SPRING '05 | VOL. 18 • NO. 01

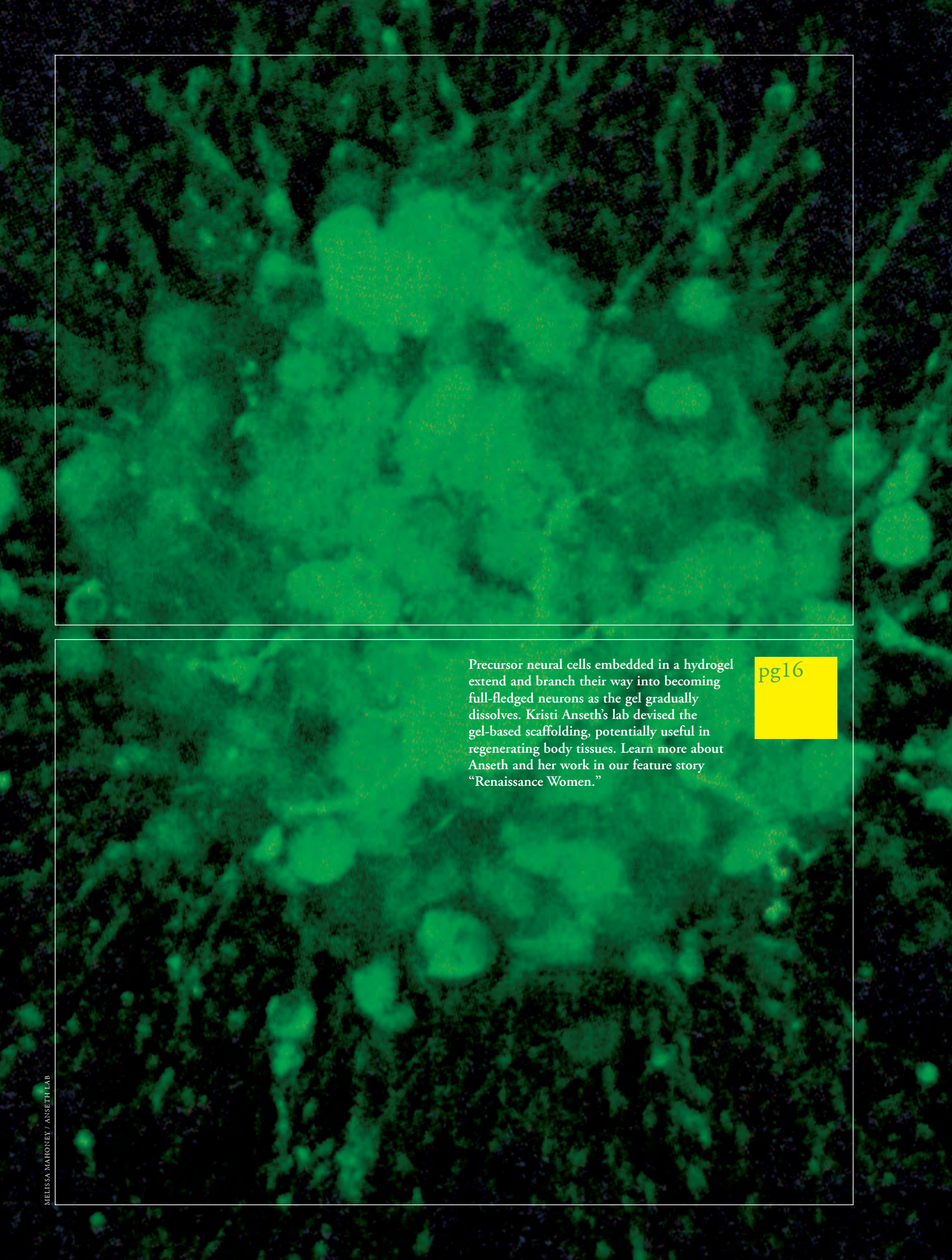
HHMI BULLETIN

Howard Hughes Medical Institute www.hhmi.org

BIO-INFORMATICS

With computers as tools, Philip Green models biology for the 21st century.

IN THIS ISSUE: THREE WINNERS OF THE WATERMAN / CANCER AND THE CLOCK / NEW INVESTIGATORS



Precursor neural cells embedded in a hydrogel extend and branch their way into becoming full-fledged neurons as the gel gradually dissolves. Kristi Anseth's lab devised the gel-based scaffolding, potentially useful in regenerating body tissues. Learn more about Anseth and her work in our feature story "Renaissance Women."

pg16

MELISSA MAHONEY / ANSETH LAB

vol. 18 / spring '05
no. 01

DEPARTMENTS

FEATURES

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Visit the **Bulletin Online** for additional content and added features.

CORRECTION. The photograph of Xiaodong Wang on page 42 of the Winter 2005 issue of the *Bulletin* was taken by Charles Ford.

COVER IMAGE: HOLLY LINDEM
PHILIP GREEN: BRIAN SMALE

EDITOR'S NOTE

TRANSFORMATION: ABOUT OUR NEW LOOK

The magazine you hold represents a transformation of the HHMI *Bulletin*. We have a new look and feel, new sections and structure, and new approaches to the way we present content.

In biology, the verb "transform" can refer to the metamorphosis of one cell into a wholly different cell through the introduction of DNA. In some ways, that's an apt metaphor for the *Bulletin*'s transformation. In the pages that follow you will find much that is familiar and much that is new. We drew considerable genetic material from the *Bulletin*'s tradition and history and added some new DNA in the form of fresh ideas to transform the magazine. This iteration honors the past as it looks to the future.

Why revise the *Bulletin*? The spark for change came when HHMI adopted a new graphic identity. It followed logically that the *Bulletin* should reflect our new logo. We also recognized that the occasion of updating the *Bulletin*'s graphic look presented opportunities for us to renew the magazine as a whole.

There is one fundamental that we have *not* altered: our mission, to report on HHMI's programs, people, and contributions to research and science education.

In its operating philosophy, HHMI urges scientists to be daring, to take risks, to be creative, and to investigate unexplored avenues. We believe the same principles should apply to this magazine. In that spirit, we hope and intend that in the process of transforming the *Bulletin* we have converted its considerable energy into a form that will be even more powerful, interesting, and informative.

You, our readers, are the ultimate judges. Let us know what you think.

The Bulletin *Staff*
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Thomas R. Cech
President
Howard Hughes Medical Institute

NEW FIELDS, NEW OPPORTUNITIES

This issue of the HHMI *Bulletin*—the first to be published in our new format—speaks to a period of energetic renewal at the Howard Hughes Medical Institute. Our recently concluded competition will bring 43 scientists into our ranks over the next several months, all at early stages in their careers. Many represent fields of research that lie at the vibrant edges of biomedical science and have not been highly represented in HHMI. Significantly as well, they include scientists at five institutions that do not currently have an HHMI investigator.

Almost a quarter of the new investigators fall outside traditional biological disciplines and are drawn from the fields of chemistry, physics, computer sciences, engineering, and geomicrobiology. And the label "traditional" hardly applies to the other scientists we selected. Whether their research focuses on dissecting the attributes of deadly pathogens, parsing the components of neural circuits, or devising novel ways to glean secrets of human disease from model organisms, they bring fresh thinking to challenging problems in biomedical science. They will be welcome additions to the Hughes community.

The promise embodied by these new investigators—and the continued creativity of their colleague scientists at HHMI, who as of May include 10 new members of the National Academy of Sciences—prompt me to reflect on two related themes: mentoring and independence.

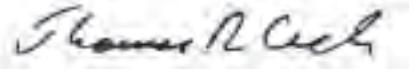
On March 31, HHMI lost one of its stars, Stanley J. Korsmeyer, M.D. While in his mid 30s, and already an HHMI investigator, Stan made pivotal discoveries that led to the identification of key genetic mechanisms governing apoptosis, or programmed cell death. Stan's research revealed how cancer cells escape death by apoptosis and pointed the way to new therapies. In fact, 6 weeks after Stan's death from lung cancer, *Nature* published preclinical studies showing that a compound that inhibits proteins in the Bcl-2 family shows promise for lung cancer treatment. Stan and his frequent collaborator, Craig Thompson, a former HHMI investigator and now chair of the HHMI Medical Advisory Board, were among the authors.

Stan loved being a Hughes investigator—he thought of his HHMI colleagues as an extended family—just as he derived so much satisfaction every day working with his postdocs and helping them become independent scientists. He was the consummate mentor.

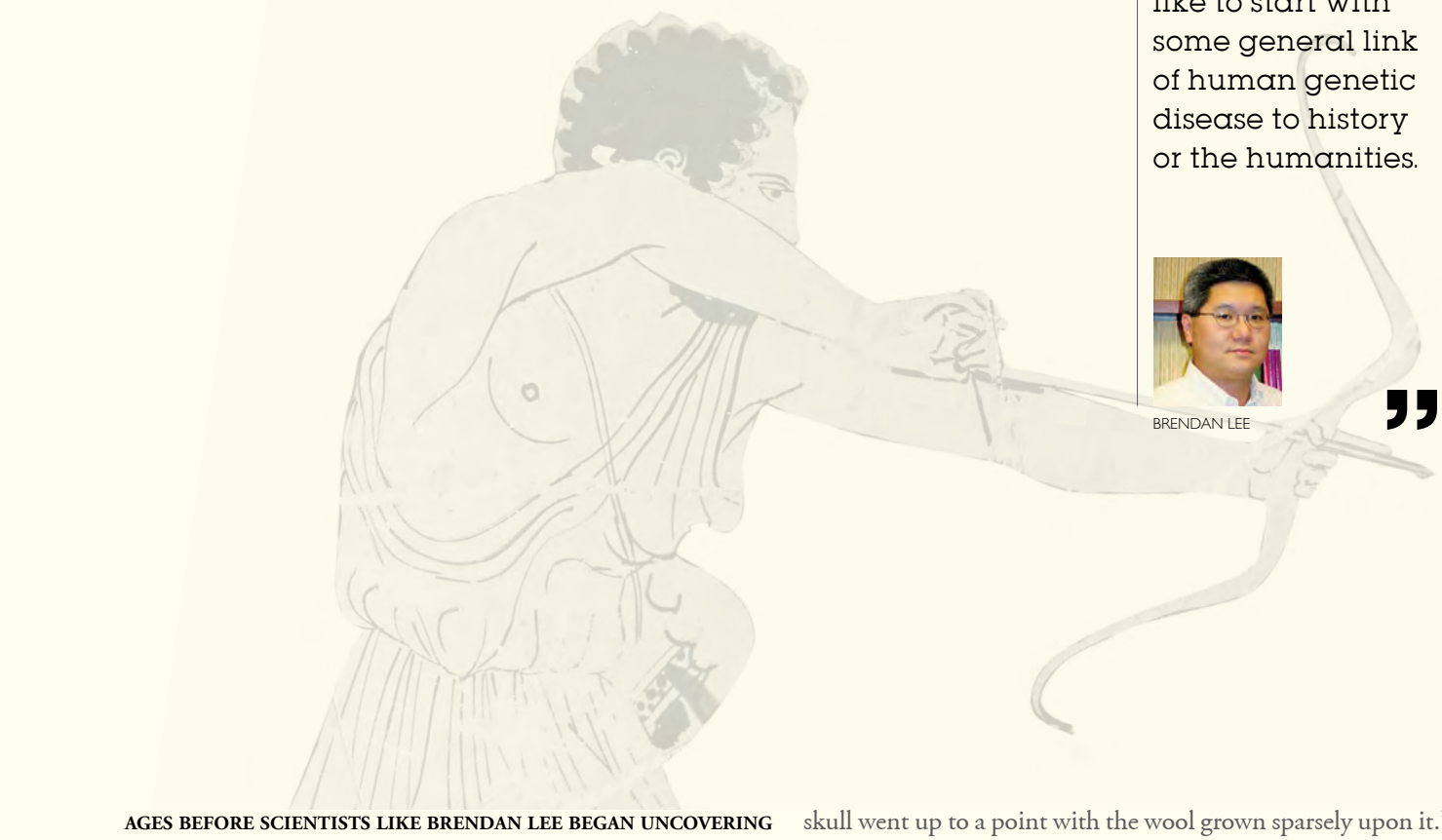
Science needs more researchers who share Stan's convictions about helping to shape scientific careers in light of the daunting barriers that young scientists face. Many linger in an extended postdoctoral limbo. On average, they have to wait until their early 40s before they receive their first independent funding from the National Institutes of Health. In 1980, 50 percent of all new grants went to scientists aged 40 or younger; by 2003, it was 17 percent. Yet by that age, Stan Korsmeyer was well established as an independent scientist and had made some of his most groundbreaking discoveries. There's no telling what path Stan might have followed today.

To its credit, the National Institutes of Health is asking the right questions. A year ago, NIH Director Elias Zerhouni asked the National Academies to examine the circumstances of early-career scientists, the impediments to independence, and the consequences for our nation. I chaired the study panel, which was aptly named "Bridges to Independence" (see page 41). I hope our recommendations will be put into effect. They include placing limits on the length of funding for postdoctoral researchers coupled with clear expectations for how principal investigators on NIH grants will prepare postdocs for independent careers. We recommend more independent awards for postdocs, including foreign scholars, and career transition grants to bridge from postdoctoral to independent research. And we suggest policies to ensure that new investigators have a fair chance to compete for R01 grants, which are the mainstay of biomedical research.

The nation needs to nurture and support scientists who are ready to move beyond "safe" research that follows well-established paths, scientists who have the requisite independence to make discoveries with a new level of impact on medicine and human health. At HHMI, we provide this freedom to a relatively small number of promising scientists through focused competitions like the one we just completed. Individual scientists, like Stan Korsmeyer, must do their part. But it is the NIH policies that have the most sweeping impact, and it is there that action is most urgently needed.



BART NAGEL



"When I'm asked to describe my research, I often like to start with some general link of human genetic disease to history or the humanities."

BRENDAN LEE

AGES BEFORE SCIENTISTS LIKE BRENDAN LEE BEGAN UNCOVERING the molecular defects behind genetic diseases, many of the more readily evident malformations that affect the face and body were entrenched in popular culture and literature. For medical detectives who enjoy the challenge of diagnosing personalities from the past, these disorders of bone and cartilage—technically known as skeletal dysplasias—provide obvious clues.

The diminutive French painter Henri de Toulouse-Lautrec, for example, is believed to have had pycnodysostosis, a bone disorder that causes short stature and fragile bones. John Merrick, the so-called Elephant Man, had a large facial tumor that was probably caused by the rare Proteus syndrome. Abraham Lincoln, ridiculed for his unusually gaunt and elongated frame, may have had Marfan syndrome, a sometimes fatal connective-tissue disorder.

"It turns out that a lot of the genetic diseases I have worked on have had connections to history," says Lee, an HHMI investigator at Baylor College of Medicine. "When I'm asked to describe my research, I often like to start with some general link of human genetic disease to history or the humanities."

In a recent science talk, Lee quoted Homer's epic The Iliad, believed to have been written in the 8th century B.C. One character, the lowly and scorned Thersites, is described as "bandy-legged and went lame of one foot, with shoulders stooped and drawn together over his chest, and above this his skull went up to a point with the wool grown sparsely upon it." (The translation comes from Richmond Lattimore's The Iliad of Homer, published in 1951 by the University of Chicago Press.) To Lee and his fellow geneticists, this description of Thersites supports a diagnosis of cleidocranial dysostosis, a skeletal abnormality whose cardinal sign is the ability to make one's shoulders meet in front.

That Homer would describe such a vanishingly rare disorder—only about 500 cases have been recorded—amazes modern researchers. Was someone he knew, or even Homer himself, afflicted by it? In any case, the disease may help solve the age-old puzzle of whether the same poetic genius wrote both The Iliad and The Odyssey. Some experts argue that the evidence points to a single author because a unique character like Thersites pops up in each of these works.

Fascinating as those speculations may be, Lee's strongest motivation is to help the living people of today—many of them children—whom he treats but cannot cure. Progress is slow in learning about these types of disorders, but Lee is convinced that the best ideas will come from the patients themselves. "In our skeletal dysplasia rounds we review the patients, look at x-rays, discern patterns, and come up with new hypotheses. We test them in the laboratory and then, hopefully, come back to the patients with a clearer understanding of the nature of the diseases and better options for care," he says. ■

~ Richard Saltus ~

LEE: COURTESY BAYLOR COLLEGE OF MEDICINE ARCHER: ERIC LESSING / ART RESOURCE, NY

Idea Farm

RIGHT _ GERALD CRABTREE'S MOUNTAIN RETREAT (DETAIL ON LEFT) IS A "WELL OF CREATIVITY."

TAKE THE RIGHT SET OF TURNS OFF winding, oak-sheltered roads and 40 minutes out of Palo Alto you might find yourself at Thistles, Gerald R. Crabtree's 8-acre refuge in California's Santa Cruz mountains. Up here, 1,700 feet above sea level, the view is of rolling hills, patches of redwood forest, and the expansive Pacific Ocean. Hawks glide overhead, making a gentle whoosh. "It's replenishing and invigorating—like living in an art gallery," says the soft-spoken HHMI investigator.

If this quiet place feels a long way from Crabtree's lab at Stanford University, where his group investigates signaling pathways critical to development, that's part of the point. But it's also true that Thistles is to a great extent the well-spring for Crabtree's scientific work.

A visitor to Thistles might find Crabtree on his patio, built of stone he laid himself. He doesn't sit still for very long, though. "When I have a problem to work on, I've got to be moving—that's when my brain starts to work," he says. Each morning he walks the countryside for up to 90 minutes, occasionally meeting and chatting over the fence with a neighbor who strolls the boundaries of his own acreage next door. Most times, though, Crabtree walks alone, a ritual that helps him mull the meaning of results from experiments or comments from his students and postdocs, plan further investigations, and integrate ideas from his many areas of interest, such as immunology, gene transcription, and neuronal circuitry. "Everything our lab is working on started with ideas from my morning walks," he says. From that point, he says, his colleagues "often take things in their own direction and improve on the initial course that I set."

Raised on a farm in West Virginia, Crabtree recognizes his retreat as a rich source for experimentation. "The barnyard and the woods are a well of creativity, where you have to constantly improvise and make things fit together," he says.

In that spirit, if you were invited to Thistles this summer, you just might find Crabtree pondering the structure of chromatin (the substance of which chromosomes are made) while he crafts an outdoor cooking area that he has in mind. ■

~ Karen Schmidt ~

THE SONG OF THE ZEBRA FINCH

The adult male zebra finch knows only one scratchy tune learned in its youth, which it performs repeatedly and intensely when females are listening. But occasionally, the finch might improvise, experimenting with a slower, more sultry variation or emphasizing different notes.

Neurobiologists studying the finch now say the improvisation arises from a component of a crucial learning circuit in a section of the forebrain that seems to generate the trial and error necessary to master sophisticated motor skills, such as singing in birds or speech and sports in humans.

"It means this part of the brain is important for instructing or allowing changes in the song," said Mimi Kao, first author of a paper in the February 10, 2005, issue of the journal Nature that demonstrates how the region modulates birdsong in real time. At the time the study was published, Kao was an HHMI predoctoral fellow in the laboratory of coauthor Allison Doupe at the University of California, San Francisco's Keck Center for Integrative Neuroscience.

TO LEARN MORE—AND LISTEN TO AUDIO CLIPS OF THE ZEBRA FINCH

www.hhmi.org/news/kao.html

BIRDS: CORBIS CRABTREE: TIM ARCHIBALD

> "My bike went flying off 25 feet to the left and I went flying off to the right. It all happened faster than anyone can imagine."
>
> RONALD VALE

Two-Wheel Fever

VALE: ANNE HAMERSKY

WILLIE MAYS PLAZA, JUST IN FRONT OF THE SAN FRANCISCO Giants' SBC Park, is inlaid with curving rows of intersecting bricks. Each engraved with the name of a charter seat holder, the commemorative bricks form a plaited pattern meant to mimic the stitching on a baseball. HHMI investigator Ronald Vale, who rides his titanium mountain bike across this plaza every morning on his way to work, had often idly noticed the bricks as he whizzed over them. But it wasn't until they felled him one rainy morning about a year ago that he came to appreciate their finer qualities.

"Turns out the bricks are highly polished. They're innocent enough until there's a little layer of water between them and your tire," says Vale. "Then there's no traction at all. My bike went flying off 25 feet to the left and I went flying off to the right. It all happened faster than anyone can imagine."

The calamity enforced Vale's belief in bike helmets but didn't dampen his love of cycling. The researcher bikes to and from his downtown laboratory at the University of California, San Francisco, 5 days a week—rain, shine, or fog. The 1-hour trek begins in Marin County, where Vale lives with his wife and their two children, a 10-year-old son and 8-year-old daughter he is already indoctrinating into the joys of cycling.

The commute, which he calls "the most glorious part of my day," takes Vale along a waterfront bike path to a ferry that carries him and his bike across San Francisco Bay, past Alcatraz and Treasure Island, to the City, where another waterfront path leads to his workplace. With his busy days at work and pleasant but hectic evenings at home, Vale says, the time commuting is good for thinking about science and experiments in general and for reflecting on the events of the day.

During the summer, when he feels a little more "luxurious" about his time, Vale crosses the Golden Gate Bridge on his 18-year-old Italian road bike, which he calls a "dear old friend." The bicycle has flown with him to a slew of far-flung scientific meetings, in places such as France, Italy, Ireland, Denmark, Sweden, Belgium, and even Moscow, where he found that bicyclers were a novelty. In the past, before his family expanded, Vale would add a week of bicycle touring to his plans. "It's the best way to see a country," he maintains.

Vale remembers spring in Tuscany, with its verdant hills and ubiquitous medieval villages, as the most spectacular of his trips. "I'd just roll into town, enjoy it for an hour or so, then move on," he says. "And sitting in a piazza eating fantastic Italian food was a terrific treat after a hard day of riding."

One day on that trip proved especially hard, and long. A turn that was 180 degrees in the wrong direction transformed a 90-mile day into a 150-mile trek. "I was hell-bent on making it to this one town," he says. "I didn't want to shortcut the circuit I had planned."

Vale hopes to resume his touring one day as a family affair. "When the kids can carry their own panniers, that'll be terrific." ■

~ Mary Beth Gardiner ~

MORE INFORMATION ON RONALD VALE'S RESEARCH

www.hhmi.org/bulletin/winter2005/kinesins/

SPRING '05

UPFRONT

CANCER AND THE CLOCK
A molecular mechanism explains why sensitivity to anticancer drugs changes with the time of day.

MODELING THE EARLY STEPS OF DNA PROCESSING
Scientist-educators—and students—join forces to solve a scientific puzzle.

FIGHTING THE PARASITES
HHMI international research scholars find promising ways to target Chagas disease and malaria.

EARLY TO BED, EARLY TO RISE
Researchers investigate a rare sleep syndrome.

IN THE EYE OF A FRUIT FLY
At UCLA, Utpal Banerjee guides undergraduates through serious research—and into the scientific literature.

FOSSIL GENES: ANOTHER GIFT FROM YEAST
Remnants of genes that fell into disuse offer clues on the process of natural selection.

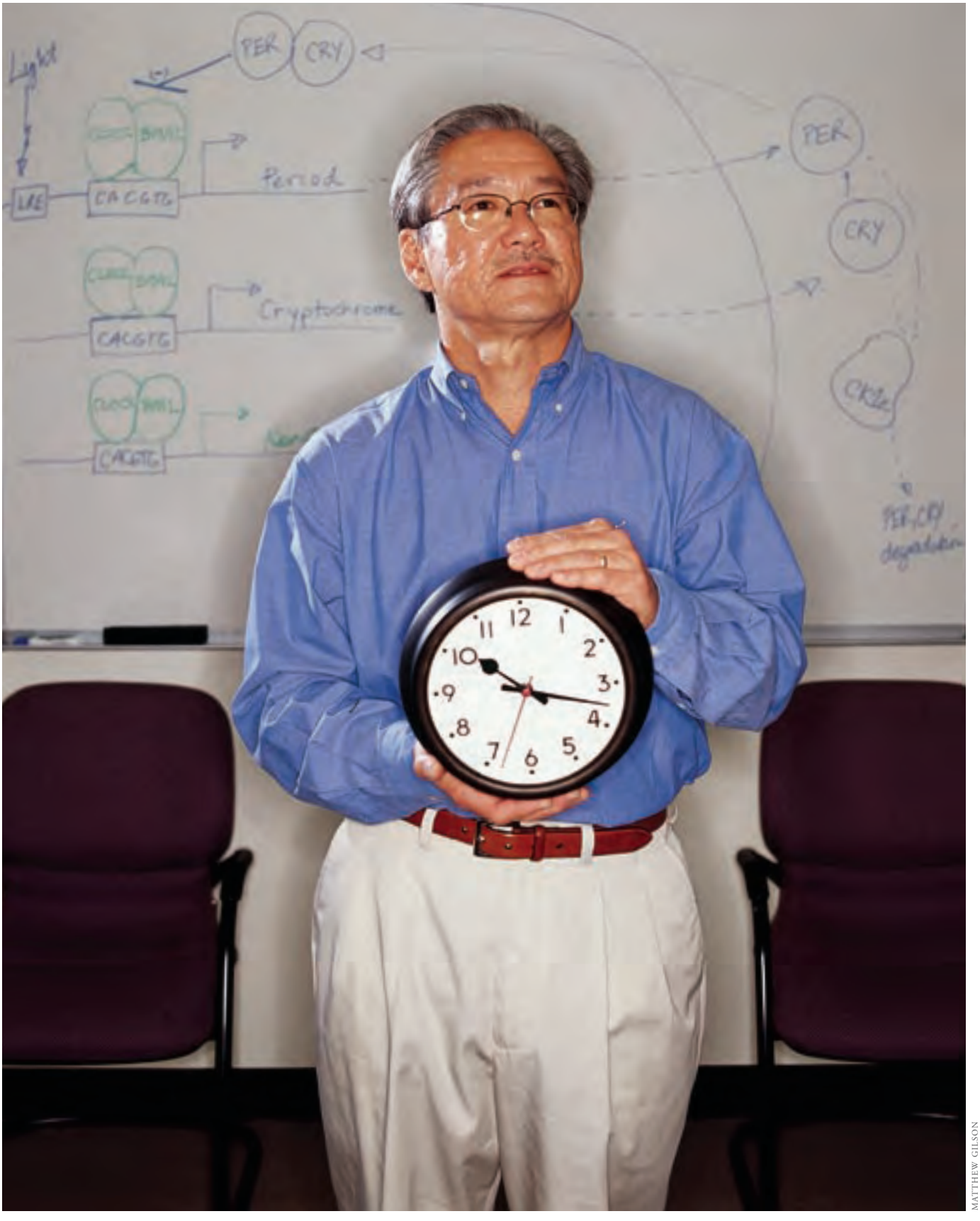
MOLECULAR FRAMEWORK PROVES A FERTILE FIND
Insights from a newly solved structure could lead to improved fertility drugs, or to contraceptives for both men and women.

At 2:00 a.m. on April 3, most of the United States adopted daylight saving time. Shortly before that date, HHMI scientists published research also having to do with time—in its biological aspects. Investigating the body's circadian rhythms, one research team discovered the molecular mechanism that explains why some cancer treatments tend to be more effective at certain times of day. A second study found a mutant gene that causes an odd "time-shift" trait that leads some of us to consistently nod off early and then wake up early.

Cancer and the Clock

A molecular mechanism explains why sensitivity to anticancer drugs changes with the time of day.

BELOW _ JOSEPH TAKAHASHI RESEARCHES THE GENETIC AND MOLECULAR BASIS OF CIRCADIAN RHYTHMS AND THE BODY'S "INTERNAL CLOCKS."



MATTHEW GILSON

ONCOLOGISTS HAVE LONG THOUGHT that cancer treatments tend to be more effective at certain times of day. Now, researchers have discovered a molecular mechanism that explains this sensitivity. In experiments with mice, they found that the body's internal biological clock affects the survival of immune cells targeted by the anticancer drug cyclophosphamide (CY).

Initial experiments with normal mice, performed by Marina P. Antoch during her tenure in the lab of Joseph S. Takahashi, an HHMI investigator at Northwestern University, confirmed that animals treated with CY in late afternoon survived better than those whose treatments were initiated early in the morning. Antoch extended these original findings—by examining the mechanism for this difference—after she moved to Cleveland, Ohio, and established a research program in the department of cancer biology at the Cleveland Clinic's Lerner Research Institute.

Antoch and her colleagues used genetically altered mice that lacked specific components of the body's internal clock. "Defects in *Clock* or *Bmal1* genes, which essentially damp the cycles of the internal clock," she reasoned, "may produce a very different effect when compared to defects in *Cryptochrome* gene, which, in contrast, 'jams' the circadian clock at the most active point in its cycle."

The researchers discovered that *Clock*-mutant and *Bmal1*-knockout mice showed high sensitivity to CY at any time it was administered—as if it were always at optimal times of day. In contrast, the *Cryptochrome*-knockout mice showed more resistance to the drug at all times than did normal mice. When the Antoch team analyzed the knockout animals' immune-system B cells, they found that the presence or absence of functional *Clock* and *Bmal1* genes determined their sensitivity to CY.

"This is not some vague metabolic difference between day and night," says Takahashi. "This is a tangible difference in the immune system that influences sensitivity" to certain anticancer drugs. The researchers' findings were published in the March 1, 2005, issue of the *Proceedings of the National Academy of Sciences*.

The results may well extend to the effects of other anticancer drugs, as well as to radiation therapy, and may provide a rationale for adjusting the timing of chemotherapy to make it less toxic. And, Antoch says, "they provide a rationale for developing drugs that can enhance the therapeutic index through the modulation of the circadian clock."

– Dennis Meredith –

A HEALTHY INTERNAL CLOCK KEEPS WEIGHT OFF

Staying up late, skipping meals, and snacking constantly resulted in weight gain, fatty livers, and high cholesterol levels for an unlucky group of mice whose internal biological clocks were genetically disrupted.

Researchers at Northwestern University—including HHMI investigator Joseph Takahashi—have identified wide-ranging molecular and behavioral changes in mice that have a faulty circadian system. In people, similar changes in body fat and metabolic activity are known as metabolic syndrome, which can lead to cardiovascular disease and type 2 diabetes.

The study suggests a surprising new angle for understanding and eventually preventing and treating obesity and related disorders in people. "Timing is critical to keep the metabolic symphony in tune," says researcher Joseph Bass, corresponding author on the paper. The work was published on April 21, 2005, in *Science Express*, which provides rapid electronic publication of select articles from the journal *Science*.

> "This is not some vague metabolic difference between day and night. This is a tangible difference in the immune system that influences sensitivity to certain anticancer drugs."
>
> JOSEPH TAKAHASHI

Early to Bed, Early to Rise

Researchers investigate a rare sleep syndrome.

MORE INFORMATION AT HHMI NEWS ONLINE
www.hhmi.org/news/ptacek5.html

A FEW OF US WHO CONSISTENTLY NOD OFF EARLY AND THEN wake up wide-eyed long before dawn can blame a newly found mutant gene. This odd "time-shift" trait—called familial advanced sleep phase syndrome (FASPS)—was recently studied in one affected family by neurologist Louis J. Ptáček, an HHMI investigator, and his colleague Ying-Hui Fu at the University of California, San Francisco.

The sleep-shifting mutation they found is in "a gene that was not previously shown in mammals to be a circadian rhythm gene," Ptáček explained.

In earlier research, Ptáček and his colleagues discovered an entirely different gene that causes a similar clock shift. Both arise because of so-called point mutations in the genes. This means that altering a single base pair in the gene's long DNA chain is enough to change a person's sleep behavior.

It's not clear how the mutant gene works to shift people's sleep time, their circadian rhythm, Ptáček says. Further studies may unravel some of the fundamental mysteries of how circadian rhythms are established and maintained in creatures that have evolved along very different paths.

The paper was published in the March 31, 2005, issue of the journal *Nature*. The lead author was Ying Xu, a member of the team in San Francisco. Other team members are at the University of Vermont and the University of Utah.

Fossil Genes: Another Gift from Yeast

Remnants of genes that fell into disuse offer clues on the process of natural selection.

DAVID NEVALA

WORKING IN THE LAB OF SEAN CARROLL (R), CHRIS TODD HITTINGER (L) MADE A BIG DISCOVERY IN ODD PATTERNS IN YEAST DATA.

THE BIG PICTURE

Chris Todd Hittinger's yeast finding is the latest in a spate of recent papers that connect physical or physiological change in an organism to its genetic evolution. One 2004 paper, for example, related jaw development in primates to a mutation in a muscle gene. This growing body of "evolutionary genomics" has implications for understanding how agents of disease, such as those involved in AIDS, make themselves difficult for the host's body and medical caregivers to target. As the field develops, "We'll have a good feeling for how evolution proceeds at the molecular and genetic level," says Hittinger. "It will likely give researchers a better perspective on how organisms will respond to various treatment regimes."

FOR THE PAST FEW THOUSAND YEARS, YEAST HAS LIVED A LIFE OF service, fermenting fruits and grains into wine and beer and breathing height into bread. More recently, yeast answered the call of science, serving as a model for countless experiments in genetics, genomics, and molecular biology. But long before it was so tamed, *Saccharomyces cerevisiae* and its single-celled cousins lived in the wilds of soil and foliage, grubbing out an existence from whatever sugar sources they could find.

At some point in that ancient history, millions of years ago, a number of those organisms lost their tastes for particular types of sugar. And as the yeasts acquired new tastes, they proceeded down different evolutionary paths. That divergence is recorded in the yeast genome today, as HHMI predoctoral fellow Chris Todd Hittinger at the University of Wisconsin–Madison has discovered. He reported the tale of this genetic and evolutionary change in the September 28, 2004, issue of the *Proceedings of the National Academy of Sciences*, in a paper coauthored with postdoctoral fellow Antonis Rokas and HHMI investigator Sean B. Carroll.

Using a menagerie of species, Carroll's lab studies the evolution of animal form and the closely related question of how animals develop from a single cell. Hittinger came to the lab in late 2001 with a double major in chemistry and biology from Southeast Missouri State University. "I was particularly interested in molecular evolution," he says.

For his graduate work Hittinger has been studying *Hox* genes, a class of genes that play a crucial regulatory role in the development of fruit flies and other animals by turning whole networks of genes on and off. Given the wealth of genomic data on yeast, he went on to examine a yeast gene that plays a similar regulatory role. The gene turns on the biochemical pathway that yeast uses to digest galactose, a common sugar that most organisms—from microbes to mammals—can consume. Galactose is an important component of mother's milk.

In searching the database of yeast genomes for the regulatory gene, "I noticed an odd pattern," says Hittinger. The gene was present in some, but not all, yeast species. He thought at first that this was a fluke of the data, so he dug further. Hittinger then found one species, *Saccharomyces kudriavzevii*, that retained the outline not only of the regulatory gene in question but of all seven genes in the galactose pathway. These genes were literally full of holes and other markers, however, indicating that they were nonfunctional: some DNA bases were missing, or the code contained "stop" instructions in the middle of the sequence rather than at the end. Without these genes intact, the yeast lacked the machinery to consume galactose—it had in essence lost its taste for the sugar.

Hittinger took his observations to Carroll, who remembers saying, "Write the paper!" What Hittinger had found was a

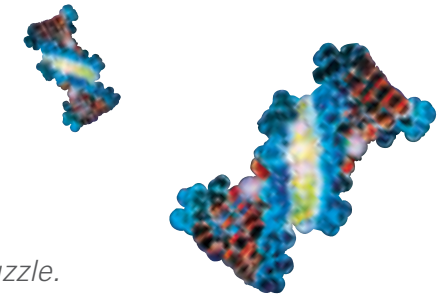
set of skeletal, or fossil, genes. "I could immediately tell him," says Carroll, "that this was a big story—a remarkable case of seven functionally related genes all in the process of decay."

Hittinger went back to the lab bench to sequence the genes in yeasts where data were incomplete. He and Rokas then pieced together a yeast family tree indicating that the ability to consume galactose was lost at least three separate times in yeast evolution. "Each one of the lineages found itself in a niche where galactose was less important for its survival," says Hittinger. In the case of *S. kudriavzevii*, which exists in the wild today only in Japan, the researchers note that it also has the unusual ability to consume a complex plant compound called inulin. They speculate that the yeast may have abandoned galactose as it acquired the specialized physiology to exploit a food source that few other organisms have the biochemistry to use. The remnants of the galactose pathway, however, can still be detected as the genes go through the evolutionary process of disappearing.

"It's such a signature of the way natural selection works," says Carroll. "It's use-it-or-lose-it. These genes fell into disuse, and they're being eroded like fossils on a shoreline." ■

~ Christine Mlot ~

> "I could immediately tell him that this was a big story—a remarkable case of seven functionally related genes all in the process of decay."
>
> SEAN CARROLL



Modeling the Early Steps of DNA Processing

Scientist-educators—and students—join forces to solve a scientific puzzle.

TWO HEADS AND THREE TOOLS ARE sometimes better than one. An HHMI professor and a colleague who mentor HHMI-supported undergraduates are using the tools of molecular biology, biochemistry, and biophysics to solve a scientific puzzle.

What has their attention is the mysterious mechanism that enables DNA replication in simian virus 40 (SV40), a mammalian model for that vital process. "We've taken what began as a biochemical and molecular genetic approach, then used structural biology to learn about protein interactions, and then returned to biochemistry to validate our structural model in a functional way," said Ellen Fanning, an HHMI professor at Vanderbilt University, in Nashville, Tennessee.

Fanning and Walter Chazin, director of Vanderbilt's Center for Structural Biology, reported their findings in the April 2005 issue of *Nature Structural & Molecular Biology*, published online March 27, 2005.

The scientists sought the mechanism by which single-stranded DNA (ssDNA) breaks free from the chains of its binding protein to allow repair or replication, a process that is not well understood. Fanning and Chazin found structural and biochemical evidence for that mechanism, providing a model of this early step in DNA processing in mammalian cells.

Every organism has an ssDNA-binding protein for DNA replication and repair pathways. In eukaryotes (organisms whose cells have a nucleus), it is called replication protein A (RPA). One of the common functions of RPA in DNA processing pathways is facilitating "hand-off," a process that ensures that the correct proteins move into place along the ssDNA to begin DNA processing.

RPA plays an important protective role for ssDNA. RPA binds with at least a dozen different repair and replication proteins. The question has been how RPA gets dislodged, allowing various enzymes access to the DNA for necessary processing.

Using SV40 as a model system, the scientists mapped atomic-level interaction on the surfaces of proteins involved in DNA processing. They used biochemical and genetic tools to determine how the interactions of those proteins promote synthesis of small segments of RNA known as primers, which are required for initiation of DNA replication.

"This provides a testable model for how the ssDNA-binding protein can be displaced from single-stranded DNA to allow a DNA processing pathway," Fanning said. "This is a general phenomenon that happens throughout all DNA processing pathways." ■

~ Cori Vanchieri ~

In the Eye of a Fruit Fly

At UCLA, Utpal Banerjee guides undergraduates through serious research—and into the scientific literature.

BELOW _ IN UTPAL BANERJEE'S LAB AT UCLA, "EACH STUDENT HAS TO DO WHATEVER IT TAKES—PCR, COMPUTER ANALYSIS, SEQUENCING—TO FIGURE OUT WHY THE MUTATIONS ARE DOING WHAT THEY'RE DOING."

AT FIRST GLANCE, UTPAL BANERJEE'S LAB at UCLA looks like any other. Across three rows of Formica-topped counters, amid lab equipment and bottles of chemical reagents, 15 microscopes stand at the ready. But the researchers who toil at these workstations are a lot younger than those in a typical lab. Mostly freshmen and sophomores, they're enrolled in an unusual biology class that's open to all undergraduates.

In this lab, which serves as one of the venues for the course, students conduct real experiments. Unconstrained by canned laboratory exercises, many of them are deciphering mutant fruit fly genes, and their research has generated publishable data that other scientists are using.

"This teaches them a different type of reasoning process," says the amiable Banerjee, an award-winning teacher and chair of UCLA's department of molecular, cell, and developmental biology. "They're able to do experiments with uncertain results and have some pride of ownership about what they uncover."

The Indian-born scientist was one of 20 HHMI professors who were awarded $1 million grants in 2002 to find innovative ways to improve undergraduate biology education. Using these funds, Banerjee, along with lecturer Allison Milchanowski and postdoctoral fellows Jiong Chen and Gerald Call, created the course to give students a real taste of the excitement of scientific discovery.

Combined with traditional classroom lectures that provide background information and a computer lab where students learn how to do genetic analysis, the bench experiments give them hands-on research experience.

Banerjee, whose research focuses on the eye, picked the fruit fly *Drosophila* as a model system because the flies reproduce rapidly, making it easier to generate large numbers of them and observe their life cycle, and because all their genes are known. What scientists don't know—and what Banerjee's students are busily uncovering—is how these genes function. The only way to discover this is to mutate a gene, says Banerjee, and then see what happens to the fly's eye.

Some of the students' research was reported in the February 2005 issue of *PLoS Biology*, published by the Public Library of Science. The paper had 148 coauthors—including 138 undergraduate students.

For their part, the students believe the course helps them refine their career goals. At the very least, it gives them a leg up on the competition when they apply to graduate school. Joy Wu, for example, who has taken the class for 6 quarters, is now headed for a career in neuroscience. "That wasn't my goal before, but as I progressed through the class I realized it's what I wanted to do," says the UCLA senior. "And when I've gone to my Ph.D. interviews, I've realized how lucky I am because my experience is different from that of most undergraduates, and I know my way around a lab." ■

~ Linda Marsa ~

BANERJEE: JOE TORENO *FLY:* AFTER SHATTUCK, 1972

Molecular Framework Proves a Fertile Find

Insights from a newly solved structure could lead to improved fertility drugs, or to contraceptives for both men and women.

WHY DO RESEARCHERS WORK SO HARD TO make three-dimensional crystal structures of molecules and their minuscule kin? "Most of these structures end up being a wellspring of ideas," says HHMI investigator Wayne A. Hendrickson. "They are often filled with unexpected things."

So it was with Hendrickson's recent work to solve the crystal structure of a particular complex—follicle-stimulating hormone (FSH) binding to its receptor. The structure not only yielded clues about how the interaction works, but opened new research avenues for fertility treatments as well as contraception. Medical practitioners already use FSH injections for treating infertility, but researchers think that if they learn how FSH binds to its receptor on the surface of cells, they may be able to improve such therapies.

One of a family of signaling molecules—including luteinizing hormone, chorionic gonadotropin, and thyroid-stimulating hormone—FSH is a key regulator in human reproduction, controlling egg development in women and sperm production in men. Each of these hormones is composed of an α and a β subunit. Because they all use the same α subunit, researchers thought the specificity they have for their own receptors had to come from the β subunit.

Hints that this might not be strictly true had already come from the x-ray crystal structure of FSH alone, which James Dias and colleagues at the Wadsworth Center in the New York State Department of Health solved in 2001. But knowledge of that structure left open some big mysteries, including how an apparently disordered (flexible) C-terminal tail in the α subunit fit into the complex.

Now that Hendrickson, a professor of biochemistry and molecular biophysics at Columbia University College of Physicians and Surgeons, and Qing Fan, a postdoctoral fellow in his laboratory, have solved the structure of the hormone bound to the extracellular domain of the receptor, it's clear why the α-subunit tail is so important. If it is mutated or deleted, the hormone can't bind to the receptor. The researchers reported their results in the January 20, 2005, issue of *Nature*.

For Hendrickson, though, the excitement of the work comes not just from the answers it provides but from the new ideas it generates. For example, in many protein-protein interactions, the interface between the molecules tends to be "greasy" and excludes water, but in this case the contact area between the receptor and the hormone was highly charged, full of negative and positive charges attracting each other.

> "Structures end up being a wellspring of ideas. They are often filled with unexpected things."
>
> WAYNE HENDRICKSON

"We knew that charge was important in the binding," says Dias, "but the new structure showed us that stereochemistry [the spatial arrangement or organization of the molecules] was also important and we couldn't have gotten that information without the structure."

The new structure provided by Hendrickson and Fan gives a picture of how the hormone interacts with part of the receptor protein, but it doesn't show how the receptor becomes activated in response to hormone binding. To observe that phenomenon, the researchers think they need to see the hormone binding to the whole receptor protein, including the membrane-spanning region. This presents a formidable challenge because proteins that are designed to reside in membranes are difficult to purify and crystallize.

CHRISTOPHER JONES

QING FAN AND WAYNE HENDRICKSON SOLVED THE STRUCTURE OF FOLLICLE-STIMULATING HORMONE (FSH), WHICH IS CENTRAL TO REPRODUCTION IN MAMMALS.

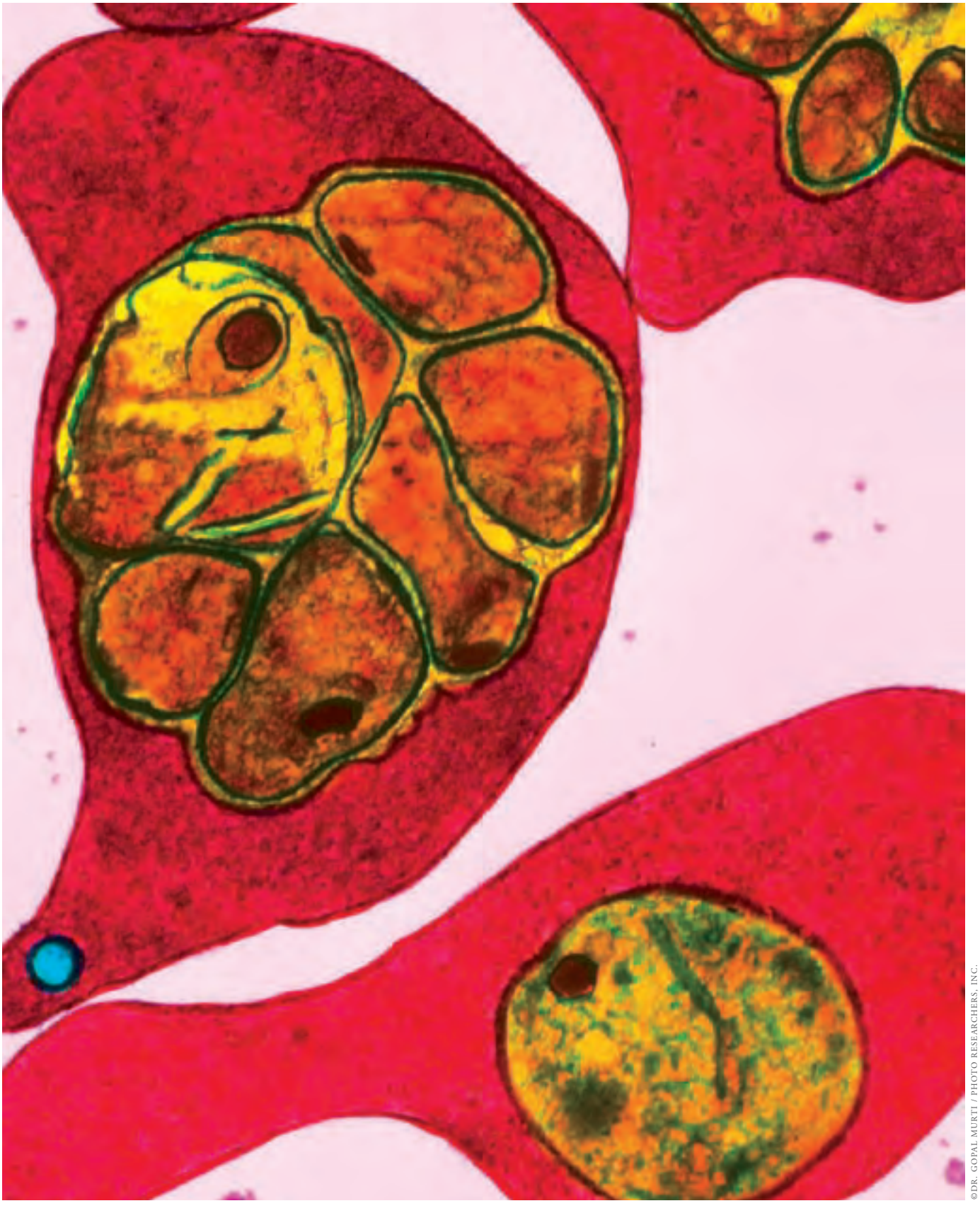
Meanwhile, the team is starting to think about how the current structure might be used in medical practice. "Protein-protein interfaces are notoriously difficult to disrupt with small-molecule drugs," says Hendrickson. "But if we could disrupt the hormone-receptor interaction, we'd instantly have a contraception approach that works for both men and women." Conversely, better knowledge of how FSH interacts with its receptor might also help researchers develop a new, orally available mimic that could be used to treat infertility by stimulating egg or sperm production. ■

~ Rabiya S. Tuma ~

Fighting the Parasites

HHMI international research scholars find promising ways to target Chagas disease and malaria.

BELOW _ MALARIA PARASITES EXIST "CLOAKED" WITHIN RED BLOOD CELLS, WHERE THEY DIVIDE INTO SMALLER CELLS CALLED MEROZOITES THAT ARE RELEASED INTO THE BLOODSTREAM WHEN THE CELL EVENTUALLY BURSTS. (SEE SIDEBAR ON MALARIA, OPPOSITE.)



THE CHALLENGE OF CHAGAS

BIOGRAPHERS AND HISTORIANS GENERALLY believe that Charles Darwin caught Chagas disease during his voyage on *The Beagle* in the early 1830s, and that the disease may have been the root cause of the chronic illnesses that affected Darwin's health until his death in 1882. Today, 123 years later, there is still no effective treatment for the chronic form of Chagas disease, which continues to kill tens of thousands of people annually. But after several decades of research, two scientists think they have found a possible cure.

The disease—caused by the parasite *Trypanosoma cruzi*, which is spread by biting insects known as "kissing bugs"—currently infects between 16 and 18 million people in Central and South America, with 120 million people at risk. Chagas disease occurs in an acute form mainly in children, but in adults there often are no acute symptoms. When the infection reveals itself a decade or two later, irreversible damage has been done to the heart, esophagus, and colon; the patient gets progressively sicker, usually dying of heart failure. The "kiss" of the parasite's vector has aptly been called the kiss of death.

"The 'kiss' of the parasite's vector has aptly been called the kiss of death."

JULIO A. URBINA, MIGUEL A. BASOMBRIO

The drugs currently used to treat Chagas disease, mainly benznidazole, have serious drawbacks. They don't work against the chronic form, which kills up to a third of those infected; they can have toxic side effects; and it is common for the parasite to have a natural resistance to them. So an alternative is badly needed. A team led by HHMI international research scholars Julio A. Urbina of the Venezuelan Institute of Scientific Research and Miguel A. Basombrio of the National University of Salta (Argentina) believes it has found that alternative in an experimental compound called TAK-187.

This compound, under investigation for a different therapeutic end as a possible systemic antifungal treatment, turns out to target the Achilles' heel of *T. cruzi*, which Urbina, Basombrio, and colleagues have discovered from 25 years of studying the basic biology of the parasite. To complete its life cycle, *T. cruzi* needs to synthesize certain types of steroids, called sterols, that are present in nucleated cells. But the parasite cannot make use of the sterol that is most abundant in the tissue of its mammalian host—cholesterol. Instead, it prefers one called ergosterol.

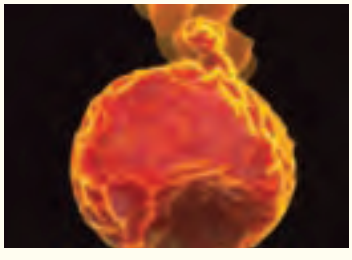
This is where TAK-187 comes in, says Urbina. "It is a compound that blocks the synthesis of ergosterol in the parasite without affecting that of cholesterol in the hosts, and it penetrates into the deep tissues where the parasite thrives."

His team infected mice with a strain of *T. cruzi*, waited until they showed symptoms in a model of the chronic form of human Chagas disease, and then treated the animals with benznidazole, TAK-187, or a placebo. The two drugs either suppressed the parasite load in the mouse blood and tissue or eliminated *T. cruzi* entirely. But TAK-187 did so at a tenth of the dose, and it worked as well when given every other day, whereas benznidazole had to be administered daily. Postmortem tissue analysis also showed that TAK-187 was more effective than benznidazole at preventing inflammation and damage in the heart and skeletal muscle of the mice.

The researchers, whose work was published in the April 2005 issue of *Antimicrobial Agents and Chemotherapy*, believe the greater efficacy of TAK-187 comes down to the fact that it strikes at the parasite's ability to replicate and that it is more slowly metabolized by the host, allowing a sustained antiparasitic action. Citing these "potentially interesting" findings together with the "urgent need for new drugs," John M. Kelly of the London School of Hygiene and Tropical Medicine says that "this preliminary report should point the way to trials on human patients." ■

~ Laura Spinney ~

THE CLOAK OF MALARIA



Once in the human body, malarial parasites spread to the liver and multiply in red blood cells such as this one, misshapen and bulging from the malarial parasites within.

In another promising advance against parasitic disease, HHMI international research scholars Alan F. Cowman of the Walter and Eliza Hall Institute of Medical Research, in Melbourne, Australia, and Brendan S. Crabb of the University of Melbourne have peered behind the invisible cloak of the malaria parasite *Plasmodium falciparum*. This parasite invades the host's red blood cells, from which it exports proteins. Some are virulence factors, aiding the parasite's spread and colonization of its host; others remodel the surface of the red blood cell, making it undetectable by the host's immune system.

In a paper published in the December 10, 2004, issue of *Science*, Cowman's group identified the common mechanism by which the parasite exports all 400-plus proteins. That mechanism "provides an extremely good target for the development of new drugs," he says.

In a follow-up paper published in the April 8, 2005, issue of *Cell*, the Cowman and Crabb groups looked specifically at the parasitic proteins that render the red blood cell invisible. The immune system eventually works out what the masking protein is, and it mounts an immune response. But the elusive *P. falciparum* then switches to another protein—and it has a repertoire of at least 50 to choose from. The researchers shed even more light on this trick by showing how the gene for the protein in question is activated while the others are silenced.

—*L.S.*

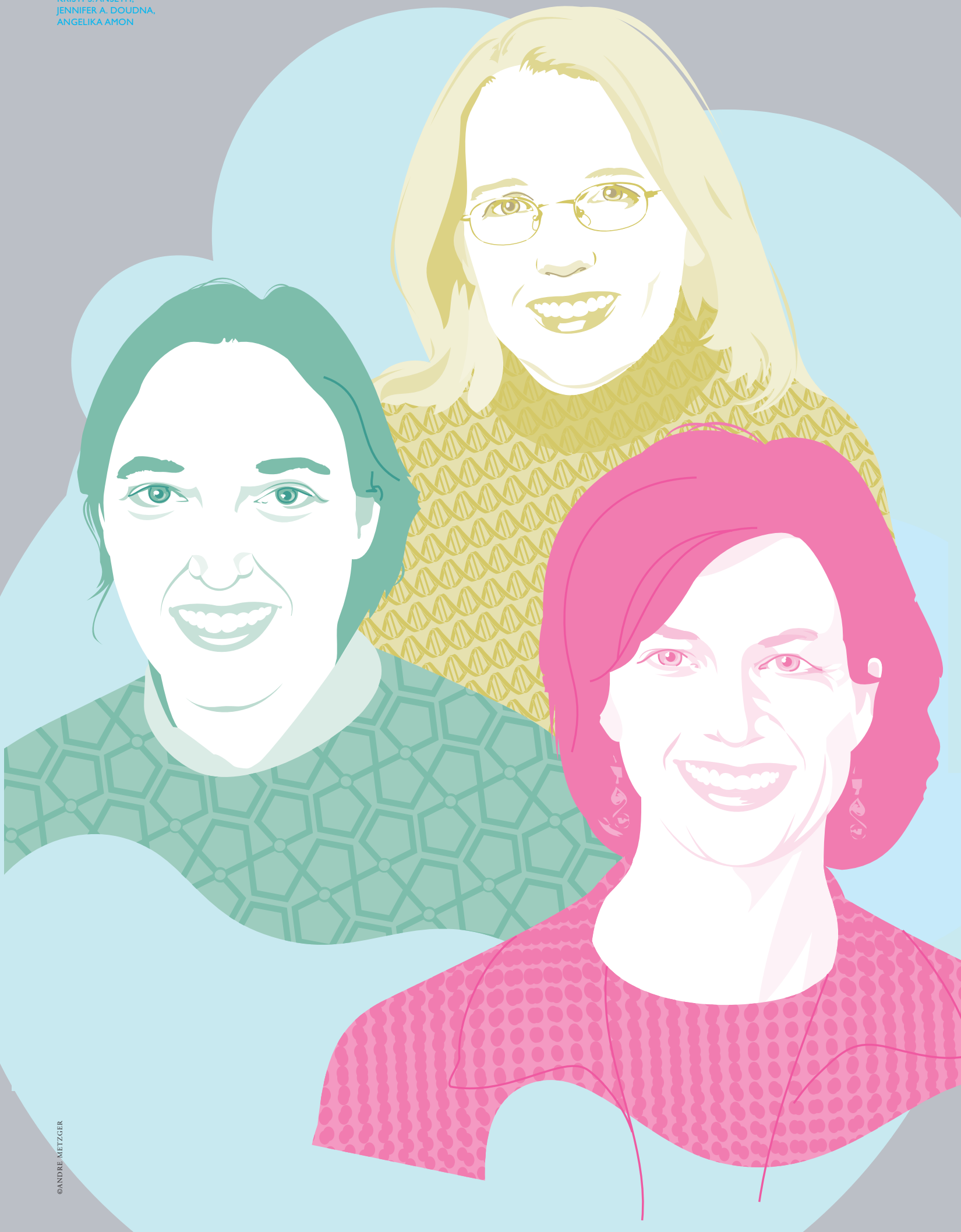
* * *

RENAISSANCE WOMEN

* * *

THREE HHMI INVESTIGATORS ARE SETTING THEIR RESPECTIVE FIELDS ON FIRE, AND EACH HAS WON NSF'S WATERMAN AWARD.

TEXT BY KENDALL POWELL



CLOCKWISE FROM TOP_
KRISTI S. ANSETH,
JENNIFER A. DOUDNA,
ANGELIKA AMON

The latest chapter of the "debate" over whether women can compete in science has been playing out recently in print and over airwaves nationwide. But Rita Colwell thinks some of the issues raised today against women in science have already been soundly refuted. "We shouldn't be reliving those arguments from the 1940s and '50s," says Colwell, a former director of the National Science Foundation (NSF) who is now a professor at the University of Maryland and Johns Hopkins University.

As evidence, she holds up three of the last five winners of NSF's Alan T. Waterman Award—three HHMI investigators who have shown "unequivocally that women scientists can compete."

Angelika Amon, Kristi S. Anseth, and Jennifer A. Doudna work in different areas of science, but they share similar career stories. Each, for example, won the Waterman award, a $500,000 honor that recognizes significant research by an investigator under the age of 35 (see sidebar). "Significant" may in fact be an understatement. Anseth's work in tissue engineering, Amon's contributions to cell-cycle regulation, and Doudna's discovery of RNA ribozyme structures have fundamentally changed the ways their peers approach critical questions.

What's more, these women stand out not only for their scientific successes, but also for the ways they run their labs and their lives. Colleagues of the three describe similar traits among them—self-assurance without arrogance, an enthusiasm that moves projects forward, boundless energy, and personal warmth. Setting an example for young scientists, their mix of optimism, confidence, and unending curiosity has resulted in successful careers.

"It's a combination of being extremely motivated and yet optimistic that things are going to work out. It's a very refreshing personality to encounter in science," James M. Berger says of Doudna, his fellow faculty member in the department of molecular and cell biology at the University of California, Berkeley.

* * *

UNBRIDLED ENTHUSIASM

In her office at the University of Colorado, Boulder (CU), as the winter sun bounces off her strawberry-blonde hair, Kristi Anseth is the very picture of scientific gusto. Animated and enthusiastic, she scrolls through slides that illustrate her research in tissue engineering—an intersection of biology, chemistry, and engineering. Her casual minilecture heats up when she starts talking about an area where she's clearly made a mark—applying the principles of light-activated polymers (chains of molecules) for regrowing tissues.

Throughout the early stages of her research career, Anseth gave those particular polymers a lot of consideration. "I thought the advantages of photo-polymers would be tremendous for biological applications," she says. "But we had been working on things for high-tech processes, so we didn't have biocompatible materials, yet." As a postdoctoral fellow and later in her own lab, Anseth persistently pursued her hunch. Eventually she developed and refined a technique in which liquid materials are injected into the body and then activated by light to form a gel-like scaffold. This structure then enables the delivery of cells and provides a framework for them to repair damage or lay down new tissue in an organized fashion. And the light-activated chemistry is safe to use around the cells.

A scaffold starts as a relatively simple mix of components. Its basic building block is a core molecule, bracketed on either side by a cross-linking molecule, with each chemical chosen to encourage a particular kind of cell to grow. The final ingredient is a tiny dash of an initiator molecule that, once activated by a particular wavelength of light, causes the cross-linker ends to polymerize, or form a compound. This chemical stew can be manipulated to change the meshwork's density, deliver growth factors to cells, and control how the scaffold degrades once its job is done.

Anseth says, however, that the biomaterials were merely "the first phase" needed for her lab to tackle specific medical problems. Nevertheless, it was a major leap forward for the tissue-engineering world—and the basis for her winning the Waterman award in 2004.

"She was one of the first to apply a combination of molecular and cell engineering to truly innovative problems of tissue engineering," says Nicholas A. Peppas, now a professor of chemical engineering at the University of Texas at Austin, who mentored Anseth when she was an undergraduate and a postdoctoral fellow at Purdue University. "What she has done is really phenomenal and seminal: to create new tissues in relatively simple biocompatible ways that can be optimized."

With new materials in hand, Anseth's team has turned to the human knee, which sits in a cushion of cartilage that can be injured or wear out. "Bone heals itself, but cartilage doesn't," notes Anseth. With an injectable scaffold—a minimally invasive procedure—the idea is to coax cartilage-producing cells, also injected, to repair damage naturally. "We're trying to get the body to heal itself when something goes awry." Not an easy task, even with the advanced technology. Engineered cartilage grown in a lab dish has stumped the group because it lacks the mechanical properties of real cartilage. Engineered cartilage grown in an animal, however, mysteriously gains the correct squishiness.

Anseth's lab has created a hydrogel scaffold now being tested in goat knees. Why goats? "Because they are very active, roaming around all day," says Anseth. The lab is also tackling problems in Parkinson's disease and heart-valve defects, which are characterized by much more complicated cellular interactions.

"Can we put in the critical components of the fetal cells' environment?" Anseth asks. For heart-valve defects, a scaffold should mimic normal heart-valve development. "Can we grow it

The Waterman Award

Congress established the Alan T. Waterman Award in 1975 to celebrate the National Science Foundation's (NSF) 25th anniversary and to commemorate its first director, who served from 1951 to 1963 under Presidents Truman, Eisenhower, and Kennedy. Awardees receive a medal and a grant of $500,000 over 3 years for scientific research or advanced study.

Candidates for the award must be 35 or under (or not more than 7 years beyond receipt of their Ph.D.). Selection is based on exceptional individual research in the mathematical, physical, medical, biological, engineering, social, or other sciences. Criteria include originality, innovation, and impact of the work.

"The Waterman first recognizes excellent scientists," says Rita Colwell, the former NSF director who presented the award to both Doudna and Amon. "But it also reaffirms the career trajectory and provides the confidence that every young scientist, male or female, will need."

"Anseth was one of the first to apply a combination of molecular and cell engineering to truly innovative problems of tissue engineering."
—Nicholas A. Peppas

ANSETH LAB: CONCENTRATION AND DISTRIBUTION OF THE EXTRACELLULAR MATRIX COMPONENT CHONDROITIN SULFATE (RED) IMPART DESIRABLE MECHANICAL PROPERTIES TO BODY TISSUES, SUCH AS THE PIG AORTIC VALVE LEAFLET SHOWN HERE—JUST ONE OF MANY CONSIDERATIONS THAT PLAY INTO THE BIOENGINEERED TISSUES THAT THE LAB DEVELOPS.

CHARLIE NUTTELMAN / ANSETH LAB

in a pulsatile bioreactor like a beating heart?" she wonders. And although she often gets grant reviews back with comments like, "This will never work," or, "Crazy idea," Anseth clearly believes that the answer to these "Can we?" questions is, "Yes."

Leslie Leinwand, a cell biologist at CU and a collaborator on the heart-valve project, says that what impresses her most "is Kristi's incredible enthusiasm for what she does." She has a particular affinity for interdisciplinary projects and bounces productively, for example, between polymer engineering and basic cell biology.

Anseth's passion for science carries outside the lab, too. Committed to basic scientific education as well as research, Anseth teaches classes like freshman introductory chemistry each year.

Off campus, Anseth and her husband, Christopher Bowman, a chemical engineer at CU, visit the local dog trail, playing with their yellow Lab puppy, Elway. And she jogs the Boulder Creek path that winds from campus into the Rockies—it is, she says, a "fun place to think in the middle of the day."

* * *

DRIVING FORCE

In her lab at the Massachusetts Institute of Technology (MIT), Angelika Amon also runs hard. On a given morning, she juggles meetings with undergraduates, calls (in German) from her husband, a side trip to do damage control on a leak in the microscope room, and a continuous stream of lab workers popping in with news. She refuels periodically from a stash of diet Coke in her office.

Amon began making headlines in the cell-cycle world as a graduate student when she published a discovery on mitosis, or cell division. Her first paper, in *Nature*, showed that a signal previously thought to be the universal trigger for entry into mitosis—the stage when the chromosomes of a dividing cell prepare to separate—was not in fact necessary for yeast cells to start mitosis. She has pursued questions about what regulates cell division ever since.

Amon won the Waterman award in 2003 for her work showing that a protein called Cdc14 was critical for making sure cells move forward through mitosis correctly. "Chromosome segregation is an irreversible event," she explains. "Nothing in mitosis comes after it. And if something goes wrong, you can't fix it later." Improper chromosome segregation in particular can lead to cancer and birth defects.

The Cdc14 discovery had an interesting twist—the protein is active only when it is released from a subcompartment of the nucleus called the nucleolus, where its inhibitor resides. That observation led to the discovery that two distinct regulatory networks release and activate Cdc14 at different times during mitosis. One network, called the mitotic exit network (MEN), was known to stimulate a sustained release of Cdc14 at the very end of the cell-division process, but Amon's group found another regulatory network that controls a very small release of Cdc14 much earlier in mitosis. The new network, fourteen early anaphase release, or FEAR (witty acronyms are a running lab joke), turns on Cdc14 as the last bits of chromosomes are separating.

"Why bother with two pathways? Cells are so clever, it's really amazing," Amon says. The small amount of FEAR-released Cdc14 stimulates MEN in a positive feedback system. "And it gives the cell a built-in delay to make sure that chromosome segregation and exit from mitosis are coupled."

This work began when Amon was a fellow at the Whitehead Institute for Biomedical Research and continued when she moved into her new lab at MIT, literally across the street.

"Some people work on a problem, but Angelika attacks it," says Gerald R. Fink, a geneticist at the Whitehead Institute and MIT and an HHMI medical advisory board member. He mentored Amon as a fellow. "She goes right to the core of what's important in a problem and solves it. She took a rather unconnected series of events in mitosis and built them into a simple model."

And while Amon's studies of the yeast cell cycle have created a nearly seamless story, there was one hiccup in her career. As a postdoc, Amon followed an adviser's suggestion that she work in a different field, germ cell development, and with a different system—fruit flies. "Flies weren't for me," she remembers, making a face. "I never got the hang of it." Fortunately, her adviser and other mentors at Whitehead were extremely understanding, encouraging her to apply for a fellowship so that she might return to her favorite questions in yeast,

"Amon's first paper, in *Nature*, showed that a signal previously thought to be the universal trigger for entry into mitosis—the stage when the chromosomes of a dividing cell prepare to separate—was not in fact necessary for yeast cells to start mitosis."

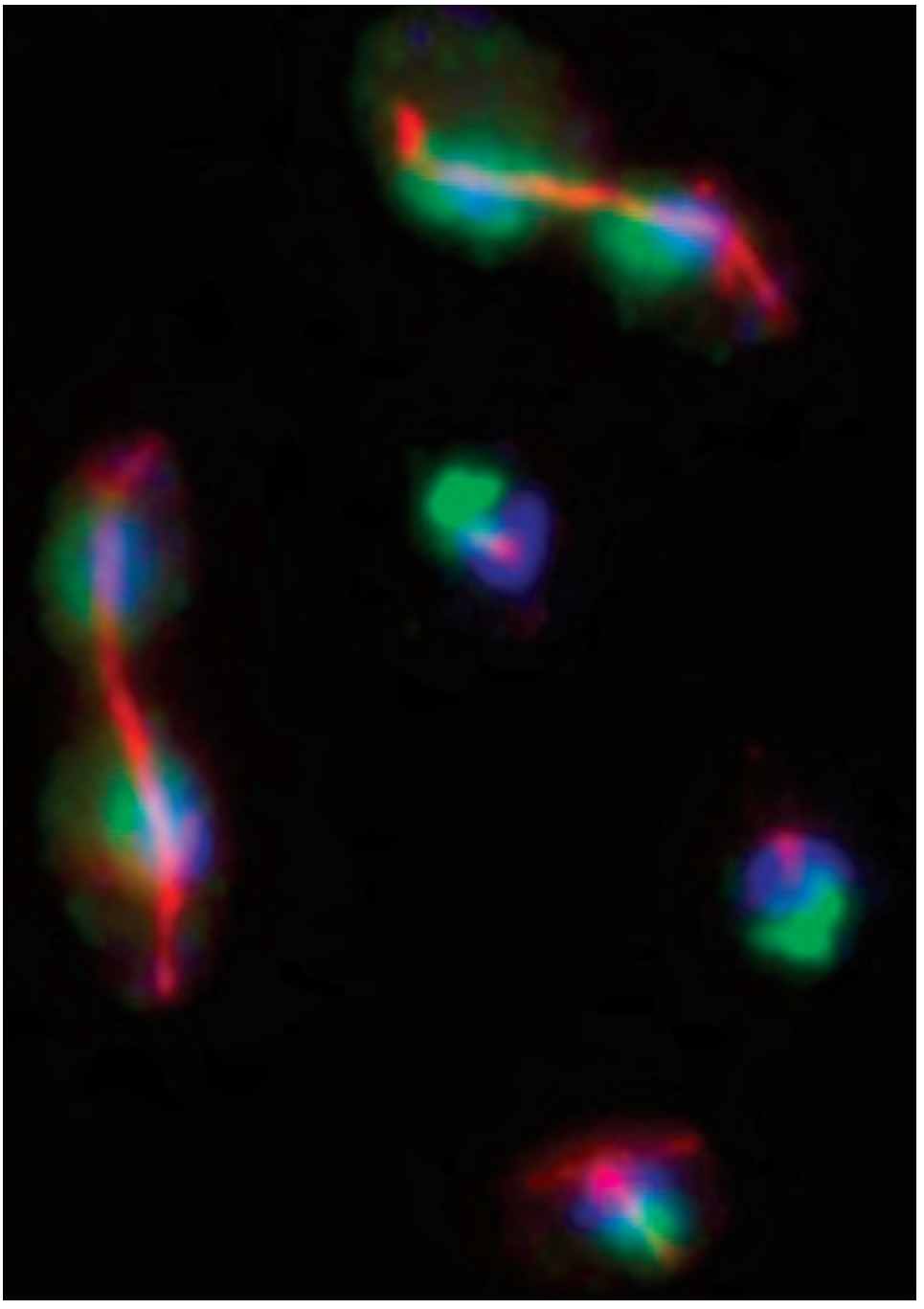
where "the only rate-limiting factor is my brain."

Amon is a strong proponent of basic research. "Like Faust, I want to know because I want to know," she says. Amon also takes her responsibility to educate young scientists seriously. "What I'm most proud of," she says, leaning forward for emphasis, "is that all of my students are doing well."

Her students return the admiration. "She's the only scientist I've met who is that smart and that warm," says Rami Rahal, a third-year graduate student.

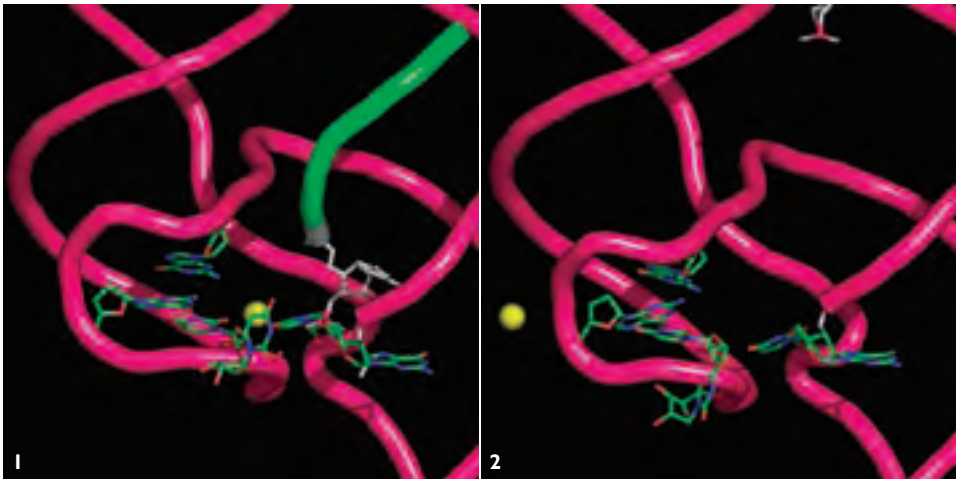
When she's not working, Amon spends time with her husband, Johannes Weis, a computer scientist, and daughters, Theresa, 6, and Clara, born April 12 this year. She is obviously proud of Theresa's contributions to the lab's decor—stick-figure portraits adorn a whiteboard.

Kim Nasmyth, her former graduate adviser at the Research Institute of Molecular Pathology in Vienna, Austria, says Amon learned an important lesson early, that "science is an impersonal thing done by personable people." When he was new to Vienna, she helped him learn German and the Viennese waltz. But in her experiments, he says, she always did what had to be done, and she was always completely fearless.



COURTESY OF AMON LAB *Adapted with permission from the cover of* Cell, *January 25, 2002; ©2002 Elsevier Science*

ABOVE _ AMON LAB: THE PROTEIN PHOSPHATASE Cdc14 HELPS REGULATE THE TIMING OF CELL DIVISION IN BUDDING YEAST. Cdc14 IS SHOWN IN GREEN, MICROTUBULES IN RED, AND DNA IN BLUE. BELOW _ DOUDNA LAB: COMPARISON OF THE CRYSTAL STRUCTURE OF THE RIBOZYME IN THE PRE- AND POST-CLEAVAGE STATES (PANES 1 AND 2, RESPECTIVELY) REVEALS A SIGNIFICANT CONFORMATIONAL CHANGE AND EJECTION OF A CATALYTICALLY CRITICAL METAL ION (YELLOW SPHERE) AFTER CLEAVAGE.



COURTESY OF AILONG KE / DOUDNA LAB *(from Ke, et al.,* Nature *429:201-5, 2004)*

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RELENTLESS PURSUIT

Colleagues also use words like fearless to describe Jennifer Doudna—a structural biologist and biochemist at the University of California, Berkeley—often in reference to the 5 years she spent in pursuit of a risky but important goal: to solve the first molecular structure of a large catalytic RNA, called a ribozyme.

"It took tremendous courage to stake her career on this," says Joan A. Steitz, a molecular biologist and HHMI investigator at Yale University School of Medicine. Steitz's department hired Doudna as an assistant professor even before she had solved the structure. "It was pretty obvious that she had the drive; and if it was going to work at all, she'd be the person to get it done."

Doudna's fascination with the biochemistry of ribozymes started in graduate school. Then, for her postdoctoral fellowship, Doudna approached Thomas R. Cech, the codiscoverer of ribozymes (and current president of HHMI), with the idea of doing x-ray crystallography on a ribozyme to learn its structure. "It was the next obvious thing to push the field forward and understand the molecular mechanisms," she says. Cech was excited by the idea, Doudna recalls, because he knew the importance of seeing what ribozymes looked like, but it was by no means a sure bet. The single-helix structure of a strand of RNA and the simple folded structure of transfer RNA had already been defined, but ribozymes were much larger and more complex molecules. Skeptics said they would not form the crystals needed to reveal their structure.

When Yale hired her, Doudna had succeeded in growing high-quality RNA crystals that would scatter x-rays into a sharply ordered diffraction pattern. That pattern is then used to back-calculate a three-dimensional structure of the molecule forming the crystals. She still had a final hurdle—the "phase problem." To calculate correctly, a crystallographer must know the phase of the x-ray waves.

CONTINUED ON PAGE 56

ALL PHOTOS: BRIAN SMALE

BIO INFOR MATICS

MATHEMATICIAN TURNED GENETICIST, THE ERUDITE PHILIP GREEN USES COMPUTERS AND EQUATIONS TO MODEL A NEW KIND OF BIOLOGY.

TEXT BY STEVE OLSON

The sequencing of the human genome—along with the genomes of organisms both similar and dissimilar to humans—has made the last few years as exciting for biologists as the beginning of the 17th century was for astronomers. "It's been absolutely revolutionary," says HHMI investigator David Haussler at the University of California, Santa Cruz. "The group of papers revealing the DNA sequences of the key organisms has made this a very special time."

But new findings must be interpreted. What does it mean when four moons are found orbiting Jupiter—or when a 779-letter DNA sequence on the human X chromosome turns out to be identical, letter by letter, to sequences in rats and mice?

Philip Green, an HHMI investigator at the University of Washington, is one of the scientists trying to make sense of genomic data. A mathematician turned geneticist, Green is uniquely qualified for the task. He has spent years analyzing DNA sequences, and the characteristic motifs of DNA have become engrained in his psyche, so that at a glance he can identify meaningful patterns in sequences that look like gibberish to anyone else. He writes relatively few papers—often just one or two a year—but his counsel and judgment are widely sought. Elected to the National Academy of Sciences in 2001, Green received a Gairdner International Award in 2002 for his contributions to the sequencing of the human genome. Genetics labs around the world use two software programs he wrote in the early 1990s to analyze the outputs of DNA sequencers—an appropriate legacy for someone working in a city teeming with software engineers. "He's the smartest guy in this field," says Robert Waterston, head of the University of Washington's department of genome sciences.

Green has taken on one of the toughest problems in biology: identifying all the functional elements in human DNA. Biological systems are both fantastically complex and inherently variable. Biologists agree that analysis of the genome will yield profound insights, but they disagree about where those insights will lead. "That's what makes these years so exciting," says Green, "finding all the genes and understanding what they do."

DARWIN'S PARADIGM

Green's computer programs are famous for their elegance and precision, but his office is a mess: stacks of books, articles, and monographs cover every flat surface. He stands partly hidden behind a wall of paper, wearing clothes appropriate for either a mathematician or a Seattle rock star—sandals, jeans, flannel shirt. His wire-rim glasses and square gray beard convey the impression of someone so unfashionable that he has become fashionable again.

Lately, his curiosity has been drawn to how and why DNA mutates. "The changes that occur in functional DNA are the raw material for evolution," Green says. "Those changes create variation in organisms, and then selection goes to work on that variation," with organisms that have advantageous mutations thriving and reproducing their DNA while deleterious mutations hit an evolutionary dead end. "That's Darwin's paradigm," he says, "and that's what drives evolution."

But Green's approach to drawing out the function of DNA is counterintuitive. He has been looking at the 95 percent or so of our genome that doesn't seem to be doing anything. "We think that part of the genome is actually quite interesting," he says, "because by studying it, you can find out about mutation. Selection is not acting on that part of the sequence, so it provides a more or less faithful record of the mutation process."

Green and graduate student Dick Hwang have analyzed, in 19 different mammals, the nonfunctional DNA sequences in a region containing the gene that is mutated in cystic fibrosis. Using a detailed computational model, they found that some kinds of mutations occur at constant rates, like the ticking of a clock, which makes them

useful for dating evolutionary events. Other kinds of mutations occur at varying rates depending on the generation times of the organism. This information in turn makes it much easier to identify parts of the genome that exhibit different patterns of change over time, indicating that the DNA in those regions is subject to selection and therefore playing a functional role. The idea, says Green, is to separate the noise of meaningless changes in DNA so that the signals of consequential changes emerge clearly from the background.

This elegant approach to a fundamental question typifies Green's work, say his colleagues at the University of Washington. "He really struggles to understand what the problem is," says geneticist Maynard Olson, whose office is a few corridors away from Green's. "And he really wants his work to address the problem—not just to be related to it."

Green earned an undergraduate degree in mathematics from Harvard and a doctorate from the University of California, Berkeley, where his dissertation combined work on abstract algebra and functional analysis. But after several years as an assistant professor at Columbia, he became dissatisfied with pure mathematics. "The math I was doing didn't seem to have any connection to the real world," he says. "I started feeling that I'd like to be working in an area where I could apply mathematical ideas to something more concrete."

About that time he read the book *Molecular Biology of the Gene,* by James Watson. The intellectual rigor and "almost mathematical" elegance of the book rekindled his interest in genetics. He moved back to the University of North Carolina, where he began working with research teams studying the genetics of heart disease and the regulation of the

This elegant approach to a fundamental question typifies Green's work, say his colleagues at the University of Washington. "He really struggles to understand what the problem is," says geneticist Maynard Olson, whose office is a few corridors away from Green's. "And he really wants his work to address the problem—not just to be related to it."

These qualities make Green especially sought after as a reviewer. Once, he wrote such a careful and detailed review of a paper submitted to the journal *Genome Research* that the editors convinced him to let them publish the review as an accompaniment to the original paper. When asked to review the paper written by the Human Genome Project announcing the completion of the human sequence, he wrote 23 single-spaced pages over the course of 7 days. "It was the deepest, most thoughtful review we received and made the paper much better," says Eric Lander, director of the Broad Institute in Cambridge, Massachusetts, and lead author on the paper. "When it comes time to publish the collected papers of Phil Green, the collected peer reviews should be published, too."

ELEMENTARY MATH

When he was in the third grade, Green came across a book of number theory problems in a local public library. He was instantly hooked. Mathematics seemed like a game to him, and when he learned a few years later that people did it for a living, he vowed to become a mathematician himself. But he also had an early exposure to computational biology. Green's next-door neighbor was a statistical geneticist at the University of North Carolina in Chapel Hill. During high school, Green worked at a summer job arranged by his neighbor that involved writing computer programs to analyze genetic data.

human fibrinogen gene. He spent a lot of time at the bench, getting a feel for the problems and potential of biological research. "I was learning to think like a biologist," he says.

In 1986, he moved to the company Collaborative Research, in Waltham, Massachusetts, to help construct a linkage map of the human genome. There he met Lander, who at that time also was making the transition from mathematics to biology. Green and Lander wrote a key computer program that allowed large amounts of data to be incorporated into the map. It was Green's first exposure to genomics—the study of large-scale maps and sequences of genetic information.

In 1989, finding that he missed the collaborative atmosphere of academia, Green moved again, to Washington University School of Medicine, in St. Louis. There he joined a genetics department consumed by the emerging challenges of genomics. Washington University was becoming a leader in the new field of high-throughput genetic sequencing. But these initial sequencing efforts were encountering major difficulties. The data emerging from automated sequencing machines were of variable quality; some "calls" for individual DNA bases were rock solid but others were ambiguous. Furthermore, geneticists did not have a good way of combining the raw data, or "reads," from the sequencing machines into longer sequences.

Green designed two computer programs to solve these problems. PHRED (for "Phil's revised editor") assigns an error probability to each base call so that the reliability of different parts of the read can be assessed. PHRAP (for "Phil's revised assembly program") takes the output of PHRED and combines the reads into longer stretches known as contigs. Their names don't have the Madison Avenue slickness of mega-selling software titles, but they don't need it. As Green began distributing his programs by e-mail to sequencing centers around the world, genome sequencers found the software to be remarkably precise and powerful. "Quality is king with Phil," says Haussler, who is director of the Center for Biomolecular Science and Engineering at the University of California, Santa Cruz, "and that comes out in his software."

In the 1990s, issues of quality became a major consideration for Green in another way. Despite his self-effacing manner, he found himself drawn into a rancorous debate over the best way to sequence the human genome. He argued that the method known as whole-shotgun sequencing, in which DNA is divided into small sequenced snippets that are then recombined by using computers, would lead to too many errors in published sequences. Other sequencers, including those at the private company Celera Genomics, vociferously countered that the shotgunning method would work. The argument sputtered out as elements of various approaches were combined. And the contretemps did not detract from Green's contributions to the effort: The 400,000 contigs that the publicly sponsored Human Genome Project combined to produce the human sequence were the output of PHRAP. "The whole edifice for doing that was based on Phil's work," says Haussler.

In 1994, Green received an offer that he found too enticing to turn down. Immunologist and technology developer Leroy Hood had been putting together a new kind of genetics department at the University of Washington, one designed to foster interdisciplinary research by bringing together people with many different backgrounds. According to Waterston, who became head of the department after Hood left to form a nonprofit research institute, the department's aim remains "to bring together the key disciplines that will be needed to make progress on the very hard problem of interpreting genomes."

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THE PARTS LIST AND THE WIRING DIAGRAM

At the University of Washington, Green devotes the bulk of his time to working on what he calls the "parts list": a catalog of all the molecules involved in biological processes in human cells. The proteins encoded by DNA are an essential component of this list, which is one reason why biologists want to identify all the functional genes in DNA. Green is a member of several research teams at the University of Washington and elsewhere that are looking for genes, typically by comparing human DNA sequences with the sequences of other organisms. "You're searching for stretches of sequence that look as if they are not evolving neutrally," he says. "In other words, you're looking for regions that have a slower rate of change, which is evidence that selection is acting on those regions."

The parts list will help biologists build a "wiring diagram" for human cells: a schematic representation of all the interactions that occur among all the elements on the list. Constructing the wiring diagram is a much harder problem because any given molecule can have many functions in a cell. DNA is a prime example. DNA molecules contain not just the specifications for proteins but regulatory regions that control when a protein will be expressed and in what quantities. "The genome is not just an information repository," says Green. "It is also an active part of the processes going on in the cell."

Once biologists have a general sense of the wiring diagram of a human cell, they can move on to what Green sees as the third main objective of human genetics research: They can begin to reconstruct, both in computers and in the laboratory, synthetic systems that mimic those in the cell. They then can perturb these systems to get a sense of how biological molecules work together, which is the goal of the new field of systems biology. They may even be able to design novel biological systems to achieve desired outcomes—the goal of the even newer field of synthetic biology.

HOWLS OF DISBELIEF

Now housed in a corner of the medical school (a new building for the department funded by Microsoft chairman Bill Gates is going up next door), the department is attacking the problem on many fronts. Computer programmers and geneticists are collaborating to analyze complex networks of genes and proteins. Research on model organisms is closely integrated with investigations of human genetics. Four HHMI investigators in addition to Green—David Baker, Stanley Fields, Richard Palmiter, and newly appointed investigator Evan Eichler—are working on problems ranging from genomic evolution to protein folding to development of the mammalian nervous system.

Green collaborates on several projects in the department and offers advice on many more. He also finds time to pursue topics that strike his interest. Several years ago, for instance, he noticed that data from the sequencing of expressed DNA fragments implied that the number of human genes was much lower than expected. When he and a colleague expressed the idea in print, their paper was met with howls of disbelief, but their number now appears to be more or less right.

Green also takes the time to think about the overall trajectory of biological research: the slow but steady progression from understanding biological systems to prediction to control. Some of his colleagues question the extent to which such an ambitious agenda can be achieved. "I'm a skeptic about systems biology, at least in its most grandiose form—the idea that we will build quantitative models of cells comparable to the models used to build bridges," says Green's colleague Olson. The cascading effects of chance and the sheer complexity of biological systems are likely to place limits on the extent to which the outcomes of biological systems can be predicted and controlled, Olson says. He believes biological research eventually will move toward more practical ends, in which the focus will be on specific interventions. "I think bioengineering is going to look very different from engineering as we've known it in the physical world," he says. For instance, in addition to searching for a drug that might cure diabetes, biologists might build sensors that carefully monitor blood insulin levels, or they may engineer artificial cells that deliver precisely calibrated amounts of insulin.

Green is more optimistic than Olson that a deeper understanding of the cell will lead to direct interventions in biological processes. "The main issue is how quantitative we're going to be able to get," he says. "Most people will accept the idea that we will know qualitatively how things are interacting with each other. But what you really want is a quantitative result, so that you can change the levels of one component and predict how it will affect the system."

PROFOUND TRANSITION

Since switching from mathematics to biology a little more than two decades ago, Green has witnessed—and has contributed to—a profound transition in biology. Biology used to be one of the least quantitative of the sciences. Its practitioners sought explanations for biological phenomena, whether the behavior of organisms or the interactions of molecules. Most did not need to couch those explanations in mathematical terms or draw on mathematical ideas to arrive at their conclusions.

That has changed. "Phil and I used to go for long walks when we were both associated with Collaborative Research," says Lander. "Back then, we wondered if there was a need for mathematics in biology. In the mid-1980s, there weren't a lot of data. Biology was about analyzing the notes in your lab book.

He believes biological research eventually will move toward more practical ends, in which the focus will be on specific interventions. "I think bioengineering is going to look very different from engineering as we've known it in the physical world." he says. For instance, in addition to searching for a drug that might cure diabetes, biologists might build sensors that carefully monitor blood insulin levels, or they may engineer artificial cells that deliver precisely calibrated amounts of insulin.

"In the last 20 years, biology has become dominated by huge data sets. Now it's an exception rather than the rule to publish a paper that does not draw on large databases of biological information. Mathematical analysis has become a fundamental part of biological research. It has turned out to be of equal importance to experimentation."

The role of mathematics in biology is only going to grow, say Lander, Green, and other quantitatively oriented biologists. As researchers continue to probe genomes for information, and as they begin to build models of biological systems, computer programs and equations will become as common as glassware and pipettes. "There's a new generation of 21st-century explorers in biology," Lander says, "and their tools for exploration are computers and mathematics." ■

MATHEMATICS, COMPUTING, AND THE NEW BIOLOGY

Modern research calls on biologists to be fluent in analytical methods.

Max Delbrück, the physicist-turned-biologist who became a founding father of molecular biology, often told his students that "if you have to use statistics to interpret your experimental results, they can't be true."

That statement wasn't meant to denigrate the power of mathematics, former colleagues say; it was simply an attempt to provoke students into designing clear-cut experiments. Nevertheless, the remark shows how far biology has come since the mid-20th century, when Delbrück began grappling with the field's big questions. Researchers today are increasingly using statistics and other analytical tools not just to interpret their results but to arrive at them.

In an essay published last year in *PLoS* (Public Library of Science) *Biology*, **Joel E. Cohen**, a population biologist at the Rockefeller University, called mathematics "biology's next microscope." In the coming years, he wrote, mathematics will "reveal otherwise invisible worlds in all kinds of data" just as early microscopes first revealed the microbial and subcellular worlds. Further, Cohen asserts, the explosive pace of biological research will spawn new branches of mathematics just as physics stimulated the development of calculus.

"We've gotten so much better at using experimental tools to study complex systems," says **Charles F. Stevens**, an HHMI investigator at the Salk Institute for Biological Studies, "that now we need mathematical approaches to make sense of it all."

"The old way of doing things was that you kept everything fixed, changed one variable, measured one other variable, and then got the relationship between them," Stevens says. "But now the kinds of questions we're asking and the kinds of experimental abilities we possess are leading us to measure many things simultaneously, and we just have to have techniques for analyzing and thinking about the data."

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CATALOGUING EVERYTHING IN THE CELL

To many, one of the boldest examples so far of the new biology has been the human genome project. **Gene Myers**, a computer scientist at the University of California, Berkeley, was at the forefront of that effort. Five years ago, when Myers was vice president of informatics research at Celera Genomics, his radical computing method for assembling DNA sequences catapulted the company to the front of the high-stakes race to read the three-billion-letter human genome sequence. Ultimately, Celera and its competitor—a government-sponsored consortium—joined forces and completed the genome sequence years ahead of schedule.

Now Myers has set even loftier goals: "Having produced the sequence of the genome, we'd like to understand what it actually says." Like the University of Washington's mathematician/geneticist **Philip Green** *(see main article)*, he wants to know how the genome is regulated and how all of the molecules in cells interact. That's going to take a lot of data crunching. "You're dealing with a system that's so large that the unaided human mind isn't going to see it," says Myers. "We're going to need the kind of help that computers are good at."

Consider his own efforts to use microscopes to track the moment-by-moment whereabouts of the hundred-or-so most important transcription factors (the proteins that turn networks of genes on and off) in the developing embryos of model organisms such as fruit flies or nematodes. "I want to see gene expression at the level of what's happening in each cell," says Myers. But he maintains that "at some point, our eyes aren't going to be able to look at all the images. We will be producing visual data at rates that require computation and interpretation by computers."

High-tech hardware alone won't be enough, however. Myers thinks that biologists have to do a better job of incorporating knowledge and approaches from other disciplines into their research. For example, "We're going to have to start thinking about the mathematical properties of these living systems from an industrial-engineering point of view—in terms of systems with feedbacks, failure modes, and redundancy."

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FEMTOSECONDS TO MINUTES

J. Andrew McCammon, an HHMI investigator at the University of California, San Diego, is pushing mathematics to the extreme in his research on the infinitesimal and varied motions inside protein molecules—movements that can provide important clues about how proteins work and interact with other molecules, such as drug compounds. McCammon's group uses supercomputers to model, in extraordinary detail, the quivers, jiggles, twists, and bends that proteins undergo, as governed by the chemical and physical forces of each of the molecule's thousands of atoms. The time scales of these various motions range widely, moreover, from femtoseconds (quadrillionths of a second) to minutes.

Modeling protein movements at that level of detail takes a lot of computing power, says McCammon. "Just to get to the microsecond (millionth of a second) time scale in simulating a medium-sized protein requires on the order of a billion small steps in time, and each step might involve as many as a million separate calculations of forces between the pairs of atoms in the protein."

His team recently simulated 50 nanoseconds (billionths of a second) of movements in a nerve-cell receptor as it binds to a neurotransmitter molecule. "The simulation model includes the receptor, a portion of the lipid bilayer it passes through, and water molecules on both sides of the bilayer, for a total of about 150,000 atoms," McCammon says. "To simulate the dynamics for about 50 nanoseconds, where we can begin to see the response of the receptor, requires about 500 processors on the DataStar supercomputer at the San Diego Supercomputer Center, running each processor for 200 hours."

Such intensely focused modeling may seem like much too much about much too little, but it can yield real-world payoffs—for instance, a new generation of drugs for treating HIV/AIDS. While inhibitors of one of HIV's enzymes, called protease, have been effective anti-AIDS drugs, in recent years protease inhibitor-resistant HIV strains have emerged. Another of HIV's enzymes, integrase, allows the retrovirus to stitch its genetic material into the genome of the human host. Although a static picture of the integrase structure was known, the enzyme hadn't been successfully investigated as a drug target when McCammon's lab started scrutinizing it a few years ago.

In modeling two nanoseconds' worth of integrase's movements, the team discovered that part of the protein chain moves in such a way that, for an instant, a "trench" opens up near the active site—the part of the protein that catalyzes the stitching reaction. McCammon and his colleagues then designed compounds that they predicted would fit into the trench, thereby jamming the enzyme so that it could no longer work. Scientists at Merck Research Laboratories have since confirmed this hypothesis by testing a number of the compounds as potential drugs to inhibit the HIV integrase, and clinical trials of one of them are expected to begin later this year. *—Paul Muhlrad*

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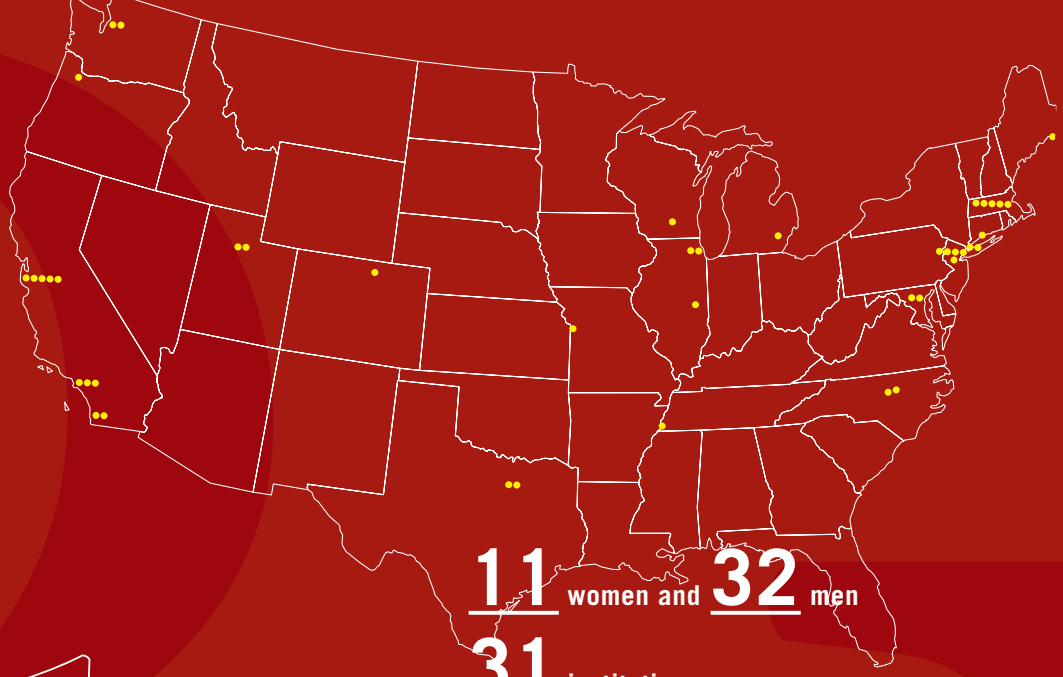

11 women and **32** men

31 institutions *(including 3 new to HHMI)*

25% from chemistry, physics, computer sciences, engineering, and geobiology

Meet the latest class of HHMI investigators…

Among the 43 promising researchers newly tapped to be HHMI investigators, nearly a quarter bring expertise from fields outside the biological sciences.

HHMI has drawn significantly from outside the biological sciences for its latest class of investigators. The group comprises 32 men and 11 women from 31 institutions nationwide. Many represent traditional biomedical research disciplines, but nearly 25 percent received their primary training in areas such as chemistry, physics, computer sciences, engineering, and geobiology.

The four scientists below are representative of the group, both in the sense that they approach the scientific enterprise from unique perspectives, and in the way they work deftly across disciplines.

BRENDA A. SCHULMAN

Science took hold of Brenda A. Schulman early. She still remembers when her high-school biology teacher revealed the myriad roles of ATP (adenosine triphosphate) in a cell. Also while in high school, Schulman worked in a university lab that was exploring how genes are activated, and she went on to win the national Bausch & Lomb Science Award, given to students who have demonstrated unusual academic achievement in science.

Now head of her own lab at St. Jude Children's Research Hospital, in Memphis, Tennessee, Schulman works to integrate her knowledge of structural biology, biochemistry, cell biology, and genetics to address a central scientific question: How can cells respond quickly to the changing demands and cues of their environments?

STEPHEN R. QUAKE

The interests of Stanford University bioengineer Stephen R. Quake unite physics, biology, and biotechnology. With a toolbox that draws on the fields of mathematics, engineering, and materials chemistry, Quake has developed technology that will allow scientists to integrate several complex experiments on a single device and devised an entirely new approach to the vexing challenge of growing protein crystals.

JOSEPH DERISI

To describe new investigator Joseph DeRisi, whose lab is at the University of California, San Francisco, as a molecular biologist who has made major contributions to malaria research would be accurate, but it would also be incomplete. He might be described more precisely as a scientific polymath who delights in tinkering with new technology, moves readily among disciplines, shares what he knows as widely as possible, and dives fearlessly into new scientific challenges. DeRisi helped pioneer the use of DNA microarray technology as a graduate student. He now uses the same approach to study the activity of the full range of malaria genes and has already generated provocative insights.

LINDA C. HSIEH-WILSON

At the California Institute of Technology, Linda C. Hsieh-Wilson brings her chemist's training—and indefatigable curiosity—to neurobiology. Instead of concentrating exclusively on the "big picture," as some neurobiologists often do, Hsieh-Wilson is focusing on a less well-studied—but perhaps even more important—area: How does the right chemistry keep the brain working properly? Her work integrates organic chemistry with neurobiology to understand how key carbohydrates, and their various derivatives, alter the structure and function of proteins in the brain.

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Princeton University–Princeton, NJ

5 ALBERT BENDELAC
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6 RONALD R. BREAKER
Yale University–New Haven, CT

7 ANDREW CAMILLI
Tufts University School of Medicine–Boston, MA

8 EDWIN R. CHAPMAN
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9 ZHIJIAN CHEN
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12 MICHAEL D. EHLERS
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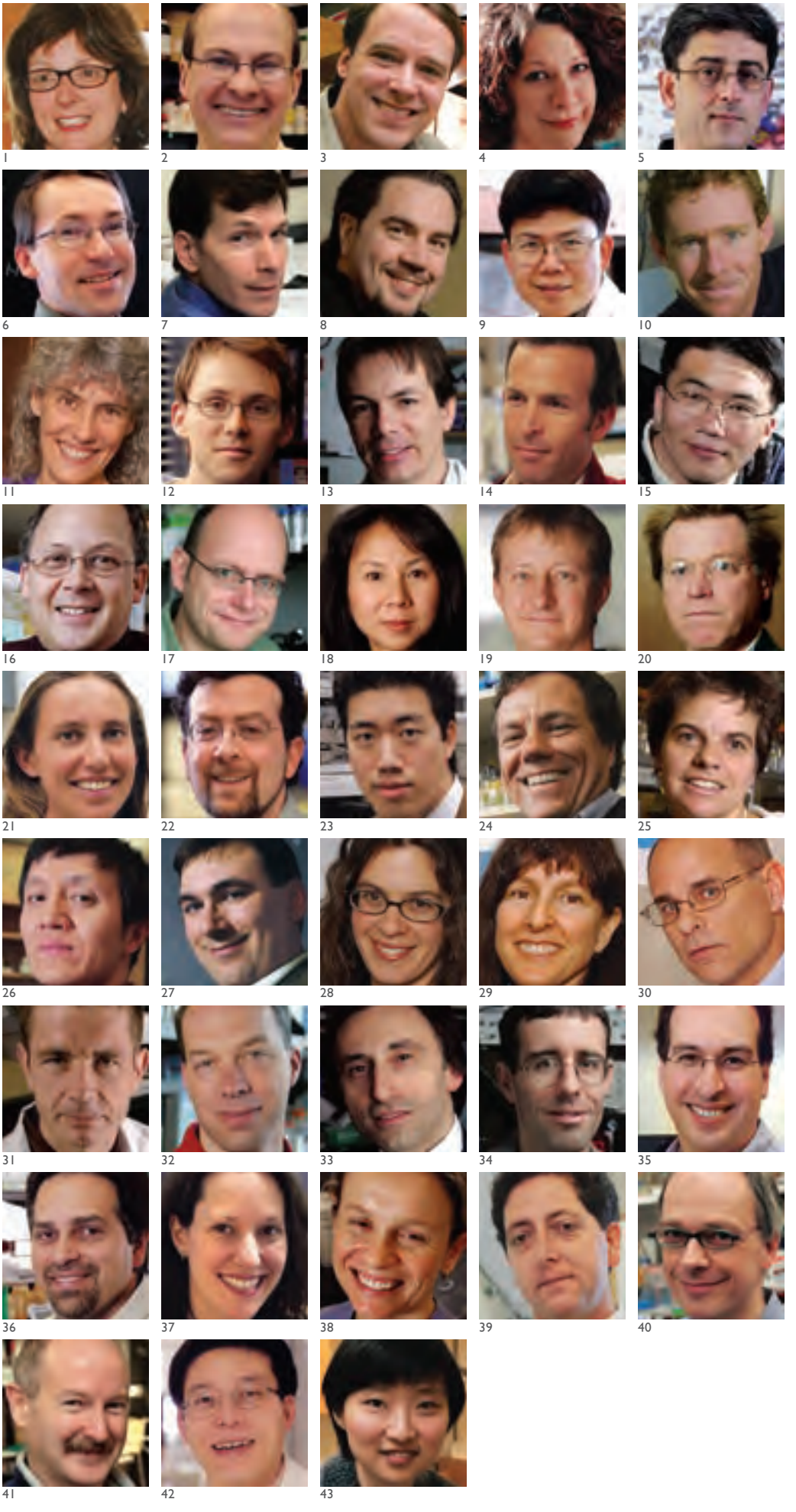

EXCEPTIONAL PROMISE

To find the new HHMI investigators, the Institute looked specifically for candidates who demonstrated exceptional promise within 4 to 10 years of their becoming independent scientists. "These scientists are on the rapidly rising slope of their careers," says HHMI President Thomas R. Cech. "We have every reason to believe that they will use their creativity to extend the boundaries of scientific knowledge for many years to come."

In a competition open to approximately 200 universities, medical schools, and institutes, more than 300 such individuals were nominated.

The outcomes represent a boon not only to those selected. David A. Clayton, vice president and chief scientific officer of the Institute, says the competition allows HHMI to respond to new areas of scientific interest and emerging fields. "The scientists we identified through this competition are impossible to pigeonhole into traditional categories—and that is good news for the future of research in the life sciences," Clayton says. "By my estimation, about 20 percent of them are drawn from the physical sciences, including chemistry and physics. And while nearly a quarter of these researchers are in the burgeoning field of neuroscience, it's fair to say that we expect the impact of their work to be felt across the full spectrum of biological research."

The competition for new investigators, HHMI's first since 2000, represents a continued expansion of the Institute's biomedical research mission. The selection of these scientists means that HHMI will invest more than $300 million in additional support for biomedical research over the next 7 years, according to Cech. (The Institute's current annual budget for biomedical research is $416 million.) HHMI is also about to conclude the first phase of recruitment of scientists for the Janelia Farm Research Campus—HHMI's community for collaborative, interdisciplinary research—scheduled to open in Northern Virginia in 2006.

The cadre of 43 new investigators includes scientists at five institutions that do not currently have an HHMI investigator: Weill Medical College of Cornell University, the University of Illinois Urbana-Champaign, Colorado State University in Fort Collins, Stowers Institute for Medical Research in Kansas City, Missouri, and the University of North Carolina at Chapel Hill. The latter three are joining the HHMI program for the first time.

SCIENTIFIC VALUE

HHMI grounds its research programs on the conviction that scientists of exceptional talent and imagination will make fundamental contributions of lasting scientific value and benefit to mankind when given the resources, time, and freedom to pursue challenging questions. HHMI urges its researchers to take risks, to explore unproven avenues, to embrace the unknown—even if it means uncertainty or the chance of failure.

Widely recognized for their creativity and productivity, the current group of HHMI investigators includes 10 Nobel Prize winners and more than 100 members of the National Academy of Sciences. HHMI investigators have made many key research advances—from the discovery of genes related to cystic fibrosis, obesity, high blood pressure, colon cancer, and other diseases to new insights into memory, vision, and olfaction.

WHAT IS THE HHMI INVESTIGATOR PROGRAM?

The Institute seeks out highly creative investigators at distinguished universities, research institutes, and medical schools across the United States whose work spans the full range of leading-edge biological and biomedical research. Investigators are identified through multilevel peer-reviewed competitions. Following a philosophy to support "people, not projects," HHMI provides long-term, flexible funding to enable its investigators to pursue their scientific interests wherever they lead.

Joining such an accomplished group, the new investigators come to the table in a swirl of high expectations. At the same time, given each new investigator's track record, there is abundant confidence and optimism about what the new class might accomplish.

"We are committed to providing these scientists—and the nearly 300 scientists who are already part of HHMI—with the freedom and flexibility they need in order to make lasting contributions to mankind," Tom Cech says. Speaking specifically of the new class, but perhaps defining a characteristic that distinguishes all HHMI investigators, he adds, "We want and expect them to be daring." ■

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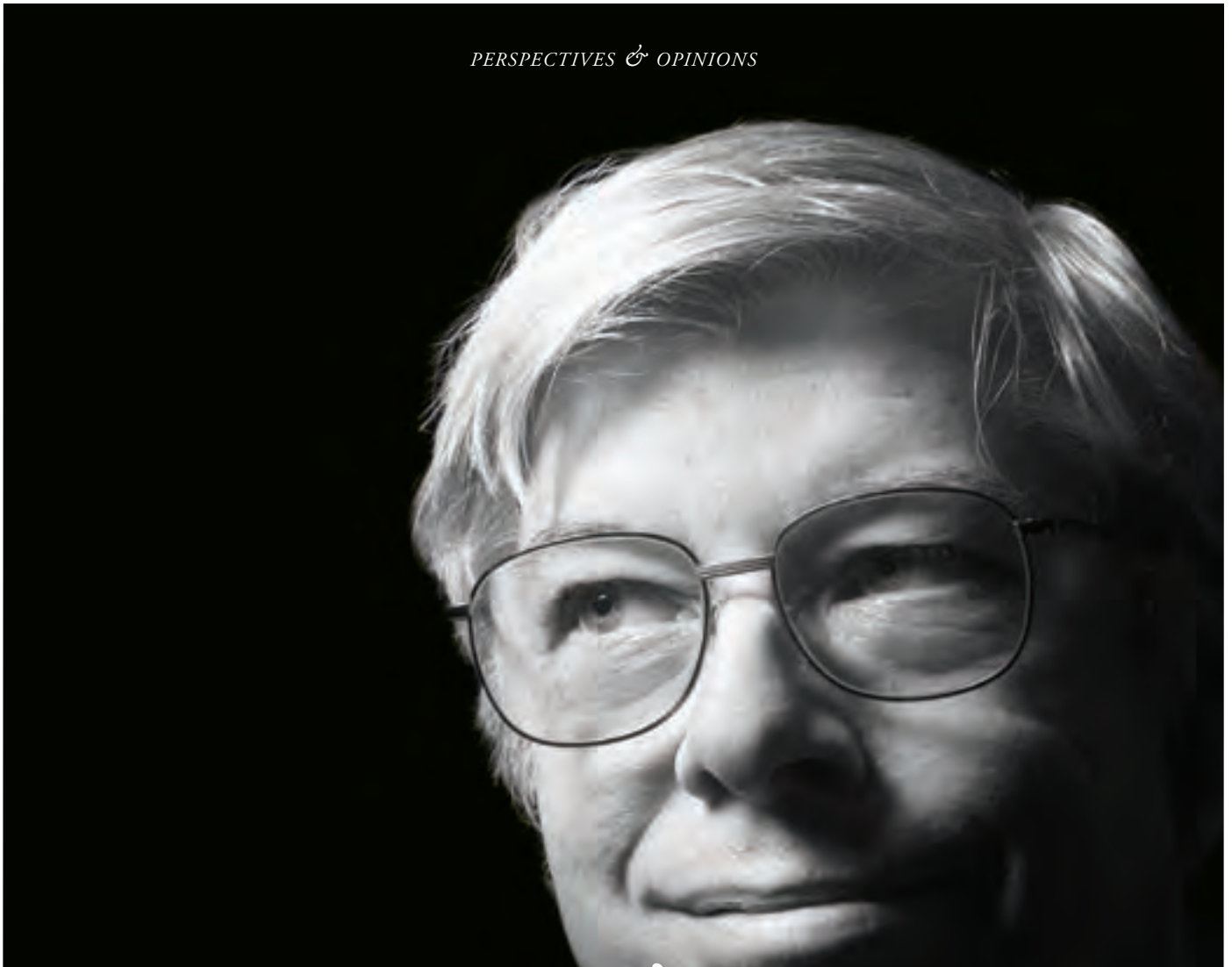
about the new investigator program: www.hhmi.org/research/investigators/
about Janelia Farm Research Campus: www.hhmi.org/janelia/



NATURE'S WAY

— ALLAN C. SPRADLING —

ALLAN C. SPRADLING'S AIM IS TO SEE THE BIG PICTURE, TO FOCUS ESPECIALLY ON FUNDAMENTAL PROCESSES IN BIOLOGY, AND TO EXPLOIT NATURE'S OWN WAYS IN ORDER TO ADVANCE SCIENCE.

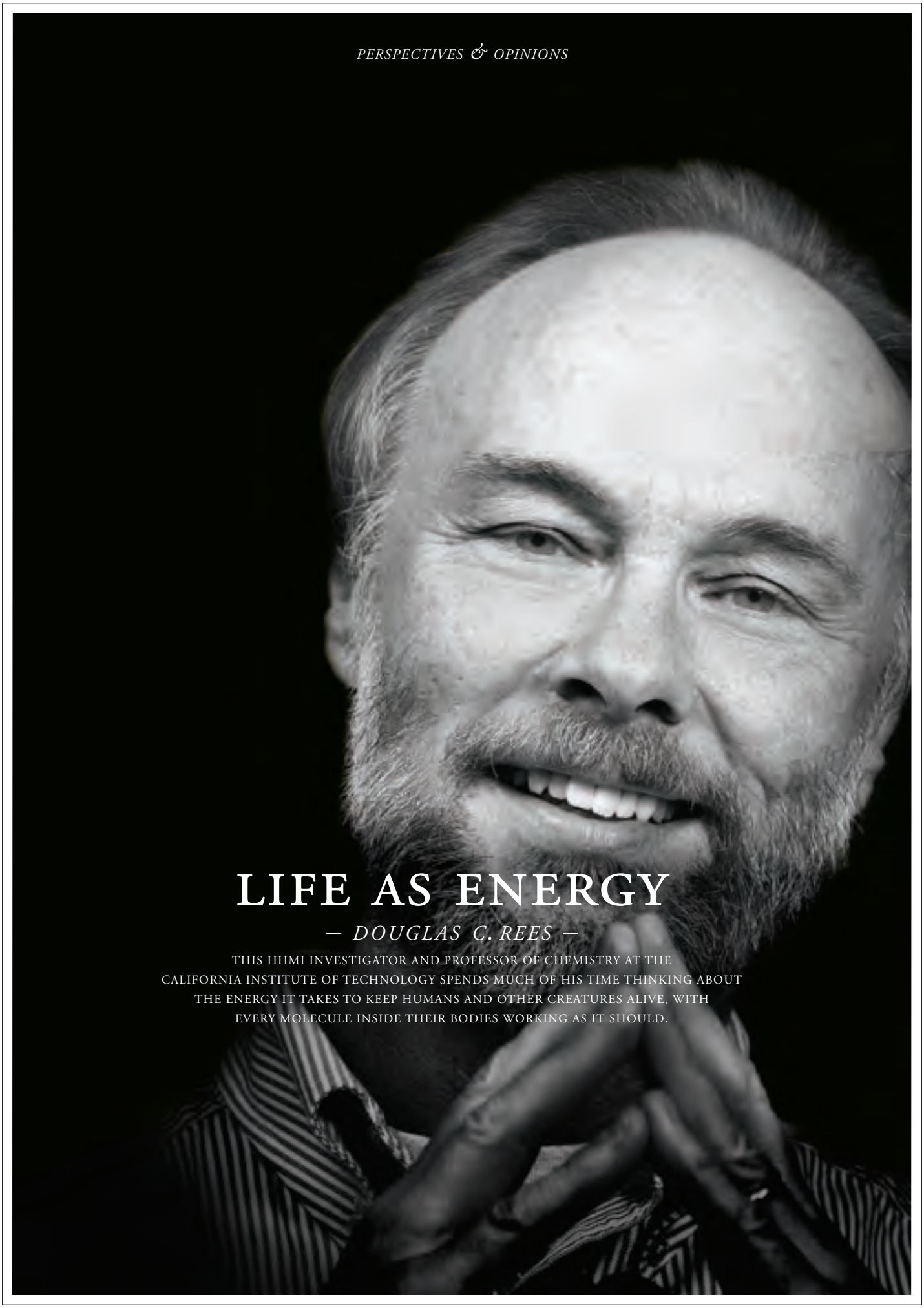
The HHMI investigator and his colleagues blend genetics with cellular anatomy to develop new tools for genetic analysis. Along the way, they have made remarkable discoveries in the fruit fly Drosophila *about stem cells and the surrounding tissue, called a niche, that supports them. When we spoke with Spradling in his lab at the Carnegie Institution of Washington in Baltimore, he offered these observations.*

Dedifferentiation may be used normally to maintain and repair tissues. There has been a great deal of success in taking an undifferentiated cell and directing its differentiation into a particular cell type. But the challenge remains to make those cells do something useful. We've started to look at the process of dedifferentiation, which is thought to take place normally in the body as part of some wound-healing and repair processes. Dedifferentiation may be a useful approach to the end goal of medically oriented stem-cell research, which is to correct adult degenerative conditions in a valuable way.

One of the problems in studying dedifferentiation has been the lack of an accessible system to study how it works. Postdoc Toshie Kai devised a method that takes germline stem cells [from which egg or sperm cells are derived], causes them to differentiate to the 8-cell stage, and then reverts them back at 100-percent efficiency. We've used these events as an assay to look for genes that turn off when the stem-cell state is lost and that come back when the stem-cell state returns. This assay has given us some new genetic handles on stem-cell regulation. But the pathways that stop development and reverse its course are still not understood.

We try to ask cells to do what they already know how to do. In approaching problems, we have attempted to use an existing biological mechanism to attain our goals, especially when developing new tools. For example, during the last 2 years, another very talented postdoc in the lab, Michael Buszczak, has been fusing genes to green fluorescent protein

CONTINUED ON PAGE 56



LIFE AS ENERGY

— DOUGLAS C. REES —

THIS HHMI INVESTIGATOR AND PROFESSOR OF CHEMISTRY AT THE CALIFORNIA INSTITUTE OF TECHNOLOGY SPENDS MUCH OF HIS TIME THINKING ABOUT THE ENERGY IT TAKES TO KEEP HUMANS AND OTHER CREATURES ALIVE, WITH EVERY MOLECULE INSIDE THEIR BODIES WORKING AS IT SHOULD.

Early in his career, Douglas Rees realized that x-ray crystallography could provide key information about how certain large molecules function in the body's energy metabolism, and he has since made good use of that tool for his own research. Last year he also became a principal investigator of a powerful new beam line, a research facility using an intense x-ray beam, now being built at the Stanford Synchrotron Radiation Laboratory. This beam line is specifically designed to help researchers solve the structures of large molecules.

HHMI: ***WHAT MAJOR QUESTION IS DRIVING YOUR RESEARCH TODAY?***

DR: We're trying to understand how ATP [a molecule that stores energy inside cells] and other large molecules are used to power the body's machinery, which is a problem I started studying as a postdoc with James B. Howard at Minnesota. We're beginning to learn how certain proteins, known as ABC transporters [for ATP binding cassette], manage to pump nutrients into living cells. These proteins use energy to accumulate molecules in cells, without letting any of the molecules leak back across the cell membrane.

X-ray crystallography has been very useful in figuring out how that's done. If you want to understand how any system works—whether it's a power plant, computer, or molecule—you have to know what it looks like. When we started, no structure of an ABC transporter had been determined, so we needed to fill the gap. We surveyed a number of different ABC transporters from different organisms before finding one—the protein that imports vitamin B12 into *Escherichia coli* bacteria—that would be appropriate for our structural studies. After producing suitable crystals of this transporter, we were able to determine its structure in atomic detail. Based on this analysis, we proposed that the transporter can pump molecules across a membrane by functioning like an airlock, where the energy provided by ATP is used to open and close the airlock doors in the correct sequence. This result, of course, helps us understand how transporters work in human cells.

Another thing that transporters do, unfortunately, is help cancer cells develop resistance to certain drugs. When these drugs enter the cancer cell, transporters may pump them out—just like bailing water out of a sinking ship—and prevent them from killing the cell. Ultimately, we'd like to know how transporters work in sufficient molecular detail to be able to stop this process.

HHMI: ***WHAT SOLD YOU ON CRYSTALLOGRAPHY IN THE FIRST PLACE?***

DR: As a graduate student, I was excited by what I saw in [current HHMI investigator] Stephen C. Harrison's lab—the power of x-ray crystallography to provide structural insights into important biological questions. My thesis adviser, William Lipscomb, used crystallographic methods to address systems ranging from small, inorganic molecules to the mechanisms of enzymes that I studied. At that time, it was just becoming easier to use x-ray crystallography to study macromolecules, but it was still not trivial—a lot of practical problems needed to be solved each day. Many of these issues have since become routine, so now the primary focus in our lab is on preparative biochemistry—how to generate and trap the samples we need for the study of molecular assemblies, the large groups of molecules that carry out the chemical processes of life. If we want to understand the structure of these molecular machines, we need a large supply of proteins. And that can be a big obstacle.

Things are starting to change, however. New crystallization techniques, such as the microfluidics methods now being developed by Stephen R. Quake of Stanford [recently tapped to be an HHMI investigator—see page 30], and others, require only one-hundredth of the material needed with older methods. In fact, every aspect of crystallography is changing rapidly.

HHMI: ***WHAT WOULD YOU SAY IS THE BIGGEST CHANGE?***

DR: At the present time, automation. Beam lines, for instance, are going to almost-complete automation. And software programs developed by Stanford's Axel T. Brunger [an HHMI investigator] and others are making it easier to decipher structures from the x-ray data. The technology is advancing really fast, to the extent that trying to capitalize on it is a real challenge. Cloning, protein purification, and crystallization are all becoming automated, which ultimately will save us both time and effort.

HHMI: ***WHERE IS ALL THIS LEADING US?***

DR: We may be embarking on another industrial revolution—this one based on molecular-scale artificial devices and powered through the types of energetic mechanisms utilized by biological systems. That would be very exciting. ■

WHY DID YOU BECOME A SCIENTIST?

SOME RESEARCHERS DISCOVER SCIENCE EARLY,
COLLECTING TADPOLES IN THE BACKYARD OR CREATING POTIONS AT THE KITCHEN SINK.
OTHERS GET INSPIRED BY A COLORFUL TEACHER OR INTRIGUING CLASS.
HERE, FOUR NEWLY APPOINTED HHMI INVESTIGATORS LOOK BACK AT THEIR OWN JOURNEYS.
WHY SCIENCE?

~ Edited by Kathryn Brown ~

BONNIE L. BASSLER
PROFESSOR OF MOLECULAR BIOLOGY
PRINCETON UNIVERSITY

"My childhood love of solving puzzles, playing logic games, and mystery stories eventually led me to enroll in science courses that had labs. Once I started, I never wanted to do anything else. I now believe a career in science is simply the grown-up, legitimized version of all those childhood games."

DOROTHEE KERN
ASSOCIATE PROFESSOR OF BIOCHEMISTRY
BRANDEIS UNIVERSITY

"I fell in love with science as a kid. Growing up in Communist East Germany also meant that social sciences were heavily influenced by the Communistic society, tweaked and manipulated. In contrast, science was much more pure and objective. My math and biology teachers were amazing, challenging me and showing the beauty of logic. I hated memorizing stuff—I always wanted to derive the answers."

KEVAN SHOKAT
PROFESSOR OF CELLULAR & MOLECULAR PHARMACOLOGY
UNIVERSITY OF CALIFORNIA–SAN FRANCISCO

"I was always fascinated with the question, 'What was the first living thing?' In college, I took a year of introductory chemistry. I had never seen the logic of chemistry before, and it excited me. Later, in graduate school, I learned how to think long and hard about a problem, find an elegant solution, and break it down into steps. That stayed with me."

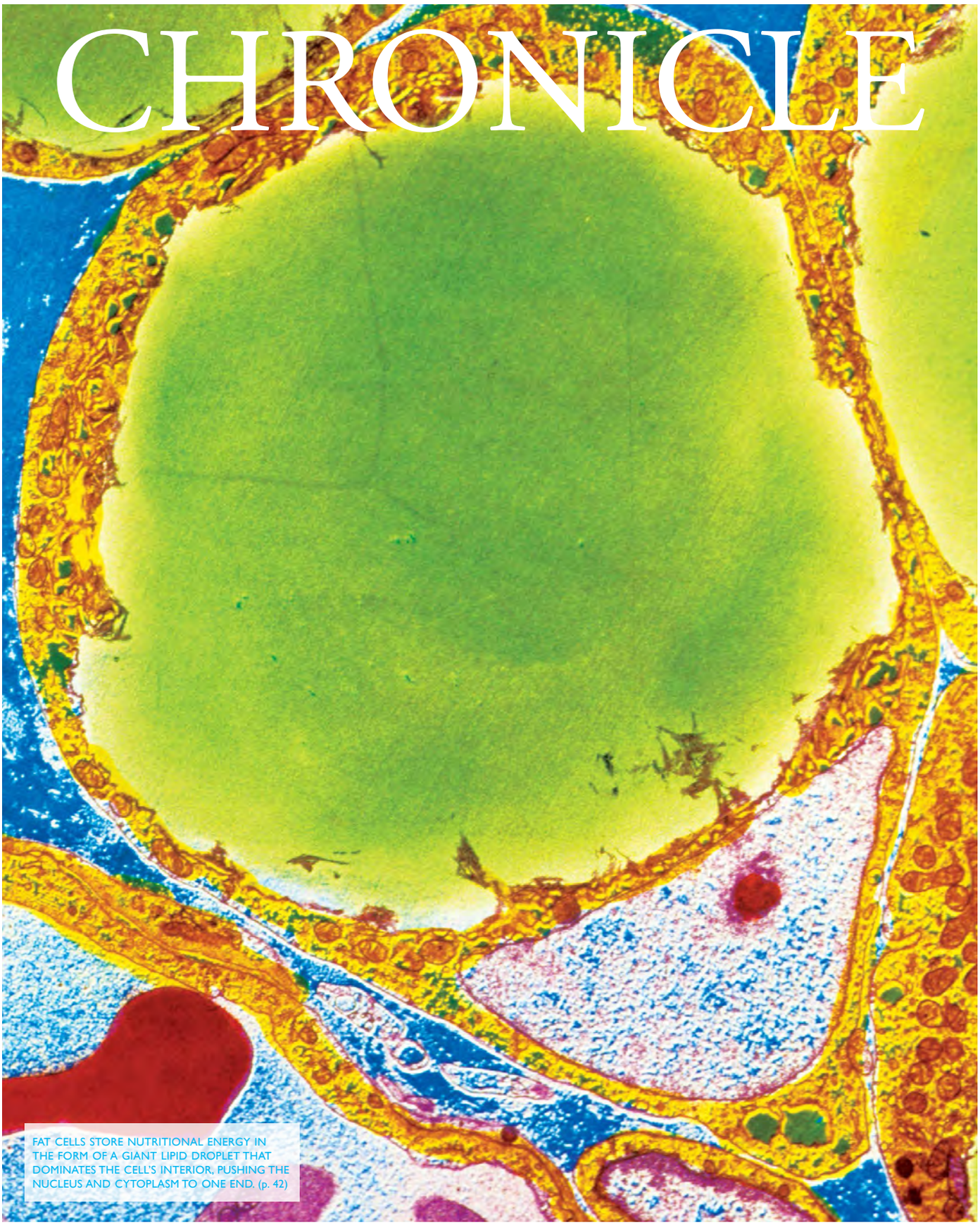
EDWIN R. CHAPMAN
PROFESSOR OF PHYSIOLOGY
UNIVERSITY OF WISCONSIN–MADISON

"How do things work? I always wanted to know. As a kid, I collected rocks, studied sea life, and played with chemistry sets. Yes, my room had a foul smell—and there were a few fires. My parents and my grandfather also gave me microscopes and electronic kits for toys. When I went to public schools and college, I naturally gravitated toward science. My career has followed the path of least resistance."

MORE INFORMATION AT HHMI ONLINE
www.hhmi.org

PHOTO CREDITS ON PAGE 34

CHRONICLE



FAT CELLS STORE NUTRITIONAL ENERGY IN THE FORM OF A GIANT LIPID DROPLET THAT DOMINATES THE CELL'S INTERIOR, PUSHING THE NUCLEUS AND CYTOPLASM TO ONE END. (p. 42)

Schmoke, Darman Elected as Trustees

Bearn announces retirement.

KURT L. SCHMOKE

KURT L. SCHMOKE, DEAN OF THE HOWARD University School of Law, and Richard G. Darman, a financial executive, have been elected Trustees of the Howard Hughes Medical Institute. Trustee Alexander G. Bearn, M.D., a Trustee for 18 years, also announced his retirement. Hanna H. Gray, Trustee chair, made the announcements.

Schmoke, 55, is an attorney who has dedicated much of his life to public service at all levels of government. He came to national prominence in 1987, becoming the first African American elected as mayor of Baltimore. During three terms in office, Schmoke focused on improving the city's school system and on broad economic development programs, with a particular emphasis on expanding home ownership and job opportunities.

A 1971 graduate of Yale University, Schmoke attended Oxford University as a Rhodes Scholar and received his law degree in 1976 from Harvard University. After spending a year in private practice, he joined President Jimmy Carter's White House domestic policy staff in 1977 and then returned to his native city of Baltimore to become an assistant U.S. attorney in 1978. Schmoke was elected state's attorney for Baltimore City in 1982.

After 12 years in office, Schmoke joined the law firm of Wilmer, Cutler & Pickering in 1999 and became dean of the Howard University Law School in Washington, D.C., in 2002. A respected and thoughtful adviser to educational and other organizations, Schmoke has served as senior fellow of the Yale Corporation, the university's governing body, and is currently a trustee of Tuskegee University.

Darman, 62, is a partner of The Carlyle Group, a global private equity firm, and chairman of the board of AES Corp., an international power company.

Darman played key roles in the development of federal tax, spending, and economic policy while serving four presidents. He held positions in the White House, the Office of Management and Budget (OMB), and six Cabinet Departments.

As deputy treasury secretary during the Reagan administration, Darman's service was recognized by the Treasury's highest award, the Alexander Hamilton medal, for his contributions to the 1986 Tax Reform Act and two international monetary policy accords. Darman served as director of OMB in the administration of President George H.W. Bush from 1989 to 1993 and was the principal executive branch negotiator for the 1990 budget agreement.

Darman joined The Carlyle Group in 1993. He became a member of the AES board in 2002 and was elected chairman in 2003. Darman is vice chairman and chairman-designate of the board of the Smithsonian National Museum of American History.

A 1964 honors graduate of Harvard College, Darman graduated in 1967 from the Harvard Business School.

Bearn, who became a Trustee in 1987, served the Rockefeller University and the New York Hospital with distinction as a physician and scientist before serving as a senior executive with Merck & Co. from 1979 to 1988. After retiring from Merck, Bearn became executive officer of the American Philosophical Society—the scholarly organization founded by Benjamin Franklin—and held that post until 2002. ■

JOSEPH D. COLLINS ELECTED AS FIRST VP FOR INFORMATION TECHNOLOGY

PHOTOS THIS PAGE: WILLIAM K. GEIGER

HHMI's Trustees have elected Joseph D. Collins as the Institute's first vice president for information technology.

Collins, who has been director of information technology since 2002, is responsible for a department with a $13 million annual operating budget and more than 50 employees. The department, which serves the Institute's Chevy Chase headquarters and field sites around the nation, had formerly been an operating unit within HHMI's Office of Finance.

"This reorganization recognizes Joe's effectiveness in managing our current information technology infrastructure and the importance of an integrated, strategic vision for mapping our future technology needs," said Thomas R. Cech, president of the Institute.

Collins has had a long career in the academic world and has held a variety of technology posts. He joined the Institute in 2002 from Howard University where he served as associate vice president for information systems and services from 1996 to 2002. Early in his career he held positions in corporate environments with IBM and Exxon. Later Collins moved to the Systems and Computer Technology Corp., where he was responsible for administrative computing at the George Washington University Center for Computing and Information Management.

Collins received a bachelor of science in electrical engineering from Howard University in 1971 and a master's degree in computer science, also from Howard, in 1980.

Nurturing Science's Next Generation

A panel chaired by Thomas Cech aims to help postdocs cross the bridge to scientific independence.

SCIENCE NEEDS THE TALENT OF YOUNG scientists, who often approach research problems with bold new ideas, to keep creativity coursing through the research pipeline. But sometimes that pipeline gets clogged.

For decades, for example, young scientists have been spending ever-increasing lengths of time in postdoctoral slots. It's hard for them to secure the funding necessary to start independent labs and set their own research directions—and perhaps make the next major discovery. Often they don't get the mentoring and range of experiences they need to prepare for transition to their own lab. And with limited openings for would-be faculty, many will ultimately pursue options other than running a lab at a university, working instead in other roles in academe, industry, or elsewhere.

Perhaps it is no wonder that, as HHMI President Thomas R. Cech recently said, "Many postdocs don't feel like they're on a career track anymore."

> "Biomedical science is not exactly what it was 20 or even 10 years ago. It is becoming increasingly interdisciplinary. That trend will continue in the future."

PAUL FETTERS

THOMAS CECH

Cech made that remark in March during a briefing at the National Research Council (NRC) in Washington, where Bruce Alberts, president of the National Academy of Sciences and chair of the NRC, and Elias Zerhouni, director of the National Institutes of Health (NIH), also spoke. The context was a report from a panel created by the National Academies at the request of NIH that was asked to study scientific career paths, particularly in relation to NIH funding, and recommend improvements. Cech chaired the group.

In their report, the panel said that NIH can promote independence among postdoctoral scholars and other early-career investigators in biomedical research by improving their training—especially through better mentoring. "Faculty mentors have a lot of responsibility for dealing with the people in their laboratory," Cech said, adding that institutions and postdocs share that responsibility.

Among other ideas, the panel suggested that NIH provide financial support directly to postdocs and early-career investigators for their own studies and limit to 5 years the time they can spend in training under senior NIH-funded scientists.

Observing that "a lot of the great discoveries tend to be made by people who bring very fresh ideas into the system," Cech said that "science would benefit from a system that actively encourages new investigators to try out novel ideas and approaches." The panel suggested that government funding ought to be more flexible in supporting researchers who want to "branch out and take a chance" in biomedical research.

Also a factor in this discussion are the ways research is changing. "Biomedical science is not exactly what it was 20 or even 10 years ago," Cech said. "It is becoming increasingly interdisciplinary. That trend will continue in the future. Should there be new funding mechanisms to encourage, maybe in completely different ways, interdisciplinary and team-based work?" ■

~ Stephen Pelletier ~

THE PANEL'S REPORT, *BRIDGES TO INDEPENDENCE: FOSTERING THE INDEPENDENCE OF NEW INVESTIGATORS IN BIOMEDICAL RESEARCH*, IS AVAILABLE FROM THE NATIONAL ACADEMIES PRESS

www.nap.edu

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ON AVERAGE, PH.D.S NOW RECEIVE THEIR FIRST INDEPENDENT GRANT FROM NIH AT AGE 42. IN 2003, INVESTIGATORS YOUNGER THAN 40 WERE GRANTED FEWER THAN 17 PERCENT OF THE AGENCY'S COMPETITIVE RESEARCH AWARDS.

IN TRAINING...

"A postdoc is supposed to be an apprenticeship that prepares one for a future career," Tom Cech says. But sometimes that apprenticeship can seem to last forever.

The average age for scientists getting their first NIH grant—typically a critical step in establishing a lab of one's own—has increased markedly over the last 20 years. On average, Ph.D.s now receive their first independent grant from NIH at age 42. In 2003, investigators younger than 40 were granted fewer than 17 percent of the agency's competitive research awards. That's down from more than 50 percent in 1980.

As one solution to this dilemma, the Bridges to Independence panel suggested that postdocs be allowed to compete for independent funding in new ways. For example, the report says, NIH could consider moving some of the resources for postdoctoral support from core R01 grants to training grants and individual awards that aid postdoctoral work.

The goal, Cech says, is to "make what is currently a great system even better."

—S.P.

Promoting Brain Gain

EMBO, HHMI join forces.

HHMI AND THE EUROPEAN MOLECULAR Biology Organization (EMBO) want to attract some of the world's most promising scientists to Central Europe. To help talented researchers establish their first independent laboratories there, the organizations are launching the EMBO/HHMI Startup Grants—3-year awards of $75,000 annually. The new grants spring from a joint initiative of HHMI and EMBO involving Croatia, Czech Republic, Estonia, Hungary, Poland, and Slovenia.

"HHMI believes it is essential that fresh new scientists with fresh new ideas start independent careers with sufficient resources to become competitive in the global world of contemporary science," says Peter J. Bruns, HHMI's vice president for grants and special programs. "By 'resources' we mean more than money; we also mean equipment, supplies, personnel, space, and time. This partnership among HHMI, EMBO, member countries, and local institutions, with each recognizing specific needs and each contributing unique resources, should make a significant difference."

HHMI will contribute $50,000 a year for 3 years for up to six grants. Another $25,000 a year per grant will come from the participating member countries and EMBO. EMBO will oversee the Startup Grants as part of its Young Investigator Programme, which has been identifying and supporting exceptional young scientists in Europe since 2000.

HHMI has supported outstanding scientists in Central and Eastern Europe, Russia, and Ukraine since 1995, reflecting the Institute's commitment to scientific excellence as a global enterprise. Through its international scholars program, HHMI currently provides grants to non-U.S. scientists in 29 countries around the world (see related article on page 44).■

~ Jennifer Boeth Donovan ~

> "HHMI believes it is essential that fresh new scientists with fresh new ideas start independent careers with sufficient resources to become competitive in the global world of contemporary science.
>
> PETER J. BRUNS

The Science of Fat

Lectures on DVD tell the story of obesity.

THE TYPICAL AMERICAN CONSUMES NEARLY a million calories a year, yet weight generally fluctuates very little. The body has mechanisms that track and carefully balance food intake and energy output. That's what makes dieting so difficult.

The science behind obesity came alive for hundreds of high schoolers late last year when two experts delivered a series of engaging lectures on the subject at HHMI headquarters. HHMI's 2004 Holiday Lectures on Science, titled *The Science of Fat*, featured HHMI investigators Ronald M. Evans, from the Salk Institute for Biological Studies, and Jeffrey M. Friedman, from the Rockefeller University. Over two days in early December, a live audience shared their lectures with viewers around the world via live Web simulcast.

Now, the complete lecture series—along with a rich collection of animations, interviews, and other special features—is available from HHMI on a free DVD. The three-DVD set can be ordered online at www.hhmi.org.■

~ Jennifer Boeth Donovan ~

RONALD M. EVANS

JEFFREY M. FRIEDMAN

©PAUL FETTERS

THE BIG PICTURE

Studying mice that are massively obese, Jeffrey Friedman and his colleagues identified the gene for leptin, a hormone produced by fat cells. Leptin—named after the Greek word for "thin"—feeds into the circuit of neurons in the brain that controls eating and energy expenditure.

Ronald Evans is an expert on a family of proteins called PPARs (for peroxisome proliferator activator receptors), which control how the body uses sugar and fat. One member of this family, PPAR-γ, acts as a master switch that drives the formation of fat cells and regulates the storage of fat.

ENGAGING SCIENCE

HHMI teams up with NOVA

HHMI has become a major sponsor of the innovative television program *NOVA scienceNOW*. An offshoot of the acclaimed TV series *NOVA*, the new program airs five times a year.

Viewers of the episode of *NOVA scienceNOW* that aired on April 17 learned about topics ranging from frozen frogs and stem cells to T. Rex and the Little People of Flores. The segment on stem cell research, by coincidence, included interviews with two HHMI investigators, Douglas A. Melton of Harvard University and Leonard I. Zon of Children's Hospital Boston of Harvard Medical School.

With a companion Web site devoted to educational outreach, *NOVA scienceNOW* meshes with HHMI's ongoing commitment to science education. Capitalizing on existing resources at the Institute, *NOVA*'s producers have plans to link to relevant online science content available through the HHMI Web site.

The next edition of *NOVA scienceNOW* is scheduled to air on July 26, 2005. To view past shows online, go to www.pbs.org/wgbh/nova/sciencenow/.

Strengthening Undergraduate Science

Collaboration, dissemination, and mentoring are at the heart of a new $86.4 million competition for universities.

WHILE MANY AMERICANS WERE dropping last-minute tax returns in the mail, FedEx envelopes bearing good news headed for more than 200 research universities. Those packets included HHMI's invitation to compete for $86.4 million in grants to strengthen undergraduate science education in the United States.

The Institute is encouraging teamwork, collaboration, mentoring, and dissemination as it searches for innovative undergraduate science education proposals. HHMI also is seeking programs that broaden access to science for women, underrepresented minorities, and nonscience majors.

Each university selected will receive a 4-year grant ranging from $1.2 million to $2.2 million. Universities may propose programs that provide undergraduate research opportunities and broaden access to science for majors and nonmajors. The grants may also support new courses in emerging fields such as computational biology, genomics, and bioimaging; mentoring programs; current and future faculty development; laboratory equipment; and cooperative programs with elementary and secondary schools. ■

~ Jennifer Boeth Donovan ~

Wanted: More Million-Dollar Professors

HHMI searches for a new cadre of scientist-educators who can inspire undergraduates in the lab and in the classroom.

- At the University of Pittsburgh, researcher Graham F. Hatfull turns high-school students into "phage hunters." Working with soil samples from backyards and barnyards—and notably the monkey pit at the Bronx Zoo—they have identified more than 30 new bacteriophages (viruses that infect bacteria). Genomic information learned from the phages has been so important, says Hatfull, that he and some of his high-school students were coauthors, together with HHMI investigator William R. Jacobs, on a research paper in the journal *Cell*.
- At Harvard University, Richard M. Losick places freshmen in research labs, where they learn, hands-on, how science is really done. Losick has also developed Web-based animations and video modules for teaching molecular biology concepts and procedures.
- Columbia University's Darcy B. Kelley and colleagues developed a course called "Frontiers of Science." Now a requirement for every entering student, it covers topics such as the origins of the universe, the evolution of language, and the future of the planet.

HATFULL, LOSICK, AND KELLEY ARE MEMBERS OF THE FIRST CLASS of HHMI professors—a group of 20 innovative research scientists, appointed in 2002, who are working to incorporate the excitement of scientific research and discovery into undergraduate education. They want everyone—science majors and non-science majors alike—to understand not only how research is done but also how it affects people's daily lives. Now, HHMI is looking for some more faculty who are similarly motivated.

One hundred research universities were invited to nominate one or two of their best scientist-educators. The deadline for nominations was May 2, 2005, and nominees must submit proposals by September 7, 2005. From this eminent group, a new class of up to 20 faculty members will be named HHMI professors in 2006, with each of them receiving a 4-year award of $1 million.

The HHMI professors program is part of the Institute's long-term plan to improve science education at all levels, to help produce the next generation of research scientists, and to create a more science-literate public. To date, HHMI has awarded more than $600 million to public and private colleges and universities as well as $20 million to the first class of HHMI professors. ■

~ Jennifer Boeth Donovan ~

Supporting Research Abroad

HHMI seeks outstanding Latin-American, Canadian researchers.

TALENTED RESEARCHERS OUTSIDE THE United States often find themselves handicapped by lack of research support and infrastructure in their home countries. HHMI's international grants program seeks to level the playing field.

To that end, HHMI is inviting scientists who have full-time appointments at nonprofit scientific research institutions in Canada, Mexico, and six South American countries—Argentina, Brazil, Chile, Peru, Uruguay, and Venezuela—to apply to the HHMI international research scholars program.

Awards will be given for fundamental biomedical research on basic biological processes and disease mechanisms. "The key criterion," says Peter J. Bruns, HHMI vice president for grants and special programs, "is the quality of applicants' research."

Each 5-year grant provides $250,000 to $500,000. The application deadline is September 14, 2005. Grants will be awarded in October 2006.

Since HHMI's international grants program was established, in 1991, scientists in 32 countries around the world have received awards totaling more than $100 million. In addition to basic researchers in Latin America and Canada, the Institute supports scientists in Eastern and Central Europe, Russia, and the Baltics, as well as parasitology and infectious-disease researchers worldwide. ■

– Jennifer Boeth Donovan –

FOR MORE INFORMATION

www.hhmi.org/grants/individuals/canlatam.html

EXAMPLES OF RESEARCH

CLOCKWISE FROM TOP LEFT: PETER ST GEORGE-HYSLOP, PEDRO LABARCA, MARCELO RUBINSTEIN, MARIANO LEVIN

International researchers supported by HHMI have made notable achievements. For example, Marcelo Rubinstein, of Argentina, founded one of the premier mouse transgenics facilities in South America and is now collaborating with Pedro Labarca to establish a similar facility in Chile. Mariano Levin, also of Argentina, helped sequence the genome of *Trypanosoma cruzi*—the parasite that causes Chagas disease, which cripples or kills tens of thousands of people annually in Central and South America and Mexico. And Peter St George-Hyslop, of the University of Toronto, discovered genes involved in Alzheimer's disease.

The Incredible Locomoting Jake

With flying snakes and clapping scallops, an inspired researcher makes science come alive.

THE FIRST TIME UNIVERSITY OF CHICAGO student James Waters saw Jake Socha giving a lecture, Socha was imitating a fish. "He was up there basically doing a dance," recalls Waters, "and he was so excited and into what he was teaching that there was no way I could miss the next class."

He didn't, having immediately enrolled in the course, called "Animal Locomotion." Socha (pronounced SO-ha), whose teaching was funded in part by an HHMI undergraduate science education grant, brought his fast-paced and theatrical teaching approach into play in virtually every class. For example, he would show short videos of animals in motion—a scallop clapping its shells together and surging forward, a web-footed "flying" frog gliding from tree to tree, a Jesus lizard running on water—and after each video, Socha would ask a student to mimic the animal's movements. Then he'd derive a formula that described its pattern. "He managed to make the course incredibly mathematical," says Waters, "yet he didn't lose anybody."

Socha, 33, who recently earned his doctorate in biomechanics from the University of Chicago, discovered the field as an undergraduate. Definable as the mechanical engineering of living things, biomechanics nicely combined his interests in physics and biology, and he had the good fortune to study with a pioneer in the field, Steven Vogel.

While visiting potential graduate schools, Socha heard from a professor that certain snakes in Asia somehow moved through the air. He came back to the idea after beginning school, thinking he'd check it out and then "move on to something real." But once Socha discovered that no one completely understood how a vertebrate without wings or any other steering appendage could control its flight path, his interest grew. The study of flying snakes became his doctoral research.

As part of his doctoral work, Socha coaxed 21 paradise tree snakes to launch themselves in turn from a scaffolding tower built for him in the Singapore Zoological Garden, and he filmed all the action. Socha's 3-D reconstruction of the snakes in flight showed that they flatten their cylindrical bodies—doubling their width—and then curl into an S-shape and undulate as they move through air (see the movies at www.flyingsnake.org). He's still trying to understand how they steer. ■

~ Cathy Shufro ~

BELOW _ *CHRYSOPELEA PARADISI*, COMMONLY KNOWN AS THE PARADISE TREE SNAKE, FLATTENS ITSELF OUT SO IT CAN GLIDE. TO LEARN MORE—AND TO VIEW THE REPTILE AIRBORNE—VISIT JAKE SOCHA'S FLYING SNAKE HOME PAGE, WWW.FLYINGSNAKE.ORG/.

JAKE SOCHA

Bacteria Fly from the Sty

Amy Chapin and her research team discover that hog farms send more than an odor into the air.

AMY CHAPIN'S CAREER PATH HAS TAKEN her to huge hog farms around the country. For several years, Chapin, with training in biology and public health, has been studying how these sites affect the environment and, consequently, human health. An HHMI predoctoral fellow when interviewed this spring, Chapin expected to receive her Ph.D. in environmental health sciences in May from the Bloomberg School of Public Health at the Johns Hopkins University.

"Wherever I go," she says, "I end up working on swine issues," which apparently have an ambience and staying power all their own. "It's definitely very stinky work," she admits. Her research equipment and notebooks exude hog odors for up to a year.

But the smell is the least of her concerns. Chapin now believes the foul breeze wafting from large-scale hog farms carries antibiotic-resistant bacteria, posing risks to the people who work or live nearby, especially those with compromised immune systems. When she and her colleagues at Johns Hopkins took air samples in the barns of one facility, for example, they found 137 types of gut bacteria—98 percent of them resistant to at least two antibiotics.

The group reported its results in the February 2005 issue of *Environmental Health Perspectives*. "The level of resistant bacteria found in the air was quite striking," says Marilyn C. Roberts, a microbiologist at the School of Public Health at the University of Washington in Seattle, who was not involved in Chapin's study. That's especially troubling because air is so difficult to control.

The main sources of the problem are the antibiotics hog farmers feed to their animals to treat infections, prevent illnesses, and improve growth. That practice causes bacteria in a hog's gut—often the same kinds that cause disease in humans—to be dominated by antibiotic-resistant variants. Such "superbugs" have been found in pork products and in nearby groundwater and soils, according to other studies. No one had fully investigated whether such bacteria could become airborne, in large part because farmers were reluctant to open their barn doors to researchers.

Getting access to the farm for their study took Chapin's team about a year-and-a-half, she says. They then made two site visits one month apart.

More barn doors—plus a few stockyard gates—may well open for Chapin once she has her Ph.D. in hand. After writing a paper this summer characterizing her work on the resistance-conferring genes in certain airborne bacteria from large-scale hog farms, she wants to expand her studies to poultry farms and cattle yards. "I think it's important to find out how far the bacteria at these sites travel and whether communities nearby may be exposed," she says. ■

~ Karen F. Schmidt ~

"When Amy Chapin and her colleagues at the Johns Hopkins University took air samples in the barns of one facility, for example, they found 137 kinds of bacteria—98 percent of them resistant to at least two antibiotics.

AMY CHAPIN

HOG FARMERS FEED ANTIBIOTICS TO THEIR ANIMALS TO TREAT INFECTIONS, PREVENT ILLNESS, AND IMPROVE GROWTH. TROUBLE IS, THAT PRACTICE LEADS TO THE DEVELOPMENT OF ANTIBIOTIC-RESISTANT BACTERIA THAT CAN CAUSE ILLNESS IN HUMANS.

CHAPIN: AMIR SAPKOTA *PIG:* VEER

Genetic Tool Reaps Rich Harvest

IN ONE FELL SWOOP, SCIENTISTS HAVE increased from dozens to hundreds the number of known genes that control crucial steps in the development of many organisms, from fruit flies to humans.

Using the power of the genetic technique known as RNA interference, the researchers identified some 238 potential regulatory genes in the Wnt signaling pathway. Understanding this pathway will provide researchers with new insight into the development of certain cancers as well as other genetic diseases.

The findings were published in the May 6, 2005, issue of the journal *Science*. The research was conducted by lead authors Ajamete Kaykas and Ramanuj DasGupta. They work, respectively, in the laboratories of senior authors Randall Moon at the University of Washington School of Medicine and Norbert Perrimon at Harvard Medical School, both HHMI investigators.

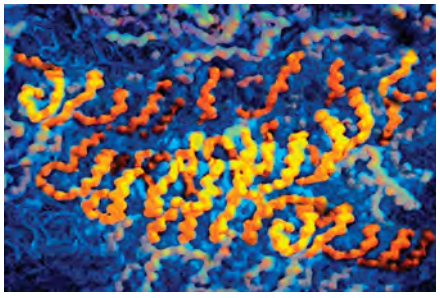
According to Moon, until the new analysis, identifying the genes that produce components of the Wnt pathway had been a long, hard, gene-by-gene slog. Basically, researchers would mutate a single gene in an organism and analyze whether it affected the pathway.

"At the time this screen was conducted, the total number of genes implicated in the pathway was probably on the order of 40 to 60," said Moon. "But this was in multiple organisms, and it wasn't really clear whether all of these components functioned in one organism or whether people were comparing different genes in different critters. There had been no systematic single-organism genome-wide screen to ask, What is an approximation of the number of genes that can affect this pathway?" he said.

Attempting to develop a more efficient approach, DasGupta and Kaykas screened fly cells for Wnt-associated genes using a technology called high-throughput RNA interference screening, developed in Perrimon's laboratory. Considered one of the most important new techniques for analyzing gene activity, RNA interference relies on the fact that a short segment of double-stranded RNA with a sequence identical to that of a specific messenger RNA—copied from a gene as a template for protein synthesis—can interfere with that messenger RNA. The interaction essentially shuts down the corresponding gene's function. Perrimon and his colleagues have created large libraries of RNA segments that together correspond to the entire genome of the fruit fly *Drosophila*.■

– Dennis Meredith –

> "I found the discovery of the involvement of this many genes in the Wnt pathway, and their diversity, to be quite stunning."
>
> RANDALL MOON



JAMES CAVALLINI / PHOTO RESEARCHERS, INC.

RIBONUCLEIC ACID, OR RNA, HIGHLIGHTED HERE IN YELLOW AND ORANGE, CARRIES THE TEMPLATE "MESSAGE" ENCODED IN DNA THAT DIRECTS SYNTHESIS OF SPECIFIC PROTEINS INSIDE A CELL.

IN BRIEF

PROGNOSIS FOR RESEARCH ON MODEL ORGANISMS

Although more than a million described species live on Earth, most basic knowledge about the properties of cells has come from studies of just a few "model organisms," including the bacterium Escherichia coli, the yeast Saccharomyces cerevisiae, the worm Caenorhabditis elegans, the mustard plant Arabidopsis thaliana, the fruit fly Drosophila melanogaster, and the mouse Mus musculus. Investments in biomedical research often are justified through their potential applications to human disease. As researchers increasingly gain the ability to study diseases directly in humans, will research on model organisms decline?

That's unlikely, said Stanley Fields, an HHMI investigator at the University of Washington, and Mark Johnston at Washington University School of Medicine in St. Louis, in an article published in the March 25, 2005, issue of Science entitled, "Whither Model Organism Research?"

Funding pressures and calls for translational research are orienting research toward humans and human diseases," said Fields. "But there's still a lot to be gained by studying model organisms."

With that said, however, Fields and Johnston believe that within the next few decades, research into model organisms will reach a pivotal juncture. Starting with yeast and progressing through the more complex organisms, the basic biology of model organisms will be "solved," they said. In other words, biologists will understand, at least in outline, all the basic mechanisms of the cell, including the functions of nucleic acids and proteins, the signaling pathways by which cells communicate, and the selective expression of subsets of genes.

HOW BITTER TASTE IS PERCEIVED

Researchers have discovered precisely how animals detect bitter tastes and how they might manage to avoid toxic and noxious substances. Their studies show that specific cells of the tongue govern detection of bitter substances.

In a particularly intriguing experiment, the researchers engineered mice to perceive bitter-tasting chemicals as sweet, and the animals relished the taste of those noxious compounds as if they were sugar. The same studies also demonstrated that taste cells are "hard-wired" to signal the presence of a particular taste to the brain, regardless of what taste receptors they possess.

This work, along with the group's recent discoveries on the biology of sweet and umami taste, opens a research pathway to tracing taste processing into higher brain regions where animals and humans make complex judgments about tastes—like going from the subtle "off taste" of spoiling milk to the complex, unique flavor of foie gras.

The researchers published their findings in the March 10, 2005, issue of the journal Nature. They were led by HHMI investigator

When Cells Are Starved for Oxygen

WHAT HAPPENS WHEN LIVING THINGS CAN'T get the critical element that's in a breath of fresh air? Within seconds of oxygen starvation, cells begin to do all they can to conserve energy, including shutting down energy-sapping processes such as cell division, protein synthesis, and ion trafficking. In a human being, says HHMI investigator M. Celeste Simon, the result can be a heart attack or a stroke.

Simon became interested in hypoxia—the term for oxygen deficiency in tissues—a decade ago, after learning about a newly discovered family of environment-sensing proteins that respond to cues such as light, electrical conductivity, and oxygen levels by switching on appropriate genes. Scientists had already established a role for one of these proteins, hypoxia-inducible factor (HIF). It activates genes—those involved in glycolysis, a process that can replenish energy reserves without using oxygen, and in building new blood cells and the vessels to transport them—that might remedy an oxygen-deprivation crisis. Under even-lower oxygen levels, HIF activates genes that control cell motility. "You have cells that want to get away," Simon explains. "They want to find where the oxygen is."

Simon suspected that HIF might serve an even more fundamental purpose—for example, in embryonic development. To find out more about the protein's other roles, her University of Pennsylvania lab bred mice lacking HIF. "Sure enough," she says, "the mutant mouse embryos had defects in vascular differentiation, blood-cell production, cardiac differentiation, and placental growth."

HIF also plays roles in cancer. "Tumors are centrally dependent upon oxygen availability," says Simon, "and that is a primary driving force for them to acquire blood vessels." Thus, one strategy for fighting cancer is to develop drugs that selectively shut down the HIF pathway in tumors, effectively asphyxiating them.

While turning on the HIF pathway can be an outcome of cancer, it can also be a direct cause of diseases—in particular, of von Hippel-Lindau disease, a rare genetic disorder that induces the abnormal growth of tumors. Ordinarily, HIF maintains a low profile in cells. As several labs, including that of HHMI investigator William G. Kaelin, Jr., at the Dana-Farber Cancer Institute, have shown, HIF gets destroyed almost as quickly as it is made, with another protein, called pVHL, directing that destruction. Only during an oxygen deficit will pVHL stop targeting HIF, thereby freeing it to trigger the hypoxia response. But mutations, like those that occur in von Hippel-Lindau disease, can render pVHL useless, so that HIF accumulates and provokes a potent hypoxia response even under normal oxygen conditions. The result is a collection of highly vascularized tumors throughout the body.

Researchers also know that oxygen-sensitive enzymes called prolyl hydroxylases must modify HIF before it can be destroyed. But Simon thinks the chain of events goes deeper than that, with her prime suspects being mitochondria, the cellular particles where oxygen is used to produce energy. Mitochondria emit "signals"—metabolites that not only affect prolyl hydroxylase activity, she surmises, but that instruct other, unidentified molecules during hypoxic stress. ■

– Paul Muhlrad –

Charles S. Zuker at the University of California at San Diego and Nicholas Ryba of the National Institute of Dental and Craniofacial Research at the National Institutes of Health.

DOPAMINE AND BRAIN CIRCUITRY

Researchers have discovered how dopamine—a molecule important for communication between neurons in the brain—stimulates the synthesis of proteins in neuronal processes. This local stimulation of protein synthesis may modify synapses in the brain during learning, said the researchers.

The new findings add to the understanding of dopamine's influence on the brain's reward circuitry that appears to be altered by addictive drugs. The research team, led by Erin M. Schuman, an HHMI investigator at the California Institute of Technology, published its findings in the March 3, 2005, issue of the journal Neuron. Lead author on the paper was Bryan Smith in Schuman's laboratory.

EVOLUTION TRACED TO SLIGHT GENETIC CHANGES

In a stunning example of evolution at work, scientists have found that changes in a single gene can produce major changes in the skeletal armor of fish living in the wild. The surprising results, announced in the March 25, 2005, issue of the journal Science, bring new data to long-standing debates about how evolution occurs in natural habitats.

"Our motivation is to try to understand how new animal types evolve in nature," said molecular geneticist David M. Kingsley, an HHMI investigator at the Stanford University School of Medicine. "People have been interested in whether a few genes are involved, or whether changes in many different genes are required to produce major changes in wild populations."

The answer is that evolution can occur quickly, with just a few genes changing slightly, allowing newcomers to adapt and populate new and different environments.

In collaboration with zoologist Dolph Schluter at the University of British Columbia and Rick Myers and colleagues at Stanford University School of Medicine, Kingsley and graduate student Pamela F. Colosimo focused on a well-studied little fish called the stickleback. The fish—with three bony spines poking up from their backs—live both in the seas and in coastal freshwater habitats all around the northern hemisphere.

Kingsley, Schluter, and their coworkers picked one trait—the fish's armor plating—on which to focus intense research, using the armor as a marker to see how evolution occurred. Sticklebacks that still live in the oceans are virtually covered, from head to tail, with bony plates that offer protection. In contrast, some freshwater sticklebacks have evolved to have almost no body armor.

Using genetic crosses between armored and unarmored fish from wild populations,

Going After the Queen

Are clues to cancer treatment hidden inside cancer stem cells?

CANCER RESEARCHERS GOT A BIG BREAK in the 1990s when they discovered that tiny numbers of mutated stem cells could spawn malignant tumors. These "cancer stem cells" turn out to be the reproductive source of other cells that make up tumors in leukemias, breast cancer, and testicular cancer. And they are suspected to exist in many more cancers.

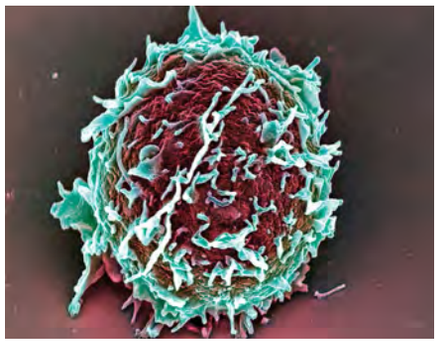
Since then, scientists have tried to determine where cancer stem cells come from, so they can deal with cancer at its source. "It's like going after a queen in a beehive," says HHMI investigator D. Gary Gilliland. "If you don't get the queen, the colony will continually replenish itself."

Brian J.P. Huntly, a postdoc in Gilliland's laboratory at Brigham and Women's Hospital in Boston, says that while most scientists presumed cancer stem cells were merely adult stem cells gone wrong, "we proposed that mature cells might be reprogrammed to regain stem-cell properties if they carried certain oncogenes" (cancer-causing genes). When cells self-renew, they typically produce a clone of themselves in addition to a "mature" cell that will eventually die. But cell death is not necessarily inevitable, Huntly says.

This hunch proved correct. In the December 2004 issue of *Cancer Cell*, the researchers reported on an oncogene that was found to turn mature blood cells into the stem cells that cause acute myeloid leukemia.

The oncogene that produced this effect is a fusion of two genes called *MOZ* and *TIF2* that—individually—engage in normal cell functions. But the *MOZ-TIF2* oncogene produces a mutant protein that allows the mature cells to survive, to self-renew like stem cells, and to accumulate further mutations that induce leukemia, according to Huntly. An additional leukemia oncogene investigated during this research—called *BCR-ABL*—did not produce this effect. "Our hypothesis is that *MOZ-TIF2* activates genes that are involved in the self-renewal process, whereas *BCR-ABL* does not," Huntly says. ■

~ Charlie Schmidt ~



GARY D. GAUGLER / PHOTO RESEARCHERS, INC.

HEMATOPOIETIC STEM CELLS CAN DIVIDE WITHOUT LIMIT, REPLENISHING BLOOD CELL POPULATIONS. RESEARCHERS NOW FIND THAT CANCER-CAUSING ONCOGENES CAN CAUSE MATURE BLOOD CELLS TO REGAIN STEM CELL-LIKE BEHAVIOR.

"If you don't get the queen, the colony will continually replenish itself."

D. GARY GILLILAND

the research team found that one gene makes the difference.

"Now, for the first time, we've been able to identify the actual gene that is controlling this trait," the armor plating on the stickleback, Kingsley said.

The gene they identified is called Eda, originally named for a human genetic disorder associated with the ectodysplasin pathway, an important part of embryonic development. The human disorder, one of the earliest ones studied, is called ectodermal dysplasia.

THE CAUSE OF A HEART DISEASE

Using genetic analyses and the translucent tail of a fish, researchers have pinpointed the underlying cause of a rare, mysterious heart disease that is preceded by hearing loss. Discovering the genetic cause of this disease provides researchers with a wealth of ideas about the molecules involved in building the developing heart as well as how diseases weaken heart muscle.

In an advance online publication on February 27, 2005, in the journal Nature Genetics, HHMI investigators Christine E. Seidman and Jonathan G. Seidman and their colleagues identified the mutation that causes the disorder, dilated cardiomyopathy preceded by sensorineural hearing loss. The Seidmans and their colleagues at Harvard Medical School collaborated with researchers at University Hospital Würzburg in Germany, Massachusetts General Hospital, Children's Hospital Boston, and the Wellcome Trust Sanger Institute in Great Britain.

GENETIC SIGNATURE MAY BE TOOL FOR BREAST CANCER THERAPIES

HHMI researchers have discovered that activation of specific components of the genetic machinery used to close a wound may also be a powerful predictor of which breast cancers are likely to spread and which women are likely to survive the disease.

The researchers said their findings would give clinicians an important tool for planning breast cancer therapies—for example, distinguishing patients who will benefit from chemotherapy from those who may not. The new findings build on earlier studies that demonstrated that activation of genes involved in repairing wounds is a characteristic shared by epithelial-tissue cancers, such as breast, lung, and gastric cancers.

Led by Marc van de Vijver of the Netherlands Cancer Institute and HHMI investigator Patrick O. Brown, the researchers published their findings February 8, 2005, in the early online edition of the Proceedings of the National Academy of Sciences. Brown, postdoctoral fellow Howard Chang, and colleagues at Stanford University School of Medicine collaborated on the studies with researchers from the Netherlands Cancer Institute, Rosetta Inpharmatics in Seattle, and the Norwegian Radium Hospital. ■

LEFT: H. SEBASTIAN SEUNG
RIGHT: RUSS TEDRAKE

"I think that robots are going to turn out to be a great tool to understand how humans work. My robot has big curved feet and no knees. It actually doesn't walk too much like a human, but we think it learns like a human.

RUSS TEDRAKE

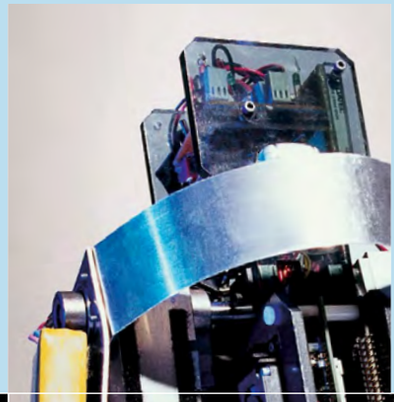
Toddler Hits Its Stride

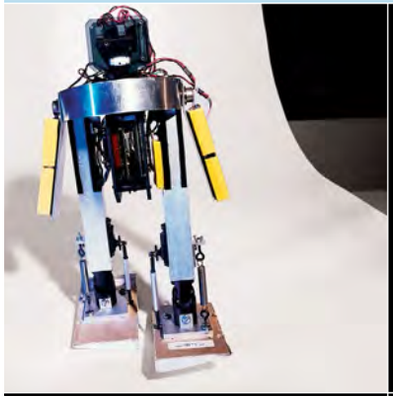
A diminutive robot helps MIT researchers study how children learn to walk.

RUSS TEDRAKE'S WIFE HAS ALREADY LAID DOWN the law: If they ever have children, he will not be allowed to experiment on them. But no matter. All the tinkering the MIT postdoc has been doing lately with his brainchild—a diminutive walking robot named Toddler—seems to be ful□lling enough. Toddler stands out because, like human children, it learns how to walk all by itself. In fact, it can master walking in about 20 minutes, a feat that would make any parent proud.

Tedrake built Toddler for his dissertation project in the lab of computational neuroscientist and HHMI investigator H. Sebastian Seung. At first blush, you might presume that Tedrake, whose undergraduate degree is in computer engineering, would be out of his element surrounded by labmates probing neurons in culture dishes. But he contends it's a match made in heaven. Because "Sebastian's lab is interested in how neurons learn," Tedrake explains, "he's interested in the computations that go on in the brain. I basically took the same ideas—the principles that we think are involved in neural learning—and applied them to a robot."

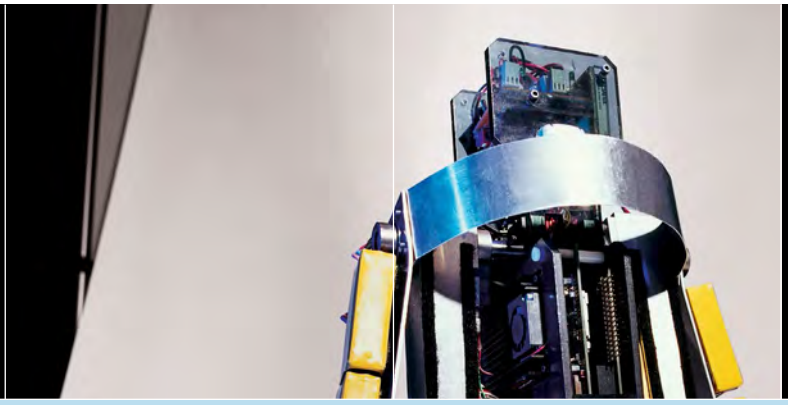
Toddler is based on passive-dynamic walkers, which, powered only by gravity, walk down ramps. Tedrake was intrigued that these simple machines, popular for generations as toys, can propel themselves with uncanny human-like gaits; the walkers seem to draw their agility simply from the design and arrangement of their moving parts. He thinks the same principle is what makes animals so good at walking without relying on too much brainwork. "The musculoskeletal system actually





Toddler owes its adroitness to its electro-mechanical design. Large, curved feet offer stability, and gyroscopic leg sensors feed position and speed data to its onboard computer.

ASIA KEPKA



simplifies the control problem that the brain has to solve," Tedrake says.

But things are a bit more challenging for machines—or living animals, for that matter—to be able to move gracefully along □at surfaces. "They have to learn to walk on a □at," Tedrake says, "because passive walking won't work there."

Seung and other computational neuroscientists speculate that learning is largely a matter of trial and error, even at the cellular level. When neurons fire, the theory goes, minuscule random fluctuations occur in the variety and numbers of neurotransmitters they release. "That means that every time a neuron fires, the result could be a little bit different," Tedrake says. Somehow, the brain keeps tabs on those variations and their corresponding results, learning with each new experience.

So, applying the theories of his mentor, Tedrake endowed his cyber-creation with a mind of its own. Beyond the four motors they added to power it, he and his assistants equipped Toddler with electronic sensors and microchips that record and evaluate its motions 200 times a second. "Every time the robot initiates an action, we add a little bit of random noise to the action. And the trick is for us to correlate the random change with a resultant change in walking performance."

Tedrake predicts that Toddler's younger sibling, still in gestation, will be more of a prodigy and provide its creators with far more useful data. It will have knees, more human-like feet, and more sophisticated circuitry to help it learn how to use them. ■

~ Paul Muhlrad ~

With each step, the computer evaluates how well Toddler is walking by comparing the data to a mathematical model of how Tedrake thinks it should walk. If Toddler's stride matches the model, the computer awards it a digital pat on the back to keep up the good work. Whenever Toddler strays from the model, the computer suggests that it try an alternative step.

WANT TO SEE TODDLER WALK? WATCH THE SHORT VIDEO

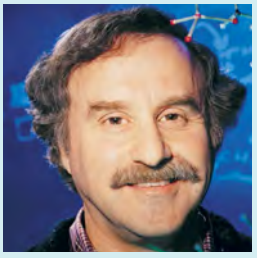
www.hhmi.org/bulletin

SPOTLIGHT

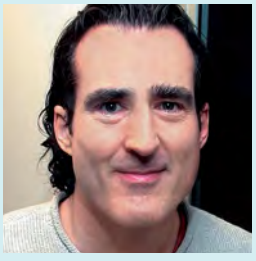

CAROLYN R. BERTOZZI


AXEL T. BRUNGER


IVA S. GREENWALD


STEVEN HENIKOFF


RUTH LEHMANN


CRAIG C. MELLO


DAVID C. PAGE


TOM A. RAPOPORT


TRUDI SCHÜPBACH


CHRISTINE E. SEIDMAN

Ten Investigators Elected to National Academy

On May 3, 2005, the National Academy of Sciences announced the election of 72 new members and 18 foreign associates from 14 countries. Among them are 10 HHMI investigators, the chairman of the Institute's medical advisory board, and an international research scholar from Mexico.

The investigators include **CAROLYN R. BERTOZZI,** University of California, Berkeley; **AXEL T. BRUNGER,** Stanford University; **IVA S. GREENWALD,** Columbia University College of Physicians and Surgeons; **STEVEN HENIKOFF,** Fred Hutchinson Cancer Research Center; **RUTH LEHMANN,** New York University School of Medicine; **CRAIG C. MELLO,** University of Massachusetts Medical School; **DAVID C. PAGE,** Whitehead Institute for Biological Research; **TOM A. RAPOPORT,** Harvard Medical School; **TRUDI SCHÜPBACH,** Princeton University; and **CHRISTINE E. SEIDMAN,** Brigham and Women's Hospital. Also elected were **CRAIG B. THOMPSON,** chairman of HHMI's medical advisory board, and **RANULFO ROMO,** international research scholar at the National Autonomous University of Mexico.

BERTOZZI: **BARBARA RIES** *BRUNGER:* **VISUAL ARTS SERVICES, STANFORD UNIVERSITY** *GREENWALD:* **COURTESY OF COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS** *HENIKOFF:* **JIM LINNA** *LEHMANN:* **COURTESY OF NEW YORK UNIVERSITY SCHOOL OF MEDICINE** *MELLO:* **TONY MACIAG / UNIVERSITY OF MASSACHUSETTS** *PAGE:* **STANLEY ROWIN** *RAPOPORT:* **GINTARAS SEKMOKAS** *SCHÜPBACH:* **COURTESY OF PRINCETON UNIVERSITY** *SEIDMAN:* **KAY CHERNUSH**

■ **Frederick W. Alt,** an HHMI investigator at Children's Hospital Boston, won the 2005 Pasarow Medical Research Award in the field of cancer, given by the Robert J. and Claire Pasarow Foundation for extraordinary research accomplishments and the likelihood of continuing outstanding achievement in biomedical science. Alt also received the 2005 Rabbi Shai Shacknai Memorial Prize in Immunology and Cancer Research from the Hebrew University–Hadassah Medical School, and the Leukemia & Lymphoma Society's 2005 de Villiers International Achievement Award.

■ **Kevin P. Campbell,** an HHMI investigator at the University of Iowa Carver College of Medicine, received the 2004 Rochester Distinguished Scholar Award from the University of Rochester. The award is given to doctoral graduates who have gone on to eminent careers in academia, industry, or government.

■ Nine HHMI investigators were elected to the 2005 class of fellows of the American Academy of Arts & Sciences. Those elected are **Gideon Dreyfuss**, University of Pennsylvania School of Medicine; **David Ginsburg,** University of Michigan Medical School; **Iva S. Greenwald**, Columbia University College of Physicians and Surgeons; **David M. Kingsley**, Stanford University School of Medicine; **Louis M. Kunkel**, Children's Hospital, Boston; **Anna Marie Pyle**, Yale University School of Medicine; **Tom A. Rapoport**, Harvard Medical School; **Louis F. Reichardt**, University of California, San Francisco; and **Gary Struhl**, Columbia University College of Physicians and Surgeons.

■ **John W. Kappler** and **Philippa Marrack,** HHMI investigators at the National Jewish Medical and Research Center, in Denver, Colorado, received the Bonfils-Stanton Foundation Award for Science and Medicine. The award is given annually to Colorado citizens for lifetime achievements in the arts and humanities, community service, and science and medicine.

■ **Mary E. Lidstrom,** an HHMI professor at the University of Washington, won an Award of Merit from the Puget Sound Chapter of the Society for Technical Communication. She was honored for developing an interactive CD to teach engineers the essentials of information transfer in biology.

■ **Roderick MacKinnon,** an HHMI investigator at the Rockefeller University, received the 2005 Hans Neurath Award from the Hans Neurath Foundation for his research on ion channels. The award honors an individual who has made a recent contribution of unusual merit to basic research in the field of protein science.

■ **Ruslan Medzhitov,** an HHMI investigator at Yale University School of Medicine, received the 2004 Emil von Behring Award from the University of Marburg in Germany. The award recognizes his contributions to scientific understanding of the innate immune system.

■ **Paul L. Modrich,** an HHMI investigator at Duke University Medical Center, received the American Cancer Society's 2005 Medal of Honor in the category of basic research for outstanding contributions to cancer control.

■ **Kunihiko Nishino,** a postdoctoral fellow in the laboratory of HHMI investigator Eduardo A. Groisman at the Washington University in St. Louis School of Medicine, was named a 2004 Young Scientist Award regional winner in the annual competition hosted by *Science* magazine and General Electric. Nishino, who studies drug-resistant bacteria, won for his essay "Analysis of drug exporter gene libraries based on genome information and study of their regulatory networks."

■ **Eva Nogales,** an HHMI investigator at the University of California, Berkeley, won the 2005 Chabot Space & Science Center Science Award from the Chabot Space & Science Center in Oakland, California. The award honors excellence in the field of scientific and technological discovery.

■ **Charles L. Sawyers,** an HHMI investigator at the University of California, Los Angeles, received the 2005 Richard and Hinda Rosenthal Foundation Award from the American Association for Cancer Research for his research involving molecularly targeted cancer therapy. Sawyers also received the 2005 David A. Karnofsky Memorial Award from the American Society of Clinical Oncology for his research on signal transduction in leukemia and prostate cancer.

■ **Nahum Sonenberg,** an HHMI international research scholar at McGill University, was among five scholars to receive a 2005 Killam Prize, Canada's distinguished annual award for outstanding career achievement in various academic disciplines. Sonenberg's prize, in the category of health sciences, recognized his contributions to molecular and cellular biology.

■ **Thomas A. Steitz,** an HHMI investigator at Yale University, won the 2004 Frank H. Westheimer Prize from Harvard University's department of chemistry and chemical biology for distinguished research in the field of chemistry.

■ **Peter Tontonoz,** an HHMI investigator at the University of California, Los Angeles, received the 2005 Richard E. Weitzman Memorial Award from the Endocrine Society, given to a scientist under the age of 40 for outstanding research in endocrinology.

■ **Roger Y. Tsien,** an HHMI investigator at the University of California, San Diego, received the 2005 Perl-UNC Neuroscience Prize, given for seminal achievement in neuroscience. Tsien won for "developing molecular indicators that have revolutionized the optical monitoring of neurons."

■ **Isiah M. Warner,** an HHMI professor at Louisiana State University, won Tuskegee University's 2005 George Washington Carver Achievement Award in recognition of his work as an educator, administrator, and humanitarian.

SPOTLIGHT

Two Investigators Win Major Awards

JEFFREY M. FRIEDMAN, an HHMI investigator at the Rockefeller University, and **CRAIG C. MELLO**, an HHMI investigator at the University of Massachusetts Medical School, were among six researchers to receive a 2005 Gairdner Foundation International Award.

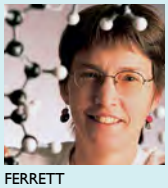
The Gairdner Foundation recognized Friedman for his "contributions to our understanding of obesity, and particularly for the discovery of the adipose fat tissue hormone, leptin." Mello was honored for "the discovery of RNA interference, which initiated a revolution in the study and use of RNA in gene silencing."

The Gairdner Foundation was created in 1957. Its prestigious awards recognize outstanding contributions by medical scientists worldwide whose work promises to substantially improve quality of life. Sixty-four of its award winners have subsequently won the Nobel Prize.

Friedman also recently received the 2005 Passano Foundation Award, given annually for outstanding contributions to medical science and research. In addition, Mello is one of four researchers working in the area of RNA-mediated gene regulation to receive Brandeis University's 2005 Lewis S. Rosenstiel Award for Distinguished Work in Basic Medical Science.

SPOTLIGHT

Faculty at Carleton, Hope Named Carnegie Scholars



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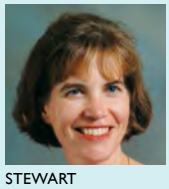


STEWART

Two college teachers supported by HHMI undergraduate science education programs are among the 21 educators named Carnegie Scholars by the Carnegie Academy for the Scholarship of Teaching and Learning (CASTL). As Carnegie Scholars on a shared project, **TRISH A. FERRETT,** HHMI program director at Carleton College in Northfield, Minnesota, and **JOANNE L. STEWART**, director of integrative studies in the sciences for the HHMI program at Hope College in Holland, Michigan, plan to assess students' ability to integrate different disciplinary approaches in addressing complex scientific problems. The assessments will be tied to particular HHMI-funded general science courses offered at the two colleges.

FERRETT: COURTESY OF TRISH A. FERRETT *STEWART:* COURTESY OF HOPE COLLEGE

IN MEMORIAM

— *STANLEY J. KORSMEYER* —

1950 ~ 2005

STANLEY J. KORSMEYER, AN HHMI INVESTIGATOR AT THE DANA-FARBER CANCER INSTITUTE AND HARVARD MEDICAL SCHOOL, DIED ON MARCH 31, 2005, AFTER A LONG STRUGGLE WITH LUNG CANCER. A NONSMOKER, KORSMEYER WAS 54 YEARS OLD.

An international leader in the field of programmed cell death, Korsmeyer published numerous research papers that opened new vistas in a quartet of disciplines, including immunology, hematology, oncology, and genetics.

"He was everybody's hero—both as a scientist and as a human being," said H. Robert Horvitz, an HHMI investigator at the Massachusetts Institute of Technology and a close friend of the late researcher. "His contributions were truly major and pioneering."

Korsmeyer's work led to the identification of many of the key genetic mechanisms that govern cell death and survival. His research also defined the role of cell death in the pathogenesis of human diseases, including lymphomas and other cancers.

Korsmeyer was best known within the scientific community for his seminal work on a gene known as *BCL-2*. In 1985, while studying patients with follicular B cell lymphoma, a cancer of the immune system, Korsmeyer, then an HHMI investigator at Washington University in St. Louis School of Medicine, discovered that these patients carried the *BCL-2* gene. The activity of this gene was increased because of a disastrous chromosomal mix-up. Shortly afterward, scientists at the Walter and Eliza Hall Institute of Medical Research in Australia announced that DNA from human *BCL-2* made mouse cells survive longer than normal; during this extra time, some of the cells acquired additional mutations and became malignant.

Korsmeyer's group continued to blaze the *BCL-2* trail to identify and characterize the roles of a host of other related proteins involved in cell death pathways, including BAX, BAD, and BID. As much as he loved basic research, however, Korsmeyer was keenly aware of the need to translate discoveries into practical therapies for patients. To that end, some of his more recent studies fashioned novel strategies for the design of cancer-killing drugs that would selectively trigger cell death.

Korsmeyer was highly respected as a mentor of young scientists. "Stan led by example," recalls Loren D. Walensky, a pediatric oncologist at Dana-Farber who conducted research with Korsmeyer. "We learned by watching him operate scientifically in a serious, meticulous, and laser-focused manner. He taught us how to frame the scientific question and then methodically drill down until all layers of the answer became apparent."

Growing up on his family's livestock farm in Beardstown, Illinois, Korsmeyer was intent on becoming a veterinarian. But a veterinarian with whom Korsmeyer worked as a high-school student suggested he take a closer look at the biological sciences. After he was accepted into the University of Illinois as a preveterinary student, Korsmeyer eventually took the vet's advice and began premedical studies.

After graduating from the University of Illinois in 1972, Korsmeyer was accepted into the University of Illinois College of Medicine, where his adviser, Paul Heller, pointed him in the direction of hematology. He graduated from medical school in 1976 as a James Scholar, successfully completing an honors program in research. To immerse himself more fully in hematology, Korsmeyer did his internship and residency in medicine from 1976 to 1979 at the University of California, San Francisco. After that, he did a postdoctoral fellowship from 1979 to 1982 in the National Cancer Institute laboratories of Thomas Waldmann and Philip Leder.

Korsmeyer published more than 250 original research articles.He was elected to membership in the National Academy of Sciences and the Institute of Medicine. His many honors include the Bristol-Myers Squibb Award for distinguished achievement in cancer research and the Charles S. Mott Prize of the General Motors Cancer Research Foundation.

Stan was deeply and genuinely concerned about the professional and personal development of the people who worked with him. His approach to mentoring was to guide you in ways that allowed the development of scientific self-confidence while gently nudging you back onto the right track. His technique was highly effective in maintaining a positive esprit de corps in the lab and in the development of postdocs as scientists.

Scott A. Armstrong
Children's Hospital Boston

FOR MORE ABOUT STAN KORSMEYER'S LIFE AND WORK

www.research.dfci.harvard.edu/korsmeyer/Home.html

STEVE GILBERT

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. "We want to help satisfy people's honest curiosity about the world around them," says Dennis Liu, program director of the Institute's public science education initiatives. "We want to answer the questions that fall outside the curriculum." Here is a sample question.

TO SEE OTHER QUESTIONS, VISIT ASK A SCIENTIST

www.hhmi.org/askascientist/

Q.

HOW DO CELLS COMMUNICATE?

SUBMITTED FROM CONCORD, CALIFORNIA

A.

This question is being investigated intensively right now.

By communicating with each other, cells in multicellular organisms maintain stability and order—otherwise, things like cancer, growth defects, and failure to specialize occur.

Cells communicate in four primary ways. The first is simply through contact. Cells can respond to direct cell-cell or extracellular-matrix–cell contact. The extracellular matrix is the protein sheath between a nerve and a muscle, which provides both structural (thus stabilizing cellular architecture) and functional (indicating where and when the nerve should establish a synapse with the muscle) signals. Through contact, a skin cell, for example, "knows" that it's on the surface of your body and not inside, like a heart cell.

The second way cells communicate is through secreted short-range signals, usually proteins. A protein is secreted from one cell, travels a short distance, and is recognized and interpreted by a nearby cell. These types of signals can tell one cell to become a skin cell, for example, and a nearby cell to become a hair cell.

The third way is through long-range signals, usually hormones. Hormones such as testosterone, estrogen, and progesterone control processes such as sexual development during puberty. However, there are also long-range protein signals such as insulin (which people with diabetes have a problem with) that control sugar metabolism in many cells in your body.

Finally, electrical and chemical signals communicate very complex messages between cells, usually between neurons or between neurons and muscle cells. The points of contact between two cells, called synapses, are where an electrical signal is converted into a chemical signal and then back into an electrical signal in the other cell. So, actions such as muscle contraction when you lift a weight are controlled by neurons communicating electrical and chemical signals to your muscle to contract. These are particularly interesting signals and may underlie learning, memory, and, ultimately, consciousness.

RESEARCHED BY DION DICKMAN / HHMI PREDOCTORAL FELLOW, HARVARD UNIVERSITY

CONTINUED FROM PAGE 21
[HHMI WATERMAN WINNERS]

For protein crystals, researchers typically solve the phase problem by infusing them with heavy metal ions to act as landmarks because they bind to the protein in predictable ways. Then, the phases from the metal ions can be used to estimate the phases for the protein atoms. In principle, a similar approach should work for RNA crystals, but because RNA is negatively charged it binds metals much more nonspecifically than protein does. The result would be an overabundance of landmarks that would obscure the RNA's structural information. "I definitely had many, many sleepless nights," worrying whether the problem was unsolvable and wondering if it was wise to pursue such a big gamble, says Doudna.

Eventually, one of Doudna's first graduate students, Jamie Cate (who years later would become Doudna's husband) suggested soaking the RNA crystals in a chemical called osmium hexamine. The compound binds only to a specific RNA base pair sequence and is chemically similar to a fully hydrated magnesium ion—which means, Doudna says, that it is "a fairly bulky kind of ion that wouldn't wedge itself into too many sites." Doudna recalls being in the lab at 3 a.m. when the "molecule was, in effect, emerging out of the computer screen. It was an incredible moment when we could very clearly see the helices of the RNA." The image revealed how the RNA molecule was folded into domains that suggested how the ribozyme's catalytic active site might form.

This work, which earned Doudna the Waterman award in 2000, led her lab and others to solve structures of RNA-protein complexes in general and of the ribosome (the cell's protein-synthesis site) in particular. Like Anseth, though, Doudna thought solving a structure was just a starting point for her lab's projects. "The structure suggested maybe this is how it binds to something. Or maybe this is how it interacts with a protein. Then we can design experiments to test those ideas," she says.

Recently, Doudna's lab has been investigating an RNA, found in the human hepatitis C virus, that directs the ribosome of infected cells to start making viral proteins. "Do these RNAs have a defined structure they are using to hijack the ribosome?" Doudna asks her students.

The question is part of a line of inquiry that Doudna wants her students to understand. She advises them to ask, at each stage of scientific research, "What is the biggest, most important question I can address?"

Doudna's healthy attitude flows in part from some of the balancing influences in her life—her 2-year-old son Andrew, retreats in Napa Valley wine country, and vinyasa yoga. She also draws inspiration from Rosalind Franklin (the essential but largely unheralded collaborator of James Watson and Francis Crick on the DNA double-helix discovery), who she describes as "a maverick who was trying to do something very hard and very interesting."

BIG SCIENCE

The "maverick" label might apply equally to Anseth, Amon, and Doudna. Their respective scientific breakthroughs have transformed the way we engineer tissue repair in the body, the way we order the events of cell division, and the way we view RNA structures. Their individual Waterman awards strongly underscore the importance of their findings.

Keys to their successes as scientists, however, transcend their curricula vitae. Any fledgling scientist would do well to take note that Doudna and Anseth both took huge leaps of faith in their post-doctoral work, which gave their fields new technologies. Anseth and Amon, colleagues say, can sort through a flood of ideas to find the best experiment to do next. All three women have stuck with a general line of inquiry they started in graduate school.

Big science, these researchers understand, requires hard work and taking risks. Each has applied the $500,000 that the Waterman award carries to push into new areas—Doudna pursued the hepatitis project and RNA's role in targeting proteins to cell membranes, Amon's lab will explore cells with incorrect numbers of chromosomes, and Anseth might choose to address cancer or the retina (she hasn't yet decided). Given their track records, it's safe to expect each will continue to make her mark in research and scientific knowledge. ■

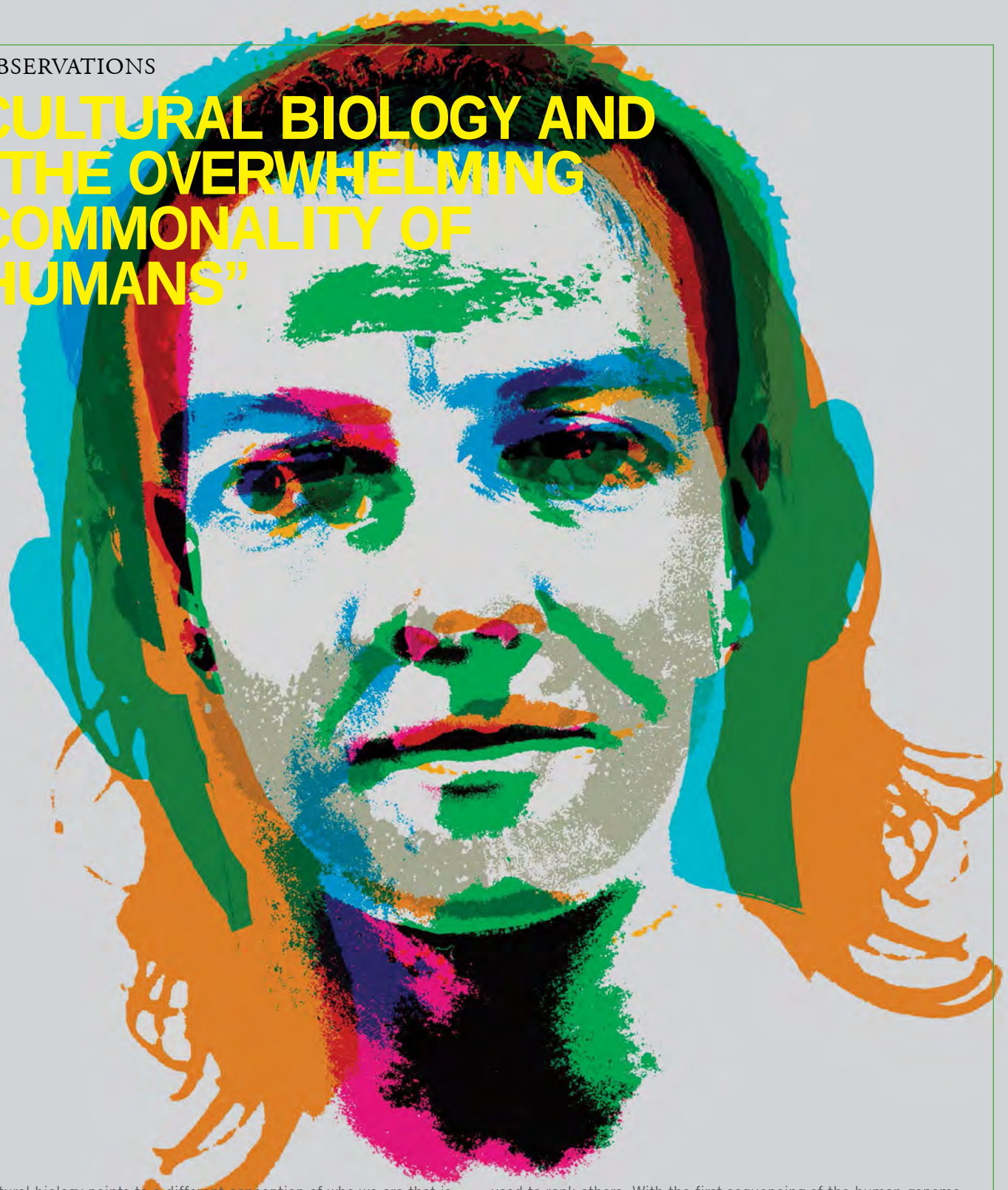
CONTINUED FROM PAGE 35
[SPRADLING INTERVIEW]

(GFP), *in vivo*, on a large scale by taking advantage of the biology of *Drosophila* transposable elements [bits of DNA that can move from place to place in an organism's genome]. About 2,000 fruit fly strains have been produced so far in which a different gene is fused to GFP. Since each of these GFP-fusion proteins is produced using the endogenous gene's normal control circuits, they are likely to reveal the gene's normal pattern of expression. There is also an excellent chance of seeing the normal tissue distribution and subcellular location of the gene product. A large collection of such strains will allow us to map the cellular structure of *Drosophila* tissues at the single-cell level and to identify genes involved in many biological processes—including stem cells. Eventually, it may be possible to insert even more sophisticated reporters—for example, those that fluoresce when certain signals are sent or when a cell activates other internal processes.

We understand relatively little of what goes on in multicellular organisms at the level of molecular processes within specific, individual cells. Not too many years ago, the general feeling was that insects didn't have stem cells. Turns out that it's not that way at all. And now, in some quarters, you'd think that biology is practically all figured out: We just need computer models and we'll understand the whole thing. In reality, we suspect that one could take virtually any tissue, even tissues that have been studied for a long time, and find new cell types and new interactions that are important and unexpected. For example, we found a new epithelial stem cell within the germline stem cell niche. It produces a small set of somatic cells that interact with early germ cells. We suspect that the interactions between these cells and early differentiating germ cells are among the most critical in determining whether reversion happens or development continues. We didn't even know these cells existed, and now we see that they are maintained by their own set of stem cells, and that both sets of stem cells and their progeny signal back and forth. It's a small example of a type of analysis that remains to be done with many metazoan tissues. ■

~ Cori Vanchieri ~

CULTURAL BIOLOGY AND "THE OVERWHELMING COMMONALITY OF HUMANS"



Cultural biology points to a different conception of who we are that is rooted in our biological commonality and combines both construction of self and connection to other. Biology provides us with the capacity to construct flexible selves by endowing us with an internal guidance system that drives our construction of self into complex, multifaceted individuals. That we can become individuals who are distinct from others, however, in no way implies that we lack commonalities. Indeed, the journey to become individuals is driven by a biological core that creates needs universal to all. Primary among these is the need for social engagement and significance....

It is an important, open question whether the new insights science offers into who we are can serve as the foundation both for a sustainable social order and for the rights we all deserve by virtue of the biology that makes us human. Ever since Darwin, the presumption was that our biology reinforces human differences among ourselves. Thus, the great irony of contemporary biology is that it provides the most compelling evidence against the divisive categories humans have used to rank others. With the first sequencing of the human genome now complete, the most surprising insight from biology is the overwhelming commonality of humans, and indeed of all of life. Consider that of the 3.2 billion base pairs in the human genome, individuals differ only by 2 million, and only a few thousand of these may account for the observed biological variability. All humans are nearly identical from a genetic standpoint....

The oldest truly human search—the search for a social order in which we answer who we are—thus continues despite the barriers modern life sometimes puts in its way. The knowledge that brain science is beginning to provide signals a remarkable opportunity to deepen our appreciation for what makes us human.

Excerpted from Liars, Lovers, and Heroes: What the New Brain Science Reveals About How We Become Who We Are, *by Steven R. Quartz and Terrence J. Sejnowski (copyright ©2002 by Steven R. Quartz and Terrence J. Sejnowski; reprinted by permission of HarperCollins Publishers). An HHMI investigator at the Salk Institute for Biological Studies, Sejnowski conducts research to understand the computational resources of brains from the biophysical to the systems levels.*

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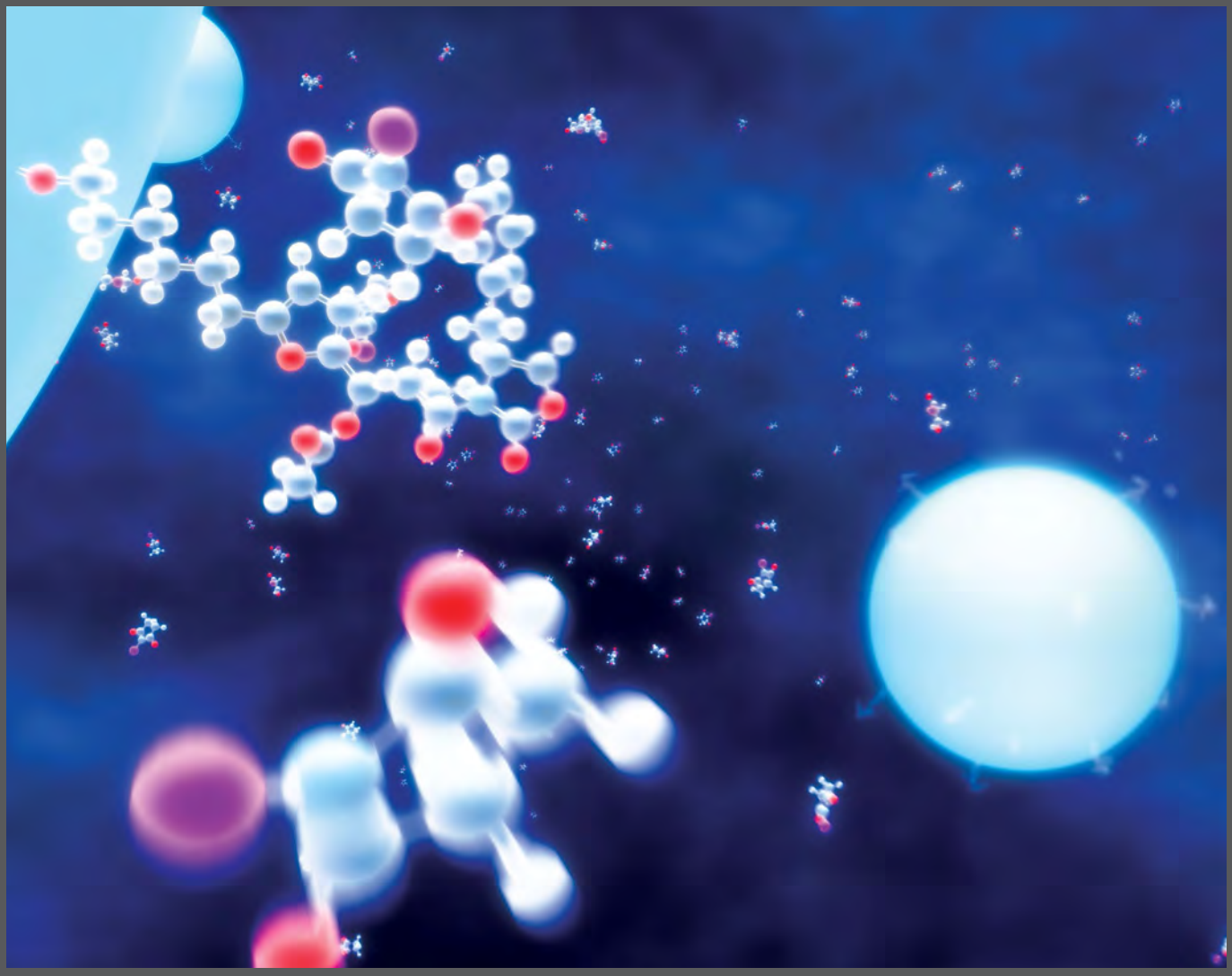

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Exploring Biology and Medicine with Chemistry

SMALL MOLECULES, USED AS MEDICINES AND AS PROBES TO STUDY CELL INTERACTIONS, ARE MADE BY A PROCESS CALLED DIVERSITY-ORIENTED SYNTHESIS IN THE HARVARD UNIVERSITY LAB OF HHMI INVESTIGATOR STUART L. SCHREIBER. INDIVIDUAL SMALL MOLECULES ARE SEGREGATED FROM ONE ANOTHER AND ATTACHED TEMPORARILY TO SOLID SUPPORTS, REPRESENTED HERE BY THE SPHERICAL OBJECTS, FOR DELIVERY TO CELLS. EACH MOLECULE IS PRECISELY SHAPED FOR THE ROLE IT WILL PLAY IN MODULATING A CELL'S MACHINERY.

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