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HHMI BULLETIN

Howard Hughes Medical Institute www.hhmi.org

Modern-Day Virus Hunters

This disease-fighting duo uses technology and clinical know-how to ID infectious culprits

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Still under construction at press time for this issue of the *Bulletin*, the tiered and glass-filled landscape building on HHMI's new Janelia Farm Research Campus in Loudoun County, Virginia, will be ready for scientists to move into by late summer.

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FEATURES

editor's letter

Every few months, a new issue of the HHMI Bulletin goes out to more than 20,000 subscribers, a diverse bunch that shares a common interest in science. You may not know it, but our readers include students and teachers, scientists and professors, deans, chancellors, heads of foundations, legislators, journalists, retirees, and homemakers. As editor, I hope to engage and inspire each of you through a story, a photograph, a moment in every issue. The assorted perspectives that you bring as readers inspire me—and the other editors and designers of the Bulletin—to make the prose snappier, the art livelier, and the science more comprehensible. We truly relish the process of taking a story from the nut of an idea to a dimensional whole that is informative, visually appealing, and a good read.

I know firsthand how much fun science and the people who do it can be—I spent more than 20 years working at the bench in biomedical research labs, in academia and industry. I moved into science journalism partly because I grew weary of worn comments about how science is dull and scientists boring. Nothing, in my experience, could be further from the truth. From learning to clone and sequence genes in Oliver Smithies' University of Wisconsin lab, in the early 1980s, to working with Genentech scientists to gain FDA approval of the cancer drug Herceptin—two of the highlights of my research career—I've encountered extraordinary creativity and inventiveness in every research lab and science classroom.

Having spent 2 years as assistant editor of the Bulletin before stepping into this new role, I am deeply committed to the mission of "communicating the elegance and significance of science through the lens of HHMI-sponsored research and grants for education." Telling the stories of the talented, energetic, and dedicated people who are the heart and soul of the Institute has been the role of the Bulletin since its inception. I intend to carry that legacy forward in new and inventive ways. If you see something in the magazine that moves you, I hope you'll let me know.

Mary Beth Gardiner

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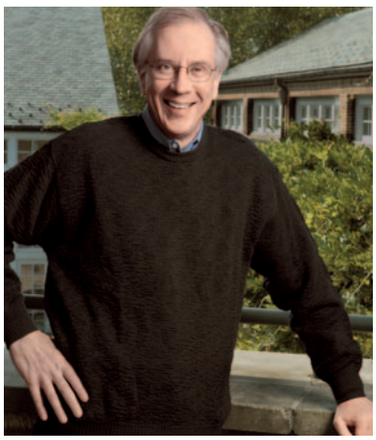
Paul Fetters

Sowing Seeds



Paul Fetters

"Our hope is to inspire in students a curiosity that prompts them to explore a new world and instill in them the intellectual and technical tools to be successful."

THOMAS CECH

MANY OF US GREW UP HEARING THE STORY OF JOHNNY Appleseed, the mythic New Englander who strode the American wilderness and sowed apple seed as he went. No one really knows what drove Jonathan Chapman into the Ohio territories in the early days of the 19th century, but he traveled ahead of the advancing settlers, clearing land as he went and planting orchards. When the settlers caught up, Chapman sold them the trees on generous terms and the apples they produced sustained many a family.

Johnny Appleseed's life of restless cultivation—one that combined idealism with a certain business practicality—provides an apt metaphor for the way we at the Howard Hughes Medical Institute think about our grant-making activities. Of course, we cultivate a different kind of ground and our orchards produce a different crop. Our hope is to inspire in students a curiosity that prompts them to explore a new world and instill in them the intellectual and technical tools to be successful. Our expectations for repayment also differ from Jonathan Chapman's—he received coins, cast-off clothes, and food; our goal is to sustain students' interests for a lifetime.

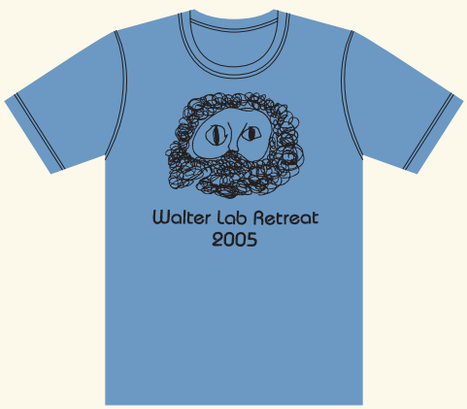
This issue of the *HHMI Bulletin* profiles several particularly fruitful initiatives at universities and liberal arts colleges that began with seed funding from HHMI. As Peter Bruns, the vice president for grants and special programs, observes, "We want to plant seeds that will grow into a new and more effective science education." At West Virginia University, for example, Ann L. Chester used modest funding from HHMI to create a winning program. The Health Sciences and Technology Academy began more than a decade ago in a handful of communities. Thanks to Chester's drive and her ability to engage students, parents, other philanthropies, and state legislators, the Academy now extends to 26 counties. Graduates of the program not only make it to college—one of Chester's main goals—but also go on to graduate and medical school.

Other examples abound. Earlier this year, HHMI announced $86.4 million in new grants for innovative science education programs at 50 research universities in 28 states and the District of Columbia. This is the first funding from HHMI for six institutions, including the University of Florida, which will create a core laboratory for undergraduate research and then collaborate with Atlanta's Morehouse College to establish a teaching postdoctoral fellowship program. Others, like Princeton University, will build on previous HHMI grants to undertake new initiatives. In the next grant period, Princeton will develop a curriculum that better integrates physics and engineering into undergraduate biology, giving students the opportunity to build the microscopes they will use to study genetics and neurobiology.

As with the investments we make in undergraduate education and outreach, HHMI's new program that provides seed funding to a group of physician-scientists is expected to generate outsized results. Focus groups of young physician alumni of research training programs run by HHMI revealed that the first few years as a junior faculty member are the most critical. Two challenges that new faculty physicians often cite as reasons for abandoning the research career path are lack of flexible funding to accommodate the needs of a new lab and lack of time to actually do research.

So, we decided to apply some resources to facilitate the transition of these young hopefuls into full-fledged researchers. This year, HHMI inaugurates a new program to jump-start the careers of some of the alumni of the two Institute-funded research fellowship programs. Thirteen physician-scientists who have just begun their tenure-track appointments will receive the first early career awards, which will include a grant of $150,000 over 3 years for research. One stipulation of the awards is that their institutions will give these individuals the freedom to spend most of their time on research, identifying mechanisms that cause disease and potential new therapies for conditions that include diabetes and cancer.

The discovery of knowledge defines a frontier no less real than the physical frontier that fed the imagination of 19th-century America. Through almost 20 years of grant making, HHMI has had the opportunity to support scientists and educators committed to nurturing the seeds of discovery. It makes for a beautiful orchard, indeed.



To see the T-shirts that inspired these renditions, as well as shirts from other years, go to http://mcb.harvard.edu/o%27shea/ and http://walterlab.ucsf.edu/Site/Home.html.

Fall Fashion

Some unusual T-shirts will make their debut among this fall's trendy fashions on certain college campuses. Most likely seen in the vicinity of science buildings, these eye-catching shirts express the creativity and camaraderie of those hardy souls who labor in research labs, day in and day out. Each summer, at least two inspired HHMI labs create a new design meant to capture the personality of the group and the essence of their year's work.

HHMI investigator Erin K. O'Shea at Harvard University began an annual tradition of lab T-shirts that has persisted for 12 years. Team O'Shea, as the lab group was dubbed while O'Shea was still at the University of California, San Francisco (UCSF), turns out designs that use cartoons or fun taglines to play on the term "Pho," referring to the pathway involved in phosphate homeostasis in yeast that O'Shea studies.

The designs consistently stop people on the street. "Many times I've had comments on the T-shirts when I'm out walking," reports O'Shea. "It's hysterical!" She's also had requests to purchase the shirts, which are posted on the O'Shea lab's Web site. "These are just random people—not scientists. I'm not sure they even know what [the designs] mean."

In fact, O'Shea admits, she sometimes doesn't fully understand the meaning. One of the more popular shirts, for example, has a simply stylized "One Two Three Pho" on the front. On the back, with the Team O'Shea logo are the words, "Someone set us up the bomb!" O'Shea laughs, "I have no idea what that means. It's clearly some pop culture thing."

Team O'Shea's creativity proved contagious, spawning a similar tradition in HHMI investigator Peter Walter's UCSF lab. The first shirt, created in 2005, sported an interpretive drawing of Walter's face by eight-year-old budding artist Mimi Lu, the daughter of a neighboring lab's manager. The second Walter lab T-shirt, unveiled in June at the lab's retreat, features Beaker, the African Grey parrot adopted by Walter and the lab after he landed on the shoulder of a postdoc's wife, out for a campus stroll, and said "Hi there." Beaker, who is bilingual and quotes Dylan Thomas, has "a spectacular vocabulary," says Alex Engel, a fifth-year graduate student. Engel took the lead on this year's T-shirt design, in which the sizeable bird—a foot long from its black beak to its red tail feathers—figures prominently as one of the many "strange birds" that make up the Walter lab. As for Walter, he's busy teaching Beaker "some useful things."

"I'm teaching him to say 'We need more data! We need more results!'" says Walter. "Instead, what he said the other day is 'Don't try so hard.' I'm trying to get that one out of his vocabulary." —*Mary Beth Gardiner*

> "I'm teaching him to say 'We need more data! We need more results!'"
>
> PETER WALTER

Courtesy of Peter Walter

A Wild-Angle View

It's a jungle inside Matthew P. Scott's office at Stanford University. Here, you might spot a dusty, wrinkled elephant munching on the branches of a bush in Zambia, or a sleek Tanzanian leopard looking down from its perch in a tree. Or you might find a Black-crowned Night Heron from the wetlands of San Francisco Bay staring grumpily back at you.

These are the kinds of vivid snapshots of nature's treasures that hang on Scott's walls and continually cycle through the screen saver of his computer, which connects to 20,000 digital photographs he has shot at locations around the world.

In his lab, Scott's experiments delve into the molecular processes that determine how cells grow and animal embryos morph into their basic forms. Yet, confessing to a particular fondness for photographing "the outcomes" of the developmental processes he studies, the HHMI investigator never loses sight of life's big picture. "When you go out into parts of Africa and see the shapes of exotic plants and animals," says Scott, "that's our friends the genes at work."

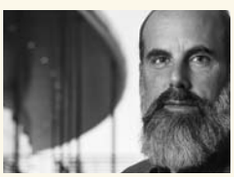
Scott grew up in Newton, Massachusetts, known as "The Garden City," where his father, a professional photographer, turned him on to the art and science of the camera. As a boy in love with nature, at age 12 he began taking black and white pictures of wildflowers and critters with a manual 35 mm Kodak Retina.

Today, delighting in the instant feedback of digital photography, Scott switches between a professional-quality Nikon D200 camera and a Sony HDR-FX1 video camcorder, which he has taken underwater on diving trips. The objects of his visual interest are oftentimes remote, such as elephants and hippos along the Zambezi River in Zambia, which he visited last summer with his family.

Scott's most fascinating wildlife encounter was in 2002, when he and his wife, Stanford biologist Margaret T. Fuller, hunkered down in Uganda's Bwindi Impenetrable National Park to watch foraging mountain gorillas. "I saw so much humanity in those eyes and so much curiosity coming right back," he says, "it wouldn't have surprised me if they pulled out a field guide to humans."

Only about 600 mountain gorillas remain. "In our lifetimes we're watching the last wild areas either disappear or become so distorted or deprived of their flagship species that the nature of the earth is changing at an incredible speed, right before our eyes," says Scott, a staunch supporter of the Natural Resources Defense Council, the Dian Fossey Gorilla Fund International, and other conservation groups.

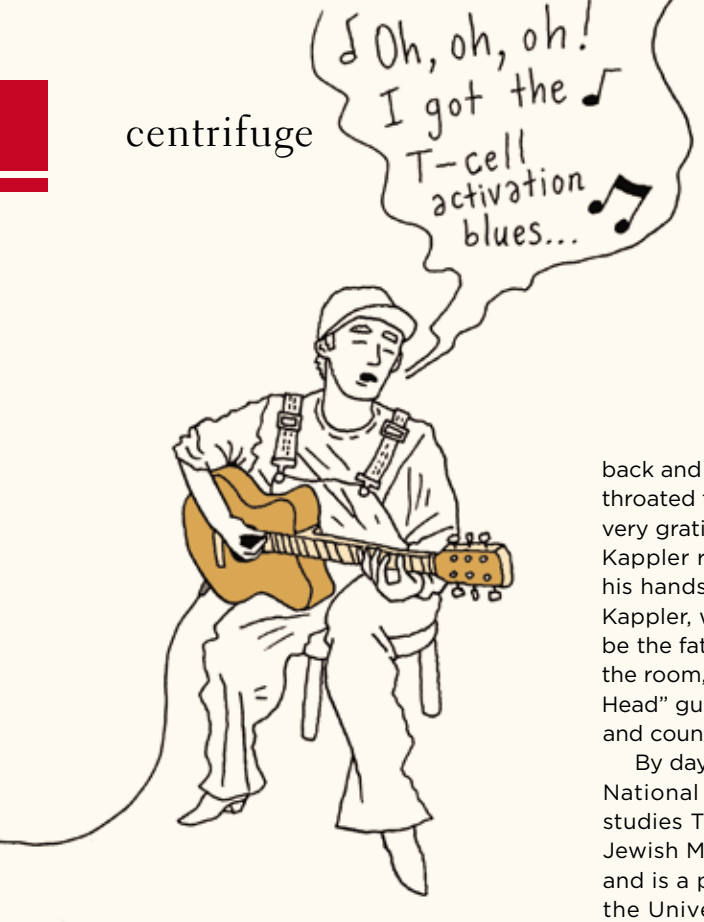
Returning from Uganda, he edited his video footage into a home movie that opens with a cluster of lighted candles. They flicker out, one by one, into darkness—a metaphorical warning about what the gorillas' future could hold. Scott sees his photography as a way of conveying the preciousness of endangered habitats to family, friends, colleagues, and, perhaps, the rest of the world. —*Ingfei Chen*



"I saw so much humanity in those eyes and so much curiosity coming right back."

MATTHEW SCOTT

Photos above: Courtsey of Matthew Scott Photo below: Robert Cardin



Dog Head Blues

It's a Sunday night in Denver and at Cricket on the Hill, a smoky neighborhood bar and musician's hangout, the place is buzzing. It's open-mike night, and young performers waiting to take the stage fill the room. As Tony Medina, host of the weekly gathering, steps to the microphone, someone in the crowd notices his gleaming guitar's engraved Celtic knot and distinctive mother-of-pearl dog's-head emblem.

"What brand of guitar is that?" he calls out.

Medina points to a gray-haired man in the crowd and says, "A wizard's wand," and with that strikes the first chord and bursts into one of his original songs.

The wizard who built that wand, HHMI investigator John W. Kappler, sits back and listens intently to the deep-throated tones filling the room. "It's very gratifying to watch him perform," Kappler remarks. "It sounds great in his hands." A few performers later, Kappler, who at 62 is old enough to be the father of nearly anyone else in the room, gets up with his own "Dog Head" guitar to do some blues, folk, and country and western tunes.

By day, Kappler, a member of the National Academy of Sciences, studies T-cell biology at the National Jewish Medical and Research Center and is a professor of immunology at the University of Colorado Health Sciences Center. Often working in collaboration with Philippa Marrack, his wife and fellow HHMI investigator, he has mapped out many of the complicated mechanisms T cells use to recognize foreign invaders and has advanced knowledge of how that process, when it goes awry, can lead to autoimmune disorders.

But he has other passions too, such as making music and making instruments that make music. Five years ago, he began studying with stringed instrument master craftsman Edward Dick and to this day serves as an apprentice in his Denver shop. Under Dick's tutelage, Kappler built guitars at first for himself. He designed an image in mother-of-pearl of Billie, the family's beloved Labrador retriever (who has since died), and the Kappler guitar brand, the Dog Head, was born.

While playing at open stages around the city, Kappler met local musicians and began taking in their guitars in need of repair. He took pleasure in fixing them as good as new, but that wasn't quite enough. "I wanted to see and hear something I built being played on stage," he explains.

Making Medina an offer he couldn't refuse, Kappler asked him what he might like in a custom guitar. "How could I say no?" Medina recalls.

Kappler says a guitar takes around 100 hours to build and that the materials—not counting tools and space—cost about $300. He makes his instruments exclusively for musicians playing on the local circuit and charges $1,000 for them, which is actually a steal. Those who have played and listened to Kappler's guitars are effusive in their praise. "I have yet to adjust to the chills and goose bumps I get when I play it," says Medina of his Dog Head. "He really is a wizard."

That's all the recompense Kappler needs: "I'm not doing this for the money." *—Marc Wortman*

> "I wanted to see and hear something I built being played on stage."
>
> JOHN KAPPLER

Labor of Love

Of all the guitars John Kappler has built, his favorite is his own personal "Jumbo," which has an extra-wide body and, he says, a "big, bass-y sound." Kappler's innovative bracing on the inside of the soundboard (the wood face of the body) gives the guitar a much cleaner sound in the higher registers. "It turned out spectacularly well," he says. "I just love it." ¶ Kappler is building another Dog Head Jumbo for a local musician, which, with the planning, carpentry, finishing, and inlay work, will take several months to complete. He is crafting a fancy rosette around the sound hole made of abalone shell and highly figured maple wood and sculpting his trademark mother-of-pearl dog's head for the guitar's headstock, that upper part of the neck that holds the tuning pegs. The guitar will have additional shell inlay as well, because the future owner, a country-and-western musician, requested some flash.

Illustration: Peter Arkle Photo: Ray Ng

upfront

Ah, the tranquility of a summer garden. Find a spot in the shade and let the fragrant blossoms and cool breezes sweep your cares away. That satisfying serenity is due in no small part to the chemicals released by the vegetation. Plants use these chemicals, called volatiles, for much more than pleasing us humans. They release volatiles into their environment to protect themselves from predatory insects, bacteria, and fungi. The volatiles also summon bees and other pollinators. HHMI investigator Joe Noel is plotting the evolutionary history of these specialized chemical communicators with the hope of one day manipulating their production pathways to create drugs with desirable properties. You may never view a walk in the park in the same way again.

The Secret Life of Plants

By tracking the evolution of volatile compounds, researchers hope to understand the past—and map out the future.

THE GARDEN AT JOE NOEL'S SAN DIEGO HOME FEATURES COASTAL SAGE, CALIFORNIA *lilacs, and other chaparral plants that once dominated the local landscape. While he appreciates his garden's vibrant colors and water efficiency, like the biochemist he is, Noel sees beyond all that: "There's a tremendous amount of chemistry happening, most evident from the very interesting smells released from the plants throughout the day." ¶ An HHMI investigator at the Salk Institute for Biological Studies, Noel is one of a growing group of scientists fascinated by the extraordinary diversity of volatile and non-volatile compounds found in plants. Plants use these* small molecules, which diffuse easily through the membranes of the cells that produce them, to communicate and interact with the outside world.

Often aromatic and almost always highly specialized for a particular ecological niche, volatiles in particular help each plant flourish in its environment, acting as an odiferous language among plants and between plants and other organisms. The chemicals attract pollinators, summon natural predators of pests, or provide protection through their antimicrobial properties.

Scientists have so far identified more than 1,000 plant volatiles. Even closely related plants produce their own unique sets of volatiles—evidence, says Noel, that the pathways giving rise to these chemicals and their biosynthetic precursors (known as secondary metabolism, because their products are not essential for a plant's growth or reproduction) are subject to rapid evolution.

"By evolving new compounds or new ways of making existing compounds, the enzymes in these biosynthetic pathways that produce volatiles and related compounds provide adaptive advantages to organisms," Noel says. "And they're evolving so rapidly that you can begin to piece together a historical record of how these systems originated, what changes they've undergone, and how they're utilized in the present. Ultimately," he adds, "I think we can also learn what changes we are in store for well into the future."

In one system, Noel and his collaborators are comparing enzymes used by members of the nightshade (Solanaceae) family—which includes tobacco, tomatoes, potatoes, and eggplant—to produce compounds closely related to volatile terpene compounds (found throughout the plant kingdom) to ward off fungal infections. In one case, the amino acids that make up two enzyme "cousins" in Egyptian henbane and tobacco plants, which diverged from their common ancestor about 10 million years ago, are 80 percent identical. But a subtle difference in the enzymes' structures means that while one produces a compound that acts against a fungus in Egyptian henbane's habitat, the other produces a chemically distinct natural compound that defends tobacco against its own fungal menace.

The gene sequence of the two enzymes is so similar, Noel says, that "in a traditional sense we would say they're the same enzyme." Yet he and his colleagues have used structural analysis to zero in on nine amino acids, of the nearly 560 comprising each enzyme, that determine which antifungal agent is produced. "When we take these nine positions in the tobacco enzyme and change them to the nine amino acids found in the Egyptian henbane enzyme,

Borrowing from Nature's Chemical Factories

Joe Noel's lab has encoded onto a single gene the entire set of enzymes that grape, peanut, and blueberry plants use to convert the common amino acid tyrosine into resveratrol—a compound particularly abundant in red wine that is known to dramatically enhance muscle tissue's ability to metabolize fat for energy. In collaboration with fellow HHMI investigator Ronald M. Evans, also at the Salk Institute for Biological Studies, Noel plans to create a mouse that expresses this "natural chemical factory" gene only in muscle tissue. Muscle cells in the mouse will then use the enzymes to transform a small amount of the tyrosine in the animal's diet to resveratrol, allowing the scientists to study how the newly produced compound affects muscle without having to feed large amounts of it to the animal. Noel is undertaking a similar project with Salk colleague Fred H. Gage to create mice that express the chemical factory in the brain—overcoming the challenges of getting a compound consumed in the diet across the blood-brain barrier—to learn how resveratrol might slow aging by altering the behavior of neural stem cells. Experiments like these may eventually enable "genetically encoded medicinal chemistry"—allowing scientists to target enzymes to specific tissues and cells in living animals, where they can create chemical variants from materials available in the diet.

"There's a tremendous amount of chemistry happening [in the garden] throughout the day."

JOE NOEL

the enzyme completely alters its characteristics," Noel explains. "It makes the chemical that the Egyptian henbane makes, and it does so with the same efficiency. The reverse experiment also works nicely."

The next step for Noel and his team is to use this information to discern the structure of the enzyme that must have existed millions of years ago in the plants' shared ancestor. "We don't have molecular fossils," he says, "but with the information now available we might be able to re-create what the ancient enzyme looked like and more importantly, how it behaved." They are proceeding by making more than 1,000 specific versions of each of the related enzymes, reflecting every possible combination of the tobacco and Egyptian henbane amino acids in the critical positions identified thus far. "We are also studying each of these variants structurally to see how the shape and dynamics change and assessing the cocktail of chemicals each produces," he says.

Eventually, glimpses like these into the structural and biosynthetic history of enzymes of secondary metabolism may help Noel and other scientists alter biosynthetic pathways to create new pharmaceuticals or other compounds with desirable properties. ■

–JENNIFER MICHALOWSKI

Illustration: Christoper Silas Neil Photo: John Hayes/AP, © HHMI

The Right Frame

Sometimes you have to tear down an old idea to find a new solution.

Elena Dorfman

Harry Dietz went back to the drawing board to rethink the cause of Marfan syndrome—and now he has a treatment in clinical trials.

"The possibility of finding a productive treatment strategy was analogous to repairing a house with a rotten frame."

HARRY DIETZ

FIFTEEN YEARS AGO, HARRY C. DIETZ AND HIS RESEARCH GROUP MADE A BIG discovery: mutations in the fibrillin-1 *gene cause Marfan syndrome, a genetic disease that weakens connective tissues in the body, including the structural meshwork of blood vessels, and can lead to sudden death if undiagnosed. ¶ The celebration, however, was short-lived. "Things began to look problematic almost immediately," recalls Dietz, an HHMI investigator at the Johns Hopkins University School of Medicine. "Because fibrillin-1 is a structural* protein—and very important during development—there was a suggestion that people with Marfan syndrome are born without a proper quotient or quality of elastic fibers." Yet he knew that figuring out a way to compensate for the missing elastic fibers—particularly during early development—was a challenge that molecular medicine was not ready to handle.

"The possibility of finding a productive treatment strategy was analogous to repairing a house with a rotten frame," he says. "There is no way you could imagine addressing the situation without tearing the house down and starting over."

As researchers considered their options during what Dietz calls "those dark days," one question in particular gnawed at Dietz: How could a disease with such complex characteristics—overgrowth of bones, thickened mitral valves, aortic aneurysm, craniofacial deformities, lung problems—be explained by structural deficiency alone? "It just didn't add up," he recalls.

To build a new intellectual framework, scientists in Dietz's lab turned to a mouse model of Marfan syndrome they had developed by genetically engineering a mutation in the *fibrillin-1* gene. They knew that people with Marfan syndrome often develop problems that resemble emphysema—with widening of the air spaces that can lead to rupture of the lungs—so they first focused on any lung abnormalities they saw in the mutant mice.

They did not expect to find lung problems in the young mice because they believed this kind of destructive emphysema occurs later in life—the cumulative result of stresses over time. "We thought that only over the course of months to years would we begin to see structural damage to the lung," Dietz recalls. "Instead, we saw a diffuse widening of the air spaces in the absence of any evidence of tissue damage or inflammation in the lung right from the day of birth."

That observation led to a radical change in Dietz's thinking. He began to suspect that many features of Marfan syndrome—for example, the fragile aorta that eventually ruptures—might not be caused by a simple weakness of the tissues imposed by deficiency of a structural protein. Instead, he started looking for abnormal patterns in a developmental program. In research spanning several years, Dietz and his colleagues proved time and again—in studies of the lungs, aorta, and mitral valve—that the culprit was excessive levels of a critical developmental signaling molecule called transforming growth factor beta (TGF-beta) that is normally regulated by fibrillin-1.

The next step was to see if they could prevent features of Marfan syndrome by blocking such signaling abnormalities, which led them to losartan, a blood pressure medication that other researchers had found to be active against TGF-beta in studies of chronic renal disease.

Dietz and his colleagues at Hopkins set up a study in mice to compare losartan, propranolol (a blood pressure agent that is used prophylactically in Marfan patients to prevent tears in the aorta), and a placebo. The study, published in the April 7, 2006, issue of *Science*, revealed that the mice that received losartan showed no progression of aneurysm formation and even an apparent reversal of aortic pathology.

"Those mice had normal aortic root growth, normal aortic root size, and normal aortic wall thickness and architecture," says Dietz. "Essentially, losartan-treated Marfan mice could not be distinguished from normal mice." Losartan improved other manifestations of Marfan syndrome in the mice, as well, including abnormal lung development.

Dietz is optimistic that additional research will show that losartan might actually remodel the abnormal architecture of the aortic wall. It is also possible, he adds, that lessons learned from these studies could be applied to other causes of aortic aneurysm. Dietz and his collaborators have recently shown that two other aortic aneurysm syndromes, Loeys-Dietz syndrome and arterial tortuosity syndrome, are also caused by altered TGF-beta signaling. "Aortic aneurysm is a major public health burden," says Dietz. "About one to two percent of the population in industrialized countries dies from it. We are now targeting the more common forms of aneurysm for study." ■

– JIM KEELEY

Children's Study Begins

Encouraged by Dietz's work, the National Institutes of Health (NIH) is launching a multicenter clinical trial to assess whether losartan might be used to prevent aortic aneurysm in children with Marfan syndrome. The trial will be coordinated by the Pediatric Heart Network, established in 2001 to improve outcomes and quality of life in children with heart disease. Recruitment of patients may begin by the end of summer 2006.

"This is the first therapy for Marfan syndrome that was born of a systematic effort to elucidate the pathogenesis of the disease," says Dietz. "It is a rare example of things living up to the promise expressed at the launch of the Human Genome Project: If we can identify the genes responsible for a disease, then we will uncover unanticipated mechanisms behind the disease and be in a better position to design rational therapeutic strategies."

Information about the clinical trial is available from the National Marfan Foundation at www.marfan.org or (800) 8-MARFAN.

Stopping a Force of Nature

Keeping a chromosomal enzyme from its appointed rounds may prevent cancer cells' immortality.

TELOMERES, THE LONG CHAINS OF DNA LETTERS CAPPING THE ENDS OF *chromosomes, seem like a Dr. Seuss creation. What they spell out, in the language of DNA, amounts to gibberish. The exact spelling varies from organism to organism but usually consists of repetitions of a single 6- to 10-letter "word." In human telomeres, the sequence is* TTAGGGTTAGG GTTAGGGTTAGGGTTAGGGTTAGGGTTAGGG*... stretching for thousands of letters. ¶ For all their senseless monotony, telomeres play essential roles in cells and organisms. Without them, the genetic legacy of higher organisms could not endure as it does through countless generations. But that same life sustenance that telomeres breathe into species can also bring* death to individual organisms, explains HHMI president Thomas R. Cech, whose laboratory at the University of Colorado studies telomerase, the enzyme that maintains telomeres on chromosomes. "Telomerase is involved in about 90 percent of cancers," Cech says.

All human cells initially contain telomerase, he explains, but most adult body cells, which typically divide only a limited number of times, lack the enzyme. As those cells age, their telomeres gradually shorten, prompting them to stop growing and senesce. But telomerase becomes reactivated in cancer cells, continually lengthening the telomeres, endowing the cells with immortality and energy-sapping dominion over the body.

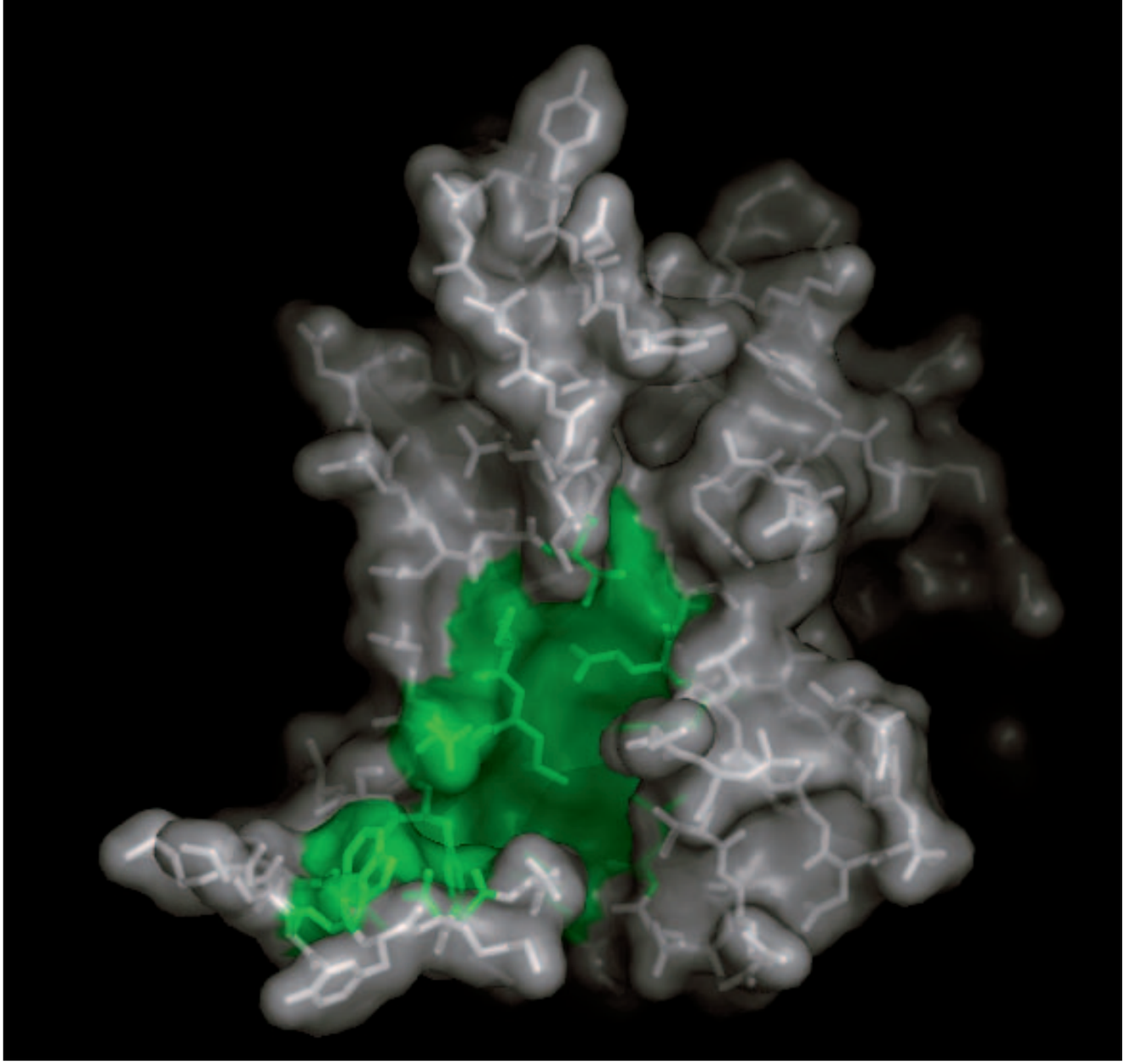
Cech's research team recently made a key finding about a crucial piece of the enzyme, called telomerase reverse transcriptase (TERT). Understanding TERT's three-dimensional structure could help scientists develop drugs to turn the renegade enzyme off in cancer cells. But until very recently, attempts to grow crystals of the enzyme, required for solving its structure, had failed. "Lots of labs have been trying to crystallize it since we discovered TERT 9 years ago, but the protein has never been very soluble," Cech says. When produced in bacteria, the enzyme molecules tend to aggregate into misshapen clumps, called inclusion bodies, which are useless for structural studies.

Finally, Steven A. Jacobs, a Damon Runyon Cancer Research Foundation postdoctoral fellow working in Cech's lab, took a new tack. His novel method and important findings were reported in February in *Nature Structural & Molecular Biology*. Rather than trying to force the entire protein to crystallize, Jacobs used genetic engineering methods to create more than 10,000 different random TERT protein fragments, each produced by a different population of *Escherichia coli* bacteria. He genetically fused each fragment to green fluorescent protein (GFP), which glows when illuminated with ultraviolet (UV) light. The GFP would serve as a biochemical beacon, alerting the scientists of any fragments that happened to fold correctly.

As expected, practically all the random fragments misfolded and formed insoluble inclusion bodies. "The inclusion bodies pulled the GFP inside them so that the proteins couldn't fluoresce nearly as brightly as they could if they were soluble—the GFP essentially goes down with the ship," Cech explains. But some of the protein fragments formed structures that could fold into their correct shape as they do in the full-length protein, and they did remain soluble within the *E. coli* cells that produced them. "You just have to shine a UV lamp on the Petri dish

THE BIG PICTURE — A Natural End

BECAUSE OF A QUIRK in the way chromosomes replicate, the DNA polymerase enzyme can't copy the letters at the chromosome tips. Consequently, newly copied chromosomes lose about 50 letters from their ends at every round of replication. >> **TELOMERES CIRCUMVENT** the shortcoming by providing meaningless DNA sequences at chromosome ends. The telomeres sacrifice their own tips to shield the chromosome's genes from being lost. Over generations, the telomeres of most of the body's cells steadily shorten, placing the genes in jeopardy of being lost. >> **FACING SUCH LOOMING DISASTER**, most healthy cells stop dividing when their telomeres become too short. But the special cells that go on to create new life, in the form of eggs and sperm, cannot afford to lose genes or to stop dividing. Either would bring the species to extinction. As a solution, cells that produce sperm and eggs continually extend their telomeres with telomerase, ensuring that species can continue into perpetuity.



In this model of part of the telomerase enzyme, green highlights the groove that "anchors" the protein near the chromosome's tip.

Science image courtesy of Steven Jacobs/ Cech lab Photo: Paul Fetters

and literally pick the bright green colonies off the plate with a toothpick," he explains.

Jacobs purified the TERT-GFP fragments from several brightly glowing *E. coli* colonies, and sure enough, one of them crystallized readily, allowing the precise atomic structure of the protein to be determined by x-ray diffraction.

That fragment was from a region of the TERT protein chain called the N terminus. By comparing the sequences of the same region of TERT from several different species, identifying the common amino acid positions shared among all the species, and mapping those positions to their structural model, the researchers inferred that a grooved cleft running through the protein must be important to the enzyme's function. After changing several of those key amino acids in the full-length TERT protein, they found that the enzyme lost its ability to assemble telomeres. "So we knew that this domain was necessary for function," Cech says. They dubbed the fragment the "TEN domain," for telomerase essential N terminus.

Further experiments showed that the TEN domain clamps onto the DNA near the end of the chromosome, positioning telomerase to begin building telomeres. "It's a part of the protein that is miles away from the active site [the part that catalyzes the chemical reaction]," Cech says, yet it's completely essential for activity." The hope, he says, is that scientists can now develop drugs targeting the TEN domain, preventing it from clamping to the chromosomes in cancer cells, and thereby nixing their immortality. ■

–PAUL MUHLRAD

> "You just have to shine a UV lamp on the Petri dish and literally pick the bright green colonies off the plate with a toothpick. "

TOM CECH

AIDED BY MICROARRAYS, AN INSPIRED PARTNERSHIP COULD FINISH THE JOB STARTED BY PAST PIONEERS.

MODERN-DAY VIRUS HUNTERS

BY STEVE OLSON
ILLUSTRATION BY JOSH COCHRAN

few days before Christmas 2005, a 28-year-old woman drove herself to the emergency room of the hospital at the Stanford University Medical Center. For 10 days, she had been running a fever, coughing, and waking up at night drenched in sweat. An x-ray had revealed fluid in her lungs, and she was taking an antibiotic to cure what doctors thought was a case of pneumonia. But she wasn't getting any better. ¶ When a new x-ray showed that her lungs were even more clogged, she was admitted to the hospital and placed on two more antibiotics. But her condition continued to deteriorate, and on her third day in the hospital she quit breathing and had to be placed on a ventilator. Hospital physicians tested her blood and the fluid in her lungs for infectious agents—they even did a lung biopsy, looking for suspicious bacteria, fungi, and viruses. "We went through every test we had in the lab," says Bruce Patterson, the director of virology at the hospital and a professor of pathology and medicine at Stanford University School of Medicine, "but everything came back negative." ¶ On the woman's eighth day in the hospital, Patterson called Joseph L. DeRisi, an HHMI investigator at the University of California, San Francisco (UCSF). Patterson had heard DeRisi talk about a new device he had built, a microarray spotted with DNA fragments that can detect DNA sequences from all known viruses. Did he think it could determine what was killing the woman? Patterson asked. ¶ Within a few hours, a medical courier was driving a sample of lung fluid up Highway 101 to DeRisi's lab in UCSF's new Mission Bay campus just south of downtown San Francisco. Less than a day later, DeRisi had a diagnosis. The woman was infected with parainfluenza 4, a virus not previously known to cause acute respiratory failure in healthy young adults. ¶ By that time it was too late to give the patient any more medications, but, miraculously, she lived. Her body got the infection under control. Within a few days she was taken off the ventilator, and 2 weeks later she went home.

This woman was lucky, DeRisi and Patterson agree, but relying on luck isn't good enough. "If her doctors had known that it was parainfluenza 4 early on in the hospital stay, treatment decisions would have been different," DeRisi says. "There would have been no reason to give her all those antibiotics plus an open-lung biopsy, which has some pretty drastic potential outcomes associated with it." As a result of that case, Patterson set up what he calls a SWAT team to deal with the handful of patients who show up in Stanford's hospital each year with infections that cannot be identified. When existing tests come up negative, samples can be sent to DeRisi's lab to look for unexpected viral infections.

After all, if doctors don't know what is making a person sick they can't propose the best possible therapies. "It's shooting in the dark," DeRisi says.

BLAST AHEAD

DeRisi is not a physician, but his work with UCSF virologist Don Ganem, also an HHMI investigator, has tremendous clinical potential. It's "bench-to-bedside research at its very best," says UCSF chancellor and Nobel laureate J. Michael Bishop.

After graduating in 1992 from the University of California, Santa Cruz, with an undergraduate degree in biochemistry, DeRisi went to Stanford University to do graduate work in the lab of HHMI investigator Patrick O. Brown. At that time, DNA microarrays were so new that the National Institutes of Health had rejected Brown's initial requests to develop the technology. But one of Brown's favorite phrases is "blast ahead," and he knew that microarrays were going to be important so he pieced together other funding to work on them.

Analogous to mailboxes in an apartment building, DNA microarrays consist of thousands of distinct DNA fragments attached to

a glass slide. DNA samples that a researcher wants to identify are tagged with fluorescent labels and washed over the slide. Just as letters are sorted into mailboxes, DNA pieces in the sample stick to matching DNA fragments on the slide, allowing the unknown DNA to be identified.

Although DeRisi went to Stanford to study retroviruses, he was soon swept up in the scientific and engineering challenges of microarrays. "The project I was doing required high-density arrays, and no one was going to make them for me," he says. After building and programming a robot that attached the DNA fragments to the slide using precision-guided metal pen tips, DeRisi and the other members of Brown's lab used the device to achieve a number of notable firsts. They were the first research group to look at the activity of all genes in yeast simultaneously, for example, and they were the first to use microarrays to explore global gene expression in human cancers.

Brown and DeRisi found they had much in common. DeRisi is a onetime black belt in aiki-jujitsu; Brown is a marathoner. Both are devoted to open-access publishing of scientific articles; Brown was a cofounder of the Public Library of Science, through which DeRisi publishes many of his papers. And both are ardent proponents of making microarrays as inexpensive and accessible as possible. DeRisi has posted instructions on his Web site for how to build a microarrayer, and he has taught highly popular summer courses at Cold Spring Harbor Laboratory in New York and UC Santa Cruz on constructing and using microarrays.

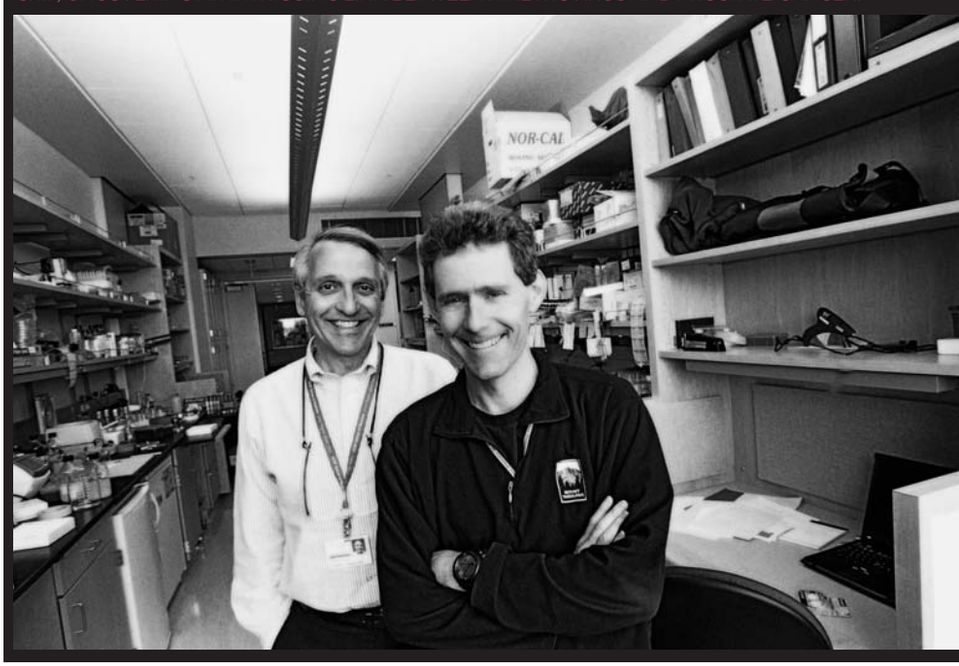
DeRisi's expertise in molecular biology, bioinformatics, and microarray technology made him a hot prospect, and a postdoctoral fellowship at UCSF was quickly followed by a faculty appointment. DeRisi used his new position to launch a major study on malaria. By tracking the expression of genes of *Plasmodium falciparum*—the parasite that causes the disease in humans—over time, DeRisi and his colleagues have uncovered particular genes that turn on and off in sequence as *P. falciparum* attacks and destroys blood cells. He is working on tests of new antimalarial drugs to see if they interfere with the process.

A FORMIDABLE PARTNERSHIP BEGINS

His malaria studies got DeRisi thinking about other possible medical applications of microarrays, but it took a frustrated postdoc to launch his work on viruses. In Ganem's lab, postdoctoral fellow David Wang, now an assistant professor at Washington University in St. Louis, had been studying a particular virus-replicating enzyme for 2 years and was making very little progress. Finally, Ganem suggested that Wang try something different by learning about microarrays in DeRisi's lab. "A couple of months later," Ganem recalls, "Dave came back to our group meeting and told us that Joe had been talking about using microarrays to detect viruses. Dave asked, 'Do you think that's a good idea?' And I said, 'It's a great idea.'"

For Ganem, working with DeRisi was a chance to do the kind of science he likes best. After his second year at Harvard Medical School, Ganem took 2 years off to do research with viruses, and after

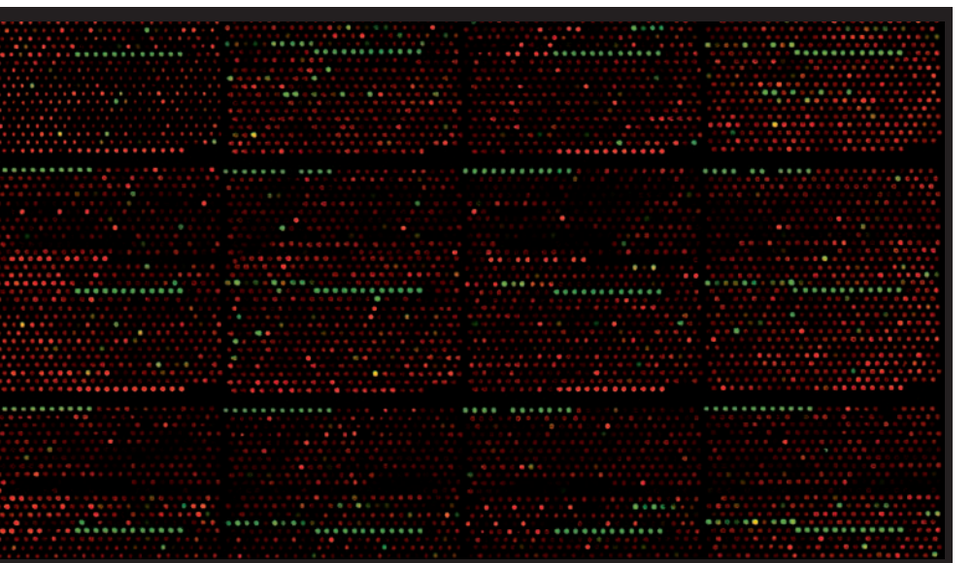
DON GANEM (LEFT) AND JOE DERISI HAVE HAD A PROMISING FIRST HIT WITH THEIR VIRUS CHIP, UNCOVERING AN INTRIGUING LINK BETWEEN A RETROVIRUS AND PROSTATE CANCER.



Olivier Laude

"IF HER DOCTORS HAD KNOWN THAT IT WAS PARAINFLUENZA 4 EARLY ON IN THE HOSPITAL STAY, TREATMENT DECISIONS WOULD HAVE BEEN DIFFERENT," DERISI SAYS. "THERE WOULD HAVE BEEN NO REASON TO GIVE HER ALL THOSE ANTIBIOTICS PLUS AN OPEN-LUNG BIOPSY."

"I LOVED THE IDEA OF TRYING TO IDENTIFY THE INFECTIOUS CULPRITS OF IMPORTANT DISEASES AND THEN DEVELOPING A COURTROOM STRATEGY TO PROVE THEIR GUILT," SAYS DON GANEM.



THE VIROCHIP V3 ARRAY, DEVELOPED AS A COLLABORATIVE PROJECT OF THE GANEM AND DERISI LABS, CONTAINS REPRESENTATION OF ESSENTIALLY ALL VIRUSES PRESENT IN GENBANK, THE GENETIC SEQUENCE DATABASE OF THE NIH. HERE, THE GREEN SIGNAL SHOWS POSSIBLE POSITIVE HITS, WHILE THE RED SIGNAL INDICATES THE ARRAY WAS CORRECTLY BUILT.

completing medical school he did a postdoctoral fellowship in virology. Drawing on those experiences, in the early 1990s Ganem and his UCSF coworkers developed a blood test for infection with herpesvirus 8 that helped establish the virus's responsibility for Kaposi's sarcoma, a deadly cancer that is common in people with damaged immune systems. "That was the best moment of my professional life," says Ganem, "when my knowledge of science and my knowledge of medicine could be used at the same time."

Wang's new postdoctoral fellowship in DeRisi's lab jump-started the virus chip project. Soon they had constructed a DNA microarray designed to identify not only known viruses but also new viruses related to those already known. The microarray contained 10,000 DNA fragments drawn from every human, animal, plant, and microbial virus described in DNA databases at that time. They began testing the microarray against viruses grown in the lab, but then events in the real world intervened.

In late 2002, several hundred people in China came down with a severe form of pneumonia caused by an unknown infectious agent. Dubbed "severe acute respiratory syndrome," or SARS, the disease soon spread to Vietnam, Hong Kong, and Canada, causing hundreds of deaths. In March 2003, DeRisi and Wang received DNA samples derived from the virus suspected of causing the disease and washed them over their microarray. Within 24 hours, they had identified the virus as a previously unidentified member of the coronavirus family, a conclusion reached at about the same time by another research group using microscopes. A day later, the Centers for Disease Control and Prevention held a news conference to announce the results. In 2004, recognizing his work on both malaria and SARS, the John D. and Catherine T. MacArthur Foundation awarded DeRisi one of its half-million-dollar fellowships—part of which he has used to support malaria studies in Uganda.

BUILDING A CASE

"Do you see those little white dots?" asks Anatoly Urisman, holding a conventional one-inch by three-inch glass microscope slide up to the window. With the sun shining through the slide, square arrays of tiny white dots float into view. "Those are the DNA spots." He slips another slide into a laser scanner, and a dense grid of green and red circles appears on a computer monitor. "This one didn't work very well," he mutters. "Those red spots should be brighter."

Urisman, an M.D.-Ph.D. student in DeRisi's lab, is heading up one component of DeRisi and Ganem's most ambitious project to date. Drawing on his clinical background, Ganem has been obtaining tissue samples from people with respiratory infections, hepatitis, meningitis, rheumatoid arthritis, multiple sclerosis, and a half dozen or so other diseases. DeRisi and his labmates then use the DNA microarray to identify viruses in the tissues. If they find suspicious viruses in patients with a particular illness, those viruses may be clues to the origins or course of the disease.

Earlier this year, the team reported the first of what it hopes will be many hits. At the Cleveland Clinic, oncologist Robert H. Silverman found a subset of prostate cancer patients with a suspicious genetic mutation. The men had a defect in a gene called *ribonuclease L*, which produces a protein that defends against viral infection. With their permission, DeRisi's lab isolated DNA from the prostate cancer tumors of men with the genetic defect and washed the DNA across its microarrays. The tests produced a clear signal: many of the men

Courtesy of Patrick Tang/Ganem and DeRisi labs

were infected with a retrovirus, called XMRV, related to a virus known to infect mice but not humans.

The nature of the link between XMRV and prostate cancer remains unknown. It's possible that infection with the virus is coincidental, especially since the virus is not of a type known to cause cancer in humans. Or XMRV could cause the cancer indirectly by contributing to inflammatory processes in the prostate. "In my heart of hearts, I don't think this virus is the direct cause of prostate cancer," says Ganem. "A hit on the array isn't the end of a project. It's just the beginning. If we get a connection, we still have to build a case for causation."

Their success with XMRV has demonstrated the potential of Ganem's and DeRisi's approach, but their partnership is not without its challenges. For one thing, they work in different parts of San Francisco. Ganem's lab is in the UCSF hospital overlooking Golden Gate Park and the Pacific Ocean, several miles from DeRisi's Mission Bay lab. The two investigators and their students have become experts at navigating the hilly urban terrain that separates the two campuses.

Organizational and professional issues are more daunting than the logistics. "There are only two outcomes in this research—a home run or a strikeout," Ganem notes. Such riskiness can be hard on graduate students and postdoctoral fellows. If a postdoc is fortunate enough to work on a project that yields a home run, everyone is happy. But a postdoc could spend a couple of years searching for a viral cause of a common disease and come up empty-handed. "I worry about that a lot," says Ganem.

Getting their research funded is another potential problem. A search for the viral causes of common diseases does not fall neatly into established research categories. Fortunately, support from HHMI has allowed the work to go forward. "Every day I thank God that there's an organization that's willing to take those risks," Ganem says.

Despite the difficulties, Ganem and DeRisi have high hopes for their joint project. According to DeRisi, "I don't think either of us on our own would be able to accomplish this project individually, but together we make a really strong team." Other researchers are equally enthusiastic. "There's no question that this technology is going to produce critically important insights," says Herbert W. "Skip" Virgin, who studies the effect of viruses on the immune system at Washington University in St. Louis. "And many more positive results will be forthcoming."

A FANTASTIC SUBVISIBLE WORLD

In 1926, Paul de Kruif, a University of Michigan bacteriologist turned writer, published a best-selling book called *The Microbe Hunters*. In it, he told stories of "the bold and persistent and curious explorers and fighters of death"—from Anton van Leeuwenhoek to Louis Pasteur to Walter Reed—who discovered and tamed the microbial causes of disease. They "peeped into a fantastic sub-visible world of little things, creatures that had lived, had bred, had battled, had died, completely hidden from and unknown to all men from the beginning of time," de Kruif wrote. "Beasts these were of a kind that ravaged and annihilated whole races of men ten million times larger than they were themselves."

Ganem read *Microbe Hunters* while in eighth grade and was profoundly affected by it—an experience not uncommon among physician-scientists of his generation. "For me, it was like a police drama," he says. "I loved the idea of trying to identify the infectious culprits of important diseases and then developing a courtroom strategy to prove their guilt."

The work that Ganem and DeRisi have undertaken is squarely within the tradition documented by de Kruif. They are searching for the elusive microbes that continue to ravage human populations. The search is a difficult one, they acknowledge, because no one knows how many viruses infect humans and what effects those viruses may have. Geneticists have begun to inventory microbes in the environment—for example, J. Craig Venter, one of the people who spearheaded the sequencing of the human genome, reported several years ago on the many previously unknown DNA sequences of microbes he found in samples of water from the Sargasso Sea. But no one has tried to do the same for human beings.

DeRisi and Ganem believe that now is the perfect time to finish the job that past microbe hunters began. As soon as researchers inventory the full range of microbes that infect humans, technologies like DeRisi's microarrays can link those microbes to specific diseases. "Forget the Sargasso Sea," DeRisi says. "Do somebody's nose." ■

BACK TO THE

GERALD RUBIN DRAWS ON THE PAST TO SHAPE JANELIA FARM'S RESEARCH STRUCTURE

BY RICHARD SALTUS

photograph by Elena Dorfman

FUTURE

HIS FOOTSTEPS crunching on unfinished floors, HHMI vice president Gerald M. Rubin walks purposefully through the curving corridors and airy laboratories of Janelia Farm's spectacular biomedical research center, a half-billion-dollar investment in creating—or, more precisely, re-creating—a highly productive scientific culture. ¶ A compact figure clad entirely in black—no fashionista, but a man who eschews clothing decisions—and wearing a white hard hat and protective goggles, Rubin points out innovative features of the three-tiered structure terraced into the side of a grassy slope in Northern Virginia's Loudoun County, 30 miles from downtown Washington. Fondly dubbed "the landscape building," its design, by renowned architect Rafael Viñoly, has made extensive use of glass. The result is a structure that is "massive yet transparent," despite the fact that it's mostly underground, says Rubin. "We've made a place where you can walk outside on any level of the building, or be indoors yet feel as if you're outside."

In execution, the Janelia Farm Research Campus is stunningly state-of-the-art, yet in concept it harks back to the heyday of legendary research-and-development powerhouses like the Medical Research Council Laboratory of Molecular Biology (MRC-LMB) in Cambridge, England, and AT&T's Bell Labs in Murray Hill, New Jersey. In those productive settings, small groups of leading scientists, internally funded and free of teaching and administrative chores, made revolutionary discoveries and won Nobel Prizes. Importantly, senior scientists worked at the lab bench alongside postdocs and junior researchers.

MRC-LMB scientists determined the structure of DNA and conceptualized the genetic code, discovered messenger RNA, and invented techniques to produce monoclonal antibodies en masse and sequence DNA, among other seminal advances. Bell Labs was the birthplace of the transistor, the laser, and the UNIX operating system.

Such examples inspired HHMI to create Janelia as an extra dimension, beyond the Institute's funding of more than 300 scientists at institutions around the country. These HHMI investigators, though assured of financial support, are limited by what Rubin calls a "conservative" academic culture that places individual achievement above collaboration and interdisciplinary research. Quoting a mentor, Rubin says, "It's amazing how much more you can accomplish if you don't care who gets the credit."

As Rubin wrote in an opinion piece in the April 2006 issue of *Cell*, "We think of [Janelia] as an experiment." He adds, "We may not get it exactly right at first," but he hopes that historians will say that "truly unanticipated discoveries started coming out after 5 or 10 years … and those discoveries might never have been made in another setting."

Clearly, he is very much the proud father, eager to see Janelia Farm peopled with busy scientists. Nobel laureate Sydney Brenner, an important mentor when Rubin studied at the Cambridge laboratory and a senior adviser at Janelia, says, "He has the wonderful intention of trying to create an openness in science and give people the opportunity to break with the conventional way in which science is done today."

Says his wife, Lynn, "It's a lot of hard work, but he's having the time of his life." And Rubin, 56, agrees. For more than three decades, he has thrived as an experimental geneticist, research director, teacher, mentor, and biotech-company cofounder. But "if you asked me to describe my dream job," he says, "this is it—and everything in my career has been preparing me for it."

Rubbing Elbows with Heroes

HANGING ON the wall of Rubin's temporary office is a framed aerial photo of Nantasket, a long, narrow peninsula that juts into Boston Harbor, south of the city. Rubin has spent part of the summer there for the past 50 years in a house belonging to his family. "I like to walk on the beach," he says, simply. "I do my best thinking when I'm walking on the beach."

Nantasket is within easy reach of the working class Boston neighborhood where Rubin was born in 1950 to parents who were both the children of Russian immigrants. Today, his speech, rapid and precise, retains a Boston flavor: "R" sounds drop from "park" and "pattern," and are translocated, like broken chromosomes, to the ends of words like "idea."

His mother taught school and his father was an electrician. His only sibling, an older brother, is a professor at Duke University.

Rubin's parents kept a Kosher house and Rubin was bar mitzvahed: "I consider myself Jewish, and am culturally in tune with my heritage," he says. The family placed great value on education, and his father earned an associate's degree at age 62. Gerry liked sports and played street basketball but was, inexplicably, an underachiever in elementary school. He caught fire in junior high and won admission to the selective Boston Latin School, graduating in 1967.

Rubin gravitated to math and science at Boston Latin, even doing extracurricular work in a cancer research laboratory at the Massachusetts General Hospital. Planning to major in chemistry, he entered the Massachusetts Institute of Technology (MIT), where he took his first formal biology courses. Rubin was deeply impressed by the humility of one professor, biologist Salvador Luria, who came to work the morning he learned he won the Nobel Prize and immediately erased a big "congratulations" message the students had written on the board. "He told us that just because he had won the Prize, it didn't mean his work was superior to that of his peers," says Rubin.

It had been 15 years since the discovery of the DNA double helix, and Rubin recognized that biology had entered a new era and that he wanted to be a part of it. He also discovered, at MIT and in the two summers he spent at the Cold Spring Harbor Laboratory, that he had a strong affinity for experimental science.

After receiving his B.S. in 1971, Rubin won scholarships to study at the MRC-LMB in Cambridge, where scientists such as James Watson and Francis Crick, as well as Brenner, Fred Sanger, and Max Perutz, were making great discoveries in biology. "All these heroes I had read about in my courses were there, walking around and doing experiments in the lab," says Rubin.

The unconventional style of the place suited him perfectly. "I liked that they didn't have required courses," he says. "Because I didn't learn well in the classroom, the MRC-LMB was wonderful for me. I liked reading and bringing in things informally, in small groups. You'd sit down with these scientists at afternoon tea in the cafeteria."

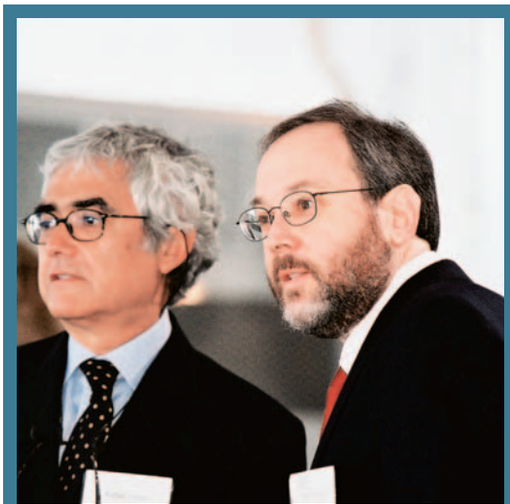
"Oh, he loved the very easy regulation of the place," recalls Brenner. "I remember he came to me and said, 'Isn't it time I put in my thesis?' And I said, 'What thesis?' I'd forgotten he was a grad student—he acted more like a postdoc, he was so completely independent."

For his Ph.D., which he received in 1974, Rubin sequenced a yeast RNA made up of 158 bases. Nowadays, he points out, automated machines can read out 10 such sequences a second. "What took 2 years of my life now can be done in one-tenth of a second!"

From England, Rubin went to Stanford University for postdoctoral studies in the biochemistry laboratory of David S. Hogness, who has been called the founder of modern genomic analysis. Hogness was using the common fruit fly, *Drosophila melanogaster*, a longtime workhorse of genetics research, in expanding the techniques of gene cloning that had just been discovered by Stanley Cohen (Stanford University) and Herbert Boyer (University of California, San Francisco). Hogness had begun cloning *Drosophila* sequences in bacterial plasmids, and Rubin's initial postdoctoral project was to compile the first library large enough to represent the fly's entire genome. "It was an exciting time to be there," recalls Rubin. "Anything you did was brand new."

A newly minted drosophilist, Rubin returned to Boston and a position at Harvard-affiliated Dana-Farber Cancer Institute, continuing work on *Drosophila* genetics. But his scientific style was at odds with Harvard's highly political and competitive academic culture, and in 1980 he accepted a position in Baltimore at the Carnegie Institution of Washington, in the embryology lab headed by Donald Brown.

Rubin's stint at Dana-Farber nevertheless brought a lasting benefit. He began spending time with the manager of another Harvard laboratory, Lynn Mastalir. "He worked all the time," she says, "so the only way he was going to meet anybody was in a lab." She soon



LEFT *Gerry Rubin talks with Janelia Farm architect Rafael Viñoly.*

RIGHT *In April 2000, Rubin testified before a Congressional subcommittee about genomic sequencing, along with (right) J. Craig Venter, founder of Celera Genomics, and (left) Robert Waterston, then head of the department of genetics at Washington University School of Medicine in St. Louis.*

PEOPLE TELL ME I'M **EVANGELICAL.** I TAKE THAT AS A COMPLIMENT.

Left: Paul Fetters Right: William K. Geiger

learned that romance with Gerry Rubin also meant that dates could be punctuated by visits to the lab—or the lab might visit them. One evening, on arriving for a date, he pulled vials of fruit flies out of his pockets and asked if he could leave them in her house while they went out. "If I leave them in the car, they'll freeze," he explained. The couple married while still in Boston and had a son, Alan, 4 days after Rubin's 30th birthday. Alan is now entering graduate school in genome sciences at the University of Washington in Seattle.

Rubin thrived at Carnegie. He and developmental biologist Allan C. Spradling, now an HHMI investigator, achieved a breakthrough by inserting, for the first time, foreign genes into the embryos of multicellular organisms—*Drosophila*—and showed that the genes were expressed in the cells of the adult. The key was harnessing a certain type of naturally occurring transposable DNA sequence, called the "P element," that can insert itself into a cell's DNA. In their much-cited 1982 paper published in *Science*, Spradling and Rubin reported that they had used P elements carrying a wild-type gene for red eye color to correct a white-eye mutation in fruit flies. The paper "jump-started our careers," Rubin says, and paved the way for bioengineering higher animals for research and biotechnology purposes.

Big Ideas

RUBIN'S growing scientific stature caught the interest of Daniel E. Koshland, a biochemist at the University of California, Berkeley, who had taken on a controversial revamping of that institution's biological sciences program. Koshland wanted a rising star like Rubin, and he heard that the Carnegie geneticist "might be movable." Koshland energetically recruited the Rubins, wining and dining and persuading, but he was foiled in his efforts to make a pitch to Lynn. "I always believed you should talk to the wife," says Koshland, formerly editor-in-chief of *Science*, "but I could never get her on the phone." Lynn, who in fact was eager to leave Baltimore, recalls the episode with amusement: "Gerry kept saying to him, 'I don't know if Lynn will come.'" The Rubins' strategy worked, says Koshland, laughing at what became a legend of academic negotiation. "I gave him more than any professor we'd ever recruited. But he was a great addition to Berkeley."

Rubin came aboard in 1983 as the John D. MacArthur Professor of Genetics and later became head of the genetics division. In 1987, a banner year, he was chosen to be an HHMI investigator and elected to the National Academy of Sciences—at the unusually young age of 37. Even after joining HHMI as vice president for biomedical research in 2000, Rubin maintained a lab at Berkeley, although it is winding down.

Robert Tjian, an HHMI investigator and molecular biologist at Berkeley who helped recruit him and became a colleague and close friend, recalls: "Gerry is the ultimate organizer, at every level, from the way the reagents are labeled to the way the lab is run. At the same time, he's not a micromanager. His philosophy is that you can be messy or you can be neat, but as long as you're thinking and working hard and tackling big ideas, you're not going to have a problem."

While in California, Rubin and two colleagues founded a biotech company, Exelixis, located in South San Francisco, for the purpose of translating discoveries about genetic pathways in the fruit fly to problems of human medicine. Today, it has about 500 employees and a number of products in the pipeline. The effort was "financially rewarding," Rubin says (he has divested himself of all interests in the company since moving to HHMI headquarters), but also is "relevant to Janelia because it was a startup experience, going from an idea to a fully functioning place."

Rubin's highest public profile emerged from his partnership with the maverick scientist-entrepreneur J. Craig Venter to sequence the *Drosophila* genome as a warm-up to the contentious race to sequence the human genome. While the National Institutes of Health (NIH)-funded effort took a more cautious path to the enormous task, Venter and his company, Celera Genomics, gambled on a faster and less expensive—but potentially riskier—"whole-genome shotgun" method.

In 1998, when Venter approached Rubin, then head of the Berkeley *Drosophila* Genome Project, and proposed that they collaborate to perform the fruit fly genome sequencing at no cost to the public, many saw the deal as akin to selling one's soul to the devil. "That took a great deal of courage on Gerry's part, because Craig was being reviled by the [publicly funded genome sequencing] community," says Michael Ashburner of the

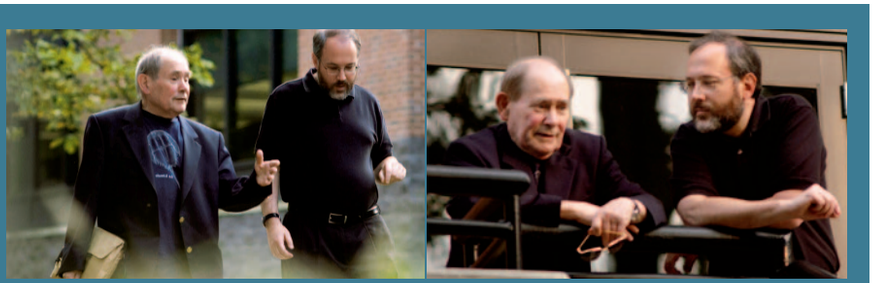
IF YOU ASK ME TO DESCRIBE MY DREAM JOB, THIS IS IT—AND EVERYTHING IN MY CAREER HAS BEEN PREPARING ME FOR IT.

University of Cambridge, a biologist specializing in *Drosophila* genetics who recently published an account of the fruit fly genome effort (see Observations, inside back cover).

The idea that the two might work together came up at a meeting at Cold Spring Harbor, just after Venter had been quoted in *The New York Times* as claiming that Celera would beat the NIH-funded effort to sequence the human genome—and do it cheaper. "It was a very tense atmosphere," agrees Rubin. "But when Craig took me out in the corridor and asked me to collaborate on the *Drosophila* genome, I was instantly delighted. Celera wanted to prove that its shotgun sequencing method would work, and I wanted to get the genome done. It seemed like a no-brainer."

Ultimately, Rubin's instincts and pragmatism, together with his insistence that the sequence immediately go into a public database, proved unerring and gained him wide respect. And, as it turns out, the collaboration worked brilliantly. In March of 2000, Venter and Rubin announced the nearly complete sequence of the 120 million units of DNA contained in the fruit fly's five chromosome arms. For this achievement, he and Venter, with their colleagues Mark D. Adams and Susan E. Celniker, shared the American Association for the Advancement of Science's Newcomb Cleveland Prize. "Gerry is a great scientific leader," says Venter. "He proved it by going against the grain and following his own path, and as a result he really helped science move forward."

With the raw sequence in hand, Rubin and about 60 *Drosophila* researchers, computer scientists, and staff gathered at Celera headquarters for a frenzied, 2-week-long "annotation jamboree." Using algorithms being refined in all-night sessions, the scientists analyzed the sequence and discovered a total of 13,600 genes on the chromosomes. Rubin calls it "the most intellectually stimulating time of his career." But he had another reason to be exhilarated: Confidentially, he had just accepted the position of vice president for biomedical research at HHMI, a job that would bring him back to the East Coast and, 2 years later, make him director of planning for Janelia.



Working among "heroes" like Nobelist Sydney Brenner, now a senior adviser at Janelia Farm, has had a lasting effect on Gerry Rubin.

Tom Kochel

Science, and Family, First

JANELIA FARM is designed to equip some 230 resident and 100 visiting scientists with advanced tools, excellent facilities, and freedom of inquiry. Its research agenda centers on two themes: discovering the basic rules and mechanisms of the brain's information-processing system, and developing biological and computational technologies for creating and interpreting biological images.

In his own laboratory at Janelia, Rubin intends to bring his *Drosophila* genetics experience and techniques to bear on issues of gene expression regulation in the brain. But he'll concentrate mainly on building Janelia's scientific programs and continuing with mentoring activities, which mean a great deal to him. More than 50 of his former students and postdocs now run their own labs; three are HHMI investigators.

Rubin believes his style is well suited to the enormous yet exciting task ahead. "I have always placed science first and politics and personalities second. I have a knack for dealing with highly creative, quirky, high-maintenance people and getting them to work together. And I am flexible."

Such standards and flexibility have served his family as well. When Janelia becomes operational, the Rubins will move to the complex from their home in Bethesda, Maryland, near his present office at HHMI headquarters. Throughout his career, Rubin has insisted on living within 2 miles of his workplace to be close to his family. "He never missed dinner at home," says Lynn, "and he could always slip out for an hour or two for all those little school plays and performances."

Running an enterprise of Janelia's scale and ambition will of course be no easy task. But colleagues have no doubt that if anyone can make Janelia a success, it is Gerry Rubin. "I think Gerry likes big science," says Tjian, "and because he's so organized it doesn't faze him to be thinking about big organizations. He has a great track record and his resources at Janelia are unmatchable."

Even competitors, such as Venter, are rooting for him. If they have any cautions, it's about the ability of a leader, no matter how capable and inspired, to make a go of an enterprise—especially in today's academically oriented, competitive biomedical-research climate—that is founded on the high ideals of science as a collaborative effort aimed at the common good.

"People tell me I'm evangelical," acknowledges Rubin. "I take that as a compliment." ■

SOMETIMES small seeds—and big dreams—can take root to solve seemingly intractable problems.

Johnny Appleseeds *of* Science

by Jennifer Boeth Donovan

ANN L. CHESTER KNOWS what it feels like, and what can happen, when kids don't believe in themselves. She remembers the sting of a mistake made in her own childhood, when a school administrator misread her test scores and placed her in a class for low achievers.

"They told me I wasn't college material," Chester recalls. "They told me my future held a job as a seamstress or a gas-station attendant." Her response was predictable. "I stopped trying to get good grades. I cut up in class and was sent to stand in the corner. That was not like me at all."

Illustration By David Brinley

Even after her mother convinced the school to revisit those test scores and Chester was moved into a high-achievers class, the self-doubt was hard to overcome. "It took me forever to regain my academic performance level," Chester says. She eventually did, however, excelling in college and earning a Ph.D. in biology. But, she notes, "if six weeks of that kind of expectation and treatment could have such an effect on me, think what a lifetime of it could have on anyone."

As a teacher at West Virginia University (WVU) in Morgantown, Chester was thus moved by the vast, unrealized potential she saw all around her. Nearly 20 percent of the residents of this small Appalachian state live in poverty. Fewer than 15 percent of West Virginians have college degrees, despite the enormous need there for qualified health-care workers and other trained professionals.

To help change the situation, Chester took charge of a federally funded campus program to draw minority and disadvantaged undergraduates at WVU to careers in science, medicine, dentistry, and pharmacy. Despite her best intentions, however, it didn't work. "We weren't getting [minority and disadvantaged] students," she recalls. They were washing out of the educational system long before they got to college. "And we weren't keeping the ones we did attract."

After this disappointing start, Chester rethought her approach and set new goals. She wanted to reach students at a younger age to support their interest in science and give them confidence in their own abilities to succeed. The program had to reach back into the high schools. And it had to root itself in the communities it served, not at the university in Morgantown.

With her new vision and determination to change the status quo, Chester, like other visionary educational mavericks, put modest resources to work to make enormous changes. And that's exactly what HHMI hopes its grantees will do with its funding. "We want to plant seeds that will grow into a new and more effective kind of science education," says Peter J. Bruns, HHMI vice president for grants and special programs.

With the blessing and guidance of Robert M. D'Alessandri, vice president of WVU's Health Sciences Center, Chester crafted a plan for the Health Sciences and Technology Academy (HSTA), including after-school science clubs in local communities plus a summer program on the WVU campus, where high school students could work in research labs and meet potential role models.

WVU won a competitive $175,000 grant from HHMI to establish HSTA in 1994 in Kanawha and McDowell counties. Kanawha, home to West Virginia's capital of Charleston, has a mostly urban population. McDowell, in the southernmost part of the state, is

"THEY TOLD ME I WASN'T COLLEGE MATERIAL" ANN CHESTER RECALLS. "THEY TOLD ME MY FUTURE HELD A JOB AS A SEAMSTRESS OR A GAS STATION ATTENDANT." HER RESPONSE WAS PREDICTABLE.

A Home on Campus

AT CALIFORNIA STATE UNIVERSITY, Long Beach (CSULB), the late Jim Jensen, then dean of the College of Natural Sciences and Mathematics, saw a need in the early 1990s for a place on campus that science students could call home. His vision was of a safe haven where students could feel they belonged and find a firm footing in the sciences, whether they were starting as freshmen or transferring—as many at CSULB do—from a community college. So he applied and received a $750,000 education grant from HHMI in 1991. JENSEN'S DREAM HAS GROWN into the James L. Jensen Student Access to Science and Mathematics Center, where entering freshmen can go on a "science safari," a weekend on-campus orientation program to introduce science-related campus resources and opportunities, and transfer students can learn about natural science majors at the university. Through the center, hundreds of students have found research opportunities and gotten advice about science careers from faculty and peer mentors. The center has become something of a science umbrella, coordinating eight student programs, including the National Institutes of Health-funded Access to Research Careers and Bridges to the Baccalaureate, and the National Science Foundation-funded Louis Stokes Alliance for Minority Participation.

mostly rural. Both counties have large percentages of economically disadvantaged people.

Steve Starks, publisher of a statewide minority newspaper and leader of West Virginia's African American community, jumped on Chester's bandwagon. "In HSTA, I saw hope for students who might otherwise fall by the wayside," he says. "I saw exposure to information that can put them in a position to succeed in life."

With Starks in her camp, Chester earned the trust of his constituents. She also reorganized the local boards that ran the programs in each county so that they might intimately involve parents, teachers, and community leaders.

"Ann was able to develop remarkable rapport with the African American community," says D'Alessandri. "She was able to identify community leaders, and she invited them to run their own programs. Ann works from a collaborative model, not a hierarchical one. She not only considers the opinions of those she's working to serve, she welcomes them."

The reforms quickly paid off. In 1995, the W.K. Kellogg Foundation added $2 million to the HSTA coffers, citing strong community-based support as a major factor in its decision to help fund the program. With this additional funding, Chester expanded HSTA to 10 of West Virginia's 55 counties.

But she wasn't satisfied. She kept applying for grants, building the program, and success bred success. Soon the Coca-Cola Foundation added another $200,000, and before long the Robert Wood Johnson Foundation, the Claude Worthington Benedum Foundation, and the National Institutes of Health joined in supporting HSTA. In 1999 and 2003, HHMI awarded new competitive grants to WVU's HSTA program.

Chester and her community-based boards even took on state government, approaching the West Virginia legislature with an audacious proposal: tuition waivers for HSTA students at state colleges and universities. It took three years and countless visits to legislators by HSTA students and their parents, but in 1997 the legislature unanimously approved tuition waivers at any state college, university, or professional school for any student finishing all four years of high school in the HSTA program.

Today, HSTA is active in 26 West Virginia counties, where 124 community residents serve as members of volunteer governing boards. Nearly 800 students and 80 teachers participate in local science clubs, an annual statewide research symposium, and summer programs at WVU and other West Virginia university campuses. Another 750—more than two-thirds of whom were the first in their families to go to college—have completed the program and are attending college, university, or graduate or professional school. In May 2006,

*"I FELT SURE THAT IF I BUILT SOMETHING THAT ADDRESSED [THE NEEDS OF STUDENTS WHO WERE MISSING OUT]," **DAVID BYNUM** RECALLS, "INSTITUTIONAL AND FINANCIAL SUPPORT WOULD FOLLOW." HE WAS RIGHT.*

Learning from Mistakes

SOMETIMES SEED MONEY CAN can serve a very different purpose—teaching educators what not *to do. Hope College in Holland, Michigan, wanted to involve minority middle and high school students in science. With a $750,000 grant from HHMI in 1991, it tried to develop a middle school recreation program, research clubs, and summer research on campus for high school students. "IT DIDN'T WORK VERY WELL, and we didn't get another HHMI grant, though not entirely because of our inability to sustain this effort," says James Gentile, then a biology professor and HHMI program director at Hope. "But we knew how important it was to reach minority students early. So we sat down and said, 'How can we do this more effectively, with less money?'" recalls Gentile, now president of the Research Corporation, a private foundation based in Tucson, Arizona, that supports college-level basic research in the physical sciences. HE CREDITS THE VISION AND INITIATIVE of Todd Gugino, director of Hope's chemistry laboratories, with helping the college shift gears and launch a science camp in 1998, initially funded through the parents of the students who participated. The camp has been such a hit with west Michigan kids and their families that almost 700 campers will attend this summer, many with scholarships underwritten by local companies and private donors, reports Gugino, who directs the program. "It is a wonderful example of staff working together to keep a vision alive until it could develop into a sustainable initiative that really works well in the Hope environment," says Gentile.*

HSTA students earned 68 bachelor's degrees, 10 master's degrees, and 3 doctorates. Emme Chapman, from remote Hodam Mountain, received the HSTA's first medical degree.

According to a 2006 study by the Bureau of Business and Economic Research at WVU, students who go through HSTA can expect to earn annual salaries on average almost $26,000 higher than their parents.

Turning On Students—and Teachers

WEST VIRGINIA ISN'T the only place where one person's resolve and a little seed money are changing lives. At the State University of New York, Stony Brook (now Stony Brook University), David Bynum found himself teaching biochemistry and cell biology in a community where enormous gaps existed between haves and have-nots, and the latter were largely absent from his classroom—and, more specifically, from science education and careers. Feeling a need to reach out to a more diverse group of potential science majors, he borrowed a lab to offer summer research opportunities to disadvantaged students at two nearby community colleges.

Using his first HHMI grant (awarded in 1994), Bynum then remodeled and outfitted two labs at Stony Brook specifically for his purposes. He developed a summer residential research program for students from three high schools in economically disadvantaged districts, and he turned another campus laboratory into a teaching center where middle and high school students could conduct hands-on biotechnology experiments. In the program's first year more than 4,000 students participated.

Bynum also created three courses and several workshops for biology teachers. Demand was so great for these courses that he sought and received New York State approval to offer a master's degree in biology teaching rooted in hands-on science. Eventually, he parlayed an HHMI grant of $1 million into more than $10 million in external funding and complete buy-in from the university.

"David is just phenomenal," says Shirley Strum Kenny, president of Stony Brook University. "It is incredible how he is able to bring kids to a love of science. He started small, and he built step by step. He's low-key and unassuming, but he knows where he wants to go, and he never wavers."

Bynum says he realized in the early 1990s that "science in the United States was grade A, while science education was more like a C. Improving science education and providing more opportunities for students who traditionally had missed out was clearly in the individual and national interest. I felt sure that if I built something that addressed those needs, institutional and financial support would follow. Besides, it's such satisfying work."

Bynum won the 2002 Presidential Award for Excellence in Science, Mathematics, and Engineering Mentoring. True to form, he used the $10,000 prize to generate more than $100,000 in fellowships for prospective science and math teachers who do their student teaching in districts designated "high-need."

More than 80 percent of the 127 school districts of Long Island (where Stony Brook is located) now participate in Bynum's programs.

Kenny credits it all to Bynum: "He is growing our scientists of the future." ■

A Role Model Who Brings Snacks

HOLLY MITCHELL GREW UP IN CHELYAN, West Virginia (population 950), where her father worked for Appalachian Power and her mother was a homemaker. Holly wanted to go to college, but she didn't see how. Her parents never had, and money was tight. As a freshman in high school, Mitchell heard about a new science club and decided to check it out. At monthly meetings, she and her classmates in the Health Sciences and Technology Academy's (HSTA) first program learned about health, nutrition, and exercise. "We did cool science projects and had amazing cultural experiences," says Mitchell. She'll never forget the club's trip to the National Great Blacks in Wax Museum in Baltimore, for instance, her first time that far from home without family.

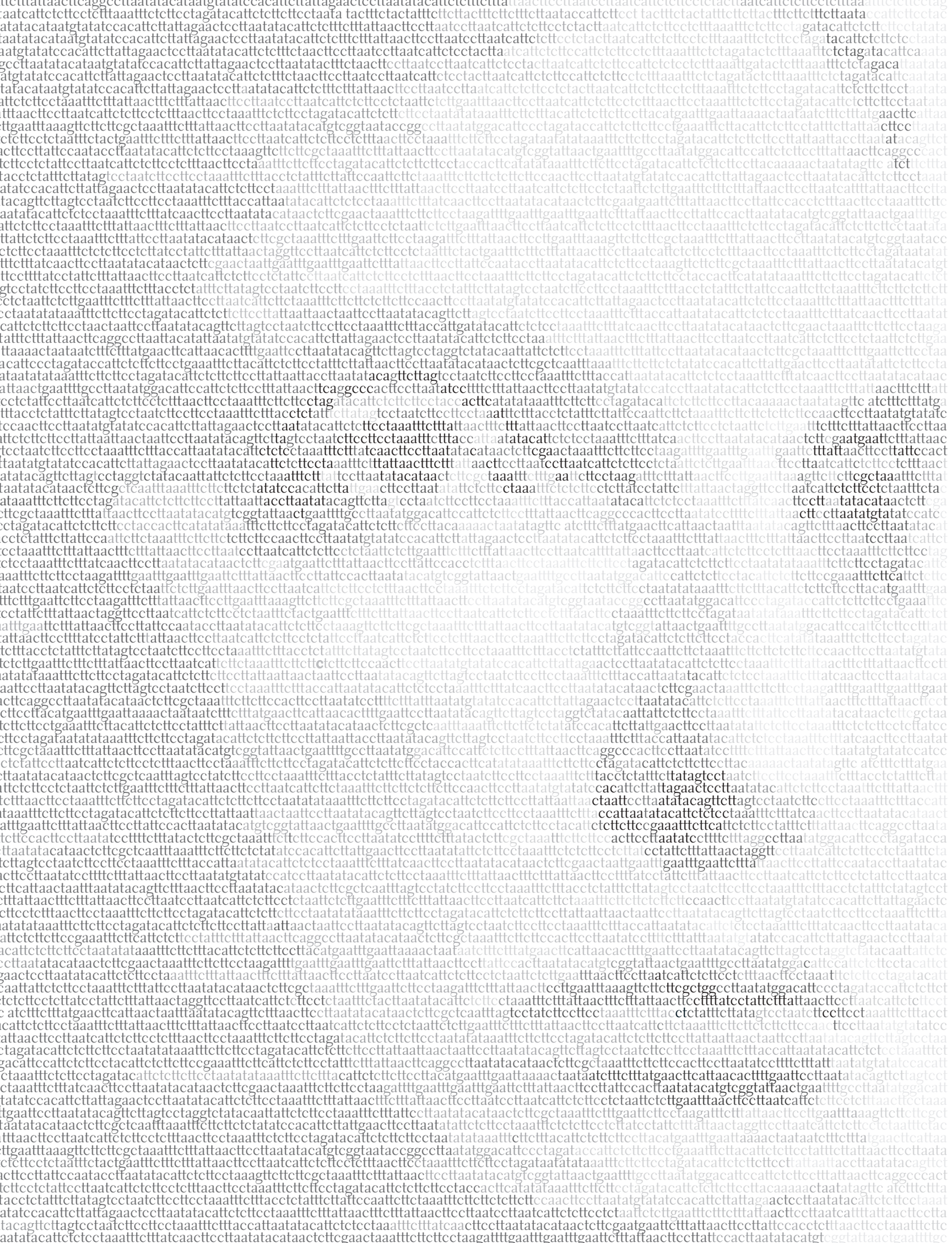
"HSTA TAUGHT US TO BE ACCOUNTABLE for our own success," she says. "We learned to say 'when I go to college,' not 'if.'" And HSTA showed them what college was like. Mitchell spent two summers on the sprawling campus of West Virginia University (WVU) in what she calls "the big city of Morgantown," taking classes, working in labs, talking with scientists and health-care professionals, and living in the dorms. By the time she graduated from high school in 1998, the West Virginia legislature had passed a tuition waiver that enabled her to enroll at WVU. "It wasn't even scary," she recalls. "I'd been there before; I knew my way around." MITCHELL MAJORED IN PSYCHOLOGY and earned a master's degree in public health. She felt so strongly about HSTA and its mission that she returned to Kanawha County to serve as an HSTA field-site coordinator, just a few miles from her childhood home, helping the younger brothers and sisters of her HSTA classmates find ways to achieve their own dreams. "I just treated them with respect and helped them find resources," she says. "Sometimes I also brought snacks." SHE RECENTLY CHANGED JOBS, moving to the Center for Organ Recovery and Education, serving southern West Virginia, educating hospital staff and their communities about organ donation. "I would never have had the confidence and networking skills to do this if I had not been part of HSTA," she says.

A Better Crystal Ball

personalized medicine promises a new level of clarity with treatments tailored to one's genes but it hinges on development of exacting gene-based tests

BY MAYA PINES

PHOTOGRAPHS BY NOAH WEBB AND PAUL FETTERS



"What's your genetic subtype?"

This sounds like a futuristic pick-up line, but it is actually the key question for researchers focused on "personalized medicine," tailored specifically for each patient's genes. They believe that, within a few years, tests to reveal patient subtypes will become part of the routine evaluation of disease.

Such tests can already show how rapidly or slowly a person metabolizes drugs, for instance, helping doctors prescribe doses that are large enough to be effective, yet not so large as to cause harm in a particular patient with heart disease, depression, or schizophrenia. Other gene-based tests can indicate whether a patient with an early tumor really needs to undergo chemotherapy—with its many side effects—after surgery. One test may soon detect the first signs of a particular cancer in a patient's blood before any symptoms appear and in time for a definitive cure by surgery.

Some of these tests will save money in the long run. Others will lead to expensive new drugs (some have already) that are targeted to specific subtypes of patients—drugs that not every patient can afford. "This is an enormous and challenging issue," says Kenneth Offit, chief of the Clinical Genetics Service at Memorial Sloan-Kettering Cancer Center in New York City. He recently took part in an Institute of Medicine conference where, he notes, several speakers emphasized the need for "more evidence-based reviews and more cost-benefit analyses to inform the discussion of access to molecular medicine."

Offit is one of many optimistic researchers who are convinced that the overall effect of gene-based tests will be to make treatment more efficient and effective, reducing the instances in which people take drugs that don't work.

"We now know that certain drugs work only in a particular subset of patients," says Charles L. Sawyers, an HHMI investigator at the University of California, Los Angeles (UCLA), "but we don't yet know how to identify subsets in an easy way." This is why Sawyers and other researchers are busy ferreting out differences in patients' genes, then using these distinctions to stratify people into smaller and smaller subgroups, each of which responds to drugs in its own particular way. This approach has already changed how certain diseases are treated, at least in leading hospitals and research centers. At the same time, it is inducing drug companies to take account of subtypes as they develop and test new treatments.

The fruits of personalized medicine are most evident in cancer. Sawyers's own work has helped revolutionize the treatment of chronic myeloid leukemia (CML) by aiming the precisely targeted and highly effective Gleevec (imatinib), and now the recently approved drug Sprycel (dasatinib), at specific genetic mutations in the cancer (see sidebar, pg 37). Research by others has revealed the genetic mutations that make the drug Herceptin (trastuzumab) effective against certain types of breast cancer, and Iressa (gefitinib) effective against a small subset of lung cancers. New tests for these mutations can identify who is most likely to benefit from these costly drugs—and who should try something else, saving valuable time and expense as well as reducing unnecessary toxicities.

While there is growing excitement among researchers about the promise of personalized medicine, only a handful of gene-based tests are in wide use at present. "Why does the community oncologist in middle America generally not use such tests?" asks Todd R. Golub, an HHMI investigator who directs the cancer program at the Broad Institute of Harvard University and the Massachusetts Institute of Technology in Cambridge, Massachusetts. "That's simply because most of the early molecular genomic tests that are predictive of response to treatment have now gone into the black hole of validation—and have yet to emerge."

Many of the initial reports of gene-expression profiles that could identify subtypes of cancer

Simplified, Early Diagnostics

The current gold standard for colon cancer detection is colonoscopy, an invasive and unpleasant procedure that many people avoid. The more widely used fecal occult blood test, designed to detect blood in the stool, catches only about 30 percent of colon cancer cases. Malignant tumors do not always bleed. **For the past decade**, HHMI investigator Bert Vogelstein and his colleagues at the Johns Hopkins University School of Medicine have sought ways to detect specific alterations of DNA in patients with very early colon cancer—first in the patients' stool cells (one test he developed to detect DNA alterations in stool samples became available in 2003), and now in blood. "**In colon cancer**, the genetic mutations are well known," points out Vogelstein, who played a major role in discovering them. So he began the ambitious project of looking for fragments of the cancer-causing gene, *adenomatous polyposis coli* (*APC*), in samples of blood. With the aid of a technique called BEAMing, in which DNA fragments of a cancer gene are attached to metal beads and amplified, he found tiny samples of *APC* in blood drawn from patients with colon cancer. He has evidence that such fragments are released into the blood when white cells destroy dead tumor tissue. **Pilot studies of Vogelstein's** experimental blood test showed that it easily identified people with advanced colon cancer and could even detect more than half of those whose cancers were in the early stages at which they could be cured by surgery—without the need for chemotherapy. "We could still find fragments of the mutant DNA in their blood, but fewer of them," says Vogelstein. "They were detectable in more than 60 percent of the early-stage patients." This could save hundreds of thousands of lives every year among people who do not undergo colonoscopies. He hopes the test will eventually become more sensitive; more advanced versions are being developed. Vogelstein expects patient compliance, once the test becomes available, to be much higher than for other tests, "because most patients routinely have blood drawn when they visit their physicians." **He adds**, "This type of blood test might apply to other early cancers, as well. That's one of the reasons we're excited about it."

were based on only tens or perhaps hundreds of patients. "Before routinely implementing them in the clinic, we need to make sure they really hold up in many other patients and many other places," Golub says. "This takes a lot of time and effort."

A few tests have gone through more extensive validation, he says, and are available commercially to physicians. Among them are predictive tests for breast cancer recurrence, such as the Oncotype DX test in the United States and MammaPrint in Europe.

INFORMED DECISIONS

The Oncotype DX test focuses on 16 specific genes related to the molecular behavior of breast cancer cells in tumors removed from women with early breast cancers that are fueled by estrogen, giving each patient a score from 0 to 100. The higher the score, the greater the danger the cancer will return. Researchers at Genomic Health, Inc., of Redwood City, California, found these 16 genes to be *least* active in the tumors of patients who survived 10 years without a relapse. The very same genes were *most* active in the tumors of patients who had suffered bad outcomes.

At New York University School of Medicine, oncologist Ruth Oratz uses the test, and it has changed the way she treats some of her patients. Recently, a woman who looked like a good candidate to receive only hormonal treatments after her breast surgery and radiation—she was older, had a very small tumor, and no signs of cancer cells in the lymph nodes under her arm—was, according to the Oncotype DX, at very high risk of having a recurrence. "So she was given chemotherapy in addition to the hormonal treatment," Oratz recalls. The test has made the pendulum swing the other way as well for some of Oratz's patients, leading them to forego aggressive chemotherapy when the test score was very low.

About 7,000 Oncotype tests were performed in 2005. Many insurers refused to reimburse the $3,460 cost because they were not convinced of the test's merits. The test received so much support from oncologists, however, that early this year Medicare decided to cover the cost for its beneficiaries. Several private insurers have begun covering it too.

Another widely accepted test called AlloMap, devised by XDx, Inc., in South

Noah Webb

"many drug companies have concluded that they must incorporate genetic tests into their drug trials."

CHARLES SAWYERS
HHMI INVESTIGATOR
UNIVERSITY OF CALIFORNIA, LOS ANGELES

Paul Fetters

"the first challenge is to discover the inherited or acquired alterations in DNA that are responsible for a disease. In most cancers, these have not yet been discovered."

BERT VOGELSTEIN
HHMI INVESTIGATOR
THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

San Francisco, recognizes the earliest steps of rejection in heart transplant patients by measuring the activity of 11 immunology-related genes. Thanks to this test, patients can now avoid many of the frequent and unpleasant heart biopsies they had to undergo to look for signs of rejection.

Tests like these may be useful, but they fall short of revealing the cause of a disease, and they don't provide any leads to better treatments. The real bottleneck in personalized medicine, according to Golub, is still a lack of specific knowledge. "We need to know more about the molecular underpinnings of a disease so we know exactly what to measure in a patient," he says. "We also need a mechanism to actually measure these molecules in a clinical setting before deciding on a treatment." He calls for "more effort in early discovery."

Bert Vogelstein, an HHMI investigator at the Johns Hopkins University School of Medicine, agrees. "The first challenge is to discover the inherited or acquired alterations in DNA that are responsible for a disease," he declares. "In most cancers, these have not yet been discovered. Only a small fraction of the alterations that contribute to breast, prostate, lung, or other common cancers have been identified. So we act like the drunk who looked for his keys, not where he lost them, but under a lamp, where the light was good. Many other places might be better."

He also complains that, "almost all 'translational' research funds now go to find new therapeutics. This is not optimal," he says. "Our best hope for reducing sickness and death—and health care costs—is through prevention and early detection, rather than therapies." Vogelstein's own research has focused on early detection of cancer (see sidebar, pg 34). "One difficulty is that if you learn how to detect a cancer at a stage when it can be cured by surgery or something simple, you have to screen 100 or 500 patients to find one that you catch early," he says. "This is not nearly as dramatic or sexy as taking a sick patient with more advanced disease and putting him or her in remission. But remember that this one patient [whose disease is caught early] will be completely cured of the cancer and won't ever die from it!" By contrast, "drugs put cancer patients in

remission only for a period of time—often a surprisingly short time, and they are surprisingly expensive."

GOOD FOR BUSINESS

Meanwhile, gene-based tests are becoming a big business. "There are about 1,000 gene-based tests that you could get today," says Kathy Hudson, director of the Genetics and Public Policy Center at Johns Hopkins. She notes that "only a dozen of them have been reviewed and approved by the U.S. Food and Drug Administration (FDA)," and wishes the government would give more attention to the validity of such tests.

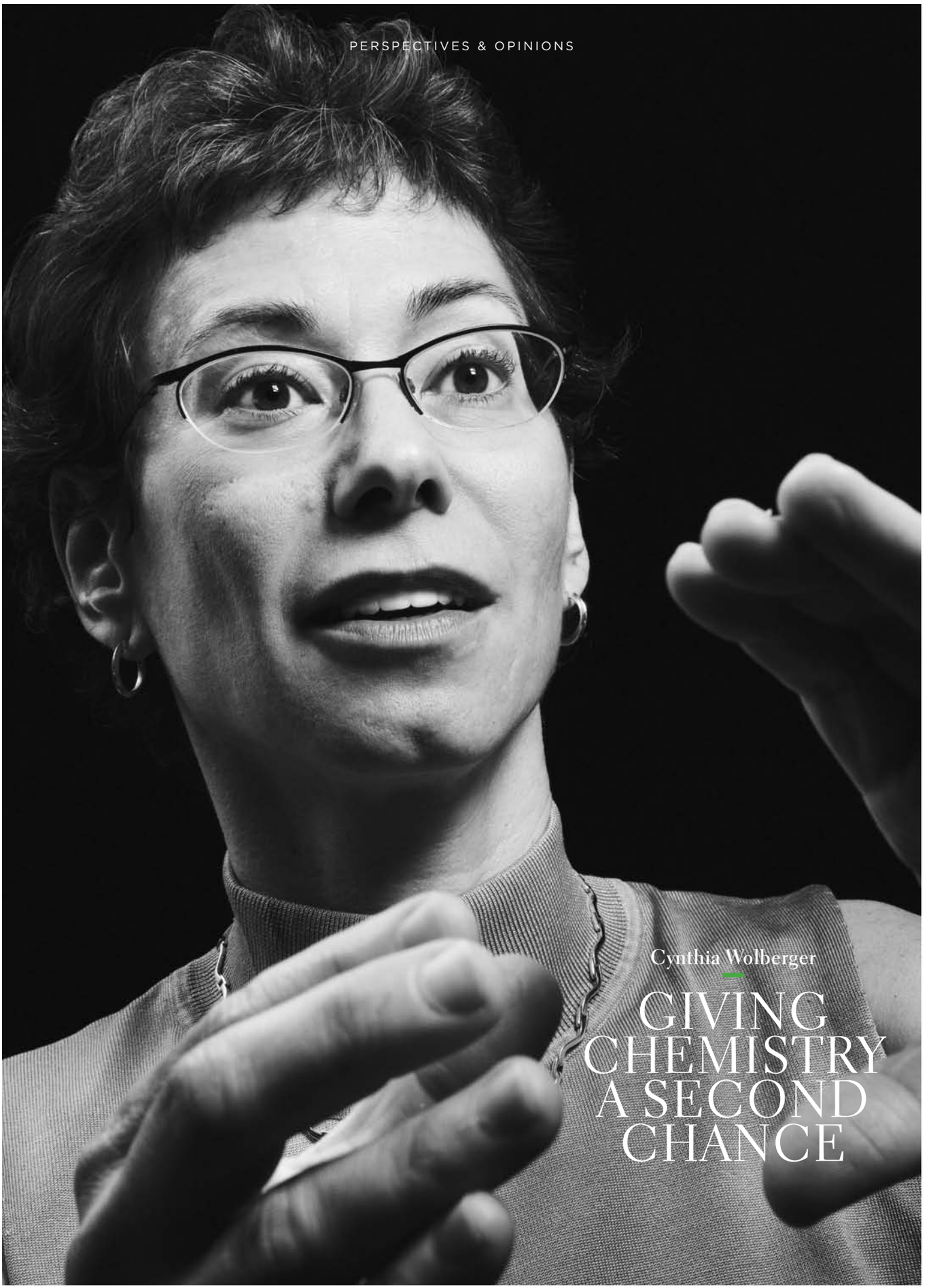
The FDA may be paying more attention. Drug companies are joining the rush to stratify patients according to their genes, and they're doing it with the blessing of the FDA, says Edward Abrahams, executive director of the Personalized Medicine Coalition, a Washington-based public-interest group. He notes that in March 2005 the FDA started asking drug companies to voluntarily share information on how specific subtypes of patients respond to the drugs submitted for review. Since then, more than 25 companies have submitted such data.

Not surprisingly, "many drug companies have concluded that they must incorporate genetic tests into their drug trials," says UCLA's Sawyers. That was his experience with Bristol-Myers Squibb, the maker of dasatinib. There had been a lot of debate about the usefulness of genetic tests in drug development, he says, "but now most parties agree that it's a good thing. The cost of drug development should go way down when you do clinical trials with the right subgroup of patients. You get faster approval, and you can go on to develop more drugs."

Insurance companies will have to come along as well, to pay for the new gene-based tests, Sawyers contends, "because these tests will guide the treatment. Insurers could avoid paying treatment costs for all patients, when in fact the treatment might help only a fraction of them." Abrahams adds that "the growing link between therapy and diagnostics" (in the form of gene-based tests) is the key to the future development of personalized medicine. "The tipping point," he says, "will come when patients refuse to accept what they often get now—trial-and-error medicine." ■

Personalized Medicine Made Real

Progress against chronic myeloid leukemia (CML), using Gleevec to halt the cancer where it starts—and now the drug Sprycel (dasatinib) when drug resistance takes hold—is "proof of principle" that personalized medicine can work, according to HHMI investigator Gary Gilliland, a cancer researcher at Brigham and Women's Hospital in Boston. "Once it is demonstrated that a specific genetic mutation causes a cancer, as for the *BCR-ABL* mutation in CML, you can reliably predict that patients will respond to its inhibitors, such as imatinib – and there are rational strategies to overcome resistance to imatinib if it develops." **In patients with CML,** the abnormal fusion gene, *BCR-ABL*, leads to an overactive form of the ABL kinase, an enzyme that regulates cell growth and differentiation. The abnormal kinase makes white blood cells grow out of control; it is fundamental to the cancer itself. Gleevec, a drug pioneered by HHMI investigators Brian J. Druker, at Oregon Health & Science University, and Charles Sawyers, at the University of California, Los Angeles, blocks ABL kinase activity, and was approved by the FDA in 2001 for CML. **Far more effective** than most other chemotherapy because it is targeted so precisely, "Gleevec puts 80 percent of patients into complete remission," says Charles Sawyers. That is a huge improvement for a disease that was once uniformly deadly. Gleevec was not the end of the story, however, because patients—about 4 percent a year—eventually develop resistance to the drug and relapse. "Three-fourths of patients are still doing well in their seventh year of therapy," Sawyers says. "But in 20 years, most of them would be expected to relapse." **Determined to solve** this problem, Sawyers teamed up with John Kuriyan, a crystallographer and HHMI investigator at University of California, Berkeley, and showed that patients whose cancer resisted Gleevec had a special subset of genetic mutations that made their kinase too rigid, keeping it in the "on" position at all times (Gleevec binds to ABL kinase only when it's in the "off" position). They began to search for a "sloppier" drug that might bind with the ABL kinase in any position, and Bristol-Myers Squibb turned out to have a good candidate, called dasatinib. **In the June 15** issue of *The New England Journal of Medicine*, Sawyers announced that dasatinib produced excellent responses in a phase 1 study. So far it has been tested only in patients who relapsed after Gleevec, but Sawyers says, "It may prove even better than Gleevec—it is much more potent and has a broader reach." In late June, the FDA granted accelerated approval for marketing of the drug under the name Sprycel for CML patients who have relapsed from or cannot tolerate Gleevec. It was also approved for certain patients with acute lymphoblastic leukemia. **Dosages of the new** drug were fine-tuned for each patient based on detailed studies that examined how well the drug inhibited its target—a technique that was pioneered by Sawyers's group for use in earlier studies in mice. In addition, each patient's resistance-enhancing mutation was sequenced by Bristol-Myers Squibb scientists. This allowed the researchers to correlate how the drug responded to each type of mutation. "**Every single patient** who was predicted to be sensitive to dasatinib based on the genotyping studies had a clinical response," Sawyers says. **This shows that all** CML patients could be genotyped (have their genes analyzed) to decide whether their condition will respond to these molecularly targeted drugs. Genzyme's new *BCR-ABL* Mutation Analysis test is already available to physicians, Sawyers notes, and "in leukemia, the tumor is in the blood, so it is easy to test for."



Cynthia Wolberger

GIVING CHEMISTRY A SECOND CHANCE

Paul Fetters

Structural biologist Cynthia Wolberger has spent much of the last decade trying to understand the behavior of Sir2 enzymes, also called sirtuins, which affect gene expression, metabolism, and aging. The key to understanding Sir2's biology, says Wolberger, an HHMI investigator at the Johns Hopkins University, is its unusual chemistry. To dig deeper, she dusted off her college notebooks and made some new friends.

What is it about Sir2 that caught your attention and inspired you to expand your knowledge of chemistry?

My lab has always concentrated on gene regulation, especially on proteins that bind DNA and control transcription. I was thinking of further aspects of transcriptional regulation that might be amenable to the tools of structural biology—my field—when I encountered sirtuins. I focused on the Sir proteins because they can shut down whole regions of a chromosome and turn off all genes located there. Sir2 in particular stands out because it makes life more difficult for itself. Instead of taking a more direct route to cleaving the appropriate molecules, it uses a more complex, energy-costly method. I wanted to explore the unusual chemistry of this process. When nature doesn't settle on the most efficient pathway to carry out a particular task, there must be a reason. Understanding Sir2's unique chemistry will be key to understanding its function and regulation. And the fact that it is universal—all organisms have at least one, if not several, sirtuins—means that its chemistry is important to all forms of life.

In what ways are you learning the chemistry you need?

Having had only the courses that most people took in college and graduate school—maybe fewer, as my background is in physics and biophysics—I'm basically playing catch-up. So I've been getting an education in chemistry and enzyme mechanisms in a number of ways, including by doing it. I asked my students to recommend some textbooks on enzyme mechanisms. I keep them here on my desk. This is a switch for me. When I first presented my work on these enzymes at an HHMI meeting, a friend came up to me afterward and said, "I can't believe you talked about enzyme mechanisms. As a student, you used to say it was so boring." It's true. My focus was thermodynamics. I was actively uninterested in chemistry back then. But it turns out to be the heart of the matter. Even though I was dragged into it by the necessities of my work, now I'm fascinated by it. Why does this enzyme do this baroque chemistry, how does it do it, and how is it being exploited by the cell? I spend time talking to different people as well. Now I tend to gravitate to enzymologists at meetings. This bouncing of ideas off people who have thought about enzyme chemistry for years has proven invaluable. Like anything in science, if there's something you need to learn, you go and learn it. A good scientist is a lifelong student.

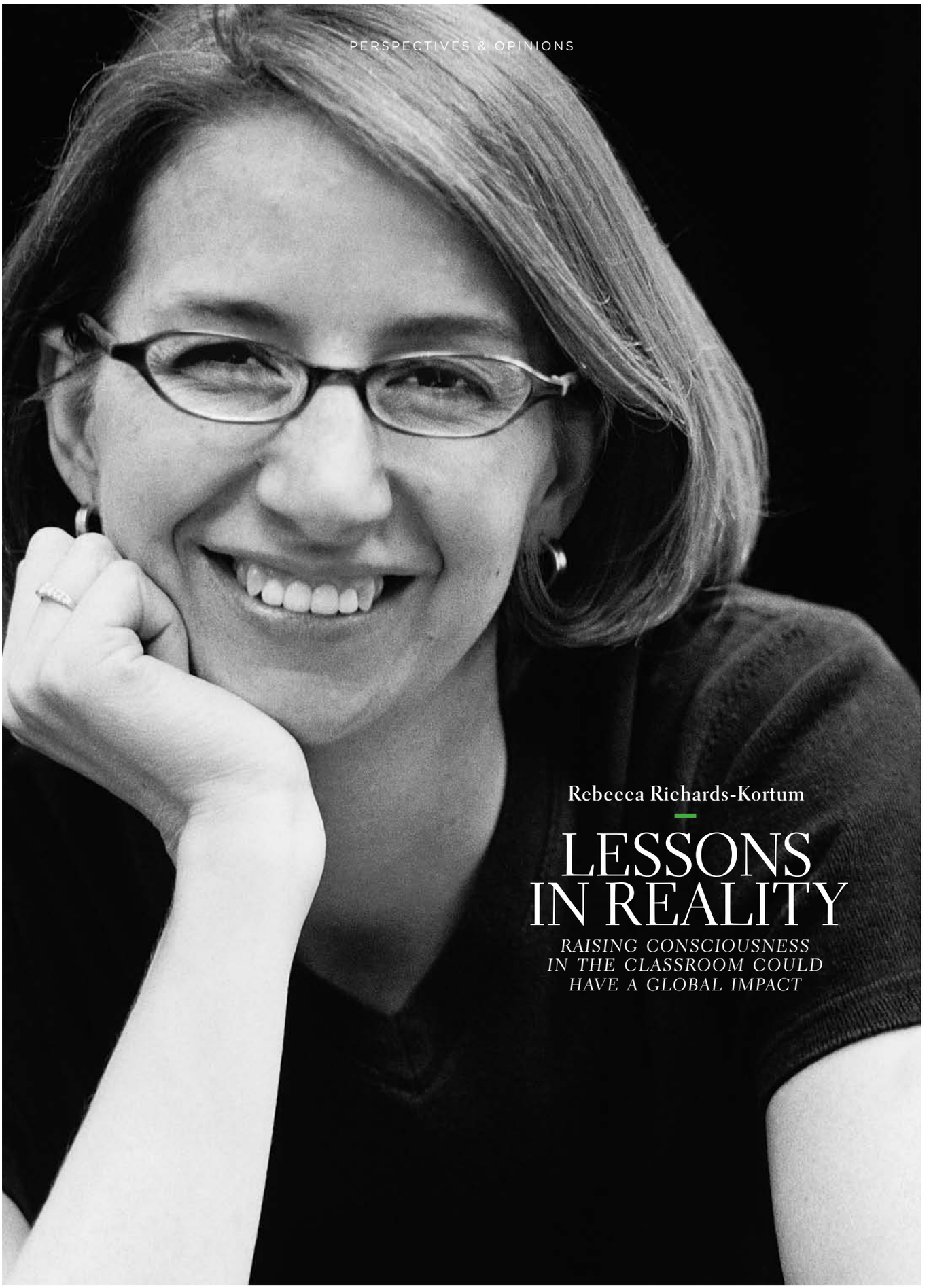
How are you applying your new dexterity in chemistry and enzymology?

In my lab, we are learning about Sir2's chemistry in particular by visualizing structures of enzymes bound to a variety of substrates and intermediates, and by trying to trap the enzyme in the crystal at different stages of the reaction. Also, we are using proteomics approaches to identify new substrates and to characterize the substrate requirements for the reaction. That, together with standard enzymology of normal and mutant proteins, allows us to put together a picture of how sirtuins work.

What is the payoff?

Besides just understanding the fundamental nature of this fascinating chemistry, there are implications for human health. One sirtuin, SirT1, seems to regulate the p53 tumor-suppressor pathway. Sirtuins have also been implicated in the insulin-signaling pathway in diabetes. In lower organisms such as yeast, losing a copy of Sir2 shortens life span and getting extra copies of the enzyme makes them live significantly longer. Restricting calories extends life span in many organisms, including mammals (though it's never been proven in humans), and Sir2 may mediate that process. Much remains to be learned about Sir2's potential role in longevity. We're constantly finding out new things about them. Giving chemistry a fresh look is a big help.

INTERVIEW BY STEVE BENOWITZ. *Cynthia Wolberger is Professor of Biophysics and Biophysical Chemistry at the Johns Hopkins University School of Medicine.*



Rebecca Richards-Kortum

LESSONS IN REALITY

RAISING CONSCIOUSNESS IN THE CLASSROOM COULD HAVE A GLOBAL IMPACT

Keith Carter

As an HHMI professor, Rebecca Richards-Kortum gives students the same early exposure to research that influenced her career. Thanks to the generosity of a college physics professor, she got a year-long taste of laboratory research. Kortum liked the work but knew she "wanted to do something to impact humanity in a much more direct way." Today, her research program at Rice University blends bioengineering with real-world health care. Kortum's special interest is building science savvy in the classroom.

Every year, nearly 10 million children in developing countries die before they turn 5. Experts believe that about two-thirds of those deaths could be prevented with technologies that are feasible to implement in low-income countries. But transferring the benefits of research from developed countries to developing countries really requires a new way of thinking—one that incorporates technology development as well as public policy and management of health care delivery. These issues were the inspiration for "Bioengineering and World Health," a college course I developed as part of my HHMI professor grant.

The course provides an overview of the major health challenges facing both developed and developing countries, using case studies to illustrate how new technologies can solve these problems in cost-effective ways. I think that students come away with a much better understanding of how precious health care resources are distributed in the world and how to make better decisions about their own health care.

While we designed the class for non-science majors, we found that it drew a broad audience, including science and humanities students. The diversity within the group brings interesting perspective to our discussions. In one assignment, for instance, students read a *New Yorker* article by Michael Specter about the scientific and ethical challenges associated with testing an HIV vaccine in Uganda. In class, we hold a town meeting to debate whether to take part in a clinical trial of the vaccine. Students play the roles of Ugandan citizens or the different scientists and policy makers quoted in the article.

Some promote the views of Marcia Angell, former editor of *The New England Journal of Medicine*, who strongly opposes research that doesn't uphold Western ethical standards. She advocates, for example, providing treatment for all trial participants who stand to later develop HIV/AIDS, a policy that is virtually impossible in Africa, given the financial and infrastructure limitations. Others put forth the views of Edward Mbidde, director of the Ugandan Cancer Institute, who asks, "If we need to go to work and we cannot afford a Mercedes Benz, should we refuse to ride a motorcycle?" As one anthropology student pointed out, it's difficult to teach people who may have a limited concept of Western medicine about how a vaccine works. Another student—one who grew up in Africa—described how the culture of hope might affect attitudes about participating in research.

The course also explores how technologies move from the lab to the bedside. One example draws from my own research, which focuses on developing small, inexpensive microscopes designed to detect cervical cancer at its earliest possible stage. Last summer, students from my lab went to Nigeria to help conduct preliminary trials of these microscopes with my long-time collaborator, Michele Follen, a gynecologic oncologist from the University of Texas M. D. Anderson Cancer Center. Cervical cancer is the leading cause of cancer death among women in developing countries, but it's completely curable when detected in the early preinvasive stage.

We have preliminary evidence that the course helps boost scientific literacy. A group of undergraduates—half had taken my class—read and discussed an article from *USA Today* about gene therapy for lung cancer. We videotaped the discussions and tallied the number of health care assessment terms they used. Health care literacy rates were twice as high among the students who had taken the class compared with those who had not.

Given that as many as half of Americans mistakenly believe that surgery can spread cancer, and that one in four thinks there's already a cure for cancer but it's being withheld by profit-driven industry, it's clear we need to increase awareness of health care issues so that they may be addressed more realistically and with greater effect.

Based on our initial success, we have begun to transform our undergraduate educational programs at Rice to more broadly meet this important need. A new program, "Beyond Traditional Borders," supported with an undergraduate science education grant from HHMI, will create a multidisciplinary educational concentration in global health. The program will feature an innovative curriculum using biotechnology and bioengineering to confront international health challenges.

INTERVIEW BY JULIE CORLISS. *Rebecca Richards-Kortum is Stanley C. Moore Professor and Chair of the Bioengineering Department at Rice University.*

Q&A

What field of science do you struggle hardest to understand?

Students aren't the only ones who may find science challenging. Scientists themselves wrestle with particular aspects — even entire fields — of science. Here, four HHMI investigators reveal some of the things that stump them. Where is the late, great astronomer Carl Sagan when you need him? – EDITED BY KATHRYN BROWN

Natalie G. Ahn

ASSOCIATE PROFESSOR OF CHEMISTRY AND BIOCHEMISTRY, UNIVERSITY OF COLORADO AT BOULDER

"There are many fields that I find difficult, but at the moment I am struggling to understand neural networks and machine-learning algorithms. The applications of computational sciences to biological problems are tantalizing, but their language, conceptual processes, strategies for validation, and controls are very different from those of experimental biology. Luckily, we have good collaborators to interact with, but we do spend a lot of time just trying to figure out if we're really talking about the same thing!"

Nipam H. Patel

PROFESSOR OF INTEGRATIVE BIOLOGY AND MOLECULAR CELL BIOLOGY, UNIVERSITY OF CALIFORNIA, BERKELEY

"For me, bioinformatics is now particularly challenging. With the current flood of genome sequencing and analysis, researchers are drowning in data. Although scientists have found countless molecular differences between even closely related organisms, it's difficult to know how to sort through all these data and then build on them with further experiments that really capture evolution at the molecular level and explain the diversity of life."

Helen M. Piwnica-Worms

PROFESSOR OF CELL BIOLOGY AND PHYSIOLOGY, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE IN ST. LOUIS

"Discussions about the big bang and related topics come up in social gatherings with close professional colleagues or when my children ask me questions related to the origins of life. But cosmology is a field that is not intuitive to me. Theories like the big bang create uncertainty in my world ... in a Heisenberg sort of way."

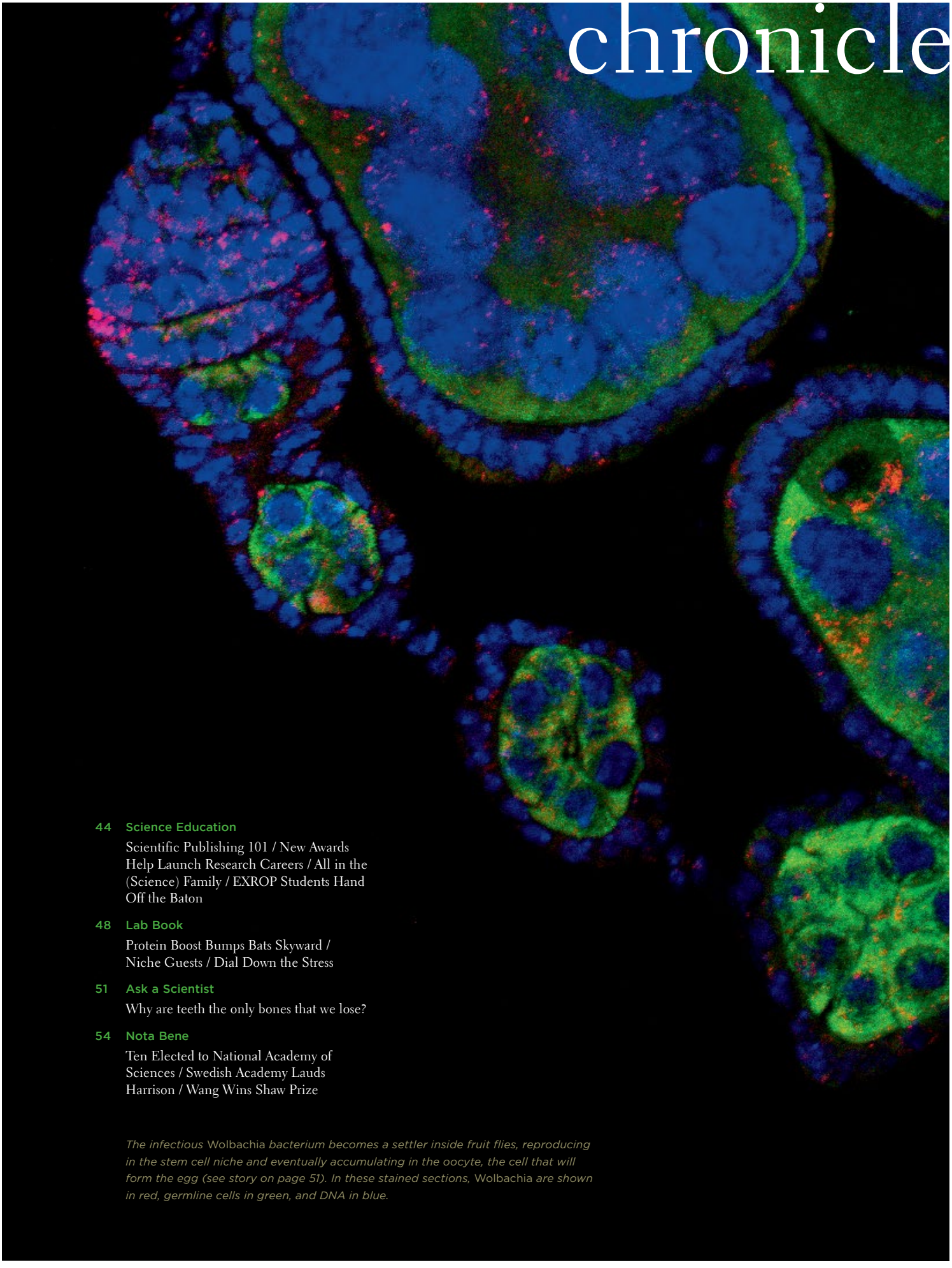
Morgan Sheng

PROFESSOR OF NEUROSCIENCE, MASSACHUSETTS INSTITUTE OF TECHNOLOGY

"Astronomy is the hardest for me to understand, due to my weakness in math and physics. Still, concepts like 'black holes,' 'supernovae,' and 'big bangs' are intellectually seductive and hard to resist. It is also healthy to feel 'small' sometimes, and nothing makes you feel small like the universe."

Ahn: Paul Fetters Patel: Todd Buchanan Piwnica-Worms: Mark Katzman Sheng: Jason Grow

chronicle



The infectious Wolbachia *bacterium becomes a settler inside fruit flies, reproducing in the stem cell niche and eventually accumulating in the oocyte, the cell that will form the egg (see story on page 51). In these stained sections,* Wolbachia *are shown in red, germline cells in green, and DNA in blue.*

Scientific Publishing 101

UNDERGRADUATES OCCASIONALLY MANAGE TO PUBLISH THEIR RESEARCH IN PROFESSIONAL JOURNALS, BUT NOW THEY HAVE A SET OF OUTLETS ALL THEIR OWN.

WHEN ALABAMA NATIVE CODY LOCKE headed to Tuscaloosa for college, he had never heard of molecular biology or even read a scientific paper. Four years later, Locke was finishing a major in biology and editing a research journal.

Locke, an HHMI undergraduate research intern, served as the editor-in-chief of the undergraduate *Journal of Science & Health at the University of Alabama (JOSHUA)* for two years and created the online version. As a sophomore, Locke jumped at the chance to get involved. "Professional journals really help further science, and I thought an undergraduate one could do the same by allowing students to learn more about different fields." Plus, he jokes, "I had papers I wanted to publish!"

Thanks to the enterprise of students like Locke, undergraduates have several opportunities to share their research in journals created by and for their peers. Students are involved at every step: writing, designing, fundraising, and even delivering.

By their very nature, these journals face unique challenges—deadlines scheduled around exams, staff turnover as students graduate, and competition with other campus activities. Locke, doing the bulk of the work, usually solicited submissions in late spring and reviewed, edited, and published the 50-page annual journal during the summer.

Despite the challenges, the journals thrive. UA undergraduates outside the biological sciences expressed interest in contributing, so *JOSHUA* started accepting articles from computer-science, physics, and engineering majors. Locke, who relinquished the editing reins before graduation, says the journal now receives enough submissions to publish multiple times a year. The articles, authored equally by male and female students, primarily describe research methods, present literature reviews, or offer perspectives on controversial issues like human embryonic stem cell research and teaching evolution. Locke says, "The journal lets the public see what students are really thinking about science."

> "The journal lets the public see what students are really thinking about science."
>
> CODY LOCKE

Alabama college students aren't the only ones getting involved. Cornell University senior Kevin Hwang started *The Triple Helix (TTH)* in 2005 as a forum for interdisciplinary ideas that intersect science, society, and law. As soon as it appeared at Cornell, Hwang says, students at other universities wanted in. So he created more than a dozen chapters in the United States and Europe (with a handful more under way) that publish local versions of the national publication.

The Journal for Young Investigators (JYI), the brainchild of five students, posts peer-reviewed research and feature articles by undergraduates, regardless of institutional affiliation. Faculty advisers critique the research articles while professional writers edit the feature stories.

Even as these student journals flourish, some observers question their value. With

The Spring 2006 issue of The Triple Helix *features articles on several hot-button topics, including "the birth of the artificial womb" (from a student at Hopkins), "pot and politics" (UC Berkeley), and "homosexuals and the national blood supply" (U. Penn).*

Courtesy of The Triple Helix, Inc.

New Awards Help Launch Research Careers

HHMI named 13 winners of its first Physician-Scientist Early Career Award Program. The grants provide $150,000 over three years to promising physician-scientists in their early years as tenure-track faculty members at academic medical centers.

These awards are designed to encourage alumni of HHMI's two physician-scientist training programs to continue to pursue their interest in research after they receive their M.D. or M.D.-Ph.D. degrees. One of these programs, the HHMI-National Institutes of Health (NIH) Research Scholars Program, enables medical or dental students to spend a year doing research in laboratories at NIH. The other program, the HHMI Research Training Fellowships for Medical Students Program, allows medical or dental students to conduct full-time research at any academic institution in the United States, except NIH.

Only alumni of these HHMI programs are eligible to apply for the Early Career Awards, which will be given annually.

The awards support individuals who have obtained full-time, tenure-track faculty positions. The money must be used for direct research expenses. The grants may not be used to replace or supplement salaries, start-up costs, or research expenses that would otherwise be supported by the institution. Also, the awardees' institutions must agree to let them spend at least 70 percent of their time doing research.

THE INAUGURAL CLASS OF THE EARLY CAREER AWARD PROGRAM:

- Atul J. Butte, M.D., Ph.D. *Stanford University School of Medicine*
- Jayanta Debnath, M.D. *University of California, San Francisco, School of Medicine*
- Emad N. Eskandar, M.D. *Massachusetts General Hospital*
- John L. Hartman, M.D. *University of Alabama School of Medicine*
- Siavash Kurdistani, M.D. *David Geffen School of Medicine at UCLA*
- David Martin, M.D. *University of Washington School of Medicine*
- Vamsi K. Mootha, M.D. *Massachusetts General Hospital*
- Scott A. Oakes, M.D. *University of California, San Francisco, School of Medicine*
- Alfredo Quiñones-Hinojosa, M.D. *The Johns Hopkins University School of Medicine*
- Stelios M. Smirnakis, M.D., Ph.D. *Brigham and Women's Hospital*
- Kimberly Stegmaier, M.D. *Dana-Farber Cancer Institute*
- Jennifer F. Tseng, M.D. *University of Massachusetts Medical School*
- Catherine J. Wu, M.D. *Dana-Farber Cancer Institute*

the high caliber of student research at universities today, argues Jim Austin, editor of *ScienceCareers.org* (a career-resource project of the American Association for the Advancement of Science, AAAS), undergraduates should strive to publish in professional journals with more rigorous standards. "Students can practice by playing the real game," he says.

But, proponents counter, when major-league journals such as *Nature* publish only about 10 percent of the papers they receive, students can benefit from the "preseason training" of publishing in student journals. Biologist Guy A. Caldwell, who coordinates the HHMI Undergraduate Research Intern Program at UA and serves as faculty adviser for *JOSHUA*, argues that student journals serve a more fundamental role: "Seeing something like *JOSHUA* makes the act of doing and thinking about science real."

Taking part in the student journals also gives contributors the opportunity to explore career interests and the self-assurance to pursue them. Mary Patyten, who created and managed *JYI's* features section as an undergraduate and now writes full-time for the California Department of Fish and Game, says, "I would have been less confident going into this field without my *JYI* experience."

Hwang's and Locke's publishing know-how also has influenced their career plans. Hwang, whose *TTH* title includes "CEO," intends to continue down the entrepreneurial path by starting a biotechnology company. Locke hopes to be a researcher and, of course, edit a professional journal. ■ –EMILY CARLSON

STUDENT MAGAZINES AT A GLANCE

Journal of Science & Health at the University of Alabama
Debut: November 2002
Founders: Nabeel Ahmed Memon and Sarah Adair (UA '03)
URL: www.bama.ua.edu/~joshua/
Circulation: 1,000 copies annually
Funding: HHMI, National Science Foundation (NSF), UA

The Journal of Young Investigators
Debut: December 1998
Founders: Andrew Medina-Marino and Tim Sibley (Swarthmore College '98), George Lui and Brian Su (Duke University '98), Neal Freedman (Brown University '98)
URL: www.jyi.org
Circulation: Available only online; new research and feature articles appear monthly
Funding: AAAS, NSF, Burroughs Wellcome Fund, universities, other organizations

The Triple Helix
Debut: March 2005 at Cornell University
Founder: Kevin Hwang (Cornell University '07)
URL: www.thetriplehelix.org
Circulation: Each chapter publishes about 1,000 copies twice a year with some chapters also publishing online
Funding: Host universities, corporate and private sponsors

> "Seeing something like *JOSHUA* makes the act of doing and thinking about science real."
>
> GUY CALDWELL

HHMI investigator Michael Summers encourages students such as Leila Njimoluh (left) and Adjoa Smalls-Mantey even before they begin their freshman studies at UMBC.

Paul Fetters

All in the (Science) Family

HHMI IS INVESTING $86.4 MILLION TO BRING INDIVIDUALIZED MENTORING AND EARLY RESEARCH EXPERIENCE TO UNDERGRADUATE SCIENCE EDUCATION PROGRAMS ACROSS THE COUNTRY.

WITH ITS 49,600 STUDENTS AND 1,251 buildings, it would be easy for a newcomer to feel disoriented, or even a little lost, on the University of Florida campus in Gainesville. Science for Life, the university's new HHMI-funded program, aims to prevent that from happening, at least for some ambitious science-oriented freshmen.

"We have these remarkable incoming classes of freshmen," says Randy Duran, an associate professor of chemistry and director of Science for Life, which received a four-year, $1.5 million grant. "We want to capture large numbers of these very talented students who otherwise may be lost in the system."

The program, which aims to build a kind of "science family" at the university, will be centered at the new HHMI Undergraduate Core Laboratory, where each year up to 100 freshmen will participate in interdisciplinary research. These students will then move on to pursue their own independent research projects, mentored by graduate students, postdoctoral fellows, and faculty members.

The grant has also allowed the university to establish, in conjunction with historically black Morehouse College, more than 300 miles away in Atlanta, Georgia, a teaching fellows program for postdocs. "Morehouse provides a very good, diverse, nurturing atmosphere for learning about mentoring and teaching," Duran explains.

The schools' postdocs will spend a year at each institution, teaching and doing collaborative research. "This background will give them experience in teaching, mentoring, and research both at undergraduate and research-intensive institutions," says Duran. As an incentive to continue their teaching and mentoring, the University of Florida will pay them $20,000 when they sign on as new faculty members at any college or university.

The grant will also allow both the University of Florida and Morehouse to make "HHMI Distinguished Mentor" awards to at least 27 current faculty members who demonstrate excellence in their mentoring. Each award, consisting of $10,000 over a two-year period, can be spent at the faculty member's discretion.

MAKING IT EASY, KEEPING THEM BUSY

About 825 miles northeast of Gainesville stands the University of Maryland, Baltimore County (UMBC). With a total enrollment one-quarter that of the University of Florida, UMBC is establishing a national reputation for attracting and retaining talented minority students interested in the biomedical sciences.

Its program, called the Hughes Scholar Program, has supported 25 students so far, 23 of whom have been African American. With a $2.2 million HHMI grant renewal, UMBC will expand the program to support seven students per year, up from five. Since the program launched in 2002, eight Hughes Scholars have graduated from UMBC, and all have gone on to M.D., Ph.D., or M.D.-Ph.D. programs at places such as Stanford University, The Johns Hopkins University, Cornell University, the University of Florida, and the University of Maryland, College Park. "They're not

just getting into graduate programs, they're getting into the very best programs," says Michael F. Summers, an HHMI investigator and the program director.

Scholars are selected as incoming freshmen, and their tuition and room and board are covered by the grant for their first two years of college. (UMBC covers expenses for the junior and senior years using a government grant.) They do research during the summer and travel to scientific meetings.

To ensure their success, scholars attend a summer "bridge" program before freshman year begins to become familiar with the campus and its research opportunities. During freshman year, they rotate through several laboratories, eventually choosing a "home" laboratory in which to undertake long-term research. They then begin working in the lab the summer before their sophomore year.

Scholars also are required to complete at least one summer of research with an HHMI investigator elsewhere in the country, usually after their sophomore year. Each scholar also has the option of spending his or her junior year in the lab of another HHMI investigator.

Besides doing research, Hughes Scholars serve as tutors and mentors to local elementary and high school students. Many also tutor fellow UMBC students in chemistry, biology, or physics. ■ –NANCY VOLKERS

2006 UNDERGRADUATE SCIENCE EDUCATION PROGRAM GRANT AWARDS

The new undergraduate research awards provide from $1.5 million to $2.2 million over 4 years. HHMI invited 214 universities—each with a proven track record in both research and undergraduate education—to apply; 158 applications were received. In May, 50 institutions received grants to develop new courses, enhance teaching and mentoring skills, improve science literacy in nonscience majors, and attract and retain traditionally underrepresented groups to the sciences.

> "They're not just getting into graduate programs, they're getting into the very best programs."
>
> MICHAEL SUMMERS

EXROP Students Hand Off the Baton

At its annual meeting in May, the Exceptional Research Opportunities Program (EXROP) honored the work of the 2005 class of students and introduced them to the class of 2006, just before the new group headed out to some of the top research labs in the country to conduct summer projects. Organized through HHMI's Office of Grants and Special Programs, EXROP pairs undergraduates with HHMI investigators and HHMI professors. The program aims to encourage disadvantaged students, including minorities underrepresented in the sciences, to consider careers in science. ¶ The event also introduced the students to the 2006 Gilliam fellows, six former EXROP students who will receive support for five years of graduate training (see May 2006 *Bulletin*). In the left-hand photo above, HHMI program officer, Andrea Stith (right), talks with Gilliam fellow Ana Cristancho (middle); Ana's mother, Maria Pia Cristancho; and friend Alyssa Alter. The keynote speaker at the event, HHMI investigator Alejandro Sánchez Alvarado (right-hand photo) of the University of Utah School of Medicine, presented findings from his studies on regeneration in the flatworm.

Paul Fetters

Protein Boost Bumps Bats Skyward

RESEARCH SUGGESTS THAT UPPING THE LEVEL OF A SINGLE PROTEIN MIGHT HAVE MORPHED BATS' HANDS INTO WINGS.

Evolution may not always plod along at the, well, evolutionary pace we all learned about in school. HHMI investigator Lee Niswander and postdoctoral fellow Karen Sears at the University of Colorado Health Sciences Center, and their colleagues at the University of Texas M. D. Anderson Cancer Center and the State University of New York Downstate Medical Center, Brooklyn (SUNY), reported in the April 25 issue of the *Proceedings of the National Academy of Sciences* on a monumental evolutionary transformation that could have occurred within just a few million years—a blink of an eye in "traditional" evolutionary timescales. The researchers posed the question: "How did bats take to the skies?"

Bat wing anatomy was essentially perfected in one fell swoop, thanks to a single genetic change.

Bats got their wings from a relatively simple change to the "hands" of their ancestors, whom Niswander and Sears say looked not so different from today's mice. In those primordial bats, the outermost three digits—their pinky, ring, and middle fingers—became extraordinarily long. Other changes, such as webbing in the spaces between the newfangled fingers, perfected the wings.

Measuring the bones of 50 million-year-old bat fossils—the oldest in existence—the researchers determined that the wing fingers in those earliest bats were just as long as those of modern-day bats. The fossil record shows no evidence of the "transitional forms" that one might expect if bats developed their wings over epochs. But what spurred the sudden bone extension?

Sears and Niswander investigated proteins known to control mammalian skeletal development and identified one key protein, called bone morphogenetic protein 2 (Bmp2), that appears to do the trick for bat wings. The forelimbs of bats and mice start out looking strikingly similar in early embryos. Then, the outer fingers of bat forelimbs experience explosive growth. At the same time, the researchers found, Bmp2 levels skyrocket in bat forelimbs, but not in hindlimbs, and not at all in mouse limbs. Amazingly, when they bathed embryonic bat forelimbs in Bmp2, the fingers grew longer; when the forelimbs were bathed in a Bmp2 inhibitor, the fingers grew shorter. Sears and Niswander hypothesize that a single genetic change boosting Bmp2 levels in bat forewings could have been the necessary developmental push to send bats skyward. ■ – PAUL MUHLRAD

IN BRIEF

TARGETING CANCER STEM CELLS' VULNERABILITY

New research on the properties of stem cells indicates a useful difference between cells that keep the blood system healthy and those that make leukemia lethal. Discovery of the difference is important, because experiments in mice show that the stem cells promoting leukemia can be killed by rapamycin, a drug already approved by the U.S. Food and Drug Administration, says lead researcher Sean J. Morrison, an HHMI investigator at the University of Michigan Life Sciences Institute.

The idea, according to Morrison, is to find some vulnerability, some chink in the cancer cell's armor, that will enable scientists to kill cancer cells while sparing cells needed for normal functioning, such as bone marrow cells. Morrison and his collaborators have found one such difference: a gene called *Pten*, which has opposite effects on the two types of stem cells. When scientists remove or inactivate *Pten*, the supply of normal stem cells declines, while the growth of cancer stem cells increases dramatically. The work was reported in the April 6, 2006, issue of *Nature*.

"We were able to target this *Pten* pathway with the drug rapamycin, which killed leukemic stem cells without harming normal stem cells," Morrison says. Having a better understanding of stem cell self-renewal may lead to more effective and less toxic chemotherapy drugs.

RIBOSWITCH FLIPS TO CONTROL MAGNESIUM

Magnesium, essential for energy production and structural integrity, is critical to cell survival. Researchers have now found that cells use specialized segments of RNA, called riboswitches, to ensure that there is an adequate supply of the mineral. The newly described riboswitch can sense magnesium levels and directly regulate production of a magnesium transport protein. When the switch detects that magnesium concentration has dropped too low, it can boost translation of the RNA—meaning the cell produces more of the transporter protein, thereby correcting the magnesium deficiency.

The discovery, reported in the April 7, 2006, issue of *Cell*, is important for two reasons, says HHMI investigator Eduardo A. Groisman, who led the study. First, the finding solves a biological puzzle about one of the cell's most important—albeit underappreciated—substances. The finding also helps advance understanding of how riboswitches regulate gene expression.

"Although we still have much work to do to understand the system, our analysis indicates that, in response to different magnesium levels, these different structures either allow or prevent the full-length messenger RNA from being translated," says Groisman. He noted that the sequence of the untranslated region is conserved across many organisms, indicating a critical regulatory role.

FRUIT FLY STUDY SHOWS HOW EVOLUTION WINGS IT

In the frantic world of fruit fly courtship, the difference between attracting a mate and going home alone may depend on having the right wing spots. Now, HHMI researchers have learned which elements of fly DNA make these spots come and go in different species. Their studies also have uncovered surprising new evidence supporting the idea that evolution is an incessant tinkerer when it comes to complex traits.

Niche Guests

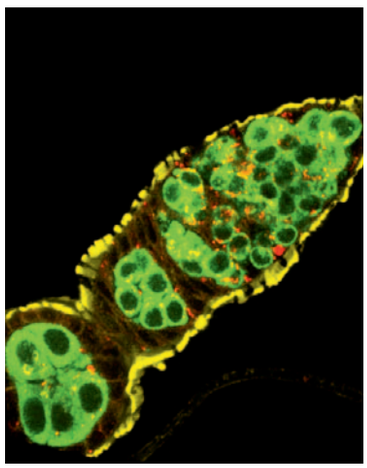
BY COZYING INTO A FRUIT FLY'S SPECIALIZED "INCUBATOR," AN ENTERPRISING BACTERIUM ENSURES ITS FUTURE.

You can learn a lot about a cell by the company it keeps. Horacio Frydman hopes to learn volumes about mysterious cells in the ovaries of fruit flies that harbor an unexpected guest, an intracellular bacterium called *Wolbachia*.

Frydman stumbled upon the cellular partnership as a graduate student with HHMI investigator Allan C. Spradling at the Carnegie Institution of Washington in Baltimore. After finishing his dissertation, Frydman joined HHMI investigator Eric Wieschaus's lab at Princeton University, where he examined the interaction more closely.

The *Wolbachia*, he found, had entrenched themselves within a smattering of enigmatic cells and their surrounding milieu, an area that Spradling, 5 years earlier, had named the "somatic stem cell niche." The specialized region, Frydman explains, provides a microenvironment that cultivates the stem cells, which eventually become eggs. The cells are a hospitable shelter for *Wolbachia*, he says, because they provide a place for the bacteria to reproduce before moving into the developing egg cells, which ultimately serve to disseminate the bacteria.

Frydman, who is an HHMI research associate, sees *Wolbachia* as a window into the workings of niche cells, of which, he says, scientists know precious little. "These intracellular microorganisms are great cell biologists, because they have been living inside cells through millions of years of evolution. If we pay attention to them, we can learn a lot of basic cell biology." And understanding niche cells could pay substantial rewards to biomedical research, he says. "Niches have become a big issue in the stem cell field." In recent years, scientists have come to realize that niche cells in general provide the nourishment and chemical signals required by stem cells. "Now we know that once you take a stem cell from the context of the niche, it loses the properties of being a stem cell."



A bacterium called Wolbachia *(red) makes itself at home inside fruit flies, proliferating alongside developing stem cells (green).*

Courtesy of Horacio Frydman/Wieschaus lab

Similarly, fruit flies offer a new window into understanding *Wolbachia*, which infect perhaps 70 percent of insect species and parasitic worms that cause devastating diseases such as river blindness and elephantiasis. "I want to learn the mechanisms for this infection process. And that might be useful to understand other epidemics and other infection processes," Frydman says. ■ – PAUL MUHLRAD

IN BRIEF

The experiments are among the first to root out "the deep mechanics of evolution" that underpin complex traits, according to the study's senior author Sean B. Carroll, an HHMI investigator at the University of Wisconsin–Madison. Carroll and his Wisconsin colleagues collaborated with researchers from the University of Cambridge and Stony Brook University on the studies, which were published in the April 20, 2006, issue of *Nature*.

"This finding is informative because it shows that the wing pattern wasn't generated from scratch," says Carroll. "The fly didn't use naïve DNA that had no job and invent this pattern out of thin air. It used a gene that was already active in the wing, already drawing some kind of pattern in the wing, and modified that pattern. We think that is a strong clue to how nature invents, which is by using material that is already available."

KEEPING AMYLOID—AND ALZHEIMER'S—IN CHECK

Researchers have identified a protein that reins in the rogue activity of the molecules that make the amyloid beta protein, which is suspected of preventing normal brain function in people with Alzheimer's disease. Their findings reveal a potentially powerful tool for designing novel Alzheimer's treatments.

Amyloid beta peptides are sticky protein fragments that accumulate, kill nerve cells, and clump together to form the distinctive amyloid plaques in the brains of people with Alzheimer's disease. They are generated when a larger, normal protein called amyloid precursor protein (APP) is cleaved or split in a series of events. Scientists believe that a protein complex called the presenilin complex is responsible for the final cleavage event.

New findings from HHMI international research scholar Peter St George-Hyslop at the University of Toronto argue against this hypothesis. St George-Hyslop's group recently pinpointed a new component called TMP21 that controls presenilin's dicing tendencies, preventing it from snipping apart APP. The researchers reported their findings in the April 27, 2006, issue of *Nature*.

Further investigation of the regulatory proteins controlling presenilin complexes may reveal other potential targets for drugs to treat Alzheimer's disease. Up to now, attempts to develop medicines to inhibit amyloid beta production have been hindered, St George-Hyslop says, because they frequently inhibit the normal and essential signaling functions too.

WHAT CONTROLS STICKINESS OF "SMART" CHROMOSOMAL GLUE?

Researchers have a new understanding of the process cells use to ensure that sperm and eggs begin life with exactly one copy of each chromosome—a process that must be exquisitely regulated to prevent problems such as miscarriages and mental retardation. The new work reveals how gluelike protein complexes, called cohesins, release pairs of chromosomes at precisely the moment of meiosis—the specialized cell division process that produces sperm and eggs—enabling them to separate properly.

The researchers, led by HHMI investigator Angelika Amon at the Massachusetts Institute of Technology, published their findings online May 3, 2006, in *Nature*.

Amon and her colleagues found that phosphorylation is important for governing

Dial Down the Stress

COULD PREVENTIVE MEASURES THAT REDUCE BRAIN HEMORRHAGE IN MICE DO THE SAME FOR HUMANS?

A gene mutation that predisposes mice to brain hemorrhages—and exists in humans as well—has led a team of basic scientists to suggest that certain preventive measures might work for humans at risk for hemorrhagic stroke.

Douglas B. Gould, a postdoc working with HHMI investigator Simon W. M. John at the Jackson Laboratory, discovered the mutation while developing a mouse model of the eye disorder glaucoma. He noticed that some mouse pups with the mutation were dying with severe cerebral hemorrhage on the day of birth.

The gene involved, called *Col4a1*, encodes procollagen type IV α1, the most abundant protein in basement membranes, which gives small blood vessels strength. When the mutation occurs, Gould says, "We think the basement membranes are disrupted and the blood vessels are weakened."

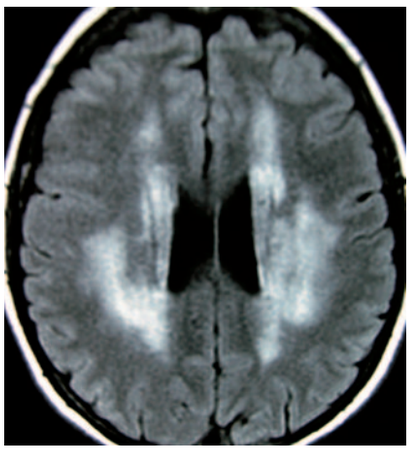
Speculating that the physical stress of traveling through the birth canal and the *Col4a1* mutation were conspiring to induce hemorrhage, the researchers tried prevention, delivering the pups by Cesarean section. It worked. But the mice weren't totally out of the woods. As adults, every mutant mouse developed small hemorrhages and about 20 percent had cavities in their brains, a condition called porencephaly.

The same may be true for humans. Four Dutch, one Italian, and one French family have so far been found to carry mutations in *COL4A1*, according to the researchers. In an April 6 paper in *The New England Journal of Medicine*, they reported on the French family, which has experienced two deaths due to cerebral hemorrhage: One adult suffered a head injury at work; the other died while on anticoagulant therapy.

The researchers think this gene's effects might be greater, extending beyond infantile stroke and porencephaly to small vessel disease, which is responsible for about 30 percent of hemorrhagic strokes and can contribute to cognitive impairment in the elderly. "We hope others will read the paper and check the next 100 hemorrhagic stroke patients who come through their clinic and start doing broader scale studies to determine the real frequency in the population," Gould says.

Gould is optimistic: "If we can identify families at risk, they can change modifiable risk factors, improving their diet, avoiding contact sports like karate, and keeping blood pressure low." ■

– CORI VANCHIERI



This MRI shows white matter abnormalities in one living member of a family that carries the COL4A1 mutation.

IN BRIEF

the stepwise loss of cohesins. In addition, they found that recombination—an exchange of DNA between chromosomes that promotes genetic diversity—was also needed for the initial removal of cohesin from the chromosome arms. Amon emphasized that these discoveries are only a beginning to understanding the intricate, critical process of cohesin loss. She and her colleagues are now exploring the possibility that the cohesin-snipping enzyme separase plays a role.

MOBILE DNA PART OF EVOLUTION'S TOOLBOX

The repeated copying of a small segment of DNA in the genome of a primeval fish may have been crucial to the transition of ancient animals from sea to land or to later key evolutionary changes in land vertebrates. The discovery is "tantalizing evidence" that copied DNA elements known as retroposons could be an important source of evolutionary innovations, says the director of the research, HHMI investigator David Haussler.

"The big question is whether this is a special case or whether it's the tip of the iceberg," says Haussler, who is at the University of California, Santa Cruz. A report on the research appeared on May 4, 2006, in *Nature*.

The researchers' results support the hypothesis that the movement of retroposons can generate evolutionary experiments by adding new regulatory modules to genes. Most of these experiments will have no effects or will harm an organism. Every once in a while, however, the movement of a regulatory element will give an organism an evolutionary advantage.

"This suggests a lot of exciting evolutionary avenues," says Haussler, "but we don't yet know how prevalent this kind of evolution is." Other labs have found similar examples of mobile elements that have changed the regulation of genes, and Haussler expects the number of reports to grow.

CLUES TO POTENTIAL TREATMENT OF CHILDHOOD BRAIN TUMORS

Using cells obtained from cancer-stricken mice, researchers at Stanford University have showed that reducing the production of sterols—chemicals, such as cholesterol, that are a vital part of cell membranes—can prevent rapid growth of medulloblastoma cells in culture. Medulloblastoma, the most common form of malignant childhood brain cancer, is due to a breakdown in normal communication between cells.

The findings of the new study, published in the May 15, 2006, issue of the *Proceedings of the National Academy of Sciences*, are important because they trace molecules connected to sterol metabolism that have powerful effects on medulloblastoma cells. The new work potentially paves the way for novel treatments, says senior researcher Matthew P. Scott, an HHMI investigator at Stanford.

Scott and his colleagues explored the use of statins, a family of cholesterol-lowering drugs, as potential agents for slowing or stopping the proliferation of medulloblastoma cells. "The growth of the cancer cells was inhibited by blocking the sterol synthesis pathway," he reports.

Though the work is still in its early stages, Scott says, results of the new study provide a basic insight that might inspire improved therapies.

Q

Submitted by a parent on behalf of his seven-year-old daughter

Why are teeth the only bones that we lose?

A

Researched by Joseph Churchill

Teeth are not really bones. One main distinction is that bones are entirely inside our bodies, while teeth are part inside—the roots—and part outside—the crowns that do all the gnashing and grinding of the food we put in our mouths. Bones, unlike teeth, are wrapped in a layer of cells called the periosteum. The periosteum and a few other cell types allow bones to grow and be remodeled over time, so bones like our maxilla (the bone that anchors our upper teeth) and mandible (the jawbone that anchors our lower teeth) can change shape and get bigger as we grow older.

Our teeth don't have this luxury. The layer of cells roughly equivalent to the periosteum of bone—cells known as ameloblasts, which are responsible for laying down the hard enamel of teeth during tooth development—get destroyed once the tooth erupts. So, after a tooth erupts through the gums, it will stay about that same size for life (if you take good care of it). If we kept our baby teeth through the dramatic size changes that happen as we grow up, we wouldn't be quite as good at chewing food. We would also look kind of funny—big jaws, little teeth.

What you're really asking is why this particular mechanism of tooth replacement evolved in humans—and, about that, precious little is known. You could imagine, for example, that we might do just as well if we were like sharks and continually grew new teeth to replace ones that had fallen out.

We probably evolved the mechanism of tooth replacement to accommodate having dramatically different jaw sizes over the course of our lives. When we're young, the mandible and the maxilla are small compared with the size they will be when we're adults. We take advantage of the bigger jaws we have as adults by developing more teeth that are bigger.

By the way, while it's true that we don't lose bones in the sense that they don't fall out like our primary teeth, we do "lose" some as we develop into our adult bodies. They fuse with nearby bones to form entirely new bones. Take the sternum, or chest bone, for example. When we are born there are four separate parts. Two additional lower parts appear between ages 1 and 6. By 25 years, everything has fused into a single bone.

RESEARCHED BY JOSEPH CHURCHILL, *dental student, State University of New York at Buffalo School of Dental Medicine (former HHMI-NIH Research Scholar)*

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 *Web site. There, working scientists field a wide range of biomedical questions.*

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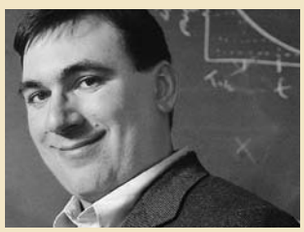
Electrifying Cells

CELLS "SPEAK" THEIR OWN, ELOQUENT LANGUAGE. HOW TO TRANSLATE THIS *biochemical banter into signals understandable by electronic gadgetry has been a major technical challenge for scientists. Using electronics is appealing, as it would eliminate the need for the bulky optical instrumentation used routinely today to visualize cellular activities.*

Now, HHMI investigator Milan Mrksich and his colleague Joel H. Collier have devised an ingenious approach to making cells that are themselves "electric" in that they produce a readily detectable electrochemical output of their own. Their achievement could create the cellular equivalent of bloodhounds—biosensors that send an electrical signal when biowarfare agents, pollutants, or clinical diagnostic molecules are present. Also, drug companies could use such cells to screen libraries of compounds to detect those that switch on specific disease targets on the cell.

Mrksich, at the University of Chicago, and Collier, of the University of Cincinnati, reported their new approach in the February 14, 2006, issue of *Proceedings of the National Academy of Sciences*.

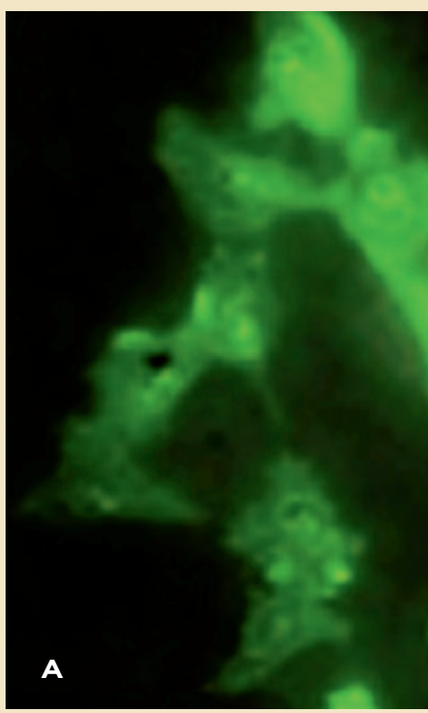


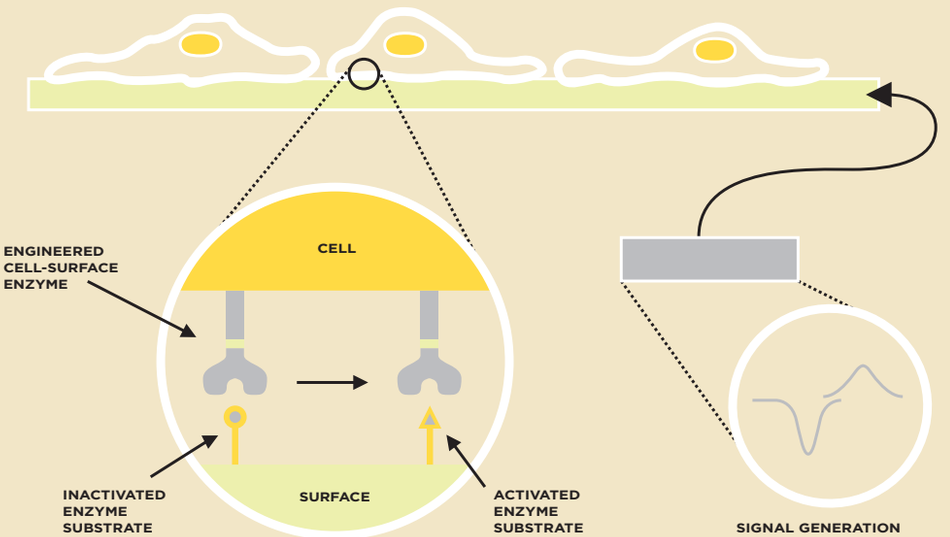
MILAN MRKSICH

JOEL H. COLLIER

First the researchers engineered Chinese hamster ovary cells to produce on their surfaces a fungal enzyme called cutinase, which is not normally made by mammalian cells. Cutinase was chosen because it catalytically transforms its target compound, or ligand, from an electrically inert substance into an electroactive one. To be able to detect this transformation, the researchers tethered a synthetic form of the ligand on an engineered electrode surface. When cutinase acts on the ligand, an electric signal materializes and is detected.

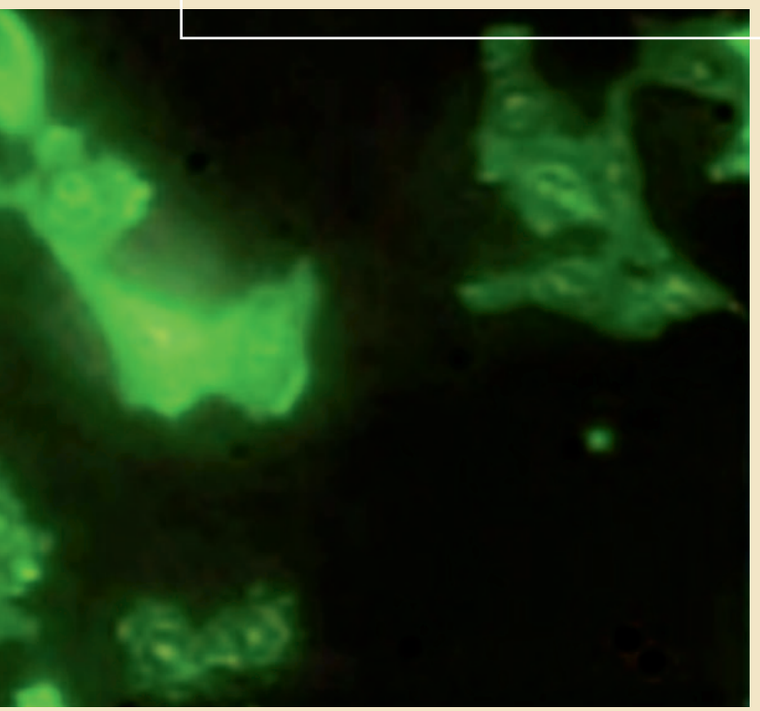
With this technique, the researchers aim to have a cell that speaks not only its own "native language" but also a telltale electrical signal. ■ –DENNIS MEREDITH

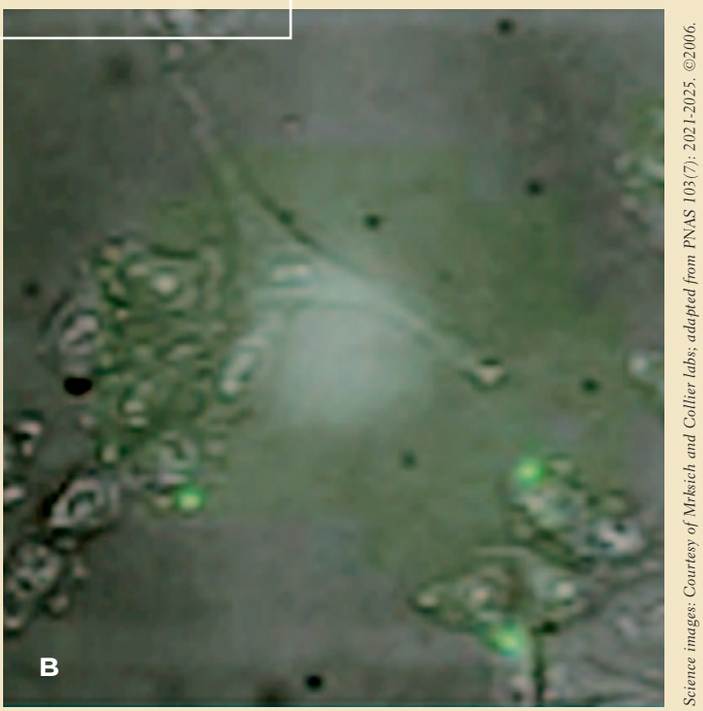




LEFT: In the technique invented by Milan Mrksich and Joel Collier, Chinese hamster ovary cells engineered to produce the fungal enzyme cutinase are adhered to a receiver surface containing the enzyme's target molecules. When the cutinase transforms its target from an electrically inactive state to an active one, the electrodes in the receiver surface can detect a signal. Importantly, the researchers found, normal cellular processes are not disrupted by either the production of cutinase or the attachment of the cells to the receiving surface. And because cutinase is not native to mammalian cells, the chemical reaction it triggers is distinct from those of its host cell, greatly reducing biochemical "noise."

BELOW: By staining their engineered cells with a fluorescent antibody to cutinase, the researchers confirmed that the cells (A) were actively expressing the enzyme, as compared to normal cells (B). The researchers believe their proof-of-concept experiment with cutinase raises the possibility of engineering cells to produce other such signaling molecules as well, thereby enabling "multichannel" monitoring of many cell processes simultaneously.





Science images: Courtesy of Mrksich and Collier labs; adapted from PNAS 103(7): 2021-2025. ©2006. Mrksich: Aynsley Floyd/AP © HHMI / Collier: Courtesy of Joel Collier

SPOTLIGHT

TOP ROW: DAVID BAKER, BONNIE L. BASSLER, DAVID E. CLAPHAM, JOACHIM FRANK, STEPHEN P. GOFF. BOTTOM ROW: DAVID HAUSSLER, MICHAEL E. O'DONNELL, RICHARD M. AMASINO, A. CARLOS FRASCH, WOLFHARD ALMERS

Ten Elected to National Academy of Sciences

Seven HHMI investigators, one HHMI professor, an HHMI international research scholar, and a member of HHMI's scientific review board have been elected to the National Academy of Sciences. Newly elected HHMI investigators are **David Baker**, University of Washington School of Medicine; **Bonnie L. Bassler**, Princeton University; **David E. Clapham**, Children's Hospital Boston; **Joachim Frank**, Health Research, Inc., at the Wadsworth Center; **Stephen P. Goff**, Columbia University College of Physicians and Surgeons; **David Haussler**, University of California, Santa Cruz; and **Michael E. O'Donnell**, The Rockefeller University. The HHMI professor is **Richard M. Amasino**, University of Wisconsin–Madison, and the international research scholar is **A. Carlos Frasch**, Institute for Research in Biotechnology, National University of General San Martín, Buenos Aires, Argentina. HHMI scientific review board member **Wolfhard Almers**, of the Vollum Institute at Oregon Health & Science University, was also elected.

CAROLYN R. BERTOZZI, an HHMI investigator at the University of California, Berkeley, was named director of the Molecular Foundry at the Lawrence Berkeley National Laboratory. The Molecular Foundry is a user facility for nanoscale materials, dedicated to supporting research in nanoscience at institutions around the world.

Five current HHMI investigators, one Trustee of the Institute, one member of the Institute's scientific review board, and one HHMI international research scholar were elected to the American Academy of Arts and Sciences. The investigators are KEVIN P. CAMPBELL, University of Iowa College of Medicine; JOACHIM FRANK, Health Research, Inc., at the Wadsworth Center; DAVID HAUSSLER, University of California, Santa Cruz; HELEN H. HOBBS, University of Texas Southwestern Medical Center at Dallas; and J. ANDREW MCCAMMON, University of California, San Diego. The Institute Trustee is SIR PAUL NURSE, The Rockefeller University; the scientific review board member is MICHAEL R. BOTCHAN, University of California, Berkeley; and the international research scholar is NAHUM SONENBERG, McGill University in Montreal, Canada.

ALAN F. COWMAN, an international research scholar at the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia, received the 2006 Lemberg Medal from the Australian Society for Biochemistry and Molecular Biology. Cowman's research focuses on how *Plasmodium falciparum*, the organism that causes the most lethal form of human malaria, invades mature red blood cells.

Two HHMI international research scholars were elected to the Russian Academy of Sciences. The scholars are PAVEL GEORGIEV, Institute of Gene Biology, Russian Academy of Sciences, in Moscow, and OLGA A. DONTSOVA, Moscow Lomonosov State University.

The 2004 Holiday Lectures on Science "Science of Fat," produced by the educational products team within the HHMI Grants department, won a 2006 Silver Telly Award. Given since 1978, the Telly Awards honor local, regional, and cable television commercials and programs, as well as video and film productions. The Silver award is the highest honor given.

B. BRETT FINLAY, an HHMI international research scholar at University of British Columbia in Vancouver, Canada, won the 2006 Killam Prize in Health Sciences from the Canada Council for the Arts. The Killam Prizes are awarded annually to distinguished Canadian scholars in recognition of exceptional contributions in the fields of health sciences, natural sciences, engineering, social sciences, and humanities.

ELAINE FUCHS, an HHMI investigator at The Rockefeller University, received the 2006 FASEB Excellence in Science Award. Sponsored by Eli Lilly and Company, the award recognizes women for outstanding achievement in scientific research. Fuchs shares the award with Marilyn Farquhar of the University of California, San Diego. In addition, Fuchs was inducted in April into the American Philosophical Society.

Baker: Brian Smale Bassler: Zack Seckler / AP, ©HHMI Clapham: John Bridges Frank: Chris Denney Goff: Ronald Morris Haussler: Tim Archibald O'Donnell: Courtesy of Rockefeller University Amasino: Brian Ebner/AP, ©HHMI Frasch: Dominic Chaplin Almers: Don Hamilton

TYLER JACKS, an HHMI investigator at the Massachusetts Institute of Technology, received the 2005 Simon M. Shubitz Award from the University of Chicago Cancer Research Center for his significant contributions to the field of cancer research.

LILY JAN and **YUH NUNG JAN**, HHMI investigators at the University of California, San Francisco, won the 2006 Presidential Award from the Society of Chinese Bioscientists in America.

THOMAS M. JESSELL, an HHMI investigator at Columbia University College of Physicians and Surgeons, was elected a fellow of the Academy of Medical Sciences. The academy promotes advances in medical science and their swift translation into healthcare benefits for society.

ERIC R. KANDEL, an HHMI investigator at Columbia University College of Physicians and Surgeons, was awarded the 2006 Benjamin Franklin Medal for Distinguished Achievement in the Sciences from the American Philosophical Society. Kandel also received the 2006 Biotechnology Achievement Award from the New York University School of Medicine.

EMMANUEL MIGNOT, an HHMI investigator at Stanford University School of Medicine, won the 2006 Outstanding Scientific Achievement Award from the Sleep Research Society for his work on narcolepsy.

JAMES PARRISH, an HHMI-supported undergraduate student at the University of Delaware, was awarded a 2006 Marshall Scholarship from the British government to study and conduct research in the United Kingdom for up to 3 years. Parrish plans to study stem cell biology at The University of Newcastle upon Tyne.

CHARLES L. SAWYERS, an HHMI investigator at the University of California, Los Angeles, received the 2007 Emil J. Freireich Award for Clinical Research from the M.D. Anderson Cancer Center. The award is given to recognize the outstanding achievement of a young researcher in clinical cancer therapeutics.

NANCY SCHUNKE, an HHMI-supported middle school science teacher, won the 2005 Presidential Award for Excellence in Mathematics and Science Teaching. Schunke has participated for almost 10 years in the HHMI Science Education Program at Texas Tech University.

PETER WALTER, an HHMI investigator at the University of California, San Francisco, was elected in May 2006 to the German Academy of Natural Scientists Leopoldina. Walter was also awarded the 2006 George E. Palade Gold Medal.

SPOTLIGHT

Swedish Academy Lauds Harrison

STEPHEN C. HARRISON

The Gregori Aminoff Prize in crystallography for 2006 was awarded by the Royal Swedish Academy of Sciences to **Stephen C. Harrison**, an HHMI investigator at Harvard Medical School. The Aminoff Prize recognizes "an individual contribution in the field of crystallography, including areas concerned with the dynamics of the formation and dissolution of crystal structures." Harrison, who is director of the Harvard-Armenise Center for Structural Biology, was honored for his work on virus crystallography.

SPOTLIGHT

Wang Wins Shaw Prize

XIAODONG WANG

HHMI investigator **Xiaodong Wang** has won the $1 million Shaw Prize in Life Science and Medicine for 2006. Wang will receive the international award from the Hong Kong-based Shaw Prize Foundation "for his discovery of the biochemical basis of programmed cell death, a vital process that balances cell birth and defends against cancer." ¶ The Shaw Prize honors individuals "who have achieved significant breakthroughs in academic and scientific research or applications, and whose work has had a positive and profound impact on mankind." ¶ A researcher at the University of Texas Southwestern Medical Center at Dallas, Wang has made groundbreaking discoveries in the biochemistry of cell death, or apoptosis. The malfunction of genes that leads to apoptosis is a hallmark of many diseases, including cancer and some autoimmune and neurological disorders. Wang's findings have provided new directions for the treatment of cancer, where natural cell death is prevented and cancer cells grow unchecked.

Harrison: Marcelo Berardi Wang: Charles Ford

Save the Date

THE BIOLOGY OF STEM CELLS

HHMI 2006 Holiday Lectures on Science

LIVE WEBCAST

November 30 and December 1

SPEAKERS

Douglas A. Melton
HHMI investigator at Harvard University

Nadia Rosenthal
Director of the European Molecular Biology Laboratory, Monterotondo, Italy

Because they are able to generate new healthy cells, stem cells are being studied for their potential to treat and cure various diseases. Doug Melton and Nadia Rosenthal, both leaders in stem cell research, will talk about where embryonic and adult stem cells come from, the biology of how they generate the body's various cells, and current progress in harnessing stem cells to treat diseases such as diabetes and muscular dystrophy.

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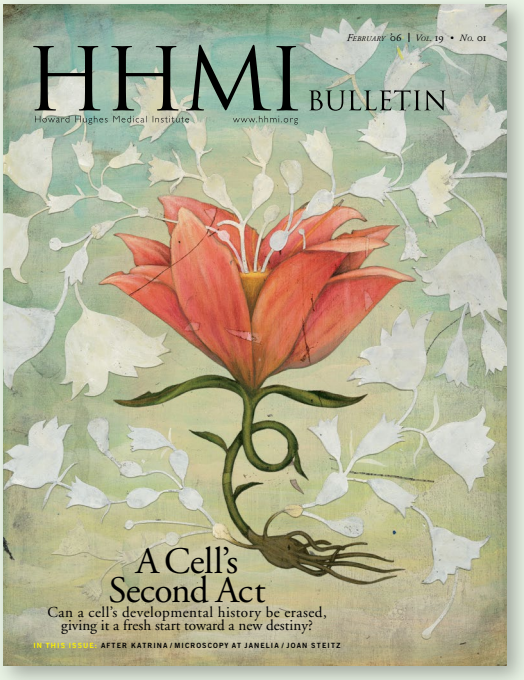

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If you can keep your head…

(With a nod to Rudyard Kipling)

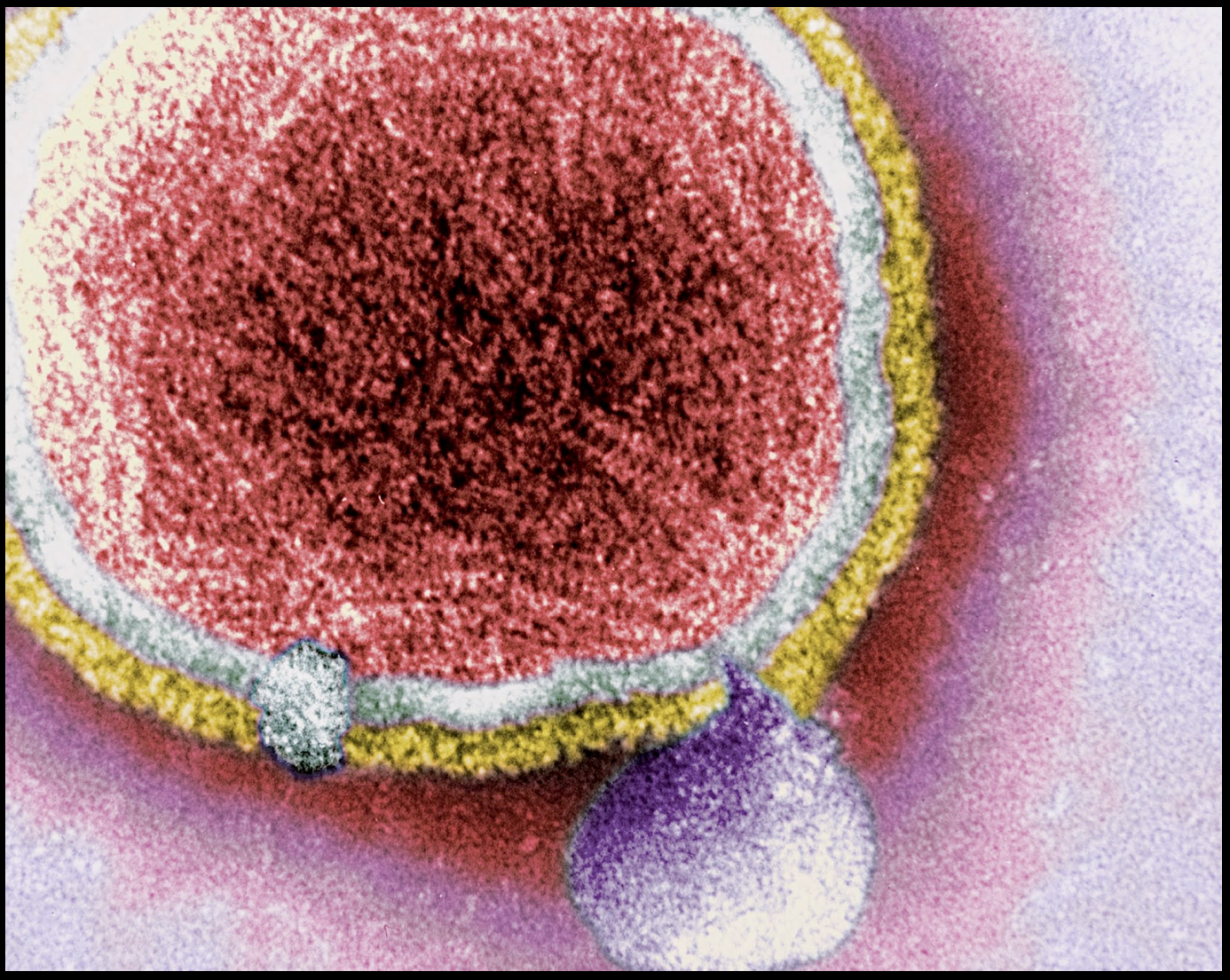
It was 1998, and the battle over who would sequence the human genome was heating up. Craig Venter had vowed that his company, Celera Genomics, would produce the sequence quickly and for profit. As a warm-up, he announced, he would test his method first on fruit flies, having won the cooperation of Gerry Rubin, whose Berkeley lab had to that point been the chief sequencer of* Drosophila. *The tale of the year and a half between announcement and completion of that undertaking was fraught with politics and intrigue, involving stellar scientific figures such as Jim Watson, of* Double Helix *fame, and Francis Collins, who headed the NIH efforts to sequence the human genome. Cambridge University Professor Michael Ashburner, who was, as he says, "close to the epicenter of the collaboration," chronicles the events of that time in a rollicking new book.

I still do not know why Craig wanted to sequence *Drosophila*—even now, when it is finished. Did he expect to make money from it? Surely not. Nobody gets rich studying *Drosophila* (well, that may not be entirely true, but let's keep it as a first approximation). Or was the reason more mundane, more pragmatic? By starting with an organism with a small genome, perhaps he could learn to do large-scale shotgun sequencing and assembly. Rather like running a 1000-meter race to see whether you can run a marathon.

Gerry is a master. How he keeps his head, I do not know. Against this man I will never play poker. There are mutterings that Gerry is collaborating with the Devil. "Remember Poland," says Jim, who recalls World War II. Jim is strong on historical analogies this week: "Will you be Chamberlin or Churchill?" he asks Francis. Jim is an Anglophile.

The world is agog. Of course, it is a pretty small world, but it is My World, the Golden Run from Cambridge to the east coast and on to Berkeley and Stanford. The e-mails begin to fly. Will Craig patent *Drosophila*? What are these new PE sequencing machines? Do they work? Why is Gerry collaborating with him? Will the sequence be public? When will it be done? Will I be scooped? What will this mean to the European *Drosophila* sequencing project? Paranoia. Pure paranoia fueled, as it is so often, by misinformation and lack of information. Gerry had his work cut out to convince the community.

Illustration: Matthew Dennis



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An Ounce of Prevention

HUMAN PARAINFLUENZA VIRUSES ARE A COMMON CAUSE OF RESPIRATORY INFECTIONS IN YOUNG CHILDREN, BUT CAN CAUSE SERIOUS ILLNESS IN THE ELDERLY AND PEOPLE WITH COMPROMISED IMMUNE SYSTEMS (AS IN THE PATIENT DESCRIBED ON PAGE 16). THE GOOD NEWS IS, THE VIRUS LIVES ONLY A FEW HOURS ON SURFACES AND IS EASILY INACTIVATED WITH SOAP AND WATER. IN THIS ELECTRON MICROGRAPH, A PARAINFLUENZA VIRUS IS MAGNIFIED 51,300 TIMES.

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