## NIH in Danger of Losing Out on *BRCA1* Patent

The discovery of *BRCA1*, a cancer susceptibility gene which in its defective forms accounts for about 130,000 breast cancers in the United States alone, was a welcome event (*Science*, 23 September, p. 1796 and 7 October, p. 66). But as reported in the 7 October issue of *The Cancer Letter*, the celebrations barely had time to die down before a duel over proprietary ownership of the gene began. At issue: whether the National Institutes of Health (NIH), which contributed both researchers and funds to the successful search, will get to share patent rights to the gene with the University of Utah and the biotechnology firm Myriad Genetics Inc. of Salt Lake City.

The stakes are high because the patent—if it issues—is a potential money spinner, providing its holders with a 17-year monopoly on the sale of diagnostic tests and therapeutics developed from *BRCA1*. If NIH owned a share of the patent, it would not only get a cut of the royalties on the sales, but it would also have a say in which companies receive licenses to develop the products and under what conditions.

The search for *BRCA1* was conducted by a mega-team—45 researchers spread across the University of Utah, Myriad, the pharmaceutical giant Eli Lilly of Indianapolis, Montreal's McGill University, and the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, North Carolina. But the patent application has been filed by the University of Utah, and the NIEHS investigators are not named as co-discoverers. The university has agreed to license commercial use of the patent exclusively to Myriad, which has sublicensed rights to Lilly, and to a Lilly subsidiary, Hybritech of San Diego.

The patent filing has spurred NIH's patent lawyers to examine their options. "It's a very sensitive issue. We're looking at it," says NIH Director Harold Varmus. Although no one contacted by *Science* would reveal exactly what NIH is demanding, Varmus's spokesperson Anne Thomas confirmed that "[NIH] patent lawyers are in discussions with their counterparts at the University of Utah."

For their part, the Utah scientists—including Mark Skolnick, who from his joint appointment at Myriad and the University of Utah oversaw the whole consortium, and Myriad director of research Alexander Kamb—defend the patent application. Without patent protection, neither Myriad nor any other company can afford to invest the resources needed to develop *BRCA1*-based therapeutics or tests, Skolnick says. What's more, Kamb points out, Myriad and its corporate sponsor Lilly contributed the lion's share of funds and personnel to the *BRCA1* isolation effort. Half of the 45 people who co-authored the *BRCA1* article are employed by Myriad, and an additional six by Lilly. Myriad's president and CEO Peter Meldrum says Lilly put $4 million into the project, and in April of 1993, Myriad raised another $10 million in a private placement offer. NIH, meanwhile, funded the six-person NIEHS team. NIH also provided approximately $2 million in research grants to the University of Utah, according to David Goldgar, a senior member of the university's *BRCA1* team.

But, in fact, the dueling parties' contributions of time, dollars, and people power have less to do with determining who is legally entitled to hold the patent than do their intellectual contributions. "To be a co-inventor," says patent attorney Max Hensley of Gilead Sciences in Foster City, California, "you must have had a role in the conception of the invention." What constitutes inventorship is one of the murkiest areas of patent law, and liable to lead to unpredictable rulings when patent disagreements result in litigation. For that reason, says Hensley, "it's certainly better for all parties to sit down and discuss these things before they go to court."

Better still would be to agree on commercial rights at the start of a collaboration. "Intramural researchers are supposed to have a formal agreement if they enter into in any form of collaboration with a partner in industry or university," says Barbara McGarey, deputy director of NIH's Office of Technology Transfer.

The NIEHS investigators had no such agreement with the University of Utah and Myriad, however. According to NIEHS team leader Roger Wiseman, the team tried to establish a Cooperative Research and Development Agreement (CRADA) with Myriad, "but it was never completed due to concerns from the Lilly cooperation." These concerns, he says, had to do with the CRADA's fair-pricing clause—a standard clause in NIH's CRADA agreements that drug companies hate because it gives the government leverage over the price of ensuing products (see *Science*, 22 October 1993, p. 496). A CRADA might not have avoided the current brouhaha, however. The agreements ensure that the industrial partner gets first dibs on a license if the government laboratory ends up holding the patent, but don't necessarily specify ahead of time who would be named on the patent.

Despite its lack of agreement regarding the commercial spoils, the NIEHS team did show foresight over how the academic glory would be divvied up: Two years ago, the NIEHS and Utah teams co-signed a document detailing the order of authorship in "the unlikely event" that they isolated *BRCA1*.

–Rachel Nowak

computers to analyze the data. They hoped to use the unique sequences of these ESTs, whose functions would be completely unknown, to reach into databases and human tissue to fish out whole genes.

Although Venter's lab continued to receive NIH intramural funding, he claims that NIH's top officials declined to provide funds to scale up his processes and zero in rapidly on cDNAs. For example, when his lab collaborated with Applied Biosystems Inc. on the first automated gene sequencer, his work was financed not by NIH but primarily by the Department of Defense. By last year, Venter and his top staff had quit the government, teamed up with HGS, and made a pledge to deliver commercially valuable data to HGS and SmithKline Beecham.

In a short time, TIGR and HGS had assembled a battalion of 80 sequencing machines and built up a collection of 300 libraries of cloned human genetic material. They poured tens of millions of dollars into computerized analysis of the sequence data, and began to sequence not only the short EST fragments but also full-length genes themselves. According to HGS president William Haseltine, this joint effort has produced more than 35,000 unique ESTs and will soon be able to identify 80% of all major human genes.

Claims like this may sound grandiose, but they recently gained credibility when Bert Vogelstein of Johns Hopkins University went hunting for genes in the HGS-TIGR database. Vogelstein, who had already identified several human colon cancer genes, was also aware of a proofreading gene in bacteria—one that corrects errors in DNA. If humans have a similar gene, Vogelstein speculated, defects in it might open another route to cancer. Vogelstein made a one-time agreement with HGS-TIGR that allowed him to search the EST database for traces of a human gene that might resemble the bacterial version. The search took minutes: Vogel-