HIV Experts vs. Sequencers in Patent Race

HIV researchers have electrified the field for the past year with a string of discoveries that revealed in detail how the AIDS virus grapples onto and enters certain human cells. At least five scientific teams zeroed in on one molecule in particular—the CCR5 receptor on immune system cells—and found that it acts like a key, opening the cell to HIV infection. If the receptor is absent or altered, the invader has trouble getting in.

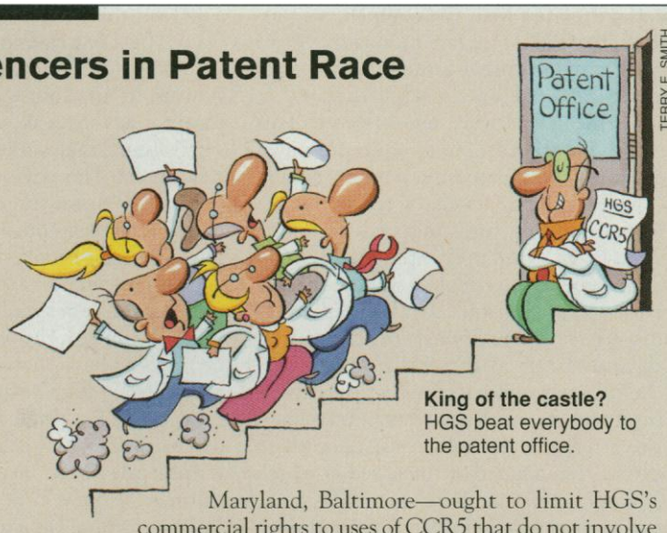
This is high-impact science, with high commercial stakes as well: Some observers predict that the CCR5 discovery will lead to new drugs designed to block HIV infections (see main text). It should come as no surprise, therefore, that half-a-dozen groups are vying for priority on CCR5, and many are filing patents. But these competitors may themselves be surprised to learn that a company that was not directly involved in these HIV studies—Human Genome Sciences (HGS) of Rockville, Maryland—appears to have beaten everyone to the patent office.

William Haseltine, HGS's chair, confirms that HGS applied for a patent on the DNA sequence coding for the CCR5 receptor back in June 1995, long before the recent scientific reports were published. HGS's early claim points up an issue that's likely to be more and more vexing to DNA patent seekers. Since the early 1990s, companies doing large-scale DNA sequencing have been filing claims on thousands of genes and gene fragments, often without knowing exactly what the DNA codes for. HGS has been among the most aggressive in this game, and CCR5 may be one of the big fish it has snagged.

HGS's chief patent counsel, Robert Benson, declines to talk about the company's pending application at the U.S. Patent and Trademark Office. (The U.S. review process is confidential.) But Benson did provide a copy of HGS's international patent filing (WO 96/39437). It was released in December, in compliance with an international treaty requiring that such applications be published 18 months after submission. An expert in this field, Edward Berger of the National Institutes of Health (NIH), after hearing the sequence, confirmed that it is the same CCR5 sequence he and others have reported.

HGS said in its patent application that it had found a gene for something it "putatively had identified as a chemokine receptor." HGS asked for rights to variations on the sequence and claimed a list of wide-ranging applications, from uses in gene therapy to drug manufacturing to disease monitoring. But HGS did not guess at CCR5's role in HIV infection. In fact, it didn't even mention HIV.

This omission, according to HIV experts like Robert Gallo—director of the Institute of Human Virology at the University of Maryland, Baltimore—ought to limit HGS's commercial rights to uses of CCR5 that do not involve HIV. But Gallo himself has a stake in this matter. He headed a team of NIH scientists that discovered in 1995 that chemokines play a key role in HIV infection. After the report was published, other researchers zeroed in on the chemokine receptors. In 1996, they identified two of them—CXCR4 and CCR5 and their variants—as key to HIV infection. Many of these teams have now filed for patents on these discoveries, including NIH, Gallo's new institute, and a group led by Marc Parmentier at the Free University of Brussels—the first to make the CCR5 sequence public last spring.



King of the castle? HGS beat everybody to the patent office.

But the quality of this scientific research may have little bearing on the authors' commercial rights. As HGS's Benson says: "Scientific credit is one thing; patent law is another." HGS's outside attorney, Jorge Goldstein of the Washington, D.C., firm of Sterne, Kessler, Goldstein & Fox, explains that whoever is first to patent a DNA sequence—for any use—can lock up subsequent uses. A patent of this type is called a "composition of matter patent," and it prevents anyone from using the DNA sequence without the patentee's permission. If a later inventor patents a new use, Goldstein says, it may create a stalemate in which neither patent-holder prevails. The common solution is to negotiate a cross-licensing agreement and share royalties.

It remains to be seen whether HGS will actually win a patent on the CCR5 sequence. If it does, several other teams of biologists will be disappointed. But Goldstein says that "for 100 years, chemists have known that getting a [composition of matter] patent on a compound is the key." And he adds that it's time for biologists to wake up and "discover the patent system in all its glory." **–Eliot Marshall**

many anti-HIV drugs to an early grave: resistance. Indeed, in theory, HIV mutants might resist drugs that block, say, one part of CCR5 but not another. Even worse, a CCR5 drug could encourage the growth of a virus that prefers CXCR4; while it's far from clear-cut, HIV strains that use CXCR4 may cause disease more quickly.

Biochemist John Moore of the Aaron Diamond AIDS Research Center (ADARC) in New York City worries that companies are going to exaggerate their early findings in HIV trials with chemokine-receptor blockers. "I think there's going to be a lot of hot air and smoke," says Moore. "Exploitation clinically? Come back in a couple of years."

Vaccine dreams

The wait for a payoff likely will be even longer when it comes to vaccines. But some researchers believe the time line can be shortened if the new chemokine work helps answer a big mystery: Why do some AIDS vaccines protect animals from "challenges" with infectious doses of the AIDS virus?

AIDS vaccines have been tested most extensively in monkeys, which develop an AIDS-like disease when they are infected by a close kin of HIV called SIV. Although several vaccines have protected monkeys from SIV infection, no one has yet convincingly elucidated the mechanism behind that protection. Some studies suggest that the protection correlates with vaccine-induced anti-SIV antibodies, which "neutralize" the virus before it infects cells. Other experiments point to cytotoxic T lymphocytes (CTLs), which selectively kill already-infected cells, as a key correlate of protection. But in yet other studies, neither CTLs nor antibodies explain much of anything. Now, primate researchers are looking for a correlation in chemokine levels—and they are finding potentially promising leads.

The first such study appeared in last July's *Nature Medicine*. Thomas Lehner of United Medical & Dental Schools of Guy's Hospital in London reported that high RANTES, MIP-1β, and possibly MIP-1α