DATELINE/

A DEGENERATE IDEA?

PATENTING HUMAN GENES RAISES STORM

NEW YORK—When does a human gene become patentable? That's the question at the heart of the controversy over the National Institutes of Health's (NIH, Bethesda, MD) application to patent 337 complementary DNA (cDNA) sequences.

Back in June, NIH quietly filed to patent gene fragments sequenced by Carl Venter, a scientist at the National Institute for Neurological Disorders and Strokes. Then news of NIH's application surfaced at an October meeting of scientists, attorneys, and patent officials who'd gathered at Cold Spring Harbor Laboratory's Banbury Center (Huntington, NY), kindling a debate that's still raging.

What makes NIH's application so controversial is the fact that Venter has virtually no idea of what these cDNA sequences do or how they might be used. "It's a degenerate idea," says David Botstein, chair of Stanford University's (Stanford, CA) genetics department. "There's no invention. I hope the patent office will have the wit to see that they're just recycling the databases."

But NIH's lawyers say they had to file for a patent prior to publication of Venter's data—or risk forfeiting the possibility of anyone ever getting a meaningful patent involving those sequences. "Failing to file the NIH patent application would have meant a loss of potential rights in most countries of the world," says Reid Adler, director of NIH's Office of Technology Transfer.

Once these sequences are published, Adler's argument goes, they would enter the public domain, where they'd be considered too obvious to form the basis for further inventions. Then further developments—the corresponding full gene sequence, recombinant expression vectors containing that sequence, expression products, and antibodies against those products—all might become unpatentable as well. Adler poses the question: "Because patent law does not require a clinical utility, at what point is a patent application too late?"

Allowing the material to enter the public domain "is an open invitation to the Japanese," says patent attorney S. Leslie Misrock of Pennie & Edmonds (New York). But disclosing and patenting the gene may prevent the granting of further patents because further inventions would then appear obvious. "The NIH is between a rock and a hard place," says Misrock.

Not all lawyers agree that NIH's patent, if granted, would preclude all future patents involving the sequences. For example, Patrick Kelly, a St. Louis patent attorney, believes that those who perform subsequent research on patented sequences could file for co-inventorship patents. The full genes and their properties also might be the basis of a further patent, suggests Albert Halluin of Fliesler, Dubb, Meyer & Lovejoy (San Francisco, CA). Though the earlier patent "would still dominate," how significant either patent might be is "the unresolved issue," Halluin says.

That kind of uncertainty could prove disastrous for the biotech industry. A patent on a cDNA partial clone would "remove much of the incentive" to see what the gene does or how it might be used, says Bruce Eisen, Genetics Institute's (Cambridge, MA) vice president and chief patent counsel.

"A company is not going to put in a lot of research dollars and time when it's going to have to pay royalties to NIH," says Richard Godown, president of the Industrial Biotechnology Association (Washington, DC). He notes that companies making major investments want the broadest possible product patents, not new-use patents. "It is just fraught with danger for the development of biotechnology," Godown says.

Even if a company were interested in licensing NIH's patent, there would be no guarantee of an exclusive license. And without an exclusive license, "everybody is really just paying a tariff," says Stephen Raines, Genentech's (So. San Francisco, CA) vice president of intellectual property.

Things could get especially sticky if a company trying to license a piece of NIH's cDNA found that competitors were working with an overlapping section of that sequence. "Then you might need a multiplicity of licenses," says Raines, to do anything with the protein. He adds, "We could be getting ourselves into a quagmire. We already have more than our share of litigation."

Raines and others also fear a logjam at the patent office if NIH gets its patent, as researchers might race to patent whatever gene is in hand. Already, a patent takes at least three or four years to work its way through the application process.

For their part, scientists fear that wholesale patenting of cDNA sequences would distort research-and-development programs worldwide. NIH's patent could send companies rushing to build cDNA libraries and patent collections "so they can trade chips" when the genes are better understood, says Mark Pearson, executive director of cancer and inflammatory disease research at Du Pont Merck Pharmaceutical (Wilmington, DE). The result would be an atmosphere of distrust that "could significantly slow down the whole human-genome project," Pearson believes.

In spite of all the concern, it's hard to find anyone who expects NIH to win its patent. "I will be flabbergasted if any patents are allowed in this area," Pearson says. "I can't imagine how people would subsequently use them."

Whatever their thoughts on NIH's application, most patent attorneys say they don't fault the agency for bringing the issue into the open. NIH "has

NIH PATENT COVERS MOST GENES EVER

NIH scientist Craig Venter has rattled biotechnology by applying to patent 337 human complementary DNA sequences. One reason is that Venter's application appears to cover more genes in one fell swoop than all previously granted gene patents put together.

The Patent & Trademark Office (Alexandria, VA) says it has no breakdown of how many genes have been patented, let alone how many human genes. CHI Research (Haddon Heights, NJ), a firm specializing in patent citation analysis, says that some three dozen gene patents were issued in the year and a half beginning in January 1990. "There are a couple of dozen or so a year, not a vast number," says Francis Narin, the company's president.

But Venter's 337 gene fragments may be just the tip of his cDNA iceberg. Using robotic sequencers that down-load to computerized databases, Venter can reportedly sequence 75 kilobases of cDNA a day, or possibly 100 genes.

"Venter is putting together several components that are state of the art or close to it, showing the kind of throughput that can be achieved," says Du Pont Merck Pharmaceutical's (Wilmington, DE) Pearson.

But Venter isn't alone in this achievement. "What's new here is the audacity to try to patent it," Pearson says.

—Mimi Bluestone