1 Gene Patent History-1980



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TIME

Monday, Jun. 30, 1980

# Science: Test-Tube Life: Reg. U.S. Pat. Off.

By John S. Demott

The Supreme Court protects the genetic engineers

When Thomas Jefferson, an an amateur scientist himself, wrote the nation's first patent law in 1793, he was deter mined to ensure that "ingenuity should receive a liberal encouragement." Under his law, "any new and useful art, machine, manufacture or composition of matter" was patentable and thus legally shielded from theft. Last week, in a 5-to-4 decision, the Supreme Court applied the Jeffersonian measure to one of the latest examples of human ingenuity. It ruled that new forms of life created in the laboratory could be patented.

The decision, climaxing an eight-year legal battle, should give a boost to an emerging industry, genetic engineering, which seeks to create new life forms. This promising field offers the prospect of advances in everything from medicine and food production to alternate energy forms. The court's ruling also revived fears — vastly exaggerated in the opinion of most responsible scientists — about the dangers of tampering with life.

The center of dispute was a new human-made variation of the common bacterium Pseudomonas. While working at General Electric's Schenectady, N.Y., labs in the early 1970s, Indian-born Microbiologist Ananda M. Chakrabarty made a significant discov ery. Chakrabarty knew that cer tain bacteria are able to break up hydrocarbons. What he found was that the genes responsible for this capacity are not contained in the bacterium's single chromosome, or principal repository of DNA, the genetic times Instead, they reside in small, auxiliary parcels of genes, called plasmids, elsewhere in the cell. Taking plasmids from three oil-eating bacteria, Chakrabarty transplanted them into a fourth, thereby creating a crossbred version with a voracious appetite for oil.

Freeze-dried until needed, then sprinkled on straw and tossed into the ocean, the superbugs could presumably make quick work of oil spills by breaking down the crude into harmless protein and carbon dioxide. Says Chakrabarty, 42, now a researcher at the University of Illinois Medical Center: "You can make tons of these microorganisms in a matter of days." Nor, he says, would the bacteria pose any danger. After the feast, they would die for want of oil.

When GE tried to patent the bacterium in 1972 under Chakrabarty's name,

U.S. patent officials balked. They argued, in effect, that if either Jefferson or Congress had intended life to be patentable, special laws would not have been needed to protect certain new plant hybrids like the Red American Beauty Rose. But when GE pressed its case, the Court of Customs and Patent Appeals rejected the Government's argument, and the Supreme Court last week went along with that position. As Chief Justice Burger explained, the issue is "not between living and inanimate things, but between products of nature—whether living or not —and human-made inventions."

Though GE was pleased by the decision, it seems in no rush to exploit the bug commercially. Ronald Brooks, head of the GE environmental unit where Chakrabarty did his work, says that the company would entertain licensing agreements with those who want to develop the oil eater. But he adds that GE does not see a market big enough for it to become directly involved.

Others are less hesitant. Awaiting the outcome of the GE appeal are patent applications for at least 100 different kinds of organisms or processes to make organisms. All are products of genetic engineering activities in more than a dozen companies and countless university laboratories in the U.S. and abroad. Most of this work does not involve the relatively simple process of plasmid reshuffling used by Chakrabarty, but the more complex and promising technique of recombinant DNA, or gene splicing. With it, scientists actually break apart DNA, using so-called restriction enzymes, and isolate certain desirable genes. These genes are then inserted into plasmids, again using enzymes, and transferred into another bacterium. The recipient bug, in effect, becomes a new life form with all the characteristics and capabilities carried by the spliced-in genes.

Even in its infancy, the technology has led to the making of new bacteria that are in fact microscopic chemical factories. Already the common intestinal bacterium E. coli, the favorite tool of such researchers, has been genetically "re-engineered" to produce human insulin and interferon, the antiviral protein that could be effective against several types of cancer, as well as the hormone that stimulates growth in humans. In the future, scientists should be able to use such reprogrammed bugs to meet other medical needs: manufacturing malaria vaccine, for example, or creating chemicals to heal burns, kill pain or stanch the flow of blood from wounds.

Yet the new technology should ixtend far beyond medicine.

Scientists are talking about creating bugs that will enable plants to "fix" nitrogen directly from the air, thereby reducing the dependence on fertilizers. Others could be created to make amino acids, a building block of proteins and thus a basic food source. Some organisms, like Chakrabarty's oil eater, might be developed to degrade metals and other materials; these could help mining companies leech ores from hard-to-reach veins or assist in the cleanup of such toxic waste sites as Love Canal. Even the energy crisis might be alleviated by the genetic engineers, who are devising new ways of using yeast to make alcohol, and other superbugs for making fuels, antifreeze compounds and plastics. Says Molecular Biologist Herman Lewis, the National Science Foundation's adviser on recombinant DNA: "Theoretically, any process occurring in nature can be harnessed for man's use. We could even learn how to duplicate photosynthesis, the basic energy-converting process in green plants." Basically, says Eli Lilly Vice President for Research Irving Johnson "You're talking about a process that could affect all living species. I can't think of a single event that is as broad as that, except maybe the discovery of atomic particles."

With so much research already going on, the Supreme Court's decision mainly gives formal sanction to what had been happening for some time, a classic example of the law's lagging behind technology. Millions of dollars have been invested without patent protection. Says Bernard Talbot, special assistant to the director of the National Institutes of Health: "Recombinant DNA work is going on in numerous labs. This would have gone on whatever the court decided." Chief Justice Burger himself acknowledged that a patent law "will not deter the scientific mind from probing into the unknown any more than Canute could command the tides."

The most important patent application now pending is for the key gene-splicing processes developed by Microbiologists Stanley Cohen of Stanford and Herbert Boyer of the University of California: both have signed over royalty rights to their respective universities, but Boyer is a major stockholder in Genentech Corp., a Bay Area genetic engineering firm, and obviously stands to make money from the process. No one quarrels with that. But there is a mixed view of just how much good will accrue from the introduction of patents to the infant industry.

Biochemist Ronald Cape, chairman of Berkeley's Cetus Corp., a rival firm, sees patents as increasing the "free flow of ideas." More companies and investors are sure to plunge into the expensive business with less fear of having ideas stolen, or at least with an assurance of legal recourse if they are. But others fear that just the opposite will happen: that scientists will be cautious about sharing information, long an essential part of the scientific process. Warns M.I.T.'s Jonathan A. King, a molecular biologist: "Now you have the prospect of keeping a strain [of bacteria] out of circulation until you have the patents." Wolfgang Joklik,

chairman of Duke University's department of microbiology and immunology, wants to see scientists rewarded for what they do. But he adds with concern, "I just don't want to see organisms patented for commercial exploitation. I would like to be sure that everything is available for basic research."

There will almost certainly be efforts to get around the patents of others through slight variations. Says James Watson, Nobel laureate and co-discoverer in the 1950s of the double-helix structure of DNA: "It will be awfully hard to show uniqueness, to prove that one man's microbe is really different from another's." That, says J. Leslie Glick, president of Genex Corp. in Bethesda, Md., could lead to modifying bacterial strains mainly for "defensive reasons, a waste of research." Lawyers especially stand to gain if patenting life becomes their way of making a handsome living. Quipped Stephen Turner, president of Bethesda Research Laboratories: "I call this the Patent Lawyer's Employment Act of 1980."

For others, the decision stirred renewed anxieties. They argue that altering life, to say nothing of patenting it, is not the wisest of human activities. Better, they say, to leave the doomsday bugs to fiction. Said the Peoples Business Commission, a Washington-based consumer group, in a hyperbolic press release greeting the court's decision: "The Brave New World that Aldous Huxley warned us of is now here." Nobel Laureate George Wald, a guru of various antiestablishment causes, echoed those concerns. If the GE bug ever gets loose in the world, he said, "it could digest petroleum that has not been spilled. You can't put bacteria on a leash once you introduce them into the environment."

Chakrabarty, who stands to make no money from his discovery because GE will own the patent, crisply dismisses such dissent. "I can't respond to imaginary scenarios," he told TIME Correspondent

David Jackson. He insists that his Pseudomonas is safe, although it was developed before the Government imposed strict containment rules for lab experiments with such organisms. Indeed, in the past few years, researchers in dozens of labs have been performing similar experiments, and as Burger put it, there has been no "gruesome parade of horribles" forecast by the naysayers to the new research. Yet with Shakespeare, Burger acknowledged, "It is sometimes better to 'bear those ills we have than fly to others that we know not of.' " If Hamlet's wisdom had prevailed, there probably would be no such thing as genetic engineering with all its potential for good. For that matter, there probably would be no science.

*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.

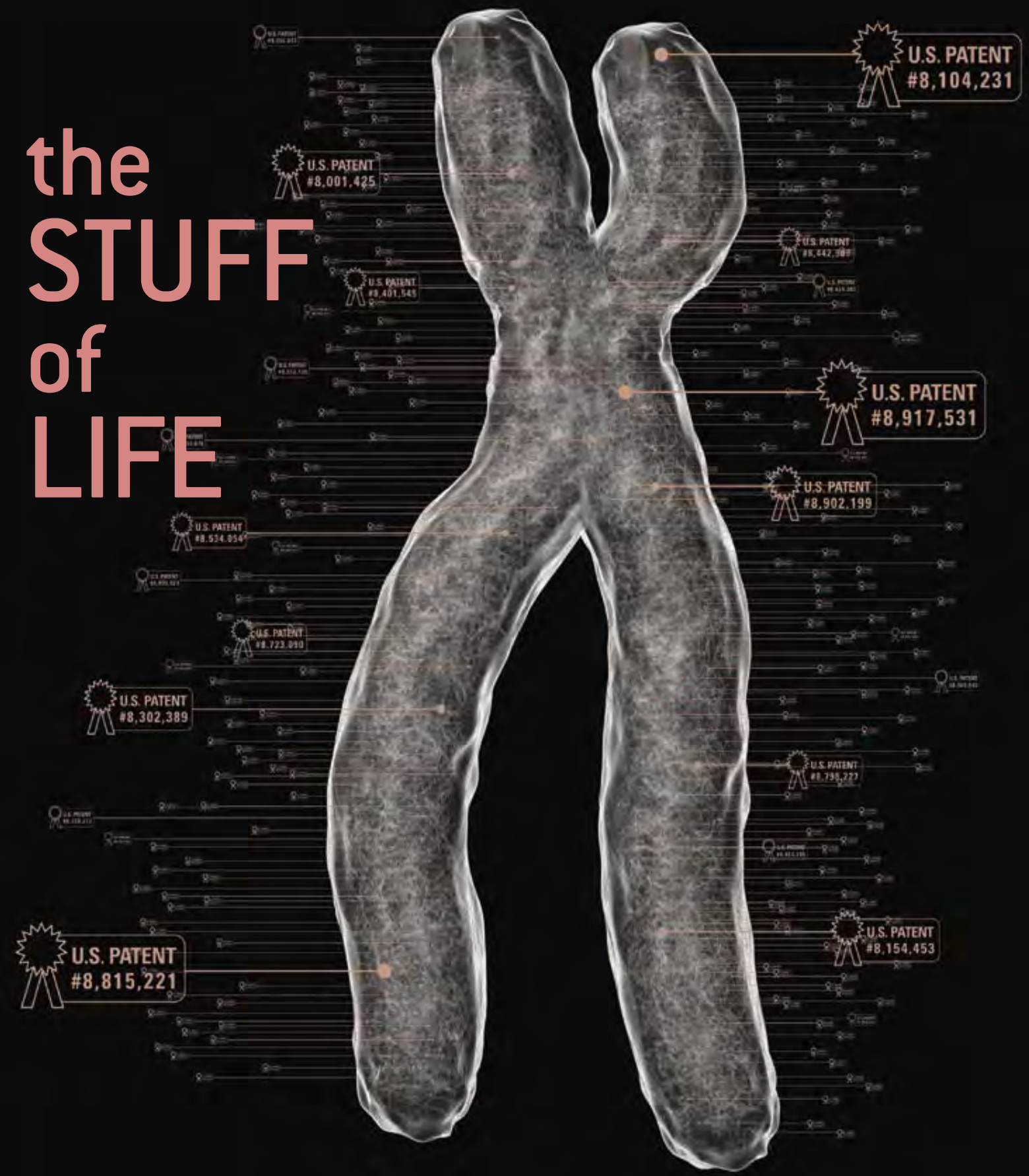
## Anything under the Sun

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

BRYAN CHRISTIE DESIGN

*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.

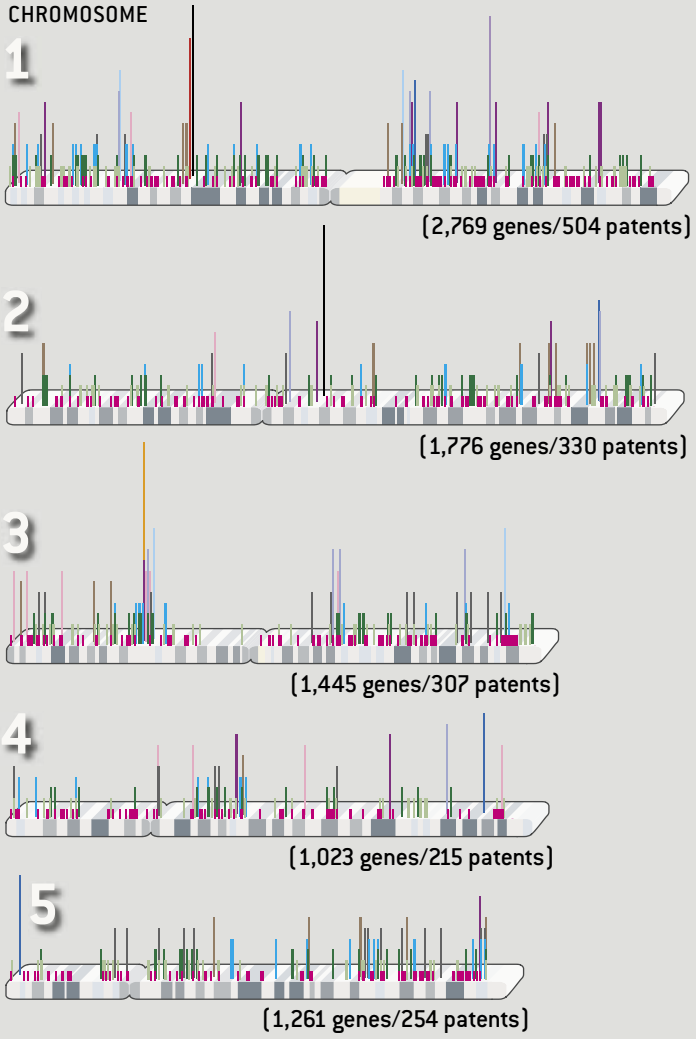
The Supreme Court justices received friend-of-the-court briefs arguing both for and against granting the claims in the Chakrabarty patent. Groups ranging from Genentech to the Regents of the University of California urged that the patent application be granted, citing benefits for pharmaceutical development,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

## 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.

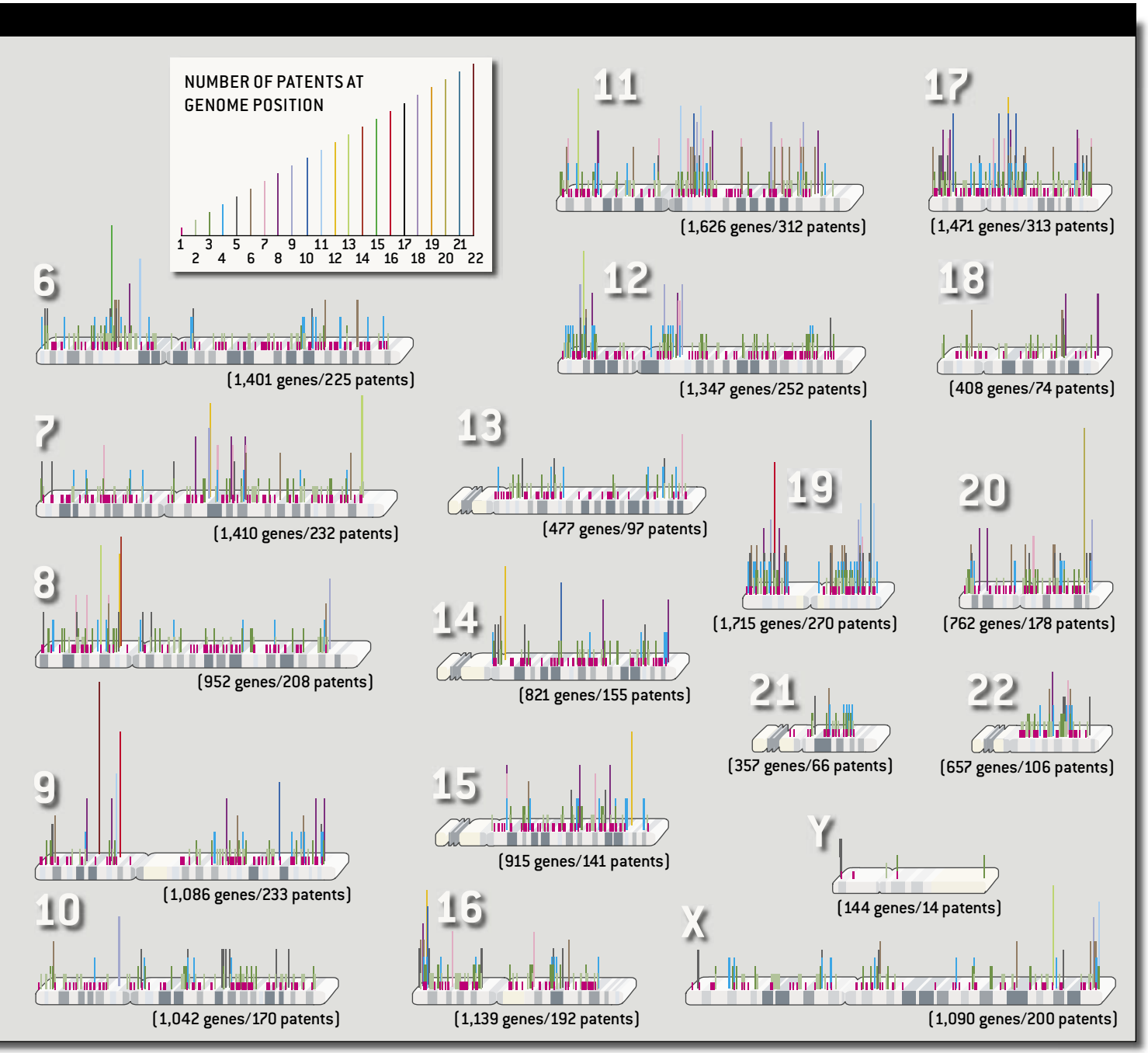
## THE HUMAN PATENTOME

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 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-

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—muddied 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.

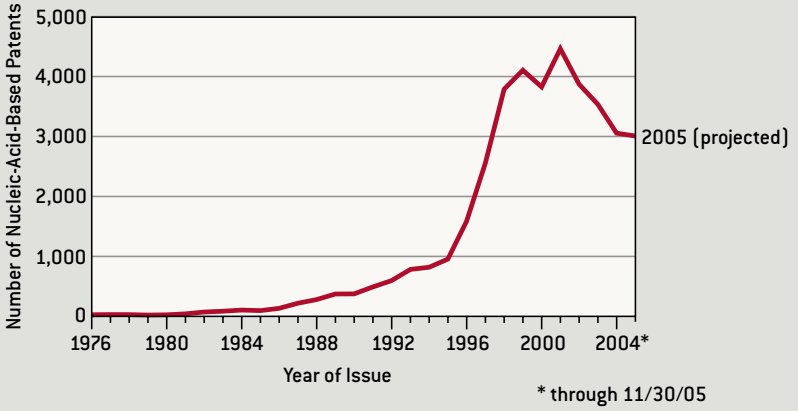
But a further, more intellectual objection to the concept of these patents was that the use of ESTs to pin down the location of genes actually occurs in a database, not in a laboratory. The value of ESTs exists more as information than as one of the tangible "processes, machines, manufactures and compositions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

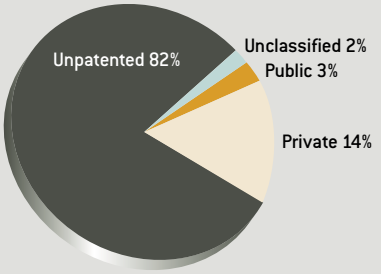
### YEARLY U.S. PATENTS RELATED TO DNA OR RNA

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 | 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*)

## 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*].

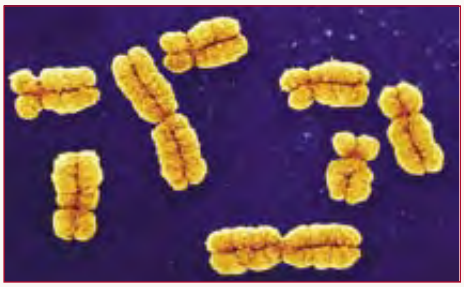
Some of the downturn may relate to the success of a de facto open-source movement in the biomedical sciences, akin to the one for information technologies. In 1996 scientists from around the world in both the public and private sectors devised what are referred to as the Bermuda Rules, which specify 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.

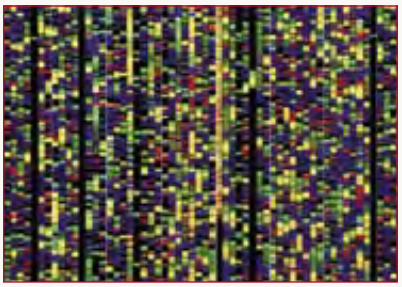
A patent thicket that blocks basic research has also failed to materialize because academics tend not to respect intellec-

**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

**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"

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 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)*

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

**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

**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

**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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SCIENCE MUSEUM/SCIENCE AND SOCIETY PICTURE LIBRARY (*mice*); REMY DE LA MAUVINIERE *AP Photo* (*chimera*)

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The New York Times

June 13, 2013

# Justices, 9-0, Bar Patenting Human Genes

By ADAM LIPTAK

WASHINGTON — Human genes may not be patented, the Supreme Court ruled unanimously on Thursday. The decision is likely to reduce the cost of genetic testing for some health risks, and it may discourage investment in some forms of genetic research.

The case concerned patents held by Myriad Genetics, a Utah company, on genes that correlate with an increased risk of hereditary breast and ovarian cancer. The patents were challenged by scientists and doctors who said their research and ability to help patients had been frustrated.

After the ruling, at least three companies and two university labs said that they would begin offering genetic testing in the field of breast cancer.

“Myriad did not create anything,” Justice Clarence Thomas wrote for the court. “To be sure, it found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention.”

The course of scientific research and medical testing in other fields will also be shaped by the court’s ruling, which drew a sharp distinction between DNA that appears in nature and synthetic DNA created in the laboratory. That distinction may alter the sort of research and development conducted by the businesses that invest in the expensive work of understanding genetic material.

The decision tracked the position of the Obama administration, which had urged the justices to rule that isolated DNA could not be patented, but that synthetic DNA created in the laboratory — complementary DNA, or cDNA — should be protected under the patent laws. In accepting that second argument, the ruling on Thursday provided a partial victory to Myriad and other companies that invest in genetic research.

The particular genes at issue received public attention after the actress Angelina Jolie revealed in May that she had had a preventive double mastectomy after learning that she had inherited a faulty copy of a gene that put her at high risk for breast cancer.

The price of the test, often more than $3,000, was partly a product of Myriad’s patent, putting it out of reach for some women.

That price "should come down significantly," said Dr. Harry Ostrer, one of the plaintiffs in the case, as competitors start to offer their own tests. The ruling, he said, "will have an immediate impact on people's health."

Myriad's stock price was up about 10 percent in early trading, a sign that investors believed that parts of the decision were helpful to the company. But the stock later dropped, closing the day down by more than 5 percent.

In a statement, Myriad's president, Peter D. Meldrum, said the company still had "strong intellectual property protection" for its gene testing.

The central question for the justices in the case, Association for Molecular Pathology v. Myriad Genetics, No. 12-398, was whether isolated genes are "products of nature" that may not be patented or "human-made inventions" eligible for patent protection.

Myriad's discovery of the precise location and sequence of the genes at issue, BRCA1 and BRCA2, did not qualify, Justice Thomas wrote. "A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated," he said. "It is undisputed that Myriad did not create or alter any of the genetic information encoded in the BRCA1 and BRCA2 genes."

"Groundbreaking, innovative or even brilliant discovery does not by itself satisfy the criteria" for patent eligibility, he said.

Mutations in the two genes significantly increase the risk of cancer. Knowing the location of the genes enabled Myriad to develop tests to detect the mutations. The company blocked others from conducting tests based on its discovery, filing patent infringement suits against some of them.

"Myriad thus solidified its position as the only entity providing BRCA testing," Justice Thomas wrote.

Even as the court ruled that merely isolating a gene is not enough, it said that manipulating a gene to create something not found in nature is an invention eligible for patent protection.

"The lab technician unquestionably creates something new when cDNA is made," Justice Thomas wrote.

He also left the door open for other ways for companies to profit from their research.

They may patent the methods of isolating genes, he said. "But the processes used by Myriad to

isolate DNA were well understood by geneticists," Justice Thomas wrote. He added that companies may also obtain patents on new applications of knowledge gained from genetic research.

Last year, a divided three-judge panel of a federal appeals court in Washington ruled for the company on both aspects of the case. All of the judges agreed that synthesized DNA could be patented, but they split over whether isolated but unaltered genes were sufficiently different from ones in the body to allow them to be protected. The majority, in a part of its decision reversed by the Supreme Court, said that merely removing DNA from the human body is an invention worthy of protection.

"The isolated DNA molecules before us are not found in nature," Judge Alan D. Lourie wrote. "They are obtained in the laboratory and are man-made, the product of human ingenuity."

Long passages of Justice Thomas's opinion read like a science textbook, prompting Justice Antonin Scalia to issue a brief concurrence. He said the court had reached the right result but had gone astray in "going into fine details of molecular biology."

"I am unable to affirm those details on my own knowledge or even my own belief," Justice Scalia wrote.

The ruling on Thursday followed a unanimous Supreme Court decision last year that said medical tests relying on correlations between drug dosages and treatment were not eligible for patent protection.

Natural laws, Justice Stephen G. Breyer wrote for the court, may not be patented standing alone or in connection with processes that involve "well-understood, routine, conventional activity."

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The New York Times

June 18, 2013

# Our Genes, Their Secrets

By ELEONORE PAUWELS

WASHINGTON — THE Supreme Court's unanimous ruling last Thursday, barring patents on human genes, was a wise and balanced decision that clears away a major barrier to innovation in the areas of biotechnology, drug development and medical diagnostics. But the decision is just a first step toward finding the right balance between protecting legitimate intellectual property and securing an open future for personalized medicine.

In Association for Molecular Pathology v. Myriad Genetics, the court ruled that "a naturally occurring segment" of DNA — genetic material that has been isolated from human chromosomes — cannot be patented because it is simply a product of nature. For policy wonks, the case was a David-and-Goliath fight, one of the most important patent cases in a decade, with an outcome sure to affect the $100 billion biotechnology industry, no matter how it was decided.

But while the Supreme Court's ruling has been welcomed enthusiastically by many, the Myriad case has been only a modest victory for the advocates of genetic-data sharing. Indeed, none of the underlying tensions have truly been resolved: we still need to find a way for the biotech industry to keep a competitive advantage without endangering the welfare of patients and slowing medication innovation.

In reality, gene patents were only one part of the problem. A more vexing, and still pressing, issue is how companies withhold genetic data as a trade secret.

The company at the heart of the case, Myriad Genetics, was awarded two patents in the late 1990s for the human genes BRCA1 and BRCA2 and offered an exclusive test to detect inherited mutations in them; certain variations in a copy of either one can markedly increase a person's risk of developing breast and ovarian cancers.

Since then, nearly one million patients have taken the Myriad test and have had their genetic data compiled in the company's proprietary database. That, in turn, has helped provide the company with an extraordinary informational advantage when it comes to interpreting patients' test results. While Myriad has published some research based on its findings and says it plans "to progressively release" more, for the most part it has designated its trove of patient data as confidential business

information: a trade secret.

Myriad was able to isolate the BRCA genes in the first place largely because it had access to government-financed public databases. But fairness aside, there are significant public health consequences when any one company gets to wall off such important human biological data from its competitors and, ultimately, from the public.

That information, stripped of any patient-identifying data, could be a boon to cancer researchers as they try to design optimal treatments for breast and ovarian cancer patients, based on the individual genetic "signatures" of their tumors. Such a trove could help scientists better understand the cancer process itself. It seems crazy to keep that potentially lifesaving knowledge away from the broad cancer research community.

Even before last week's Supreme Court decision, the importance of gene-related trade secrets, compared with that of outright patents, was clear. Myriad had already announced that it would begin, this fall, to replace its BRCA test with one that examines multiple genes implicated in hereditary cancers — most of which were outside the scope of its gene patents before Thursday's ruling. The new test, likewise, is expected to use complex proprietary algorithms, developed from its prodigious patient data, and therefore be largely protected from competition.

If anything, the court's decision may prompt biotech companies to rely even more heavily on that strategy than they do now — an unintended consequence that could stall research in many critical areas. Those with established beachheads on a gene-related disease or condition will be able to deter competition, much as they did before last Thursday's gene-patent ruling.

In the end, it will be patients and the public who pay.

We shouldn't wait as long to fix this problem as the Supreme Court waited to remedy its 1980 decision that enabled the patenting of human genes until now.

As a first step, the United States Food and Drug Administration should immediately investigate the impact of trade-secret protection on innovation in personalized medical treatments. The F.D.A. could also mandate public disclosure as a condition of market approval for genetic testing. Insurers too have some leverage: they could refuse reimbursements unless clinical data is shared for interpretation. But perhaps an even more effective remedy would be for scientific researchers themselves to get genetic information out into the public domain before any one company can call it a secret.

Ad hoc efforts in this regard, including that by the Personal Genome Project at Harvard Medical School, have already put an impressive amount of genetic and molecular information into open-access databases. But to make sure no company gets an exclusive hold on human genetic data, we need a data-disclosure effort that reaches critical mass.

On June 5, a consortium of 69 organizations in 13 countries made a great stride toward this end, agreeing to facilitate the sharing of DNA sequences and clinical information. But the effort still needs financing for researchers to work together on technical standards for sharing and interpreting genetic data. An annual public investment of just $1 million would be a start. Research funders like the National Institutes of Health could induce more institutions to join by asking grantees to abide by standards set by the consortium. This would help keep open-access efforts viable and help make sure no one company is able to keep an essential diagnostic test or treatment out of the public's reach.

*Eleonore Pauwels is a researcher with the Science and Technology Innovation Program at the Woodrow Wilson International Center for Scholars.*

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The New York Times

June 13, 2013

# After Patent Ruling, Availability of Gene Tests Could Broaden

By ANDREW POLLACK

Almost immediately after the Supreme Court ruled that human genes could not be patented, several laboratories announced they, too, would begin offering genetic testing for breast cancer risk, making it likely that that test and others could become more affordable and more widely available.

The ruling in effect ends a nearly two-decade monopoly by Myriad Genetics, the company at the center of the case.

“It levels the playing field; we can all go out and compete,” said Sherri Bale, managing director of GeneDx, a testing company, which plans to offer a test for breast cancer risk. “This is going to make a lot more genetic tests available, especially for rare diseases.”

Just how many other tests are affected is a bit unclear. Experts say there are not that many tests offered exclusively by one company because of patents.

But some other patents, like those on bacterial genes that might be useful in producing enzymes or biofuel, might also now be in jeopardy.

Still, biotechnology industry officials and patent lawyers said on Thursday that the decision should have little effect on the pharmaceutical industry and on developers of genetically engineered crops. That is partly because while the court held that isolated DNA could not be patented because it is a natural product, it did allow patenting of a more synthetic form of DNA that is more commercially valuable.

“The Supreme Court got it exactly right,” said Eric Lander, the president of the Broad Institute, a genetic research center affiliated with Harvard and M.I.T. “It’s a great decision for patients, it’s a great decision for science, and I think it’s a great decision for the biotechnology industry.”

It is not necessarily a great decision for Myriad Genetics, which held the patents on the two genes, called BRCA1 and BRCA2, at issue in the case.

Women with certain mutations in either of these genes have an extraordinarily high risk of developing breast or ovarian cancer. The actress Angelina Jolie, who has one of those mutations, recently had both breasts removed to sharply reduce the risk of getting cancer.

Myriad, which charges about $4,000 for a complete analysis of the two genes, had used its patents to keep others from offering such tests.

The company, based in Salt Lake City, said it did not anticipate any impact on its business from the decision, which it said affected only a small number of its patent claims.

“We have 24 patents, more than 500 patent claims, the vast majority of which are still valid and enforceable,” Richard Marsh, Myriad’s general counsel, said in an interview.

But the groups that sued Myriad and some testing laboratories said the patents that were invalidated were the main barriers to competition.

Besides GeneDx, which is a subsidiary of Bio-Reference Laboratories, others that said that they would offer testing of the BRCA genes include Ambry Genetics; the University of Washington; Montefiore Medical Center and Quest Diagnostics, the nation’s largest clinical laboratory company.

Mr. Marsh declined to say whether Myriad would try to enforce its remaining patents against any of these companies.

Robert Cook-Deegan, a research professor at Duke University’s Institute for Genome Sciences and Policy who has closely studied gene patenting, said he doubted that would happen.

“I think there might be some blustering or saber rattling, but I would be really surprised if they sue anybody for patent infringement for a diagnostic test,” he said.

Myriad’s stock initially shot up 10 percent after the court’s opinion was issued, but it then retreated as investors realized that competition would indeed be coming for BRCA testing, which accounted for about $132 million of Myriad’s $156 million in revenue in the most recent quarter. Myriad shares ended the day at $32.01, down 5.63 percent.

The company, however, had also faced other challenges from the rapid improvement and declining costs of gene sequencing.

“Many academic labs, including our own, will soon be offering panel tests for dozens, or even hundreds of genes, for the same price Myriad historically charged for just two genes,” said Dr.

Kenneth Offit, chief of the clinical genetics service at Memorial Sloan-Kettering Cancer Center.

Myriad itself has announced plans to phase out its BRCA gene tests by the middle of 2015 and replace them with a test that will analyze 25 genes that contribute to the risk of breast cancer and several other types of cancer. The price is expected to be similar to what the BRCA analysis costs now.

Also becoming more practical is whole genome sequencing. Some experts had feared that having numerous patents on individual genes would impede the ability to sequence and analyze a person's entire genome, though others doubted that. In any case, that threat is now removed.

Some experts say that other genetic tests that are exclusively controlled by a patent holder include the test for spinal muscular atrophy and the test for an inherited form of deafness.

Dr. Bale of GeneDx said the deafness gene also caused a skin disease. Her company is allowed to test for mutations that cause the skin disease, but if it discovers a mutation for hearing loss, it cannot tell the doctor. Instead, a new blood sample has to be drawn and sent to Athena Diagnostics, which controls the testing for the deafness gene. Dr. Bale said the court's decision should eliminate the need for that arrangement.

It is often said that patents cover 4,000 human genes, or about 20 percent of all human genes, meaning the decision could have a large impact.

But many of these patents were obtained in the genomics gold rush of the late 1990s and are either close to expiring or have been allowed to lapse for not being useful.

Moreover, said Christopher M. Holman, a biotechnology patent expert at the University of Missouri-Kansas City School of Law, many of the gene patents are actually patents on complementary DNA, or cDNA, which is essentially a gene with extraneous parts removed. The Supreme Court said cDNA was eligible for patenting because it was not naturally occurring.

Complementary DNA is commercially valuable because it is generally used to genetically engineer a cell, a plant or an animal.

Still, the Supreme Court ruling could have some broader effects — on bacterial genes, for example. An analysis in Nature Biotechnology in May concluded that more than 8,000 genes might be at risk in the Myriad decision, less than half of which were human genes.

It is also possible that the decision could make it hard to patent things other than genes that are

isolated from natural products, like drugs derived from microorganisms or plants.

Patents on human genes are “almost yesterday’s I.P.” said Hans Sauer, deputy general counsel for the Biotechnology Industry Organization, a trade group, using the abbreviation for intellectual property. But inability to patent bacterial genes could slow innovation, he said.

“Paradoxically enough,” he said, “the case bites harder in areas that have the least to do with human genes.”

VIEWPOINT

# The Future of Gene Patents and the Implications for Medicine

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**On June 13, 2013,** in *Association for Molecular Pathology v Myriad Genetics Inc*, the US Supreme Court unanimously ruled that naturally occurring genes cannot be patented. Synthetic transcripts of genes, however, can be patented.[1] The case involved patent claims covering *BRCA1* and *BRCA2*; mutations in these genes are linked to an increased risk for breast and ovarian cancer. Both sides quickly claimed victory. Harry Osterer, MD, a clinician and one of the plaintiffs, declared that the Court's decision would help society "feel more of the impact of the genomics revolution."[2] The Biotechnology Industry Organization claimed that the decision left intact patents on the synthetic transcripts, "the commercially most important form of DNA used in biotechnology."[3] On the day the decision was announced, Myriad Genetics stock initially jumped 12% but finished down 6%. So what does this decision really mean, for both patent law and medicine?

The *Myriad* decision concerned one particular legal doctrine in patent law, termed "patentable subject matter" or "patent eligibility." Simply put, a patent can be granted only to someone who "invents or discovers" a "new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof."[4] Historically, courts and the US Patent and Trademark Office have interpreted these terms broadly to encompass "anything under the sun made by man." This has not included "laws of nature," "natural phenomena," "abstract ideas," or "products of nature."[5] Yet, a famous 1911 lower court decision concluded that "products of nature" may constitute patentable subject matter if they were "isolated and purified" from their surroundings.[6] Precisely what constitutes a "product of nature," or the propriety of this "isolated and purified" exception, has long been a puzzle. Nonetheless, human genes have been eligible for patent protection since at least 1982 under the theory that they were "isolated and purified" from their surrounding chromosomes. The *Myriad* case is the first time the Supreme Court addressed this practice.

In *Myriad*, the Court considered 2 types of patent claims for human genes. The first type covered "isolated genomic DNA," that is, DNA fragments of various sizes that have simply been removed from the surrounding genome. The second type were claims directed to "complementary DNA" (cDNA), specifically, reverse transcripts of messenger RNAs (mRNAs). The Court ruled that claims on isolated genomic DNA were not patent eligible—even if the genomic DNA were "isolated and purified" from the surrounding chromosome. Claims for cDNA, however, were patent eligible.

The Court's decision primarily focused on whether either type of DNA existed as such in nature. Because the Court viewed isolated genomic DNA as a stretch of DNA simply excised from a larger chromosomal region, it concluded this was more like a "product of nature" than "a product of human ingenuity."[1] These DNAs did not have "a distinctive name, character [and] use," nor did they possess "markedly different characteristics from any found in nature."[1] Although the Court was careful not to negate Myriad's work in sequencing the *BRCA* genes, it declared that "separating [a] gene from its surrounding genetic material is not an act of invention"[1] and that "[g]roundbreaking, innovative, or even brilliant discovery does not by itself satisfy"[1] patent eligibility. Under these circumstances, the Court was reluctant to extend the "isolated and purified" doctrine, despite its historical pedigree. Therefore, claims on isolated genomic DNA are now patent ineligible because they are "products of nature."[1]

But cDNA does not exist, as such, in nature. Even though the "nucleotide sequence of cDNA is dictated by nature," in mRNA transcripts, "the lab technician unquestionably creates something new when cDNA is made," according to the Court.[1] Thus, claims on cDNA are potentially patentable, although, as the Court noted, other legal doctrines might still bar patenting of cDNA sequences in some cases. For example, patents covering cDNA sequences, although *eligible* for patent protection, might still not be patentable, if obvious or if previously disclosed elsewhere.

One result of *Myriad* is fairly clear: testing for *BRCA* genes should be cheaper. Within hours after the decision, several companies announced that they would offer *BRCA1* and *BRCA2* testing for much less than Myriad's then-current prices. Myriad has charged as much as $4100 for full-sequence testing; some competitors have announced prices in the range of $1000 to $2200 for the same level of testing. These price declines will probably stick. Because Myriad's cDNA claims cover only testing methods that require the creation of cDNA, other companies will be able to compete with Myriad using newer sequencing technology that does not involve cDNA. (Myriad's claims for the method of assessing breast cancer risk based on *BRCA1* and *BRCA2* sequences were struck down at an earlier stage of the case.) Myriad will likely lower its prices for *BRCA* testing as it responds to the competition, although not without a fight; on July 10, 2013, Myriad sued one of its new *BRCA* testing competitors for patent infringement.

Yet, it remains to be seen just how much more widely available *BRCA* testing will be. Although Myriad no longer has a monopoly on sequencing the genes, it does have an extensive—and exclusive—database of its past customers' mutations. That database may help Myriad determine whether a patient with an unusual genetic variation has a higher risk of cancer or not, although patients with either wild-type *BRCA* sequences

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or well-known mutations will likely not need the added precision that the database can provide. In addition, others are actively trying to replicate Myriad's database of mutations.

What the *BRCA* testing landscape would have looked like if the Court had upheld all of Myriad's patent claims is unclear. The now-invalid claims for the most basic of Myriad's patents would have expired in February 2016, and new testing technologies might have produced *BRCA* tests that would not have infringed on those patents anyway.

What about the world beyond *BRCA*? Thousands of genes have been patented, and thousands of genetic tests are available, but almost no genetic tests have caused patent controversies. For example, the gene involved in Huntington disease, *HTT*, has long been patented, but there have been few complaints about Huntington's testing because the patents were either not asserted or licensed nonexclusively and on easy terms.[7] The "gene patent problem" has been almost entirely a Myriad Genetics problem. Other firms that might have been tempted to enforce their gene patents aggressively would have confronted the same impending patent expirations and noninfringing technological advances that Myriad faces now. Thus, although the Court's decision brings some reassurance to those worried that hundreds of patents might be asserted against broad gene-sequencing technologies, that risk never seemed great. The end of Myriad's monopoly on *BRCA* testing is to be applauded, but the Court's decision is likely to have only have limited effects on genetic testing.

Will the *Myriad* decision chill investment in genetic research? Probably not. Fewer and fewer researchers have been receiving patents for isolated genomic DNA sequences. Many gene researchers are publicly funded, and many researchers are not substantially motivated by the potential for profits. Synthetically created, novel, nonobvious DNA sequences—important for purposes other than diagnostic testing, such as for creating recombinant biological products—are still eligible for patents, although it is not clear how important those patents might be. Nonetheless, some interpretations of the Court's decision might chill pharmaceutical research. If, for example, a drug company discovers a medically important molecule naturally produced by a fungus, the decision might prohibit the firm from patenting the molecule itself. But the company still should be able to patent medicinal uses of that molecule, as well as useful variations made in a laboratory. And, if the company shepherds that new chemical entity through FDA approval, the approval will include the exclusive right to sell the drug for 5 years.

In fact, on July 2, 2013, public interest organizations filed their brief in the appeal of their suit, *Consumer Watchdog v WARF*, to invalidate claims to human embryonic stem cells in patents of the Wisconsin Alumni Research Foundation. The appellate brief argues, among many other things, that the cells are "products of nature" and thus not patent eligible under the Myriad decision. It is not at all clear that those arguments will prevail, but it is more evidence that the decision will be good for the patent litigation business.

So what does the *Myriad* decision ultimately mean? In the short term, it means more competitive markets for diagnostic genetic testing, at least for testing for *BRCA1* and *2*. But in the long term, probably not very much.

ARTICLE INFORMATION

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