Yet electroplating does not work on silicon either. So the researchers used wet-chemistry techniques to deposit nickel or titanium on the floor as a seed layer for zinc to stick to during electroplating. Growing zinc in a uniform manner so that there were not small mountains of zinc in some places and none elsewhere required laborious trial and error by fiddling with temperatures, electric current and concentrations of chemicals. "Looking back, I'm surprised it took only a year," Simon remarks.

After the scientists had a prototype working, they began to talk to potential customers. These discussions triggered a radical revamping of the battery. The initial design was a sandwich, with the cathode on top, the zinc chloride electrolyte solution in the middle, the nanograss under it and the anode on the bottom. Officials at the U.S. Army Research Laboratory in Adelphi, Md., expressed concern about how constant contact between the electrolyte and any electrode could result in unwanted chemical reactions. After the redesign, electrolyte now rests on top, the anode and cathode compounds occupy physically separated patches on the bottom, and a nanosilicon barrier is suspended in between, which, when activated, enables the electrolyte to penetrate and immerse the electrodes.

The team originally used nanopillars to separate the electrolyte from the anode because the pillar took up the least amount of space, allowing more surface area for chemical reactions between those electrodes. But the difficulty of manufacturing the nanopillar battery design prompted researchers instead to develop a nanohoneycomb membrane to isolate the electrolyte from the electrodes. Creation of the electrowetting membrane, with pores 20 microns across and thin, fragile walls 600 nanometers wide, was also a challenge. First the scientists used a plasma to etch the delicate honeycomb structure from wafers of silicon covered in silicon dioxide. Then they grew silicon dioxide on the bare silicon walls of the pores in furnaces heated to 1,000 degrees Celsius and suffused with oxygen. Finally, they coated the entire honeycomb with fluorocarbon.

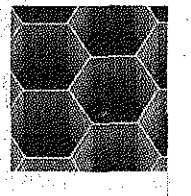
The researchers developed their first redesigned samples in October 2005. One of the great advantages of the system is that it now helps the team avoid having to laboriously find the exact conditions required to grow a uniform anode layer amid a forest of nanopillars every time it wants to try out a new anode-cathode combination. Instead the scientists can simply lie the electrode patches down on otherwise featureless surfaces. At the same time, the experience they gained in electroplating should make creating the patches far easier, Simon notes. Bell Labs and mPhase are currently collaborating with Rutgers University on incorporating the kind of lithium-based battery chemistries found in digital cameras and cellular phones.

The nanobattery might also allow for a more environmentally friendly power source that includes compounds that can entomb the electrolyte. "That would keep it from leaching into the ground or, if soldiers got shot, would keep the battery from leaking all over them," Krupenkin says. Plastic nanostructures might also be used in place of employing silicon, Simon adds, potentially paving the way for flexible nanobatteries.

The scientists are not seeking to replace disposable batteries, since mass production of those "is in the fractions of cents per AA battery," Krupenkin says. Instead they are targeting more specialized applications, such as sensors dropped from military aircraft that may have to use their radio transmitters just once or twice in their lifetimes, to signal the presence of intruders, for instance, or toxins or radiation. "If the sensor sees nothing interesting, it has nothing to transmit, but if it does, it needs a lot of power," Krupenkin explains. Alternatively, devices monitoring environmental change could use that extra juice to transmit over larger distances, thereby cutting down on the number of sensors needed. Emergency reserve batteries might also be incorporated into medical implants, cell phones or radio-transmitting pet collars.

The team has considered a rechargeable version of their device. A pulse of current could run through a depleted nanobattery, causing the surface on which the electrolyte rests to heat. That could evaporate a tiny layer of the liquid, forcing the droplet to jump up back on top of the nanostructure. "In principle, it's possible. In practice, it's really far out," Krupenkin cautions. For instance, mPhase expects to get product samples to potential first adopters in two to three years. A nanobattery would demonstrate how power sources are finally beginning to keep pace with the revolution in miniaturization that has driven the rest of the electronics industry for decades. SA

A nanomembrane separated the electrolyte from the electrodes in a later battery design.



Charles Q. Choi is a frequent contributor to Scientific American.

(nanomembrane)

MORE TO EXPLORE

From Rolling Ball to Complete Wetting: The Dynamic Tuning of Liquids on Nanostructured Surfaces. T. N. Krupenkin, J. A. Taylor, T. M. Schneider and S. Yang in *Langmuir*, Vol. 20, pages 3824–3827; May 11, 2004.

A film about one phase of development of the nanobattery is available at **www.mphasetech.com/video/mphase.mov**

A Novel Battery Architecture Based on Superhydrophobic Nanostructured Materials. V. A. Lifton and S. Simon. **www.mphasetech.com/nanobattery_architecture.pdf**

Patents on DNA have not caused the severe disruption of biomedical research

OWNING

By Gary Stix

There is a gene in your body's cells that plays a key role in early spinal cord development. It belongs to Harvard University. Another gene makes the protein that the hepatitis A virus uses to attach to cells; the U.S. Department of Health and Human Services holds the patent on that. Incyte Corporation, based in Wilmington, Del., has patented the gene of a receptor for histamine, the compound released by cells during the hay fever season. About half of all the genes known to be involved in cancer are patented.

Human cells carry nearly 24,000 genes that constitute the blueprint for the 100 trillion cells of our body. As of the middle of last year, the U.S. Patent and Trademark Office had issued patents to corporations, universities, government agencies and nonprofit groups for nearly 20 percent of the human genome. To be more precise, 4,382 of the 23,688 genes stored in the National Center for Biotechnology Information's database are tagged with at least one patent, according to a study published in the October 14, 2005, *Science* by Fiona Murray and Kyle L. Jensen of the Massachusetts Institute of Technology. Incyte alone owns nearly 10 percent of all human genes.

The survey of the gene database confirmed that the patenting of life is today well established. Yet it still strikes a lot of people as bizarre, unnatural and worrisome. "How can you patent my genes?" is often the first question that comes up. How can someone own property rights on a type of mouse or fish when nature, not humans, "invented" its genes? What happens to the openness of scientific research if half of all known cancer genes are patented? Does that mean that researchers must spend more time fighting in the courts than looking for a cure?

Ethicists, judges, scientists and patent examiners continue to immerse themselves in these debates, which will only grow more acute in a new era of personalized medicine and of genomics and proteomics research that examines the activities of many different genes or proteins at the same time. Doctors will rely increasingly on patented tests that let clinicians match genetically profiled patients with the best drugs. Investigators are already assessing the functioning of whole genomes. Potentially, many of the biological molecules deployed in these complex studies could come burdened with licensing stipulations that would prevent research leading to new therapies or that would fuel the nation's already robust health care inflation.

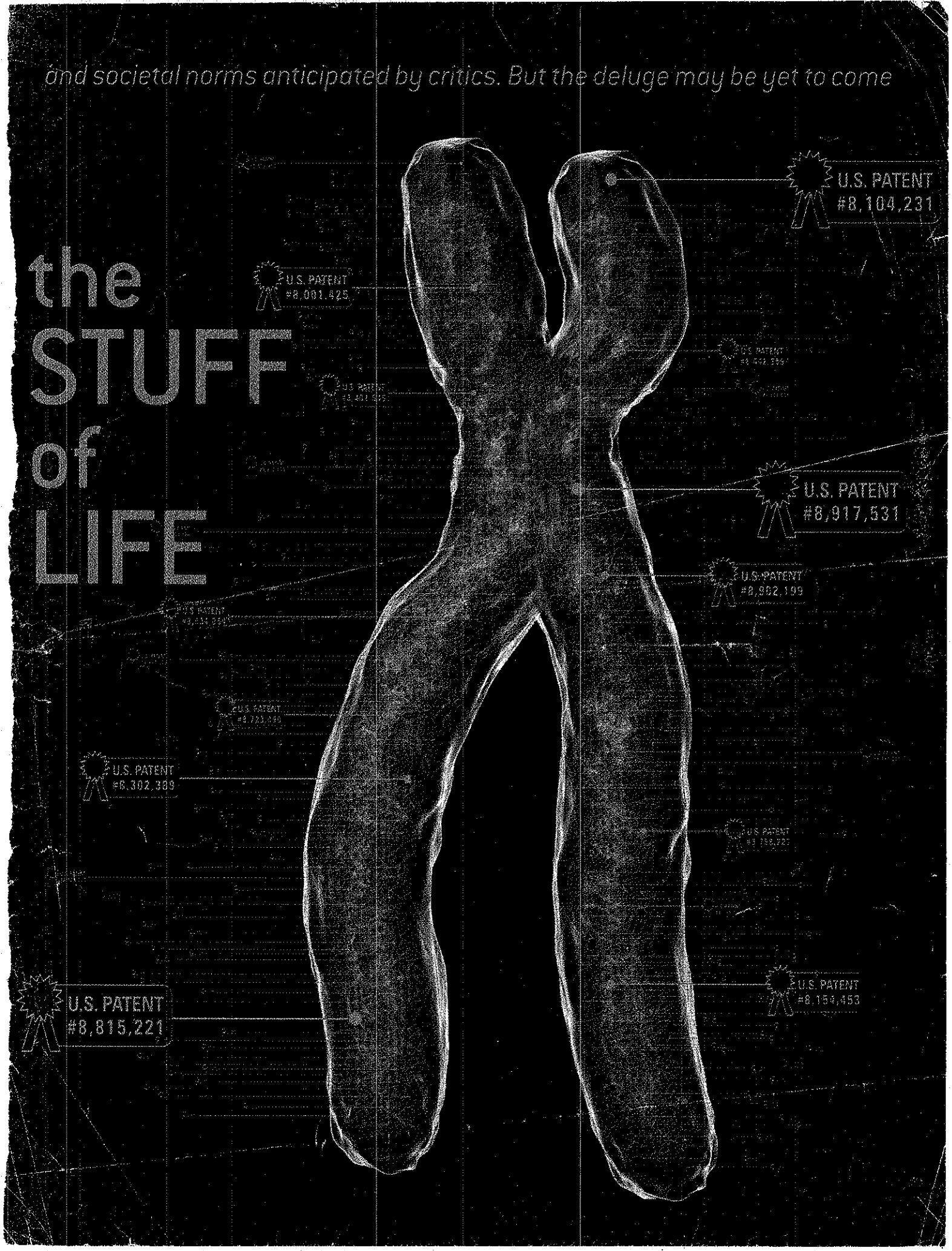
Anything under the Sun

THE QUESTION of "who owns life" has been asked before. But the M.I.T. researchers' taking stock of the intersection of intellectual property and molecular biology came fittingly at the 25th anniversary of a landmark decision by the U.S. Supreme Court that

BELL LABS, LUCENT TECHNOLOGIES

and societal norms anticipated by critics. But the deluge may be yet to come

the STUFF of LIFE



held that living things are patentable—as long as they incorporate human intervention—in essence, that they are "made" by humans.

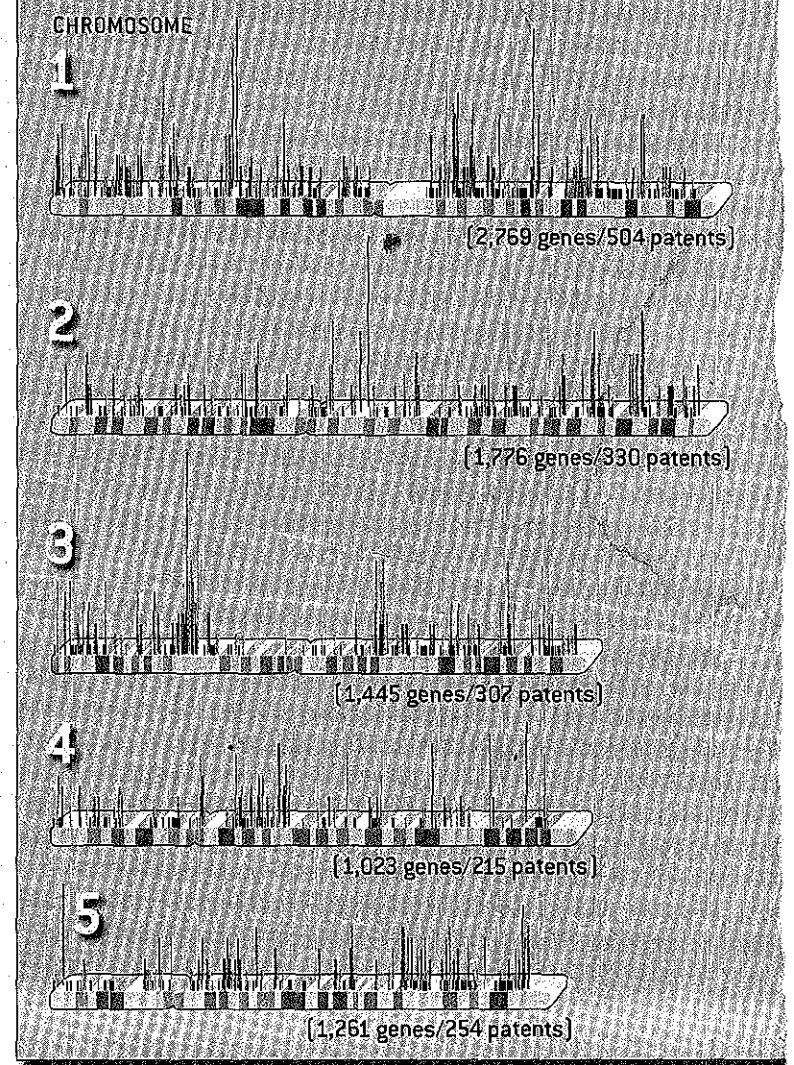
Ananda M. Chakrabarty, a General Electric engineer, filed for a patent in 1972 on a single strain of a *Pseudomonas* bacterium that could break down oil slicks more efficiently than if a bioremediation specialist deployed multiple strains for the task. Chakrabarty did not create his strain by what is usually meant by genetic engineering—in fact, recombinant DNA splicing methods were not invented until the year of his filing. Instead he tinkered with the bacterium in a more classical way and coaxed it to accept plasmids (rings of DNA) from other strains with the desired properties. The patent office rejected Chakrabarty's application, saying that "products of nature" that are "live organisms" cannot be patented.

By the time the Supreme Court decided to hear the appeal of the case in 1980, the landscape of molecular biology was changing radically. The splicing of DNA from one organism to another had become commonplace. A new firm called Amgen had formed that year to take advantage of the nascent technology of cutting and pasting DNA. A paper had just appeared detailing how recombinant methods had been used to synthesize interferon. Stanley Cohen and Herbert Boyer received a patent on a key technology for manipulating DNA. Technological boosterism was in the air. Congress passed the Bayh-Dole Act, which allows universities to engage in exclusive licensing agreements for technology they have patented. The Stevenson-Wydler Act let the National Institutes of Health and other federal agencies do the same.

The Supreme Court justices received friend-of-the-court briefs arguing both for and against granting the claims in the Chakrabarty patent. Groups ranging from Genentech to the Regents of the University of California urged that the patent application be granted, citing benefits for pharmaceutical development, environmental remediation and new sources of energy, to name a few. The Peoples Business Commission, co-directed by activist Jeremy Rifkin, decried the commodification of life and described environmental disasters in the offing.

THE HUMAN PATENTOME

This map of the chromosomes offers an indication of how often genes have been patented in the U.S. Each colored bar represents the number of patents in a given segment of a chromosome, which can contain several genes. Patents can claim multiple genes, and one gene may receive multiple patents. As a result, the number of patents indicated for each chromosome does not necessarily match the sum of the values represented by the colored bars.



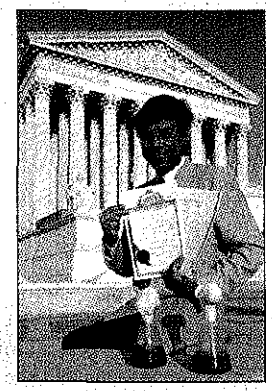
LAURIE GRACE; SOURCE: KYLE JENSEN AND FIONA MURRAY *Massachusetts Institute of Technology*

Overview/*Genetic Patenting*

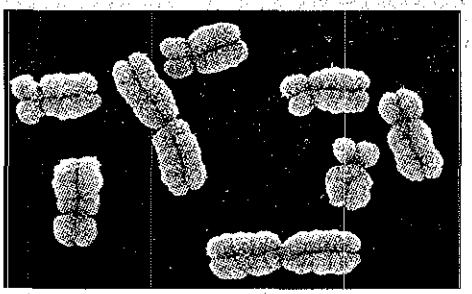
- Last year marked the 25th anniversary of the landmark court decision that opened a floodgate of patenting on both DNA and even whole organisms.
- Nearly one fifth of the nearly 24,000 genes in the human genome have one or more patents on them. Almost 50 percent of known cancer genes have been patented.
- Overall the feared blocking of basic research by ownership of both gene-based tools and critical knowledge has not yet occurred, but it still could materialize as genomic and proteomic discoveries are commercialized.
- In the U.S., ethical issues about patenting life have been largely ignored in enacting legal decisions and policy, but they are still a consideration in Europe and Canada.

In the majority opinion, Chief Justice Warren Burger waved away the objections to patenting life as irrelevant, saying that "anything under the sun that is made by man" could be patented. The only question for the court was whether the bacterium was a "product of nature" or a human invention. "Einstein could not patent his celebrated law that $E = mc^2$; nor could Newton have patented the law of gravity," the opinion acknowledged. But as a "product of human ingenuity," Chakrabarty's engineered bacterium was different. Dismissing Rifkin's "gruesome parade of horribles," the court suggested that it was incapable of standing in the way of progress. "The large amount of research that has already occurred when no researcher had sure knowledge that patent protection would be available sug-

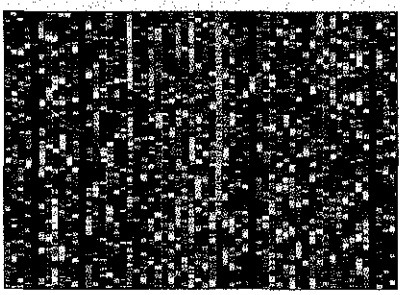
1980
The Supreme Court rules that Ananda Chakrabarty's bacterium is not a "product of nature" and so can be patented; other living things "made by man" are declared patentable as well



Ananda Chakrabarty



Human chromosomes



DNA sequencing

1980
Congress passes the Bayh-Dole Act (the Patent and Trademark Laws Amendment), which allows universities to enter into exclusive licensing for their intellectual property

1988
Harvard University gets a patent for the OncoMouse, a rodent with a gene inserted that predisposes it to cancer

1990
The Human Genome Project is launched

1996
Both public- and private-sector scientists from all over the world involved in DNA sequencing pass a resolution—the Bermuda Rules—that states that "all human genomic sequence information, generated by centers funded for large-scale human sequencing, should be freely available and in the public domain"

tual property. Noncommercial research, in their view, receives an exemption. Yet a 2002 case decided by the CAFC—*Madey v. Duke*—disabused universities and other nonprofit institutions of any notion of special status. The court decided that noncommercial research furthers the "legitimate business objectives" of a university, and so both research tools and materials, which would include DNA, do not merit an exemption. (An exemption does exist for research that is specific to preparing an application to file for a new drug.)

Patent holders generally have little interest in beating down lab doors to track down infringers. In the wake of the *Madey* decision, the level of notification from patent owners has picked up a bit, according to the NAS survey, but this increase has not caused major disruption. A growing awareness of the absence of an exemption, however, could lead to a more restrictive research environment, which is why the NAS panel recommended that Congress put in place a statutory research exemption.

Major intellectual-property hurdles may begin to appear as genomics and proteomics—fields in which many genes or proteins are studied together—reach maturation. "The burden on the investigator to obtain rights to the intellectual property covering these genes or proteins could become insupportable, depending on how broad the scope of claims is and how patent holders respond to potential infringers," the NAS panel remarked.

Genomics and proteomics are only starting to bear fruit in the form of medical diagnostics and drugs. "You really get ownership issues coming up when things get closer to market," says Barbara A. Caulfield, general counsel for Affymetrix, the gene-chip company that has opposed DNA patenting because it could impede research with its products.

Already, Caulfield says, examples of patents with a very broad scope burden both industry and academia. Genetic Technologies Ltd., an Australian company, holds patents that it is using to seek licensing arrangements from both companies and universities that conduct research on the noncoding portion of the genome. The breadth of its patents—covering methods of obtaining information from the approximately 95 percent of the genome that is sometimes erroneously called junk DNA—would make most scientists rub their eyes. Genetic Technologies, however, has already entered into licensing arrangements with the likes of U.S. biotechnology giant Genzyme and Applera, the parent of Celera and Applied Biosystems.

Keeping the *Ordre Public*

U.S. POLICYMAKERS and courts have, in general, taken a no-holds-barred approach to the commercialization of new biotechnologies. Though often debated by government advisory panels, ethical, philosophical and social questions have seldom entered into actual decision making about whether to extend patent protection to living things. In *Chakrabarty*, the Supreme Court justified its decision, in part, by quoting the statement of the first patent commissioner, Thomas Jefferson, that "ingenuity should receive a liberal encouragement."

One of the obvious questions raised by the *Chakrabarty* decision was, Where does patenting life stop? Does it extend to creatures above the lowly *Pseudomonas* on the phylogenetic tree? In 1988, eight years after *Chakrabarty*, the patent office issued No. 4,736,866, the patent for the Harvard OncoMouse, which contained a gene that predisposed the animal to contract cancer, a valuable aid in researching the disease. The justification for granting the patent could be traced directly to the reasoning of the justices in *Chakrabarty*: the addition of the oncogene meant that this was a mouse "invented" by a human.

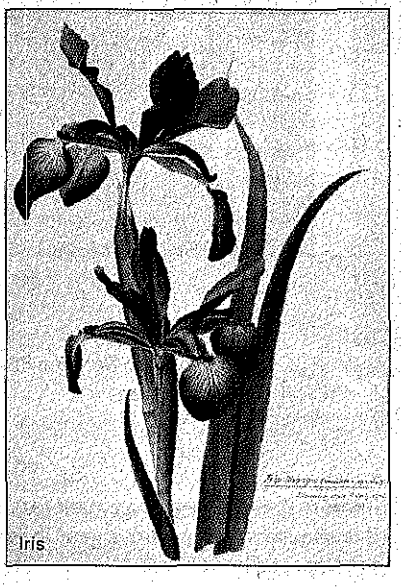
Not every country has handled the issue of patenting higher organisms with the same utilitarian bent demonstrated by U.S. courts and bureaucrats. Much more recently, Canada reached an entirely different decision about the small mammal with the extra gene. On appeal, the Supreme Court of Canada rejected the Harvard OncoMouse patent. In 2002 it decided that the designation "composition of matter"—in essence, an invented product that is eligible for patenting—should not apply to the mouse. "The fact that animal life forms have numer-

TED SPIEGEL *Corbis [Chakrabarty]*; BIOPHOTO ASSOCIATES/PHOTO RESEARCHERS, INC. *[chromosomes]*; DAVID PARKER *Photo Researchers, Inc. [DNA sequencing]*

PATENTING LIFE: A CHRONOLOGY

The patent system—both courts and patent examiners—has always wrestled with the question of what is truly an invention (and therefore deserving of a patent) and what constitutes a mere attempt to expropriate in unaltered form a physical law or material from the natural world, a reason for rejecting an application.

1889
The commissioner of patents determines that plants, even artificially bred ones, are "products of nature," and therefore ineligible for patenting. The applicant in this case—*Ex parte Latimer*—had tried to patent fibers separated from the plant and was turned down


Iris

1930
The U.S. Congress passes the Plant Patent Act, which allows the patenting of new plant varieties that reproduce asexually

1948
A Supreme Court ruling held that simply combining bacteria does not count as an invention (*Funk Brothers Seed Company v. Kalo Inoculant Company*)

1971
Cetus, the first biotechnology company, opens its doors

Continued on next page

mere act of using that information in the course of conducting scientific research run the risk of infringement?

In response to some of these pressures, in 2001 the U.S. patent office made final new guidelines that directed examiners to look for "a specific and substantial utility" in granting biotechnology patents. In most other technological pursuits, the requirement that a patent be useful is secondary to criteria such as whether an invention is truly new, because most inventors do not seek protection for worthless inventions. In the arena of life patents, the assessment of an invention's usefulness has become a crucial filter to maintain a check on patent quality. Designating a sequence of DNA simply as a gene probe or chromosome marker is not enough to meet the new rules.

These changes have had an effect. So far only a small number of EST patents have been issued, according to the NAS. An important affirmation of the patent office's approach to weeding out useless and overly broad patents came in a decision on September 7, 2005, by the U.S. Court of Appeals for the Federal Circuit (CAFC), which hears appeals of patent cases. The court upheld the patent office's denial of Monsanto's application for a patent for five plant ESTs that were not tied to a given disease. The patents would have amounted to "a hunting license because the claimed ESTs can be used only to gain further information about the underlying genes," wrote federal circuit chief judge Paul Michel.

Data on the extent of a feared anticommons have just begun to emerge in recent months. A survey performed as part of an NAS report—"Reaping the Benefits of Genomic and Proteomic Research," released in mid-November 2005—received responses from 655 randomly selected investigators from universities, government laboratories and industry about the effect of life patents on genomics, proteomics and drug development research. The study found that only 8 percent of academics indicated that their research in the two years prior had anything to do with patents held by others; 19 percent did not know if their research overlapped; and 73 percent said that they did not need to use others' patents. "Thus, for the time being, it appears that access to patents or information inputs into biomedical research rarely imposes a significant burden for academic biomedical researchers," the report concluded.

The number of patents actively being sought has also declined substantially. Patents referring to nucleic acids or closely related terms peaked at about 4,500 in 2001, according to a recent report in *Nature Biotechnology*, and declined in four subsequent years—a trend that may result, in part, from the patent office's tightening of its utility requirement [*see box on opposite page*].

Some of the downturn may relate to the success of a de facto open-source movement in the biomedical sciences, akin to the one for information technologies. In 1996 scientists from around the world in both the public and private sectors devised what are referred to as the Bermuda Rules, which specify that all DNA sequence information involved in the Human Genome Project should be placed immediately into the public domain. Data sharing was later encouraged in other large-scale projects, such as the Single Nucleotide Polymorphism Consortium, which mapped genetic variation in the human genome. In some cases, researchers have taken out patents defensively to ensure that no one else hoards the knowledge. Both companies and public health groups involved with discovering and sequencing the SARS virus are trying to form a "patent pool" to allow nonexclusive licensing of the SARS genome.

This embrace of the public domain torpedoed the idea of building a business on public information. Both Celera Genomics and Incyte—two leaders in the genomics field—restructured in the early years of the new century to become drug discovery companies. J. Craig Venter, who spearheaded the private effort to sequence the human genome, left Celera and turned into an open critic. "History has proven those gene patents aren't worth the paper they were written on, and the only ones who made money off them were the patent attorneys," Venter commented at a 2003 conference.

A patent thicket that blocks basic research has also failed to materialize because academics tend not to respect intellec-

ANONYMOUS/PRIVATE COLLECTION/BRIDGEMAN ART LIBRARY (*Iris*)

An expressed sequence tag (EST) is a sequenced segment of DNA only a few hundred nucleotides long located at one end of a gene. It can be used as a probe to rapidly fish out the full-length gene from a chromosome. Researchers started filing patents on ESTs—sometimes by the hundreds. They did so without really knowing what the ESTs in question did: the applicants often guessed at the biological function of the gene fragments by poking through protein and DNA databases. "This involves very little effort and almost no originality," once remarked Bruce Alberts, former president of the National Academy of Sciences.

The justification for patenting DNA sequences of unclear function was that these ESTs could serve as research tools. Yet this reason was precisely what concerned much of the scientific community. Owners of patents on EST probes might demand that researchers license these tools, adding expense and red tape to medical research and possibly impeding the development of new diagnostics and therapeutics.

In a 1998 article in *Science,* Rebecca S. Eisenberg of the University of Michigan Law School and Michael A. Heller, now at Columbia Law School, worried about the emergence of an "anticommons," the antithesis of the traditional pool of common knowledge that all scientists share freely. Those concerns were heightened by the audacious scope of some of these applications, which staked out not only the ESTs but any DNA that resides adjacent to them. Such a claim could translate, in theory, into granting property rights for an entire chromosome.

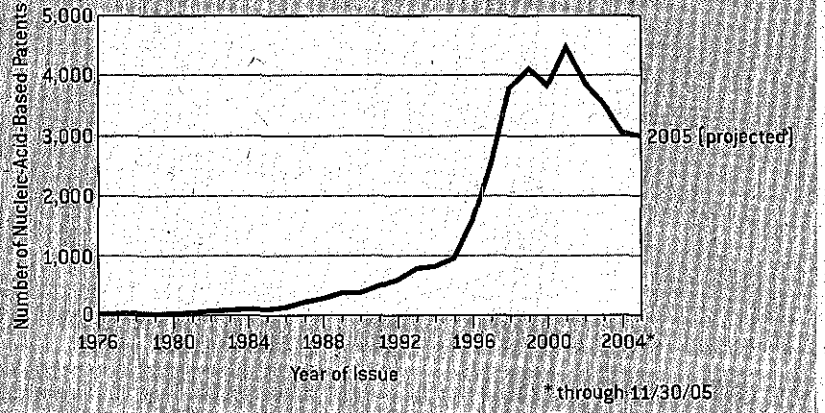
But a further, more intellectual objection to the concept of these patents was that the use of ESTs to pin down the location of genes actually occurs in a database, not in a laboratory. The value of ESTs exists more as information than as one of the tangible "processes, machines, manufactures and compositions of matter" that are eligible for patenting. Abstract ideas have traditionally been considered outside the realm of patentable subject matter, although a number of federal court cases have blurred this distinction during the past 10 years.

Allowing information to be patented would tend to undermine the balancing act that is a cornerstone of the whole system. In exchange for a 20-year monopoly, the patent applicant must disclose how to make an invention so that others can use that knowledge to improve on existing technology. But how does the traditional quid pro quo work if the information disclosed to others is the patented information itself? Does the

WHO OWNS THE PATENTS?

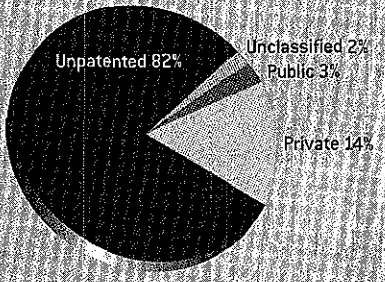
YEARLY U.S. PATENTS RELATED TO DNA OR RNA

The granting of patents involving nucleic acids, including from nonhumans, peaked in 2001 and then declined (*graph*), probably because of tightening requirements. The holders of many of the patents are listed in the table (*right*).



PATENTS ON HUMAN GENES

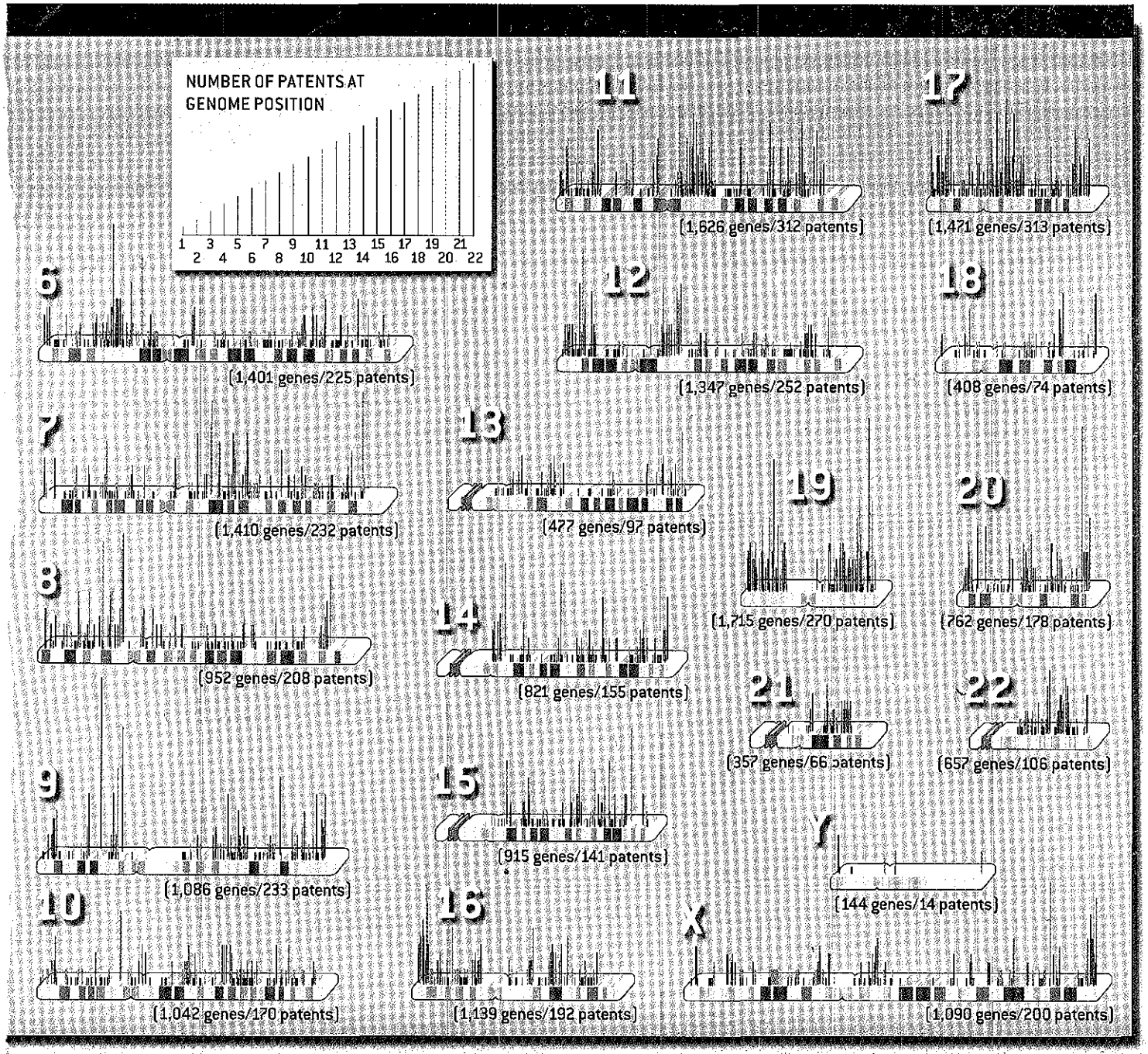
As the pie chart shows, private interests in the U.S. were the largest holders of patents on the 23,688 human genes in the National Center for Biotechnology Information database in April 2005.



LARGEST PATENT HOLDERS	NUMBER OF PATENTS†
University of California	1,018
U.S. government	926
Sanofi Aventis	587
GlaxoSmithKline	580
Incyte	517
Bayer	426
Chiron	420
Genentech	401
Amgen	396
Human Genome Sciences	388
Wyeth	371
Merck	365
Applera	360
University of Texas	358
Novartis	347
Johns Hopkins University	331
Pfizer	289
Massachusetts General Hospital	287
Novo Nordisk	257
Harvard University	255
Stanford University	231
Lilly	217
Affymetrix	207
Cornell University	202
Salk Institute	192
Columbia University	186
University of Wisconsin	185
Massachusetts Institute of Technology	184

† as of 9-14-05

LAURIE GRACE; SOURCES: KYLE JENSEN AND FIONA MURRAY *Massachusetts Institute of Technology (pie chart and graph);* LORI PRESSMAN, ROBERT M. COOK-DEEGAN AND LEROY WALTERS ET AL. IN *NATURE BIOTECHNOLOGY* (IN PRESS) AND MELISSA SOUCY *Kennedy Institute of Ethics, Georgetown University (table)*



gests that legislative or judicial fiat as to patentability will not deter the scientific mind from probing into the unknown any more than Canute could command the tides," Burger noted.

After the close 5–4 ruling, industry and academia have looked to the broad interpretation of patentability in the Chakrabarty case as justification for patenting not only genes but other stuff of life, whole organisms and cells—including stem cells—to give but an incomplete list. The early patents on genes followed closely in the tradition of patents on chemicals. Incyte does not actually own the rights to the gene for the histamine receptor in your body but only to an "isolated and purified" form of it. (At times, patent examiners or courts have invoked the U.S. Constitution's prohibition of slavery to explain why a patent cannot be issued on an actual human or on his or her body parts.) A patent on an isolated and cloned gene and the protein it produces grants the owner exclusive rights to market the protein—say, insulin or human growth hormone—in the same way that a chemical manufacturer might purify a B vitamin and file for a patent on it.

Little Effort, Less Originality

BY THE 1990S the inexorable pace of technological development had overturned the status quo again. The high-speed sequencing technologies that emerged during that decade—which powered the Human Genome Project—muddied the simple analogy with chemical patenting.