A hint of what might be happening in the jets comes from recent three-dimensional computer simulations created by Kazunari Shibata, a theorist at Kyoto University's Kwasan Observatory in Kyoto. Based on magnetohydrodynamic equations, his simulations show gas and dust ejected from the core swirling into knots and rings. The knots and rings are more or less stationary, wobbling slightly toward and away from the core while the material that forms them continues on its way.

So far, even the most sophisticated simulations can only model systems a tiny fraction of the size of the AGNs radio astronomers are observing. The complexity of the forces involved stretches the limits of supercomputers and their programs, Shibata explains. Still, astronomers say the simulations are coming of age. "We're seeing a convergence of the magnetohydrodynamic modeling and observations," says Junor, and this will make simulations an increasingly useful tool for testing theories.

Twinkle, Twinkle, Little Quasar

One of radio astronomy's longest running debates centers on distant objects whose radio emissions vary over time. Do the emissions really wax and wane, or is the variation caused by some sort of scintillation in the interstellar medium, the gas and dust between the stars? Astronomers generally accept that variability on the order of months or years comes straight from the source. But change over less than a day, so-called intraday variability, is harder to explain. Astrophysicists believe that the shorter the period of the variability, the more compact the source has to be. Yet these highly variable quasars are emitting thousands of times more radiation than theory would allow highly compact sources.

David Jauncey of the Australia Telescope National Facility and colleagues have now pinned the intraday variability of at least one radio source on the interstellar medium. The source, known as PKS 0405-385, is extremely variable: Its emissions nearly double in intensity and then fade within an hour.

Jauncey and his colleagues theorized that they might be able to tell where the variability was coming from by precisely timing when changes in the radio signals arrived at radio telescope arrays on opposite sides of Earth. Because PKS 0405-385 is halfway across the universe, signals due to changes in the source itself would reach the arrays simultaneously, give or take a few milliseconds. But if the variability arises in the relatively nearby interstellar medium of our own galaxy, the signals reaching two arrays might form different patterns or arrive at different times.

Using the Very Large Array, a set of 27 radio telescopes near Socorro, New Mexico, and the Australian Telescope Compact Array, a set of six telescopes in Narrabri, New South Wales, the astronomers found that both arrays detected very similar patterns of variability. But the signals arrived in New Mexico about 2 minutes before reaching Australia—much too long to be explained by one array being closer to the source or by experimental error.

"The conclusion is inescapable," Jauncey says. "It is interstellar scintillation that is at least a major cause of this intraday variability." William Junor, an astrophysicist at the University of New Mexico, Albuquerque, agrees: "It looks pretty conclusive and comprehensive."

If other groups get similar results with other sources, the technique could provide a means of probing the interstellar medium. "I think this result is going to motivate a lot of work on other [intraday variable] sources," says Bernard Burke, a radio astronomer at the Center for Space Research at the Massachusetts Institute of Technology.

–DENNIS NORMILE

BIOMEDICAL PATENTS

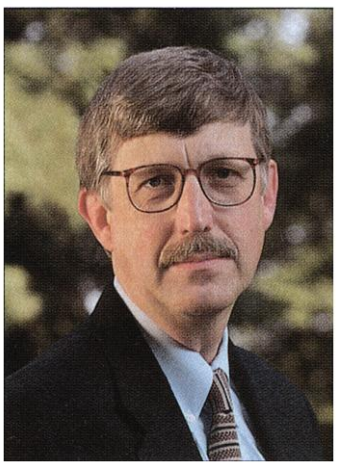
Patent Office May Raise The Bar on Gene Claims

But NIH officials worry that the bar might not be high enough to keep out unwarranted claims, which they say threaten to stymie research

The U.S. Patent and Trademark Office (PTO) is inching toward resolution of an issue that has dogged it, and the biomedical research community, since the early 1990s: What sort of genetic information is patentable? Over the past decade the PTO has been deluged with applications for patents on millions of gene fragments. Yet most have been stalled because of enduring questions over exactly what can be patented.

Now, in a major shift, the PTO has proposed a policy that will raise the bar for patent applications on DNA—a change that could lead to the rejection of many of those idling claims. Although the proposed change is welcomed by many in the research community, some, including top scientists at the National Institutes of Health (NIH), argue that it still does not go far enough. Unless the PTO tightens its rules further, they warn, research and innovation could be stifled by a quagmire of overlapping rights and claims. "This could be a big disincentive for biomedical research," says Maria Freire, director of the Office of Technology Transfer at NIH.

By all accounts, the stakes are enormous. To reap the harvest of the genome era, companies have invested hundreds of millions of dollars in uncovering genes on which new drugs and diagnostic tests can be based. Analysts say their business strategies are at least partly based on the assumption that they will own the rights to exploit that genetic knowledge. Few in the biomedical community argue against that basic position. Without some form of intellectual property protection, pharmaceutical companies would not bet large sums on developing gene-based drugs, and those drugs would never reach the market.



Patent worries. NIH's Francis Collins is "very concerned."

CREDIT: SAM KITTNER

The question, then, is how much someone needs to know about the usefulness of a piece of DNA—its "utility," in patent law terms—to merit a patent. NIH officials and many other publicly funded scientists argue that no DNA patent should be granted unless researchers know a gene's full sequence and have figured out what protein it produces and what that protein does in the cell. The first hard-won gene patents, issued in the 1970s and 1980s, met those criteria, because researchers often started with a known protein and worked their way back to the encoding gene—a difficult and laborious process.

Since then, new and less cumbersome ways to find genes have emerged. In the early 1990s, scientists discovered a way to identify short scraps of DNA—called expressed sequence tags (ESTs)—about which they knew little more than that they belonged to some gene that was switched on somewhere in the body. That didn't deter researchers from applying for patents,

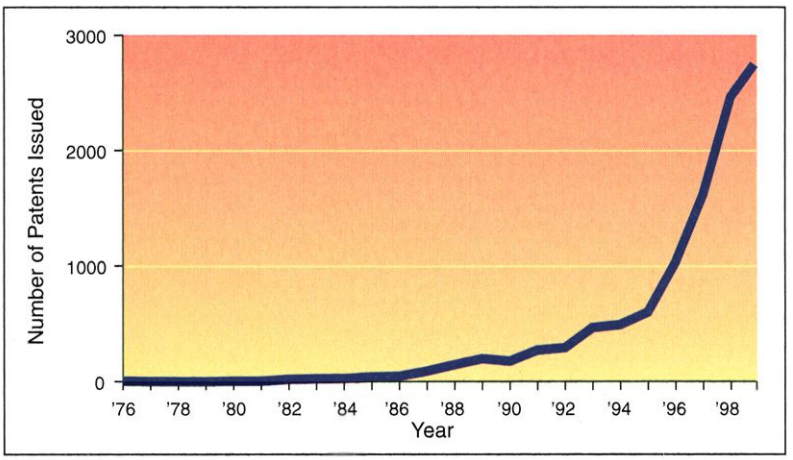
however. Often, ESTs were ascribed some unspecific type of utility—for instance, that the sequence could be useful in forensic science or could help find genes on a chromosome. Nobody knows exactly how many EST applications have been filed, but millions are believed to be in the queue at the patent office. Until recently, the agency had indicated it would award such general claims—for instance, John Doll, PTO's director of biotechnology, outlined such a policy in a commentary published in *Science* (1 May 1998, p. 689).

But, in what Doll concedes is a "significant change" in policy, the agency has decided that patent applicants must demonstrate a more "substantial, real-world utility; not some throwaway utility." As a result, many EST applications "will have a difficult time" meeting the utility requirement, says Doll. This proposed change is spelled out in a set of new guidelines for the agency's patent examiners—the people who judge the validity of claims. Published in the *Federal Register* on 21 December, the guidelines are open for public comment until 22 March.

Experts say the proposed change could hurt companies that have applied for patents on large numbers of ESTs, such as Incyte of Palo Alto, California, and Human Genome Sciences, based in Rockville, Maryland. But Lee Bendekgey, general counsel at Incyte, says his company is confident its 1.2 million ESTs are patentable. "We never filed applications where we didn't know what the EST did," says Bendekgey. A spokesperson at Human Genome Sciences said the company is studying the proposal and declined to comment.

For its part, NIH is "very pleased" by the proposed change in policy, says Freire. NIH officials worry that under the current regime, an EST patent might give the patent holder rights over not just that snippet but also the full-length gene, if it is later characterized by somebody else. Because many ESTs can originate from the same gene, several patent holders could all have a share in a single gene—a recipe for disaster. "That was indeed a frightening prospect," says Iain Cockburn, a finance and economics professor at Boston University School of Management.

But NIH is decidedly unhappy about the PTO's position on another class of gene patents, also contained in the proposed guidelines. Since the advent of sophisticated gene-hunting software, researchers have been able to take a gene, or even just a piece of a gene, plug it into a computer, and instantly turn up vast amounts of intriguing but theoretical information about it. For instance, a gene might resemble one that produces a protein involved in intracellular transport in the fruit fly. Or it might produce a protein that, judging by its hydrophobic nature, probably floats in a cell membrane. Such searches have become the mainstay of companies like Rockville-based Celera Genomics and Incyte. Already, thousands of patent applications have been filed on genes that have been characterized only through computer searches—without doing a single experiment or "getting your pipette wet," as one critic explains.



Gene boom. The number of patent applications containing a genetic sequence has exploded over the past decade.

SOURCE: IAIN COCKBURN/BOSTON UNIVERSITY

Much to the dismay of NIH, patent officials say that under the new guidelines, such applications will likely pass muster. Searching sequence databases for similar genes has become common practice in genomics, explains Doll: "Scientifically, it's very well established and very well accepted in the academic community." Indeed, the patent office has already awarded one such patent, to Incyte in 1998, on a set of ESTs believed to encode a family of 44 enzymes called kinases.

In a polite but spirited letter-writing campaign in December, then-NIH director Harold Varmus and Francis Collins, director of the National Human Genome Research Institute, voiced their opposition to PTO Commissioner Q. Todd Dickinson. Varmus and Collins wrote that they were "very concerned with the PTO's apparent willingness" to grant claims based on such "theoretical" functions. Varmus and Collins argue that although databases may give researchers tantalizing hints about what a gene could do, they don't prove anything, let alone give researchers new ideas for drugs. Therefore, such searches should not be sufficient to enable scientists to lay claim to a gene. NIH officials worry that, if approved, such claims could impede research by other investigators. "In 3 or 5 years, people can come and say: 'Hey, you can't be working on that gene. That's mine,' " says Freire. "That's a very scary proposition."

Not surprisingly, the genomics industry is pleased with this part of the proposal, arguing, as does Doll, that homology searches are an accepted way to ascribe function to a gene. "Everybody uses these techniques," says Incyte's Bendekgey, "and they are virtually 100% correct."

In the end, determining what is and isn't patentable will likely be decided in court, as the PTO's decisions must stand up to legal challenge. Doll says that if the PTO rejects a patent application based on a database search, that decision is likely to be overturned by the court. Patent experts tend to agree. The courts have never enforced the utility requirement very strictly, says Rebecca Eisenberg, a patent law scholar at the University of Michigan, Ann Arbor. As far as existing law is concerned, she says, the new policy "is probably on pretty safe ground." The only way to be sure is to take it to court. That's why the PTO is now preparing a test case: It will issue a patent to an applicant who has volunteered to have it challenged by a third party. The agency declines to reveal details about the case.

No one is willing to bet on the outcome. Nor is anyone certain what would happen if genomics companies actually get patents on the thousands of genes they claim to have found but have not fully characterized. "Are we heading for a situation where nobody can do business without negotiating 400 agreements? That's a possibility," says Cockburn. On the other hand, NIH officials may be overly pessimistic, and such complexities may be sorted out in the marketplace. Whatever the outcome, he says, it's likely to lead to several high-profile patent infringement lawsuits.

That's nothing new. Virtually every major therapeutic product to emerge from the biotech field has been the subject of intense and often bitter litigation, says Cockburn: "It's one of the sad features of the biomedical industry."

—MARTIN ENSERINK