identifying some 50,000 genetic markers in individuals that are linked to specific abnormalities or diseases. Now that the human genome has been nearly sequenced (see p. 2294), Ledley and BU are betting that biotech firms also will find the Framingham data a valuable tool.

Before Ledley can realize that dream, however, the company must win the support of residents, other universities involved in the study, and the National Heart, Lung, and Blood Institute (NHLBI) in Bethesda, Maryland, which has put up $34 million over the years. NHLBI director Claude Lenfant could not be reached for comment, but his staff says he plans to visit BU soon to discuss the new company and the institute's concerns about privacy, data access, and conflict of interest. NHLBI officials and researchers outside BU want continued access to the data, whereas residents—who for the past decade have signed consent forms for genetic analyses of their blood and tissue—want to safeguard their health records, which include psychosocial data. The relationship of BU researchers to the new company must also be resolved. "This is a difficult dance," says Caplan.

But Ledley and BU managers say they know the moves. The revamped database will remain available to researchers at no cost. "We're not taking any data out of the public domain, and we're not selling patient data," Ledley says. "We're selling tools to analyze that data." In addition, BU researchers involved in the study will be precluded from owning company stock, although they will be able to serve as consultants. "We want to preserve the integrity of the study," says BU associate vice president David Lampe.

A 25 April letter to the 1000 or so surviving study participants spoke about "entering an important new era of medical research" and promised to maintain "exemplary ethical standards." It also proposed an ethical review group, to be based in Framingham, and said "a portion of its resources"—perhaps a chunk of stock—would be put in a trust controlled by a community board. "You can never pay people back, but you can show social responsibility," Ledley says.

Jay Lander, a Framingham attorney and vice chair of an organization called Friends of Framingham Heart Study which represents participants, says so far the community feels "surprised and somewhat apprehensive" about the new company. Pending a clearer idea of how the venture might affect the study, he says, "this thing isn't going anywhere." But some ethicists are intrigued by the plan and see its potential value to society. "I would caution against a knee-jerk reaction about this. It's not a bad thing," says Norman Fost, director of the medical ethics program at the University of Wisconsin, Madison.

To signal its good intentions, the company intends to give the proposed board $150,000 to hire an ethicist. Ledley has suggested native son Caplan, noting that "he would be accountable to the community, not to us." Caplan says the unusual arrangement would be workable if the company's contribution doesn't come with any strings attached. And he thinks that BU officials realize they are under close scrutiny. "This is a monumental study," he adds. "Doing it right is crucial."

—ANDREW LAWLER

PATENT DISPUTES

## Biotech Giants Butt Heads Over Cancer Drug

Mountain sheep settle disputes by knocking their heads together until one of them gives up and walks away; biotech companies do much the same, except they enlist patent lawyers to do the head-butting. The most recent display of this kind centers on an important new breast cancer drug, Herceptin. Developed by Genentech Inc. of South San Francisco in the 1990s, Herceptin has been generally available only since November 1998. Already, though, it has won acceptance as an adjunct to other therapy and is earning big revenues for the company—$68.7 million in this year's first quarter alone, according to Genentech. But success breeds competition. On 8 June, Chiron Inc. of Emeryville, California, challenged Genentech's patent claims and sued for a share of the profits.

**Chiron accuses Genentech of "willful, wanton, and deliberate" patent infringement.**

Chiron's 4-page complaint, filed in the federal district court in Sacramento, California, accuses Genentech of "willful, wanton, and deliberate" infringement of one of its patents. It seeks an unspecified amount of money for damages, including a trebling of normal penalties "due to the willful nature of Genentech's infringement." Sean Johnston, vice president for intellectual property at Genentech, says Chiron's patent is "invalid"; the company plans to say so in an answer to be filed with the court in August. The case is being closely watched in the biotech industry not just because of the money at stake but also because it involves one of the first therapies to emerge from the burgeoning field of cancer genetics.

Chiron launched its attack after winning what some observers call a "submarine patent"—one that had been quietly wending its way through the U.S. Patent and Trademark Office (PTO) for the past 16 years. On 25 April, PTO awarded Chiron U.S. Patent 6,054,561, which traces its lineage back to an application filed at the PTO in February 1984 by scientists from another California biotech firm, the Cetus Corp. Cetus was merged into Chiron in 1991. Among the patent's 31 claims is the invention of a monoclonal antibody that binds to a cell surface receptor called c-erbB-2, also known as HER2—the very target that Herceptin binds.

For its part, Genentech owns six or seven patents in the area, according to a spokesperson, including one (U.S. Patent 5,677,171) that claims "a monoclonal antibody which specifically binds to the extracellular domain of the HER2 receptor and inhibits growth of SK-BR-3 breast tumor cells. ..." Genentech filed for its patent in 1988 and received it in 1997.

It's "not uncommon at all" to have patents appear to overlap, says Robert Blackburn, Chiron's chief patent counsel. He suggests that the Cetus-Chiron patent is broader and, more important, was filed earlier. Blackburn claims Genentech talked about getting a license from Chiron several years ago, but "they seemed to lose interest and go away."

"If [Chiron is] saying they offered reasonable royalty terms, I would disagree," says Johnston, who acknowledges that the two companies did discuss a license. Johnston argues that in this case Chiron owes its success at the PTO more to clever management of a fragmentary legal claim than to diligent investigation of the clinical uses of HER2. "We're confident that we can demonstrate that the Cetus-Chiron scientists were not the first to make antibodies [to the c-erbB-2 receptor]," Johnston adds. For example, he notes that Robert Weinberg of the Whitehead Institute in Cambridge, Massachusetts, identified the key protein in 1982. This and other early research, Johnston claims, can be used to disprove Chiron's claim of priority in 1984. Blackburn, without going into details, dismisses these arguments as "a red herring."

Why is it taking so long for these disputes to surface? "Unlike chip technology," says Rachel Krevans, lead outside counsel for Genentech at the firm of Morrison & Foerster in San Francisco, "biotech products take a long time to mature." Questions about who profits from them take even longer to answer, "and that's why we're litigating the science of the early 1980s in the year 2000."

—ELIOT MARSHALL