NEW POLICY UNDEFINED

ROCHE FREES PCR FOR CLINICAL TESTS

NEW YORK—As director of the DNA Diagnostic Lab at Yale University (New Haven, CT), Allen Bale conducts research that includes testing for the mutations that cause cystic fibrosis (CF). Bale wanted to offer the tests clinically, too. So Yale began negotiating with Hoffmann-La Roche (Nutley, NJ) for a license to use its polymerase chain reaction (PCR) amplification system in CF and other tests.

Yale was about to find out that although Roche doesn't restrict use of PCR for research purposes, it does restrict PCR for some clinical tests.

Roche offered a PCR draft contract "that was just completely out of our ballpark," Bale recalls. It called for yearly payments of $15,000, creditable against royalties equal to 15 percent of revenue for each test performed, plus 15 percent of every test after that. "If we were billing $30,000, we would have paid them half," Bale notes.

Even if Yale were willing to accept those terms, Roche would not offer a PCR license that included CF testing. To top things off, Roche insisted on a grantback clause that would give it rights to any process patented at Yale involving PCR technology.

Yale said no. For Bale, the consequences have been serious. "This has been a very unprofitable operation, because we can't do cystic fibrosis testing," he says. "I don't know how much longer my department is going to support a diagnostics lab that's losing money."

Scientists cry out

The university has tried further negotiations, and Bale believes that a new contract is imminent that will include CF testing and eliminate the yearly $15,000 payment. But his difficulties in dealing with Roche are not unique. "There's been such an outcry from the scientific community, including me, that the company has started listening," he says.

Late in January, anger over Roche's handling of PCR licensing boiled over—and the company promised to change its ways. The issue arose at a meeting on the commercialization of biology at Cold Spring Harbor Laboratory's Banbury Conference Center (Cold Spring Harbor, NY). Douglas McQuilkin, vice president of business development for Roche Molecular Systems, told the gathered group of scientists, journalists, congressional staffers, and corporate leaders that Roche would make the technology available to any lab without restrictions and would also revise its financial terms for licenses.

Roche has yet to define its new licensing policies, saying that it will make them known within "several weeks" of the Cold Spring Harbor meeting. The company has said, though, that it will make available the PCR-based tests that it had previously offered only on a highly restricted basis, including tests for HIV, tuberculosis, and Lyme disease, as well as paternity testing.

"I'm not sure anyone could demonstrate that the Roche policy already had retarded clinical development of PCR," says Philip Reilly, executive director of the Shriver Center for Mental Retardation (Waltham, MA), who is a member of the board of directors of Vivigen (Santa Fe, NM), a commercial reference lab. There was "a potentially very serious problem had Roche not changed its mind, which it apparently has." On the other hand, Reilly says, Roche's policies "were not so restrictive that they discouraged companies from developing the test" for CF, as he notes several labs have done.

Fluid situation

"The whole situation is very fluid," says Gerald Vovis, senior vice president for research and development at Collaborative Research (Waltham, MA), which offers PCR-based genetic testing under a license from Cetus (Emeryville, CA), the company that sold Roche the rights to PCR last year. So far, Vovis says, Collaborative has viewed the more generous license it negotiated with Cetus as "a competitive advantage" against labs holding PCR licenses from Roche.

Researchers' resentment over Roche's licensing rules is not the only reason for the company's turnabout. "It had a lot to do with James Watson orchestrating the meeting" at Cold Spring Harbor that included a number of government officials, notes Thomas Reed. One of Roche's most vocal critics, Reed is Vivigen's chairman and chief executive officer.

Roche needs to recover the $300 million it spent to acquire the technology from Cetus. The PCR patent expires in about a decade, yet many researchers argue that Roche would benefit more if the technology were used more widely. With more licenses made available, "there may be more incentive for others to develop the technology," including devising new tests, says Frank Fujimura, scientific director of molecular biology at Nichols Institute (San Juan Capistrano, CA), a commercial reference lab.

Roche also may be in danger of losing some business to competitors. Elizabeth Wagar, assistant director of the microbiology lab at the University of California-Los Angeles Medical Center, wanted a license from Roche to develop new cytomegalovirus (CMV) tests using PCR amplification. But Roche, she says, has not answered her requests. "They promise they'll call back and they don't," she says.

Alternative amplification methods

So Wagar is talking now with Baxter Diagnostics' MicroScan (W. Sacramento, CA) about using its 3SR reverse transcriptase amplification system. MicroScan, she says, may bring in equipment in March for preliminary CMV testing.

Vivigen is also looking into alternative amplification methods. One possibility, says Vivigen's Reed, is called Nasba and is offered by Akzo (Arnhem, the Netherlands). Vivigen is also holding talks with Abbott Laboratories (Abbott Park, IL) about using its ligase chain reaction (LCR) amplification system. "LCR appears to have magnitudes greater specificity than PCR," Reed says. With LCR, he adds, "you could pick out a cube of sugar from Lake Michigan. The real world is, you'd probably like to have them both, and I think that's the real world as Abbott sees it."

Reed acknowledges that LCR needs "much more careful handling than PCR" and would call for "a substantial capital investment," more than PCR requires. Nonetheless, Vivigen has signed a confidentiality agreement with Abbott, although it has not yet negotiated a license. Yet another signal amplification method, Q beta replicase, is under development at Gene-Trak (Framingham, MA).

It particularly galls Reed that his lab and others like it would be competing directly against Roche's reference lab, Roche Biomedical Labs. "They're setting us up to make prices high and give them a predatory opportunity to come in under those prices," Reed charges. Roche's CF-test terms for Vivigen, he says, called for a $15,000 annual payment against charges of $24 a test or 15 percent of revenues per test, whichever was greater. In addition, Roche stipulated that Vivigen could not deviate more than 10 percent from the listed price for a test.

Despite his efforts to find an alternative, Reed acknowledges PCR as an indispensable method for anyone running a diagnostics lab today. "It really is to molecular genetics as yeast is to baking bread," he says. **—Mimi Bluestone**