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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.

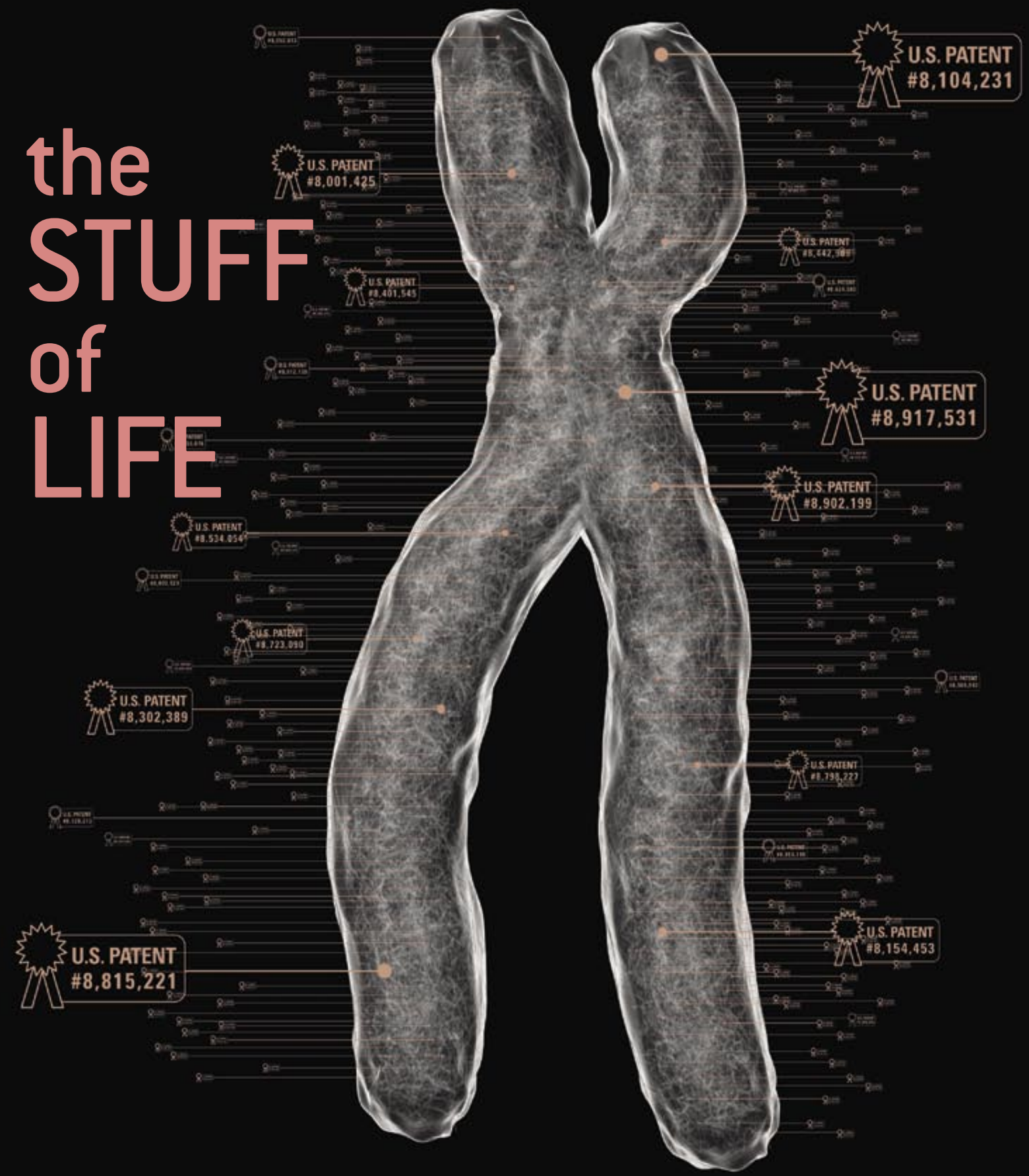
Anything under the Sun

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.

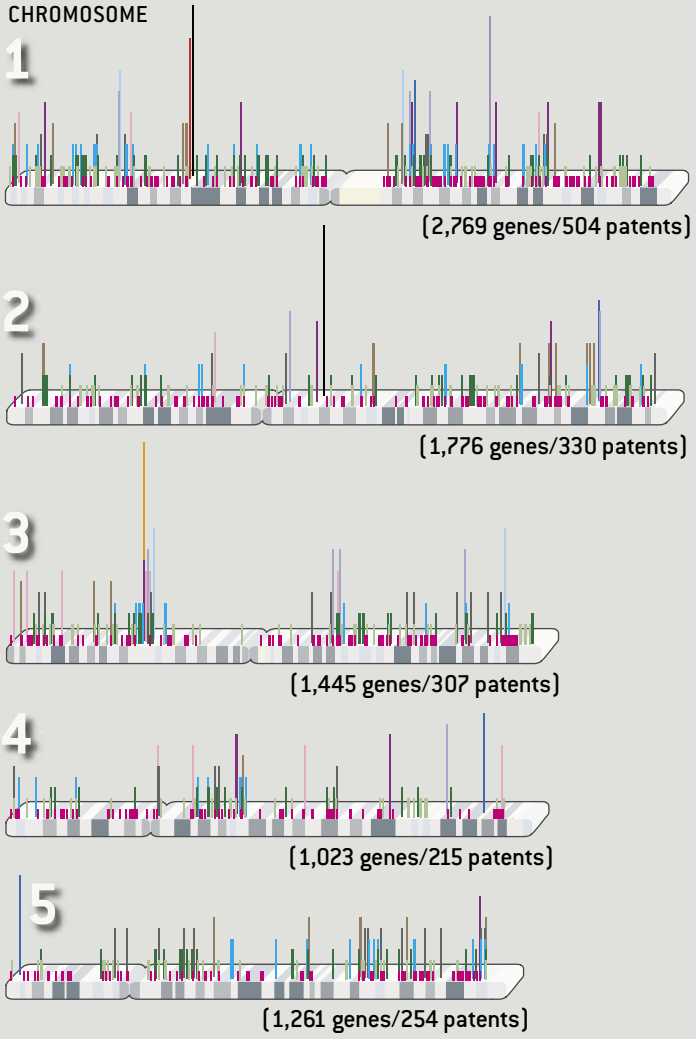
The Supreme Court justices received friend-of-the-court briefs arguing both for and against granting the claims in the Chakrabarty patent. Groups ranging from Genentech to the Regents of the University of California urged that the patent application be granted, citing benefits for pharmaceutical development,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

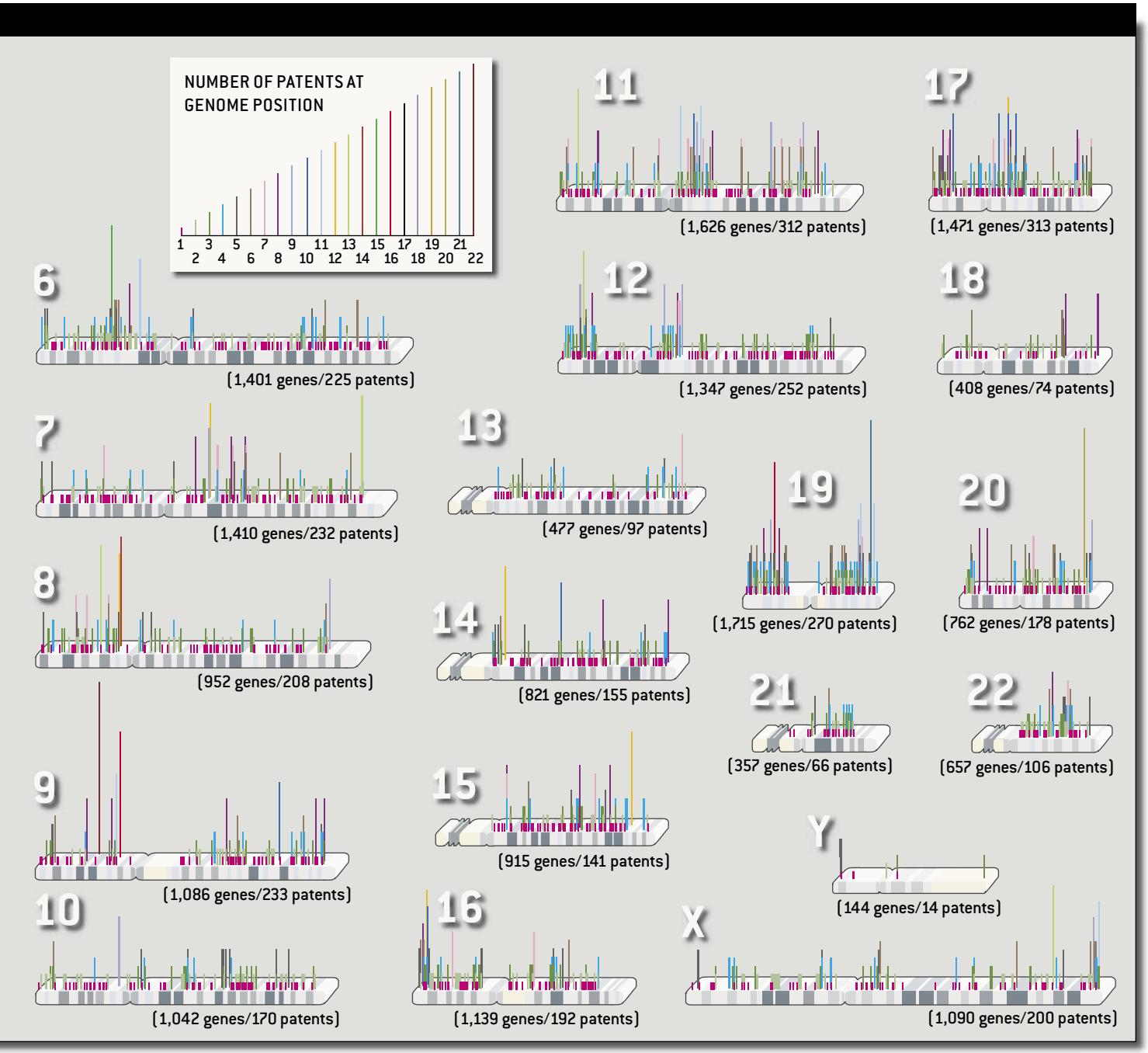
THE HUMAN PATENTOME

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.

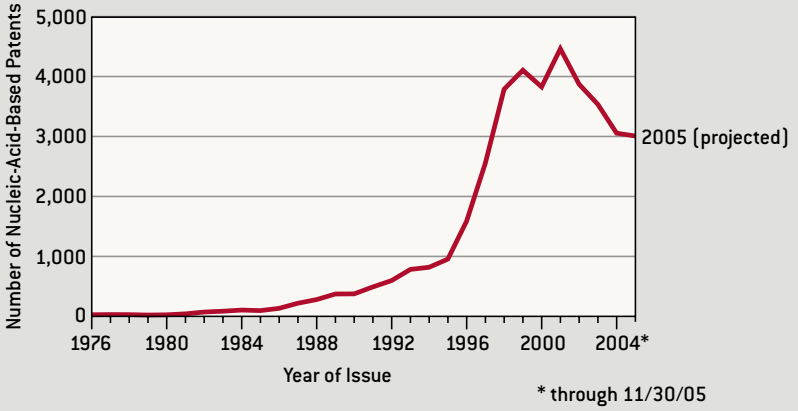
But a further, more intellectual objection to the concept of these patents was that the use of ESTs to pin down the location of genes actually occurs in a database, not in a laboratory. The value of ESTs exists more as information than as one of the tangible "processes, machines, manufactures and compositions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

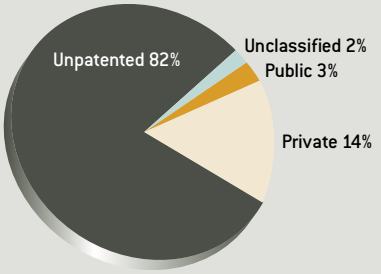
YEARLY U.S. PATENTS RELATED TO DNA OR RNA

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*].

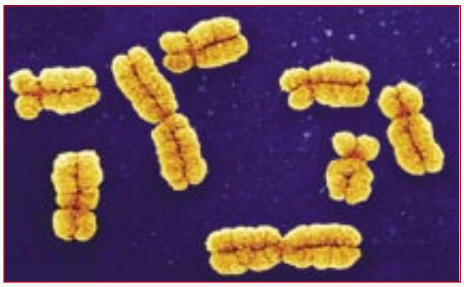
Some of the downturn may relate to the success of a de facto open-source movement in the biomedical sciences, akin to the one for information technologies. In 1996 scientists from around the world in both the public and private sectors devised what are referred to as the Bermuda Rules, which specify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

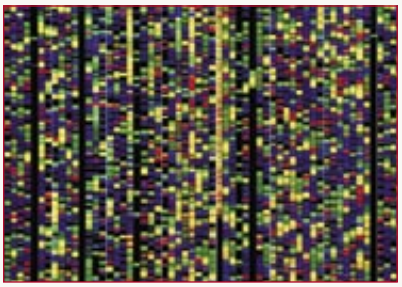
A patent thicket that blocks basic research has also failed to materialize because academics tend not to respect intellec-

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

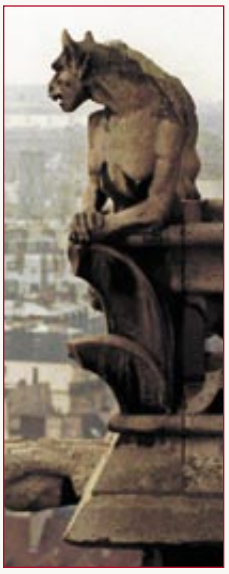
Heads of state Bill Clinton and Tony Blair issue a statement that "raw fundamental data on the human genome, including the human DNA sequence and its variations, should be made freely available to scientists everywhere." Biotechnology stocks drop sharply

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

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.

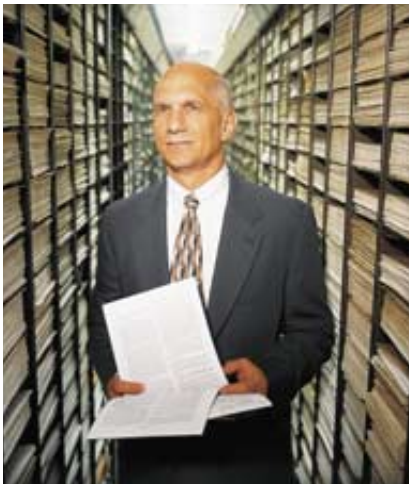
SCIENCE MUSEUM/SCIENCE AND SOCIETY PICTURE LIBRARY (*mice*); REMY DE LA MAUVINIERE *AP Photo* (*chimera*)

Talking Gene Patents

JOHN J. DOLL, director of biotechnology for the U.S. Patent and Trademark Office, tells SCIENTIFIC AMERICAN about granting exclusive rights to make, sell and use a gene

The idea of patents on genes is still inherently counterintuitive to some people. Would you explain briefly why genes are patentable?

Genes are complex organic molecules, and when you isolate and purify them from the chromosomes where they reside, they are eligible to be patented as chemical compounds. And that is the extent of the patent protection that is given. We're not giving patents on whole chromosomes, and we certainly don't give patents on anything as it exists in nature.



How many genes have been patented in the U.S., and how many applications for patents are still outstanding?

The only number that I have is a guesstimate: since 1980 we have granted more than 20,000 patents on genes or other gene-related molecules [for humans and other organisms]. And we also know that we have more than 25,000 applications outstanding that actually claim genes or related molecules.

Can you describe why you recently tightened the rules for gene patent applications?

The four main criteria for getting a patent are that the invention must have a utility; it must have an adequate written description; it must be nonobvious to one of ordinary skill in that particular field; and it must not have been done exactly before. The biggest hurdle that genomic inventions face is the utility standard.

In 1995 we issued guidelines, and we very clearly stated that if you had a secreted protein from a gene and you didn't know what role it played in disease or the diagnostics of disease, but the protein was secreted in a diseased cell line [breast cancer cells, for instance], you could use that protein as an additive in a shampoo. You could have done that, and we would have allowed you to cross the utility hurdle for getting a patent. So that if anybody else wanted to make, use, sell or import into the United States this protein, your patent rights could be used to stop any of those actions.

That is the major change instituted by the new utility guidelines. We've gotten rid of proteins being used as shampoo additives or proteins being used as animal food or nutritional supplements. We've gotten rid of transgenic mice being used as snake food. And that is exactly what the utility bar has been raised to do—to exclude throwaway utilities and to make sure that when you have a genomic-type invention that you have a real-world and specific utility that is credible.

One of the major findings of the Human Genome Project was just how common it is for a gene to code for multiple proteins. What if someone applies for a patent for a gene that expresses a particular protein and someone else applies for a patent for the same gene coding for another protein? Does the owner of a gene patent have rights to all the proteins expressed by a gene?

When you have a patent on a particular gene, it's made up of a series of nucleotide sequences called exons that code for a particular protein. Let's say you have six blocks of exons that came together to express a particular protein. Under a different condition in that cell line, maybe all six of the exons don't function. So now there are maybe four blocks of exons that come together to express a totally different protein. That new set of exon blocks would be a separate patentable invention, and the people who had the patent to the first six would not gain exclusive rights to the protein expressed by the four new blocks of exons. SA

Please let us know about interesting or unusual patents. Send suggestions to: patents@sciam.com

KATHERINE LAMBERT

July 29, 2011

Ruling Upholds Gene Patent in Cancer Test

By ANDREW POLLACK

In a closely watched case, a federal appeals court ruled on Friday that genes can be patented, overturning a lower court decision that had shocked the biotechnology industry.

The Court of Appeals for the Federal Circuit, which specializes in patent cases, said that Myriad Genetics was entitled to patents on two human genes used to predict if women have an increased risk of getting breast and ovarian cancer.

The court ruled that DNA isolated from the body was eligible for patents because it was "markedly different" in its chemical structure from DNA that exists inside the chromosomes in the body. As a result, the isolated DNA is not simply a product of nature, which would not be eligible for a patent.

The 2-to-1 decision on the gene patenting issue was also a rejection of arguments made by the Obama administration, which had filed a friend of the court brief arguing that isolated DNA should not be patented. That brief went against the long-standing policy of the United States Patent and Trademark Office to grant such patents.

The appeals court ruled against Myriad in another part of the case, however. The court said that Myriad's patent claims on the process of analyzing whether a patient's genes had mutations that raised the risk of cancer was not patentable because it involved only "patent-ineligible abstract mental steps."

The case may eventually reach the Supreme Court.

The decision on the patentability of genes and DNA cheered much, though not all, of the biotechnology industry. Thousands of human genes have been patented, and some biotechnology executives say such patents are essential for encouraging innovation.

"It basically adhered to the policy the Patent Office has pursued since the early '80s, when the

biotech industry was born," said Gerald J. Flattmann Jr., a patent lawyer at Paul Hastings in New York, who represents pharmaceutical companies but was not involved in this case. "Isolated gene patents are the cornerstone of the biotechnology industry."

Critics say it is unethical to patent something that is part of the human body or the natural world. Some also say that the cost of testing might be reduced if companies did not hold testing monopolies because of their patents. Myriad, which holds the patents on the genes called BRCA1 and BRCA2 with the University of Utah Research Foundation, charges more than $3,000 for its breast cancer risk test.

A lawsuit challenging the patents on the breast cancer risk genes was filed in 2009 by the American Civil Liberties Union and the Public Patent Foundation, acting as the lawyers for various cancer patients, medical researchers and medical societies.

In an opinion issued in March 2010, United States District Judge Robert W. Sweet in Manhattan ruled the patents were invalid. The importance of DNA, he said, was the information content it carried in terms of how proteins should be made. In that aspect, he said, the isolated DNA was not really different from the DNA in the body. The argument that isolating the DNA made it different, he said, was just "a lawyer's trick."

But the appellate decision Friday rejected Judge Sweet's reasoning, saying that since DNA is a chemical, the chemical structure is what matters and that "informational content is irrelevant to that fact."

"The claims cover molecules that are markedly different — have a distinctive chemical identity and nature — from molecules that exist in nature," Judge Alan D. Lourie wrote for the court.

Peter D. Meldrum, chief executive of Myriad, said Friday that he was "absolutely delighted with the ruling." He said the patent claims that the court ruled invalid were not important and that patent protection for the company's test was as strong as before the lawsuit was filed.

Daniel B. Ravicher, executive director of the Public Patent Foundation, which helped file the suit, called the decision a partial victory for the plaintiffs. Noting that one judge dissented on the gene patents, he said, "They can't agree among themselves."

Mr. Ravicher said the plaintiffs were considering either asking the entire appellate court to rehear the gene patenting aspects of the case or appealing to the Supreme Court.

While Judge Lourie's opinion spoke for the court, the other two judges wrote their own opinions.

Judge Kimberly A. Moore agreed that genes were patentable but cited somewhat different reasoning, including that only Congress should change Patent Office policy to grant such patents.

"Judicial restraint is particularly important here because an entire industry developed in the decades since the Patent Office first granted patents to isolated DNA," Judge Moore wrote. "Disturbing the biotechnology industry's settled expectations now risks impeding, not promoting, innovation."

But the third judge on the panel, William C. Bryson, dissented, saying that the genes should not be patented just because they were isolated from the body. In some respects, he wrote, "extracting a gene is akin to snapping a leaf from a tree."

Judge Lourie, in the prevailing opinion, rejected that analogy, saying that isolating DNA created a new chemical entity. It was not simply a matter of separating or purifying the DNA, he said, and not like snapping off a leaf or extracting a mineral from the earth.

The patent claims that the appellate court ruled invalid involved analyzing a patient's genes to see if they had deleterious mutations. Many diagnostic tests involve analyzing some gene or chemical in the body, and whether such tests can be patented is an issue that the Supreme Court has agreed to consider in another case.

Lisa A. Haile, a patent lawyer at DLA Piper in San Diego who is not involved in the Myriad case, said the appeals court on Friday suggested Myriad's claims would have been upheld if there was another step, such as sequencing the genes, in addition to just mental steps.

"You can't say diagnostic claims aren't patentable," Ms. Haile said. "It's just the way these claims were written."

The New York Times

November 30, 2012

Supreme Court to Look at a Gene Issue

By ADAM LIPTAK

WASHINGTON — The Supreme Court announced on Friday that it would decide whether human genes may be patented. The justices considered but took no action on requests that the court hear one or more cases concerning same-sex marriage.

The case the court added to its docket concerns patents held by Myriad Genetics, a Utah company, on genes that correlate with increased risk of hereditary breast and ovarian cancer.

The patents were challenged by scientists and doctors who said that their research and ability to help patients had been frustrated. “Myriad and other gene patent holders have gained the right to exclude the rest of the scientific community from examining the naturally occurring genes of every person in the United States,” the plaintiffs told the Supreme Court in their petition seeking review. They added that the patents “prevent patients from examining their own genetic information” and “made it impossible to obtain second opinions.”

The legal question for the justices is whether isolated genes are “products of nature” that may not be patented or “human-made inventions” eligible for patent protection.

A divided three-judge panel of a federal appeals court in Washington ruled for the company. Each judge issued an opinion, and a central dispute was whether isolated genes are sufficiently different from ones in the body to allow them to be patented.

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

The company urged the justices not to hear the case, saying that the “isolated molecules” at issue “were created by humans, do not occur in nature and have new and significant utilities not found in nature.” It has long been settled, the company’s brief went on, that “the human ingenuity required to create isolated DNA molecules” is worthy of encouragement and that its fruits are worthy of protection.

The plaintiffs in the case, Association of Molecular Pathology v. Myriad Genetics, No. 12-398, were

supported by friend-of-the-court briefs filed by the American Medical Association, AARP and women's health groups.

The justices were also scheduled to consider on Friday 10 closely watched appeals in cases concerning same-sex marriage, but they gave no indications about which ones, if any, they will hear. It is not unusual for the justices to discuss petitions seeking their attention more than once, particularly when the cases present complex and overlapping issues.

The court is widely expected to agree to hear one or more cases on the constitutionality of the part of the federal Defense of Marriage Act of 1996 that forbids the federal government from providing benefits to same-sex couples married in states that allow such unions.

The court has also been asked to hear cases about Proposition 8, the ballot initiative that banned same-sex marriage in California, and an Arizona measure that withdrew state benefits from both gay and straight domestic partners.