

# OWNING

**T** 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?

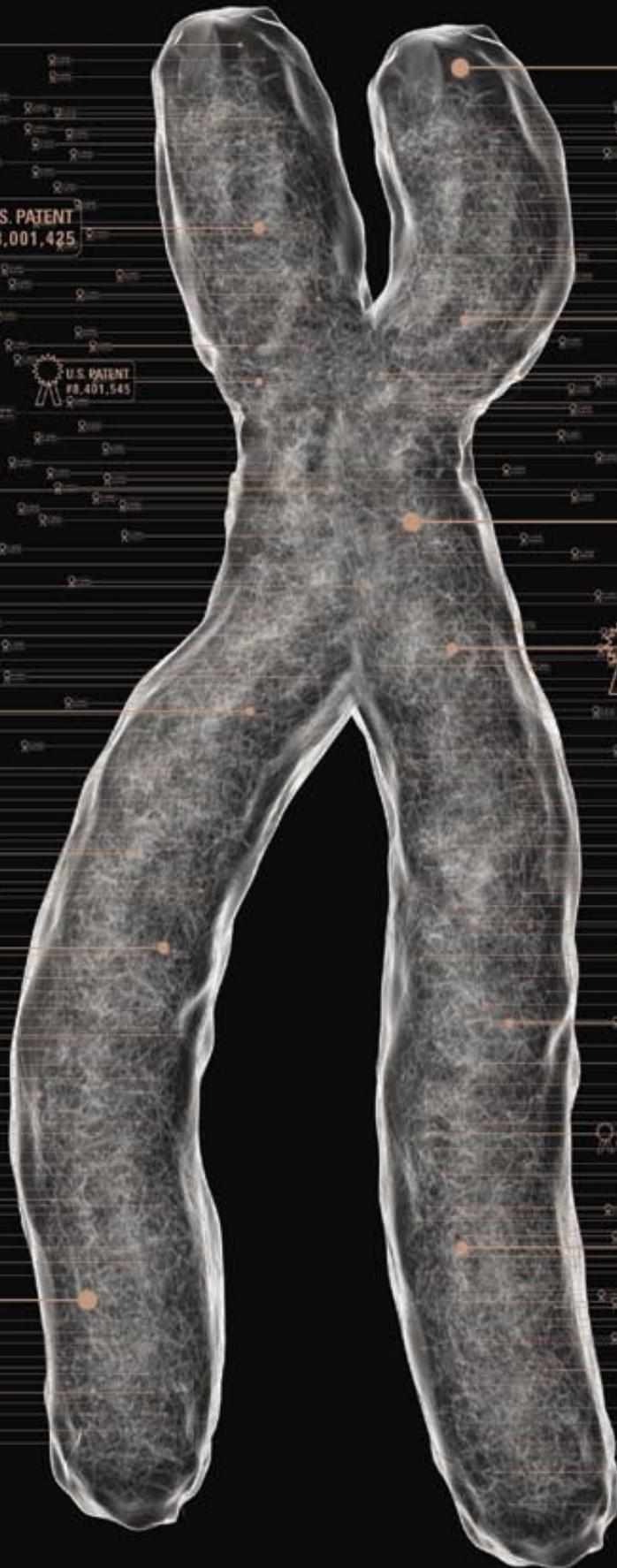
Ethicists, judges, scientists and patent examiners continue to immerse themselves in these debates, which will only grow more acute in a new era of personalized medicine and of genomics and proteomics research that examines the activities of many different genes or proteins at the same time. Doctors 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

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

# the STUFF of LIFE



**U.S. PATENT**  
#8,104,231

**U.S. PATENT**  
#8,001,425

**U.S. PATENT**  
#8,401,545

**U.S. PATENT**  
#8,447,389

**U.S. PATENT**  
#8,917,531

**U.S. PATENT**  
#8,902,199

**U.S. PATENT**  
#8,534,854

**U.S. PATENT**  
#8,800,124

**U.S. PATENT**  
#8,723,090

**U.S. PATENT**  
#8,302,389

**U.S. PATENT**  
#8,128,813

**U.S. PATENT**  
#8,798,227

**U.S. PATENT**  
#8,815,221

**U.S. PATENT**  
#8,154,453

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.

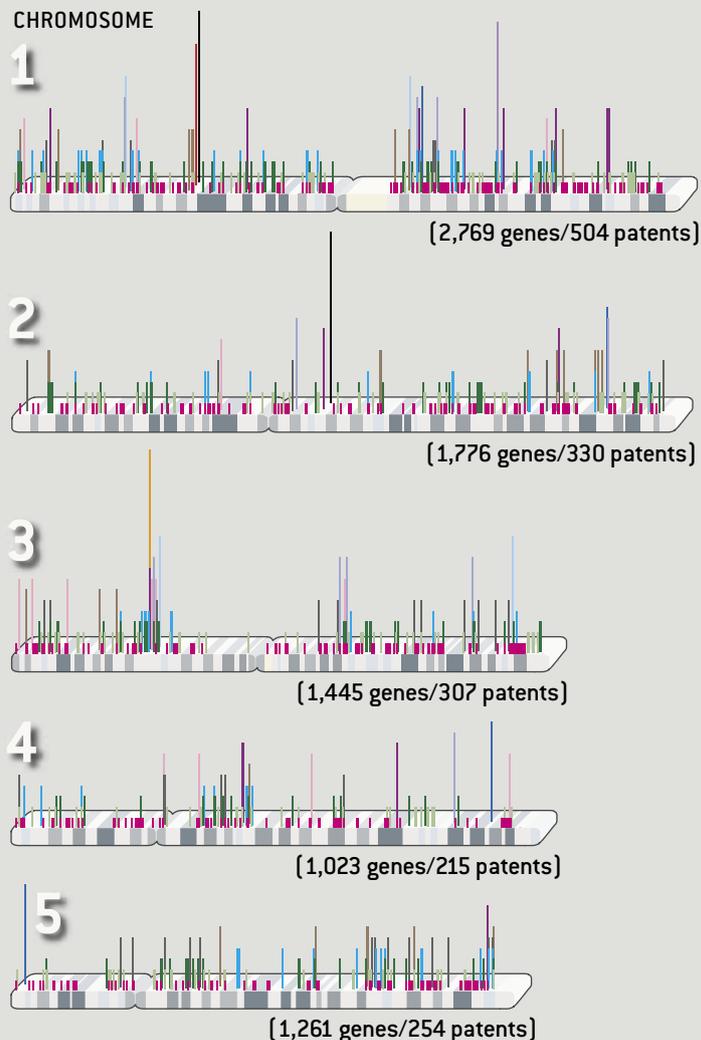
The Supreme Court justices received friend-of-the-court briefs arguing both for and against granting the claims in the Chakrabarty patent. Groups ranging from Genentech to the Regents of the University of California urged that the patent application be granted, citing benefits for pharmaceutical development, 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.

## 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.

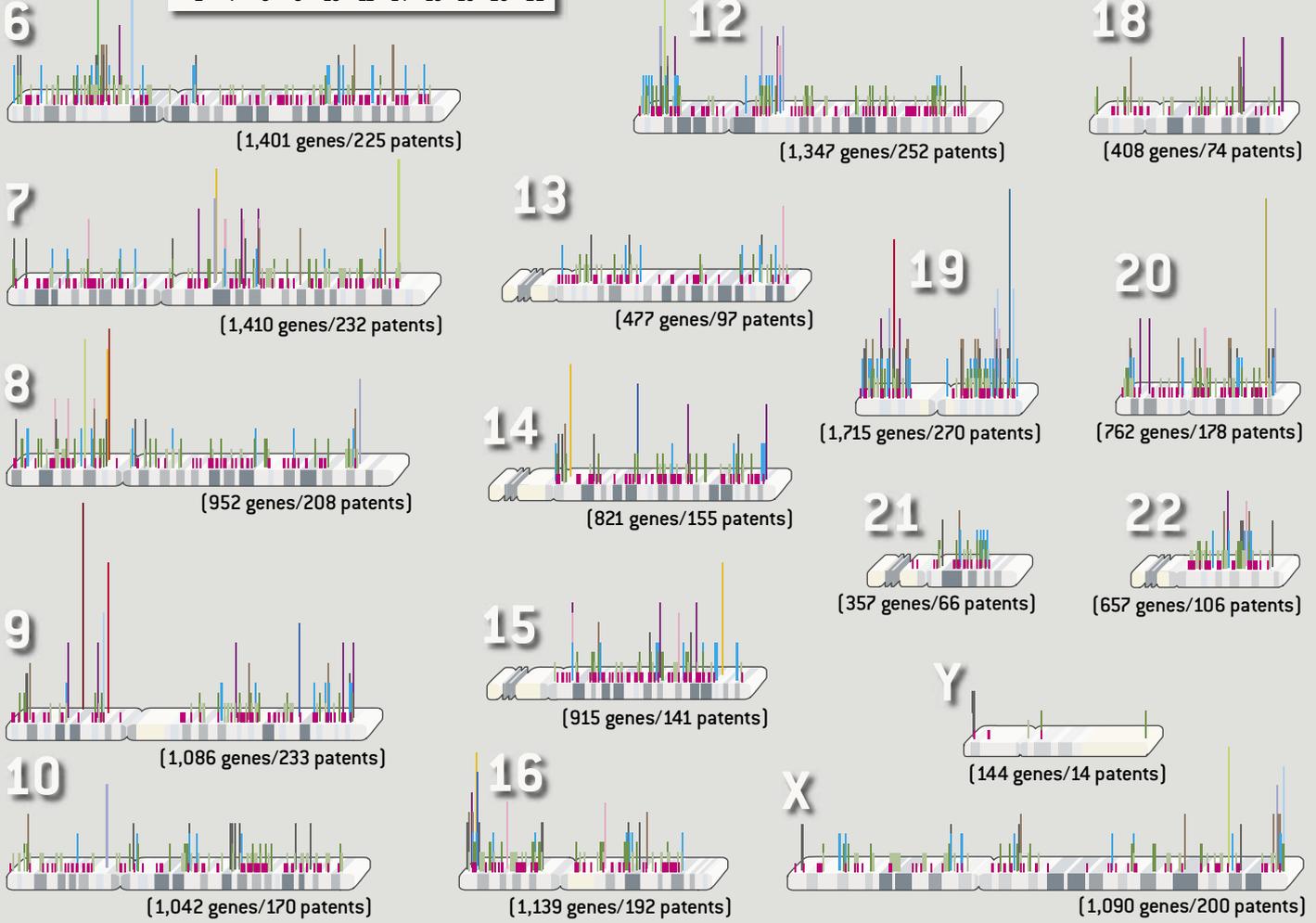
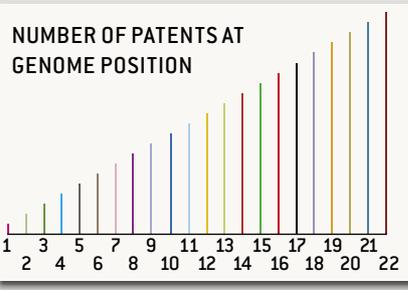
## THE HUMAN PATENTOME

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.



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 horrors,” 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-

Laurie Grace; Source: Kyle Jensen and Fiona Murray, Massachusetts Institute of Technology



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—muddled the simple analogy with chemical patenting.

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.

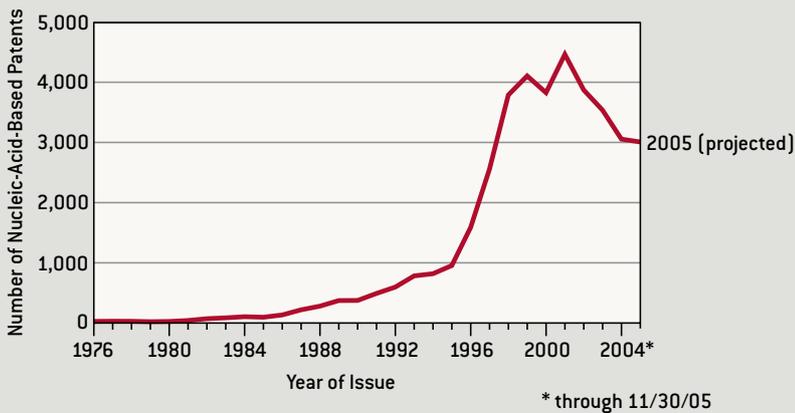
But a further, more intellectual objection to the concept of these patents was that the use of ESTs to pin down the location of genes actually occurs in a database, not in a laboratory. The value of ESTs exists more as information than as one of the tangible “processes, machines, manufactures and compositions 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?

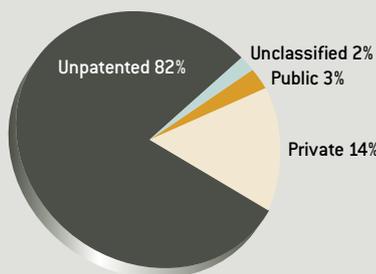
### YEARLY U.S. PATENTS RELATED TO DNA OR RNA

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

| 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 MATURE BIOTECHNOLOGY (IN PRESS) AND MELISSA SOUCY KENNEDY INSTITUTE OF ETHICS, GEORGETOWN UNIVERSITY (table)

## 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



**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.

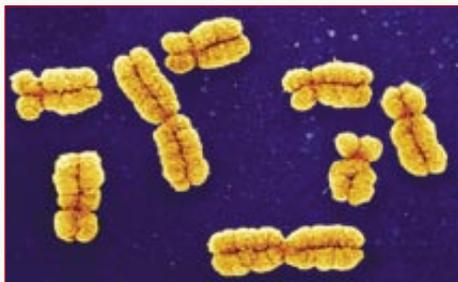
A patent thicket that blocks basic research has also failed to materialize because academics tend not to respect intellec-

## 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



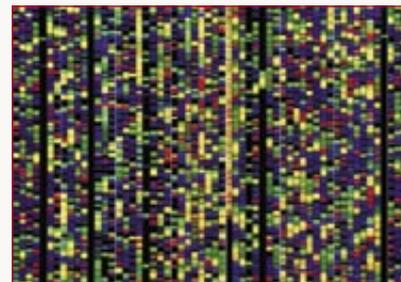
Ananda Chakrabarty



Human chromosomes

## 1990

The Human Genome Project is launched



DNA sequencing

## 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"

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

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 onco-gene 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-



Cancer mice

## 2000

A working draft of the human genome is announced

Heads of state Bill Clinton and Tony Blair issue a statement that “raw fundamental data on the human genome, including the human DNA sequence and its variations, should be made freely available to scientists everywhere.”

Biotechnology stocks drop sharply

## 2002

The Supreme Court of Canada hears an appeal that results in the refusal of a patent for the Harvard OncoMouse

## 2003

Congress puts a provision in the patent office budget prohibiting patents on a “human organism,” a codification of the office’s existing policy

## 2001

The U.S. patent office issues final guidelines that raise the standard for usefulness and the amount of disclosure of details of an invention needed for granting, in part, patents—an action prompted by the many patent applications on gene fragments

## 2005

The patent office issues a final rejection of a patent application filed by Stuart Newman and Jeremy Rifkin for a hypothetical chimera: a part-human, part-animal hybrid. The two opponents of patents on living things want to obtain a patent to block anyone from ever creating such an animal



Chimera

ous unique qualities that transcend the particular matter of which they are composed makes it difficult to conceptualize higher life forms as mere ‘compositions of matter,’ ” Justice Michel Bastarache asserted. “It is a phrase that seems inadequate as a description of a higher life form.”

Europe, too, was more circumspect than the U.S. about embracing the cancer mouse. The European Patent Office narrowed the scope of the OncoMouse patent to cover only mice instead of all rodents. It did so by invoking a provision of its patent law that has no comparable clause in U.S. statutes. It brought to bear Article 53 of the European Patent Convention, which bars patents that threaten “‘*ordre public*’ or morality.”

European regulators have also eviscerated the patent portfolio on breast cancer genes held by the Utah-based Myriad Genetics. In the U.S., patents on diagnostic genes, more than other DNA patents, have inhibited both research and clinical medicine. Myriad has used its patents to stop major cancer centers from devising inexpensive “home-brew” tests for the breast cancer genes *BRCA1* and *BRCA2*. In Europe, a coalition of research institutes challenged Myriad’s patents, invalidating some and limiting others. Because of the paring back of Myriad’s rights, the tests are now free for everyone except Ashkenazi Jewish women, who must pay Myriad’s licensing fees. The mutations that are still covered by Myriad’s remaining patents are most commonly found in Ashkenazi women. By law, a doctor must ask a woman if she is an Ashkenazi Jew, which has provoked howls from geneticists.

A replay of these scenes is unlikely in the U.S. In *Chakrabarty*, the Supreme Court remarked that the type of ethical questions raised by Rifkin’s group should be addressed by Congress, but most legislative attempts have foundered so far. If any fundamental change does come, it will most likely happen through the Supreme Court’s examination again of one of the key decision points in *Chakrabarty*: the definition of the ever shifting line between laws of nature and invention.

Legal analysts are eagerly awaiting a Supreme Court decision expected this year that may help clarify how far to push

back the borders of what was once considered unpatentable. The high court has agreed to hear a case—*Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc.*—that will determine whether the simple correlation of an elevated level of the amino acid homocysteine with a deficiency of two B vitamins “can validly claim a monopoly over a basic scientific relationship used in medical treatment such that any doctor necessarily infringes the patent merely by thinking about the relationship after looking at a test result,” in the language of *Laboratory Corp.*, the plaintiff. The patent claim covers only the correlation itself, not the electrical and mechanical equipment that is used to carry out the test. The case is of intense interest not only to a biotechnology industry in which raw information has become increasingly valuable but also to the information technology industry, where the patentability of software and business methods has also been a matter of dispute. “This could have an impact not just on DNA patenting but on emerging areas such as nanotechnology and synthetic biology,” says Arti K. Rai, a law professor at Duke University.

Friend-of-the-court briefs will argue that the Jeffersonian doctrine of promoting invention should prevail. But the case also resonates with *Chakrabarty* and case law that preceded it. As technology advances, courts will have to come to grips again and again with defining the meaning of the phrase “anything under the sun that is made by man.” Should tinkering with a single gene in a mouse—or the mere act of detecting an inverse relation between two molecules—suffice always to confer on an “inventor” a limited monopoly for two decades? SA

### MORE TO EXPLORE

**Who Owns Life?** Edited by David Magnus, Arthur Caplan and Glenn McGee. Prometheus Books, 2002.

**Intellectual Property Landscape of the Human Genome.** Kyle Jensen and Fiona Murray in *Science*, Vol. 310, pages 239–240; October 14, 2005.

**Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health.** Committee on Intellectual Property Rights in Genomic and Protein Research and Innovation. National Research Council, National Academies Press, 2005.