Diabetes Detectives || $$$ to Databases || Anthrax 101 || Fighting Parasites in Bangladesh

DECEMBER 2001

HHMI

Howard Hughes Medical Institute Bulletin

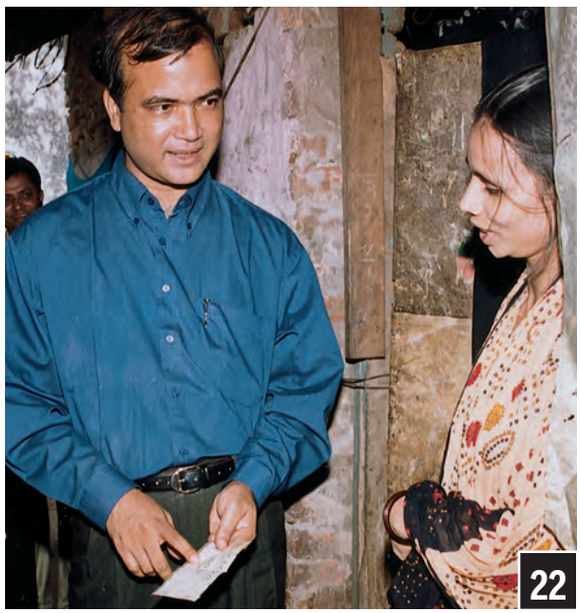
Gleevec's Glory Days

The Long Journey of a Celebrated Anticancer Drug

FEATURES

In Starr County, Texas, an alarming 2,500 Mexican-American residents have type 2 diabetes. These women, at the Starr County Health Studies Office, undergo regular monitoring of their disease, which has strong genetic and evironmental components.

DEPARTMENTS



DAN COHEN (LEFT), FAKRUL ALAM (TOP RIGHT), STUART BRADFORD (BOTTOM RIGHT)

On the Cover: Illustration by Stuart Bradford

HHMI

Howard Hughes Medical Institute Bulletin

DECEMBER 2001 ‖ VOLUME 14 NUMBER 5

HHMI BULLETIN STAFF

CORI VANCHIERI, *Editor*

JIM KEELEY, *Science Editor*

JENNIFER DONOVAN, *Education Editor*

PATRICIA FOSTER, *Manager of Publishing*

KIMBERLY BLANCHARD, *Editorial Coordinator*

ELIZABETH COWLEY, *Copy Editor*

MAYA PINES, *Contributing Editor*

STEVEN MARCUS, PETER TARR, LAURIE VAUGHAN, *story editing*

KATHY SAVORY, *copy editing*

DAVID HERBICK DESIGN, *Publication Design*

Telephone (301) 215 8855 Fax (301) 215 8863 www.hhmi.org
The Bulletin is published by the HHMI Office of Communications, ROBERT A. POTTER, *Director.*

Letters to the editor: We invite your comments. Send your letters via e-mail to bulletin@hhmi.org or regular mail to Letters, Office of Communications, Howard Hughes Medical Institute, 4000 Jones Bridge Road, Chevy Chase, MD 20815-6789. We reserve the right to edit for space and clarity. Please also include your name, address (e-mail or postal) and phone number.

NOTA BENE

Stephen P. Bell, an HHMI investigator at the Massachusetts Institute of Technology, won the 2001 American Society for Biochemistry and Molecular Biology/Schering-Plough Research Institute Award for contributions to biochemistry and molecular biology.

Günter Blobel, an HHMI investigator at The Rockefeller University, was named a member of the Orden Pour le Mérite, a German honorary society. Membership is limited to 30 Germans and 30 foreign members who have been recognized internationally for their contributions to science and culture.

Patrick O. Brown, an HHMI investigator at Stanford University School of Medicine, received the 2001 Millennium Pharmaceuticals Distinguished Achievement Award for Genomics Research in Clinical Immunology.

R. David Bynum, director of the HHMI-supported undergraduate biological sciences education program at the State University of New York at Stony Brook, received the American Society for Cell Biology's 2001 Bruce Alberts Award for Excellence in Science Education. He is an associate professor of biochemistry.

Kevin P. Campbell, an HHMI investigator at the University of Iowa College of Medicine, received the 2001 S. Mouchly Small Scientific Achievement Award from the Muscular Dystrophy Association. The award recognizes a researcher whose work in neuromuscular disorders shows particular promise.

Mario R. Capecchi, an HHMI investigator at the University of Utah, won the 2001 Albert Lasker Award for Basic Medical Research. He shared the award with Martin Evans, Cardiff University, Wales, and Oliver Smithies, University of North Carolina at Chapel Hill, for the development of the technology for manipulating mouse embryonic stem cells to create strains of mice in which a gene is disabled, or "knocked out."

Ana Belén Elgoyhen and **Hugo J.F. Maccioni**, HHMI international research scholars in Argentina, won the 2000 Bernardo A. Houssay Award from the Argentine Biological Society. The award is given biennially to recognize contributions to biological sciences research.

Joseph Heitman, an HHMI investigator at Duke University Medical Center, won the 2002 American Society for Biochemistry and Molecular Biology–Amgen Award. It is given in recognition of a new investigator's achievements in applying biochemistry and molecular biology to the understanding of human disease.

Barry Honig, an HHMI investigator at Columbia University College of Physicians and Surgeons, will receive the 2002 Founders Award from the Biophysical Society, recognizing his achievements in biophysics.

Arthur L. Horwich, an HHMI investigator at Yale University School of Medicine, won the 2001 Hans Neurath Award from the Protein Society for his contributions to basic research in protein science.

Four teachers from the **Fred Hutchinson Cancer Research Center Science Education Partnership**, supported by a grant from HHMI, were honored for teaching excellence. Krestin Bahr, MaryMargaret Welch and David Ziegler won the 2001 Washington Award for Excellence in Education. Jim Boyce won the 2001 Christa McAuliffe Fellowship, named in honor of the first teacher selected to travel in space.

Investigators **Thomas M. Jessell**, Columbia University College of Physicians and Surgeons; **Douglas A. Melton**, Harvard University; **Bert Vogelstein**, The Johns Hopkins University School of Medicine; and Scientific Review Board member **Gregory A. Petsko**, Brandeis University, were elected to the Institute of Medicine of the National Academies.

Robert J. Lefkowitz, an HHMI investigator at Duke University Medical Center, received the Jessie Stevenson Kovalenko Medal from the National Academy of Sciences. The award is given approximately every three years for contributions to the medical sciences. Lefkowitz also received the Louis and Artur Lucian Award for Research in Circulatory Diseases from McGill University in Montreal.

Ben Margolis, an HHMI investigator at the University of Michigan Medical School, won the university's 2001 Faculty Recognition Award.

Nebraska Wesleyan University won the 2001 Council of Independent Colleges Heuer Award, funded by the Russell Pearce and Elizabeth Crimian Heuer Foundation, for a program supported by a grant from HHMI. The award, recognizing achievement in undergraduate science education, is given to two institutions in the United States.

Daphne Preuss, an HHMI investigator at the University of Chicago, won the 2001 American Society for Cell Biology/Promega Early Career Life Scientist Award. Another HHMI investigator, **Erin O'Shea**, University of California, San Francisco, won the award in 2000.

Joseph S. Takahashi, an HHMI investigator at Northwestern University, received the W. Alden Spencer Award from Columbia University College of Physicians and Surgeons for contributions to neural research.

Wayne M. Yokoyama, an HHMI investigator at Washington University School of Medicine, shared the 2001 Novartis Prize for Basic Immunology with Klas Kärre of Sweden and Lorenzo Moretta of Italy. The prize recognized their contributions to an understanding of the molecular function of natural killer cells.


KAY CHERNUSH

Biomedical Research in a Changed World

Until September 11, the biggest issues being discussed at the Howard Hughes Medical Institute centered around research involving human embryonic stem cells and the continuing development of Janelia Farm, the Institute's new research campus being built in nearby Virginia. Then came the horrifying news from New York and Washington, on a morning when we were holding a neuroscience meeting. We turned off the scientific slides and watched events unfold on television, holding our collective breath as colleagues attempted to call their families and friends. With all flights canceled, our travel office struggled to get everyone home safely, renting cars and even a bus for destinations as far away as California. Some conferees waited it out in the conference center, donating blood at a nearby facility and checking e-mail at temporary terminals set up by headquarters computer staff.

Messages soon began arriving from HHMI's international research scholars. "The events in your country have shocked us beyond words," Francisco Sepulveda wrote from Chile. Tatyana Azhikina inquired from Russia about our families and friends, adding that "all of us here are shocked and full of grief." Ana Belén Elgoyhen sent a message from Buenos Aires, saying, "This does not only affect the U.S., I think it involves the entire world." Here in the United States, colleagues urged us to proceed with planned scientific meetings. To do otherwise, one wrote, "would be handing the profoundly sick masterminds of last week's horrors a victory that they do not deserve."

No sooner had we begun to absorb the reality of September 11, however, than the anthrax attacks were upon us—and the awful realization that some scientists among us might be using their specialized knowledge and training for bioterrorism. Suddenly, the biomedical sciences took center stage in a rapidly developing drama that could change the world forever.

In the wake of these events, every major institution in the United States is reexamining its future, HHMI among them. We all need to seek a balance between long-range plans and responsiveness to the current situation. Inevitably, there will be calls upon our time, energy and resources that must be met but that will distract us from the careful agendas that existed before September 11. The biomedical research community will certainly be looked to for advice and ideas about how the country should prepare for the possibility of bioterrorism far more deadly than we have faced to date from anthrax. The need for public education about science, particularly biology, clearly has become critical to our well-being and must now be viewed as a national priority.

Public education about biomedicine has always been an important part of the Institute's mission. Through the years, we have invested substantial resources in publications for the general public, educational programs for young students and their families, support for science museums, televised lecture series for high-school students (see page 34), a highly informative Web site (*www.hhmi.org*) and numerous other activities.

The *Bulletin* is an excellent example. The cover story in this issue is about Gleevec, an anticancer drug that was approved by the Food and Drug Administration in the remarkably short time of 10 weeks. This fast turnaround, however, belies the years of painstaking basic research that preceded the development of the drug by HHMI investigator Owen Witte and others (see page 10). A second article takes the reader to a Bangladeshi slum, where HHMI international scholar Rashidul Haque combines epidemiology with molecular biology in his study of parasitic diseases in the children of Mirpur.

In closing, I want to remember one of our HHMI research technicians at The Rockefeller University, Mohammed Salman Hamdani, who lived in New York. He has been among the missing since the towers collapsed on September 11. His family and coworkers are convinced that Sal, 23, a trained emergency medical technician, ran to the World Trade Center to help, and was lost. All of us at the Institute are privileged to have been among his colleagues. Sal and countless other researchers throughout the world are the true face of the life sciences.

Finally, let me share our sadness on the death of Irving Shapiro, one of the original HHMI Trustees. Much of what HHMI is today was made possible by Irv's dedicated efforts on behalf of the Institute (see page 44).

Thomas R. Cech
President
Howard Hughes Medical Institute

Up Front

Mouse Model Closely Mimics Human Cancer

In research labs throughout the world, cancer researchers have long been frustrated that animal models do not faithfully reflect the way tumors form in people. Now, HHMI investigator Tyler Jacks and colleagues have created a strain of cancer-prone mice that more closely mimics nature.

Their model, based on activation of the oncogene most commonly mutated in human cancer, promises a more accurate way to test potential chemotherapy agents and gives scientists a new window on the cell-signaling pathways involved. In addition, unlike most other genetic mouse models, it reliably produces tumors in 100 percent of the animals.

Allan Balmain of the University of California, San Francisco, who uses the improved laboratory mice in his research, considers Jacks' novel "knock-in" mice "one of the most important in vivo cancer models to have emerged in several years."

Jacks, who recently became director of the Center for Cancer Research at the Massachusetts Institute of Technology (MIT), has made cancer-prone mice his specialty since the late 1980s, when he was a postdoc working with the Whitehead Institute's Robert Weinberg, a pioneer in cancer genetics. Jacks began his career during the emergence of gene targeting, or "knockout," technology. The technique enables scientists to introduce germline mutations into lab animal embryos, which means that the genetic flaws will be present in every cell of the organism that develops from it. He was among the first group of researchers to use the knockout method to create mice with mutations in the tumor suppressor genes, including *Rb, p53, Nf1* and *Nf2*. Each of these mutant genes causes cancer when protein function is lost through inactivation of a cell's second gene copy. Hundreds of researchers around the world have used the knockout mice to study these genes, he says.

Jacks' new technique also results in mice that are highly susceptible to cancer. Unlike the knockout method, however, in which specific genes and the proteins for which they code are deactivated, the new method calls for activating, or "knocking in," an oncogene. That gene, *K-ras*, is mutated in 30 percent of human tumors, including 90 percent of pancreatic cancers, 50 percent of colon cancers and 30 percent of non-small cell lung cancers.

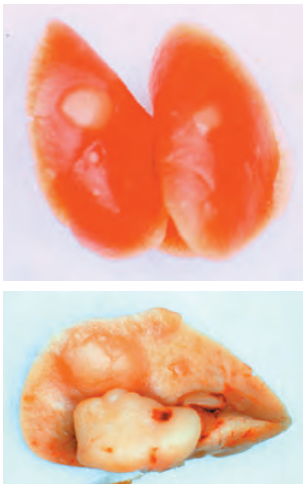
The tumor suppressor's functional opposite, a mutated oncogene such as *K-ras* causes cancer when protein function is revved up, not shut down. Gene targeting with oncogenes is tricky: Many oncogenes in their normal form are essential to cell development; therefore, animals with germline mutations are likely to die in utero. Jacks and his colleagues set out to circumvent this obstacle and, at the same time, recreate the events that lead to sporadic (noninherited) cancers, which arise from a single mutated cell. Although hereditary cancers have led to many discoveries about cancer genetics, sporadic cases make up the vast majority of human cancers, making them especially important to study.

Jacks adapted the "hit-and-run" technique developed by Allan Bradley, formerly an HHMI investigator at Baylor College of Medicine in Houston and now director of the Sanger Centre in Cambridge, England. In Bradley's method, a mutant gene is inserted into embryonic stem cells (the "hit"). In some of these cells, the mutant copy replaces the normal copy via recombination (the "run"). In Jacks' adaptation, "we do the 'hit' step in culture, and let the 'run' step take place in vivo," he explains. "We introduce an inactive form of *K-ras*—a kind of genetic Trojan horse—into embryonic stem cells. We grow a mouse from the stem cells, and by random, spontaneous recombination, the mutant gene becomes activated in individual cells," giving rise to cancer.

In the April 26, 2001, *Nature*, Jacks and coauthors, including lead author Leisa Johnson, now at Onyx Pharmaceuticals in Richmond, California, reported that the knock-in mice "were highly predisposed to a range of tumor types, predominantly early onset lung cancer" that resembles non-small cell lung cancer. They also crossed the *K-ras* mice with mice carrying a mutation in the tumor suppressor gene *p53* and discovered that offspring with both mutant genes had shorter survival, more malignant lung tumors and more tumor types than mice with single mutations.

"This model provides us with an opportunity to isolate and characterize lung tumors from the most benign to the most advanced stages of the disease," says Johnson. "This has been difficult to achieve with human lung tumors, as patients generally present with advanced stages of the disease." The researchers have also discovered that tumor development can be suppressed by cross-breeding the *K-ras* mice with other strains that have a particular genetic makeup, and Balmain, in collaboration with Jacks' lab, is using this strategy to identify lung tumor modifier genes.

Jacks, meanwhile, is making the *K-ras* mice available to other researchers through a new repository at the National Cancer Institute. The Fred-



Tumor growth in the lungs of mice with K-ras mutation. Top shows 30-day-old mouse lungs with numerous tumors. Bottom shows advanced lung tumors in the lungs of a 150-day-old mouse.

KIM MERCER, JACKS LAB. REPRINTED WITH PERMISSION FROM *NATURE* 410: 1111 - 1116 (2001) FIG. 3 A,B. © MACMILLAN PUBLISHERS LTD.

STANLEY ROWIN

Tyler Jacks has developed a mouse model that relies on a "genetic Trojan horse" to give rise to cancers that more closely reflect human cancer development.

erick, Maryland, facility is part of the Institute's Mouse Models of Human Cancers Consortium (*web.ncifcrf.gov/ researchresources/mmhcc/default.asp*).

Jacks' knock-in mouse is likely to have an important impact on drug development, because the K-ras protein is the target of several investigational anticancer compounds. The new model allows companies to directly test a drug candidate's effect on K-ras protein's signaling pathways. Today, many pharmaceutical companies use xenografts, in which human tumor cells are transplanted under an animal's skin, to test anticancer compounds on the animal. "The xenograft models are fast, and the drug companies know what to expect from them," Jacks says. "But we've always argued that they don't accurately reflect how cancer arises in a person: not as a bolus of cells growing under the skin, but rather a developmental process over a long period of time."

"The companies are starting to buy in—to recognize that if a model better reflects the natural history of human cancer, they should use it to test their drugs," he adds. "It might give them more accurate answers and avoid the costs of doing clinical trials on something that's fated not to work." Numerous companies have expressed interest in the new model, and Jacks is licensing the mice to several of them. According to Johnson, the knock-in mouse also "has tremendous potential" for quickly screening not only chemotherapeutics, but also potential chemopreventive drugs, for lung cancer.

One problem with Jacks' current model is that the mice develop too many tumors, too fast. They die before most of their tumors progress, limiting their utility for studying invasion and metastasis. Members of his team are now developing a second-generation mouse in which they can control the "run" step, allowing them to observe later stages of tumor progression.

Perhaps even more important, a new system developed by David Tuveson, an HHMI postdoctoral research fellow in Jacks' lab, promises to expand the model's potential far beyond the original *K-ras* mice. A transcriptional stop element—a chunk of DNA that blocks the process by which a gene issues instructions for protein production—is inserted next to the oncogene. The stop element can be deleted at will, activating the oncogene. This is accomplished by using an adenovirus to introduce an enzyme called Cre recombinase. As a next step, the researchers plan to develop techniques to deliver the virus carrying the enzyme directly to different tumor sites, including the colon and pancreas.

"The beauty of the Cre-mediated approach is we can control the timing, the frequency and the site," Jacks says. "We can activate other genes in the same fashion as we did *K-ras* or inactivate them in a variety of different combinations. And we can put in markers such as green fluorescent protein that allow us to track the cells. Looking ahead a few years, we think we'll be in a position to follow tumor cells very precisely from their origin to later stages of invasion and metastasis." **—TOM REYNOLDS**

Database Science Forcing New Standards for Openness

When the journal *Science* announced last December that it would publish an article written by researchers at Celera Genomics describing the sequence of the human genome, many scientists sounded an alarm. The journal's editors, going against long-established tradition, had agreed to print a report based on scientific data that would not be freely available for public inspection. Rather, the data could be accessed only on a restricted basis as agreed upon by Celera and the journal.

Critics warned that the decision would have serious repercussions for future research, noting the stark contrast between Celera's restrictions and the open access to the draft sequence being published simultaneously in *Nature* by the publicly funded international consortium. The consortium had made a point of depositing its raw data daily in GenBank, a database established for the express purpose of keeping information about the genome in the public domain.

For Donald Kennedy, editor-in-chief of *Science*, the journal's decision was simply pragmatic, consistent with what he called in a February 2 editorial, "the real world" of scientific research —"the world as it is, without hopeful presumptions." For many scientists, however, *Science* was setting a troubling precedent at a time of dramatic change in the life sciences. Since the 1970s and the birth of biotechnology, biological research has become increasingly proprietary and an ever-more complex web of interactions has been woven among universities and biotech and pharmaceutical companies. The relationships have been marked by the escalating use of patents and legal instruments called material transfer agreements (MTAs) designed to protect research tools and data.

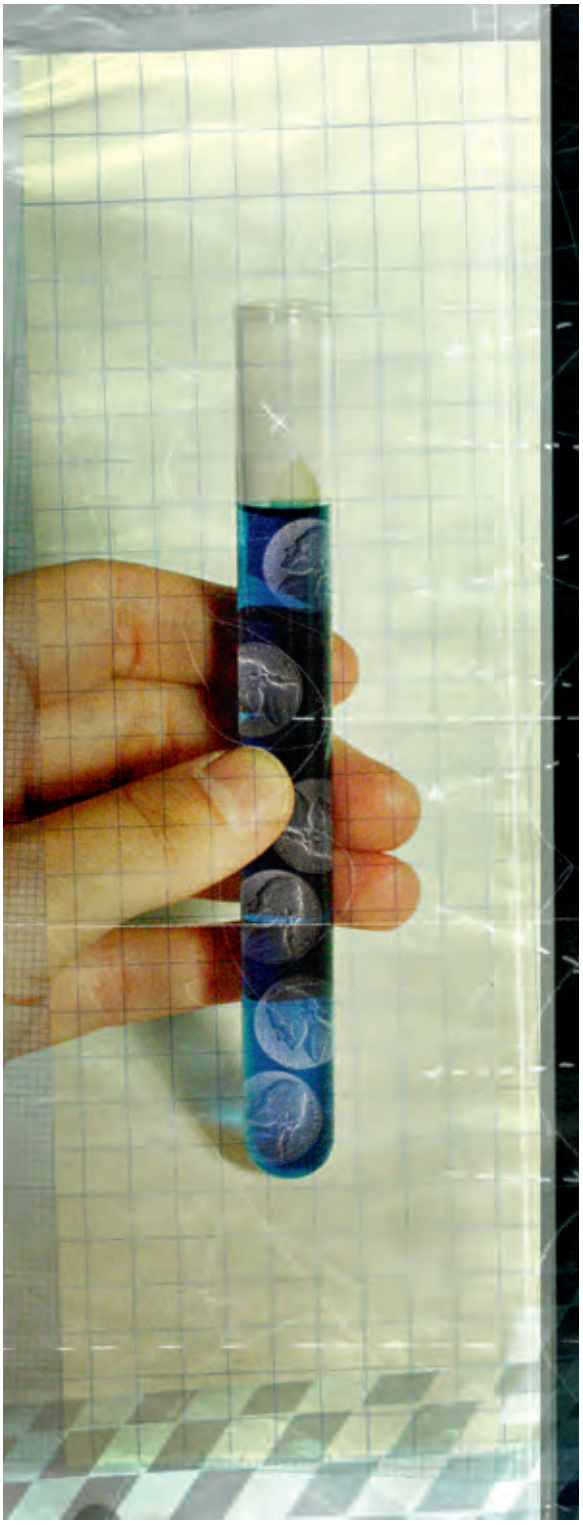
According to Rebecca Eisenberg, a professor of law at the University of Michigan and an expert on scientific intellectual property, the convergence of public and private interests "makes it difficult to maintain a domain of open research science where people abide by the traditional norms of science and exchange material and information freely."

The uncertain relationship between public and private research is especially important in light of an emerging trend in the life sciences. The "reductionist" biology of the 20th century, characterized by attempts to describe individual components of complex biological systems, is giving way in many labs to a systemic approach that focuses on how individual components—whether genes, proteins or entire signaling pathways—work together in networks.

Systemic Biology

This system-wide approach to biology has made databases—such as those assembled by GenBank and Celera containing gene sequence information—among the most ubiquitous and powerful tools in the research arsenal. Recent efforts of public enterprises and private companies have yielded a rich harvest of databases for gene sequences and entire genomes, as well as for RNA sequences, protein sequences and protein structures. There are databases in the works for the human proteome—a compendium of information about every protein produced by human genes—and databases that will link disease characteristics with individual genetic variations. In addition, researchers are just beginning to create massive databases of microarray data, readouts of the expression levels of tens of thousands of genes under a potentially infinite range of physiological conditions across a diversity of tissue and cell types.

Biologist Robin Schoen, who studies science and policy issues at the National Academy of Sciences, believes the growing list of bioinformatics databases is most valuable



STUART BRADFORD

when the information is freely and easily accessible and interconnected, "like a huge online encyclopedia with lots of cross-links.

"Say you're studying protein 'x' in your laboratory," she states. "Now you want to take the information you gather and go into these databases to look at all the other proteins that have the same activity or look at families of proteins segregated by function or by type of enzyme. Or you want to see when that protein is expressed and in what cell tissues. If you're creating models of how a cell works, as people are doing now, think of all the different kinds of data you might want to pull together.

"Ideally, you would want people adding in data to make the databases more comprehensive and also pulling out data to use and test in their models. All of this requires that the data be freely accessible, which gets extraordinarily complicated when the private sector is involved."

The catch, acknowledged by all parties to the discussion, is that databases cannot be patent-protected, making it difficult for a private company to protect its investment if its database is made publicly available. Biotech firms have thus far dealt with gene sequence data by first patenting the sequences and then publishing a paper and releasing the data, confident that their patent would protect the investment they made in generating the data. Academic researchers often do the same.

Databases, however, are protected by copyrights rather than patents, and those copyrights do not protect the actual data, only its presentation—just as copyrights do not protect the actual words in a book, only the order in which they are placed. "A copyright is a pretty limited protection for a database," says Robert Cook-Deegan, an expert on scientific ethics at the Kennedy Institute of Ethics at Georgetown University.

In 1996, the European Union addressed this problem by passing a law that gives database content at least 15 years of patent-like protection. Similar provisions have been debated in the U.S. Congress, but so far no action has been taken. "The scientific community here gets very agitated about it," says Schoen. "They are very heavy users of databases, and they don't want to have to sign a piece of paper every time they use them." At

the same time, she points out, companies such as Celera have legitimate business reasons for not wanting to put all of their information in a database whose contents "could be copied wholesale."

Paying for Access

In the case of Celera's human genome publication, the editors of *Science* hammered out an agreement with the company that enabled Celera to restrict the data to its own company Web site so long as academic, nonprofit and government researchers could have free access to the database with minimal restrictions—such as downloading no more than one megabase (which could contain a dozen or so genes) per week. In certain cases, these users would be given access only after signing an MTA. Scientists employed by private-sector companies could use the data at no cost to validate the results of the *Science* paper, after signing an MTA promising not to use the data for commercial purposes. Further access would require a paid subscription.

Although the public consortium would publish its competing version of the human genome in the journal *Nature*—data that were freely accessible on GenBank even as it was being assembled—Celera concluded that researchers would also be willing to pay for access to an expanded database that integrates the public information with added features available only with a subscription. These extras include updates to Celera's human sequence information, special software tools for analyzing the genome and access to Celera's other sequences, most notably a mouse genome sequence that was unavailable elsewhere.

Despite the relative ease of access for academic researchers who want to study the Celera genome, *Science's* agreement with the company continues to generate discussion. HHMI President Thomas Cech and Vice President Gerald Rubin believe it's a reasonable compromise that works to the benefit of both Celera and researchers throughout the life sciences community. According to Cech, better that Celera publish the data and offer limited access than withhold the data and offer no access without a subscription. "The truth is you almost never get anything—any published reagent or information—from a for-profit company without some sort of material transfer agreement," he says.

LINDA A. CICERO/STANFORD NEWS SERVICE

Donald Kennedy says the decision to publish Celera's human genome sequence in the February 16* Science *(left) was a pragmatic one.

Other researchers are considerably less sanguine, directing their criticism at *Science* rather than at Celera, which they acknowledge is acting in the best interests of its shareholders. David Lipman, director of the National Center for Biotechnology Information at the National Library of Medicine, calls the *Science* decision a "terrible precedent," while dismissing as "unlikely" the argument that publication of Celera's data—even on restricted terms—would make it more available to researchers. As Lipman points out, only a handful of companies—in particular, Incyte Genomics, Gene Logic and Human Genome Sciences—are generating genetic data for the purpose of selling it to others, and those companies, unlike Celera, have been willing to forego the academic accolades that go with publishing their data so long as they still hope to profit from it. "Most companies that generate proprietary data," he says, "don't make it available publicly, not because they want to sell it themselves, but because they want to use it themselves. Usually you publish data when you no longer want to keep it secret."

As the Celera/*Science* controversy has cooled, several major institutions—HHMI and the National Institutes of Health among them—are now allowing their researchers to use institutional funding to purchase subscriptions to Celera's private database in order to get unrestricted access to the company's data and analysis tools. The Wellcome Trust in England, however, which contributed funding to the public human genome project, has told researchers that if they want to access the Celera database, they can't use Wellcome funding to pay for it. The key determinant for individual researchers may prove to be utility: in particular, the benefits of having access to Celera's mouse genome and the software analysis tools the company packages with its data.

Larger questions of how public and private research should interact remain unresolved, however. Private companies continue to generate a host of new databases even as public and academic researchers argue for a world in which all genomics data are accessible online through the modern equivalent of one-stop shopping. In February 2002, parties to the debate will have a chance to exchange views face-to-face, at a workshop hosted by the National Academy of Sciences. Cech, who will serve as chair, hopes participants will be able to agree about what should and should not be made publicly available when researchers decide to publish a paper, and about whether "the rules should be different" for commercial companies than for academic or government labs. "There are some issues here that we just didn't have 10 years ago," he says, "and it would be useful for people in the community to arrive at a consensus on them."

—GARY TAUBES

Anthrax 101

A Conversation With William Dietrich

In spite of its status as an ancient disease and modern bioweapon, most people knew little about anthrax before it was spread through the U.S. mail in October. When the assault-by-letter began, however, the public suddenly needed detailed information on how the deadly bacteria wreak their havoc and how they might be stopped.

In early October, William Dietrich, an HHMI investigator at Harvard Medical School, found himself in demand among the media. By chance, just as the first attacks occurred, the journal *Current Biology* published some of Dietrich's findings on anthrax. He had identified a gene in mice that governs their susceptibility to the deadly anthrax toxin. A change in a single letter of the gene's sequence can alter the mouse's resistance to the toxin. The discovery could potentially hold true in humans as well. Here, Dietrich provides the *Bulletin* with answers to some frequently asked questions about a disease that has moved to the forefront of the country's consciousness.

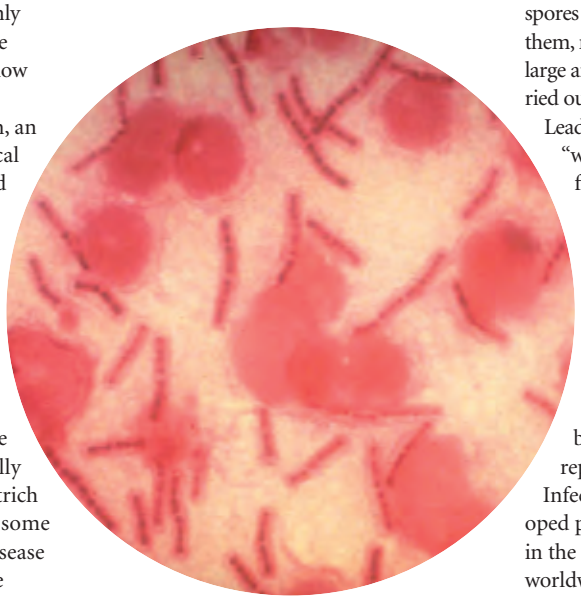
ARMED FORCES INSTITUTE OF PATHOLOGY

What are possible sources of the anthrax spores used in the attacks on the United States?

Dietrich: They include research laboratories, bacterial-stock clearinghouses, government-sponsored biological weapons programs in the United States and abroad and isolates obtained from soil that was contaminated from naturally occurring anthrax outbreaks.

Why is anthrax an attractive weapon to terrorists, especially considering that the infection isn't contagious?

Dietrich: It is probably easier to obtain, package and deliver than some other possible choices, such as smallpox. Anthrax is lethal if inhaled and the infection is not immediately treated. Clearly, anthrax can be a significant weapon if prepared and dispersed in the most effective manner. For example, in 1993, a report by the Congressional Office of Technology Assessment estimated that between 130,000 and 3 million deaths could follow the aerosolized release of 100 kg (220 lb) of anthrax spores upwind of the Washington, D.C., area. Also, the fact that the spores are resistant to temperature, humidity and other factors makes anthrax more stable and long-lasting than other potential agents.



What is the difference between the cutaneous (skin), inhalation and gastrointestinal forms of the infection?

Dietrich: It is simply the route the bacteria take to enter the body. The vast majority of infections are cutaneous. Any of the forms can be deadly, though, and the severe symptoms—blood poisoning, plummeting blood pressure, shock, bleeding and fluid in the lungs—can occur whenever a systemic infection gets established.

How do the anthrax bacteria cause such severe and life-threatening effects on the body?

Dietrich: The bacteria target macrophages, cells of the immune system that seek out and engulf foreign substances. The bug produces a toxin that enters the macrophages and disrupts the function of key proteins. This poisoning causes the cells to burst, which releases biological molecules that send the body into shock.

What makes anthrax "weapons-grade"?

Dietrich: I do not have direct experience in "weaponizing" anthrax. From my reading of secondary sources, part of it is related to isolating spore preparations that are of such small diameter they can float for long distances and effectively penetrate the respiratory tract. It also seems that there are ways of treating the spores to remove the electrostatic charge on them, making them easier to disperse over a large area. This treatment reportedly was carried out on the anthrax sent to Senate Majority Leader Tom Daschle's office. The term "weapons-grade" is also perhaps related to forms of the bacillus that are specifically created to be antibiotic-resistant.

Excluding a deliberate attack, what are the average person's chances of contracting anthrax?

Dietrich: If you live in the United States, your chances are virtually nil. Until the October attacks, there hadn't been a case of inhalation anthrax reported in this country since 1978. Infections are more common in less developed parts of the world. I have seen numbers in the tens of thousands of cases annually worldwide, though these estimates seem excessive to me.

Should everyone buy antibiotics and keep them on hand in case of an anthrax outbreak?

Dietrich: In most cases, it would be a waste of money. You are unlikely to know whether you've been exposed to anthrax unless the government and public health officials are involved, and in the unlikely event that you were exposed, you'd be able to receive prophylactic antibiotic treatment right away.

Is there a vaccine that could protect the entire population?

Dietrich: No. The existing anthrax vaccine stock is sufficient only to protect members of the armed forces. Even if there was an ample supply, it can have some serious side effects and must be administered in a series of injections over months and years.

—RICHARD SALTUS

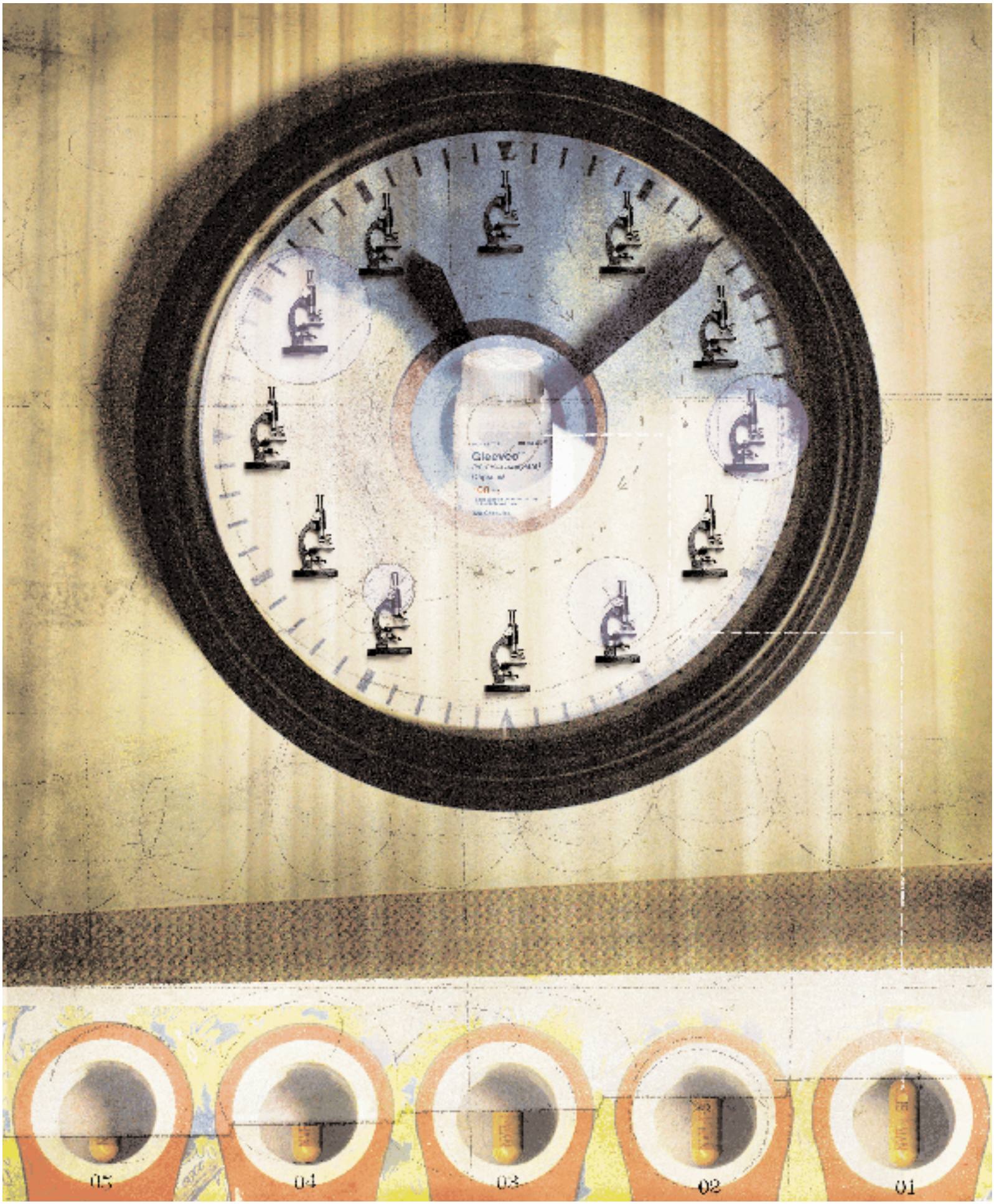
An apparent overnight success, this new leukemia drug has decades of research behind it. By Jill Waalen

Gleevec's Glory Days

Gleevec seemed to spring up overnight. "Powerful Anti-Cancer Drug Emerges from Basic Biology," trumpeted *The New York Times* on May 8. Two days later, the Food and Drug Administration (fda) announced its approval after a record-breaking review period of only two and a half months. With words such as "fantastic" and "incredibly important," an impressive array of scientists welcomed the new drug as the first demonstrable success among a new generation of cancer weapons targeting aberrant signaling molecules within cells. Before the month was out, *Newsweek* was luring readers with a headline that teased "A Cure for Cancer?"

Gleevec, a.k.a. compound STI-571, is not a sure cure for any cancer, and in fact has shown clear benefit in only two diseases so far: a

STUART BRADFORD


05
04
03
02
01

rare blood cancer, chronic myelogenous leukemia (CML), and an equally rare stomach malignancy, gastrointestinal stromal tumors. Aside from that important qualifier, however, most researchers believe that the compound—and, more important, the biological rationale behind its development—holds enormous promise.

Taken as a simple daily pill, it causes few side effects and has brought dramatic remissions, with up to double the effectiveness of other treatments. This is largely because the underlying treatment strategy—to halt the cancer right where it starts—is so specific and efficient. By targeting a particular rogue molecule, STI-571 prevents a signaling cascade inside cells that would otherwise turn cells cancerous. Most cancer treatments, in contrast, target more general processes of cell division, often damaging normal cells and causing intolerable side effects. With Gleevec's meteoric clinical success, researchers probing the molecular origins of cancer are more excited than ever about designing comparable drugs that offer hope to a broader range of patients.

Neither the strategy nor the treatment sprang up overnight, however. Last May's splashy headlines notwithstanding, the accomplishment took nearly four decades, more than a few odd coincidences and convergences, and one gloomy period near the end when market limitations seemed likely to scuttle it all.

Owen Witte watched with excitement as his basic research from the 1970s resulted in a viable cancer therapy.

TWO PATHS CONVERGE

When you're a basic scientist, of course, a few decades can still seem a relatively short time. It did for Owen N. Witte, a key player since the early days of the Gleevec story and now an hhmi investigator at the University of California, Los Angeles: "In one scientific lifetime, to see the fruits of your basic science evolve and end up in a therapeutic that actually makes a major difference in people's lives is an extremely rewarding feeling."

When Witte started his career in the 1970s as a postdoc at the Massachusetts Institute of Technology (mit), he joined a crowd of junior researchers jostling for lab space and face-time with the boss. Last May he joined his former boss, David Baltimore, now president of the California Institute of Technology, and three other researchers, Brian Druker of Oregon Health Sciences University, Nicholas Lydon of Amgen, Inc., and Alex Matter of Novartis, to receive Harvard Medical School's prestigious Warren Alpert Foundation Prize for their discoveries leading to the development of STI-571.

At the outset, Witte had no idea his work would play a role in CML. He and Baltimore were studying the Abelson murine leukemia virus, which was known to trigger another type of leukemia in mice. Their research built on what was then a recent discovery by the Nobel Prize-winning team of J. Michael Bishop and Harold Varmus at the University of California, San Francisco. Bishop and Varmus had found that another cancer-causing virus, one that produced sarcomas in chickens, worked by commandeering a normal gene from the chicken genome and changing it into a cancer-causing gene called *src*. At mit, Witte, Baltimore and colleagues found that the Abelson virus seemed to work in the same way in mice, seizing a normal mouse gene, named *Abl*, and adding its own genetic material. The hijacked gene caused the resulting ABL protein to overstimulate cell growth.

On a seemingly unrelated front, other scientists had been gathering clues about the origins of CML, a type of leukemia characterized by white blood cell counts up to 50 times higher than normal. CML strikes up to 8,000 people in the United States each year, most of whom are in their 50s and 60s. While studying chromosomal "snapshots," or karyotypes, in the 1960s, Peter Nowell and David Hungerford of the University of Pennsylvania School of Medicine and the Institute of Cancer Research (now Fox-Chase Cancer Center) in Philadelphia had noticed that chromosome 22, which is short to begin with, was almost invariably even shorter in the white blood cells of CML patients.

The significance of that stubby fragment, which came to be known

as the Philadelphia chromosome, remained a mystery for another decade. Then, in 1973, new techniques for staining chromosomes with barcode-like patterns enabled Janet Rowley of the University of Chicago to discover that the piece from the shortened chromosome 22 was not missing but in fact had jumped to chromosome 9—and, in exchange, a shorter piece of chromosome 9 had shifted to chromosome 22.

The Philadelphia chromosome discoveries were part of "a complete sea change in our understanding of cancer at the time," says Witte. "They made us realize that cancer did not necessarily result from random chromosome changes and that it could be caused not only by a loss or gain of information, but also by a rearrangement of information." Understanding how the swap between chromosomes 9 and 22 might lead to CML, however, required knowing which genes were disrupted in the process. Another new technique at the time enabled scientists to pinpoint genes on chromosomes, which led in 1982 to the unexpected convergence of Witte's work and the Philadelphia chromosome: As it turned out, the piece of chromosome 9 that shifted to chromosome 22 in CML contained the human version of the *ABL* gene.

Now able to pinpoint genes involved in the chromosomal exchange, Witte and others found that just as the Abelson virus' genetic material had increased the ABL protein's activity in mice, genes near the site where the *Abl* gene landed on the Philadelphia chromosome (called the breakpoint cluster region, or BCR) combined with *Abl* to encode a protein that was an overactive switch for cell division. Although it would take several more years to demonstrate that the *Bcr-Abl* gene could cause CML in animal models, "we knew then that we had our molecular target for CML," says Witte.

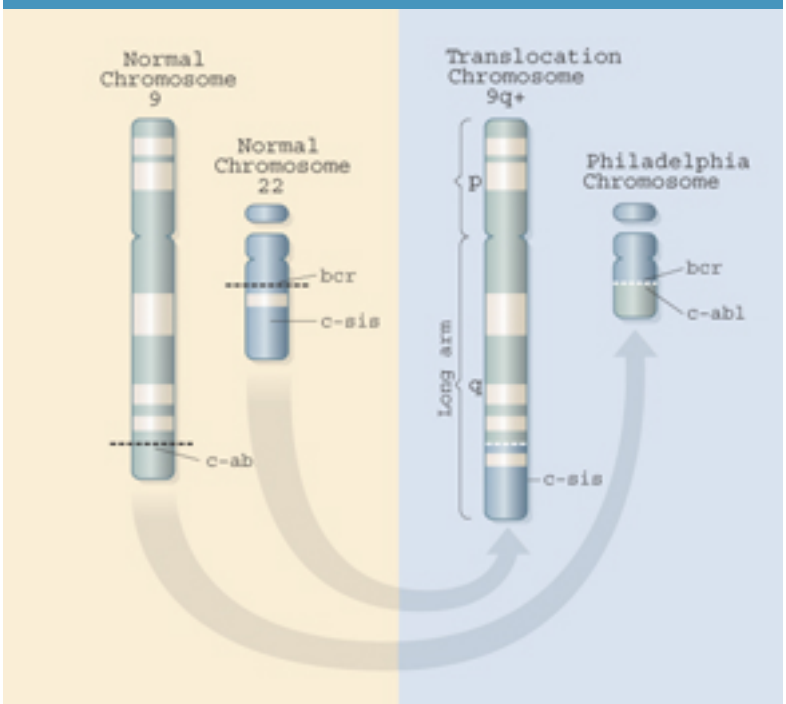
KATHY TARANTOLA

Owen Witte, Nicholas Lydon, Brian Druker, Alex Matter and David Baltimore shared the 2000 Warren Alpert Foundation Award for their work leading to the development of Gleevec.

TOM KELLER

Chromosome Swap in Chronic Myelogenous Leukemia

In chronic myelogenous leukemia, segments of chromosome 9 and chromosome 22 switch places. The shortened chromosome 22, called the Philadelphia chromosome, forms a gene called *BCR-ABL*, which causes overactive white blood cell division.



NEW MOLECULAR M.O.

It was now clear that stopping CML would require stopping the hyperactive BCR-ABL protein. Important clues about the workings of the *Bcr-Abl* gene and proteins coded by similar cancer genes were emerging from experiments conducted in the late 1970s and early 1980s in, among others, the laboratory of molecular biologist and hhmi Medical Advisory Board member Tony Hunter at The Salk Institute in San Diego.

Many signaling proteins, including ABL and SRC, were already known to work by triggering cascades of chemical reactions that drive cell division. They set off the chain of reactions by "tagging" certain proteins with phosphate groups, a process called phosphorylation. At the time, researchers knew of only two amino acids that could accept phosphate tags: serine and threonine. Then, in 1979, while Hunter was running a routine experiment on SRC and other signaling proteins, he found a phosphate-tagged form of a third amino acid, tyrosine. At about the same time, Witte found that a viral protein, later identified as the functional part of BCR-ABL, also worked by phosphorylating tyrosine. Signaling proteins had another means of flipping the switch for cell division.

The discovery that tyrosine could be phosphorylated led to a flurry of retesting other important cell signalers thought to tag only serine and threonine. "Within about a year, many tyrosine kinases [the signaling proteins that phosphorylate tyrosine] came out of the woodwork," Hunter says. The number is now estimated to be more than 90, including not only SRC and ABL, but also other important regulators of cell division, such as receptors for epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF).

BLOCKING SIGNALS

By the mid-1980s, Witte had taken to the road to try to stir interest in developing drugs to jam BCR-ABL's signals, which triggered CML. "I gave a lot of seminars and kept telling people this would be a great target," says Witte. Because CML does not affect large numbers of people, it was very hard to interest drug companies in developing inhibitors specifically for BCR-ABL, he explains.

The pharmaceutical companies had their sights set on bigger markets. Novartis (then Ciba Geigy), taking the lead in the search for inhibitors of tyrosine kinases, focused on the PDGF receptor, which was not only implicated in many different cancers, but also was considered a good target for preventing reblockage of coronary arteries following angioplasty. A number of researchers persisted in their efforts to find an inhibitor for BCR-ABL, however, including oncologist Brian J. Druker of the Oregon Health Sciences University in Portland, who was supplying reagents for Novartis' tests. In 1993, Druker heard that Novartis had generated one inhibitor, known as STI-571, which was only moderately active against the PDGF receptor but was active and specific for stopping ABL.

For the next few years, he worked to convince the company that CML was a worthwhile market. Druker collected preclinical results showing that STI-571 could stop proliferation of leukemia cells without harming normal cells, both in animal models and in blood samples from CML patients.

"The question was whether STI-571 was going to be any better than tumor necrosis factor or other compounds that look extremely potent in mice but aren't as good in clinical trials," Druker says. The answer came quickly when phase I clinical trials began in June 1998. Remissions occurred in 100 percent of the first 31 patients who participated in the trial, with remarkably few side effects. These patients and the majority of other patients treated since have maintained their normal white blood cell counts for more than one year, according to Druker.

Anticipating increased patient and physician demand for the drug when the results were unveiled at an American Society of Hematology meeting in December 1999, Druker and other investigators lobbied the company to make more of the drug available for the next phase of patient studies. Their efforts, backed by a petition sent to the Novartis CEO from 4,000 members of the Leukemia and Lymphoma Society of America, led to rapid expansion of clinical trials, from 100 patients to 1,000 within a year and to 6,000 within two years.

If Novartis' early efforts in developing STI-571 could be characterized as slow, says Druker, "they more than made up for lost time by responding quite remarkably when the demand was there." After the spectacular initial results held up in the later trials, STI-571 sailed through the drug approval process faster than any other cancer drug in the history of the FDA.

Even while STI-571 triumphed in clinical trials, its specificity for ABL—the key to its success against CML—remained unexplained. Why, researchers wondered, did the drug inhibit ABL while leaving other tyrosine kinases essentially unaffected? "Tyrosine kinases share similar active sites because they catalyze the same reaction. When they're in the active conformation, they all look the same, like soldiers at attention," says John Kuriyan, an HHMI investigator who recently moved from The Rockefeller University to the University of California, Berkeley. Thus, most inhibitors that bind to active forms of the enzymes are fairly nonspecific, able to short-circuit multiple cellular processes, which could lead to a generalized meltdown of cells, including normal ones.

By contrast, inactive tyrosine kinases assume their own unique shapes, like soldiers standing at ease, Kuriyan explains. Using x-ray crystallography to visualize the interaction between STI-571 and the active site of ABL, Kuriyan and colleagues found unexpectedly that STI-571 binds to ABL in its inactive—and therefore more unique—conformation. "The result is that STI-571 specifically blocks ABL, but not serine/threonine kinases or other tyrosine kinases," Kuriyan says.

Although the explanation lies in the molecular realm, the difference that specificity makes is palpable to patients. Before STI-571, CML patients faced two main treatment options: bone marrow transplant, available only to the one-third of patients for whom a donor could be found, or daily injections of interferon, which often resulted in side effects likened to having the worst case of the flu every day for a lifetime.

Now these patients take STI-571 almost as if it were a daily vitamin. The lack of major side effects was a surprise, even to the scientists who designed it that way. "It really is remarkably without side effects," Witte says. Although these results are encouraging, says Druker, follow-up is

Bullets With Limited Magic

It's remarkably potent against two cancers so far, but will the same targeted strategy work with other malignancies? Researchers are hopeful but are keeping their expectations in check.

With Gleevec's dramatic success in muzzling the tyrosine kinases underlying chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GISTs), the search is on for compounds that inhibit other cancer-causing tyrosine kinases. One such drug, Herceptin, for patients with metastatic breast cancer and excess levels of the growth factor receptor Her2, was approved in 1998. Other inhibitors are in patient studies, including several that target tyrosine kinases serving as receptors for epidermal growth factor or vascular endothelial growth factor (VEGF). The VEGF receptor is of particular interest because it promotes growth of new blood vessels that feed tumors.

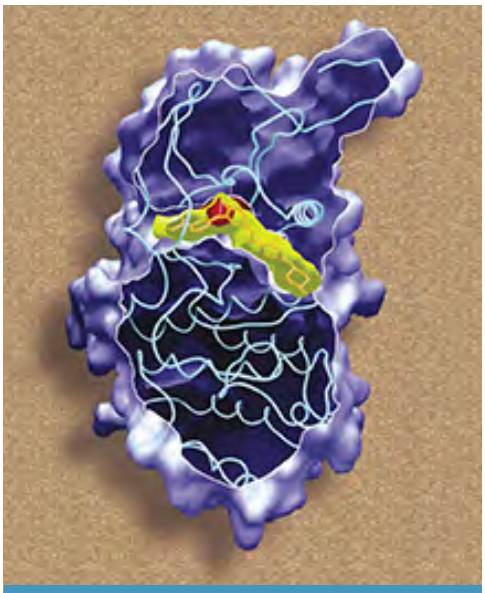
None of these inhibitors, however, are likely to match Gleevec's knockout performance against CML and GISTs, predicts Brian J. Druker, at Oregon Health Sciences University in Portland. Although they could be at least as effective as other cancer chemotherapies directed toward general growth processes, most will not squelch the cancer at its molecular source, Druker says. Even if they inhibit tyrosine kinases that are expressed in many cancers, expression is not enough. For inhibitors to strike with power and precision, their targeted molecules must be part of the cancer's root cause.

Indeed, Gleevec itself—now being tested in lung cancer patients—is unlikely to match its earlier successes. That's because although the drug's specific targets, ABL and c-KIT tyrosine kinases, may participate in the growth pathways of other cancers, they are less likely to be the root cause in those diseases, Druker explains.

Owen N. Witte, an HHMI investigator at the University of California, Los Angeles, is enthusiastic about testing Gleevec in other cancers, but he thinks the drug will prove most useful as part of combination chemotherapy. "When you have a drug that has limited side effects and can have efficacy in different settings, it should be tried," Witte says. "You may need to combine it with other drugs, but that's the history of chemotherapy for cancer—combinations of drugs work better for certain tumors." Likewise, inhibitors of the majority of other tyrosine kinases are expected to be most helpful as part of a multipronged treatment approach, stemming a cancer's growth while leaving its roots intact. **—JW**

CHRISTOPHER DENNEY

John Kuriyan showed that STI-571 is so specific because it binds to ABL's more unique, inactive form.



LORE LEIGHTON, KURIYAN LAB

Resistance in Late-Stage Disease

STI-571 (orange) can shut down the overactive BCR-ABL protein (purple), except during blast crisis, when a mutation (red circle) changes the shape of the protein's active site. The drug can no longer bind tightly and is less effective.

needed to see how long the response lasts and whether STI-571 prolongs survival compared with standard treatments.

RESISTANCE TO STI-571

Although STI-571 remains effective in treating most patients with CML, the drug has proven less active, and eventually fails, in patients in blast crisis, the rapidly progressing end stage of the disease. Many researchers have attributed this resistance to an accumulation of molecular abnormalities that occur late in the disease and are altogether separate from BCR-ABL.

However, another and more surprising story is emerging from studies of blood cells from patients in blast crisis by oncologist Charles Sawyers, a former Witte trainee, and his colleagues at ucla. Those findings, reported in the August 3, 2001, *Science*, suggest that end-stage resistance results from a change in the ABL protein's active site, which Kuriyan had found to be important for STI-571 binding.

"These results suggested that BCR-ABL is still the right target" even in late-stage blast crisis, Druker says. "The remarkable finding is that STI-571 as a single agent has any effect at all on blast crisis," Witte notes. Experiments show that BCR-ABL continues to drive the cancer at that stage, suggesting that STI-571 could still be used in combination with other drugs to treat blast crisis, a common strategy in cancer treatments, he adds.

GIST REWARDS

On the heels of its dramatic success in CML, STI-571 held one more surprise. David A. Tuveson, an oncologist working as an hhmi postdoctoral fellow in the laboratory of hhmi investigator Tyler Jacks at mit, heard about the drug's success against the BCR-ABL protein. He wondered whether it would work against another defective protein called c-KIT, which is the central cause of solid (non-blood-cell) tumors known as gastrointestinal stromal tumors, or GISTs. This relatively rare cancer, which strikes up to 5,000 adults in the United States each year, is notoriously resistant to chemotherapy. Tuveson, Jacks and colleagues found that the drug blocked the growth of GIST cells in the lab. Follow-up studies in patients have shown that tumors shrink in 60 percent of those treated—a victory similar to that over CML.

Ironically, the key to STI-571's effectiveness against CML and GISTs—its specificity—is also the reason the drug is not likely to work against other cancers, Druker says. In CML and GISTs, STI-571 strikes the root cause, the defective BCR-ABL and c-KIT proteins (see box). For other cancers, although STI-571 may help stop processes that contribute to cell growth, other specific inhibitors aimed at the root causes of the cancers still need to be developed. That prospect has scientists searching for all kinds of molecular triggers and their inhibitors, hoping to discover a drug like STI-571 during their lifetimes—a rare and inspiring event.

Confronting Diabetes From All Angles

To combat this growing epidemic, researchers are hunting for genes, exploring cell-signaling pathways and looking at obesity's role. BY KAREN HOPKIN

MEXICAN-AMERICAN SISTERS EUGENIA MONTALVO (LEFT) AND JESUSA SALMON HAVE TYPE 2 DIABETES. THEY VISIT THE STARR COUNTY HEALTH STUDIES OFFICE IN RIO GRANDE CITY, TEXAS, TO HAVE BLOOD DRAWN BY TECHNICIAN CLARA TREVINO, AS PART OF THE STARR COUNTY STUDY THAT HELPED RESEARCHERS FIND A GENE INVOLVED IN THIS WIDESPREAD DISEASE.

DAN COHEN (2)

The more scientists learn about diabetes, the more complex the disease becomes. Multiple genes, intricate cell-signaling disruptions and environmental insults all play important roles, although their precise mechanisms are unclear. Meanwhile, the pressure to find ways to combat this disease is greater than ever. ¶ "It really is an epidemic," says Alan Saltiel, a diabetes researcher at the University of Michigan in Ann Arbor, "and it's on the rise." Because diabetes is linked with obesity, its incidence increases as people become older and less active. An estimated 143 million people worldwide have the disease—almost five times more than just a decade ago. In the United States, diabetes has been diagnosed in more than 16 million people. ¶ When glucose concentrations rise in the blood of healthy individuals—after a meal, for example—the pancreas produces the hormone insulin, which tells muscle and fat cells to extract the sugar from the blood. The insulin also instructs liver cells to stop producing glucose. In people with diabetes, however, glucose levels in the blood remain too high. This is true for

both type 1 and type 2 diabetes, though for different reasons (see box below).

Four hhmi researchers have chosen different targets, hoping their findings will improve treatments for diabetes or provide clues for a cure. Graeme Bell is searching for culprit genes, Morris White and Morris Birnbaum are studying the cellular pathways of insulin and glucose and Gerald Shulman is investigating the impact of fat on diabetes development. Their work is part of a larger effort being made in scores of laboratories worldwide. Each new discovery of a component of any of these pathways provides a potential target for future drugs. "This is a really exciting time," says Saltiel. "We now have a lot of ideas for how to attack the disease."

Find Faulty Genes

Graeme Bell, an hhmi investigator at the University of Chicago, launched his career as a prospector for diabetes genes some 20 years ago at the University of California, San Francisco. Bell wondered whether mutations related to the human insulin gene might be involved in the development of diabetes—and he soon discovered a genetic variation associated with increased risk for type 1 diabetes. The variation, in a region next to the human insulin gene, turned out to modulate the gene's expression.

"It was a surprising discovery," Bell says, because type 1 diabetes was known to be caused by the outright destruction of the insulin-producing pancreatic beta cells by the immune system. "For 10 years, no one believed it," he recalls.

Although there is no longer any doubt that Bell had identified a gene that increases susceptibility to type 1 diabetes, Bell, Craig Hanis of the University of Texas Health Science Center at Houston and their colleagues now face similar skepticism over their discovery of a gene that appears to be linked to increased risk for type 2 diabetes, the more common type of the disease. Eight years ago, they turned their attention to a long-studied population of Mexican-Americans who are highly prone to the disease. In this population in Starr County, Texas, 2,500 of the 60,000 residents have type 2 diabetes; half of the adults over age 35 are either diabetics themselves or have a relative with the disease. Bell and Hanis obtained DNA samples from 330 pairs of diabetic siblings from 170 families and searched hundreds

TODD BUCHANAN

Graeme Bell has mined hundreds of DNA samples and located genetic variations involved in both type 1 and type 2 diabetes.

Two Types, Two Causes

- Type 1 diabetes, the early-onset, or "juvenile," form of the disease, occurs when the body's immune system destroys the beta cells in the pancreas that produce insulin. Patients with type 1 diabetes require insulin injections.
- Type 2 diabetes, the more common, adult-onset, form of the disease, arises when a person becomes less responsive to insulin—often by gaining weight or reducing physical activity. The muscle and liver cells resist insulin's influence, and too much sugar stays in the blood. The beta cells of the pancreas compensate by expanding in number or size to produce extra insulin. When the pancreas can no longer keep up with the body's demand for more insulin, type 2 diabetes results. About one-third of patients require insulin treatment; the rest try to manage their sugar levels with diet, exercise and oral medications.
- Insulin resistance, a first step toward type 2 diabetes, can arise from a long list of defects along the multistep insulin-signaling pathway. Changes can occur, for example, in expression of genes or proteins that are targets of insulin action. Metabolic abnormalities, some brought on by aging, others by obesity, can cause the body to defy insulin's commands.
- The vast majority of people with diabetes—about 90 percent—have the type 2 form. More than 80 percent of people with type 2 diabetes are overweight.
- In a study of more than 3,200 people at high risk for developing type 2 diabetes—who had impaired glucose tolerance and were overweight—a low-fat diet and 30 minutes of daily exercise resulted in an average 15-pound weight loss and a 58 percent reduction in the risk of getting type 2 diabetes.
- Diabetes is the main cause of kidney failure, limb amputations and new-onset blindness and is a major cause of heart disease and stroke.

of locations throughout the genome for a link to disease susceptibility. By 1996, they had narrowed their search to a region of chromosome 2—but they still had to locate the gene and identify the variants that increased the people's risk for diabetes.

In October 2000, they finally announced their success. "People were incredulous," says Bell. Instead of finding a gene known to be involved in insulin action, the team had zeroed in on a gene encoding calpain-10—a protease, which is an enzyme that breaks down proteins. In people at increased risk for disease, the researchers discovered small genetic variations, called single-nucleotide polymorphisms (SNPs), in a region of the gene that controls how much calpain-10 is produced. As a result of the SNPs, these individuals have lower concentrations of calpain-10 in their muscle cells, and their cells are not as sensitive to insulin's commands. The mechanism by which calpain-10 affects how glucose is taken up and used by cells, however, remains unknown.

Bell is anxious to forge ahead. "Once you find a gene, you then have to show how it plays a role in disease." He and his colleagues are trying to learn how calpain-10 might influence insulin signaling or glucose metabolism, particularly in cells involved in diabetes, such as muscle, fat and liver cells.

Unblocking Signals

Morris White focuses his studies on the signals that are switched on and off inside the cell after insulin makes contact with the cell surface. An hhmi investigator at the Joslin Diabetes Center at Harvard Medical School in Boston, White is looking for molecules involved in insulin action and then attempting to learn how they become compromised in people with diabetes. In normal cells, the insulin binds to a specific protein on the cell's surface, called the insulin receptor, triggering a chain reaction in which one protein activates the next to pass insulin's signal deep into the cell. How the cell responds depends on what type of cell it is: Insulin directs muscle cells, for instance, to import and store glucose and tells liver cells to shut down glucose production. It might even alert the brain that enough food has been consumed. In people with diabetes, this signaling cascade fails at some point—but where, and how?

In the early 1980s, researchers discovered that when insulin binds to its receptor, the receptor takes on a particular chemical "tag" called phosphotyrosine. White and his colleagues exploited this tag when they set out to identify proteins involved in insulin action. Using the sort of brute-force biochemistry that was the only approach back then, the researchers ground up 200 rat livers—100 from animals that had been treated with insulin, another 100 from animals that hadn't. Then, using an antibody designed to recognize the phosphotyrosine tag, they set out to isolate any proteins that were tagged in the presence of insulin. As it turned out, the protein they were looking for was relatively scant in cells, making the search nearly impossible. After eight long years, however, they had purified enough of the insulin-activated, tagged protein to learn something about it. No one had seen anything like it before, and unfortunately, when White examined the protein more carefully, he could detect no obvious function. It appeared to have no activity at all.

At this point, White's efforts, like Bell's, were raising a few eyebrows. The protein, which he dubbed IRS-1 (for insulin receptor substrate 1), picked up a phosphotyrosine tag within seconds after cells were exposed to insulin. But how was it involved in insulin signaling? While White continued to ask this question, other researchers produced mice that lacked IRS-1, because sometimes the fastest way to figure out what a protein does is to see what happens when it's eliminated.

Mice without IRS-1 were small, but they never developed diabetes—not what one would expect if IRS-1 were critical to insulin's action. "People started asking me what I was going to do with my career," White recalls with a chuckle.

In 1992, Jacalyn Pierce at the National Cancer Institute told White about a line of blood cells that was resistant to insulin and was missing a protein that looked a lot like IRS-1. "It was just different enough to convince me that there was a second IRS protein," White explains. The researchers then succeeded in isolating and cloning that protein, which they called IRS-2.

Mice lacking IRS-2, they found, develop diabetes as they enter

Morris White is looking for molecules involved in insulin action to learn how they become compromised in people with diabetes.

ASIA KEPKA

DAVID GRAHAM

Morris J. Birnbaum's interest in figuring out how insulin stimulates glucose uptake led him to the IRS-2 pathway.

puberty, when insulin requirements increase. What's more, these mice show defects both in the way they respond to insulin and in the amount of insulin they produce—as do people with type 2 diabetes. To White, this meant that IRS-2 not only mediates insulin action in liver and muscle, it also appears to help the beta cells meet the body's need for insulin. "This was the most exciting moment for me in years, because it meant that a single problem might cause both insulin resistance and reduced insulin secretion—which leads to type 2 diabetes."

Interestingly, most people with diabetes do not show mutations in the *IRS-2* gene. So a simple genetic explanation doesn't fit this puzzle. "Some other component in the insulin signaling pathway, perhaps calpain-10, or something not yet discovered, might break the IRS-2 branch of the pathway just enough to cause diabetes," White says. "Finding this defect may point to a relatively simple way to increase production of IRS-2, reduce insulin resistance and promote beta cell function and insulin secretion."

Enable Glucose Transport

White's research dovetails with that of Morris J. Birnbaum, an hhmi investigator at the University of Pennsylvania, whose interest in figuring out how insulin stimulates glucose uptake led him to the IRS-2 pathway. While a faculty member at Harvard Medical School in the late 1980s, Birnbaum cloned the gene for Glut4, the "transporter" protein that brings glucose into cells in response to insulin stimulation. He then set out to understand how insulin lures this transporter from inside the cell to the cell membrane, where it works to remove glucose from the bloodstream.

At Penn, Birnbaum focused on PI 3-kinase (phosphoinositide 3-kinase), a protein needed for insulin to stimulate glucose uptake. As it happens, PI 3-kinase is activated when it binds to the IRS proteins discovered by White. PI 3-kinase, in turn, activates a protein called Akt. When Birnbaum and colleagues tried adding an overactive form of Akt to fat cells, they found that it stimulated glucose uptake by causing Glut4 to journey to the cell membrane. "In fact, most of the things that insulin does were mimicked by putting activated Akt into cells," he notes.

To learn more about this protein's role in insulin signaling, the researchers also produced mice lacking the *Akt2* gene, because the Akt2 protein is the form of Akt prevalent in insulin-sensitive tissue. As published in *Science*, June 1, 2001, the mutant mice showed marked insulin resistance and had elevated blood-sugar levels—the same problems experienced in type 2 diabetes. These data establish *Akt2* as an essential gene in the maintenance of normal glucose balance, the authors wrote. Further studies of these mice, in collaboration with hhmi investigator Gerald Shulman (see below), showed that their insulin could no longer shut down glucose production in the liver, another hallmark of diabetes.

"I think this is the first time anyone has proven that a downstream signaling pathway governs insulin action in a mammal," says Birnbaum. "People have been working on this for over 40 years."

Determine Fat's Role

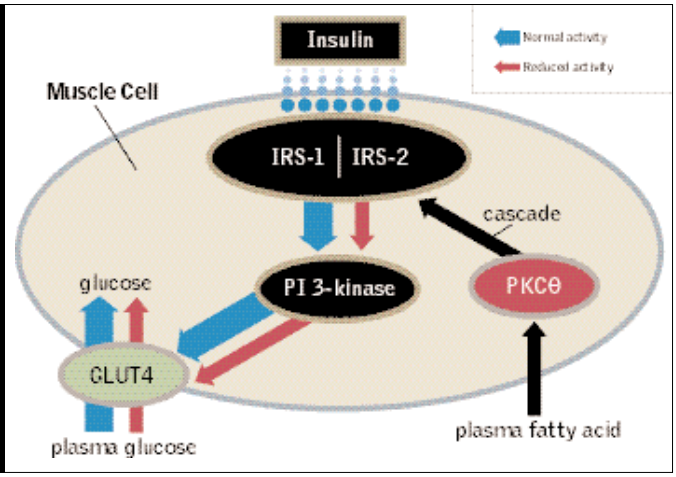
Obesity and type 2 diabetes often go hand in hand—and both are on the rise (see Perspective, page 42). Gerald Shulman, an hhmi investigator and clinical endocrinologist at Yale University School of Medicine, is getting to the heart of what links weight gain with altered glucose metabolism and an inability to respond properly to insulin.

Most insulin-resistant individuals have elevated levels of fatty acids in their bloodstreams. To investigate how fat might cause insulin resistance in humans, Shulman and his colleagues used nuclear magnetic resonance spectroscopy to measure fatty acids, sugars and their metabolites in the tissues of two groups of human volunteers: one healthy, the other insulin resistant. People who are resistant to insulin had greater amounts of fat inside their muscle cells than did their healthy counterparts.

To go a step further and find out how fat might block muscle's response to insulin, they developed a method to measure the concentration of glucose and an intermediary metabolite, glucose-6-phosphate, in muscle. When healthy volunteers were given intravenous fat, they temporarily became severely insulin resistant and had lower levels of glucose and glucose-6-phosphate in their muscle cells. "These data

challenge conventional beliefs by strongly suggesting that fatty acids cause insulin resistance in muscle by directly interfering with insulin activation of glucose transport activity," says Shulman. "This is the same step found to be defective in patients with type 2 diabetes."

How does fat interfere with insulin-stimulated glucose transport in muscle? Does it directly interfere with movement of the glucose transporter Glut 4 to the cell's membrane, or does it interfere with the insulin signaling cascade? To find out, the scientists examined insulin activation of PI 3-kinase, a key enzyme that stimulates glucose transport activity. Using muscle biopsies from the earlier subjects, they found that an intravenous infusion of fat totally abolished insulin activation of PI 3-kinase. Shulman's group teamed with Morris White to figure out how, and they discovered which steps in the insulin signaling pathway are blocked by excess fats (see figure).



How does excess fat cause insulin resistance? Shulman and colleagues propose that fatty acids block glucose movement from the bloodstream into the muscles. By activating an enzyme called PKCθ, the fatty acids set off a cascade that causes defects in activation of insulin receptor substrates (IRS-1 and IRS-2). This, in turn, blocks PI 3-kinase, an enzyme that stimulates GLUT4 to transport glucose into the muscle cell.

What do these findings mean for diabetics? Because accumulation of fatty acids in liver and muscle has such a profound effect on insulin sensitivity, researchers could try to develop drugs that block their action. In an August 2001 article in the *Journal of Clinical Investigation*, Shulman's group and Steve Shoelson's group at the Joslin Diabetes Center showed that high-dose aspirin can prevent insulin resistance caused by high levels of fat in mice, and they determined where in the pathway the impact occurred.

More directly, people with type 2 diabetes can clear fatty acids from their own muscles: "Exercise and/or weight reduction is a great way to do this," notes Shulman. Meanwhile, he plans to continue moving back and forth between his studies of mice and of humans. "The transgenic mice are an incredibly powerful system for testing hypotheses," Shulman says, "but in the end, what you really care about is the patient with the disease."

Gerald Shulman is getting to the heart of what links weight gain with altered glucose metabolism and an inability to respond properly to insulin.

GALE ZUCKER

The University of Michigan's Saltiel says he is encouraged by the many scientists who are tackling diabetes and the varied routes they are traveling. "No single approach will work," he says, and "no one researcher can move forward alone." Birnbaum, White, Shulman and others hope to identify all the molecules involved in the disease and to discover how these components act together to disrupt metabolism. With access to DNA samples from almost all of the 2,500 diabetic residents of Starr County, Bell is hoping to conduct an exhaustive search for all the factors—genetic and environmental—that contribute to type 2 diabetes in that population. With a closer look at calpain-10, he may discover that the enzyme somehow controls the activity of a protein in the IRS signaling pathway.

"What has emerged," says Bell, "is an appreciation that individuals can have diabetes for very different reasons." As the genetic work comes together with biochemical and physiological studies, the reasons for those differences should become clearer.

Mirpur's Children

A SLUM IN BANGLADESH YIELDS CLUES ABOUT IMMUNITY, INFECTION AND AN ILLNESS THAT AFFLICTS MILLIONS WORLDWIDE. BY DAVID JARMUL

PAVEL RAHMAN/AP

Dhaka, the capital city of Bangladesh, is home to 10 million people. Researchers are studying deadly childhood infections in Mirpur, one of Dhaka's overcrowded neighborhoods.

Rashidul Haque steps over a gutter filled with human waste as he visits a neighborhood that holds answers to scientific mysteries about infection and immunity. The bamboo homes in this Bangladeshi slum are pressed so close together that light barely penetrates. In tiny rooms, children work at wooden looms. Water drips from corrugated roofs onto goats, broken bricks and mud. Music blares from a nearby bazaar.

A woman stops Haque to discuss her daughter, one of 235 children he is monitoring to learn about amebiasis, a parasitic disease that each year causes about 50 million illnesses and up to 100,000 deaths worldwide. Haque is an HHMI international research scholar who heads the parasitology lab at the Center for Health and Population Research in Dhaka, Bangladesh's capital city.

Haque and the anxious mother review the familiar questions. Does the child have diarrhea? For how long? Is there blood in her stool? Haque's colleague, Lutfar Rahman, who accompanies him on these weekly tours and lives in a house around the corner, arranges for the girl to receive free treatment.

Hasna. Sultana. Amir. Rafique. Kalim. They are the children of Mirpur, one of many such neighborhoods in Dhaka, and they get amebiasis at an alarming rate. In some children, infection from the parasite *Entamoeba histolytica* does not necessarily lead to illness, and when illness does occur, it tends to be less acute than other diarrheal diseases such as cholera and rotavirus. In children and adults of poor families who are already malnourished, however, the bug can sap strength and cause liver abscesses.

Haque has been studying the children of Mirpur for several years and recently published what a reviewer for *The Journal of Infectious Diseases* called "critical insights" into why some become infected more than others. Combining epidemiology with molecular biology, Haque showed that children with antibodies to *E. histolytica* in the mucous lining of their digestive tracts were less likely to become re-infected (see figure, page 25). Their immunity was only partial and short-lived, but the fact that it existed and was mediated by antibodies in the gut—rather than in the bloodstream—caught the attention of amebiasis researchers and others interested in the underlying science of how deadly parasites infect the children of the developing world.

"Until recently, scientists were using traditional techniques like microscopy to study parasitic diseases," says David Sack, a Johns Hop-

kins University researcher who directs the Dhaka center. "Now, with new molecular tools, we're in a position to make real progress. It's essential that we not limit these tools to places like Hopkins, Harvard and Stanford, where you don't get the reality check of patients coming through the door with these diseases every day."

Haque gets his daily reality check as he walks up to his office. Beside the stairs are rows of beds from the Center's hospital, still known locally as "the cholera hospital." The beds have mattresses with holes in their centers for patients too weak to rise during bouts of diarrhea.

The children's wards are the most crowded, filled with mothers who dab at their children's bottoms with pieces of saris and feed them water mixed with sugar and salts. Last year, the Bill & Melinda Gates Foundation presented its first $1 million global health award to the Center for its role in developing oral rehydration therapy, which has saved countless lives in Bangladesh and elsewhere.

FAKRUL ALAM

Rashidul Haque monitors children for amebiasis. His center provides free medical treatment.

Upstairs, in Haque's laboratory, a poster displays "eggs and larvae found in faeces." A tray holds test tubes with saliva samples from the children, which Haque's team will test for antibodies. Inside a drawer are the latest stool samples, to be tested with an assay that Haque helped develop to distinguish between *E. histolytica* and *E. dispar*, a nonpathogenic infection that looks identical under the microscope. About two decades ago, the discovery that there are genetically distinct varieties of the parasite cast doubt on the validity of much of the previous research on amebiasis.

Haque's laboratory has curiosities such as a huge jar filled with 2,269 *Ascaris lumbricoides* worms gathered from 114 people, but it lacks expensive equipment such as the fluorescence-activated device he'd like that would speed the sorting of different cell types from samples. Still, Haque has been able to probe how T cells, B cells and other players in the immune system respond when parasites invade.

"Recently, I've been focusing on the cellular immune response,

Meanwhile, in West Africa ...

While Rashidul Haque carries out research in the slums of Bangladesh, Jan ter Meulen has been facing different problems in the small West African nation of Guinea. An attack by rebels from neighboring Sierra Leone forced many of ter Meulen's staff members to flee their town. Even now, with calm restored, refugee camps are filled with people whose arms were chopped off.

Ter Meulen, a German citizen and HHMI international research scholar, says the turmoil adds to the "tremendous logistical problems" he already faces in his studies of the human immune response to Lassa virus. This virus infects an estimated half-million people in the region annually, causing everything from flu symptoms to death. One in six patients suffers permanent hearing loss from Lassa fever, which is a cousin to other viral hemorrhagic fevers such as Ebola.

"Almost everything has to be imported for our research," ter Meulen explains, who adds that refrigeration is erratic, roads are unpaved and educated workers are scarce. Not long ago, electricity spikes destroyed two sophisticated PCR (polymerase chain reaction) machines.

Yet, because Lassa fever occurs only in West Africa, ter Meulen remains in the Guinean capital, Conakry, returning to Germany occasionally to carry out more sophisticated experiments at his home base, the University of Marburg. His research is thriving as he uses new biological techniques to reveal how the human immune system recognizes and fights Lassa fever at the molecular level, work he hopes will lead to a recombinant vaccine.

"I have the unique opportunity to bring together field work and state-of-the-art molecular biology," he says. "The work in Conakry gives me access to patients who survived Lassa, which is a great advantage over studying the disease in animal models."

Fellow scientists in Germany and other developed countries often regard his work as "strange and exotic," ter Meulen acknowledges. "It's nearly impossible to build a career as a young scientist on field research on tropical diseases unless you already have a permanent position. Few scientific institutions are interested in researchers working on 'exotic' diseases, except if there are interesting molecular aspects. Money for applied research is hard to get because the diseases do not play a role in the Western world, and the affected countries have no buying power."

But ter Meulen has no plans to leave his tropical laboratory. He says he is intrigued by his work and grateful for the perspective that his stay in Africa has given him. Moreover, his commitment is paying off. One of his recent scientific papers, in the March 2000 ***Journal of Virology***, described for the first time how human T cells respond to Lassa virus. And lately, ter Meulen has been receiving repeated invitations to "give talks on my exotic subject."

"I've always enjoyed traveling and working in a developing country," he says, "and I'm lucky that the woman I've been together with for almost seven years also doesn't want to settle down. We both enjoy the freedom and privilege of being able to regularly change our environment and our perspectives." **—DJ**

Finding Their Niche

How can biomedical scientists in countries with limited resources compete against their counterparts at large, well-equipped laboratories in places such as the United States? Rashidul Haque in Bangladesh and Jan ter Meulen in West Africa have taken advantage of their locations by focusing on diseases—amebiasis and Lassa fever—that are prevalent locally but uncommon in the West. Other scientists whom HHMI has funded around the world have adopted different strategies.

Near Mexico City, Carmen Clapp is making the most of her environs as she pursues one of biology's hottest topics. A researcher at the National Autonomous University of Mexico, Clapp is studying a protein involved in angiogenesis, the process of blood vessel formation that has fascinated several prominent cancer researchers in recent years. Clapp derives the protein from tissue, provided by local eye surgeons, from children with premature retinopathy. "In more developed nations, doctors use laser surgery, so these samples can rarely be obtained," Clapp says.

Krisztina Kovács at the Hungarian Academy of Sciences in Budapest has found a comparatively quiet niche at the intersection of immunology and neuroscience. Her lab studies how allergies affect the central nervous system, a topic she says "nobody cares much about" despite its intellectual vitality and potential clinical importance. "It's a new field and very interesting, but it's completely neglected," she explains.

Scientists in distant locales have a range of views about how to select a research topic. "It depends in part on your personality," says Grzegorz Hess, a neuroscientist at Jagiellonian University in Kraków, Poland, whose research techniques "don't require a constant flow of resources." Ivan Shatsky of Russia, for one, says "if you can't compete, it's not worth bothering." A researcher at the A. N. Belozersky Institute of Physico-Chemical Biology at Moscow State University, Shatsky says "you should try your own original way, but it should be interesting. To just repeat someone else's results is stupid."

Ultimately, many scientists around the world say they're guided more by their own interest in a topic than by calculated career strategies. "In the end, you need to be happy," says Fernando Lopez-Casillas of the National Autonomous University of Mexico. "You can't just work on something because a pile of money will be there." **—DJ**

which involves the T cells," he explains. "We're hoping to begin some new kinds of genetic analysis, since there has to be a reason why some children get infected more easily than others, and why only a few get sick while most are asymptomatic. Their genes may play a role."

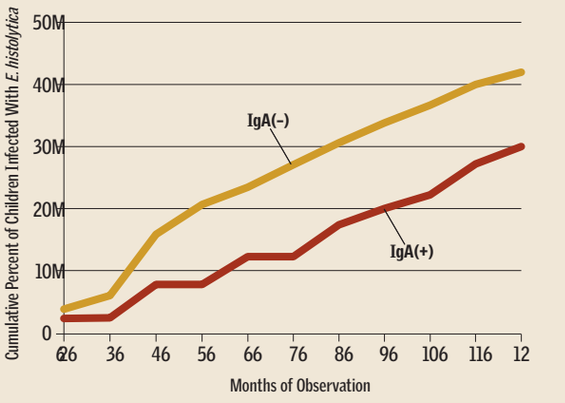
Haque's collaborator, William Petri, Jr., of the University of Virginia, has identified and characterized the part of the parasite that latches onto human cells, and demonstrated that the attachment sets off intracellular signals that cause the cells to commit suicide. Working in vastly different settings, the two men have become close friends, communicating daily by e-mail and meeting at each other's laboratories, although Haque jokes that he still cannot persuade Petri to eat spicy Bengali cuisine.

"Sometimes when you have a collaboration, you give more than you get," Petri says. "It's been just the opposite for me. This is definitely not a program that's intellectually driven from the United States." Petri notes that it was Haque who suggested they check the children for antibodies in their digestive tracts as well as their blood. "It didn't occur to me to test for an immune response in the stool," Petri recalls, "but Rashidul was familiar with the cholera literature and thought we should do it."

Both men say their goal is to develop a vaccine for amebiasis, which afflicts people throughout the world. "Understanding the natural history and immune response to amebiasis is essential," says Petri, who has begun talking with companies about such an effort. Vaccine developers may well seek to mimic the immune response that Haque and the others discovered in the gut, but they'll need to boost this protection and make it last longer—and provide it cheaply to children in places like Mirpur.

Immune Resistance to Amebiasis

Rashidul Haque found that children with antibodies to the *E. histolytica* parasite in their digestive tracts [IgA(+)] were less likely to become reinfected than children without antibodies [IgA(–)] in the gut. To make a difference, the antibodies had to be found in the gut, not the bloodstream.



Walking through the slum during his weekly visit, Haque reflects on the special problems he faces carrying out biomedical research, which he began pursuing as a doctoral student in Bulgaria. During this two-hour visit to Mirpur, the power has gone out three times, the water stopped and a political demonstration blocked the roads. Haque is also concerned about the delivery of supplies from abroad and about his three-year-old daughter, who just got diarrhea after eating at a fast-food shop.

Still, he remains focused—and remarkably optimistic. "There are very few of us working on amebiasis around the world," he says. "It doesn't get as much attention as a lot of diseases that affect fewer people, but with all of these new tools, we really are making progress."

Petri concurs, emphasizing that high-tech research into everything from the molecular structure of the antigen to the genetic variations among both people and parasites must be accompanied by studies in places like Mirpur. "If you're doing laboratory research, you need to see if your ideas will work in the real world," he says. "I couldn't possibly do the kind of study that Rashidul is doing, even if I was there every day. His team knows the people and can relate to them. They provide them with free medical care. If it weren't for them, we'd have no idea whether the research we're doing here in the States makes sense." H

Scientific Outliers

How teachers and students in rural America can learn good science

BY MITCH LESLIE

In 1993 Robbie McCarty was fed up, burned out and ready to resign. For six years she had been the lone science teacher at a 300-student school in Duke, a small agricultural town in far southwestern Oklahoma, about a three-hour drive from Oklahoma City. Her dream to teach science in an inspired and hands-on way—as opposed to the traditional lecture system with its overemphasis on vocabulary—began to fade as she faced the realities of teaching at a small, isolated school with meager resources. "There was so much I wanted to do—and so little to do it with," she recalls.

When McCarty arrived, the school allotted no money for science teaching and had almost no supplies for her labs and classes. Although her superintendent managed to scrape together some of what she needed, McCarty grew increasingly frustrated at having to make do, and she began to think that she was failing her students.

Rural science teachers nationwide echo McCarty's story of frustration. To teach science is a challenge everywhere, but rural teachers confront a trio of special problems that can sap their morale and undermine the quality of education they offer their students, problems that directly affect the one in four children who attend school in rural areas with populations less than 25,000:

- *A scarcity of money*. Although some rural schools boast generous budgets and well-stocked labs, many others, like the one in Duke, must scrimp to acquire basic equipment and supplies. According to the Rural School and Community Trust, 244 of the 250 poorest counties in the nation are rural.
- *Isolation from the world of science*. Rural teachers and students rarely get to meet scientists or see how they work. Enriching activities that urban teachers take for granted—trips to a zoo, planetarium or lab, as well as classroom visits from scientists—are difficult to arrange.
- *Isolation from colleagues.* Many rural science teachers have no colleagues nearby, leaving few opportunities for swapping ideas with peers or for commiserating. These teachers often feel they are struggling alone in a sea of troubles.

McCarty almost quit, but she didn't because she was chosen to participate in a program supported by hhmi at the Oklahoma Medical Research Foundation (omrf) in Oklahoma City. There, she spent the summer working in Philip Silverman's molecular biology lab, isolating viruses from cow manure. She says that mundane-sounding experience changed her outlook and teaching style, renewed her confidence and reignited her zeal. She stayed at the school in Duke for

LISA HOKE

JOSEPH MILLS

Frustrated by isolation and poor funding while teaching science in rural Oklahoma, Robbie McCarty (above) entered a program run by Philip Silverman (left) and found ways to make science teaching work.

another three years, then moved to a nearby high school to continue teaching science.

OKLAHOMA'S RAW MATERIAL

Silverman loves to say that manure is the magic ingredient for the teacher education program he heads. Every summer, Silverman and colleagues invite a select group of four to six science teachers to omrf for the nine-year-old Foundation Scholar Program, part of Silverman's Oklahoma Science Project, which is one of several programs around the country designed to improve rural science education and tackle the problems of insufficient resources and teacher isolation.

Many of these programs immerse teachers in lab work for a few days or weeks. In designing the Foundation Scholar Program, however, Silverman discarded the format and content of the traditional summer workshop. The last thing most rural teachers need, he says, is to spend time mastering state-of-the-art laboratory equipment and techniques that are impossible to reproduce in their classrooms. Instead, they need to learn simple, inexpensive experiments that students can do, experiments that drive home fundamental concepts such as natural selection, genetic inheritance and gene regulation.

"We went back to some of the classic molecular genetic experiments that are very simple technically, very inexpensive and intellectually very rich," he says. The summer scholars isolate the snippets of DNA called plasmids that confer antibiotic resistance, for instance, or trap bacteria-killing viruses called bacteriophages and measure their rate of multiplication.

These experiments are easy to set up and run, and they use a raw material—animal manure—easily available on the farms and ranches of rural Oklahoma. Thus, teachers can duplicate the studies in their schools, Silverman says, and students can see the relevance of their work in the classroom. Instead of just reading about natural selection,

Scientists Recall Country Roots

Some of the world's greatest scientists grew up in the hinterlands. Mathematician Isaac Newton was on his family farm in England when the famed apple fell on his head. Gregor Mendel, the father of genetics, was raised on a farm and orchard in Austria. HHMI also has its share of scientists whose interests in biology or chemistry were germinated in the wide-open spaces of their youth.

"I grew up in a small Midwestern town called Paris, Illinois—not exactly the City of Lights," recalls **Stephen J. Elledge**, an HHMI investigator at Baylor College of Medicine in Houston. "I had two good science teachers in high school, but I was already a scientist at heart long before I knew them." Elledge went through several chemistry sets, eventually blowing up something in his grandmother's kitchen. As a junior in high school, he wasn't sure he wanted to go to college; no one in his family had gone. His science teachers pushed him to go. With a first-place award in a science competition, he went to the University of Illinois on a scholarship.

Stephen J. Elledge studies the cell's response to DNA damage and works on genetic technologies to improve drug development.

Daphne Preuss, an HHMI investigator at the University of Chicago, would have appreciated a female role model as she grew up in the small town of Akron, Colorado. "Most of the people I knew were farmers. The women were wives of farmers. The thing that would have meant the most to me was to see a woman, even on television, who was a scientist." A series of books on adventurers—including Thomas Edison, Booker T. Washington and Marie Curie—helped Preuss see that she could be a scientist too. Her natural curiosity was cultivated by her rustic surroundings. "A rural environment, where kids have a chance to walk out into the fields and look at the world around them," she says, "can be incredibly nurturing for someone developing as a scientist."

Daphne Preuss uses genetic and biochemical approaches to identify how plants recognize each other, a critical component in understanding interactions within species and between species.

Powtrock Hollow, West Virginia, population 13, was the childhood home of **Gerald R. Crabtree**, an HHMI investigator at Stanford University Medical School. "People on farms are confronted with the realities of biology, physics and chemistry," he says. "We raised chickens, I learned how to plow with a horse and I could fix the hay baler." It was a loving, supportive community that encouraged him to pursue his heart's desires, he recalls. It was also a patient community: One of Crabtree's pleasures in those days was building rockets and entertaining his friends by setting them off in the nearby hills.

Gerald R. Crabtree studies calcium signaling within the cell and is a member of the National Academy of Sciences.

» Elledge, Preuss and Crabtree share more of their childhood experiences on our Web site: *www.hhmi.org/bulletin*.

FROM TOP: PAUL FETTERS, MARK SEGAL, BARBARA RIES

they can observe it in action by using antibiotic-resistant bacteria isolated from samples they collected themselves—often from their own animals. Instead of just reading about viruses, students can grow them on dishes of bacteria and see their effects.

Silverman also likes to let the teachers struggle. Instead of following defined steps leading to a predetermined "discovery," they choose which investigations to pursue and which procedures to follow. This approach approximates how scientists really work and forces teachers to collaborate, getting the peer interaction they crave, Silverman says.

To make sure collaboration continues, the summer scholars leave omrf with computers to keep in touch with Silverman and their fellow participants. The foundation provides other help as well—often lending equipment, for example, or shipping supplies for experiments. As a result, "teachers don't feel alone and insecure," says McCarty, who is studying the interactions among the participants for her doctoral dissertation.

Silverman is planning to integrate the program into the undergraduate curriculum for teachers-in-training, and McCarty is helping to lead the way. This fall, she began teaching future science teachers at Southwestern Oklahoma State University at Weatherford, and she plans to adopt the methods of the omrf program in her classes whenever possible.

OUTSIDE WITH EXPERTS

For rural teachers who have few opportunities to work with scientists, a summer program sponsored by the New Mexico Museum of Natural History and Science in Albuquerque, with a grant from hhmi, provides experts to lead the teachers and their students through field ecology courses.

Using many of the tools and procedures of professional ecologists, middle- and high-school students and their teachers from around New Mexico dip into streams and rivers to sample water chemistry and collect aquatic invertebrates, according to Tim Aydelott, the museum's ecology education coordinator. They compare a range of locales—from near-pristine mountain springs to heavily developed rivers—to see how human interventions such as agriculture and urbanization affect water quality. With support from a local education group called New Mexico's Math, Engineering and Science Achievement Program, Aydelott and his staff at the museum provide training and equipment for this and other courses, and they dispatch experts on every field trip who demonstrate techniques and help identify specimens. The teachers adapt the program to their own needs and resources, select the field sites and set their own goals, Aydelott says.

Without the museum's help, says Margaret Lewis, her students could never have pursued their current in-depth investigations. Lewis is a science teacher at Memorial Middle School in Las Vegas. (That's the *authentic* Las Vegas, locals like to point out, founded two centuries before the upstart in Nevada.) "The kids are doing things—water-chemistry tests, working with macroinvertebrates—that they usually wouldn't be able to do until college," she says. Lewis and colleague Nancy Jeffrey taught the five-week course last summer, and their students worked at three sites—including the untouched headwaters of the Gallinas River in the mountains above Las Vegas and a spot just below the outflow of the city sewage-treatment plant. In addition to their scientific value, the studies acquaint students with their own environment. "What surprises the kids most is how good the water is that flows through Las Vegas," she says.

Lewis' students have reaped other intellectual benefits. At the culmination of the aquatic ecology program, all the classes meet in Albu-

GEOFF JOHNSON

Joan Christen has won accolades and expanded young minds as the lone science teacher in small town Stella, Nebraska.

From Exhausted to Outstanding

Joan Christen teaches life science, earth science, physical science, biology, advanced biology, physiology and anatomy, physics, advanced physics, chemistry, advanced chemistry and environmental science. At the Southeast Consolidated School in tiny Stella, Nebraska, where 234 students attend grades 1 through 12, she is *the* science teacher.

After Christen's first year of teaching, the school almost lost her. Recruiters at the Cooper Nuclear Station, a Nebraska power plant where she had done an internship during college, offered her a job in their environmental department at a hefty pay raise.

"My first year had been exhausting, and the increase in salary was awfully tempting," Christen recalls. But she had already signed up for a summer program at Nebraska Wesleyan University, so before she made a decision, she spent 15 days in Lincoln with 11 other rural science teachers. The science and instructional-technology workshops of the HHMI-supported K–12 Science Teaching Institute were packed with hands-on lessons in biology, chemistry and physics, as well as ways to use computer-based technology and the World Wide Web to teach science.

Fall found Christen back at Southeast Consolidated, revitalized and eager to make a difference in young people's lives. In the four years since her summer at Nebraska Wesleyan, she has gone on to win $233,000 in grants to upgrade the school's computers and build an outdoor environmental-education classroom and greenhouse. She has added courses in advanced biology and second-year chemistry to her school's curriculum, completed work for a Master's of Science degree in entomology and convinced her school board to consider hiring a second science teacher. The National Association of Biology Teachers named her Nebraska's outstanding biology teacher of 2001.

Christen says she's glad she stuck with teaching. "I have had some exceptionally talented students, and I feel like I am making a difference in their lives," she says. "The children are our future, and I want and need to do my part." **—JENNIFER BOETH DONOVAN**

» For more on the Nebraska Wesleyan University K–12 Science Teaching Institute, visit: *www.biology.nebrwesleyan.edu/hhmi/index.html*

» For more on HHMI's Undergraduate Biological Sciences Education program, visit: *www.hhmi.org/grants/undergraduate*

querque so the students can present their research results. This meeting is one of the most valuable parts of the program, says Lewis, because it gives these rural kids the opportunity—and the motivation—to prove themselves in the eyes of students from around the state.

VIRTUAL MAGNET SCHOOL

Some rural communities bypass the barriers facing teachers by reaching out directly to students. That's what West Virginia is doing with a statewide *virtual* magnet school created to interest students in health-related professions.

Founded in 1994 with a grant from hhmi, the Health Sciences and Technology Academy (hsta) is directed at minority and financially disadvantaged kids—most from rural schools—who would be the first in their families to attend college, explains program head Ann Chester, assistant vice-president for health sciences at West Virginia University in Morgantown. The year-round program aims to identify students early and inform and motivate their career choices.

The 600 students enrolled in hsta study at their home schools for the most part. They do, however, commit to spending part of each summer, starting after eighth grade, at West Virginia University. During these one- to three-week summer stints, the students immerse themselves in projects that are designed to be practical and lively, says Chester.

In their first summer, the kids compete to design the most efficient digestive tract. "This has a gross component that kids love," she says. In following years, they try to solve a fictional missing persons case from forensic clues and study heart anatomy and function by dissecting cadavers and conducting stress tests. In the final summer, the kids take either a college prep or advanced math class. "They all walk out of here at college level or higher in math before they hit their senior year," says Chester.

To keep the students engaged all year long, she enlisted help from teachers in 21 counties throughout the state. They created after-school "learning clubs" that focus on health-related issues important to their communities, such as water quality or particular diseases. One club in Webster County, for example, used records from the county courthouse to identify heart disease as the leading cause of death in the area. The students then surveyed local people to find out which risk factor was most prevalent. When the predominant one turned out to be lack of exercise, the students laid out a walking trail, indicating on the trail the number of calories people might burn by walking that distance.

Chester says that about 95 percent of the participants in the magnet school attend college; by comparison, the statewide average among high-school graduates is 50 percent. So impressed was the state legislature that it has granted free tuition at any state college or university to students who complete the hsta program.

Although these programs are good first steps, they aren't panaceas. Even the best-designed, most generous programs can't boost tax revenue or conquer geography, and rural teachers will continue to struggle with challenges unknown to their urban and suburban colleagues. Yet, programs such as these can open teachers' eyes to underappreciated resources and help them make the most of their assets. As McCarty puts it: "After my experiences at the omrf, I began to see ways to make the impossible possible."

HANDS ON

Building Interest in the Human Body

Eight middle-school science teachers have come to Omaha to "Build a Human." First they must take one apart.

Wearing lab coats and latex gloves, they gather gamely around a cadaver in the basement anatomy lab of Creighton University School of Medicine. "That's part of the large intestine," says Thomas Quinn, professor of anatomy and director of the Build a Human Project. "You can touch it if you want." No one wants.

A two-week summer program supported by an HHMI grant, Build a Human gives middle-school teachers and students some close-up experiences to help them learn about the structure and function of the human body. They acquire a more visceral understanding, so to speak, of the body, from the molecular level on up through cells, tissues, organ systems and the organism as a whole.

Only the teachers come face to face with a cadaver. In morning labs, however, students and teachers work together to build models of sugar molecules, "eyeballs" of Styrofoam and cotton, and "skin tissue" of felt, sponge and yarn. Cracking fertile eggs into Petri dishes, they observe the development of chicken embryos. They color diagrams of the parts of the human brain and dissect a real one. In a bone-naming competition, tosses of a die determine who must identify different parts of a human skeleton.

Everyone goes home with plenty of souvenirs. Teachers get models their students can build as well as hands-on lesson plans they've designed themselves (including at least one with extensive modifications for students with special needs). They also earn three hours of graduate credit and a stipend for their summer effort.

The seventh- and eighth-graders take home packets of practical health and medical information—on topics such as diabetes, heart disease, lead poisoning and organ donation—to share with their families. They also return with experiences they will never forget: looking at motor neurons under a microscope, experimenting with digestive enzymes to see how they break down food, dissecting cow eyes, touring a medical school and hospital and getting to know the culturally and ethnically diverse graduate students who serve as lab assistants—and role models. As a bonus, students and teachers share the remarkable experience of working side-by-side as colleagues and even friends.

—JENNIFER BOETH DONOVAN

» For more on the Build a Human Project, visit: *puffin.creighton.edu/edu/BuildAHuman/index.html*

» For information on HHMI's precollege science education biomedical initiative, visit: *www.hhmi.org/grants/precollege/overview/biomed.htm*

■ **Above: Examining a human brain is one of the students' favorite hands-on activities in the Build a Human project. Teachers and students learn the location and function of the frontal, temporal, occipital and parietal lobes, the ridges called gyri and the valleys called sulci, the cerebellum and the brain stem. Creighton University School of Medicine assistant professor Andrea Zardetto-Smith quizzes seventh grader Jonathan Van Erdewyk and sixth grader Gordon Walls, Jr., on brain anatomy.**

■ **After cracking fertile eggs into glass cups and placing them in an incubator, Carvie Erwin, a seventh grade teacher at Jesuit Middle School in Omaha, sixth grader Camille Keaulana and seventh grader Petrolyn Stephenson chart the daily progress of the shell-less chick embryos as they develop. In addition to a developmental biology lesson, the activity enables students to apply fundamentals of the scientific method, such as observing, measuring, predicting and interpreting data.**

■ **At left: Seventh grade twins Allison and Katie Gorga use vinyl, foam, cotton batting, felt and colored yarn to build a model of the skin. As they glue the layers together, they learn about the structure and function of the epidermis, dermis, collagen, muscle tissue, blood vessels and nerves. They also learn the role of melanin in skin pigmentation, using varying shades of tan and brown vinyl for the "epidermis" and discovering that under the top layer, people really are all made the same.**

■ **Below: Using balloons in plastic soda bottles, sixth graders Andrew Taylor and Peter Koneck-Wilcox see how changes in air pressure caused by the movement of a flexible diaphragm force air in and out of the lungs. Libby Putz, who teaches eighth grade at Anderson Middle School, explains that decreasing pressure in the bottle—or the chest cavity—causes inspiration, the intake of air to fill the lungs. Increasing the pressure causes expiration or air movement out of the lungs.**

MEDIA SERVICES, CREIGHTON UNIVERSITY (4)

To Think Like a Scientist

Patricia Giesler teaches deaf and hearing-impaired students at Norman S. Weir Elementary School in Paterson, New Jersey—and she's been searching for a way to teach science well. "I watched dedicated and well-intentioned teachers make magic shows out of science," she says. "It's fun, but after the demonstration is finished, so is the thinking process. There is no time to reflect, to analyze, to experiment, to do things 'wrong' and try to come up with better solutions."

Giesler wanted to teach her students to think like scientists. Realizing, however, that she did not actually know how real scientists think, she signed up to spend a summer working in a research lab in an HHMI-supported program that brings together teachers and researchers.

Fittingly, this teacher of the deaf ended up working in the laboratory of A. James Hudspeth, an HHMI investigator at Rockefeller University in New York City. Hudspeth studies the biophysical and molecular bases of hearing and equilibrium, particularly in the hair cells that are the sensory receptors of the inner ear.

Molecular biology was foreign territory, however, so Giesler had to spend long hours learning how to prepare bioassay plates and cell cultures, use filters and probes and identify clones. Her project was to assist research associate Stefan Heller, her mentor in the lab, to screen a "bullfrog library" of DNA from the inner ears of frogs. They used the library to search for the messenger RNA that might encode for an ion channel that is involved in the cellular detection of osmotic pressure, a mechanism of inner ear function. Using a previously cloned ion channel from a chicken as a probe, they failed to find an equivalent channel in the bullfrog.

How did she deal with negative results after so much work? "I learned that one must never give up if an experiment seems to fail, that one must persevere and try new avenues and that every experiment is just one small piece in a very large puzzle," she says. "I took these important concepts back to teach my students."

Returning to the lab at Rockefeller the following summer, Giesler learned to breed zebrafish (there are some 20,000 in Hudspeth's lab) and screen them for mutations that affect hearing and balance. Hudspeth says Giesler's dedication strengthened his own commitment to a long-term project to identify the genes that cause deafness or balance problems.

CHRISTOPHER DENNEY

Teacher Patricia Giesler and HHMI investigator A. James Hudspeth show a small sample of the 20,000 zebrafish used in Hudspeth's lab to study the genetics of hearing and balance.

Led by former research associate Richard Kollmar, a research team in Hudspeth's group has now identified 39 mutant lines of zebrafish that have trouble with hearing, balance or orientation in the water. "Our hope is to learn the functions of genes that we have found to be expressed uniquely or dominantly in the ear," Hudspeth says. "Several of these genes are candidates for involvement in human hearing loss."

Giesler's dedication was clearly evident when this past summer she returned to the lab for the third time. "We injected fish embryos with an antisense oligonucleotide, a short piece of DNA that is like a mirror image of part of the messenger RNA molecule, to block the manufacture of a specific protein," she says—now clearly at home with the language of molecular biology.

Her students have visited the lab and last year adopted eight zebrafish for their classroom. Geisler showed them many things about the fish, including how to determine their sex. "The males are pinkish with a yellow belly and a streamlined body," she pointed out. "The females have swollen-looking bellies, yellow dorsal fins and bolder stripes on their bodies."

The children have gained a great deal more than zebrafish, however. Their observation techniques have improved, and they've learned a new vocabulary, Giesler says. Now they're breeding the fish to study reproduction. Last year, one of her students presented an award-winning project at the school science fair in sign language, with Giesler—who learned sign language because an uncle was deaf—voicing his comments for the rest of the student body. This year, her goal is for every one of her students to participate in the science fair.

"People like Pat are the teachers who can keep the spark of scientific aptitude and curiosity alive in kids" says Hudspeth. "It doesn't take fancy equipment. You can extract DNA from spit. We need more teachers with Pat Giesler's attitude."

—JENNIFER BOETH DONOVAN

» For more information about The Rockefeller University Science Outreach Program for teachers, visit: *www.rockefeller.edu/outreach/teachers.html*.

Undergraduate Taps Into Tomato Communication

Scientific discovery involves more than developing and testing hypotheses: Attending to unexpected results is equally important. Such flexibility helped Wynnelena (Wynn) Canio, who received undergraduate research support under an HHMI grant to the University of California, Davis, uncover a novel communication mechanism that regulates leaf development in plants.

PHOTO DISC

Working with plant biologist Neelima Sinha and graduate student Minsung Kim, Canio discovered the first indication that messenger RNA (mRNA) can move from the leaves of a plant's root stock to the leaf cells of a different plant variety that has been grafted onto the root stock, and the mRNA can produce the proteins it encodes in that new and distant location. Previous research showed that other types of RNA can traverse such a course in plants—but Canio's work revealed not only that mRNA can travel long distances between cells, but that it can be expressed when it reaches its destination. Canio reported her findings as co-lead author of a paper published in the July 13, 2001, issue of *Science*.

She started by grafting a tomato strain with yellow, normal-shaped leaves to a variety with green, abnormally shaped leaves, called "ME" (for mouse ears). Canio wanted to create a mixture of yellow and green cells, called chimeras, in the grafted shoot's new leaves, but she noticed something altogether different happening to the hybrids. "I told Dr. Sinha that the leaves on top were looking a lot like those at the bottom," she says. The new leaves of the grafted stems were shaped like the ME leaves of the root stock.

How was the ME stock sending its blueprint to the new leaves? The work of other scientists in Sinha's lab had revealed the cause of the ME leaf's appearance: a mutation that caused inappropriate expression of a transcription factor that altered leaf shape. Canio and her professor wondered whether the change in leaf shape in the hybrids was the result of the mutant transcript's movement through the stock into the graft, where it was translated into protein.

"Testing this idea was a big challenge for an undergraduate," says Sinha, and Canio, who grasped much of the theory, needed to learn a variety of techniques. "Wynn was great," says Sinha. "I would say 'We need to do this,' and she would ask, 'Who can show me how to do it?'"

How has doing research affected her? Canio, who received her bachelor's degree in biochemistry in June, says that before doing this work she was "a determined premed. Now I have also found research to be stimulating and challenging." She is thinking about working in the biotechnology industry for a couple of years and then pursuing an M.D./Ph.D. **—BETH SCHACHTER**

A Course Set by Example

Diana Albay remembers waiting in a van with her four siblings while her mother, unable to find a baby sitter, took high school classes at night. "My mom hadn't finished high school, and she wanted to finish to make a point to us kids," Albay says. "I remember seeing her go to college afterward, and that was a motivating factor for me. I decided when I was still an undergraduate that one day I wanted to do research at the National Institutes of Health (NIH), and now here I am getting that very opportunity. It's an incredible feeling to see one's dreams coming true."

Albay is one of 45 medical students who took up residence this past summer at the Cloister on the NIH campus in Bethesda, Maryland. Formally known as the HHMI-NIH Research Scholars Program, it gives students (who've completed their second or third year of medical school) the opportunity to spend a year doing research in an NIH lab.

Hailing from the University of California, Los Angeles (UCLA) School of Medicine, Albay says the experience has been exciting and awe-inspiring. Upon arriving at the NIH campus, the Cloister fellows first meet with program advisers to identify labs of interest. Then they must contact researchers with whom they'd like to work to discuss possible projects.

It's quite a pleasure to be taken so seriously as a colleague, Albay says. "Here, these researchers are doing all this fascinating work, and they take the time to talk to me about it. It's like getting a personalized hour-long lecture about the latest breaking research in the field."

Albay wanted to find a project studying cardiovascular disease or diabetes; her grandmother had died from cardiac complications of diabetes, and her mother also suffers from diabetes. In a lab at UCLA, she had already studied the molecular events that cause restenosis, or narrowing, of cardiac-bypass grafts in a rat vein-graft model; and at Houston's Texas Heart Institute, she had worked to prevent blood clots in patients with left ventricular-assist devices (by lining the devices with smooth muscle cells that would express nitric oxide synthase).

PAUL FETTERS

Her mother's commitment to education against difficult odds kept Diana Albay focused on her goal of studying at the National Institutes of Health.

Then she just needed to find a good fit for her year at NIH. "We're really not rushed into making a decision about our lab," says Albay, "and that's a great thing." At the same time, she admits to placing pressure on herself to make up her mind and get moving.

Albay ultimately decided to work with the National Heart, Lung and Blood Institute's Vandana Sachdev to study a new form of gene therapy that delivers DNA, embedded in microbubbles, directly to the heart with a blast of ultrasound. Researchers have already shown that the process is feasible; however, it isn't efficient. She'll work to optimize the system in cell lines and rats before the procedure is tried on humans. Albay says she finds the project fascinating because it addresses one of the biggest problems with gene therapy—making sure the gene goes exactly where you want it to.

—LISA CHIU

HOLIDAY LECTURES

Who's Who in Genes and Gender Research

HHMI investigator Barbara J. Meyer has loved numbers and problem-solving for as long as she can remember. It's one of the reasons why the researcher, based at the University of California, Berkeley, took on the puzzle of how sex is determined in the worm *Caenorhabditis elegans*. David C. Page, an HHMI investigator at the Massachusetts Institute of Technology's Whitehead Institute, calls scientific research "absolutely intoxicating." Page studies the genes that control the development of sperm and eggs in mice and humans.

Meyer and Page are scheduled to talk about their work and their love of science at the 2001 Holiday Lectures on Science, November 29 and 30. To view their lectures, learn about their lives and research and find related educational resources and interactive activities, visit *www.holidaylectures.org*.

A Rising Star in Gene Therapy

Calvin Kuo's brisk pace is fueled by Oreo cookies and Goldfish crackers as he escorts a visitor to the "mouse room" at Stanford University. "I have hypoglycemia, so the snacks help," Kuo explains cheerfully.

What he doesn't say is that regular meals are hard to come by when you're putting in the kind of hours needed to start a new lab. "When you're starting a lab, you have to do everything yourself," Kuo says, grinning. He has good reasons, both professional and personal, to be excited. Considered a rising star by his mentors and in hot pursuit of major advances in cancer research, Kuo was recently named an assistant professor in hematology at Stanford, where he also earned his M.D./Ph.D. in 1994. Then there is his upcoming wedding to fellow scientist Cecile Chartier, with whom he is renovating an historic home in Stanford's Professorville neighborhood.

Trained in basic biochemistry and in clinical oncology, Kuo is working on inhibiting angiogenesis, the process by which tumor cells send out chemical signals that induce the growth of new blood vessels to feed their expansion. By depriving tumors of blood, antiangiogenesis agents cause them to wither and die—or at least stop growing. Several proteins have been found to act in this way to inhibit tumor growth, in both mice and humans, no matter where the tumor is located in the body. Clinical trials of several antiangiogenic compounds are now in progress.

Delivering these compounds as conventional drug therapy, however, promises to be an expensive—and life-long—way to keep tumors in check. Instead, Kuo is exploring gene therapy. "The thought is that you can give patients the gene that encodes these antiangiogenic proteins and turn their bodies into factories that make the proteins for their whole lives," he explains.

Working as an HHMI postdoctoral fellow in the laboratory of Judah Folkman at Children's Hospital in Boston and with Richard Mulligan at Harvard University, Kuo used the quickly replicating cold virus called adenovirus to introduce into mice the gene for the vascular endothelial growth factor (VEGF) receptor. In the April 10, 2001, issue of the *Proceedings of the National Academy of Sciences*, Kuo reported that the virus with the gene infects the liver, which then produces enough circulating VEGF receptor in the blood to bind and inactivate VEGF, thus inhibiting the growth of tumors in distant locations, such as the brain, prostate and skin.

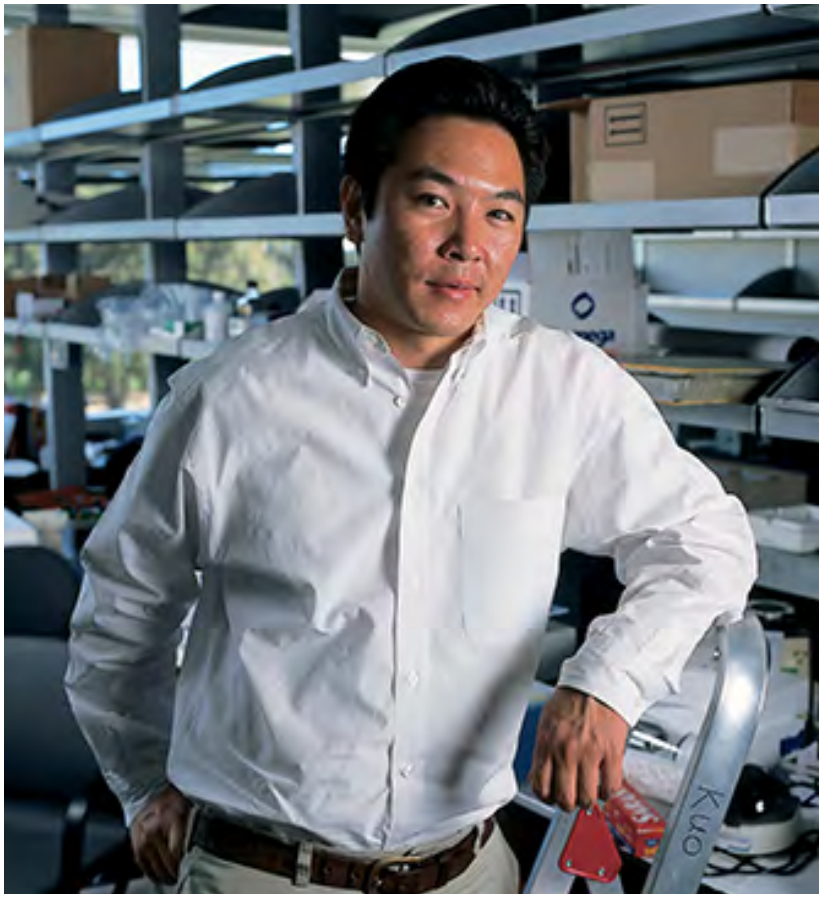
Kuo continues to search for additional blood-supply-choking compounds in his new lab at Stanford. "We hope to find cocktails of antiangiogenic agents that could even more potently suppress tumor growth," Kuo says. The eventual goal, of course, is to extend this work to humans.

Judah Folkman, considered the patriarch of the antiangiogenesis field who first proposed the theory and demonstrated its potential, says he is watching Kuo's progress with anticipation. "He has laid the groundwork" for the use of gene therapy to deliver antiangiogenic compounds, Folkman says, and "he has a very distinguished career ahead of him."

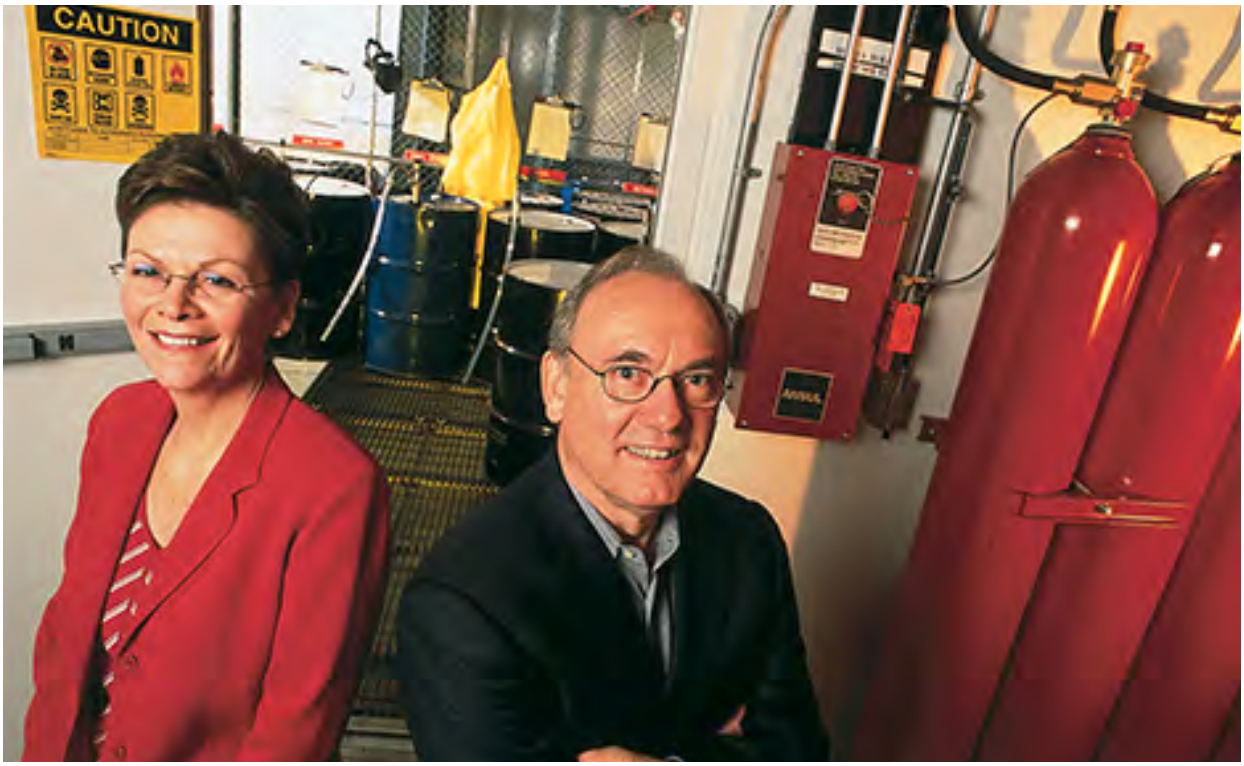
Kuo left his HHMI postdoctoral fellowship seven months early to accept his new position, and he was soon named one of six Burroughs Wellcome Fund new investigators in the basic pharmacological sciences, an award that includes $210,000 over three years. His thesis adviser, HHMI investigator Gerald R. Crabtree, was instrumental in luring Kuo to Stanford. "He's really in love with science," Crabtree says, "and he's wonderfully good at it."

—CAMILLE MOJICA REY

Stanford's Calvin Kuo is attempting to use gene therapy to turn the body into a factory to churn out compounds that cut off a tumor's blood supply.



FRED MERTZ



KAY CHERNUSH

HHMI's Emmett Barkley and Cheryl Warfield worked with 10 universities to devise and test better waste-management practices.

Smarter Waste Management

A demonstration project led by HHMI, which included 10 universities and the U.S. Environmental Protection Agency (EPA), tackled hazardous-waste management problems that have plagued scientists for two decades. Among the promising results: The transport of laboratory-generated hazardous waste for disposal—inherently risky—would be dramatically reduced if the waste were treated on site. Some 740,000 fewer pounds of chemical waste would be transported over the nation's highways each year, just from the participating universities.

Many hazardous-waste problems exist at universities because the standards issued by the EPA in 1981 were written for big industrial plants—by far the largest generators of waste. University labs, which produce less than 0.01 percent of the waste stream, are subject to the same stringent rules, which often focus on process rather than outcome. "It's a case of standards not fitting the situation," says Emmett Barkley, director of HHMI's Office of Laboratory Safety.

The result is a thicket of paperwork—and nonstop training in university laboratories because students and fellows are constantly coming and going. Moreover, EPA rules are inconsistently enforced by the states, which exacerbates the situation. In the Northeast, for example, every laboratory in a university is treated as a separate waste generator and carries the full burden of categorizing, labeling and disposing of its waste. In the Southeast and the Northwest, by contrast, each university's environmental health and safety office is considered the official "waste generator," permitting a core of trained waste-management officers to manage the output of the whole school.

The difficulties arising from this situation were serious enough that in 1999 HHMI decided to take a leadership role in improving waste management at universities. The Institute's Office of Laboratory Safety assembled a team—including environmental health and safety directors from 10 universities (all of whom are hosts for HHMI investigators), researchers and regional and national EPA representatives—to formulate a consensus on best practices. The universities then carried out demonstration projects to evaluate the proposed changes.

The participants believe their efforts show promise because they address the source of the problem. "This initiative has allowed us to shift our point of emphasis," says Wayne Thomann, director of occupational and environmental safety at Duke University Medical Center. "Instead of committing energy and resources solely on enforcement of strict compliance, we have been able to focus on ways to reduce the volume of waste produced." For example, Duke's switch from using mercury-containing fluorescent bulbs and thermometers has, in the past two years alone, prevented almost 16,750 pounds of toxic mercury-contami-

nated waste from ending up in landfills.

In the Stanford University laboratory of former HHMI investigator Sharon Long (now dean of Humanities and Sciences), 18 people handle more than 800 chemicals, all requiring different types of storage and disposal. "This project allowed us to come up with our own way of dealing with the situation and gave us a closer working relationship with our environmental health and safety officers," says lab manager Carol Toman. "We've done a better job of not over-ordering chemicals, and we can send the unused chemicals we don't need to surplus now, where someone else can use them, instead of to hazardous waste."

According to HHMI's Barkley, the demonstrations showed that simply shifting from a punitive to a collaborative waste-management strategy generates innovative ideas and enthusiasm. "A performance-based approach will achieve compliance," says Barkley, but that's not enough. "What's equally important is that the approach promotes stewardship and responsibility for health, safety and the environment, while respecting the culture of the university."

When the U.S. Congress learned of the initiative last fall, it encouraged the EPA to partner with HHMI and the 10 participating universities in carrying out the project. Congress also requested a report on the project's findings and recommendations, which the EPA submitted in October; it was written collaboratively by the HHMI group.

Although it is too soon to know whether regulatory change will result, Barkley says that "improvements in hazardous-waste practices will surely result." **—KARYN HEDE**

Lost in World Trade Center Attack

At 9:55 a.m. on Tuesday, September 11—when the south tower of the World Trade Center collapsed—Mohammed Salman Hamdani should have been at his lab bench at The Rockefeller University about 100 blocks away, learning to purify radioactively labeled samples. His parents believe, however, that Hamdani must have changed trains on his subway trip into Manhattan from Queens and gone to the World Trade Center instead. A trained emergency medical technician who volunteered at the Jamaica Hospital Emergency Room, Hamdani must have decided to try to help after the planes hit the New York landmark. No one has heard from him since.

Those who knew the 23-year-old Hamdani, known as Sal, are not surprised that he would have headed for the World Trade Center after hearing news reports of the attack. He was determined to become a physician and constantly shouldered extra responsibilities. "There are 15 doctors in the family," explains Talat Hamdani, his mother, who teaches at a middle school in Queens. "I told all of my children they must become doctors."

Sal, the oldest of three boys, graduated from Queens College with a degree in biochemistry, working in three university labs along the way to gain experience. That was why Brian Imai, director of Rockefeller's Protein/DNA Technology Center, hired him as a research assistant in July. "It is unusual to find young people with his level of experience," Imai says, "and Sal was hard working and enthusiastic." The center, which is a resource lab run jointly by HHMI and Rockefeller, analyzes samples from dozens of labs on campus.

The family emigrated from Pakistan 22 years ago. Sal was a devout Muslim—and thoroughly American. He wore tee shirts and jeans, played baseball and was a *Star Wars* fanatic.

Mrs. Hamdani, who still wears the traditional shalwar kameez (a long tunic over flowing trousers), described her son's religious views to a *Washington Post* reporter a week after the attacks: "He believes in mankind. When he was rescuing people, he wouldn't care if they were Christians, Jews, Muslims or Hindus. Even if someone had insulted him and his religion only 10 minutes earlier, he would still go and save them." **—JONATHAN BEARD**

Doing Their Part

HHMI employees around the country found ways to contribute in the wake of the September 11 terrorist attacks. Some gave blood, and others donated money, food or clothing. Many of them organized prayer vigils or participated in memorial services. The Institute donated $100,000 to disaster relief funds, half to the Red Cross, the rest to The September 11th Fund.

A few of the ways HHMI people offered help include the following:

- Four postdoctoral fellows from investigator Thomas M. Jessell's lab at Columbia University processed blood donations at the New York Blood Center in the hours immediately following the World Trade Center attack.
- As president of the Michigan Chinese Women Association, Angela Yang, research specialist in the University of Michigan Medical School lab of HHMI investigator David Ginsburg, shifted the focus of a planned banquet to raise funds for the Red Cross instead. Ginsburg, his wife and several lab members attended.
- Catherine Lutz, administrative assistant to investigator Morris J. Birnbaum at the University of Pennsylvania School of Medicine, organized a building-wide relief drive. Surgical masks, gloves, eye drops, batteries and the like were contributed to Operation Brotherly Love, a local radio station's disaster-aid effort.
- The Department of Genetics at Duke University Medical Center established a fund to help New York University Downtown Hospital, where 320 victims were treated in just the first two hours after the attack. Only five blocks from the World Trade Center, the hospital also provided shelter for another 500 people. Mariano Garcia-Blanco, a colleague of investigator Joseph Nevins, organized the fund.

HHMI LAB BOOK

RESEARCH NEWS FROM HHMI SCIENTISTS

IN BRIEF

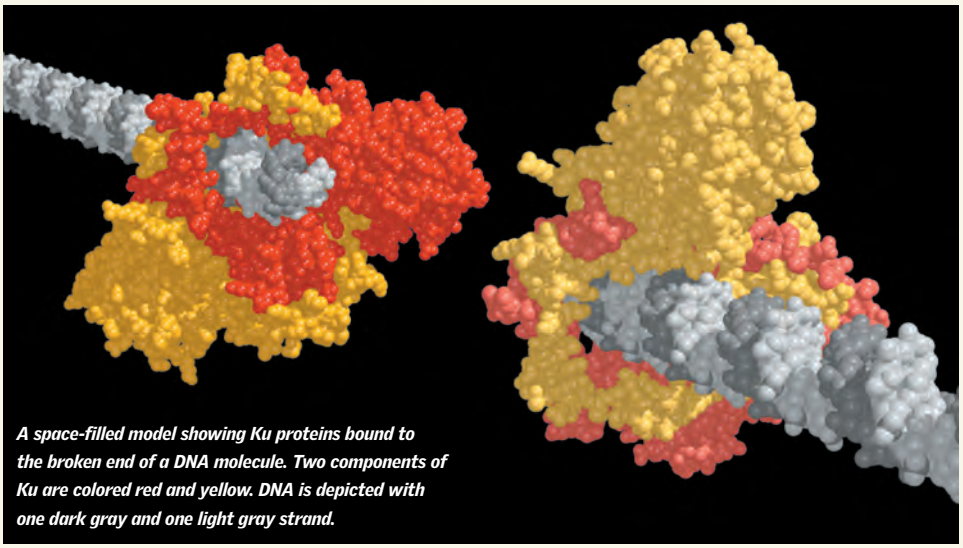
New path to blood-pressure control
Researchers have identified two related genes that control blood pressure in humans. When altered, either of the genes can cause a rare hereditary form of high blood pressure called pseudohypoaldosteronism type II. The genes underlie a newly discovered metabolic pathway that helps control blood pressure.
Researcher: **Richard P. Lifton**
www.hhmi.org/news/lifton4.html

Evolutionary insights The centromere, a part of a chromosome that is key to cell division, has been something of a paradox: Despite having DNA that rapidly evolves, it is stable enough to carry out its job during cell division. Scientists believe that the underlying mechanism may hold vital clues to the ways in which newly evolving species soon become genetically incompatible.
Researcher: **Steven Henikoff**
www.hhmi.org/news/henikoff.html

Examining electrical fields Researchers have devised a new computer-modeling method to study electrical interactions within large biological molecules. The scientists, who used the model to examine electrical fields on the surfaces of microtubules and ribosomes, say that such modeling will help in the development of specific new drugs and therapies.
Researcher: **J. Andrew McCammon**
www.hhmi.org/news/mccammon.html

Genetic switch for Alzheimer's The protein that produces the brain-clogging amyloid plaque deposits in Alzheimer's disease may actually be a genetic switch. By studying how fragments of amyloid beta-precursor protein affect gene activity, researchers may better understand the origins of some forms of the disease.
Researcher: **Thomas C. Südhof**
www.hhmi.org/news/sudhof.html

Brain cells never forget Researchers have discovered how fruit fly brain cells "remember" the order in which they are "born" from stem



JONATHAN GOLDBERG

A space-filled model showing Ku proteins bound to the broken end of a DNA molecule. Two components of Ku are colored red and yellow. DNA is depicted with one dark gray and one light gray strand.

How DNA Gets Its Fix

Researchers have produced the first detailed pictures of a protein that detects broken strands of DNA and helps repair them. The images reveal how the protein, called Ku, is built to cradle DNA while it's being fixed.

The DNA repair system protects against gene mutations and rearrangements of chromosomes, some of which cause leukemias and lymphomas. Fixing breaks in double-stranded DNA, a complex yet surprisingly accurate process, is no small feat. Scientists knew that Ku is a key member of a family of proteins that repairs DNA and that when Ku encounters damaged DNA, it initiates a repair process, called "nonhomologous end joining," that stitches double-stranded broken ends back together. What they didn't know was how Ku sensed the damage and orchestrated the process.

Researchers, led by HHMI investigator Jonathan Goldberg at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York, used x-ray crystallography to visualize the interplay between Ku and DNA. They discovered that the protein is essentially ring-shaped, with a long cradle and a narrow bridge. "It's beautifully simple," Goldberg says. "Ku is sitting in the nucleus ready to sense DNA damage and to bind to DNA ends." When a break occurs, Ku molecules more or less surround broken strands, threading themselves onto the strands like beads on a string.

The Ku ring encircles and cradles one side of the DNA, exposing much of the other side to repair factors. Goldberg and MSKCC colleagues John R. Walker and Richard A. Corpina published images of the Ku protein in the August 9, 2001, issue of *Nature*.

The researchers still have many unanswered questions. They would like to know, for example, how Ku recruits other factors to help in the repair, and they want to better understand the step-by-step process by which DNA ends are fused together. In particular, they plan to explore how Ku proteins hold the DNA in precise alignment to allow rejoining by repair enzymes. "The structure gives us a starting point to test ideas," Goldberg says, "and by understanding how the system works, we hope to learn when and why it falters."

» *www.hhmi.org/news/goldbergj.html*

Chromosome 4: Live Long and Prosper?

Does the key to long life reside on chromosome 4? A group of researchers in Boston believes it does.

HHMI investigator Louis M. Kunkel at Children's Hospital and Harvard Medical School and geriatrician Thomas Perls at Beth Israel Deaconess Medical Center, together with their coworkers, searched the full genomes of 137 sets of two or three siblings (308 individuals in all). Every subject was at least 90 years old, and one member of each set was at least 98 years old. The researchers looked for shared regions of DNA that might turn up more often than expected by chance inheritance.

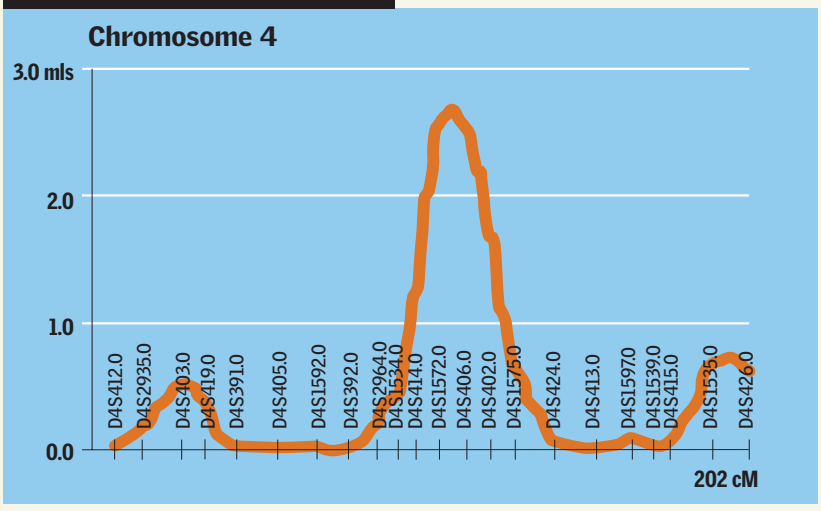
Kunkel and colleagues hypothesized that those who live well into old age may have subtle variations in a few genes that may somehow afford them longer life. They eventually zeroed in on a segment of DNA on chromosome 4. "We believe there is a gene (or genes) on chromosome 4 that is positively influencing life span," Kunkel says. They reported their results in the August 28, 2001, issue of the *Proceedings of the National Academy of Sciences*.

Those in the study "were fortunate enough not to have 'bad' versions of genes, or alleles, at a particular genetic location involved in age-related diseases," (such as heart disease, cancer, diabetes and Alzheimer's disease) Kunkel says. "Plus they had alleles that enabled them to live often 20 years beyond their life expectancy and remain active and in reasonably good health."

The scientists will try to replicate their results in another 100 or so sibling groups, but pinpointing the genes that influence longevity won't be easy. There may be as many as 500 genes in the region, and finding one or two that contain subtle variations will be difficult. Kunkel is the first to admit that "until the results are replicated or the gene is found, we're still unclear if we are right or not." Still, Kunkel is optimistic. "We believe that we can find the genes that allow humans to live to be much older than average, as well as the metabolic pathways they influence."

» *www.hhmi.org/news/kunkel.html*

A scan of the genomes of 137 sibling groups with exceptional longevity showed several similar gene segments on chromosome 4, in the location of the peak on this chart, that appear at a higher frequency than would be expected by chance.



HHMI Lab Book written by Steven I. Benowitz

IN BRIEF

cells. This molecular memory appears to determine the connections these neurons make, and in some cases, the neurotransmitters they use. Scientists hope to use this knowledge to learn how to manipulate neural stem cells to produce specific types of neurons and thereby develop treatments for disease. Researcher: **Chris Q. Doe**
www.hhmi.org/news/doe.html

Sounding off Epilepsy researchers have identified a mutated gene in mice that develop spontaneous seizures in response to loud noises, similar to the way in which human episodes of epilepsy are sometimes triggered by strobe lights. The scientists have also identified the human version of the gene and now hope to determine whether it is responsible for some cases of epilepsy. Researcher: **Louis J. Ptáček**
www.hhmi.org/news/ptacek4.html

Plants know their pollen Researchers are closer to understanding how plants recognize pollen from their own species. This knowledge may ultimately lead to methods that help prevent genetically engineered plants from cross-breeding with other strains. The scientists have identified the genes responsible for proteins that coat the pollen of the flowering plant *Arabidopsis thaliana*. Researcher: **Daphne Preuss**
www.hhmi.org/news/preuss.html

Getting a grip on protein folding
By devising an advanced computer program, researchers have designed proteins that fold into their three-dimensional shapes 100 times faster than their real-world counterparts. This work indicates progress in understanding how proteins assume their three-dimensional structures, which determine their functions as enzymes or other key cellular components.
Researcher: **David Baker**
www.hhmi.org/news/baker2.html

Restoring the will to eat Researchers have used gene therapy to revive feeding behavior in mice that had stopped eating as a result of low levels of dopamine in their brains. The scientists were able to restore dopamine production in specific areas of the animals' brains.
Researcher: **Richard D. Palmiter**
www.hhmi.org/news/palmiter.html

Skin Bares Its Secrets

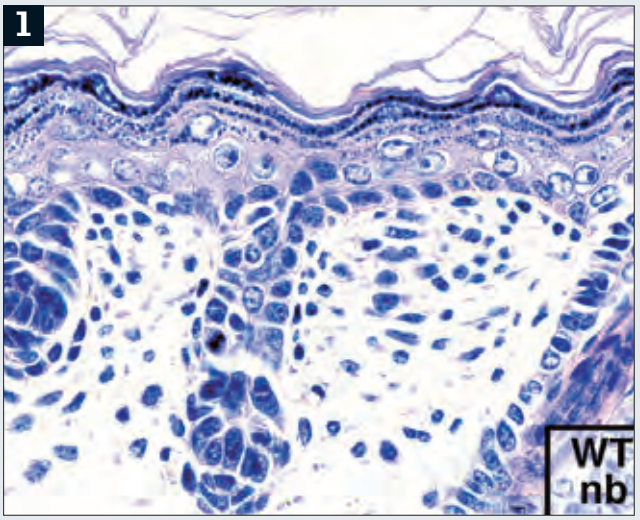
Skin is literally all around us, yet as a model system for studying human development and disease, it has kept a low profile. Now, two HHMI investigators, Elaine Fuchs at the University of Chicago and Greg Barsh at Stanford University School of Medicine, are helping skin's dynamic structure reveal its innermost self.

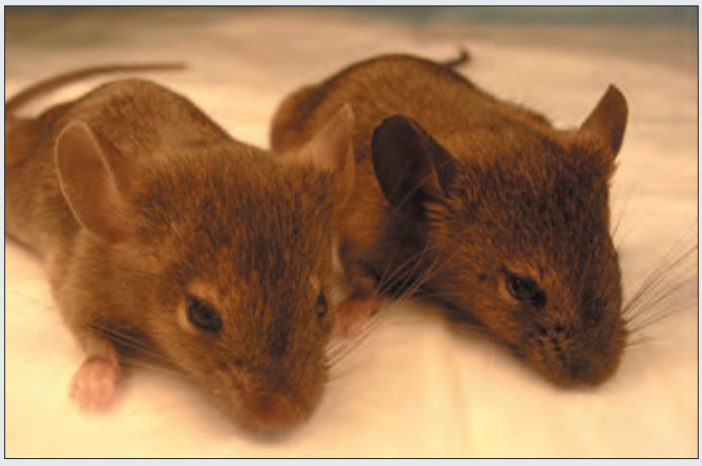
Even as a postdoctoral fellow in the late 1970s, Fuchs believed that the layers of interacting skin cells were far more than a nine-pound organ with a neglected pedigree. "There is a reservoir of stem cells in adult skin that drives the organ to nearly renew itself every two weeks. These cells can be maintained and propagated in a laboratory petri dish over generations," Fuchs explains. As such, skin cells offered a perfect opportunity for studying the three D's: development, differentiation and disease.

With the advent of mouse genetics in the late 1980s, Fuchs and her colleagues moved from cell cultures to a living mammalian model in which they could track the consequences of genetic changes. The results have been dramatic. They've discovered some fundamental facts about skin and have revealed the genetic foundations of several human skin disorders. Most recently, they've learned how skin cells of the outer layer epidermis and hair follicle stick to each other to form sheets and why this process is essential to the skin's function as a barrier. They also have determined the genetic basis of a tumor of the hair follicles called pilomatricomas, and they believe they're close to understanding the mechanisms by which precancerous lesions form in the skin.

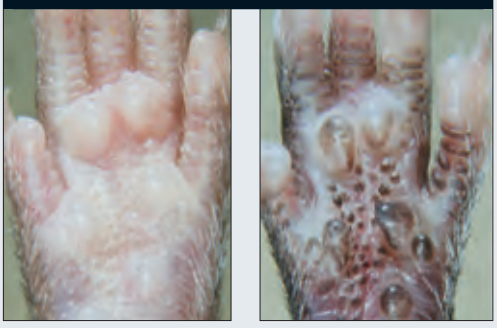
The Fuchs team began its research by determining the genetic interplay that produces a part of the epithelial skin cell's internal scaffolding, or cytoskeleton, made of an extensive network of thin filaments called keratin filaments. Defects in the genes encoding keratin proteins cause blistering diseases in humans.

Skin sections of a newborn mouse illustrate the multiple layers of the epidermis. Panel 1 shows a wild-type, or nonmutant, mouse. The top layer is the skin surface. The arm-like projections beneath are the hair follicles. Panel 2 shows a skin section of a mutant mouse lacking the protein alpha-catenin. Hair follicles do not form and the skin epidermis becomes overly thick, as in skin disorders involving excess cell division in the skin. In panel 3, also showing skin from a mouse lacking alpha-catenin, the epidermis has invaded the inner-layer dermis and formed a large mass of cells. This condition is similar to that seen in squamous cell carcinoma in situ, a precancerous lesion in the skin.





The mouse on the right carries a mutation that causes dark skin. An increase in pigment cells in the epidermis leads to darkening of the ears, footpads (below right) and tail.



GREG BARSH (3)

They also studied a second cytoskeletal network of filaments composed of a different protein, called actin: The actin cytoskeleton aids in cellular movement. It is actin that enables epithelial skin cells to begin their ascent to the skin surface, swarm to close a wound or assemble into a hair follicle.

Fuchs and her colleagues have been studying how skin cells use their filament networks and cell-to-cell adhesion to orchestrate cellular movements and maintain structural integrity. In research reported in the January 21, 2000, issue of *Cell*, Fuchs and her colleagues showed how actin filaments attach to some cell-surface proteins to bring cells together while keratin filaments work with other cell-surface proteins to clamp the cells into place. Genetic mutations in the cell-surface proteins that normally "clamp and hold" give rise to skin blistering defects similar to the consequences of genetic mutations in the keratin genes. In contrast, genetic mutations in the cell-surface proteins that associate with the actin cytoskeleton give rise to disorders in which cells multiply excessively, including cancer.

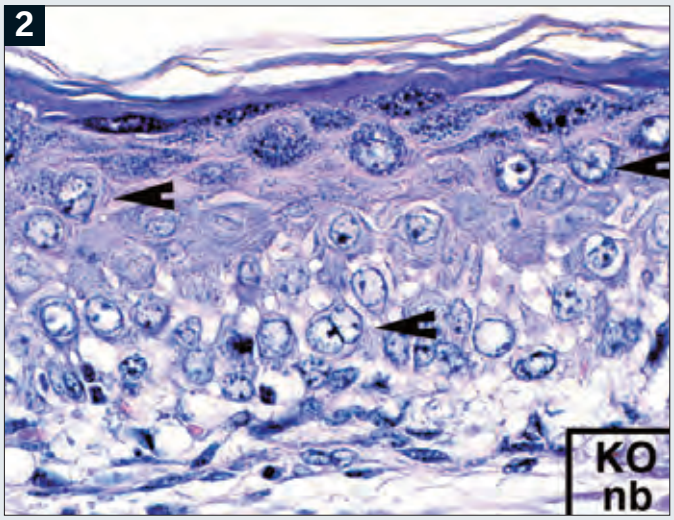
As an HHMI postdoctoral fellow in Fuchs' lab, Valeri Vasioukhin, now at the Fred Hutchinson Cancer Center in Seattle, found that a protein called alpha-catenin helps skin cells touch and stick to each other. The protein also plays a role in proliferation, an absolute necessity when an organ is taking shape, but a dangerous quality when cells stall on their way to becoming specialized and instead start down the pathway to cancer development. "The studies help us to begin to understand how cells coordinate cell-to-cell adhesion with proliferation during development or wound healing and how this process goes awry in skin cancer," says Fuchs.

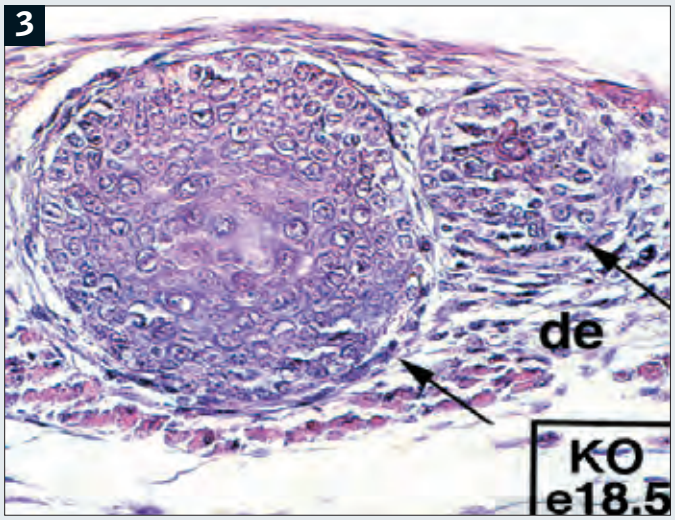
Greg Barsh studies the genetics of skin and hair color. Although variations in these traits provide one of the most obvious signs of human diversity, Barsh's interest is based on the variations' ability to offer a sensitive measure of gene expression for pathways involved in the same three D's Fuchs is studying: development, differentiation and disease.

For more than 10 years, he has analyzed mutations that affect pigment type-switching, which is the ability of melanin-producing cells in the hair follicle to switch from black/brown to red/yellow. Along the way, Barsh and his colleagues discovered a connection between hair pigment and regulation of body weight. A hormone that causes red hair in mice, Agouti protein, is very similar to a neuropeptide that causes overeating and obesity.

Two years ago, however, Barsh saw spots. That is, he noted that some mutant mice had pigment accumulations in varying patterns on the skin. "No one had really thought much about these color spots before," says Barsh. "Some occurred on the pads of the feet, others between the pads. Some were superficial. Some were deep." What intrigued him in particular were the genetic controls that governed the travels of the pigment cells from the neural tube (during development) to the epidermis and from there to the hair follicles, and the failures in this system that caused the pigment blotches. "No one had studied this developmental pathway before," he says with some amazement. Because mice and humans are only 80 million years apart on the evolutionary scale, discovering a pathway in one is likely to reveal a similar process in the other.

To that end, Barsh and his colleagues have zeroed in on 12 specific genetic mutations and are cataloging which dark patches are the result of a cell surplus and which are caused by excessive pigment in an otherwise normal number of cells. Either way, "I would be very surprised if the pathways used to make dark skin patches are not used in other parts of the body," he says. As in the link between pigment type-switching and obesity, what hair and skin reveal, genes conceal—at least, until now. "That is one of the interesting possibilities. The mutations may turn out to have nothing to do with skin disease and may be more relevant for entirely different systems." **—JEFF MILLER**





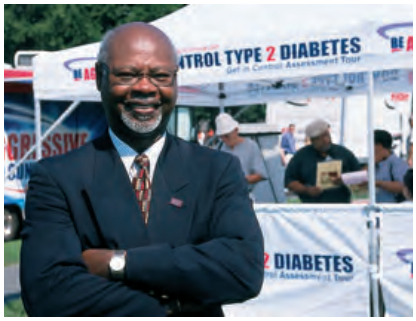
VALERI VASIOUKHIN AND ELAINE FUCHS (3)

PERSPECTIVE

Diabetes in High-Risk Minorities

By James R. Gavin III

Recently, when I was traveling to a conference sponsored by the American Diabetes Association, my cab driver turned around and said, "I've taken quite a few passengers to this hotel today. Are you a doctor, too?" It turned out that she had just married a man with type 2 diabetes. Our conversation soon became a replay of countless others I've had in taxicabs and other settings.



GREG HADLEY

The true nature and scope of the diabetes problem is staggering: 16 million persons known to have diabetes and at least $105 billion spent annually on related medical care. These numbers assume real meaning when they become personal, as they did for me when I became aware that my sister suffered from diabetes.

My taxi driver, for example, apologized for asking so many questions but felt obliged to learn more so she could "take better care" of her new husband. While I applauded her sentiment, I had to point out that it's necessary for him to assume responsibility for managing his disease, with her providing encouragement and assistance. For starters, they both need to know the medical specifics, and I explained the importance of being familiar with the details of her husband's treatment. We also discussed what kind of actions are important to prevent and delay complications for people with diabetes, especially those at highest risk.

Indeed, one of the most important recent insights about diabetes is that it behaves differently across population groups. The focus of our taxi conversation was an African-American man in his early sixties and "a little on the heavy side," according to his wife, who said diabetes ran in his family. She went on to say she was concerned because she had heard diabetes affects African Americans more than other groups.

What she had heard is absolutely true. There is more diabetes in African Americans and other minorities than in Whites. In fact, for African Americans and many Latino groups, the disease is twice as prevalent. Rates are even higher among American Indians, and they are skyrocketing in Asian Americans. While we have the benefit of powerful epidemiological evidence that establishes associations between various risk factors and diabetes, we do not know the genetic or molecular mechanisms that account for the disease, nor why it is more common and severe in certain groups.

The relative impact of diabetes on minorities is similarly staggering. End-stage kidney disease, for example, is four to six times more common in African Americans than in Whites, and lower-extremity amputations are up to three times more common in African Americans, especially in women. Likewise, the rates of coronary heart disease deaths associated with diabetes are higher in African-American women. What emerges from many studies is a clear conclusion that the development of diabetes and its complications is driven by a complex set of interactions, both genetic and environmental. Moreover, there are nuances within different population groups that defy a "one-size-fits-all" approach.

There is also an urgent need to focus on basic research—to advance the level of knowledge about factors that underlie whole ranges of diseases. This is not intuitively obvious to many people. People often ask me about HHMI's "diabetes research program" and are astonished when I reply that we have no such program. Neither do we have a heart disease program, a cancer program or any other research program for specific diseases. That does not mean, however, that we are uninvolved in research that directly addresses these diseases (see story page 16).

The great appeal of basic biomedical research is that the work of a single investigator may reveal insights into the basic mechanisms of many diseases. When we understand the biology of the stem cell and can successfully direct its differentiation, for example, it will be possible to generate a variety of cell types to replace those affected by disease, such as new insulin-producing beta cells that might prevent or cure multiple forms of diabetes. Likewise, as we learn why certain populations of cells age rapidly and prematurely undergo programmed death, or apoptosis, we may be able to prevent the gradual failure of beta cells in type 2 diabetes.

Similarly, the more we understand the mechanisms of autoimmunity, the greater will be the likelihood that we can prevent the onset of type 1 diabetes. And the more we learn about the genetic and molecular mechanisms involved in obesity, hypertension and lipid disorders, the better we will be able to design preventive measures and treatment strategies for diabetes and its complications.

In other words, we need basic research that is as complex as diabetes itself, with multiple investigators exploring its fundamental mechanisms. That's the best way to answer the questions posed by people like my cab driver and to provide new hope to the people they love—in minority communities and everywhere else.

James R. Gavin III, a senior scientific officer at HHMI and director of the HHMI-NIH Research Scholars Program, is past president of the American Diabetes Association. In 2002, he will become president of Morehouse School of Medicine.

To Pay for Biomedical Research, Buy Low, Sell High and Act Fast

It's Ellen Hanlin's third call in five minutes to her broker. "Let's pick up 5 at 75," she says, placing an order to buy 5,000 shares of an oil services company at $21.75 per share. Moments earlier, she bought 5,000 shares at $21.80, adding to her first block of 5,000 purchased at $21.85. Just as she hoped, the price is dropping, and her eyes don't waver from one of her five computer screens as she calls the broker in New Orleans, a specialist in oil industry stocks who sends her orders to a trader at the New York Stock Exchange.

Hanlin is also a trader, making this latest acquisition in small batches to avoid raising the price, and she works at HHMI headquarters in Maryland. She buys and sells stocks for the Institute's endowment at the direction of Rich Pender and his team, who manage the "in-house equities" portion of HHMI's investment portfolio. Although the Institute invests most of its endowment—recently valued at approximately $12 billion—with outside firms, its internal staff invests more than a third of the money directly.

Hanlin and her colleagues know that their performance affects HHMI's spending on biomedical research and science education, because the endowment funds nearly all of the Institute's $650 million annual budget. "Who knows what dollar it might be that finds a cure for some disease?" she says. "I feel like we're actually doing some good here."

Guided by HHMI's Trustees and led by Vice President Nestor Santiago, the investment department allocates the Institute's resources among many categories—from equities to bonds to timber holdings—to smooth out returns and limit exposure to upheavals such as the recent plunge in technology stocks. Just as in a research laboratory, many people work together to bring these decisions to life. For instance, Lisa Snyder, who is part of the private equities team headed by Mark Barnard, monitors HHMI's stake in more than 150 limited partnerships, making sure they distribute earnings and provide updates on schedule. Every day, she checks that wire transfers—which routinely total in the millions of dollars—reach HHMI's bank in time to earn an extra day's interest.

KAY CHERNUSH

Ellen Hanlin is part of the team that invests HHMI's funds.

Meanwhile Margaret Hotchner produces detailed reports on all of HHMI's internal and external accounts. "As volatile as the markets have been lately, Nestor and the others want to see updates several times a month," she says. "When there's a big jump, I'll prepare a report that shows the latest values of the endowment's different asset classes and compares these with the targets that the Institute has previously established." Hotchner jokes that the names of the various asset classes, such as leveraged TIPS and currency overlay, "may be as incomprehensible to some scientists as their reports are to me."

From her trader's perch, Hanlin also watches developments closely, knowing that the slightest rumor can affect a stock she's been instructed to buy or sell. While talking to the broker in New Orleans, for instance, she awaits a speech by Federal Reserve Board Chairman Alan Greenspan, whose face decorates her wall, as does a photo of her family's farm in West Virginia. After hanging up, she recalls that "my parents traded cattle and sheep. They would say to someone, 'How much do you want for that cow? We'll give you this much money and the first cut of hay from that field over there.' In a way, I do the same thing. I'm always trying to get a high price when I sell and a low price when I buy."

Hanlin started out as a bank teller and advanced through the financial world before landing at HHMI in 1988. "I've seen a lot of changes since then," she says, nodding toward her computer screens. "But it's not just the technology. The number of players and the volume have just exploded. When I started out, I sold 35,000 shares of Heinz and took the price down by four points. Now, the market would barely notice."

Such experience also provides perspective. "When the tech prices were going up and up, I just knew it was a bubble," Hanlin says. "People were gambling without knowing that the house always wins. We're not day traders here. We go over companies with a fine-tooth comb, and our performance shows it."

Santiago says that Hanlin—like Snyder, Hotchner and others in the investment department—needs to be "both diligent and flexible" to take advantage of opportunities while preserving the resources that fuel HHMI's activities. "You need everyone on the team working together," he emphasizes. "All of us regard the scientific operations as a national treasure, and we want to provide the maximum financial support."

—DAVID JARMUL

A Tribute to Irving S. Shapiro

Irving S. Shapiro, one of the original Trustees of the Howard Hughes Medical Institute appointed by the Delaware Court of Chancery in 1984, died on September 13, 2001, in Wilmington, Delaware. Shapiro served as chairman of the Trustees from 1990 to 1997 and was still an active member of the board at age 85.

Shapiro became a public figure while he was chairman and CEO of DuPont from 1974 to 1981. During that period, he emerged as an articulate spokesman and advocate for corporate America. He became especially noted for his thinking and writing about corporate governance, which he dealt with in his book *America's Third Revolution—Public Interest and the Private Role*. He was a strong proponent of greater openness in all institutions.

JOHN MCGRAIL

"Irv Shapiro was a remarkable person," said Hanna H. Gray, former president of The University of Chicago, who succeeded Shapiro as chairman of the HHMI Trustees in 1997. "He was totally dedicated to the mission of HHMI, and his guidance was critical in securing and strengthening the institution as we know it today. Irv was a great public servant. He was also a tough-minded businessman and a business strategist of the first order. He played the critical role in the sale of the Hughes Aircraft Company to General Motors in 1985, which established the Institute's endowment, and his service as chairman of the finance committee and later as chairman of the Board was always, and effectively, directed to enhancing the welfare of HHMI and furthering its work. He will be greatly missed."

Shapiro was born in Minneapolis in 1916, the son of Lithuanian immigrants. He graduated in 1939 from the University of Minnesota, where he also received his law degree. In 1941, he joined the federal government, where he helped establish a rationing program during the early days of World War II. Later, at the Justice Department, he specialized in practice before the Supreme Court and the U.S. courts of appeals.

Shapiro's spectacular career with E.I. duPont de Nemours & Company began in 1951, when the company persuaded him to join its legal staff following his service in the Roosevelt and Truman administrations. In January 1974, Shapiro was named chairman and CEO of DuPont, which he remained until he retired in 1981.

After he retired, he joined the New York law firm of Skadden, Arps, Slate, Meagher & Flom as a partner. Shapiro was a member of the American Academy of Arts and Sciences and the American Philosophical Society.

Earlier this year, Shapiro was interviewed as part of the Institute's oral history project. Here are some of his observations:

Q: Why was the 1987 sale of the Hughes Aircraft Company, which the Institute owned, so important?

Shapiro: It gave new life to the Institute's operations because the scientists then knew for sure that there was plenty of capital around to finance what they were doing. We managed our money very resourcefully and we happened to be around when the stock market really got hot. We are spending more than a half-billion dollars a year now—when we started in 1984 we were spending $40 million.

Q: The Institute spends about 5 percent of its endowment each year, although it is required to spend much less. Is that a deliberate policy of the Trustees?

Shapiro: We've operated on the premise that our function is to put the money to work, not just to collect capital. As our income increased, we wanted programs to use up that income. It just didn't make any sense to collect cash and husband it. The whole point is to put that cash to work.

Q: Do you think it is best for large philanthropies to find a certain area to address in depth rather than trying to solve everybody's problems?

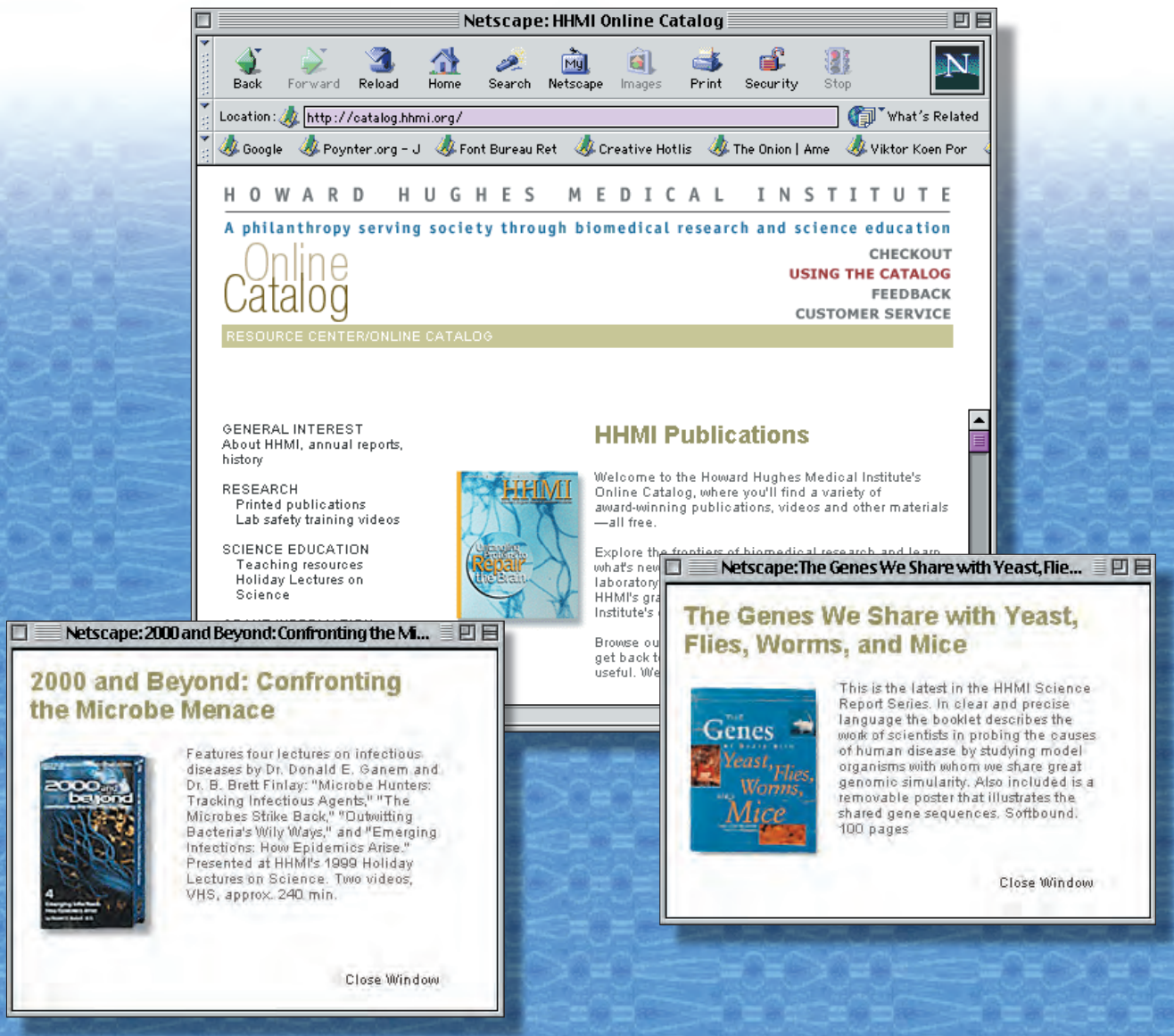
Shapiro: Well, I would agree, and that's what Hughes is really about, dealing with research on the human body, and no matter how hard we work, we'll never complete that job. As a result of the work over the last 20 years, the practice of medicine is going to be quite different from anything we've seen before. The knowledge of the genome, for example, is so valuable that you start rethinking everything. I know there are going to be people who are saved because some bright doctors figured out how to put an effective gene in the body.

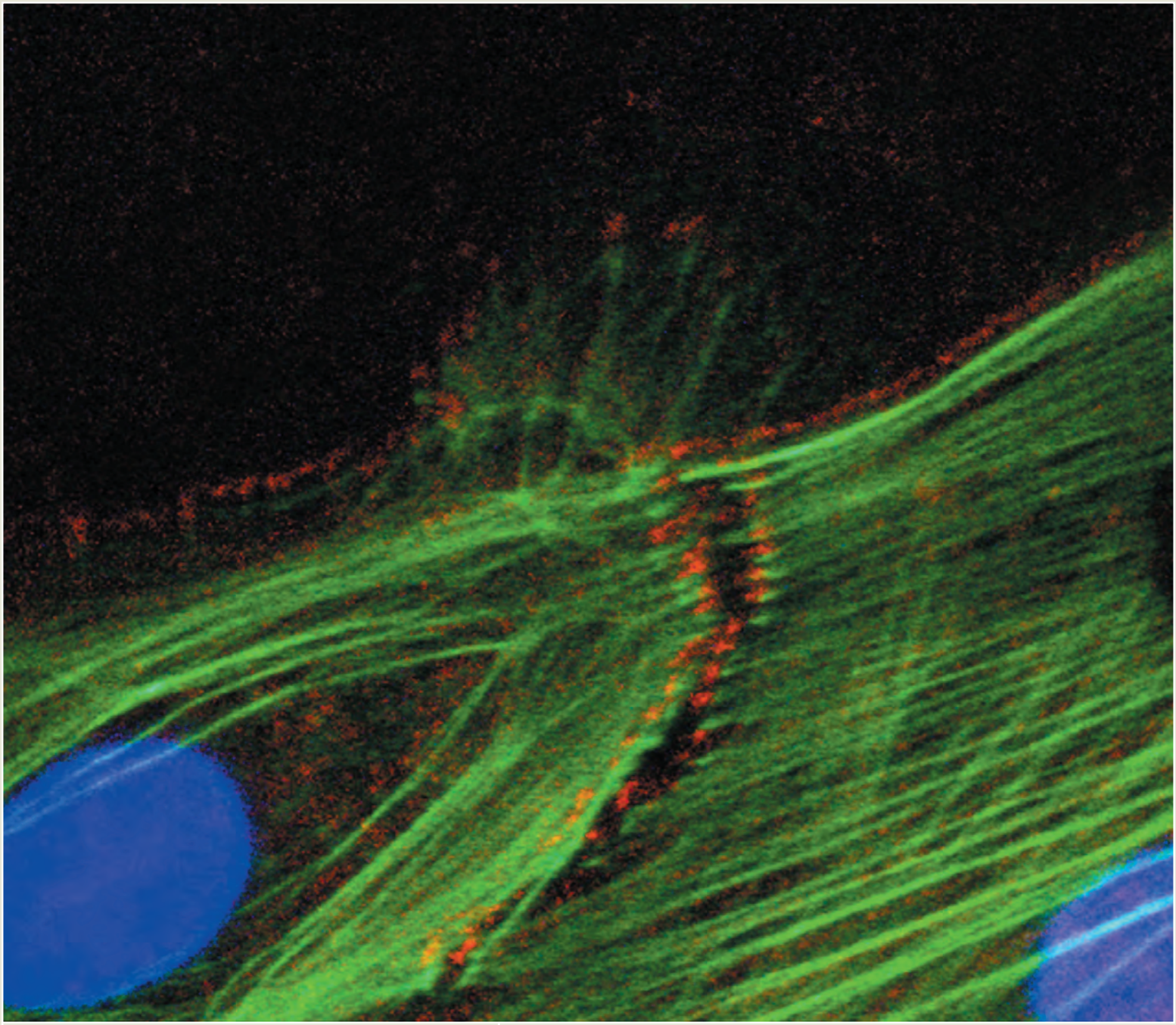
Order HHMI Materials Online

It's not exactly *amazon.com*, but now you can find all HHMI publications, CDs and videos in one place at *catalog.hhmi.org*.

The materials, organized by category, can be searched by topic, format and media type. Join the mailing list to receive the current issue of the *HHMI Bulletin* by mail, order the latest in the HHMI science report series, *The Genes We Share*, or enjoy a tour through a virtual lab on CD-ROM. The online catalog contains numerous links to reference material on *www.hhmi.org* and to the online versions of several HHMI publications. Many print items, particularly grant-application materials, are available in PDF format.

After registering on their first visit, all users are offered streamlined shopping on subsequent visits. Special orders can be accommodated by sending an e-mail to Customer Service.





HHMI investigator Elaine Fuchs produced this image of two skin epidermal cells in culture. They are in the process of making contact to form a tight adhesive seal. The green is the actin cytoskeleton and the red is E-cadherin. The cell's nucleus is blue. Fuchs is studying how this process goes awry in skin cancer. Story on page 40.

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

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