BIOTECHNOLOGY PATENTS

Chiron Challenged on Hepatitis-C Patent

A protracted dispute between a prominent hepatitis researcher and Chiron Corp. of Emeryville, California, landed in court last month. At stake: royalties—potentially amounting to millions of dollars—from a test for the virus that causes hepatitis-C (sometimes called non-A non-B hepatitis). The test, used to screen blood donations in the United States and many other countries, is one of Chiron's major revenue sources.

On 20 December, Daniel W. Bradley, a virologist who spent 23 years at the Centers for Disease Control and Prevention (CDC) in Atlanta, filed a federal suit against Chiron, claiming the company had used his research to isolate and clone the hepatitis-C virus and then shut him out of a patent resulting from the discovery. (Bradley also sued the federal government over an agreement it reached with Chiron, which he signed.)

Chiron, in a public statement issued on 28 December, said Bradley did not contribute to the key part of the research; the company characterized the suit as part of a "desperate strategy" by companies that have tried unsuccessfully to challenge Chiron's hepatitis-C patents. Chiron noted that Bradley is being represented by Leslie Misrock, a prominent biotechnology patent lawyer whose firm represents a Dutch company that has fought Chiron's claims on hepatitis-C.

This legal battle stems from what was once a fruitful collaboration between Bradley and Chiron. Bradley, who retired from CDC in May 1994 and is now chair of the World Health Organization's Steering Committee on Polio and Hepatitis Vaccines, says in his complaint that he became interested in hepatitis in 1977, when he was approached by a company that provided Factor VIII to hemophiliacs. The company was concerned that non-A non-B hepatitis might be transmitted through its product.

Bradley managed to infect chimpanzees with the suspect Factor VIII and concluded that the animals were an appropriate model to study non-A non-B hepatitis. In particular, he discovered that levels of certain liver enzymes provided a key marker for high titers of hepatitis virus in the blood during the chronic phase of the disease.

That discovery caught Chiron's attention, and in 1982 Chiron entered into a collaboration with Bradley. Over the years, Bradley says he supplied Chiron with "over 2500 milliliters of a very rare commodity, a unique commodity,"—the high-titer plasma. In May 1988, Chiron announced that it had isolated the hepatitis-C virus from these samples and cloned its genome. The achievement brought scientific recognition to Bradley and Chiron researchers Michael Houghton, Qui Lim Choo, and George Kuo, in the form of several joint awards.

But harmony did not last long. One of the first breaks in the apparent amity came when Chiron filed a patent application that did not include Bradley as a co-inventor. Bradley says federal lawyers challenged the claim in 1989 and proposed an agreement that would assign CDC a half interest in patents relating to hepatitis-C. Chiron would be given a 10-year exclusive license and would pay a royalty of 3% of net sales. Chiron declined to go along and hired former Department of Health and Human Services Secretary Joseph Califano to represent it. Califano sent a letter disputing Bradley's claims and arguing that the company did the key work in isolating and cloning the virus. Califano noted in particular that the hepatitis-C clone was "obtained by using a specific protocol designed by a Chiron scientist."

In 1990, the government reached an agreement with Chiron under which the company would pay Bradley $67,500 a year for 5 years "in recognition of his contributions to the field of [non-A non-B] research," and enter into a $2.5 million, 5-year cooperative research and development agreement with the federal government on hepatitis-C research and tissue culture. Bradley says he did not take part in the negotiations. He signed the agreement (in March 1990), he says in his complaint, because he had been diagnosed with prostate cancer and was concerned about his ability to provide financially for his family. Chiron was awarded a U.S. patent for a hepatitis-C test on 27 September 1994; the company has 26 similar patents in 20 other countries.

If Bradley's suit goes to trial, the outcome is likely to hinge on whether Bradley's level of collaboration was sufficient to be named co-inventor—a legal standard more stringent than the requirements for co-authorship. Bradley claims his development of the capacity to produce high-titer material "was a critical step that enabled the [non-A non-B] viral genome to be cloned." But Chiron Vice President Robert P. Blackburn says the work, while important, was not sufficient to give Bradley co-inventor status. "It's not enough to make the clone, but you have to select the proper clone out of millions of wrong ones," he says.

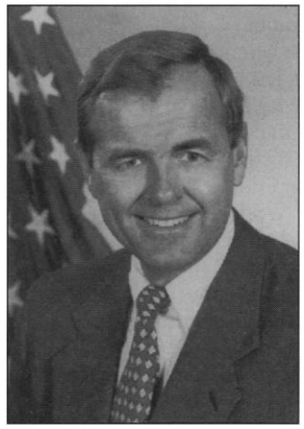
–Victoria Slind-Flor

Victoria Slind-Flor is in the San Francisco bureau of the National Law Journal.

BIOTECHNOLOGY PATENTS

Rules Would Drop Need for Clinical Data

The biotechnology industry has wrung a significant concession from the U.S. Patent and Trademark Office (PTO). Last month, PTO Commissioner Bruce Lehman announced that patent examiners will no longer require companies to back up their patent applications with clinical data showing a product works in people. From now on, less expensive animal tests or in vitro data will be sufficient evidence that a product is likely to be effective, at least as far as PTO is concerned.



Responsive. Patent chief Bruce Lehman has listened to concerns of biotech companies.

The industry has long argued that the PTO has usurped the role of the Food and Drug Administration (FDA) in forcing companies to spend millions of dollars to conduct clinical trials to prove that their products will be effective. This requirement, they say, presents them with a Catch-22: It's hard to raise venture capital to test a product that isn't patented, but they can't get a patent until they have conducted the tests (*Science*, 28 October 1994, p. 537). Biotech officials have also complained that patent applications are frequently stalled for months because PTO examiners challenge the clinical data. David Beier, vice president of public policy for Genentech Inc., says, for example, that "well over half" of his company's 212 patent applications snagged on the requirement for clinical data before a patent was issued. "This is an unrealistic standard," says Daniel Chambers, counsel for Viagene Inc.

Lehman concedes that this has been a problem. "Many people say that some examiners routinely challenge the sound scientific conclusions of recognized experts in the field. This practice will not be condoned under the new guidelines," Lehman said at a press conference last month. The PTO's new policy, which is expected to be published this week in the *Federal Register*, requires patent examiners to have compelling evidence that an invention will not be useful in order to reject it on those grounds. "No longer will examiners act like

inquisitors," predicts Lisa Raines, vice president for government relations at Genzyme Inc. To ensure compliance with the new guidelines, the PTO plans to supplement its staff of 165 biotech examiners—about half of whom have Ph.D.s—with at least two people who will review all actions taken on biotech patents.

Biotech officials insist that the new guidelines will not jeopardize public health because the FDA will still require clinical data before approving a new drug or device. "It's not the job of the patent office to serve as a supermedical agency to decide whether or not a drug works," says Beier. The guidelines—for which the patent office is accepting comment until 24 February—"will assure the division of responsibility between the patent office and the FDA," he says. FDA officials agree. "As far as we can tell, the patent office's decision will not impact our operations or procedures," says an FDA spokesperson.

–Richard Stone

NATIONAL INSTITUTES OF HEALTH

Broder to Join Exodus From NCI

Samuel Broder, director of the National Cancer Institute (NCI), surprised top officials at the National Institutes of Health (NIH) last month when he disclosed that he will leave the government in April to join a private company. After 22 years at NIH, six as NCI director, Broder told *Science* he has been in government long enough and looks forward to the "enormous freedom" scientists in the private sector enjoy. Broder will become vice president and chief scientific officer of the IVAX Corp. of Miami, a producer of generic drugs and cancer therapeutics, which is developing a synthetic form of the anti-cancer agent taxol. Broder is credited with strengthening clinical research at a time when NCI's total budget was under pressure.

Broder's decision to quit is the latest in a string of resignations and retirements that leaves NCI "hollowed out," as one senior staffer puts it. With a budget of $2 billion and more than 2000 employees, NCI is the largest unit of NIH. The change of leadership comes at a difficult time for NCI, as the institute recovers from criticism of alleged lax oversight of clinical trials and struggles to cope with austerity measures affecting all government agencies.

The institute has been without a deputy director since early 1994, when Daniel Ihde, the former deputy, left to join the faculty of Washington University in St. Louis. He was followed in August by Richard Adamson, former director of the division of cancer etiology, who left NCI to head the Washington office of the National Soft Drinks Association. And Bruce Chabner, director of the division of cancer therapy, announced recently that he will leave in April to direct cancer therapy at the Massachusetts General Hospital in Boston. Others who have left NCI since 1993 without being replaced include Peter Howley, chief of the laboratory of tumor virus biology, who moved to Harvard Medical School; Stuart Aaronson, chief of the Laboratory of Cellular and Molecular Biology, to the Mount Sinai Medical Center in New York City; and Takis Papas, chief of the Laboratory of Molecular Oncology, to the Medical University of South Carolina in Charleston.

Still more will leave this year: Michael Sporn, chief of the Laboratory of Chemoprevention, plans to retire in April to join Dartmouth Medical School, and Robert Gallo, chief of the Laboratory of Tumor Cell Biology, says he is considering several outside offers and will accept one of them soon.

This exodus, according to some observers, has been prompted in part by the growth of attractive nongovernment jobs in cancer research. Biomedical centers have begun to recognize the scientific and economic value of having a powerful oncology department, says one top NCI official, who points out that a recent study done for Johns Hopkins University shows that the average cancer patient runs up a hospital bill two to three times that of the average noncancer patient. This is an important business consideration for university hospitals, which have hired away some of NCI's top researchers with lucrative job offers. Broder, who was recruited to his new job by IVAX chair Phillip Frost, member of an NCI advisory board, will reportedly at least double his current $120,000 government salary.

B. BRANSON/NCI

Under the microscope. Broder says distrust of public officials is making government service hard to take.

But the environment at NCI may also be partly to blame. Broder, who notes that he served as the "lightning rod" for critics of the federal war on cancer, has harsh things to say about public and congressional distrust of public officials. "You would not believe the number of restrictions that have been placed on high-level employees," such as limits on honoraria or rules against involvement in nongovernment projects. "Life has gotten a lot harder for government service," Broder says. At the same time, the job of managing NCI is getting tougher. Broder points out that, in constant dollars, the institute's budget for cancer-related activities has not increased since the early 1980s, while other parts of NIH have grown. And he adds, "I don't particularly look forward to the level of extreme budget austerity that is coming down the line."

An even harsher assessment comes from former NCI staffer Adamson, who says the institute has been harried by political lobbies, stressed by a shortage of resources, and subjected to "micromanagement" from Congress and the Administration. And he contends that Varmus has attempted to interfere "for political reasons" in the NCI director's choice of appointees, emphasizing ethnic and gender diversity, all of which has led to a loss of morale.

Both Broder and Varmus contest this bleak interpretation. "All biological systems go through a cycle of renewal," and that's what NCI is doing now, says Broder. "There was an influx of very strong people in the late 1960s and 1970s, and their term of government service is now coming to an end." Broder also brushes aside reports that he and the NIH director have clashed, saying his resignation has nothing to do with "rumored personality differences" between himself and Varmus. Varmus agrees, saying that "any suggestion that [Broder] and I are not on good terms is ridiculous. ... We've gotten along very well; he's got a good sense of humor, and he's given me a lot of good advice." That good relationship was not evident, however, in Broder's leave-taking: Because Varmus missed a phone call from Broder, he learned of his plans the day Broder announced them at a staff meeting.

Given the difficulties any new NCI director will face, it could be hard to recruit a new chief. But Varmus is optimistic. The NCI director is appointed by the president, and Varmus expects the Administration will get a search under way quickly and have a candidate ready for consideration by April.

–Eliot Marshall