

SPRING 2004

A magazine of life sciences inquiry from Whitehead Institute

paradigm

featuring: The fly vs. the worm

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[Inside cancer: The tale of a tumor]



AN ENGAGING CONVERSATION

“[D]irect dialogue with the public should move from being an optional add-on to science-based policy making and to the activities of research organisations and learned institutions, and should become a normal and integral part of the process.”

With these words from the Select Committee on Science and Technology, Great Britain’s House of Lords in 2002 signaled a sea change in how and why scientists communicate their research to the public that pays for the bulk of it. No longer is it sufficient to count on citizens’ goodwill to support science, their report explains; the public must have a real place at the table in establishing and evaluating national research programs.

In Britain, this report emerged following more than five years of public anger over governmental missteps on mad cow disease and suspicion about misregulation of genetically modified crops. But the public engagement approach to science has since been echoed in the United States, with organizations from the American Association for the Advancement of Science to the National Science Foundation now actively promoting inclusion of the public in discussions that lead to science policy.

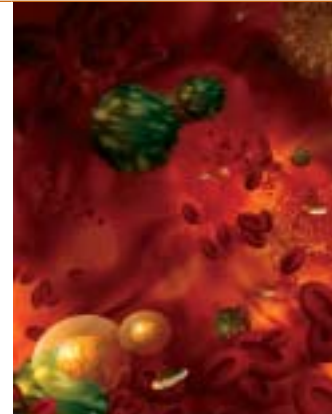
Noble as this sentiment is, many in the scientific community just now are beginning to understand the full ramifications of this approach: If you engage members of the public, you must abide by what they say.

Nowhere was this clearer than in Britain’s largest experiment in public dialogue to date. In June 2003, the government launched a national series of debates and discussions across the country, in pubs and churches, schools and shopping malls. For a month, Britons turned their attention to the health and safety issues raised by genetically modified (GM) crops. At the end of this exhaustive public debate, supporters of research and commercialization of genetically modified plant and animal crops had to face a hard reality: The more people engaged in GM issues, the harder their attitudes and more intense their concerns became.

This has profound implications for how we communicate the results of biomedical research at Whitehead and elsewhere. We are funded primarily by public dollars, and the public deserves a voice in the conduct of the research we do. But it is a mistake to think that simply informing the public about biomedical research will swell the ranks of science advocates.

Support, communications research suggests, only comes if stakeholders feel they have a meaningful role to play in the enterprise. If we are serious about public engagement as our communication strategy of choice for science, it must be meaningful and our responses to public concerns genuine. The scientific community cannot afford to simply pretend to be inclusive.

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



on the cover:

To illustrate a cancer tumor in the human body, artist Christina Ullman studied cellular images taken with a high-powered microscope camera. She then created the illustrations by digitally painting the scenes in Adobe Photoshop.

our contributors

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cover story

- 20** **Biography of a tumor**
by David Cameron
The life story of a tumor begins innocently enough. But the chapters that follow that introduction are a complex tale of biology that researchers only now are beginning to understand.

features

- 8** **Hook, line, & model**
by Steve Mirsky
What has science learned from the fly and the worm? Just about everything we know about genetics, genomics, and development.



[8]

- 10** **The big picture**
by David Cameron
Say goodbye to the one-gene-at-a-time approach to disease research. To truly understand human ailments, scientists say, you have to take a global view of the entire genome.

[16]



- 16** **The biology of behavior**
by Charles Schmidt
Scientists use a new form of an old technology to study the intricacies of human consciousness.

- 28** **The price of publication**
by Richard Saltus
Researchers around the country are issuing a wake-up call to the \$3.5 billion scientific publishing industry. Are open-access journals the answer?

[10]



departments

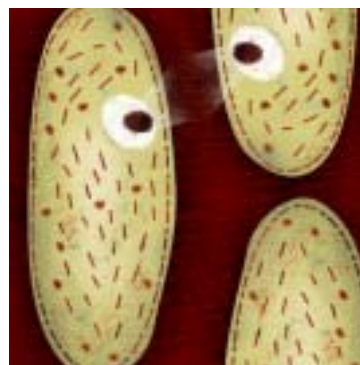
- 2** **Science digest**
Research news in brief
- 32** **Science and society**
Issues in education and policy

- 34** **Extra credit**
Life sciences 101

- 36** **On topic**
Exploring science headlines

- 37** **www.whitehead.mit.edu**
On the Web

[5]



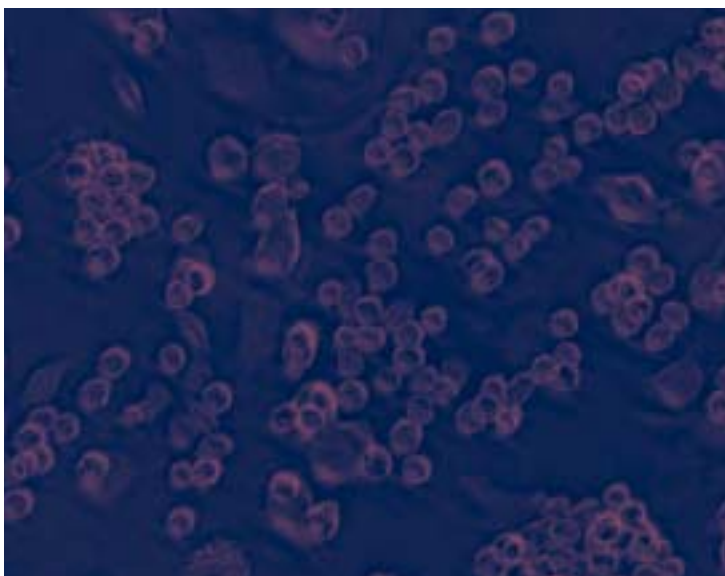
[CELL GROWTH]

Lab-grown adult stem cells could ease bone marrow transplants

Hundreds of thousands of patients worldwide seek blood stem cell or bone marrow transplants each year to treat a variety of blood disorders, cancers, and autoimmune diseases. But even with more than 5 million volunteers on the National Marrow Donor Program potential donor registry, finding a match is tricky. And once a match is found, collecting enough blood stem cells is a challenge. These cells, which are able to generate all the blood and immune cells of the body, are very rare; just one out of every 100,000 cells in the bone marrow is a blood-forming, or hematopoietic, stem cell.

Most experiments to grow these stem cells in the lab have failed. But Chengcheng Zhang, a postdoc in the lab of Whitehead Member and MIT Professor Harvey Lodish, has identified a protein called IGF-2 that could help scientists rapidly reproduce hematopoietic stem cells extracted from bone marrow. Researchers examined IGF-2 and found that it accelerates the production of blood stem cells in cultures of mouse fetal liver or bone marrow cells. They published the work last fall in the journal *Blood*.

Noting that hematopoietic stem cells multiply rapidly during fetal liver development, Zhang suspected that fetal liver cells might contain growth factors that could promote rapid stem cell expansion in culture. In a study funded by the Leukemia and Lymphoma Society, he pinpointed IGF-2 in 15-day-old fetal liver cells in mice. When he combined IGF-2 with two other growth factors and applied them to hematopoietic stem cells isolated from the 15-day-old mouse fetal liver or bone marrow, the cells doubled within three days.



chengcheng zhang

MAKING MEMORIES

STUDY EXAMINES PROTEIN INVOLVED IN LONG-TERM MEMORY STORAGE

Scientists have discovered a new process for how memories might be stored, a finding that could help explain one of the least-understood activities of the brain. What's more, the key player in this process is a protein that acts just like a prion—a class of proteins that includes the deadly agents responsible for mad cow disease.

The study, published in the journal *Cell*, describes how a protein related to memory storage behaves just like a prion when placed in a yeast cell. These findings challenge the widely held belief that prions are always bad news.

“For a while we’ve known quite a bit about how memory works, but we’ve had no clear concept of what the key storage device is,” says Susan Lindquist, Whitehead director and coauthor of this new study. “This study suggests what the storage device might be—but it’s such a surprising suggestion to find that a prion-like activity may be involved.”

Prions are proteins that can suddenly alter their shape, and in doing so cause other proteins to follow suit. A protein’s shape is central to its function, and in all known cases, these clusters of misfolded proteins either die or kill the cell—and ultimately the organism.

Zhang next plans to collaborate with hematologists at Boston’s Dana-Farber Hospital to determine if combining IGF-2 with other growth factors can expand human hematopoietic stem cells.

The ability to expand the number of blood stem cells is a topic of interest to doctors treating patients and to scientists studying the potential for using a patient’s own hematopoietic stem cells for therapies that would correct faulty genes implicated in disease.

“In the near term, this could be useful for bone marrow transplants,” says Lodish. “In the long term, it could be used for doing gene therapy on stem cells.”

Mark Dwortzan

Growth factors: Scientists applied a combination of growth factors to hematopoietic stem cells isolated from 15-day-old mouse fetal liver cells, like those shown here. The stem cells doubled within three days.

For this reason, Kausik Si, a postdoc in the lab of Columbia University neurologist and study coauthor Eric Kandel, was surprised to find that a protein related to maintaining long-term memory contained certain distinct prion signatures. Working with the Lindquist lab, the group extracted the protein from a sea slug and observed its behavior in yeast. While the protein altered its form and caused other proteins to follow—as prions do—it was not toxic to the cell. In fact, the protein carried out its normal function in the prion state. The next step is to see if the protein behaves like a prion in neuron cells.

Lindquist, who also is a professor of biology at MIT, suggests this won't be the last time prions are found to play normal biological roles. She long has speculated they may be essential to many cellular functions. Kandel adds that he wouldn't be surprised if this sort of prion mechanism was discovered in cancer maintenance and even organ development.

“This is remarkable not just because the protein executes a positive function in its prion-like state,” Lindquist says. “It also indicates that prions aren't just oddballs of nature but might participate in fundamental processes.”

David Cameron

For more information on prions, visit the Whitehead news archive at www.whitehead.mit.edu/nap/features/nap_feature_memory.html.



brian w.l. lse

[AN UNLIKELY MODEL]

Scientists use baker's yeast to study neurodegenerative diseases

What do humans and baker's yeast have in common? More than you think. Over the last few decades, researchers have plumbed the depths of human biology by using yeast cells as living test tubes, studying everything from cellular growth to neurodegenerative diseases.

Tiago Outeiro, a graduate student in the lab of Whitehead Member and Director Susan Lindquist, has used baker's yeast to duplicate some of the most critical features of Parkinson's disease. Focusing on a Parkinson's-related neuronal protein called alpha-synuclein, or α Syn, Outeiro developed a method to observe the protein's behavior in response to various stimuli.

In research published last fall in the journal *Science*, Outeiro assembled a group of yeast cells, each containing various levels of the α Syn protein. “I wanted to see what happens in the cell when we produce just a bit more of this protein than the quality-control system can handle,”

Outeiro says. “Does the biology of the protein change? Does it cause problems to the cell?”

When α Syn was produced at low levels, it made its way to the cell membrane and appeared to regulate chemical trafficking and fat metabolism—perhaps normal functions for this protein. However, when α Syn levels were increased—even slightly—some of the proteins misfolded and caused others to do the same. The proteins began to form large clusters, and the cell began to die.

In the future, Outeiro believes this system may be useful for screening drugs to tip the balance back, an objective that will soon be explored with corporate partners.

“At the basic level, yeast cells are very similar to mammalian cells. So in a sense, yeast is perfect for this,” he notes.

DC

For more information on this research, visit the Whitehead news archive at www.whitehead.mit.edu/nap/features/nap_feature_alpha_syn.html.

TOOLS OF THE TRADE

Gene silencing goes digital

In the film *It's a Wonderful Life*, an angel shows a suicidal George Bailey how his small town would have fared had he never been born. For years, scientists have conducted countless George Bailey experiments on genes, identifying their function by knocking them out with specially designed complex molecules, then observing what happens to the cell.

In the past, such complex molecules took months to engineer. But since 2001, more scientists are adopting a new method that shuts down a single gene within days using small segments of RNA called short interfering RNA, or siRNA. Now, Whitehead Institute's Bioinformatics and Research Computing group has developed a Web-based tool to increase the technique's accuracy and speed.

When placed in a cell, these short strands of RNA interfere with a gene's ability to produce protein. Several academic labs and drug companies have pursued siRNA's ability to immobilize key genes involved in viral and immunological diseases, cancers, and other illnesses. But sorting out which siRNA sequences block which genes is cumbersome; scientists must randomly select siRNA segments from thousands of possibilities in the hopes of hitting the bull's-eye.

The siRNA Selection Program, completed in February 2003 by Whitehead's bioinformatics group, could make the

process less cumbersome—and faster. In September, the group received a grant from the National Science Foundation to improve its accuracy. Developed by Bingbing Yuan, the siRNA Selection Program enables scientists to quickly pinpoint a small number of specific siRNAs that likely will knock out a specific gene. Users enter the DNA sequence for the human or mouse genes they're studying, and the program returns potential siRNA sequences that can be used to target the gene.

A recent survey in *Genome Technology* magazine ranked Whitehead's program as one of the top three most used siRNA design tools. "The advantage of our tool over other available software is that we identify sequences that exclusively target the gene of interest, and provide information as to why the resulting siRNA candidates got selected," says Fran Lewitter, director of the bioinformatics group.

In collaboration with Thomas Tuschl, former Whitehead postdoc and a pioneer in siRNA research, and other leading siRNA researchers, the bioinformatics group now is developing a public database that will help further refine the program. Lewitter's team also has launched a new project to produce additional experimental data that could yield an even more sophisticated program.

MD

View the siRNA tool online at jura.wi.mit.edu/bioc/siRNA.

NOSE TO NOSE

STUDY USES OLFACTORY CELLS TO PRODUCE VIABLE CLONES

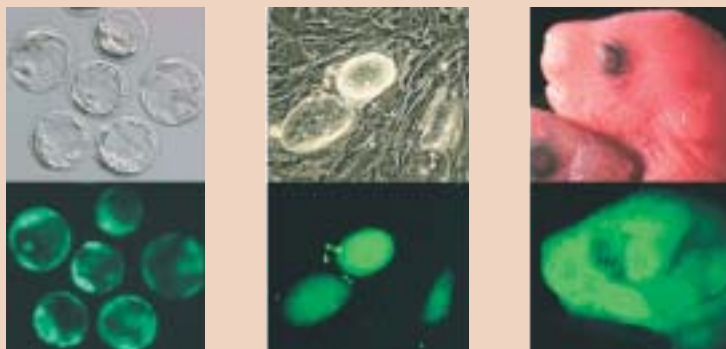
In the Woody Allen film *Sleeper*, a group of geneticists want to clone their dictator using tissues from the only body part that survived an assassination attempt—his

nose. Thirty years later, a group of researchers at Whitehead Institute and Columbia University have carried out the spirit of what Woody Allen's character couldn't do. But rather than salvaging an evil despot, they have cloned mice from olfactory neuron cells in a study that questions certain assumptions about how cloning works.

To produce a clone, scientists remove all genetic material from an egg cell and insert a nucleus taken from a donor cell. The egg cell reactivates this donated nucleus and, if all goes well, develops into an embryo. Many researchers believe that this reactivation can occur only when the donated nucleus is taken from a cell close to the embryonic stem cell stage. But in this study, Whitehead's Rudolf Jaenisch and Andrew Chess, in collaboration with Columbia University researcher Richard Axel, show that even a cell as highly specialized as an olfactory neuron—a cell that can't even divide—can produce successful clones.

These findings, published early this year in the journal *Nature*, "shift the spotlight away from the type of cell used to produce a clone to the more fundamental question of how the egg cell reactivates the donated genetic material," says Jaenisch, who also is professor of biology at MIT.

The experiment also counters current theories on how central nervous system cells develop. Many researchers



From neurons to mice: Original neuron cells are stained green, allowing researchers to trace their development and prove that the clones originated from these neurons. (l-r) Early stage embryos cloned from neuron cells; embryonic stem cells derived from these embryos; *in utero* mice.

CELLULAR SELF-AWARENESS

Study examines how cells tell each other apart

The idea of self vs. nonself may sound more like an existential identity crisis than a question in cellular biology. But to Whitehead Institute Associate Member Andrew Chess, the concept could offer information about how cells tell each other apart, a cellular self-awareness that ensures the correct wiring of neurons in the brain.

In research published earlier this year in the journal *Nature Genetics*, Chess and collaborators from his lab examined the role a gene called *Dscam* plays in allowing neuron cells to distinguish themselves from each other. *Dscam* is a cell-adhesion molecule that helps to guide axons to their intended targets. While the majority of genes produce, at most, just a handful of proteins, *Dscam* can generate some 38,016 different proteins in fruit flies, each having a slightly different structure and function. That quality alone would be enough to make the gene an interesting target of study. But *Dscam* made an attractive subject for other reasons as well.

“We knew *Dscam* was extremely complex, that it was expressed in neurons in the brain, and that other cell adhesion molecules had been shown in other species to be important in how neurons connect to each other,” says Chess, who also is an associate professor of biology at MIT. “It made us think that studying *Dscam* may allow us

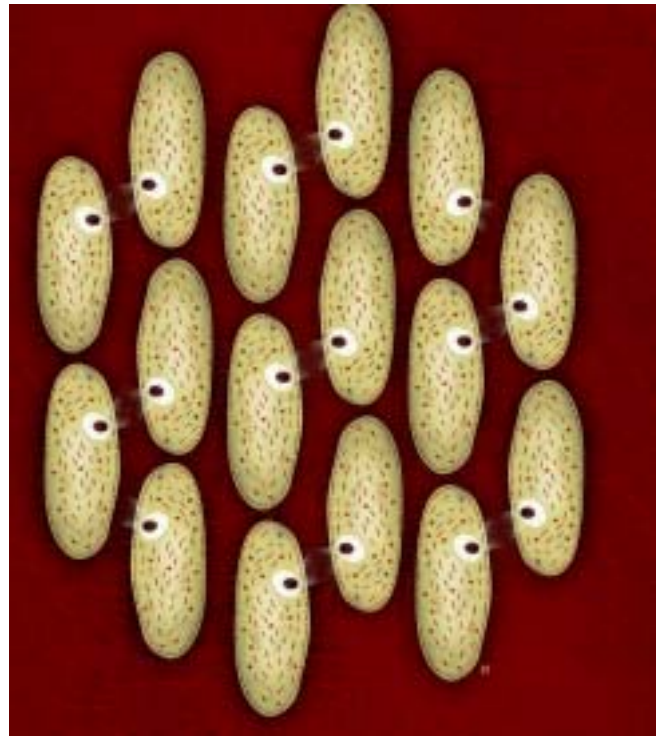
believe that neuron cells distinguish themselves in the same way that immune system cells do—by removing all pieces of genetic information that the cell doesn’t need for its particular function. The cells scramble this unnecessary genetic data in such a way that it can’t be restored, meaning that mice cloned from immune system cells would have compromised immune systems. If the central nervous system acted in the same way, a mouse cloned from an olfactory cell should have a very limited sense of smell. However, the mice in this experiment maintained full olfactory range.

“So there must be some other unique mechanism for gene expression in mammals which is still not yet defined,” says Kevin Eggan, the study’s lead author and former postdoc in Jaenisch’s lab, now a Junior Fellow in the Harvard Society of Fellows at Harvard University.

Researchers in Jaenisch’s lab plan to further explore such gene expression mechanisms, work that could lead to a better understanding of genomic reactivation.

DC

For more information on this research, visit the Whitehead news archive at www.whitehead.mit.edu/nap/features/nap_feature_olfactory.html.



brian.will.lee

to uncover some kind of new mechanism for how cells or groups of cells tell each other apart.”

Anxious to study the gene in individual cells, Chess and a research team that included postdoctoral associate Guilherme Neves, scientist Jacob Zucker, and Whitehead Fellow Mark Daly developed a technique for single-cell analysis in fruit flies. The team discovered that different cells in the brain make different types of *Dscam* protein.

According to Chess, this means that each cell contains a distinct *Dscam* repertoire. “That’s what led us to this idea that *Dscam* might be used to help identify self from nonself,” Chess says.

A similar notion of self vs. nonself has been examined widely in studies of the immune system, where a cell’s ability to tell itself apart from foreign cells is crucial to the destruction of virus-infected cells.

“This is a new concept for neurons,” Chess says. “It suggests that even while they’re driving along, following pathways, they are somehow aware of which parts of the cell membrane surrounding them are their own and which parts belong to different cells.”

This single-cell analysis technique can be used to study other genes, Chess notes. The team plans to do just that, examining genes in cells of both flies and mammals.

Kelli Whitlock

[BRANCHING OUT]

Scientists explore the Y chromosome family tree

The names and dates constituting a family tree contain branches that can extend backward centuries in time. People use these diagrams to discover their ancestral roots. Scientists use them to study the genealogical origins of entire species.

Biologist Steve Rozen has explored the family tree of the male-determining Y chromosome, looking for information about a genetic mutation that raises interesting questions about the evolution of the Y.

Large genetic deletions of all or most of a section of the Y called the Azoospermia Factor c region almost always cause poor sperm production. The variation usually is passed down only through *in vitro* fertilization. It's a rare mutation, affecting only about one in 4,000 men.

But Rozen and others in the lab of Whitehead Member and MIT professor David Page have found a new deletion in the same region that doesn't always cause infertility. It can be passed from father to son through normal reproduction, making it far more common in the general population.

While the discovery, reported in the journal *Nature Genetics*, offers new information about male infertility, it

raises even more questions about the evolution of the Y. Though this deletion doesn't always affect fertility, somewhere along the line, some men who inherit the deletion will be left with poor sperm production. The deletion should get weeded out. That's how human evolution works.

But when Rozen began to investigate the deletion's genealogical origin, he and his colleagues found one population where this mutation is thriving: Japan.

The Y's genealogical chart is vast and while the finer branches just now are being discovered, the major limbs already tell the stories of Y chromosome variants that arose tens of thousands of years ago in different parts of the world. The scientists looked for evidence of chromosomes containing this particular deletion, and found this type of Y amidst others on 14 different branches of the chromosome's family tree, including one where every single Y chromosome had the deletion. The scientists traced the origin of this particular branch to Japan and discovered that 30 percent of all Japanese men have this chromosomal type.

"On the one hand, we have evidence that this deletion is being weeded out, somewhat slowly, but being weeded out nonetheless, because on average, the men with this deletion are at greater risk of having sperm production problems," Rozen observes. "But on the other hand, we have a case where a branch with this particular deletion has gone to a very high frequency in one population. It's contradictory and we don't know how to resolve the contradiction."

The scientists hope they won't be stumped for long. The next step of this work will involve further analysis of this new deletion to unlock more secrets of this family tree.

KW

For more information on research on the Y chromosome, visit the Whitehead news archives at www.whitehead.mit.edu/nap/features/nap_feature_page_y.html.

[ON TARGET]

Study identifies 400 likely gene targets for microRNAs

Fascinated with microRNAs' ability to mediate the chemical translation of DNA into protein—effectively silencing a targeted gene—scientists are exploring the role these miniature marvels play in normal cell development and how they might be used to treat disease. Scientists recently identified more than 400 human genes likely targeted by microRNAs, taking an important step toward defining the relationship between them, the genes they target, and the processes they control.



100 AND COUNTING

SCIENTISTS EXAMINE THE GENETICS OF LONGEVITY

What separates those who live to 100 years old and beyond from the rest of us? While scientists have identified low cholesterol as a key factor, simply cutting back on bacon and eggs may not guarantee a ticket to the golden years. According to new research, much of low cholesterol—the kind that helps you make it to 100—is controlled by the genes.

Recent work by Whitehead Fellow Mark Daly and collaborators in Boston and Paris indicates that a genetic mutation linked to a favorable cholesterol profile (a proper balance between the good and the bad cholesterol) is very common among centenarians. The results were published last fall in the *Proceedings of the National Academy of Sciences* in a study funded by genomics-based drug discovery company Elixir Pharmaceuticals.

While most researchers probing the causes of longevity have looked for genes responsible for shortening our lifespan, Daly and his colleagues tried a different approach. “We focused on the other end of the spectrum,” he says. “Assuming you can live beyond childhood, is there any genetic predisposition to *how long* you live?”

The research team mapped a sequence of genes in more than 1,200 Americans—half aged 98 or older and half younger than 50—in a section of a chromosome associated with longevity. They found a noticeable difference in a single gene called *MTP*, which plays a critical role in metabolizing fat. The older individuals were significantly



christina ulman

more likely than those under 50 to carry a mutated version of *MTP* associated with a favorable cholesterol profile.

“Discoveries like these may have an immediate pharmaceutical value,” says Dr. Nir Barzilai, director of the Institute for Aging Research at the Albert Einstein College of Medicine. Drugs targeting the proteins that regulate genes involved with aging may ultimately reduce age-related infirmities.

The study also underscores the promise of using the genomes of centenarians to identify genes affecting longevity. “Centenarians can serve as a super-healthy control population for many age-related diseases,” Daly explains. “A more powerful way to study those diseases is to compare people who have acquired age-related diseases versus those who have not.”

MD

“MicroRNAs are one of the many types of regulatory molecules important in determining which genes are on or off in a particular cell,” says David Bartel, a Member at Whitehead Institute and professor of biology at MIT. “Understanding what they do may provide the answers to some unsolved mysteries of gene regulation and help us better understand human biology and disease.”

In 2003, Bartel and Chris Burge, an assistant professor of biology at MIT, developed a way to detect microRNA genes in different animals, estimating that microRNAs constitute nearly 1 percent of genes within the human genome. Now, the pair have developed TargetScan, a new computational method used to define the relationship between microRNAs and the genes they target.

Using TargetScan, the team identified more than 400 genes in the human, mouse, and rat genomes likely to be regulated by the same microRNA. In addition, TargetScan predicted another 100 microRNA targets that are conserved in human, mouse, rat, and pufferfish.

According to Burge, 70 percent of targets predicted by TargetScan are likely to be authentic.

The researchers, who reported the work in the journal *Cell*, also identified parts of the microRNA that are more important than others in ensuring that it silences the correct target. Such insights, useful for finding the natural targets of the microRNAs, also will be helpful for those trying to use microRNA-like molecules for drug therapies.

“A detailed understanding of this mechanism will aid in the engineering of new small RNAs that regulate particular target genes while avoiding undesired side effects,” says Burge. “MicroRNAs or related molecules could potentially be used to therapeutically manipulate gene expression in cases where malfunctioning genes contribute to disease.”

Melissa Withers

For more information on microRNAs, visit the Whitehead news archive at www.whitehead.mit.edu/nap/features/nap_features_microrna_2_04.html.

Hook, line, &

Scientists use **fruit flies** and **worms** to fish

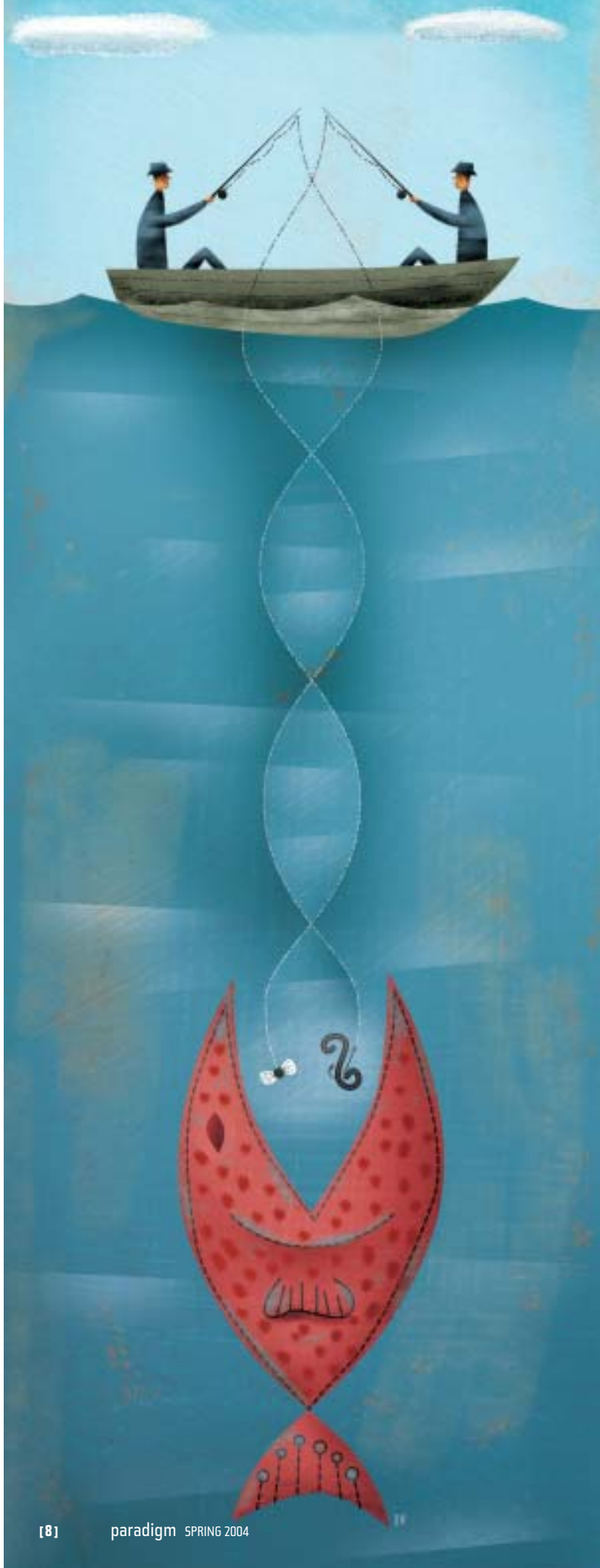
TEXT BY STEVE MIRSKY
ILLUSTRATION BY BRIAN WILLISE

Hamlet provided one of the zippiest summations of the connections among life forms: “A man may fish with the worm that hath eat of a king, and eat of the fish that hath fed of that worm.” Of course, fishing with flies hath also been popular. The flies and worms in this story differ from those preferred by fisher-folk. Nevertheless, these Lilliputian creatures have caught some big ones; most of what we know about genetics, genomics, and development can probably be credited to this one fly and one worm.

The organisms in question are the old laboratory workhorse, the fruit fly *Drosophila melanogaster*, and the newer, but no longer new, kid on the block, the soil nematode *Caenorhabditis elegans*.

The meek really did inherit the world of biological research. The male fruit fly is about 2 millimeters long, the female about 3. The worm is about 1 millimeter long and there’s no need to divvy that figure up further by sex because they’re hermaphrodites. (Okay, one in 700 is a true male, the odd man out.) They have brief lives and they fly/crawl under the radar of people who ordinarily take umbrage over animal research. They’re the perfect guinea pigs, much better than, well, guinea pigs.

One of the worm’s key qualities is that “it was small enough for slices to fit under an electron microscope,” Andrew Brown writes in his *C. elegans* history, *In the Beginning Was the Worm*. The transparent nature of *C. elegans* made it a window for John Sulston, who in the 1970s painstakingly traced the appearance of each of the 959 cells that constitute a complete worm. He saw an additional 131 cells that come into being and then self-destruct as the worm molds itself into its final form.



model

for biological treasure

The lab also produced a complete diagram of the connections among the worm's 302 nerve cells.

Meanwhile, one of the unusually visible things about fruit flies is their honking big chromosomes. In many cells, notably in the salivary glands, chromosomes keep getting copied and line up neatly together, but the cell doesn't divide. The result is a big, beautiful "polytene" chromosome with a distinctive banded appearance. "Those chromosomes were really important for providing a physical map, visible under the light microscope," says Terry Orr-Weaver, a Member at Whitehead Institute and MIT professor who studies links between development and cell growth and division. Those giant DNA strands have, for almost a century, given researchers a peek at the hereditary material they ordinarily study indirectly, usually by mucking with the genes and following the freaky effects.

The results often are quite dramatic. Antennapedia mutant fruit flies get a leg up—up on the top of their heads, in fact. Such mutations shed light on the genetic sequences that govern fundamental genetics of development, in flies and us. Famous *C. elegans* mutations tend to be less Frankensteinian, but one gruesome one is known as bag o' worms. The hermaphroditic worm self-fertilizes its eggs, but in this mutation the organism can't expel them. The eggs hatch in the parent and, as Brown puts it, "with nematode pragmatism, eat it alive, from the inside, until they can burst out." And, because this is a heritable mutation, the same thing happens to the perpetrators when they mature in a few days. It's Oedipus and Electra all wrapped up in one tiny, clear package.

Each organism has its patron saint. Almost a century ago, Thomas Hunt Morgan was looking for good research animals with which to study evolution. *Drosophila* literally flew in Morgan's window at Columbia University in New York City.

Morgan initially hoped to study evolution, and tinkered with some 50 species. Gregor Mendel may have glimpsed the first, simple rules of heredity working with peas, but it was Morgan's fruit flies that would spill the beans.

Mutations are rare. But flies, producing large numbers of offspring in short amounts of time, eventually popped out a few obvious ones. Tracking mutations over generations meant producing more offspring, which led to more mutations. Robert Kohler, author of *Lords of the Fly*, a history of the early years of *Drosophila* research, writes that fruit flies had become "a biological breeder reactor, creating more material for new breeding experiments than was consumed in the process." Morgan, who got his Nobel Prize in 1933, was a smart guy—he realized that his research subject was dictating the experiment, and he quickly mutated himself from an evolutionist into a geneticist.

Sidney Brenner, at the Laboratory of Molecular Biology, in Cambridge, England, on the other hand, made a concerted effort in the 1960s to find a suitable organism for his almost mind-numbing purpose, which was basically to find out everything possible about how a specific multicellular organism works. Fruit flies were too complicated for that ambition. In a proposal to the Medical Research Council, he wrote, "To start with we propose to identify every cell in the worm and trace lineages." And that's exactly what he and other researchers, including Sulston and Robert Horvitz, now at MIT, did. Except that the worm turned—the species in the original proposal was *C. briggsae*. Shortly

thereafter, Brenner switched to *C. elegans*. It was a good choice, with the three sharing a 2002 Nobel Prize.

Drosophilists, with a 50-year head start, still outnumber *elegansers*: 1,662 people subscribe to Flybase, a Web site devoted to all things fruit fly, whereas Jonathan Hodgkin, an early member of the Brenner lab, reported in January that 479 scientists were registered with the Caenorhabditis Genetics Center. Everybody plays nice now, but there have been minor turf tensions between the two communities. "They're fruit flies that don't pupate," was how a *Drosophila* researcher once disparaged *C. elegans*. But the worm had the first laugh; in 1998, it became the first multicellular organism to have its entire genome sequence published. *Drosophila* had to wait until 2000.

"The topic should not be considered as *C. elegans* vs. *Drosophila* but rather as *C. elegans* plus *Drosophila*," says Horvitz, who got his Nobel for figuring out the genetics behind apoptosis in worm development and discovering analogous processes in us. "It is the combined analysis of these two highly tractable experimental animals that has provided and that will continue to provide repeated breakthroughs in basic biology and insights important for the field of biomedicine."

Indeed, insights from the two organisms have revealed that there has been a remarkable conservation throughout history of basic genetic systems: Studying flies or worms thus often is an efficient way to study ourselves. Orr-Weaver was at a meeting at which fly guy Gerald Rubin cited the implications of this gene conservation by saying, "When you see the fly, you should think of little people with wings." "Then," Orr-Weaver recalls, "someone in the audience said, 'Gerry, I think those are called angels.'"

[For more information, visit Flybase at www.flybase.org/ and Wormatlas at www.wormatlas.org/index.htm.]

the picture

For years, scientists studied human disease one gene at a time. Today, their view is more global, a vantage point that offers a new look at disease.

text by David Cameron photography by Sam Ogden

Like many researchers who have their hands in a number of academic and industry collaborations, Richard Young's calendar is filled with meetings with lab members and collaborators, conference calls, and lectures. To make this triple-booked schedule worse, many of his appointments take him out of town. Travel is one area, however, where he has learned to tame the chaos.

Four years ago, when this wayfaring started to pick up, Young took matters into his own hands and got his pilot's license. Now, no longer at the mercy of commercial airline schedules, he can fly to and from Washington, D.C., or Chicago and make it home for dinner with his wife and 7-year-old daughter.

"It has its drawbacks," he observes. "I can't sit back and break out my laptop or just read a book. I need to stay focused on flying the aircraft

and trying not to have too much fun." An important aspect of flying, Young says, is maintaining situational awareness—knowing precisely where the aircraft is in three dimensions and projecting where it needs to be at any time throughout the rest of the flight.

There's a phrase for what happens when pilots lose the situational awareness that Young describes: "falling behind the plane." While communicating with air traffic controllers or changing flight plans due to poor weather, the pilot may lose his sense of where the plane is and where it needs to be. The technicalities of how to fly and land a plane may have been mastered, but when a pilot loses his grasp on the big picture, Young notes, "the fun ends right there."

It's here that biologists might learn something from the world of aviation.

In 1996, while attending a conference at Cold Spring Harbor Laboratory, Young began to get the uneasy feeling that the world of biology was, in a sense, "falling behind the plane." Sitting in the lab's Grace Auditorium, he and a few dozen researchers presented findings about the individual genes they'd been studying. They debated the details of how these few genes are regulated, but there was no talk of the big picture: how all genes work together to produce living cells and organisms.

The problem, in Young's opinion, was that biology was stuck in the one-gene-at-a-time approach; genes were studied in isolation from the larger context of the genome. It was like trying to understand how to fly an airplane by studying the engine in great detail while knowing nothing of the principles that make precise flight possible. If scientists didn't step back to look

at all an organism's genes at once, to see the individual parts in the context of the whole, then all this genetic research would never get off the ground.

"Biology is undergoing a revolution right now. Everything from how we train undergraduates to how we conduct science is becoming more and more genome-based."

—Richard Young

That was eight years ago. Today, the 50-year-old scientist, like many of his fellow biologists, has long eschewed the one-gene-at-a-time approach. "Biology is undergoing a revolution right now," he says. "Everything from how we train undergraduates to how we conduct science is becoming more and more genome-based."

Young's gaze in this revolution is focused on the complex networks through which genes and proteins communicate. In particular, Young is studying the more than 2,000 proteins called transcription factors that switch genes on and off in humans. Dozens have been linked to any number of diseases. Young's plan is to locate them all and figure out which genes they control. Drafting such a map could change the face of drug development and help doctors pinpoint an individual's risk for diabetes, hypertension, and other health problems with a simple analysis of their genetic profile. While the possibilities of such work are limitless, scientists are constrained by the limitations of conventional technology. Creating this intricate protein map would take centuries using available tools.

Young doesn't have centuries. If he is to map the interactions of genes, proteins, and disease in his lifetime, he must find a new way to do what, until now, wasn't possible.

The science of everything

Young is by no means alone in his aim to tackle the biological big picture through a multidisciplinary approach. Research centers and programs combining the work of biologists, engineers, chemists, and computer scientists are cropping up around the country, part of an emerging field called systems biology. Although the term was first coined in the 1960s, it has become increasingly popular in recent years.

At its most basic level, systems biology is an examination of cellular life as an integrated system rather

than as individual molecules. Systems biologists typically take the data from multiple experiments and use computer algorithms to weave the parts into a whole, almost like re-creating an atlas of the U.S. by analyzing bits and pieces of maps from individual states. One technological advance that has made this possible—and which also is central to Young's current research—is the microarray chip, a quarter-sized slice of either glass or silicon that can contain up to 100,000 gene fragments. These chips provide snapshots of the genome at work, showing, for example, which genes are turned on or off at any given time.

"When you describe systems biology, it's almost like saying you're trying to understand the science of everything," says Wendell Lim, associate professor of cellular and molecular



Leader of the pack: HNF 4α , adapted here from the *Journal of Biological Chemistry*, is the transcription factor par excellence in the pancreas and liver, controlling nearly half the genes that create these organs—and leading to diabetes when mutated.

pharmacology at University of California, San Francisco. “In many ways it’s a much more vague term than genomics.”

The phrase “science of everything” certainly seems fitting when one looks at the human genome as a whole. The genome, two copies of which fit inside a single cell, is composed of about 3 billion nucleotides—the DNA building blocks represented by the letters A, C, T, and G.

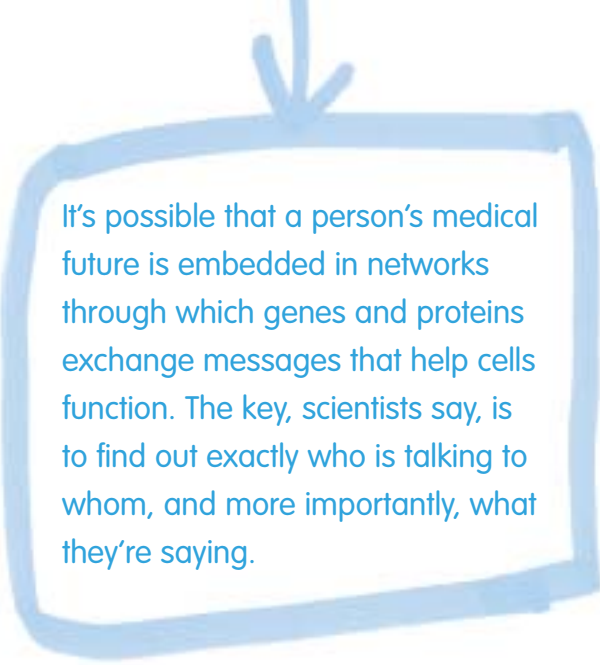
However, the typical human gene averages anywhere from just a few hundred to a few thousand nucleotides. For Young to study groups of genes and proteins within the context of the whole genome is like a marine biologist studying a particular species of fish with an eye on the entire population of the Atlantic.

In many ways, though, the genome is an entire population. Thirty thousand genes produce hundreds of thousands, perhaps even millions, of proteins. These genes and proteins all communicate with each other through intricate networks responsible for carrying out the cell’s work. Young and many other scientists believe that a person’s medical future is embedded in these communication networks. And he’s determined to find out exactly who is talking to whom, and more importantly, what they’re saying.

From yeast to humans

To eavesdrop on this conversation Young turned first to common baker’s yeast. It might seem strange that the desire to uncover the deepest biological mysteries of human life would lead a scientist to one of the main ingredients of beer and pizza dough. But yeast is a proven testing ground for biologists, the perfect context in which to hone scientific exploratory techniques before moving to the bedlam of human cells.

The human genome contains vast terrains of DNA that don’t serve



It’s possible that a person’s medical future is embedded in networks through which genes and proteins exchange messages that help cells function. The key, scientists say, is to find out exactly who is talking to whom, and more importantly, what they’re saying.

any known purpose. In fact, this so-called “junk DNA” makes up over 90 percent of our genome. To complicate matters further, one gene can produce dozens, sometimes even thousands, of different proteins. The yeast genome, by contrast, is simple, neat, orderly—and small. There are only 6,000 genes in all, and each gene produces only one protein. For these reasons, yeast was the logical starting point.

Young’s particular approach for viewing the entirety of the genome has a self-evident logic to it. If you want to find out what any “organization” is all about, find out who’s running it. With the genome—yeast or human—that part is easy. The whole show is run by transcription factors, proteins that bind to genes and act as control switches, flipping the genes on and off. Transcription factors give the orders; genes follow them. So, then, to understand how the genome runs, there was no better place to begin than by first locating all the transcription factors and finding out what they’re telling the genes to do. “The only problem,” says Young, “was that with traditional laboratory tools, this would take over a hundred years to pull off—even in yeast.”

In the late 1990s, microarray technology hit the biology scene, at last providing scientists with a method to quickly analyze genes en masse.

But to make sense of the reams of data microarrays provided, some intense computational power was required. Young put together a team that included, among others, postdoctoral associate Duncan Odom and David Gifford, a computer scientist at Massachusetts Institute of Technology where Young also is a professor of biology. Young’s lab assembled the microarray chips; Gifford constructed the algorithms to crunch the data.

In October 2002, the research team reported in the journal *Science* that they had discovered the binding points of 106 of yeast’s 200 transcription factors. The technology they developed—which reduced to a matter of months what would take centuries using conventional methods—enabled the scientists to create a map of sorts, a schematic that diagramed how transcription factors and genes in yeast communicate with each other. It was a complex picture, since one transcription factor can bind to and regulate multiple genes. In addition, transcription factors send signals to each other, as well as communicating with genes—a system that Young calls a regulatory network. For the first time, scientists had a working set of operating instructions for an entire genome.

“But this was simply a proof of context experiment,” says Young. “Doing this in yeast just proved that the tools worked.”

The real test, he says, was to try the system out on the human genome. Transcription factors are known to play key roles in many common diseases, but no one had yet developed a process for hunting them down and identifying all their points of operation. If Young’s technique worked in human tissues, the payoff could be immense.

Tuning into the networks

For human genes, Young had two choices. He could use readily available and plentiful lines of cultured cells, but most of these cell lines have, over generations, developed genetic abnormalities that might compromise study results. Far more challenging, but equally rewarding, would be to use donor-grade human tissue samples, the same quality used in transplant procedures. This would be as close to a living, breathing body as the researchers could get.

Acquiring these tissues is no easy task. It requires persistence, patience, and a willingness to respond quickly to a call from a donor center. Last year, one of those first calls came through on Odom's cell phone during a weekly lab meeting. Odom checked his caller ID: It was the Joslin Diabetes Center. Staff there had pancreatic tissue samples for his research, and he needed to pick them up fast. He quietly ducked out of the meeting, loaded some plastic test tubes into a cryogenic carrier, threw on his coat, and ran for the subway.

When he arrived at Joslin, he transferred the tissue into the test tubes, filled the tubes with formaldehyde, and capped them with brightly colored lids. The process, Odom recalls, was "pretty anti-climactic." The end result, however, could be a windfall of insight into human disease.

Odom spent the next week extracting all the genetic information from these tissue samples and applying it to a new suite of microarray promoter chips. An algorithm developed by Gifford, a modified version of the one used in the yeast research, interpreted the data and displayed the complex networks that these genes and proteins form. Odom examined the

networks, looking at four transcription factors associated with type 2 diabetes.

His task was to take the donated pancreatic tissue from Joslin Diabetes Center and liver tissue that he received from another donor program at the University of Pittsburgh, comb the entire genome in both types of samples, locate every single point to which each of these transcription factors bind, identify each gene that they control, and learn how these transcription factors communicate both with these genes and with each other.

"It's an extremely complex and deeply integrated network," says Odom, "one that orchestrates the creation and maintenance of the pancreas and other human organs." If a transcription factor is damaged, the cell may end up producing the wrong amounts of any number of proteins. The entire network can be thrown off balance, causing a change in insulin release that could lead to diabetes.

The researchers were successful in their hunt, and in February, they reported the location of every genome binding point of these four transcription factors—again completing in months what in the past would have taken centuries. The team discovered that one of the transcription factors regulates nearly half of the 3,000 genes necessary to make both a pancreas and

a liver. In a world where scientists tend to examine individual genes and proteins to find the molecular causes of disease, pinpointing this one transcription factor could yield a wealth of genetic information. Perhaps, Young suggests, researchers might be able to develop medications that modify the activities of mutated forms of this transcription factor. Doing so would correct the activity of 1,500 genes and possibly even prevent type 2 diabetes in at-risk individuals.

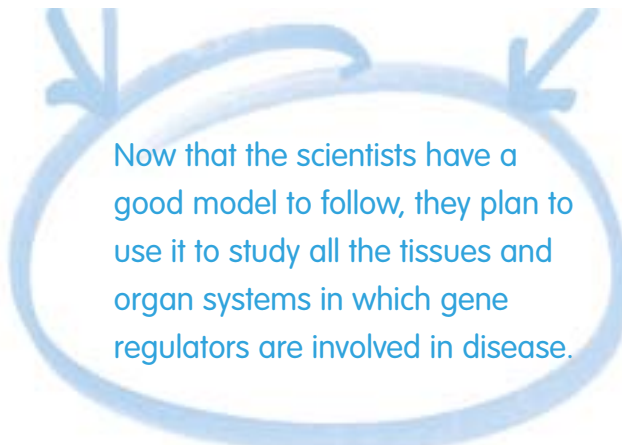
The study, which was published in *Science*, in addition to uncovering some compelling basic biology about type 2 diabetes, demonstrated that the technology works in human tissue, signaling a new phase in human genomic research.

"Before, we were just looking at conditions one gene at a time," says Graeme Bell, molecular biologist at University of Chicago and coauthor of the latest *Science* paper. "Now we can see the whole playing field, and more importantly, we can see the players."

Making a list

Now that the scientists have a good model to follow, Young plans to use it to study all the tissues and organ systems in which gene regulators are involved in disease. And that is why he's compiling a list—a very long list—of every known transcription factor related to diseases and conditions such as cancer, hypertension, birth defects, neurological disorders, and obesity, among others. His goal is to map every gene-protein communication network that each of these transcription factors regulates and do this in every human tissue.

"In the end," says Bell, "these efforts will provide a detail of understanding of the regulation of gene expression that will open doors and possibly lead to a whole new approach to many of the



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In the tube: The donor-grade human pancreatic tissue Duncan Odom transported from Joslin Diabetes Center in bright-capped test tubes last year was used for his studies on transcription factors, including one that controls half the genes needed to make a healthy pancreas.

most common diseases.” Still only a few months old, this most recent *Science* paper has caused a surge of interest in the therapeutic value of identifying these gene-protein networks. Scientists such as former Whitehead Fellow Trey Ideker are developing technologies to analyze the new information about gene-protein interactions that researchers like Young are discovering.

“In the next five to 10 years, we’re going to see the study of these networks dominating the scene in biology,” says Ideker, who now is an assistant professor of bioengineering at University of California, San Diego. “I’d say that right now, this field is where the Human Genome Project was in 1985.”

Of course, back then sequencing the human genome was still something

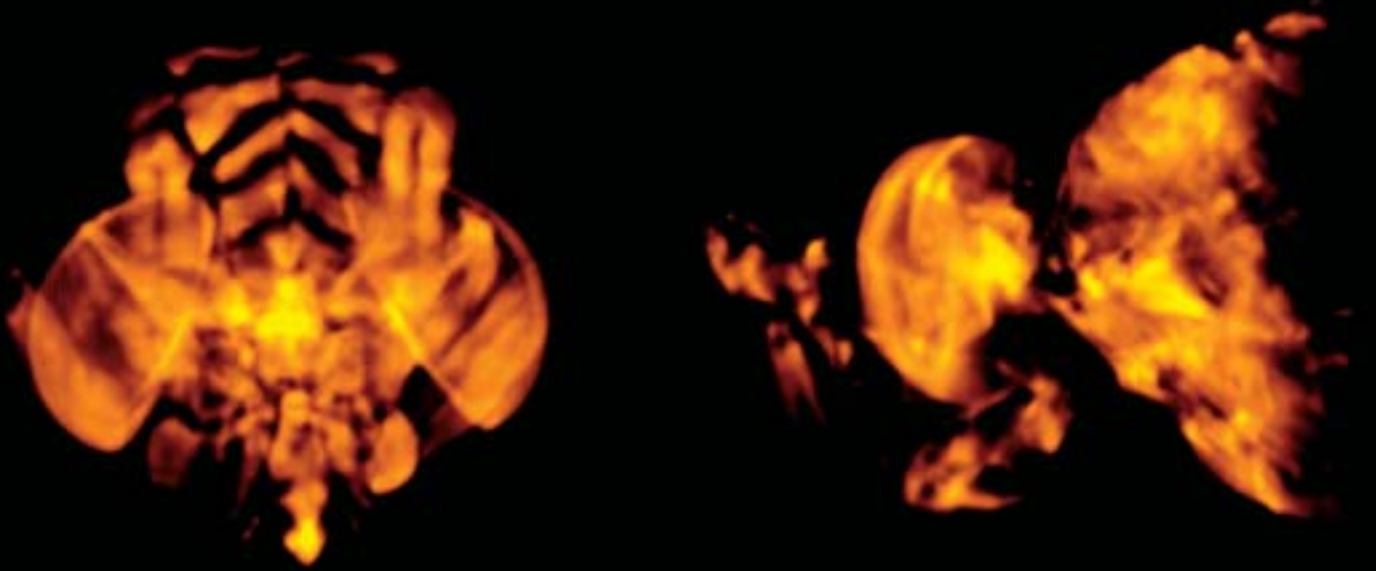
of a dream. Today, the completed project, essentially a massive “parts list” in which the chemical building blocks of DNA are laid out in a linear line, often has been compared to dissecting a Boeing 747 and placing every last nut and bolt on the ground next to each other. Although we can see the entire body of the aircraft from the inside out, there’s nothing to indicate what goes where—let alone how the machine stays airborne.

By understanding the complexities of how genes and proteins interact, Young and others in the field are developing an instruction manual scientists can use to shape the information from the genome project into a map of human disease. In a sense, they’re figuring out how to build an airplane, a daunting task even for the most seasoned pilot. The key for Young, it seems, will be

to recall the lessons of aviation that have guided him from the runway, to 20,000 feet above ground, and back down again: Keep your eyes on the horizon. Know where your plane is and where it should be at all times. And never lose sight of the big picture.

[For more information on this research, visit the Whitehead news archive at www.whitehead.mit.edu/nap/features/nap_feature_young_diabetes.html.]

The **Biology** of



*How do the **brain** and **mind** work together
to produce **action** and **reaction**?*

by Charles Schmidt

Behavior



image courtesy of alan jasanoff

The human body is assaulted by hundreds of thousands of stimuli every day. Sights: A car is coming down the street, so you step out of the way. Sounds: Someone calls your name and you answer. Touch: A glossy magazine arrives in your mailbox and you thumb through its pages.

We take in these and other sensations and use them in ways that help us adapt and survive in our physical world. But human life is much more than such simple response mechanisms might suggest. We feel emotions, have memories, and process myriad thoughts about who we are and what we're experiencing. Responding physically to our senses is an action controlled by the brain. The voice of reason that tells us why we react in a particular way and allows us to interpret the

larger significance of that response is the mind at work.

For centuries, scientists have sought to understand how the brain—a physical entity that can be touched and observed—gives rise to the mind, that intangible amalgamation of thoughts and perceptions that makes us who we are. That the two are linked is without question: Kill a portion of the brain and some part of the mind goes with it. But the biological basis of this connection and the way it changes when someone is sick or injured is a mystery.

Today, scientists are using a new form of an old technology to study the intricacies of human consciousness and brain functioning. This tool, known as functional magnetic resonance imaging, or fMRI, is providing insights into the biology

On the fly: Alan Jasanoff built an MRI device that collects images of the brain in living animals noninvasively at extremely high resolution. These scans of the brain of a blowfly, which show detail near the cellular level, proved the setup works.

of behavior, perception, and emotion. Most people think of MRI as a means to visualize brain tumors and other medical anomalies. But in behavioral studies, scientists use the tools of fMRI to generate rapid, time-sequenced snapshots of the brain in action, watching the flow of blood as it meanders throughout the brain, delivering oxygen where it is needed. By tracking blood flows, it's possible to identify which areas of the brain are activated by certain activities and feelings, such as learning or fear. This



sarah o'neill

Sharper image: Using fMRI technology to study the intricacies of human consciousness and brain function offers insight into the biology of behavior, perception, and emotion, says Whitehead Fellow Alan Jasanoff.

information is critical to understanding how the brain processes stimuli and stores information, says Alan Jasanoff, a Whitehead Institute Fellow who is among a handful of scientists pushing new uses of fMRI to analyze the basic elements of brain function.

“In terms of brain physiology, even these basic behaviors are complex and difficult to study,” Jasanoff says. “So today, we focus our efforts on simple processes, which are building blocks to more ‘cognitive’ phenomena, like how the mind experiences hope or helps you play chess.”

A NEW TWIST ON AN OLD TECHNIQUE
MRI’s origins date to the 1940s. At first, the technique was used mainly for experiments in chemistry and physics. But in the 1970s, MRI was adapted for medical uses, an advance spearheaded by Paul Lauterbur, an American chemist, and Peter Mansfield, a British physicist. The pair shared the 2003 Nobel Prize in Medicine or Physiology for their efforts.

Functional uses of MRI first emerged in the early 1990s, when Seiji Ogawa, then a physicist at Bell Laboratories, modified the technique to monitor blood flows in the brains of rodents. Later research at Massachusetts General Hospital performed by Kenneth Kwong, who now teaches radiology at Harvard Medical School, led to fMRI’s use in humans. Kwong pioneered the use of injected “contrasting agents”—liquids that enter the brain through the bloodstream and make blood flows easier to detect. Since then, fMRI has become an indispensable tool for research in neuroscience and cognitive psychology. fMRI methods also are improving treatments for a broad range of neurological ailments.

Nancy Kanwisher, a psychologist and professor at Massachusetts Institute of Technology, says her fMRI studies of the brain’s organizational structure help her understand the mind itself. Much of her current research focuses on how the brain processes visual images. Kanwisher’s studies have shown that image recognition is highly localized to specific areas of the

brain. Faces, for instance, are processed in a tiny region of the cortex measuring barely 1 square centimeter. Kanwisher has dubbed this region the “fusiform face area.” All other human body parts are processed in a different part of the brain, she says.

Recently, Kanwisher’s lab began an exploration of how the brain coordinates its perceptions of other people. In a remarkable finding, her graduate student, Rebecca Saxe, demonstrated that our understanding of other people’s beliefs is processed in one region of the brain while our understanding of their goals is processed in another. “Both these regions help us to understand people,” Kanwisher says. “But each is involved in a different aspect of that activity.”

While some mental functions are therefore highly localized, others—for instance, number processing—may engage what Kanwisher calls “general purpose brain machinery,” which does many different things. But getting to the core of this functionality—and the organic foundations that make us cry, or laugh, or cheer at a football game—require increasingly more detailed investigations into how different regions of the brain are coordinated.

Describing this coordination is pushing the current resolution of fMRI technology. Larry Wald, a radiologist at MGH’s Athinoula A. Martinos Center for Biological Imaging, one of the top imaging research facilities in the world, says current fMRI techniques are limited in part because they don’t measure the brain’s primary response to stimulus. Blood flow actually is a secondary response, triggered by electrical impulses in neurons. The time-lag between these electrical triggers and a blood surge can be several seconds—a significant lapse, notes Wald, because it hides the interplay between activated regions.

“We might be able to say that two regions are involved in memory, for

example, but we can't see how they interact," Wald explains. "We need to figure out how these activated regions form a network."

Identifying such networks is a goal that drives Jasanoff, who is pioneering new fMRI techniques that go beyond blood flow to expose the brain's electrical activity—a series of impulses that transmits messages between neurons. The techniques are still experimental, so Jasanoff works with laboratory animals to isolate neural circuits involved in simple behaviors. "What we learn about simple behaviors in animals guides us toward an understanding of more complex behaviors in humans," Jasanoff says. "Our findings can influence the direction of human research."

Researchers trying to "get inside the brain" during experimental research traditionally have relied on electrodes wired directly into neural tissue. This process is not only invasive and cumbersome, it's also limited in terms of its spatial coverage—electrodes gather data only from the area to which they are attached. Jasanoff's research is offering another option, namely, a set of MRI contrasting, or imaging, agents that can selectively be activated by the brain's electrical currents. "My approach will provide a direct assay for neural activity deep within the brain," Jasanoff says. "This is unlike anything that is currently available."

To date, Jasanoff's focus has been on establishing a way to test imaging agents for fMRI in single brain cells of an oversized housefly called a "blowfly." He presented the blowfly brain imaging approach in a 2002 article in the *Journal of Magnetic Resonance*, and demonstrated an oxygen imaging application using the setup in a 2003 article in the journal *Magnetic Resonance in Medicine*. Now Jasanoff is completing work on two new brain imaging agents, and intends to adapt the agents so they can be used safely in higher organisms, for instance, rodents. Studies

in animals are necessary before the agents can be used in experiments with human subjects, a step in the research that Jasanoff notes is many years away.

BEYOND THE BRAIN-MIND CONNECTION

With the aid of fMRI technology, scientists are expanding their understanding of not only the brain-mind connection, but also chemical and structural changes in a diseased or injured brain. fMRI techniques now are being developed to quickly identify salvageable brain tissue in stroke patients. Targeting these tissues quickly with drugs greatly increases the likelihood they can be saved, Wald says. "This is a lot better than giving a drug and then waiting and watching to see how the patient responds, for instance, by how well they speak," he adds. "You want a good functional assessment that can tell you quickly how well a drug is working."

Scientists also are using the technique to study how the brain "rewires" itself after a stroke or physical injury. Evidence suggests that some brain regions actually may take over for other areas that die after these events, says Christopher Moore, assistant professor of neuroscience at MIT. Researchers use fMRI to define these regions with the aim of harnessing recovery mechanisms using rehabilitative physiotherapy.

Moore's own studies with fMRI have shown that brain rewiring might inflict deleterious effects, including "phantom limb" pain among amputees or patients suffering from paralysis, for example. In these patients, Moore explains, brain activity is reorganized by a dramatic loss of sensory input from the affected parts of the body. Brain regions that used to respond to being touched on the arm, for instance, could be activated by the sensation of being touched on the chest. This aberrant activation may induce misperceptions of painful

input. Clinicians can use the information gleaned from fMRI to develop therapies for pain management. "Sometimes you can train these patients to shift their perceptions away from pain," Moore says.

Today, many different specialists are using fMRI—each with a distinct focus, but all with a common goal of understanding brain function and the mysteries of human perception.

Today, many different specialists are using **fMRI**—each with a distinct focus, but all with a common goal of **understanding** brain function and the **mysteries of human perception.**

In the future, Wald says, scientists increasingly will seek higher resolution fMRI tools to study the neural circuits that drive mental processes. Jasanoff's imaging agents, Wald suggests, represent an important advance that will uncover the molecular events that drive these systems. Meanwhile, scientists such as Jasanoff, Wald, and Kanwisher say fMRI will produce ever more valuable research contributions that someday may bring that elusive mind-body connection into greater focus.

"It's a lucky fact that the mind lives in the brain," Kanwisher quips. "So, if we want to really understand how the mind works, then studying the basic organization of the brain is a pretty good place to start."

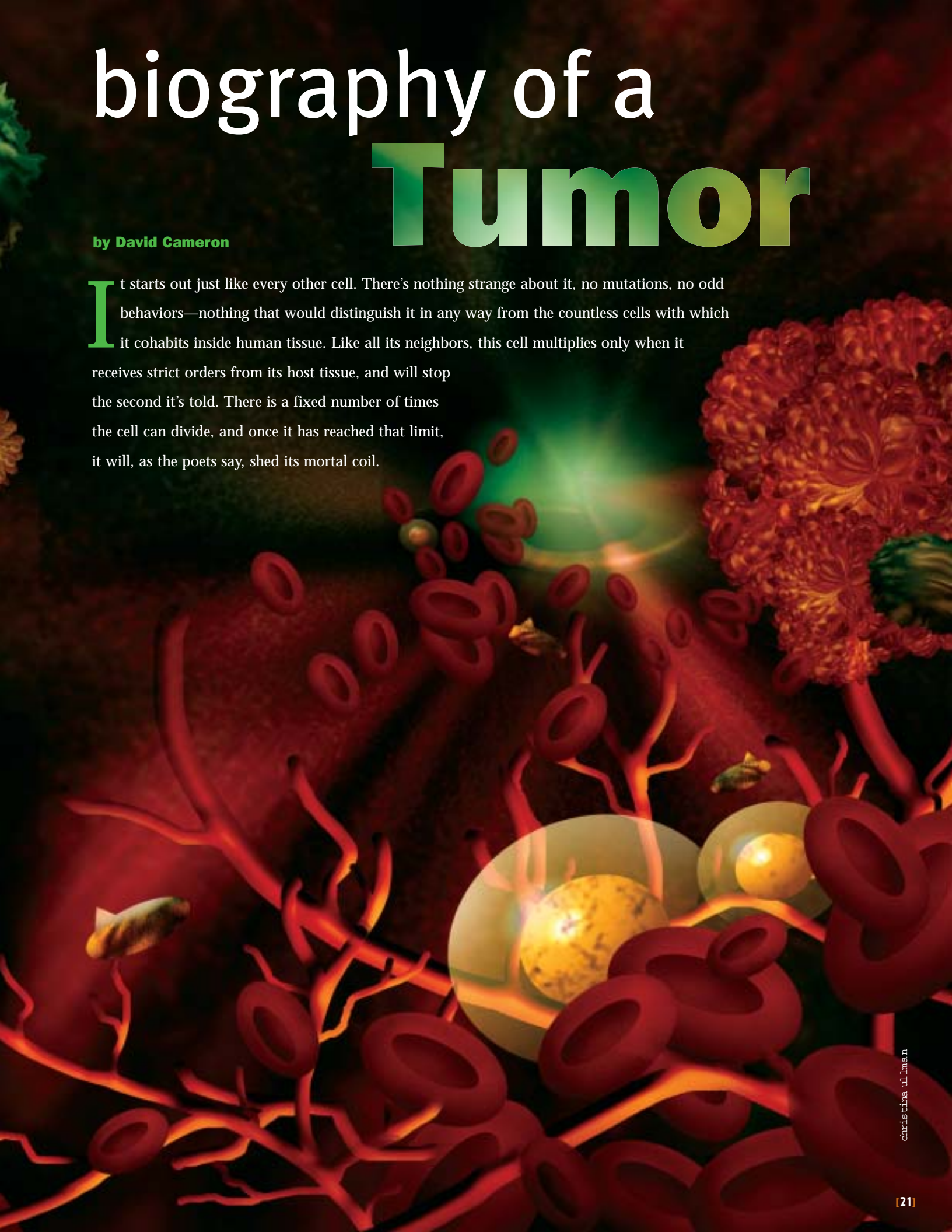
[For more information on MRI technology, visit the Web at www.howstuffworks.com/mri.htm.]



biography of a Tumor

by David Cameron

It starts out just like every other cell. There's nothing strange about it, no mutations, no odd behaviors—nothing that would distinguish it in any way from the countless cells with which it cohabits inside human tissue. Like all its neighbors, this cell multiplies only when it receives strict orders from its host tissue, and will stop the second it's told. There is a fixed number of times the cell can divide, and once it has reached that limit, it will, as the poets say, shed its mortal coil.



This cell is such a team player that if it transgresses any of these barriers it will immediately commit suicide for the greater good of the organism, like a captured secret agent who pops a cyanide pill rather than divulge secrets to the enemy.

Over the years, however, this cell will sustain a mutation that sparks the development of a tumor mass, surpassing insurmountable odds in an exercise in Darwinian evolution that becomes the body's nightmare. Just like the microscopic organism that slugged its way through primordial soup, evolving over billions of years into a creature capable of writing *Hamlet* and splitting atoms, this cell also will evolve, and over the course of a few decades, it will survive and grow and multiply in an environment so hostile, it's amazing any tumor ever manages to survive.

Still, the life story of a tumor shows that ultimately, everyone is vulnerable to cancer. The human body comprises hundreds of billions of cells, and because many cells continue to divide throughout their lifetime, cancer remains a threat, however remote. In fact, many researchers believe that if we were spared death from all other diseases and lived virtuous lives complete with healthy diet and ample exercise, we all still would get cancer sooner or later, perhaps at age 170 rather than 70.

Tumors don't develop overnight. Their growth is a long and arduous process that can take decades. To mature, tumors must circumvent a powerful biological defense system designed to kill the rogue cells that make up the mass. Not all tumors progress in exactly the same way. The stages may occur in a different order depending on the cancer, and

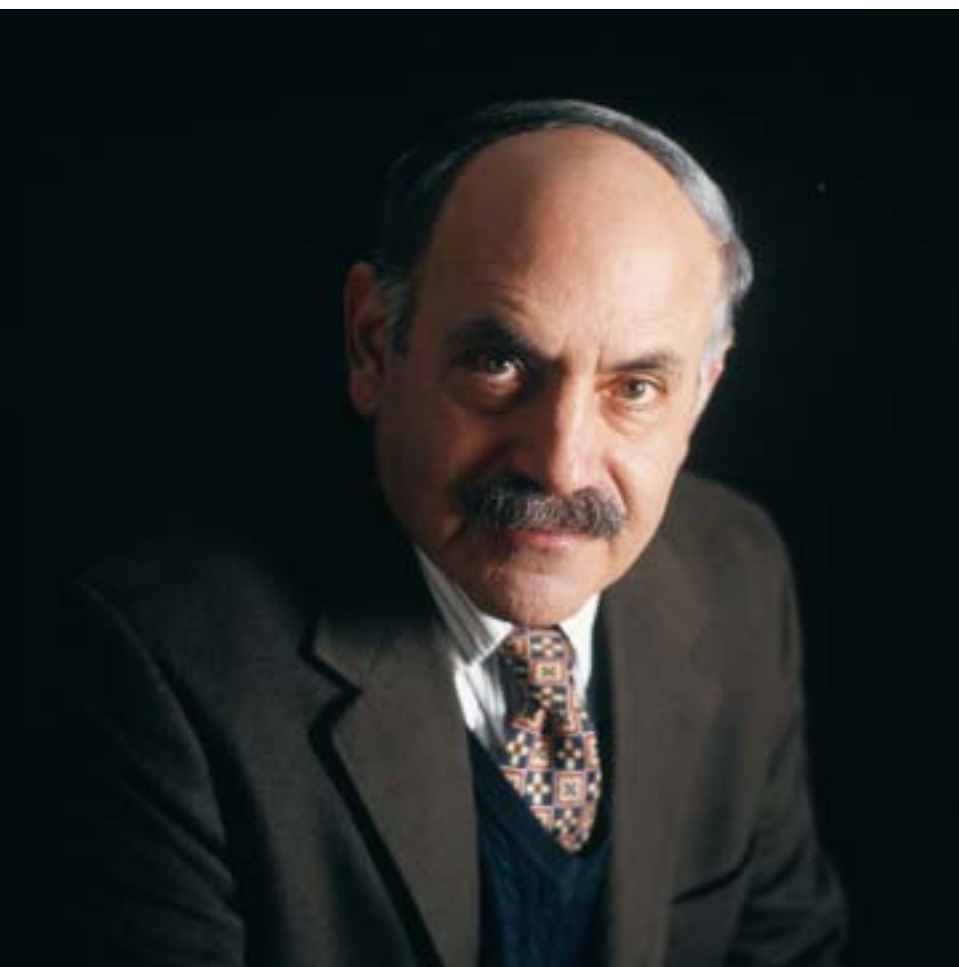
the same type of cancer can progress quite differently from one patient to another. But there is a common script that most cancers follow, and while a person's lifestyle choices certainly can enable a cancer's progression, those stages occur mostly through the slow and random process of natural selection.

The biography of a tumor, then, is not a story about cancer's prowess. It is about our vulnerability to random chance.

From Humble Beginnings

And so, we begin with an ordinary cell that lives harmoniously with its fellow cells somewhere deep inside the regions of a particular human tissue. Living harmoniously means, among other things, that there exists a perfect equilibrium between cell births and cell deaths. The cell will divide, birthing a replicate, or clone, of itself, only when another cell has died. Its genetic wiring ensures this.

However, when the cell divides and makes a copy of itself, it's never a perfect replica. Each time, a minuscule mutation, sometimes only an alteration in a single letter of DNA, alters the new cell's genome ever so slightly. In addition, toxins that enter the human body from, say, cigarette smoke, charred meat, or pollution, often affect some of the genes in this and other cells. In his book, *One Renegade Cell*,



sam o'gden

Final frontier: A growing number of scientists are turning their attention to cancer metastasis, what Whitehead Member Robert Weinberg calls the "last great frontier in cancer research."



Whitehead Founding Member Robert Weinberg writes, “the genome of the human cell is constantly under attack, pelted by a hailstorm of damaging chemicals.” This happens all the time, and the cell is used to it. So far, none of these mutations has troubled this cell.

And then, one day, it happens.

Purely by chance, a toxin, perhaps a component of tobacco that makes the substance so deadly, finds its way deep into regions of the cell’s nucleus and damages what’s called an oncogene, a class of normal genes that, when mutated, cause a cell to grow out of control. Weinberg, who identified the first human oncogene in 1982, compares the effect of a damaged oncogene to a gas pedal stuck to the floor. And that is why this cell, although oblivious to any of the other mutations it has experienced in the past, notices this one.

The equilibrium in the tissue is disturbed. The cell divides, and divides again, but this time not in response to another cell’s death. It copies itself at will. When it divides, each new clone retains the ability to divide, unprompted, on its own. And so on. But this new genetic twist affords only that particular cell and its progeny limited unfettered reproduction. The cell is held in check by a tumor suppressor gene, another class of genes that acts as a sort of emergency brake system to slow down the effect of this stuck pedal. With tumor suppressor genes acting vigilantly, this micro-cluster of a few extra cells is harmless. The tumor suppressors create a firewall that prevents the cell from growing out of control.

The cell and its small cohort remain in this state for years, until one day a new toxin defeats seemingly insurmountable odds and disables a single tumor suppressor gene in this small cell cluster. Now, gas pedal stuck, brake system disabled, the cell division picks up speed.



seam ogden

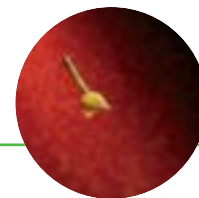
Gradually, a small and irregular—and, at this point, still inoffensive—gathering of cells takes shape.

The tissue that houses this cluster has seen this sort of thing before. Over the years, other tiny groups of cells have experienced similar mutations and started to grow at random. “In a sense, our bodies are constantly developing microscopic pre-cancerous growths,” says Tan Ince, a scientist in Weinberg’s lab and pathologist at Brigham and Women’s Hospital in Boston. “It’s just that 99.999 percent of the time, the body is able to take care of them.”

The body does this by using a group of proteins whose sole purpose is to maintain cell-growth equilibrium within the tissue. When a cell starts growing out of synch with its neighbors, the tissue sends these proteins to the cells instructing them to stop. Some cells, as a result, never grow again; others are only temporarily held at bay.

This cluster of a few thousand cells, which is still benign, receives these anti-growth signals and obediently stops in its tracks. For the tumor, that’s just fine. After all, it’s only following the dictates of both its internal and environmental biology, and when it’s told to stop, it stops. And this tumor isn’t alone. Others like it have been stopped at this particular stage, never to grow again—and we are none the wiser.

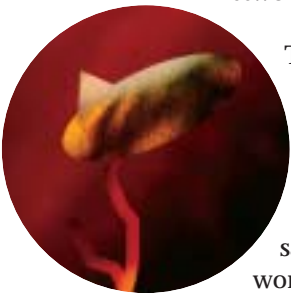
Biology’s Internet: Just like damage to a single computer server can bring down an entire network, a small mutation to a single gene can wreak havoc in the cell and spur cancer growth, says scientist Tan Ince.



Of course, toxins from a variety of sources—environment, food, chemical substances—continue to travel through the tissue. Some even cause more mutations in this microscopic tumor, but in every case, the mutations occur in areas that don’t affect its behavior. A few of the cells in the tumor still are able to divide, a process that can cause slight mutations. But again, like most mutations resulting from cell division, nothing happens. And the tumor remains in this state for years, perhaps even a decade or more.

Eventually, a random toxin finds its way through the tumor and mutates a single gene in a cell inside the mass. This time, the damaged gene happens to be a critical node in the cell’s network through which it processes the anti-growth signals that have been keeping it in check.

“Think of it as the World Wide Web,” says Ince. “You can hit any number of nodes in the network, and it won’t be a problem. But then you hit one that has a ripple effect and it brings the whole network down.”



That one cell, embedded deep within the tumor, already with oncogene and tumor suppressor gene damaged, is now deaf to anti-growth messages. The network isn’t working as it should. It begins dividing again, creating clones which, in turn, contain these same mutations.

Then, a roadblock: Orders from the host tissue instruct individual cells in the tumor to kill themselves. A succession of mass suicides begins. The tumor does nothing to stop it.

The Sacrificial Cell

Biologists call this apoptosis—also known as programmed cell death. The process, named by British biologist Andrew Wyllie in 1972, refers to the ancient Greek term for leaves falling from a tree. In the cell, however, the process isn’t nearly as pastoral as the changing of seasons. Proteins on the cell surface receive these suicide orders and deliver them to other proteins deep within the cell. Additional signals may even originate within the cell itself. The message continues, protein to protein, via an intricate network that converges on the mitochondria, a group of cellular internal organs whose responsibilities include, among other things, turning food into energy. These mitochondria release a chemical catalyst that launches the suicide process. The cell membrane begins to crumble, the chromosomes degrade, the nucleus fractures, and within the space of a few hours the cell is a microscopic cadaver, swallowed up by nearby cells.

It very well could all end here. The growth rate of the tumor has been significantly curbed by the scores of

cells sacrificing themselves for the greater good of the organism. While the tumor won’t disappear as a result, it can stop growing altogether.

“Scientists are researching new forms of therapy designed to induce cancer cells to enter apoptosis,” says Weinberg, noting the effectiveness of this natural process. Drugs that target this process in tumor cells while sparing healthy cells, however, still are in early developmental stages.

It’s not easy to coax a cell into killing itself. The entire process is complex and many proteins need to be recruited for it to work. But there is one star player, a gene called *p53*. This gene was first discovered by Princeton University biologist Arnold Levine in 1979, but it wasn’t until the late 1990s that Levine and other researchers realized it was a critical component in this suicide network. *p53*, along with the protein it produces, assesses the health of a cell and its genome and, when necessary, acts as a conduit through which signals reach the suicide machinery.

But somewhere inside the tumor, a single cell that has not yet received its suicide order divides, and in doing so introduces a mutation that disrupts its *p53* gene, a mutation that is found in more than half of all human cancers. With *p53* damaged, the new cell produced by this division contains a suicide network in disarray. A suicide order enters the cell, but the passing of information breaks down and never reaches the mitochondria. And when this cell then divides and divides again (its hyperactive oncogene continually pushing for more rapid cell divisions) the tumor will enter a new phase as all of its progeny quickly form a new clump of cells, each containing disabled suicide networks.

It’s important to remember that in spite of how far this fledgling tumor has come, it really isn’t any “smarter” than when it started.

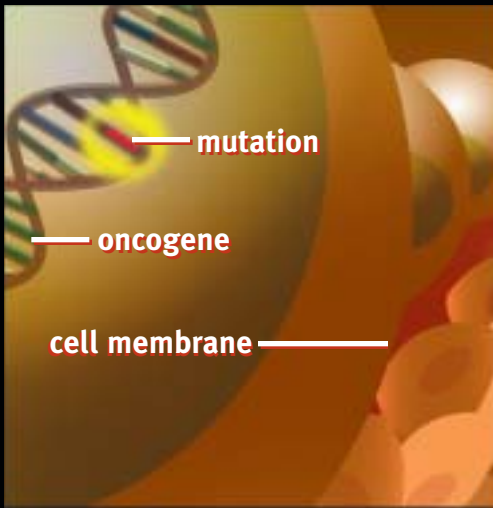
Each new capability it gains is the result of a series of random mutations. “There’s no ‘learning’ going on here,” says Bert Vogelstein, professor at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. “The tumor isn’t developing any new skills. This is all chance. In macro-evolution, organisms don’t learn anything, they’re just selected. Here it’s the same thing on the cellular level.”

Evolution may have rejuvenated this tumor’s reproductive power, but the tumor, like all other organisms, can’t live forever. Its ability to grow apart from what its environment dictates is trumped by an internal machinery that is programmed for a specific amount of cellular division. Even the most mutated cell eventually enters into its golden years, and when it finally reaches its division quota, quietly passes on.

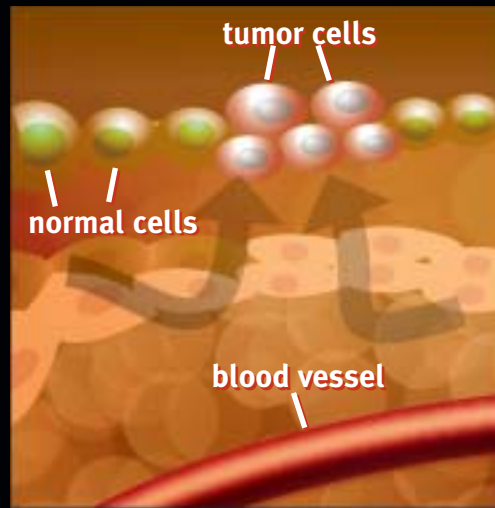
Forbidden Fruit

The original lineage of cells that triggered the tumor growth is gone. Since typical human cells divide anywhere from 60 to 70 times—sometimes once a day, and other times once a month or even once a year—we can then assume that this cell and its daughter cells passed on some time ago. That’s because cells possess an internal clock controlled by something called the “telomere,” a region of DNA that lives at the endpoints of each of the 46 chromosomes. The telomere preserves the chromosomes, but with each cell division, the new cells lose some of this region, until eventually this protective shield is gone altogether—a process that James Watson, co-discoverer of DNA’s double helix, predicted in 1972. And so, when the original cell divided into two daughter cells, and those two resulting cells subsequently divided, each new cell contained less of the telomere than its predecessor. And so on.

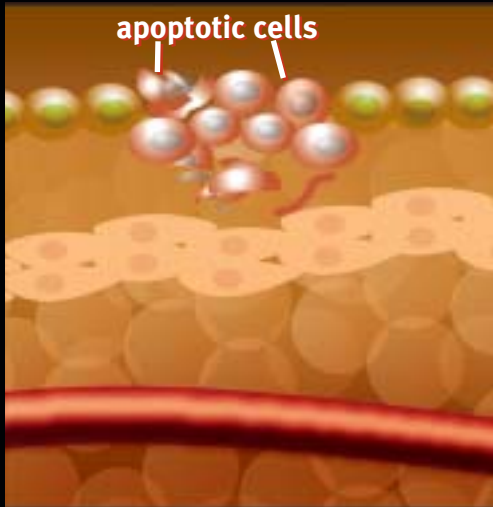
“Certain cells, such as sperm or stem cells, contain an enzyme that preserves the telomere through each



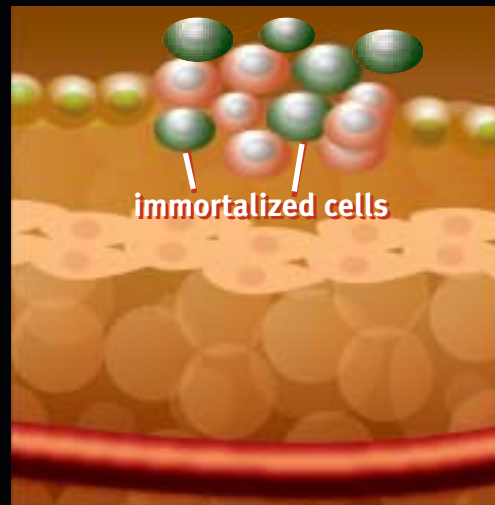
1. A single mutation in a gene called an oncogene causes the cell to divide at a much faster rate.



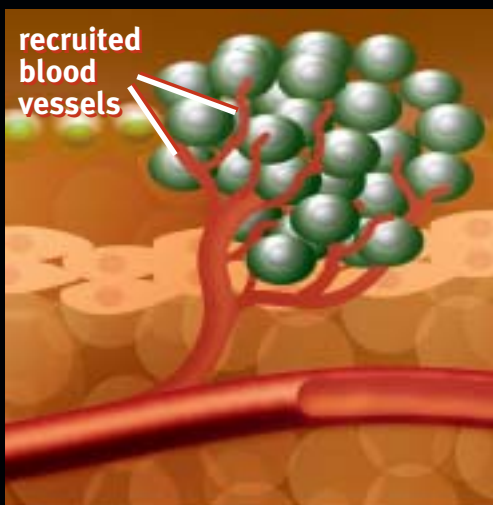
2. The tissue sends anti-growth signals to this small cluster of cells, but the fledgling tumor becomes deaf to these signals.



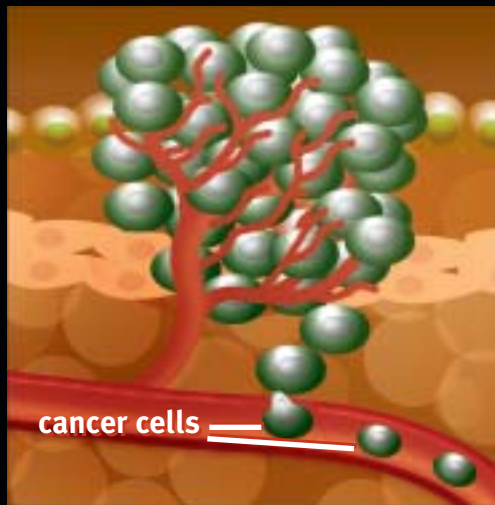
3. Cells inside the tumor receive orders to commit suicide, a process called "apoptosis." Further mutations in the tumor enable the individual cells to eventually evade this process.



4. Most cells have a fixed number of times that they can divide, and eventually their lineage dies off. But tumor cells pass on to their successors the ability to divide without any limit whatsoever, creating an "immortal" lineage.



5. The tumor has been relying on the surrounding tissue to supply it with blood, but now it has developed its own vascular network.



6. Breaking through tissue layers that have been keeping the tumor confined, the tumor can now enter the bloodstream and spread to distant sites in the body.

graphic by: tom dicesare
 source: the hallmarks of cancer
 cell, vol. 100, 57-70, january 7, 2000

cell division and as a result, these cells become ‘immortal’,” able to replicate endlessly without any limitation, says Douglas Hanahan, a professor of biochemistry at University of California, San Francisco. All cells in the body contain the gene that creates this telomere-producing enzyme, but with the exception of sperm cells and stem cells, it is inaccessible. Weinberg describes this gene as the genetic “apple from the Tree of Knowledge, forbidden to most normal cells in the body.”

However, through a process that researchers don’t fully understand, the tumor breaches this mortality barrier. In some tumors this happens early on; with others it’s later. But somehow, a group of cells manages to activate this “forbidden” gene, starting the production of that immortality-giving enzyme. With each subsequent cell division, the telomere remains intact, and so the cells divide 70, 100, 140 times, each time passing on perpetual youth to their cellular offspring.

Because almost all types of cancer possess this ability to replicate unchecked, disabling the process is a tempting target for drug makers. “Attempts to make telomerase inhibitors that could shut down the enzyme are attractive in principle,” says Weinberg, “but have, until now, proven difficult.”

For now, this tumor, which has transformed itself over the years from a simple collection of otherwise normal-looking cells to a tissue with its own uniquely abnormal architecture, has achieved an immortality of sorts.

Tripping the Malignant Switch

Even though it has evolved beyond so many of its environmental constraints, and despite its gradually mounting size, the tumor remains benign. It may have grown resistant to the host tissue’s attempts to restrain it but, ultimately, the tumor still needs the tissue to live. The tumor requires a steady supply of

blood to grow, and although it has siphoned blood from the host, the lack of its own vascular network keeps it in a relatively immature state.

But over the life of the tumor, a slow and steady process innate to the body’s immune system has gained momentum. Early in this particular tumor’s development, when it was no more than a small lesion, the immune system detected it, but misdiagnosed it as a wound. The immune system’s primary healing response is to enable a wound to grow blood vessels—a process known as angiogenesis.

“Remember,” says Hanahan, “the immune system isn’t smart enough to say, ‘Hey, that’s cancer!’ It hasn’t evolved to the point where it recognizes cancer as an enemy.” Instead, it looks for foreign invaders like viruses and bacteria. The immune system, mistaking the identity of the tumor, feeds it with proteins that spawn a vascular network. “It can literally bathe the cells with these angiogenic growth factors,” says Hanahan.

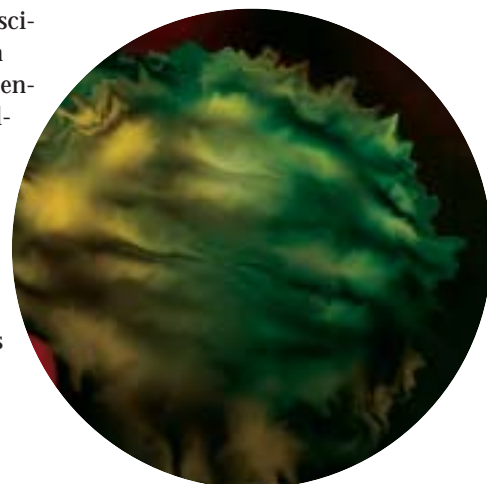
Slowly, over many years, scores of small capillaries have developed, some growing into larger, more robust blood vessels. Eventually, the vessels reach maturity, and now, with the blood flowing freely and abundantly, the tumor has become a self-contained system, a sort of organ within an organ. With no constraints, and wholly independent, it continues to grow.

Few areas of tumor development have gained as much attention in recent years as angiogenesis. Unlike research on apoptosis or telomere, angiogenesis is one area in which scientists have experienced success in drug trials. Harvard University scientist Judah Folkman, who often collaborates with Hanahan, has developed drugs that block these growth-factor proteins, one of which received approval from the Food and Drug Administration in February. “It’s too early to tell just how successful these therapies will be,” Hanahan says, “but the early signs are promising.”

At this stage of the tumor’s development, it has remained within the confines of particular tissue membranes, contained by a sheath of proteins that prevent it from invading other areas of the organ housing it. Therefore, if a physician were to remove or destroy it, the patient could be assured that all traces of the cancer are gone and that there will be no recurrence whatsoever.

But as the tumor grows, its sheer size becomes a threat. For many years it has been slowly chafing away at this inner sheath of proteins that has enveloped it since its inception, generating enzymes that slowly eat away at this layer. As it expands, it degrades the shield, and eventually, the tissue tears. A small section of the tumor works its way into this tiny perforation. More enzymes deepen the wound. The tumor expands, the tear increases, and the tumor breaks through this layer, gaining access to tissues in the organ that before were inaccessible.

Like many of these stages of tumor development, this can happen early, or, as this example describes, at a later stage. But either way, “the malignant switch has finally been tripped,” says Weinberg. “At this point the tumor can invade anywhere it wants in the body. Breaking through this tissue layer is a harbinger of its ability to invade in more distant sites and trigger metastasis.”





The Final Frontier

Now, were a surgeon to remove the tumor or destroy it with a few blasts of radiation, there is no certainty that the patient would recover: Since the tumor broke through that protective protein layer and made its way deeper into the tissue, it is no longer bound to any particular location. Now it has full access to the inner workings of the organ in which it's been living for so many decades, including the vascular networks that branch throughout the entire body. The tumor begins to scatter individual cancer cells into the bloodstream, in much the same way that a plant scatters its seeds to the four winds. The original tumor can be destroyed, but the vagrant seeds cannot be gathered.

Yet just as few plant seeds find fertile soil, the cells scattered by this tumor will find few, if any, areas in the body hospitable to them. These cells have evolved to bypass all the body's strategies for curbing their growth, but they have developed these capabilities within the context of a single organ tissue. Weinberg sees these cells less like an army that sweeps through foreign lands conquering and pillaging and more like the first pilgrims who landed on American soil and were nearly devastated by their first New England winter. The tragedy of the pilgrims is that almost half died; the tragedy of the cancer cells is that one or two out of millions manage to survive.

When the tumor cells leak into the bloodstream, many die there. Even those that survive don't have an easy time. "Exhausted by the rigors of the voyage," says Weinberg, "a few remaining cells finally land in new organ tissues and are assaulted right away by a brand new biochemical milieu."

However, in one region of the body that has vanquished just about every cancer cell that tried to settle there, one cell survives. The process

of evolution that occurred so long ago, initiating the formation of the first tumor, begins again in this single cell. Because the cell inherited the immune system-defeating mutations from the original tumor, it matures at an accelerated rate. It, too, soon will become a tumor, and at some point, it will send cells into the bloodstream to settle in distant sites. And because the primary tumor may have gone unnoticed, this secondary tumor may be the patient's first indication that something is wrong.

On a molecular level, this process, called metastasis, is poorly understood. "It's really the last great frontier in cancer research in the sense that we really don't understand how the primary tumors succeed in dispatching cells to distant sites, and how they succeed then in creating new colonies of tumor cells," says Weinberg. "This is a complex issue that we barely understand at present."

For the moment, there are far more questions than answers. Do tumors acquire the ability to metastasize, or do they draw upon an existing store of information housed in their genomes? Are there specific genes that enable a cell to become invasive or metastatic, the equivalent to oncogenes and tumor suppressor genes? What exactly is it that enables, or prevents, wandering cancer cells from successfully founding new colonies at distant sites? "Right now it's a pretty wide open field, and there are many competing theories," Weinberg observes. "There's an enormous amount of data but little conceptual clarity."

Today, Weinberg's lab at Whitehead is focusing on five genes involved in early embryonic development, genes colorfully named *Slug*, *Snail*, *Gooseoid*, *Twist*, and *Mesenchyme forkhead* after the bizarre embryos that their mutated forms can cause in flies. Weinberg is exploring the

hypothesis that tumors opportunistically resurrect these genes and use them to acquire traits for metastasis and invasiveness.

While this theory hasn't yet been fully demonstrated, scientists know that once the tumor has acquired these abilities, it is profoundly difficult to control. "It's always an uphill battle for the tumor," says Ince. "Now, though, it has everything it needs to keep marching on."

The original tumor and its progeny are by no means invincible. Doctors soon will know the full extent of the disease. The original tumor and the obvious secondary tumors will be destroyed. A few cells likely will escape these treatments and seek refuge deeper in the tissue or the bloodstream, only to be poisoned by a flood of chemotherapy. Fledgling tumors might starve to death from the newer therapies that choke off their ability to grow blood vessels. Or, some tumors might experience therapeutic assaults specially designed for them alone, thanks to recent advances in genetic profiling.

But even the most aggressive treatments can leave a single, lone cancer cell unscathed. Once again, everything will depend upon the unpredictable outcome of natural selection. That cell can thrive, or it can die, or it can form a kind of tumor that the body constrains for the rest of the patient's life. No one knows.

The ending of this tumor's biography is, for now, uncertain. Evolution has no favorites, and that's both a blessing and a curse.

[For more information on this research, visit the Whitehead news archive at www.whitehead.mit.edu/nap/features/nap_feature_kuperwasser.html.]



The price

Text by Richard Saltus
Illustration by Nathan Wagoner

The scientific publishing industry has taken a public beating for its high subscription rates. Are open-access journals the answer?

Pier Paolo Pandolfi, a molecular biologist at Memorial Sloan-Kettering Cancer Center, is no stranger to the benefits of publishing in the “best” scientific journals: greater impact, wider readership—and career-boosting citations for his junior colleagues’ CVs. Of his 145 published papers, a number have appeared in the top-ranked journals: *Science*, *Cell*, *Nature* and its offshoots, and *The New England Journal of Medicine*.

So it was a radical departure last year when he decided to submit an important prostate cancer paper to a startup journal launched in October 2003. *PLoS Biology* had no track record or guarantee of survival, but it did have an editorial board of scientific heavyweights and a \$9 million capital cushion. Moreover, Pandolfi supported the journal’s mission: By giving away its content for free, the journal’s creators hoped to shake up the entrenched and increasingly expensive world of scientific publication.

In economic terms, librarians in many countries are fed up with years of journal prices skyrocketing much faster than the cost of living, to a level the libraries say is unsustainable. (As recently as 2001, for example, an annual print subscription to the journal *Nature* cost \$650; today the fee is \$1,280—almost twice as much.) With more journals being started all the time and library budgets static or shrinking, critics say publishing monopolies and high profits are hampering the mission of disseminating the fruits of the research enterprise so that other scientists can build on them to create new knowledge. Revenues suggest the scientific journal industry has benefited greatly from its citizenship in the publish-or-perish academic world. Now, some are asking, “Has the industry lived up to its civic duty?”

Open access

Scientists such as Pandolfi are all too familiar with peer review, a process many first encounter as

In part, the revolt over journal access stems from what advocates say is a fairness issue: “The public pays for our work; why shouldn’t everyone have easy, early access?” Dr. Harold Varmus asked participants in a New York Academy of Sciences briefing last winter. The outspoken Nobelist, a supporter of what many call the “open-access” movement, is cofounder of Public Library of Science (PLOS), a nonprofit organization of scientists aiming to create demand for open-access journals by publishing their own.

The launch of *PLoS Biology* last year and *PLoS Medicine*, due out this spring, represents the latest strategy of the open-access movement. Traditional journals cover the costs of reviewing and publishing scientific papers through annual subscriptions, which cost users (mainly research libraries) hundreds, thousands, or even tens of thousands of dollars annually. Access to articles is possible only

of publication

“We reasoned that contributing this paper could be a good initiative from a political point of view,” says Pandolfi, adding that he believes *PLoS Biology* “could be the new *Science* of 2010.”

Pandolfi isn’t alone in his desire to send a wake-up call to the \$3.5 billion scientific journal industry. Other scientists, librarians, legislators, and even the general public have protested the exorbitant subscription costs of many of the top-tier journals. Disenfranchised populations, critics say, include scientists in poor countries and private citizens without easy access to libraries and who have to pay fees to access journals online.

graduate students. When a researcher completes a study, the findings are written up in a technical article and submitted to a journal for review by a panel of scientific peers. Much of scientists’ reputation and future career path rests on how often and where they publish the findings of their research. But many scientists like Pandolfi also want to share the findings of their work with colleagues and a public that may not have easy access to traditional journals. What’s more, many funding agencies now ask grant seekers to explain how they plan to share their findings with others. And therein lies the dilemma: Who should bear the cost of publication?

through a subscribing library or by purchasing individual articles from a journal’s Web site for fees as high as \$20 per article.

PLoS Biology charges readers nothing at all. As soon as articles are accepted and posted on the Internet, they can be read, downloaded, copied, and redistributed at will—along with original data provided by the researchers. Instead of the readers, it is the authors who pay the bills: *PLoS Biology* collects \$1,500 for each accepted paper to offset its costs in screening, reviewing, editing, and posting the articles. Authors may post their papers on their own Web sites, and they retain the copyright, rather than

signing the rights over to the journal as is customary.

As with traditional journals, manuscripts submitted to *PLoS Biology* are reviewed by unpaid, unbiased scientists who check the papers for scientific soundness and ensure that the authors' claims are justified by the data. Often the reviewers ask for more data or clarifications before accepting them for publication, also a common practice with traditional journal reviewers.

Changing the culture of science and publishing to an open-access world runs into much skepticism. Although Pandolfi's prostate cancer paper ultimately was published by *PLoS Biology* in December, the scientist admits that his junior coauthors were resistant to the idea at first. "Convincing the postdocs was not easy," he says. "They wanted to publish in a journal that is certified top-notch now, not in three years. One of the two first authors is going to be looking for a job soon, and he felt that if his first paper were in *PLoS Biology* it wouldn't have the same weight on his CV as one in *Cancer Cell*."

At Whitehead Institute, Director Susan Lindquist (a *PLoS* board member) gets similar responses. "I've had a horrible time getting people in my lab to submit papers there (*PLoS Biology*). They think their jobs depend on getting papers in particular journals, and they think it's risky."

Under review

The commercial journal publishing industry is dominated by a handful of European mega-companies that publish thousands of journals, creating a captive audience of libraries and researchers, say observers. The key players are Reed Elsevier and Wolters Kluwer in Amsterdam, Blackwell Publishers in England, and BertelsmannSpringer in Germany. All have been the target of hostility and activism, but the largest, Reed Elsevier, which publishes about 1,500 journals,

including the elite publications from Cell Press, has been the most harshly criticized.

Last year, two faculty members at University of California, San Francisco called for a boycott of the Cell journals, and asked scientists not to review papers for them. The reason: On top of the \$8 million that the UC system pays Elsevier for access to its electronic journals, the publisher was asking a surcharge of \$90,000 a year for access to the six Cell journals, which the libraries said they couldn't afford. After arduous negotiations, the UC libraries and Elsevier reached an agreement in early 2003, but the terms were not made public.

Other universities have made similar protests. Stanford University, Massachusetts Institute of Technology, Harvard University, the University of Connecticut, Duke University, Cornell University, and North Carolina State University all have passed resolutions criticizing high journal subscription fees. In their resolution, Stanford's Faculty Senate also called upon faculty to consider submitting their research to open-access journals instead of traditional publications.

Customers complain that publishers use strong-arm tactics to maintain their profit margins, which at some companies have exceeded 30 percent. A common practice is "bundling" several journals that must be purchased together. An extreme case is *Brain Research*, which costs about \$21,000 a year in a package with five other journals—you have to buy them all to gain access to just one.

The high profitability of the commercial publishers seems outrageous to many librarians and scientists, especially given the nature of the business. That outrage boiled over earlier this year when the editorial board of a computer science journal, *The Journal of Algorithms*, resigned en masse, charging that Elsevier makes the publication too

expensive for many students and libraries. Before Elsevier took the journal over in 2001, a subscription cost \$600; by 2003 it had jumped to \$700, according to a statement by the editors.

Judith Messerle, a librarian at Harvard University's Countway medical library, says that when she arrived there 15 years ago, a budget of \$500,000 paid for 5,000 journal titles. Today, the library's budget of \$1.7 million buys just 2,700 titles.

Moreover, as publishers "migrate" customers to online versions of journals with their ease of access and searchability, Messerle says libraries like Harvard need to maintain their shelves of print journals as well "because the publishers don't guarantee access to the content in the future." So, Messerle says, if a library decided to cancel an online-only subscription, "The day you do that is the day you lose access to the content." But to get both electronic and print journals now, she adds, the library has to pay publishers surcharges of 15 percent to 25 percent.

David Richardson, who runs Whitehead's library, says the Institute has discontinued two-thirds of its print journals in part because of financial reasons, and also because the journals are available at the MIT library, where Whitehead scientists are on faculty. "Every five to seven years, they double in price, in my experience," he says.

Doubts abound

The growing backlash against large publishers has stung them. But executives of these companies say they provide an excellence that justifies the high prices. And while some mainstream, subscription-based journals acknowledge the pressure for change, most are not convinced that open-access publications will survive.

"I think the numbers just don't add up," says Emilie Marcus, editor of

the journal *Cell* and executive editor of Cell Press, referring to the author-pays system of PLoS. “That’s why they have a large private grant”—the \$9 million startup fund from the Gordon and Betty Moore Foundation that protects them from real-market dynamics for some time. Marcus says she welcomes attempts to create an open-access industry, but believes proponents have glossed over the potential downsides of their model—such as whether the economics of the author-pays format will enable the journals to survive and maintain high standards.

Doubts also abound in the editorial offices of *The New England Journal of Medicine* and other leading journals about the author-pays PLoS business model. “For us, the most important thing we do is ensure the quality of the material we are publishing,” says *NEJM* Executive Editor Gregory Curfman. The necessary infrastructure includes editors, technical experts, manuscript reviewers, proofreaders, printers, and Web specialists. “We can’t do that at \$1,500 per article,” he says, referring to the PLoS author charge. “It would be a different kind of journal.” Quality could suffer if author-pay journals have a financial incentive to accept more articles to recoup their costs, Curfman adds, potentially letting standards slide.

PLoS says it has taken great pains to hire distinguished editors (in fact, a top editor came from *Cell*) and to refer manuscripts to highly credible reviewers. Says Peter Suber, a professor at Earlham College and open-access advocate, “Open-access removes the barrier of price, not the filter of quality control.”

There are those who would challenge the assertion that an open-access journal industry would be cheaper for subscribing libraries than the current publishing system. At Yale University, associate librarian Ann Okerson did a quick run of the numbers, based on Yale researchers’ annual output of at

least 4,400 articles. If the university paid, for example, \$1,125 for each published paper, Okerson says it would cost Yale approximately \$4,950,000—in excess of the estimated \$3.6 million to \$4 million it pays now for its science, technology, and medicine journals. Says Okerson, “It is much too early to estimate accurately the financial impact of open access.”

Removing barriers

While the debate over open access continues, national legislators, the National Institutes of Health, and private funders such as the Howard Hughes Medical Institute and the Wellcome Trust have taken steps aimed at lowering cost barriers to dissemination of research findings. HHMI has announced that it will pay the authors’ fees for its 350 investigators to publish in open-access journals such as *PLoS Biology*. And NIH has decreed that researchers applying for grants of \$500,000 or more must describe how they will share their results—or explain why this can’t be done. In another open-access initiative, the National Library of Medicine’s PubMed Central offers free access to papers made available by willing publishers through PubMed links.

Not all journal publishers are commercial enterprises. Nonprofit scientific societies put out a large number of journals—the American Association for the Advancement of Science’s widely read publication *Science*, for example. The societies depend on journal revenues to support educational activities and meetings, and complain that open-access models might leave them short of revenue to underwrite these. In response, Varmus suggests that they raise these funds through means other than subscriptions.

However, according to AAAS Chief Executive Officer Alan Leshner, *Science* provides so much added value—such as its reporting on science news and policy, and commentaries on the papers it publishes—that it would have to

charge \$10,000 per paper if it adopted a PLoS-style author-pays model. As for open access in general, “We applaud the experiment, and we’re just waiting to see how this plays out.”

Some publishers, while hewing to their traditional business models, have made changes to lower barriers to access. In several cases, readers can access journal issues online free six months or a year after publication. Many, like *The New England Journal of Medicine*, have waived subscription fees for scientists in Africa and other countries with limited capital. *NEJM* research articles also are free online after six months, says executive editor Curfman. The journal, he adds, is sensitive to complaints about per-article fees from people who want access to up-to-the-minute research on diseases for themselves or their families. Curfman says, “To be perfectly honest, if someone called us up and said, ‘My daughter has disease X and needs an article,’ we’d just send it to them.” And, he adds, for individuals in or out of medicine who want the latest research news immediately, an online subscription is only \$99 a year.

Still, open-access supporters such as Varmus, the PLoS cofounder who also is president and chief executive officer of Memorial Sloan-Kettering and former director of NIH, believe that over time, open-access journals will capture many of the best research papers. At the New York Academy of Sciences meeting last year he predicted that traditional publishers will be forced to change, or risk going out of business.

“If they fold, that is fine,” he said. “If they adapt by becoming open access, that is better.”

[For more information on the Public Library of Science, visit the Web at www.plos.org.]

[RISKY RESEARCH]

Scientists advise government on preventing bioterrorism

Imagine this scenario: A researcher at an American university develops a technique for genetically manipulating bacteria and publishes the findings in a major journal. Someone else reads the study and uses the research to develop a strain of anthrax that resists the only known vaccine, then sells the new super bio-killer on the black market to the highest bidder.

This depiction is, for now, pure fiction. But the dilemma of how to publish legitimate research that can serve such dual purposes is all too real. It's the subject of national debate and was the focus of an 18-month study by a committee commissioned by the National Research Council and headed by Whitehead Member Gerald Fink.

In a report released last fall, the committee recommended a review process in which local scientific communities and the federal government assess research proposals. A scientist, for example, working with a viral agent that conceivably could threaten national security would first need to have the work approved by his or her own institution's review board and then by the National Institutes of Health

Recombinant DNA Advisory Committee. The federal component of this review could then advise the NIH to withhold public money from a particular project.

In order to ensure that the process runs smoothly, the report also suggested that the Department of Health and Human Services create an advisory committee to oversee the entire review process.

Biologists often have been asked to view their work in terms of national security, Fink notes. "Biologists aren't surprised to learn that their work can be used for something harmful," he says. "They think in terms of 'disease' all the time. Theoretical physicists, on the other hand, probably had a hard time at first thinking about how their work related to national security issues."

In March, Health and Human Services Secretary Tommy Thompson responded to the committee's recommendations by announcing the new National Science Advisory Board for Biosecurity, a 25 member committee to be managed by NIH. Rather than work directly with scientists, the board will advise institutional biosafety groups according to the guidelines suggested by the National Research Council.

Says Fink, "The government saw the importance of our report."



DC

For a summary of the report, visit the Web at books.nap.edu/execsumm_pdf/10827.pdf.

[INFORMED SKEPTICS?]

Study examines link between science literacy and public opinion

Many scientists claim public opposition to biotechnology is primarily a product of ignorance. But a report published by researchers at the University of Trento in Italy may contradict that belief. After conducting two large-scale surveys of public opinion on biotechnology in Italy, researchers found that access to scientific information does not necessarily promote positive attitudes about biotechnology, particularly for controversial science, such as genetically modified foods and embryonic stem cell research.

CLONING CONTROVERSY

UNITED NATIONS POSTPONES CLONING RESOLUTION FOR ONE YEAR

When the United Nations began debate on the issue of human reproductive cloning in December 2001, the goal may have seemed fairly straightforward: The international body wanted to develop a resolution condemning the cloning of a human being, a practice opposed by most scientists and nonscientists alike.

But science seldom is clear-cut. The debate soon split into a question of whether such a ban should encompass all cloning, including therapeutic cloning, where the aim is not to clone a human being, but rather to develop lines of embryonic stem cells that can be used in therapies for a variety of diseases.

The international organization had hoped to work out the details of a resolution by last year, but in November, members voted 80 to 79 to table the discussion for two years. One month later, a 68-nation coalition led by the United States lobbied successfully to reduce that delay to one year. U.N. discussion of the ban will resume in September.

Some scientists have criticized the U.N. resolution because it lumps reproductive and therapeutic cloning together. While both practices replace the nucleus of an unfertilized egg cell with that of a donor cell, reproductive cloning—which most scientists oppose—places the egg in a uterus to produce a fetus that's genetically identical to the donor. In therapeutic cloning, which many scientists

support, the egg is placed in a dish where it can develop into embryonic stem cells.

Although the proposed U.N. law would be purely symbolic, Whitehead Member and MIT professor Rudolf Jaenisch speculates that countries abiding by such a ban would lose many of their top stem cell scientists: "If you criminalize therapeutic cloning, the research will go somewhere else."

Some nations, including Britain, Singapore, and Israel, already have enacted laws that prohibit reproductive cloning, while allowing therapeutic cloning. In the U.S., however, Congress has remained divided over legislative efforts to restrict all cloning. Taking matters into their own hands, 10 states have passed laws banning all forms of human cloning and three have outlawed therapeutic cloning research, but two—California and New Jersey—have explicitly legalized therapeutic cloning. If the U.N. legal committee bans cloning in 2004, it could take up to two years to become international law. Still, "Certain countries will never adopt a U.N. resolution that bans all cloning, and it will not affect their policies," says LeRoy Walters, a bioethicist at Georgetown University.

MD

For more information on the United Nations' debate on cloning, visit the Web at www.un.org/law/cloning/#2003.

According to study leader Massimiano Bucchi, debate about the impact of science news exposure on public attitudes about biotechnology historically has occurred without reliable data, particularly in Europe. "Scientists and policy makers always assume that negative attitudes to certain research fields are only due to lack of information on the part of the public," says Bucchi. "We wanted to test this assumption on an empirical basis and tried to show that it is not so simple."

Bucchi cites public attitudes toward human embryo research as a prime example of where old ideas about science literacy promoting positive public opinion break down. According to the article in the Italian publication *Journal of the History of Medicine*, where the survey results were published, those with the highest level of exposure to science news, 64 percent, deemed research on embryos ethically unacceptable; just 59 percent of the group with less exposure to science news opposed human embryo research.

Participants with high exposure also wanted stricter state regulations on biotechnology and reportedly had less faith in scientists' ability to self regulate. Similarly, results suggest that there is a strong demand for public involvement in scientific decision-making—almost one-third of survey participants claimed they would like to participate in public discussions about scientific issues.

"It is surprising to see that in certain cases, the more people know about biotechnologies, the more skeptical they become," says Bucchi. "But it is surprising only insofar as you buy the argument that more science communication equals better understanding, which equals more favorable attitudes."

Does Bucchi's argument hold water in the United States? Most likely, says Joann Rodgers, public affairs deputy director and director of media relations at Johns Hopkins University School of Medicine. "This paper brings into strong relief the experience that I and many of my colleagues in science communications have had: You cannot just throw information out there and expect it to 'win' you anything," says Rodgers. "Trust is not built on a sea of facts, but on the solid ground of experience."

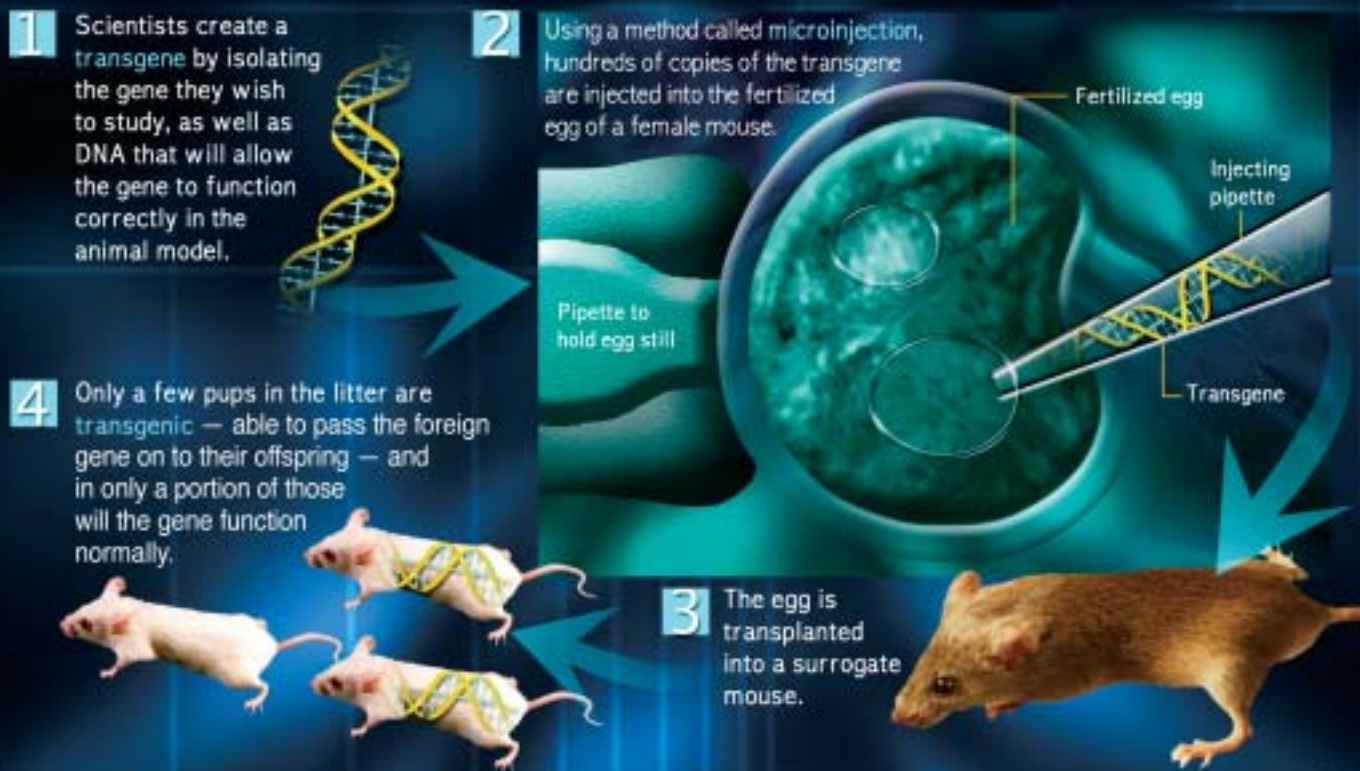
[THE SCIENCE OF TRANSGENICS]

Our bodies are made up of some 30,000 genes, many of which are involved in diseases such as hypertension, diabetes, cancer, and other illnesses. To study how these genes work, scientists often introduce the gene they are studying into an animal model through a process called transgenics. For example, researchers examining the biological causes of breast cancer may engineer a mouse model to contain a gene linked to breast cancer. By studying the gene in animals, scientists can gain information about human disease that can be used to develop new therapies to treat the illness.

Scientists use a number of different techniques to create transgenic animals, but the most common is a process called *microinjection*. Scientists isolate the gene they want to study, inject hundreds of copies of it into a fertilized egg, and transplant that egg into a surrogate animal. Some of the animal's offspring will contain the foreign gene (also called a *transgene*) and will be able to pass it on to the

next generation. These animals are called transgenic. Genes can be added to an animal with microinjection, but they cannot be deleted with this technique.

When scientists use microinjection, the gene is inserted randomly into the animal's genome. Sometimes, however, researchers want to see how a particular gene behaves in a particular tissue. For this type of study, researchers often develop transgenic animals using a process called *embryonic stem cell transfer*, or the *gene-targeted transgenic approach*. Scientists delete or substitute a specific gene in *embryonic stem cells* in a Petri dish and inject the modified stem cells into a clump of cells called a *blastocyst*, which is derived from a fertilized egg. The blastocyst is implanted into a surrogate animal; some of the animal's offspring will carry the gene the scientists want to study.



[Embryonic stem cell transfer] This method, also called *gene-targeted transgenics*, is used when scientists want to see a particular gene expressed in a specific site of the animal's genome.



SOURCES: NATIONAL INSTITUTES OF HEALTH; NATIONAL HEALTH MUSEUM; BIO TECH LIFE SCIENCES DICTIONARY; AGRSEARCH; EXPERT REVIEWS IN MOLECULAR MEDICINE; RUDOLF JAENISCH; KONRAD HOCHEDLINGER

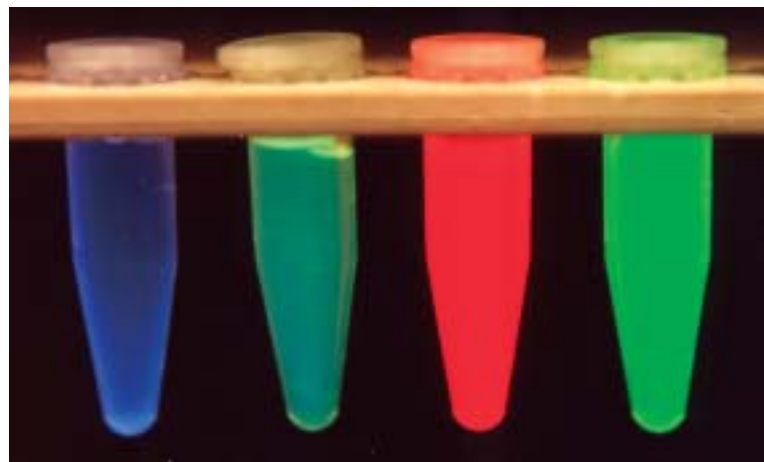
GRAPHIC BY: CHRISTINA ULLMAN

EMERALD CITY

How a jellyfish helped advance science

Salmon fishermen trolling along the waters off Puget Sound in Washington often are witness to an awesome sight when they haul in their catch: salmon captured in nets that glow brilliantly against the nighttime sky. This unnatural sheen is caused by the Northwest Pacific jellyfish *Aequorea victoria*, whose cellular makeup includes a bioluminescent protein called aequorin that emits a deep blue light. Another protein called green fluorescent protein, or GFP, absorbs this light, and through a biophysical process, turns it into a glowing emerald green.

The jellyfish has given off its evening shine for millenia, but in the early 1990s, scientists developed a way to use



william ward

BY DEFINITION

Blastocyst: An embryo in the early stages of development that resembles a hollow ball of cells and consists of between 30 and 150 cells. The outer layer of cells ultimately will become the placenta; the inner layer of cells are a source of embryonic stem cells.

Chimera: An organism created by combining DNA from two or more different organisms.

Embryonic stem cells: Cells that have the ability to develop into any tissue in the body.

Embryonic stem cell transfer: A method used to make a transgenic animal that allows scientists to introduce a gene into a specific location in the animal's genome by altering embryonic stem cells in a Petri dish and injecting those cells into an embryo during the blastocyst stage.

Gene: A section of DNA that holds information about traits an organism inherits from its parents. Humans have about 30,000 genes, each of which has a unique influence on the function of cells in the body.

Genome: The full set of genes that constitutes an organism.

Microinjection: A technique used to create a transgenic animal by which a foreign gene is injected into a fertilized egg which is then transplanted into a female animal. Some of the animal's offspring will contain the foreign gene.

Transgene: A gene from one organism that is introduced into a different organism.

Transgenic: An organism whose genome contains a foreign gene from another organism.

GFP in biological studies. Researchers removed the gene for GFP from jellyfish, cloned it, and introduced it into the cells of the bacterium *E. coli* and in *C. elegans*, a soil nematode widely used as a biological model. In the experiments, GFP clones were fused to specific proteins in the study models, causing those proteins to glow when illuminated with blue light. Under a microscope, these GFP-labeled proteins shine in a steady glow, allowing scientists to easily track and observe the proteins' movements and behaviors. Some 10,000 studies a year now report findings related to GFP's use in the laboratory. GFP has even been used to make "transgenic art," notably a fluorescent rabbit named Alba, who was bred in 2001 with this jellyfish protein imbedded into her genetic code.

Structurally, GFP looks like a barrel that surrounds a light bulb in its interior. The interior bulb, which is known technically as a chromophore, doesn't produce its own light, but rather absorbs and alters light from another source. In a jellyfish, that source is the aequorin protein, which transfers its blue light to GFP by a quantum process that some scientists compare to mind-reading—unlike sound waves, energy moves from one molecule to the other in the absence of any medium. In the laboratory, artificial light substitutes for aequorin's natural role.

Today, scientists use GFP to determine where proteins are located during different stages of a cell's life, or to watch how proteins interact to produce disease. GFP also helps scientists track the introduction of foreign genes into DNA, a strategy used to create transgenic models to study cancer, diabetes, and other diseases.

GFP one day could play a role in treating illnesses like cancer. Scientists hope to be able to incorporate GFP directly into tumor cells, causing them to glow as a distinct population, easily separated from healthy cells and tissues. Ultimately, GFP use in research will only grow. The little green protein looks to have a bright—indeed, a glowing—future in biomedical research.

Charles Schmidt

For more information on GFP, visit www.ascb.org/teachers/green.html.

[**ON MAD COWS AND BIRD FLU**]

The facts about animal-to-human disease transmission

A disease that jumps from animals to humans makes for a compelling headline. Indeed, this phenomenon, called zoonosis, led many a nightly newscast in the last year, as reporters followed stories on avian flu and mad cow disease. It's easy to feel overwhelmed by all the information, and difficult to sort the fact from the hype. So, we asked scientist David Franz to explain the basics. Franz is chief biological scientist for the Midwest Research Institute and director of the National Agricultural Biosecurity Center at Kansas State University. He is a former commander of the U.S. Army Medical Research Institute of Infectious Diseases and has served on the National Academy of Sciences' Committee on Genomic Databases for Biological Threat Agents and the Department of Homeland Security Science & Technology Advisory Committee, among others.

How are illnesses such as mad cow disease, West Nile virus, and avian flu transmitted from animals to humans?

Mad cow disease, or Bovine Spongiform Encephalopathy (BSE), is transmitted in nature when one animal ingests body materials (typically brain, spinal cord, and possibly certain glandular materials) containing infected tissue from another animal. Most cases have been transmitted within the same animal species. There have been, however, instances in which a human has eaten certain cuts of meat from an "infected" cow and acquired a disease called "variant Creutzfeldt-Jakob Disease." West Nile encephalitis is typically transmitted to humans through the bite of an infected mosquito that has taken a blood meal from a bird, horse, or other animal infected with the virus. Some varieties of avian flu may cause disease in humans. It can be transmitted through the air, by direct contact with birds, or by fomites, inanimate objects carrying the virus from bird to human.

Is the virus or pathogen that infects humans the same that infects animals?

As in the case of flu virus, there may be strains which infect animals, but not humans. However, if a strain of virus is transmitted from an animal to a human, and causes disease in the human, it would be the same virus. It is possible for a virus to be "carried" by an animal species and/or a human but cause disease only in one or the other, but not both. This is why, during the foot-and-mouth disease outbreak in the United Kingdom in 2001, for example, humans were required to cleanse their nasal passages before leaving an infected farm. There essentially was zero risk of human disease, but they might have virus from animals in their nose which could spread to other animals.

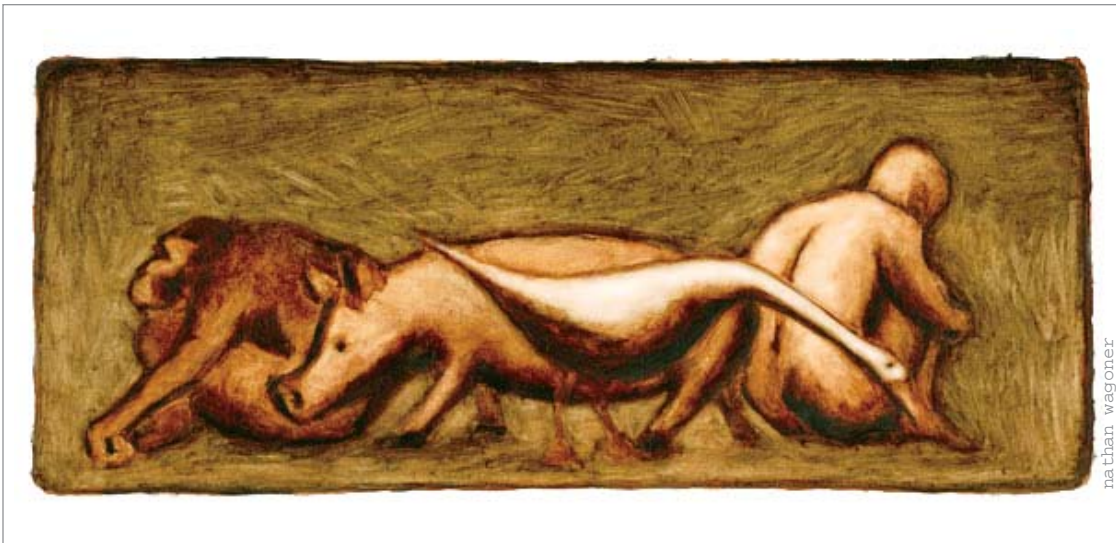
Historically, what are some of the most significant instances of a virus jumping from animals to humans?

HIV is believed to have jumped from a nonhuman primate to humans. This would be, no doubt, the most significant species adaptation by a virus during our lifetimes. It is likely, however, that many viruses that now infect humans originated in animals. The filoviruses, Marburg and Ebola, are popular examples of animal viruses that occasionally jump to man. Although they probably are feared more than HIV, they actually are less dangerous to the population because they kill the host quickly, reducing the spread of disease.

Have cases of animal-to-human disease transmission increased, or is it just media coverage of the topic that's on the rise?

As the world has gotten smaller—more travel, more movement of animals from their natural environment to homes and farms as pets, and more humans traveling into the environments of strange animals—there has been more

human contact with animal species that previously were not exposed to humans. When this happens, it's always possible that a virus will jump from one species to another. Also, as animals harboring similar but distinct viruses like influenza have been/are being kept in close proximity, the distinct viruses (which might only initially infect one species) can "share" parts, making new viruses, some of which can jump to humans. Media coverage is certainly better than it was 50 years ago, making us more aware of what is occurring in the world around us.



nathan wagoner

[NEW MODEL FOR BREAST CANCER]

A team in the lab of Whitehead researcher Robert Weinberg has grafted human breast tissue into the mammary glands of mice, creating animal models that have functional breasts capable of producing human milk. Some of these mice were engineered to form early stage breast tumors like those found in humans, creating the first experimental mouse model of human breast cancer. To see live footage of these new mouse models, visit wi.mit.edu/nap/features/nap_feature_kuperwasser.html.



sam ogden

[RESPECT, AT LAST]

David Page claims that the Y chromosome is the Rodney Dangerfield of the human genome: It gets no respect. Until lately. Page recently gave a lecture on new research that is finally giving the Y the respect it deserves. Watch the lecture online at mitworld.mit.edu/video/178/.

[DISEASE, DEVELOPMENT, AND DARWIN]

If it weren't for yeast, flies, worms, and frogs, biomedical science wouldn't be close to where it is today. On September 27 of this year, leading researchers will gather for Whitehead Symposium XXII to discuss methods for using these model organisms to unravel the secrets of human biology. For information on the speakers and program, visit wi.mit.edu/cee/cee_conf_symposium.html.

[NOT JUST FOR MAD COWS]

Prions, the tiny proteins linked to such neurological disorders as mad cow disease, have shown the capacity to be surprisingly useful. In fact, engineers may one day use them to build computer chips. Whitehead Director Susan Lindquist recently spoke with ScienCentral News about her studies of proteins. See the interview online at www.sciencentral.com/articles/view.php3?language=english&type=&article_id=218392080.



courtesy of u.s. dept. of agriculture - animal and plant health inspection service, aphs



COURTESY OF THE PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES

[RETOOL FOR SCHOOL]

The human genome contains the alphabet of life, but the grammar and syntax all are embedded in the complex networks through which genes and proteins talk to each other. Learn more about a new software program that helps make sense of these networks, possibly yielding medically useful information, at wi.mit.edu/nap/features/nap_feature_pathblast.html.

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Whitehead bioinformatics scientist Robert Latek overlaid four distinct immune-system proteins in this image to demonstrate their structural similarities and disparities. Each of these proteins was assembled through a process in which computer-aided design generated hypothetical 3-D models of each protein. While the sequence of amino acids for each was known, the structures were a mystery. Using related proteins with known structures as templates, the applications traced the sequences along the backbone of the template molecule, creating the protein models.



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