Genome Patent Fight Erupts

An NIH plan to patent thousands of random DNA sequences will discourage industrial investment and undercut the Genome Project itself, the plan's critics charge

AT A CONGRESSIONAL BRIEFING ON THE Human Genome Project last summer, molecular biologist Craig Venter of the National Institute of Neurological Disorders and Stroke dropped a bombshell whose repercussions are still reverberating throughout the genome community. While describing his new project to sequence partially every gene active in the human brain, Venter casually mentioned that his employer, the National Institutes of Health, was planning to file patent applications on 1000 of these sequences a month.

"I almost fell off my chair," says one briefing participant who asked not to be named. James Watson, who directs the genome project at NIH, did more than that, exploding and denouncing the plan as "sheer lunacy." With the advent of automated sequencing machines, "virtually any monkey" can do what Venter's group is doing, said Watson, who in one sentence managed to insult Venter, his dismayed postdocs, and Reid Adler, the director of NIH's Office of Technology Transfer, who advised Venter to pursue the patents. "What is important is interpreting the sequence," insisted Watson. If these random bits of sequences can be patented, he said, "I am horrified."

Watson may have been the most outspoken, but he was not the only one to be horrified. The scheme has engendered a firestorm of criticism from genome scientists and project officials alike, including David Galas, Watson's counterpart who oversees the genome effort at the Department of Energy (DOE), which will begin funding some of Venter's work in November; Stanford's David Botstein, a prominent genome project researcher; and Walter Bodmer of the Imperial Cancer Research Fund, who is also president of the International Human Genome Organization in London. The critics argue that these sequences probably can't be patented in the first place—and even if they can, they shouldn't be.

What galls Watson and the other critics the most is the notion that by simply sequencing a short piece of an unidentified clone with an automated sequencing machine—"a dumb, repetitive task," as one critic describes it—someone could conceivably lay claim to most of the human genes. This, they say, would undercut patent protection for those who labor long and hard at the real task of elucidating the function of the proteins encoded by the genes, thereby driving industry away from developing inventions based on that work. "No one benefits from this, not science, not the biotech industry, not American competitiveness," asserts Botstein, who also attended the hearing last summer and has since been trying to mobilize the genome community to oppose the idea.

The scheme's critics envision a mad scramble for patents. "If Craig can do it, so can the UK," Watson told *Science*. Indeed, Bodmer has warned that if Venter continues with this wholesale patenting, the British may have to follow suit—even though it could double the price of obtaining the sequence of the human genome, he says. And the critics worry that the patenting scheme will impede the open exchange of information on which the Human Genome Project depends. The critics add that they are not opposed to patenting per se in the genome project but think that it should come later in the game, once a gene is fully characterized.

Venter and Adler seem taken aback by all the fuss. They argue that Watson and company are wrong about the effect on industry, insisting that patent and license protection will help—not hinder—technology transfer. What's more, they say that, given the uncertainty over whether the clones are even patentable, they were just doing what is prudent by filing now.

How it all began

What started all this ruckus is the project Venter launched about a year ago to find and partially sequence the 30,000 or so complementary DNAs, or cDNAs, from the human brain. cDNAs are simply clones made from messenger RNAs and thus represent the coding regions of all the genes expressed in a tissue. Venter and his group randomly select cDNA clones from commercial brain clone collections and then sequence a short stretch of each one, about 300 to 500 bases, to create what Venter calls an expressed sequence tag, or EST. From that sequence, which is stored in a database, other investigators can then re-create the 300-base tag using polymerase chain reaction techniques. And with the tag in hand, it is relatively straightforward to pull out the entire cDNA clone from a clone collection (*Science*, 21 June, p. 1618).

With the help of an automated sequencing machine, Venter is now churning out 50 to 150 of these tags a day, thereby making a major dent in finding the entire complement of 100,000 or so genes in the human body, he maintains. Even so, Venter is the first to admit that once he has tagged a cDNA, he still has no idea what it does, unless it's a sequence from a gene whose function is already known. Of

the first 600 clones Venter pulled out, however, 350 represent unique genes, never seen before.

Venter insists he never intended to patent all these clones until Max Hensley, a patent attorney at Genentech in south San Francisco, got into the picture. Hensley had heard about Venter's project and suggested to Adler at NIH's technology transfer office that NIH consider patenting the sequences. Adler bit, convincing Venter in turn that it would be a "tragic mistake" not to, recalls Venter. "We were told that if we did not patent them, we risked greatly undercutting the U.S. biotech effort."

Adler argues that once the sequence is published, it and the entire gene would be in the public domain, which might render further discoveries unpatentable or at least dramatically reduce the extent of patent protection available for them. "If everything goes into the public domain, there is much less incentive for companies to invest time and money in developing a product," he insists. "Our concern was to protect the invention early enough to give meaningful patent protection to the companies that might seek a license from NIH."

So, at the same time that Venter's first article on his cDNA project came out in *Science* last June, NIH filed a patent application on the first 350 unique cDNAs. The claim covered each EST as well as the entire coding sequence for the longer clone, its protein product, and the method for obtaining and interpreting cDNAs. Adler concedes he is "not completely certain" the patent will issue, though he is fairly confident it will. Others are not so sure—indeed, there seem to be as many opinions on the patentability issue as there are experts.

Can they be patented?

The general consensus among the genome scientists *Science* spoke with is that the patent scheme won't fly, though it is unclear how much of that is simply wishful thinking.

For NIH and Venter to get their patents, the raft of clones will have to meet the U.S. Patent and Trademark Office's three tests: novelty, non-obviousness, and utility. The biggest, though probably not insurmountable, hurdle is utility, say numerous patent attorneys. In other words, how can you patent something when you don't know what it is, much less what it will be used for? Indeed, when British genome officials earlier sought advice from patent attorneys about their own cDNA project, they were told that "generating cDNA sequences was a routine exercise involving no inventive step," says Tony Vickers of the Medical Research Council's Human Genome Mapping Project Resource Center. "There was nothing we could patent without having an idea of what the gene could be used for, except in a broad, generic sense."

"The Patent Office has already issued patents on gene sequences, so the subject matter is patentable," responds Adler, who nonetheless concedes their application is "unusual" because the function of these genes is unknown. Lacking specific information, Adler and Venter say they made their claim in broad terms, asserting that these partial sequences would be useful as probes for identifying particular tissue types or chromosomes and for recovering the entire gene. They also assert that at least some of them will be useful in "antisense" technology to develop new drugs.

Adler believes, as do Hensley and others, that those claims should suffice, pointing out that under patent law "you don't have to know all the uses for an invention but just some sort of threshold activity." Others say there is at least room for doubt. Rebecca Eisenberg, a law professor at the University of Michigan, cites *Brenner* v. *Manson*, a 1966 case in which the Supreme Court ruled that if an invention is useful only in research, it is not patentable.

To Steve Bent, a patent attorney with Foley & Lardner in Washington, the key question is whether the patent will be broad enough to be worth much, even if it does issue. In other words, will NIH receive a patent just on the ESTs, the short stretches of DNA Venter's group has sequenced, or on the entire cDNA and its protein product, which they have yet to sequence or characterize? Bent, for one, is skeptical that they will receive broad coverage. "The scope of their claim will probably be limited very literally" to what they are actually doing—that is, sequencing ESTs. "If so, then that is not a very useful patent," he says. So why do it? Good question, he answers. "I don't want to say that NIH is wrong, but my feeling is maybe they entered the patent process too early," he adds.

Bent and the other patent attorneys *Science* spoke with do agree on one point: that even if the first patent issues, subsequent ones will probably be harder if not impossible to obtain because the methods of generating these cDNA sequences will become obvious and routine. Charles Cantor, senior scientist in DOE's genome effort, sums up the view this way, referring back to Watson's original complaint: "At the point when monkeys really can do it, it won't be patentable."

And even if the patent issues, would it be enforceable? Botstein is convinced it would not withstand challenge—though he notes that the case could be tied up in the courts for 10 years or so, allowing ample time for chaos to ensue.

Even Hensley, one of the prime movers behind this scheme, is skeptical. "When I look at any one sequence in a cDNA catalog patent, I have a hard time coming up with a statutory reason why it shouldn't be valid. But the tummy feel to this is not quite right. You ask, 'Where's the beef?'" he says, adding that these views are his own and do not reflect those of Genentech or the biotech industry. "When patent lawyers are done debating, you need to step back and do a reality check," says Hensley. "If it was 10 or 50 genes a year, I could make that fly. But when you start talking about 20,000 genes, a buzzer goes off and you wonder, How will I get that by a judge?"

Should they be patented?

But it is not the legal question as much as the societal one that has gripped the genome community: Even if these partial cDNAs can be patented, should they be? Much of the argument is cast in terms of the effect on industry; indeed, if the rhetoric on both sides is to be believed, the very competitiveness of the nation hangs in the balance. Adler and Venter insist that the biotech industry will be leery of touching these inventions without adequate patent and license protection from NIH. Watson, Galas, and Botstein are equally convinced that this wholesale patenting will drive industry away.

But Washington attorney Bent thinks arguments on both sides have been blown out of proportion. He maintains that if lucrative products are at stake, biotech and pharmaceutical firms will find a way to develop them, whether or not NIH can offer them license and patent protection. Adler does have a point, Bent and others say: if Venter does publish without filing for a patent application, it probably won't be possible to patent the gene sequences themselves later. But even so, it's not necessary to have a patent on the sequence to protect a drug or diagnostic kit

derived from that sequence.

Watson and Galas are also worried about the effect of the NIH patent application on the genome project itself. Specifically, they ask, will it impede sharing of information among researchers, both in the United States and overseas? In the United States, at least, there seems to be no problem so far; Venter submitted all his data to Genbank at the time he published and filed his application. "We did not delay Craig's publication by one minute," insists Adler. But, adds Robert Strausberg, director of technology transfer at the NIH genome center, "Just because Venter published right away doesn't mean it will always happen that way. A company might not."

DOE's Galas is more concerned that these patents might have a chilling effect on efforts to build an international database. Already, there are signs of tension in England, where the Medical Research Council is pursuing a cDNA project similar to Venter's. Vickers, who heads the database and resource center there, says that in a "rational" world, European, Japanese, and U.S. scientists would all compare their cDNA data so they could avoid wasting time mapping the same cDNA. "But suppose we check our database against Venter's and find there is 10% overlap. Is he going to lay claim to [our clones]? We certainly want to share our data. But we want the issue of patents sorted out first."

And then there is the price tag for pursuing the patents, which has people on both sides of the Atlantic fuming. Patent attorneys say it could reach $30,000 to $50,000 for one application, and there is the very real prospect that NIH will have to break its bulk applications down into smaller chunks, perhaps even single sequences—at which point the cost becomes prohibitive by any reckoning. Bodmer and numerous investigators fear that the tab, whatever its total, will come out of money that would be better spent on research. But Adler notes that NIH will not pursue patents unless industry is interested, and that the agency typically asks its technology licensees to bear the brunt of patent expenses. "It will be the company bearing the cost, not the taxpayer."

Striving for resolution

With Watson and Adler visibly feuding, the Europeans are wondering just what U.S. policy is. "There is no coherent government policy, and we need one—quick—since the sequence is just pouring out," says DOE's Galas. He says he and Watson plan to seek a ruling from the Patent Office, adding, "It would be a big mistake to leave this one to the lawyers."

At NIH, Strausberg has been meeting with Adler and Venter. The topic had gotten "very emotional," he says, and "my role is to cool it down." After being hit with such a violent backlash, Adler insists his views are not set and that he is still formulating a policy on the issue. Despite Venter's earlier statements, Adler says it is unclear whether NIH will attempt to patent all the cDNAs Venter turns up, and he says that cost will certainly be a factor. Controversy aside, says Adler, "I still think filing the application was the prudent thing to do."

Meanwhile, Venter is still churning out cDNA sequences, at an ever-increasing rate—up to 2000 a month now. Adler has scheduled a meeting with industry representatives on 14 November to "announce that this invention is ready for licensing." By gauging their interest, he says, he can decide whether the patents are worth pursuing. At the same time, Adler is preparing a second patent application, this one on 1500 additional cDNAs, to coincide with Venter's next publication. ■ LESLIE ROBERTS

Edelman: Bye, Bye Rockefeller

What's going on at Rockefeller University? Two months ago aging-research luminary Anthony Cerami announced he was leaving Rockefeller to become president of the Picowar Institute for Medical Research. Not alone, mind you: He took his 30-member lab with him. And not because he was unhappy at Rockefeller, he said, or with David Baltimore, whose 1989 election to head the university Cerami had opposed. Rather, Cerami said, he was leaving because his new offer was such "a unique opportunity." Now that story is being repeated, as Nobel Prize–winning neuroscientist Gerald M. Edelman gives similar upbeat reasons for jumping ship after three decades at Rockefeller.

This week Edelman announced he's leaving Rockefeller for the Scripps Research Institute in La Jolla, California, where he will become chairman of a new department of neurobiology in July. Like Cerami, Edelman is taking his entire lab, with 11 scientists, as well as the 14-member staff of the Neuroscience Institute (an independent think tank on the Rockefeller campus, which he heads). Like Cerami, he insists he is going elsewhere for "overwhelming positive reasons."

But could one of those positive reasons be that he won't have to put up with Rockefeller president David Baltimore's well-publicized troubles with Congressman John Dingell or with the opposition to Baltimore that some say is building at Rockefeller? Edelman has long been cited by insiders as a leader of the opposition to Baltimore's appointment as president of Rockefeller and has reportedly been unhappy with Baltimore's administration of the university. But if such feelings played a role in his decision, Edelman isn't talking publicly. To *Science*, he declined to confirm or deny any influence of Baltimore on his departure.

Instead, Edelman points to the "upbeat environment and sense of hopefulness about the future" he finds at Scripps. That was one of the drawing cards offered by Edelman's long-time friend, Scripps president Richard Lerner, who says he's been trying to interest Edelman in making that move for years. The discussion became serious only 9 months ago, Lerner says, but that can be attributed to the fact that Scripps sweetened the deal by offering to construct a new building for the Neurosciences Institute on its spectacular ocean-view campus.

Edelman plans to keep raising funds as the director of the institute and to build the new department of neurobiology at Scripps. His early work was on the structure of immunoglobulins—the active molecules of the immune system—for which he won the Nobel Prize in medicine in 1972. Thereafter, he branched out into neuroscience, particularly the study of the neural cell adhesion molecules (N-CAMs), which have a key role in giving form to the developing nervous system. Edelman's lab will continue its research on N-CAMs. And Edelman will continue to avoid direct comment on why he left what he calls "my home for 34 years." Except for adding, in his interview with *Science*, that he identifies "very closely with the spirit and style of the old Rockefeller." ■ ANN GIBBONS