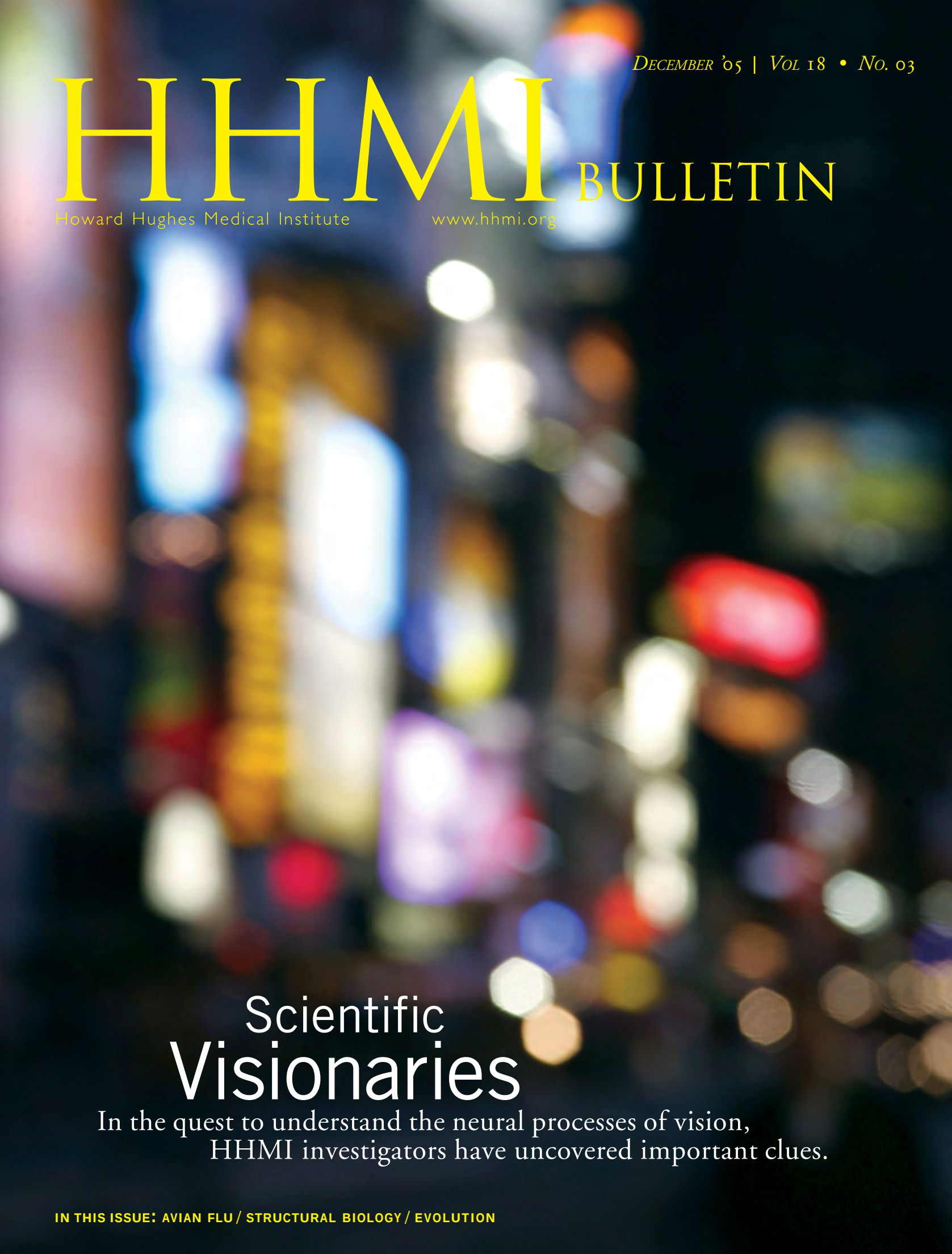
December '05 | Vol 18 • No. 03

HHMI BULLETIN

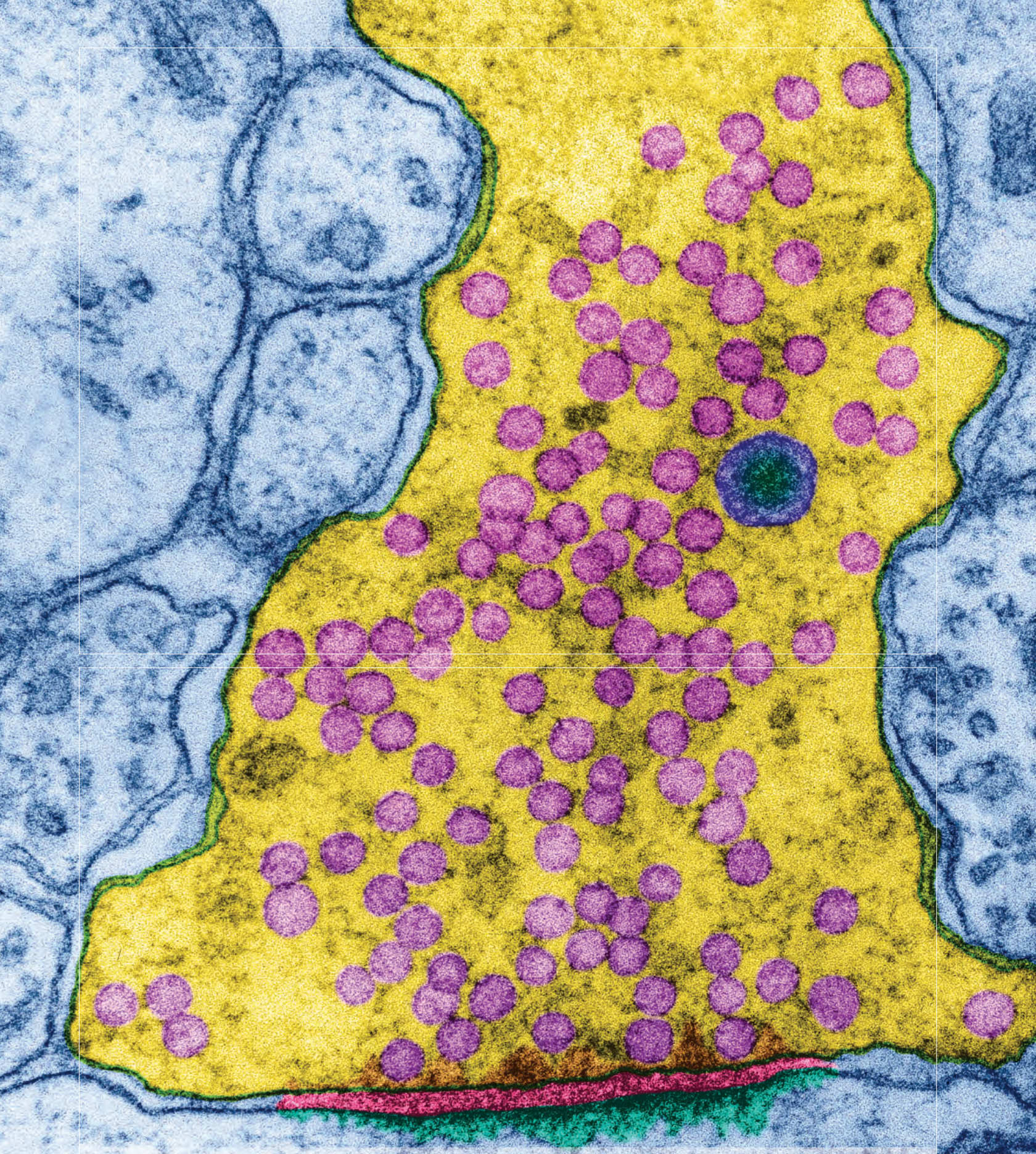
Howard Hughes Medical Institute www.hhmi.org



Scientific Visionaries

In the quest to understand the neural processes of vision, HHMI investigators have uncovered important clues.

IN THIS ISSUE: AVIAN FLU / STRUCTURAL BIOLOGY / EVOLUTION



pg 10
pg 52

At the junction between brain nerve cells, known as the synapse, chemicals congregate, creating electrical impulses that control, among other things, motor movements, mood, and memory. Scientists in three HHMI laboratories who study synaptic events from very different perspectives have learned some surprising things, including the fact that transmission of chemical messages can occur in areas other than the synapse. In this colorized electron micrograph of an excitatory nerve cell, the synaptic zone is pink; chemical-filled vesicles are shaded purple.

DENNIS KUNKEL/PHOTOTAKE

vol.18/december'05
no.03

DEPARTMENTS

3
President's Letter
"Grandeur in This View of Life"

4
Centrifuge
The physics of roller coasters / Argentina's Mr. Wizard / An undergraduate's wayward mosquito / A lab manager's run-in with a car

7
Upfront
Neurodegenerative diseases / Synapses / Better mouse models / Rules for proteins

37
Perspectives and Opinons
Simon W.M. John, Valerie Mizrahi, and Q&A

42
Chronicle: *Institute News*
Janelia Farm Construction Update / Loudoun County Science Academy / Janelia Farm Graduate Track

46
Chronicle: *Science Education*
Bringing the Sizzle to Science in the Schools / Interdisciplinary Crosstalk

48
Chronicle: *Lab Book*
The fate of brain cells / A mechanism for coordinating genes / New screens for colon cancer

51
Chronicle: *Excerpts*
Ask a Scientist

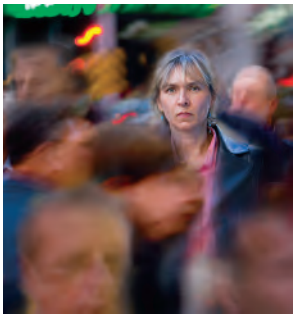
52
Chronicle: *Tool Box*
DReAMM Scheme: Tools for better images at the subcellular level

54
Chronicle: *Nota Bene*
News of recent awards and other notable achievements

Inside Back Cover
Observations
Life: The Most Remarkable of All Emergent Systems

FEATURES

14



Scientific Visionaries

[COVER STORY]

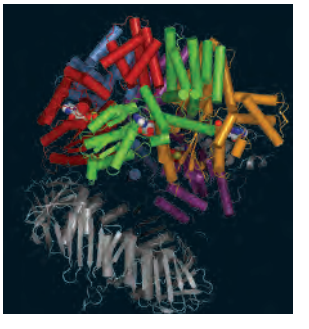
Neuroscientists strive to map the brain's remarkable visual system.

20

Evolution Is Our Laboratory

Studying how evolution acts on all levels—molecular, cellular, organismic, ecological, social—investigators find thematic threads that draw the disciplines together.

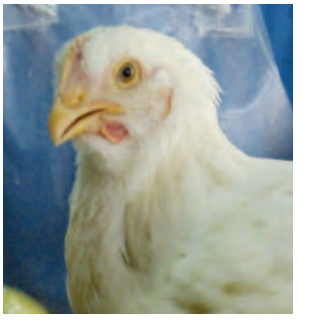
26



Viewing Vital Structures

Researchers angle for better 3-D structures of the molecular machines that produce our proteins, repair our DNA, defend us against microbes, and, in effect, control our health.

32



A Bout With Flu

As influenza smashes evolutionary barriers, scientists wonder: Is this the coming of the next human pandemic?

WEB EXCLUSIVE

Chronicle: International Science
Is There a Junior Doctor in the House? The story of the successful program "Mini Médicos"

WWW.HHMI.ORG / BULLETIN

Visit the *Bulletin Online* for additional content and relevant links.

COVER IMAGE: MOSHE KATVAN

CONTRIBUTORS

Steve Mirsky is an editor at *Scientific American* magazine. He also writes the magazine's Antigravity column. A freelance contributor to numerous other publications, Mirsky studied chemistry in college and became a science writer after being awarded a AAAS Mass Media Fellowship in 1985. He was a Knight Science Journalism Fellow at MIT in the 2003–04 academic year. (1)

Maya Pines edited and was the principal writer of HHMI's book *Exploring the Biomedical Revolution* (1999), which includes reports on genetics, development, the senses, and microbes. She has written four books in the fields of science and education, as well as numerous articles for national magazines. She is a contributing editor of the *HHMI Bulletin*. (2)

After earning a master's degree in biomedical sciences from the University of California, San Diego, Kendall Powell attended the science writing graduate program at the University of California, Santa Cruz. She writes news and features regularly for the journals *Nature*, *Nature Medicine*, *Nature Biotechnology*, and the *Journal of Cell Biology*, among others. Powell happily works from her home office near Denver, Colorado, with her two Labrador retrievers for company. (3)

A freelance science writer and novelist based in London and Paris, Laura Spinney writes for *New Scientist*, *The Economist*, and the *Guardian*, among other publications, on biological subjects, and particularly on neuroscience. Her novel, *The Doctor*, was published by Methuen in the UK in 2001. A second novel is coming soon. (4)

(1)

(2)

(3)

(4)

ELLIS MIRSKY (MIRSKY); KAY CHERNUSH (*PINES*)

HHMI TRUSTEES

James A. Baker, III, Esq.
Senior Partner / Baker & Botts

Richard G. Darman
Partner / The Carlyle Group
Chairman of the Board / AES Corp.

Frank William Gay
Former President & CEO / SUMMA Corporation

Joseph L. Goldstein, M.D.
Professor & Chairman, Department of Molecular Genetics / University of Texas Southwestern Medical Center at Dallas

Hanna H. Gray, Ph.D., *Chairman*
President Emeritus & Harry Pratt Judson Distinguished Service Professor of History / The University of Chicago

Garnett L. Keith
SeaBridge Investment Advisors, L.L.C.
Former Vice Chairman & Chief Financial Officer / The Prudential Insurance Company of America

Jeremy R. Knowles, D.Phil.
Dean Emeritus & Amory Houghton Professor of Chemistry & Biochemistry / Harvard University

William R. Lummis, Esq.
Former Chairman of the Board of Directors & CEO / The Howard Hughes Corporation

Kurt L. Schmoke
Dean / Howard University School of Law

Anne M. Tatlock
Chairman & CEO / Fiduciary Trust Company International

The opinions, beliefs, and viewpoints expressed by authors in the HHMI Bulletin *do not necessarily reflect the opinions, beliefs, viewpoints, or official policies of the Howard Hughes Medical Institute.*

HHMI OFFICERS

Thomas R. Cech, Ph.D. / *President*
Peter J. Bruns, Ph.D. / *V.P. for Grants & Special Programs*
David A. Clayton, Ph.D. / *V.P. & Chief Scientific Officer*
Stephen M. Cohen / *V.P. & Chief Financial Officer*
Joseph D. Collins / *V.P. for Information Technology*
Joan S. Leonard, Esq. / *V.P. & General Counsel*
Avice A. Meehan / *V.P. for Communications & Public Affairs*
Gerald M. Rubin, Ph.D. / *V.P. & Director, Janelia Farm Research Campus*
Landis Zimmerman / *V.P. & Chief Investment Officer*

HHMI BULLETIN STAFF

Stephen G. Pelletier / *Editor*
Jim Keeley / *Science Editor*
Jennifer Donovan / *Education Editor*
Patricia Foster / *Associate Director of Communications for Web & Special Projects*
Mary Beth Gardiner / *Assistant Editor*

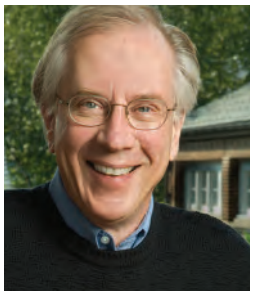
ADDITIONAL CONTRIBUTORS

Steven Marcus, Cay Butler, Kathy Savory / *Editing*
Laura Bonetta, Katherine Wood / *Fact Checking*
Maya Pines / *Contributing Editor*
VSA Partners, NYC / *Concept & Design*
David Herbick Design / *Publication Design*

HHMI
HOWARD HUGHES MEDICAL INSTITUTE

Telephone (301) 215.8855 • Fax (301) 215.8863 • www.hhmi.org

© 2005 Howard Hughes Medical Institute



Thomas R. Cech
President
Howard Hughes Medical Institute

PAUL FETTERS

"GRANDEUR IN THIS VIEW OF LIFE"

As we approach the bicentennial of the birth of Charles Darwin (in 2009) and the 150th anniversary of the publication of The Origin of Species, the subject of evolution remains as central to scientific discourse today as it was in the mid-19th century. Pick up a newspaper or magazine, turn on the television or radio, cruise the Web and you will invariably encounter a discussion about evolution—from reports about new scientific insights that deepen our understanding of the connectedness of life forms, to debates about whether evolution should be taught in tandem with creationism or intelligent design, and data that point to deep public ambivalence about science as a way of understanding the world.

A plurality of Americans believe that human beings and other creatures have evolved over time—a central premise of Darwin's theory of evolution—but an almost equal number (41 percent) believe that all living things have existed in their present form since the beginning of time, according to research by the Pew Center for People and the Press. Moreover, fully one-third of the public believes there's no consensus among scientists about evolution, and a clear majority of those polled (65 percent) believes that creationism should be taught alongside evolution.

So what is the role of the Howard Hughes Medical Institute? As an organization focused on basic biomedical research and science education, our stand is clear. We are committed to the scientific investigation of the natural world—what Darwin's contemporary Thomas Huxley described as "the mode at which all phenomena are reasoned about, rendered precise and exact."

The work of numerous HHMI investigators bears witness to the evolution of biological molecules, of viruses, and of living creatures. Over and over again, we scientists have identified genes in simple organisms such as baker's yeast or the fruit fly and then used this DNA information to isolate a human gene with a similar function—a pathway predicated on the evolutionary relatedness of all living things. This issue of the HHMI Bulletin provides a lively sampling of research that makes use of evolution and, at the same time, helps fill in missing details. As investigator Sean B. Carroll observes, "Many biologists would now agree that a grounding in evolution is fundamental to biology. Before, I think they would have said that evolution is a branch of biology but not an integral foundation."

But our interest in evolution extends beyond the discoveries that emerge from HHMI laboratories. We are developing educational resources and programs to serve a broad spectrum of students and teachers. One vibrant component is our annual Holiday Lectures on Science, which have an immediate impact on the Washington-area high school students in attendance and then an ongoing impact through television rebroadcasts and the thousands of DVDs and educational materials we distribute. This year's Holiday Lectures—"Evolution: Constant Change and Constant Threads"—feature Sean Carroll, an investigator at the University of Wisconsin–Madison and author of a popular book about evolution, and David M. Kingsley, an investigator at the Stanford University School of Medicine. Their talks can be viewed at www.holidaylectures.org.

Carroll and Kingsley use tools of genetics and molecular biology that Darwin could hardly have imagined. Although focused on different questions, these scientists have shown that an understanding of the function of key genes can elucidate general rules of evolution that can then be applied to diverse organisms. For example, Kingsley has demonstrated that changes in a single gene triggered a major shift in the armor plating found in wild populations of stickleback fish. Interestingly enough, the gene that controls the armor plating in sticklebacks also plays a role in human development; mutations result in a syndrome that Darwin himself observed while traveling through the Indian subcontinent.

What is most important about the Holiday Lectures is that they provide the nation's high school students and the general public with access to topflight scientists and exposure to an experimentally testable approach to understanding the world. It's not the only way to think about the world, but it does represent a scientific consensus. In that context, the magisterial final sentence of Darwin's The Origin of Species is worth recalling: "There is grandeur in this view of life, with its several powers, having been originally breathed into a few forms or into one; and that, whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved." Indeed.

Thomas R Cech

RIGHT _ ROLLER COASTERS FRIGHTEN, EXHILARATE—AND DEMONSTRATE PRINCIPLES OF MATH AND PHYSICS.

On the Fast Track

YOUR AVERAGE UNDERGRADUATE IS unlikely to whoop and holler in math class. But at Bates College in Lewiston, Maine, more than a few mathematics students have been known to actually shriek. No, the course is not "Partial Differential Equations." The Bates students may find themselves screaming while pulling serious G forces in "Math s45K," also called "Roller Coasters: Theory, Design and Properties."

The kernel for this odd pedagogical marriage was the discovery by Bates mathematics professors Meredith Greer and Shepley "Chip" Ross of a common love of roller coasters, which evolved into a wish to use the technology as a vehicle, so to speak, for reaching more students. "We hoped that we might draw a few people in who otherwise wouldn't have gone on to take another math class," says Greer. So with the aid of a small math-and-science-curriculum-development grant from HHMI, the month-long coaster course opened with a dozen students this past April.

Coaster designers have to be able to perform serious engineering mathematics, but the Bates course is designed for students who may have only an introductory calculus course as background. "That's enough for them to follow all the concepts," Greer says. "And it gives us the opportunity to expose them to parametric equations." Such equations look at, for example, familiar *x* and *y* variables when both of them are dependent on yet another variable. For roller coastering, the other variable is *t*—for time.

"It's a tough concept to get across to a lot of students," says Greer. "They think we're complicating things unnecessarily with the *t*'s. But here we're able to show that although roller coasters clearly follow a path, there's also this time element involved—it matters how fast you traverse that path. Not fast enough and you don't make it up the next hill. Too fast around a curve and it can get ugly."

Not many math classes have a field trip, but the coaster course shipped out to Cedar Point Amusement Park, in Sandusky, Ohio—home to 16 coasters, from old warhorses to state-of-the-art scream machines. Old and new coasters side by side offered a history lesson in materials science, engineering, and the use of mathematics. Students spent 3 days analyzing the rides and, of course, hopped on a few.

> "We hoped that we might draw a few people in who otherwise wouldn't have gone on to take another math class."

MEREDITH GREER

Almost all the students in the class had a preexisting condition—they loved roller coasters. "Only one of them really didn't," says Greer, "but had been talked into taking the class by friends. He went on some of the tallest and fastest rides and ended up loving them. So the class helped him conquer his fear of coasters. We just hope it helps most students conquer their fear of math." ■

-Steve Mirsky-

COURSE WEB SITE:
http://abacus.bates.edu/~mgreer/maths45/maths45.html

BRIAN PFOHL (2)

Media Man

PARASITOLOGIST HUGO D. LUJAN STUDIES *GIARDIA*, A SINGLE-celled organism that spreads waterborne diarrheal disease. But to much of the media in Argentina, where the HHMI international research scholar conducts research at the Mercedes and Martin Ferreyra Institute for Medical Reseach at Cordoba, Lujan has become something akin to a Latin American Mr. Wizard.

When HHMI announced its first infectious diseases and parasitology grant to Lujan in 2000, the Argentine scientist says national newspapers such as *La Nación* and *Clarín*, as well as radio and TV stations from around the country, began calling. First they wanted to know about his research and why he was selected for the prestigious American grant.

Then the questions got harder. "If you are a good enough scientist to be selected by such a prestigious institution, why do you stay in Argentina?" reporters asked.

"I kept changing my answer, according to my state of mind," Lujan recalls. "Sometimes I said, 'I like to work here,' and other days, 'I wish I could go back to the United States,' where I did postdoctoral work at the National Institutes of Health."

Over time, the Argentine media adopted Lujan as something of a scientific adviser. They started calling for his input on everything biomedical, from dengue fever to human cloning.

Lujan estimates that he receives four or five media calls a month. "I find myself responding to questions on topics far away from my specific area of research," he says, "and it keeps me under high pressure to stay informed of new advances in many areas of the medical sciences."

Why doesn't Lujan just tell the journalists that their questions are beyond his field of expertise? "I feel that if I do not answer these questions, the public will get the information anyway, and they may get it inaccurately. Also, if I can present scientific discoveries in an understandable way, many more young people will come to study science. More scientists will produce more discoveries, and more discoveries will produce a better life for everyone." ■

-Jennifer Boeth Donovan-

THE UNDERGRAD'S WAYWARD MOSQUITO

ABOVE _ FOR STEPHANIE GALLITANO, AN UNEXPECTED DISCOVERY DURING FIELDWORK MADE FOR AN AWESOME SUMMER—AND A PUBLISHED PAPER.

Undergraduate Stephanie Gallitano spent this past summer doing routine fieldwork outside St. Louis, studying breeding patterns of mosquitoes. But her research turned into anything but routine when she discovered a species that had never been seen in the Midwest: the Asian mosquito *Ochlerotatus japonicus*, a suspected carrier of the West Nile virus.

Gallitano's sighting was the first report of *Oc. japonicus* in Missouri and the farthest west the species has ever been seen in the central United States.

Gallitano originally set about to investigate how native mosquitoes select a habitat for egg laying. She conducted her fieldwork at Washington University in St. Louis's Tyson Research Center in Eureka, Missouri, as part of an HHMI summer undergraduate research project. But some of the eggs she collected developed into larvae she didn't recognize. "Both the body dimensions and hair distribution were really different from anything I'd seen before," Gallitano says. It took expertise from the Rutgers University lab of ecologist Leon Blaustein to identify the mysterious insect.

Gallitano, a chemistry major in her junior year; her mentor James Vonesh; and Blaustein reported their findings in the December 2005 issue of the *Journal of Vector Ecology*.

Oc. japonicus is native to Japan and elsewhere in eastern Asia, where it carries West Nile virus to swine. "But has this mosquito ever transmitted it to a human? That we don't know," says Vonesh.

Assessing the mosquito's impact as a human disease vector, researchers say, will require learning more about its interactions with other kinds of mosquitoes—perhaps a future challenge for Gallitano or one of her colleagues. ■

—Doug Main

ILLUSTRATION: JUD GUITTEAU; PHOTO: SCOTT FERGUSON

> "There are bicycles out there and they have a legal right to use the road. People have to be accommodating to them."
>
> SHAWN FIELDS-BERRY

RIGHT _ TRAINING FOR AN AIDS CHARITY BIKE RIDE, HHMI LAB MANAGER SHAWN FIELDS-BERRY WAS STRUCK BY AN AUTOMOBILE. HIS INJURIES KEPT HIM FROM THE RIDE, BUT HE STILL MANAGED TO RAISE $9,000.

Watch for Bikes

JULY 27, 2005, WAS SUPPOSED TO BE A blazing hot day in Massachusetts, so Shawn Fields-Berry figured he'd finish his daily 50-mile bike ride while the sun was still low in the sky. Then he'd catch a midday train to Boston, where he manages the Harvard lab of HHMI investigator Constance L. Cepko.

He never made that train. Instead, Fields-Berry's morning bike ride landed him an emergency helicopter ride to Massachusetts General Hospital. A Pontiac sedan struck the cyclist, leaving him with a concussion, broken collarbone, several broken ribs, fractured shoulder blade, and collapsed right lung. He has no recollection of the accident or the 4 days he spent in the hospital, heavily sedated by anesthetics and pain medication.

Seven weeks after the crash, his bones have healed enough so that physical therapy may begin, but the concussion's effects linger. "Imagine yourself really intoxicated, but take away the euphoria and fun," says Fields-Berry. "That's my baseline." Damage to a cranial nerve means his eyes don't track properly, and he is plagued by double vision. His balance is not what it should be, nor is the sensitivity of his skin. The doctors say these neurological problems will disappear over time. "They told me the time frame would be months to a year," he says.

With his symptoms slowly improving, Fields-Berry has returned to work part time, scheduling his hours around appointments with neurologists, orthopedists, and physical therapists. He focuses on tasks such as handling e-mails and ordering supplies—things that don't require the hand-eye coordination he still lacks. "I'm at the point where I can concentrate enough to work on the computer, and I feel like now I can make contributions to the lab. But I'm not confident enough yet to handle anything delicate or toxic," he says.

Fields-Berry talks freely about the accident, knowing awareness of the incident is the best way to glean some good from the broken bones and mangled mess of titanium that used to be his custom-made bicycle. "I'm up to my ears in lemons," he says. "So let's make lemonade."

The calamity helped draw attention to the Mass Red Ribbon Ride that Fields-Berry had been training for—a charity event he helped local AIDS organizations launch after the popular New York-to-Boston AIDS Ride was discontinued in 2002. Although unable to ride the 175-mile course (which starts at Pittsfield in the Berkshires and ends in suburban Boston) this August, he still managed to bring in nearly $9,000 in donations for AIDS service providers in the state—making him the event's top fundraiser.

Just as important to Fields-Berry, who also served on the charity ride's safety committee, is an enhanced awareness among riders about self-protection: "Some people I know who never wore helmets before are wearing helmets now." If he had not been wearing a helmet at the time, he is certain that the crash would have been fatal. ■

-Jennifer Michalowski-

JASON GROW

december '05

UPFRONT

TOO MUCH OF NORMAL PG.8
A routine interaction between two proteins, when exaggerated, causes neurodegenerative diseases.

SYNAPTIC SHAPE SHIFTERS PG.10
Three HHMI laboratories chart the landscape of nerve connections.

BUILDING A BETTER MOUSE TRANSPOSON PG.11
A breakthrough in mouse molecular genetics may mark a significant research advance.

PROTEIN DETECTIVES PG.12
To discern the twists and folds of these basic biological machines, David Baker relies on the kindness of strangers.

In this holiday season, those of us prone to excess might readily agree that too much of a good thing can sometimes indeed be bad. Evidence from the laboratory of HHMI investigator Huda Zoghbi can attest to the truth in that old saw in regard to certain proteins associated with neurodegenerative disorders. The sharp observation of a first-year grad student led to the discovery that an overabundance of a normal, workaday protein found in the nervous system—rather than a malformed protein—can have debilitating effects.

Too Much of Normal

A routine interaction between two proteins, when exaggerated, causes neurodegenerative diseases.

HUDA Y. ZOGHBI LONG WANTED TO know how one mutant protein can wreak such havoc in people who have spinocerebellar ataxia type 1 (SCA1). A chance observation by a first-year graduate student shed light on the problem—in what might be a case where too much good is actually bad.

SCA1 belongs to a group of neurodegenerative disorders called the polyglutamine diseases, each of which is characterized by a mutant protein with an abnormally long stretch of a single amino acid—glutamine.

"Most people have naturally focused on the polyglutamine tract [that stretch of glutamine repeats] when studying the pathogenesis of these polyglutamine diseases," says Zoghbi, an HHMI investigator at Baylor College of Medicine in Houston. But she sees things differently. If each disorder causes a unique constellation of symptoms, Zoghbi reasons, then the shared polyglutamine tract cannot be the only part of the protein that is culpable. The challenge, then, is how to identify other regions of the protein—ataxin-1 in the case of SCA1—that contribute to the problem.

A lucky break came when first-year graduate student Matthew F. Rose was deciding whose lab to join for his dissertation work—Zoghbi's or that of Hugo J. Bellen, also an HHMI investigator at Baylor, who works on development of the nervous system in the fruit fly *Drosophila melanogaster*. While trying out Bellen's lab, Rose combed through the results of an experiment, designed by postdoctoral fellow Hamed Jafar-Nejad, to identify proteins that interact with the *Drosophila* protein Senseless. Rose noticed in particular that dAtx-1—the fly equivalent of ataxin-1—binds to Senseless.

Scientists knew that in humans the polyglutamine tract slows down ataxin-1 degradation, leaving cells with too much of the mutant protein in the same way that overexpression does. But, unlike its human counterpart, dAtx-1, which was being studied by Hiroshi Tsuda, a postdoctoral fellow in the Zoghbi lab, has no polyglutamine tract. Nevertheless, when Tsuda engineered flies to make too much dAtx-1, sensory neurons were killed. This result implied that fly and human pathways might not be so different. Jafar-Nejad provided fly strains that allowed the group to study the effects of dAtx-1 on Senseless.

> "We don't think pathogenesis will be the result of a single protein-protein interaction. It may involve multiple interactions, some that are inconsequential, and some that are devastating for the cell."
>
> HUDA ZOGHBI

When Tsuda and the team investigated how excess dAtx-1 kills neurons, they found that the AXH domain—a portion of the protein conserved between flies and humans—binds directly to the Senseless protein. That interaction targets Senseless for degradation, and without Senseless the sensory neurons die. Moreover, when the team removed the AXH domain from dAtx-1, neuron death was no longer a problem.

The team then turned to a model system that is a bit more like humans than *Drosophila*—the mouse. They found that mammalian ataxin-1 binds to growth factor independence-1 (Gfi-1), which is the mouse version of the Senseless protein; and, as in flies, too much ataxin-1 degrades Gfi-1 and leads to neuronal death. The researchers concluded that the AXH domain in mammalian ataxin-1, not the polyglutamine domain, is what is required for binding ataxin-1 to Senseless and Gfi-1. The research bolsters an emerging theory that neurodegenerative disorders can be caused by having extra copies of a normal protein, not just a mutated one.

Tsuda, Zoghbi, Bellen, and colleagues published the work in the August 26, 2005, issue of *Cell*. Harry T. Orr, Zoghbi's research collaborator for 18 years, contributed to the work.

Other groups have found evidence that the polyglutamine tract alone does not kill neurons. Michael R. Hayden's group at the University of British Columbia found that overexpression of a somewhat shortened huntingtin protein did not induce Huntington-type neurodegeneration in mice, even though it included a large polyglutamine stretch. But this is the first time that scientists have identified what region of the protein is necessary and understood the mechanics behind the cell death.

A lot of work remains to be done, says Zoghbi, but her team's findings to date suggest that an exaggeration of a normal interaction between ataxin-1 and Gfi-1 causes the problem in polyglutamine diseases. The polyglutamine tract simply produces the accumulation—the exaggerated amount of ataxin-1 available for binding.

The research team—including Matt Rose, who ultimately joined Zoghbi's lab—is now on the hunt for other ataxin-1 binding partners. ■

-Rabiya S. Tuma-

LEFT _ HIROSHI TSUDA (LEFT), HUDA ZOGHBI, AND COLLEAGUES DISCOVERED A NEW FACTOR IN THE DEVELOPMENT OF NEURODEGENERATIVE DISORDERS.

ROCKY KNETEN

SCA1 AND HUNTINGTON'S DISEASE

While all the polyglutamine diseases kill neurons, the particular set of cells affected in each disease differs, leading to distinctive problems. For example, individuals with SCA1 gradually lose coordinated movement and speech, eventually losing control of breathing and swallowing. In contrast, patients with Huntington's disease have tremors as well as emotional and intellectual disturbances.

ON THE WEB:

For more information about polyglutamine diseases, visit *www.hhmi.org/biointeractive/neuroscience/polyglutamine_disease.html*.

Synaptic Shape Shifters

Three HHMI laboratories chart the landscape of nerve connections.

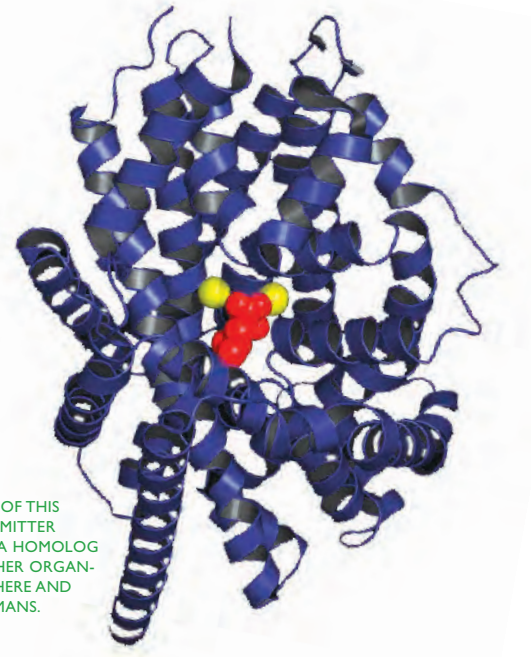
HHMI INVESTIGATOR ERIC GOUAUX ONCE JOKED THAT HIS lab studies "how the garbage is taken out" of the synapse, the junction between two nerve cells. But it's really no joke: Excess chemicals can lead to chaos in the nervous system.

Gouaux and colleagues published new work on synapses in July 2005, around the same time that two other HHMI laboratories also announced discoveries about how synapses work. The three labs took different approaches, as if viewing the synapse junction through various photographic lenses.

Gouaux's group (then at Columbia University, he has since moved his lab to the Vollum Institute at Oregon Health & Science University in Portland) took a high-resolution close-up of a transporter molecule. Robert B. Darnell's laboratory at the Rockefeller University in New York shot a panoramic view of a whole genome's worth of synapse proteins. And Terrence J. Sejnowski's team at the Salk Institute for Biological Studies in La Jolla, California, modeled synaptic function using a computer simulation. Their collective results may change how researchers define the synapse and its role in the brain cells controlling motor movement, mood, and memory.

First, the close-up. The transporters that move the neurotransmitter serotonin back into nerve cells are a target for antidepression drugs. How those transporters work, though, is still a mystery, which means the drug action also remains unknown. Gouaux's group solved the atomic structure of a bacterial transporter that is structurally similar to the human transporters. Its symmetry and shape suggest which portions of the molecule are involved in binding to the neurotransmitters, which may give clues to where and how drugs will act.

Zooming out from the atomic to the genomic level, Darnell's group searched for nerve cell proteins whose production is regulated by one RNA splicing molecule, called Nova. To do that, they used a gene microarray tool that would show which RNAs were present in a nerve cell when Nova was present but not when Nova was absent. They found 49 such RNAs and, surprisingly, found that some 80 percent of the corresponding proteins function at the synapse. (The other 20 percent are involved in axon guidance.) In addition, 75 percent interact with each other.



THE ATOMIC STRUCTURE OF THIS BACTERIAL NEUROTRANSMITTER TRANSPORTER (LEUTAA), A HOMOLOG OF ONES FOUND IN HIGHER ORGANISMS, MAY ILLUMINATE WHERE AND HOW DRUGS ACT IN HUMANS.

"There's an aspect of gene regulation going on here that wasn't clear before," says Darnell. "Nova is acting in a complex way to change the nature of the synapse." And by changing the quality of synapse proteins, Nova may also modify synaptic plasticity—the mechanism used by repeatedly activated synapses to form memories.

Both Gouaux's and Darnell's work details synapse proteins at a specific point in time. But synapses are dynamic, releasing and recycling neurotransmitters and firing nerve impulses. In the past, neuroscientists charted these dynamics by measuring electrical activity but without visualizing individual synapses.

Now, through computer simulation, Sejnowski's group has designed an animated prediction of what happens in one particular type of synapse in the chick ciliary ganglion. They used data from three-dimensional tomography imaging—a type of electron microscopy in which a thick tissue slice is imaged at different angles to show its 3-D structure—to generate a topographic map of the synapse's crinkled surfaces. To this map, they added electrical and chemical measurements taken from wet lab experiments to simulate neurotransmission.

"It's as if we had a simulated microscope that could zoom into the synapse," says Sejnowski. The simulation program, called MCell, surprised him when it showed that most of the nerve cell transmission was occurring outside the "active zone," the area in the synapse where researchers thought most nerve transmission occurs. (For more about MCell, see this issue's Tool Box column on page 52.) "We suspect that a similar thing is happening at other synapses in the brain," says Sejnowski. He says this type of ectopic transmission may serve to increase the background activity level of neurons, sensitizing them during times of rest to be fire-ready when needed. MCell could also help drug developers "watch" the effects of candidate drugs.

Each of these three groups has added new ways to envision synapse functions. Their work shines a searchlight on new pathways to treating disorders of the central nervous system like depression, epilepsy, and movement disorders. ■

-Kendall Powell-

SYNAPSE INVESTIGATORS

Eric Gouaux
Gouaux studies the molecular mechanisms of communication between nerve cells by studying the receptors and transporters that detect and remove neurotransmitters from synapses.

Robert B. Darnell
Darnell's research seeks a basic understanding of a group of rare brain diseases. These studies are producing insights into tumor immunology, autoimmunity, and neuronal cell biology.

Terrence J. Sejnowski
Sejnowski's goal is to discover principles linking brain mechanisms and behavior. His laboratory uses both experimental and modeling techniques to study biophysical properties of neurons

ILLUSTRATION: ERIC GOUAUX; GOUAUX; PAUL FETTERS; DARNELL; ROCKEFELLER UNIVERSITY/DIRK WESTPHAL; SEJNOWSKI; MARK HARMEL

Building a Better Mouse Transposon

A breakthrough in mouse molecular genetics may mark a significant research advance.

BY INACTIVATING EACH MOUSE GENE one by one and assessing the biological consequences, geneticists can deduce a gene's functions. HHMI investigator Mario R. Capecchi of the University of Utah in Salt Lake City pioneered targeted mouse gene knockout technologies some two decades ago, unleashing a flood of knowledge about mammalian biology. Despite such successes, progress toward being able to delete all the mouse's 30,000 or so genes has been slow. The method is technically challenging, expensive, and time-consuming—it can take more than a year of full-time work to generate a single knockout mouse. So far, researchers have managed to inactivate only about 10 percent of mouse genes.

Tian Xu, an HHMI investigator at Yale University School of Medicine, has been searching for a faster and easier approach for the past 7 years. In the August 12, 2005, issue of *Cell*, Xu and collaborators—HHMI investigator Min Han of the University of Colorado at Boulder, Yuan Zhuang at Duke University Medical Center, and colleagues at China's Fudan University—reported they had finally succeeded.

The new method takes advantage of a transposon—a short segment of DNA that can "hop" to another position of an organism's genome and that is capable of landing squarely inside a gene and inactivating it. For decades, geneticists had exploited transposons to disrupt genes in plants, worms, and fruit flies, among other models, but they hadn't worked very well in mammals. "About 40 percent of the sequences in our genome, and in the mouse genome, are actually transposon sequences," Xu says. Those transposons are no longer active, however, but are the molecular relics of an era when transposons ran rampant through mammalian genomes. "Evolution managed to make all these transposons inactive, probably so that they wouldn't destroy our genomes," Xu says.

Xu's lab tried to modify several of the standard transposons used in other organisms to prod them to hop to mammals, but the researchers' efforts were unsuccessful. Then they tried an unusual transposon called piggyBac, discovered a decade ago by University of Notre Dame professor Malcolm J. Fraser, Jr. PiggyBac appears to be evolutionarily distant from other known transposons and has properties that make it unique. "I thought maybe it's so strange it will work," Xu says. And when Fudan graduate student Sheng Ding introduced piggyBac into mouse and human cells, it did work. In one pilot experiment, Ding and fellow researcher Xiaohui Wu, each working only half-time in their Shanghai research laboratory, generated 75 different knockout mouse mutants in just 3 months.

> "Evolution managed to make all these transposons inactive, probably so that they wouldn't destroy our genomes."
>
> TIAN XU

ABOVE _ AFTER SEARCHING FOR 7 YEARS FOR A BETTER WAY TO INACTIVATE MOUSE GENES, TIAN XU AND COLLEAGUES HAVE SOME GOOD NEWS TO REPORT.

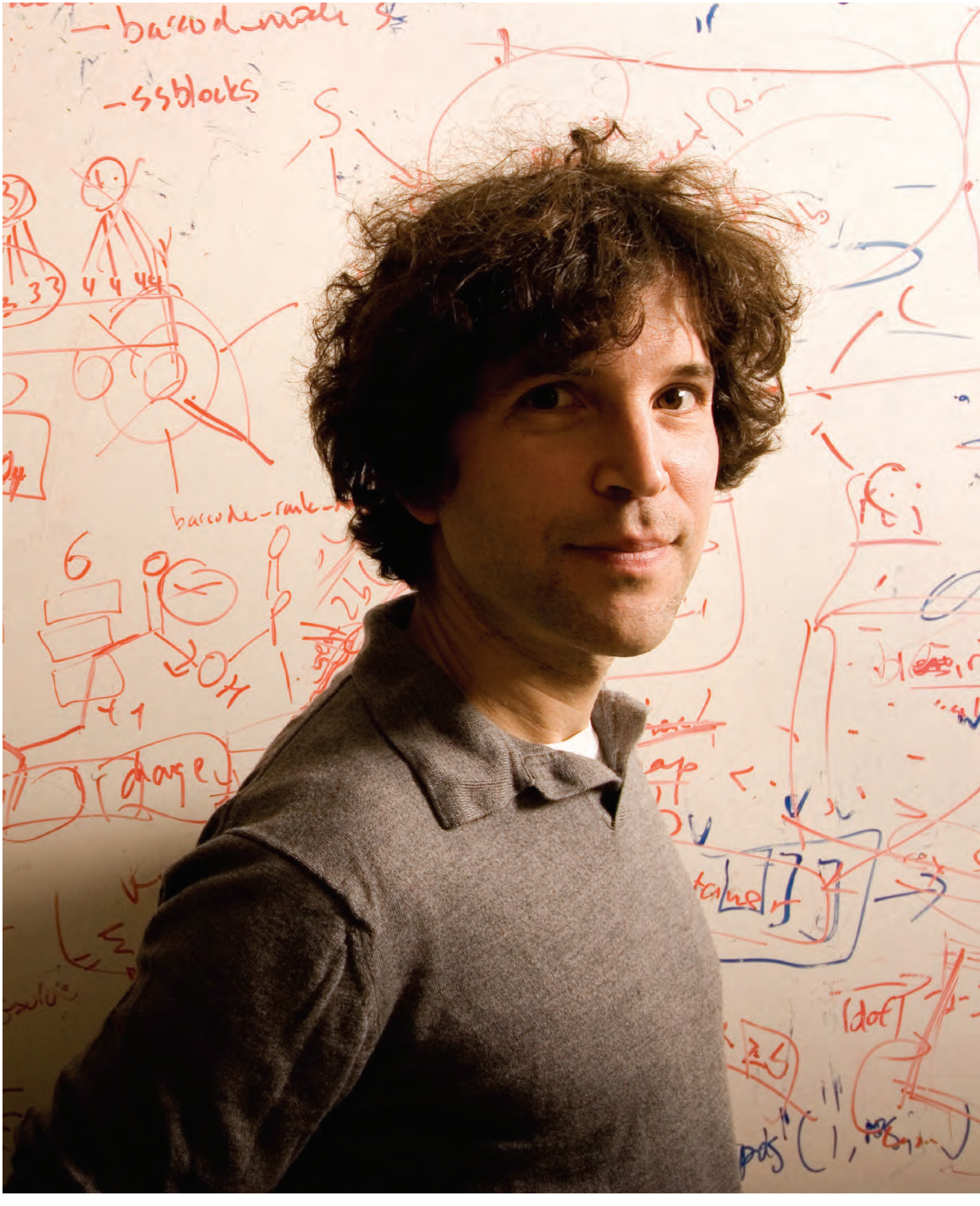
RICHARD FREEDA

Besides the agility with which piggyBac lodges itself in mammalian genes, one of its most practical properties is that it can carry additional genes within it, without losing its ability to hop. Xu's team inserted a marker gene that encodes a red fluorescent protein into piggyBac. "You just look at the mice in the next generation, and if they're red you know you have your transposon" without the need for further testing, Xu says. Another advantage is that, like a normal gene, the transposon carries just one copy of the transferred gene into the chromosome, in contrast to traditional transgenic methods that result in multiple copies being inserted. "These features make piggyBac a dream tool for mutating genes," Xu says. He predicts that this new technique will become the method of choice for creating mouse knockouts.

Notre Dame's Fraser, who maintains a Web site for disseminating information about piggyBac to the scientific community, appreciates witnessing the fruits of his discovery: "I congratulate [Xu and colleagues] on the thoroughness of their analysis. It's gratifying to have been involved with finding something that other people can use for such great advantage. That's why you get into science."

For his part, Xu intends to continue Fraser's spirit of scientific openness. "We plan to inactivate the majority of the mouse genes in the next 5 years," he says. "We're going to make those mutant mouse strains available to the scientific community, and I believe this will significantly advance science." ■

-Paul Muhlrad-


-ssblocks
barcode-rank-
change
idot

LEFT _ DRAWING ON COMPUTER POWER FROM VOLUNTEERS WORLDWIDE, DAVID BAKER SEES "A COMMUNITY-BASED SOLUTION TO A LONG-STANDING SCIENTIFIC PROBLEM."

Protein Detectives

To discern the twists and folds of these basic biological machines, David Baker relies on the kindness of strangers.

MOST SCIENTISTS CULTIVATE COLLABorations to advance their work. But we're betting only David Baker has colleagues in Andorra, Belarus, and the Pitcairn Islands. Not to mention the rest of the world.

An HHMI investigator at the University of Washington, Baker relies on collaborators worldwide to help him uncover nature's rules for protein folding—the process by which a protein shapes itself to fulfill its function. Determine a protein's structure, researchers believe, and you can learn how this essential biological machine works. But getting to that point, from a mere amino acid sequence, requires computer power on a gargantuan scale. That's where Baker's far-flung friends come in.

Software that Baker and colleagues created taps participants' PCs during downtime—the computers perform protein-folding calculations while their owners, in effect, sleep. Harnessing that vast capacity, Baker has made considerable progress in the quest to compute protein structures from their sequences of amino acids. Progress has been so good, in fact, he now predicts that many, if not most, protein structures and interactions will one day be computable—a level of confidence that protein researchers have previously lacked.

Three recent accounts from the Baker lab (published in the September 16 and October 28, 2005, issues of *Science* and the August 1, 2005 issue of *Proteins*) report that given enough computing power his protein-modeling software, called Rosetta, can produce protein models that look like their natural counterparts at least about a third of the time. And Baker's results with determining the structure of a protein once it "docks" onto a partner are even better. Together, the papers demonstrate that it's possible to achieve high-resolution prediction of protein structure by first sampling a large number of potential variations at low resolution and then refining the best candidates with modeling that accounts for all of the atoms in the molecule.

"These results suggest not that the critical problems of protein-structure prediction are solved," says Baker, "but rather that accurate modeling now appears to be an achievable goal." To take it to the next level of accuracy, he says, will require still more computing power and better understanding of how linear sequences of amino acids transform into fully functional folded proteins.

> "Each computer is like an explorer parachuting into a particular place on a huge landscape, exploring the neighborhood, and reporting back on the lowest elevation point it found."
>
> DAVID BAKER

Some kinds of proteins resist prediction more than others, however. "It's very difficult right now to accurately calculate interactions involving charged atoms," Baker says. "These are often in places like the active sites of enzymes, so this is a critical problem to solve. But more computing power will definitely help us search these landscapes better."

Even before Rosetta is refined to the point that it can accurately predict the structures of large proteins, it can be used to create altogether new proteins (see www.hhmi.org/news/baker3.html).

"There's no reason to rely strictly on what nature has provided through evolution," says Baker. "For example, we are interested in designing novel enzymes that catalyze reactions not catalyzed by naturally occurring proteins, and new endonucleases—proteins that can cleave DNA at a specific place—which could be useful in controlling pathogens. And we are very excited about our work using computational design methods to try to design a vaccine for HIV. You can imagine that the perfect vaccine might be a very stable, carefully designed protein that would guide the immune system to the Achilles heel of the virus, and that you could make in large amounts and ship all over the world." ■

-Karyn Hede-

BACK STORY: ROSETTA

The Rosetta Web site (http://boinc.bakerlab.org/rosetta/) details how participants can volunteer their computers in the hunt for low-energy protein structures. Once they sign up from the site, a server in Baker's lab automatically sends out jobs to participants' computers, which run protein-folding calculations in the background.

Predicting protein structure involves finding a structure that has lower energy than any other structures the protein could adopt. So each individual computer is on a search for the lowest energy structure. "Each computer is like an explorer parachuting into a particular place on a huge landscape, exploring the neighborhood, and reporting back on the lowest elevation point it found."

Participants are fully engaged in the project, he says. They can see the results of the explorations their computers are performing, and active in helping other users, and are even suggesting ways in which the search could be improved.

"This project gives us a wonderful opportunity to convey the excitement of scientific research to a very broad audience. Many of our participants are very sharp and are contributing more than just computing power—responding to their questions has led to a number of new ideas. A really neat thing here is that we could have a community-based solution to a long-standing scientific problem."

BRIAN SMALE

Scientific Visionaries

Neuroscientists map the brain's remarkable visual system.

By Richard Saltus

PHOTOGRAPH BY MOSHE KATVAN

Waiting for a friend

on a busy corner in New York City, you take in the towering buildings, flashing electronic signs, and rivers of pedestrians. Suddenly, you spot your friend's familiar face in the crowd and dart across the street—deftly avoiding many passing cars—to reach out and embrace her.

Our functioning in such a scenario seems routine—to us. But to neuroscientists it is filled with dazzling performances by the human visual system, truly a marvel of evolutionary bioengineering.

As you scan that New York street, your power of attention allows you to screen out irrelevant inputs and focus on small but important targets. The brain, a wondrous supercomputer, calculates the direction, speed, and acceleration of passing people and approaching cars based on inputs of various types of motion-detecting cells. Other cells encode the jumble of colors, shapes, and patterns in this visual field, which higher-brain resources then transform into meaningful perceptions of city street life.

When your friend comes into view, certain key features of her face strike a match with those encoded in your facial-memory bank—a positive identification! When you and she reach out in greeting, a frenzy of mental computations in 3-D space guide both sets of hands and arms along trajectories, with on-the-fly midcourse corrections, to join in an embrace.

No wonder that nearly one-third of our higher brain, the cerebral cortex, is dedicated to making sense of what we see. Strictly speaking, what registers on the eye's retina is essentially light and shadow; the brain constructs all the rest. The welter of reflected light from thousands of sources that constantly floods the retina has to be captured, filtered, and processed at diverse places along the visual pathways of your brain to construct a perception in your mind's eye of what you are looking at. And then there's the depth problem: A 3-D world is projected onto your 2-D retinas, but the brain has to transform it into three dimensions.

Vision has been studied for centuries, though in fits and starts. The initial tracing of nerves from the eye to certain brain regions came in the 1600s, for example, and theories of color vision were also first proposed in that century. But a quantum leap in vision research came in the 1960s when David Hubel and Torsten Wiesel carried out experiments that would eventually win them a Nobel prize. These pioneers showed that they could record electrical activity from individual neurons "and that they could describe what turns the neurons on and learn about the nature of sensory representation at early stages of the visual hierarchy," says David C. Van Essen, a veteran vision researcher at Washington University in St. Louis School of Medicine and a member of the HHMI Scientific Review Board, who was a postdoctoral fellow under Hubel and Wiesel.

Since then, Van Essen says, "we have certainly made progress." There have been numerous discoveries about the wiring of the brain areas that process visual signals, particularly information about motion, and we understand better how the eye/brain system uses viewers' memories and emotions to help interpret what they see. But it may take many more years to fully understand the neural processes of vision. Scientists are ardently working toward that goal, however, and among them four HHMI investigators in particular are making major contributions.

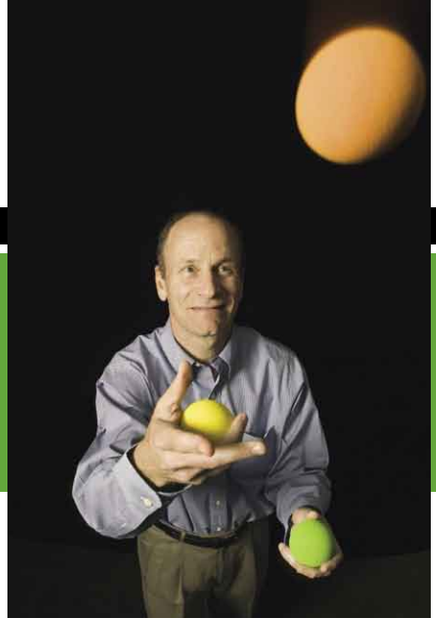
Perception to Decision

WILLIAM T. NEWSOME, an HHMI investigator at Stanford University School of Medicine and one of the acknowledged leaders in the field of visual neurosciences during the past few decades, has expanded on leads uncovered by Hubel and Wiesel—such as their discoveries of different types of brain cells specialized to respond to specific kinds of visual signals transmitted from the retina. Newsome credits recent progress to the field's move away from anesthetized laboratory animals to the more flexible and realistic system of humanely using alert, unsedated monkeys, whose brain activity can be recorded while they respond to visual cues and perform carefully designed tasks.

WILLIAM T. NEWSOME

➡ Recently, William Newsome has been interested in the processes that transform perceptual information into decisions for action. "Exactly where and how the sensory signals are evaluated to reach a categorical decision about an appropriate behavioral response is still quite mysterious," he says. Millions of neurons represent visual inputs in various parts of the brain, but only one or a limited number of actions can be taken.

TIMOTHY ARCHIBALD



PAUL FETTERS

STEPHEN G. LISBERGER

➡ Stephen Lisberger has discovered that visual pursuit—tracking an object in motion—is not a reflexive action, but is actually a "complex voluntary behavior that comprises many components." The eye and brain must choose which moving object to track, estimate the direction and speed of the target with respect to the moving eye, and command the eyeball to rotate along the object's path at the correct speed.

When he explains his work to engineers, Newsome says, "I tell them we have monkeys looking at visual displays and 'telling' us what they see. Our goal, in turn, is to go into the brain with tiny microelectrodes and attempt to understand how the brain 'sees' by studying the electrical activity of single neurons one by one. It seems outrageous in principle—somewhat like taking the back off a Cray supercomputer and understanding how it works by measuring the activity of single resistors and capacitors one by one—but the amazing thing is that we can really make progress this way."

The "single most exhilarating moment" of his research career, says Newsome, came in 1989 when he and Daniel Salzmann, a Stanford medical student at the time, showed that they could do more than just locate the neurons responsive to incoming visual signals—they also could artificially stimulate them. The neurons in question were cells that respond exclusively to motion in a particular direction. When Newsome stimulated cells that respond to upward motion while the animal was watching a downward-moving target, the monkey's reaction indicated that it "saw" the target moving in the opposite direction.

"This was proof of principle," says Van Essen, "that you can go into a collection of neurons and with these moderately sized jolts of electricity actually produce subtle and precisely measurable changes in what the animal perceives."

More recently, Newsome has been interested in the processes that transform perceptual information into decisions for action. "Exactly where and how the sensory signals are evaluated to reach a categorical decision about an appropriate behavioral response is still quite mysterious," he says.

Moving from perception to decision is something like electing a nation's president: Millions of voters have many different views of the candidates, but, when the votes are in, one bloc carries the day. Similarly, millions of neurons represent visual inputs in various parts of the brain, but only one or a limited number of actions can be taken.

For example, if a monkey is presented with visual targets moving in random directions but overall in a downward direction, how does the animal's brain "pool," or process, the cavalcade of information coming from different motion-detecting cells? "We realized there has to be some decision mechanism that takes the sensory evidence and reaches a judgment about whether the overall direction is up or down," says Newsome. "The monkey has to put all of his eggs in one basket."

Some of Newsome's newest work incorporates research on the brain's reward system—a field of study called "neuroeconomics." This name reflects the fact that the expectation of a reward influences an individual's decision about taking action—a fisherman, for example, throws a line into a part of the river that has produced catches before. "The question," says Newsome, "is whether we can measure emotional arousal, manipulate those responses, show that they have effects on choice and behavior, and track the underlying neural signals."

Sensation to Action

STEPHEN G. LISBERGER, an HHMI investigator at the University of California, San Francisco, is investigating a complementary phenomenon. "I'm interested in how you take a visual sensory signal and convert it into a command for movement," he says. For a window into this critical area, Lisberger has long studied the neuronal circuitry that enables monkeys to move their eyes smoothly while "pursuing"—that is, tracking—an object in motion.

Visual pursuit is a highly developed faculty in primates, and Lisberger likes to point out the virtuosity with which it performs in, for example, an outfielder turning and sprinting to the exact spot where a flying, curving baseball will come to earth. This feat depends on two separate faculties within the brain: keeping the eyes locked on the speeding ball, and compensating for the jerky, bouncing movements of the running fielder's head.

Scientists used to think that smooth pursuit was a straightforward reflexive action. But over the past several years, Lisberger has discovered that pursuit is actually a "complex voluntary behavior that comprises many components." The eye and brain must choose which moving object to track, estimate the direction and speed of the target with respect to the moving eye, and command the eyeball to rotate along the object's path at the correct speed.

One of the most interesting components Lisberger discovered is an "online volume control" that selectively dials up

JOHN H.R. MAUNSELL

➡ Visual inputs flow from the retina through a series of processing centers in the brain, climbing a ladder of increasingly higher-level stages until the image is in a "finished" form that, John H.R. Maunsell says, has been "edited to suit the immediate goals of the viewer." Maunsell's aim is to understand how changes in attention alter the responses of visual nerves involved in this editing process.

PAUL FETTERS

or down the strength of visual inputs to the motor system. Analogous to Newsome's experiments, where stimulation in the brain area labeled "MT" changed what the monkey reported he "saw" for a given moving stimulus, Lisberger's laboratory demonstrated that stimulation in a part of the frontal motor cortex can change how the monkey's pursuit system responds to a given visual stimulus. The effect of stimulation seems to be mediated by altering the setting of the volume control.

Another longtime interest of Lisberger's is how the proverbial outfielder, despite running along and turning his gaze rapidly from place to place, manages to perceive the world as stable. It's due to the vestibulo-ocular reflex, or VOR, which occurs when, for instance, in watching someone pass by, you turn your head to the right: This action produces a smooth eye rotation to the left. Remarkably, even though the VOR is a simple reflex, it is capable of learning, so that any errors in stabilizing the world are quickly eliminated. Lisberger's lab has pinpointed the neural loci of learning to two places in the cerebellum and has begun to explain how learning at specific loci in the brain can be converted into organized changes in motor output.

Attention Improves Perception

VISUAL INFORMATION from the outside world falls on our retinas in an overwhelming jumble of stimuli, like the incoherent babble of voices at a cocktail party. Fortunately, the brain is equipped to focus on small, important parts of a scene while screening out what is irrelevant. Attention, as this filtering process is called, sharpens our perception of the target and enables the brain to make better-informed decisions about responding.

Visual inputs flow from the retina through a series of processing centers in the brain, climbing a ladder of increasingly higher-level stages until the image is in a "finished" form that, HHMI investigator John H.R. Maunsell says, has been "edited to suit the immediate goals of the viewer." Maunsell's aim is to understand how changes in attention alter the responses of visual nerves involved in this editing process.

Maunsell and his colleagues at Baylor College of Medicine have worked with monkeys trained to fix their gaze on a central spot on a computer screen and then—without moving their eyes—shift attention to other targets. Meanwhile, a computer-aided sensing system records the electrical activity of the neurons in the brain that are receiving stimuli from the retinal cells that capture the object of the animal's attention.

This research has shown that when monkeys thus shift their attention, a surge of electrical activity occurs in those neurons. The investigators have demonstrated such an effect in many areas of the brain, in nerve cells specialized for different features such as detecting edges and motion as well as recognizing patterns.

More recently, the researchers changed the test conditions. The monkeys were trained to concentrate on a single dot. When dedicated neurons detected the target dot, their electrical activity spiked to twice the normal firing rate, and the same cells "turned down" their response when they encountered a similarly moving dot that wasn't the one on which they were trained to focus.

"The behavioral result is that you get improved perception or faster reaction times when the monkeys detect a small change or respond to it," Maunsell says. "What attention is doing is just altering the sensory representation the animal will use to make his decisions."

Maunsell emphasizes, however, that the allocation of attention is a dynamic, constantly changing process, and the strength of responses in the brain cells "can fluctuate over a fraction of a second as the animal directs more or less attention to different parts of the visual scene."

Maunsell is currently conducting experiments to discover how the brain translates a visual image's information into a motor response. So far, it looks as if this process is based on information from a limited voting body, so to speak, rather than a large population. A relatively small number of neurons—

hundreds, perhaps—are involved in different areas of the cortex.

This kind of research, Maunsell says, reflects a new stage in the daunting journey to understanding the workings of the brain. "I view the last 30 years as coming to grips with how things are laid out in the brain and where visual images are represented," he says. "We have a decent first draft."

Now, he says, researchers are delving into the still-mysterious processes "by which, using the 1.2 billion neurons in the visual cortex, the important bits of information are extracted and an appropriate motor response is determined."

Context: "The Brain's Best Guess"

WE'VE ALL SEEN puzzling photos of objects that are unrecognizable until we're told or eventually figure out that they are small parts of something larger—an architectural detail, perhaps, of a familiar building. What was initially lacking was a context for the otherwise meaningless shape we were looking at. As soon as the context became apparent, recognition was a snap.

In one area of his wide-ranging vision research, Thomas D. Albright, an HHMI investigator at the Salk Institute for Biological Studies, in La Jolla, California, has been studying the crucial importance of contextual clues to visual perception. Context can mean many things, from the physical features of a visual target's environment to memories stored in the brain that are associated with the object. Context, says Albright, helps us "recover" information that's missing from the original image captured on our light-sensitive retinas.

At the first of several stages of increasingly sophisticated processing and interpretation, the retina senses mainly a patchwork of light, dark, and color—contrasts without recognizable shape or significance. In the next round of processing, Albright explains, brain cells that respond exclusively to certain features of an image begin providing rough interpretations of the visual scene. Some specialized cells are activated when they sense an edge or a contour, others when they detect motion in a specific direction, and still others when certain colors or brightness levels are present.

Next, these growing sensory impressions, not yet full-fledged perceptions, are fleshed out at the highest level—cognitive processing that integrates context in the form of memories, emotional responses, anticipated rewards, and the "mental set" of the viewer.

Up to this point, says Albright, context is supplied mainly by hard-wired rules of interpretation, so that most people's perceptions of a scene are in agreement—we all pretty much see the same objective reality. But in the cognitive stages, the perception takes on more personal guises, with greater variation among viewers.

"People who've been deprived of many sensory experiences may have a very limited interpretation," says Albright. "On the other hand, an artist like J.M.W. Turner, the English pre-Impressionist painter, may have a radically different view of the world." Turner, whose landscapes and sunsets often were rendered in multihued, brilliant colors that were far from straight realism, once was told by a viewer, "I've never seen a sunset that looked like that," recounts Albright. The artist responded, "Don't you wish you could!"

Another form of contextual influence that Albright studies involves the visual system's ability to "fill in" gaps in the eye's image caused by events that obscure part of the scene. One omnipresent gap, for instance, is a "hole" in the retina's image caused by the lack of light-detecting cells in a small circular area where the bundle of neurons forming the optic nerve leave the back of the eye and connect to the visual centers at the rear of the cortex. "The visual system has to have a mechanism to keep you from seeing a blind spot," Albright explains.

How does it compensate? By sampling the image surrounding the exit hole in the retina so that we see "the brain's best guess as to what's there," he says. "The brain will fill that space with the representation of the space around it," Albright says. "And the remarkable thing is that it happens so fast."

Or, as David Van Essen characterizes the overall context-establishing process, "The brain doesn't have access to truths but to evidence, which is always incomplete. So what the brain has to do is make inferences." ■

PAUL FETTERS

THOMAS D. ALBRIGHT

➡ In one area of his wide-ranging vision research, Thomas D. Albright has been studying the crucial importance of contextual clues to visual perception. Context can mean many things, from the physical features of a visual target's environment to memories stored in the brain that are associated with the object. Context, Albright says, helps us "recover" information that's missing from the original image captured on our light-sensitive retinas.

Evolution Is Our Laboratory

Studying how evolution acts on all levels—molecular, cellular, organismic, ecological, social—investigators find thematic threads that draw the disciplines together.

BY STEVE OLSON

ILLUSTRATION BY DAVID PLUNKERT

PLUNKERT

A great irony of the recent upsurge in creationist sentiment in the United States is that research in evolutionary biology has never been more dynamic or exciting. ¶ Biologists in many fields are discovering that they cannot answer critical questions without first understanding how living systems evolved. "Many biologists would now agree that a grounding in evolution is fundamental to biology," says Sean B. Carroll, an HHMI investigator at the University of Wisconsin–Madison. "Before, I think they would have said that evolution is a branch of biology but not an integral foundation." ¶ Several developments underlie this trend. Biologists have come to recognize the many ways in which evolution has forged commonalities among organisms. "There are much greater similarities at the genetic level than biologists had appreciated, profound similarities," says Carroll. "That forced a rethinking. It meant that a generation of biologists had to learn not only about the connections among organisms but also about how those connections could be used as research tools." ¶ New genomics data have highlighted these evolutionary links. Whereas biologists used to rely on similarities in shape or behavior to draw evolutionary connections, they now can reconstruct evolutionary lineages by analyzing DNA sequences. "You can document the dramatic genetic events that changed the nature of an organism over evolutionary time," says HHMI investigator David Haussler at the University of California, Santa Cruz. ¶ In addition, biologists increasingly have realized that questions involving evolution have important connections to other scientific fields. And as they have forged multidisciplinary collaborations with chemists, geologists, computer scientists, and social scientists, new ideas and techniques have flooded into the biological sciences. ¶ The growing prominence of evolutionary biology is apparent in the work of many HHMI investigators. **Here are five examples.**

1. The Origins of Life

SZOSTAK

In principle, evolution is remarkably simple. Among assemblages of molecules able to reproduce themselves, some copies turn out slightly different from the original. When a variant appears that is better able to survive and reproduce, it will become more numerous. And as these entities continue to copy themselves and change, some will come to exploit existing resources in new ways or move into new environments.

Biologists may never know exactly which molecules came together to form the first living organisms, but HHMI investigator Jack W. Szostak, a geneticist at Massachusetts General Hospital and Harvard Medical School, is very close to demonstrating how the process could have occurred early in Earth's history. In his laboratory at Massachusetts General Hospital, Szostak and colleagues synthesized chains of nucleic acids that can latch onto other nucleic acid chains (including copies of themselves) and partially copy those chains. On the early Earth, reproducing chains of nucleic acids could have formed within vesicles composed of fatty acids, which could have been plentiful in certain places. This compartmentalization is critical, Szostak points out, because otherwise, highly efficient replicators will make copies of all the nucleic acid chains around them. If they are isolated inside a vesicle, however, they will make more copies of themselves and thereby increase in number.

A major challenge for Szostak's team has been devising a way of coordinating the growth and division of the vesicle with the replication of its contents. After examining several possible mechanisms, "we worked out an idea that was relatively simple," he says. They found that putting nucleic acid chains inside a vesicle creates osmotic pressure inside the membrane. These highly pressurized vesicles are able to absorb fatty acids from less-pressurized vesicles and grow. If these growing cells divide randomly or at a certain size threshold, they reproduce faster than less rapidly growing cells. In this way, says Szostak, a highly efficient nucleic acid replicator could outcompete less efficient replicators.

The outcome is natural selection among membrane-encapsulated nucleic acid chains. "It's a nice simplification of the whole process," says Szostak. Different replicator-vesicle packages compete with each other to become more numerous, so Darwinian evolution can occur with relatively simple molecular systems. Once these simple cells start competing, Szostak believes, there is a "snowball effect. You start to get additional functions evolving, and that's going to lead to changes in the membrane composition. The whole system is going to be under pressure to get a lot more complicated pretty quickly."

Szostak, well-known in biology for his work on chromosomal recombination, notes that his interest in evolution has caused him to establish strong collaborations with chemists: "I have people in my lab who are doing synthetic chemistry, and because we have to make molecules to build these systems, we collaborate with a number of other chemists, too." This connection between disciplines is being further strength-

MARK WILSON

A RELATIVELY SMALL CHANGE IN A REGULATORY REGION CAN HAVE A DRAMATIC EFFECT ON THE BODY PLAN OF AN ORGANISM.

ened by the creation of a new center at Harvard to study the origins of life. "Both in chemistry and biology," he says, "the origin of life is a fundamental issue."

2. The Coevolution of Life and Earth

NEWMAN

For more than a billion years, single-celled organisms were Earth's only inhabitants. But these cells were evolving and diversifying, and in so doing they began to change their environment. As California Institute of Technology geomicrobiologist and HHMI investigator Dianne K. Newman puts it, "Life and Earth have coevolved."

The earliest organisms lived in a forbidding world. Earth's atmosphere contained virtually no oxygen and would have killed many of the organisms that live on the planet today. Instead, scientists believe, the atmosphere contained substances such as nitrogen, carbon dioxide, and water vapor. As a result, our ancient predecessors had to rely on these atmospheric components, not the oxygen that now sustains us.

Newman studies modern-day organisms that essentially breathe metals—they transfer electrons from one metal ion to another to produce metabolic energy. The distant ancestors of these metal-breathing bacteria ruled Earth early in its history, but bacteria evolved that released oxygen into the atmosphere. For many millions of years this oxygen was sequestered in rocks, producing the ore deposits now known as banded iron formations. Eventually, oxygen began to build up in the atmosphere, triggering an environmental and biological "crisis" by changing the composition of rainwater, streams, and oceans.

Newman's work on metal-breathing bacteria has led her to consider the broader question of how bacteria have changed Earth's environment over evolutionary time. For instance, she and a group of colleagues recently proposed that a particular kind of bacterium played a key role in deposition of the banded iron formations. "I'm not an evolutionary biologist," says Newman, who studied German as an undergraduate at Stanford before receiving a Ph.D. in civil and environmental engineering from the Massachusetts Institute of Technology. "What I hope to contribute is an understanding of the mechanisms whereby these putatively ancient bacteria do what they do, and then make connections back to the rock record."

Like Szostak, she stresses the importance of interdisciplinary collaboration. "It's imperative for someone like me to have good colleagues who are experts at looking at ancient rocks," she says. "We're also beginning to design experiments with bacteria in the lab to help geologists interpret certain structures they see." To that end, she recently visited South Africa with a team of geologists and biologists to investigate the banded iron formations there.

Newman's work has many practical applications. For example, because some metal-breathing bacteria can convert toxic metals into less toxic compounds, these descendants of Earth's first occupants may someday be hard at work cleaning up pollution produced by humans.

3. Experimenting with Body Plans

CARROLL

PATEL

KINGSLEY

About 2.4 billion years ago, the atmosphere began to harbor appreciable amounts of oxygen. A few hundred million years later, according to the fossil record, new kinds of cells appeared. They were larger and more complex, possibly because they had evolved ways of using oxygen to support metabolic processes. Shortly thereafter, organisms appeared that were large enough to be seen without a microscope (had one existed)—algae consisting of cells in spiral chains.

For more than a billion years, these simple multicellular organisms evolved internally without great changes in external form. But beginning about 545 million years ago, during a period known as the Cambrian, evolution headed down a different path. A wealth of new organisms suddenly appears in the fossil record; they have hard shells, segmented bodies, and wildly different kinds of legs, antennae, spines, and claws. All the major types of animal lines—including organisms that would evolve into the vertebrates—appear during the Cambrian period, along with many bizarre biological experiments that proved unsuccessful.

The sudden appearance of these different body plans

NEWMAN: JOHN HAYES/AP; CARROLL: MICHAEL KIENITZ; PATEL: TODD BUCHANAN; KINGSLEY: KAY CHERNUSH

HUMANS EVOLVED IN THE MOST RECENT FEW MOMENTS OF EVOLUTION'S GRAND PAGEANT—APPEARING JUST 150,000 YEARS AGO.

has always puzzled biologists. How did all these animals evolve so quickly? Was it the result of abrupt and dramatic genetic changes?

HHMI investigators Sean Carroll, David M. Kingsley at Stanford University School of Medicine, and Nipam H. Patel at the University of California, Berkeley, have been investigating these questions from a relatively new perspective. They are leaders in the new field of evolutionary developmental biology—evo devo, for short—which relates the development of organisms to the regulation of genes. According to these investigators, evolutionary changes in body plan do not necessarily require changes in the number of genes or in the protein products of genes. Instead, evolution can create new kinds of organisms simply by experimenting with how genes are turned on and off as an organism develops from a single fertilized cell to its mature form. "If you want to tinker with body patterns, you tinker with genetic switches," says Carroll.

Besides containing the genetic sequences that dictate the order of amino acids in proteins, DNA contains noncoding sequences that tell cells when and where specific proteins should be expressed during development. These regulatory regions undergo evolutionary changes just as the coding regions of DNA do. But a relatively small change in a regulatory region can have a dramatic effect on the body plan of an organism. It can change the number of segments of an organism, and it can alter the appendages—themselves often segmented—that emerge from a body segment.

Patel, for example, studies this process in crustaceans, the segmented organisms that first appeared in the Cambrian period. "The particular animal we work on [the crustacean *Parhyale hawaiensis*] is remarkable because each segment comes from an individual row of cells in the embryo, so it's very easy to keep track of what goes on," he says. Patel and his colleagues have identified a number of genes that play a role in the segmentation process, and they have begun modifying the regulation of these genes to gauge the effects on development. They also have been relating changes in expression of the genes to changes in the segmentation of fossilized crustaceans. "In different species, different appendages have become specialized to do different things, and we're trying to develop a molecular understanding of how that occurs."

Patel, Kingsley, and Carroll all emphasize the importance of understanding how ecological forces have shaped an organism's evolution. Kingsley, for example, studies the evolutionary genetics of the stickleback—a small bony fish that lives in lakes, oceans, and coastal habitats throughout the Northern Hemisphere. He chose the stickleback as a model organism, he says, because different forms can be crossed and because thousands of papers have been written about the fish and its adaptation to different environments. "We were able to leverage a rich history of biological work to develop a full picture of this organism, from its DNA to its ecology," he says.

4. Diversification of Life on Land

HAUSSLER

After the Cambrian period, animals moved from oceans onto land and evolved into insects, amphibians, and reptiles. The dinosaurs that came to dominate suddenly went extinct, quite likely because a giant asteroid hit Earth. In the absence of dinosaurs, early mammals diversified and spread, eventually producing many of the creatures familiar to us today.

Until recently, biologists studied this grand saga largely through the fossil record. But in the past few years they have gained access to an entirely new way of studying evolution. As genome sequencers have derived the complete or partial DNA sequences of different organisms, evolutionary biologists have been able to track how these organisms diverged genetically from a common ancestral species. In so doing, "you can feel the DNA evolving," says HHMI investigator David Haussler.

Haussler leads several teams that have been developing mathematical algorithms and software to analyze and display the genetic differences among organisms. Using these bioinformatic techniques, one team has reconstructed with an estimated 98 percent accuracy part of the genome of the common ancestor of most placental mammals—a small, shrewlike creature that lived about 100 million years ago. "It sounds implausible," Haussler admits, "but there's enough information to reconstruct quite a good approximation to the ancestral genome on the basis of mammals alive today."

Building on this reconstruction, Haussler and his colleagues have been putting together a database that can trace the changes in any given nucleotide from the common placental ancestor to humans or other living mammals. "We hope to literally show you evolution working," he says. In turn, Haussler's group has been using this tool to study the functional significance of various parts of our genome. Only 1.5 percent of the human genome actually codes for proteins. But by comparing genomes across organisms, Haussler and his colleagues have estimated that an additional 3 to 4 percent of the human genome is constrained in its changes—presumably because it regulates the expression of genes or helps organize other functions of our DNA. "There's a huge amount

TIMOTHY ARCHIBALD

of uncertainty and discussion right now about what these areas are doing," he says. "We're mapping them out to try to understand how they have changed over time and beginning to explore their function in the lab."

5. The Evolution of Humans

WALSH

LAHN

Humans evolved in the most recent few moments of evolution's grand pageant. The evolutionary lineage leading to humans split off from the lineage leading to chimpanzees some 6 to 8 million years ago. But anatomically modern humans—people who looked as we do today—appeared only about 150,000 years ago (less than one three-thousandth of the time between us and the Cambrian period).

The lineage leading to humans obviously underwent profound changes since the time of our common ancestor with chimps. HHMI investigators Christopher A. Walsh at Harvard Medical School and Bruce T. Lahn at the University of Chicago have been studying those changes in the brain. The human brain is much larger in relation to our body size than the brain of any other animal, and it "has a more complex organization," says Lahn, "particularly in terms of the subdivision of regions for specific tasks."

Walsh points out that three genetic mechanisms could have caused the human brain to diverge from the chimpanzee brain. New genes may have been added to the human genome that are not present in the chimpanzee genome. Some of the genes that the two organisms share could encode subtly different proteins. Or the regulation of genes could vary—shared genes might be more or less active in the two organisms during different periods of development and in different tissues.

"We have some evidence for the action of all three of those mechanisms, and we're sorting out which of them is likely to be most important," says Walsh. Publication of the chimp genome a few months ago revealed that a number of genes in humans have been duplicated and then altered since the days of our common ancestor, and some of those genes may influence the development of human brains. Similarly, many of our genes are slightly different from the corresponding genes of the chimp, although that animal's genome reveals a striking similarity in coding sequences across the two species.

But Walsh thinks that regulatory changes eventually will prove to be the most important distinguishing factor. Small changes in the expression of a gene can have dramatic effects on an organism. Researchers also have shown that levels of gene expression have changed more over time in the human lineage than in the chimpanzee lineage. Unfortunately, says Walsh, "Our tools for studying changes in noncoding DNA are very poor."

To understand the complex development of the human brain, Walsh and Lahn both stress the importance of studying genetically transmitted neurological disorders. With a human genetic disease, says Walsh, "You can really learn something about why a gene is essential in our brains, and you can learn that only in humans." For example, Walsh and Lahn have been studying inactivating mutations in a gene called *ASPM* (for "abnormal spindle-like microcephaly associated") that can produce brains much smaller than normal. Both their labs have demonstrated that the protein product of the gene has undergone significant evolutionary changes since the time of our common ancestor with chimpanzees, implicating the gene in our ancestors' dramatic brain expansion.

In fact, Lahn believes the gene is still under significant positive selective pressure in human populations. He and his colleagues have identified variants of the *ASPM* gene that have arisen relatively recently, and they have found one variant that appears to be spreading through the population. Lahn thinks that people with the variant *ASPM* gene have some sort of selective advantage, enabling them to have more children and thereby producing more copies of the gene. "This [work] is very relevant to behavioral evolution studies," says Lahn. "We have to start thinking about how social structures and cultural behaviors in the lineage leading to humans differed from that in other lineages."

We tend to think of ourselves as distinct from the rest of the biological world, as if our appearance marked the end of evolutionary history. That's clearly not true. We are the products of a vast evolutionary process that will continue indefinitely, whether we are here to influence it or not.

As Sean Carroll says in his 2005 book *Endless Forms Most Beautiful: The New Science of Evo Devo and the Making of the Animal Kingdom*, humans are "ensemble players working from a shared evolutionary script."

And, just as studies of evolution have revealed a profound unity among biological organisms, so have they fostered an appreciation of the unity among biological disciplines. In the past, different fields of biology were relatively isolated, Carroll points out. "Paleontologists and molecular biologists never used to meet," he says. "People published in different journals and ran in different circles. There was a pronounced split in the biological community."

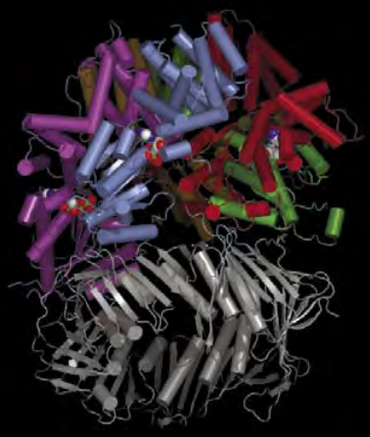
In recent years, the study of evolution has been drawing the disciplines together. Researchers are increasingly appreciating that evolution acts on all levels—from the molecular to the cellular to the organismic to the ecological to the social—and that all aspects of biology reflect the workings of natural selection. Thus, a major challenge facing biology today, says Patel, is to "integrate all of the various fields of biology and get a more holistic view of how evolution works." ■

WALSH: ASIA KEPKA; LAHN: MARK SEGAL

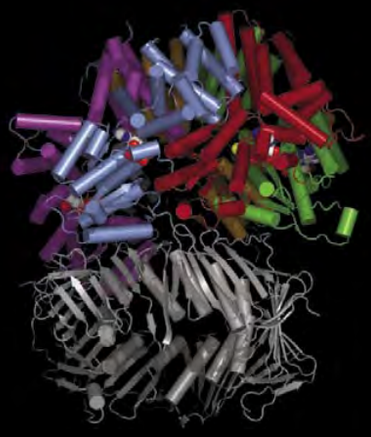
▶ 0° ▶

▶ 21° ▶

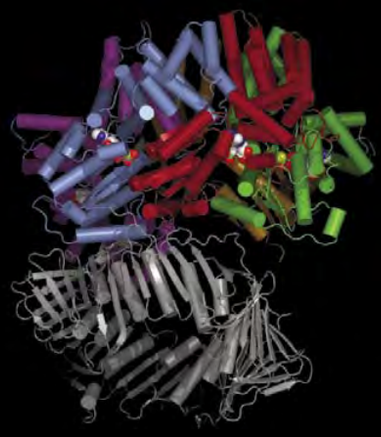
▶ 42° ▶



▶ 127° ▶



▶ 148° ▶



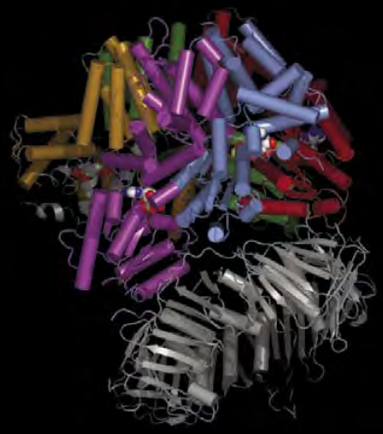
▶ 169° ▶

▶ 254° ▶

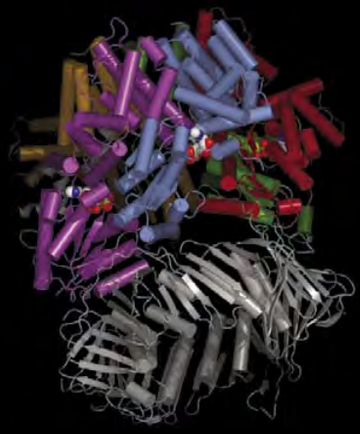
▶ 275° ▶

▶ 296° ▶

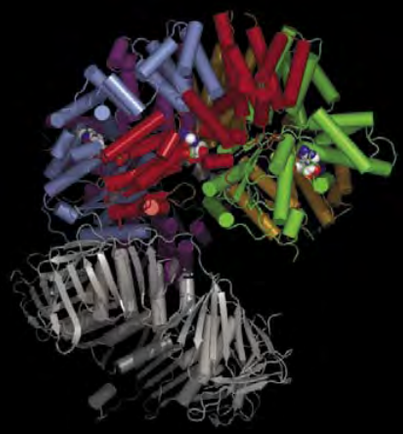
64°



85°

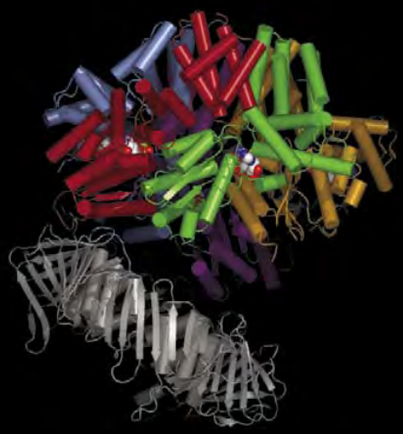


106°



191°

212°



233°

VIEWING VITAL STRUCTURES

RESEARCHERS ANGLE FOR BETTER 3-D STRUCTURES OF THE MOLECULAR MACHINES THAT PRODUCE OUR PROTEINS, REPAIR OUR DNA, DEFEND US AGAINST MICROBES, AND, IN EFFECT, CONTROL OUR HEALTH. **BY MAYA PINES**

PHOTO ILLUSTRATIONS BY GREGORY BOWMAN

THE PHOTO ILLUSTRATION SEQUENCE DEPICTS A 360° ROTATION OF THE CLAMP LOADER ASSEMBLY (SEE PAGE 29). DEGREES OF ROTATION ARE APPROXIMATED.

318°

339°

360°

"This virus is really sneaky," says Karolin Luger, a newly minted HHMI investigator at Colorado State University, describing the agent that causes Kaposi's sarcoma, a cancer of the connective tissue below the skin. With the help of x-ray crystallography, a technique that enables scientists to deduce the positions of individual atoms in a structure, Luger and her collaborator Kenneth Kaye of Harvard Medical School have just discovered the devious way in which the Kaposi virus spreads: It piggybacks onto segments of chromatin, a protein- and DNA-containing structure inside the cell's nucleus, forcing the cell to produce more viral genes every time it copies its own DNA.

Luger made this discovery while analyzing the shape of a nucleosome, the basic repeating unit of chromatin, to which a fragment of the Kaposi virus was attached. "The structure shows that the nucleosome can act as a docking platform for a virus," she says. "This is a new role for it—and potentially this interaction could be prevented with antiviral drugs."

Now she hopes to tackle a much bigger problem: discovering the shape of chromatin itself. "Our genetic information, which is stored in DNA, is not read linearly but packed into these highly convoluted and organized structures, and a lot of cancer comes from the wrong readout of genes," she says. "To discover how this happens, we need to understand the structures involved."

Luger's goal illustrates a new trend in structural biology: focusing on the shapes of ever more intricate "molecular machines," groups of molecules that self-assemble to do key jobs in living cells. Until about 15 years ago, scientists were happy to determine the structure of a single protein at resolution high enough so they could see the position of each of its atoms. Then, spurred by more efficient methods of growing crystals, better computers, and the more intense x-rays produced by a new generation of synchrotrons, they began to solve the atomic structures of single proteins bound to single receptors. Now they want more. They want to see the 3-D structures of the powerful molecular machines that produce our proteins, repair our DNA, defend us against microbes and, in effect, control our health.

These complex functional units consist of perhaps five to a dozen different proteins or nucleic acids that have come together for specific purposes. At times several different molecular machines unite to form even larger functional units.

"We're now able to visualize molecular assemblies of such complexity that I would never have predicted they could be crystallized," says John Kuriyan, an HHMI investigator at the University of California, Berkeley. Kuriyan's lab recently solved the intricate structure of a "clamp loader assembly," a cluster of proteins that positions the machines that replicate DNA. It is difficult enough to grow a well-ordered crystal—the essential first step in x-ray crystallography—when dealing with just one or two components, he points out (see sidebar, "First, Grow a Crystal"). But, in 2000, Thomas A. Steitz, an HHMI investigator at Yale University, Peter B. Moore of Yale, and their colleagues solved the atomic structure of a complicated molecular machine—the large subunit of the ribosome, the cell's protein-building factory—at high resolution. This relatively enormous machine contained 3,000 nucleotides of RNA as well as 31 different proteins.

"When I first heard Steitz describe this work … I felt much as I did when humans first stepped on the moon," Kuriyan recalls. It was the largest molecular-machine structure that had ever been solved in such detail. Around the same time, the smaller subunit of the ribosome was also visualized, and this year the total ribosome structure—which shows how the ribosome produces new chains of protein, one amino acid at a time—was solved at reasonably high resolution.

BOLD COLLABORATIONS

The conquest of the large ribosome subunit emboldened scientists to tackle other molecular machines that in the past had seemed forbiddingly large. Their efforts have had some early and potentially useful results, such as leading biologists to learn exactly how certain classes of antibiotics kill bacteria and why certain bacteria are resistant to drugs. In order to prevent bacteria from producing new proteins, drugs actually target the bacteria's ribosomes. Recent studies in Steitz's lab and elsewhere have identified the specific crevices of bacterial ribosomes into which particular antibiotics fit. This discovery could lead

FIRST, GROW A CRYSTAL

▶ **The first commandment of x-ray** crystallography—grow a crystal of the molecule you're interested in so you can peer at its atomic structure—can be a scientist's biggest stumbling block. ▶ **A crystal is a form of perfection,** in which all the atoms of each molecule are arranged in precise order and their pattern is repeated regularly in three dimensions. X-rays beamed at such crystals are then diffracted in regular patterns, which scientists can use to figure out the positions of the atoms that make up the molecule. But obtaining such crystals used to require enormous luck. It is still particularly difficult when dealing with large, complex, and flexible molecules. And in some cases it may be impossible, as Karolin Luger knows in connection with chromatin, the subject of her next experiments. "Chromatin's structure is not regular enough to produce a good crystal," she says. She realizes she will have to use different tools, such as an analytical ultracentrifuge or an atomic-force microscope. ▶ **Recently, scientists** have made several improvements in their methods of growing crystals. For example, it is now possible to test in a few minutes whether a particular protein is likely to crystallize in certain conditions, saving hours of trial and error. Instead of depending on just one set of conditions to make things crystallize, scientists can rapidly set up about 1,000 different conditions for growing crystals with the aid of new robotic dispensers that operate on the level of a nanoliter (one-billionth of a liter). All this can be done with just one milligram of protein. Then the results can be read with an automated microscope. According to David Agard, "Such methods are completely changing how we do crystallography."

CLAMP LOADER ASSEMBLY

THE INTRICATE STRUCTURE OF A CLAMP LOADER ASSEMBLY, A CLUSTER OF PROTEINS THAT HELPS POSITION DNA DURING REPLICATION, WAS RECENTLY SOLVED IN THE LABORATORY OF HHMI INVESTIGATOR JOHN KURIYAN.

to drugs that fit more tightly, are more effective at low doses, and have fewer side effects.

Some biologists have been using the ribosome's structure as a jumping-off point to examine what happens to newly born protein chains when they emerge from the ribosome. Good health depends on proteins getting where they're supposed to go, but no one knew precisely how new protein chains make their way across various cell membranes—or how some of these chains become lodged inside the membranes. In 2004, cell biologist Tom A. Rapoport and structural biologist Stephen Harrison, both HHMI investigators at Harvard Medical School, led a team that solved the atomic structure of a surprisingly narrow membrane channel that new proteins must squeeze through, as through a birth canal. Docking next to this channel, the ribosome extrudes limp nascent protein chains right into the channel opening and pushes them in. Once on the other side of the membrane, the chain folds into its active shape and gets to work.

The channel turned out to have a very tricky structure—it is shaped in part like a clamshell that opens and shuts, allowing a number of proteins to cross the membrane while holding back millions of others. It also directs some proteins sideways, to positions inside the membrane.

"The system is extremely ancient," Rapoport explains. Every bacterial or mammalian cell that has an outer membrane or some internal compartments must be able to transport proteins across these membranes to their destination as well as find ways to respond to its environment. Proteins such as insulin need to exit from the cell and travel to other parts of the body. All cells need certain proteins to be embedded in their membranes, to act as receptors for signals from other cells. The membrane channels that conduct such proteins in different species are amazingly similar. If they malfunction—if essential proteins are misdirected, misfolded, or destroyed—a variety of diseases can result.

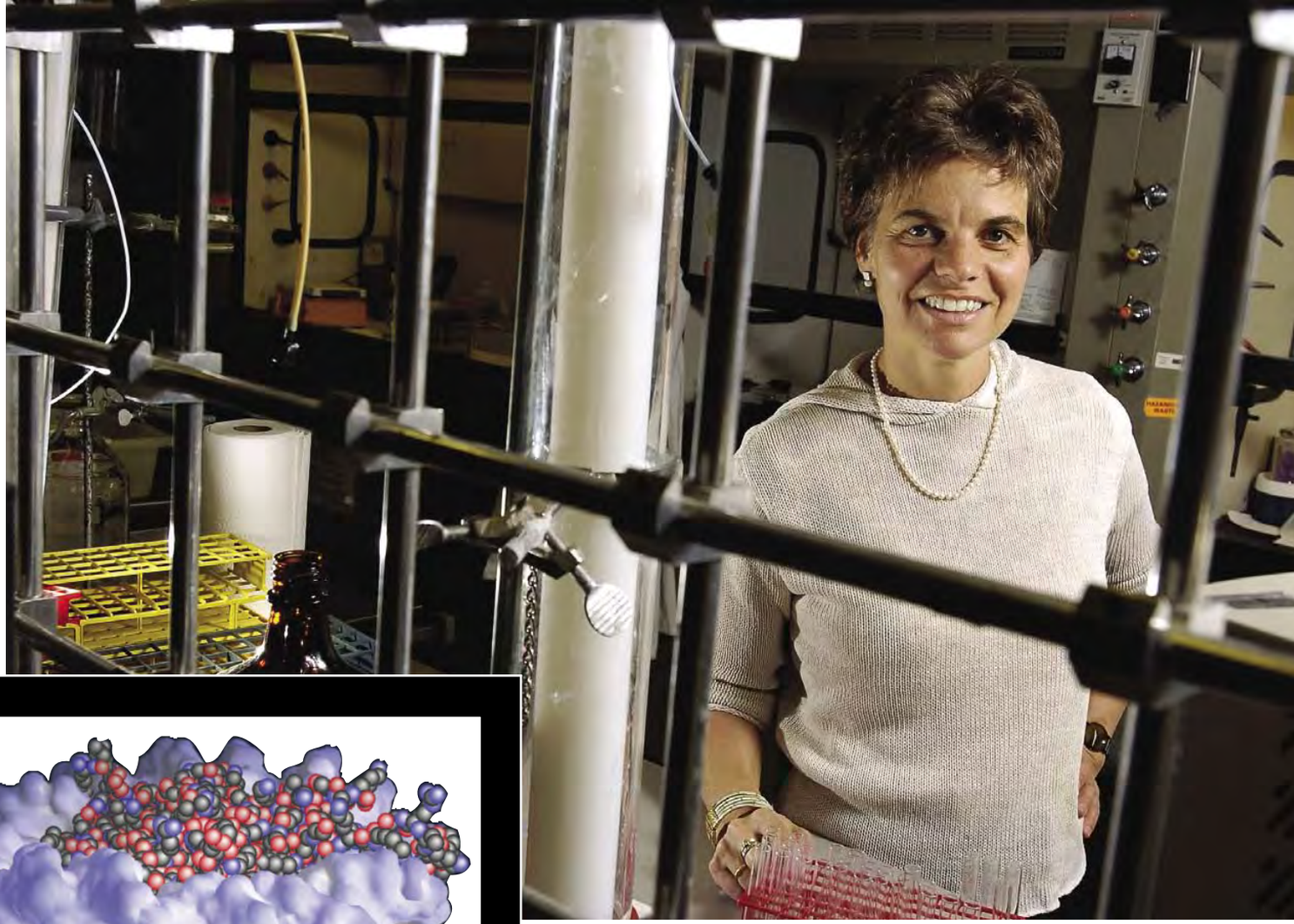
Meanwhile, scientists have been pursuing the 3-D structures of several other "large molecular machines that control the birth, growth, and death of proteins," says Kuriyan. Some researchers are even studying machines as dynamic as the spliceosome, a structure in the cell nucleus that is put together very loosely from different components that keep shifting location as the machine does its work. The spliceosome acts on RNA molecules that are copied from genes; its job is to excise any noncoding intervening sequences (introns) from mRNA and stitch together coding (exon) sequences to make "mature" mRNA that is then translated to proteins encoded by the gene.

At Brandeis University, HHMI investigators Melissa J. Moore and Nikolaus Grigorieff are collaborating in an effort to map the spliceosome's structure, and the scope of the challenge is clear. The spliceosome must be exceedingly precise while splicing out introns, because a mistake that shifts even one nucleotide in a splice site will throw the entire gene-coding region "out of frame" and produce possibly dangerous mutations. Splicing errors are the basic cause of genetic diseases such as retinitis pigmentosa, some forms of dementia, cystic fibrosis, spinal muscular atrophy, and cancer. To prevent such outcomes in humans, the spliceosome must accurately identify more than 100,000 introns in diverse sequences of RNA.

Using electron microscopy, the scientists obtained a low-resolution structure of the spliceosome that showed several asymmetric sections forming an unusually large number of tunnels and bridges—an intriguing start. They could not use x-ray crystallography for these studies, Grigorieff explains, because

A BEAM GLOWS IN BERKELEY

▶ **A billion times brighter** than the sun and traveling at the speed of light, a thin beam of x-rays streams out of the ringlike Advanced Light Source (ALS) synchrotron in Berkeley, California. After hitting a small crystal, it bounces off, producing patterns that enable scientists to decipher the crystal's atomic structure. ▶ **Researchers who want to discover** the 3-D shape of a biological molecule—and have obtained a crystal of it—need the help of x-rays so intense they can be produced only by synchrotrons. In these large facilities, electrons that travel at nearly the speed of light are forced off their normal straight paths and into a circular route by magnets. At each bend, the electrons emit beams of light ranging from bright ultraviolet to x-rays. ▶ **Two years ago,** HHMI opened two "dedicated" beamlines at this synchrotron facility—with the cooperation of the U.S. Department of Energy, which operates it—to enlist these x-rays for regular use by structural biologists. ▶ **"It's been super-successful,"** says David A. Agard, an HHMI investigator at the University of California, San Francisco, who notes that much of his own work on the shapes of large molecules that play important roles in protein folding would have been impossible without ALS's new beamlines. At the Rockefeller University, Roderick MacKinnon, who won a Nobel prize in 2003 for solving the structure of a potassium channel, used the ALS to gain important clues about the channel's shape. John Kuriyan and scores of other researchers, both in and out of HHMI, also sing the praises of the ALS. ▶ **Despite its prodigious power,** the ALS is not the most brilliant—or expensive—x-ray source in the United States. The Advanced Photon Source (APS) of the Argonne National Laboratory in Argonne, Illinois, outside Chicago, holds that distinction. To solve the structure of the ribosome's major subunit, for instance, Thomas A. Steitz and his colleagues used the APS to build on their earlier results with the Brookhaven National Lab's Synchrotron Light Source on Long Island, where HHMI installed its first dedicated beamline a decade ago. ▶ **The beauty of the ALS,** scientists agree, is its power combined with its ease of operation. In addition, says Douglas Rees, "it is moving toward complete automation." This should make it possible for biochemists and others who are not crystallographers to solve structures there—and greatly speed up the discovery rate of important molecular shapes.



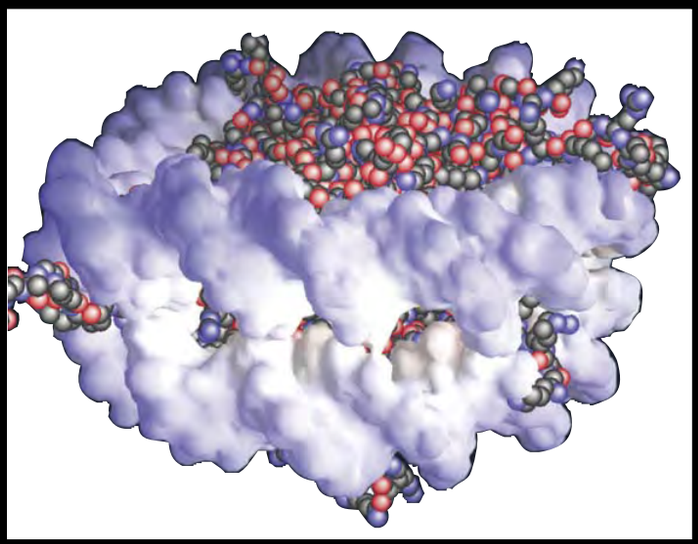


PHOTO ILLUSTRATION: COURTESY OF KAROLIN LUGER *KAROLIN LUGER:* JOSHUA LAWTON © HHMI

◀ **NUCLEOSOME CORE** SOLVING THE STRUCTURE OF THE NUCLEOSOME—A FUNDAMENTAL CHROMATIN COMPONENT MADE UP OF A DISK OF PROTEINS SURROUNDED BY DNA—WAS A STARTING POINT FOR KAROLIN LUGER. SINCE THAT ACHIEVEMENT, SHE HAS SHIFTED HER FOCUS FROM WHAT THE NUCLEOSOME IS TO WHAT IT DOES, AND HOW THE STRUCTURE CHANGES AS IT INTERACTS WITH OTHER MOLECULES. IN THIS SIDE VIEW OF THE NUCLEOSOME CORE PARTICLE, DNA IS DEPICTED AS A LIGHT BLUE SURFACE; ATOMS OF THE HISTONE OCTAMER ARE REPRESENTED AS SPHERES.

there are relatively few spliceosomes in a cell nucleus—far too few to grow into a crystal—and because "for crystallization, all spliceosomes would have to assume essentially the same shape." Nevertheless, he says, "We have collected and averaged thousands of images of spliceosomes, which should give us a detailed structure at a higher resolution."

BETTER TOOLS FOR THE JOB

Many factors have come together to produce the current crop of new findings in structural biology. "All operations are faster," says Douglas C. Rees, an HHMI investigator at the California Institute of Technology. "It's also easier to decipher structures on the basis of data, thanks to computational programs developed by Axel Brunger [an HHMI investigator at Stanford University] and others."

In addition, all research on structures has benefited greatly from recent progress in genomics. "Now, when we're interested in understanding a particular mechanism, we can pull out the proteins that carry out that function from many different genomes," says Kuriyan. "Sometimes the genes from one organism produce proteins that for some reason are more stable and crystallize better than the human or other genes that you were working on originally."

Scientists are also learning how large and shifting molecular machines can be caught in the act and crystallized as a whole. "Some of it is just luck," says Kuriyan. "But some of it is the result of doing experiments that tease out how the molecules work at a biochemical level. It's like photographing a tiger at the water's edge. You need to understand that the tiger comes to the water, know when it comes to water, position yourself by the pool—finally you get that moment when everything is right, and you snap it."

As these methods improve, researchers will have more opportunities to see for themselves "how a structure talks to you," as Nobel prize winner Roderick MacKinnon, an HHMI investigator at the Rockefeller University, once described the value of structural biology. Eventually this work will lead to a better understanding of how living cells function and how to repair them when they fail. ■

By Kathryn Brown

A Bout with FLU

As influenza smashes evolutionary barriers, scientists wonder: Is this the coming of the **next human pandemic?**

PHOTOGRAPH BY STUART RAMSON / AP

A WORKER PROCESSES A CHICKEN AT A PROCESSING PLANT IN SHANGHAI. IN NOVEMBER, CHINA CONFIRMED ITS FIRST THREE CASES OF AVIAN FLU IN HUMANS AND, TO TRY TO STEM THE SPREAD OF THE VIRUS, RUSHED TO VACCINATE BILLIONS OF CHICKENS AND OTHER FOWL.

Last year, a shortage of flu vaccine helped focus public attention on the medical consequences of influenza, to say nothing of its economic impact. This year, flu is again in the news. A lethal strain of avian influenza—bird flu—is spreading. Because this strain can infect humans as well as birds, scientists fear that in a worst-case scenario the avian flu could trigger a human pandemic.

In this context, influenza is a challenge to public health officials. But to scientists, the virus also presents a unique opportunity—a way to study evolution in action.

Since 1933, when scientists first isolated influenza A type viruses from ferrets, they have watched it break evolutionary barriers with alarming ease—infecting not only humans, but also birds, pigs, horses, dogs, and other species.

"Really, it's a numbers game," says Robert G. Webster, a virologist at St. Jude Children's Research Hospital in Memphis. "The more that chickens are infected and the broader the virus's geographic range, the faster it all adds up. It's just a matter of time before a new pandemic emerges."

Flu pandemics in 1918, 1957, and 1968 caused millions of deaths. Both strain H2N2 (the cause of the 1957 pandemic) and strain H3N2 (1968's pathogen) are believed to have arisen by the exchange of genes between avian and human flu viruses, possibly following dual infection in humans. The deadliest pandemic, in 1918, was different. It was the result of strain H1N1, thought to be derived wholly from an ancestor that originally infected birds.

Concerned about the likelihood that history will repeat itself—and that it will look more like 1918 than 1957 or 1968—Webster has been sounding the avian influenza alarm for years—to the point that some researchers dismiss him as preachy. "I've been accused of being a Chicken Little," he says. "But someone's got to do it. The H5N1 strain has some very disturbing characteristics."

Circulating in Southeast Asia since at least 1997, the highly pathogenic H5N1 has killed more than 150 million birds. And the virus is on the move. Wild waterfowl such as geese have been carrying H5N1 across Asia, along migratory routes where they come in contact with domestic poultry, typically near rivers and lakes. In August, officials in Russia and Kazakhstan confirmed the first reported outbreaks of H5N1 influenza among poultry in those countries.

So far, it's unclear how dangerous H5N1 is to humans. The virus, however, is clearly capable of infecting humans who come in contact with infected poultry—authorities have reported more than 110 confirmed cases, resulting in over 60 deaths, in Vietnam, Thailand, Cambodia, Indonesia, and China.

These numbers are likely to be underestimates—with spotty surveillance data, it's impossible to reliably gauge the rates of disease incidence or fatality. But, at least for now, H5N1 does not appear to be easily transmitted from human to human—a basic feature of pandemics.

Many scientists think they're playing a waiting game, however. "H5N1 has been around for 9 years, and I find myself asking, 'Why *hasn't* a human pandemic happened?'" says Robert A. Lamb, an HHMI investigator at Northwestern University in Chicago. "The fact is, it wouldn't necessarily take much. With these H5 viruses, even a single-point mutation can make the difference between the virus's ability to kill lab mice or not."

ESSENCE OF EVASION

Influenza's threat is not limited to this particular avian type. H5N1 belongs to the H5 influenza virus family, just 1 of 16 subtypes. Labeled H1 to H16, each subtype is named for the distinct structural biology of two key influenza surface proteins, hemagglutinin (HA) and neuraminidase (NA). All H5 viruses, for instance, share a similarly shaped HA protein. The influenza viruses within the H5 family as well as in the other families are further distinguished by the shapes of their NA proteins, of which there are nine.

Like a coat of armor, the HA and NA surface proteins stud the tiny influenza virus particle. When the virus mutates, it can essentially "change coats," altering the shape of its exterior surface and becoming unrecognizable to the human (or animal) immune system. This is the essence of immune evasion, a hallmark of influenza. The virus can under-

MAKATO TAKEDA

"H5N1 HAS BEEN AROUND for 9 years, and I find myself asking, 'Why hasn't a human pandemic happened?' With these H5 viruses, even a single point mutation can make the difference between whether the virus kills lab mice or not."

–ROBERT LAMB

go two types of changes. Small changes in the virus coat's proteins happen continually and result in new strains. This is a main reason why people can get the flu more than once and why they need to get a new flu vaccine every year. The virus coat can also change abruptly into a new subtype that has an HA protein or an HA-NA protein combination that has not been seen in humans, at least not for many years. Most of us would have little or no innate protection against this new virus. And if the virus can spread easily from person to person, a pandemic may occur. If influenza viruses rarely changed shape, immune evasion wouldn't keep researchers up at night. But they constantly evolve, and their physical structure is again the reason. Inside its spherical shell, the virus particle houses eight separate RNA segments—which encode genes for at least 11 proteins—and this kind of segmented genome is ripe for recombination. If two different influenza viruses infect the same cell, for instance, they can easily exchange gene segments—generating, by some estimates, up to 256 different offspring. Scientists call this phenomenon a genetic "reassortment."

In the case of the H5N1 avian flu strain, waves of genetic reassortment have pushed the virus from geese into chickens, then ducks, and beyond. What are the molecular mechanics behind these interspecies jumps? Scientists are beginning to find out. In the past year, researchers have published several studies of mammals in Asia infected with H5N1—including humans, tigers in a Thai zoo, and mice. Each case appears to harbor the same mutation: a single amino acid substitution, glutamine to lysine, in position 627 of the virus's PB2 protein, a polymerase protein that renders the virus more pathogenic by helping it replicate. The specific cause of the jump from one species to another remains something of a mystery, but many researchers believe it has to do with changes in the HA protein, which is responsible for recognizing receptors on the cells the virus infects.

TRANSMISSIBILITY

Although pathogenicity is a key influenza feature, it's only part of the health equation. Equally important, scientists

AP PHOTO/STUART RAMSON

CURRY, A 5-YEAR-OLD BICHON FRISÉ, IS ONE OF THE LUCKY ONES. CURRY RECOVERED FROM CANINE FLU, WHICH IS CAUSED BY A VIRUS THAT JUMPED FROM HORSES TO DOGS IN THIS COUNTRY.

THE FLU STRIKES CLOSE TO HOME

FOR A REAL-LIFE EXAMPLE OF INFLUENZA jumping the species barrier, look no further than the family pet. In a study published in the October 21, 2005, issue of *Science,* researchers reported that a decades-old variety of equine (horse) influenza has emerged in dogs.

This discovery began unfolding in 2004, when greyhounds at a Florida racetrack fell ill with an unidentified respiratory disease. Lab studies at the University of Florida failed to turn up the usual pathogens behind "kennel cough" and similar canine conditions, so researchers sent the samples to the veterinary diagnostic lab at Cornell University.

Fearing an influenza virus, Cornell scientists forwarded suspect viral samples to the U.S. Centers for Disease Control and Prevention (CDC). Sure enough, CDC staff recognized the pathogen as H3N8 equine influenza virus. Having occurred for at least 40 years in horses, this virus suddenly made a complete jump into greyhounds. Moreover, this newfound canine influenza, dubbed canine/FL/04, quickly began to spread. Since the winter of 2004 it has been confirmed in outbreaks at racetracks in at least 11 states, affecting thousands of greyhounds. Pet dogs, too, are susceptible, with confirmed cases among many breeds in Florida clinics and 16 other states, although the illness is mild in most dogs.

Nevertheless, "For scientists worried about interspecies transfer of influenza, this is a rare and striking example," says Ruben O. Donis, a CDC scientist and senior author of the *Science* paper. "Interspecies transmission of influenza happens quite frequently, but what we usually see is the scenario in Asia, where H5N1 avian influenza jumps to a person and then stops. That's a dead end for the virus, because it can't be transmitted from person to person. What's new, in the canine case, is the establishment of a new virus in a new host—the dog—with efficient transmission. Dogs catch this flu from other dogs. In other words, influenza has found a new host, adapted to it, and is thriving."

How? Donis says that, although the equine and canine influenza strains are at least 96 percent genetically homologous, the canine virus appears to carry 8 to 10 amino acid changes in its hemagglutinin—an important surface protein on influenza particles that is critical for determining host specificity. Changes in other proteins, still under study, may also promote the virus's interaction with its new canine host.

CDC scientists, in collaboration with scientists at the University of Florida and University of Kentucky, plan to continue comparing recent equine and canine influenza isolates—as well as to survey equine samples that are older. "We have equine influenza virus isolates, taken every year, back to 1963," Donis says. "So we can look at all of them and ask, 'Which mutations at what time enabled H3N8 to cross the species barrier into dogs?'"

That may be the top question among scientists, but for pet owners another concern looms. If the flu can jump from horses to dogs, why not from dogs to people? The historical record provides some assurance, as well as uncertainty. "H3N8 has been in horses for more than 40 years," Donis notes. "In all this time, there has not been a single documented case of human infection. On the other hand, dogs have been living next to horses for the same period of time, and they didn't catch the equine flu virus until now. The reality is, we just don't know."

say, is transmissibility within a species. Peter Palese, a virologist at Mount Sinai School of Medicine, in New York, has lots of questions in that regard: "What makes an influenza virus transmissible from human to human? What are influenza's rules for this transmission? And how can we study it in the lab, using animal models?" He acknowledges that "we just don't have good answers right now."

HHMI investigator Stephen Harrison, a structural biologist at Harvard Medical School, adds that these questions require scientists to blend different approaches. "To understand influenza's molecular evolution, we must rephrase natural history questions in molecular terms," Harrison says. "In other words, we have to capture that moment when a virus jumps to a new species, and learn the detailed dynamics of viral infection."

If H5N1 did trigger a human flu pandemic, the World Health Organization (WHO) estimates it could kill anywhere from 5 million to 150 million people, although WHO says a valid prediction is possible only after a pandemic begins. Even at the lower end of that range, the numbers are astounding; public health officials cannot afford to wait for influ-enza to reveal its secrets. The National Institute of Allergy and Infectious Diseases (NIAID) has contracted with two companies to develop H5N1 vaccines.

One of the companies, Sanofi Pasteur, has already demonstrated the feasibility of an H5N1-specific vaccine in preliminary clinical trials of a vaccine candidate. The other company, MedImmune, announced in September that it will collaborate with NIAID scientists to systematically develop a library of vaccines for all 16 influenza virus HA subtypes. And an H5N1 vaccine is on the list. ■

PANDEMIC PROTECTION: BUILD HIGHER LEVEES, NOW

INFLUENZA RESEARCHERS ARE KNOWN to disagree on the finer points of avian flu, including just how great a threat it may pose to human beings. But the scientists are virtually unanimous on one point: Should this flu cause a pandemic, the world is not prepared for it. "The science is way ahead of the political will to solve these problems," says Robert G. Webster of St. Jude Children's Research Hospital in Memphis.

At a September influenza briefing on Capitol Hill sponsored by HHMI and the Center for Strategic and International Studies, Webster and several other researchers highlighted the importance of stockpiling influenza drugs, modernizing vaccine production, and planning for a worldwide disaster.

For many, it was a familiar refrain. "Ten years ago, I attended an influenza-pandemic preparedness meeting with some of the same people in this room," says Dominick Iacuzio, medical director at the pharmaceutical company Hoffman–La Roche, at the briefing. "Here we are again a decade later, still talking about being prepared."

Along the way, the scientists have actually made significant progress—in science. Hoffman–La Roche has released the antiviral drug Tamiflu (oseltamivir phosphate), designed to alleviate flu symptoms if taken early in the illness. Webster has probed the molecular biology and epidemiology of the H5N1 avian flu strain. Briefing participant Peter Palese of Mount Sinai School of Medicine and collaborators have reconstituted the 1918 flu strain to reveal its molecular secrets. And attendee Robert A. Lamb, an HHMI investigator at Northwestern University, has discovered the function of important elements of the replicating influenza virus. Other scientists have made similarly impressive gains.

Yet science can only go so far. "At the end of the day, public policy and government planning will make the difference," says Lamb. "European countries and Australia have done a much better job than the United States at stockpiling Tamiflu, for instance. In the U.S., all the available drugs would probably go to Congress and specific primary-care providers. What would happen if 20 percent, or 5 percent, or even 1 percent of Americans got sick?"

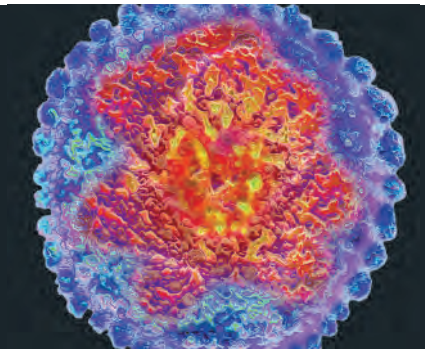
In one revealing moment at the September briefing, when an audience member pointedly asked the panel of scientists how the United States would cope with an influenza pandemic, they replied that the U.S. Department of Homeland Security (DHS) would ultimately be responsible for coordinating the day-to-day management of the crisis. To slow the flu virus's spread, they suggested, DHS might close schools and offices, shut down public transportation, and basically send the country home.

Weeks after the briefing, Webster reflected on this scenario and felt a lot less sanguine. Americans have since lambasted the federal government, including DHS, for its uneven response to the devastating Hurricane Katrina on the Gulf Coast. "There are so many indicators that a pandemic is brewing," says Webster. "We really can't be caught short. As in New Orleans, our levees have got to be built higher."

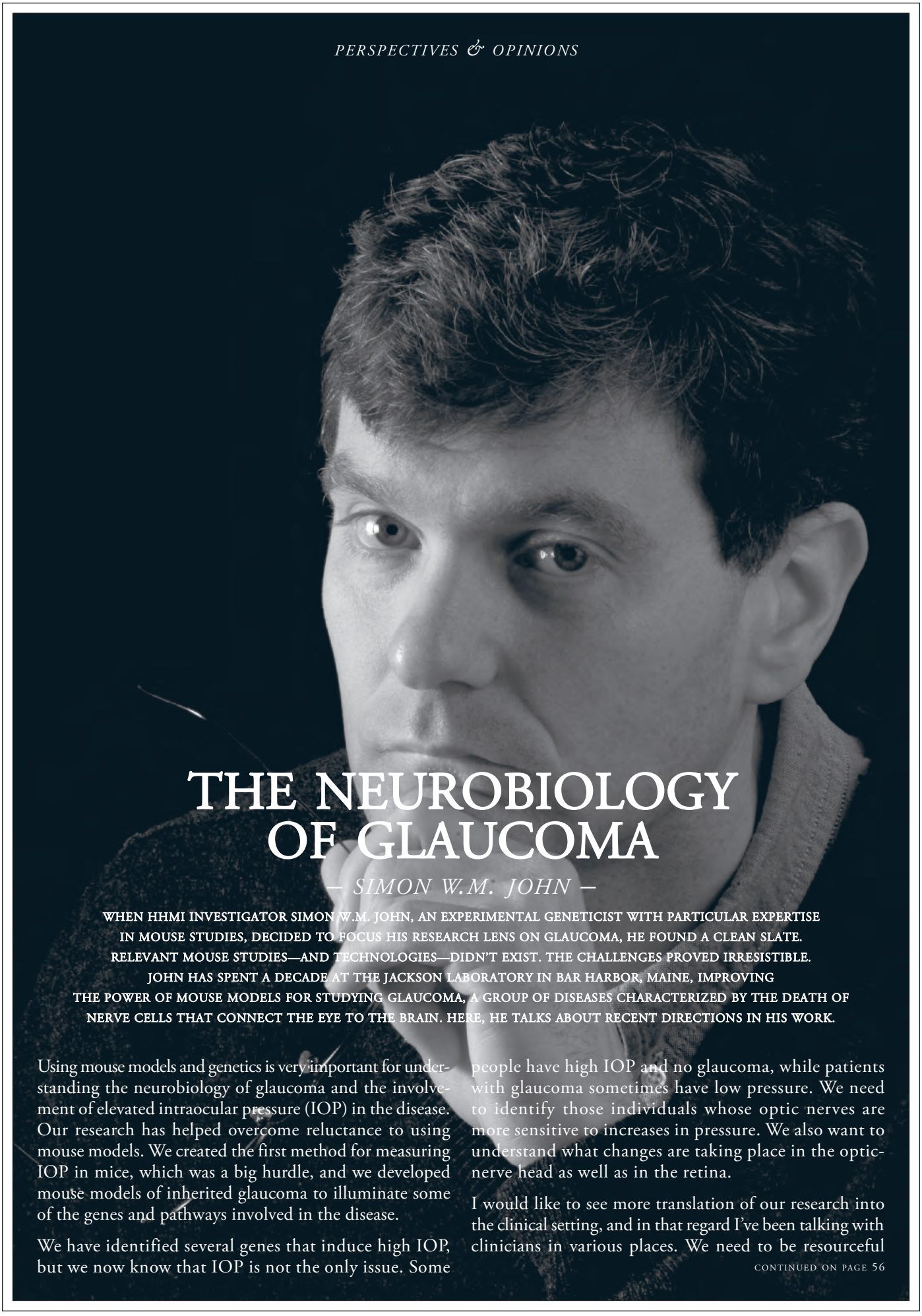
READY OR NOT

Influenza scientists widely agree on one point: The world is not prepared for a flu pandemic. Scientists have expressed concern that public policy lags the need for action. As Peter Palese of Mount Sinai School of Medicine says: "We have markets for F16 fighters, but not vaccines."

Currently, no vaccine is available to protect humans against the avian virus known as H5N1 (right). According to the Centers for Disease Control and Prevention, research studies to test a vaccine to protect humans against H5N1, which is known to have infected people in southeast Asia, began in April 2005.



JAMES CAVALLINI / PHOTO RESEARCHERS, INC.



THE NEUROBIOLOGY OF GLAUCOMA

— SIMON W.M. JOHN —

WHEN HHMI INVESTIGATOR SIMON W.M. JOHN, AN EXPERIMENTAL GENETICIST WITH PARTICULAR EXPERTISE IN MOUSE STUDIES, DECIDED TO FOCUS HIS RESEARCH LENS ON GLAUCOMA, HE FOUND A CLEAN SLATE. RELEVANT MOUSE STUDIES—AND TECHNOLOGIES—DIDN'T EXIST. THE CHALLENGES PROVED IRRESISTIBLE. JOHN HAS SPENT A DECADE AT THE JACKSON LABORATORY IN BAR HARBOR, MAINE, IMPROVING THE POWER OF MOUSE MODELS FOR STUDYING GLAUCOMA, A GROUP OF DISEASES CHARACTERIZED BY THE DEATH OF NERVE CELLS THAT CONNECT THE EYE TO THE BRAIN. HERE, HE TALKS ABOUT RECENT DIRECTIONS IN HIS WORK.

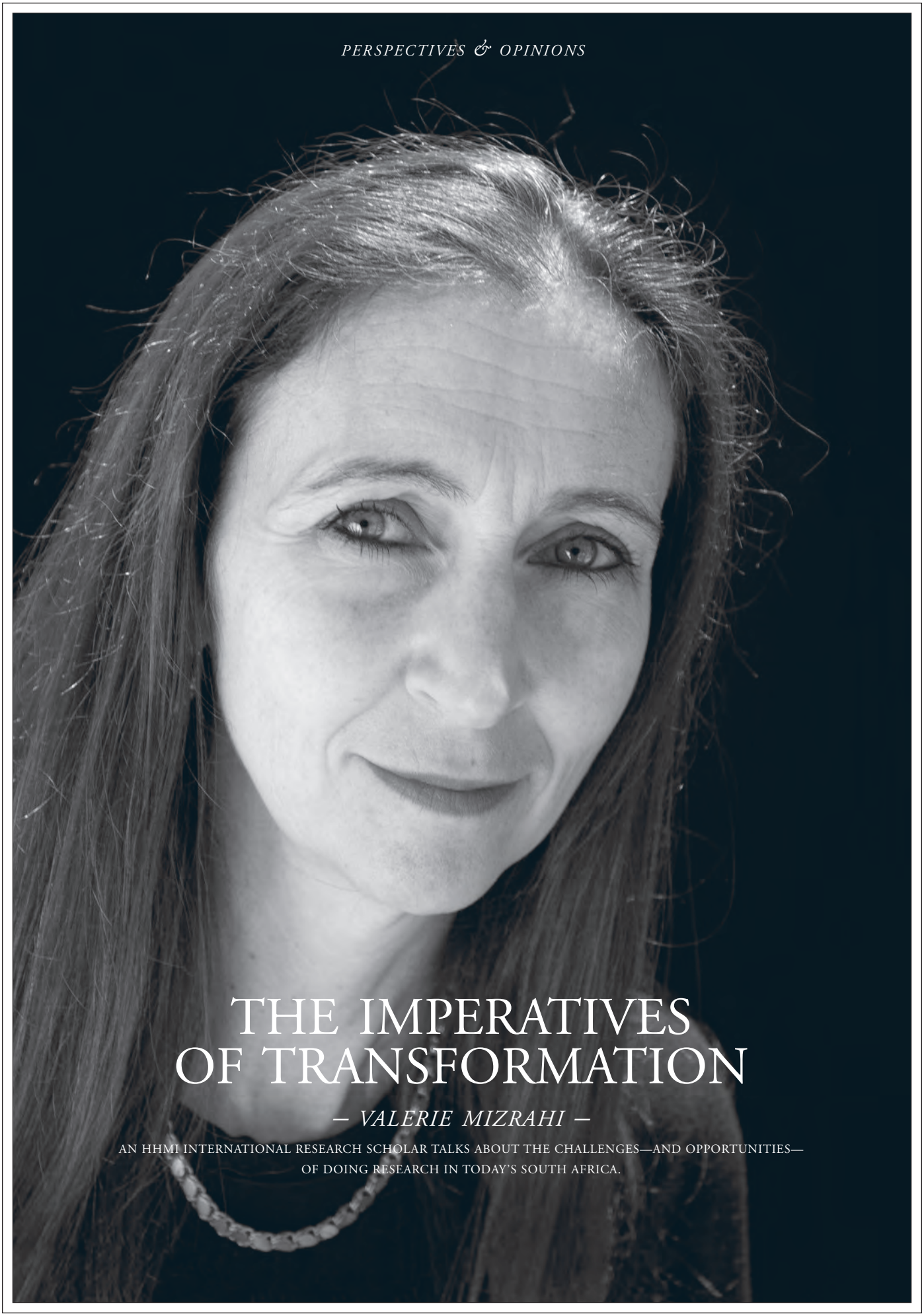
Using mouse models and genetics is very important for understanding the neurobiology of glaucoma and the involvement of elevated intraocular pressure (IOP) in the disease. Our research has helped overcome reluctance to using mouse models. We created the first method for measuring IOP in mice, which was a big hurdle, and we developed mouse models of inherited glaucoma to illuminate some of the genes and pathways involved in the disease.

We have identified several genes that induce high IOP, but we now know that IOP is not the only issue. Some people have high IOP and no glaucoma, while patients with glaucoma sometimes have low pressure. We need to identify those individuals whose optic nerves are more sensitive to increases in pressure. We also want to understand what changes are taking place in the optic-nerve head as well as in the retina.

I would like to see more translation of our research into the clinical setting, and in that regard I've been talking with clinicians in various places. We need to be resourceful

CONTINUED ON PAGE 56

JOSE AZEL



THE IMPERATIVES OF TRANSFORMATION

– VALERIE MIZRAHI –

AN HHMI INTERNATIONAL RESEARCH SCHOLAR TALKS ABOUT THE CHALLENGES—AND OPPORTUNITIES—OF DOING RESEARCH IN TODAY'S SOUTH AFRICA.

LOUISE GUBB

Valerie Mizrahi—a professor at the University of the Witwatersrand Medical School in Johannesburg and director of the Molecular Mycobacteriology Research Unit of the South African Medical Research Council—is an HHMI international research scholar and one of South Africa's most outstanding scientists. The African recipient of a UNESCO-L'Oréal *For Women in Science* Prize in 2000, awarded annually to one woman scientist from each continent, she recently was named co-director of a new Centre of Excellence for Biomedical TB Research—one of six such centers funded by the South African government and the only one devoted to health sciences.

Mizrahi studies the mechanisms of DNA metabolism and resuscitation in *Mycobacterium tuberculosis*, the organism that causes human TB. M. tuberculosis has a remarkable ability to adapt to adverse conditions and persist in a dormant state from which it can reactivate to cause disease. By better understanding these mechanisms, she hopes to enable of more effective tools for TB control to be developed.

HHMI: *WHAT IS THE GREATEST CHALLENGE FACING SCIENCE AND SCIENTISTS IN SOUTH AFRICA?*

VM: To become a leading African country in science and technology as well as compete meaningfully in the rest of the world, we must find ways to overcome the legacies of apartheid, particularly the enormous inequities in access to high-quality schooling. We need to prepare all South African students to be internationally competitive, and we need to create conditions so that people will want to stay and do serious science.

HHMI: *ARE YOU INVOLVED IN EFFORTS TO CHANGE THINGS ACCORDINGLY?*

VM: Yes, by trying to help level the playing field for talented black Africans and women. My mentoring philosophy is to provide as stimulating and supportive an environment as possible so that gifted and motivated students may realize their potential. And because I want them, as part of that goal, to be equipped to do internationally competitive science, every Ph.D. student in my lab is given the opportunity to travel abroad at least once during his or her doctoral studies. In that way, students can present their work at a conference, for example, or work in a collaborating lab.

HHMI: *YOU OFTEN REFER TO THE "TRANSFORMATION IMPERATIVE." WHAT IS THAT?*

VM: The practice of science in South Africa is still dominated by white males. I believe it is imperative to transform South African science in order to create opportunities for gifted black Africans and women. In my own lab, 80 percent of the scientists are women and 30 percent are black South Africans.

HHMI: *THE SOUTH AFRICAN GOVERNMENT RECENTLY NAMED YOUR LAB AS ONE OF TWO PARTNERING LABS IN THE NATIONAL CENTRE OF EXCELLENCE FOR BIOMEDICAL TB RESEARCH, ONE OF SIX SUCH CENTERS IN THE COUNTRY AND A GREAT HONOR. WHAT DOES THIS MEAN, AND HOW DOES IT CHANGE THINGS?*

VM: It is a very important statement by the government that it plans to invest in lab-based science, significantly and over the long term—the funding is for up to 10 years and totals several million dollars. And the university had to commit to matching a part of that amount. I was able to hire two researchers and an administrative assistant. For the first time in years, I'm more free to do science.

HHMI: *WHAT IS LIFE LIKE FOR A WHITE SOUTH AFRICAN IN JOHANNESBURG TODAY?*

VM: The country is undergoing massive changes, and as such it is a very exciting place for people who see themselves being part of the "New South Africa," which I do. When I think back on how things have changed since I was a student in apartheid South Africa in the 1980s, I realize how much better life is today for all of us. We live in a free and democratic society protected by a remarkable Constitution. I've watched my children grow up without the overwhelming burden of guilt that I felt as a privileged white child.

HHMI: *DO YOU FEAR FOR YOUR OWN AND YOUR FAMILY'S AND STUDENTS' SAFETY?*

VM: Johannesburg is a big, bustling city with a very high level of crime. This limits one's personal freedom

CONTINUED ON PAGE 56

Apart from professional literature, what books are you reading now?

SCIENTISTS CAN READ THE LETTERS A, T, C, AND G—THAT UBIQUITOUS ALPHABET FOR EVERY ORGANISM'S GENETIC CODE—FOR ONLY SO LONG. BETWEEN LAB EXPERIMENTS OR LATE IN THE EVENING, HHMI INVESTIGATORS REACH FOR A WIDE RANGE OF BOOKS. HERE, THEY OFFER A PEEK AT THE STACKS ON THEIR BEDSIDE TABLES.

-Edited by Kathryn Brown-

BRIAN W. MATTHEWS
PROFESSOR OF PHYSICS,
UNIVERSITY OF OREGON

"My family and friends frequently recommend books, and that's where I get my reading list. I've recently read Devil in the White City by Erik Larson, You Cannot Be Serious by John McEnroe, Bobos in Paradise: The New Upper Class and How They Got There by David Brooks, and A Voyage for Madmen by Peter Nichols."

LEE NISWANDER
PROFESSOR OF PEDIATRICS,
UNIVERSITY OF COLORADO

"When I was a child, The Hobbit and Lord of the Rings by J.R.R. Tolkien were my favorite stories. Now I'm reading them with my son—and he's enjoying them as much as I did. I've also been reading Dan Brown's The Da Vinci Code and Angels & Demons. They're fun, fast-reading novels. I wanted to find out what all the hype is about!"

EVA NOGALES
ASSOCIATE PROFESSOR OF MOLECULAR AND CELL BIOLOGY,
UNIVERSITY OF CALIFORNIA, BERKELEY, AND
LAWRENCE BERKELEY NATIONAL LABORATORY

"I am reading El Quijote (Don Quixote). It has been 400 years since the first edition, and I got the most recent version, which is annotated, from the Cervantes Institute in Spain. I'm also reading a historical novel, from a collection called El Capitan Alatriste, about a former soldier who became a hero of Spain's 16th-century imperial wars. This collection was recommended to me by another HHMI investigator—Carlos Bustamante."

RANDY SCHEKMAN
PROFESSOR OF MOLECULAR AND CELL BIOLOGY,
UNIVERSITY OF CALIFORNIA, BERKELEY

"I like history, particularly biography. I recently finished American Prometheus, about Robert Oppenheimer. I'm just starting 1776, by David McCullough. I'm also a sucker for Garrison Keillor, who is my favorite humorist. This summer I read his Lake Wobegon: Summer 1956, and one of his short-story anthologies."

LEARN MORE ABOUT THESE INVESTIGATORS ONLINE
www.hhmi.org

MATTHEWS: PAUL FETTERS, *NISWANDER*: JASON TANAKA BLANEY, *NOGALES*: ROY KALTSCHIDT/LAWRENCE BERKELEY NATIONAL LAB, *SCHEKMAN*: BARBARA RIES

INSTITUTE NEWS PG. 42
Construction Update: Janelia Farm Research Campus / Turning Science Education Rightside Up / Janelia Farm Announces a Graduate Track

SCIENCE EDUCATION PG. 46
Bringing the Sizzle to Science in the Schools / Interdisciplinary Crosstalk

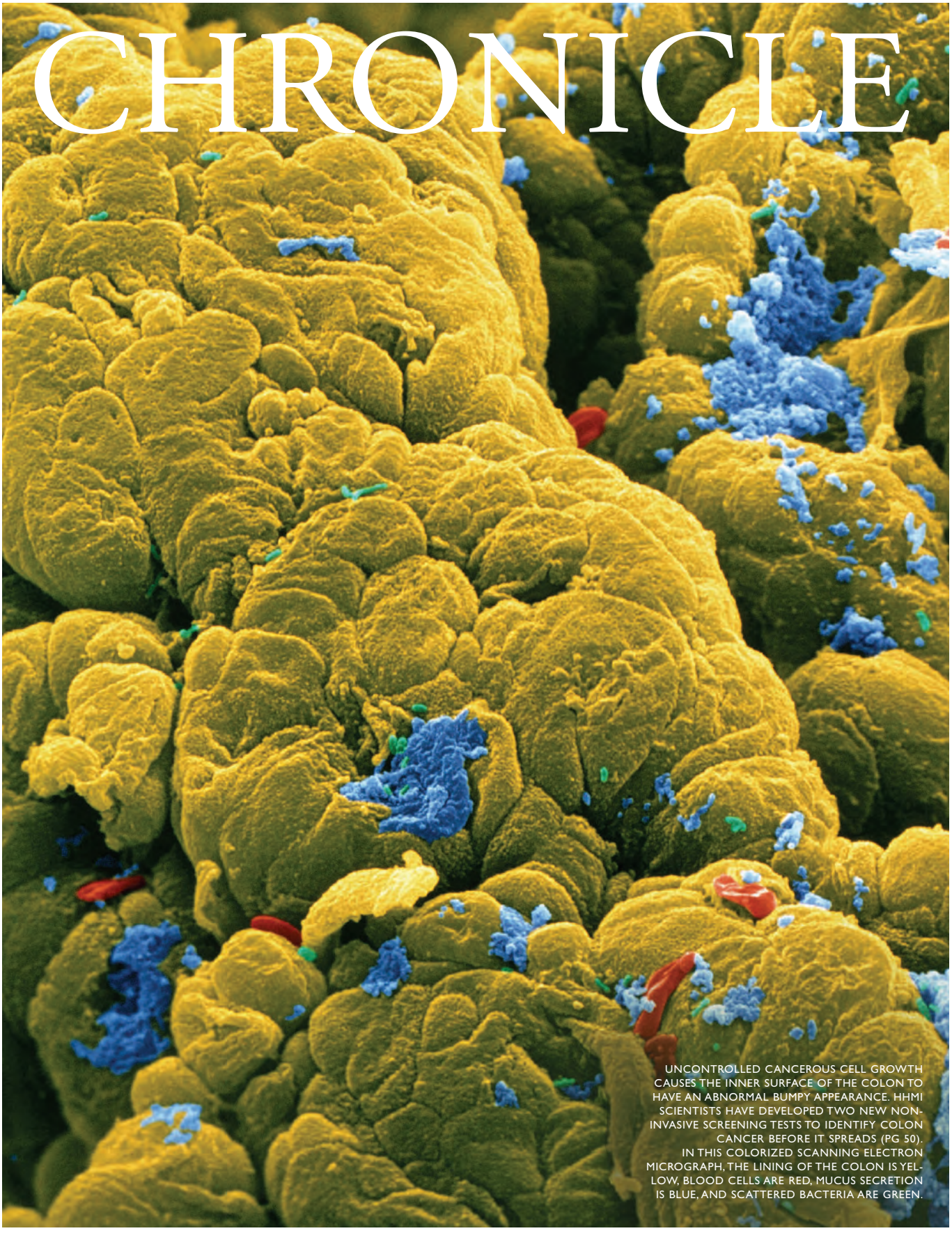
LAB BOOK PG. 48
Coordinated Genes / Developing an Easier Screen for Colon Cancer / The Fate of Brain Cells

EXCERPTS PG. 51
Ask A Scientist

TOOL BOX PG. 52
DReAMM Scheme

NOTA BENE PG. 54
News of recent awards and other notable achievements

CHRONICLE



UNCONTROLLED CANCEROUS CELL GROWTH CAUSES THE INNER SURFACE OF THE COLON TO HAVE AN ABNORMAL BUMPY APPEARANCE. HHMI SCIENTISTS HAVE DEVELOPED TWO NEW NON-INVASIVE SCREENING TESTS TO IDENTIFY COLON CANCER BEFORE IT SPREADS (PG 50). IN THIS COLORIZED SCANNING ELECTRON MICROGRAPH, THE LINING OF THE COLON IS YELLOW, BLOOD CELLS ARE RED, MUCUS SECRETION IS BLUE, AND SCATTERED BACTERIA ARE GREEN.

EYE OF SCIENCE / PHOTO RESEARCHERS, INC.

JANELIA FARM UPDATE

The Shape of Things to Come

An army of workers hustles to complete this imaginatively designed research facility on schedule.

A year from now, the corridors and labs of the Janelia Farm Research Campus will be swarming with scientists. Today, however, the site swarms with carpenters, electricians, metal workers, and others with construction know-how, all bearing down to complete the facility for the fall 2006 opening.

Text by Mary Beth Gardiner | Photography by Paul Fetters

ABOVE_ The low-rise, terraced "landscape" building—a glass-filled structure that snakes along a hillside overlooking a small lake—will be home to researchers' laboratory and office space as well as to administrative, meeting, and dining areas. Two arching steel-and-glass stairways span the three floors of the building, providing visual as well as physical access—and enhancing the sense of openness and accessibility.

A short walk away, a semicircular "hotel" for conference attendees is also taking shape. An underground tunnel will connect the landscape building to the two-story conference-housing structure, which will include space for social gatherings and a fitness center. Just beyond, longer-term housing for visiting scientists—from studio to four-bedroom apartments clustered around a central open-air pedestrian area—nears completion.

ABOVE_ Electricians wire an intricate lighting grid in the ceiling of the main auditorium, located on the first floor of the landscape building. This circular 250-seat room will be the central spot for official gatherings, including many of HHMI's regular science meetings.

ABOVE_ Dawn's first light is enough to set things in motion at the Janelia Farm construction site. In the foreground, vertical supports outline the units of the hotel-like conference-housing structure. Just behind, the three-tiered landscape building climbs the hillside. The sweep of the building's two feature stairways adds flourish to the rhythm of the regularly spaced square office pods that line the rooftops of the second and third floors.

LEFT_ More than 1.1 million feet of data cable for computers and telephones are being strung through the ceilings and floors of the landscape building. The cable will feed 1,865 user outlets in the building, with the capacity to support 5,460 devices.

Turning Science Education Rightside Up

A new HHMI-supported science academy for high school students puts first things first.

AS 84 HIGH SCHOOL STUDENTS AT THE Loudoun County Academy of Science conduct science experiments this year, they will be in the forefront of an even bigger experiment. The students are part of a program that's recasting the way high school science is taught.

The Loudoun County Academy of Science—in northern Virginia, where HHMI is building its Janelia Farm Research Campus—opened its doors to 62 freshmen and 22 seniors when school started in September. Its six teachers include a physicist, a chemist, a biologist, an environmental scientist, and two mathematicians. Accomplished educators, most also have professional experience in their field beyond the classroom. The academy is one of several Loudoun County education programs supported by a $1 million a year grant from HHMI.

The academy curriculum is turning traditional science education upside down, and director George Wolfe is proud of that fact. Wolfe came to Loudoun County from an inner city school in Rochester, New York, where a similar program he helped to pioneer helped earn the school a national ranking in Newsweek for the number of students enrolled in advanced placement and international baccalaureate courses. "We've been doing it backwards," he says. "Most schools teach earth science, then biology, then chemistry, and then physics, if the students even get to physics."

At the Loudoun science academy, freshmen and sophomores begin with a 2-year curriculum that integrates earth science, physics, and chemistry with math. Then, with a fundamental understanding of the physical sciences and the math that supports them, students will take biology as juniors.

Wolfe strongly advocates this approach. "Physical science is the application of math to data, and you can't do biology without a grounding in physics and chemistry," he argues.

Odette Scovel, science instructional supervisor for the Loudoun County Public Schools (LCPS), agrees. "I think a lot of teachers would teach this way if they were given a choice," she says.

ABOVE_IN LOUDOUN COUNTY, VIRGINIA—CLOSE TO HHMI'S JANELIA FARM RESEARCH CAMPUS—ODETTE SCOVEL AND GEORGE WOLFE EXPERIMENT TO RECAST HIGH SCHOOL SCIENCE EDUCATION.

> "We've been doing it backwards. Most schools teach earth science, then biology, then chemistry, and then physics, if the students even get to physics."
>
> GEORGE WOLFE

The classes all are inquiry-based, which Wolfe defines as "kids figuring out what the question is before they look for the answer." This approach, he adds, "is crucial to great science teaching and learning."

The integrated physical sciences curriculum of the first 2 years will be team-taught by all the academy teachers. "It's going to be a collaborative effort," Wolfe explains. "Bench scientists do it all the time, but teachers don't usually have the opportunity."

Because it takes a special kind of teacher to teach that way, Wolfe and the LCPS staff conducted a nationwide search for faculty. They found three already teaching in the Loudoun County schools: James Bond, who taught physics; Jennifer Andrews in environmental science; and Diana Virgo, a math teacher. The others are Dick Sisley, who came from California, and Linda Gulden and Jacqueline Curley from other districts in Virginia. "The challenge," Wolfe says, "was to find educators diverse enough to teach all these subjects or flexible enough to pick them up."

Although the science academy is an unknown quantity, and to attend, some students have to ride a school bus up to an hour and a half round-trip to Dominion High, where the academy is housed, there were 205 applicants for the freshman slots. The students spend alternate days at the academy, taking their nonscience classes at their home high schools, where they can also participate in sports and other activities. (When the present freshmen are sophomores next year, cohorts of juniors and seniors, in addition to another freshman class, will have been recruited.)

PAUL FETTERS

From the beginning of their freshman year, students begin to learn research and writing skills commensurate with high-quality research. In their sophomore year, they begin to take specialized research courses leading to independent studies in topics of their choice during their junior and senior year, under the mentorship of one of the teachers. Throughout their years at the academy, each student will have the same teacher/adviser, who will also be a liaison with the student's family. "With small classes, group teaching, and the unique advisory role of the teachers, we hope that a science academy family will develop," says Wolfe.

HHMI support enabled the academy to purchase, among other equipment, a "Smart Board" for each classroom—a computer-driven, interactive, white board linked to student laptops by a wireless network. Similarly, the labs will have microscopes with video capabilities and equipment to carry out research in DNA technology.

With technology as with curriculum, however, Wolfe is determined that his students learn to walk before they try to run. "We're dedicated to keeping the technology simple until the kids master the concepts behind it," he says. "I want them to know how to graph before they do it with a "black box."

Wolfe, guidance director Jayne Fonash, and the teachers firmly believe that the Loudoun County Academy of Science could become a model for high school science education. HHMI will be observing the progress closely,

CONTINUED ON PAGE 56

JANELIA FARM UPDATE

Janelia Farm Announces a Graduate Track

HHMI and two major research universities join forces in a unique program.

IN SEPTEMBER, HHMI'S JANELIA FARM RESEARCH CAMPUS established partnerships with the University of Cambridge and the University of Chicago to launch an interdisciplinary graduate program. The program aims to attract a small number of outstanding graduate students who will benefit from doing their Ph.D. dissertation research in the collaborative environment at Janelia Farm.

When Janelia Farm—HHMI's first freestanding research facility—opens in the summer of 2006, resident and visiting scientists will focus on two main goals: identifying the general principles that govern how neuronal circuits process information, and developing imaging technologies and associated analytical methods.

The small size of the research groups and the highly interactive culture planned for Janelia Farm will provide a strong training and mentoring environment for graduate students, says Kevin Moses, the facility's associate director for science and training. "At the same time, Ph.D. students will add to the vitality of Janelia Farm. Graduate students often provide a unique perspective, communicating across unexpected lines and initiating innovative avenues of collaborative research."

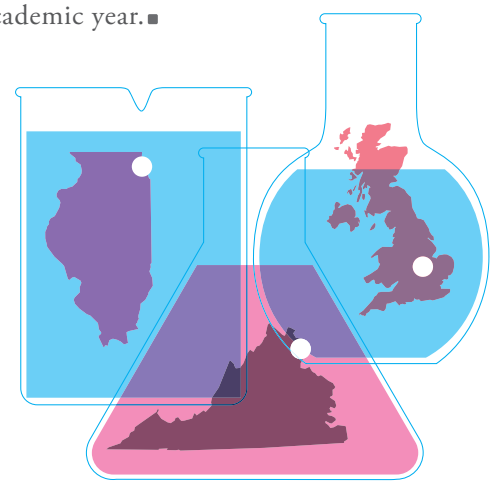
The new program, moreover, will allow students to benefit from Janelia Farm's unique research environment as well as both universities' outstanding academic resources. "The University of Cambridge has a longstanding history of major contributions to the biological sciences," says Roger Keynes, a reader in neurobiology at Cambridge and director of the Cambridge/Janelia Farm joint graduate program. "This highly innovative collaboration will give students the benefit of the university graduate-training facilities, coupled with access to the state-of-the-art labs at Janelia Farm."

The joint training partnership between HHMI and the University of Chicago's division of the biological sciences will be administered through Chicago's new Interdisciplinary Scientist Training Program, led by HHMI investigator Harinder Singh. That program features flexible training and diverse faculty participation and will grant jointly trained students a Ph.D. in biology.

"As biologists we are always drawn to bold innovative experiments and thus are delighted with this collaboration with HHMI, which fits squarely into such a category," says James Madara, dean of the biological sciences division and university vice president for medical affairs at the University of Chicago.

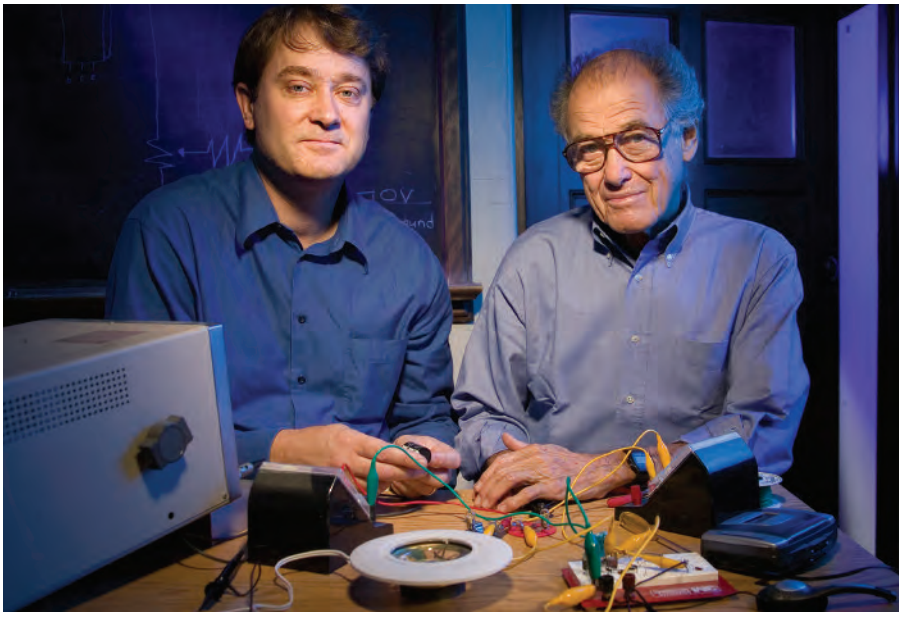
Each student will have two advisers—a Janelia Farm group leader and a faculty member at the partner university—who will work together to develop an individualized education plan. The two universities will provide the academic training required to support this interdisciplinary program. Students will generally spend their first year at the home university, pursuing academic courses and perhaps commencing a collaborative research project; the remaining years of their dissertation research will be at Janelia Farm. It is expected that they will earn their degree, awarded by the partner university, in 4 to 5 years.

The first class of graduate students will enter the program in the fall of 2007 after recruitment during the 2006–2007 academic year. ■



Bringing the Sizzle to Science in the Schools

This innovative program nurtures the natural scientist that's in all students.



ABOVE_ SCOTT PHELPS, LEFT, A HIGH SCHOOL SCIENCE AND MATH TEACHER, COLLABORATES WITH JERRY PINE, DIRECTOR OF A CALTECH PROGRAM TO IMPROVE SCIENCE EDUCATION IN THE SCHOOLS.

A STATELY MANSION ON A TREE-LINED street in Pasadena is the unlikely nerve center of a national effort to transform the way science is taught to America's youngsters. While the once-grand house at the edge of the California Institute of Technology campus has seen better days, there's nothing dated about the program it houses. The Caltech Precollege Science Initiative (CAPSI) aims to make science appealing to all students, not merely to those who plan to pursue science-related careers.

"Every student should have a quality science education—it shouldn't be just for the elite," says Wayne Snyder, project director at CAPSI. "Children are natural scientists. If they are nurtured, they will become scientifically literate citizens. But if science instruction is minimal or consists of being force-fed rote facts, kids get turned off."

Funded in part by grants from HHMI and the National Science Foundation, CAPSI is the brainchild of two Caltech professors, Jerry Pine and Jim Bower. CAPSI builds on Project SEED (Science for Early Educational Development), which Pine and Bower founded after noting with dismay the lack of decent science education programs in Pasadena's elementary schools. Starting in 1984, the pair worked in tandem with teachers and administrators in the school district to develop an innovative and successful science program for the city's youngest students (see sidebar).

But Pine, Bower, and colleagues noted that when SEED graduates moved on to junior high and high school, there wasn't a corresponding program for them in Pasadena. So they decided to create courses for grades 7 and 8. They expected not to have to reinvent any wheels. "Initially we thought we'd find a good secondary-school program somewhere else and use it as our model," says Snyder. But then, he says, they found that "there were no good programs."

Consequently, they had to start virtually from scratch. It took nearly 9 years to finish a project they originally thought would take 3. But this fall, CAPSI finally unveiled its first four units for secondary schools. The Matter and Forensic Chemistry module allows students to form a mini-CSI (crime-scene investigation) squad and do chemistry experiments to solve their cases. The Human Body Under Attack unit enables students to study bodily processes such as digestion, respiration, and circulation, as well as their delicate interplay. The Microbia module focuses on the world of microorganisms, and the Forces & Rocketry unit looks at Newton's laws of motion in the real world. Each module gives students 6 to 8 weeks of intensive hands-on science investigations.

Early next year, three more modules should debut, focusing on areas such as vision and hearing, force and motion, and electrical circuits. "The trick is making something advanced enough for eighth graders," says Snyder, "but easy enough so that all levels can succeed."

CAPSI has also developed inquiry-based science courses for in-service and pre-service teacher education, and it has established a nationally known science-education research group (see www.capsi.caltech.edu).

CAPSI staff's concerns aren't merely academic. If the upcoming generation doesn't have an appreciation for or interest in science, they point out, there could be a shortage of scientists and engineers, with serious consequences for the nation's economy.

"Will we be farming out all our science and technology along with manufacturing?" asks Pamela Aschbacher, CAPSI's director of research. "As it stands now, we haven't brought along nearly enough of our own." CAPSI and other programs like it, she and her colleagues believe, may help turn things around. ■

-Linda Marsa-

BACK STORY

SEED, which includes units on biology, physics, and earth science, is an inquiry-based program, meaning that it emphasizes hands-on experimentation as a way of exposing children to the scientific method, and it brought in scientists and engineers from the community as collaborators. By 1994, the pilot program was so successful that all of Pasadena's elementary schools had adopted it; later, 12 other poor and predominantly minority districts throughout the state also adopted the program. The innovative curriculum has since become a widely copied model.

STEVE LABADESSA

Interdisciplinary Crosstalk

Needed: "Bilingual" scientists to help biologists and engineers communicate.

DANNIE DURAND, NOW A PROFESSOR AT CARNEGIE MELLON University, remembers sitting down to breakfast at the Marine Biological Laboratory in Woods Hole, Massachusetts, during a workshop on molecular evolution. Her classmates were discussing one of their favorite single-celled organisms, radiolarians, a family of marine plankton that take on a variety of geometric forms. Durand was unfamiliar with them. "Are they protists?" she asked, referring to a class of organisms that cannot be classified as animal, plant, or fungus but that exhibit characteristics of all three.

The table went silent. "Do you work on mammals?" someone asked—perhaps the ultimate put-down from an organismal biologist.

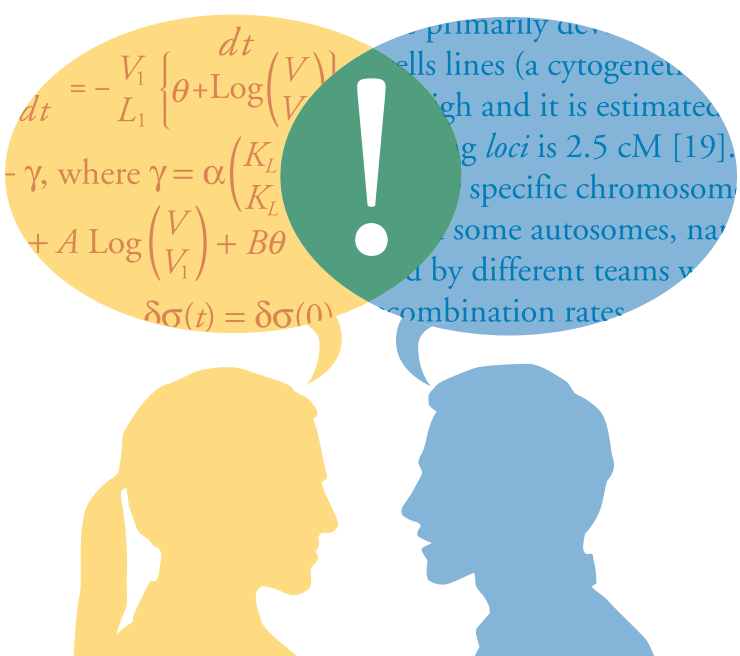
"No, I'm a computer scientist trying to learn to be a computational biologist," Durand replied.

"Oh, that's all right then," her challenger conceded.

Biologists, computer scientists, and engineers speak different languages. Mention "vector" to a molecular biologist and a plasmid (a circular piece of bacterial DNA used in gene cloning) comes to mind. Say "vector" to an engineer, and she thinks of a mathematical concept. Similarly with "expression":
To a biologist, it means protein production from a gene; to an engineer, it's an equation.

This communications divide is becoming more of a problem now that research so often requires collaboration across disciplines. One-third of the engineers at the Massachusetts Institute of Technology now work on biological problems, according to MIT biology professor Graham C. Walker. Yet it can be challenging for biology and engineering students to understand each other.

The divide, deeper than mere semantics, can touch on basic cultural differences, he says. "Even among top-level scientists, our fundamental ways of conducting inquiry differ, depending on our interests and training."



DANIEL FAZER

Teaching introductory biology, Walker experiences the disciplinary disconnect firsthand. "It's a constant challenge," he says, "to find ways to make biology comprehensible and relevant to students who think like engineers."

As an HHMI professor—1 of 20 research scientists nationwide who received $1 million each from HHMI to find innovative ways to stimulate undergraduates' interest in science—Walker is ever on the lookout for solutions to this problem. Last spring he invited Mary E. Lidstrom, a fellow HHMI professor, to MIT to discuss how she grapples with it at the University of Washington.

Lidstrom, who teaches a biology class for engineers, has found that biologists are motivated by the "what" while engineers are motivated by the "how." She told a packed room at MIT that "engineering students tend to view biology as magic because they don't see us using differential equations. And often they don't even necessarily want to understand the 'what' of biology—they just want to use it."

"So we actually teach biology to engineers using a function-based approach, with the idea of nature as the designer and evolution as the design tool," Lidstrom says. "That's real engineering. And that's the way we feel biology should be taught—start with how it works, then talk about the parts."

To help her engineering students feel comfortable in this strange new territory, she says, "We talk about the functions of life, about information transfer, about adaptability. Engineers understand systems, and ecology is the perfect example of a system."

But while Lidstrom's approach may be useful for engineering students, says Julia Khodor, a graduate student who helps teach Walker's introductory biology course at MIT, it may be limited to engineering students. "Because our lectures need to reach all students, regardless of background," she says, "they are likely to remain mostly in the language of biology."

Lidstrom suggests an option—in effect, double majors. "The new research workforce will always need people firmly based in the core disciplines of biology and engineering," she says, "but it also needs translators who have the understanding and the tools to communicate about the other field."

Douglas A. Lauffenburger, a biological engineer who helped develop MIT's new major in that field, agrees. "The world of science keeps expanding," he says. "For a synthesis to be effective, we have to educate a third kind of person—a 'bilingual' one." ■

-Kathleen Cushman and Jennifer Boeth Donovan-

The Fate of Brain Cells

New technique tracks the long life of neural stem cells.

A FOUNTAIN OF YOUTH SPRINGS FROM WITHIN THE BRAIN OF every mammal, report HHMI investigator Alexandra L. Joyner and her former postdoctoral associate Sohyun Ahn in the October 6, 2005, issue of *Nature*. No, the two researchers haven't unlocked the secret to immortality. But their discovery of a method to visualize an elusive population of stem cells that has the potential to regenerate nerves and other brain cells may explain how certain regions of the brain rejuvenate themselves. Moreover, the findings may allow researchers to tap the revitalizing powers of stem cells for repairing injured and diseased brain tissue.

Two regions of the mouse brain—the hippocampus, which controls short-term memory, and the olfactory bulb, which processes odors—contain neurons that are continually replenished throughout adult life. Some neurobiologists have thought that these fresh brain cells arise from a population of rapidly dividing but short-lived stem cells called transient amplifying cells, but others have proposed that these cells must derive from infrequently dividing "quiescent neural stem cells" lurking within the brain. Indirect evidence has hinted that such quiescent cells do exist, but, until now, says Joyner, no one had effectively pinpointed the cells in living brains.

Ahn and Joyner, working at New York University's Skirball Institute of Biomolecular Medicine, devised a method to mark all stem cells and their descendants in the brains of live laboratory mice over the animals' lifetimes. After marking the stem cells, the researchers administered a drug called AraC, which efficiently kills only rapidly dividing brain cells. "We killed off the transient amplifying cells and then showed that there is another population of cells still capable of replenishing," Joyner explains. "And then we did it a year later. We killed off the transient amplifying cells again, and the cells we had marked the year earlier could still replenish," proving the existence of long-lived quiescent stem cells in living animals.

Because the normal life span of a mouse is only about 1 year, the results imply that the quiescent stem cells survive throughout the life of the animal. "The idea in humans is that they would lie mostly dormant for 80 years," says Joyner.

Now she wants to learn how to harness the cells for regenerating new tissue types. "If we could infuse the right type of growth factors into the brain after injury or disease, perhaps we could mobilize them to do more than what they normally do."

Some other potential applications may involve selective destruction rather than harnessing, as Joyner says that similar stem cells elsewhere in the body may be involved in spreading cancer. "There's this idea that there are stem cells in cancers, the ones that allow aggressive tumors to escape therapies. There may be quiescent stem cells in cancers, which produce the rapidly dividing cells that eventually are lethal." ■

~ Paul Muhlrad ~

IN BRIEF

LEARNING HOW SARS SPIKES ITS QUARRY

Researchers have determined the first detailed molecular images of a piece of the spike-shaped protein that the SARS virus uses to grab host cells and initiate the first stages of infection. The structure, which shows how the spike protein grasps its receptor, may help scientists learn new details about how the virus infects cells. The information could also be helpful in developing antiviral drugs or vaccines.

The research team, led by HHMI investigator **Stephen C. Harrison** at Children's Hospital Boston and Harvard Medical School, and colleague Michael Farzan, also at Harvard Medical School, reported its findings in the September 16, 2005, issue of the journal *Science*.

"One of the critical issues in a SARS epidemic would be to predict whether a given variant of the virus will jump species or move laterally from one human to the other," says Harrison. "Understanding the structure of this complex will help us understand what mutations in the spike protein mean in terms of infectivity."

RACE AGAINST ANTIBIOTIC RESISTANCE

Antibiotic resistance has put humans in an escalating "arms race" with infectious bacteria, as scientists try to develop new antibiotics faster than the bacteria can evolve new resistance strategies. But now, researchers have a new strategy that may give them a leg up in the race—reproducing in the lab the natural evolution of a class of bacterial enzymes that confer resistance.

A team of scientists from Argentina and Mexico identified mutations that increased the efficiency of a bacterial enzyme that renders penicillin and cephalosporin antibiotics useless. The results could lead to more effective enzyme inhibitors by giving drug designers a sneak peek at the next generation of resistance.

Alejandro J. Vila, an HHMI international research scholar, and colleagues at the Institute of Molecular and Cellular Biology of Rosario, in Argentina, and at the Biotechnology Institute of the National Autonomous University of Mexico reported their findings in the September 27, 2005, issue of the *Proceedings of the National Academy of Sciences.*

SUPERCHARGING BLOOD-FORMING STEM CELLS

Researchers studying a colorfully named zebrafish mutant, mind bomb, have discovered a way to replenish blood cells more quickly after exposure to radiation. The studies identify key genetic regulators that boost production of blood-forming stem cells.

The finding could lead to ways to supercharge production of hematopoietic stem cells in cancer patients who have received bone marrow transplants to restore their blood-forming system after chemotherapy or radiation. Supercharging could also enhance effectiveness of such transplantations to treat disorders such as aplastic and sickle-cell anemias, say the researchers.

A Mechanism for Coordinating Genes

Chromosomes reach out and touch each other.

STUDYING HOW CELLS OF THE MOUSE IMMUNE SYSTEM MATURE and differentiate, researchers at Yale University recently discovered a surprising strategy. HHMI investigator Richard Flavell and his team observed the first instance of genes from separate chromosomes coordinating their activities by touching each other.

The researchers studied helper T cells (T_H cells), which can develop into T_H1 or T_H2 cells that use slightly different tactics—turning on distinct groups of genes—to fight infections. The Yale researchers had previously found out that in T_H2 cells a master control element on chromosome 11—called the locus control region (LCR)—turns on three nearby but widely separated genes that encode interleukins (proteins the cells use to neutralize pathogens). With the aid of a recently developed method, called chromosome conformation capture, to map physical contacts between different regions of DNA, Flavell's group learned that the LCR orchestrates the activities of the three interleukin genes by actually contacting parts of all three genes.

At around the same time, the researchers noticed that early in development T cells produce small amounts of both the T_H2-specific interleukins and the T_H1-specific cytokine interferon-γ, whose gene lies on chromosome 10. (Cytokines are proteins that stimulate or inhibit the joint action of immune cells.) Because the interferon-γ and interleukin genes seemed to be regulated in concert, Flavell surmised that the LCR on chromosome 11 might somehow bind both its neighboring interleukin genes and the interferon-γ gene on chromosome 10. That was a bold hypothesis. "In the past, people have thought that chromosomes acted independently," says Flavell. But the hunch turned out to be right.

Using fluorescent-microscope-imaging techniques, the Yale researchers directly witnessed the predicted regions of chromosomes 10 and 11 come in contact during early T_H cell development and then move apart as the cells committed to their final fates as T_H1 or T_H2 cells. The work was published in the June 2, 2005, issue of *Nature*.

Although questions remain about how the chromosome contacts regulate gene expression, the Flavell team suspects that the LCR serves to escort genes to regions of the cell's nucleus that offer a favorable environment for gene activation. Given nature's inherent efficiency, they speculate that chromosome contacts will prove to be a general mechanism for coordinating the activity of genes. ■

~ Paul Muhlrad ~

BIOPHOTO ASSOCIATES / PHOTO RESEARCHERS, INC.

IN CONTRAST TO THE SCENE IN THIS COLORIZED SCANNING ELECTRON MICROGRAPH, CHROMOSOMES IN A CELL'S NUCLEUS ARE SNUGLY PACKED—AND THEY AREN'T JUST RUBBING ELBOWS.

IN BRIEF

(continued)

Leonard I. Zon, an HHMI investigator at Children's Hospital Boston, and his colleagues reported their findings in an article published in the October 2005 issue of the journal *Genes and Development*.

GETTING TO THE HEART OF CELL SIGNALING

Researchers have discovered new details about how one of the cell's most commonly used messenger molecules, cyclic AMP, can trigger several distinct responses within cells. The studies point the way toward new drug targets for heart disease and other disorders.

John D. Scott, an HHMI investigator at Oregon Health & Science University, and his colleagues published their findings in the September 22, 2005, issue of the journal *Nature*.

Cyclic AMP is a cellular chemical that, among other things, can control heart rate and muscle contraction. Cyclic AMP also regulates the passage of calcium through ion channels in the cell membrane, another important cellular process in the heart.

In their new study, Scott and his colleagues explored a group of proteins called muscle-specific A-kinase anchoring protein (mAKAP) complex, which acts as a sort of central molecular clearing house for cyclic AMP signals. An earlier study had found that mAKAP includes phosphodiesterase, which Scott's study identified to be the key protein for regulating cyclic AMP signaling. Scott said their findings suggest that new treatments for heart disease could target phosphodiesterase to influence cyclic AMP signaling, since "changes in the cyclic AMP pathway are known to be linked to heart disease, and heart contraction is linked to calcium and cyclic AMP signaling."

NEW FORM OF NERVE CELL PLASTICITY

Researchers have discovered a new form of synaptic plasticity, the changes to nerve cells in the brain that underlie learning and memory. The phenomenon, the scientists say, may help govern how a single neuron integrates and processes multiple stimuli.

The researchers, led by HHMI investigators **Lily Yeh Jan** and **Yuh Nung Jan** at the University of California, San Francisco (UCSF), published their findings in the October 7, 2005, issue of *Cell*. Coauthors include the Jans' colleagues at UCSF and **Robert B. Darnell**, an HHMI investigator at the Rockefeller University.

In experiments designed to answer whether slow inhibition of electrical impulses between nerve cells undergoes long-term potentiation (LTP), long-lasting changes in the connectivity between two nerve cells, the Jans showed that the same pathway could generate LTP of both excitatory and inhibitory synapses. The scientists then wondered whether this plasticity might be controlled by a "master" regulatory protein. A good candidate, they thought, was a protein found in the brain called Nova-2 that controls a network of other proteins, many of which are involved in inhibitory synaptic transmission. Using mice engineered by the Darnell

Developing an Easier Screen for Colon Cancer

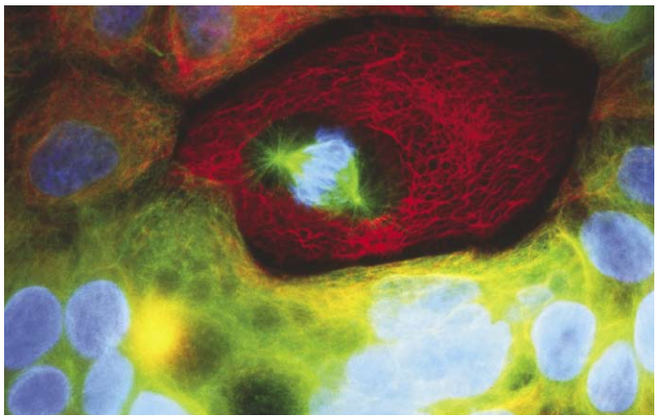
A noninvasive and inexpensive test might soon displace colonoscopies.

COLORECTAL TUMORS TAKE THE LIVES OF MORE ADULT Americans than any other cancer except lung cancer, even though colon cancer is almost always curable by surgery if detected early enough.

Yet most people never undergo a colon cancer screening test, says HHMI investigator Sanford Markowitz of Case Western Reserve University. Colonoscopy can detect more than 90 percent of colon tumors. But the procedure is expensive and unpleasant, and carries some degree of risk. Meanwhile, the fecal occult blood test (FOBT), the standard noninvasive screen that detects blood in the stool, catches only 15 percent of colon cancers.

Markowitz and his colleagues have now developed a noninvasive test, 3 times more sensitive than the FOBT, that relies on a telltale chemical signature in a gene called *vimentin*. While the gene in cancerous colon cells displays chemical modifications called methylations, it is rarely, if ever, methylated in healthy cells. On this basis, Markowitz's lab devised a biochemical assay that can detect the aberrant gene modification in as few as 15 cancer cells—a sensitivity that allows the test to be performed on DNA shed in a stool sample. In a clinical trial, the test detected *vimentin* methylations in 46 percent of colon cancer patients, and it caught early-stage tumors as effectively as it did late-stage tumors.

New progress toward a comprehensive noninvasive screening test for colorectal cancer has also been made by HHMI investigator Bert Vogelstein and his colleagues at the Sidney Kimmel Cancer Center at the Johns Hopkins Medical Institutions. The researchers recently reported that they could detect DNA fragments of mutant forms of a key cancer gene, called APC, in blood plasma from patients with certain types of colon cancer. "The test we developed for plasma DNA mutations can also be used to study fecal DNA mutations," says Vogelstein. "We are working with Sandy Markowitz's group to develop the optimal combination of DNA markers to use for this purpose." ■



NANCY KEDERSHA / PHOTO RESEARCHERS, INC.

UNDER A MICROSCOPE, COLON CANCER IS CHARACTERIZED BY IRREGULARLY SHAPED CELLS WITH LARGE NUCLEI AND EVIDENT CELL DIVISION. HERE, NUCLEI ARE BLUE, TUBULIN SPINDLES ARE GREEN, AND MUSCLE FIBER (MYOSIN) IS RED.

~ Paul Muhlrad ~

IN BRIEF

lab to lack Nova-2, they found that the protein is indeed required for LTP of slow inhibition. It is not, however, necessary for LTP of excitation. "It was totally surprising to us, but it's really intriguing that there could be controls at that level," Lily Jan says.

GENETIC CLUE TO TOURETTE'S SYNDROME REVEALED

Researchers have identified the first gene mutation associated with Tourette's syndrome (TS), opening a new avenue for understanding the complex disorder that causes muscle and vocal tics. Until now, causes of TS, which afflicts as many as 1 in 100 people, have eluded researchers because the disease appears to be caused by subtle mutations in many genes.

The researchers published their findings in the October 14, 2005, issue of the journal *Science*. Matthew W. State of the Yale University School of Medicine was senior author of the paper. His research was supported by an HHMI institutional award to support early research by promising scientists at Yale. Other coauthors at Yale included HHMI investigator **Richard P. Lifton**, and neurobiologists Nenad Sestan and Angeliki Louvi from the Yale Child Study Center.

State and his colleagues searched near the breakpoints of an inversion on chromosome 13 discovered in a TS patient. They identified one gene, called *SLITRK1* (for Slit and Trk-like family member 1), that is expressed in the brain in the regions implicated in TS, and is associated with the growth and interconnection of neurons. The gene was then confirmed to be linked to TS in other patients.

Lifton points out that State's approach is somewhat different from his own strategy of analyzing rare genetic abnormalities that tend to run in families. "The idea of looking for clues from chromosomal anomalies is a very powerful one that has paid off in this case," says Lifton. "The findings point for the first time to a pathway that appears to contribute to the pathogenesis of TS and enables further studies not only from a genetic perspective, but also from a pathophysiologic one."

NEW VIEW OF THE BIOLOGICAL LANDSCAPE

A new technique for analyzing the network of genetic interactions promises to change how researchers study the dynamic biological landscape of the cell. The technology, called epistatic miniarray profiles (E-MAP), has already been used to assign new functions to known genes, to uncover the roles of previously uncharacterized proteins, and to define how biochemical pathways and proteins interact with one another. E-MAP will enable new understanding of how genes and proteins function in the cell, says **Jonathan S. Weissman**, an HHMI investigator at the University of California, San Francisco, and leader of the team that developed the technique. The work was published in the November 04, 2005, issue of *Cell*.

ASK A SCIENTIST

WHAT IS THE MOLECULAR MECHANISM FOR STRIPES IN ZEBRAS?

Q.

SUBMITTED BY AN UNDERGRADUATE STUDENT FROM NEW DELHI, INDIA

A.

BY JAYATRI DAS

Among the three living species of zebra, the common (or plains) zebra has 26 stripes per side, the mountain zebra has 43 stripes, and the Grevy's zebra has 80 stripes. Why these differences?

During vertebrate development, groupings of neural crest cells give rise to the brain and then the spinal cord, as the cells migrate down the axis of the animal. Some neural crest cells along the spinal cord differentiate into melanocytes—cells that produce colored pigment—which then migrate perpendicular to the spinal cord, developing into pigmented skin.

Jonathan Bard, of the University of Edinburgh, proposes that the original pattern of melanocyte differentiation is the same in all three species, but the differentiation occurs at different developmental times.

Differentiation is predicted to occur earliest in the common zebra—around the third week of development. If melanocytes are produced this early, they proliferate more (creating fewer, broader stripes) and will be pulled, as the rump continues to grow, into a pattern parallel to the spinal cord axis.

By contrast, however, differentiation in the Grevy's zebra is not predicted to occur until the fifth week. Because the embryo is larger then and more developed, there are more melanocytes (creating more stripes) that do not proliferate as much (so the stripes are thinner). The larger size of the embryo affects the patterns of stripe growth. (Melanocyte differentiation in the mountain zebra is predicted to be at four weeks.) No two individuals within a species have the same pattern of stripes because of individual differences in growth.

What determines which cells produce pigment and which remain white? The exact molecular pathway is not known. Scientists predict that this process requires an "activator" that produces pigment and an "inhibitor" that suppresses the activator.

RESEARCHED BY JAYATRI DAS, POSTDOCTORAL RESEARCHER, UNIVERSITY OF PENNSYLVANIA

FOR MORE INFORMATION, VISIT THESE WEB SITES:

Search for "zebra" at www.devbio.com (discusses Bard's theory of the development of stripes, with diagrams of embryos)

http://grace.evergreen.edu/artofcomp/examples/zebra/Zebra.html (a simulation illustrates how a random process mimicking a reaction-diffusion system can produce an ordered pattern like zebra stripes)

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."

TO SEE OTHER QUESTIONS, VISIT ASK A SCIENTIST

www.hhmi.org/askascientist

Right: A broad view of a reconstructed nerve cell showing the flow of chemical signals.

DReAMM Scheme

Using high-tech tools, scientists see nerve cell communication in a whole new light.

Combining high-resolution serial electron microscopic tomography, neuroelectrophysiological measurements, mathematical modeling, and computer graphics, a multi-institution team led by HHMI investigator Terrence J. Sejnowski at the Salk Institute for Biological Studies has overturned a half-century's dogma in neurobiology. The researchers proved that the flow of chemical signals from nerves isn't restricted to the ends of nerve fibers, as scientists had previously believed, but that more than 90 percent of a nerve's signals emanate from parts of the cell away from the nerve terminals.

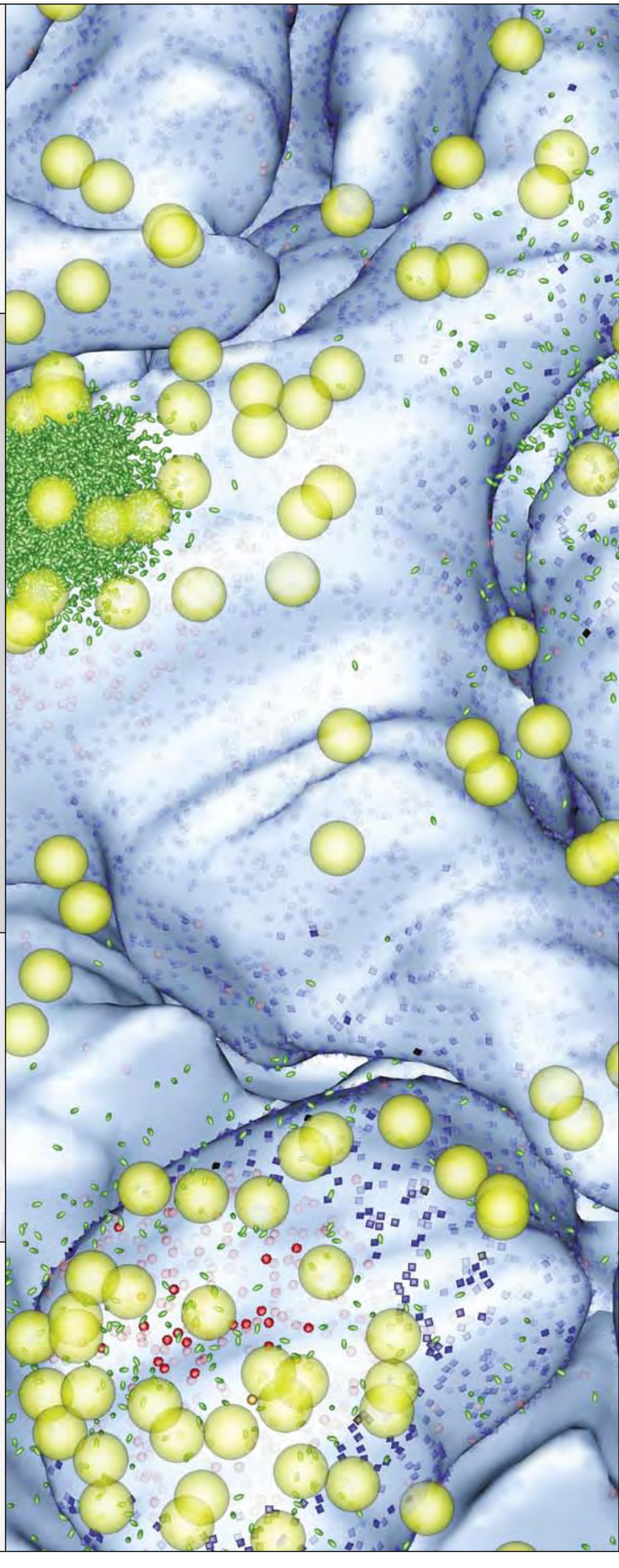
A custom-graphics program with the acronym DReAMM (Design, Render, and Animate MCell Models) gives researchers unprecedented capacity to visualize activity at the subcellular level. MCell software uses 3-D models and algorithms to simulate molecular activity within and between cells. Investigators like Terrence Sejnowski use DReAMM to design, edit, and visualize the simulations and parts of cells derived via MCell.

~ Paul Muhlrad ~

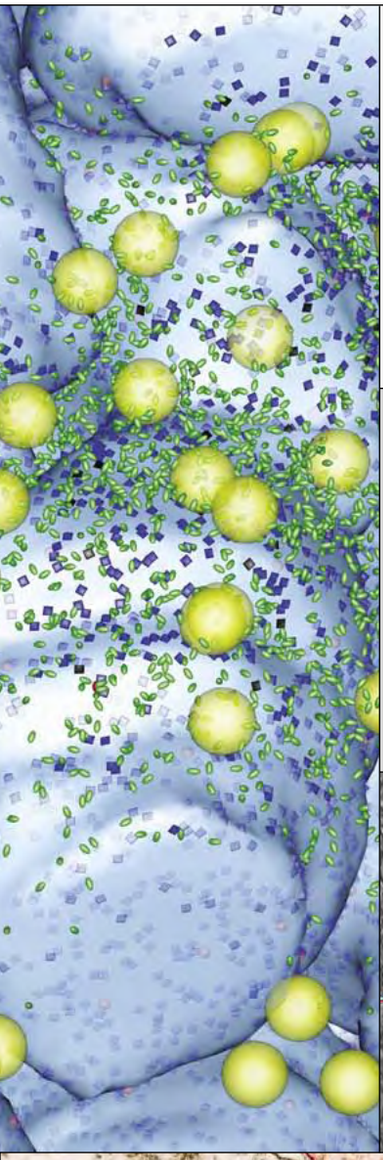
"It's like having another communications channel in the brain."

TERRENCE J. SEJNOWSKI

MARK HARMEL

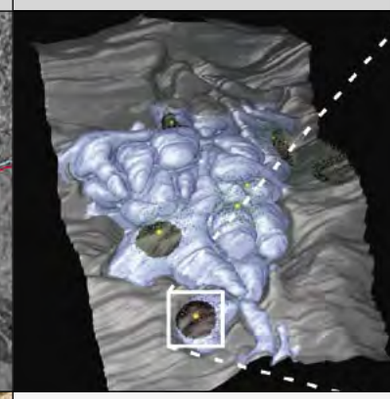


THOMAS BARTOL, JR.

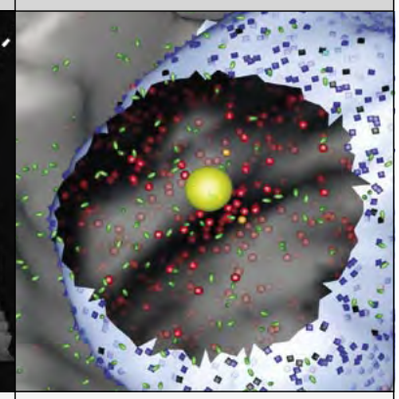


Below: This cross-sectional view through a junction between two nerve cells was constructed by computer-aided tomography of a thin slice of the nerve, imaged in an electron microscope. The red lines outline neurotransmitter-filled vesicles flowing from the cell that is transmitting the nerve impulse. The area above the blue line is the cell that will receive the nerve signal.

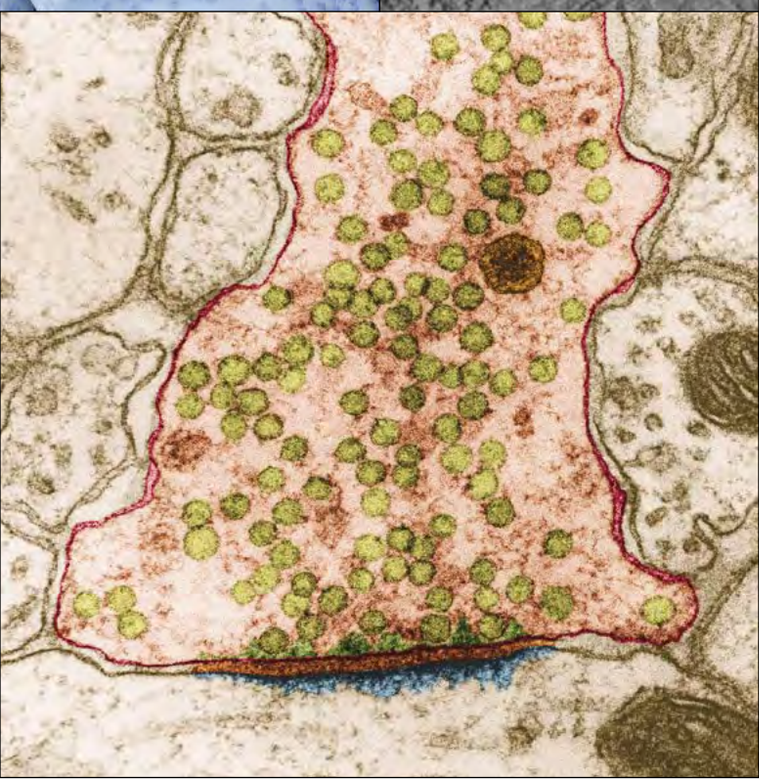
Below: DReAMM (see box at far left) renders data from many nerve cross-sections into a 3-D dynamic image of the cell. The program also superimposes mathematical modeling data describing the movements and positions of vesicles, signaling molecules, and signal receptors in the nerve tissue.



Below: A close-up view of the boxed region in the previous image (at left). The blackened surface shows the "postsynaptic zone," the region through which scientists had previously thought nerve signals must flow. The yellow sphere is a vesicle, green dots are neurotransmitter molecules, and the red and blue dots are two different kinds of neurotransmitter receptors.



(3) REPRINTED WITH PERMISSION FROM *SCIENCE* 15 JULY 2005, VOL 309, PP 446–451 / © 2005 AAAS



© DENNIS KUNKEL / PHOTOTAKE, INC.

Left: Membrane vesicles (green) filled with chemical signals flow toward the tip of the transmitting cell where they will cross the synaptic zone and then enter the receiving nerve cell. While the traditional view of nerve cell signaling comes from electron micrographs such as this one, more careful scrutiny has revealed that vesicles release their signaling molecules through the entire surface of the cell.

TO SEE AN ANIMATION IN MOTION

Click the link at the bottom of this Web page: www.mcell.cnl.salk.edu/Publications/ectopic_sciencemag_2005/

SPOTLIGHT

PIETRO DE CAMILLI

JEFFREY M. FRIEDMAN

EMMANUEL MIGNOT

VAL C. SHEFFIELD

GERALD I. SHULMAN

JOAN A. STEITZ

LEONARD I. ZON

Seven HHMI Investigators Elected to Institute of Medicine

Seven HHMI investigators and four advisory board members were elected members of the Institute of Medicine of the National Academies in October 2005. The investigators are **PIETRO DE CAMILLI,** Yale University School of Medicine; **JEFFREY M. FRIEDMAN,** the Rockefeller University; **EMMANUEL MIGNOT,** Stanford University School of Medicine; **VAL C. SHEFFIELD,** University of Iowa Roy J. and Lucille A. Carver College of Medicine; **GERALD I. SHULMAN,** Yale University School of Medicine; **JOAN A. STEITZ,** Yale University School of Medicine; and **LEONARD I. ZON,** Children's Hospital Boston of Harvard Medical School. HHMI board members elected are **PETER C. AGRE,** Duke University; **J. LARRY JAMESON,** Northwestern University Feinberg School of Medicine; and **STEVEN L. McKNIGHT,** University of Texas Southwestern Medical Center at Dallas—all members of the scientific review board—and **JONATHAN D. MORENO,** University of Virginia, a member of the bioethics advisory board.

PIETRO DE CAMILLI: CLAUDIA BUZZI DE CAMILLI *JEFFREY M. FRIEDMAN:* MARC BRYAN-BROWN *EMMANUEL MIGNOT:* COURTESY OF MIGNOT LAB *VAL C. SHEFFIELD:* DENISE AGUIAR CROUCH *GERALD I. SHULMAN:* GALE ZUCKER *JOAN A. STEITZ:* COURTESY OF YALE UNIVERSITY SCHOOL OF MEDICINE *LEONARD I. ZON:* PAUL MEAD

■ **Ronald R. Breaker,** an HHMI investigator at Yale University, received the 2005 Eli Lilly and Company Research Award from the American Society for Microbiology. The award honors Breaker's research program, which explores the more exotic functions of RNA and DNA, as well as his most recent work showing that metabolites are directly bound by messenger RNA elements called riboswitches.

■ Three HHMI investigators were selected to receive 2005 World Technology Awards by the World Technology Network, an organization dedicated to putting important emerging technologies of all types into practice. The awardees and the categories in which they were honored are: **Patrick O. Brown,** Stanford University School of Medicine (Media and Journalism); **David Haussler,** University of California, Santa Cruz (IT Software); and **David R. Liu,** Harvard University (Materials and Nanotech).

■ **Brian J. Druker,** an HHMI investigator at the Oregon Health & Science University, won the 2005 Robert Koch Award for his work in advancing the therapeutic treatment of chronic myeloid leukemia.

■ **Stephen J. Elledge,** an HHMI investigator at Brigham and Women's Hospital, received the Hans Sigrist Foundation Award for outstanding research in the field of quality control in living cells. The award is given by the University of Bern, Switzerland.

■ **Helen H. Hobbs,** an HHMI investigator at the University of Texas Southwestern Medical Center at Dallas, received the inaugural American Heart Association 2005 Clinical Research Prize, created to "recognize an individual making outstanding contributions to the advancement of cardiovascular science and who heads a notable clinical research laboratory." Hobbs was cited for her discoveries of multiple genetic mutations responsible for abnormalities in lipid metabolism and cholesterol transport in humans, which have led to more effective treatment approaches. Her work was also recognized with the 2005 Heinrich Wieland Award, sponsored by Boehringer Ingelheim.

■ **H. Robert Horvitz,** an HHMI investigator at the Massachusetts Institute of Technology, won the 2005 Alfred G. Knudson Award from the National Cancer Institute for his work in the field of cancer genetics. He also received the 2005 Graduate School of Arts and Sciences Centennial Medal given by Harvard University to recognize the work of former graduates.

■ A University of Washington team headed by HHMI professor **Mary E. Lidstrom** was recognized with a 2005 Premier Award for Excellence in Engineering Education Courseware for a CD-format tutorial created with funding by HHMI. The tutorial, titled "Biological Information Handling: Essentials for Engineers," was one of two honored by the award, which is administered through the

National Engineering Education Delivery System, supported in part by the National Science Foundation.

■ **Liqun Luo,** an HHMI investigator at Stanford University, was one of six researchers to receive the 2005 Senator Jacob Javits Award in the Neurosciences. The award is given by the National Institute of Neurological Disorders and Stroke to recognize individual scientists it supports "who have demonstrated exceptional scientific excellence and productivity in research."

■ **Philippa Marrack,** an HHMI investigator at the National Jewish Medical and Research Center, was selected to receive the 2006 Avery Landsteiner Prize by the German Society of Immunology.

■ Two HHMI investigators were selected to receive the 2004 Presidential Early Career Award for Scientists and Engineers. The awardees are **Teresa Nicolson** of the Oregon Health & Science University and **Brenda A. Schulman** of St. Jude Children's Research Hospital. The awards were presented in a White House ceremony on June 13, 2005.

■ **Stuart H. Orkin,** an HHMI investigator at Children's Hospital Boston of Harvard Medical School, won the 2005 Award for Distinguished Research in the Biomedical Sciences from the Association of American Medical Colleges.

■ **Olivier Pourquié,** an HHMI investigator at the Stowers Institute for Medical Research, in Kansas City, Missouri, was honored recently with two awards, the 2005 Victor Noury Grand Prize from the French Academy of Sciences and the 2005 Pierre-Joseph and Édouard van Beneden Prize from the Royal Academies for Science and the Arts of Belgium, for his research on the genetic and developmental mechanisms that control segmentation.

■ **Sandra R. Schmookler,** director of the HHMI precollege science education program in Montgomery County, Maryland, received a presidential citation from the American Psychological Association (APA) for her multipronged efforts supporting collaboration between APA and Montgomery County Public Schools.

■ **Michael Segal** was awarded Best in Category in Biochemistry at the 2005 International Science and Engineering Fair for his HHMI-supported project titled "Bioinformatics Discovery of Novel Stem Cell Regulatory Mechanisms." Now an undergraduate at Harvard University, Segal carried out his summer research project in Jon Geiger's Jackson Laboratory research lab while still a student at Philadelphia's Central High School.

■ **Robert F. Siliciano,** an HHMI investigator at the Johns Hopkins University School of Medicine, and Bruce D. Walker, an HHMI investigator at Massachusetts General Hospital, were recently honored with lifetime memberships in the International Association of Physicians in AIDS Care.

SPOTLIGHT

DAVID HAUSSLER

Haussler Wins Dickson Prize

The 2005 Dickson Prize has been awarded to **DAVID HAUSSLER,** an HHMI investigator at the University of California, Santa Cruz. Given by Carnegie Mellon University, the annual award recognizes individuals making outstanding contributions to science in the United States.

Haussler is known for his trailblazing work in the fields of computational learning theory and bioinformatics. As a collaborator on the international Human Genome Project, his team posted the first publicly available computational assembly of the human genome sequence on the Internet and went on to develop and maintain an interactive Web browser for the genome sequence (www.genome.ucsc.edu) that is used extensively by biomedical researchers around the world.

In ongoing research, Haussler and his team develop new statistical and algorithmic methods to explore the molecular evolution of the human genome. By integrating cross-species comparative and high-throughput genomic data, the group has identified mammalian gene sequences that have been extremely well conserved throughout millions of years of evolution.

TIMOTHY ARCHIBALD

SPOTLIGHT

Production on DNA Wins Emmy Award

An international team that created a multimedia television production on DNA with support from HHMI won an Emmy Award for its efforts. The team won in the category of Outstanding Science, Technology, and Nature Programming for the episode "The Human Race," which was televised internationally. The National Television Academy presented the award at the 26th Annual News and Documentary Emmy Awards on September 19, 2005.

SPOTLIGHT

Scientific Illustrator Wins Major Award

Scientific illustrator **GRAHAM JOHNSON** won *Science* magazine's 2005 Science and Engineering Visualization Challenge illustration award for his depiction of a brain cell synapse, which he created for HHMI. The illustration appeared in the fall 2004 edition of the HHMI *Bulletin*, in support of the story entitled "The Synapse Revealed." *Science* magazine, with the National Science Foundation, organized this year's Science and Engineering Visualization Challenge to encourage and celebrate imaginative use of graphics to communicate scientific achievement.

Johnson earned a master's degree in medical and biological illustration from the Johns Hopkins School of Medicine in 1997. This fall he began a Ph.D. program in molecular biology at the Scripps Research Institute, where he hopes to advance techniques for visualizing interactions within cellular contexts.

CONTINUED FROM PAGE 37
[SIMON JOHN]

and energetic to make that happen—for example, our research has shown that Bax is a gene that needs exploration in the human population. Is it a susceptibility gene in humans? Bax codes for the BAX protein and induces apoptosis. To explore retinal ganglion cell death, Richard T. Libby, a postdoc in my lab, crossed our glaucoma-prone mice with mice deficient in BAX to generate mice that were either completely missing BAX or had lower amounts of it. Importantly, even the mice missing just one copy of the Bax gene are profoundly protected from glaucoma because the nerve cells in the retina do not die. These mice don't lack BAX, they just have lower levels of it—a more realistic model for treating humans since it is easier to reduce the levels of a protein in patients than completely turn it off. We want to encourage clinicians to look at BAX inhibitors to see if they might be helpful for glaucoma patients.

Our discovery of the role of the tyrosinase gene is another area ripe for a clinical look. We discovered that mice with a mutation in the tyrosinase gene, coupled with a second culprit gene, Cyp1b1, had severe eye-drainage structure malformations similar to those that cause glaucoma in people. When we put L-DOPA, a product of tyrosinase, in the drinking water of pregnant mice deficient in CYP1B1 and tyrosinase, their pups did not have severe structural abnormalities. We want clinicians to take this result and run with it, though it may be safer to modulate the tyrosinase gene than to directly manipulate L-DOPA.

David K. Dueker is a clinician in Saudi Arabia, where early-onset glaucoma involving CYP1B1 is common, often resulting in childhood blindness. Dave would like to study the impact of fava beans, a dietary staple in the region that is rich in L-DOPA. He wants to ask: "If a woman with the CYP1B1 mutation has a baby with a milder form of glaucoma, was she eating a lot of fava beans? That is, was she medicating herself with L-DOPA without knowing it?" We'd like to complement this epidemiology with mouse studies, which I hope can do his patients some good. These L-DOPA studies may also help patients with glaucoma caused by several other genes that affect tyrosine hydroxylase, another enzyme that makes L-DOPA. Disturbances in L-DOPA may be a unifying theme in these glaucoma cases.

The last area I want to mention is furthest from clinical application, but still very exciting. Through serendipity, we discovered that radiation plus bone-marrow transfer in mice provides complete protection from glaucoma! While studying a form of the disease called pigmentary glaucoma, we observed that none of the glaucoma-prone mice we irradiated had any glaucoma damage. This was a hugely surprising outcome that we just couldn't fathom. So we did it a second and third time, and got the same results. In about 96 percent of the animals, protection was complete. We seemed to stop the disease dead in its tracks—long-term.

This effect doesn't seem to be unique to the mouse strain. A group studying atom-bomb survivors of Hiroshima and Nagasaki found that the people with the highest radiation exposures seemed to be protected from glaucoma. Now our challenge is to understand the mechanisms involved. Maybe there's a way those mechanisms can be "bottled" and turned into medications or preventive measures down the road. ■

-Interview by Cori Vanchieri-

CONTINUED FROM PAGE 39
[VALERIE MIZRAHI]

and has led people who can afford it to retreat into secure neighborhoods protected by barbed wire fencing—not a great way to live. The safety of my family is foremost in my mind at all times, of course, but you can't let the fear of crime dominate your life. Also, I don't worry about the safety of my staff and students—at least, not during normal working hours—because my lab site is very secure. I do worry a little about their safety after hours, but most of them have grown up in Johannesburg or lived here for a while, so they tend to be street-smart.

HHMI: ***WHY DON'T YOU LEAVE?***

VM: I am a second-generation African, and South Africa is my home. I love the beauty of this country, its sounds, its smells, and the wonderful climate. Every time I step off a plane here, I feel glad to be home. There is also the issue of relative impact. The reality is that I can make more of a difference here than elsewhere.

HHMI: ***WHAT WOULD YOU LIKE TO BE REMEMBERED FOR?***

VM: Actually, I want to be put out of business by my graduates—by students like Limenako Matsoso and Betty Mowa, two talented black African women who are working toward their Ph.D.s in my lab.

Betty is from the Limpopo Province of northeastern South Africa. She is in her first year of doctoral studies and has won a prestigious bursary, which is like a graduate fellowship, from the South African government.

Limenako is from Lesotho, a small independent country located completely within South Africa. She played a central role in establishing DNA microarray technology in our lab, using a partial-genome microarray of Mycobacterium smegmatis—a close cousin of the organism that causes TB. Because the M. smegmatis microarray was constructed by former HHMI international research scholar Ross Coppel in Australia, the requisite interaction with our Australian colleagues exposed Limenako to the world of international collaborative science. After completing her Ph.D. this year, she plans to do postdoctoral training in the United States, but I want her to know that she can then come home and do great science here. ■

-Interview by Jennifer Boeth Donovan-

CONTINUED FROM PAGE 45
[SCIENCE EDUCATION]

hoping to disseminate the academy's ideas across the country.

"We see this as a unique opportunity that goes beyond simply providing money," says Peter J. Bruns, HHMI vice president for grants and special programs. "Our network of scientists and educators are contributing ideas and their own findings, so this experiment in science education is not going it alone."

The 9th- and 10th-grade academy curriculum is designed to meet Virginia state standards, which are based on national science standards. Fortunately, Virginia doesn't require earth science, biology, and chemistry to be taken in the traditional sequence, Wolfe says, although students must pass a test at the end of each course. He isn't worried about these exams. "Our kids will have such a strong understanding of the sciences," he says, "that they'll be able to handle anything the tests throw at them and probably a whole lot more." ■

-Jennifer Boeth Donovan-

OBSERVATIONS

LIFE: THE MOST REMARKABLE OF ALL EMERGENT SYSTEMS

THE TRIFID NEBULA IS A GIANT STAR-FORMING CLOUD OF GAS AND DUST LOCATED 5,400 LIGHT-YEARS AWAY IN THE CONSTELLATION SAGITTARIUS. USING A SPECIAL INFRARED SPACE TELESCOPE, NASA HAS DISCOVERED, ALL TOGETHER, 30 MASSIVE EMBRYONIC STARS AND 120 SMALLER NEWBORN STARS THROUGHOUT THE TRIFID NEBULA'S DARK LANES AND LUMINOUS CLOUDS.

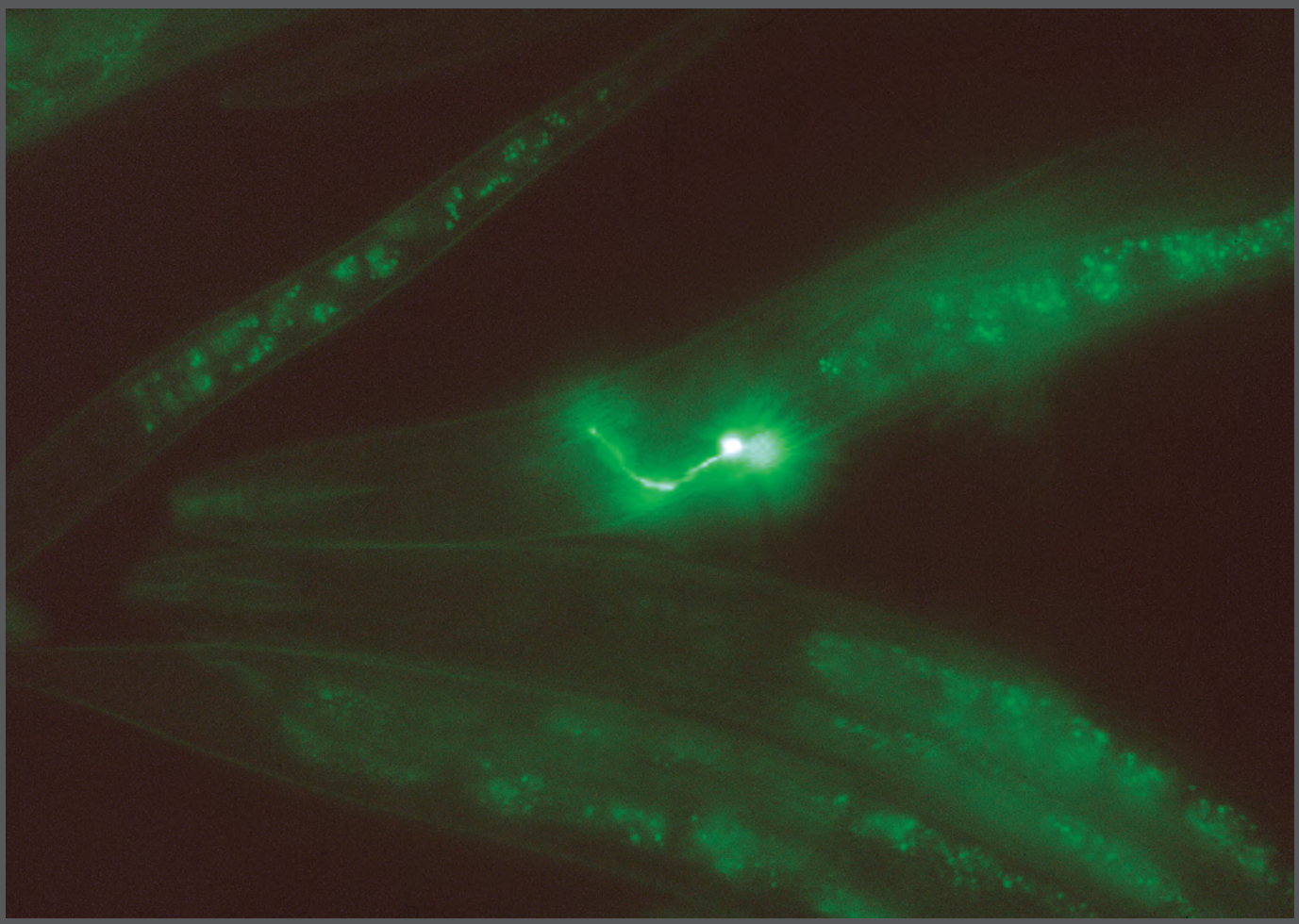
CREDIT: VISIBLE-LIGHT IMAGE COURTESY OF THE NATIONAL OPTICAL ASTRONOMY OBSERVATORY, TUCSON, AZ.

The science of emergence seeks to understand complex systems—systems that display novel collective behaviors that arise from the interactions of many simple components. From gravitational interactions of individual stars emerge the glorious sweeping arms of spiral galaxies. From the chemical interactions of individual ants emerge the extraordinarily complex social behavior of ant colonies. From the electrical interactions of individual neurons in your brain emerge thought and self-awareness. Emergence is nature's most powerful tool for making the universe a complex, patterned, entertaining place to live.

Life itself is arguably the most remarkable of all emergent systems. Many origins-of-life experts adopt the view that life began as an inexorable sequence of emergent events, each of which was an inevitable consequence of interactions among versatile carbon-based molecules. Each emergent episode added layers of chemical and structural complexity to the existing environment. Intensive experiments at laboratories around the world reveal, step-by-step, the essential life-triggering reactions that must occur throughout the cosmos. First came the carbon-containing biomolecules, synthesized in unfathomable abundance on comets and asteroids, in the black near-vacuum of space, on the surface of the young Earth, and deep within our planet's restless crust. Then came the emergence of larger molecular structures—the selection, concentration, and assembly of life's membranes, proteins, and genetic molecules, built in part on a scaffolding of rocks and minerals. Eventually, these biomolecular structures formed self-replicating cycles—chemical systems that copied themselves and competed for a finite and dwindling supply of resources. Ultimately, competition between different self-replicating cycles triggered evolution by natural selection, and life was on its way.

From the book Genesis: The Scientific Quest for Life's Origin, by Robert M. Hazen. © 2005 by Robert M. Hazen. Reprinted here with permission of the publisher, the Joseph Henry Press, an imprint of the National Academies Press.

An astrobiologist at the Carnegie Institution of Washington, Robert M. Hazen is also the Clarence Robinson Professor of Earth Science at George Mason University. Genesis describes scientific advances in labs worldwide that are transforming our understanding of the quest for life's origins. The book refers to the work of several HHMI investigators, including an extensive look at research by HHMI investigator Jack Szostak at Massachusetts General Hospital and Harvard Medical School.



COURTESY OF OLIVER HOBERT

Lessons from the Nerve Cells of Roundworms

THE ROUNDWORM *CAENORHABDITIS ELEGANS* GETS BY IN THIS WORLD WITH A MERE 302 NERVE CELLS. SCIENTISTS UNDERSTAND THE ROLE OF EACH OF THOSE NEURONS, SO THE EYELASH-SIZE WORM IS AN IDEAL ORGANISM FOR STUDYING HOW NEURONAL CIRCUITS ARE ASSEMBLED AND HOW THEY AFFECT BEHAVIOR. HERE, THE AIY INTERNEURONS, A MULTIFUNCTIONAL NEURON CLASS THAT INTEGRATES A VARIETY OF SENSORY INPUTS, GLOW BRIGHTLY DUE TO SPECIFIC LABELING WITH A FLUORESCENT MARKER.

HHMI
HOWARD HUGHES MEDICAL INSTITUTE

4000 Jones Bridge Road
Chevy Chase, Maryland 20815-6789
www.hhmi.org

NONPROFIT ORG.
US POSTAGE
PAID
HYATTSVILLE, MD
PERMIT NO. 61

Change Service Requested