Biotech Nightmare: Does Cetus Own PCR?

The biotech company is locked in combat with DuPont over the patent on a crucial DNA technology

FOR A BIOTECH COMPANY STRUGGLING TO build applications out of basic research, the main problem is getting a product on the market. Cetus Corporation solved that problem in a big way in 1987 with the polymerase chain reaction, or PCR, arguably the most important new DNA technology of the past decade. PCR has not only revolutionized research in molecular biology, it could be the basis of a $500-million diagnostic market. But now Cetus has another problem: PCR's success has attracted others who want a piece of the action.

E. I. DuPont de Nemours & Company is marketing kits that Cetus claims violate its patents on PCR. The biotech pioneer and the chemical giant have wound up locked in a lawsuit that is being tried in San Francisco, where a decision could come as early as next week. DuPont claims that PCR cannot be patented because work done by an MIT professor in the early 1970's put it in the public domain. The suit embodies the worst fears of fragile biotech companies: that their precious inventions could fall prey to legal attack by giant corporations who have little to lose and lots to gain. "Pharmaceutical companies may be able to afford [patent wars], but can biotech companies?" asks Pamela Bridgen, executive director of the Association of Biotechnology Companies. "If we're not careful, [issues of patent rights] will come down to money, and that's scary for the biotech companies."

It's particularly scary for Cetus, still reeling from $61 million in losses last year—a year in which the Food and Drug Administration failed to approve its application for interleukin-2, a potential cancer drug that Cetus had hoped would be a big seller.

The history of the invention of PCR is simple—at least according to former Cetus scientist Kary Mullis, who has told it countless times in various media. The idea came to him one April evening in 1983 as he drove through the mountains of Northern California: a way to amplify a chosen DNA sequence, without having to purify it first. The scheme he envisioned would make any piece of DNA instantly detectable and available to the researcher, without having to clone it.

Mullis' plan was to use short DNA primers to flank the sequence, then separate the DNA strands with heat, cool them to let the primers find their places, and use an enzyme called a DNA polymerase to extend the primers, making new copies of the adjacent sequence. Using alternating cycles of heating, cooling, and polymerization, he reasoned, one could easily amplify that particular sequence a billionfold or more.

More to the point, when Mullis tried the technique, it worked. After several years of refinements, Cetus received a patent on the PCR process in 1987. By now they have the market pretty well locked up: 3 patents issued and 50 more in the works. Last year sales of PCR kits and equipment brought Cetus and its partner Perkin-Elmer $26 million, and the technique's research applications are growing. Cetus, moreover, has joined with Hoffman-LaRoche to develop PCR-based medical diagnostic kits for a market some experts value at $500 million.

By the early 1970's PCR "had been invented. It was in the public domain."

— ARTHUR KORNBERG

In August 1989, DuPont challenged Cetus' patents in a lawsuit. DuPont contended that PCR had been described, 15 years before Cetus' patent was filed, in several papers* from the MIT laboratory of H. Gobind Khorana. In the concluding paragraph of the first of those papers, published in 1971, Khorana and his coauthors suggested that transfer RNA genes could be copied by denaturing the DNA, hybridizing it to "appropriate primers," extending the primers with DNA polymerase, and repeating the cycle again and again. As a first approximation, this sounds like PCR. "Experiments based on these lines of thought are in progress," the paper says, but such experiments were never published.

How good is DuPont's case? That depends a bit on whom you ask. DuPont first asked the U.S. Patent Office—which didn't think their argument amounted to much at all. Last summer the patent office reexamined the Cetus patent on the PCR process, and decided the Khorana papers did not make it invalid.

After that decision, DuPont doesn't have much of a chance, says Jim Johnson, a biotech patent attorney with the Atlanta firm of Jones, Askew and Lunsford: "The courts tend not to overturn what the Patent Office has done. The judge herself [in a pretrial opinion] said it would be an uphill battle."

Others aren't so sure. DuPont's argument hinges on the notion that the Khorana papers made PCR so obvious as to be unpatentable, says Iver Cooper, a biotech patent attorney with the Washington, D.C., firm of Browdy and Neimark—and that kind of argument has succeeded in some past biotech cases. Cooper also notes that DuPont will present more testimony and evidence in the trial than the Khorana papers and other written testimony they gave to the patent office.

Some of that testimony will consist of opinions from scientific luminaries such as Arthur Kornberg, who won the Nobel Prize for his studies of DNA polymerase. "The patent examiner blew it," says Kornberg. "Every one of his statements is either wrong or just not responsive to the information that was available to him." Anyone with a basic knowledge of biochemistry could have deduced how to perform PCR from the papers, Kornberg asserts, adding that the only reason no one did was that the technique was ahead of its time. Neither DNA sequences nor primers were available in the early 1970s, and by the time they were, cloning had been invented and had become the chosen method for copying DNA. PCR may have fallen out of sight, says Kornberg, but "it had been invented. It was in the public domain."

If Kornberg is right and DuPont prevails, it could leave the PCR market up for grabs to all the companies lined up to get a piece of the action. "I've got clients developing PCR who are very interested in how this case goes," said one patent attorney who requested anonymity. But Jacqueline Siegel, a biotech analyst with Hambrecht and Quist, says things may not be that bad for Cetus because of its head start in the field.

And what about a Cetus victory? "If DuPont loses, then those [Cetus] patents are incredibly strong," says Johnson. Bolstered by its victory, he says, Cetus is likely to go after other companies that—while they don't sell complete kits with instructions for doing PCR, as DuPont does—sell reagents or equipment that is tailored for the procedure.

*Kleppe, *et al., Journal of Molecular Biology*, v. 56, p. 341-361 (1971); Khorana *et al., Journal of Molecular Biology*, v. 72, p. 209-217 (1972); Besmer, *et al., Journal of Molecular Biology*, v. 72, p. 503-522 (1972); and Panet, *et al., Journal of Biological Chemistry*, v. 249, p. 5213-5221 (1974).

Even related processes may be vulnerable to an attack by Cetus, such as a constant-temperature method of DNA amplification being developed by several companies.

There are, however, a few skeptics who argue that even if Cetus does prevail, it will find that PCR is not the golden egg the company expects it to be. Although it will clearly continue to be a key technique in research and in forensics, PCR might not turn out to be a diagnostic bonanza, partly because other methods are coming along that may provide stiff competition. According to Siegel, "The issue...in terms of human diagnostics is how fast can you develop an accurate but sensitive and user-friendly format to diagnose human diseases and genetic conditions. I do think there will be some competition in this area."

So, whatever the verdict, there will remain many unknowns about how Cetus will fare. Patent disputes cost millions, and Cetus, with austerity measures in place after its interleukin-2 debacle, is not the kind of financial giant that can afford to take on every challenger. The same could be said of many fledgling biotech companies, which is why so many eyes in the industry are now turned to San Francisco.

■ MARCIA BARINAGA

British Science Under the Ax—Again

British scientists, who have been squeezed by tight budgets for the past several years, got more bad news last week. The Science and Engineering Research Council (SERC), the chief source of funds for academic research, announced that it will slash the number of new grants it will fund next year by 50% and cut the number of studentships by 15%. These reductions are part of a plan to balance SERC's books in the face of spiralling cost increases and a budget that council chairman Sir Mark Richmond describes as "lousy."

SERC's problems arise primarily from larger than expected pay awards, which resulted in a projected shortfall of £40 million (about $76 million) in the 1991-92 financial year, which begins in April. And the government added insult to injury by giving the council a budget increase of only 3% for 1992-3—much below the rate of inflation, which is currently running at around 9%. Faced with these dismal prospects, SERC last year asked each of its four subject boards to identify savings of 10%, and the council last week announced where the ax would fall.

Some boards found the task relatively straightforward, though painful. The Engineering Board spends 85% of its budget on research grants and studentships (see table). SERC agreed that it should cut these by 10%.

The Science Board had more trouble. It agreed to postpone a planned European high-power laser, a decision that Richmond said suited the other European partners in the project. More significantly, it currently supports two important neutron sources, ISIS at the Rutherford Appleton Laboratory outside Oxford, and the Institut Laue Langevin in Grenoble, France. It cannot afford both, but it could not decide which to abandon. So it proposed a "thoroughgoing review" of the need for neutron factories in coming years. That will take the best part of a year, during which the combined costs of ISIS and ILL will be met by cutting grants and studentships within the science board.

The Astronomy and Planetary Science Board is in a somewhat different position from the other three boards as much of its money is tied up in long-term projects. The board will make its promised contributions to the 8-meter telescope proposed by the U.S. National Science Foundation, though it will delay payments for 2 years, and it will continue to participate in the SOHO/Cluster mission of the European Space Agency, a solar satellite due for launch in 1995. But it may not be able to contribute to many other planned projects. The international Polar Cap Radar, due to be built above the Arctic Circle in Spitzbergen, and the joint Anglo-German Gravitational Wave Observatory have been cut, and British contributions to a U.S.-ESA ultraviolet satellite called Lyman/FUSE and the Polar Platform Earth Observatory are in jeopardy.

Spectrum X, a Soviet-led mission to map the cosmos in wavelengths from far ultraviolet to hard x-rays due for launch in 1993, is also in doubt. The first component of the x-ray telescope, being built at Leicester University, arrived from the USSR at London's Heathrow airport last week on the day before the SERC council meeting. One council member quipped that it was a pity Iraqi terrorists had not blown the shipment up; that would have cured at least one of their financial headaches. Though SERC now has no money in its budget for Spectrum X, it will be politically difficult for Britain to pull out of the venture because it is the subject of an intergovernmental agreement.

Intergovernmental agreements have proved especially troublesome for the Nuclear Physics Board's efforts to find ways to cut its spending. Of its £80 million budget, £48.5 million goes to membership of CERN and another £11.5 million provides grant support for British scientists at CERN. "If you're paying £50-odd million to join the club, you've got to pay the money to play the game as well," explains Sandy Donnachie, chairman of the Nuclear Physics Board. The SERC council ruled out any changes in the board's dealings with CERN, which left just £20 million from which to find a cut of £8 million. Donnachie offered to sacrifice the world-renowned Nuclear Structure Facility at Daresbury, near Manchester, which costs about £7 million a year.

The SERC council decided not to accept the offer, for the time being. "The work being done by the nuclear structure facility is first class," said Richmond, a sentiment echoed in more than 500 letters received since news of the threatened closure leaked out 2 weeks ago. And, because SERC would have to make substantial severance payments to lay off workers at Daresbury, closure of the laboratory would save little over the next 2 or 3 years. Instead, the facility will continue to operate at least until 1992 while Richmond tries to extract additional funds from the government for nuclear physics. "He has a very good case," said Donnachie, "but it's also a very high risk strategy." Richmond denied he was taking a gamble by bankrolling the Daresbury lab for another year. The alternative, he pointed out, would be unthinkable: Nuclear Physics could "save £5 million almost instantly by not awarding grants."

■ JEREMY CHERFAS

HOW SERC SPENDS ITS FUNDS

BOARD	TOTAL BUDGET (million pounds)	DISTRIBUTION (% OF EACH BOARD'S TOTAL)				
		GRANTS	STUDENT-SHIPS	CENTERS	INTER-NATIONAL	OTHER
ASTRONOMY AND PLANETARY SCIENCE	73.2	20.3	2.7	37.1	39.0	1.3
ENGINEERING	123.8	62.5	23.3	9.0	0.0	5.2
NUCLEAR PHYSICS	78.0	8.7	2.0	26.6	62.2	0.5
SCIENCE	128.4	40.2	22.1	25.8	9.9	2.0

* each row may not add up to 100 because of rounding