Gene Splicers Square Off in Patent Courts

Several disputes over patent rights, currently in preliminary stages, could eventually shape the biotechnology industry

A variety of patent disputes has erupted between biotechnology companies during recent months. Though not unexpected—the companies have been stepping all over one another's feet in setting their early research goals—the outcomes of these contests could have a big effect in shaping the biotechnology industry. Not only could they influence which small companies survive but also how they conduct their research.

The need to seek patents is virtually unavoidable for biotechnology companies. For one thing, some investors insist on using patents as an important index of a company's technical abilities. For another, the alternative of relying on trade secrets is not very effective when so many research groups are working on similar problems using nearly identical methods. Consequently, biotechnology patent applications have been flooding in. Genentech, for example, boasts of having more than 1400 applications under consideration around the world. Neighboring Cetus says it budgets $1 million per year for its patenting efforts and has more than 100 U.S. patent applications pending. For both companies the basic conclusion is the same: patents matter. "Billions are at stake," says Genentech patent attorney and vice president Thomas Kiley. "Biotechnology will be a litigious industry for some years to come."

By itself, acquisition of a patent does not offer much in the way of security. For example, Stanford University, which soon will be awarded a broad and fundamental product patent covering many uses of recombinant DNA techniques—the Cohen-Boyer patent (*Science*, 20 April, p. 264)—already is setting aside funds to defend the patent against infringement. Other similarly broad biotechnology patents sometimes are being ignored, industry sources say, with the expectation that they will not withstand legal challenges.

Particularly for small companies, the costs of legal actions involving patents can prove staggering not only because of the companies' limited budget resources but also because key personnel from small staffs may be forced to devote precious time to dealing with legal maneuvers. "We'll tend to see these suits in biotechnology because the small companies are vulnerable," one patent attorney told *Science*. "Some companies will try to go after the fledgling upstarts if they have good technology but not much in the way of legal reserves." In the process, the most vulnerable companies could be destroyed or absorbed by their challengers. Lawsuits also can provide a means to a less extreme but also damaging result, offering a way to delve into a company's research—before it is ready for disclosure—to see whether a patent is being infringed.

Against this backdrop, several biotechnology patent contests have begun. Most are in their early stages—indeed, the participants themselves liken their legal maneuvers to those of warships letting loose shots across the bow. However, if some of the contested products prove their clinical worth, these preliminary patent maneuvers could prove crucial. The contests include:

> Some companies will go after the fledgling upstarts that have good technology but small legal reserves.

- Genentech and Hoffmann–La Roche in partnership against Biogen and Schering-Plough over rights to α-interferon (a comparable battle soon will extend to γ-interferon).
- An impending battle over interleukin-2, a polypeptide that modulates the immune system, that could include more than a half-dozen major contestants.
- A patent infringement suit over purification of blood factor VIII. This was filed in November 1983 by Revlon, which has licensed technology from Scripps Clinic and Research Foundation, against Chiron and Genentech, which announced 25 April that its scientists have produced this protein using recombinant DNA techniques.
- A patent infringement suit filed early in March by Hybritech against Monoclonal Antibodies that could affect the latter's freedom to develop a range of immunodiagnostic products.
- Claims by GCA/Precision Scientific Group to hold patent rights on a technique for fusing cells with pulsed electric charges. These claims could hamper efforts of DEP Systems, which is marketing an electrofusion device that operates on the same principles (see box).

The first official movements in the interferon skirmishes revolve around α-interferon, which is being tested clinically for its antiviral and anticancer activities. "If it [interferon] turns out to be of clinical importance, it will be a major battle between giants," says one insider. Those giants include Biogen and Schering-Plough, whose α-interferon collaboration became widely known 4 years ago, and Genentech and Hoffmann–La Roche, whose officials plan to contest the validity of the α-interferon patent. Biogen was notified recently by the European Patent Office that a patent soon will be issued, beginning a 9-month period when it may be challenged (*Science*, 9 March 1984, p. 1047). This debate could be joined by others—Cetus, for example, says that it is considering raising objections.

Early in 1980 Biogen announced that its scientists in Switzerland had cloned the gene for α-interferon. "Putting Biogen on the map" is what former Harvard professor and Biogen cofounder Walter Gilbert then called it. Little was then known about the interferon molecule, and no one realized that it contains a peptide sequence that is lopped off when the protein leaves the cell where it is made. This difference between the precursor and "mature" forms of α-interferon is the central issue of the patent debate.

Attorneys representing Genentech and Hoffmann–La Roche say that collaborating scientists from these two companies, not from Biogen, were the first to clone and express the mature form of α-interferon—the form being clinically tested. But Schering patent attorney Bruce Eisen, who has a major responsibility for defending the Biogen patent, contends that "the [Biogen] patent application discloses 'mature' interferon" because it undoubtedly was present in the mixtures. Moreover, he claims that "the heart of this invention was identifying the [α-interferon] human gene. All the rest is 'state of the art.' "

A spokesman for Hoffmann–La Roche

counters, "They [Biogen] updated their application to disclose mature interferon. Once their patent application is examined, it will show they produced the mature protein after Genentech [did]." Hoffmann–La Roche patent attorney George Gould adds, "Our argument is that making the mature form was an advance."

Regardless of which companies obtain the European patent to α-interferon, the fact that such a patent may be granted is noteworthy. The genetically engineered version of the molecule resembles that made naturally, and there has been considerable speculation whether that similarity would eliminate the possibility of obtaining a product patent. "Products of nature" customarily are not patentable.

A comparable argument over γ-interferon has begun, although it has not advanced quite so far because none of the parties yet has been notified that they are to receive a patent. Both Genentech and Biogen have filed applications. Genentech is likely to be cast in the defender's position on γ-interferon, because its application was filed earlier than rival Biogen's.

A key issue in the impending battle over γ-interferon, with wide implications for the biotechnology industry, is whether a company must deposit its genetically engineered organism in a central bank, such as the American Type Culture Collection. (This has been a common practice for the drug industry, for example.) Some patent attorneys argue that failure to do so may invalidate a patent application, which by statute must describe an invention fully enough to be used by others "skilled in the art."

"We have not deposited a γ-interferon producing microorganism," says Genentech's Kiley, explaining that this is considered unnecessary for describing how to make γ-interferon. "We now have the capability to synthesize genes as a matter of routine, once their sequence has been revealed." Knowledge of that sequence is adequate for describing the invention and satisfying the patent law, he claims. "There are real economic consequences to making deposits of valuable microorganisms where the law does not require such deposit," he continues. "If deposit is required . . . then your patent claims [could] be limited to the very microorganism you have deposited [and] your competitors free to put your gene into others."

However, it is being argued in some circles that, no matter what other qualities may be embodied in Genentech's patent application for γ-interferon, the company's refusal to deposit the organism may be construed as a "failure to properly describe its invention."

A similar issue has arisen in the debate over the validity of patent claims for interleukin-2, one of a family of scarce proteins of the immune system being eyed for their potential in treating cancer and other diseases. Published European patent applications indicate that Takeda Chemical Industries in Japan appears to have filed earliest for a cloned version of interleukin-2, claiming a priority of late 1981. However, Biogen among others has questioned whether the Takeda scientists deposited their genetically engineered organism upon filing.

Another potential problem, according to Cetus' patent attorney Albert Halluin, could be a contest over whether the Takeda patent application covers steps beyond cloning the gene. Another Japanese scientific group, headed by Tadatsugu Taneguchi, has generally been credited by the scientific community with first cloning and expressing the interleukin-2 gene. But this group, whose patent application assigns rights jointly to the Japanese Cancer Research Foundation and Ajinomoto, filed its application a few months later than Takeda.

Many eager corporate contenders are thronging to the study of interleukins, and some are counting on new technological twists to establish a niche in what is expected to be a substantial market. Cetus, for example, has developed genetically engineered versions of interleukin-2 that it calls "muteins." The name

Fusion Technique Causes Fission

Herbert Pohl of Oklahoma State University and Ulrich Zimmermann of the Nuclear Research Center in Jülich, West Germany, once were collaborators. They worked together on an esoteric use of pulsed electric fields, which can induce living cells to fuse. This technique, which now is recognized to have wide application to biotechnology because it can be used for constructing hybridomas, is being developed commercially by two competing companies in the United States: GCA/Precision Scientific Group, which claims to have exclusive licenses to technology developed by Zimmermann, and DEP Systems, which has had an uneasy alliance with Pohl.

Pohl says he began to work on dielectrophoresis, the action of a nonuniform electric field on a neutral particle, as far back as World War II while in the Navy. Much later, he began applying some of the principles he developed as a physicist to biological problems. In 1972, he says he studied his own blood cells and observed that they lysed (were destroyed when their membranes ruptured) when subjected to too strong an electric field but fused when treated with a weaker electric pulse. "I didn't know the importance of this, so I just made notebook remarks," he says.

Zimmerman says his own studies in this field date back at least to 1973, when he observed the breakdown of cells in an electric field. Around 1980, Maja Mischel, a graduate student from West Berlin, and her adviser Ingolf Lamprecht, were informally collaborating with Zimmermann and observed cell fusion in his laboratory. According to Lamprecht, Mischel, who was familiar with Pohl's work but did not know of his unpublished cell-fusion studies, saw cell membranes fusing under the microscope. By this time, the importance of this process for forming hybridomas, which can make monoclonal antibodies, was widely recognized.

Zimmermann and Pohl soon became collaborators. However, Pohl says he neglected then to tell Zimmermann of his 1972 observations. Their partnership was short-lived.

Meanwhile, Zimmermann apparently had applied for patents, and he told *Science*, "I have invented both effects, electrofusion and electric breakdown of cells. I'm surprised Pohl can claim this invention." Zimmermann says he described both phenomena at a Gordon Conference in 1980. He also worked out an agreement with GCA/Precision to develop and market cell fusion devices. Pohl threw his support to DEP Systems, with whom he has since quarreled. The latter company is aggressively developing products, including devices to fuse cells or to sort them, based in part on technology that Pohl claims to have developed. The company's rights remain in doubt, however. An attorney for GCA says that the whole question has been referred to outside counsel.—**J.L.F.**

derives, in part, from the fact that mutation-like amino acid substitutions are introduced—in the case of interleukin-2, a particular cysteine is changed to serine. The scientific objective is to get the protein to fold properly, according to Halluin. The patenting strategy is to make an improved derivative that will be patentable—a well-established practice in the drug industry. "This whole approach opens new vistas, with many opportunities for patents," Halluin says. "There has been considerable debate about whether regular proteins made by recombinant DNA are patentable. I have a much better feeling of how ours will stand up." Besides the two Japanese companies and Cetus, Hoffmann–La Roche, Biogen, and several other biotechnology companies are developing interleukin products.

Another crowded and potentially lucrative race to produce factor VIII, a blood-clotting protein used by hemophiliacs, has also become mired in a patent infringement fight. It carries wide and disturbing implications because the suit pertains to alleged infringement of a patent only while doing research.

Factor VIII is currently purified from blood and is marketed by several companies, including Revlon. Several genetic engineering groups have been trying to clone the factor VIII gene, including the Genetics Institute, Chiron, and Genentech. The first two companies have partly cloned the gene and, late in April, Genentech announced that it cloned the complete factor VIII gene and made from it a biologically active protein.

In November 1983, Revlon filed suit against Chiron and Genentech, alleging that they infringed on a patent describing how monoclonal antibodies can be used to purify factor VIII. "We're not selling anything, and we're not using that patent," says Chiron research director Pablo Valenzuela.

According to attorneys separately representing Chiron and Genentech, shortly after the suit was filed an application to correct the Scripps patent was filed. "We think they are seeking to broaden the patent," says William Green, a San Francisco attorney representing Chiron. Use of the Scripps patent "to prevent the study of factor VIII is an assertion by the patentee of a monopoly not only of his invention but of future inventions," Genentech's Kiley says.

Genentech's latest accomplishment naturally makes the market prospects for a synthetic version of factor VIII appear that much closer, with estimates now moved up to 2 years from the start of clinical trials, which now are pending. Revlon's actions could impede an early introduction of a low-priced competitor to natural factor VIII. Revlon patent attorneys did not respond to repeated telephone inquiries.

A contest between Hybritech of San Diego, California, and Monoclonal Antibodies of Mountain View could have broad implications for the potentially vast market for medical diagnostic kits. Early in March, Hybritech filed a patent infringement suit in the U.S. District Court of Northern California seeking triple damages from and an injunction against Monoclonal Antibodies for allegedly using a process outlined in U.S. patent 4,376,110.

If patent disputes are decided in ways that do not correspond with what researchers expect by more conventional criteria . . . the allure of biotechnology companies could be greatly diminished.

Both companies are actively developing medical diagnostic techniques that rely on monoclonal antibodies. Such antibodies, which are made by hybridomas formed by fusing certain antibody-producing cells with freely reproducing cancer cells, are highly specific and thus suited for many diagnostic procedures. Hybritech's patent lays broad claim to procedures that use dual sets of such antibodies where one is present in soluble form and another is bound to a carrier, to detect an antigen they recognize in common.

Neither company is willing to say much about the suit, and Monoclonal Antibodies still has not filed its official response with the court. In papers filed with the Securities and Exchange Commission, however, Monoclonal Antibodies questions the validity of Hybritech's patent and alleges it covers "obvious processes."

Everybody is waiting to see what happens," says one industry source, who notes that Hybritech's patent seems to graft the use of monoclonal antibodies onto techniques developed with conventional, polyclonal antibodies. Hybritech's decision to single out Monoclonal Antibodies from other companies probably reflects "the commercial realities," this same source says. The latter is already selling a simple test for detecting pregnancy that can be used reliably without recourse to expensive equipment. It is speculated that Hybritech is attempting to use its lawsuit to cut Monoclonal Antibodies' early lead while it catches up. Monoclonal Antibodies, which sees many of its competitors as imitators, expects the patent infringement battle to be "a drawn-out affair."

The Hybritech versus Monoclonal Antibody suit is not the only legal action involving biotechnology-based diagnostic products. Cetus has recently petitioned the patent office to reexamine U.S. patent 4,358,535, held by Stanley Falkow now of Stanford University and Stephen Moseley, his former collaborator at the University of Washington. The patent grants them broad coverage of the use of DNA probes for diagnostic purposes, and Cetus currently holds an option to license the patent. The company's seemingly hostile action could go either of two ways, according to attorney Halluin. The patent could be declared invalid, thus freeing the procedures for anyone, or its scope could be narrowed, thus leaving Cetus "with a stronger patent we have rights to." This use of relatively new petitioning procedures represents another way companies can maneuver around or manipulate important biotechnology patents.

Another new, but largely untested component of major patent battles is the Court of Appeals for the Federal Circuit. Instituted late in 1982, this court will serve as a central arbiter of appeals emanating from patent infringement suits. Before this court was created, such appeals could be heard in 11 districts in the United States, a situation that led to wide discrepancies in the way patent decisions were interpreted.

A great deal is at stake in the biotechnology industry, and some of that stake must be measured in terms other than corporate profits. Some companies have been aggressively seeking patents, not only to protect their future market positions but also as a way of rewarding their scientific staffs. Filing patents frees them to publish their research in journals and to speak at meetings, allowing scientific reputations to be established. If patent disputes are decided in ways that do not correspond sensibly with what researchers expect by more conventional criteria or if patents are awarded on technicalities to inventors who appropriated some competitors' superior idea, the allure of these companies could be greatly diminished.—**JEFFREY L. FOX**