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.

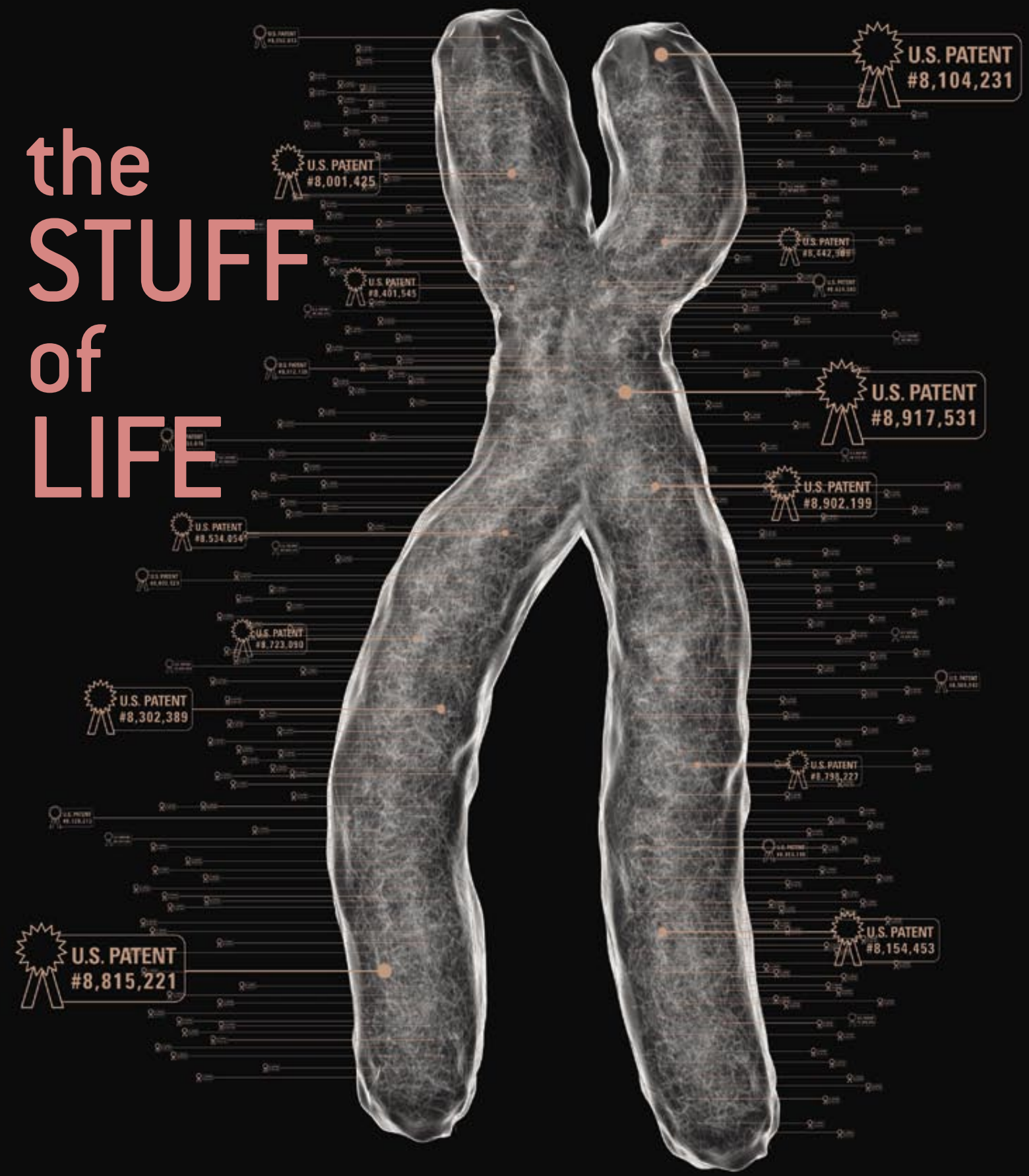
Anything under the Sun

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.

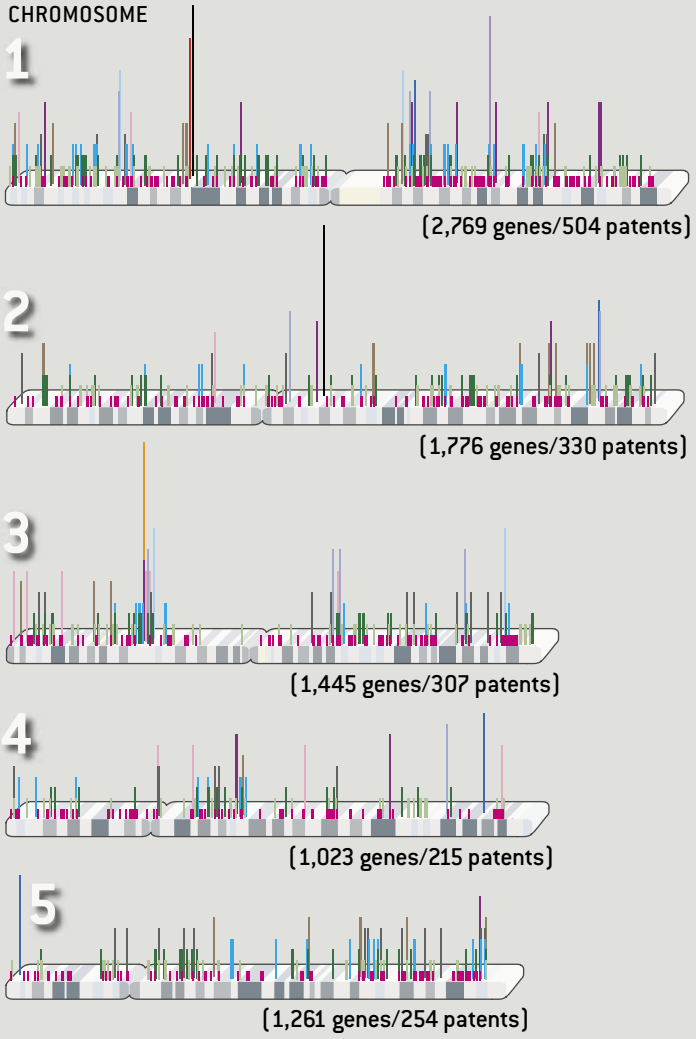
The Supreme Court justices received friend-of-the-court briefs arguing both for and against granting the claims in the Chakrabarty patent. Groups ranging from Genentech to the Regents of the University of California urged that the patent application be granted, citing benefits for pharmaceutical development,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

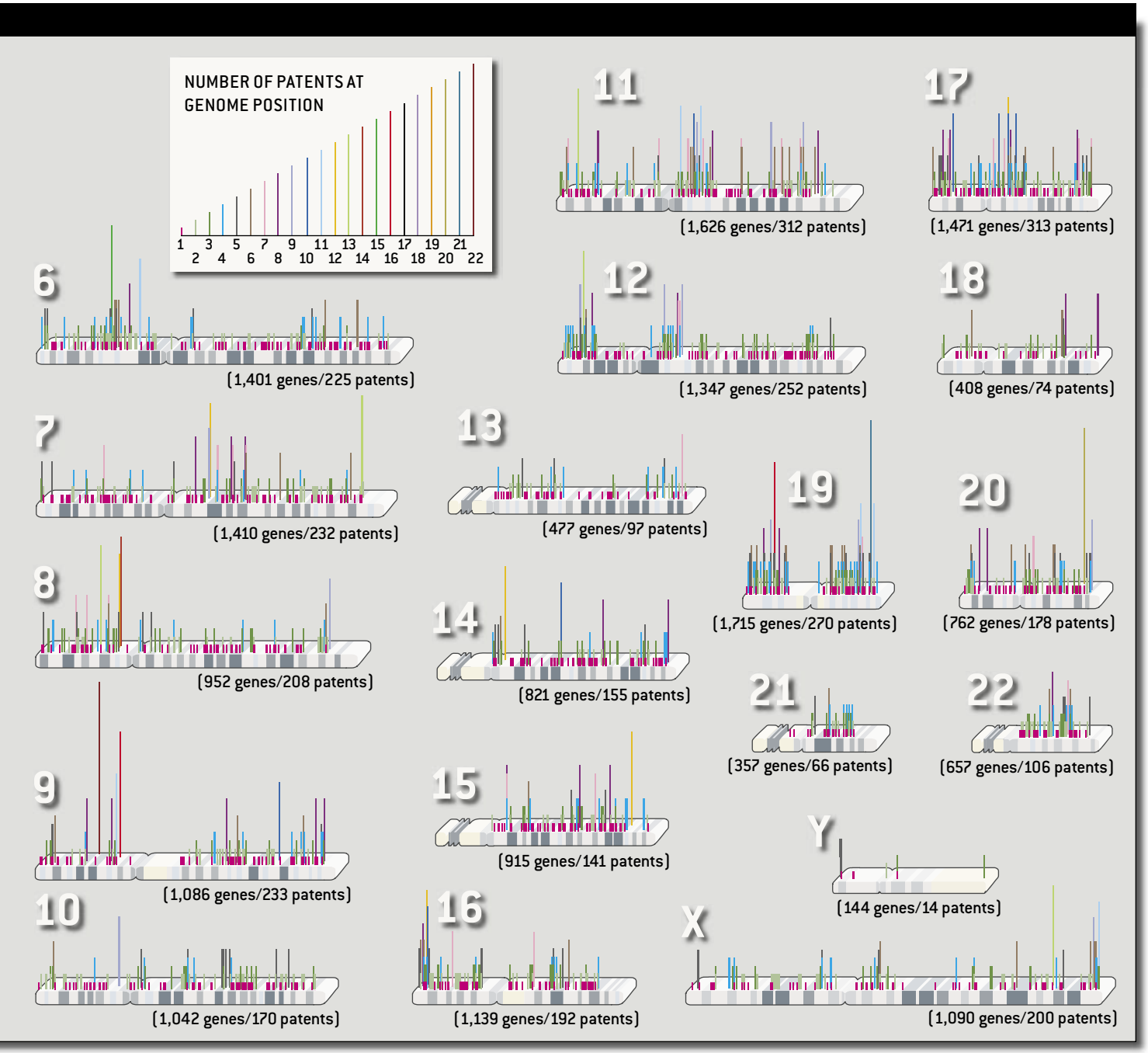
THE HUMAN PATENTOME

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.

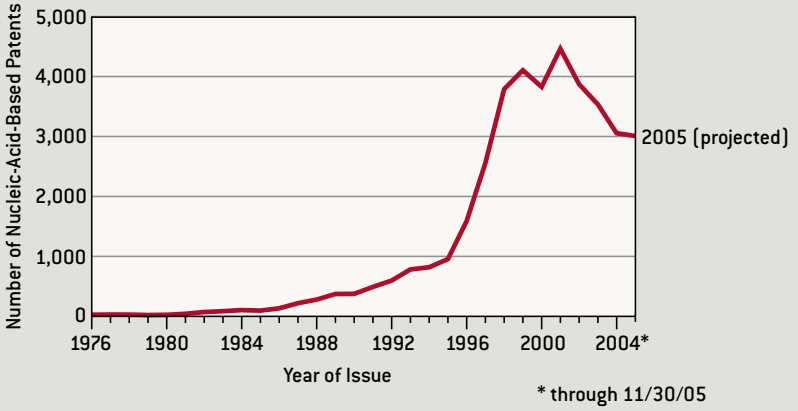
But a further, more intellectual objection to the concept of these patents was that the use of ESTs to pin down the location of genes actually occurs in a database, not in a laboratory. The value of ESTs exists more as information than as one of the tangible "processes, machines, manufactures and compositions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

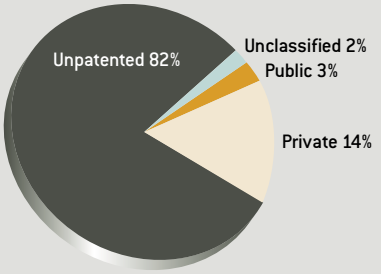
YEARLY U.S. PATENTS RELATED TO DNA OR RNA

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*].

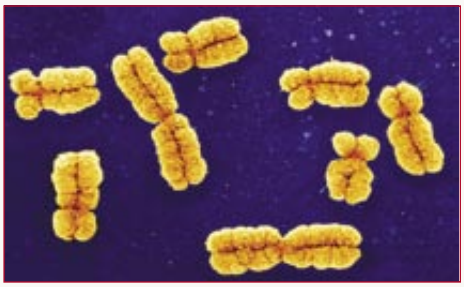
Some of the downturn may relate to the success of a de facto open-source movement in the biomedical sciences, akin to the one for information technologies. In 1996 scientists from around the world in both the public and private sectors devised what are referred to as the Bermuda Rules, which specify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

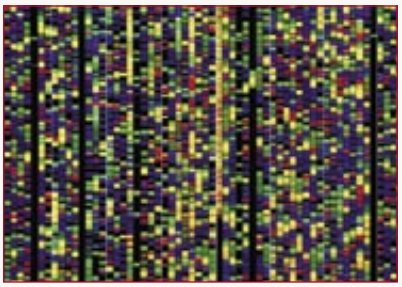
A patent thicket that blocks basic research has also failed to materialize because academics tend not to respect intellec-

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

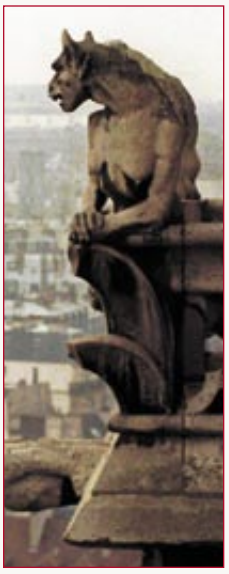
Heads of state Bill Clinton and Tony Blair issue a statement that "raw fundamental data on the human genome, including the human DNA sequence and its variations, should be made freely available to scientists everywhere." Biotechnology stocks drop sharply

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*)

The New York Times

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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."

CRISPR Patent Fight Now a Winner-Take-All Match

by Antonio Regalado April 15, 2015

Lab notebooks could determine who was first to invent a revolutionary gene-editing technology.

In a legal maneuver with billion-dollar implications, the University of California has asked the U.S. Patent & Trademark Office to decide who was first to invent a powerful gene-editing tool called CRISPR-Cas9.

In a request filed Monday, the regents of California's public university system asked the patent agency to reconsider ten patents issued starting last year to the MIT/Harvard Broad Institute, in Cambridge, Massachusetts, saying the hugely valuable rights should belong to them.

The technology, called CRISPR-Cas9, acts as a kind of molecular scissors, cutting and replacing DNA letters in an organism's genome with exquisite precision and ease. The technique is revolutionizing the study of species from mice to potatoes, and is likely to open powerful new avenues in gene therapy to treat human disease as well (see "Genome Surgery").

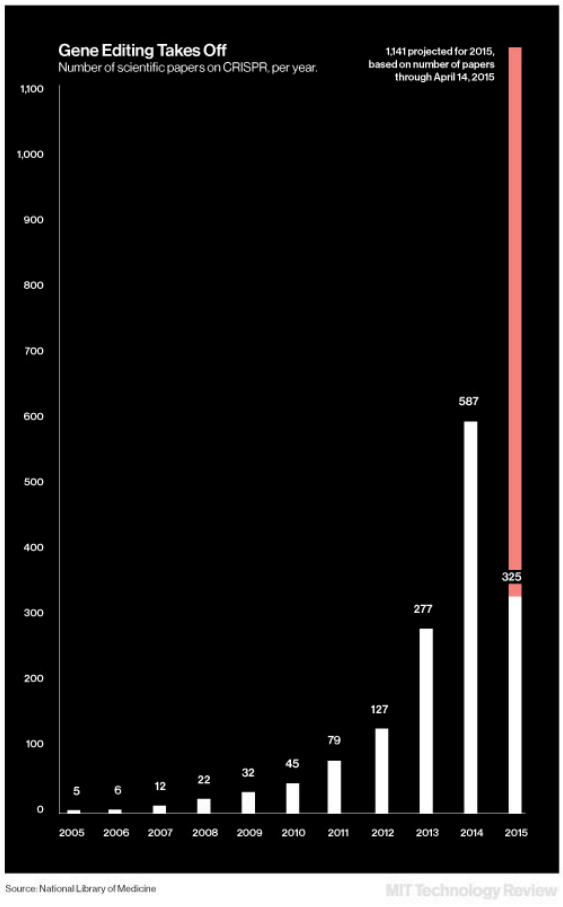
If the patent office approves it, the request for a "patent interference," as the process is known, sets up a winner-takes-all challenge in which either the Broad Institute, or the University of California and two co-petitioners, including the University of Vienna, will come away with all the rights to the gene-editing system, leaving their rival with nothing.

"Expect this battle to be very expensive, very contentious, given the stakes involved," says Greg Aharonian, director of the Center for Global Patent Quality, which works on patent issues. "I can see many hundreds of thousands of dollars being spent."

The CRISPR-Cas9 editing technology was publicly described in the journal Science in 2012 by Jennifer Doudna, a biologist at the University of California, Berkeley, and

the French microbiologist Emmanuelle Charpentier. But Feng Zhang, a scientist at the Broad Institute, was first to win a patent on the technique after submitting lab notebooks he says prove he invented it first (see “Who Owns the Biotech Discovery of the Century?”).

The system uses a cutting protein, Cas9, attached to a short RNA molecule that guides it to precise locations in a genome. Already, scientists have used it to disable HIV, cure muscular dystrophy in mice, and make wheat that’s resistant to crop diseases.



Under current rules, known as “first to file,” patent rights go to whoever submits a patent application first. That would mean an easy victory for Doudna and Charpentier, because their earliest application is dated May 2012, seven months before Zhang’s. But because of the dates of the discoveries, the case is being carried out under older “first to invent” rules, where the winner is whoever is able show—by any means—they were first to make an invention work, or simply conceive of it. “That person gets the patent,” says Aharonian.

Some experts say the confusion around CRISPR patents is slowing down commercial efforts. Tom Adams, vice president of global biotechnology at Monsanto, says his company had begun working with the technology to create plants with useful traits, but remained reluctant to employ it widely. “It’s a very complicated set of inventions,” says Adams. “Until we understand the intellectual property it’s hard to do much.”

If products or treatments are delayed, the high-profile legal fight could end up reflecting badly on the universities, who all used public tax dollars or philanthropic gifts to make the inventions.

UC Berkeley’s technology transfer office declined to comment, citing the legal case, as did Doudna. A spokesperson for the Broad Institute, Paul Goldsmith, said that Broad has made “repeated efforts and trips since the beginning of 2013 to resolve this situation outside the legal system.”

Other technology disputes have been resolved by creating patent pools which offer wide access to basic innovations, or via cross-licensing. But that hasn’t happened yet with CRISPR-Cas9, precisely because it’s not clear who really owns the key rights. “It would be mutually beneficial to develop as many products as possible with the technology, because it’s the products that will generate the revenue,” says Dan Voytas, a gene-editing researcher at the University of Minnesota. “With CRISPR, it’s still anyone’s guess how it’s going to work out.”

The patent dispute started last April when Zhang, a scientist at the Broad, appeared as the lone inventor on a broad patent covering CRISPR-Cas9. To win it, he filed a declaration with the patent office saying he’d invented the idea on his own and offered lab notebooks to back up the claim. Zhang told MIT Technology Review in December that other evidence, like grant applications and correspondence, could offer further proof.

But lawyers for UC Berkeley, in counterclaims filed with the patent office this week, say pages and diagrams from Zhang’s lab notebooks show only some related experiments, and don’t prove he invented the system. “Dr. Zhang is wrong,” they conclude. Their conclusions rely, in part, on a technical analysis provided to the patent office by Dana Carroll, a gene-editing expert at the University of Utah. (A copy of the interference request is here, not including more than 100 exhibits.)

Broad says it will stick to its position. “It’s hardly shocking that Berkeley’s lawyers support Berkeley’s claim,” says Broad lawyer Ellen Law. “In fact, Dr. Zhang’s notebooks make it clear his invention of CRISPR-Cas9 dates back to 2011.”

Both Zhang and Doudna devote substantial time and effort to supporting and publicizing CRISPR. Doudna stars in an explanatory video being passed around social media sites, while Zhang’s lab has set up a website and made laboratory materials widely available to other scientists.

The stakes involved are huge. Not only does a Nobel Prize for gene editing seem likely, but several heavily financed startups have been created to start developing gene-therapy treatments. Zhang is involved in Editas Medicine, Doudna's startup is called Caribou Biosciences, and Charpentier is a founder of CRISPR Therapeutics. The number of scientific publications on the technique has also been skyrocketing, and is likely to surpass 1,100 this year.

Ryan Honick, a spokesman for the patent office, says interference proceedings are decided by a special board of examiners, which hears evidence in about 100 cases a year. The process can take as much as two years to resolve, he says. Overall, the patent office approves about 300,000 patents annually.

Interferences have helped to decide control over some of the most lucrative inventions ever, including the telephone, the sewing machine, and television. In 1885, a competitor managed to strip Thomas Edison of a patent on a lightbulb with a paper filament, although by that time Edison had invented a better one.

Similarly, given the pace of innovation in gene editing, today's legal fights could end up serving little purpose. Improved versions of CRISPR-Cas9 have already been invented, and entirely new methods are likely.

TaggedCRISPR, genome editing, patents, genome editing tools

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I am the senior editor for biomedicine for MIT Technology Review. I look for stories about how technology is changing medicine and biomedical research. Before joining MIT Technology Review in July 2011, I lived in São Paulo, Brazil,… More

Crispr: Scientists' hopes to win Nobel prize for gene-editing technique at risk over patent dispute

A looming patent dispute threatens to overshadow next week's announcement and may well scare off the Nobel committee from going anywhere near Crispr-Cas9

- Steve Connor Science Editor
- @SteveAConnor

- Friday 2 October 2015

University of California, Berkeley Professor of Chemistry Jennifer A. Doudna and Ulmea University Professor and Microbiologist Emmanuelle Charpentier (R) speak onstage during the Breakthrough Prize Awards Ceremony

There are no prizes for coming second, at least no Nobel prizes which is why everyone's eyes will be on Stockholm next week when the greatest accolades in science will be announced.

Hot favourites for the chemistry prize are two scientists widely credited with discovering a revolutionary gene-editing technique that is changing the scientific landscape of everything from genetic medicine to the development of new crops and bio-products.

American Jennifer Doudna and French-born Emmanuelle Charpentier co-authored a key study published in August 2012 that demonstrated the technical power of Crispr-Cas9 to cut and splice genes with extreme efficiency down at the highest resolution possible on the DNA molecule of life.

Since then, Crispr-Cas9 has been shown to work in lifeforms ranging from bacteria, insects and plants to fish, farm animals and humans. It has snowballed into a force that has taken the world of molecular biology by

storm, promising new cures, new drugs, and even the possibility of eradicating some inherited diseases by the creation of "genetically modified" babies.

But a looming patent dispute threatens to overshadow next week's announcement and may well scare off the Nobel committee from going anywhere near Crispr-Cas9 – the committee is notorious for two things; its obsessive secrecy and an institutional aversion to controversy. And the patent row is now making Crispr exceedingly controversial.

While the world's media have focussed their attention on the contributions of Professor Doudna of the University of California, Berkeley, and Professor Charpentier, now at the Helmholtz Centre for Infection Research in Braunschweig, Germany, the US Patent and Trademark Office has quietly awarded many of the key patents on the Crispr technique to a third scientist, Feng Zhang of the Broad Institute and the affiliated Massachusetts Institute of Technology (MIT) in Cambridge, Massachusetts.

Twitter CEO Dick Costolo, Ulmea Universtiy Professor and Microbiologist Emmanuelle Charpentier, University of California, Berkeley Professor of Chemistry Jennifer A. Doudna, and Actress Cameron Diaz attend the Breakthrough Prize Awards Ceremony

So far, Professor Zhang and his institute have bagged an impressive portfolio of 13 out of 20 Crispr patents issued by the US patent office – and another four by the European Patent Office. Meanwhile Doudna and Charpentier have been left largely empty handed when it comes to the protection of their intellectual property – and the licensing money that comes with it.

The issue has become so serious that it has pitted the mighty MIT against the equally mighty University of California, with its Berkeley campus openly calling on the US patent office to think again. Earlier this year, the university filed an official request for a "patent interference" which, if allowed, will force the US patent office to decide which academic institution owns the intellectual rights over Crispr in a "winner-takes-all" decision.

The US patent office has yet to respond to our enquiries about whether it intends to grant the review.

Patent disputes of course are nothing new in business. Equally, there has always been competition (as well as collaboration) in science. But when the patent lawyers move in on academia, things can turn personal, especially when tens of millions of dollars are already invested and hundreds more are promised for whoever has control over the key Crispr patents.

Last month, after the Economist magazine put Crispr on its front cover with the headline "The age of the red pen", a leading figure at the MIT, Robert Desimone, wrote a tart letter disputing the magazine's assertion that Doudna and Charpentier had "worked out" and demonstrated the gene-editing technique.

“Actually, their [scientific] paper studied the properties of a purified protein in a test tube: it involved no cells, no genomes and no editing. Rather, the paper simply highlighted the potential that genome editing might be possible,” Professor Desimone wrote.

To comprehend what the dispute is about, it is first necessary to understand the nature of the Crispr-Cas9 system. As the name implies, it is made up of two elements. The Crispr part is the programmable molecular machinery that aligns the gene-editing tool at exactly the correct position on the DNA molecule, while the Cas9 is a bacterial enzyme that cuts the DNA rather like a pair of molecular scissors.

Although the discovery of Crispr in bacteria goes back many years, putting it together with Cas9 and getting it to work was the brilliant inventive step of Professor Charpentier and her one-time colleague Professor Doudna. The trouble is, according to the MIT and Broad Institute, the two scientists and Nobel prize favourites only went so far with it.

This is where Professor Zhang comes in. In early 2011, more than a year before Doudna and Charpentier published their paper in Science, Zhang had learned about Crispr at a scientific meeting and immediately realised it was a game-changing technology. At that time, the professor of biomedical engineering at the MIT was just setting up his own research group at the affiliated Broad Institute so he decided to start work on the technique.

Professor Zhang focussed on adapting Crispr, which was essentially a natural gene-editing tool that protects bacteria from viruses, for use in human cells. His key scientific paper came out in January 2013 showing that Crispr-Cas9 can be used to edit the human genome in living cells. As

it happened, his paper was published alongside another paper showing much the same thing by Professor George Church at Harvard.

However, Zhang claimed an inventive edge over competing patent claims by producing laboratory notebooks going back to 2011 showing that he was working on the development of a practical use for Crispr-Cas9 in "eukaryotic" cells like those in humans, rather than in the simpler cells of bacteria.

Professor Zhang was unavailable, but the Broad Institute directed us to a prepared statement.

"Zhang's patent application and published paper included an actual method, one that was the result of nearly two years of independent, focused and successful effort at the Broad Institute and MIT – a method that has since become the standard for genome editing," the Broad Institute said.

"Broad was not the first to file a patent request related to Crispr. However, Broad was the first to file a patent that described an actual invention – experimental data regarding a successful method for mammalian genome editing," it said.
It is not possible to patent a natural process, and both Crispr and Cas9 are natural, at least in bacteria. Putting both together and showing how the molecular complex can be used in mammalian cells was the key "inventive step" that the Broad Institute believes swayed the US patent office – but not before the institute instigated a "fast track" patent application to the chagrin of Berkeley's patent lawyers.

READ MORE

- Crispr: Breakthrough announced in technique of 'editing' DNA to fight
- Crispr: The science behind a 'game-changing' gene-editing technique

- CRISPR gene therapy: Scientists call for more public debate around
- Exclusive: 'Jaw-dropping' breakthrough hailed as landmark in fight

In patent parlance the fast-track is called “accelerated examination” and it meant that although Zhang and his institute applied for patents after Doudna and Charpentier, he was awarded them first. The Broad Institute insisted there is nothing underhand, just that it “simply means” its application was considered more quickly than that of the Berkeley’s.

“It does not change the level of scrutiny applied to the application….In this case, Broad’s applications were considered against those from UC Berkeley and other institutions, as they would have been regardless of whether the patent had been examined via the accelerated review process or otherwise,” the institute said.

But routine or not, it now appears that there is much bad blood flowing in the veins of American academia as a result of the escalating patent row over Crispr-Cas9. And bad feelings between scientists, and especially between their academic institutions, are not going to go down well with the Nobel committee in Stockholm.

Profiles

Feng Zhang is a synthetic biologist and professor of biological engineering at the Massachusetts Institute of Technology. He is also a “core member” of the Broad Institute, which is affiliated to MIT and taking the lead on the patent dispute over the Crispr gene-editing technique. Professor Zhang is named on most of the patents so far awarded and has claimed that his key inventive step, published in January 2013, was to show that Crispr-Cas9 works in mammalian cells, including human cells.

Jennifer Doudna is professor of chemistry and molecular cell biology at the University of California, Berkeley. She co-authored a key scientific paper published in the journal Science in August 2012 showing that

Crispr-Cas9 has the potential to work as an incredibly efficient and effective gene-editing tool. Professor Doudna has been a leading figure in the group of scientists who have called for a wide-scale public debate on whether the technique should ever be used to change the human "germline" of sperm, eggs and embryos.

Emmanuelle Charpentier started her research in Paris before moving to the United States. She also worked in Sweden where she is credited with discovering the potential of the Cas9 enzyme to edit genes with the help of the Crispr system. One of her key studies was with Jennifer Doudna, and she was a co-author of the August 2012 paper in Science. She has since returned to Europe and is now based in Germany at the Helmholtz Centre for Infection Research.

Better than Crispr?

Scientists have discovered an even more powerful tool for editing the genome than Crispr-Cas9 thanks to a trawl through a library of biological enzymes used by bacteria to defend themselves from invading viruses. Feng Zhang of the Broad Institute in Cambridge, Massachusetts, and his colleagues found that they could replace the Cas9 enzyme that has proved so good at snipping the DNA of genes with another bacterial enzyme called Cpf1.

Crispr, which stands for clustered, regularly-interspaced, short-palindromic repeats, is a complicated name for the relatively simple process of aligning a "guide" molecule, which is made to order to match a specific DNA sequence, against a precise position on the DNA double helix where editing it required.

The second element of the gene-editing technique is to cut both strands of the DNA double helix with the Cas9 enzyme used by some bacteria to attack invading viruses. But now Professor Zhang and his colleagues have found that they can replace Cas9 with a smaller and more effective enzyme called Cpf1, which they found in another bacterium.

The scientists, who reported the discovery last week in the journal Cell, said another advantage is that Cpf1 requires a guide molecule of RNA – a molecular cousin to DNA – that is only made of a single strand, whereas Cas9 needs two strands. This means the new gene-editing tool is even smaller than Crispr-Cas9, meaning that it should be easier to insert into the cells and tissues where the gene-editing is needed – for instance the muscles if treating muscular dystrophy with gene therapy.

A second advantage is that the Crispr-Cpf1 complex cuts DNA in a slightly different way to Crispr-Cas9. While Cas9 cuts both strands of the helix as precisely the same place, leaving "blunt ends", the Crispr-Cpf1 complex cuts each strand at slightly different points, leaving short overhanging bits or "sticky ends" which scientists believe will make gene editing even more accurate.

"This has dramatic potential to advance genetic engineering…[it] shows that Cpf1 can be harnessed for human genome editing and has remarkable and powerful features. The Cpf1 system represents a new generation of genome editing technology," said Eric Lander, director of the Broad Institute and one of the scientists who led the human genome project.