the mice to a series of behavioral tests, which confirmed that the mice could indeed see red.

In essence, says Nathans, the brains of the mice completed all the necessary rewiring to make their new color receptors function. He views the findings, published in the March 23, 2007, issue of *Science*, as a lesson on how color vision, and possibly other sensory traits, might have evolved in humans. "Maybe the principal way in which sensory systems evolve is by genetic change at the front end—at the receptor cells," he says, "and the brain is flexible enough to immediately take advantage of those changes." ■ —PAUL MUHLRAD

IN BRIEF

The study, published May 1, 2007, in *Current Biology*, offers a new model for scientists to study transmission of infectious disease and could help identify therapeutic targets to block the spread of pathogens.

KEY ELEMENTS CONTROLLING PRION FORMATION IDENTIFIED

HHMI researcher Susan L. Lindquist at the Whitehead Institute for Biomedical Research and others have identified small regions within a yeast protein that control its conversion to infectious agents known as prions.

Prions are proteins that can fold into self-templating configurations, allowing proteins of the same type to adopt the same configuration. In the prion state, such proteins accumulate into masses known as amyloid, which can cause human disorders such as Creutzfeldt-Jakob disease.

Lindquist's group looked at *Saccharomyces cerevisiae* yeast protein Sup35, which normally regulates the flow of information from DNA into the cellular machinery that produces proteins. When Sup35 converts to a prion state, its activity is reduced, which changes expression of the yeast's DNA and alters biological function.

As described in their May 31, 2007, *Nature* article, the researchers attached Sup35 middle (M) and end (N) segments to a glass slide and exposed them to a solution containing fluorescently labeled copies of Sup35 in its nonprion state. The soluble Sup35 accumulated over a very small set of the peptides, which corresponded to two regions of the M and N segments previously found to be sites of protein-protein contact in assembled fibers. Under electron microscopy, these accumulated proteins showed fibers characteristic of amyloid prions.

Though the underlying process remains unclear, the researchers hypothesize that specific peptides cause the protein to adopt a prion configuration.

ANALYSIS REVEALS EXTENT OF DNA REPAIR ARMY

A database developed by HHMI investigator Stephen J. Elledge at Harvard Medical School and colleagues are providing the first detailed portrait of the army of more than 700 proteins that helps repair and maintain cellular DNA's integrity.

The DNA damage response is a routine event in the life of any cell. Stress caused

by environmental factors such as exposure to ultraviolet light, ionizing radiation, or other environmental phenomena can cause DNA to break apart or rearrange its nucleotide base pairs in unhealthy ways. Left unchecked, such mutations can accumulate over time and ultimately lead to conditions such as cancer and diabetes.

Elledge, senior author of a study published May 25, 2007, in *Science*, likened the DNA damage response to a command and control center. Two critical enzymes, known in scientific shorthand as ATM and ATR, act like sensors to detect trouble and initiate DNA damage response by engaging the cell's molecular repair apparatus. The researchers found this multiprotein army by looking at how these enzymes reacted to damage in human cells caused by ionizing radiation and ultraviolet light.

The revelation promises insight into a spectrum of diseases. In a companion paper published in the same issue of *Science*, Elledge's group used the database to identify two proteins, known as Abraxas and RAP80, critical to recruiting the breast and ovarian tumor-suppressing BRCA1 protein to sites of DNA damage.

Q

A

Why do medicines expire after a certain period of time?

Rupesh, a high school student from India

Like all chemicals, drugs are subject to changes that can alter their structures and properties. These changes, such as an interaction with water or oxygen molecules, or reaction to light energy, often occur slowly. Any alteration of its structure, however, will change the drug's ability to interact with its target, regardless of the length of time involved. Consequently, the drug may lose its efficacy.

To indicate how long a particular drug is therapeutically beneficial, the United States Food and Drug Administration (FDA) requires that most drugs have a stated expiration date. This date reflects the time after which the drug will likely be "changed" to the point where it is not as effective as it should be. The drug manufacturer cannot simply determine this date via a "best guess." A detailed protocol and extensive data must be included with any new FDA drug application, providing clear evidence of the drug's shelf life under specific conditions. To meet FDA standards, tests must be conducted on the drug in its final packaging material, to mimic consumer storage conditions. These guidelines help to ensure that the expiration date you see on a particular drug is backed by documented experimental evidence.

So what to do with drugs that are past their expiration date? Throwing

them away might seem harmless. More and more drugs, however, are being found in rivers and streams, presumably from careless disposal. Recently, the United States Geological Survey reported traces of drug compounds in 80 percent of the 139 streams tested.¹ These active drugs have the potential to reach drinking water and subsequently act on consumers.

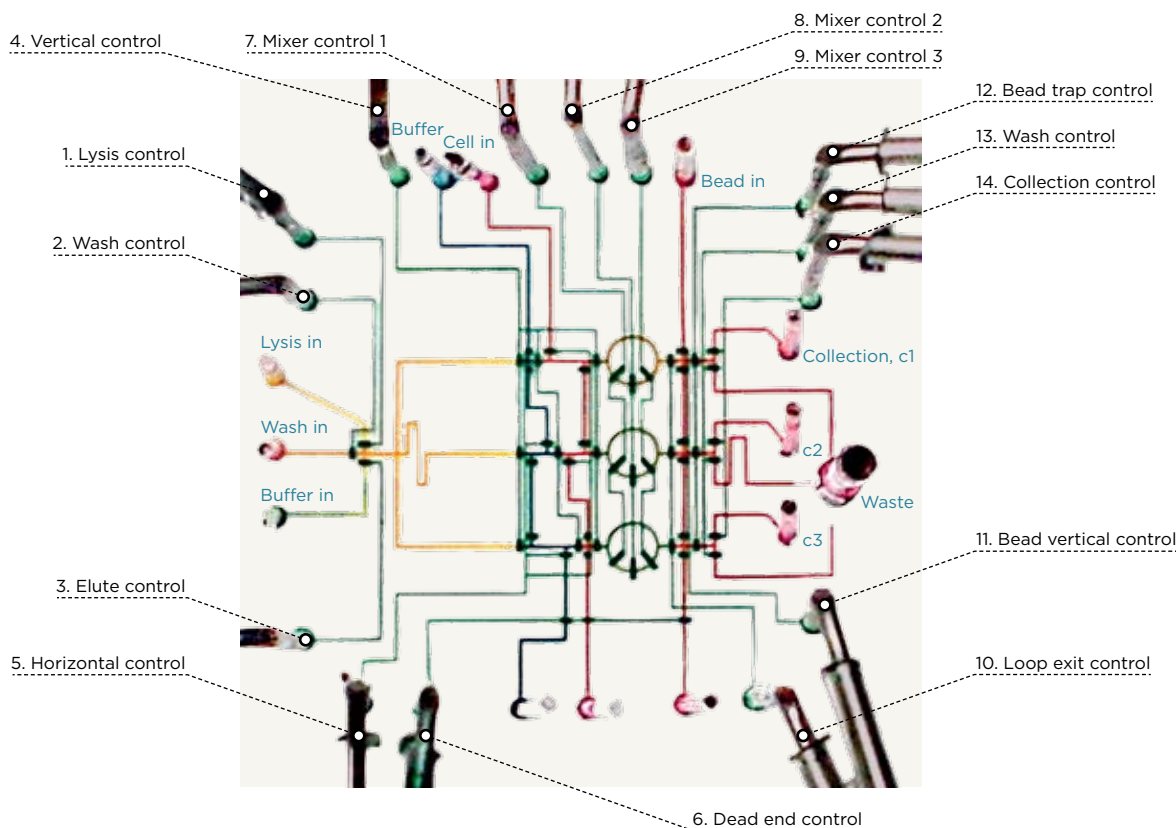
Drugs should not be poured down the drain or flushed down the toilet, as conventional wisdom suggests, and even landfill disposal may result in eventual seepage into the water supply. The province of Alberta is combating this problem through a program that charges pharmacies with drug disposal, according to the National Association of Pharmacy Regulatory Authorities in Canada. Alberta pharmacies treat the expired drugs as medical waste destined for incineration, thus ensuring no contamination of the water supply. In March 2007, the American Pharmacists Association and the United States Fish and Wildlife Service launched a media awareness campaign, called SMARxT DISPOSAL, to build public awareness of the hazards posed by improper disposal of unused medications.²

ANSWER RESEARCHED BY MARK LARSON, assistant professor, Department of Biology, Augustana College, South Dakota.

¹Underwood, Anne. Rivers of doubt. *Newsweek*, 4 June 2007.

²Sax, Barbara. Proper drug disposal target of new campaign. *Pharmacy Times*, 22 March 2007.

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.



Actual Size: 20 x 20 mm

Small-Scale Solutions Miniaturized experiments on a chip could make biomedical research easier and faster.

STEPHEN R. QUAKE WOULD HAVE BEEN THE PERFECT Mr. Fix-it for the Lilliputians, the little people of *Gulliver's Travels*. "I spend a lot of time doing plumbing," he says—on a most diminutive scale. His tinkering is focused on dense networks of tiny pipes, valves, and sinks that are cast within clear rubber microchips no larger than a credit card.

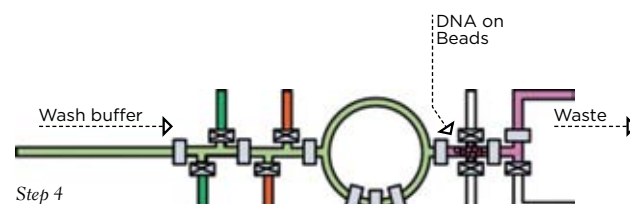
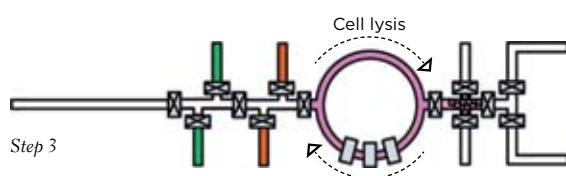
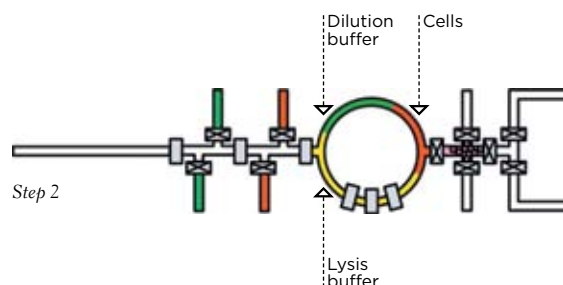
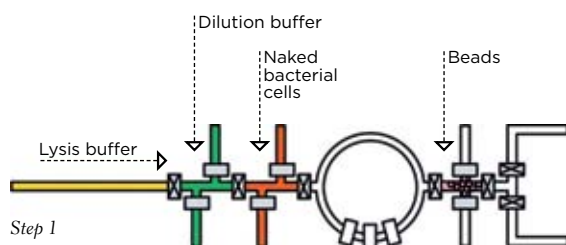
Such devices are the promising new tools of microfluidics, the science of manipulating fluids at nanoliter volumes—one-hundredth to one-thousandth that of a human teardrop. As Quake, an HHMI investigator and biophysicist at Stanford University, has cleverly demonstrated, his plumbing arrangements are capable of running miniaturized molecular biology experiments. In some cases, thousands of reactions can run in parallel—all without the standard muss and fuss of test tubes and fluid-dispensing pipette tips or the hulking robotic machines used in large-scale, automated genetic studies.

Chemists first invented lab-on-a-chip devices to analyze gases in the 1970s, but the effort to make practical microfluidics tools for biological studies has gained traction only in the past decade. One major advance, led by George Whitesides at Harvard University in

the late 1990s, was to fabricate the chips from cheap, flexible rubber rather than the expensive, stiff silicon used to manufacture computer chips. In a method dubbed "soft" lithography, Whitesides and his colleagues started with the same photographic processes that computer-chip companies use to cast an integrated-circuit blueprint in a single wafer of silicon, but they poured rubber into the chip-making molds instead.

Still, microfluidics researchers needed a way to pipe in reagents and flush them around. "The most powerful way to manipulate fluids on a chip is to have mechanical valves—just like the valves in your sink—so that you can have absolute control over the fluids," says Quake. Creating valves proved difficult, however, and scientists had been able to put only one to three of them on a chip. Quake solved that problem as an associate professor at the California Institute of Technology in 1999, with his students and Caltech physicist Axel Scherer. "We found a way to break through that bottleneck," he says.

The solution was to use two layers of rubber, each containing a channel about 100 micrometers wide—a tad thicker than a human hair—by 10 micrometers high. The thin layers are stacked and sealed



This particular lab-on-a-chip by Stephen Quake isolates living bacterial cells, lyses them open, and extracts their DNA—all within a footprint the size of a postage stamp. **LEFT** This chip's parallel design allows processing of three samples at once. Food coloring is used here to differentiate the channels. Those filled with green control the opening and closing of the chip's 54 valves. The yellow-, blue-, and red-filled channels bring in reagents. **THIS PAGE** Cells and buffers are moved in and out of a processing unit through fine tubing connected by stainless steel pins. Valves, represented by small rectangles, are marked with an x when closed.



on top of each other, with the channels running perpendicular to each other. Applying pneumatic pressure through the top “control” pipe deflects the walls of the bottom “flow” pipe downward, closing it.

“You squish it,” says Quake. “It’s just like stepping on a garden hose.” In 2002, his team successfully developed multilayered chips with thousands of pneumatic valves—now known in the field as “Quake valves”—connecting hundreds of chambers.

Since then, looking for ways his invention could be used to speed up bench work, Quake and his collaborators have used labs-on-chips to crystallize proteins (a first), to purify DNA from bacterial cells (see diagram), and to calculate the energy it takes for a protein to bind to a piece of DNA.

Most recently, Quake has been working on “interrogating” single cells for genetic data. Several years ago, he read in a journal article by Stanford microbiologist David Relman that many disease-causing pathogens remain unknown because more than 99 percent of microbes cannot be grown in lab cultures. Microbial ecosystems are complex little societies of so many interacting bugs that it is technically challenging to pick out and learn about any one player.

Quake contacted Relman and joined him in studying the microbial jungle of the human mouth. Quake’s group designed a device with nine processing units to analyze bacteria that thrive within tooth plaque. By routing the sample through a series of chambers, each unit could isolate an individual bug, lyse it open, and make hundreds of thousands of copies of its genome. With further work off-chip, the team successfully sequenced most of the genome of one microbe called TM7—the first of its bacterial class for which researchers have any genetic information. They published the results in July in the online early edition of the *Proceedings of the National Academy of Sciences*.

At Stanford, Quake has set up a foundry with a clean room for producing microfluidics chips—2,680 of them last year—for academic researchers. At age 38, he holds more than 30 U.S. patents and is cofounder of two companies that have been developed around his technology, Fluidigm and Helicos BioSciences.

Quake has a big goal for his small devices: he envisions lab-on-a-chip technology accelerating biology research in the same way the silicon computer chip revolutionized mathematical computation.

■ -INGFEI CHEN

SPOTLIGHT

National Academy of Sciences Elects Ten HHMI Investigators



TOP ROW: DAVID AGARD, DAVID ANDERSON, TANIA BAKER, SEAN CARROLL, BRIAN DRUKER
 BOTTOM ROW: DAVID GINSBURG, HELEN HOBBS, CHRISTOPHER MILLER, GERALD SHULMAN, WAYNE YOKOYAMA

Ten HHMI investigators have been elected to the National Academy of Sciences. Newly elected HHMI investigators are **David A. Agard**, University of California, San Francisco; **David J. Anderson**, California Institute of Technology; **Tania A. Baker**, Massachusetts Institute of Technology; **Sean B. Carroll**, University of Wisconsin-Madison; **Brian J. Druker**, Oregon Health & Science University; **David Ginsburg**, University of Michigan Medical School; **Helen H. Hobbs**, University of Texas Southwestern Medical Center at Dallas; **Christopher Miller**, Brandeis University; **Gerald I. Shulman**, Yale University School of Medicine; and **Wayne M. Yokoyama**, Washington University School of Medicine in St. Louis.

The HHMI-supported **ACADEMY OF SCIENCE** at Dominion High School in Loudoun County, Virginia, received the 2007 Claes Nobel School of Distinction award from the National Society of High School Scholars for its “commitment to academic excellence and community service.”

HHMI investigators **ADAM ARKIN**, University of California, Berkeley; **ANN M. STOCK**, University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School; and **WAYNE M. YOKOYAMA**, Washington University School of Medicine in St. Louis, have been elected fellows of the American Academy of Microbiology.

Ten HHMI investigators and two HHMI professors were elected to the American Academy of Arts and Sciences. The investigators are **BRENDA L. BASS**, University of Utah School of Medicine; **BONNIE L. BASSLER**, Princeton University; **NANCY L. CRAIG**, Johns Hopkins University School of Medicine;

BARRY HONIG, Columbia University; **LILY Y. JAN**, University of California, San Francisco; **YUH NUNG JAN**, University of California, San Francisco; **ROBERT A. LAMB**, Northwestern University; **GAIL MANDEL**, Oregon Health & Science University; **MICHEL C. NUSSENZWEIG**, Rockefeller University; and **HELEN PIWNICA-WORMS**, Washington University School of Medicine in St. Louis. The HHMI professors are **BALDOMERO OLIVERA**, University of Utah, and **SUSAN R. WESSLER**, University of Georgia.

University of Delaware undergraduate **CHARLES DRUMMER IV** received the United Negro College Fund–Merck Undergraduate Science Research Scholarship Award. Drummer is a member of the HHMI-sponsored NUCLEUS program and was an HHMI EXROP student in 2006.

LUIS R. HERRERA ESTRELLA, an HHMI international research scholar at the National Polytechnic Institute in Irapuato, Mexico,

was awarded the 2007 Trieste Science Prize by TWAS, the academy of sciences of the developing world, and Illycaffè.

HHMI investigators **RONALD M. EVANS** of the Salk Institute for Biological Studies and **ROBERT J. LEFKOWITZ** of Duke University Medical Center were awarded the 2007 Albany Medical Center Prize in Medicine and Biomedical Research. Solomon H. Snyder of the Johns Hopkins University School of Medicine shared the award. The awardees were recognized for discoveries that reveal how cells use receptor molecules to communicate with their environment.

RONALD M. EVANS, an HHMI investigator at the Salk Institute for Biological Studies, and **BALDOMERO OLIVERA**, an HHMI professor at the University of Utah, were elected to the American Philosophical Society.

D. GARY GILLILAND, an HHMI investigator at Brigham and Women’s Hospital, received

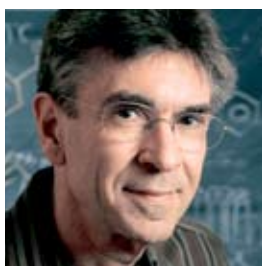
the American Society for Clinical Investigation's 2007 Stanley J. Korsmeyer Award for "his contributions to the understanding of the genetic basis of human hematological malignancies."

HHMI investigator **STEPHEN C. HARRISON** of Harvard Medical School received the 2007 UCSD/Merck Life Sciences Achievement award for his "discoveries and groundbreaking work on protein research."

The **JANELIA FARM RESEARCH CAMPUS** was named "2007 Lab of the Year" by *R&D* magazine for its flexible lab design and role in promoting the culture of science.

SPOTLIGHT

Lefkowitz Lauded with Shaw Prize



ROBERT LEFKOWITZ

HHMI investigator **Robert J. Lefkowitz** will receive the \$1 million 2007 Shaw Prize in Life Science and Medicine. The international award, given by the Hong Kong-based Shaw Prize Foundation to researchers whose work has achieved world-wide significance, honors Lefkowitz for "his relentless elucidation of the major receptor system that mediates the response of cells and organs to drugs and hormones." A researcher at Duke University Medical Center, Lefkowitz is renowned for his work on G protein-coupled receptors, transmembrane receptors found throughout the body that are the targets of many well-known pharmaceutical drugs.

SUSAN L. LINDQUIST, an HHMI investigator at the Massachusetts Institute of Technology, was awarded the Desert Research Institute's 2007 Nevada Medal for her work on protein folding.

KAROLIN LUGER, an HHMI investigator at Colorado State University, received the 2007 Vorarlberg State Science Prize from Austria, her native country, for her contributions to elucidating the structure of chromatin.

HHMI investigator **TOM A. RAPOPORT**, a cell biologist at Harvard Medical School, received the 2007 Sir Hans Krebs Medal from the Federation of European Biochemical Societies for "outstanding achievements in biochemistry and molecular biology or related sciences."

REBECCA RICHARDS-KORTUM, an HHMI professor at Rice University, received the 2007 Chester F. Carlson Award from the American Society for Engineering Education.

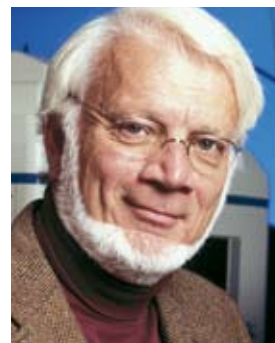
HHMI vice president and director of Janelia Farm Research Campus **GERALD M. RUBIN** and HHMI investigator **MORGAN SHENG** of the Massachusetts Institute of Technology were elected to The Royal Society, the national academy of science of the United Kingdom. Rubin was inducted as a foreign member; Sheng was elected as a fellow.

CHRISTINE E. SEIDMAN, an HHMI investigator at Brigham and Women's Hospital, and her husband and colleague, Jonathan G. Seidman, also at Brigham and Women's, have been awarded the 2007 Grand Prix de la Fondation Lefoulon-Delalande from the Institut de France for their "seminal contributions to understanding inherited cardiac disorders."

HHMI investigator **CHRISTOPHER A. WALSH** of Harvard University and the Beth Israel Deaconess Medical Center received the 2007 George W. Jacoby Award of the American Neurological Association for his "especially meritorious" work on identifying genes that regulate the development and function of the human cerebral cortex.

SPOTLIGHT

Steitz Wins Gairdner Award



THOMAS STEITZ

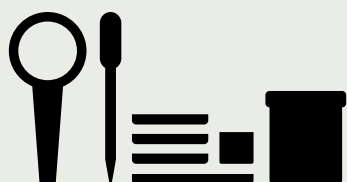
Thomas A. Steitz, an HHMI investigator at Yale University, is among the five researchers to receive the 2007 Gairdner International Award for achievements in medical research. Given by the Gairdner Foundation for significant contributions to medical science, the prestigious award was bestowed on Steitz and University of California, Santa Cruz, molecular biologist Harry F. Noller for work that led to the structural and functional identification of the ribosome, the subcellular organelle where proteins are synthesized. Their findings that the ribosome is a target of many well-known antibiotics are now leading to the creation of antibiotics to circumvent resistance, a major health concern worldwide.

SUSAN R. WESSLER, an HHMI professor at the University of Georgia, was honored with the first Distinguished Scientist Award from the Southeastern Universities Research Association for her work on transposable genetic elements in plants.

HHMI investigator **XIAOWEI ZHUANG** of Harvard University received the 2007 American Chemical Society Award in Pure Chemistry for her optical imaging of single molecules.

PLANARIA POWER

Teachers interested in enabling their students to observe firsthand the powers of tissue regeneration (see “Regeneration for Repair’s Sake,” page 32) might want to try this simple classroom exercise using flatworms called planaria. A quick overview of the experiment is shown below. To download the complete lesson plan, visit www.hhmi.org/biointeractive/activities/.



A few inexpensive items are all that's required—a magnifying glass, one plastic pipette, one plastic coverslip, three small plastic petri dishes, one large petri dish, and a bottle containing about 10 planaria.



Planaria live in some freshwater ponds and rivers, but you'll probably want to order yours from a biological supply company.



Students dissect a planarian into two pieces at any one of three locations on the body.



Day 1 Day 3 Day 6 Day 8

In a matter of days, the animal will regenerate its missing part. Around day eight, one of the two pieces will have completely regenerated its head.

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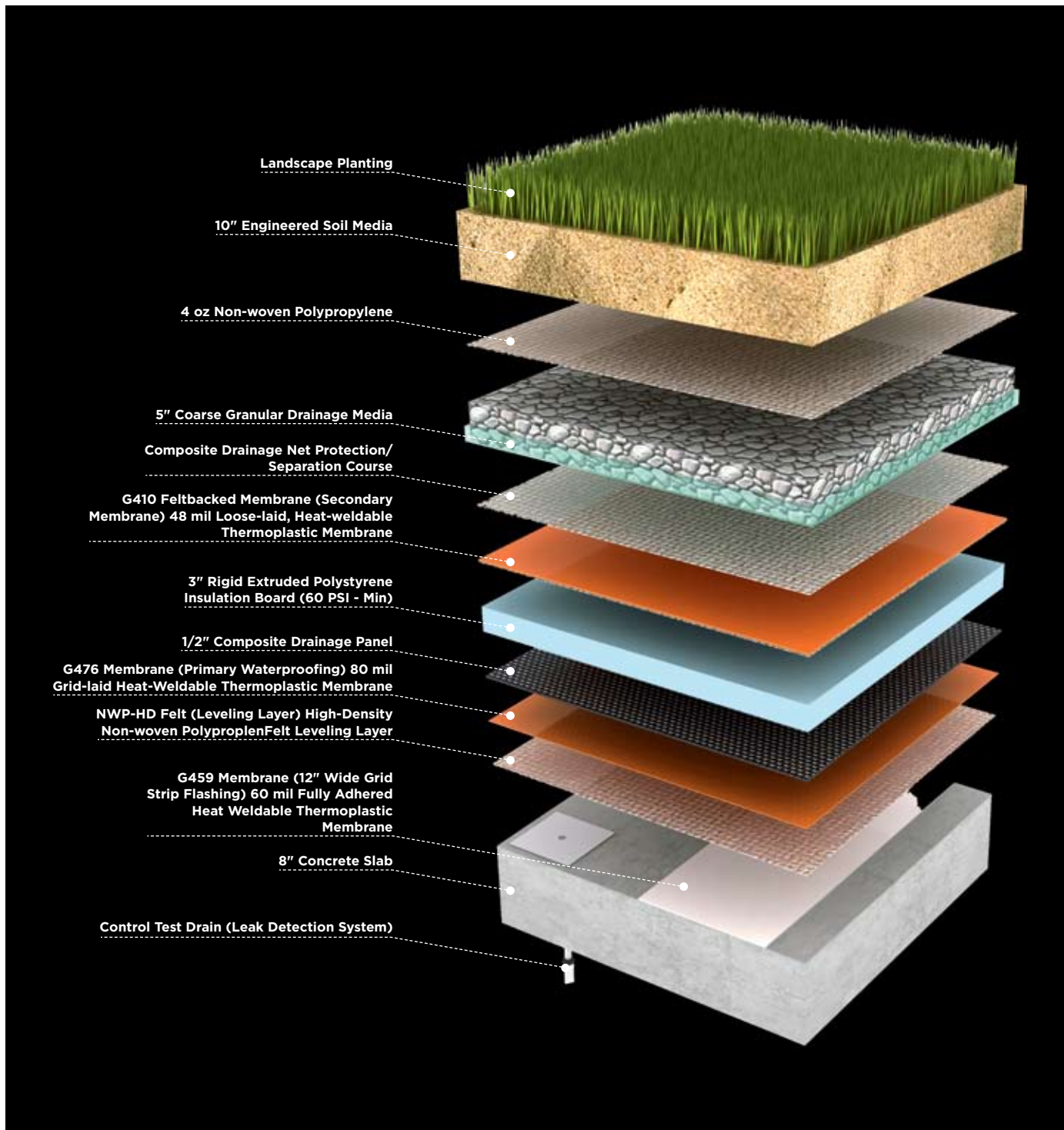
These four key components of HHMI's work also guide and define the mission of the Institute's quarterly magazine, the *HHMI Bulletin*.

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While you're online, read the Web edition of the *Bulletin*.

HHMI BULLETIN



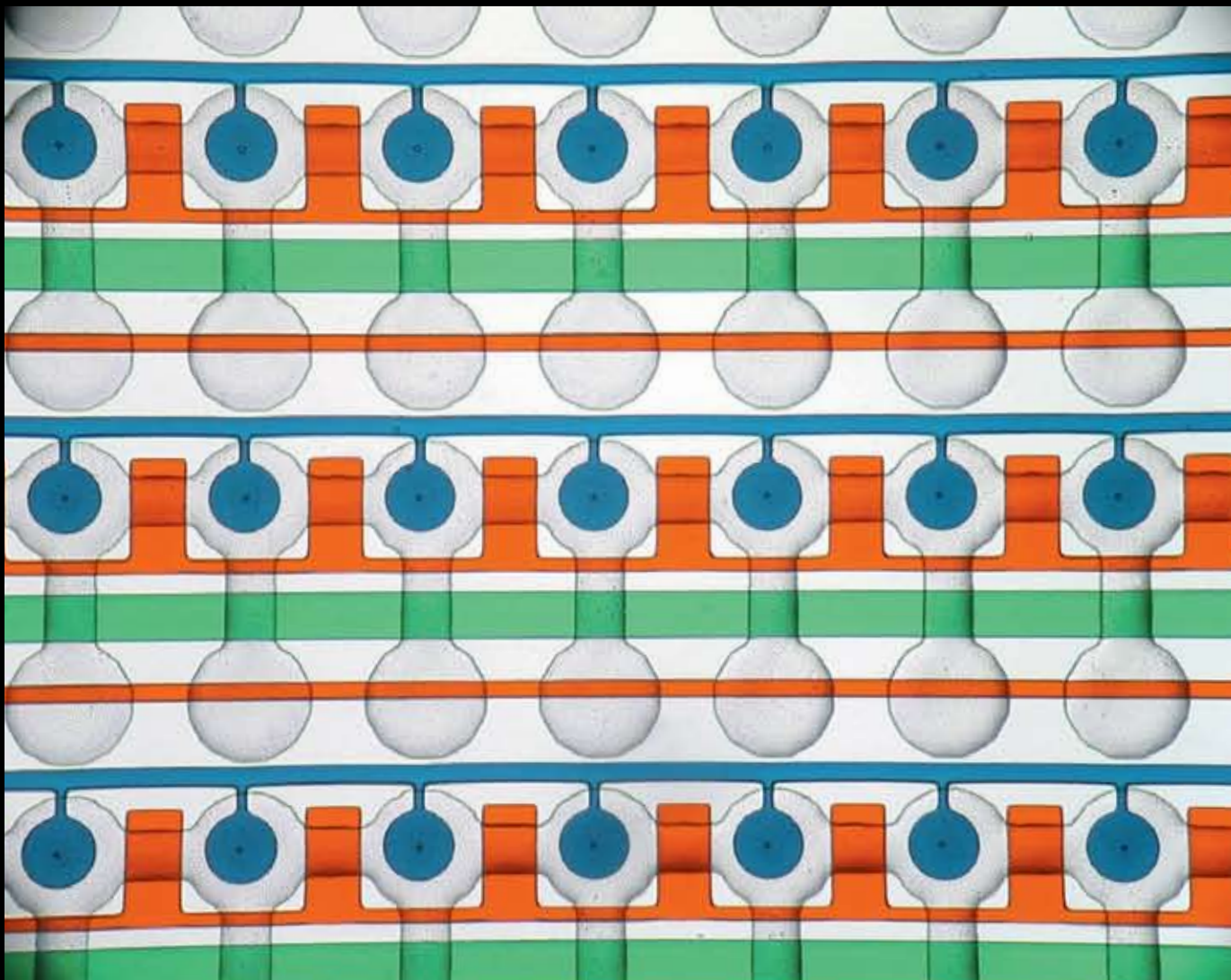


FROM ROAD TO ROOF

Green roofs, buildingtops covered with vegetation, like the one on the Janelia Farm Research Campus, hold the promise of contributing an environmentally sound solution to the world's energy needs. These roofs can reduce the heating and cooling needs of a building, filter pollutants and CO₂ out of the air, and extract pollutants and heavy metals out of rainwater. But it all depends on the layers beneath the green. As a research fellow at Rafael Viñoly Architects, Joe Hagerman put a lot of thought into how the materials used at Janelia stack up. Inspired by his trademarked Biopaver design, which embeds storm water pollutant-filtering plants into city roads, parking lots, and sidewalks, Hagerman

thought a similar design could be used to improve all green roofs. The resultant design (shown above) for Janelia's roof incorporates his use of interlocking blocks of plant "bio-islands." "Part of Joe's thinking evolved as a kind of critique," Viñoly's director of research and training Ned Kaufman, told *BusinessWeek*. "He thought, 'How can we do things better, or differently?'"

Diagram provided by Rafael Viñoly Architects. Quote from "Roofs paved with green." BusinessWeek, February 22, 2007, © 2007 The McGraw-Hill Companies. Reprinted with permission from the publisher.



Sebastian Maerkl / Quake Lab

A Rivulet Runs Through It

ABOUT THE SIZE OF A QUARTER, THIS GROOVY PATTERN IS ACTUALLY A MICROLABORATORY, DESIGNED BY HHMI INVESTIGATOR STEPHEN QUAKE AND HIS GRAD STUDENT SEBASTIAN MAERKL AT STANFORD UNIVERSITY. IT ENABLES SCIENTISTS TO OBSERVE 2,400 POSSIBLE CHEMICAL INTERACTIONS SIMULTANEOUSLY AMONG SINGLE MOLECULES SUCH AS DNA AND PROTEIN TRANSCRIPTION FACTORS. THE MECHANISMS OF THIS MICROCHIP (THE ORANGE AND GREEN VALVES DIRECT THE MOLECULES' FLOW TOWARD THE BLUE REACTION CHAMBERS) COME FROM THE BURGEONING FIELD OF MICROFLUIDICS (SEE PAGE 52), THE SCIENCE OF MANIPULATING FLUIDS AT NANOLITER VOLUMES—ONE-HUNDREDTH TO ONE-THOUSANDTH THAT OF A HUMAN TEARDROP.

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