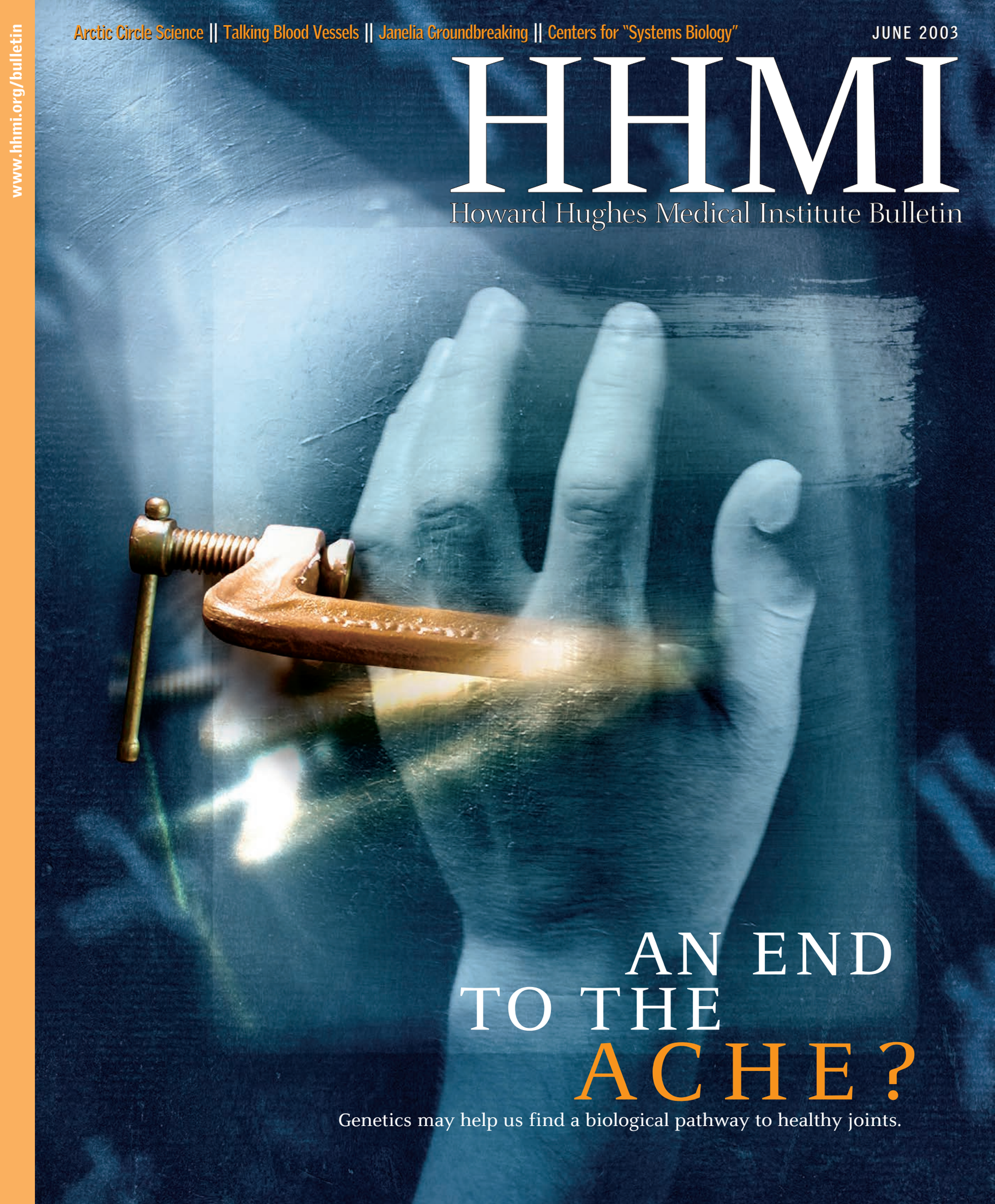
www.hhmi.org/bulletin

JUNE 2003

HHMI

Howard Hughes Medical Institute Bulletin



AN END TO THE ACHE?

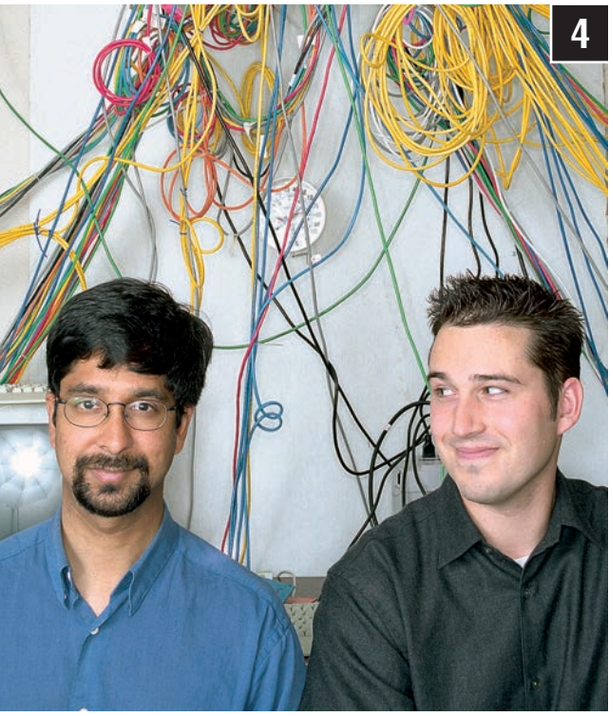
Genetics may help us find a biological pathway to healthy joints.

FEATURES

22

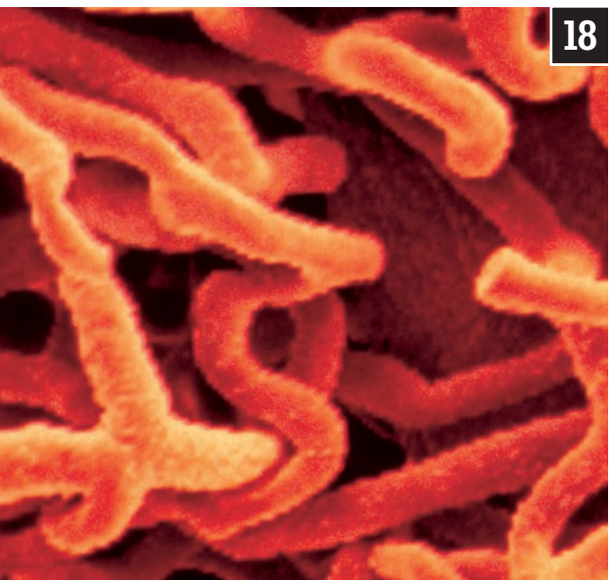
Freelance model-maker Jeremiah Bailey incorporates design changes into a working model of HHMI's Janelia Farm Research Campus.

PAUL FETTERS



TIMOTHY ARCHIBALD

JENNIFER BOETH DONOVAN



COLLECTION CNRI

DEPARTMENTS

On the Cover: Illustration by Richard Tuschman

HHMI
Howard Hughes Medical Institute Bulletin

June 2003 || Volume 16 Number 2

Telephone (301) 215 8855 ■ Fax (301) 215 8863 ■ www.hhmi.org
The *Bulletin* is published by the HHMI Office of Communications and Public Affairs.

Supporting Science Education

Awards for Community Outreach

Nineteen biomedical research institutions in 15 states will receive grants from HHMI to bring science education to their communities. The new awards total $9.78 million.

The grants are designed to encourage biomedical research institutions to use their unique resources, including their scientists, to stimulate young people's interest in science and improve the general public's understanding of science. Since 1994, HHMI has awarded nearly $33 million to biomedical research institutions to support community outreach.

Nearly 300 institutions were invited to compete for the most recent grants. A panel of scientists and educators then reviewed proposals and made recommendations to the Institute. Awardees are:

- Baylor College of Medicine
- Columbia University College of Physicians and Surgeons
- Duke University School of Medicine
- Fox Chase Cancer Center
- Fred Hutchinson Cancer Research Center
- Jackson Laboratory
- Lovelace Respiratory Research Institute
- Massachusetts General Hospital
- Oklahoma Medical Research Foundation
- Pennsylvania State University College of Medicine
- University of California, San Francisco, School of Medicine
- University of Cincinnati College of Medicine
- University of Michigan Medical School
- University of Mississippi School of Medicine
- University of Nevada School of Medicine
- University of Rochester School of Medicine and Dentistry
- University of Texas Medical Branch at Galveston
- Wake Forest University School of Medicine
- West Virginia University School of Medicine

New Undergraduate Grants Competition

HHMI is conducting a new grants competition in undergraduate science education. The Institute will fund collaborations among colleges and programs that provide teaching and mentoring experiences for graduate students and postdoctoral fellows, as well as efforts to help foster communities of undergraduate science students. The competition also asks colleges to address issues raised in *Bio2010*, a report issued recently by the National Research Council. *Bio2010* encourages science departments to create interdisciplinary curricula, provide student research experiences, and improve the quantitative and computational skills of future scientists.

The Institute has invited 198 colleges and universities that grant baccalaureate and master's degrees to compete for these awards. The institutions were invited because of their proven records of preparing students for graduate education and careers in research and medicine. Included are historically black colleges and universities and other institutions with large enrollments of minority students.

The proposal deadline is October 15, 2003. Four-year grants ranging from $800,000 to $1.6 million will be awarded in 2004. This is the sixth competition over the past 15 years that targets life-sciences education at colleges and nonresearch universities; to date, HHMI has awarded $186 million to 121 such institutions. The Institute awards similar grants to research universities.

Regional Awards Extended

The majority of HHMI's grants to Washington, D.C.-area K–12 science education programs will be extended through the 2004 fiscal year. One-year awards totaling $800,000 will support programs for elementary and secondary school students and science teachers in the Montgomery County and Prince George's County (Maryland) public schools and at the Chesapeake Bay Foundation and Audubon Naturalist Society, both of which conduct science education programs in the metropolitan area.

Since 1990, the Institute has awarded almost $9 million in grants for K–12 science education in the Washington, D.C., area, where HHMI headquarters is located.

Assessing Undergraduate Research

Many scientists and science educators believe that research experience is good for undergraduates. But no one really knows whether that's true, because the educational value of undergraduate research is only now beginning to be assessed systematically.

Such a process is about to get under way with a two-year project led by Washington University in St. Louis. Using a $50,000 minigrant from HHMI, a consortium of 43 colleges and universities will design an assessment tool to collect and analyze data on the impact of undergraduate research on student intellectual development and career-related goals. Sarah C. R. Elgin, HHMI program director at Washington University, will head the project.

In October 2002, the Institute invited directors of HHMI-supported undergraduate science education programs to submit proposals for a collaborative minigrant. The undergraduate grants program staff reviewed 15 proposals before selecting Washington University's project.

Support Extended for Cold Spring Harbor and Marine Biological Laboratory

New grants totaling more than $3.5 million will continue HHMI support for postgraduate education at Cold Spring Harbor Laboratory (CSHL) in Cold Spring Harbor, New York, and the Marine Biological Laboratory (MBL) in Woods Hole, Massachusetts. The four-year grants include $1.32 million to CSHL and $2.2 million to MBL.

At CSHL, the grant will support 10 laboratory and 5 lecture courses, including new courses on stem cells and proteomics and advanced courses in neurobiology. MBL's award will support 13 courses, including a biology of parasitism course made available to HHMI international research scholars through special fellowships.

Over the past 15 years, HHMI has awarded a total of $10.4 million to CSHL and $8.2 million to MBL to support postgraduate courses that span the biological disciplines and the computational and physical sciences.

"Both programs represent the latest scientific knowledge presented by outstanding teachers," says William R. Galey, who heads HHMI's graduate grants programs. "Our support continues our commitment to exceptional graduate education opportunities."

— JENNIFER BOETH DONOVAN

PRESIDENT'S LETTER

Hybrid Vigor at Janelia

KAY CHERNUSH

With the mist-shrouded vista of Sugarloaf Mountain as a backdrop and sheltered by a small city of tents, we formally broke ground for HHMI's Janelia Farm Research Campus on a cool, wet morning in early May. Nearly 300 civic, business and governmental leaders from the greater Washington area—among them Virginia Governor Mark Warner and Scott York, chair of the Loudoun County Board of Supervisors—joined the Institute's trustees and leadership for this historic occasion. The ceremony provided a welcome opportunity to look ahead and think about the kind of science we hope to nurture in this extraordinary new environment.

Some 70 years ago, the Pickens family named the land now owned by HHMI for their two daughters, Jane and Cornelia. It was a kind of genetic recombination of the two names and, as many of you will appreciate, a lot of hybrid vigor can accompany the union of two different varieties.

So we have decided to keep the name "Janelia Farm," both as homage to the rich history of the place and in recognition of the evolving research that will occur in its laboratories. If you think ahead a decade or more, a "Proteomics Center" or "Genomic Institute" might seem scientifically outdated, even a little quaint. The scientific focus at Janelia Farm will evolve as new opportunities emerge and, therefore, the name "Janelia Farm" conveys both a sense of timelessness and a sense of place.

The "farm" also provides an excellent metaphor for what we are about to undertake, as Julie Graf, the HHMI program director at the University of Colorado at Boulder, pointed out to me. Julie, who grew up on a farm, sees many analogies between farming and biomedical research. After all, what is a farm? It's a place of fertile soil, where crops are nurtured. A farmer chooses what to plant, and then fertilizes and waters those crops to support a process of continual renewal.

We will do something similar at Janelia Farm: We will identify the best scientists and nurture their research in a fertile environment that will help them to work at the forefront of their fields. Through a process of renewal—not unlike the planting, growing and harvesting of the farmer's seasonal routine—we will establish a research culture that evolves and refreshes itself as new opportunities arise.

It's useful to remember that the farmer is the quintessential "multidisciplinarian." He has to have more than superficial knowledge about many things: equipment repair, botany, meteorology, soil chemistry and how to birth a calf. Likewise, the research at Janelia Farm will be interdisciplinary in nature and will involve scientists who are excited to work in an environment that brings biologists together with physicists, computer scientists, engineers and chemists.

That vision for a multidisciplinary, collaborative community of science emerged from the early conversations that David Clayton, Gerry Rubin and I had with the Trustees. We sought ways to expand the boundaries of HHMI's biomedical research program, to create a place that would also serve as a scientific nexus for our investigators and for scientists from around the world. Each step toward fulfilling the vision has required creativity and multidisciplinary collaboration among scientists, architects, engineers and building contractors.

As director of planning for Janelia Farm, Gerry Rubin has worked closely with Robert McGhee, the Institute's architect, and consulted not only with HHMI investigators, but also with scientists from around the world. That knowledge has guided Rafael Viñoly's architectural vision for the new campus and kept the design tightly linked to the scientific program. In the coming months, as the design is finalized and construction moves ahead, the focus of attention will be on refining the details of how the Janelia Farm program will be organized and on the early stages of scientific recruitment. The first step in that direction has been taken—in August, Gerry will officially become the first director of Janelia Farm. Later this year, we will also announce the creation of a committee of eminent scientists—among them Joseph Goldstein, a member of the HHMI Board of Trustees, and Craig Thompson, chairman of the Medical Advisory Board—that will help advise us on various aspects of the Janelia program.

In short, we hope that HHMI and the entire scientific community will be beneficiaries of hybrid vigor—through the interdisciplinary research that our scientists will perform at this new technology campus—as exemplified in the hybrid name, Janelia Farm.

Thomas R. Cech
President
Howard Hughes Medical Institute

Up Front

Science Behind the Screens

Tapping the power of distributed computing, biophysicists push the rate of their protein-folding simulations toward warp speed.

Although its name may evoke visions of washcloths and towels, the Folding@Home project is in fact serious science. Project volunteers offer the power of their home computers to help researchers study protein folding. In the process, they help speed the collection of data that could lead to answers about disorders such as Alzheimer's disease.

The really great thing about the project is the scale, says HHMI predoctoral fellow Christopher Snow. "If I have an interesting idea, I can come in over the weekend and get 10,000 computers working on it!"

Snow, a Ph.D. candidate in biophysics at Stanford University, can tap that kind of computing capacity courtesy of individuals around the world who loan him unused processing power online. Their common goal is to help scientists figure out how protein molecules fold into their final shapes—a challenge that ranks as one of the toughest and most important in biology.

Properly folded proteins are nature's "nanomachines," serving as molecular gatekeepers and cellular scaffolding, among other functions. Cells couldn't work without them. Indeed, life would not be possible without them.

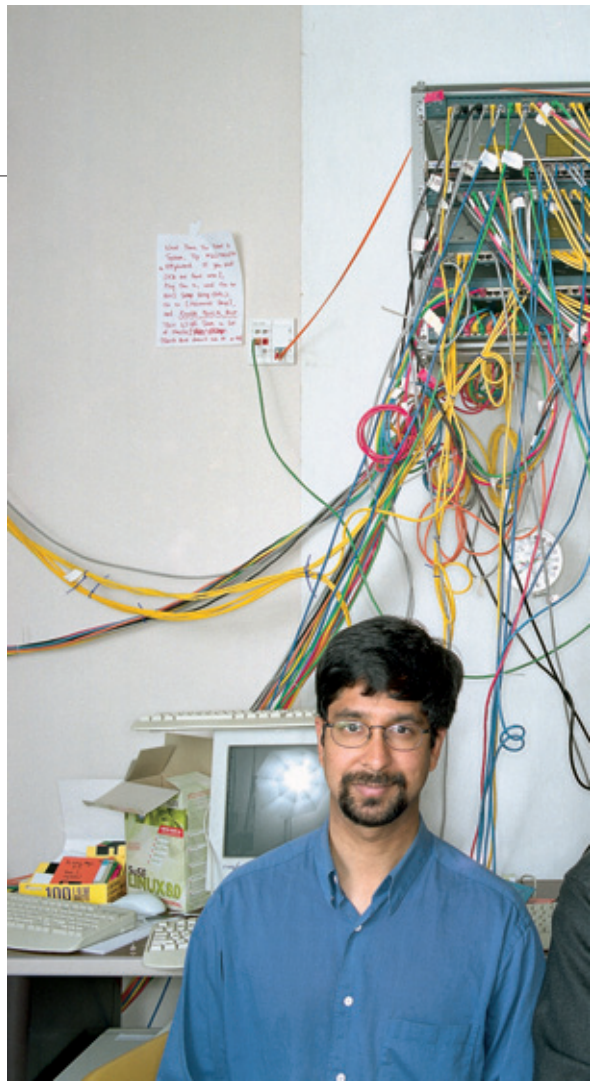
By contrast, improperly folded proteins are like tiny time bombs. The mutated molecules not only fail to perform their jobs in the cell, but also can form sticky, insoluble clots that arrest or even kill the cell. A wide variety of disorders—including Huntington's, Parkinson's, and Alzheimer's diseases—are thought to derive from improper protein folding. Folding@Home research could therefore help scientists discover the origins of, and possible treatments for, this rogues' gallery of maladies.

Ever-Morphing Molecule

Folding@Home software, which is free for the downloading, currently runs on an average of almost 100,000 personal computers around the world every day, and Snow could potentially draw on any or all of them. Not that he'd be bothering their owners in the slightest: From the user's perspective, Folding@Home is just a stark-looking screen saver in which a molecule of some sort keeps reappearing from different points of view. Like any good screen saver, Folding@Home vanishes at the first keystroke; it pops up again only after the machine has been sitting idle for a while.

The magic is in what's happening behind the scenes. This screen saver is actually a small but sophisticated molecular-simulation package that takes advantage of the computer's unused processing power. The image on the screen is actually a simulated protein molecule, temporarily frozen at one instant in time while the computer calculates what it will look like an instant later. The results are automatically transmitted back to the researchers at Stanford each time the PC connects to the Internet. And in the meantime, the user will get quite a show, gain some insight and enjoy the good feeling of contributing to scientific knowledge.

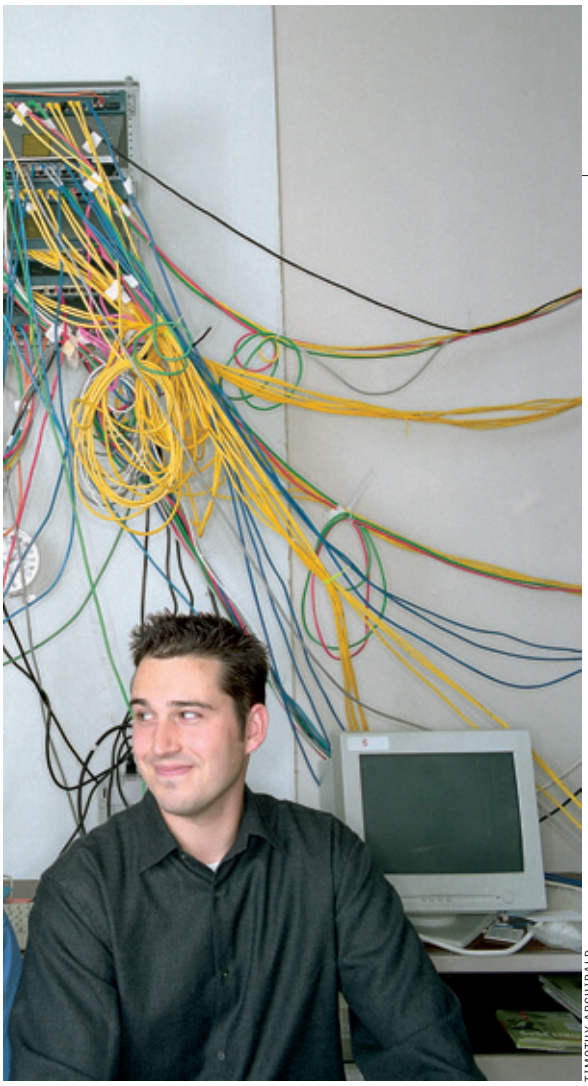
This is what draws people into the project, says Vijay Pande, the Stanford biophysicist who launched the Folding@Home project three years ago. When you look at who's downloading the software, he says, "it varies from people with an interest in computers, to people interested in biology, to people interested in helping fight disease"—not to mention a fair number of high school students, whose teachers find that Folding@Home is a unique way to get their classes excited about science. The users have also formed dozens of teams, with names such as "Dutch Power Cows" (706 members) or "Overclockers Australia" (3,184 members), and keep tabs on who has contributed the most processing time.



To help analyze protein folding, Vijay Pande (left) and Christopher Snow can borrow the power of tens of thousands of computers worldwide.

"This is like having a whole new kind of 'funding agency' for research—namely, the general public donating its computers," says Pande. "When you factor in the maintenance they're doing, the operating system upgrades, and so on, that's a gigantic resource!" It's also a godsend, he adds, because the scientists who work on this problem need all the help they can get.

When a protein molecule is constructed inside the cell, Pande explains, it starts out as a simple chain of amino acids: smaller compounds that are linked together like so many beads on a string. The sequence of amino acids—there are 20 different kinds—determines the type of protein. But even as the



TIMOTHY ARCHIBALD

protein is forming, subtle interatomic forces cause the chain to start tangling like a nanoscale telephone cord. Every chemical bond in the molecule is involved—potentially thousands of them—each one stretching, twisting and bending until at last the chain achieves stability. Indeed, the complexity of the folding process goes far beyond anything that can be measured in the laboratory, says Pande; the only way to understand it in detail is by computer simulation.

But simulation has its own problems. Proteins typically take about a millisecond (one thousandth of a second) to fold, yet this process is so complex that the fastest PC in existence can simulate only a nanosecond (one billionth of a second) in a day. "That's a million times slower," says Pande. "So it would take you a million days, or roughly 3,000 years, to finish—and then you'd only see one result." By being artful about the programming and the analysis, however, one could get away with "only" 10,000 days, he notes.

That's still 30 years. But if researchers can't wait that long, Pande says, they can find the capacity to do 10,000 simulations at once by breaking up the calculation into that number of pieces. Each of 10,000 computers may then work independently and simultaneously on one piece. So the only problem remaining, he recalls, was "Where were we going to get 10,000 computers?" Forget about buying them; a computer farm that large would cost $10 million or more and be a nightmare to administer. Pande and his colleagues would have to borrow them.

Previous distributed-computing projects, such as distributed.net and SETI@home, showed them how. Distributed.net was the first major Internet distributed-computing project, and its goal was factoring large numbers, important in cryptography and code breaking. SETI@home had already enticed some half-million people around the world to run screen savers that processed radio signals for the search for extraterrestrial intelligence. "So in October 2000," says Pande, "my group started Folding@Home." With some strategic help and advice from Adam Beberg (founder of distributed.net and now with the Cosm Project), Pande's team developed the software for Folding@Home. They found their first volunteers from Cosm's mailing list. From there, Folding@Home grew rapidly as a result of several reports in the press as well as by word of mouth. In the relatively brief period since then, more than 400,000 processors have contributed at least some time to the project, Pande reports.

The Speed of Simulation

Snow joined the group as a graduate student just a few months after the project began, and Pande gives him considerable credit for nursing the software through its infancy. "Chris did a lot to shape things up and make it more solid," he says. Snow then went on to help validate the approach by running multiple simulations of a small artificial protein, BBA5, that could easily be compared with experimental results.

The results, which agreed quite closely with those obtained in laboratory experiments by Martin Gruebele and his students at the University of Illinois at Urbana-Champaign, were published in the November 2002 issue of *Nature*. "What they did was almost unheard of," says a deeply impressed Gruebele. Until then, the longest protein simulation on record covered only about one microsecond (one millionth of a second), he explains. "But Vijay and his group just blew away that timescale completely. They got 700 microseconds"—long enough to simulate BBA5's folding all the way.

Of course, as Pande and everyone else on the project takes care to emphasize, they're still far away from simulating most real proteins—and even farther from finding cures for diseases. The BBA5 chain is only 23 amino acids long; naturally occurring proteins often have hundreds or even thousands of amino acids. This computational challenge dwarfs Folding@Home's resources.

Still, Folding@Home needs to grow in processing power only by another factor of 50 to 100 to be robust enough to take on the big molecules. Given computer science's famous Moore's Law, which states that machine processing power doubles every 18 months or so, "that's not a factor that frightens you," Gruebele points out. Nor is the Folding@Home group waiting around.

Snow, for example, is already planning to take on the amyloid precursor protein, a protein that seems to be critical in Alzheimer's disease. This protein misfolds and then forms aggregates; these aggregates are believed to lead to Alzheimer's disease. "Understanding the structure of these aggregates is fundamental to understanding Alzheimer's disease," says Pande, "and that's what we'd like to simulate."

In the meantime, graduate student Bojan Zagrovic, another HHMI fellow working in Pande's group, has been looking at the structure of proteins before they are fully folded. "For a long time this was ignored," says Zagrovic. "But thanks to the huge sampling from Folding@Home, our research seems to indicate that the unfolded state is not random." As the simulated molecules begin to bend and twist, he says, "you find that they very quickly crumple into all these weird-looking shapes"— like spaghetti as it softens in boiling water. "And if you average all that crumpled spaghetti, you find that the average shape is already very close to the final folded state!" That's a totally unexpected result, he says, and no one quite knows what to make of it. "But that" he says, "will be my thesis project."

—M. MITCHELL WALDROP

» For more information, see *folding.stanford.edu.*

Better Learners

Educators are counting on the Web to help students tackle science's tougher concepts.

When Bethany Lye's suitemate at Ohio's Kenyon College was diagnosed with a brain tumor, Lye vowed to help. She attended her friend's introductory biology class and took voluminous notes, complete with detailed diagrams and sketches of molecules, cell division, cellular structure, enzymatic reactions and the mechanics of metabolic energy production.

Thanks to surgery and radiation therapy, Lye's friend, Marissa Boyan, recovered, returning to Kenyon after a six-month absence, although she never did complete that biology course. And Lye, now a senior majoring in biology and English, ended up helping more than her friend.

Encouraged by Kenyon professor Chris Gillen to share her material with other students, Lye adapted her notes and drawings for a new Web page. Her "Success in Intro Biology: A Student's Guide" debuted in fall 2001. Initial student feedback says it's a hit. "Some people get bored" reading textbooks or printed handouts, Lye says. "This is something different. This could be someone's ticket to finally getting it."

Helping students "get it" online is the aim of "Courses on the Web," a multisection Kenyon Web site that includes lecture materials, supplementary information and links, as well as exercises and interactive quizzes. Supported by HHMI grants, the site contains three Web-based Kenyon courses for biology majors and two for nonmajors.

Kenyon's site is part of a trend at colleges and universities to use online tools in support of learning. At one extreme is the Massachusetts Institute of Technology, which turned heads last year when it announced its plans to make available on the Web, at no cost, the contents of every university course—some 2,000 in all—by 2007. Other institutions, such as Columbia University, make proprietary course materials available to the public for a fee.

Kenyon's Web focus is its own students, hoping to make them better learners through online access to syllabi, course content, tutorials and links to "external" knowledge-rich sites such as the National Institutes of Health and the Library of Congress.

Net Enhancements

David Lampe, an assistant professor in biological sciences at Duquesne University, runs a portion of a Web-based course called SuperLab I that gives students their first experiences in the techniques of molecular biology. Lampe's students have spent the past three years cloning and sequencing human DNA and using the Internet to analyze their samples.

"When you're dealing with DNA sequences, the Web is indispensable; that's where all the [sequence] data is located," Lampe says. In the process, he says, his students "realize how much stuff they can figure out": Did they get a gene, or is their sequence near a known gene? Are there any diseases associated with the gene? What's the structure of the gene, and what is its protein like? Are there any homologs in the human or other genomes? In fact, Lampe adds, students "get pretty revved up about the process, because they don't know what they're going to get, and neither do I. That level of uncertainty, which is eventually resolved by using the Internet, is something that gets them very involved and something that they like a lot."

Paul Beam, a professor of English at the University of Waterloo in Ontario, Canada, has written about the Web's potential to transform learning. What the Internet adds, he says, is around-the-clock accessibility to course materials for both students and teachers, the capacity to make instant updates on assignments or schedules and the introduction of the interactive communication tools that have become ubiquitous over the past decade: e-mail, private chat rooms and Web bulletin boards.

Ed Dole, coordinator of the introductory biology course at the University of Illinois, Urbana-Champaign, weaves Web-based features into the curriculum "not as a replacement, but rather an enhancement." Students taking the course are required to participate in two "Web Crossing" lab assignments, in which they use a restricted, password-accessible space on the Internet to exchange ideas and critique each other's work. University teachers who advocate integration of the Web often point out that this sort of peer exchange opens lines of

Web sites like these at Kenyon College enable students to study science at their own pace, and may help them become better learners.

communication that might never have been established otherwise between students and teachers and among students themselves.

The Internet is also credited for its capacity to convey visual information in compelling ways; complexity can be rendered vividly in three-dimensional visuals. Tom Susman, a junior at Kenyon majoring in molecular biology and political science, elected to take a hands-on lab class that included examination of cat anatomy. During and after dissection, Susman and his fellow students used workstations in the lab to access Kenyon's "Cat Anatomy Tutorial," authored by biology professor Patricia Heithaus, which displays detailed pictures of feline physiology and provides arrows and other markers identifying organs, muscles and bones. "I thought it was very helpful," Susman says. "It was easier and clearer to see the actual anatomical structures and know what they were. It was also a good way to quiz yourself outside the lab."

Indeed, working on their own, students can digest information at their own pace—another of the Web's potential advantages. "You actually benefit from your mistakes," says Joan Slonczewski, a Kenyon biology professor and program director of the college's HHMI grant. "You get instant feedback. You're testing things out and getting an immediate response. It's very different from traditional quizzes."

She points to an interactive multiple-choice quiz in her introductory genetics and development course. She built the quiz by using Hot Potatoes software, which is free to nonprofit educators. If a student selects an incorrect response, a reply explains why the choice was incorrect and offers a hint toward the correct response. When the student finally selects the correct answer, he or she receives a score discounted for the number of attempts required. "They learn something every time, no matter which responses they pick," Slonczewski says.

Biology in Three Dimensions

Slonczewski credits the Kenyon Web tutorial on genetics and its three-dimensional images with helping her students "learn as much Mendelian genetics and gene-product interaction in a week as I used to teach in a month in the traditional lecture-and-learn course." She also reports that Kenyon's student-authored "Biomolecules" tutorials have enabled her sophomores and juniors to accurately "recognize amino acid residues within protein model structures." Slonczewski now tests students on this material, something she "never would have thought of doing" in pre-Web days, when such knowledge, in her view, was beyond the grasp of most students. Web graphics have helped make it palpable, she says.

"Doing things in the electronic medium adds an interactive dimension that really does not exist in a medium like the standard textbook," says Ron Stevens, professor of microbiology and education at the University of California, Los Angeles, School of Medicine. Over the past decade, in part with HHMI grants, Stevens has developed a learning tool called IMMEX that has gained a foothold in classrooms ranging from kindergarten to medical school. The med school version presents students with a series of real-world "problem sets" in immunology, microbiology, pediatrics, respiratory therapy and clinical practice.

During a two-hour session, groups of four students sit at a workstation and are presented with three patient cases, replete with symptoms, results of a physical exam and lab assays of tissue and fluid samples. As in an actual hospital or clinic, the fledgling doctors cooperate to diagnose and recommend courses of treatment. The idea is for doctors-in-training to acquire important skills before entering the clinic, where the stakes are high.

Enthusiasts like Stevens say that helping students of all ages put facts they've learned to work is "just the tip of the iceberg." Web-based learning is no replacement for classroom instruction, they say, but it can tell educators new things about how students learn and therefore help them learn more effectively.

—JAMES SCHULTZ AND PETER TARR

WEB-TEACHING RESOURCES

Kenyon's "Courses on the Web": *biology.kenyon.edu/HHMI*

Hot Potatoes quiz-making software: *web.uvic.ca/hrd/halfbaked*

IMMEX: *www.immex.ucla.edu*

My Computer, My Writing Coach

Whether they're taking Biology 101 or an advanced course on genetics, students need to be able to write coherently about what they're learning. Now they can help each other improve their writing skills, with an Internet-based program for networked computers.

With support from an HHMI grant, UCLA chemistry professor Orville Chapman developed a program called Calibrated Peer Review (CPR) that teaches students to read critically for content and style and to write clearly and persuasively about science. Based on the peer-review model of modern science, CPR trains students to analyze the writing of—and to profit from being reviewed by—other students. It includes a growing library of ready-to-use assignments, although instructors can also write their own.

CPR, now being used by UCLA and more than 100 other colleges and universities nationwide, works like this: A student logs on to get an assignment, reads recommended source materials and then writes a brief essay (150–350 words) that's intended to answer a set of questions. The student then reviews and grades three sample essays on the same subject, using criteria such as "Does the text contain unexplained jargon?" The CPR program scores the reviews and gives feedback on how they compare to a model review.

When the student does well enough on test reviews, he or she gets to analyze and score three real essays submitted by other students. Finally, the writer scores his or her own essay and can access other students' reviews to see what peers thought of it.

CPR provides individual feedback, even for students in large lecture courses, without overburdening the instructors. The educational payoff of peer review can be enormous, says Chapman. "Writing about science produces a different kind of learning about science—real understanding."

—JENNIFER BOETH DONOVAN

» For more information see *cpr.molsci.ucla.edu/cpr_info/main.asp*

By ELIA T. BEN-ARI

Illustration by Richard Tuschman

# of Joints and Genes

Genetics research could help spell relief for aching joints.

Each time a healthy person takes a step, bends a finger, or raises an arm, the ends of the two bones that come together in a joint slide across one another gracefully, with less friction than that of a skate gliding on ice. A smooth, lubricated layer of cartilage tissue that covers the ends of the bones makes that action possible. This tough, somewhat elastic material also acts as a shock absorber in the joint.

But joints can take only so much stress. Damage resulting from injury, obesity, overuse, repetitive movements or improper joint alignment such as bowlegs or knock-knees can contribute to cartilage degeneration and the development of osteoarthritis—the most common type of arthritis. A leading cause of disability among adults, osteoarthritis accounts for billions of dollars in health-care costs and lost wages, not to mention considerable pain and suffering each year.

Researchers used to think that osteoarthritis, whose incidence increases with age, was a simple case of age-related wear and tear. Recent studies, though, suggest that the disease process is more complicated.

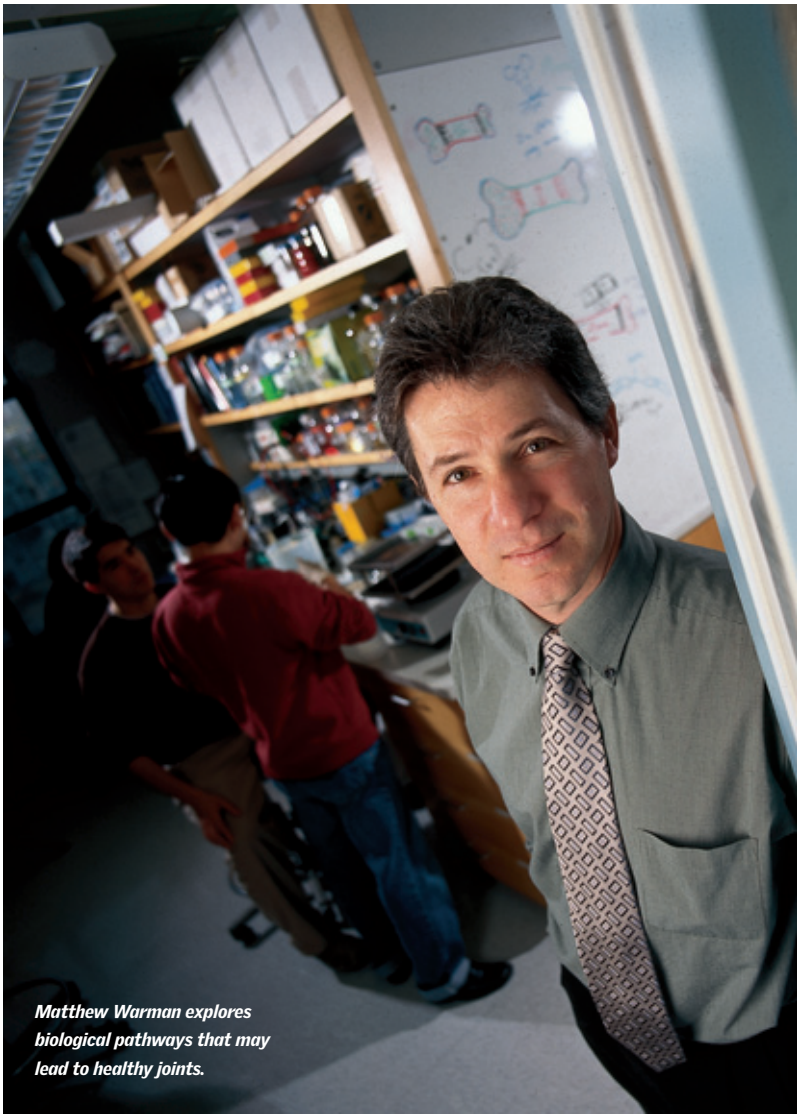
The Joint-Gene Connection

In his laboratory and in the clinic at Case Western Reserve University School of Medicine in Cleveland, HHMI investigator Matthew L. Warman studies rare hereditary disorders that affect the joints. Through these studies, Warman hopes "to understand what the essential biological processes are that get a joint to last for an entire lifetime of use and not fail." Following that, the challenge is "to figure out how to intervene in these biological pathways to minimize the risk of joint failure in common joint diseases."

Once you find a [rare-disease-causing] gene," Warman says, "it gives you an entrée to a biological pathway." That pathway is also likely to be involved in maintaining healthy joints for all people.

There is strong precedent for using unusual genetic diseases as a starting point for insights into more common diseases, notes HHMI investigator David M. Kingsley, a developmental biologist at Stanford University School of Medicine. One of the strengths of the genetic approach, Kingsley says, is that "genetics is great for taking a complex problem and breaking it into manageable bits." Genetics also allows researchers to create model organisms for human diseases, which can be used to test potential treatments or explore the effects of various gene mutations on disease.

The study of rare genetic syndromes that cause severe heart disease in young children helped researchers identify the mechanisms and pathways that control cholesterol and lipid metabolism and the role that problems in these pathways play in adult heart disease. For example, Michael S. Brown and Joseph L. Goldstein's Nobel Prize–winning work on severe familial hypercholesterolemia, which results in abnormally high levels of cholesterol in the blood, led to new approaches for treating and preventing atherosclerosis. "We're at a very early stage in the arthritis field," says Kingsley. "But having seen the impact of genetic approaches in heart disease, I'm optimistic that a concerted attack on what may look like rare or more severe forms of arthritis … will help provide molecular targets that can be manipulated to make joints healthier or repair [damaged] joints."

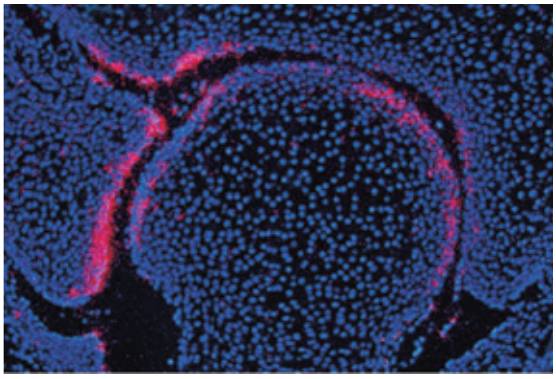


Matthew Warman explores biological pathways that may lead to healthy joints.

The Promise of Lubricin

Warman's studies of the "one-in-a-million" inherited joint disorder known as camptodactyly–arthropathy–coxa vara–pericarditis syndrome, or CACP, exemplify how genetic approaches are providing new perspectives on what keeps joints healthy and how things can go wrong. CACP can cause joint deformities such as permanently bent fingers and symptoms similar to those of osteoarthritis, including stiff, painful and swollen joints and limited mobility. In youngsters with CACP, symptoms of joint swelling and stiffness begin in mid-childhood, and joints are destroyed at an early age. Cells in the synovium—the thin layer of tissue that lines the joint and produces the synovial fluid that nourishes cartilage—grow abnormally in these children. When joint symptoms become so severe that they limit the activities of everyday life, the only effective treatment is joint replacement surgery.

In 1999, an international consortium of researchers led by Warman found that mutations in a particular gene on human chromosome 1 cause CACP. Around the same time, other scientists, including Gregory D. Jay of Brown University, discovered that this same gene is switched on in human synovial cells and codes for lubricin, long thought to be a key joint lubricant. This convergence of research not only showed that inherited defects in lubricin could lead to damaged joints, but also underscored that lubricin is important for the health of joints generally.



PATRICK SMITS AND VERONIQUE LEFEBVRE

Lubricin mRNA is expressed by cells at the surface of a developing mouse elbow joint. Cell nuclei, stained blue, delineate the three skeletal elements (humerus, radius, and ulna) that form the joint. Cells at the surface of these elements surround the newly forming joint and express lubricin mRNA (pink).

DANIEL LEVIN

"This protein is a major contributor to reducing friction in joints," Warman says. "When lubricin is genetically deficient, joints wear out from the surface down." In the future, he hopes, doctors may be able to treat CACP by replacing lubricin directly or through gene therapy.

To study lubricin in action, Jay—an emergency physician and bioengineering researcher—uses a friction apparatus that simulates the mechanics of abutting cartilage surfaces in a joint. His findings suggest that lubricin made and secreted by synovial cells and chondrocytes in the joint normally reduces friction and wear by coating the cartilage layer and "keeping the two surfaces apart at the nanoscale," he says. Warman likens the apparent effects of lubricin at the joint surface to that of Teflon on a nonstick frying pan. "Teflon firmly adheres to the metal underneath," he says. "It's not floating on the surface of the frying pan, like oil might be."

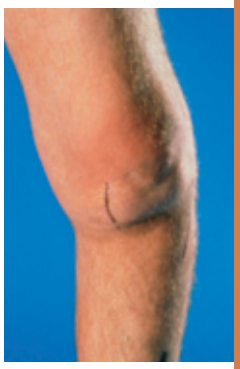
Results of recent studies in mice by Warman, John D. Carpten of the National Institutes of Health and Jay lend support to the importance of lubricin in joints. Mice in which the lubricin gene has been "knocked out" via genetic engineering have signs and symptoms like those of humans with CACP; studying them can lead to new insights into the protein's role in maintaining joints. For example, Jay found that there was increased friction in the limb joints of these mice. Warman's studies revealed that lubricin may also normally keep the brakes on synovial cell growth. In the absence of lubricin, Warman says, "we think the synovial cells … become much more aggressive and can potentially invade the cartilage surface," a phenomenon also seen in rheumatoid arthritis. This inflammatory autoimmune disease affects more than 2 million Americans, causing pain, swelling, stiffness and progressive loss of function in the joints.

Extrapolating from what goes wrong in CACP and from knowledge of how lubricin works, Warman says, it's not hard to imagine how acquired, nongenetic defects in lubricin might play a role in common joint diseases. He and Jay have joined forces to test the hypothesis that breakdown of lubricin by enzymes released in inflamed or injured joints, or diminished production of lubricin in aging joints, might contribute to joint damage in osteoarthritis and rheumatoid arthritis. If enzymes are chewing up lubricin, impairing its ability to keep joints moving smoothly or to curb uncontrolled synovial cell growth, drugs that inhibit these enzymes might help prevent disease. In addition, if lubricin levels are low, Warman says, doctors might someday be able to prevent or treat disease by injecting new

PRINCESS MARGARET ROSE ORTHOPAEDIC HOSPITAL/SPL/CUSTOM MEDICAL STOCK PHOTO (KNEE)

When Cartilage Breaks Down

Articular cartilage consists of cells called chondrocytes in an extracellular matrix made up of a fibrous network of collagen proteins and proteoglycans—proteins with chains of sugar molecules attached. "Collagens give cartilage strength, and the proteoglycans are able to hold water and give resistance to compressive forces," explains biologist Mary B. Goldring of Harvard Medical School.



"Somehow, biomechanical damage [caused by factors such as joint injury or overuse] stimulates the chondrocytes to start making enzymes that break down cartilage," Goldring says. As the cartilage surface gradually erodes under this attack, the underlying bones begin to grate against each other, causing chronic joint pain and swelling. Bony outgrowths often form at the edges of the joint and protrude into the joint space, exacerbating the disease.

Goldring is familiar with these and related phenomena from her own research. She uses a chondrocyte cell-culture system she developed to study how proteins produced in response to inflammation in osteoarthritic joints not only stimulate production of enzymes that break down cartilage but also impair the ability of chondrocytes to repair the damage.

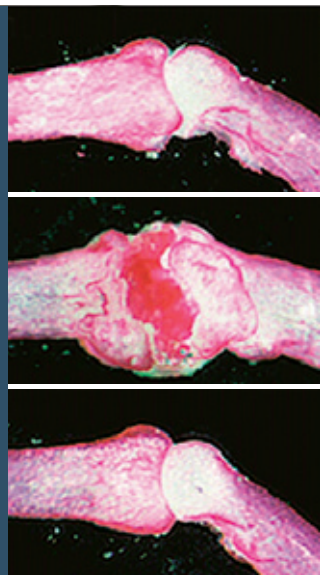
The prevailing view is that the initial stages of osteoarthritis involve an imbalance between production and breakdown of collagen and proteoglycans, which normally turn over at a low level, says Roland W. Moskowitz, a rheumatologist at Case Western Reserve University and president of the Osteoarthritis Research Society International. "We're not sure what kicks off this imbalance," he says, but multiple risks—including aging as well as metabolic factors and various mechanical stresses—could all contribute to the acceleration of cartilage breakdown. Some people also have a genetic predisposition to osteoarthritis. "You may need one or several genes" that predispose to disease, Moskowitz says, "and then something else makes you more susceptible"—for instance, a job involving lots of kneeling, squatting or heavy lifting.

The effects of osteoarthritis range from mild to disabling. People with the disease may awaken with stiff, achy joints or have trouble walking, climbing stairs, getting up from a chair or even holding a pen. Although the best available therapies, which include medication and proper exercise, relieve some of the pain and improve function, they can't stop disease progression. If impairment becomes severe, joint replacement or other surgery is usually the only remaining option. Clearly, as the aging baby boomers now begin to swell the ranks of the roughly 21 million Americans affected by osteoarthritis, the need for new treatments is becoming more urgent. **—ETB**

lubricin into people's joints or giving them drugs that cause cells in the joint to pump out more lubricin.

Recent work in Jay's laboratory suggests that lubricin breakdown may play a role in the early stages of osteoarthritis that develops as a consequence of joint injury. As an emergency physician, Jay sees people whose joints are swollen with fluid as a result of sports injuries or other blows to the joint that could lead to osteoarthritis somewhere down the line. It turns out that lubricin in the fluid removed from these patients' joints is degraded and has reduced lubricating capacity. In addition, he says, their articular cartilage (cartilage in the joint) shows signs of early erosion. The injection of new lubricin into a joint after injury could help prevent arthritis from developing in patients like those Jay sees.

Interest in lubricin, a protein that "had not been on the radar screen a few years ago," is growing, Warman says. At this year's annual meeting of the Orthopaedic Research Society, an entire session was devoted to the biology of lubricin. Scientists described studies on the distribution of lubricin in osteoarthritic cartilage and the susceptibility of lubricin to be broken down by enzymes that may be found in arthritic joints, and they reported on efforts to tailor lubricin production and secretion in tissue-engineered cartilage being developed to repair damaged joints. Researchers also revealed that simulating natural joint motion in engineered articular cartilage increases lubricin expression by chondrocytes. This finding may not only enhance the quality of engineered cartilage but could also help explain why physical therapy involving passive motion is beneficial for injured and arthritic joints, Warman says.



The joint from a hind limb of a progressive ankylosis (ank) *mouse (center photo) is stiff and swollen and shows abnormal calcification (bright red). Joints of* ank *mutant mice that have been "rescued" by addition of a normal* ank *gene (bottom) are virtually indistinguishable from joints of normal mice (top).*

FROM HO, A.M., JOHNSON, M.D., AND KINGSLEY, D.M. 2000. *SCIENCE* 289:265-270. © 2000 BY THE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE.

Tartar Control

At his lab in Palo Alto, Stanford's Kingsley is also dreaming up new ways to use genetic approaches to understand joint maintenance and improve arthritis treatment. About three years ago he and his colleagues identified the gene responsible for a severe progressive form of arthritis in mice that shares many features with human arthritis, and they showed that a single mutation in this gene, known as *progressive ankylosis* (*ank*), causes the disease.

In mice with the *ank* mutation, crystals of calcium phosphate

Studying the Embryo to Heal the Adult

The Holy Grail for many orthopedic surgeons is the ability to rebuild or replace not only damaged joint cartilage but tissues, such as tendons and ligaments, that support the joints. Basic research in pursuit of this objective, by HHMI investigator David M. Kingsley of Stanford University School of Medicine and other scientists, often focuses on factors that control the formation of joints during embryonic development. "Everyone hopes that a better understanding of the process by which joints are originally built may in the long term help devise strategies for repairing joints that are damaged in adulthood," Kingsley says.

In a developing embryo, joint formation takes place largely within dense regions of cells called skeletal condensations, which develop first into cartilage and then into bones and joints. "Along the length of those skeletal condensations, at reproducible times and places during development, you'll see the beginnings of the segmentation process," which splits a bone-to-be into smaller pieces connected by joints, Kingsley explains. If this precisely orchestrated process is disrupted, bones and joints form abnormally.

Among the players in this process are members of a family of growth factors known as bone morphogenetic proteins (BMPs), which control many aspects of joint development by binding to specific cell-surface receptors and triggering a chain of signaling events within the cell. Kingsley and other developmental biologists have shown that mice with genetic defects in particular BMPs have abnormal cartilage and joint formation in different regions of the skeleton. Studies by HHMI investigator Matthew L. Warman, at Case Western Reserve University School of Medicine, and others show that mutations in some of these BMPs, and in factors that interact with BMPs, also cause a range of human hereditary disorders of limb and joint development.

In the developing mouse embryo, the gene for one BMP, called *growth/differentiation factor 5* (*Gdf5*), "turns on in a beautiful pattern of stripes at all of the sites where joints are going to form," Kingsley says. "It's one of the strongest and earliest known markers for the joint-formation process." Two genes closely related to *Gdf5* "also turn on in stripes, but only in some of the stripes," suggesting that BMPs can control formation of specific joints. Indeed, "when we've trawled through the [BMP] genes … we have found small stretches of DNA that will tell a gene to turn on in the elbow, but not in the finger," he says.

"We're interested not only in whether the BMP-signaling pathway plays an important role in stimulating early events of joint formation but also in whether it may be required for later stages of joint maintenance," Kingsley says.

Orthopedic researchers who are developing tissue-engineering techniques to repair damaged joints will also be interested in the results of ongoing studies on BMPs. In fact, Kingsley says, many scientists who spoke at the most recent international conference devoted to BMPs are already exploring the use of these growth factors to help transplanted articular cartilage cells heal cartilage defects. They're also looking at the effects of BMPs on tissues such as tendons and ligaments. **—ETB**

David Kingsley wants to know more about how joints form in the developing skeleton.

KAY CHERNUSH

form in most joints, triggering inflammation and erosion of articular cartilage. "In the latter stages of the disease, the articular cartilage is heavily damaged," Kingsley says. "But even worse than that, [the joints] form osteophytes—bony struts that go from one bone to another all the way across the joint," making the joint rigid. By the time these mice reach six months of age, most of their joints are completely frozen, and they die.

Kingsley and his colleagues found that the *ank* gene codes for a previously unknown protein, ANK, which spans the cell membrane and is produced in articular cartilage and other tissues. Cell-culture and biochemical studies showed that the *ank* mutation leads to a drop in extracellular levels of a small molecule called pyrophosphate—the active ingredient in tartar-control toothpaste. Pyrophosphate is known to inhibit the formation of calcified mineral deposits typically found in tartar, and in the crystals that cause arthritis in *ank* mice. Kingsley's findings suggest that ANK normally provides the equivalent of tartar-control for the joints by stimulating transport of pyrophosphate out of cells and into joint fluid, where it acts to prevent crystal formation.

More recent studies indicate that defects in this tartar-control system also play a role in human joint disease. In the October 2002 issue of the *American Journal of Human Genetics*, an international collaboration led by Kingsley reported that mutations in the human version of the *ank* gene cause a rare hereditary form of a common joint disease known as chondrocalcinosis, or "pseudogout." Among people with this disease, which is less severe than the mouse disorder, calcium-containing crystals build up in the articular cartilage of some joints before age 40, causing pain and inflammation. "In the disease state, the ANK protein is either overly active, which stimulates one type of crystal formation, or it's not active enough, which triggers the formation of a different type of crystal. But in both cases, you end up with joint disease," Kingsley says. "ANK activity has to be within a window—too much may be bad, too little may be bad."

He notes that 60 percent of people with osteoarthritis also have an excess of one or both of these types of crystals in their synovial fluid. However, scientists have long debated whether this is a cause or an effect: Do the crystals play a role in triggering osteoarthritis or are they a by-product of other damage in the joint? In the case of the *ank* mouse, it is clear that the defect in crystal formation is the primary cause of joint disease in the animals, not a by-product of joint damage. Moreover, "regardless of whether crystal formation is a primary or secondary event," Kingsley says, "once the crystals are formed they can act in an amplification loop that probably increases the severity of disease."

For those with the genetic form of chondrocalcinosis, which appears to result from an overly active ANK protein, "a compound that inhibited ANK activity might be something you could give to prevent the formation of crystals and try to prevent that sort of joint pain," Kingsley says. What researchers don't yet know is whether changes in ANK activity play a role in the common, nonhereditary forms of chondrocalcinosis, or in osteoarthritis or other joint diseases. If this turns out to be the case, drugs that affect the protein's activity might be useful in these diseases as well.

As baby boomers age, the human and financial costs of osteoarthritis will only escalate. Still, as Roland W. Moskowitz, a rheumatologist at Case Western Reserve University and president of the Osteoarthritis Research Society International, says, "it may be a while" before safe and affordable treatments for this joint disease are available. Researchers are just starting to understand the complex interplay of factors involved in osteoarthritis, not to mention figuring out reliable ways to diagnose the disease in its earliest stages and measure its progression. Moskowitz may be disinclined to forecast immediate cures, but he has hope for meaningful treatments in the not-too-distant future. Of that promise, he says, "I think we can see light at the end of the tunnel." H

Cold School

A blizzard couldn't stop an Eskimo village above the Arctic Circle from connecting with science.

By Jennifer Boeth Donovan

When the blowing snow of an Arctic blizzard blurs the line between ground and sky in the North Slope village of Wainwright, Alaska, the people who live there call it a whiteout. But it takes more than a whiteout to keep Elsie Ahmaogak and dozens of her neighbors from trudging to the village school for a science festival.

Ahmaogak, an Iñupiaq Eskimo home-to-school coordinator, grins as she watches giggling groups of children try to close their hands around a hologram of a pig. "We like it when science comes to the village," she says, "because a lot of us can't take the long plane rides to get to the science."

Perched on the edge of the Arctic Ocean, 300 miles north of the Arctic Circle, Wainwright is a whaling and trapping village. It's home to 493 Iñupiat Eskimos, 150 of them preschool through 12th-grade students at Alak, the village's only school. The science festival that drew them out in that February blizzard is part of an HHMI-supported outreach program of The Imaginarium, a science museum in Anchorage that takes hands-on science to remote villages all over the nation's largest state. Since 1992, HHMI has awarded $700,000 in grants to The Imaginarium. The museum uses HHMI support to develop the hands-on science activities that The Imaginarium brings to more than 300 native villages. Corporations such as ConocoPhillips, the largest oil producer on the North Slope, or the schools themselves, foot the substantial bill for delivering the programs to the villages.

ON THE "ROAD" AGAIN

When they take their science show "on the road," Imaginarium outreach workers Ramon Wallace and Amy von Diest don't travel light. They stuff into six 50-gallon Rubbermaid crates nearly 800 pounds of things that fly, float, light up, fall down and spin around; an additional, large black container holds their sound equipment; and of course there's the indispensable complement of parkas, snow boots and sleeping bags. "On the road" is actually a bit of a misnomer, though, because there are no roads to most of their destinations.

On this North Slope trip, for example, Wallace, von Diest and their ample cargo fly Alaska Airlines to Barrow—a town of 4,500 and the northernmost point in the United States. From Barrow, it's bush planes to Wainwright, Atqasuk, Point Lay, Nuiqsut and Kaktovik for two weeks of double-digit below-zero weather outdoors and lively science classes, assemblies and community science festivals indoors.

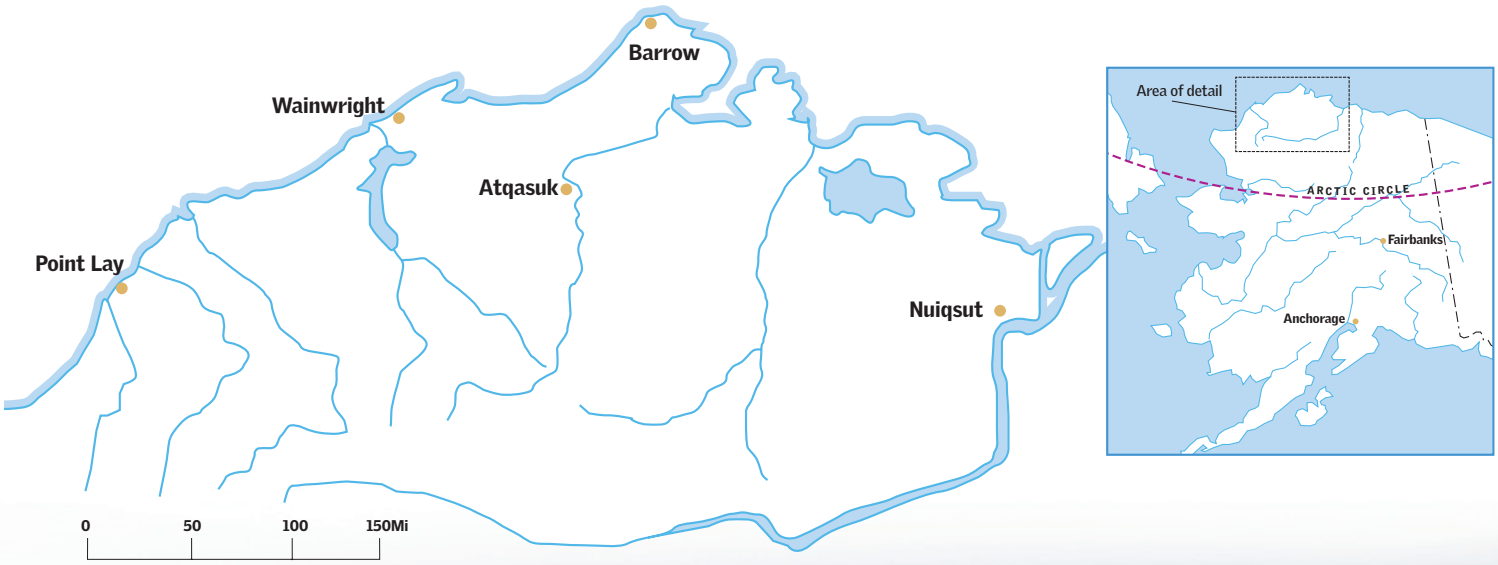
For people of all ages in the remote Alaskan villages, it's as if the circus has come to town. Word spreads rapidly, and excitement runs high. As one little boy told his mother, "the imaginary people are coming." Whole villages turn out for their science festival, with the adults as rapt as the children.

The Imaginarium offers outreach programs on reptiles, insects, electricity, chemistry and flight. The North Slope schools have chosen flight. It's a science subject central to everyday life in villages that rely on planes for their bread, milk and toilet paper; for the citizens band radios that keep them in touch with their neighbors; for the snow machines that have replaced dog sleds as everyday transportation; and for mail, emergency medical care and basketball games with teams from other villages.

In Atqasuk, an inland village of 228 where caribou paw through the ice-encrusted snow to graze, black-haired children ages 5 to 18 stampede up the bleachers of the Meade River School gym for an all-school assembly on "Flights of Fantasy."

JENNIFER BOETH DONOVAN

At the community science festival in Wainwright, Alaska, Eskimo children try to move objects using a battery-powered robotic arm.



JEFF SCHULTZ/ALASKA STOCK

"What flies?" asks von Diest, tossing Wilbur, a rubber chicken, into the air. Not Wilbur—as the fowl prop nosedives to the floor, giggling children shriek their answers: "Planes! Rockets! Ravens!" Von Diest has their attention. "Why can they fly?" she continues. Enlisting students to toss Frisbees, hurl gliders and launch a hot-air balloon, she explains and demonstrates the four forces of flight: weight, lift, drag and thrust.

After the assembly, von Diest shows kindergarten through second-grade children how to make balloon-powered "rockets." A soft buzz fills the classroom as pairs of students help each other send their rockets toward the ceiling. The squabbling and competition that often accompany such projects in primary-grade classrooms elsewhere is conspicuously absent. "Together we have an awesome power to accomplish things," says a poster extolling cooperation, one of a series illustrating Iñupiat cultural values that lines the corridors of the school.

A couple of fifth graders are coaching von Diest in Iñupiaq, now taught as a second language to school children of North Slope villages in an effort to preserve the culture of a people who, a generation ago, were sent away to residential schools and forbidden to speak their native tongue. "Aaka," Stacey says, pointing to a gray-haired woman seated at a school-cafeteria lunch table reserved for village elders. "Grandmother." Von Diest gives it a try: "Anak." The girls collapse in 11-year-old hysterics. "That's the word for poop," gasps one.

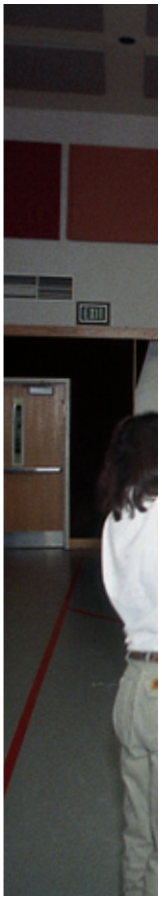
FLYING EGGS

Third through sixth graders are exploring air and gravity with Wallace, making parachutes out of squares cut from large plastic bags, string, orange sticky dots and washers wired together to simulate the weight of a person. Wallace's parachute carries a more fragile payload: a raw egg in a bubble-wrap flight suit. He drops the 'chute, and the egg hits the floor. "He's hurt," shouts a fifth grader, pointing to cracks spreading across the eggshell. "He has a concussion," Wallace agrees, checking the egg for leaks. Nothing is seeping through the cracks. "At least it wasn't fatal."

"While they're having fun making and dropping parachutes, they're learning that air is a real thing with mass, a thing that reacts in predictable ways to pressure and motion, acceleration and free fall," Wallace explains. He gazes around the classroom at some of the parachutes floating gracefully and others hurtling toward the floor, at David repositioning the strings on his 'chute to give it more lift and Josie removing a washer to help her pilot lose weight. "I get so much energy from doing this," says Wallace, "especially when one of the kids 'gets it.' You can see that lightbulb come on in their eyes. There is nothing more exciting."

The high school students are a harder sell. A class called "Wacky Wings" is designed to teach 7th through 12th graders the Bernoulli principle, which says that the faster air moves, the lower the pressure it creates, and Newton's third law of motion—for every action, there is an equal and opposite reaction. "Anybody play baseball?" Wallace asks. Silence. "Anybody a baseball fan?" More silence. The teenagers of the frozen tundra, where ball games of necessity are indoor sports, are not relating to the aerodynamics of a curve ball that makes the air move faster as it spins.

Wallace hands out "puddle jumpers," rigid sticks topped with angled plastic blades. The teens try spinning them clockwise, which propels them straight to the floor, and counterclockwise, which shoots them upward. "What do you feel on your hands?" he asks. He waits a



JENNIFER BOETH DONOVAN

Eleven Ways to Say "Snow"

Iñupiat is the tribal name of the Eskimo peoples of Northern Alaska. It means "real" or "genuine" people. The same word used in the singular form—*Iñupiaq*—refers to "a real or genuine person." Iñupiaq is also the language spoken by the Iñupiat.

The name of the town Atqasuk stems from the Iñupiaq words *atqaq* (to descend, go down) and *atqasalik* (to travel downward). "My best grammatical and geographical analysis of the village name would be something like 'a place that slopes down,' " says Steve Culbertson, an Iñupiaq-language teacher at Eben Hopson Sr. Memorial Middle School in Barrow, Alaska.

Iñupiaq is rich in words describing the same or comparable things under varying conditions. For example, the English words:

snow

nutagaq: *new fresh powder snow*
qiqsruqaq: *glazed snow in thaw time*
sitliq: *hard crusty snow*
auksalaq: *melting snow*
aniu: *packed snow*
aniuvak: *snow bank*
natigvik: *snow drift*
qimaugruk: *snow drift blocking a trail or a building*
aqiluqqaq: *soft snow*
milik: *very soft snow*
mitailaq: *soft snow on ice floe covering an open spot*

caribou

pagniq: *a caribou bull*
kulavak: *a caribou cow*
tuttugaurat: *a few caribou*
tuttugaagruich: *a herd of caribou*
tuttuqpauragatat: *a huge herd of caribou*
kavraq: *a wounded caribou that is running away unobserved*
tuttutullaturuq: *someone who likes to eat caribou*

These terms are language-teacher Culbertson's English transliterations from Iñupiaq. They are necessarily approximate, as the language includes some characters not found in the English alphabet.

TIM MACDONALD (2)

Clockwise from top left: Science educator Amy von Diest explores principles of flight with Eskimo children in Atqasuk; and in Barrow, Alaska; a microscope and slides captivate a family at a community science festival.

beat or two, then answers himself: "Air, right?" The high school students are busy shooting puddle jumpers at each other. "What's the air doing?" says Wallace. "It's pushing down. And what happens when you push air down?" He looks expectantly around the classroom. No one replies. "Come on, work with me, people. You get lift, right?"

MOTIVATING STUDENTS AND TEACHERS

In Atqasuk, four seniors are due to graduate this year. There are no juniors. "We have several sophomores, but who knows how many will be back next year," says a secondary-grades teacher at Meade River School. "Most of the kids here drop out when they hit 16." Like most of the teachers and all of the principals in the North Slope schools, this teacher is not an Alaska native, but a transplant from the part of the United States that Alaskans call "the lower 48." If he follows the trend, he'll move on in another year or two.

Most students can't see much reason to stay in school. Home to Prudhoe Bay and the trans-Alaskan oil pipeline, the North Slope Borough School District is the richest in Alaska. Oil company leases and royalties have brought running water and sewer systems to the Eskimo villages across the North Slope, and they have built and equipped school facilities that stack up against virtually any of their lower-48 counterparts.

Every permanent resident of Alaska receives an annual payment from the oil income, the statewide Alaska Permanent Fund Dividend. The Alaska natives also get income from the native corporations that run the Eskimo villages. It's enough to put a color TV in almost every house and a satellite dish outside to bring in 100 channels. Medical care is free. But there is no industry in Atqasuk, Wainwright or the other Eskimo villages. Unless they work for the school or in village maintenance, the people live on subsistence hunting, trapping, whaling and fishing, as their ancestors have for centuries. Ilisagvik College in Barrow offers associate degrees and vocational certificates, but moving to Barrow—accessible from Atqasuk or Wainwright only by bush plane—takes enormous determination, motivation and just plain guts.

When Marjorie Angashuk's son Wilbur turned 18, he said to his mother, "What am I going to do with my life?" She blinked at him, uncomprehending. "Get a trap, like your father," she said. Stanley Afcan, 24, dropped out before finishing high school, and, although he has taken a couple of distance-learning courses, he doesn't have the grades or credits to seek a college degree. Besides, his girlfriend grew up in Atqasuk and has no interest in leaving her family. "I always liked science," Afcan says wistfully as he watches the village children and their parents experimenting with magnets and microscopes at the science festival. "I was good at science. I was the one who asked all the questions in science class. Now I just wish I could find a job."

Greg Danner, outreach program manager at The Imaginarium, and his colleagues hope the museum's programs will reach and help motivate young people like Stanley to stay in school and perhaps even pursue careers in science. Science teachers say that the programs are increasing student interest in labs and experiments. English teachers report that vocabulary introduced during the traveling science programs crops up in student compositions for months afterward.

"However, rarely does one experience of 45 minutes or even 45 hours make a lifelong positive change that may be counter to the student's environment, upbringing or personal goals," Danner points out. "We will need to make sustained contact with these students over years. Even then, the ones who are in elementary school now are those whom we are most likely to affect. We may need to recognize that simply improving older students' attitudes toward science is a worthwhile goal."

Meanwhile, The Imaginarium is working with the Native Educators Association and the Alaska Federation of Natives to help bring more regional science training to village teachers and teachers' aides and to inspire more Alaska natives to become teachers and return to village schools. In 2004, the museum's outreach staff of five will take the helm of a network of rural science fairs that focus on linking traditional native and modern Western science.

They are well aware that they can't solve a complex educational, cultural and economic problem by themselves. For now, "our main mission is getting kids excited about science," says Mia Jackson, The Imaginarium's director of programs and exhibits. "We're bringing the science circus to town." H

» Visit The Imaginarium Web site at *www.imaginarium.org*. See a thumbnail profile of The Imaginarium's HHMI-supported program at *www.hhmi.org/news/071001b.html*.

Blood Works

More than mere plumbing, the pipes that carry our blood play important roles in development, from coordinating their own formation to initiating organ growth.

By Karen F. Schmidt

ARTERIES AND VEINS, SCIENTISTS ARE NOW learning, deserve more respect. Beyond their mundane function as the plumbing system for moving blood around the body, they also serve more complex purposes.

Recent research shows that arteries and veins appear to converse with each other as they form a mature network, listening to the surrounding tissues for cues about where to route themselves, and giving orders for many organ tissues to start forming. Indeed, blood vessels play an active role in embryonic growth, and in the progression of some diseases.

Enhancing our understanding of human development, these findings also open doors to potential treatments for cancer, diabetes, and cardiovascular and liver disorders.

Model Systems » In the 1990s, researchers realized it might be possible to keep cancer from spreading by blocking blood vessel development in tumors—or, alternatively, to encourage blood vessels to grow in damaged tissues such as those of the heart or liver. But before they can realize the goal of manipulating blood vessel development, scientists must first understand how this network is created, and which molecular players are crucial. Although researchers have now identified a few dozen factors involved in blood vessel development, they are just beginning to put the puzzle together. "There are a lot of pieces to fill in," acknowledges Leonard I. Zon, an HHMI investigator at Children's Hospital Boston and Harvard Medical School. Yet the answers may ultimately be found in any creature that walks, flies or crawls. "Studying multiple organisms as model systems," he notes, "is now helping us do that."

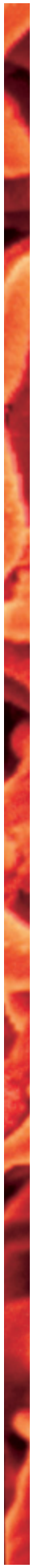
For all vertebrates, the textbook picture of how blood vessels normally develop begins with the embryonic layer known as the mesoderm. That tissue gives rise to hemangioblasts—stem cells that can become either hematopoietic cells (red and white blood cells) or endothelial cells (the precursors of tubular blood vessels). Although it seemed a strange notion that these two very different cell types have a common progenitor, Mark A. Krasnow, an HHMI investigator at Stanford University School of Medicine, has discovered what he believes is an evolutionary clue. Krasnow found that blood cell growth in fruit flies is regulated by vascular endothelial growth factor (VEGF), which is also important for the development of blood vessels in mammals.

Fruit flies have no true blood vessels, only an open circulatory system through which runs a network of tracheal tubes that transports oxygen and serves as the respiratory system. But Krasnow believes that the blood cells and VEGF signaling system found in fruit flies were adapted in some ancient animal to become the closed cardiovascular system of mammals. "Maybe some subset of blood cells acquired the ability during evolution to form associations with other blood cells and assemble into tubular structures," he hypothesizes. "The tubes connected up, and because the VEGF signaling system was already in place, they recruited and used this receptor and ligand to build a vascular network."

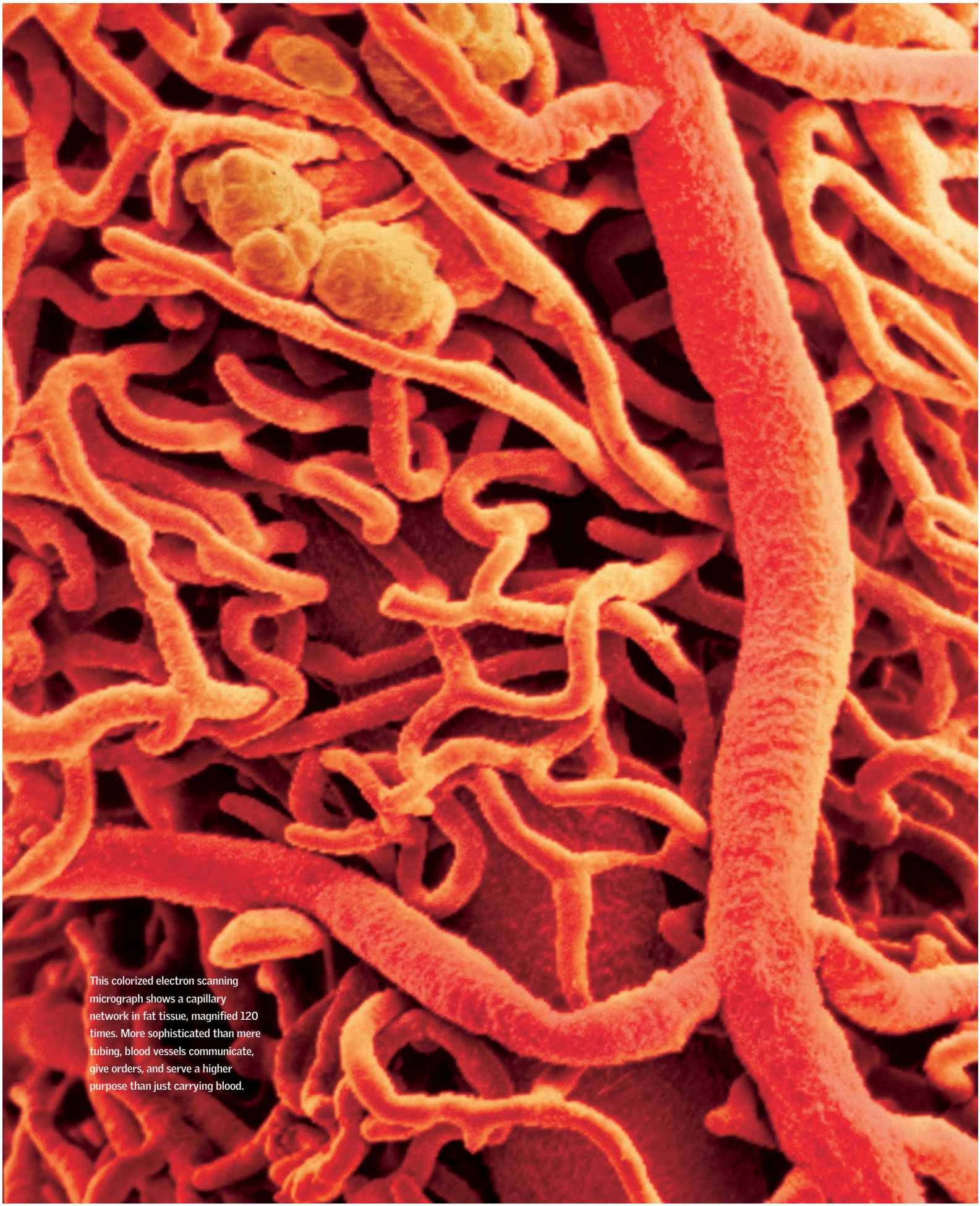
Birth of a Blood Vessel » The story of how a mammalian embryo develops a full-fledged vasculature goes basically like this: In the mouse, the hemangioblasts give rise to endothelial cells. Around embryonic day 8, those cells form tubules and, in a process called vasculogenesis, a loose vascular net. Next, the tubules organize, hook up to a heart that starts beating at about day 9, and remodel into a complex network by day 10. This remodeling process, called angiogenesis, can occur later in other parts of the body, such as limbs, and even during adulthood when tissues repair themselves or when tumors grow.

Although many researchers study blood vessel development in mice, some also study the process in zebrafish, which grow an intact circulatory system in just 24 hours. "You can't beat the zebrafish for a model of blood vessel development," Zon says. "I can watch vasculogenesis, angiogenesis, see the blood cells go around the circulation, see how cells get recruited to form a functional vasculature—all under a microscope and in the short lifetime of a fish."

He can also manipulate changes in gene expression and witness their effects on embryonic development. That has led Zon's group to identify some key genes in blood vessel development. For instance, *cloche* mutant zebrafish embryos show a severe reduction in hemangioblasts and don't develop blood vessels or blood cells. A knockdown of the transcription factor SCL leads to a failure in angiogenesis and a lack of blood cells. "We don't know if these are the first genes to set in motion vasculogenesis and hematopoiesis, but we think both *cloche* and *scl* are critical genes," says Zon. While subtle species differences exist, these genes and their pathways appear to be conserved in higher vertebrates as well, he adds. Other genes, called *notch*, *mindbomb* and *gridlock*, appear to be important in triggering the remodeling that occurs during angiogenesis—they



COLLECTION CNRI



This colorized electron scanning micrograph shows a capillary network in fat tissue, magnified 120 times. More sophisticated than mere tubing, blood vessels communicate, give orders, and serve a higher purpose than just carrying blood.

help determine which blood vessels become arteries and which ones become veins.

Molecular Difference » For the past century, scientists believed that the two kinds of blood vessels were essentially the same tubular plumbing, differing only in function: Arteries carry oxygenated blood to the body's tissues, while veins return deoxygenated blood to the heart. That view was shattered six years ago in a serendipitous discovery in the laboratory of David J. Anderson, an HHMI investigator at the California Institute of Technology.

Anderson remembers the day that his graduate student, Hai Wang, came to him very excited about a pattern of blue staining he was seeing in mouse embryonic tissue. It suggested they had found a factor involved in guiding nerve development. Ten minutes later, Wang returned disappointed, saying that the staining pattern did not involve the nerves after all but rather the blood vessels.

LEONARD I. ZON

PAUL MEAD

"There are a lot of pieces to fill in. Studying multiple organisms as model systems is now helping us do that."

However, Anderson noticed something strange: The carotid artery in the embryonic mouse's head was clearly stained, but none of its veins were. "Everywhere we looked, we found that the factor—ephrinB2—was expressed in arteries but not in veins," Anderson recalls. The group then decided to look at veins more closely. They found that veins expressed ephrinB4, but arteries did not. Anderson consulted with an expert on blood vessels, who told him that no one had ever observed such a difference between arteries and veins before. Says Anderson: "I knew then that this was important. Not only was there a molecular difference between veins and arteries, but we had a ligand-receptor pair that interacts physically with each other."

Anderson's group found that arteries and veins become distinct by day 8 in mouse embryonic development, at the beginning of angiogenesis and before the heart beats. At that time, arteries start expressing ephrinB2, and veins ephrinB4. The ephrins—which are glycoproteins anchored in cell membranes—allow arteries and veins to communicate. When a primitive artery and a primitive vein come in close contact, ephrinB2 and ephrinB4 click together, triggering a change in the interiors of the two cells.

In later studies, Anderson's group found that knocking out the ephrinB2 gene in mice disrupted angiogenesis and caused embryos to die later. "What's particularly interesting about this pair of molecules is that usually one thinks of signaling as going in a single direction—with the receptor listening and the ligand talking," Anderson says. "In this case, the arteries were talking and the veins listening. But the whole network of arteries and veins was disrupted. That suggests bidirectional communication."

Signaling Components » Several groups have recently shown that developing blood vessels will even talk to cells outside their own system, thereby influencing the growth and differentiation of organs. It's as if the developing organs must know that a blood supply will be in place before they continue to grow. "The way you guarantee the proper physical interaction is that the development goes hand in hand," explains Douglas A. Melton, an HHMI investigator at Harvard University. "You never make a pancreatic islet cell without a blood vessel. They're made together."

Melton, a biologist who studies pancreas development, came to that conclusion after pondering the special reciprocal relationship that blood vessels have with organs—blood provides sustenance to the pancreas, for example, but the pancreas also monitors the blood's sugar level and secretes the appropriate amount of insulin. That raised an interesting developmental question: When you build an animal, how do you get these two separate systems to come together?

Although it's known that most organs—the lungs, liver, pancreas, gastrointestinal tract—arise from the embryonic endoderm layer, only recently have researchers begun to understand how they bud off from the primordial tube and become full-fledged organs. In studies of mouse embryos, Melton has found that the endoderm begins to receive signals for pancreatic development at or before day 7.5. By day 9, the prepancreatic endoderm starts expressing a gene specific to pancreas development, and by day 10.5, the tissues begin expressing insulin. Notably, these last two events occur just after contact with endothelial cells. Melton and his colleagues Ondine Cleaver and Eckhard Lammert wondered whether endothelial cells and prepancreatic cells were signaling to each other.

In a series of experiments reported in the October 19, 2001, issue of *Science*, Melton's team did find evidence of two-way signaling. It was already known that many tissues, including pancreatic, attract blood vessels to grow nearby by secreting VEGF. But the group found that another factor is also required to come from the endothelial cells. "It says, 'Grow up and make yourself into an islet cell,'" he explains. "But we don't know what that signal is." His lab is presently pursuing its identity—for Melton, one more piece in the larger quest of finding all the steps for converting stem cells into pre-islet cells. That knowledge, he expects, could one day be used to treat patients with diabetes.

Melton's group isn't the only one uncovering this new role of blood vessels in organ development. In the same issue of *Science*, a research team led by Kenneth S. Zaret of the Fox Chase Cancer Center in Philadelphia reported similar findings in the liver. Using a reagent for tagging endothelial cells in mouse embryos, the team found that contact with these cells was critical for getting the liver to bud from the endoderm. Moreover, when they looked at mouse embryos mutated to

"Maybe some subset of blood cells acquired the ability during evolution to form associations with other blood cells and assemble into tubular structures."

MARK A. KRASNOW

FRED MERTZ

have no endothelial cells, no liver buds formed at all. Says Zaret: "Endothelial cells need to be considered as important signaling components in the growth of organs and might even be important in responses to tissue damage in adults and cancer."

His group is now trying to determine whether this mystery signal coming from endothelial cells is used broadly to influence the development of other organs. So far, based on the work involving the pancreas and liver, Zaret predicts that more than one signaling system exists. Endothelial cells signal liver cells to rapidly multiply, whereas they seem to be telling pancreatic cells to specialize to become islet cells. "This underscores the diversity," he says, "of signaling systems that are out there and likely to be discovered for endothelial cells."

DAVID J. ANDERSON

MARK HARMEL

Chicken Soup Hypothesis »

Learning more about how blood vessels influence organ development could yield novel medical treatments. A research group led by Jennifer LeCouter at Genentech Inc. in South San Francisco has shown that it's possible to stimulate endothelial cells in adult liver tissue in mice and thereby spur liver growth. Reporting in the February 7, 2003, issue of *Science*, the Genentech group also manipulated the signaling system in a way that protected mice from liver damage caused by carbon tetrachloride, which is known to damage essential cells in the liver. This is an exciting and important finding, says Zon. "It supports what's called the 'chicken soup hypothesis'—that the endothelial cells are making all these goodies to make tissues and organs happy, even in adulthood."

Still, real therapies for repairing tissues are not likely to come quickly. It's not clear yet that tweaking one factor in a complex pathway would have therapeutic benefits and no serious side effects. So far, researchers have only a broad outline of how the body builds a well-functioning vasculature, and many questions remain.

For instance, how are the cardiovascular system's intricate branching patterns created? Indeed, by sight alone it's hard to tell whether blood vessel patterns are the result of precise control or random events. But molecular clues now suggest that the positioning of blood vessels is most likely a highly regulated process involving other organ systems and two very different mechanisms.

Krasnow at Stanford has studied the general question of how patterning occurs in the fruit fly tracheal system. The main branches that arise early in development show a highly stereotypic arrangement and appear to be governed by a hardwired genetic program, he says. His group has found that a secreted signaling molecule, called fibroblast growth factor (FGF), directs where each major branch sprouts and grows and where the next generation of branches sprouts.

But what about the finer tertiary branches that must reach out and contact every cell? Here he sees more variability in the tracheal pattern, as the mechanism seems to switch to one based on physiological needs. "A target cell in an oxygen crisis sends out a signal that attracts a new branch, which grows out to the cell and supplies it with more oxygen. Another cell goes through a crisis, and on and on," explains Krasnow. The result is a densely patterned and customized network designed to serve the specific tissue. Surprisingly, the same signaling molecule, FGF, is adapted for new use in this physiological phase. "The same factor and same receptor are used," says Krasnow, "but there's a switch from hardwired control of its gene expression to oxygen-controlled expression that happens in a matter of hours, at the precise time when the tracheal pattern also changes dramatically."

FRED MERTZ

Factors in Patterning »

The parallels between the fruit fly tracheal system and the mammalian cardiovascular system are striking, although in mammals the key signaling molecule is VEGF. At about day 8 in mouse embryos, still in the hardwired genetic phase of development, VEGF promotes early patterning of the blood vessel network. Then at day 8.5, hypoxia (oxygen deficit) begins to play a role, says M. Celeste Simon, an HHMI investigator at the University of Pennsylvania's Abramson Family Cancer Research Institute. Hypoxia triggers more VEGF, which then stimulates vascular remodeling at the finer level.

> "Not only was there a molecular difference between veins and arteries, but we had a ligand-receptor pair that interacts physically with each other."

Simon also has learned something about how the switch from hardwiring to physiological control occurs. Although it's still unclear how cells detect when oxygen levels get low, once they do so a transcription factor called hypoxia-inducible factor, or HIF, comes into play. "As soon as cells become oxygen deprived, HIF responds within minutes—it's a very rapid and reversible response," explains Simon. Her group has found that HIF turns on about 100 genes, 10 of which—including the genes for VEGF and FGF—are related to blood vessel development. From gene-knockout studies, Simon concludes, "we now know that HIF is important in just about every aspect of the cardiovascular system of the developing embryo: the heart, vasculature, placenta and blood cells."

Still, when it comes to blood vessel patterning, hypoxia is not the only guide. Anderson's group at Caltech examined how blood vessels lay down their patterns in limb skin, which develops around day 15 in mice. It turns out the arteries align themselves with developing peripheral nerves. "We found that when we misrouted the nerve pattern, the arteries were still aligned with the nerves," says Anderson. "That really told us that the nerves were leading and the arteries were following." What signal were they following? Once again it was VEGF, which is secreted by some nerve cells. Interestingly, VEGF also seems to tell the blood vessels to become arteries and not veins, Anderson says.

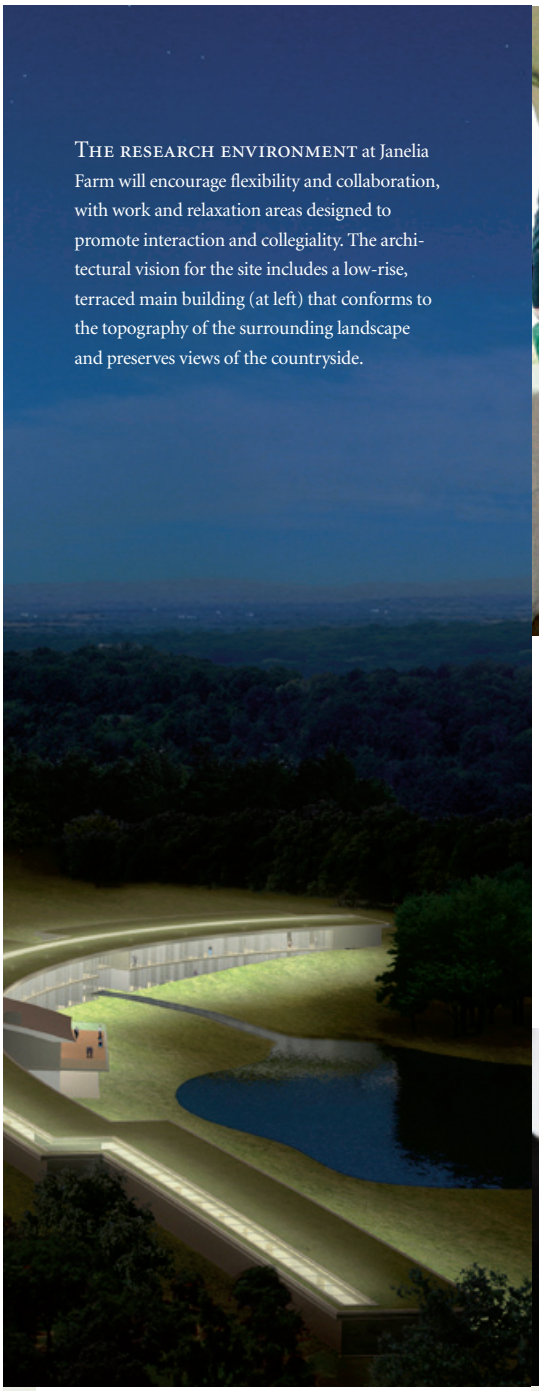
Applying all these new insights is clearly a challenge for the future. Drugs that manipulate VEGF, ephrins or HIF activity, for instance, would be excellent candidates for blocking blood vessel development in tumors. Many pharmaceutical companies are interested, but so far they are only cautiously optimistic about the potential for such cancer therapies. "We're learning that the way the body gets it right during development is by using a lot of factors working together," says George D. Yancopoulos, president of Regeneron Research Laboratories in Tarrytown, New York. "We need to know all the players and how they act in time, space and amount during blood vessel development. While it's getting more interesting, it's also getting more complicated." H

Transforming the Research Landscape

Construction begins on the Janelia Farm Research Campus, HHMI's new venture in collaborative technology-driven research.

ARCHITECTURAL RENDERINGS BY RAFAEL VIÑOLY ARCHITECTS ▪ PHOTOGRAPHS BY PAUL FETTERS

"The Human Genome Project and other recent breakthroughs have transformed the landscape of opportunities in the biomedical sciences, and that's going to have a transforming effect on medicine," said HHMI President Thomas R. Cech. "Janelia Farm will be a robust part of that new landscape. As a center for intensive, hands-on, interdisciplinary research, Janelia will be a distinctive, exciting environment for sparking creativity and great ideas."

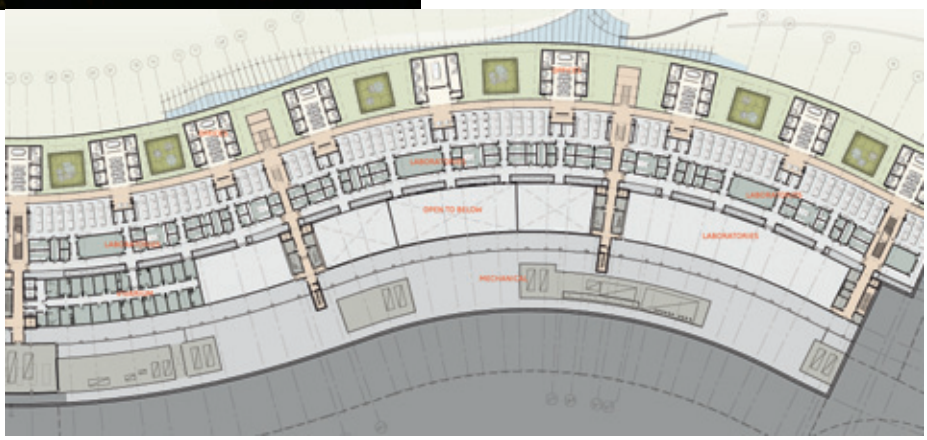


THE RESEARCH ENVIRONMENT at Janelia Farm will encourage flexibility and collaboration, with work and relaxation areas designed to promote interaction and collegiality. The architectural vision for the site includes a low-rise, terraced main building (at left) that conforms to the topography of the surrounding landscape and preserves views of the countryside.

WITH THE PRESS OF A CEREMONIAL shovel into the soil at Ashburn, Virginia, on May 5, 2003, HHMI officially began its venture to cultivate a bold new approach to scientific discovery. The Janelia Farm Research Campus, scheduled to open in 2006, will house biologists, chemists, physicists, engineers and researchers from other disciplines who will collaborate to create and apply new tools and knowledge that advance biomedical science. Here, dignitaries from Virginia join HHMI representatives for the ceremonial groundbreaking.

HHMI VICE PRESIDENT GERALD RUBIN confers with Janelia Farm architect Rafael Viñoly. In May, Rubin was appointed director of the Janelia Farm Research Campus. With input from numerous people worldwide, he collaborated with HHMI President Thomas R. Cech, Vice President and Chief Scientific Officer David A. Clayton and Institute Architect Robert H. McGhee to frame the Janelia Farm concept. A competition to translate that concept into architectural reality then followed, and Viñoly's firm was selected.

A PLAN FOR THE SECOND-floor laboratory space at Janelia Farm. HHMI's new research campus will provide facilities and freedom for scientists to work in small interdisciplinary teams for periods ranging from a few weeks to several years. Projects at Janelia will encourage creativity, originality and scientific risk taking. To select participants, HHMI will seek proposals from Institute investigators as well as the scientific community at large.



HANNA H. GRAY, chairman of the HHMI Board of Trustees, joins architect Rafael Viñoly (left) and HHMI President Thomas R. Cech (far right) in showing a model of the Janelia Farm Research Campus to Virginia Governor Mark R. Warner. HHMI expects to spend about $500 million to build the campus and put its scientific programs in place. In remarks at the groundbreaking, Warner called Janelia Farm "the single largest biotech investment" in Virginia's history.

Building is booming for new "systems biology" research centers, but getting specialists from diverse disciplines to talk, much less make beautiful science together, is no simple matter.

Bringing the Sciences Together

ILLUSTRATIONS BY MICK WIGGINS

BY MAYA PINES

"Interdisciplinary," "innovative" or "integrative" research centers are sprouting up on dozens of campuses across the country, most of them prompted by the gusher of information about genes, proteins, their signals and their interactions that is streaming out of labs associated with the Human Genome Project.

"The emergence of these data completely changes the way biology can—and will—be done," says David Botstein, director of the Lewis-Sigler Institute for Integrative Genomics at Princeton University. "From now on, biologists will design their experiments so as to look at the activity of an entire genetic system, rather than one gene at a time. But to do this, they will need to focus on quantitative biology—with, ultimately, an exact and predictable understanding of biological systems."

The planners of these centers all want to bring the "hard sciences," such as physics or computer science, into close contact with biology. One such advocate, HHMI Vice President Gerald M. Rubin, was appointed in May to be director of the Institute's interdisciplinary biomedical research campus, Janelia Farm. "People are generating information much faster than they can analyze it," Rubin explains, "and much of this information can't be analyzed without using physical, statistical and computational techniques."

The question now is how to arrange a productive marriage between these two cultures. Should the new centers be located in universities or in freestanding research institutes? Should they focus on provoking new discoveries in biomedical science, or on enlightening the rest of the scientific community? Moreover, each center has its own interpretation of "interdisciplinary." And some scientists are grumbling that money will be taken away from their own projects to finance what they see as a gamble. But the founders and directors of these centers are full of hope.

"We need to stir up the pot and create new flavors," says Matthew P. Scott, an HHMI investigator at the Stanford University School of Medicine who now heads an interdisciplinary program there called Bio-X. He notes that some Stanford biologists have been collaborating with researchers in the hard sciences for years. "For example, the cell sorter was invented here by immunologists working with engineers, and in recent years geneticists such as [HHMI investigator] Pat Brown teamed up with engineers to design microarrays—an amazing technology that allows us to systematically look at whole genomes." Yet, Scott says, "many biologists are not taking advantage of chemistry, physics or engineering in any way. As a result, they are running up against challenges that could be overcome by the techniques—or even ideas—of people in these other fields."

Of course it is not enough to simply throw people from different disciplines into the same building, Scott points out. "Proximity alone will not work," he says. "It will be necessary for people to talk, share ideas, explore possible collaborations. That's why we plan to have social events, scientific presentations and meetings—they are a key part of the picture. In fact, the social experiment is the most challenging part."

To spearhead the Bio-X program, Stanford built the Clark Center, an ultramodern structure scheduled to open this summer. The center was named after Jim Clark, a former Stanford professor and cofounder of Netscape, who pledged $150 million to set up Bio-X. (Clark later reduced his gift to $90 million in a protest over national policy on stem cell research.) Its 42 faculty members are being recruited from more than 25 departments in fields including biology, chemistry, medicine, surgery, electrical engineering, mechanical engineering, physics and computer science. Part of the building will be used for teaching—in labs, not classrooms.

In addition, Bio-X wants to connect with more distant disciplines. "It's important to remember that this is a university, not a research institute," says Scott. "One of our goals is to provide educational opportunities, some of which will, I hope, spur creativity in arts as well as science, and also consideration of the social impact of science. With all that we are learning about life and human origins, migrations of people traced with genetics, and the ways brains work, there's food for thought for philosophers, historians and sociologists. Law, too, has major connections to biology in bioethics, stem cell regulations, transgenic plants in agriculture, etcetera."

According to Scott, 260 Stanford professors have expressed interest in being affiliated with the Bio-X program. "We're identifying groups with overlapping interests," he says. "For example, robotics experts who want to work with surgeons, or microbiologists who want to collaborate with physicists and computer scientists to do simulations of cell circuits—it's surprising how many there are!"

A New "Systems Biology"

In California alone, half a dozen other universities are starting centers for interdisciplinary biomedical research. For instance, three campuses in the University of California system—the University of California at San Francisco (UCSF), UC Berkeley and UC Santa Cruz—

have banded together to develop the California Institute for Quantitative Biomedical Research (QB3), and each of the three universities is building a center for it. UCSF's center is located at Mission Bay, in a new campus that is going up in what was previously an area of dilapidated warehouses and abandoned rail yards. The wide-ranging group of researchers being hired for it is expected to develop tools for a new "systems biology."

As Marvin Cassman, executive director of QB3, explains, "Biology is now ready to move on from its recent focus on individual genes and molecules to 'networks of interaction' at every level—molecules, genes, cells, tissues, organs and even entire organisms—in other words, systems biology. Organisms are determined primarily by networks, not individual genes, and we want to understand all the architecture of the networks on a systems level, the way engineers think about it."

"You need many disciplines for systems biology," continues Cassman, who was formerly director of the National Institute of General Medical Sciences in Bethesda, Maryland. "You need genetics, genomics and proteomics so you can analyze the components (genes and proteins) that interact. You need physical chemistry and biochemistry to measure these interactions, and imaging tools to record where and when they occur. Then you need structural biology to understand why and how the molecules interact." In addition, he says, "you need computational expertise to integrate all these elements," as well as expertise in building models.

Not to be left behind, the University of Southern California has started construction of a Molecular & Computational Biology Building for "interdisciplinary research at the forefront of the biological sciences," according to a university announcement. Its "hybrid" labs will be designed for "a new kind of biologist who combines the approaches of computational biology with those of molecular biology."

Other parts of the country are showing similar activity. "Everywhere I go," says David A. Clayton, who travels a great deal as HHMI vice president and chief scientific officer, "it's déjà vu all over again: new centers for biotech and proteomics, combined with computational biology and chemical synthesis. But staying at the edge of rapidly evolving technology is a big challenge. Only the most research-intensive institutions will have a chance of success."

The Models for Janelia Farm

Groundbreaking for HHMI's interdisciplinary biomedical research campus, Janelia Farm, took place May 5, 2003 (see photo essay on page 22). When completed in 2006, the facility will house a variety of scientific programs that will integrate many disciplines.

In helping to plan the Janelia Farm campus, HHMI vice president Gerald Rubin—tapped in May to be director of the new facility—began by asking himself which of the world's many scientific-research institutions had proved most productive in the past, and he came up with two. The first was the Medical Research Council (MRC) Laboratory of Molecular Biology in Cambridge, England, which he describes as "the world's leading molecular biology research center for a 30-year period, between 1950 and 1980." During that time, the MRC's scientists, who never numbered more than 300 at any one time, made landmark discoveries that won them the Nobel Prize on eight separate occasions. The second was AT&T's Bell Laboratories in Murray Hill, New Jersey, the site of many important advances in solid-state physics and electronics, including the development of the transistor and the laser.

Despite the differences in their fields of inquiry, these two labs shared a wide range of operating principles, according to Rubin. Although the MRC lab was a small operation in the public sector while Bell Labs was a large institution in the private sector, individual research groups were kept small in both places. At the MRC, one group leader worked with two to six other scientists; at Bell Labs, a group leader typically had one or two. "Small group size was considered essential to promote collaboration and communication, as well as good mentoring," Rubin says. "In contrast, the average HHMI investigator today has a group size of about 15."

Another characteristic feature of the two labs was that "group leaders were active bench scientists; that is, they carried out experimental work with their own hands, even if they were Nobel Prize winners," Rubin points out. By contrast, starting assistant professors at many of the "best" universities today are often advised by their senior colleagues that it would be counterproductive for them to work at the bench. "The period when a young scientist can be both fully independent and directly engaged in the conduct of research, as opposed to simply directing the work of others, has been greatly shortened and in some cases totally eliminated," he says. (See our survey of HHMI scientists on page 28.)

Rubin is particularly concerned about these young scientists, many of whom want to continue working on their own experiments but are pressured into very different activities: motivating and supervising others, writing grant applications, hiring people, teaching, attending meetings or doing other types of administrative work. "It's like being trained to be a goldsmith, then having to run a jewelry store!" he declares. While some scientists manage this balancing act successfully, "it's not for everyone."

In both the MRC and Bell Labs, all research was funded by internal sources; outside grant applications were not permitted. The emphasis was on "tackling difficult and important research problems, as opposed to more typical criteria such as publication number, service on editorial boards and speaking invitations," Rubin says. Finally, tenure was either limited (MRC) or nonexistent (Bell Labs). This meant that in both places the staff kept turning over. "Most scientists were at an early career stage," he says. "They generally moved on to university positions after 5 to 10 years."

"No institution in operation today fully fits the above description," Rubin maintains. The funding mechanism that supported Bell Labs was destroyed by the breakup of the AT&T monopoly, and the MRC suffered numerous changes after the British civil service imposed a strict tenure system. "Only a private organization with a large endowment, such as HHMI, could support such an enterprise," he says. "This offers the Institute the opportunity to create a truly unique research facility."

That opportunity will in fact be pursued at Janelia Farm, which will be very different from the other centers that are going up at present, according to Rubin. "It will be modeled directly after the MRC and Bell Labs," he says. "We will have no departmental structure, no lifelong tenure. No undergraduates. No classroom teaching. No committees. No need to seek outside funding. But plenty of time for one-on-one mentoring and meaningful interaction with people from other disciplines. The scientists will be encouraged to tackle difficult problems. And since they won't need to worry about guiding the research of a large group of scientists in their labs, they will be expected to spend most of their time working in the lab with their own hands." **–MP**

In the Midwest, the University of Michigan is about to open a Life Sciences Institute building, which will bring together researchers from three broad areas of biology—genomics and proteomics; molecular and cellular biology; and structural, chemical and computational biology. Its charter members include HHMI investigators David Ginsburg, a geneticist, and John B. Lowe, a pathologist. Its director, Alan R. Saltiel, is a cell biologist who believes that at the center of the institute's three fields lies "a deeper understanding of life at the cellular level."

From left: The Life Sciences Institute at the University of Michigan, Stanford University's Clark Center for Biomedical Engineering and Sciences, and Duke University's Center for Human Genetics.

"The Life Sciences Institute…is somewhat of an experiment," states a University of Michigan news release, because it will try to break down the traditional walls of academic departments and because its scientists will work in a new "lab without walls" that is designed to foster interaction. Saltiel hopes these scientists will develop and use new research tools to "advance the life sciences into the next level of sophistication." As in most centers that are based in universities, however, the scientists will be there only half the time. The other half will be spent teaching and carrying out normal duties in their own departments, where they will have dual appointments.

One university that seems particularly interested in bringing a message about genomics to its entire campus is Duke University in Durham, North Carolina. Its Institute for Genome Sciences and Policy, which was launched in 2000, includes a Center for Genome Ethics, Law, and Policy, as well as four centers dealing with genetics, human disease, genome technology, and bioinformatics. Huntington F. Willard, its new director, declares that "the genomic revolution will have as much impact on our lives as did the industrial revolution," but acknowledges that it may create "fear and confusion, as well as knowledge and progress, along the way." He believes that besides producing fundamental changes in medical science, genomics will affect law, ethics, religion, business and other fields, altering everything from the foods we eat to how we view ourselves. Therefore, he says, Duke wants to ensure that "every student, from freshmen up to graduate and professional students in all fields, will have contact with the genome and its implications."

Meanwhile, not surprisingly, Ivies such as Harvard and Yale have developed ambitious plans of their own for stimulating interdisciplinary research. And many other colleges, universities, medical schools and research centers are also building new structures in which biologists and other scientists with overlapping research interests can use adjacent labs, share equipment and, it is hoped, interact creatively.

With so many centers out there, often using the same buzzwords, will they be able to deliver on their promises?

Easier to Say Than Do

The success of the new centers will depend in part on who is chosen to direct them and where these leaders place their bets. (Right now the competition for qualified, imaginative directors is said to be fierce.) It is also contingent on whether funds will still be available for the centers after they are built. And it especially hinges on whether deliberate attempts at cross-fertilizing diverse disciplines really work—and, if so, which research structures are most effective.

Princeton's Botstein observes that when one is educated in a particular discipline, one acquires a certain set of skills. However, he adds, "You also acquire a set of prejudices and ways of looking at the world. Along with those perspectives comes a specialized language that's often ineffective in communicating with people in distant—and even not-so-distant—disciplines. It's a Tower of Babel out there! It's very difficult to get biologists to learn math and even more difficult to get mathematicians to take biology seriously—they don't want to be beginners all over again and have to assimilate a huge amount of information. It's like the difference between a 13-year-old and a 20-year-old who are placed in a new environment where they have to learn a new language. The 13-year-old will learn to speak it without any accent, but that's much more difficult for the 20-year-old, who will always sound foreign."

Botstein's solution to this problem is to start earlier—with college freshmen and sophomores. He just moved from Stanford to Princeton's Lewis-Sigler Institute for Integrative Genomics, which was founded by Shirley M. Tilghman before she became president of Princeton in 2001. "The institute has now acquired a major focus on teaching at the undergraduate level," he says. "We'll try to put in place an introductory course for freshmen and sophomores that will include biology, chemistry, physics and computation right from the start. It will be an alternate route for students who want to major in science. Premeds make up the overwhelming majority of science students, so most undergraduate education in biology is focused entirely on pleasing medical examining boards. Yet that is not what biologists of the future really need—which is more math. They will get it here."

Another problem is that most of the new centers are being erected within existing colleges and universities, where their founders must overcome traditional barriers between academic departments. Only a few of the new interdisciplinary centers—including the

FROM LEFT: KARL BATES/UNIVERSITY OF MICHIGAN; MATTHEW SCOTT; DUKE UNIVERSITY MEDICAL CENTER

Institute for Systems Biology, founded by Leroy Hood in Seattle, Washington, and HHMI's Janelia Farm Research Campus in Ashburn, Virginia, which is scheduled to open in three years—are freestanding.

In academia, "the tenure system works against collaborations among research scientists," explains Gerald Rubin. He believes this is true even when the scientists are in the same department, because such collaborations may make it hard to distinguish one person's achievements from the other's—thus retarding the career advancement of both. But it is even more of a hurdle for researchers who collaborate across disciplines, because the joint product of such collaborations may seem unimportant to each discipline.

Rubin often points to the growth of bioinformatics for biological research. "A reason why it got developed in the commercial sector, and not in universities," he says, "is that people in academic biology departments didn't think bioinformatics was real biology, while people in computer science didn't think it was real cutting-edge computer science. To get tenure, you have to do what the guild says is the pure stuff of your discipline."

Leroy Hood, a long-time advocate of new techniques for advancing biological research—he led the team that developed the automated DNA sequencer, the tool that made the Human Genome Project possible—recently abandoned academia to start the Institute for Systems Biology. "The university culture and bureaucracy just could not have sufficient flexibility" for the cross-disciplinary work he was planning, Hood said.

Starting with a blank slate has both advantages and disadvantages, notes Matthew Scott of Stanford's Bio-X program. "Janelia Farm won't have to deal with any of the entrenched subdivisions you have in universities," he says. "On the other hand, we have certain strengths of our own. We already have a fantastic group of people with different skills, even though some of them don't know each other yet."

As to what will constitute success for the new centers, "Janelia Farm will be a success story depending on the degree to which we have been able to do something that other places can't do," says David Clayton.

According to Scott, success will be measured by the ability "to graduate students who have a remarkable breadth and can bring to bear multiple approaches on problems in biology," as well as by new discoveries that emerge from the efforts of Bio-X participants.

For Marvin Cassman of QB3, success will be developing an infrastructure that stimulates collaborations so that large numbers of students and postdocs work across disciplines. "They will be the key," he says. "They always are."

For now, however, we'll just have to wait. "It's too early to tell how successful any of the centers will be," comments Clayton. "We'll know 10 years from now." H

No Time for The Bench

"What is the difference between Dr. X and God?" goes an old joke about a prominent scientist. The answer: "God is everywhere, while Dr. X is everywhere except in his lab."

Such is the image of scientists who run highly successful research labs. They face so many urgent demands on their time, and have so many skilled postdocs and graduate students in their labs, that they find it counterproductive to actually work at the bench. To learn whether there is more than a germ of truth in this impression, we ran a brief survey of HHMI's 329 scientists to see how some of the nation's leading biomedical researchers allot their time—their most precious commodity. We received answers from 236 of them, or 72 percent.

A surprisingly large number (129, or 55 percent) of those who replied said they spent no time at all on Item 1, "doing experiments with your own hands in the lab" (which is expected to be the dominant activity of scientists at Janelia Farm). Several of those who answered "none" to this question took the trouble to express the frustration this caused them. "My answers are a sad commentary on what happens to the time of successful scientists," wrote one. "None—except when I am on leave," wrote another. A third added, "None. Are you kidding? I wish!!!"

Some of those who are mathematicians or structural biologists explained that for them, "doing experiments with your own hands in the lab" meant doing computational experiments or solving 3-D structures.

Another 58 scientists reported spending between 1 and 5 hours a week doing experiments with their own hands in the lab. Only a handful managed to carve out more time for such work. One scientist who wrote that he spent between 20 and 30 hours a week at it commented, correctly, "I'll bet my reply is different from average."

Regardless of how much time they worked at the bench, most of the scientists said they spent roughly 10 to 20 or 20 to 30 hours a week on Item 2, "talking to people who are doing experiments in your lab, or looking over their data." One researcher noted that much of this time was actually spent "talking to people about things that are not directly related to experiments. There is a lot of informal teaching, career advice, psychotherapy, and discussing things related to getting jobs and grants (like writing letters of recommendation, helping to prepare talks and proposals, talking about what constitutes the right job, etcetera)"—activities that would naturally take more time in a larger lab.

The remainder of the workweek was split almost evenly. The median scientist spent roughly 16 hours on Item 3, "writing grants applications, writing/editing papers, or thinking about results and future research plans directly related to experiments in your lab," as well as on Item 4, "teaching; writing review articles; attending scientific conferences, faculty or committee meetings; reviewing grants or papers; consulting for companies; or doing other scientific or professional tasks not directly related to experiments in your lab." However, some of the researchers spent an astounding 50 percent of their time on this final group of activities.

Several researchers questioned the accuracy of such a survey. "Since schedules vary widely from month to month," respondents' answers must necessarily be guesses, wrote one. He explained that "in the part of the year when I am teaching, or writing a long review, these activities will take up nearly all my time," but during other periods the allotment is quite different.

Finally, one scientist questioned whether such measurements made sense, or even had to: "Scientific research is not a job that one measures in hours. I am not sure when I am working during the day and when I am not. The good news is that the time doesn't seem to matter." **–MP**

INTERVIEW

A Force for Free Access

A conversation with Patrick O. Brown

Most scientific journals own and control all rights to the articles they publish and limit access to the articles to paying subscribers. The content is thereby often unavailable to many scientists, especially in developing countries, as well as to the general public. Frustrated by this limited access to cutting-edge publications, Patrick O. Brown, an HHMI investigator at Stanford University School of Medicine, did something about it. In 2000, Brown, along with Michael B. Eisen of Lawrence Berkeley National Laboratory, Michael Ashburner of the University of Cambridge and Nobel laureates Harold E. Varmus of Memorial Sloan-Kettering Cancer Center and Richard J. Roberts of New England Biolabs, helped create the Public Library of Science (PLoS), a nonprofit organization dedicated to making scientific publications available online and free of charge, with no restrictions on access or use.

An early effort of the group was an open letter urging scientific journals to make original research articles freely available online within six months after their first publication. Signatories to the letter, who eventually numbered more than 30,000, pledged to subscribe to and publish in only those journals that made content freely available. However, many signatories subsequently disregarded the pledge. And most journals, including *Science* and *Nature*, stayed their ground. Therefore, the PLoS announced last year that it would establish its own journals, *PLoS Biology* and *PLoS Medicine*, in the second half of 2003, buoyed by a $9 million grant from the Gordon and Betty Moore Foundation.

What's the effect of the recent announcement that Vivian Siegel would leave her position as editor of the journal *Cell* to become executive director of the new PLoS publishing arm?

Brown: Instant credibility. Because Vivian is an outstanding and widely recognized scientific editor, the fact that she made this decision is a very strong public endorsement of the seriousness of the Public Library of Science as a scientific publisher. The other thing, of course, is that Vivian is terrific, which attracts the first-rate scientists and experienced editors needed to make this whole operation a success. We now have a fantastic editorial board that's growing every day.

Q&A

The PLoS did not initially seek to publish its own journals. Why did you decide it was time to go into the publishing business yourself?

Brown: I had not appreciated how much institutional inertia there is in the scientific publishing world. At the time I wrote "the letter," I thought it would serve a simple catalytic purpose. But the letter didn't succeed at what it was intended to do. And we felt that the only way to make sure someone does it, is for us to do it ourselves.

KAY CHERNUSH

Patrick Brown has a different angle on scientific journals.

The current plan to is bill authors some $1,500, with that fee eventually going down as economics allows. HHMI has announced that it will cover its researchers' fees. How do you keep the PLoS from becoming the "Online Journal of HHMI"?

Brown: Well, in fact, to be more precise, HHMI has done something even better. It will cover reasonable author charges for its investigators for all open-access journals, regardless of who publishes them. So it's not just for the PloS—it's a carrot for any journal that wants to offer open access. In any event, I think there's very little danger of the PLoS only publishing the more affluent researchers. It's in fact extremely common already for journals to charge authors part of the publication costs. And those charges are, not at all uncommonly, well over $1,500 per paper. I don't want to be "let-them-eat-cake" about this, because I appreciate the fact that for a lot of authors this is serious money; I still swallow hard every time I have to pay it, too. But the PLoS fee is not out of line with the industry standard. And we will waive charges for authors who can't afford to pay them.

Are you personally active in the new journals, or have you stepped back from day-to-day involvement?

Brown: I'm extremely active at the moment. I'm in communication with our editors and involved with planning on a daily basis.

And you're also thinking about rolling out additional journals in the future.

Brown: Yes. Our broader vision is that there are people in all scientific disciplines and even in other academic disciplines—the humanities and the arts—who are generating new ideas and discoveries. There's no reason why all these things couldn't be put in the public domain and made freely accessible as an international information resource—an online, world-class library for everyone to use.

What was it about this issue that got under your skin to the point where you had to do something?

Brown: I love the idea of public libraries. It's one of the best social inventions ever. And every single day I'm reminded of how much better my own work would be—and everybody's in the science community would be—how much more efficient it would be, how much public benefit there would be, if all that information were in the public domain. It seemed to me that there were very few things more valuable for me to spend my time on than trying to help make this happen.

—STEVE MIRSKY

PAUL FETTERS

As HHMI meals prove, Sante Mastrangelo knows his way around a kitchen.

Food, Glorious Food

The tiny village of Roio del Sangro, near the Adriatic Sea in Italy's Abruzzo region, has a proud tradition of producing fine chefs. Boys here begin learning the art of cooking at an early age, and they often leave home in their teen years to hone their skills under the tutelage of culinary masters in the big cities.

So it was for Sante Mastrangelo, HHMI's head chef, whose father warned him when he left for Rome at the age of 13: "Make sure you don't come back too soon—because if you are not successful, the door will be locked." As harsh as they may sound, Mastrangelo remembers his father's words being filled with wisdom and love. "It was a good thing for him to say—it made me grow up in a hurry," he recalls.

He listened to his father and worked hard in Rome, serving as an apprentice to the head chef of the Swedish embassy and later cooking for the embassies of Argentina and Malta. In 1969, at the age of 18, Mastrangelo left Italy for America. He landed in Washington, where his two brothers, also chefs, had come before him. Mastrangelo then spent 14 years as a chef at the Australian embassy, returning briefly to his village in 1972 to marry Giuseppina, the girl he had left behind. Today the couple lives in Maryland. They have two sons.

In 1986, a friend in the restaurant business stuck a piece of paper into Mastrangelo's pocket, saying, "Call this number. They're looking for a chef." The number was HHMI's.

In those days, the Institute was beginning to transfer its administrative functions from Florida to Maryland, although it had not yet moved to its current Chevy Chase location. Mastrangelo would travel to Coconut Grove, Florida, the site of many scientific conferences, to cook. Or he would transport food from HHMI's Bethesda building to meeting sites. Most events occurred without mishap—but not all.

Shuddering at the memory, Mastrangelo recalls one evening in 1990. He and his staff were moving tureens of soup and platters of vegetables and swordfish steaks from Bethesda to a warming oven at the meeting site. When an assistant opened the oven, the escaping heat set off the sprinkler system. "Everything was flooded," Mastrangelo says. "We had to take everyone to a Chinese restaurant. I felt like I wanted to disappear from the face of the earth." Fortunately, such disasters are rare.

Today Mastrangelo enjoys not only the appreciation of the HHMI staff but also the loyalty of his own kitchen team. Mastrangelo's wife Giuseppina works in the kitchen. The team also includes Hector Aicon, Anna Corsini, Armando Ferreira, Laura Greiner, Durmus Karaman, Armerina Malandrucco, and Maria Rodrigues, as well as four members of another family—two brothers originally from Turkey, Ibrahim and Yusuf Sisman, and their wives, Hacer and Gulseven.

"I am very lucky to have such a nice group of people," Mastrangelo says. "We work very well together, and we think of HHMI as our home. We are all proud of what we do."

Mastrangelo crafts the daily dining-room menus, as well as those for conferences, to favor menus that balance the likes of prime rib and cheeseburgers with fish and other alternatives to red meat. "We make everything from scratch," Mastrangelo says. "Almost everything is fresh. We almost never open cans. And we never keep a big inventory—nothing goes in the freezer."

HHMI conferees often praise his work. "It's typical for a scientist to return to his or her lab from a conference exclaiming, 'the talks were really good, but the food was bad,' " says HHMI President Thomas Cech. "After a conference at HHMI headquarters, the comment is likely to be that 'the talks were great, and the food was *fabulous!*' "

As a true Italian, Mastrangelo wishes he could serve a bit more pasta, but that's a love that he indulges at home, where he is also the chief chef.

Their sons are now grown, and although neither of them became a chef (one attends graduate school; the other works as a comptroller), they seem to have profited from their dad's influence much as he did from his own.

"I admire my father because he is wise and deals with difficult situations calmly," son Donato wrote in a homework assignment in 1986 when he was 12 years old. "I also admire him because, from a poor boy growing up in a small town in Italy, he earned enough money to get an education … But most of all, I admire him for his knowledge, which he got when he was growing up, from his father."

The framed composition hangs on the wall of Mastrangelo's office, and as he tells a visitor, "He got an A."

—MARLENE CIMONS

PERSPECTIVE

Teaching Scientists to Teach

We should train graduate students to be educators as well as researchers.

By Jo Handelsman

Imagine if music schools trained pianists to play with only the right hand, leaving them on their own to figure out the left hand's responsibility. Ridiculous? Yes. But that is not unlike the way research universities train scientists.

On the one hand, so to speak, research-university graduates excel at doing science, given their institutions' focus on rigor, intensity and high standards in the practice of scientific research; on the other hand, they emerge largely untrained to teach science—to the public, to students generally and even to the next generation in their own fields—simply because graduate programs pay little attention to teaching scientists to teach.

UNIVERSITY OF WISCONSIN-MADISON

The future scientist's teacher training, such as it is, is a casual and ad hoc affair with little design in the process or passion in the delivery. Some students serve as teaching assistants or mentors for undergraduates; others don't. Some receive supervision while engaged in teaching activities; others are left to learn—or flounder—on their own. It is unimaginable that students would complete the nation's best graduate science programs unable to deliver a compelling research seminar, defend an experimental design or write a scientific paper. Likewise, we ought to require that our graduate students also know how to craft a lecture, design a pedagogically sound learning exercise, successfully mentor an undergraduate student and communicate science to broad audiences.

In short, as we train the next generation of scientists, we should help students develop skills as educators—and expect that in that pursuit they would aspire to the same levels of knowledge, creativity and spirit of experimentation that we require of their research.

Whether they formally teach or not, scientists need to explain and make science compelling to nonscientists—industrial managers, government policymakers, patent examiners, the world. Every researcher has a responsibility to share his or her results with the public that supports the research and uses its products. With sound instruction in the art of teaching, scientists will be much better equipped to meet this responsibility. And those who enter the professoriate, where teaching is an explicit job requirement, will do so with skill and grace, having developed a theoretical framework about learning, cognition and the objectives of science education as well as a toolbox of teaching techniques to draw upon. Thus, strong teaching skills strengthen a Ph.D. scientist's career, whatever direction it may take.

Jo Handelsman *is an HHMI Professor at the University of Wisconsin–Madison. Her research focuses on the structure, function and networks of microbial communities.*

Scaffolding for Growth

Some might say there is no spare time in graduate education—for graduate students to master their discipline's rapidly expanding knowledge base is challenge enough. But training students to teach will not add years to their degree programs. Just a single semester of learning and practicing teaching as part of an intense, supportive and critical community, can build ample scaffolding for a student's future growth as a teacher. And for graduate students who are flagging or unfocused, successful teaching may renew a love of science. Their teaching can stimulate them to spend more time in the lab, plan their work with greater care and effectively direct the resources available, including the undergraduates they mentor.

Graduates of U.S. research universities become faculty at both undergraduate education institutions and research universities. Thus, if their own mentors embrace the goal of training graduate students in the art and science of teaching, the effect will cascade through the higher-education system. Such reform would improve the education of undergraduates at all institutions of higher learning, leading to a citizenry that not only has an enhanced sense of the power and limits of scientific inquiry but can also profit from the intellectual and experimental foundations of that inquiry. Programs by public and private agencies, including the HHMI Professors Program, help stimulate such important reforms.

We need to adjust our priorities and correct this historic imbalance of learning how to practice science but not how to teach it. In so doing, we will educate an entirely new generation of scientists who offer improved classroom teaching and more accessible public communication about science. That, in turn, will foster more informed discussion about the myriad science-rich issues that are unfolding before us at an ever-escalating pace, and wiser use of our country's resources, both material and human.

Research universities should raise a generation of future scientists who, like pianists who play with both hands, practice their art with a dynamic complement of skills, to the great benefit of society.

Quebec Feels the Power of Genomics

By his own admission, physician-scientist Vamsi K. Mootha is no Lance Armstrong. But when he saddles up this summer for a bike-a-thon in Canada, he'll likely get a hero's welcome.

Using a sophisticated technique of his own invention, Mootha recently isolated the genetic mutation behind a fatal disease prevalent in French Canadian children from an isolated corner of Quebec. Based on his finding, scientists believe a treatment for the disorder—called Leigh syndrome, French Canadian type (LSFC)—is now within reach. So local families have fresh reason for hope. As one way to honor Mootha for his work, the grateful community insisted that he join its annual LSFC-fundraising bike ride this summer.

Rare elsewhere in the world, LSFC is common in the Saguenay/Lac-Saint-Jean region of Quebec. Most of the 300,000 French Canadians who live there trace their origins to some 100 families who settled the region in the early 1800s. At least one member of those founder-families carried the genetic mutation for LSFC, and today, 1 in 23 of their local descendants possesses it. One out of every 2,000 children born there has LSFC, a rate comparable to cystic fibrosis and other more common diseases in the United States.

When both parents carry the mutant gene, they have a one-in-four chance of bearing a child with LSFC. The child appears developmentally delayed in infancy and then most often dies before age six from metabolic shock induced by a cold, a viral infection or other common physical stresses resulting in a lactic acid buildup in the bloodstream. Most parents do not realize their children even have LSFC, or that they themselves are carriers, until a child becomes sick.

Mootha began doing research on mitochondria (the sites of cells' energy production) at Harvard Medical School and at the National Institutes of Health (NIH), where he was an HHMI-NIH research scholar. While a clinical resident in internal medicine at Brigham and Women's Hospital in Boston, he continued working on mitochondrial biology at the Dana-Farber Cancer Institute with HHMI investigator Stanley J. Korsmeyer.

ASIA KEPKA

Vamsi Mootha never thought that riding a bike would be part of his scientific career.

Mootha's next step as a scientist was in the fall of 2001, when he arrived at the Center for Genome Research at the Whitehead Institute for Biomedical Research as an HHMI physician postdoctoral fellow. At the suggestion of institute director Eric S. Lander, a prominent researcher in the Human Genome Project, Mootha began to work with an in-house team studying LSFC.

Whitehead researcher John Rioux, a French Canadian who had previously directed a project to map another genetic mutation found in Quebec, invited Mootha to apply his knowledge of genomics and mitochondrial biology, which was believed in part to underlie LSFC, to find the gene mutation causing LSFC. Rioux's team, including groups from McGill University in Montreal and the University of Toronto, had already identified the chromosomal region where the mutation would likely be found, but the area was still enormous, containing 2 million base pairs. The researchers estimated that given the available resources, sequencing all those base pairs to locate the gene in carriers of the disease would take nearly two years.

Mootha had a better idea: Conduct a "neighborhood analysis," using a computerized technique of his invention to find associations among the expression signatures—

the active state as indicated in microarray experiments—of different genes. Mootha's method is essentially an efficient search algorithm that exploits similarities in those signatures across vast sets of publicly available data such as those generated by the Human Genome Project, gene expression profile sources and proteomics datasets.

Mootha used his computer-based, integrative genomics method to reduce the 2 million candidates to 5,000 likely base pairs—a far more manageable target—within a week. "It was such an incredible moment when the research assistant, Katie Miller, showed me the site of the mutation," recalls Mootha. The excitement was just beginning.

Within those base pairs, a single mutated gene, *LRPPRC*, stood out as a likely suspect. Mootha and his colleagues tested the gene in patients, parents and control subjects and, less than four months later, proved it was indeed the cause of LSFC. Published in the January 21, 2003, issue of the *Proceedings of the National Academy of Sciences*, the finding rated national news coverage in Canada.

Meanwhile, a provincial government program has begun to screen families from the Saguenay/Lac-Saint-Jean region for the LSFC mutation. Rioux leads a Whitehead Institute effort to clone the gene in mouse models of the disease and begin testing therapeutic compounds. "We are confident," he asserts, "that we'll have an effective treatment in the next 5 to 10 years." And although the team's research has been marked by elegance of technique, high speed and demonstrable results, it has another distinguishing characteristic. "This was very different from any other disease project I'd been involved in," Rioux says. "Usually the subjects are anonymous, but we got to know them and their parents, who really took a leading role in energizing the research groups."

One of those parents was Pierre Lavoie, a local factory worker who lost two children to LSFC. Also a competitive athlete—an age-group winner of the renowned Ironman of Hawaii world championship triathlon—Lavoie embarked on a whirlwind bike tour of the region to raise LSFC awareness; he covered a phenomenal 650 kilometers in 24 hours. Lavoie's trek was transformed into a regular event in which he collects donations for LSFC research en route. LSFC researchers also get involved: Last summer, Rioux rode with Lavoie in the last 150 kilometers—and Mootha is next.

When he elected to conduct laboratory research after completing medical school, Mootha worried that he would wind up "doing abstruse work with no relevance." In light of his work on LSFC, he can set that concern aside. In fact, his technique has significance far beyond its immediate promise for the afflicted community in Canada; it is already being applied to other, more common disorders such as diabetes and Crohn's disease.

Putting on his other hat when reflecting on his LSFC work, Mootha says that "as a physician, it was very gratifying to see how basic work actually impacts the population with the disease." And thinking ahead to his ride with the LSFC bike-a-thon, Mootha observes that "I didn't figure that getting on a bike would be part of my scientific career." Nevertheless, his place of honor with Lavoie and company will only underscore the relevance of that career. **—MARC WORTMAN**

Stevolution

GORDON STUDER

What's in a name? Ask the National Center for Science Education (NCSE), a group that promotes the teaching of evolution. NCSE, an Oakland-based nonprofit, issued a brief proevolution statement in February that at press time was signed by 378 Ph.D. scientists—all of whom, in a striking example of selection, were named Steve.

"Project Steve" is both homage to the late Stephen Jay Gould and a wry response to a habit of creationists to circulate antievolution statements signed by a handful of carefully selected people with science doctorates. "We did it as a joke, but the antievolutionists are serious," says NCSE executive director Eugenie Scott.

Several HHMI investigators joined their fellow science Steves (and four Stephanies) in the tongue-in-cheekiness. "I thought it was a rather interesting idea because humor really gets through to people," says Steven Henikoff, HHMI investigator at the Fred Hutchinson Cancer Research Center in Seattle. "But there is a message there."

The list counters the creationist argument that evolution is widely doubted in the scientific community. Because Steves make up about 1 percent of the population, this nonrandom Steve sampling may be seen as the tip of the iceberg, representing tens of thousands of non-Steve scientists. "It suggests that the organizers didn't simply go after some corner of the National Academy of Sciences," notes signatory Stephen R. Sprang, HHMI investigator at the University of Texas Southwestern Medical Center at Dallas.

Feedback from the science community was supportive, both of the message and the medium. "I've had a lot of e-mail saying that this is hilarious," says NCSE deputy director Glenn Branch. But the other side wasn't laughing. "I've also had a couple of e-mails," Branch added, "from creationists who have missed the point, saying, 'Well, science isn't decided by majority vote.' We're aware of this."

HHMI investigator Nipam H. Patel, of the University of Chicago, agrees: "I think it's a nice illustration of how united the scientific community is, and it's a great way to poke fun at what's going on." Does Patel look forward to a Project Nipam? "Well," he admits, "we may not get too many signatories on that." **—STEVE MIRSKY**

Predoc Designs Breakthrough Gene Screen

Here's a tale of the fast track: A predoctoral student gets to do research in one of the most exciting areas of biology, helps build a tool to identify the functions of genes rapidly and on a large scale and becomes first author on a *Nature* paper for his groundbreaking results. HHMI predoctoral fellow Ravi Kamath can lay claim to all these accomplishments.

In a "News and Views" article that accompanied Kamath's paper in *Nature* (January 16, 2003), Thomas Tuschl of the Laboratory of RNA Molecular Biology at The Rockefeller University said that Kamath's work set "a new standard for systematic, genome-wide genetic studies."

While working in the lab of Julie Ahringer at the Wellcome Trust/Cancer Research UK Institute at the University of Cambridge, Kamath and his team systematically silenced each of 17,000 genes of the roundworm *Caenorhabditis elegans* and analyzed the resulting offspring to see how they were affected. Given that more than half of the worm's genes have human counterparts, the researchers' findings will likely shed light on the role our own genes play in development and disease.

The technique that made their achievement possible is based on the manipulation of an ancient cellular immune system called RNA interference (RNAi). Five years ago, a group of scientists—led by Andrew Fire at the Carnegie Institute of Washington in Baltimore and Craig Mello at the University of Massachusetts Medical School, now an HHMI investigator—found a way to trigger this system to silence genes selectively .

The trigger was double-stranded RNA (dsRNA)—two RNA strands entwined in much the same way that DNA strands manifest themselves in the double helix. In cells, RNA normally occurs in single strands, but in some viruses, it occurs as dsRNA. So when a cell detects dsRNA, it assumes a virus is attempting to hijack its protein-manufacturing machinery and tries to foil that perceived invader by shutting down the gene whose sequence matches the offending dsRNA.

In 1998, when Fire and Mello published their discovery, Kamath was studying for his M.D. degree at Harvard Medical School and had become interested in pursuing a Ph.D. in genetics. The *C. elegans* genome had been recently sequenced, and with the promise of a powerful new analytical tool in RNAi, Kamath recognized the potential of this combination. He approached Ahringer, who studies the genes in *C. elegans* that are involved in early development, and between them, they hammered out the idea of developing a genome-wide RNAi screen.

ASIA KEPKA

Predoc Ravi Kamath set a new standard in genetic studies.

Soon Kamath was ensconced in Cambridge, England, searching for the most efficient way to induce RNAi in living worms. In the lab, *C. elegans* feeds on the bacterium *Escherichia coli*. Other researchers had discovered that simply by feeding the worm *E. coli* that had been modified to express dsRNA corresponding to a given *C. elegans* gene, they could selectively knock out the product of that gene in all the worm's cells. And this was the approach that Kamath chose to pursue.

At the time, the feeding method was far less effective than microinjecting the dsRNA directly into the worm's gonads—the standard (and far more labor-intensive) method of the day. But with a little tweaking, Kamath and his colleagues managed to improve it until it was just as effective as microinjection. They also developed methods allowing them to efficiently engineer bacteria containing fragments of *C. elegans* genes suitable for use in RNAi. Kamath says that although these studies weren't groundbreaking, "they were very important because they formed the basis for all of our subsequent work." Within two years, they had built a library of 17,000 *E. coli* strains, each of which carried dsRNA corresponding to a different *C. elegans* gene.

The construction of the library itself was tedious, he says. But when it came to executing the screen—that is, feeding the bacteria to the worms and observing the effects on their offspring—things got exciting. "Every single day we were silencing genes and discovering phenotypes—hundreds at a time—that had never been seen before," says Kamath. "It enabled us to do genetics in a way that I don't think people could even have imagined five years ago."

Among the wealth of data they generated, several important findings emerged. They found, for example, that the genes whose loss proved lethal tended to be the oldest in evolutionary terms and were the most likely to be found in a wide range of species. This discovery in turn suggested that younger genes control more species-

specific adaptations but are not necessarily crucial to survival.

Meanwhile, the screen has already been seized upon by researchers keen to apply it in order to better understand the role of genes in the functioning of the organism. In the same issue of *Nature* as the Kamath paper, one group working in collaboration with the Cambridge team used the screen to identify some 300 *C. elegans* genes whose silencing led to a reduction in body fat, providing plenty of potential targets for obesity drugs.

"These studies," says Ahringer, "are yielding information on a vast range of biological processes—from the mechanism of aging, to the migration of axons, to the repair of DNA damage and the control of cell division."

Since the summer of 2002, Kamath has been back at Harvard, completing his M.D. degree. He's still enjoying the thrill of his achievement but hasn't decided what to do next; however, he and Ahringer are already involved in collaborations with labs all over the world that want to apply their RNAi screen.

"One of the things I'm most proud of is that this huge project was done by a small lab like ours," says Kamath. "That really speaks to the time we spent doing proper controls and streamlining our methods, and also to the really hard work we put into it."

—LAURA SPINNEY

DNAi: Molecular Biology's *Cinéma Vérité*

The scene: a cell nucleus. A multiprotein-replication machine straddles a naked stretch of DNA. At its head, a protein pries apart the intertwined strands of the double helix, exposing the nucleotide bases that spell out how the cell will function. At its tail, a sliding clamp protein locks the complex into place. The enzyme that copies the DNA nuzzles closer—but wait! Hold everything.

Drew Berry, molecular animator, sees a problem. He's preparing this action-packed thriller, which shows how cells copy their genes, for "DNA Interactive" (DNAi)— a multimedia extravaganza that was produced to celebrate the 50th anniversary of James Watson and Francis Crick's discovery of the structure of DNA. But as he begins to build his three-dimensional (3-D) model, Berry realizes that something is missing—something that relates to the protein that lies at the very center of the replication machine. "We know how big the protein is, and we know who it touches," he explains. "But nobody knows what it looks like." So Berry has to guess.

"I bounced it off a number of experts afterward," he says. "They thought it looked okay. But I'm sure Mother Nature has a more elegant design."

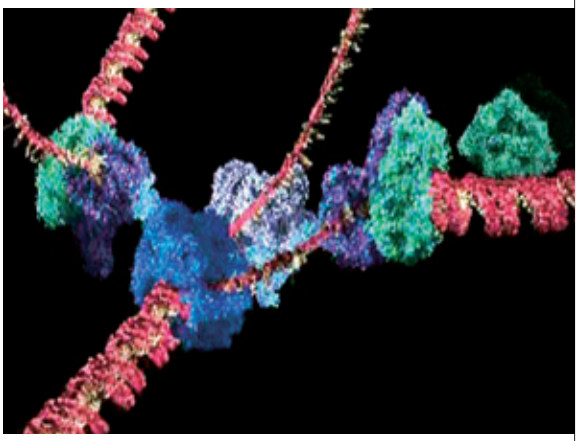
While Berry may be modest, his animations are anything but. "Drew's animations are going to blow everyone away," predicts Dennis Liu, the HHMI program officer who served as liaison between the Institute and the various players taking part in the DNAi project. "The 3-D animations really pull you into the molecular world. It's like *cinéma vérité* for molecular biology." The lively clips appear on the DNA Interactive Web site, *www.dnai.org*, which was developed by the Dolan DNA Learning Center at the Cold Spring Harbor Laboratory (CSHL). The animations are also featured in a related television series that aired in April in the UK and is expected to run soon on PBS. HHMI funded the animations and Web site, along with a DVD for teachers that features interviews with key scientists and animations for classroom use.

Berry's animations, which cover several areas of modern molecular biology—including how DNA is copied, packaged and used to produce proteins—all begin with some intensive time in the stacks. "I hit the journals," says Berry, "and then I build the models based on the data. It makes my job easy, because the science is fascinating."

Berry, who works at the Walter and Eliza Hall Institute in Melbourne, Australia, received his master's degree in cell biology but then took a job in advertising. "I had intended to do a Ph.D.," he explains, "but I ran out of gas." Although the ad job was "a bore," Berry says it taught him how to cut through the jargon and get to the point—useful skills for his work as an animator. "Once you convert the science into an animation, it's amazing how simple the ideas really are. It's just that they're usually buried in jargon."

So Berry has taken decades of scientific research and boiled down the results into scores of six-second snippets that reflect, with painstaking accuracy, what we understand about the biology of DNA.

The resulting animations are part of a larger package that includes video interviews with Watson, Crick and other scientists who have been involved in unraveling the mysteries of DNA. The DNAi Web site and DVD will be used by high school teachers and students—and anyone else looking to learn more about DNA.



DREW BERRY, © HHMI

A frame from the DNAi animation showing how DNA is copied.

Berry, for one, is honored to have done his part in bringing the DNA story—the basis of life—to life. "It's hard to describe how rewarding it was to be included in this project," he says. "For me it was an absolute coup—a step beyond anything I could have dreamed of."

—KAREN HOPKIN

Collaborations Cross Borders

They could have been admiring the Pacific coastline or gazing at the British Columbia mountains during the dinner train tour from Vancouver, but Valerie Mizrahi and Ross Coppel, two HHMI international research scholars, spent the evening talking shop. They barely noticed the scenery, but forged a promising partnership.

Such is often the case at HHMI's annual meeting of international research scholars. Bringing together scientists from far-flung countries for several days of talks, field trips and social events, these meetings inspire collaboration. At the 2002 meeting in Palm Cove, Queensland, Australia, last summer, for instance, 121 researchers attended and 52 new collaborations were reported. Much of that teamwork began outside lecture halls, as scientists casually compared notes. "It's amazing what you can learn on a bus ride," remarks B. Brett Finlay, an HHMI international research scholar at the University of British Columbia.


MIZRAHI


COPPEL

Or on a train. When Mizrahi met Coppel during the 2001 HHMI meeting in Vancouver, Canada, they had much to discuss. Both are microbiologists who study tuberculosis —Mizrahi at the University of Witwatersrand in Johannesburg, South Africa, and Coppel at Monash University in Victoria, Australia—and they decided to team up. Their collaboration has generated both modified TB bacteria and DNA microarrays of a similar organism, *Mycobacterium smegmatis*, that will help identify key TB genes.

Both labs benefit. "Mizrahi and her colleagues have a lot of expertise in the molecular genetics of TB," Coppel says, "and they are helping us with the notoriously difficult knockout technology." Coppel sends Mizrahi microarray slides for her experiments, as well as DNA plasmids containing modified genes he'd like to test in TB bacteria. She then engineers the desired TB bacterial strains and ships them back to him for further analysis.

As a South African scientist, Mizrahi adds, she considers such outside collaborations vital. "Not only does this make scientific sense, but it is extremely important for young researchers in a developing country such as mine to feel as though they are part of the bigger picture." And their partnership may one day have an even bigger payoff in better drugs for treating TB.

"As science grows ever more complex, collaborations make economic sense, too," says Jill Conley, director of HHMI's international research scholars program. By sharing experimental results, Conley notes, researchers save both time and money, while exchanging new ideas. "Other people come to the same problem from different approaches, and they all benefit from a different perspective," she says.

At the 2001 Vancouver meeting, for example, Finlay and HHMI international research scholar José Puente of the National Autonomous University of Mexico in Cuernavaca planned a new project, using Finlay's mouse model to study the regulatory genes and virulence factors behind *Escherichia coli*-like bacteria. Puente's lab does the *E. coli* molecular microbiology while Finlay concentrates on the animal experiments. "If we find anything about regulation of *E. coli* virulence, we ship it to [Puente] and his lab," Finlay says. "He makes mutants for us and ships them back here." Each scientist also has spent time in the other's lab.


FINLAY


PUENTE

Finlay calls this partnership a "gem of a collaboration." Modest labs across the developing world, he adds, offer considerable talent. "Many scientists who succeed in poor countries are stellar scientists," Finlay says. "They will come with ideas, and we have the means."

HHMI meetings sometimes inspire collaborations that quickly travel from idea to clinic. At last summer's meeting, for example, three scholars—Mariano Jorge Levin of the University of Buenos Aires and Miguel Angel Basombrio of the National University of Salta, both in Argentina, and Julio Urbina of the Instituto Venezolano de Investigaciones Cientificas in Caracas, Venezuela—brainstormed ways to combine their efforts against Chagas disease. Caused by an insect-borne parasite, the illness has affected an estimated 18 million people worldwide, primarily in South and Central America. Chagas can become chronic, weakening the heart; there is no cure.

Urbina's lab designs antiparasitic drugs that may be useful in treating Chagas. While Basombrio tests one of Urbina's drugs in animal models, Levin prepares the first clinical studies of another. In addition, they have plans for extending the collaboration—with the addition of other HHMI scholars from Argentina, Uruguay, Brazil and Russia—to develop novel experimental models for Chagas disease, using transgenic mice and parasites.

"As a result of the meeting in Australia, a wealth of collaborations has actually sprouted," says Levin.

—KATHRYN BROWN


LEVIN


BASOMBRIO


URBINA

KENT KAHLBERG (COPPEL, MIZRAHI, PUENTE AND URBINA), DOMINIC CHAPLIN (BASOMBRIO, FINLAY AND LEVIN)

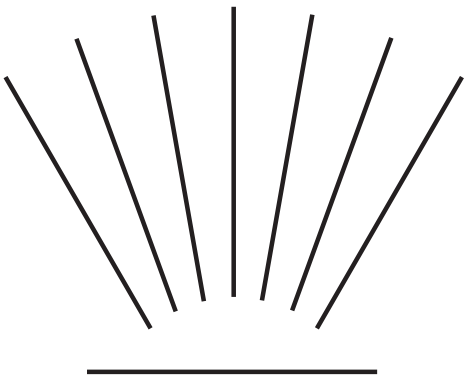
Optical Illusions: Why Do We See the Way We Do?

When Catherine Howe studies optical illusions, she's interested in more than visual tricks. Howe, an HHMI predoctoral fellow at Duke University, studies illusions to learn about the processes of brain signaling that enable our normal, everyday ability to see.

We all take vision for granted, Howe says. Like our other senses, vision usually works without calling attention to itself. Yet this very unobtrusiveness makes it difficult for scientists to understand how vision works, and some basic aspects about sight remain unexplained.

From her workstation in the lab of neurobiologist Dale Purves at Duke University Medical Center, Howe seeks to resolve what she calls "the fundamental problem of vision." We receive visual input by way of two-dimensional retinal images that have no fixed relationship with their three-dimensional sources—any single image that falls on the retina can, in theory, be generated by an infinite number of real-world scenarios. How then do we manage to map the two-dimensional image on the retina back onto its source to somehow make our way in a three-dimensional environment?

Howe's explanation begins with an optical illusion that has intrigued scientists for more than 100 years. Given an assortment of lines of equal length, one line horizontal and the others vertical or leaning outward like the rays of a stylized sunrise, human vision will unfailingly perceive the horizontal line as shorter than all the rest, regardless of their angle of orientation. In other words, we seem to add length mentally when we see vertical or leaning lines. This phenomenon soon becomes deeply ingrained in the way we process visual images, as anyone can demonstrate simply by drawing a square without the aid of a ruler.

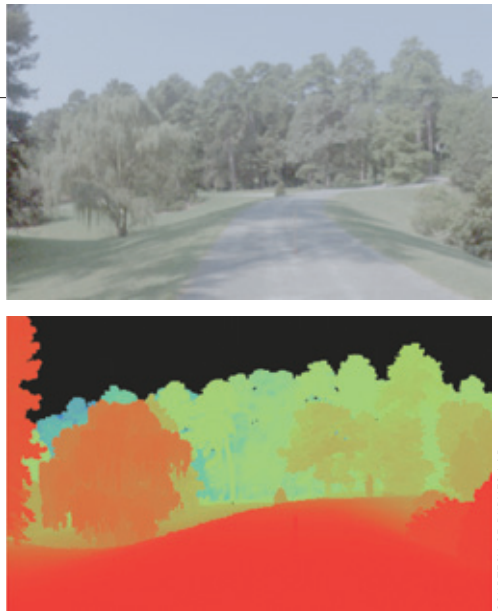


Which is longer, the single horizontal line or the lines above it? See the story for the answer.

"If you think you've drawn a perfect square, you haven't," says Howe. A square that is really perfect will always appear slightly taller than it is wide, "because the brain will automatically add length to the vertical lines in the course of normal visual processing." What is perplexing about this and other optical illusions is the question of why the brain "misperceives" in these circumstances.

For human beings and all other seeing animals, the world contains far more variety in the size, shape, orientation and location of physical objects than any single formula for vision could address. Howe and her colleagues proposed that our interpretations of retinal images, therefore, can only be probabilistic. That is, the brain receives an image on the retina, generates a range of more or less likely interpretations and "sees" the most probable one in the light of previous visual experience. (Optical illusions, by this reasoning, occur when the most likely interpretation happens to be different from the actual circumstances giving rise to the retinal image.)

To test this hypothesis, Howe and her colleagues built a database of natural scenes, using a laser range scanner to record the three-dimensional location of each of a large sampling of points in each scene. Then, in a statistical analysis involving a massive number of calculations from the database of some 15,000 images, the scientists determined the relationship between the length of a line in the retinal image and the length of the source of that line in the three-dimensional world. It turned out that, on average, the length of the physical source in three-dimensional space varies in accordance with the orientation—the angle of "leaning"—of the line in the retinal image. Basically, the real-world objects that produce standing or leaning lines in the retinal image tend to be physically longer than those that give rise to horizontal lines.



COURTESY OF PURVES LAB

Comparing a true-color image (top) with one that maps its three-dimensionality (bottom), researchers tested a hypothesis that the brain generates a range of more or less likely interpretations of an image and "sees" the one that is most probable.

These findings confirmed their hypothesis: The reason we see vertical or "leaning" lines as being longer than horizontal ones is that in the most probable real-world scenario, the physical sources of the former are longer than the sources of the latter. Howe and Purves reported their statistical analysis last September in *Proceedings of the National Academy of Sciences*.

Howe is now at work applying her probability theory to several more optical illusions; she thinks it holds the potential to explain a great many things about the phenomenon of vision. Her mentor, Purves, concurs. "Dale likes to say that all visual perception is basically illusion," says Howe. That thought may be disturbing, mystifying or even enlightening—depending on how you see it.

–SANDRA J. ACKERMAN

HHMI LAB BOOK

RESEARCH NEWS FROM HHMI SCIENTISTS

IN BRIEF

A Window on the Brain
Researchers have developed sophisticated microscopy techniques to watch how the brains of live mice are rewired as they adapt to new experiences. The rewiring process involves forming and eliminating synapses, the connections between neurons. The techniques offer a new way of examining how learning can spur changes in brain cell connections.
Researcher: **Karel Svoboda**
www.hhmi.org/news/svoboda2.html

Genetic Trigger A genetic defect triggers heart failure by disrupting the flow of calcium in heart muscle cells. The finding could lead to targeted treatment for dilated cardiomyopathy, an inherited disorder that causes the heart to become so enlarged it can no longer pump blood effectively.
Researchers: **Christine E. Seidman** and **Jonathan G. Seidman**
www.hhmi.org/news/seidman3.html

Mending a Broken Heart A zebrafish can regenerate its two-chambered heart after injury. Studies suggest that this phenomenon may lead to specific strategies to repair damaged human hearts, perhaps by enhancing their regenerative potential.
Researcher: **Mark T. Keating**
www.hhmi.org/news/keating5.html

Eyes on Glaucoma When studying mice with a mutant gene whose counterpart causes inherited glaucoma in humans, researchers found a second gene mutation that affects L-DOPA production and worsens the eye defect that causes certain types of glaucoma. Physicians might someday be able to prevent glaucoma by administering L-DOPA, currently used in treating Parkinson's disease.
Researcher: **Simon W. M. John**
www.hhmi.org/news/john.html

Location, Location, Location

Some heart ailments involve defects in ion channels, the tiny pores through which sodium, calcium and other ions move in and out of cells. The coordinated back-and-forth flow of these ions helps regulate the heart's electrical activity and the rhythmic pumping of blood. But the work of an international team of scientists shows that even when ion channels are defect-free, the improper location of proteins can also cause heart problems.

This discovery represents an emerging class of clinical disorders that may be more common than previously thought. "It's a large new area of biology," says HHMI investigator Vann Bennett, who led the research, along with HHMI postdoctoral fellow Peter J. Mohler, at Duke University Medical Center. "Ion channels not only need to function properly but have to be organized properly with respect to each other and other cells. Understanding the organization of ion channels will be increasingly important."

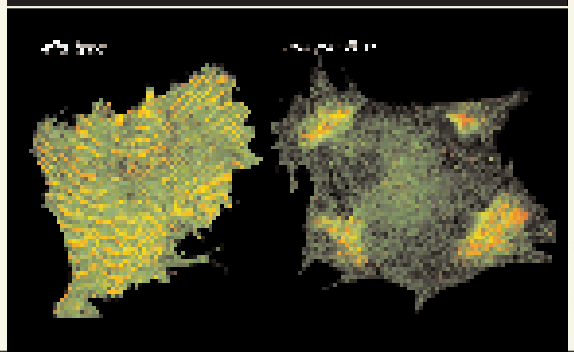
A case in point is a condition called long QT syndrome (LQTS), the subject of the Bennett team's research. A mutation in a protein that helps coordinate the location of ion channels on heart cells can cause this rare but fatal condition. The "QT" in LQTS refers to a specific interval on an electrocardiogram—the period that includes the deflections produced by ventricular contractions. In LQTS, that interval is abnormally long. Some patients with the disorder never have symptoms, but others are at risk of developing abnormal heartbeats and arrhythmia. In one family in France, two normal-seeming individuals died suddenly—a 37-year-old while climbing a hill and a school-aged child after being startled.

In studies of the French family with a form of inherited LQTS, along with experiments in mice, Bennett and his colleagues at Duke and the University of Maryland and in France determined the condition's cause: a specific mutation in the gene for ankyrin-B, a protein in heart muscle cells that helps position and anchor their ion channels. The researchers reported their findings in the February 6, 2003, issue of *Nature*.

Bennett discovered the first ankyrin protein—one of three known types—in 1978 in human red blood cells, though he and his coworkers subsequently found that ankyrins are present in most cells of the body. They also knew that another type, ankyrin-B, is highly expressed in the brain. So when the team created knockout mice lacking both copies of the ankyrin-B gene, they were not surprised that the mice had structural problems in the brain and died soon after birth. But the mice also had signs of muscle weakness, and their heart cells showed abnormalities in calcium uptake and release.

Given that the knockouts died early in development and were therefore of limited value to research, Bennett turned to heterozygous mice, or animals missing only one ankyrin-B gene, so that they could live long enough to manifest whatever developmental

Calcium Dynamics ***The proteins ankyrin-B (red) and the Na/Ca exchanger (required for regulating calcium and shown in green), in neonatal heart cells isolated from a wildtype mouse (left) and an ankyrin-B (+/-) mutant mouse. Both proteins are reduced in the ankyrin-B (+/-) heart cell, except in some regions where they are expressed at wildtype levels.***

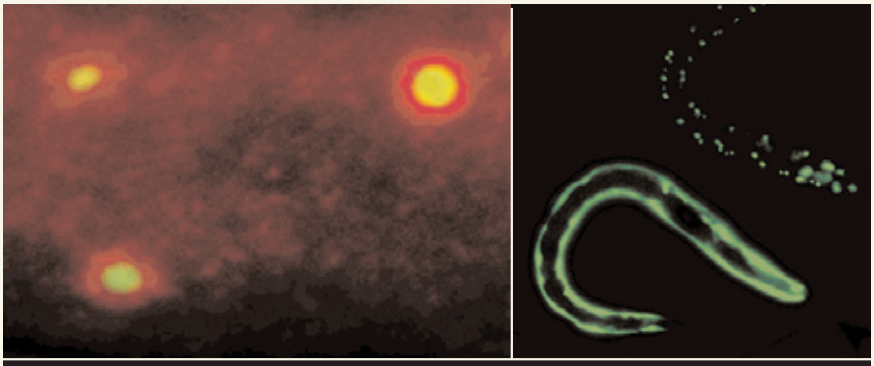


PETER MOHLER

effects were caused by the loss. (LQTS is a genetically dominant disease, meaning that the absence of only one copy of the gene can cause the syndrome.) These mice indeed had slow, irregular heartbeats and LQTS—deficits similar to those observed in the French family.

How did the ankyrin defect cause arrhythmia? The Bennett team knew that ankyrin binds to so-called protein transporters that help move calcium and other ions out of the cell. With the help of John Lederer at the University of Maryland, they showed that each time the heart cells of the knockout mice contracted, more calcium than normal was released, upsetting the calcium dynamics and causing abnormal heartbeats.

These findings may lead to new therapies. "People with arrhythmia can be difficult to treat," notes postdoc Mohler, who was the first author on the *Nature* paper. "Regulating ankyrin or related proteins might be a new way to help."



KIM CALDWELL, THE UNIVERSITY OF ALABAMA

Glow Worms ***Left:* C. elegans *torsin protein (red) moves to sites where the fluorescent protein aggregates (green) in worm cells. Right: Torsin halts the clumping of proteins in* C. elegans. *In the worm at top, fluorescent protein aggregates in its cells. The worm on the bottom contains the same aggregation-prone protein in the presence of torsin.***

Brain Drain

Might it one day be possible to unclog brain cells littered with malformed proteins? Guy A. Caldwell thinks so. He's hot on the trail of torsinA, a protein that may serve as a model for a "molecular clog remover" as it reverses the cellular catastrophe associated with protein misfolding—a characteristic common to Parkinson's, Alzheimer's and Huntington's diseases.

Scientists knew that a mutated gene, *TOR1A* (or *DYT1*), had been linked to early-onset dystonia, a severe hereditary movement disorder. But the role of its protein, torsinA, had been a mystery. Caldwell, an assistant professor of biological sciences whose work is partially supported through an HHMI undergraduate science program grant, and his colleagues at the University of Alabama turned to *Caenorhabditis elegans* for answers.

The researchers transplanted another protein that causes jellyfish to glow into *C. elegans* and induced the worm to create aggregates of misfolded proteins. When they added torsinA, the number of glowing clumps dropped dramatically. They then genetically altered worms to produce a mutated form of torsin similar to the one linked to dystonia. The mutated torsin subsequently could not prevent protein clumping. The Alabama team reported its findings in the cover story of the February 1, 2003, issue of the journal *Human Molecular Genetics*.

In addition to defining a possible role for torsinA in dystonia, this research could have major implications for other human diseases. A protein, α-synuclein, has been found in clumps in the brains of Parkinson's patients, and Caldwell already has early results indicating that torsins can suppress α-synuclein clumping—at least in worms.

HHMI Lab Book written by Steven I. Benowitz

IN BRIEF

Mouse Coat a Clue to Mad Cow

A gene mutation that colors a mouse coat black also causes degeneration of nerve cells similar to the effects of brain diseases such as Creutzfeldt-Jakob disease and mad cow disease. The findings could improve understanding of how renegade proteins, called prions, destroy the brains of infected humans, cattle and sheep.
Researcher: **Gregory S. Barsh**
www.hhmi.org/news/barsh2.html

Chemical Escort Service Receptors for pheromones, chemical signals that animals use to identify one another, need escort molecules in order to be ferried to the surface of sensory neurons, where they are needed to translate chemical cues. These escort molecules, members of a family of important immune system proteins called the major histocompatibility complex (MHC), might also modulate an animal's response to pheromones, thereby aiding in the recognition of other animals.
Researchers: **Catherine Dulac** and **Kirsten Fischer Lindahl**
www.hhmi.org/news/dulac2.html

Pheromone Images Scientists have made the first-ever recordings of a mouse's brain activity patterns as it explores the sex and identity of a newly encountered animal. Their results show that pheromones trigger highly specific patterns of neural excitation in the brain, providing vital information about the sexual receptiveness of females and the dominance hierarchy in males.
Researcher: **Lawrence C. Katz**
www.hhmi.org/news/katz2.html

All in Good Taste A research team has shown that information about sweet, bitter and umami (monosodium glutamate) tastes reach the brain, where taste perception occurs, through a common biological pathway. The discovery opens the way for more precise manipulation of taste sensations to discover how different tastes are encoded in the tongue and perceived in the brain.
Researcher: **Charles S. Zuker**
www.hhmi.org/news/zuker4.html

New Views of Molecular Machines

Using the power of electron microscopy to look deep inside the living cell.

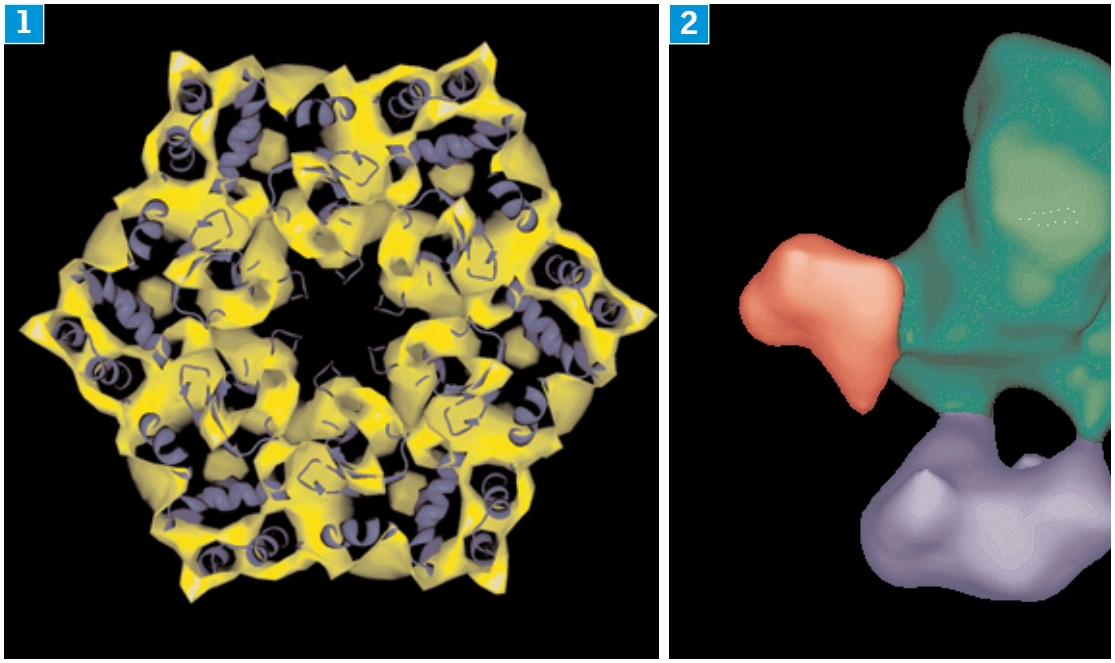
Nikolaus Grigorieff likes to see how things work. But seeing the things that pique his interest—intricate molecular machines, such as protein complexes, that perform their jobs inside living cells—presents a series of daunting challenges. These include extracting proteins from cells in pure form without distorting their natural shape, imaging myriad copies of them with sufficient clarity, and making spatial sense of the resulting chaotic data while filtering out copious "noise."

Grigorieff, an HHMI investigator at Brandeis University, addresses that challenge with single-particle electron microscopy (EM)—a method that's emerging as a key tool in structural biology to complement the traditional methods of x-ray crystallography and nuclear magnetic resonance (NMR). While those more established techniques can be used to visualize proteins and study how they function in three dimensions, they have serious limitations.

Crystallography, which uses crystals of purified protein with many copies of the same molecule joined to form a rigid lattice, requires purified samples of protein complexes in amounts often difficult to collect. With NMR, large molecules do not tumble fast enough in solution to produce clear signals—and protein complexes are huge by molecular standards.

With single-particle EM, Grigorieff says, "the big advantages are that we can work with small quantities of material and there's no upper size limit." Molecules or complexes are immobilized through freezing and then imaged one at a time. However, as the microscope's electron beam passes through a protein molecule, radiation destroys the molecule's structure and distorts the results, meaning that each individual particle can be visualized only once and produces a "noisy," indistinct image. To get a clear three-dimensional image, the microscopist must take a succession of electron snapshots, imaging perhaps 100,000 individual particles on 500 separate micrographs over a month's time.

"We need to visualize the structure from many different angles, then determine how the different views relate to one another," Grigorieff explains. A computer sorts each image according to its orientation (front, back, top, bottom or side views) and then



MOLECULAR STRUCTURES: THE BIG PICTURE

1. Exocytosis is one step in the basic cellular job of vesicular trafficking, in which tiny sacs, or vesicles, ferry their molecular cargo—such as neurotransmitters or hormones—between cells. During exocytosis, the vesicle fuses with the membrane target, releasing its contents. The protein NSF (*N*-ethylmaleimide-sensitive factor) is part of a complex network of protein and lipid interactions that control this process. NSF's ring-like structure, with six molecules of protein forming a functional unit, can be seen in Nikolaus Grigorieff's electron-microscopy image of the NSF D2 domain (yellow) extracted from nerve cell synapses. The superimposed blue portions of the image depict an atomic model of D2 built by Grigorieff's collaborator, HHMI investigator Axel T. Brunger of Stanford University, using x-ray crystallography data. Grigorieff's image of the entire NSF molecule helped complete the picture begun by Brunger. The composite image exemplifies how the two methods complement one another: Crystallography reveals finely detailed but partial structures of large molecules, while electron microscopy shows the bigger picture. Although the material used to make this

averages all the images within each group to minimize noise and amplify the signal, he says. The computer finally rounds out the picture by placing the optimized views, like pieces of a 3-D puzzle, in their proper spatial relationship.

Further complicating the process is the fourth dimension: time. Protein complexes are dynamic mechanisms with many moving parts. As they go through their cycles of activity, their appearance changes rapidly and radically. Grigorieff illustrates this problem with the spliceosome, a machine that removes noncoding introns after the transcription of DNA to RNA.


GRIGORIEFF

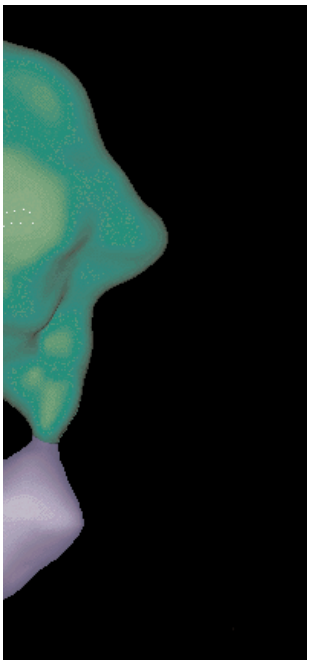
KATHLEEN DOOHER

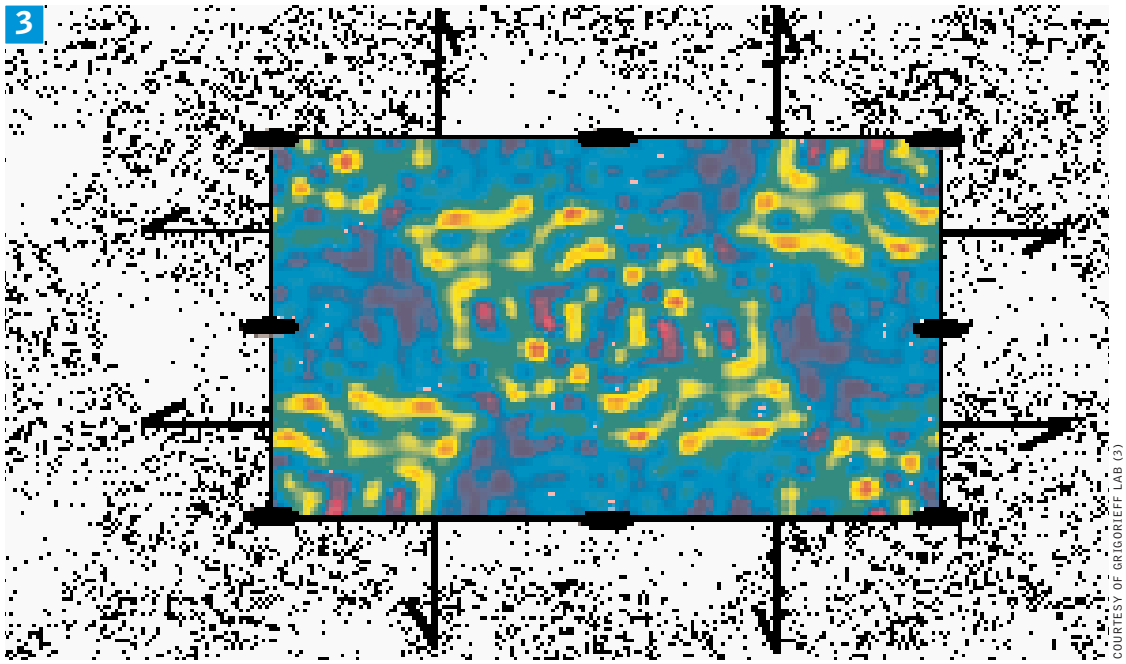
"If you let the spliceosome go freely, it would go through cycles of assembly and disassembly, and at any point in time, you would see a wild mix of different complexes," Grigorieff says. "So you have to lock the machine somehow into one stage" in which all particles look the same. His Brandeis colleague and collaborator Melissa J. Moore, an HHMI investigator, found a way to jam spliceosomes this way chemically, allowing Grigorieff to produce the first-ever EM images of this molecular machine.

A physicist by training, Grigorieff's passion is driven both by curiosity about how proteins function within cells and by the challenge of overcoming technical obstacles to create better images. His goal is to visualize structures with atomic resolution—fine enough detail to build molecular models down to the individual atoms.

He sums up the simple motivation behind his high-tech research: "When you find something you don't understand and you want to know how it works—it could be a car engine or an object from outer space—the first thing you do is take it apart to see what's inside, how the bits and pieces fit together and act together."

—TOM REYNOLDS





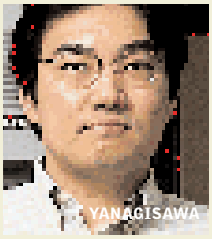
COURTESY OF GRIGORIEFF LAB (3)

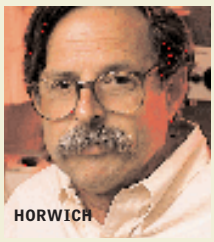
image was originally derived from a hamster's nervous system, the process and proteins involved are similar in other organisms, including humans.

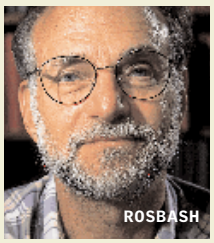
2. Grigorieff created the first image of the spliceosome, the molecular machine that removes noncoding segments, or introns, after the transcription of DNA to RNA. Using material derived from the long-lived HeLa cell line, and with the aid of a technique developed by HHMI investigator Melissa Moore, also of Brandeis University, that jams the spliceosome at the C-complex stage—when the actual RNA cut-and-stitch operation is performed—Grigorieff depicts the spliceosome frozen in time at that stage. This electron-microscopy image depicts three distinct sections within the complex, a result obtained in previous research. But it also provides the first visual information about how these three components of the C complex are positioned and suggests clues about how they may work together.

3. The first image of a chloride ion channel, made by electron microscopy of two-dimensional crystals from the bacterium *E coli*. Similar channels in higher organisms are involved in many physiological processes, such as blood pressure control and intracellular trafficking. The crystals were obtained by Grigorieff in collaboration with HHMI investigator Christopher Miller, also at Brandeis. The image shows the channel from a view perpendicular to the bacterial membrane. Solid-line contours represent protein density; dotted-line contours represent areas with lipid. HHMI investigator Roderick MacKinnon of The Rockefeller University later determined a three-dimensional x-ray crystallography structure of this channel.

Ten Tapped for NAS







Nine HHMI investigators were elected in April to membership in the National Academy of Sciences, and an HHMI international research scholar was named a foreign associate of the Academy. The researchers are **Cornelia I. Bargmann**, University of California, San Francisco; **Linda B. Buck**, Fred Hutchinson Cancer Research Center; **Stephen J. Elledge**, Baylor College of Medicine; **Arthur L. Horwich**, Yale University School of Medicine; **Robert A. Lamb**, Northwestern University; **Michael Rosbash**, Brandeis University; **Joseph S. Takahashi**, Northwestern University; **Arthur Weiss**, University of California, San Francisco; **Masashi Yanagisawa**, University of Texas Southwestern Medical Center at Dallas; and **Luis Herrera-Estrella**, an HHMI international research scholar and professor at the Center for Research and Advanced Studies, National Polytechnic Institute, Guanajuato, Mexico.

Sarah Adair, an HHMI undergraduate research intern at the University of Alabama, was one of 20 college students named to *USA Today*'s 2003 All-USA Academic First Team.

Frederick W. Alt, an HHMI investigator at Children's Hospital, Boston, received the 2003 Excellence in Mentoring Award from the American Association of Immunologists.

Angelika Amon, an HHMI investigator at the Massachusetts Institute of Technology, won the American Society of Microbiology's 2003 Eli Lilly and Company Research Award, which recognizes original research of exceptional merit in microbiology or immunology.

Kristi S. Anseth, an HHMI investigator at the University of Colorado at Boulder, received the 2003 Curtis W. McGraw Research Award from the American Society of Engineering Education. The award recognizes important research advances by engineering faculty under age 40.

HHMI investigators won three of five 2003 Gairdner Foundation International Awards. **Richard Axel** and **Wayne A. Hendrickson**, Columbia University College of Physicians and Surgeons, and **Linda B. Buck**, Fred Hutchinson Cancer Research Center, received the awards, which recognize contributions by medical scientists whose work will significantly improve the quality of life. Axel and Buck were also co-recipients of the 2003 Perl-UNC Neuroscience Prize in recognition of seminal achievement in neuroscience.

Bonnie Bassler, a Princeton University molecular biologist who teaches an HHMI-supported genetic engineering research seminar for secondary school science teachers and students, won a 2002 MacArthur Foundation fellowship.

R. David Bynum, director of an HHMI-supported undergraduate science education program at Stony Brook University, received a 2003 Presidential Award for Excellence in Science, Mathematics and Engineering Mentoring. Ten individuals and six organizations were honored for success in increasing the participation of minorities, women and disabled students in science, mathematics and engineering.

Mario R. Capecchi, an HHMI investigator at the University of Utah School of Medicine, received the 2003 Pezcoller Foundation–AACR International Award for Cancer Research, given annually for a major scientific discovery in the field of cancer. Capecchi also shared the 2002–2003 Wolf Prize in Medicine for techniques he developed to create mutations of selected genes in mammalian cells.

HECTOR X. AMEZQUITO (HERRERA-ESTRELLA), KAY CHERNUSH (BARGMAN), PAUL FETTERS (ELLEDGE AND TAKAHASHI), JOHN KLEIN (WEISS), DAN LAMONT (BUCK), NANCY NEWBERRY (YANAGISAWA), STANLEY ROWIN (ROSBASH), HAROLD SHAPIRO (HORWICH), MAKATO TAKEDA (LAMB)

HHMI investigators **Harry C. Dietz**, The Johns Hopkins University School of Medicine; **Joseph Heitman**, Duke University Medical Center; and **Peter S. Klein**, University of Pennsylvania School of Medicine, were among 80 new members elected to the American Society for Clinical Investigation.

HHMI investigators **Brian J. Druker**, Oregon Health & Science University, and **Charles L. Sawyers**, University of California, Los Angeles, were co-winners of the 2003 UCSD-*Nature Medicine* Translational Medicine Award. Druker also shared the 2002 Novartis-Drew University Award in Biomedical Research with Harold Varmus, Memorial Sloan-Kettering Cancer Center, and Fred McCormick, University of California Cancer Center and Cancer Research Institute.

Ronald M. Evans, an HHMI investigator at the Salk Institute for Biological Studies, won the 2003 March of Dimes Prize in Developmental Biology, awarded to a scientist who has discovered a new principle relevant to birth defects.

Adam Farley, an undergraduate at Murray State University in Kentucky, was selected by the Council on Undergraduate Research to present at the council's 2003 "Posters on the Hill" event in Washington, D.C. His research is supported by an HHMI undergraduate science education grant to Murray State.

D. Gary Gilliland, an HHMI investigator at Harvard Medical School, won a 2002 Doris Duke Charitable Foundation Distinguished Clinical Scientist Award, given to five physician-scientists who apply advances in science to the treatment of disease.

Joseph L. Goldstein, a member of the HHMI Board of Trustees and chairman of molecular genetics at the University of Texas Southwestern Medical Center at Dallas, was co-winner with Michael S. Brown of the 2003 Albany Medical Center Prize. The $500,000 prize is the largest prize in medicine in the United States. Goldstein and Brown, who is also on the UT Southwestern faculty, shared the 1985 Nobel Prize in Physiology or Medicine for their pioneering work on the mechanism underlying cholesterol metabolism. The Albany Medical Center Prize recognizes the pair's research since winning the Nobel, including work on LDL-receptor regulation and related research into the mechanisms underlying some forms of diabetes and cancer.

Todd R. Golub, an HHMI investigator at the Dana-Farber Cancer Institute, won the 2002 Cornelius Rhoads Memorial Prize from the American Association for Cancer Research. The award recognizes pivotal contributions to cancer genetics.

Mark Gottfried and **Barbara Rothstein**, teachers at North Miami Beach (Florida) High School and participants in HHMI's Holiday Lectures DVD Project, were southern regional winners in a Young Epidemiology Scholars competition for teachers, cosponsored by the Robert Wood Johnson Foundation and the College Board. They were honored for a science education activity they developed, based on the 1999 Holiday Lectures on infectious diseases.

Two endowments honoring **Hanna H. Gray**, chairman of the HHMI Board of Trustees, have been established by the Andrew W. Mellon Foundation, whose board she also chaired until her recent retirement. Grants totaling $4.5 million will establish graduate fellowships at the University of Chicago, where Mrs. Gray is president emeritus, and an undergraduate research program in the humanities at Bryn Mawr College, her alma mater.

Thanh N. Huynh, an HHMI-NIH research scholar and a medical student at the University of California, Los Angeles, won the 2003 Saul R. Korey Award in Experimental Neurology from the American Academy of Neurology.

H. Robert Horvitz, an HHMI investigator at the Massachusetts Institute of Technology, received the 2003 American Cancer Society Medal of Honor for basic research.

Eric R. Kandel, an HHMI investigator at Columbia University College of Physicians and Surgeons, won the 2002 Centenary Medal from the Royal Society of Canada. The medal recognizes exceptional achievement in scholarship and research.

Roderick MacKinnon, an HHMI investigator at The Rockefeller University, received the 2003 Fritz Lipmann Lectureship Award from the American Society for Biochemistry and Molecular Biology. The award recognizes conceptual advances in biochemistry, bioenergetics or molecular biology.

Philippa Marrack, an HHMI investigator at the National Jewish Medical and Research Center, won the 2003 Lifetime Achievement Award from the American Association of Immunologists.

Craig C. Mello, an HHMI investigator at the University of Massachusetts Medical School, received the 2003 National Academy of Sciences Award in Molecular Biology, which recognizes a notable discovery in molecular biology by a young scientist. Mello shared the honor with Andrew Z. Fire of the Carnegie Institution of Washington.

Sean J. Morrison, an HHMI investigator at the University of Michigan Medical School, was named *Wired* magazine's 2003 scientist of the year.

Pirelli Honors HHMI

Dennis Liu, program director of HHMI's public science education initiatives, accepted the top prize in the Pirelli INTERNETional Awards for "best product of multimedia education produced by an institution." The award recognizes HHMI's virtual labs. **Satoshi Amagai**, a member of Liu's staff at HHMI, played a key role in developing the virtual labs, with support from the rest of the Institute's educational materials team.

NOTA BENE

Michel C. Nussenzweig, an HHMI investigator at The Rockefeller University, won the Solomon A. Berson Award for Basic Science from New York University.

Jacek Otlewski, an HHMI international research scholar in Poland, has been elected to membership in the European Molecular Biology Organization.

HHMI investigators **Gerald M. Rubin** (now HHMI vice president and recently selected to be director of the Janelia Farm Research Campus) and **Allan C. Spradling** were co-winners of the 2003 George W. Beadle Award from the Genetics Society of America in recognition of outstanding contributions to the community of genetics researchers. Spradling is an investigator at the Carnegie Institution of Washington.

Randy Schekman, an HHMI investigator at the University of California, Berkeley, received Columbia University's 2002 Louisa Gross Horwitz Prize, which recognizes outstanding basic research in biology or biochemistry.

Terrence J. Sejnowski, an HHMI investigator at the Salk Institute for Biological Studies, has been elected to membership in the Johns Hopkins Society of Scholars. Election recognizes former postdoctoral fellows and junior or visiting faculty at Johns Hopkins who have gained marked distinction in their fields.

Charles J. Sherr, an HHMI investigator at St. Jude Children's Research Hospital, won the 2003 Landon-AACR Prize from the American Association for Cancer Research. The award honors researchers who have made basic and translational research discoveries that have accelerated the progress against cancer.

Jonathan S. Stamler, an HHMI investigator at Duke University Medical Center, was elected an alumni member of the Lambda Chapter of the medical honor society, Alpha Omega Alpha, at Mount Sinai School of Medicine.

Donald F. Steiner, an HHMI investigator at the University of Chicago Pritzker School of Medicine, received the 2002 Davis Award in Diabetes Research from the Carousel of Hope, sponsored by the Children's Diabetes Foundation.

Joan A. Steitz, an HHMI investigator at Yale University School of Medicine, received the 2003 Excellence in Science Award from the Federation of American Societies for Experimental Biology.

Joseph S. Takahashi, an HHMI investigator at Northwestern University, won the German Biochemical Society's 2003 Eduard Buchner Prize, which recognizes a scientist who has pursued his or her research goals with great perseverance and success.

David L. Valle, an HHMI investigator at The Johns Hopkins University School of Medicine, received the 2003 Colonel Harland Sanders Award for lifetime achievement in genetics research and education. The award is presented by the March of Dimes.

Isiah M. Warner, an HHMI professor at Louisiana State University, won the 2003 American Chemical Society Award for Encouraging Disadvantaged Students into Careers in the Chemical Sciences, sponsored by the Camille and Henry Dreyfus Foundation.

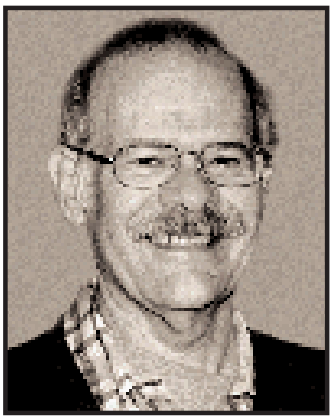
IN MEMORIAM

IRA HERSKOWITZ

1946–2003

Geneticist Ira Herskowitz died on April 28, 2003, of pancreatic cancer. He was 56. Herskowitz was the Hertzstein Professor of Genetics in the department of biochemistry and biophysics at the University of California, San Francisco (UCSF), and codirector of the UCSF program in human genetics. His studies on the yeast *Saccharomyces cerevisiae* yielded major insights into the fundamental aspects of cells. Herskowitz was also a pioneer in pharmacogenetics, the study of the effect of natural variations in individuals' genes on their responses to drugs.

"I knew and worked with Ira over the past 20 years," said David A. Clayton, HHMI vice president and chief scientific officer. "He was recognized internationally as a leader in yeast molecular biology and genetics as that area emerged in importance. Ira also served the Institute with distinction as a member of both the Scientific Review Board and the Medical Advisory Board. With his innate wisdom, he invariably contributed thoughtful and substantive ideas."



CHRIS T. ANDERSON

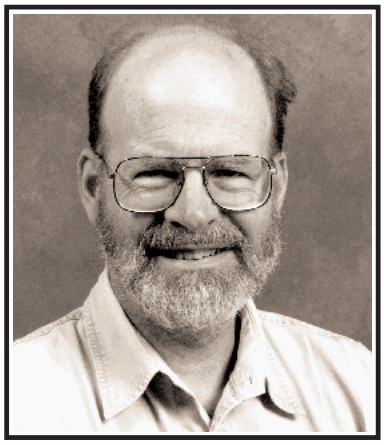
Among many honors and awards during his productive career, Herskowitz was elected to the National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts and Sciences, and he was a MacArthur Foundation Fellow. Most recently, Herskowitz received the 2003 Lewis S. Rosenstiel Award for Distinguished Work in Basic Medical Research.

IN MEMORIAM

Charles A. Janeway, Jr.

Charles Alderson Janeway, Jr., an HHMI investigator at Yale University School of Medicine since 1977, died on April 12, 2003, after a long struggle with B-cell lymphoma. He was 60.

Janeway is credited with formulating many of the concepts that are the basis of modern immunology. He made major contributions to the understanding of T-lymphocyte biology and is widely known for his discoveries on innate immunity—an evolutionarily ancient mechanism to distinguish "self" from "non-self." Largely as a result of his work, scientists now know that innate immunity is a "first response" system to fend off invading microorganisms until the adaptive immune response is mobilized.



YALE UNIVERSITY

Born in Boston, Janeway was educated at Phillips Exeter Academy in Exeter, New Hampshire, and at Harvard College, from which he graduated *summa cum laude* in 1963 with a bachelor's degree in chemistry. He earned his medical degree from Harvard Medical School in 1969.

Janeway came from a long line of physicians. His father, Charles A. Janeway, Sr., was physician-in-chief at Boston Children's Hospital from 1946 until 1974. His grandfather, Theodore C. Janeway, was the first full-time professor of medicine at The Johns Hopkins University School of Medicine, and his great-grandfather, Edward G. Janeway, was the health commissioner of New York City. His mother, Elizabeth Janeway, was a social worker at the Boston Lying-In Hospital.

Janeway trained as a researcher at Harvard, the National Institute for Medical Research in England, and Cambridge University. He completed an internal-medicine internship at Boston's Peter Bent Brigham Hospital. Following seven years of immunology research at the National Institutes of Health and Uppsala University in Sweden, he joined the Yale faculty in 1977. He was promoted to professor of pathology in 1983, and in 1988 became one of the founding members of the newly created section of immunobiology at the school of medicine.

Janeway published more than 300 scientific papers. He was the editor of the highly regarded textbook *Immunobiology: The Immune System in Health and Disease*, now in its fifth edition. He was elected to the National Academy of Sciences and won a number of awards, including the American Association of Immunologists' Lifetime Achievement Award and the Avery-Landsteiner Award, the highest honor of the German Society of Immunology. He served on the board of directors of several research institutions, including the Trudeau Institute, The Jackson Laboratory and the Federation of American Societies for Experimental Biology. He was president of the American Association of Immunologists from 1997 to 1998.

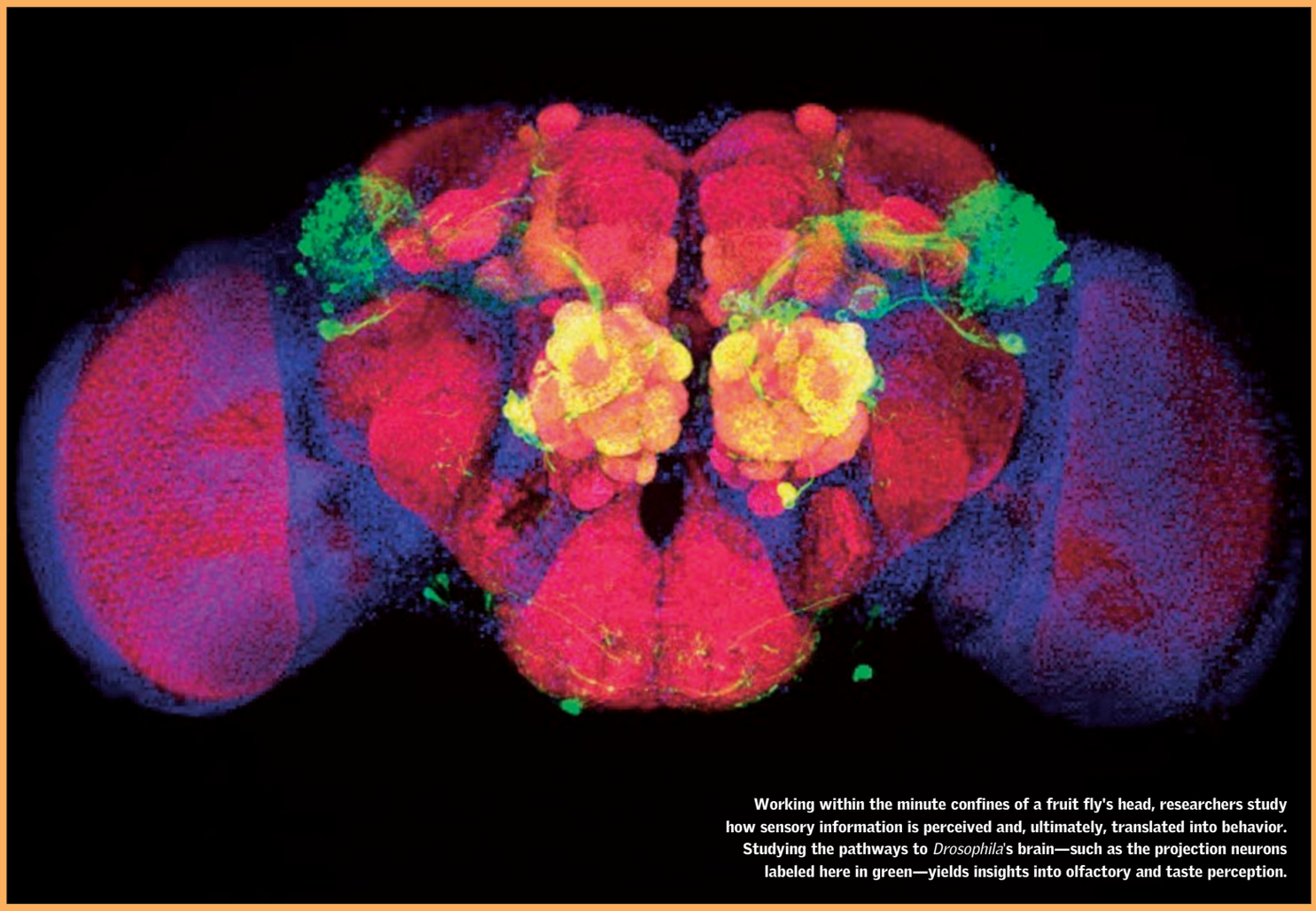
Those who knew Janeway recall his generosity, perseverance and commitment to his research and his students. "Charlie Janeway had an enviable talent of being able to grasp complex problems and lay them out as elegant concepts that provoked further questions and experiments," said Ruslan Medzhitov, one of his colleagues at Yale and an HHMI investigator. "He was famous for his distinctly original ideas that penetrated many areas of immunology. He had a rare encyclopedic knowledge of immunology and could put disparate pieces of experimental data into a broader context, unified by a simple concept with a characteristic intellectual appeal."

In addition, "Charlie was a talented teacher and a great mentor," Medzhitov noted. "His immunology course for Yale medical students was legendary, and his dedication and devotion to science inspired everyone who trained with him."

David A. Clayton, HHMI vice president and chief scientific officer, observed that "Charlie was a true leader in immunology, with a special ability to analyze research from a big-picture perspective. His provocative thinking regularly led researchers to look at problems in new ways, and he thus had a wide and profound influence across the field."

"It is appropriate to remember some advice from Charlie," said HHMI President Thomas R. Cech, "that we would all do well to heed: 'Be inspired by the knowledge that exists at the time you enter research but be irreverent toward this knowledge…for this is the road to true understanding.'"

Janeway is survived by his wife and colleague of 25 years, H. Kim Bottomly, also a professor of immunobiology at the Yale School of Medicine, and by daughters Katherine, Hannah and Megan. H



Working within the minute confines of a fruit fly's head, researchers study how sensory information is perceived and, ultimately, translated into behavior. Studying the pathways to *Drosophila*'s brain—such as the projection neurons labeled here in green—yields insights into olfactory and taste perception.

IN THE NEXT ISSUE

Computing the Genome

Tools from the realms of computation and mathematics can help biologists better understand gene evolution, structure and function.

Big Science in Small Places

Open-heart surgery on a tiny zebrafish...looking inside a fly's brain... giving a mouse an EKG—scientists who conduct their research in such small places have developed some remarkable and inventive techniques.

Learning by Doing

In Philadelphia, high school students learn science by doing science, as partners with medical-center scientists in ongoing cancer research.

Howard Hughes Medical Institute
4000 Jones Bridge Road
Chevy Chase, Maryland 20815-6789
301.215.8855 www.hhmi.org

NONPROFIT ORG.
US POSTAGE
PAID
SUBURBAN MD
PERMIT NO. 6561