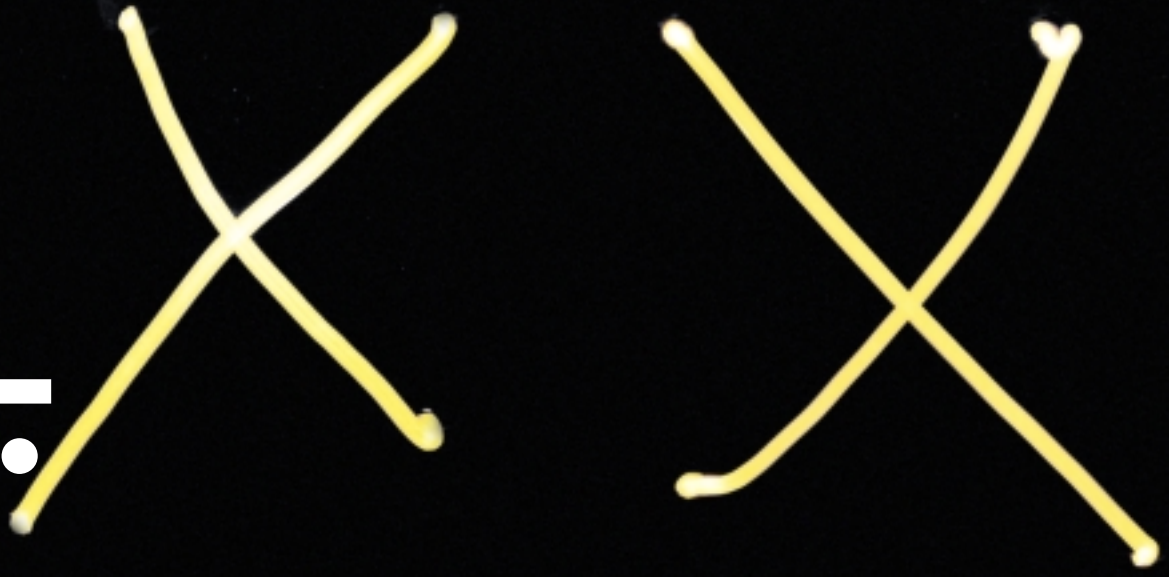
FALL 2003 A magazine of life sciences inquiry from Whitehead Institute

Terrain



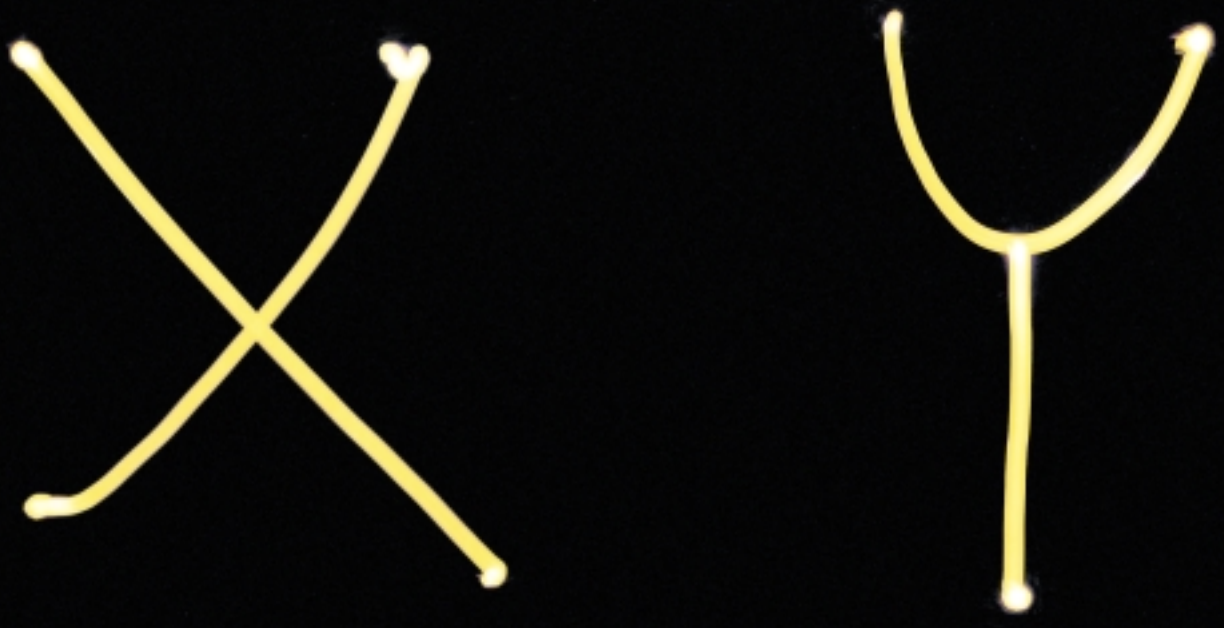
featuring:

The power of proteins

[The Y finds a mate]

A stand for stem cells

Fending off a biological invasion



notepad

par•a•digm (par´ə dīm´) n. *a philosophical and theoretical framework of a scientific school or discipline within which theories, laws, and generalizations and the experiments performed in support of them is formed.*
Webster's Collegiate Dictionary, Tenth Edition

I once gave a talk about a career in science writing to a group of young journalism students, one of whom asked why I enjoyed writing about things like T-cells, tectonic plates, and elliptical galaxies. I don't recall my answer, but I do remember her response.

"I could never write about science," she said. "I'm not smart enough."

Her attitude is shared by many. We live in a society that is ravenous for science news, but intimidated by science. That fear not only compromises our ability to make sound decisions about such things as the environment and health care, but also impacts how we vote on election day. Now, perhaps more than ever, scientists and nonscientists alike have a vested interest in who is sent to Washington, D.C., and to the nation's statehouses. Government always has been in the business of regulating science and research funding. In these days of limited access to scientific data and ever-tightening federal budgets, an informed electorate is crucial to scientific discovery, which in turn is vital to the health of the nation.

What to do? Many people, like that college student, think of science as an alphabet soup of chemical symbols, formulas written in white chalk on a dusty blackboard, liquid dancing in a beaker warmed by a Bunsen burner.

In truth, science is much more than that. It's understanding why Mars shone so brightly in the August sky. It's figuring out how West Nile virus crossed an ocean four years ago, ultimately spreading across the United States and killing hundreds. It's drafting a map of the 30,000 genes that constitute the human genome—and learning what those genes do.

These are the stories of science. And there are many more: Hundreds of tales are waiting to be told in the life sciences alone.

Paradigm was created with this in mind. Whitehead Institute was founded in 1982 to promote scientific inquiry in an environment that embraces basic research for all the knowledge such studies yield. Findings uncovered in our labs impact work under way across the nation and around the world, just as discoveries in those distant places affect studies here. In *Paradigm*, we'll share the stories of science through text, photography, and art that add social and scientific context to studies under way at Whitehead and beyond.

Humans are naturally curious creatures. We want to know why and how things work and what happens when they don't. Engaging stories about science can offer knowledge that leads to a more informed—and less intimidated—public.

And besides, everybody loves a good story.

Kelli Whitlock
Editor, *Paradigm*

ON THE COVER:
To illustrate the X and Y chromosomes, photographer Sam Ogden drew the letters in the air with a flashlight, capturing the light on film. The images have not been digitally enhanced.

our contributors

Work by photographers **SAM OGDEN** and **MARK OSTOW** is featured throughout this issue. Ogden, whose photos have been published in magazines in 27 countries, specializes in high-tech, science, and medical photography. He lives in Newton, Massachusetts. Ostow shoots location portraits for magazines and ad agencies. He has photographed Andie MacDowell, Ben Affleck, and John Kerry, among others. He lives in Cambridge, Massachusetts.

CHARLIE SCHMIDT ("The Protein Universe") writes frequently about genomics and molecular biology. He is a recipient of the 2003 National Association of Science Writers' Science in Society Journalism Award for magazine writing. He lives in Portland, Maine.

Since 1997, **MARK DWORTZAN** ("The Weeds Within Us") has contributed news and feature articles on science, technology, business, and the environment to national magazines, Web sites, and Boston-area universities and research centers.

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A CHEMICAL LIBRARY

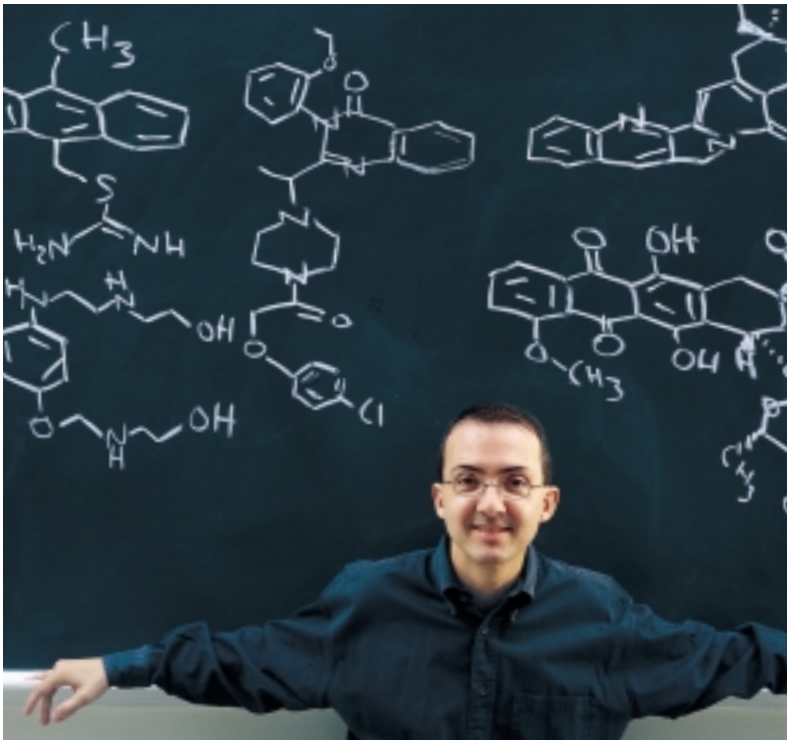
Most cancer patients face an all or nothing dilemma: While aggressive chemotherapy kills cancerous cells, it also kills healthy cells, causing severe side effects like anemia, organ damage, and memory loss.

But a new strategy that identifies compounds active only in the presence of certain cancer-causing genes and proteins could aid in the search for drugs that destroy disease while leaving healthy cells unharmed.

Whitehead Institute Fellow Brent Stockwell and his colleagues used a novel screening technique to survey more than 23,000 chemical compounds and test for their ability to selectively target human cancer cells.

The results, published earlier this year in the journal *Cancer Cell*, were fed into a database that scored the compounds based on their effectiveness. The team discovered nine compounds that passed the test, including one compound that has never been studied as an anticancer drug.

According to Stockwell, such selective screening represents an emerging paradigm in drug discovery. "The old method to find drug candidates was to take tumor cells from a human tumor and find things that killed them, without really understanding how they would ultimately affect other cells in the body," he explains. "Drug candidates identified by this method often turn out to be severely toxic to healthy cells and thus not usable as a therapy."



SAM OGDEN

Compounding Interest: Brent Stockwell has developed a strategy to identify chemical compounds that act only on certain cancer-causing genes and proteins.

RNA RENAISSANCE

Once thought to serve only as a bridge between genes and protein production, RNA is quickly shedding its reputation as being all brawn and no brain. RNA's research renaissance is due, in part, to the discovery of a class of genes called microRNAs (miRNAs for short). Rather than code for proteins, miRNAs serve as regulators—genetic trump cards that turn protein-coding genes off.

Researchers estimate that miRNA genes constitute nearly 1 percent of human genes. They are one of the more abundant types of regulatory genes in humans.

"Having this extra layer of gene regulation may have enabled the emergence of the multicellular body plans found in both plants and animals," says Whitehead scientist David Bartel. "The developmental processes that give rise to an adult plant or animal require a lot of turning on and off of genes."

Researchers in the labs of Bartel and MIT's Christopher Burge have developed a computational method to estimate the number of miRNAs in different animals. In work published in *Science*, the pair used their approach, called MiRscan, to determine how many miRNAs likely exist within the genomes of humans and other vertebrate animals.

Four of the compounds Stockwell's team identified currently are used to treat tumors. A better understanding of how these drugs work may help doctors custom-tailor chemotherapy to fit a patient's unique tumor type, he says.

The one previously unidentified compound, which the scientists named erastin, is especially interesting because it seems to kill cancer cells in a different manner from many drugs currently on the market. "The most immediate thing is to figure out how erastin works and try to understand that molecular mechanism in detail," Stockwell adds.

In addition to investigating the screening method's therapeutic implications, Stockwell and his colleagues also are using the technique to study the mechanisms driving tumor growth.

Melissa Withers

Using MiRscan, the researchers compared miRNA sequences from mice and humans to those found in the puffer fish *Fugu rubripes*. They found 15,000 genomic segments existing outside the protein-coding regions conserved across the human, mouse, and puffer fish genomes. Lee Lim, then a postdoctoral researcher in the Bartel and Burge labs and the tool's chief architect, used MiRscan to cross-examine these segments and predict which were likely to be miRNA genes. MiRscan found most of the known human miRNAs, estimating that the upper limit of human genes coding for miRNAs is between 200 and 250.

Bartel and his colleagues also have found nearly all the miRNA genes in the worm *C. elegans*, a model used to study animal development. Those found so far represent 48 gene families, of which 22 are conserved in humans.

"The abundance of these tiny RNAs only increases the mystery as to why they hadn't been found earlier," says Bartel. The next step, he adds, is to figure out what role miRNAs play in the machinery of cell growth and differentiation. His team has made substantial progress toward this goal in plants, having matched the first 16 microRNAs found in plants with target genes that they control.

M W

JUMP-STARTING GENES

Only 1 percent to 3 percent of animals cloned from adult cells survive to birth; many die mysteriously around the time of implantation. There likely are many reasons for their failure, and uncovering them has been a challenge for scientists.

"Most animals cloned from somatic cells fail in all seven species, while animals cloned from embryonic stem cells survive much better," says Rudolf Jaenisch, a Member at Whitehead Institute. "We wanted to know why embryonic stem-cell-derived clones survive so well while those derived from somatic cells do so poorly."

Earlier this year, Whitehead scientists identified a set of genes important in early development that fails to reactivate in adult, or somatic, cell-derived clones—a finding that could help scientists skirt a major roadblock in cloning.

Among the genes essential to normal embryonic development is the *Oct4* gene, which prompts embryos to create pluripotent cells—cells that can form any tissue in the body.

Researchers from the labs of Jaenisch and fellow Whitehead scientist David Page identified more than 60 genes expressed in normal mouse embryos. With an eye toward the *Oct4* gene, they isolated 10 of those genes that behave similarly to *Oct4*.

Scientists at Whitehead and the University of Hawaii cloned mouse embryos derived from embryonic stem cells and another group created from somatic cells. Those made from embryonic stem cells expressed all 10 *Oct4*-like genes normally, while only 62 percent of somatic cell-derived clones correctly expressed the genes.

"This finding suggests that other genes that function together with *Oct4* in control of early development also might be inefficiently expressed in somatic clones," says Alex Bortvin, a postdoctoral associate in the Page lab and lead researcher for this work, which was reported in the journal *Development*. Now, Bortvin and others in the Page lab have demonstrated important roles of several such *Oct4*-like genes for normal mouse development.

As the debate over embryonic stem cell research continues, scientists must look to adult stem cells for cloning studies that could yield vital information about disease and cell development. So, helping somatic cell-derived embryos survive to birth is high on researchers' minds.

"The issue now," Jaenisch says, "is to make therapeutic cloning more efficient."

Kelli Whitlock

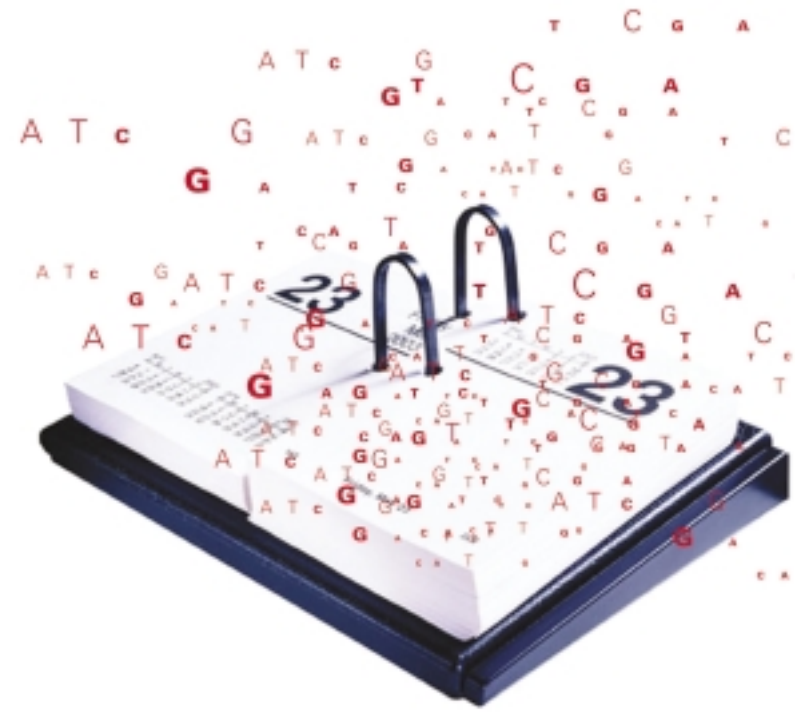
Cloning Conundrum: Why do only 1 percent to 3 percent of animals cloned from adult cells survive to birth?

7 MILLION LETTERS, AND COUNTING

Almost 150 different genomes have been sequenced to date, including the human genome. But sequencing needs are growing faster than ever: In March 2003 the Bush administration announced it will spend $1 billion over five years to increase forensic analysis of DNA, which included a backlog of up to 300,000 samples. And the success of the growing field of genomic medicine, which promises to deliver better therapies and diagnostics, depends on faster sequencing technology.

This fall, researchers at Whitehead Institute will test new technology that could aid in these and other endeavors. The BioMEMS 768 Sequencer can sequence the entire human genome in only one year, processing up to 7 million DNA letters a day, about seven times faster than its nearest rival. Scientists began working on the project in 1999 with a $7 million National Human Genome Research Institute grant. The technology eventually will help scientists quickly determine the exact genetic sequence of the DNA of many different organisms, and could lead to faster forensic analysis of DNA gathered in criminal cases.

The heart of the new BioMEMs machine is a large glass chip etched with tiny microchannels called "lanes." It tests 384 lanes of DNA at a time, four times more than existing capillary sequencers. Each lane can accommodate longer strands of DNA: about 850 bases (the nucleic acids found in DNA, abbreviated by the letters A, C, T, or G), compared to the current 550 bases per lane.

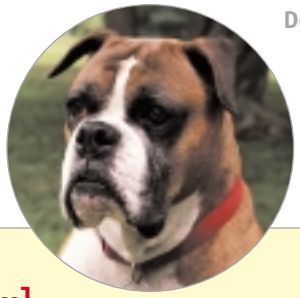


It takes about 45 minutes to read the DNA from one of the BioMEMS' 768 lanes. The machine has two chips; one is prepared as the other is sequenced, so that the machine is sequencing at all times. The new sequencer saves not just capital costs, the developers say, but day-to-day expenses as well.

"It's not only the cost of the machine, but the cost of the materials it uses," says Brian McKenna, senior software engineer at Whitehead Institute. The target, he says, is to use the same amount of consumables—liquid, chemicals, and other materials used to prepare the DNA—as existing sequencing machines. BioMEMS also uses a DNA loading process that eventually will need only 1 percent of a typical DNA sample.

While developed at Whitehead, the machine is being commercialized by network biosystems, a company in Woburn, Massachusetts, started in 2001 by Whitehead Member Paul Matsudaira, BioMEMS Labs Director Dan Ehrlich, and research scientist Lance Koutny. Shimadzu Biotech in Japan will manufacture the sequencer.

David Appell



Dog Days: A Boxer named Tasha was picked over 120 other dogs for the sequencing project.

BEST OF SHOW

It was the scientific version of the Westminster Kennel Club Dog Show. A project to sequence the genome of *Canis familiaris* (a.k.a. man's best friend) was on the minds of researchers at the Whitehead Institute/MIT Center for Genome Research, and they needed just the right dog.

120 dogs and 60 breeds under consideration. The winner: a Boxer named Tasha.

"The dog genome sequence will be a powerful basic resource that will rapidly propel the discovery of disease genes forward in both the dog and human," says Kerstin Lindblad-Toh, lead researcher on the project.

Scientists say the sequencing effort, which began earlier this year, will reveal genetic information crucial to the study of human and canine diseases. The Boxer genome has less variation than that of other dog breeds, which should make the sequence easier to assemble.

FOR WHOM THE CELL TOLLS

Making a medical diagnosis today often relies on symptomology, bacterial cultures, stain tests, experience—and luck. But new research by systems biologists at Whitehead Institute aims to offer physicians new diagnostic tools by uncovering important differences in the way immune cells respond to bacteria that cause botulism, diphtheria, strep throat, staph, and a range of other infections.

The work focuses on molecules called "Toll-like receptors" that have evolved to serve as docking clamps for specific molecules on the surfaces of bacterial cells. In research published in *The Journal of Immunology*, Whitehead scientist Richard Young led a team that applied microarray technology to study how genes in human immune cells are modified when they encounter bacteria. It's a first step, Young says, not only toward the development of a bacterial infection diagnostic tool, but also "an approach to dissecting out the molecular details of the pathways by which these cells are fighting the infection."

Studies of the human genome reveal 10 Toll-like receptors densely packed on the surfaces of immune cells called macrophages. When bacterial microbes attack these cells, signals sent through the Toll-like receptors change the level of protein production by genes in the macrophage. The scientists found 101 genes whose protein expression changed significantly when exposed to the two major classes of bacteria, Gram-positive and Gram-negative.

BRIAN WILLSE

Using microarray ("gene chip") technology that's become a key tool in genetics research, Young and former postdoctoral researcher Gerard Nau studied the expression of hundreds of genes activated by a single bacterium, a view that offered a detailed display of the complexities of gene response to infection.

Their results focused on a molecule found in the cell walls of a Gram-negative bacteria called lipopolysaccharide—LPS for short—which helps give the cell wall membrane its fluidity. LPS joins with a Toll-like receptor called TLR4, forming a pair the analysis identified as crucial to the differences in gene expression seen in the presence of Gram-negative and Gram-positive bacteria.

The detection of this unique gene expression profile could help physicians identify the Gram status of the bacterial agent immediately and prescribe the most effective antibiotic.

"If I could tell that a patient coming into the emergency room had, with a 99 percent certainty, a Gram-negative infection, that would skew how I would approach the patient," says Nau, now an assistant professor at the University of Pittsburgh who is an immunology researcher and infectious disease physician. "That could be a useful diagnostic test."

It's a view shared by Douglas Golenbock, chief of the Division of Infectious Diseases and Immunology at the University of Massachusetts Medical School: "I think this research represents a basic science advance that may soon have real impact on our ability to take care of patients."

D A

So far, scientists have published the complete or partial genomes of fungi and the human, mouse, rat, worm, and fly. *Canis familiaris* has an estimated 2.8 billion base pairs in its genome—similar to that of humans and other mammals, scientists say. Adding Tasha to the list of sequenced organisms will offer another good model for the study of disease.

Selective breeding by dog owners has yielded more than 300 purebreds during the past 300 years, offering great genetic variation among different breeds with regard to size, color, and temperament. What's more, key traits within each breed are passed down from generation to generation, including more than 400 inherited disorders.

Once researchers sequence Tasha's genome, an effort they hope to complete by June 2004, they will study it alongside sequences from other dog breeds to examine genetic variation within the species.

K W

BREAKING THE MOLD

Scientists love that fuzzy, green stuff that grows in your breadbasket. Known as *Neurospora crassa*, the common bread mold has served as a staple laboratory model for genetics, biochemistry, and molecular biology for more than 60 years. Researchers have studied *Neurospora* more comprehensively than any other mold, mushroom, or other filamentous fungi. But until this spring, they lacked a map of its genetic makeup.

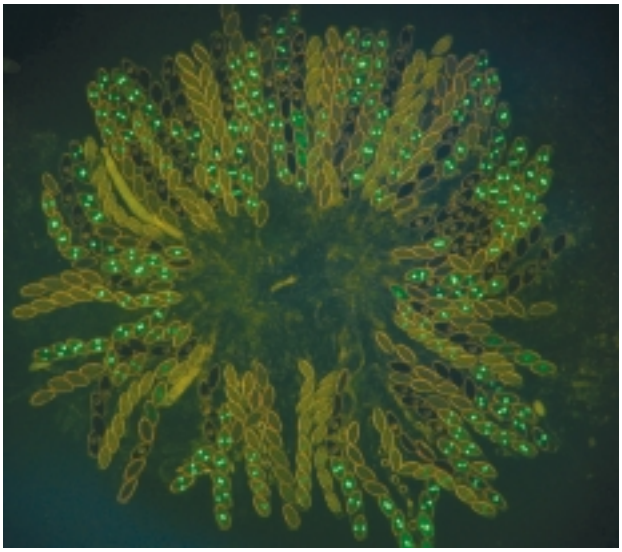
Scientists in the Whitehead Institute/MIT Center for Genome Research and their collaborators have completed a first draft sequence of the *Neurospora* genome, work they hope will boost researchers' understanding not only of the biology of the bread mold and related fungi, but also of more complex organisms that share many properties with *Neurospora*. As a result, the study leaders say, scientists should be better equipped to probe the pathogenesis of fungal relatives implicated in plant diseases that destroy corn, rice, and soy crops, and animal diseases such as athlete's foot and valley fever.

"Because fungi are biologically close to humans, it's hard to come up with medicines that kill fungi without also killing the patient," says James Galagan, a scientist at the genome center and leader of the study, which was published in the journal *Nature*. "The more we understand about what makes a fungus pathogenic, the more we can combat fungal diseases."

The genome encodes about 10,000 protein-coding genes, researchers discovered, a figure that's about one-third the total for humans, and twice that of common baker's yeast. The scientists' analysis suggests that a fungi-specific genome defense mechanism called repeat-induced point mutation (RIP) has wielded a powerful impact on the evolution of *Neurospora* by impeding the creation of new genes through genomic duplication. RIP accomplishes this by efficiently mutating and eliminating repetitive segments of DNA. The genome analysis also revealed new insights into cell signaling, growth, differentiation, and metabolism in the bread mold.

The research team sequenced the genome's 40 million base pairs using whole genome shotgun (WGS), a standard method in which the genome is shredded and systematically reassembled. "The technique is similar to ripping a note into several pieces, throwing it to the ground, picking up the pieces, reading the letters on the front and back of each piece, and then putting the pieces back together," Galagan explains. To achieve a high degree of accuracy, the WGS process determined the identity of every base in the genome an average of 20 times. The scientists still must account for a number of very small missing or ambiguous segments that constitute about 5 percent of the genome, but they expect to produce a final sequence by year's end.

Mark Dwortzan



NAMBOORI RAJU

Green and Fuzzy: Scientists have mapped the genome of *Neurospora crassa*—common bread mold.

CELLULAR CODE

Despite the rich knowledge scientists now have of the genes that constitute the human genome, researchers have yet to unravel the precise choreography by which they work—or malfunction—together in the cell in response to triggers from the outside world.

"There is a code we need to understand that would give us a tool to determine what happens to a cell under many different conditions, and ultimately to make predictions of how an entire genome is regulated," explains Julia Zeitlinger, a postdoctoral associate at Whitehead Institute.

Key to cracking this code, she says, is a set of proteins called transcription factors, which bind to specific genes to produce proteins. Akin to computer programs that return different results depending on the input data, transcription factors can carry out multiple functions in the cell in response to distinct stimuli.

For example, a transcription factor in yeast called Ste12 induces mating in response to a pheromone from a mating partner, or filamentation (growth in the form of threadlike strands) when subjected to a lack of sufficient nutrients. Pinpointing the mechanism that makes transcription factors such as Ste12 respond differently under different environmental inputs could enable scientists to better predict cellular behavior and disease pathology.

In a study published earlier this year in the journal *Cell*, Zeitlinger and colleagues at the Whitehead/MIT Center for

CANCER PUZZLE

About four years ago, a group of researchers at Whitehead Institute created the first genetically engineered human cancer cells in the lab. They infected normal cells in mice with cancer-causing genes, and waited for tumors to form. Some cells formed large tumors. But others yielded only small, harmless bumps, much to the scientists' surprise.

What went wrong? they wondered. Or, from the perspective of a group of scientists who'd like to figure out how to keep cancer from spreading, *What went right?*

"We had these two cell types that for all intents and purposes were the same," says Randolph Watnick, lead researcher on the project. Only one thing set them apart: One had high levels of a mutated protein involved in tumor cell and blood vessel growth, while the other had low levels. Still, Watnick maintains, since most human tumors have low levels of this mutated protein, "they both should have been able to form tumors."

BRIAN WILLSE

Watnick knew what the end result looked like, but was missing key pieces to the puzzle. He decided to examine the systems involved with blood vessel growth—a process called angiogenesis. In a healthy body, growth factors turn the process on and anti-angiogenic factors turn the process off. But in cancer patients, one or both of these protein switches can malfunction, leading to the uncontrolled growth of blood vessels that not only deliver nutrients crucial for cancer cell growth, but also give the cells a conduit through which they can travel around the body.

Watnick uncovered a previously unknown pathway used by cancer cells to control the system that regulates blood vessel growth, and throw it out of balance. The study, published earlier this year in the journal *Cancer Cell*, identifies a communications channel used to turn off the expression of Tsp-1, a key anti-angiogenic protein. With this protein out of commission, the ingrowth of new blood vessels into the tumor proceeds unchecked, leading to tumor growth. For Watnick, the pieces of the puzzle began to fit together.

Now that the pathway has been revealed, researchers want to know more about the signals it carries. In September, Watnick, who was a postdoctoral associate in the lab of Whitehead Member Robert Weinberg when he did this study, joined Harvard Medical School as an assistant professor in the surgical research department. He plans to examine this new pathway further, a project that could lead to a new protein target for drug development.

K W

Genome Research discovered that when a multipurpose transcription factor is exposed to a particular environmental condition, it directly orchestrates a global change throughout the genome in binding sites involved in the cellular behavior induced by that condition.

The team monitored all binding sites of the transcription factor Ste12 in yeast while exposing the genome to the pheromone that induces mating and to butanol, an alcohol that mimics the conditions that promote filamentation. They used a technique called genome-wide location analysis, a process pioneered by Whitehead Member Richard Young that uses DNA microarrays to enable rapid analysis of protein interaction with the DNA of an entire genome.

"When we profiled the binding sites of Ste12 under the two developmental conditions, we found that Ste12 indeed undergoes the predicted global switch in binding," recalls Zeitlinger, who works in Young's lab. The researchers found that the transcription factor, rather than activating further transcription factors in the cellular network, directly determines which genes are activated under each condition.

Zeitlinger plans to investigate if this mechanism occurs generally in yeast and higher organisms, work that ultimately could help physicians better understand, diagnose, and disrupt certain diseases at the cellular level.

M D

In the heated debate over human embryo stem cell research, voices become muddled and motivations misunderstood. Scientist Willy Lensch is among those speaking out in support of this research. His reasons are complex, he says, but his cause is clear.

with respect and conscience

When he was 15 years old, Willy Lensch rode with his father in the back of an ambulance to the Salt Lake City Veterans Hospital in Utah. Critically ill with a rare form of blood cancer, Martin Lensch never returned home to the family farm in nearby Lehi.

Twenty years later, Lensch, a postdoctoral fellow at Whitehead Institute, speaks candidly about the impact of his father's death. "Watching him wither away during the course of his illness left an indelible mark on my family. I still miss him."

These early experiences shaped his professional choices, says Lensch, admitting that his decision to study blood disease was motivated in part by the loss of his father. As a graduate student at Oregon Health Sciences University, Lensch worked with leukemia patients and people suffering from Fanconi anemia, a devastating genetic disease that causes bone marrow failure. There was an unfortunate familiarity, he recalls, in his work with terminally ill patients and their families.

After completing his doctorate, Lensch joined the lab of George Daley, a former Whitehead Fellow who now is a visiting scientist at the Institute and an associate professor of biological chemistry and pediatrics at Harvard Medical School and Children's Hospital. Lensch planned to use human embryonic stem (ES) cells to study blood cell formation, a decision that ultimately put the 36-year-old researcher into the precarious position of defending the field of human embryo research.

Most embryos used in stem cell research are created by in vitro fertilization (IVF) at fertility clinics. Couples undergoing treatment may decide to store, destroy, or donate surplus embryos to science. The cells that Lensch studies are culled from donated embryos that are about a week old. These embryos contain a few dozen undifferentiated "master" cells that have the potential to form any cell type in the body. Researchers extract these cells and culture them in the lab, after which they can be used in experiments. As a therapy, researchers want to coax "uncommitted" stem cells into becoming specific cell types, such as nerve and cardiac muscle, which potentially could be used to repair damaged tissue.

Opponents of ES cell research argue that the destruction of human embryos, even just days following fertilization, is unconditionally wrong. Some, including the Catholic Church, compare it to murder.

Lensch, himself a Catholic, says he believes this research can be conducted respectfully and with conscience to benefit those suffering with disease. In today's political climate, however, defending these complicated virtues carries considerable risk. Taking these risks, Lensch says, is part of being a responsible scientist. In the past year, he has testified at a committee hearing on Boston's Beacon Hill, presented his research to Utah's House of Representatives Democratic caucus, and braved a hometown audience of high school students, many of whom were appalled by his work. He has broached the subject with his family—some Mormon, some Catholic—and felt the sting of their rebuff. Lensch even faced the threat of losing his fellowship funding when an otherwise inconsequential phone call turned to the topic of embryonic stem cells.

"I've been compared to a Nazi doctor, accused of subjugating women, and told that I am morally complicit in the murder of children," says Lensch, who, despite being deeply troubled by these accusations, feels obligated to publicly discuss his research. "We don't make discoveries, write them in our notebooks, and then throw them in the fire. If you can't give the salient points of what you're doing and why you're doing it, I think you're missing the mark."

Text by Melissa Withers
Photography by Mark Ostow

"I've been compared to a Nazi doctor, accused of subjugating women, and told that I am morally complicit in the murder of children." — *Willy Lensch*

The issues for Lensch are complex: His science is his livelihood. Should the political tides turn and embryonic stem cell research be outlawed, Lensch, a husband and father of two, could lose his research funding. "This whole thing could turn out badly," he says, visibly frustrated. "Work could be banned, no new cell lines introduced, no professorship down the line—never mind the stigma of working in a blackballed field."

In 2001, President Bush restricted federal funding for stem cell research to work using only certain approved stem cell lines. Rather than settle debate, the announcement stranded the research in a legislative no man's land. At the time, the Bush administration claimed that there were more than 60 approved cell lines available. Two years later, only 12 are listed on the National Institutes of Health's stem cell registry, six of which are controlled by foreign countries. Scientists claim that the additional lines are inaccessible, either held by private companies or unfit for research purposes. Without the introduction of new cell lines, Lensch and his colleagues argue, the science will stagnate.

"It's very frustrating to imagine entering into research, investing time and energy into your work, and then not being able to do anything with it," he laments. "We are interested in developing therapies, and if the legislative climate becomes darker, that won't happen."

Mounting frustration over these restrictions has prompted several scientific and research advocacy groups around the country to petition their state legislatures to challenge Bush's decision. In May 2003, a Massachusetts legislative subcommittee convened to hear arguments about Senate Bill 515, which mirrors a similar measure passed in California last year and declares Massachusetts a safe haven for stem cell research. Supporters of the bill invited Lensch to testify at the hearing and share his perspective.

Dressed in his one and only suit—a simple green, tweed jacket with matching pants—Lensch arrived at the courthouse on the morning of the hearing freshly shaven, hair trimmed, and far less experienced than many of the other witnesses. Nervous about his legislative debut, he shared the cab ride from Whitehead to Beacon Hill with laboratory leader George Daley, who also was scheduled to testify.

Inside the hearing chamber, a cavernous auditorium lined with stiff, theater-style chairs, the committee and a gallery of about 100 people heard more than five hours of testimony. First were the patients who shared stories about coping with disease and disability. Daley and a handful of other scientists testified next, recounting the difficulties they faced working under current restrictions. Then came the opponents, those who testified that stem cell research was an immoral project led by immoral people.

Lensch labored over his testimony in the days leading up to the hearing. When preparing, he didn't know he would speak last, addressing a committee that already had heard a glut of contentious testimony: scientists both for and against ES cell research, members of the clergy, children with diabetes, a young paraplegic, a doctoral student who compared stem cell research to 20th century eugenics. When Lensch finally took the stand—a lone podium in front of the committee bench—he offered the committee an improvisational redress of testimony given by those other witnesses.

"I am testifying today because I sincerely believe that [embryonic stem cell] research holds great promise to substantially improve medical practice," he told those gathered. "I am committed to remaining in the field despite its uncertain future…and I have put my credibility on the line."

Although Senate Bill 515 is still in review and has not been enacted (even if it is, it won't trump federal legislation), Lensch feels satisfied with the experience. "Scientists could be better at communicating what they do," he notes. "To go to a public forum and talk about the rationale for what you do is your responsibility as a citizen."

Lensch could easily blame circumstance for his foray into politics—the Bush announcement came just days after he agreed to join the Daley lab. But he doesn't. "I have an incredibly overdeveloped sense of responsibility," he says, smiling. "I don't want to sit on the wayside and let other people be intimately involved in things that affect my life."

Taking action has meant learning to speak publicly about his research to people who only faintly understand the scientific process. Lensch likens this to an experience he once had operating a wood-fire cook stove during a winter camping trip. The stove, which took hours to stoke, tested his companions' patience, who were dismayed that a can of beans could take so long to cook.

"People naturally want to know what cures will come from stem cells, and when. If you say that you don't know, there's the perception that [the research] is probably not worthwhile," he says. "I think that it's difficult, even for me, to appreciate how slowly science moves."

Helping people understand how science happens in the lab is not optional, particularly for publicly funded researchers, Lensch contends. "It's too easy for people to think that it's sterile, godless scientists working in the lab. It's part of my responsibility to put a face on who's in that laboratory."

Ironically, it was a group of school children, not politicians, who first pushed Lensch to publicly account for his work with embryonic stem cells.

Last November, seven months before his Beacon Hill testimony, Lensch was invited by a childhood friend to speak at his hometown high school in Lehi, a mostly Mormon community in northwestern Utah. The friend, now a teacher at the school, was convinced that her students would benefit from hearing his story.

Lensch arrived to a packed auditorium. He discussed his academic journey and his experience studying disease. "But when I got to the part of the talk where I brought up stem cells, you could have heard a pin drop," he recalls. The teacher who had invited Lensch knew only about his work studying leukemia and bone marrow transplantation. The stem cells were a surprise.

Lensch was moved by some of the students' almost visceral reaction to his research. "After the talk, a group of very brave students came up and told me that I was wrong, and that what I was doing was immoral," he remembers. "I tried to explain why I thought my research was moral, and I asked them to share their point of view. Although most of the students

"It's too easy for people to think that it's sterile, godless scientists working in the lab. It's part of my responsibility to put a face on who's in that laboratory." — *Willy Lensch*

didn't really know how to respond, I was incredibly proud that they came up to tell me I was a jerk. That took a lot of guts."

The experience gave Lensch a better sense of what stem cell supporters like Senator Orrin Hatch, a Utah Republican, are up against in persuading their constituencies to support ES cell research. Recently, facing sharp criticism in his home state, Hatch has wavered in his support. "As a Utah native, I wanted to tell Hatch that I supported the work he was doing and find out what I could do." Lensch wrote Hatch and eventually met with the senator's staff in Washington, D.C.

Eternally optimistic but not naïve, Lensch doesn't expect to single handedly change legislative opinions about embryonic stem cell research. But, he adds, communication can change ideas.

"I remember watching Bush's speech on stem cell research together with Willy," says Lensch's wife, Andrea Fiorillo. "There was an uncertainty, an insecurity, about what would happen in terms of his livelihood if this was the road that he went down."

Fiorillo, who studied religion, is attuned to the ethical issues that characterize the stem cell debate and mindful of the deep personal feelings it evokes. She remembers reading about embryonic development when pregnant with their son, Dante. She and Lensch's daughter from a previous marriage, Annie, followed a week-by-week calendar illustrating a fetus's growth in utero. "I can't say that I don't think about the conflicts, because I do," she admits. "But I believe that he is doing [the research] for ethical reasons. He's a good person, and I support him."

In discussing his work outside scientific circles, Lensch and Fiorillo tread lightly. When Lensch began studying ES cells, he was hesitant to discuss it, concerned about the judgments people might make. It wasn't until recently that he finally felt comfortable sharing details about his work with his family, some of whom strongly disagree with his choices.

"Discussing my work has always been a tough bet," says Lensch. "My current work is just another nuance of that, the difference being that with ES cells, I haven't met anyone who doesn't have an opinion."

What will Lensch do if embryonic stem cell research is outlawed? If forced to choose, Lensch predicts that he will transition back into traditional leukemia research, although it's clear that the move would not be easy.

"All I want to be able to say is that I did my best. That's just an aspect of being a member of a community," he says, slightly shrugging his shoulders. "I guess you can be an advocate wherever you're at."

[*For more information on stem cell research, visit the web at* www.wi.mit.edu/nap/features/nap_feature_daley_stemcell.html.]

The Protein

IN THE WAKE OF GENOMICS, THE SCIENCE OF PROTEINS

TEXT BY CHARLES SCHMIDT
PHOTOGRAPHY BY SAM OGDEN

Like any other birth, the birth of a protein is a remarkable event. The fledgling molecule is a chain of amino acids linked together like a string of beads. It slips from the ribosome—its womb in the cell—and in a series of quick steps, folds into an exquisitely complex 3-D shape perfectly suited to its role in biology. As it jostles through the cell, it links up with other proteins to create the cellular machinery that produces life.

The story of life and its associated processes takes place within a vast universe of proteins and their interactions. Proteins are the cell's workhorses, active in nearly everything cells do. They control cell structure, storage, signaling, movement, and defense. As enzymes, they control chemical reactions. As hormones, they control growth, development, and even mood.

Usually, proteins rapidly become perfectly shaped entities ready for normal behavior. But in some cases, they fold into abnormal shapes, wreaking havoc in the body. Indeed, dysfunctional proteins are the root cause of most genetic diseases. They can lose their ability to recognize protein partners or fail to engage in necessary reactions. In these cases, they degrade and the cell might suffer from a loss of its vital activities.

Rogue, misfolded proteins can clump together and cause problems in the cell, as seen in patients with disabling illnesses like Alzheimer's and Parkinson's disease. Understanding how proteins function under both normal and diseased states is critically important to life sciences research.

In the wake of genomics, the science of proteins is a bountiful frontier. Genomics has provided the celebrated "blueprint of life," but in and of itself, that blueprint is just a catalogue of anonymous gene sequences, explains Matthias Mann, a professor of bioinformatics who studies proteins at the University of Southern Denmark. Scientists at research centers such as Whitehead Institute, Harvard University, the Scripps Research Institute, and others now are assessing the biological function of these genes by studying the proteins they generate.

It is largely via protein research, scientists say, that the genome's role in life, disease, and evolution will be elucidated. But studying entire proteomes—meaning the complete diversity of proteins in individuals—is a monumental challenge. The proteomes of higher species comprise tens of thousands of protein conformations and

IS A BOUNTIFUL FRONTIER, RIPE FOR EXPLORATION

millions of untold molecular interactions. Nevertheless, scientists are taking on the challenge. But is this challenge beyond the scope of modern science?

"We will absolutely be able to do this," says Whitehead Director Susan Lindquist. "There's no question it's going to take some time. But in the next decade we're going to see some profound changes."

Researchers now are tackling the proteome on two fronts. In the more traditional approach, the intricate details of individual pathways are deconstructed and exposed. These studies generally begin with a hypothesis: Scientists first postulate a role for a class of proteins, then investigate those assumptions experimentally in the laboratory. Meanwhile, researchers who work in a new field called proteomics systematically are charting protein networks in cells and tissues. Unlike hypothesis-based research, these studies tend to be very broad. One might view them as missions to discover entirely new realms of protein activity. The proteome's true nature will be revealed, Lindquist suggests, as findings from hypothesis-based and proteomic research begin to converge.

WITHIN THE FOLD

For the most part, every gene in the body gives rise to one protein or class of proteins. But in recent years, evidence has shown that, even with the same amino acid sequences, proteins can fold into multiple conformations in the cell. One class of small, infectious proteins called prions not only change their own shape, but also transmit folding instructions to other proteins of the same type, prompting them to misfold as well. Prions can be lethal in humans and animals, causing a variety of neurological illnesses that cause the brain to slowly waste away. Prions have been linked to mad cow disease, an illness in cattle that can be transmitted to humans, causing Creutzfeldt-Jakob disease.

Lindquist is among the world's leading experts on protein folding. In most cases, she emphasizes, protein folding is a vital part of normal biology. Her research has revealed the key role a group of proteins called "chaperones" plays in getting other proteins to fold correctly. Because they are dedicated to this task, protein chaperones are indispensable to maintaining good health. "Probably half of all diseases are caused by protein folding problems," Lindquist says. "A few of the very big diseases are clearly

Living test tubes: Susan Lindquist uses yeast cells as living test tubes in her lab at Whitehead to study alpha synucelin, the protein believed to be responsible for Parkinson's disease.

induced by misfolding—Alzheimer's, cystic fibrosis, and Parkinson's disease, for instance. It's also clear that certain cancers develop because proteins don't fold properly. They lose their regulatory functions—some proteins that are supposed to stop cell growth become disabled and others that stimulate cell growth take off their brakes."

In a surprising finding, Lindquist's research has shown that protein folding also plays an important evolutionary role. Much of her work in this area addresses a protein called Hsp90. This chaperone helps other proteins fold correctly when exposed to stressful conditions that might induce them to misfold in harmful ways. More important, it also helps a special class of very unstable proteins fold at normal temperatures. These proteins are known as "signal transducers." They are meant to be unstable because that helps them to be highly sensitive to signals for growth control and development. By exposing fruit flies to stress or drugs, her group has been able to test the effects of extra demands on Hsp90 function. This causes flies to morph into a number of bizarre forms.

"We saw strange eyes, wings, and legs in a few individuals," Lindquist recalls. When the malformed insects were bred together and selected to have the same unusual development in subsequent generations, they eventually maintained their forms even when normal Hsp90 function was restored. "We deduced that taxing Hsp90 function reveals hidden variation in the genome," Lindquist explains. Hsp90 normally suppresses genetic changes that can alter body shape. When Hsp90 levels are dramatically reduced—say, in response to overwhelming stress—these genetic changes occur and malformations begin to appear. Some scientists now attribute sudden evolutionary changes in the fossil record to the release of hidden genetic variations by corresponding drops in protein chaperones' response to environmental stress.

In addition to using fruit flies, Lindquist performs many initial studies in yeast before turning to animal models. Like mammalian cells, yeast cells are eukaryotic, meaning they have a membrane-covered nucleus and many other biological features of "higher" cells. Prion proteins cause deadly diseases when they misfold in human brains, but when this occurs in yeast cells, Lindquist notes, the effects aren't toxic.

But while using yeast cells as a living test tube to study prion folding mechanisms, she and her postdoc Jiyan Ma, now an assistant professor of molecular and cellular biochemistry at Ohio State University, stumbled upon an interesting finding: When the prion proteins appeared in the interior of the cells, they sometimes folded into a highly unusual conformation known to be associated with human illnesses. Could this internalized prion also cause mammalian disease?

To find out, Lindquist and Ma generated a transgenic mouse that expressed the same interior prion. The mouse became sick, suggesting that some human neurological illnesses arise from a breakdown in the "quality control" machinery that normally degrades misfolded proteins from inside the cell.

"This mouse is showing us that when prions remain [inside the cell], they exist there in a highly toxic form," Lindquist explains. "Does this finding have relevance for all prion diseases? I don't know. But I do think the findings give us a new way to think about these diseases."

What's more, she adds, the research establishes something the scientists have suspected all along. "Protein folding problems are very ancient and the mechanisms cells use to cope with them are fundamental to biology," Lindquist notes. "That means we can use simple organisms to gain important insights into much more complex ones."

PROTEINS AND DISEASE

In many cases, protein investigations drive the search for new ways to prevent disease and treat patients. For instance, Whitehead Member Harvey Lodish is examining the role that a protein hormone called erythropoietin, or Epo, plays in controlling red cell formation. Epo is secreted by the kidneys when the level of oxygen in the blood drops and more red blood cells are needed—as happens with severe bleeding. The hormone binds to a receptor, identified several years ago in the Lodish lab, that is located on the surface of bone marrow cells called erythroid progenitors.

Typically these cells die soon after they are formed. But in response to Epo binding, the progenitors undergo a series of divisions and differentiate into red blood cells. His work with mice has shown that the Epo receptor activates a number of complex signals that together prevent progenitor cells from dying and stimulate their division.

Recently, scientists discovered that administration of Epo prevents the death of brain cells that normally follows a stroke or blow to the head. Lodish wants to know if the "anti-death" signals induced by Epo in nerve cells are similar to those in the red cell progenitors. This property of Epo, if harnessed, could lead to new methods to limit brain damage caused by neurodegenerative diseases.

Lodish's research also may have an impact on treatment for patients undergoing bone marrow transplants for cancers. After the procedure, donor cells in the marrow can attack a patient's organs and tissues, causing debilitating side effects. Scientists long have hoped to reduce the incidence of side effects by using the patient's own hematopoietic stem cells, adult stem cells that produce all the blood and immune cells in the body. But the cells are rare and often located with other, cancerous cells. Producing them in sufficient quantities for therapy is challenging.

Lodish's goal is to ease the burden of locating and purifying hematopoietic stem cells. Toward this end, he recently identified a surface protein called endoglin that is abundant on these stem cells and helps distinguish them from other cells in bone marrow and blood. Endoglin, also necessary for the growth of blood vessels, "flags" hematopoietic stem cells, making them easier to purify. The protein may help clinicians spot stem cells during cultivation, Lodish says, perhaps enabling them to produce enough for effective transplants.

Cell control: Whitehead scientist Harvey Lodish is investigating how the protein hormone erythropoietin regulates red blood cell formation.

THE EMERGENCE OF PROTEOMICS

Research such as this represents the cutting edge of an established, hypothesis-driven approach to protein chemistry. However, a new force—proteomics—also is beginning to shape the field's future. Niroshan Ramachandran, a postdoctoral researcher in the lab of Joshua LaBaer at the Harvard Institute of Proteomics, is part of the next generation of scientists working in this developing area. He and LaBaer have joined with Eugenie Hainsworth, an engineer at the Harvard Technology and Engineering Center, in a project that takes them into the hidden circuits of a devastating killer: breast cancer.

In his workstation at Harvard, Ramachandran points to a computerized map of breast-cancer protein combinations. This map—which looks like a maze of connected dots—merely hints at the true complexity of the cancer process, Ramachandran says. "You can see how it gets more complex as we get to higher densities of proteins," he explains. "We're looking for patterns and stories in these interactions."

Currently, the Harvard map is limited to 30 proteins known to participate in transitional phases of cell replication. If these transitions are disturbed, replication can be amplified, causing the cells to produce tumors. Ramachandran's first goal is to identify protein interactions that might trigger the loss of cell cycle control. The long-term goal, he says, is to map interactions among 1,000 breast cancer proteins. This more complete dataset will portray breast cancer as a biochemical ecosystem, replete with clues to the origin of the disease and new opportunities for drug intervention.

To create the map, Ramachandran relies on a set of high-throughput technologies that scientists use to rapidly assess biomolecules. Indeed, while traditional protein chemists focus on specific pathways, proteomic scientists produce enormous datasets that describe protein locations and activities under normal and diseased states. Ramachandran and his fellow researchers at Harvard are advancing the development of one high-throughput method called the protein microarray. The arrays they work with are made by first spotting gene sequences onto a glass slide. The slide is bathed in a solution containing protein-making machinery, and the genes go into action. Within a few hours, they produce proteins, which remain on the slide after the solution is washed away. The array is then used to assess protein interactions under a range of conditions.

Whitehead Associate Member David Sabatini also has developed an alternate array for studying proteins directly within cells (See story, page 36). Sabatini's arrays are "in vivo"—they are done in living cells, whereas the Harvard arrays are "in vitro," meaning "in glass." The approaches are highly complimentary. In-vivo arrays provide a more natural setting within which to elucidate protein function. But the in-vitro arrays allow for the manipulation of proteins during an experiment.

Proteomics also has been propelled by advances in a high-throughput instrument called the mass spectrometer. This device, used by British researcher Sir J. J. Thomson in his 1897 discovery of the electron, measures the mass of individual molecules as they are converted to electrically charged particles called ions. Biologists use the instrument to sequence biomolecules, including proteins, and to identify their locations. This once was a cumbersome task: Sequences were read by painstakingly feeding molecules into a spectrometer one piece at a time. Today, scientists can identify proteins simply by matching amino acid fragments to nucleotide sequences contained in a variety of genomic databases.

Mass spectrometry has become so powerful, connections among literally thousands of molecular components can be assessed rapidly. With this systems-level view, scientists can obtain highly sophisticated perspectives on the cellular changes associated with disease. The technology has fostered the creation of a new field called systems biology, which combines the work of biologists, computer scientists, engineers, and other scientists to decipher the working relationship among proteins, genes, DNA, and all the other biological elements in a cell that, when put together, produce living creatures. Growing numbers of Whitehead researchers are beginning to think deeply about systems biology, among them Member Richard Young. In research published last fall in the journal *Science*, Young combined a new technique with microarray technology. He and his colleagues conducted their studies on baker's yeast, which has a cellular structure similar to human cells. The technique they developed, with the aid of computer scientists and engineers, allows them to locate regulatory proteins across an entire genome, something never done before. The result is a picture of how the genome is regulated to produce a living cell.

Today, a host of companies are hopping on the proteomics/systems-biology bandwagon, looking for venture capital and funding. But researchers caution that it will take time for systems biology to yield any major new findings. The field is in its infancy, an era of massive data collection. High-throughput methods applied to genomics, proteomics, and other related fields are producing data at a rate that far exceeds analytical capabilities.

"Right now, systems biology is a very trendy thing; it's very exciting and justifiably so," says Whitehead's Lindquist. "But it also provides a very broad overview. Sometimes you can't see the forest through the trees, so you need to narrow your focus with hypothesis-based research. I think the real power will come from going back and forth between these two approaches."

While more Whitehead researchers are looking toward systems biology in their studies, and are working with proteomic methods, Lindquist says much of the faculty's research addresses the more nuanced, hypothesis-based investigations of protein chemistry.

Lodish's work with erythropoietin receptors provides a ready example. These proteins activate multiple signaling pathways within blood progenitor and nerve cells, he says, and a systems perspective is needed to understand how they all are integrated to control cell behavior. However, many of these signaling proteins are "low abundance," too few in numbers to be picked up by current proteomic instruments. Mass spectrometry, for instance, still is unable to detect many of the proteins involved in disease. Epo receptor proteins, which Lodish cites as an example, constitute just "one part in a million to one part in 10 million of the total cell protein."

So, Lodish must apply more traditional tools to assess the function of these proteins. Among them are "gene knock-out" mice in which specific genes have been inactivated to allow scientists' studies of disease. Epo receptor knock-outs enable Lodish to deduce the receptor's role by observing how red cell dynamics change in the absence of the protein. In yet another technique, the proteins can be over-expressed by deliberately introducing large numbers of receptor-coding genes into the cell's DNA. This approach floods the cell with receptor proteins, causing the related signaling pathways to be hyperactivated.

Whitehead scientists also are employing a new method to assess protein function that many believe could revolutionize biology. This technique, called RNA interference (RNAi), enables gene expression—and thereby protein chemistry—to be selectively controlled. In RNAi experiments, tiny molecules called "short interference RNAs" bind with the targeted messenger RNAs that carry a gene's protein building instructions. The RNA binding effectively blocks the gene's activity, so that targeted proteins are never formed. RNAi has the advantage of being fast and efficient—a sharp contrast with gene-knockout methods that can take months or even years to develop. "RNAi is extremely popular now," Lodish says. "We use it routinely in our studies. You can use it to look at effects in whole animals or in cultured cells. You can also screen

thousands of RNAi's, but that's very tedious; it will require robotics. But that's a direction in which a number of our projects may go."

DISCOVERING NEW CLINICAL OPPORTUNITIES

Ultimately, scientists are confident that proteomic research will produce clinical advances. Especially promising opportunities lie in the diagnostic arena. The more scientists learn about how proteins function in healthy and diseased states, the better they get at identifying proteins that predict the course of a given illness. Such proteins, also called "biomarkers," will someday be easily identified on the basis of clinical screening. Armed with proteomic data, clinicians will have better opportunities to select the best course of treatment.

Proteomics may enhance drug development efforts, but experts caution that at least five to 10 years will pass before the technology yields new, marketable products. Experimental methods are still under development, experts say, and the process of ushering new drugs through the Food and Drug Administration is time consuming.

Nevertheless, scientists are optimistic that new therapeutic opportunities await. For instance, it may someday be possible to develop drugs that repair deformed proteins as a means of curing a patient. These would represent a whole new class of drug targets. Most drugs on the market today inhibit enzymes involved in disease processes. Drugs that target folding problems could greatly expand the clinician's arsenal. But designing protein-fixing medicines is challenging, in part because scientists often don't know the actual 3-dimensional shape of a protein, let alone how to restore it to some target conformation. Revealing protein structure is difficult, particularly for large molecules that can be thousands of amino acids in length.

According to University of Southern Denmark's Mann, misfolded proteins often exist in a flexible, random structure that is particularly hard to elucidate, especially for drug targeting. "Normally, we design small molecules that simply bind with proteins and inhibit what they do. Here, we're asking for something completely different: We're asking the drug to bind with the protein and change it from one structure to another. That's a lot to ask. Nevertheless, many neurodegenerative diseases act by these folding pathways. So, this research is very cutting edge and has great promise for the future, even though it's very speculative."

Conformational changes also are the bane of computer modelers trying to develop complex models of cell behavior. These efforts require that biochemical processes be reduced to a series of mathematical equations, so that cell changes resulting from a given stimulus can be predicted and quantified.

The participation of computer scientists in these endeavors reflects the multidisciplinary nature of modern protein research. Today, computer scientists and other information technologists work side by side with biologists in the laboratory. In many instances, the academic lines are blurred—computer scientists become biologists and vice versa. It's a marriage of necessity: Proteomics is generating data at a rate that far exceeds the analytical capacity of the mere mortal. Sophisticated computer algorithms are necessary to wade through it all. And the arrangement is by no means one sided. Just as information technology enables biology, so does the latter enable the former. Researchers now are using electronic circuits to manipulate DNA and control protein expression.

Lindquist also is wading into the information technology arena. In a recent project, she began to construct tiny wires for nanoscale

Making a map: Harvard's Niroshan Ramachandran used the Nucleic Acid Programmable Protein Array to generate a map that illustrates interactions among proteins that may play a role in cancer development.

electronics out of a protein derived from yeast. The self-assembling protein forms fibers that can be coated with mixtures of silver and gold. The resulting metal wires are as narrow as the span of a few dozen atoms. The most ancient structures in biology therefore serve as the backbone for some of the most advanced electronics currently in existence.

Clearly, proteins have much to teach us. And the future will provide many years of opportunity to study the lessons they offer.

[*For more information on protein studies, visit the Lindquist lab at* www.wi.mit.edu/far/far_lindquist_lab_page1.html*; the Lodish lab at* web.wi.mit.edu/lodish/*; and the Harvard Institute of Proteomics, at* www.hip.harvard.edu/.]

A national report says postdoctoral researchers are “indispensable” to the advancement of science, a fact often overlooked by institutions and funding agencies. Now, postdocs are pushing for change. And people are listening.

Drivers

by Kelli Whitlock

It's a windy Monday afternoon in July and 5-year-old Luke, a rough and tumble fellow with dark hair and curious eyes, is in his backyard with his 2-year-old brother, Jared. The pair zip across the grass and scramble atop their jungle gym with the kind of verve that seems to fade soon after adolescence. Their mother looks on with admiration. If only she had their energy.

The brothers and their parents, Laurie and David Boyer, returned

# of discovery

the day before from a week's vacation on Cape Cod. Monday is Laurie's day off, and she's spent part of the time unpacking from their trip—suitcases full of clothes, bags of toys, her laptop. Like many working parents with demanding careers, Laurie had to take care of things back in the office while she was away. There were e-mails with her supervisor, articles to review for a paper she's writing. Laurie's office is a laboratory at Whitehead Institute and her demanding job is that of a postdoctoral fellow.

It's been a challenging road for the 35-year-old postdoc. There have been times when the rigors of the lab have clashed with the trials of motherhood, moments when she questioned her ability to find that perfect balance between work and home. She adores her children. She has a passion for science. The strength of each—and the support of her husband—has provided the leverage she needed to move past uncertain times when she thought about leaving her career behind.

Her challenges are no different from those of any working parent, she says. While she is representative of hundreds of thousands of professional women seeking that balance between home and career, she also is symbolic of today's postdoctoral researcher. These future academic and industrial scientists are older than postdocs of the 1950s, the first period in history to see a dramatic rise in the number of postdoctoral researchers. Most are married and many have young children. The life of today's postdoc comes with many new issues, but much remains the same: low salaries, minimal benefits, a competitive job market.

A 2000 report from the National Academy of Sciences maintains that the 52,000 postdocs in the U.S. are drivers of discovery and innovation in science, medicine, and engineering, crucial to the nation's scientific prowess. Their importance has long been dismissed by institutions that employ them and funding agencies that cover their wages, claims the report, which offers a laundry list of recommendations to improve postdocs' quality of life and scientific experience. Topping that list are higher wages and better benefits. But there are other issues. Most of the nation's postdocs are in the life sciences, doing work in such cities as Boston and Palo Alto, where the cost of living is extraordinarily high. Access to affordable childcare is limited and many postdocs lack retirement benefits. The average postdoc stint is five years and a weak job market leads many to do more than one rotation. Mentoring and professional development are in short supply, while the feeling of isolation haunting many postdocs is widespread.

Some institutions responded to the academy's findings with plans to increase wages and expand benefits. But improvements vary from institution to institution. To truly effect change, explains the academy report, the nation must first ask: Just what is a postdoc, anyway?

A national resource

Postdocs historically have been viewed as research apprentices, a philosophy developed in the mid-1870s at Johns Hopkins University. Fifty years later, the Rockefeller Foundation formalized the postdoc position by creating a fellowship program designed to allow physicists more time to learn the nuances of their science, a feat that no longer could be done within the confines of traditional doctoral study.

The number of postdocs increased marginally until the late 1950s, when the race for weaponry and technological superiority spurred the government to increase funding for science and engineering and heightened the demand for scientists. Between 1960 and 1970, the U.S. postdoc population tripled. Then and today, the majority of postdoctoral positions are in the life

Having it all: Balancing parenthood with postdoctoral research is far more common today than in years past. Whitehead postdoc Laurie Boyer plays with sons Jared (foreground) and Luke.

MARK OSTOW

MARK LEE

Strength in numbers: A report on the value of the country's 52,000 postdocs sparked the creation of the National Postdoctoral Association, says executive board chair Carol Manahan.

sciences. The mix includes scientists who completed graduate degrees outside the United States, but traveled to this country for advanced training. International postdocs account for about half of all those in the U.S., a trend that began in the 1970s when federal fellowships—and subsequently the number of American graduate students—decreased.

Today, about 80 percent of postdocs work in academia. According to a 2001 National Science Foundation report, Harvard University has the most postdocs in the nation—3,597. Stanford University is second with 1,210 and Johns Hopkins is third with 1,159. Massachusetts Institute of Technology, with 828, ranks No. 11.

Institutions haven't always tracked such statistics. When the Committee on Science, Engineering, and Public Policy—COSEPUP for short—began collecting data for the 2000 National Academy study, "Enhancing the Postdoctoral Experience for Scientists and Engineers," it found that many universities didn't even know how many postdocs they had.

"Some places had postdocs as students, some had them as faculty, some had them as staff," says Maxine Singer, chair of the committee that published the 2000 report. "No one had really focused on the fact that there was this population of people called postdocs."
Four years ago, Stanford University launched a university postdoc association, one of the first institutions in the nation to do so. (Johns Hopkins was the first, in 1992.) In addition to a desire for better pay and benefits, one motivation for forming the group was to educate people at the university about just what a postdoc was, recalls Mark Siegal, cochair of the organization.

"Even going into your department office and asking to check out a slide projector became a difficult thing," Siegal says. "They assumed that you were not very valuable at all, because you weren't a grad student and you weren't faculty."

Things are different today, he says. And yet, the classification at Stanford is proof of the confusion across the country. At Stanford, postdocs are labeled "nonmatriculated graduate students" and are assessed tuition of $125 a quarter. (It was nearly $1,000 a quarter until last year.) At Harvard University, all postdocs are called fellows. At Whitehead, postdocs with independent funding are fellows and those whose salary is covered in their advisers' grants are associates.

Developing a standardized definition is one goal of the National Postdoctoral Association, created last spring with a $450,000 grant from the Alfred P. Sloan Foundation and supported by the American Association for the Advancement of Science. The organization held its first annual meeting in March, an event that emphasized key issues on the minds of postdocs around the nation, says Carol Manahan, chair of the association's executive board and a Johns Hopkins postdoc.

"People have tried to start nationwide postdoc organizations in the past, but they have not been successful," Manahan says. "I think when the reports on postdocs came out, people began debating these issues. A lot of things came together to make this time right."

A study of demographics

Timing is everything for working parents, a mantra Laurie Boyer knows well. A postdoc working with Whitehead Member Rudolf Jaenisch, Boyer works long hours in the lab Tuesday through Friday (and sometimes on weekends) so that she can be home with Luke and Jared on Mondays. Her husband David, an engineer with the Massachusetts Department of Environmental Protection, rearranged his work schedule to be at home with the kids on Fridays. Tuesday through Thursday, the boys have a nanny.

"We wanted to minimize the amount of time our kids spent with someone other than a parent," Laurie says. "It was very important to us."

Equally important is *how* she spends time with her kids, adds Laurie. When she's with them, she tries to focus exclusively on them. The science waits until they go to sleep, when Boyer sets up a makeshift office at the kitchen table. It's often in the wee hours of the morning before she calls it a day.

"I don't think I'm doing anything extraordinary compared to other postdocs," Laurie says. "Maintaining a balance between family and career is challenging, but it has been my choice." She runs her hand along a pink cloth heart filled with fragrant lavender, a gift from Luke, and struggles to find words to express her thoughts.

"Being a postdoc is a great opportunity. I didn't want to have to give up on that," she explains. "But I want to be good at both—being a

mom and a scientist. I think it's important for my children to see that it is possible."

The drive to excel in parenthood while also holding onto a science career is growing more common, according to the COSEPUP report. A survey conducted two years ago by Whitehead's postdoc association suggests about one-third of the Institute's postdocs have at least one child. Other institutional surveys yield similar results.

It's a matter of math, really. People are taking longer to complete their doctoral training and rather than starting a postdoc in their mid- to late 20s, many folks are in their 30s by the time they begin that level of professional training. At Whitehead, the average postdoc is 32 years old.

"I think it's much harder to have a family when you're doing a postdoc," says Whitehead Member Hazel Sive, a faculty adviser to the Whitehead Postdoc Association, which formed last fall. "But if you are in your 30s, putting things off can have devastating consequences. It is an enormous problem, especially for women, and I think it needs to be addressed on a national level."

Standards of living

Susan Lindquist was in her mid-20s when she began her postdoc at the University of Chicago in 1974. The current Whitehead Institute director doesn't recall her exact salary, but remembers that "It was considerably more than I was making as a graduate student, but not enough to get started on a life of your own."

For many, starting a research career is more about a yearning for science than it is about money. "I was just so compelled to go into science, I just didn't think about the salary," Lindquist says. "In retrospect, I really don't think it was right to have to live that way."

According to the COSEPUP report, a postdoctoral scholar in the late 1990s earned an average of $30,000 a year within six years of completing a PhD. In that same time period, the salary of a 25- to 34-year-old bachelor's degree recipient was around $35,030.

"Postdocs are supposed to be getting advanced training, learning how to be independent scientists, getting mentoring," says Singer, who was named chair of Whitehead's Board of Directors earlier this year. "They are getting something of value, whereas if you just go for a job, you don't expect to get something of value for your future other than a salary."

Even so, Singer says, the wages some institutions historically paid was unjustifiably low.

"For many senior scientists, the situation as it existed was acceptable," she says. "They got highly skilled, highly educated people, working for very moderate sums. The mentors were getting very cheap, very fine labor."

Most universities and research centers have for decades used the minimum postdoc pay scale set by the National Institutes of Health as a guide for their institutions' salary ranges. That was never the intention of the agency, the single largest funder of postdocs in the U.S. That scale applied to individual recipients of NIH postdoctoral fellowships, not to postdocs who were paid through their principal investigators' grants, which is how most postdocs in this country are paid. Setting the range for those postdocs, the agency argues, is up to the investigator. Some investigators argue it should be set by NIH.

Many institutions, recognizing this isn't an easily solved battle, have charged ahead with their own salary and benefits changes, choosing not to wait for federal agencies to set the standard for postdoc pay. Whitehead Institute began a review of its postdoc salaries and benefits packages three years ago.

In 2000, when that review began, Elizabeth Wiellette, a postdoc in the Sive lab, received an NIH fellowship. Wiellette went from a classification of postdoctoral associate to postdoctoral fellow. She brought nearly $100,000 into the Institute to cover her salary—and immediately lost her benefits package. At the time, only associates received full benefits because they were Whitehead employees—their salaries were paid by the Institute. Fellows were paid by outside agencies and were subject to IRS rules that made it difficult to offer them regular employee benefits.

"Seeing other people in the lab who were ineligible for fellowships or who hadn't won them getting really good benefits, while I, who was bringing money into the Institute and the lab, lost my benefits, seemed wrong," Wiellette recalls.

So, when Wiellette learned that the administration was forming a

GLEN MATSUMURA

Defining moment: Postdoc Mark Siegal was part of the group that created a postdoc association four years ago at Stanford University to lobby for better pay and benefits.

committee to lead a postdoc compensation and benefits review, she volunteered to help. Realizing the challenges presented by strict tax laws and inflexible benefits providers, the postdocs, faculty, and administrators on the committee knew that finding equitable solutions would be difficult. The group spent the next year gathering data and building a proposal to increase postdoc minimum salaries and help equalize benefits for fellows and associates.

The plan, which would cost nearly $1.5 million to implement, was expansive: Minimum first-year postdoc salaries would be increased from $28,260 to $36,000; the Institute would subsidize the difference between postdoc fellowship stipends and the new Institute minimum. Fellows would continue to receive their fellowship salary after their grant expired and they moved to associate status. Associates and fellows would receive access to similar health insurance plans, which would be funded either out of a central funding pool or through other Whitehead or lab resources; all postdocs would have free access to dental insurance. Postdoctoral associates hired before July 1, 2002 would continue their participation in the Institute's employee retirement plan as long as they retained associate status, while postdoctoral fellows and any associate hired after July 1, 2002 would receive an annual cash stipend of $2,000 to invest in a Roth Independent Retirement Account. Implementing such a broad and expensive plan during tough economic times would require a keenly persuasive argument before Whitehead's Board of Directors.


MARK OSTOW

Plan of action: In 2002, Whitehead raised postdoc salaries and improved benefits, welcome news to postdocs like Elizabeth Wiellette, who helped draft the new compensation plan.

"I wanted the Institute to be known as the most ideal place to do postdoctoral research in the country," says Lindquist, who made improving conditions for postdocs a priority when she was named director in 2001. "And that means a good salary, opportunities for mentorship, career development. We have to pay attention to all these things."

Lindquist knew mentoring and professional development needed to be addressed. But improving salary and benefits had to come first. She and the postdocs, faculty, and staff on the committee made their case before the board, and the plan was approved.

"Before the committee started this whole process, everybody said, 'You can't do this,'" Wiellette says. "But we did it."

Other institutions have enacted salary increases and changes in benefits packages, but according to the National Postdoctoral Association's Carol Manahan, Whitehead set the stage.

"Whitehead was the only place that actually made a comprehensive review of postdoc salaries and benefits," Manahan says. "It's really one of the models to look toward when other people ask how they should set up their policies."

Among the other institutions experimenting with new salary plans is Stanford University, which raised its first-year minimum postdoc salary to $36,000 this fall.

Harvard University introduced a new benefits plan July 1 that offers most postdocs access to dental insurance, short-term and long-term disability, life insurance, a choice of four or five health plans, discounted mass transit passes, tuition assistance, and other perks. Most responses to the plan have been positive, says Roz Orkin, assistant dean for faculty affairs who oversees Harvard Medical School's postdoc office. However, Orkin admits that there have been complaints from some postdocs who receive stipends from external funding agencies, who now must pay more for health care insurance. Before the roll-out, these postdocs had access to a lower-cost, limited-coverage health plan available to all Harvard students. That plan is no longer an option for them. But even if it were, Orkin notes that plan's cost is set to increase by 59 percent this year.

MIT is heading down a similar road with plans to explore ways for the university to equalize health insurance benefits for all postdocs. The provost hopes to devise an initiative by the fall. But the question, says MIT Special Projects Director Marilyn Smith, will be "How to pay for it?"

Something of value

There couldn't be a worse time for the nation to experience a record-high number of postdocs. The harsh economy is unforgiving when it comes to job creation in the sciences, especially in academia, which is where most postdocs want to work. When asked where they hoped to find work after their postdocs ended, nearly all the participants in Whitehead's postdoc survey pointed to academia. When asked if they were certain that their careers would go in that direction, two-thirds rated their confidence as low to medium.

"I think good people definitely fall through the cracks and don't get jobs," says Stanford's Siegal, who is in his fourth year as a postdoc. "Some people stay in postdocs and just keep trying year after year. Some go into industry. Some take jobs they never would have taken otherwise."

Industry is an option many are considering. A report released earlier this year by the nonprofit research group Commission on Professionals in Science and Technology found that the number of people entering industry after completing a PhD increased from 20 percent to 30 percent over the past two decades. Those choosing academia over industry cite as their primary motivation the ability to publish, something they fear would be limited in a business setting. Many also wish to teach, another reason to continue the search for a collegiate position.

There is little to be done about a slumping job market, except to be vigilant in the job search and examine all options. Aside from that concern, most postdocs agree that salary and benefits are areas that need immediate attention. Among those issues that remain is the need for professional development and a desire to foster a stronger sense of community among postdocs.

"Every point until now, you come into a new situation with a group of people who are going through it at the same time. Everyone is starting at the same point and you have this built-in support network," says MIT Postdoc Association member Penny Beuning. "For postdocs, you don't have that. Everyone comes in at different times from different places, with little orientation or training."

Building community and offering professional development are on the planning boards at many institutions. One project under development at Whitehead is a Second Mentoring Program, an initiative involving the work of several postdocs and the faculty adviser, Hazel Sive. The program will offer postdocs an opportunity to work with several mentors who might offer counsel on a variety of topics. Other initiatives, such as programs on lab management and grant writing, are in the works.

Meanwhile, attacking salaries, benefits, and professional development concerns goes a long way toward meeting the guidelines set out in the National Academy's COSEPUP report. But universities want more.

"It provides a wonderful list of recommendations, but no road map for implementation," says Harvard's Orkin.

Perhaps that's because the map will be different for each institution. Although conceiving some standard guidelines on postdocs would be helpful—for example, a uniform definition to ease the fiscal confusion surrounding management of postdoc salaries and benefits—there likely never will be one right way to structure a postdoc position.

However, the academy's report suggests, there is one thing to keep in mind when contemplating the value of postdoctoral researchers: "As a whole, the postdoctoral population has become indispensable to the science and engineering enterprise, performing a substantial portion of the nation's research in every setting."

Their role isn't likely to diminish any time soon, the report continues. Other agencies will be looking to gather data on the nation's postdocs in the near future. The National Science Foundation plans to do a better job of tracking the postdocs that agency funds; both NSF and NIH have plans to raise postdoc minimum salaries, a trend they hope all research institutions will strive to match. Indeed, it's a goal worth attaining, Lindquist remarks, and not just for the postdocs.

Community of scholars: Penny Beuning joined MIT's Postdoctoral Association to help create a sense of community among that university's postdoc population.

"I think it's extremely important for the well-being of science and the future of our country," she says, "that we make science a profession that is not associated with self sacrifice."

Laurie Boyer couldn't agree more. She talks to her children often about the value of choices, the privilege of mapping your own course in life. It's a concept 5-year-old Luke is just beginning to process. "Mom says we have choices," he says in a small, unsure voice, glancing at his mother to make sure he got it right. Teaching her sons such lessons is something Laurie's not willing to sacrifice. If the recent move to improve the postdoc experience continues, she and those who follow won't have to.

[*For more information on postdoctoral researchers, visit the National Postdoctoral Association at* www.nationalpostdoc.org.]

The Y chromosome has been called the Rodney Dangerfield of the genomic world. New studies suggest it's time to give the chromosome a little respect.

the "Y" files

Text by Kelli Whitlock

Photography by Sam Ogden

Not everyone believes in chance—the fortuitous twist of fate that takes a person down an unforeseen path. David Page believes in chance. For him, fate came along on the tip of a light brown wooden toothpick.

Page was a first-year medical student and research assistant in Cambridge, Massachusetts, in 1979 when he signed up for a study to map all the genes in the human body. (Seven years later, this effort would become known as the Human Genome Project.) His first task was to analyze thousands of recombinant DNA clones, searching for those most suitable for study. Each clone was selected randomly, and rather unceremoniously, from a sea of thousands. The instrument used for this scientific experiment: a toothpick.

It was summertime and Page was spending hours in the lab, waving a toothpick above trays of DNA clones, choosing one, examining it, and choosing another. One afternoon in particular stands out in his memory. What ended up on the bottom of his toothpick that day was a clone of DNA shared by the X and Y chromosomes—the sex chromosomes whose combination determines whether a human is male or female. He examined the clone, pondering its potential for his project, just as he had done with dozens of others. It's only in hindsight, 24 years later, that the magnitude of that random selection became clear.

"When people ask how I picked the Y chromosome for my research, I often say, 'I didn't. It picked me,'" Page says. "If I hadn't picked that clone out of hundreds of thousands I'd probably be a cardiologist."

Not a cardiologist, but a scientist at Whitehead Institute and an investigator with Howard Hughes Medical Institute, Page is considered to be among the world's leading experts on the Y chromosome, the defining biological determinant that makes males male. In 1992, his lab announced the first successful cloning of a human chromosome—the Y chromosome—and in June of this year, he led a team that published the complete sequence of the Y on the cover of *Nature*, work that offers not only a road map for scientists who study male infertility, but also casts doubt on a decades-old theory that destined the Y to extinction.

And it all began with a fateful stab of a tiny wooden stick.

Drawing board: Research by Whitehead Member David Page is helping scientists draw a clearer picture of the male-determining Y chromosome.

The Y's demise

Scientists marvel at the nuances of the human genome, the mysterious alphabetical configurations of DNA and the construction of cells and genes and chromosomes that work together to help us live, reproduce, and evolve. At the heart of human evolution is the body's ability to repair genetic flaws through a process called sexual recombination.

All humans receive a set of chromosomes from Mom and a matching set from Dad. Over the course of many generations, chromosomal pairs can swap damaged genes for good ones and fill in gene sequences that may be missing on one chromosome but present on its mate. This swap—called recombination—doesn't fix all damaged or missing gene sections. It's up to natural selection to eliminate those that make it through without repair.

If all chromosomes had a matching partner, the story would end here. But the complexities of human biology make things messy. Of the 24 chromosomes in the human genome, 22 come in identical pairs in both males and females. Women have another matching set—two X chromosomes that together cast a developing fetus in a female role. But men have a mismatched arrangement of sex chromosomes—one X and one Y. Lacking a mate, the Y can't swap its defective genes for good ones.

The Y has paid dearly for this bachelor status over time. When sex chromosomes first evolved some 300 million years ago, the X and Y each had about 1,000 genes, which they swapped with each other.

Somewhere along the way, the Y lost its ability to share genes with the X. As defects in the genetic structure appeared, the Y was stuck with them and most of the chromosome's genes weakened or died out altogether.

Indeed, in the biological battle between the sexes, the Y chromosome has suffered defeat after defeat. The male-determinant has seen its gene supply shrink to what scientists thought was only a handful of genes; some speculated that there was just one lone gene on the Y—the one responsible for maleness. It was a downward trend predicted to continue until the Y disappeared altogether.

The male-determinant has seen its gene supply shrink to what scientists thought was only a handful of genes; some speculated that there was just one lone gene on the Y—the one responsible for maleness.

X marks the spot...or does it?

David Page is a lone Y in a house full of Xs. He and his wife Elizabeth have three daughters, an irony not lost on a man whose research subject often provides fodder for only half-feigned derogatory sarcasm from the double-X gender. The Y chromosome long has been the whipping post for all stereotypical male traits—all *negative* stereotypical male traits—including everything from an inability to ask for directions to the bewildering memory skill that allows for instant recall of exact dates of historical sporting events but not dates of anniversaries and birthdays.

Subscribing to the "If you can't beat 'em, join 'em" philosophy, Page's research presentations often include a slide featuring certain "genes" identified along the Y chromosome: the genes for channel flipping (FLP), spitting (P2E), the ability to identify aircraft from a distance of 10,000 feet (DC10), and selective hearing (HUH?).

Obviously, the 47-year-old Pennsylvania native has a healthy sense of humor. He also has a fondness for treading on uncharted territory. As a high school senior in a small rural town near Three Mile Island, Page applied to Swarthmore College, a private, liberal-arts college, while many of his other classmates chose to remain closer to home. He was accepted and enrolled as a freshman intent on a career in environmental law. While Page enjoyed a rich exposure to chemistry, physics, and biology in high school (he calls the experience a "Sputnik education," sparked by the nation's 1950s desires to outpace the Russians in space and science), he also enjoyed the debate team, and law seemed a natural step.

"When I was growing up, science was very much an abstraction because I'd never met a scientist. I had no idea what a scientist looked like or, for that matter, if anyone actually was a scientist," Page recalls. It took a while for the science to take hold, but by his junior year at Swarthmore, he "came back to the Sputnik stuff."

Page spent two summers as a research assistant in biology labs, first at Brookhaven National Laboratory on Long Island, New York, and then at the National Institutes of Health in Bethesda, Maryland. At NIH, he studied nucleosomes, basic subunits of the chromosome. He was hooked.

He applied to the Health Sciences and Technology Program, a joint initiative between Harvard University and Massachusetts Institute of Technology that integrates education and research in science, engineering, and medicine. To fulfill a research thesis requirement, he joined the lab of David Botstein at MIT, a pioneer of the Human Genome Project who now leads Princeton University's

genomics institute. It was there that Page had the chance meeting with a gene clone shared by the X and Y. The Y wasn't all that interesting to genetic scientists at the time. Seemed like a perfect fit for a man who enjoyed forging paths rather than following them, so when Page received his MD and joined Whitehead as a Fellow in 1984, he continued the work he began at MIT—a project to map the Y's gene sequence.

Making a map

In 1992, four years after being named an Associate Member at the Institute, Page's lab cloned the Y chromosome—the first time anyone had cloned a human chromosome. Over the next 10 years, the scientist's work revealed new information about the evolution of the Y and the function of its genes. In the late 1990s, the biologist and his collaborators published findings that suggested that infertile men who father children through a common type of in vitro fertilization can pass along to their male offspring the very genetic flaws that caused their own infertility.

But the biggest advance—the completion of the Y mapping project—was announced at a Washington, D.C., press conference in June 2003. The effort, led by Page and collaborators from Washington University School of Medicine in St. Louis, yielded 78 genes on the chromosome—far more than the handful rumored to remain on what had come to be called the "rotting Y."

And there's more: While it's true that over millions of years the male sex chromosome has lost hundreds of genes and seen many others crippled, the biggest concern has been gene health in the regions of the Y that control sperm production. But this new genetic map reveals a series of massive palindromes—stretches of gene copies that are 99.9 percent identical to one another. A palindrome is something that reads the same forward and backward (i.e., MADAM I'M ADAM), and the researchers found eight of them in the region of the Y responsible for sperm production. The scientists suspect that this genetic "hall of mirrors" provides a mechanism for self-repair, a way for the Y to prevent the erosion of these critically important genes.

Technology has not yet provided a window to watch the chromosome in action, which leaves the researchers to infer the function of these duplicate gene sequences. Say a gene copy along one of these palindromes suffers a mutation. By bending into a hairpin formation, the injured gene pairs with its copy, and the good gene may overwrite the bad one. Essentially, the Y combines with itself.

"This study shows that the Y chromosome has become very efficient at preserving its important genes," says Richard K. Wilson, director of the Genome Sequencing Center at Washington University School of Medicine in St. Louis, where the Y was sequenced. "It's found different ways to do the things chromosomes must do to evolve, survive, and thrive."

But this secret weapon was not revealed easily. While other chromosomes are known to have duplicate genetic sequences, none contains quite as many. Wilson's team recently completed sequencing chromosome 7, a task he considered among the biggest challenges his lab has tackled. Duplicate sequences constitute about 8 percent of that chromosome; they make up half of the Y.

"There are some things that just don't like to be sequenced," Wilson says. "They can be a bit resistant to being deciphered by the usual biochemistry methods we use. So, we had to use some alternative biochemistry for the Y."

Researchers mapped the gene sequence of a Y chromosome from an anonymous male, as well as parts of a Y chromosome from a chimpanzee. This technically challenging process involved delicately unwrapping the two arms on each of the eight palindromes and analyzing the near-identical gene sequences inside.

"Most chromosomes are like a typical thousand-piece jigsaw puzzle—a pretty picture split into pieces with easily identifiable markings," says Wilson. "The Y chromosome, on the other hand, was like a picture of a small sailboat on the ocean with lots of blue sky, no clouds, and hundreds of pieces that looked exactly alike. Determining exactly where each piece went in the grand scheme required a lot of work."

Key to these findings is that researchers identified this gene repair technique not only in a human Y chromosome, but also in a chimp Y.

"When we look at the human Y, compared with the chimp Y," Page says, "what we can infer is that during the last 5 million years, since we and chimps parted company, this overwriting of one gene copy by another has been going on frequently in our Y chromosome and in the chimp Y chromosome."

Questions answered, questions raised

Studies of the Y chromosome in humans and other species haven't always caught the collective eye of biologists. In fact, the Y chromosome has not been studied in comparable detail in any other species.

But the small number of people interested in the Y has steadily increased in the last few years. Today, the field is populated with researchers interested in a variety of projects in which the Y chromosome is implicated, including the mystery surrounding the origins of modern populations (called the search for Y-Chromosomal Adam) and male infertility.

Millions of couples in the United States alone have trouble conceiving a child. In about 30 percent of

those cases, the problem is related only to male infertility. Steve Rozen and Helen Skaletsky, scientists in the Page lab and coauthors of the *Nature* studies, are interested in applying the information they've learned about the Y's genetic make-up to their male infertility studies. Of all the genes the team identified on the chromosome, all but 18 are active in the testes, Rozen says.

"Some of these genes are essential for normal sperm production. For others, the fact that the gene is active in the testes merely suggests a role in sperm production," Rozen notes. "We are interested in looking for damage to these genes in men who do not produce normal numbers of sperm. Finding a newly damaged gene in a man with poor sperm production tells us that the damage caused the sperm production problems."

Understanding the structure of the Y chromosome may be a significant step forward in the effort to treat male infertility. But, Rozen cautions, science moves at its own pace, which is hardly ever fast.

For some scientists, though, the payoff of this work is more immediate.

"I thought about, talked about, wrote about the Y as a rotting chromosome that really only had one important gene—the one that determines sex," says Scott Hawley, a biologist with the Stowers Institute for Medical Research in Kansas City, Missouri, who studies chromosomal pairing. But these new findings make "perfectly good sense," Hawley adds. "It's one of those 'Ah-ha!' experiences that, after you hear it, you think, 'It had to be that way. Why didn't we think of this before?' It's just revolutionary work."

The research could perhaps have the most significant effect on studies of heterochromatin, highly condensed chromatin (portion of a cell nucleus that contains all the nucleus's DNA) strains once thought to be useless genetic wastelands but now known to be essential for normal chromosomal behavior.

"David's really given us an analytical approach to studying heterochromatic regions on a larger scale," says Hawley, who authored a review of the Page lab findings for the journal *Cell*. "It's a new paradigm for thinking about the structure of the heterochromatic regions, and there are a lot of people who think about this kind of stuff."

Getting a little respect

"I often say that the Y chromosome is the Rodney Dangerfield of the chromosome world," Page jokes. "It gets no respect."

No respect and little credence: When the completion of the mouse genome was announced in 2002, it was not really complete. The mouse Y has not yet been sequenced.

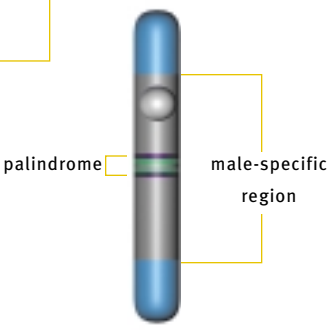
A 2002 article in *Nature* by two Australian scientists rang a death knell for the Y chromosome, claiming that "The original Y chromosome contained around 1,500 genes, but during the ensuing 300 million years, all but about 50 were inactivated or lost… . At the present rate of decay, the Y chromosome will self-destruct in around 10 million years."

There's no denying the Y has problems. While this new research shows that there are more genes on the chromosome than once thought, as Page points out, the Y still has lost a lot of genes. But to expend its energy on protecting the genes that are most important, the ones that keep it from extinction—now that, Page says, is clever.

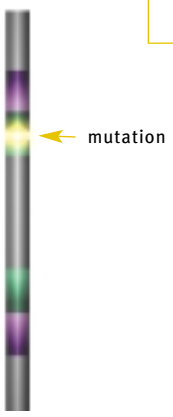
A pair of ordinary chromosomes: One from Mom and one from Dad.

Ordinary chromosome pairs can swap parts, which allows injured (mutated) genes to be replaced over many generations.

The X and Y chromosomes swap parts only at their tips.



1 of 8 palindromes in the male-specific region of Y chromosome.

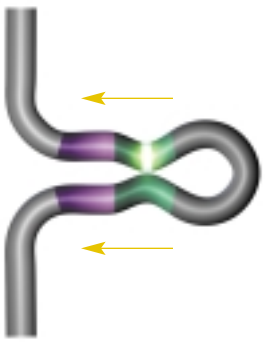


Enlargement of a palindrome. One gene copy injured by mutation.

"The Y has found a way to keep these genes coherent despite a rather unstable structure," says Robert Waterston, now a scientist at the University of Washington who was a lead researcher at the Genome Sequencing Center at Washington University during these studies. "That instability of structure could be disastrous for a particular individual, but it won't be disastrous for the Y, because the deleted Ys would not be passed on."

Still, not everyone is convinced that this justifies a newfound respect for the Y chromosome. The oft-targeted male chromosome took a thrashing in a column published in early July in the *Boston Globe* by David Bainbridge, a fellow of St. Catharine's College in Cambridge, United Kingdom, and author of *The X in Sex: How the X Chromosome Controls our Lives.*

"Page's research appears to demonstrate that the Y chromosome contains clear evidence of trying to patch up its wounds by swapping bits with itself. Of course, this is still an inefficient way of losing damaged genes. It may hold things together in the short run, but it's no healthy way for a self-respecting chromosome to carry on," Bainbridge wrote.



Correction of mutation by copying from near-identical partner on opposite arm of palindrome.

COURTESY OF HOWARD HUGHES MEDICAL INSTITUTE

"The idea of the Y as a shiftless, no-good degenerate chromosome is entirely too appealing and attractive to resist for reasons that have little do with science and lots to do with sexual politics." — *David Page*

Attacks such as this confound Page at times. He acknowledges that the Y likely will always be the butt of many jokes. Still, when the abuse is heaped on by other scientists, it gives him pause.

"The common perception of boys and girls, of men and women, greatly impacts biologists' perceptions of the X and the Y," Page says. "The science and the sexual politics become blurred. The idea of the Y as a shiftless, no-good degenerate chromosome is entirely too appealing and attractive to resist for reasons that have little do with science and lots to do with sexual politics."

The road ahead

Over the last two decades, the Y chromosome has revealed itself to be far more complicated than anyone thought. What many scientists overlooked for other, seemingly sexier research topics has provided Page with a biological challenge that is far from over.

"There are many points in the course of a line of experiments where you choose to believe or disbelieve something and you choose to follow it up or let it go," he says. "The history of Y chromosome research is strewn with prematurely abandoned lines of work."

But there was something about the chromosome that demanded Page's attention. As the sequence of the Y was coming together, scientists learned bits and pieces about the chromosome. But until the map was complete, Page says, they were fumbling along in the dark. Now, the team will use the human Y as a reference for the study of the Y chromosomes of other organisms.

Already under way are projects to sequence the male-determining chromosome in the chimpanzee and the mouse. The chimp Y should be complete in 2004 and the mouse Y the following year.

"We've seen the Y in humans and we've started to see little bits in the chimp and we're beginning to see that there's something a little different," Wilson says. Filling in those missing pieces would go a long way toward understanding how sex chromosomes have evolved and learning why different organisms choose the specific type of reproductive strategy they use.

Of course, the studies of the Y's genetic self-repair system will continue, as will plans to identify how genes in the testes region function, and what happens when they don't.

When Page began this journey, he had no idea where it would lead. It was a chance stab at a gene clone that marked his first brush with what would become a lifetime study. Today, he travels a more purposeful path in his research. Still, he says, smiling, there is much to be said for happenstance.

[*For more information on this research, visit the web at* www.whitehead.mit.edu/nap/features/nap_feature_page_y.html.]

the weeds within US

Fungi and yeast can spread through the body like weeds in a lawn, a biological invasion that has caught the attention of physicians and scientists

Text by Mark Dwortzan Photography by Sam Ogden

When a few dandelions appear on your lawn, you can pick them off easily one by one. But if they spread, the picking becomes laborious, and you may need a chemical weed-killer to keep the invaders in check. After several applications, however, the weeds could become resistant, requiring more powerful herbicides. The stronger the herbicide, the more collateral damage to the lawn you are trying to protect. Meanwhile, the survival of your lawn hangs in the balance.

Like weeds in a lawn, pathogenic fungi and yeasts (single-celled fungi) can invade and overtake our bodies. In people with healthy immune systems, cells called macrophages, dendritic cells, and neutrophils engulf these pathogens. But when the immune system is weakened, fungi can grow unchecked, much like weeds in a garden. In patients with compromised immune systems, an invasion of the common yeast *Candida albicans* can spread to various organs—possibly leading to death.

Physicians often turn to antifungal drugs to keep the yeast under control. Over time, yeasts and fungi can develop resistance to the treatments, forcing doctors to prescribe more potent drugs. The more potent the drug, the greater the potential for harmful side effects. Meanwhile, the patient's health hangs in the balance.

From harmless to harmful

Yeasts and fungi have long enjoyed relatively good relations with humans. Despite their abundance—they appear on plant leaves, and in soil, salt water, baked goods, beer, our gastrointestinal tracts, and on skin surfaces—very few yeasts and fungi trigger disease in healthy people. Present in about half of us, the most common fungal pathogen, *Candida albicans*, can cause easily treatable ailments such as vaginitis, diaper rash, and oral thrush. But according to recent reports, more immunocompromised patients are succumbing to fungal pathogens, leading to thousands of deaths each year.

"Fungal pathogens are becoming much more prevalent in systemic infections because we have a larger immunocompromised patient population," says Robert Wheeler, a postdoctoral fellow in the lab of Gerald Fink, a Member and former director at Whitehead Institute. This includes cancer, AIDS, and organ transplant patients. If infected by the *Candida* species—the fourth most common bloodstream infection in hospitals—these patients face a nearly 40 percent mortality rate.

Treatment is limited to a few marginally effective drugs that produce significant side effects and to which the pathogens are becoming increasingly resistant. "Antibiotics can kill bacteria without bad side effects," Wheeler explains, "but because fungi contain cellular machinery and proteins similar to our own, it's hard to find agents to kill fungi that don't have negative effects on us."

Probing the immune system response

Containing the "weeds" within us requires novel approaches. Researchers in Fink's lab are investigating more virulent forms of fungi to improve scientists' understanding of how fungal pathogens engage the immune system, and to develop more effective antifungal agents.

"People used to study pathogens by taking a microorganism and debilitating it by making a mutation," observes Fink. "But these debilitated organisms weren't always very informative about the healthy pathogen. A much more fruitful

approach is if you make something that's hypervirulent, because genes that lead to a souped-up microbe tell you a great deal about how pathogens behave."

Case in point: An experiment on the yeast *Saccharomyces cerevisiae* conducted by Wheeler, Fink, and collaborators at Boston University and Israel's Tel Aviv University. Used in bread baking, beer brewing, and wine fermentation, *Saccharomyces* often appears in immunocompromised patients, raising questions about its origin, survival, and virulence in humans. In their study, published earlier this year in the journal *Proceedings of the National Academy of Sciences*, the scientists compared the virulence in laboratory mice of *Saccharomyces* strains isolated from the human bloodstream, a rotting fig, and a carefully cultivated, fully sequenced strain of baker's yeast. These comparisons were made before and after knocking out *SSD1*, a gene that influences the yeast cells' surface characteristics and ability to grow at higher temperatures.

In mice without gene modification, the fig isolate was virulent, but the lab strain and human isolate were not. When scientists knocked out the *SSD1* gene, the virulence of the plant and clinical strains rose substantially, suggesting that the removal of *SSD1* changed the composition and cell wall architecture of the yeast cell surface. The mutant yeast also evoked a more powerful response from immune cells. As a result, the immune system's macrophage cells may have misrecognized the yeasts and overreacted, provoking a systematic inflammatory response that ultimately caused the mice to die of septic shock.

The study probes the minimum conditions required for fungi to cause disease, says Phil Robbins, professor of molecular and cell biology at Boston University's School of Dental Medicine. "Defining the subtle mutations that lead to this pathogenic lifestyle will provide important new insights into the primary or underlying mechanisms used by other, more aggressive fungi to produce disease," he maintains.

More to explore

Researchers at Whitehead are combining new genomic approaches and genetic techniques to boost scientists' knowledge of how fungal pathogens infect human, animal, and plant hosts. One key area of this research focuses on the mechanisms that enable yeasts such as *Candida albicans* to change forms. For example, when *Candida* infects the body, the spore-like yeasts germinate and become elongated, filamentous cells. Like other yeasts, they multiply through cell division, or grow as filaments. This filamentation binds *Candida's* cell walls to different tissues.

Studies in Fink's lab of *Candida albicans'* interactions with immune system cells expand our understanding of how the immune system recognizes and defends against different fungal pathogens. Fink and others also want to learn why these pathogens resist antifungal drugs. A better understanding of these processes could help researchers develop more accurate and effective drugs to contain them.

Work by Wheeler and Fink on *Saccharomyces* could lead to a number of beneficial clinical applications. For example, Wheeler notes that both *Saccharomyces* and a bacterium found in yogurt called *Lactobacillus* are used as a probiotic to restore a healthy balance of intestinal microbes. This probiotic can decrease the severity and duration of diarrhea associated with antibiotic use. In addition, he says, *Saccharomyces* eventually may be employed as a vaccine delivery vector.

Looking further down the pipeline, the Institute has applied for a patent to help develop novel antifungal drugs that target specific fungi. Whitehead researchers also are using *Saccharomyces* to explore communities of drug-resistant yeast cells—fungal biofilms—that attach to solid surfaces. These microorganisms potentially are a major cause of untreatable fungal infections.

And these ideas only skim the surface. As researchers learn more about pathogenic fungi and yeast, more questions are bound to arise, the answers to which could offer a larger arsenal against the disease-causing agents.

For more information about this research, visit the Fink lab at www.wi.mit.edu/far/far_fink_bio.html. *For more information about yeast and fungi, visit The Microbial World at* helios.bto.ed.ac.uk/bto/microbes

In the weeds: Whitehead scientist Gerald Fink (left) and postdoctoral researcher Robert Wheeler study fungi and yeast, which can overtake our bodies much like weeds in a lawn.

TEACHING SCIENCE IN SILICO

Teachers face an enormous challenge bringing contemporary biology into the classroom. Gone are the days when Bunsen burners, test tubes, and a microscope served as adequate tools for probing complex biological questions. But for most communities, recreating big-budget science in a high school lab is financially impossible.

BRIAN WILLSE

There is a silver lining to this technological cloud: Much data gathered from federally funded research, like the Human Genome Project, is stored online in central databases. Scientists use computational tools, many of which also are publicly accessible, to investigate genes, proteins, drug candidates, and other biological systems. Teachers can use this strategy—an approach called bioinformatics—to bring students to the front lines of biological research.

"I use bioinformatics tools to help students master concepts in the curriculum," says Massachusetts high school teacher David Form. "My feeling is that bioinformatics should become part of the educational toolkit of all high school biology teachers."

Form, a participant in Whitehead Institute's Seminar Series for High School Teachers, is working with Institute staff and scientists to develop a bioinformatics workshop for other teachers. The program will offer participants an opportunity to get hands-on experience with bioinformatics tools and develop classroom lessons and lab protocols.

Form has introduced bioinformatics to his students in recent years, integrating a variety of tools, including those available through the National Institutes of Health's National Center for Biotechnology Information. The center has several databases and bioinformatics tools for scientists, all available online. For example, students can access GenBank, a database of all publicly available DNA sequences, including the human genome. Students can use such tools to compare the genome sequences of different organisms, find evolutionary similarities, hunt for disease genes, or study proteins.

In one activity, Form coached his students to use bioinformatics to study obesity. The class used online tools to locate genes linked to obesity, sequence related genes, select model organisms that might be used for comparative genomics, and study proteins involved in metabolism. Form also taught students how to use PubMed, an online catalog of science journal citations and abstracts, to research a novel artificial sweetener.

But jumping on the bioinformatics bandwagon comes at a cost. Tools like those Form uses in his class run best on quality computers, a luxury many schools don't have. A slow Internet connection or uncertainty about how to use a tool can sink a lesson plan, and most tools offer instructions meant for scientists, not educators. Form also is unusually lucky: His classes are small enough that there are enough computers to go around.

The Whitehead bioinformatics workshop will offer teachers tips on how to overcome such technical hurdles and strategies for developing customized lessons for classes with limited access to computers and high-speed Internet connections.

Until classrooms can catch up with the lab, teaching some science lessons in silico may be the next best thing.

M W

TAKING A STAND

Stating concerns that restrictions on embryonic stem cell research may one day hinder U.S. hospitals' ability to provide optimal care, editors of the *New England Journal of Medicine* announced in July plans to seek out "highly meritorious" embryonic stem cell studies. It's an uncharacteristic move from a journal that does not have a reputation for igniting either political or social controversy.

"As a physician who has cared for patients who suffered and died from conditions that we are currently unable to treat, I hope that this research can progress rapidly," wrote Editor in Chief Jeffrey Drazen.

The editors were compelled to take this stand, Drazen added, in part because of a decision earlier this year by

UNLIKELY ALLIES

According to the National Association of Biology Teachers, outstanding educators present new concepts in a "conceptually concise fashion," continually reassess their approach "to ensure a fresh, relevant curriculum," and model the "inquiring behavior typical of scientists." Tack on classroom management, administrative duties, and lab upkeep and it's no surprise many teachers feel overwhelmed.

Some Massachusetts educators are enlisting the help of Whitehead Institute scientists, and together these unlikely allies are showing students that biology is anything but boring.

"A visit from a scientist brings the reality of science right into the classroom," says Lexington High School biology teacher Susan Offner. "It's a high point of the year for my students."

This year and last, Tsu-shuen Tsao, a postdoctoral fellow in Whitehead Member Harvey Lodish's lab, visited Offner's class to discuss obesity and diabetes, using his work to explain why the disease wreaks havoc on the body.

Offner, who participates in Whitehead's Partnership for Science Education program, teamed up with Tsao in 2001 when he became her "Whitehead Partner." Scientist partners like Tsao act as "lab insiders," answering questions, sharing information about their research, and giving classroom presentations.

This kind of support, says Offner, creates a classroom experience that couples current research with a lesson in real-life science, a strategy that encourages students to appreciate the research process.

"As a student, I attended biology classes where the learning process involved mostly the memorization of facts and terminology. The processes from which the facts were derived were never emphasized," says Tsao. "I think it is very important for students to see the research processes underlying biology."

Students and teachers aren't the only ones who benefit from the partnership. "I love meeting with the teachers," says Julie Wallace, a graduate student in Whitehead Member Terry Orr-Weaver's lab. "It's satisfying to learn how science is being taught and to think creatively about what a high school student can do. I learn as much from them as they learn from me."

Working with the students and teachers also helps scientists improve their communication skills.

"As someone who is used to talking about research in terms that only other researchers understand, it was difficult to develop a presentation accessible to high school students," says Tsao. "But it gets a little easier as I learn what is appropriate and what is too difficult for the students to comprehend."

Teachers and students get more than just straight science from working with their partners, says Hudson High School teacher Julie Snyder. Snyder spends one evening a month attending the Whitehead program, which includes having dinner with Wallace, her Whitehead partner. Dinner is more than just a chance to talk shop for the pair; it's a chance to learn about each other.

For the students, meeting researchers helps defy the myth that scientists are "geeks." "All of the partners are really neat people who have done a lot of neat things," says Snyder. "You can bring back to the class the idea that you don't have to take the typical route to becoming a scientist."

M W

the U.S. House of Representatives to ban nuclear transfer—also called therapeutic cloning—a process by which genetic information from a cell is placed into an unfertilized egg whose DNA has been removed. When placed in a Petri dish, this egg develops into a line of stem cells; when placed in a uterus, a procedure known as reproductive cloning, it eventually can develop into a fetus.

Two similar bills are pending in the U.S. Senate. A moderate version would allow therapeutic cloning and a competing bill mirrors the House decision. If the latter is passed and signed into law, therapeutic cloning would be illegal in the U.S. Nevertheless, Drazen claims that nuclear transfer undoubtedly will "be used to develop treatments for conditions that are currently incurable," if not in the U.S., then elsewhere.

Several other articles on the subject accompanied Drazen's editorial, including two by researchers at Whitehead Institute. Member Rudolf Jaenisch and postdoctoral associate Konrad Hochedlinger wrote that faulty reprogramming of the genome most likely is the culprit behind abnormalities common in cloned animals. However, the "abnormalities associated with reproductive cloning are not expected to impede the use of this technique [nuclear transfer] for therapy."

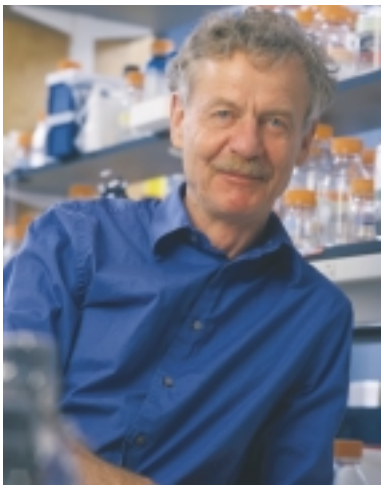
Whitehead visiting scientist George Daley authored a piece addressing the legislative quagmire of stem cell-research politics, warning that "Legislation that unduly restricts the pursuit of nuclear-transfer studies will cripple innovation."

David Cameron

HIGH HONORS

Rudolf Jaenisch has a new mark of distinction to add to his teeming CV, and he owes it all to mice.

Last April, the German-born biologist was elected to the National Academy of Sciences. Election to NAS is hardly just another appointment—the Academy is widely considered to be one of the scientific world's premier honors.



SAM OGDEN

Academy Accolades: Whitehead Member Rudolf Jaenisch was recently elected to the National Academy of Sciences.

The coauthor of more than 300 research papers, Jaenisch is a founder of transgenic science, an area of biology in which researchers alter an animal's genetic makeup to produce a variant of a human disease. Jaenisch's work has focused on creating transgenic mice that enable his team to study forms of cancer and neurological diseases that have long baffled researchers.

Jaenisch also is a proponent of nuclear transfer, also called therapeutic cloning, in which the genetic information from one cell is transplanted into an unfertilized egg from which DNA has been removed. When placed in a Petri dish, this egg develops into a line of stem cells. However, Jaenisch is a vocal opponent of reproductive cloning, in which the egg is placed not in a Petri dish but into the uterus of a female, where it eventually may develop into a fetus. He has made his case against reproductive cloning frequently to the scientific community and U.S. Congress.

As for his election to the Academy, "It's a great recognition," Jaenisch says. "The NAS is the most respected body of scientists in the country. I feel very honored."

Comprising 1,922 active members, the Academy was formed in 1863 with a mission to advance scientific discovery for the common good. Jaenisch is the sixth Whitehead scientist to be elected to NAS. Gerald Fink, Eric Lander, Susan Lindquist, Harvey Lodish, and Robert Weinberg also are members.

D C

BUILDING A GENOMIC TOOLKIT

Most medicines treat the symptoms and not the cause of disease, making it difficult for doctors and patients to effectively manage chronic illnesses like diabetes and hypertension. With the human genome sequence in hand, researchers are hoping to hone in on the genetic roots of disease, creating tailor-made treatments that correct, rather than mask, disease-causing defects.

Realizing the promise of genomic medicine is the goal of a new partnership announced earlier this year among Whitehead Institute, Massachusetts Institute of Technology, and Harvard University. The cornerstone of the collaboration is the evolution and expansion of the Whitehead/MIT Center for Genome Research, which will become the foundation of The Broad Institute, a new initiative aimed at bridging the gap between genomics and clinical medicine.

Under the direction of Whitehead Member Eric Lander, The Broad Institute will leverage the strengths of its three founding institutions to create a new toolkit for genomic medicine. The institute is named for philanthropists Eli and Edythe Broad, who have committed $100 million over 10 years to support the endeavor. Harvard and MIT also have pledged to raise additional funds for the institute's research programs.

The outgrowth of The Broad Institute from the Genome Center represents the tradition of innovation and risk-taking that best characterizes Whitehead's commitment to nurturing promising scientists like Lander, who joined the Institute as a Whitehead Fellow in 1986, says Whitehead Director Susan Lindquist.

"Whitehead's mission is to identify people of extraordinary talent, nurture them, and empower them to fulfill their greatest potential," she says. "We want them to produce work that is of fundamental importance, establishes new paradigms, and benefits humankind. It is with enormous pride that we point to the work that Eric Lander and all members of the Genome Center team have done at Whitehead and eagerly await the landmarks that lie ahead."

The Broad Institute is expected to support 12 core faculty and about 30 associated faculty members from MIT, Harvard, and Whitehead. MIT will administer the new institute on behalf of the three partners. It will be housed in the Center for Genome Research facilities in Cambridge until a permanent space can be established nearby.

M W

SHARPER IMAGE

Scientists viewing the magnified structures of a cell once were like pilots looking at buildings from an airplane: They could see the physical forms of the structures but little of the bustle within them.

Today, scientists are using the modern tools of bioimaging to observe the activities of genes and the busy traffic of proteins in an emerging field that is opening new windows into the study of cell biology.

"You can learn a lot from biochemistry. But to really understand proteins, you need to know where they are and when, while things are happening. This is information that bioimaging provides," says Paul Matsudaira, a Member at Whitehead Institute and director of the Whitehead/MIT Bioimaging Center, a collaboration launched in July 2001 to promote advancements in imaging throughput and resolution and resolve computational challenges in the analysis of imaging data.

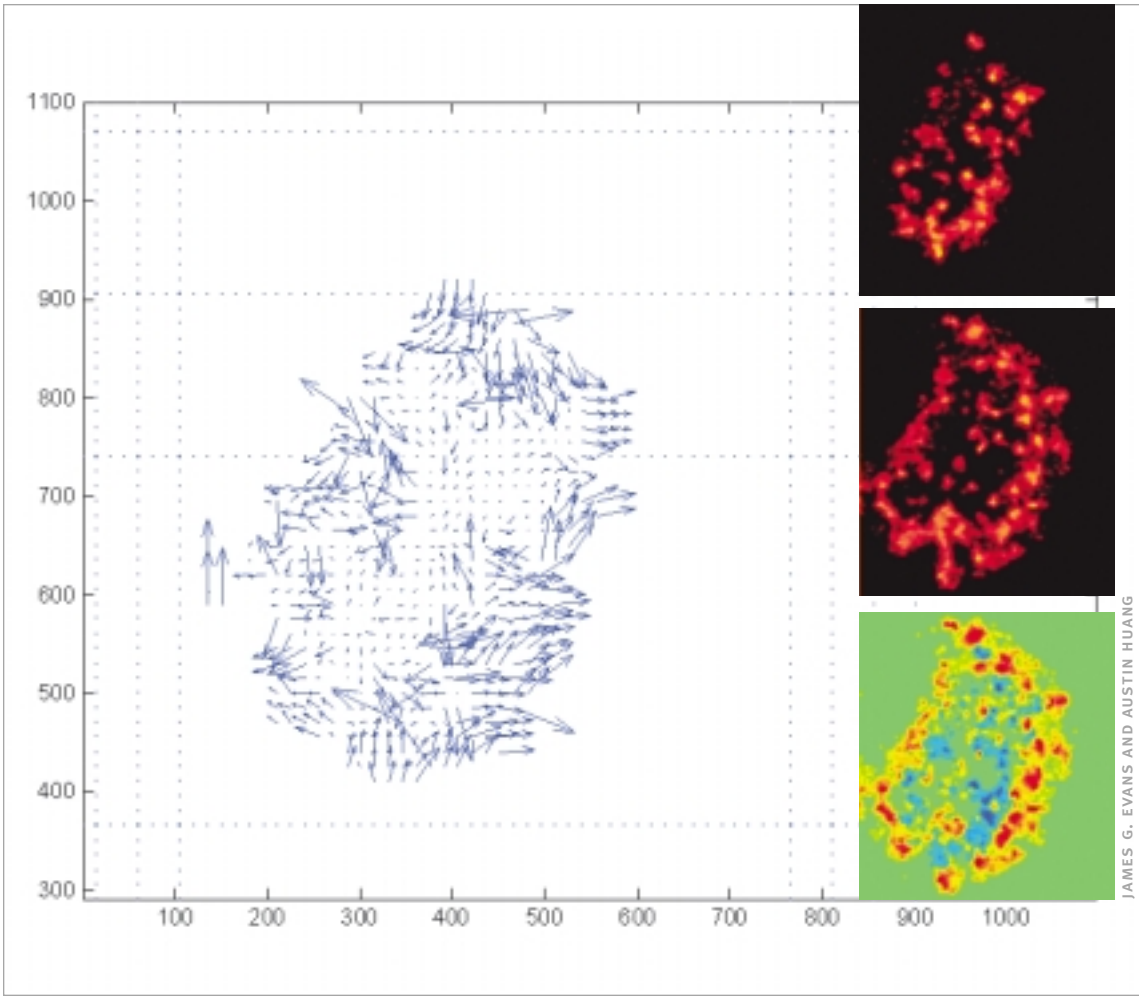
The center's goal, Matsudaira says, is to give researchers with shared interests access to the instrumentation they need to further a variety of studies. A next-generation, all-digital cryoelectron microscope, purchased with a $2 million grant to the center from the Keck Foundation, allows researchers to peer deeply into cells at resolutions that illuminate protein arrangements and interactions. Other instruments rapidly produce images on a massive scale, what researchers call "high throughput, high content imaging." These include fast, automated light microscopes.

One of the center's upcoming projects is a five-year effort to image every gene product in a cell in 4-D (the fourth dimension is time), which will produce tens of terabytes (1 terabyte=1 trillion bytes) of data.

"This is all very exciting," says Sanjoy Ray, director of computing for the center. "It's allowing us to directly visualize processes that we've never seen before."

Funding for the center, currently $8 million, comes from the Keck Foundation's initial support, as well as other Whitehead and MIT sources. Industry partners include Cellomics, Perkin Elmer, IBM, Network Appliance, and EMC, among others. The center is housed in two buildings on the MIT campus.

C S



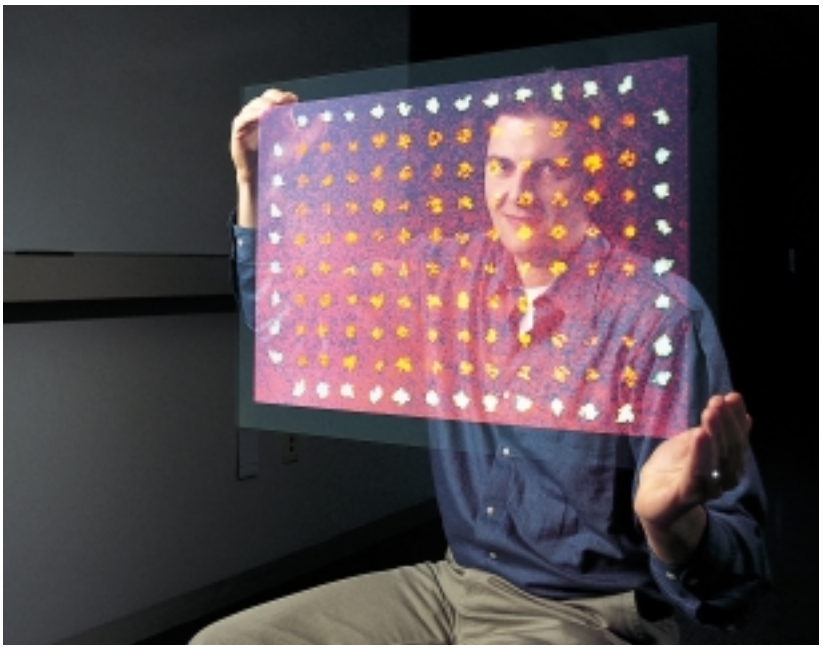
In motion: 3-D time-lapse imaging with a confocal microscope reveals protein movement in a living cell over time. The first two color images were taken 11 minutes apart; the bottom image compares the changes in protein position by a process called "optical flow." On the left, arrows indicate the direction and magnitude that the proteins moved. Whitehead scientists are developing technology to allow quantitative 3-D time-lapse imaging of many cells at once, which would allow researchers to observe how proteins interact with each other under different conditions and in response to different drugs.

CELLULAR MAKEUP

David Sabatini was studying a group of proteins that control cell growth when he hit a roadblock. He needed to examine gene and protein function in thousands of living cells all at once, in real time—something not possible with conventional technology.

So, Sabatini did what many scientists do when faced with such a dilemma: He invented a new technique to help him figure out the relationship between genes, proteins, and human diseases.

That was two years ago. This spring, Sabatini and Whitehead Institute, where Sabatini is an Associate Member, received a U.S. patent for the technology. Cell microarrays, as they're called, make possible the study of thousands of proteins simultaneously in a living cell. The invention also gave Sabatini an opportunity to merge intellectual curiosity with a process that has aided many scientists with unlimited ideas, but limited resources: commercialization.



SAM OGDEN

Hands on: David Sabatini's cell microarray technology allows high-throughput screening of biologically active molecules in live cells, such as these shown in red and green.

BUSINESS LESSONS IN THE LAB

As a graduate student at Johns Hopkins University School of Medicine, Sabatini entered the lab knowing that commercialization was an important part of scientific discovery. His first steps into that field weren't as tentative as they may have been for researchers prior to 1980. That year, Congress passed the Bayh-Doyle Act, which removed barriers preventing institutions that receive federal funds from jumping into the world of technology transfer—a process by which universities and research institutes transfer their faculty's inventions and discoveries to businesses for commercial development. A 2000 report from the Association of University Technology Managers found that more than 300 new products—drugs, materials, diagnostics, etc.—were made available to consumers in that year alone, all developed from academic discoveries.

"I came in knowing that commercialization could be useful, and in fact, interesting," Sabatini says. His discovery launched Akceli, a Cambridge-based company that Sabatini helped create.

"This is all an extension of the intellectual domain of the lab," Sabatini says. "They're doing things at Akceli that I don't have the resources or time to do in my lab here."

Many biologists like Sabatini have created tools to carry their research to the next level. But they must direct their time and resources to their science, not product development. By licensing the cell microarray to Akceli, Sabatini could focus on his research without worrying that his technology would languish. Akceli will prepare the microarrays for distribution and, in the future, researchers around the world can use them to advance genetic studies.

THE PATH TO DISCOVERY

When Sabatini joined Whitehead in 1997 as a Fellow, available arrays allowed him to study only a fraction of what high-throughput technology makes possible today. When the first high-throughput arrays were put into use, scientists finally were able to run assays on thousands of cells and genes all at once, an advance that led to a better understanding of life at the molecular level.

Sabatini took things a step further with his cell microarray, which uses small glass slides printed with as many as 10,000 pieces of DNA that encode individual proteins or RNA molecules that inhibit the expression of specific proteins. Clusters of live cells are grown on the surface of the slide in defined areas called "features," where the DNA is imprinted. The cells absorb the DNA, and begin expressing whatever protein for which the DNA in that feature codes. Sabatini's technique can be used to assay the location of proteins, study their function, and predict their reaction to pathogens and drugs designed to attack those pathogens.

Adding "inventor" to his list of accomplishments gives the 33-year-old biologist pause. To him, creating the cell microarray technology was a necessary step along the path of scientific discovery. "It was just something we developed along the way."

K W

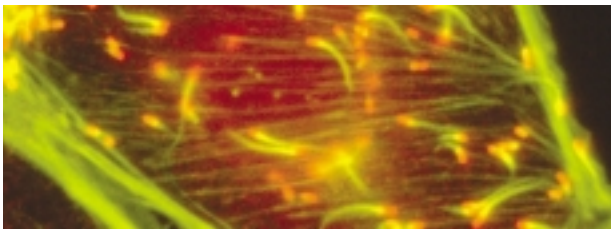
RIDING THE RNA ROLLER COASTER

Whitehead researcher David Bartel is re-evolving evolution in his lab. Exploring the theory that about 3.5 billion years ago RNA called all the shots, Bartel is evolving RNAs that can create other RNAs, knocking both DNA and protein out of the biological equation. Bartel describes these creations as an RNA theme park, a fragmented re-evolution of the RNA world. So far, these displays have caught the attention of the scientific community. Learn more about this long-lost RNA world at *www.whitehead.mit.edu/nap/features/nap_feature_bartel_park.html*.

TOM DICESARE

SILVER SCREEN

The images of science can be colorful, delicate, striking—and bizarre. Imagine an up-close-and-personal view of the bacteria *Listeria*, the disease-causing fungus *Candida albicans*, or a fruit fly's lymph gland. Now, imagine these pictures fading across your computer monitor. Whitehead's science art screensaver is a collection of images created from a variety of research projects on everything from plants to insects. The screensaver is available free for Mac and Windows users. To download the images, visit the web at *www.whitehead.mit.edu/photos/screensavers.html*.



JULIE THERIOT

SAMETZ BLACKSTONE ASSOCIATES

SCRIPTS FOR LIFE

The biology of drug discovery, the human genome, biological challenges to humanity—these are just a few of the subjects to headline the annual Whitehead Symposium since the program launched in 1982. Speakers at the event are among the nation's leading researchers in the life sciences, a draw that attracts more than 1,000 registrants each year. This year's symposium, slated for October 3, examines the grand scheme—or the script—that orchestrates the complex life of the cell. Keep an eye on the Institute's website *www.whitehead.mit.edu* for reports from the Scripts for Life symposium. Meanwhile, to view video of speakers from the 2002 symposium, visit the web at *www.whitehead.mit.edu/cee/cee_conf_sympo2_pro.html*.

RETOOL FOR SCHOOL

No doubt it's a struggle for high school science teachers—and even the interested student—to stay current on the newest developments in science. Whitehead Institute's Partnership for Science Education offers some solutions to this problem by providing resources that update teachers on the latest trends in life sciences research, while also helping students explore possible science careers. For more information on the partnership and this year's lecture series for teachers, "Life in Process: Evolution, Diversity, and Change," visit our website at *www.whitehead.mit.edu/cee/cee_scied_teach.html*.

paradigm FALL 2003

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Paradigm is published twice a year by the Office of Communications and Public Affairs at Whitehead Institute for Biomedical Research. The magazine reports on life sciences research and innovations at Whitehead and beyond, and explores issues related to the conduct of research in general. Its goal is to encourage scholarly inquiry and public discourse on science through the publication of articles and images that place science in the context of the world around us.

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Photographer Kunie Sugiura has made "photograms" since 1980. Subjects are placed on or in front of light-sensitive photographic paper, which is exposed to a brief flash of light, capturing the subjects' shadows. She recently began a new series on scientists, including Whitehead Institute's Susan Lindquist and Eric Lander. Selections from this series will be on exhibit this fall at the Leslie Tonkonow Artworks and Projects gallery in New York City. More images from this series will appear online at *www.tonkonow.com/sugiura*.

Whitehead Institute

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