

# paradigm.

## A political science

Once, biology was left to researchers—  
now, everyone wants to get into the game

DO  
NO  
HARM

vote  
**YES**  
on stem cell  
research

## THE UNITED STATES OF BIOLOGY

As I write this in the waning days of summer, it appears that the 2004 national election may turn in large part—and for the first time in history—on an issue of biomedical science. At question is the use of embryonic stem cells, taken from embryos only a few days old, to reverse diseases by replacing damaged or defective cells with new, undamaged ones grown in the laboratory.

That such a complicated scientific issue should rise to the top of the political heap in a hotly contested presidential election has stunned pollsters and pundits alike. Driven by a desire to leverage a wedge issue that divides many otherwise loyal conservatives—notably Nancy Reagan and Utah Republican senator Orrin Hatch—partisans on both sides of the issue are ramping up the volume of political rhetoric to maximum stridency. Not surprisingly, the election-watching press has responded with a barrage of coverage about an issue that most Americans had never heard of a year ago.

For years, those of us who advocate increased public understanding of science as essential to democratic governance have bemoaned the lack of attention paid to scientific issues in electoral dialogue. Well, now we have our chance. By the time this edition of *Paradigm* rolls off the press, we will be able to see what we've made of this opportunity to broadly educate the public about an important and exciting line of scientific inquiry.

The first salvos during the Democratic and Republican national conventions, however, have not been encouraging. Stem cell research was hyped as an imminent cure for practically every human ailment, or demonized as a threat to the sanctity of life.

Missing so far is a national public dialogue about the science itself. There still are fundamental questions about just how stem cells morph into the various cell types that make up our bodies, about how elastic that differentiation can be under different circumstances or with different kinds of cells, and about whether stem cells from other sources are acceptable substitutes for the research now under way.

But these questions won't be addressed in bumper stickers, campaign slogans, or 30-second media spots paid for by special-interest groups. If the campaigns truly are interested in dialogue, this year's presidential contenders will resist the temptation to reduce stem cell research to a sound bite, choosing instead to help us understand the scientific and medical issues that inform their political positions.

*Rick Borchelt, director of Communications & Public Affairs at Whitehead, serves on the American Association for the Advancement of Science Committee on Public Understanding of Science and Technology.*



### ON THE COVER:

Biological research is caught in the headlines during this election year. In this issue, we examine three of the issues that now embroil investigators. Photo by Stuart Darsch.

## our contributors

**SUSAN GAIDOS** (“Of peas and patterns”), a first-time contributor to *Paradigm*, writes about basic research, health, medicine, and the environment. Her freelance stories appear frequently in the *Dallas Morning News*. She has received gold and silver awards in medical and science writing from the Council for Advancement and Support of Education. She lives in Cape Elizabeth, Maine.

**ERIKA JONIETZ** (“RNA’s regular role”) is a former senior associate editor of *Technology Review* magazine. After 11 freezing winters, she fled Boston and now is a freelance writer in Conroe, Texas. This is her first article for *Paradigm*.

**BARTON REPERT** (“Battle over bio-defense”) is another first-time contributor to *Paradigm*. Previously he worked for 18 years as a reporter and editor with the Associated Press in Washington, New York, and Moscow. He currently writes about science and technology from his home in Gaithersburg, Maryland.

**STEVE MIRSKY** (“This guy’s the limit”) is an editor at *Scientific American* magazine. **RICHARD SALTUS** (“Visa denied”) is a science writer and editor for the Dana-Farber Cancer Institute. Work by photographers **STUART DARSCH, SAM OGDEN, MARK OSTOW**, and illustrators **CHRISTINA ULLMAN, DAVID WHEELER, and BRIAN WILLSE** is featured throughout this issue.

## cover story

## 12 A political science

Do science and politics make strange bedfellows? Not this year. Never have so many issues related to biological research taken center stage in political battles.

## 14 Life, death, and stem cells

by David Cameron

Most scientists, politicians, and ethicists agree that human reproductive cloning should be banned. The issue of using embryonic stem cells for therapeutic cloning doesn't inspire quite the same solidarity.

## 20 Battle over biodefense

by Barton Reppert

The proposed federal budget for the next year calls for \$1.7 billion for biodefense research. What some scientists welcome with open arms, others call a political reaction that's siphoning funds away from research on cancer and AIDS.

## 26 Visa denied

by Richard Saltus

No one denies the importance of national security in a post-9/11 world. But some argue that new regulations regarding visa issuance are ineffective, hinder research, and make it harder for reputable scientists to do work in the United States.



## features

## 6 This guy's the limit

by Steve Mirsky

Meet NASA scientist John Rummel, your Planetary Protection Officer.



[6]

## 8 Of peas and patterns

by Susan Gaidos

The search for genetic patterns is revealing important information about human disease.



## 30 The genome club

by Eric Bender

The completion of the Human Genome Project was far from the last word on genome sequencing. Welcome to the mammal-of-the-month plan.

## departments

## 2 Science digest

Research news in brief

## 32 Science and society

Issues in education and policy

## 34 Extra credit

Life sciences 101

## 36 Fast FAQs

Exploring science headlines

## 37 www.whitehead.mit.edu

On the Web



[36]

**[ PROTEIN PUZZLE ]**

*Study offers insight into target for anti-obesity drugs*

Obesity researchers in the laboratory of Whitehead Member and MIT professor Harvey Lodish made an intriguing discovery in 2001 when they found that large doses of adiponectin, a fat-cell protein that they had identified and cloned, caused obese mice to lose weight. Although these findings placed adiponectin in the center of the search to develop an anti-obesity drug, the exact mechanism of the protein remained a mystery, as did the other potential cellular players.

The picture became clearer this summer when the team led by Lodish identified another key player in fat metabolism. In research published in the journal *Proceedings of the National Academy of Sciences*, Lodish's team identified T-cadherin, a protein that lies on cell surfaces in blood vessel linings, the heart, and muscle tissue and serves as a receptor for adiponectin.

“Discovering a protein that adiponectin interacts with now provides us a way to learn more about adiponectin itself,” says Christopher Hug, a visiting scientist in the Lodish lab and the study's lead author.

In particular, the discovery eventually may enable scientists to develop a molecule that mimics adiponectin. “This is one of our long-term goals, since we saw earlier how effective the molecule is in treating obesity in mice,” says Hug. This may one day help in counteracting type 2 diabetes, as well as other obesity-related illnesses, he adds.

The incentive to develop such a treatment is huge. Last year, U.S. surgeon general Richard Carmona reported that the nation spent \$177 billion on health conditions stemming from obesity. And this summer, a long-time Medicare policy against labeling obesity as an illness was abandoned when the agency announced it was expanding its coverage to include obesity treatments.

Although Lodish and his collaborators are excited about their findings, as they note in a second journal article published in the same issue of *PNAS*, it will be some time before researchers develop anti-obesity therapies.

In that study, postdoctoral researcher Guang Wong discovered a new protein, mCTRP2, which, like adiponectin, helps cells metabolize fat. Because this new molecule belongs to a larger class of related proteins, this implies that metabolic regulation may be far more complex than previously thought. “It has opened up a huge area of investigation for many years to come,” says Wong.

– David Cameron



**[ THE mTOR STORY ]**

*Protein targeted by drug developers not open and shut case*

Discovery of the mTOR protein and the role it plays in cell growth, a process often linked to diseases such as cancer, was part serendipity and part good detective work. And like any good whodunit, the mTOR story wouldn't be complete without an unexpected twist.

The mTOR tale begins with rapamycin, an immunosuppressant used to prevent organ rejection in transplant patients. Initially, doctors knew rapamycin was effective but didn't know exactly why. Scientists then discovered that rapamycin works by blocking the activity of a protein responsible for sensing nutrients in a cell's environment. By inhibiting this protein, rapamycin tricks cells responsible for organ rejection into believing that they are starving, causing them to stop growing. Scientists dubbed the protein mTOR, mammalian target of rapamycin.

Studies conducted in Whitehead Member David Sabatini's lab found that rapamycin was inhibiting a complex of proteins that, together with mTOR, sense nutrients and control cell growth. As Sabatini and others studied mTOR in greater depth, its role in disease became more apparent, raising hopes that mTOR could be targeted by drug therapy. But new research from the Sabatini lab suggests that the investigation into mTOR's function is far from over.

“When you completely snuff out mTOR activity, cells die. Yet rapamycin, which we know inhibits mTOR, isn't toxic to patients or cells in culture,” says Dos Sarbassov, a

## CANCER CLUES

### MICE CLONED FROM MELANOMA CELLS SUGGEST CANCER MAY BE REVERSIBLE

Scientists at Whitehead Institute and the Dana Farber Cancer Institute have cloned mice from an advanced melanoma cell, a study that suggests nature can reset the clock in certain types of cancer and reverse many of the elements responsible for causing malignancy.

“This settles a principal biological question,” says study coauthor Rudolf Jaenisch, Whitehead Member and professor of biology at MIT. “The epigenetic elements of cancer are reversible; the genetic elements, as expected, are not.”

Researchers have known for decades that cancer begins when certain key genes in an otherwise healthy cell mutate. They also know that tumor growth depends on continuing, multiple mutations. But only recently have scientists begun to understand the “epigenetic” components of cancer—that is, other molecules in a cell that affect genes without actually altering the sequence of DNA. Many of these epigenetic components, such as methylation, can determine whether a gene is silent or active.

Konrad Hochedlinger and Robert Blelloch, postdoctoral researchers in the Jaenisch lab, studied whether any of these epigenetic influences can be reversed. First, they removed the nucleus from a melanoma cell and injected it into an egg cell whose nucleus had been removed. (This process is known as nuclear transfer.) After the egg cell

developed into a blastocyst, Hochedlinger and Blelloch harvested embryonic stem cells, which they then incorporated into a group of healthy mouse blastocysts. Many of these blastocysts developed into normal adult mice. The work was reported this summer in the journal *Genes and Development*.

“It’s important to note,” says Blelloch, “that the stem cells from the cloned melanoma were incorporated into most, if not all, tissues of adult mice, showing that they can develop into normal, healthy cells” such as those for skin pigmentation, immunity, and connective tissue. But in spite of this, when certain cancer-related genes in these mice were activated, they developed malignant tumors at a much faster rate than the control mice.

According to Lynda Chin of Dana-Farber’s oncology department, a coauthor of this new work, the research opens the door to developing cancer animal models in which researchers could ask epigenetic questions.

“Although studies are ongoing, these findings have provided initial clues of the relative contributions of the epigenetic versus genetic lesions in the development of cancer,” she says. “Drugs that target the cancer epigenome may prove to be a key therapeutic opportunity for diverse cancers.”

— David Cameron

postdoctoral researcher in Sabatini’s lab. This, he says, suggests that rapamycin does not inhibit the essential mTOR function.

In a recent issue of the journal *Current Biology*, the group reported the discovery of a protein called rictor that helps explain why rapamycin is not toxic to patients and provides new evidence that mTOR plays a more complex role in the cell than previously thought. Despite rapamycin’s destructive effect on some mTOR proteins, mTOR that is bound to rictor remains unaffected and able to perform other jobs within the cell.

“When given to patients, rapamycin is inhibiting only a fraction of mTOR’s activity,” says Sabatini. “This has important ramifications for pharmaceutical companies developing drugs to inhibit mTOR activity.”

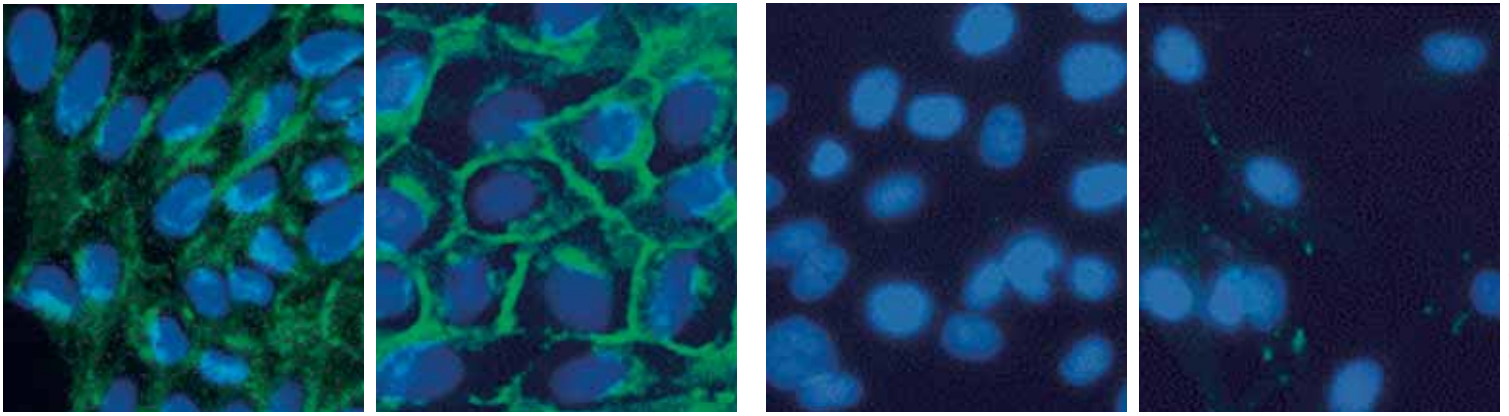
Now, researchers in the Sabatini lab are investigating what other roles mTOR may play in mammalian cells, work that could lead to an even better understanding of the protein.

— Melissa Withers

**Rethinking rapamycin:** Dos Sarbassov studies a new player in mTOR behavior.



MARK OSTOW



IMAGES COURTESY OF CELL PRESS

## [ TWIST OF FATE ]

*Scientists examine how tumors spread*

There is no shortage of scientific data on how cancer originates and develops. For decades researchers have been investigating the complex circuitry of genetic mutations that fuels a tumor's growth. But data on how a tumor spreads and metastasizes have remained relatively scant. Now, a team of researchers led by Whitehead Member Robert Weinberg has discovered that tumors spread by reactivating and commandeering a "sleeper" protein that should have been shut off permanently in early embryo development.

"As a result, cancer cells acquire in one fell swoop many of the abilities they need to execute the complex stages of metastasis," says Weinberg, who also is a professor of biology at MIT.

Metastasis is a highly inefficient, multi-step process that requires cancer cells to jump through many hoops, Weinberg notes. The cells first must invade a nearby tissue, then make their way into the blood or lymphatic vessels. Next they must migrate through the bloodstream to a distant site, exit the bloodstream, and establish new colonies. The entire operation involves so many steps that it raises an obvious question: How do cancer cells cobble these behaviors together and acquire the ability to do all this? According to the new study, they don't. Instead, they hijack an existing cellular process and use it to disperse throughout the body.

In research reported this summer in the journal *Cell*, the researchers tracked how a breast carcinoma in mice misappropriates a protein called Twist. Twist is a gene regulator that tells genes when to turn on and off. But Twist mainly is active only in early embryonic development, when it enables cells to move from one part of an embryo to another and allocates these cells to different tissues. As an embryo develops, Twist's functions no longer are necessary, and it soon becomes dormant in most tissues throughout the rest of an organism's life.

**Breaking up:** In the two images on the left, the gene that codes for the Twist protein is dormant, and the cancer cells are held together. In the right two images, Twist is expressed in the tumor, and the cancer cells lose their adhesion to each other. As a result, the cells can now disperse throughout the body, making metastasis possible.

The scientists found that tumor cells reactivate this long-dormant protein and acquire the ability to move throughout the body, although exactly how the cells accomplish this remains unclear.

"Twist is probably the first gene regulator that has been tied so definitively to human cancer metastasis," says Jing Yang, a postdoctoral researcher in Weinberg's lab and lead author on the paper.

Andrea Richardson, a pathologist at Brigham and Women's Hospital and coauthor, correlated these findings with her lab's data taken from human breast cancer studies. She found that Twist is highly active in invasive lobular carcinoma, a unique type of breast cancer where breast tumor cells completely lose their cell-cell adhesion and infiltrate other tissues.

"In many mouse studies you have great models and come up with something and it cures the mice, but then it never seems to work in people," says Richardson. "In this case we were seeing the exact same phenotype and gene expression correlation in human breast tumors."

While the authors speculate about the kinds of clinical or diagnostic applications these findings may have, Weinberg is certain that Twist is only the beginning: "There are a number of other regulatory proteins that have been studied in other labs and have properties very similar to those of Twist," he notes. "The other regulators undoubtedly will play important roles in other types of human metastatic cancer."

— David Cameron

## [ YEAST FIGHTS BACK ]

*Protein dissolves the tough fibers found in Alzheimer's sufferers*

Amyloid fibers, clumps of plaque-like proteins found in the brains of Alzheimer's patients, have perplexed scientists with their robust structures. In laboratory experiments, they withstand extreme heat and cold and powerful detergents that cripple most other proteins. Although there's debate about whether they necessarily cause Alzheimer's, they are associated with it and many other neurological conditions.

Researchers have struggled to create a way to assail these resilient molecules. Now, a study at Whitehead Institute suggests that yeast may succeed where detergents have not. The research, published earlier this year in the journal *Science*, reports on a natural process by which yeast cells dismantle amyloid fibers.

"These proteins are remarkably stable," says Susan Lindquist, a Whitehead Member and lead researcher on the project. "This is the first time that anyone has found anything that can catalytically take apart an amyloid fiber."

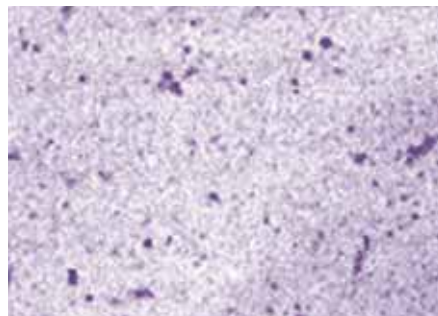
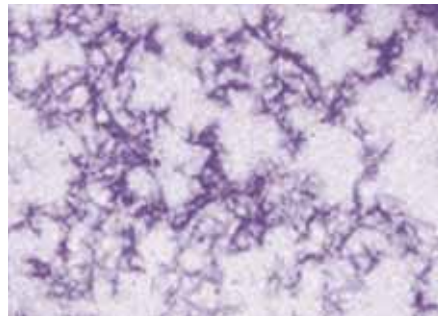
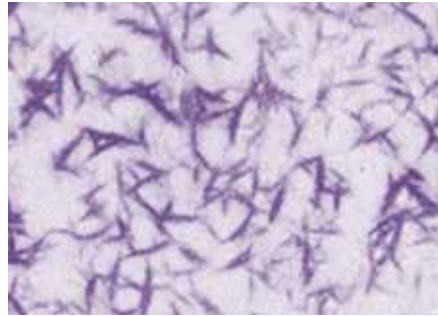
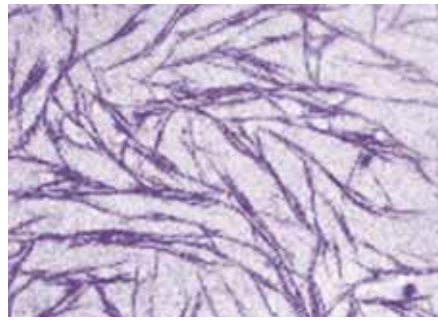
The finding follows years of study focused on a yeast protein called Sup35, which helps a protein that helps cells translate genetic information into strings of amino acids—the key components of proteins. Sometimes Sup35 suddenly forms amyloid fibers similar to those found in Alzheimer's patients. In yeast, this is part of the cell's normal biology, changing the types of proteins that the cell makes—changes that may be beneficial.

Previous research in the Lindquist lab described how a protein called Hsp104 seemed to affect Sup35's ability to form amyloid fibers, but it didn't make clear how the process worked.

In their new study, Lindquist and postdoctoral researcher James Shorter isolated the two proteins and found that small amounts of Hsp104 catalyzed the formation of amyloid fibers, while large levels of the protein actually caused the fibers to dissolve.

"Given their resilient structure, the fact that a protein can take apart these amyloids is remarkable," says Lindquist. "It has huge implications for our understanding of the protein-folding process in amyloid-related conditions."

This research also may contribute to scientists' understanding of evolution, Lindquist notes. Prions, those infectious proteins implicated in conditions such as mad cow disease, are a subclass of amyloids. In yeast cells, Sup35 technically is a prion, although it is not toxic to the cell.



IMAGES COURTESY OF SCIENCE MAGAZINE

**Protein busters:**  
At top, amyloid fibers at first resist any attempt to disrupt their structure. Hsp104, however, breaks them apart until they have been completely dissolved.

Hsp104 belongs to a class of proteins called "heat shock proteins" that sometimes are influenced by environmental conditions. It is conceivable, Shorter explains, that different environments affect the levels of Hsp104, which would, due to its effect on Sup35, create different traits in the yeast cells that could be passed on to subsequent generations.

This, he notes, would be an example of environment guiding evolution. "This is speculation that hasn't been demonstrated yet," says Shorter. "For obvious reasons it's hard to prove any evolutionary argument. But this paper is one indication that this might be the case."

— David Cameron

# This guy's the limit

by Steve Mirsky

The toughest part of John Rummel's job may be informing a new acquaintance what it is. "Sometimes I say I'm a faceless bureaucrat," the NASA employee admits. "I mean, that works pretty well." It has to be tough to tell people you're the Planetary Protection Officer.

Those lithe, silvery, bipedal, large-domed aliens that allegedly come here in their own ships to carry out proctological examinations are not

## THE MAN WHO STANDS BETWEEN US AND,

Rummel's concern, however. His responsibility is smaller: "I try to keep us from taking microbes to other planets where the microbes could grow and thrive," your PPO explains, "and I try to make sure we don't bring back anything to cause us all a problem with our biosphere."

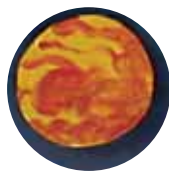
Intraplanetarily speaking, history offers examples aplenty of bad things coming in small packages. "Those are the invaders that have wreaked the most havoc here, little creatures that are easily overlooked," says May Berenbaum, head of the entomology department at the University of Illinois at Urbana-Champaign.

She has done fun studies of invaders in science fiction films, an exercise that sheds light on reality. Typical movie aliens are large, slow-growing organisms that arrive in small numbers. "Such aliens are not good colonizers generally," she points out. On the other hand, small organisms that grow rapidly and produce lots of progeny can do quite well in a new environment. Just ask a zebra mussel in the Great Lakes, or the variola virus that inflicted smallpox upon the Aztecs.

Making sure that the meek don't inherit the Earth is thus a more reasonable planetary protection strategy, says Rummel, than is watching the skies for an incoming armada.



DAVID WHEELER



## IF THEY'RE THERE, THEM

Rummel came to NASA, for the second time, in 1998. “I always like to say that I complained enough about the idiots in Washington that they offered me a chance to be one,” he cracks. He has the right academic background for a job that requires the consideration of organisms and environments—he received an undergraduate degree in environmental population and organismal biology from the University of Colorado and did his Ph.D. work at Stanford in evolutionary ecology.

His first NASA stint, starting in 1985, was at the NASA Ames Research Center as a National Research Council postdoctoral fellow. Within a few months, he was running NASA’s exobiology program, whose goal is to “understand the origin, evolution, and distribution of life in the universe.” He left NASA for the Marine Biological Laboratory at Woods Hole for five years in the 1990s, where he did research and administrative work, but returned in 1998 to head the Planetary Protection Office.

That office makes policy based on recommendations from two major sources: the Committee on Space Research, part of the International Council of Science that works with the United Nations, and the Space Studies Board of the National Research Council. Figuring out the details of complying with those recommendations, however, is up to Rummel. On recent Mars missions, for example, equipment set to actually land on the red planet’s surface was cleaned and decontaminated more thoroughly than Karen Silkwood.

It’s the issue of back-contamination—bringing back some native Martian life form—that can get contentious. A few critics believe that the risk of us inadvertently bringing back a pathogen

outweighs any benefits gained by having pieces of Mars available for study in Earth laboratories. On the other side are those who claim that the chances of bringing back something pathogenic are small enough to ignore. But Rummel once wrote, “Not until seven months after Viking 1 landed on Mars did we know about life at deep-sea hydrothermal vents right here on Earth. And Mars is big. We have, literally, only scratched its surface. Mars may indeed be a living planet.”

One reason for cautious optimism about the safety of bringing back Mars samples: Earth is already lousy with them, sent packing when cosmic collisions blow bits of Mars into space. “We get 40 kilograms of Mars rocks every year on this planet, so they’re here,” Rummel says. “We have this natural interchange. As my friend Chris McKay [at the NASA Ames Research Center] likes to say, ‘The Earth and Mars have been spitting at each other for billions of years.’”

And in evolutionary terms, it’s hard to imagine a malevolent Martian microbe. “If you’re a human pathogen,” Rummel explains, “the last place you want to be right now is Mars. There are no humans there to infect—it’s a very bad place to make a living. So we don’t anticipate that there should be a problem. But we will be very careful, both because it’s a good idea and because the National Research Council in their document in 1997 recommended that we contain something until we prove that it’s not a biohazard.”

Rummel is already thinking about the design of containment facilities for processing any Mars samples that could arrive on Earth by 2016, if proposed missions do indeed get off the ground. So some scientist a dozen years from now may get first crack at

looking for life on Mars in a lab on Earth. “If we bring something back, we’ll look at it in two different ways, essentially,” Rummel says. “We’re going to be smart and figure out what life must have, and these kinds of informed tests will then look for things we would associate with life—whether it’s morphology, so it’s something that looks like it’s alive, or chemistry, something that does something that we wouldn’t anticipate would happen in a natural chemical system without some kind of anti-entropic life form.”

What will Rummel be doing then? “Watching my successor struggle with the setup that we have,” he says.

Meanwhile, should any probing, translucent Alpha Centaurians land and ask to be taken to our leader, Rummel’s job description lets him off the hook. “I would hope to be consulted as an exobiologist,” he says, “but it’s the sort of thing that—what would lawyers say—it’s certainly of interest, but it’s not actionable.”

[ To learn more about the Planetary Protection Office, visit <http://planetaryprotection.nasa.gov/pp> ]



# The field of genetics began with Mendel's peas. Today, scientists are pushing the boundaries of science to reveal the underpinnings of disease.

In the 19th century, mathematical formulas didn't figure much into biology. But when Austrian monk Gregor Mendel crossed and counted his round and wrinkled peas, he found something unexpected: a pattern. His studies showed traits pass from parent to offspring in a predictable fashion, following well-understood rules of mathematics.

Carefully transferring pollen from flower to flower, he bred thousands of pea plants to study the patterns that appeared in succeeding generations. Round or wrinkled, green or yellow, short or tall. From these garden variety traits Mendel learned that pairs of characteristics organize and combine themselves in specific and predictable ways. His study, sadly ignored for years, helped establish the laws of heredity and, ultimately, the field of genetics. It also changed the way biologists approached their work. Mathematics and quantifiable measurement became part of the equation in biological studies.

Today, scientists poring over the human genome catalog are using

mathematical and statistical analyses to discover additional patterns of genetic variability. What Mendel did with pencil, paper, and patience now is done with computers and sophisticated mathematical formulas. The studies are revealing combinations that can contribute to disease and point the way to new treatments.

Three years ago, researchers at the Whitehead/MIT Center for Genome Research were working on just such a study when they discovered groups of genes that travel together in the human genome in large, tidy units called "haplotype" blocks. The find was uncovered when DNA analysis expert Mark Daly found a pattern.

## A GENETIC INHERITANCE

It was early 2001, and the recently completed Human Genome Project had, for the first time, made it possible for scientists to compare different parts of the genome, the catalog of chemical units called bases that spell out the genetic code. It's a catalog written in an alphabet of Cs, Ts, As, and Gs—the letters signifying the bases—and divided into 23 volumes,

one for each chromosome in a cell's nucleus. Sitting in his office at Whitehead Institute, Daly was settling in for a good read.

"It was at a time when the expectation was that these data were going to be very complicated, and that there was going to be no structure or recognizable patterns that we could take advantage of," says Daly, who is a Whitehead Fellow. "So it was really just a matter of taking an unfettered look at the data, not looking for a particular answer, but simply looking at it for what it was."

Reading through a series of base pairs, he found that over long stretches of DNA—say 50,000 letters—only a few common genetic variations arose. Scores of people shared the same series of letters across long sequences, as though their genetic inheritance had been handed down in large, prepackaged chunks.

Working with his colleagues in the genome center, Daly further analyzed the blocks using sophisticated analysis techniques. The scientists ended up

# Of

# and



hypothesizing that these long segments of the genome passed from generation to generation undisturbed by recombination. The group, which included Whitehead Member Eric Lander and research scientist John Rioux, published their findings in *Nature Genetics* in October 2001.

Additionally, the researchers made a case for using haplotype patterns to study disease, identifying a variant that could put people at high risk for Crohn's disease, a chronic inflammatory bowel disorder.

Daly then collaborated with Whitehead Affiliate Member David Altshuler to see if haplotype blocks occurred throughout the human genome. "The limitation of that [first] study was that it was just one region of the genome, and it was just one population—a European population," says Altshuler, who now serves as a founding member of the Broad Institute, a research collaboration headed by Lander that was launched in 2003 by Whitehead, Massachusetts Institute of Technology, and Harvard University and its affiliated teaching hospitals. "Also, it was a disease gene, so it was possible there was something unusual about this region because it caused disease."

The researchers analyzed 50 different regions of the human genome in samples from Africa, Europe, and Asia. Their findings, published in *Science*

in June 2002, showed that haplotype patterns do indeed appear throughout the entire genome.

#### CREATING A NEW MAP

The highly conserved segments of DNA the team uncovered provide an efficient way to wade through the

"The enthusiasm for [HapMap] was really sparked by Mark's observation and his work with collaborators," Altshuler says. "No one told him to go find this pattern. He looked at the data, he saw what he saw, and he described it clearly.



And everyone went and looked and found it in their data, too."

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**SAW WHAT HE SAW, AND HE DESCRIBED**

**IT CLEARLY."** —DAVID ALTSHULER

enormous amount of data produced by the Human Genome Project, Daly observes. The findings also helped serve as an impetus for building a haplotype map of the human genome—called HapMap—to describe the common patterns of variation that are found in DNA.

Launched in the fall of 2002, the HapMap project will allow scientists to more rapidly identify the links between genetic variation and complex diseases, such as diabetes, arthritis, cancer, stroke, heart disease, and asthma. These illnesses can result from an unfortunate conflux of genes and environmental factors, such as diet, smoking, and lack of exercise.

Scientists have had difficulty pinpointing the molecular underpinnings of these diseases because, in most cases, multiple genes are at play.

But haplotype mapping may change that. The power of the haplotype pattern lies in its ability to correlate places in the genetic code where DNA differs from one person to the next by a single letter. Called single nucleotide polymorphisms, or SNPs, these tiny changes occur about once in every 1,000 base pairs in the genome, transposing a C to a T or an A to a G.

For the most part—99.7 percent—your genetic blueprint reads just like everyone else's. But the differences in your code and that of your neighbor are almost all found in these single molecular flips.

What's more, scientists learned that though a single SNP may have only a subtle effect on a gene or its encoded protein, that small influence can make

# Patterns

BY SUSAN GAIDOS





LAUNCHED IN THE FALL OF 2002, THE HAPMAP PROJECT WILL ALLOW SCIENTISTS TO MORE RAPIDLY IDENTIFY THE LINKS BETWEEN GENETIC VARIATION AND COMPLEX DISEASES, SUCH AS DIABETES, ARTHRITIS, CANCER, STROKE, HEART DISEASE, AND ASTHMA.

a person more susceptible to disease, or influence her response to environmental factors and therapeutic drugs.

**LOOKING FOR PATTERNS**

While everything they'd learned to this point suggested the researchers were going in the right direction, the road ahead looked long. Just how were they supposed to decipher that .3 percent of genetic code that makes individuals, well, individual?

Then, Daly uncovered a pattern. When SNPs do occur, he learned, they tend to do so in a predictable fashion, making it possible to predict the identity of dozens of neighboring SNPs. Common patterns emerged, so for any particular gene region, only a handful of common SNP variants, or haplotype patterns, exist. This means that instead of searching base-by-base through all the differences in a particular region of the genome to find one responsible for a disease, researchers may examine a smattering of key SNPs rapidly in large populations.

HapMap researchers in Canada, Japan, the United Kingdom, China, Nigeria, and the United States now are rounding up DNA samples from local families to find genes that affect health, disease, and responses to drugs and other factors. For each genetic variation pattern, scientists eventually will tally the numbers to see how

many people carry that version, and of those, how many get the disease and how many don't.

In developing the haplotype map, scientists also are learning more about how genes organize and sort themselves out to create genetic variation.

Take recombination, for example, the scrambling process used in

meiosis to create new genetic recipes.

As cells divide to produce eggs or sperm, chromosome pairs split in half so that daughter cells wind up with only one set of chromosomes. But before separating, the chromosomes swap some of their genetic ingredients so that new genetic combinations are formed. Up until a few years ago, scientists thought recombination was random, and could happen anywhere in the human genome.

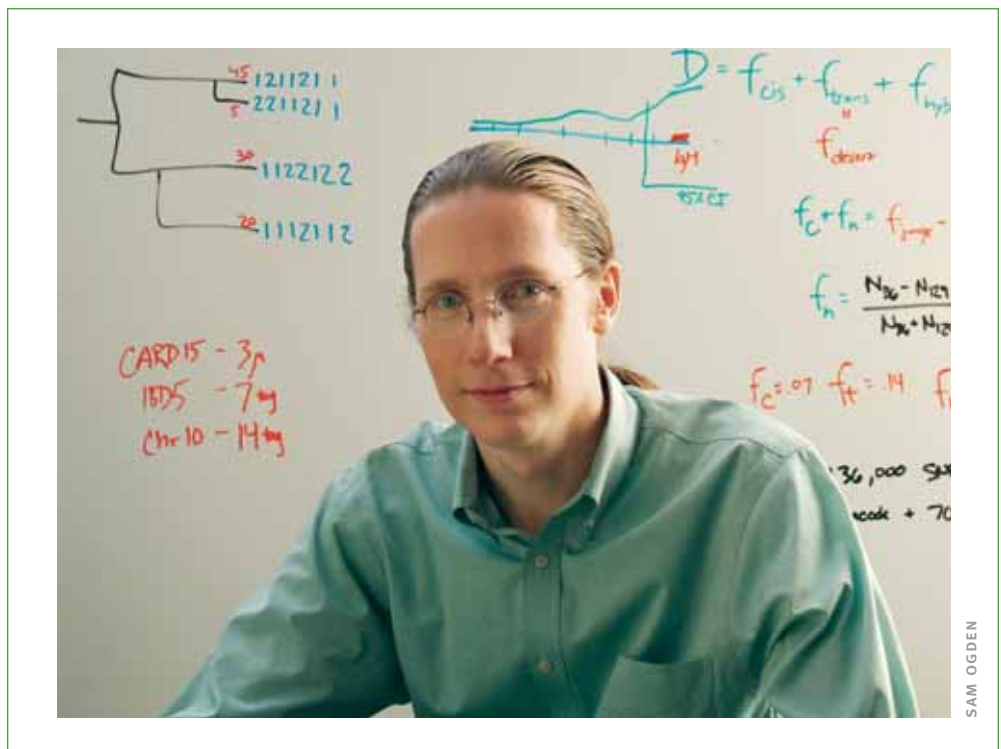
Daly's 2001 study that described haplotype patterns, along with seminal findings from another group, suggested that, perhaps, recombination wasn't a random process at all. Since then, studies have shown that recombination in the human genome is, instead, clustered in a small number of recombination "hotspots."

"One of the ancillary benefits of the haplotype map is it's also providing us a map of all these hotspots," Altshuler says, "which is useful both in terms of disease-gene mapping and in understanding basic biology."

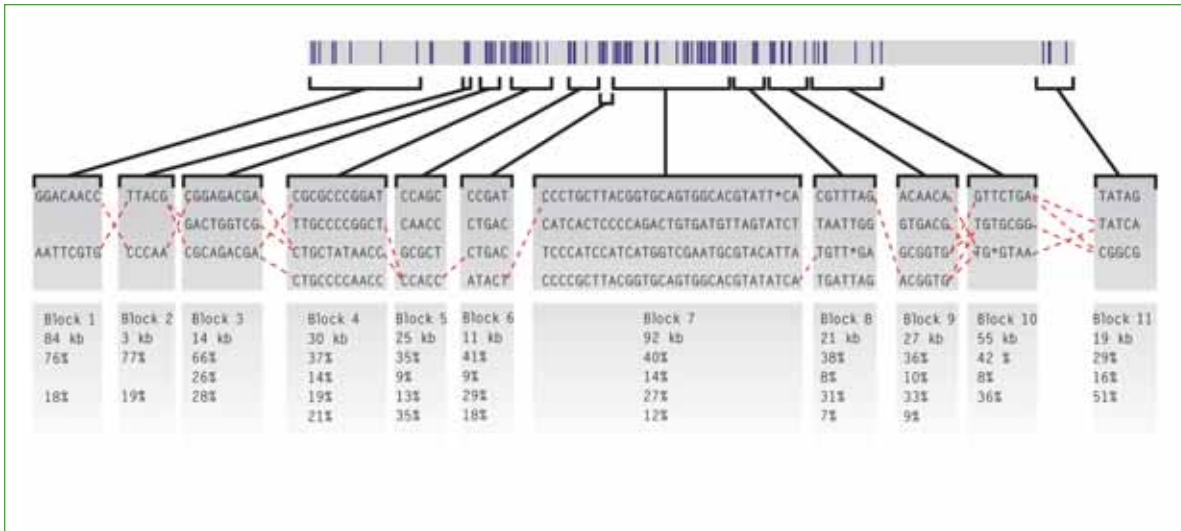
**TOOLS OF THE TRADE**

As a participant in the analysis group for the HapMap project, Daly is working to develop ways to systematically sort through the information. His talent for sifting through data was recognized soon after he entered Whitehead 18 years ago as a physics undergraduate at MIT. Using his knowledge in computational science and mathematics, Daly has developed numerous analytical tools to help researchers find and understand patterns in all types of data. His

**Blocking in:** Mark Daly unravels the secrets of haplotype blocks, groups of genes that travel together in the human genome in large, tidy units.



SAM OGDEN



**Map reading:** A haplotype map of a portion of chromosome 5 that includes a gene involved in Crohn's disease. Each of the 11 haplotype blocks comes in two to four "flavors," represented by unique combinations of single nucleotide polymorphisms—places in the genetic code where DNA differs from one person to the next by a single letter. The dashed lines show common relationships between the blocks. The percentages indicate the occurrence of each of the common flavors found in the patients studied.

Haploview software, for example, allows researchers worldwide to access, visualize, and interpret data made available through the Human Genome Project.

"Most of the computational work that we do is not about discovering and developing new mathematical algorithms and techniques. It's adopting and modifying a lot of well-established techniques in other areas of science to address specific problems," Daly says.

Ultimately, the HapMap may help scientists uncover genetic nuances that not only lead to disease, but can provide new clinical insights into subtypes

ease of the gastrointestinal system." Such findings may change how scientists search for and use information on the genetic foundations of disease, Daly says. "People would say, 'Because disease is complex, we have to use our clinical knowledge to figure out what the distinct subtypes of that disease are so that we can more efficiently make use of the genetics.' This work suggests in some cases, that may work in reverse—genetics may help lead us to better clinical classification."

And some benefits, such as using information from an individual's genetic profile to predict a therapeutic outcome, might come sooner rather than later.

**"ONCE WE HAVE A HAPMAP AND CAN CHARACTERIZE GENETIC VARIATION, WHAT DOES THAT ENABLE US TO DO IN MEDICAL GENETICS THAT WE CAN'T DO TODAY?" — MARK DALY**



of disease. Scientists are beginning to extract such information, Daly says. "In our Crohn's disease data we have been able to show that this particular risk factor promotes widespread dis-

"We have an expectation that some of the discoveries spawned from HapMap will be along the lines of finding genetic variation to predict one's response—either positively or adversely—to different drugs used to treat disease," Daly says.

"Wouldn't it be nice to know, for your particular form of diabetes, which of the many treatment options may be most effective for you or have the fewest side effects?" he asks.

The HapMap project, scheduled to be completed next year, is producing "reams of data." Scientists will begin tabulating preliminary results to describe genetic variation this fall. The real challenges, Daly says, lie ahead in decoding the information to figure out how that variation is involved in complex disease.

"The question is, once we have a HapMap and can characterize genetic variation, what does that enable us to do in medical genetics that we can't do today?" he suggests. "It's only a tool, which we need to apply intelligently. And depending on the true complexities of these diseases, we don't know how much work that's going to be."

He's now looking ahead, working to develop mathematical methodologies to help scientists decode the information from the HapMap. When the project is completed, scientists will be able to leaf through millions of human variations. Hidden in there, somewhere, scientists will surely find a pattern.

[For more information on the HapMap project, visit [www.hapmap.org](http://www.hapmap.org).]



# A political

Once biology was left to researchers—now, everyone wants to get in. In this special issue of *Paradigm*, we present three reports on how

OPENING PHOTOS BY STUART DARSCH

It's test tube babies all over again.

The debate over embryonic stem cells sounds very much like the one about in vitro fertilization three decades ago. That argument faded away long ago, and a million babies worldwide have been conceived with the technique.

But with stem cells, the controversy just keeps rising. Is the ban on federal funding for embryonic stem cell

research a necessary prohibition, to safeguard human life even in its earliest forms? Or will it simply shift this highly promising research overseas, delaying the potential for life-or-death medical advances? In "Life, death, and stem cells," assistant editor David Cameron dissects the issues, scientific and otherwise.

Another high-stakes discussion: Is the massive buildup in biodefense research





# science

into the game.  
politics and science are driving each other.

safeguarding us from bioterrorism—or increasing our risks? What’s its effect on funding for studies in other areas, such as cancer or AIDS? And if you’re studying highly infectious diseases with no cure, is the middle of Boston the best place to put your lab? Barton Reppert analyzes the programs and politics in “Battle over biodefense.”

And in our unending “war on terror,” the hardest task is figuring out who’s

friend and who’s foe. As the U.S. tightens its visa policies, it often bungles its treatment of legitimate foreign scientists working here. In “Visa denied,” Richard Saltus describes the troubling case of one scientist couple.

As these stories suggest, biological science is now caught under a political microscope—and that will last long after the ballots are counted this November.

**curing disease is NOT a sin**

**News Focus**  
Although the investigation seems focused, some experts say that’s improbable  
**Anthrax Po**  
When the anthrax outbreak passed the stage, “YOU CAN NOT STOP US HAVE THIS ANTHRAX” the threat is a chilling message that remains largely unrecognized. “ARE YOU AFRAID?” the attackers. “Yes,” should have been according to some biologists.

**When Bioterror Moves**

**HA**  
Stem Cells  
The science, the ethics

# Life, death, and stem cells

Both sides of the debate on therapeutic cloning are fighting for life and against death. It's probably the only thing they have in common.

BY DAVID CAMERON

Your doctor has some bad news. Turns out your heart isn't working right. In fact, due to deterioration in the muscle tissue, it's only operating at 10 percent capacity. That explains your chest pains, difficulty breathing, and inability to exert yourself without getting winded. Unfortunately, you know what the diagnosis means: getting on a donor list, staying at home, and waiting for the hospital beeper to go off if a

donor organ becomes available. And even if that does happen—and the chances are slim—you'll always be wondering how long the transplant will last, worrying that your immune system will wise up to this foreign mass of muscle and attack it with everything it's got.

But your doctor has another idea. He will



collect cells from the surface of your skin and put them in a dish. You'll go home, with orders to stay in bed and rest. About six weeks later, you will arrive at the hospital and be wheeled into the operating room. The last thing you'll remember is the anesthesiologist placing a mask on your face and asking you to count backward from 10. When you wake up in recovery, groggy and achy, your doctor will say that you're going to be fine. Even as the two of you speak, your heart muscle will be renewing itself. Tissue will have been engrafted into your heart—tissue created from your very own DNA. No red flags to alert your immune system. In a few weeks, you'll be completely restored.

For now, the above scenario is speculative fiction—highly controversial speculative fiction. Politicians, lawyers, ethicists, religious leaders, United Nations delegates, and scientists are embroiled

in a debate over whether the process used to “heal your heart” is morally flawed.

For that new heart tissue to be created, researchers would need to remove the nucleus from one of your skin cells and implant it into a donor egg cell from which the nucleus had been removed. They would coax the egg cell to divide into a blastocyst, a mass of about 100 cells. In the center of that mass they'd find the payload—embryonic stem cells, microscopic dots with nothing but pure potential. The cells are able to form any type of cell in the human body, including those from which scientists could conceivably grow your heart tissue. Or liver tissue. Or pancreatic tissue. Or brain tissue. Or spinal cord tissue. And so on. To do that, they would need to destroy the cloned blastocyst, and that's where it gets messy.

If, rather than harvesting it for stem cells, scientists instead placed that blastocyst, grown from your skin cells, inside a human uterus, it would have the potential to develop into a fetus. Nine months later, if all went well, a baby would be delivered. But not just any baby. It would be a carbon copy of you, cell for cell. It would be your clone, the “twin” you never had.

Just the prospect of creating a human being in this way is an ethical minefield in and of itself. But so is destroying the blastocyst. And so is creating it in the first place. To make matters worse, for researchers today to learn how to create “your” heart muscle tomorrow, they need to experiment on

# National Report

The New York Times



## First Lady Defends Limits On Stem Cell Research

By RANDY KENNEDY  
ROYAL OAK, Mich., Aug. 9 — Venturing forcefully into one of the most contentious areas of the debate over embryonic stem cell research, the first lady said today that she would support any effort to create or abate by stem cell research.

## Cells May Yield Unending Supply of Islets

...important because ... in major journals over ... few years have suggest ... there is widespread

... President, DiabetesPortal.com

...ous that the limiting factor ... let transplantation is the ... of insulin-producing islets.

...ximate 6,000 cadaver donors ... ch year through United Network ... aring (UNOS), only half are ... transplantation—and these are ... to candidates for whole-organ ... nsplants.

...e time, there are approximately ... people living with type 1 ... in the United ... 30,000 ... of type ... ed each

in the pancreas are the source for creating new cells to replace those that have been damaged or destroyed. In this study, Melton and his colleagues inserted a gene marker into the insulin-producing “beta” cells of mice. These markers allowed them to observe that new cells were coming from existing beta cells.

Melton's observation validates the work of others, like Alberto Hayek, MD, the Director of Islet Research at the Scripps Whittier Institute in San Diego, who has been trying to grow beta cells for some time with the goal of creating a supply of cells for human transplantation.

Melton, who is the

### Cruising for a Cure

#### Fresh Islets Better Than Cultured Ones for Islet Transplantation

In mice studies, researchers from Boston, Massachusetts, found that fresh islets are better than cultured islets at reversing high blood glucose.

In research presented at the June 2004 ADA Scientific Sessions in Orlando, Florida, islets were transplanted into diabetic mice either freshly or after culture for

## Stem cell research

ANN PARSON

Stem cell research

Respect developing human life.

## Stem Cells



MARK OSTOW

human embryonic stem cells. Until now, scientists in the field have used leftover blastocysts that stock the freezers of fertility clinics for their studies. These blastocysts are fertilized embryos that have the potential to develop into healthy babies.

Welcome to the ethical bouillabaisse known as embryonic stem cell research, where issues related to religion, abortion, cloning, and human disease are dumped together into a single scientific stew. Rarely has an issue of basic science been so hotly debated on every imaginable front, from family dinner tables to political platforms.

The Bush administration remains firmly behind the stem cell research policy announced in 2001, which restricted federally funded embryonic stem cell research to existing stem cell lines. But last May, Nancy Reagan, Republican icon and wife of the late President Ronald Reagan, asked the sitting president to change his policy on embryonic stem cell research, calling it the best hope for people with Alzheimer's disease, the illness that plagued her husband in his final years. And in July, the Reagans' son, Ron, carried the same message to the Democratic National Convention.

**“We know a tremendous amount about mouse embryonic stem cells and how to culture and differentiate them,” notes Harvard Medical School professor George Daley. “Our understanding of how to do the same in human embryonic stem cells is much more primitive.”**

But behind all the political sparring, where is the science? Critics claim that embryonic stem cell advocates are inflating their case; advocates say it is the most exciting development in biology in decades. Still, fundamental questions remain: How advanced is the research? Can therapeutic cloning actually work, delivering on its promise to cure the incurable? And what of the arguments both camps cite to prove their points? Do the current findings somehow manage to achieve a weird combination of ambiguity and promise in such a way that both sides can claim science is on their side?

#### **THE MONSTER IN THE GONAD**

In 1953, cancer researcher Leroy Stevens discovered teeth and hair in mouse testicles, and the field of stem cell biology was born. A major tobacco company had awarded a grant to Jackson Laboratory in Bar Harbor, Maine, where Stevens was a scientist, for a study the company hoped would prove that the paper in cigarettes—not tobacco—caused cancer. After exposing mice to large amounts of cigarette ingredients, Stevens noticed that a few were developing gigantic scrotums. When he dissected the scrotums, he was taken aback by what he found inside: a hodgepodge of random tissue, including cartilage, teeth, and hair.

This particular type of tumor is called a teratoma, taken from the Greek word “teraton,” which means monster. It’s a tumor that originates from a germ cell (precursors for both egg and sperm cells), hence its ability to form such a bizarre array of tissue. Stevens quickly abandoned his tobacco research and spent the next few decades studying these teratomas, trying to get at their cellular roots.

Eventually he came across what he called a “pluripotent embryonic stem cell,” that is, a cell that can give rise to a variety of tissues. Stevens’ work was limited in that the cell lines he discovered always maintained the potential to form these monster-like cancers.

Nearly 30 years after Stevens’ initial discovery, scientists in the United States and the United Kingdom isolated embryonic stem cells from a mouse blastocyst, a find that energized the field. Still, research in the area remained safely cloistered in the walls of academic study. Then, in 1998, two groups independently announced that they had isolated human embryonic stem cells. One group from the Wisconsin Regional Primate Research Center had used leftover blastocysts from a fertility clinic. The second team, from Johns Hopkins University School of Medicine, harvested their stem cells from aborted fetuses.

For researchers, this was a watershed discovery. For opponents of embryonic stem cell research, it was a call to arms. The ethical and political question of “should we find therapies this way?” came head to head with the scientific question “can we find therapies this way?” The stew began to bubble.

#### **OF CLONED MICE AND MEN**

Whitehead Institute’s Rudolf Jaenisch knows a thing or two about mice. Years ago he was among the first scientists to incorporate foreign DNA into a mouse’s genome in such a way that the new genetic information could be passed down to subsequent generations. Called “transgenics,” this procedure is now commonplace in labs around the world. For well over a decade, Jaenisch, who also is

a professor of biology at MIT, has cloned thousands of mice, trying to decipher all the factors involved in what he calls “reprogramming”—the process by which the host egg cell reactivates the entire genome of the donor nucleus. While much of the basic biology of how cloning works remains a mystery, one thing is clear to Jaenisch: There is no such thing as a normal clone.

“The vast majority of cloned embryos die in utero,” he says. “Others are stillbirths.” The slim percentage that grow to adulthood “are ridden with all sorts of genetic-related health conditions. They’re obese; they die young. I suspect many have neurological damage which is hard for us to detect. Out of all the animals ever cloned, I’m not sure whether any normal clone has yet been produced.”

The problem, Jaenisch says, is that it’s impossible for an egg cell to reactivate every single gene in the donor nucleus. Something inevitably goes wrong. “This isn’t a technical issue,” he maintains. “It’s not like the early days of in vitro fertilization, where we simply needed to improve the techniques. This is a principal biological issue.” For this reason, he and most other scientists in the field believe that human reproductive cloning should be universally—and permanently—banned. “Human reproductive cloning would be the conscious and willful creation of a grossly malformed person. The very thought of doing it is reprehensible.”

While the fetus created from a cloned blastocyst is not normal, the embryonic stem cells derived from it are. In 2002, Jaenisch collaborated with George Daley, then a Whitehead Fellow, on a study of a mouse that had no functional immune system due to a genetic defect—for all intents and purposes, a “bubble boy.” The team removed a cell from the tip of the mouse’s tail, extracted the nucleus, and placed it into a de-nucleated egg cell. It became a blastocyst from which they culled embryonic stem cells. The stem cells, because they were taken from the diseased mouse, contained that same genetic flaw. The scientists

corrected the defect in the stem cells and grew them into mature blood stem cells, which they then injected into the mouse. It was, essentially, the same kind of procedure used in the hypothetical repair of your damaged heart. And it had the same outcome: The mouse was cured.

This study, published in the journal *Cell*, was “the first proof-of-principle experiment proving that therapeutic cloning can work,” says Jaenisch.

Last summer, Mayo Clinic scientists reported in the *American Journal of Physiology* that they used embryonic stem cells to repair damaged heart tissue in rats.

Obviously, neither mice nor rats are men. Still, “Human cells are no more complex than mouse cells,” says Lawrence Goldstein, a professor of cellular and molecular medicine at the University of California, San Diego. “It’s like a Cadillac versus a Volkswagen.

The parts don’t necessarily go in the same places, but the principles are the same.”

But figuring out which “parts” go where requires a steep learning curve.

“We know a tremendous amount about mouse embryonic stem cells and how to culture and differentiate them,” says Daley, now a professor at Harvard Medical School. “But for

## [HOW THERAPEUTIC CLONING MIGHT WORK]

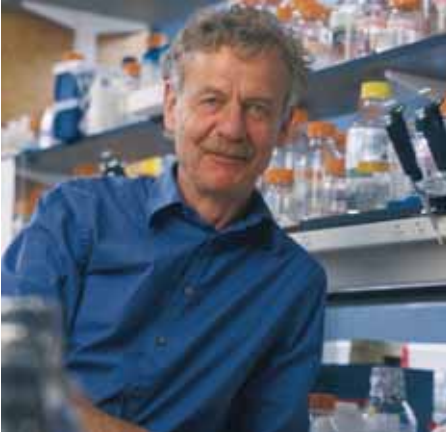
Although scientists have achieved some preliminary success in mice and rats, therapeutic cloning has not yet been attempted in people. Here is an example of how it might work in a patient who suffers from damaged heart muscle, a condition that often requires a heart transplant. This is just one of many illnesses that researchers hope to one day treat with therapeutic cloning.



SOURCES: GEORGE DALEY AND KONRAD HOCHEDLINGER GRAPHIC: CHRISTINA ULLMAN

now, our understanding of how to do the same in human embryonic stem cells is much more primitive. There are issues of cell viability and engraftability that have yet to be explored in greater detail. I’m sure there are challenges that we don’t even know yet.”

Still, researchers have begun to see some success in creating mature tissue from human embryonic stem cells. So far, they’ve derived heart cells called cardiomyocytes, blood precursors (which can become either red or white



blood cells), and certain classes of neurons. Goldstein is using human embryonic stem cells to create Alzheimer's cells. "Our goal is to make human embryonic stem cells that carry the mutations that cause hereditary Alzheimer's disease and use those cells to test hypotheses that we've gotten from animal models of the disease," says Goldstein. Using funding from Howard Hughes Medical Institute allows him to take advantage of human embryonic stem cells outside the limited number approved for federal funding in 2001 by President Bush.

But what about human therapeutic cloning, performing in a person the same kind of procedure Jaenisch and Daley performed in a mouse?

The first—and so far only—breakthrough here occurred earlier this year when Woo Suk Hwang and Shin Yong Moon of Seoul National University reported in the journal *Science* that they had successfully cloned a human blastocyst and removed viable embryonic stem cells from it. Notes Jaenisch, "This paper proves that human therapeutic cloning is possible."

The American Medical Association, the National Academy of Sciences, and such publications as the *New England Journal of Medicine* have issued statements supporting this work, creating the impression that all scientists stand united against those trying to prevent embryonic stem cell research on moral and religious grounds.

But first impressions can be deceiving.

**“Human reproductive cloning would be the conscious and willful creation of a grossly malformed person,” declares Whitehead Founding Member Rudolf Jaenisch. “The very thought of doing it is reprehensible.”**

#### A DISSENTING VOICE

James Sherley is blunt. "I do not subscribe to the majority view at all," the MIT associate professor says. "I'm just one of many scientists who feels this way. Ask yourself, 'What are we destroying?' It really is nonsensical to debate the whole question of when life begins. We know that embryos are alive. With therapeutic cloning, we're talking about destroying one human being for another human being's gain. That's something that we as a society must not do."

This argument essentially is the same as the one posed by the anti-therapeutic-cloning, anti-embryonic-stem-cell research faction: Whether the blastocyst is cloned or taken from a fertility clinic, they claim, acquiring embryonic stem cells destroys a human life. (Jaenisch counters by pointing out that a cloned blastocyst has little, if any, chance of ever developing into a normal baby.)

But Sherley has another problem with this area of research, one that his fellow critics seldom, if ever, mention.

A researcher at MIT's Biological Engineering Division, Sherley works with adult stem cells. Unlike embryonic stem cells, adult stem cells are generally thought to become only the type of tissue from which they've been taken. A familiar example: bone marrow transplants in which the adult stem cells from the donor marrow help the cancer patient. Ideally, a person's own adult stem cells could be used in treatment. A cancer patient could have adult stem cells taken from his blood samples, multiplied in a dish, and administered without any danger of rejection.

Adult stem cell researchers have hit two significant roadblocks: These cells are hard to identify and difficult to grow.

But according to Sherley, embryonic stem cell researchers soon will face the same obstacles.

"You have to ask, 'What do you need in order to produce tissue for long-term replacement therapy?' The answer is, 'You need adult stem cells,'" Sherley says. "If these embryonic stem cell therapies will be successful, they must produce adult stem cells. So these researchers will soon have the same problems that we have. They'll have to figure out ways to locate and then multiply the adult stem cells from the tissue cultures that they created using embryonic stem cells."

Sherley says that mature tissue alone won't suffice for long-term replacement therapy. Even with bone marrow transplants, if the marrow doesn't contain adult stem cells, the procedure fails.

The solution, as he sees it, is to bypass altogether the moral quagmire of experimenting with human blastocysts and focus exclusively on adult stem cells. Besides, "I just can't accept that reproductive clones are unhealthy but stem cells from reproductive clones are fine," he says. "The data aren't convincing."

But many of his fellow scientists aren't persuaded. "The real issue," says Jaenisch, "is that so far, it's impossible to propagate and grow adult stem cells. And adult stem cells haven't been shown to have therapeutic value, except for blood cells."

What's more, Daley notes, not every tissue has adult stem cells. "For the pancreas, the heart, and much of the brain, there does not appear to be active regeneration from adult stem cells. For these tissues, embryonic stem cells are likely to be the best source of replacement cells."

As for the moral question regarding when life begins, “I just spent the other day working with a number of ethicists and philosophers discussing this very issue,” says Goldstein, “and very smart, experienced people with different viewpoints confront the issue differently and arrive at different answers. This sort of debate is a standard thing to happen when we have new technologies that test our conceptions of who we are and what we’re about.”

#### **TOWARD A PUBLIC-POLICY TRAIN WRECK**

In 2002, Bernard Siegel was channel surfing when he stumbled on a press conference in which spokespersons for the UFO cult the Raelians announced that they had cloned the first human baby. Siegel, an attorney, decided that the manner in which the cult members were manipulating this alleged baby was evidence for a child abuse investigation. So, he filed for guardianship.

“Then came the media firestorm,” he says. (Because of this case, the Raelians refused to do a DNA test on the child—who Siegel is certain does not exist.)

Even after the case was dropped, Siegel noticed how the Raelians had affected the world of stem cell research. Rael,

their leader, had testified in a congressional hearing and appeared before the National Academy of Sciences to make his case in favor of human reproductive cloning. Conservatives seized on his testimony and used it as evidence that all forms of cloning—including therapeutic cloning—should be banned.

“There was no single, unified group of scientists that could answer to this,” says Siegel. And so he founded the Genetics Policy Institute (GPI), a Coral Gables, Florida-based science advocacy group whose membership includes many top stem cell researchers.

This fall will mark the first real test of the group’s effectiveness.

Toward the end of this year, delegates with the United Nations will renew a debate on two competing treaties that were tabled last year. The first, the Costa Rican treaty—which is supported by the U.S.—bans all forms of cloning, including therapeutic. The second, the Belgium treaty, would allow therapeutic cloning while banning the procedure for reproduction.

It is too early to tell how the vote will go. If delegates adopted the Costa Rican treaty, “it would cast a pall on

says Siegel. Coming to a head are the U.N. vote, a U.S. presidential election in which embryonic stem cell research has been a key issue, and a California initiative that would provide up to \$295 million annually for embryonic stem cell research. “These will all, in one fell swoop, influence the landscape of stem cell research,” he says.

Meanwhile, both scientists and the public must be patient. It will be many years before we see whether therapeutic cloning will ever treat, for example, “your” heart muscle. And there still is the possibility that researchers will find ways to cure myriad diseases in mice and rats, yet never apply those techniques successfully in people. Until someone does, in fact, make the transition to humans, the debate will rage on, forcing scientists to work under a cloud of public controversy.

But researchers push forward, confident that this field eventually will deliver on some of its promises.

Goldstein, for one, is optimistic that his efforts one day will yield treatments to rid the body of cancer, diabetes, and other ailments. “Sure, it’s possible for this to be a huge failure, but I don’t see that,” he predicts. “The science and the

**“With therapeutic cloning, we’re talking about destroying one human being for another human being’s gain,” maintains MIT biologist James Sherley. “That’s something that we as a society must not do.”**

the research, declaring it an affront to human dignity and morally reproachable,” Siegel says. But what he fears most is that it would breathe life in the Brownback Bill, a bill authored by United States senator Sam Brownback (R-Kan.), that proposes to make the very process of nuclear transfer with human cells a criminal offense, punishable with mandatory jail time for any scientist who attempts it.

This fall, “we’re heading straight toward a public-policy train wreck,”

data are sound enough so that a guy like me, who’s done this for 25 years and has a reasonably good scientific track record, is willing to put substantial resources and energy into this. I’m willing to take risks, but I wouldn’t do this if I thought there was a high likelihood it would fail.”

[For more information about cloning, visit Whitehead’s On Topic resource at [www.wi.mit.edu/news/ontopic/cloning.html](http://www.wi.mit.edu/news/ontopic/cloning.html).]



MARK OSTOW

# Battle over biodefense

As the U.S. pumps billions into research on everything from anthrax and plague to military biohazard suits, what's the effect on our science—and our security?

BY BARTON REPERT

Like a proud father who puts his first-born on display for family and friends, Alan Cross shows off his new infectious-diseases laboratory with flourish. The 7,000-square-foot lab is equipped with highly sensitive alarm systems, special ventilation hoods, decontamination showers, a hacker-proof computer system, and a variety of other trappings that give rich meaning to the phrase “state of the art.”

The \$2 million facility at the University of Maryland School of Medicine in Baltimore soon will be home to researchers studying anthrax, tularemia, and other potential bioterrorist pathogens. So, it follows that the lab would be equipped with a little more than run-of-the-mill safety systems.



“The biosafety efforts are extraordinary,” says Cross, an affable, engaging researcher who enjoys discussing his work. A professor of medicine affiliated with the school’s Center for Vaccine Development, Cross was an infectious-diseases scientist for many years with the United States Army before going into academic research.

The design and equipment for the Maryland lab must be approved by federal authorities—a safety precaution that was put into place following the 2001 anthrax attacks, which left five people dead, sent another 17 to the hospital, and forced some 30,000 to take prophylactic antibiotics. The government also mandates strict screening and registration procedures

for all personnel with access to dangerous biological agents.

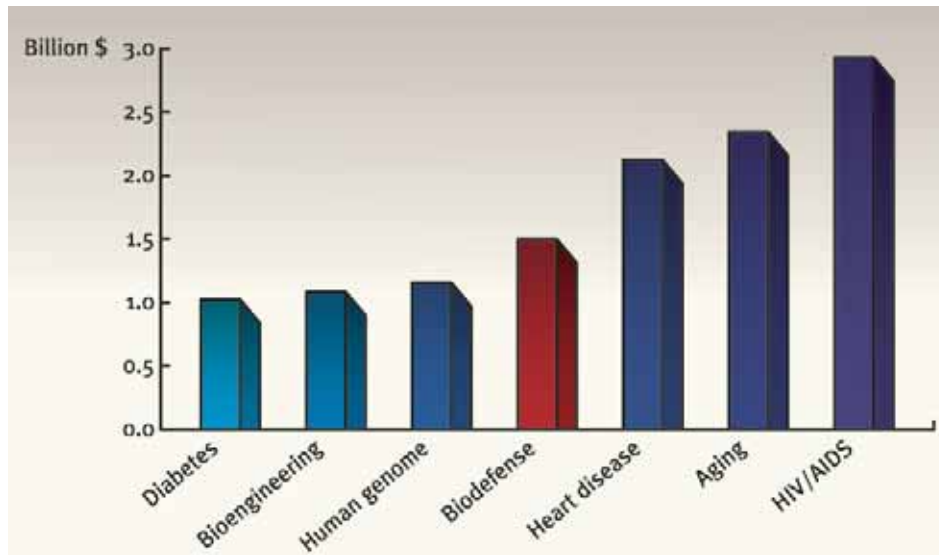
This scrutiny has led to the advanced safety systems that outfit Cross’s new lab: an independent ventilation system in each of the seven workrooms to prevent leakage of airborne microbes; electronic locking systems on every freezer housing test specimens; and monitoring systems that track the number of times that specimens are removed from the freezer—and who removed them.

The health sciences building that houses the laboratory was opened in May 2003, but Cross and his colleagues still are awaiting the official go-ahead from the Centers for Disease

Control and Prevention to begin working in the facility. “And after they review all the safety features of the facility, and also check the qualifications of each of the investigators—taking months and months and months—then the next level is the FBI,” Cross says. “The FBI investigates every single person who is on that application.”

Built with a construction grant from the National Institute of Allergy and Infectious Diseases (NIAID for short), the Baltimore lab represents a relatively modest component of an ambitious, heavily funded federal effort intended to build up counter-measures against bioterrorism and





### Biodefense joins the big players:

The National Institutes of Health will spend about \$1.5 billion on biodefense research in fiscal year 2005, up from only \$53 million four years ago. Here's how that funding compares to selected other major NIH programs. Total annual U.S. civilian spending on biodefense is now estimated at \$7.6 billion.

biological warfare agents, as well as naturally occurring pathogens.

Despite vocal criticism from some quarters of the scientific community and organized opposition by citizen activist groups, the government is moving ahead with plans to construct at least 11 new high-security infectious-disease laboratory buildings at universities across the country, and to pump out funds for biodefense research involving eight consortia of universities and other institutions.

NIAID's spending on biodefense now exceeds the support it provides for HIV/AIDS research, which previously was the biggest item in the institute's budget. (NIAID makes up about half of total National Institutes of Health spending on the disease.)

Government officials and other proponents of the new labs say they are badly needed to deal with incidents such as the anthrax letter episodes. Supporters also argue that the biodefense effort serves to guard against the specter of large-scale bioterrorist or state-sponsored biological warfare attacks against the United States.

Critics, however, contend that the civilian biodefense program—involving NIAID and the CDC, along with the Department of Homeland Security and other federal agencies—amounts to a politically motivated overreaction to a

relatively limited threat. In addition, they charge, the rapidly ramped-up biodefense effort is putting significant pressure on federal funding for other areas of biomedical research.

Their complaints aren't falling on deaf ears. Strong local opposition factored into NIAID's decision last year not to build an infectious-diseases lab complex at the University of California, Davis. Vocal criticism from community groups and scientists may succeed in delaying, scaling back, or possibly stopping construction of a similar facility planned for Boston University.

Only a major policy change will alter the government's plans for a significant expansion in the nation's biodefense research infrastructure. Still, the battle over biodefense is far from over.

### BUILDING UP, AND UP

President Bush has singled out bioterrorism as a "real threat" on more than one occasion. "Armed with a single vial of a biological agent ... small groups of fanatics, or failing states, could gain the power to threaten great nations, threaten the world peace," Bush told senior military officials at the National Defense University in Washington, D.C., earlier this year. "We must confront the danger with open eyes and unbending purpose." This "unbending purpose" will not be cheap. A study by University of Pittsburgh biosecurity analyst Ari

Schuler, published this summer in the journal *Biosecurity and Bioterrorism*, offered a detailed look at federal biodefense spending. The United States has spent about \$14.5 billion on the overall civilian biodefense effort from 2001 to 2004, according to Schuler's study. The president's budget request for 2005 is \$7.6 billion, 18 times higher than the amount budgeted just four years ago. About \$1.7 billion of this is earmarked for biodefense research.

NIAID biodefense research spending jumped from only \$53 million in 2001 to an estimated \$1.4 billion in 2004, and is budgeted to reach nearly \$1.5 billion in 2005. For other civilian agencies, the administration's budgeted biodefense outlays for 2005 include: Department of Homeland Security, \$2.9 billion; CDC, \$1.1 billion; Health Resources and Services Administration (particularly hospital preparedness and infrastructure), \$504 million; Department of Agriculture, \$381 million; Food and Drug Administration, \$246 million; Environmental Protection Agency, \$92 million; and National Science Foundation, \$32 million.

NIAID is funding two large National Biocontainment Laboratories at the Boston University Medical Center and the University of Texas Medical Branch in Galveston, with construction grants of about \$120 million apiece. Annual operating costs for each of these facilities are expected to be about \$70 million.

They'll each include BL-4 labs with the highest biosafety rating assigned by the Centers for Disease Control and Prevention.

BL-1 labs, such as those used by high school biology students and college undergraduates, are for work with microbes not known to cause disease in healthy adult humans. BL-2 applies to work performed with biological agents of moderate potential hazard, such as measles virus and salmonella. BL-3 labs, such as the new facility at the University of Maryland, include those with such pathogens as anthrax, tularemia, and tuberculosis.

BL-4 laboratories, such as those planned for the Boston and Galveston labs, have been described as “submarines inside a bank vault.” Heat, pressure, chemical, and incineration systems housed in the vault area process all liquid and solid wastes completely to render them sterile or safe. High-efficiency filtration removes any airborne material. Researchers wear positive-pressure suits connected to independent air sources through breathing tubes. To prevent possible exposure through punctures to the suits, glass and

most sharp objects are not permitted. Researchers exiting the workspace must go through a multi-stage shower, including a chemical disinfectant cycle, to wipe out any infectious agents.

Along with the two large National Biocontainment Laboratories, nine smaller Regional Biocontainment Laboratories with BL-2 and BL-3 labs are planned at universities around the country, with federal construction grants of between \$7 million and \$21 million each. In addition, NIAID is supporting the establishment of eight Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research, involving consortia of universities and other institutions.

The University of Maryland School of Medicine, home to Cross’s lab, is lead institution for one of these centers. Federal grants for these centers total about \$350 million over five years.

Aside from such biodefense research initiatives, the Bush administration’s “Project BioShield” involves large-scale government outlays to procure and stockpile vaccines and drugs to cope with anthrax, smallpox and other pathogens, and to set up a national network of sensors for potential bioterror agents.

#### **BIGGER PROGRAMS, BIGGER RISKS?**

Officials emphasize that all these initiatives are strictly defensive measures.

## LIFE IN A BL-4 BLUE SUIT

When Bobbie Rae Erickson goes to work in the morning, she deals with a dress code that few nine-to-fivers would accept. But most of us don’t earn a living tinkering with Ebola virus.

In high school, Erickson read *The Hot Zone*, a thriller by Richard Preston about an onslaught of Ebola in the United States, and became fascinated with the world of dangerous viruses. Now, she’s a microbiologist at one of the Centers for Disease Control and Prevention’s BL-4 labs in Atlanta, Georgia—facilities that also study anthrax, smallpox, and bubonic plague, to name a few.

When Erickson arrives at the “office,” she first needs to make sure that she has all her supplies, since once she’s in the lab, it’s too late to realize she’s short one pipette. Next she changes into scrubs, just like a surgeon.

Then comes the blue suit (shown here on another researcher). This maximum-containment attire is made from chlorinated polyethylene and feels like thick Saran wrap. The suit covers her entire body except her hands. These she protects with a pair of latex gloves and a pair of thick rubber gloves, both attached to the suit with duct tape.

Next Erickson checks her air regulator, a small silver box attached to her waist. Now she’s ready to go to work.

She enters the lab and makes her way to the bench. She reaches up and grabs one of the air hoses hanging from the ceiling. When she plugs it into the side of her suit, a high-pitched whistling sound assaults her ears. That air keeps the suit positively pressured, and it’s why all BL-4 workers wear ear plugs. To speak with her lab neighbor, or to talk on the phone, she needs to unplug the air hose and yell.

Getting out of the suit takes almost a half-hour. For this, she first takes a chemical Lysol shower while wearing the suit, followed by a thorough personal shower. Only then may she leave the lab area.

What if, while working at the bench, she suddenly needs to use the restroom? “Simple,” Erickson says. “I don’t. If I know I’ll be spending four hours in the lab, I just won’t drink anything that morning.”

— David Cameron



The United States renounced biological weapons during the Nixon administration. But some critics of the biodefense program contend that it might lay the groundwork for reconstituting a bioweapons capability. This is partly because research at the infectious-disease labs could be turned to developing more virulent, genetically engineering, drug- and vaccine-resistant strains of pathogens.

“The intent, or at least the expressed intent, of the U.S. bioweapons agent program is defensive,” says Richard Ebright, a professor of chemistry and chemical biology at Rutgers University in Piscataway, New Jersey. “However, in practice, this is a de facto offensive bioweapons agent program. It has all the characteristics, all the properties. The scale is larger, in terms of dollar volume and also in terms of research personnel, than the Soviet offensive bioweapons program.”

**“IN PART, THE CURRENT RESPONSE IS ONE THAT IS  
DICTATED BY POLITICAL REASONS RATHER THAN  
SCIENTIFIC REASONS.” – STANLEY FALKOW**

Ebright, a laboratory director at the university’s Waksman Institute of Microbiology, is one of the most outspoken critics of the biodefense program. He worries that the biodefense effort will lead to an unnecessary excess of infectious-disease lab space and increase the risk of an intentional or accidental release of a deadly pathogen.

In addition to the new BL-4 facilities at the new National Biocontainment Laboratories in Boston and Galveston, Ebright notes that construction on other high-risk labs is planned in Hamilton, Montana, at the NIAID Rocky Mountain Laboratory; in Fort Detrick, Maryland, with new labs there for the Defense Department, NIAID, and the Department of Homeland Security; and also in Atlanta, Georgia, for the CDC.

According to Ebright, this new BL-4 space will amount to between 200,000 and 300,000 square feet—10 to 15 times more than the amount of similar lab space being operated in 2001.

These concerns are heightened by the number of research personnel now approved for work with anthrax, plague, and other “select agents.” The CDC has inspected and fully certified 235 facilities and given provisional approval to 82 more, a spokesperson says. An official at the FBI’s Criminal Justice Information Services Division says the bureau has processed about 12,000 applications to work with such agents.

Research on potentially dangerous organisms “isn’t just going on unfettered and unmonitored,” emphasizes Gerald Fink, Whitehead Founding Member and chair of the National Academies Committee on Research

Standards and Practices to Prevent the Destructive Application of Biotechnology. “The government is setting up a system to review it. Of course, the devil is in the details.”

As Fink’s committee advised last year, the government is establishing a National Science Advisory Board for Biosecurity. Managed by NIH, the new board is described as a critical component of a set of federal initiatives to promote biosecurity. It will provide security guidance and leadership about dual-use bioresearch (studies with legitimate scientific purpose that may be misused to pose a biological threat).

**DRAINING THE FUNDING POOL?**

Ebright and other opponents of the biodefense effort say that it will end up siphoning away federal support for basic scientific studies in other biomedical areas that affect the health of

tens of millions of people. “There’s a tremendous waste of funding,” declares Ebright.

Since 2001, Ebright says, biodefense has seen the largest targeted increase in any research area at an NIH institute in the history of NIH—higher growth than the buildups for the War on Cancer and for HIV/AIDS. “No agency at NIH can absorb a targeted increase of that magnitude without effectively eliminating peer review,” he maintains.

Other scientists, such as world-renowned microbiologist Stanley Falkow at Stanford University, also worry that this strategy could cut funding for other disease studies.

“It’s going to be done at the expense of some organisms that are causing serious health problems in the United States but are not getting the same emphasis, like drug-resistant staphylococci, pneumococci, and the like,” says Falkow. “There’s a need to be vigilant about biodefense, without any question,” he adds. “On the other hand, I think, in part, the current response is one that is dictated by political reasons rather than scientific reasons.”

“I don’t think anybody would argue that biodefense isn’t important, and certainly we learned that with the anthrax thing and 9/11. But we still have 1,500 people or thereabouts a day dying from cancer,” says Wendy Selig, vice president for legislative affairs at the American Cancer Society. “Pressure on the budget, forcing these arbitrary ceilings on spending, is causing very difficult choices.”

One potential indicator of this stress: Following a five-year period in which funding for the National Cancer Institute jumped by 81 percent, the institute received only a 3.9 percent increase in 2004.

**DOING DOUBLE DUTY**

NIAID chief Anthony Fauci, a key architect of the current biodefense effort, flatly denies that politics are driving research or that the program has reduced allocations for other areas of biomedical research. “It is brand

## BANNED IN BOSTON?

For Mark Klempner, the infectious-diseases facility planned for Boston University Medical Center is “a dream come true.” But for some local citizen activists and scientists, the big lab isn’t a dream but a nightmare—right in the middle of Boston’s densely populated South End.

As currently planned, the National Emerging Infectious Diseases Laboratories will be located in a nine-story building with 223,000 square feet of space, about a fifth larger than Whitehead’s headquarters. Housing research on anthrax, plague, and other dangerous disease agents, the \$178 million structure will be among the most “cautiously designed and onstructed types of buildings in the world,” Boston University officials stress. It will hold its own ventilation, electrical, decontamination, and waste disposal systems plus a state-of-the-art security system.

And the lab will aim purely at advancing basic science, says Klempner, shown here at the proposed site. “Emerging infectious diseases are one of the highest-priority areas for research around the world,” he says. “This is money incredibly well spent.”

But the plan upsets many in the Boston community. In September 2003, the citizen action group Alternatives for Community & Environment (or ACE) served notice that it was bringing suit against the project for “flagrant viola-

new money,” he insists. “It wasn’t money that was moved around from one research direction to another.” Fauci also emphasizes that the research being supported is dual-purpose.

“Because of the threat of bioterror on this nation, we need to be prepared from the standpoint of understanding the microbes that could be used and developing countermeasures, which is probably the most important

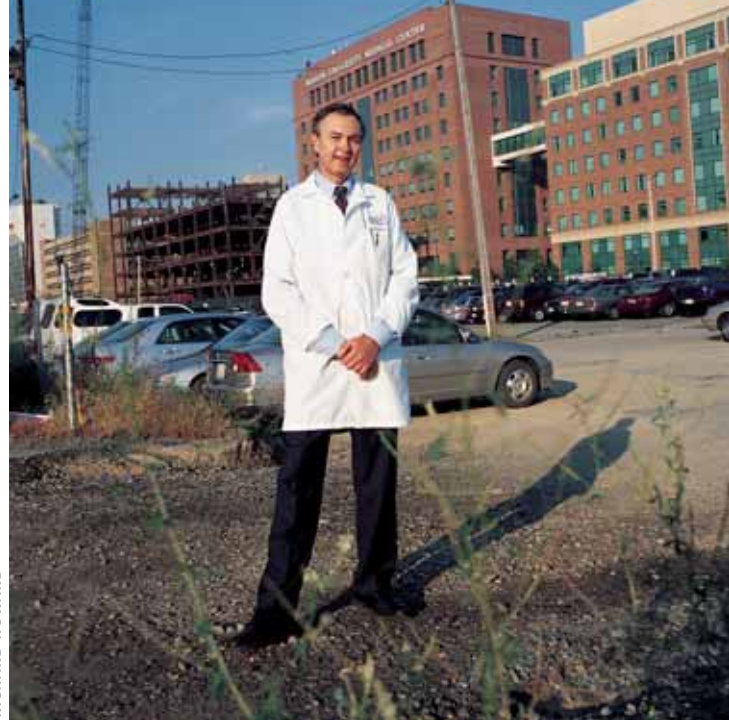
tions” of the Massachusetts Environmental Policy Act. In March of this year, ACE and another community group, Safety Net, sent a letter to the National Institutes of Health detailing a series of environmental and safety objections to the planned new biodefense lab. They argued that the facility “would likely constitute an appealing terrorist target because the pathogens located inside could be used for bioweapons and could decimate large human population centers.”

Some scientists in the Boston metropolitan area also vigorously oppose the project, among them David Ozonoff, a professor of environmental health at Boston University School of Public Health. Although Ozonoff initially supported the facility, he changed his mind. “I became convinced that it was not serving the public health agenda,” he says, adding that he believes the project is “part of a process that was harming public health.”

“We have been very clear that this is entirely about public health-related matters,” Klempner responds. “All of the research will be public health-related, and there won’t be any that will be related to weapons in any way.”

component of the research,” he says. But he maintains that programs to study naturally occurring infectious diseases also will play a significant role.

“In fact, a naturally evolving catastrophic epidemic is incredibly more likely than a deliberately released one,” Fauci says. “The intellectual capital, the resources, the amount of effort you put into understanding the natural evolution of microbes is



RICHARD HOWARD

“We’re trying to provide as much detailed information as possible about the safety and environmental impact of this laboratory,” he adds.

If the university fares well in regulatory processes, groundbreaking could come by next summer.

– Barton Reppert

absolutely complementary to work that’s done on trying to develop countermeasures for deliberately released microbes,” he emphasizes.

Infectious-disease specialist Cross agrees, saying that the biodefense program is spinning off some very good basic science, pointing to advances such as sequencing the whole genome of the anthrax bacillus. “We have a whole new database to work with,” he says. “We have a whole new concept of how toxins work.”

Additionally, the University of Maryland researcher says he isn’t particularly concerned about the possibility of draining down money for other fields of research. “Obviously, there is a limited pot,” he acknowledges. “Some choices will have to be made.”

# VISA

# DENIED

BY RICHARD SALTUS

## Tighter visa restrictions are making it harder for foreign researchers to work in the United States. What's the effect on science—and scientists?



As with many things that go terribly wrong, it began with a simple plan.

Elena Casacuberta and her husband, Joan Roig, postdoctoral researchers in biology labs at the Massachusetts Institute of Technology and Harvard University, respectively, flew to Barcelona in December 2003 for a three-week holiday visit with their families. At the same time, they would dutifully renew, at the United States embassy in Madrid, their one-year visas allowing them to work and study in America. Then, they'd jet back to Boston and resume their busy lives.

Casacuberta, in the United States since 2000, and Roig, since 1998, customarily traveled to Spain once a year. On past visits, the renewals had gone

smoothly, despite the drastically intensified security measures and new layers of visa application requirements prompted by the terror attacks of September 11, 2001.

### NOT THIS TIME

Embassy officials told the pair that because their common occupation—"molecular biologist"—appeared on a classified Technology Alert List, their passports and visa applications would be held while Washington agencies ran their names through an extensive background check known as "Visas Mantis." The delay, they were told, would be about six weeks.

"I tried to explain my work, but the guy had never heard of *Drosophila*, and he knew nothing about biology,"

recounts Casacuberta, who studies fruit fly chromosomes. "I don't know how they could assess whether or not I was potentially dangerous."

Before 9/11, Visas Mantis security reviews in response to occupations on the Technology Alert List were conducted at a rate of about 1,000 annually. Today, there are about 20,000 a year. Established during the Cold War, the list now contains many broad fields potentially related to terrorism such as biochemistry, genetic engineering, artificial intelligence, architecture, and urban land-use planning.

For Roig, who does basic research on the cell cycle at Massachusetts General Hospital, the wait stretched from six to nine weeks. "These are lives of real



people they are playing with,” he says, with more than a tinge of bitterness. “They should be able to pay somebody to know what [occupation] is dangerous and what’s not.”

When Roig finally arrived home, the couple’s names had been removed from the mailbox at their apartment. He did what he could to resume a normal schedule in Boston, and began waiting for his wife. It would be a long wait.

#### SCIENTISTS NEEDED

Today, the proportion of non-U.S. science students and scholars in the U.S. is at an historic high. Nearly 60 percent of postdoctoral researchers and almost 50 percent of doctoral staff at the National Institutes of Health are

foreign nationals. At MIT, 36 percent of graduate students are non-U.S. citizens.

The international influx has helped shore up this nation’s scientific and engineering workforce, whose oldest contingent, *Sputnik*-inspired baby boomers, is near retirement. From where do their replacements come? Fewer and fewer hail from the ranks of American students, who in recent years have tended to shun fields like science in favor of the perceived quicker rewards in business.

Given the nation’s reliance on international intellect, there couldn’t be a worse time for foreign students and scholars to feel unwelcome in America. Yet there’s a rising tide of resentment

and frustration as international students and scientists find the new, daunting homeland security restrictions to be barriers to entering the United States, and sometimes just as much a problem when trying to return after a short trip abroad to attend a scientific conference or visit family.

Just ask Casacuberta. Months after her husband returned to Boston, the MIT researcher remained in a bureaucratic limbo. Feeling like a character in a Kafka novel, she called Madrid every day, and every day was told, “nothing yet,” or “sorry, we have no information.” Prior to 9/11, a visitor undergoing Visas Mantis checks was waved through if nothing had been heard back within two weeks. Now, the embassy must wait for a positive

report from the security check, no matter how long it takes. Much to her frustration, all Casacuberta could do was wait.

### HELP OR HINDRANCE?

No one in the research community disputes the need for heightened security around foreign visitors and access to technology that could be useful to terrorists. After all, the pilot who flew a hijacked plane into the Pentagon on 9/11 entered the U.S. on a student visa.

But many see the rush to implement widespread and often inefficient security systems as an overreaction, resulting in unintended but aggravating problems for legitimate foreign researchers. Overall, the new systems “have been a major hindrance to the flow of international knowledge,” according to a statement by the National Academy of Sciences.

Many complaints involve the Student Exchange Visitor Information System, SEVIS for short. Rushed into service by the Department of Homeland Security in response to the terror attacks, it is designed to track the comings and goings of about 800,000 foreign students a year, whose names must be placed in the SEVIS database.

That database “is full of glitches and problems,” says Marjory Gooding, director of international offices at the California Institute of Technology. Caltech also suffers disproportionately from visa snags with the State Department because of its heavy concentration in technology, she adds.

As Casacuberta waited in Barcelona, she was forced to move between the homes of her parents and her husband’s parents. For a while, she used a small bit of lab space in the office of her brother, also a scientist. She wondered if she should have some of her research materials sent to her in Spain. She spent time appealing by fax and mail to U.S. officials in Madrid, to her congressman, and to Senator Edward Kennedy (D-Mass.).

She missed her husband of three years. She turned to technology to maintain

her ties to the states, relying on e-mail and instant messaging. There was always the phone, but the six-hour time difference between Barcelona and Boston was a hindrance.

Misunderstandings crept into e-mails with her two undergraduate students as she tried to direct them from afar. Finally, others in her lab had to step in to help the students. “And for my own work, the wait was quite bad,” she says. In a competitive endeavor like science, says Casacuberta, a loss of several months can be critical. The publication of a paper on her chromosome project will be delayed, for example. The scientist who heads the lab in which Casacuberta works, Mary Lou Pardue, was affected. “Indirectly, the objectives for the NIH grant of Professor Pardue have been delayed, too,” Casacuberta says. “That will show up in this year’s report.”

Pardue remained supportive, as did Roig’s supervisor at Harvard. “They were really supportive all the time, trying to keep us motivated and calming us down,” Casacuberta says. “It’s because of them I was able to hold on so long and not give up my job.”

### TWEAKING THE SYSTEM

Among the most galling consequences of the new regulations, according to Gooding at Caltech, is that some foreign scientists who visit U.S. collaborators frequently “get checked every single year,” and some of them “get backed up for six or eight months because of this.”

For example, a research director with the Institute of Applied Physics of the Russian Academy of Science complained to the NAS that he had applied for a multiple-entry visa in January 2004 and had received no response by late July. This was a man who had visited the U.S. several times a year since 1991. In the new security climate, he says, “huge delays and uncertainty in getting United States visas [make it] impossible to set concrete plans” for longtime international research collaborations with the United States. In August, the scientist reported that he finally got his visa—



but only for a one-time entry. Federal agencies are not deaf to the criticism and complaints. They have taken a variety of steps to tweak and streamline communication among departments—chiefly State, Homeland Security, and Justice (the FBI).

Asa Hutchinson, undersecretary for border and transportation security in the Department of Homeland Security, told a hearing of the House Committee on Science last February that the SEVIS response team, since its formation in August 2003, had



MARK OSTOW

**Stop signs:** Elena Casacuberta and Joan Roig planned a quick trip home.

smoothed the way for 8,000 foreign students and scholars entangled in SEVIS delays. At the same time, he pointed out, “We identified over 200 individuals posing as foreign students, and when we called their academic institutions, they hadn’t heard of them. These individuals were denied entry into our country.”

In September, the Department of Homeland Security disclosed plans to extend security clearances beyond a year for foreign students and scientists.

The logjam may be easing, say observers, but problems remain. A report by the Government Accountability Office found that at American consulates abroad, visa applications requiring security checks were delayed for an average of 67 days.

At the National Academy of Sciences, Wendy White says her office on international programs has fielded 2,000 appeals from students and researchers tangled in visa bureaucracy. “Up to a few months ago, our average wait time was five to six months,” she says. “Now we’re down to two and three months.”

That’s still too long, argue student and educational organizations, which call for more improvements in the system.

One tangible effort in that direction is a bill introduced by U.S. representative Michael Capuano (D-Mass.). The bill, cosponsored by Congressman Don Manzullo (R-Ill.), would streamline the Visas Mantis process in several ways. Among the provisions: refining the Technology Alert List; improving information-sharing among the FBI and Departments of State and Homeland Security; making security clearance good for three years instead of one; and allowing those who are cleared to have multiple-entry visas.

In all likelihood, it seems the post-9/11 visa process will become somewhat more rational, flexible, and easier to navigate through legislation, if not negotiation. But the hurdles will remain higher than before.

One foreboding prospect, say American educators and professional-society officials, is that many foreigners will opt for training in their own countries or apply for welcoming spots in Australia, the United Kingdom, and Europe, countries only too happy to accommodate them.

“We risk losing some of our most talented scientists and compromising our country’s position at the forefront of technology innovation,” Harvard president Lawrence Summers warned in letters he fired off last April to Secretary of State Colin Powell and Secretary of Homeland Security Tom Ridge. Summers pointed to a survey last spring showing that foreign applications for graduate study dropped by one-third at 113 U.S. institutions.

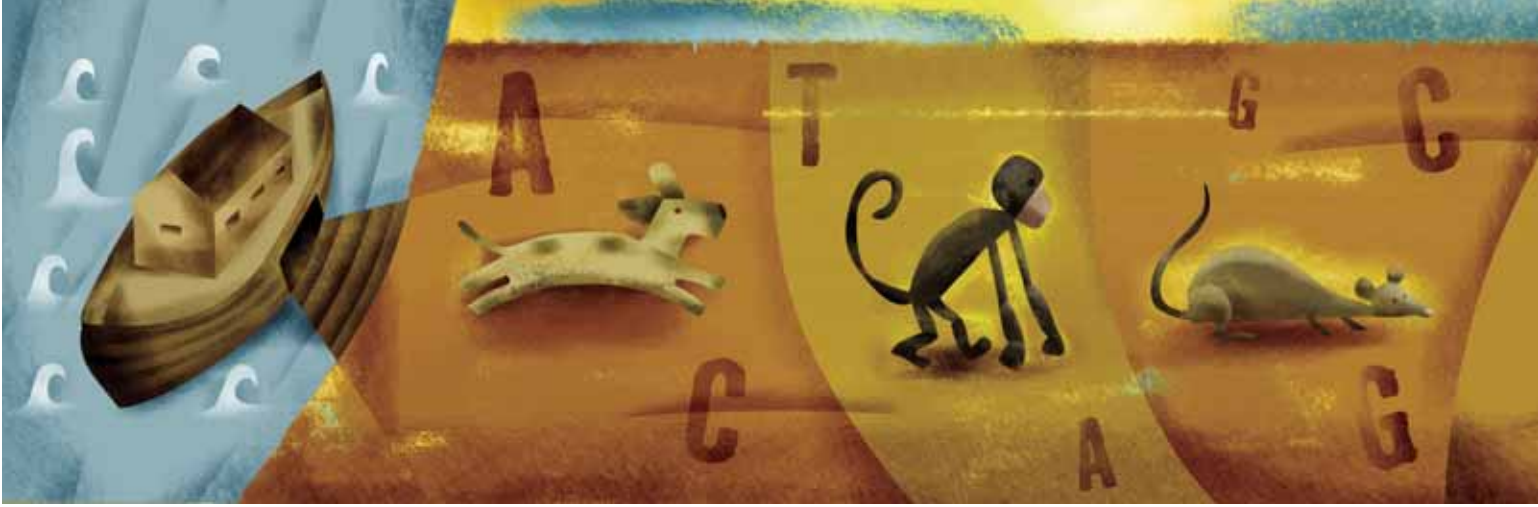
The situation is “extremely complex,” says White at the National Academy of Sciences. As universities in many countries are becoming more competitive with those in the United States, she says, they create more incentives for students to stay closer to home. “We don’t know how many people are choosing not to come to the U.S., and for what reasons,” says White.

“Are we just seeing a little blip on the radar screen here, a failure to get a certain number of students here in 2004? Or is this a generational thing?” White asks. “If so, you’re turning a lot of students to other countries, and it’s going to be hard to get them back.”

And what of the international students already here? If America is to maintain its scientific prowess, some must stay in the U.S. to pursue their professional careers.

Casacuberta and Roig won’t be staying. It took five months for Casacuberta to get her visa stamp. When she finally made it back to her lab at MIT, it took her nearly two months to catch up on the backlog that accumulated during her absence. “Even to look into a refrigerator and remember which tube you had been working with five months ago was hard—and I’m an organized person,” she says.

Casacuberta and her husband plan to look for work in Spain soon, as they had planned from the beginning. “I was always the one saying, ‘Maybe we shouldn’t leave America,’” she says. “Now, I don’t say that anymore.”



# The Genome Club

THE LIST OF MAMMALS  
WITH NEWLY GENERATED  
GENETIC MAPS IS  
GROWING FAST

BY ERIC BENDER

This is the Year of the Rat. It's also the Year of the Dog and the Opossum. Next year will be the Year of the Cow, the Rhesus Macaque, and maybe a few other assorted creatures with hot blood and fur.

They're all joining humans, mice, and chimpanzees in the exclusive club of mammals whose whole genome has been sequenced—giving complete and matching sets of each animal's DNA, and offering researchers the opportunity to rebuild biology and medicine from the ground up.

The technology yielding this treasure works by deciphering an organism's genetic code, which is held in its chromosomes in DNA "base pairs" that combine adenine and thymine or cytosine and guanine (commonly referred

to with the letters A, T, C, and G). Mammals have about three billion base pairs. Scientists tackle the intimidating task of reading them all in exactly the right order with an entirely counter-intuitive approach.

"If you think of the genome as an encyclopedia, you break up the whole encyclopedia and get lots of strings of letters. You then try to put the strings together like a puzzle," notes Kerstin Lindblad-Toh, codirector of the Genome Sequencing and Analysis Program at the Broad Institute in Cambridge, Massachusetts.

Scientists separate DNA fragments, read them, then reassemble them using supercomputers and some very, very clever programming. The researchers then repeat the process over and over to make sure they've created the most accurate genetic map possible. While this is a Herculean task, the efficiency and volume of current sequencing techniques "have surpassed everybody's wildest dreams," comments George Weinstock, codirector of the Human Genome Sequencing Center at Baylor College in Houston.

The resulting mammalian DNA "parts lists" give an effect greater than the sum of their parts, says Jane Peterson, associate director of the National Human Genome Research Institute's Division of Extramural Research.

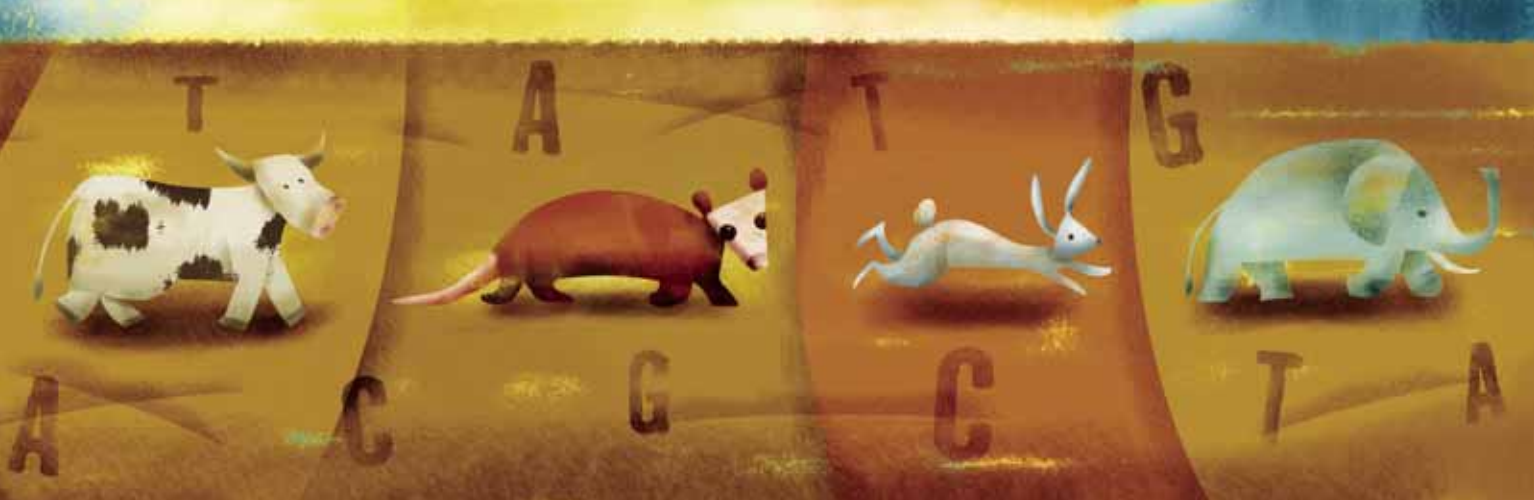
These projects are opening the floodgates not just for understanding individual organisms, but for comparative genomics studies, revealing what genetic material is conserved over time, and how these genomes relate to each other—and to humans.

"It's important to understand how this effort relates to human health," Peterson emphasizes. "The sequenced assembly of genes at different evolutionary distances starts to give clues as to what's important in the human genome and even why it's important. This really is the major tool for improving understanding of the human genome."

## Mammals on the march

While organisms from yeast on up are being sequenced in large numbers, scientists are particularly interested in mapping mammalian genomes—especially those mammals employed as biological research models.

Given its lead role in medical studies, "the mouse was a no-brainer" as the national institute picked targets, Peterson remarks. A high-quality draft sequence was published in 2002. Since then, scientists have re-sequenced the mouse over and over and plan to release this final highly polished map in late 2005. The rat, extensively studied in behavioral research and other investigations, was another



BRIAN WILLESE

early choice. A first draft was published this spring. Last December, scientists published the first draft of the chimp genome sequence.

Another critical model organism, the dog, has been under study in two different labs. Man's best friend shares many diseases with humans and even lives in the same environments. Dogs come in wildly diverse breeds, often have well-documented pedigrees and veterinary records, and show different susceptibilities to specific genetic diseases. Last year, The Institute for Genomic Research in Rockville, Maryland, sequenced the genome of a poodle; this July, Broad Institute and partners in the National Human Genome Research Institute completed a much more detailed draft of a boxer.

And it won't end there. Scientists are hard at work to uncover the genomes of other mammals, including the Rhesus macaque monkey (the major primate for biomedical research) and the cow (key not just in agriculture but in studies of everything from cardiovascular disease to reproduction). Also in the works are plans to sequence the gray short-tailed South American opossum, tammar wallaby, African elephant, European common shrew, European hedgehog, guinea pig, lesser hedgehog tenrec, nine-banded armadillo, rabbit, cat, and orangutan. "One of my headaches recently has been *finding* these organisms," Lindblad-Toh says wryly.

#### Reading a map

It's still early days for analyzing the initial wave of mammalian genomes. The first paper on the chimpanzee

whole genome, for instance, isn't expected until late this year or in early 2005. What's more, the mammals don't come two by two. Analyzing male Y chromosomes can be exasperatingly difficult due to the chromosome's intricate makeup, so most sequencing projects examine DNA samples from female animals. To fill in some missing Ys, Whitehead collaborates with Washington University in Saint Louis. For example, the chimp Y should give insight into human male fertility, says Jennifer Hughes, a postdoctoral researcher in the lab of Whitehead Member David Page.

Even within this exclusive club of mammals, not all animals are equal. They get quite different levels of effort and expense, particularly in the number of times their complete DNA is scanned and in the effort made to fill in the trickiest gaps in the genetic code. "It takes much more time to finish a genome than to get the first 95 percent," as Lindblad-Toh puts it.

At one extreme, the mouse will get about the same scrutiny as the human, with each DNA base read at least seven times. At the other, wallaby DNA will be scanned only twice. Scientists in the National Human Genome Research Institute may use this abbreviated approach to sequence most of the other mammals on their to-do list. Some researchers complain the approach will give insufficient data, muddying the waters for interpretation. The pros and cons still are being kicked around, Peterson responds. As they start to decode the draft sequences, she adds, scientists will get a better grip on what will be most efficient.

#### Doggone important

It's no surprise to learn that investigators hail these new cornucopias of data. This year's dog draft is an "enormous step," says Gustavo Aguirre, professor of medical genetics and ophthalmology at the University of Pennsylvania in Philadelphia. "It allows us to now do work that we could only have hoped to do several years ago."

Previously, when Aguirre's lab isolated a protein of interest, the next step was to clone the gene in the lab. Poring through a huge library of physical complementary DNA "might take as long as six months to a year," Aguirre says. Now, the researchers usually can find the gene target by crunching through the dog sequence database.

"We're eternally grateful for it," says Aguirre, "but we're not satisfied."

Fortunately, the advances in sequencing technologies are keeping pace with scientists' demands. "Now a single center can finish a mammalian genome in a year," notes Baylor's Weinstock. "Almost everything of significant value will be sequenced at some level in the next few years."

[ For more information on comparative genomics, visit [www.nhgri.nih.gov/11509542](http://www.nhgri.nih.gov/11509542). ]

## [ LAW OF THE LAND ]

*Treaty will preserve vital plant genetic resources*

Bananas are a staple in most American kitchens. We eat them on cereal, dip them in chocolate, and slice them for peanut butter and banana sandwiches. Unfortunately, this favored yellow fruit faces a widespread fungal threat called ‘black sigatoka.’ Although farmers grow five modern banana varieties for consumption, all share very similar DNA—and all are susceptible to the fungus. If such a fungal attack goes unchecked, bananas could become a thing of the past.

The fruit’s plight is just one example of the importance of sustainable agriculture, scientists say, a movement that has a new ally in the International Treaty on Plant Genetic Resources. Ratified by 55 countries, the treaty finally became law in June.

The accord aims to preserve as much plant genetic material as possible, whether in gene banks or in cultivation. Maintaining a large plant gene pool will ensure that scientists and farmers can access the basic DNA to improve current crops and develop new ones, either by traditional breeding or biotechnology. Should a future climate change, blight, or pest destroy plants that feed entire populations, the agricultural diversity that this new treaty protects will allow farmers to rebound.

According to the United Nations Food and Agriculture Organization, the world’s farmers have developed approximately 10,000 plants for human and livestock consumption over the millennia. Today only 150 different types of crops feed the majority of the world’s population, and only a dozen—including rice, wheat, corn, and potato—account for 80 percent of plant-derived dietary energy. A vast number of crops have succumbed to genetic erosion. Of 7,098 apple varieties documented in the United States between 1804 and 1904, approximately 96 percent no longer exist. The same is true for 95 percent of the different kinds of cabbage, 91 percent of field maize, 94 percent of the pea, and 81 percent of the tomato.

The treaty’s goal is to stop that trend by protecting hundreds of thousands of plant species, including the world’s most important gene bank collections, about 600,000 samples held by the Consultative Group on International Agricultural Research (CGIAR).

The accord’s framework allows plant breeders, farmers, and researchers easier access to plant genes for research and development, simplifying the process and cost of obtaining resources from other countries. Countries that commercialize plants developed within this system will contribute some revenues to a trust fund for the sustainable use of plant genetic resources in developing nations.



“The types and harvested amounts of crops that feed the world today likely will not be sufficient to feed our growing population in the future,” says Allison Mallory, a post-doctoral fellow who studies plant development in the lab of Whitehead Member David Bartel. “The treaty establishes an avenue for sharing the resources that have resulted from decades of plant breeding. It is an invaluable contribution to establishing environmentally sound and sustainable agriculture that will strengthen the world’s economy and help feed our growing population.”

— Jennifer Tomase

## [ CONFLICTING INTERESTS ]

*What dealings are appropriate between NIH scientists and industry?*

A number of high-level National Institutes of Health scientists have received significant money and stock for consulting to drug and biotechnology companies—and that’s a conflict of interest that could seriously damage public trust in the NIH, claims House Energy and Commerce Oversight and Investigations Subcommittee chair James Greenwood (R-Penn.).

After Congress raised this concern last year, NIH director Elias Zerhouni appointed a blue-ribbon panel to investigate ethics policies in his organization. The panel, which presented its report in May, recommended prohibiting NIH senior managers with funding responsibilities from consulting with industry. It also advised improving internal and public disclosure of financial relationships, and teaching supervisors how to review financial disclosures.

## A DRAIN ON THE BRAIN TRUST

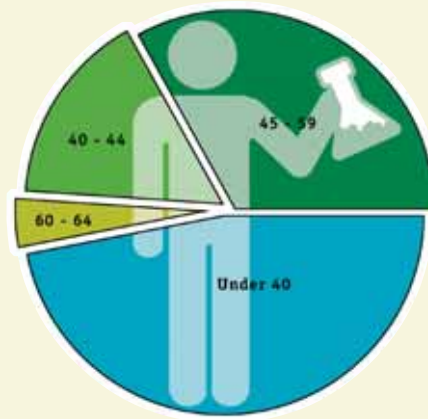
### A NEW REPORT SUGGESTS PROBLEMS AHEAD FOR SCIENCE AND ENGINEERING FIELDS

Much has been done to dispel the myth that the nation's scientific brain trust consists only of men with graying beards and copious collections of tweed jackets. A recent report suggests that at least part of that description is true. Although women, minorities, and young researchers represent a vital contingent of the nation's scientific and engineering workforce, the study found that scientific leadership in the United States actually *is* graying around the temples.

According to the 2004 Science and Engineering Indicators, a report published annually by the National Science Foundation, 53 percent of all science and engineering degree holders in the United States are age 40 or older. Furthermore, the 40 to 44 age group, which accounts for nearly 16 percent of all degree holders, is nearly four times as large as the 60 to 64 age group, a figure that suggests that the number of retirees leaving the workforce will dramatically increase in the coming decades.

More troubling is the unimpressive rate at which scientific veterans are being succeeded by younger recruits.

Although the number of students enrolled in American universities has risen steadily, the number of those attaining science and engineering degrees has risen only slightly—and in the cases of engineering and math, decreased. The report attributes the disparity between the rising



**Well-aged:** A National Science Foundation study found that 53 percent of all science and engineering degree holders in the U.S. are age 40 or older.

ranks of college-educated Americans and the number of those entering science and engineering to increased enrollment among minority students—groups that remain underrepresented in science and engineering.

To make matters worse, chides the report, post-9/11 restrictions are reducing the number of foreign-born scientists entering the workforce, many of whom come to this country early in their careers.

In an accompanying report, the National Science Board warned that reversing these trends could take upwards of 20 years. According to report authors, the students entering the science and engineering workforce in 2004 decided to take the necessary math courses to enable this career path when they were in middle school. Students making those same decisions today won't complete advanced training until 2018.

— Melissa Withers

“We are severely restricting the ability of NIH employees to consult with industry,” Zerhouni testified before the Oversight and Investigations Subcommittee in June. He added, however, that “I do not want to discourage the kind of intellectual excitement and curiosity that leads our scientists to want to work with industry. I am working to strike a careful balance—whereby those individuals in key decision-making positions will be prevented completely from consulting, while stringent limits will apply to other employees.”

Concerns remain despite the NIH report, due partly to financial information compiled by the subcommittee on deals made over the last five years. “Information received from the drug companies has revealed a significant number of troubling discrepancies,” Greenwood noted in June. “So far, the committee staff has identified about 100 situations in which the drug company reported a consulting agreement but the NIH did not include the agreement in the data given to the committee. This is especially disturb-

ing given that the committee sent request letters only to the 20 companies that had the most agreements out of the hundreds of companies on the NIH lists.”

Also in June, the House Energy and Commerce Committee broadened its ethics investigation when it requested that 15 other federal agencies—among them the Environmental Protection Agency, the Food and Drug Administration, and the Departments of Commerce, Energy, and Health and Human Services—disclose their employees' awards, contracts, and other agreements with outside organizations.

“We hope that the disturbing practices discovered at NIH are not commonplace in our government, but we mean to discern the facts in a thoughtful and expedient manner,” said House Energy and Commerce Committee chair Joe Barton (R-Texas).

In September, NIH officials disclosed they were contemplating a one-year agency-wide moratorium on outside consulting.

— Jennifer Tomase

## [HOW RNA INTERFERENCE WORKS]

Often hailed as the most powerful new biochemical tool in decades, RNA interference was first demonstrated in animals in the *C. elegans* worm in 1998 and is now cited in thousands of scientific papers. The process selectively disables gene expression by attacking the messenger RNA created by a specific gene — without destroying the gene itself. RNAi naturally occurs in a wide range of organisms, and its roles are studied by Whitehead Member David Bartel and many other investigators (see next page).

RNAi begins with double-stranded RNA, which is sliced into short interfering RNAs (siRNAs). Integrated into RNA-inducing silencing

complexes (RISCs), the siRNAs then attach to complementary messenger RNA molecules and break them.

This pathway doesn't work in mammals, whose cells are shut down by the introduction of the double-stranded RNA. But in 2001, Thomas Tuschl, who earlier had worked as a postdoc in the Bartel lab, announced an RNAi variant that overcomes this barrier by slipping synthetic siRNAs into mammalian cells. Labs worldwide now have developed a number of approaches to exploit RNAi in mammals, and are furiously investigating potential research and medical applications.

### [RNAi in plants and animals]

**1** Long double-stranded RNAs are introduced to the organism.

**2** The double-stranded RNAs are chopped into short interfering RNAs (siRNAs) by an enzyme called Dicer.

**3** The siRNAs are assembled into RNA-inducing silencing complexes (RISCs), unwinding as they do so.

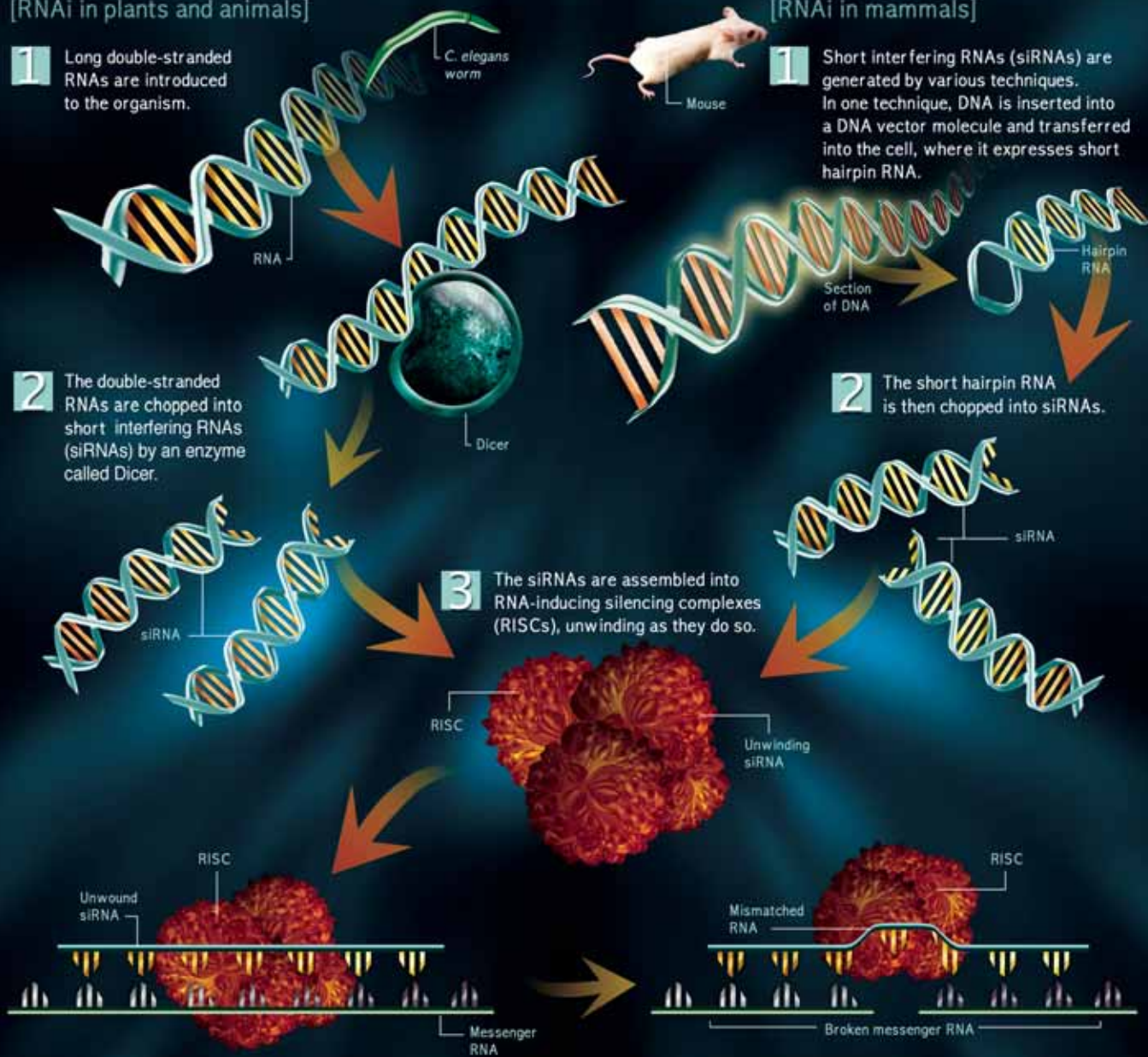
**4** The unwound siRNA strands guide the RISCs to complementary messenger RNA molecules. They attach to and then break the messenger RNA, silencing gene expression.

### [RNAi in mammals]

**1** Short interfering RNAs (siRNAs) are generated by various techniques. In one technique, DNA is inserted into a DNA vector molecule and transferred into the cell, where it expresses short hairpin RNA.

**2** The short hairpin RNA is then chopped into siRNAs.

SOURCES: LABORATORIES OF DAVID BARTEL AND MICHAEL MCMANNIS, NATURE REVIEWS GENETICS AND INVITROGEN GRAPHIC: CHRISTINA ULLMAN



## [ RNAi's REGULAR ROLE ]

*How built-in RNAi machinery helps plants develop*

In 1990, University of Arizona plant biologist Rich Jorgensen was trying to make purple petunias more vibrant by inserting a supercharged copy of the gene that controls production of purple pigment. Surprisingly, he got white petunias instead. It seems Jorgensen had stumbled across a natural mechanism for plants to turn off genes—a process we now call RNA interference (RNAi)—in which double strands of RNA quickly and efficiently turn off genes.

Biologists didn't actually figure out what was going on until 1998, but since then, double-stranded RNAs have become the latest laboratory craze, used by researchers worldwide to study favored genes in not only plants, but also worms, flies, and mice. Universities and drug companies are investigating applying such molecules to human disease, and the first human trials begin this fall.

A few researchers, though, have been studying the natural roles of the RNAi machinery. Three years ago, Whitehead Member and MIT professor of biology David Bartel and his colleagues discovered a large class of genes that encode little, double-stranded RNAs, called microRNAs, found in creatures large and small. These genes are so similar in so many different organisms that biologists suspected they must play key roles in regulating cells' normal growth and development. The Bartel lab is pursuing this idea not only in animals, but also in plants. Bartel's recent research into the microRNAs of *Arabidopsis*, a flowering mustard plant, has helped the understanding of those roles to blossom.

Studies of several *Arabidopsis* microRNAs by Bartel and others have shown they are crucial for proper plant development. Working with Bartel's sister Bonnie Bartel at Rice University, for instance, the researchers showed that eliminating microRNA regulation of a gene important in both early plant and flower development, called *CUC-1*, caused the plant's flowers to have extra petals and fewer sepals (the leaf-like structures that support the petals). If the plants produced too much of the microRNA that regulates *CUC-1*, however, other abnormalities appeared.

Most gene regulation happens simply by turning off the machinery that transcribes a gene from DNA into messenger RNA. "MicroRNAs," says David Bartel, "give you another layer of regulation that we think probably has been very useful for the emergence of complex, multicellular body plans."

Why would a cell need this extra level of control? MicroRNAs can "dial down" the amount of protein produced by a gene much more quickly than turning off transcription, allowing a cell, say, to switch much more quickly from a precursor cell into a petal cell during the course of development. With multiple methods of gene regulation, Bartel says, "you can get much more complex patterns of gene regulation that you need to define all the different cell types that you have in these organisms."

While this new knowledge may help in developing new plant varieties, Bartel's own interests lie in learning the roles microRNAs can play in plant development. "It's basic research for understanding how you get from a seed to a mature plant, and how you get the seed in the first place," he says.

— Erika Jonietz

### BY DEFINITION

**Dicer:** An enzyme that slices double-stranded RNA into short interfering RNAs.

**Double-stranded RNA (dsRNA):** Long RNA duplexes that may be formed by viruses, transposons (transposable elements—segments of DNA that randomly insert themselves elsewhere in the genome), or other processes. Most forms of RNA are single-stranded.

**Messenger RNA (mRNA):** A class of RNA that acts as a template for synthesizing proteins. In RNA interference, short interfering RNAs are designed to attack specific complementary messenger RNAs, whose molecular structure matches up with the siRNAs.

**MicroRNA (miRNA):** One class of short (about 21 nucleotides) RNAs, similar to short interfering RNAs. Each microRNA originates with a gene that produces RNA that folds back on itself to form a short hairpin-like structure that is in turn processed (with help from Dicer) into a microRNA. In contrast, siRNAs derive from long, double-stranded RNA.

**RNA:** Ribonucleic acid, which accepts genetic information from DNA and aids in protein synthesis and gene regulation. Messenger RNA, transfer RNA, ribosomal RNA, microRNA, and short interfering RNA are different RNA classes.

**RNA-inducing silencing complex (RISC):** A multi-protein complex that brings short interfering RNA together with complementary messenger RNA, which then is destroyed or degraded.

**RNA interference (RNAi):** An activity that starts with introducing RNA into a cell and ends with the degradation of complementary messenger RNA, thus stopping or otherwise affecting gene expression.

**Short hairpin RNA (shRNA):** DNA from a target gene can be inserted into a DNA vector molecule and transferred into mammalian cells, where it is expressed in a short hairpin RNA. Transferred from the nucleus to the cytoplasm, the shRNA is chopped by the Dicer enzyme into short interfering RNAs, which can direct an RNA interference process.

**Short interfering RNA (siRNA):**

A short (about 21-nucleotide) RNA duplex that specifies RNAi activity.

## [ ONE PERSON'S JUNK IS ANOTHER'S TREASURE ]

*Sorting through the human genome's vast wastelands*

Nobelist Sydney Brenner had a pithy description for the huge stretches of the human genome that don't seem to code for genes: "junk DNA." Since he coined the term, scientists have debated which of these hapless-looking strands of DNA are really junk and which are key players in biological or disease processes we don't yet understand. David Haussler, director of the Center for Biomolecular Science & Engineering at the University of California, Santa Cruz, explains recent advances in sorting out our junk.

### How do you separate genes from "junk"?

We haven't located every human gene precisely, but we're getting close, with somewhere between 20,000 and 25,000 protein-coding genes. Altogether, those genes account for less than 1.5 percent of the DNA in the human genome. Even the simplest species can't be pure protein-coding; there's got to be some DNA that helps to guide the process of making the protein-coding genes. But there seems to be extra bloat of material in the human genome, beyond what you would expect is needed to guide the protein-coding genes.

### What do comparisons with other mammals tell us?

Most recently, we looked at the most extremely conserved things in the human genome—everything that was completely identical in the human, mouse, and rat for hundreds of DNA bases. No one knows what these segments are doing. Most of them are not making proteins. But they're definitely not junk. Those similarities have been preserved through evolution, probably because those pieces of DNA are important.

It's amazing to think about how conserved these segments are, and it makes it all the more exciting to try to figure out what they do. We have some indications that they regulate genes in the neighborhood. What's amazing is that the neighborhood can be up to a million bases away from the gene. And a very statistically significant number of these ultra-conserved elements are near genes involved in embryo development.

Overall, while it's not all ultra-conserved, another 3.5 percent of the human genome is more conserved with other species than was expected. Most of this additional conserved DNA could be regulating the protein-coding genes, but this remains to be proven. Much of it could also be making RNAs that don't code for proteins. We just don't know yet.

### What else is lurking in the "junk"?

There's a lot of DNA in the human genome that seems to be evolving neutrally, just accumulating mutations through the eons. It's been called selfish DNA.



BRIAN WILLISE

Occasionally a segment of selfish DNA can make a copy of itself in a cell that's destined to become a sperm or an egg. That copy gets inserted back at a different place in the genome. If that happens, then you pass on an extra piece in your genome to your child. Through millions of years, you end up with more and more copies of these things in the genome. More than half of the human genome is stuff left over from these "transposons." They're essentially the rotting carcasses of these old selfish DNA elements. And you carry them in your genome and pass them on to your children!

### Do transposons play active roles?

There was an exciting paper in *Nature* this year about one kind of transposon called long interspersed nuclear elements [LINEs]. When LINEs make copies, if they randomly insert themselves in between the protein-coding parts of a gene, they can slow down the rate at which you use that gene. Also, they occasionally can take a bit of a nearby gene with them, and when they make the copy, they put down a new bit of gene somewhere else in the genome.

### Beyond genes and transposons, what makes up the rest of our DNA?

We don't know about the in-between stuff. Some will be transposons that have decayed so much from their original versions that we can't even recognize them. But some may be DNA that's doing important stuff that we just haven't recognized yet.

**[NOW IN SITE]**

Whitehead Institute's newly updated Web site at [www.whitehead.mit.edu](http://www.whitehead.mit.edu) offers easier navigation and a host of new features, including:

- Quick access to each faculty member's research summary and latest scientific papers
- Access tailored for educators, scientists, and other specific groups
- Updated collections of information on stem cells, cloning, and other popular research topics
- Archives for our *Paradigm* and *Discovery* magazines, plus a handy online subscription form
- The ability to e-mail news stories to friends



JUSTIN KNIGHT

**[PUBLIC OFFERINGS]**

Whitehead opens its doors for a number of public events, including a seminar series for high school teachers in the fall and a three-day program for high school students in the spring. (Both are free but require registration.) For details on all of the Institute's educational and outreach programs, visit [www.whitehead.mit.edu/programs](http://www.whitehead.mit.edu/programs).

**[WELCOME TO THE ACADEMY!]**

Take a seat in our new virtual lecture hall, where senior Whitehead researchers introduce their work to nonscientists in QuickTime videos. For instance, Member David Page describes recent discoveries that changed our understanding of how sex chromosomes evolve. You can enter the Whitehead Academy at [www.whitehead.mit.edu/academy](http://www.whitehead.mit.edu/academy).



SAM OGDEN

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EDITORS  
Eric Bender  
Kelli Whitlock

ASSISTANT EDITOR  
David Cameron

WRITERS  
Melissa Withers  
Jennifer Tomase

DESIGN  
Sametz Blackstone Associates,  
Boston

Rick Borchelt  
*Director, Office of Communications  
and Public Affairs, Whitehead  
Institute for Biomedical Research*

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The horseshoe crab sperm cell has an interesting way of penetrating the egg cell's membrane: It shoots out a molecular harpoon made up of the protein actin. Kazuyoshi Murata, a researcher at the Whitehead-MIT Biolmaging Center, used a new, state-of-the-art electron microscope to image these spear-like bundles of proteins at a resolution of 20 angstroms, roughly two-billionths of a meter. The microscope ultimately will reach a resolution of 3.5 angstroms.



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