Stanford's Gene Patents Hit Snags

An omission in a patent claim may imperil two fundamental and potentially lucrative gene-splicing patents

An application for a fundamental patent covering products of gene-splicing may be in jeopardy because the applicants' attorney omitted possibly important information from the claim, according to some patent lawyers. If the application is ultimately rejected by the United States Patent and Trademark Office, Stanford University and the University of California stand to lose lucrative licensing fees and royalty income. Patent lawyers, market analysts, and researchers are closely watching federal review of the patent claim because of its wide implications for the burgeoning field of biotechnology.

The claim was filed in 1978 by researchers Stanley Cohen of Stanford and Herbert Boyer of the University of California at San Francisco. It is a broad claim that covers products of gene-splicing used to transfer genes from one cell to another.

In August, the patent office issued a preliminary rejection of the claim. On 1 November, Cohen and Boyer's attorney filed a response—in effect, an appeal—of the rejection. Assistant commissioner of the patent office, Rene Tegtmeyer, said that the office will decide the fate of the patent application by the end of the year.

If the August rejection stands, market analysts and lawyers predict that another closely related and fundamental patent—issued to Cohen and Boyer in 1980—is likely to be challenged. The 1980 patent covers the process of making proteins with hybrid plasmids prepared by gene-splicing. The second claim seeks to patent the plasmids themselves. Based on the process patent, Stanford and the University of California have already collected $1.2 million in licensing fees and royalties. (Cohen and Boyer assigned the patent rights to Stanford, but the two universities share the income.)

The patent office rejected the researchers' second application for several reasons, but attention has focused on one main point. Federal officials discovered that the application gave inaccurate instructions to produce a key plasmid. The error came to light when the patent office learned that an article published in 1977 in the *Journal of Bacteriology* had revised the plasmid-making procedure. Cohen was the lead author.

The error, the patent office argued, meant that the patent would not enable another person to duplicate the same product. "Enablement" is a crucial test to win patent approval.

In a document responding to the rejection, the lawyer representing Stanford, Bertram Rowland, told the patent office that he did know of the error well before the application was filed. He said in the statement that he apologized for his "inadvertent failure" to mention the 1977 article in the patent application.

> Stanford's attorney said that although the omission was "unfortunate," he believes the patent will be issued.

Rowland's description of his omission could raise two points of contention. Some lawyers suggest that the application is now vulnerable to charges that knowledge of the article was deliberately withheld or resulted from gross negligence. Either charge could lead to a final rejection. Some lawyers venture that even if the patent is granted, the issue is a potential time bomb because companies are likely to challenge the patent in court if they have to pay out substantial royalties.

One lawyer said he found it "unusual" that Rowland did not disclose the error earlier. Another said he was "flabbergasted" to see Rowland's statement. "In my judgment, the characterization that it [his action] was inadvertent won't cure the deficiency," he said. Rowland "is in a real pickle."

Rowland said in an interview that the error "was not done in bad faith. I had no reason to hide it," especially because the error was disclosed in the public literature. "I got busy and it [reference to the article] got lost." Rowland said that although the omission was "unfortunate," he believes the patent will be issued.

The patent office is also trying to determine the seriousness of the error. Rowland argued that the application gives sufficient detail to duplicate the product. To support his point, he gathered affidavits from six scientists who testified that the application was enabling. Five of the scientists, however, are employed by Stanford or the University of California. Bernard Weisblum of the University of Wisconsin at Madison provided the sixth opinion.

According to a Cetus Corporation lawyer, the five affidavits are in legal terms "self-serving," but not invalid. Shyamala Rajender said that they carry less weight than those provided by outsiders.

The award of the patent is complicated by two other issues, although they are minor, according to the lawyers. The patent office also rejected the application because it was unconvinced that a previous collaborator with Cohen and Boyer should be excluded as a coinventor. It cited the fact that Robert Helling, now a professor at the University of Michigan, has refused to sign a disclaimer to inventorship.

Rowland responded that Helling, among others, was "instrumental in performing the steps essential to the success" of the invention. But, he said, the original concept was discussed between Boyer and Cohen in 1972 at a "now famous delicatessen" in Hawaii. He contended that he had repeatedly tried to persuade Helling to sign a disclaimer or to describe his role as a possible coinventor. Rowland said Helling never responded to his queries.

Helling, in an interview with *Science*, said that he does consider himself a coinventor. He has not signed a disclaimer because "I didn't want to perjure myself." In his opinion, he, Cohen, and Boyer were "equals" in collaborating on the project. "I was part and parcel to the whole thing."

He said his desire to be included as a coinventor stems from an interest in proper recognition rather than any promise of financial reward. "I doubt if there's anything in it for me or the University of Michigan," he remarked. An attorney at the University of Michigan, James Dautremont, said that Michigan and Stanford were engaged in "amicable discussions" and that Michigan was

0036-8075/82/1126-0868$01.00/0 Copyright © 1982 AAAS

more concerned about due credit than money.

Another possible problem centers on an article published by the *New Scientist*, which described in rough outline conference lectures delivered by Boyer about his plasmid work. The problem could affect both the process patent already issued and the second application.

The law requires that a patent application be filed within one year after an invention is publicly disclosed or published. The *New Scientist* article was published in 1973, a year and one week prior to the filing date of Cohen and Boyer's first patent. The scientists filed their second patent claim in 1978.

The patent office raised two matters related to the *New Scientist* story: whether the article was enabling and whether the lectures publicly disclosed Boyer's work for which he later sought a patent. Rowland contended that, at the time the article was published, important steps in the experiment had not yet been developed. Furthermore, the key plasmid in the experiment was not available to others at the time. He said the Boyer's talks did not constitute public disclosure because the participants at the meeting pledge in advance to hold all discussions in confidence.

In the short term, Stanford and the University of California have more at stake with the patent issuance than licensing companies. A market analyst for Sutro and Company, M. Kathy Behrens, said that if the claim is rejected, then the universities may have to pay back the royalties already received. Industry, however, is only paying nominal fees for licensing and royalties, she said.

Market analysts and lawyers seem to agree that even if the second application is issued, the universities are not home free. Once companies begin to market widely commercial products derived from genetic engineering, their outlays for royalties will jump significantly. One lawyer said that the companies may then find it more attractive to challenge the patents.

The same lawyer predicted that the "hard-nosed chemical companies" would be the most likely sector of industry to sue over the patents. Biotechnology firms and pharmaceutical companies are less likely to take the universities to court because they have long-standing ties to academia that they would prefer not to strain. The lawyer suggested that it is probably no coincidence that the large chemical firms, such as Exxon, which are now venturing into biotechnology, have not taken out a license on the Cohen-Boyer patent.—**MARJORIE SUN**

Global Energy R & D Stalls

Paris. The rapid world-wide growth in government-sponsored energy research that characterized virtually the whole of the 1970's has come to an end, dragged down largely by reduced efforts in the United States. The total budgets devoted to such activities in the major Western countries remained virtually constant between 1980 and 1981, according to figures just published in Paris by the International Energy Agency (IEA) of the Organisation for Economic Cooperation and Development (OECD).

The outcome was predictable from the trends of the past few years. Energy research spending by the 23 members of the IEA (which includes all the major OECD members apart from France) increased by 14 percent between 1977 and 1978, by 11 percent in 1979, and by only 6 percent in 1980. The drop to level funding in 1981, however, was almost entirely due to the cuts made by the Reagan Administration in the research budget of the U.S. Department of Energy. Energy R & D in the United States accounts for almost half (48 percent) of the total spent by the countries covered in the IEA report.

Furthermore, the drop in overall research funding would have been even greater if several other OECD countries, particularly those hit hardest by the rapid rise in oil prices in 1979 and who lack a significant indigenous supply of energy resources, had not reported significant increases. In West Germany,

Conservation and solar R & D are shrinking while nuclear research is expanding.

for example, spending on energy research increased by 11 percent in real terms between 1980 and 1981, in Japan by 10 percent, and in Italy—reflecting a major new commitment to research in both conventional and unconventional sources of energy by the Italian government—by a massive 76 percent.

The same three countries figure at the top of those spending the most on energy research as a proportion of gross national product, headed by Italy at 0.152 percent. Japan tops the list when it comes to comparing expenditure on energy research to total primary energy demand, with a figure of $4.21 per tonne of oil equivalent, compared to $2.08 in the United States.

A slackening in the growth of the price of oil after 1979—and the reduction in the role of the U.S. government in sponsoring energy research introduced by the Reagan Administration on the grounds that private industry should shoulder more of the responsibility—is reflected in a significant overall drop in the amount of money devoted to research in conservation. For the 23 countries covered by the survey, the total invested in conservation R & D dropped for the first time since data began being collected, falling from $562 million to $496 million.

In contrast, total spending on conventional forms of nuclear energy research continued to increase, climbing by over 10 percent between 1980 and 1981—with the most significant increases occurring in Italy (50 percent increase), Japan, and the United States. As for research into advanced nuclear energies—primarily fast breeders and fusion technology—total funds dropped slightly, mainly reflecting reductions in the U.S. and U.K. budgets from $2.205 billion in 1980 to $2.170 billion, although here again there were large increases in the efforts of both Italy and Japan.

Not to be put off by this drop, however, the report, prepared under the auspices of the IEA's Committee on Energy Research and Development chaired by Donald M. Kerr, director of the Los Alamos National Laboratory, has some enthusiastic words for advanced nuclear research. It points out that funding for breeder technology accounts for 17.6 percent of the total amount of energy research supported by the countries covered in the report, and describes this as "a remarkable commitment to the future of nuclear energy" which "reflects the belief that no alternative technology can currently hold the same ultimate potential."—**DAVID DICKSON**

0036-8075/82/1126-0869$01.00/0 Copyright © 1982 AAAS