Companies Vie over New Heart Drug

Genentech and Wellcome battle each other over patent rights to the clot-dissolving drug TPA, while other companies gear up to compete, too

This is the second of two articles on TPA. The subject of the first article, which appeared in last week's issue, was the decision by an advisory committee to the Food and Drug Administration to postpone approval of the drug.

As Science *went to press, the British High Court ruled on 7 July that Genentech's TPA patent was invalid because the claims were too broad. Unless Genentech narrows the claims, the patent will be revoked. Wellcome called the ruling a "vindication." Genentech said it might appeal.*

In what Genentech Inc. executives thought was a key victory over their competitors, the company won a broad patent in Britain 15 months ago on a powerful new heart drug that dissolves blood clots. The drug, tissue plasminogen activator or TPA, is expected to be the first $1-billion drug of the biotechnology industry and could help as many as 750,000 heart attack victims in the United States every year.

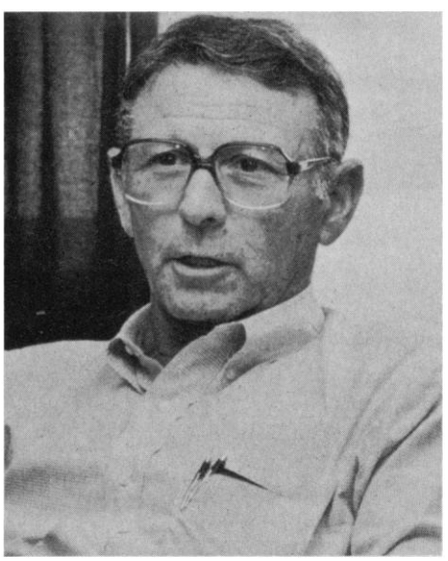
Within hours of receiving the patent, however, Genentech was sued by Wellcome Foundation Limited, the British pharmaceutical company, over the validity of the patent, contending that no patent should be issued because Genentech allegedly did nothing novel to make TPA. Genentech responded a few days later by charging in a countersuit that Wellcome, which is also producing TPA, had illegally infringed its British patent.

The battle for TPA was joined. And it is sure to broaden and intensify because more than a half-dozen companies in the United States alone have research programs under way to make the drug. These companies, including Genetics Institute, Inc., and Integrated Genetics, Inc., both located in the Boston area, are jockeying for shares of a potentially huge market with an unusual combination of legal and scientific strategies. With the help of genetic engineering, companies can now make large quantities of TPA, a substance produced in small amounts by the body.

The race has heated up in recent weeks. It took a dramatic turn when an advisory panel to the Food and Drug Administration (FDA), contrary to expectations, voted on 29 May not to approve Genentech's applications to market its version of TPA called Activase. Although the panel members acknowledged that TPA effectively dissolves clots, they said they wanted more data to show that the drug actually improves a patient's heart condition and lessens the risk of dying from a heart attack.

But eventual approval is widely anticipated because preliminary results from clinical trials currently under way support the effectiveness of TPA, according to researchers at the National Heart, Lung, and Blood Institute. FDA could decide to approve the drug despite the advisory committee's advice, but such an action would be highly unusual. In terms of the race to market, any delay will narrow the substantial lead that Genentech has had so far.

TPA is expected to have broad use as a clot dissolver. In addition to its value as a heart drug, TPA has also helped patients who suffer from blood clots in the lungs and may be useful in treating clots in the deep veins of the legs. According to Genentech, TPA could be useful to a total of 1.5 million patients in the United States, 1 million in Europe, and 600,000 in Japan. So far, however, the drug has been approved for use only in France, the Philippines, and New Zealand. Activase was approved for use in these countries last year and is actually on the market just in New Zealand.



Paul Berg *of Stanford says, "Genentech had undertaken the most difficult cloning project to date."*

A week after the FDA committee met, Wellcome's patent suit went to trial before the High Court of Justice in London. Both Genentech and Wellcome agree that the proceedings are an important test of biotechnology patents in Britain, and some observers expect the outcome to influence patent applications pending on TPA in the United States, where a patent on TPA has yet to be issued.

Genentech's British patent is a broad one, covering the natural TPA molecule itself, the process by which it was made, and the animal cells that produce the drug. One of the main arguments in Wellcome's lawsuit is that Genentech's cloning techniques to develop TPA were not novel. In many countries, including the United States, Japan, and Britain, patents may not be awarded for something that is obvious but are granted based on novelty in order to reward inventors for their efforts.

Wellcome's principal line of attack is that "Genentech did the obvious," says Bruce Eisen, chief patent counsel at Genetics Institute. Genetics Institute has a substantial stake in the outcome of the patent trial, because it licensed its TPA technology and awarded worldwide marketing rights to Wellcome. Eisen says that "no special knowledge was needed [to clone TPA]. All the tools were in place." Wellcome asserts, for example, that Genentech's use of genetic probes to isolate the TPA gene is common. Eisen says, "It was only a matter of horsework" for Genentech to clone TPA.

"That is the point where all the fur flew," says Thomas Kiley of Genentech. "We argue that obtaining the clone was unusual and that molecular biologists didn't know how to apply the probes."

During the British trial attorneys paraded expert after expert before bewigged Justice John Whitford to prove the obviousness or novelty of the cloning techniques. Wellcome's witnesses included Tom Maniatis of Harvard, who is also the scientific founder of Genetics Institute, as well as other top scientists at Genetics Institute. (Another Wellcome witness, William Brammar of the University of Leicester wrote a 30-page

primer on recombinant DNA technology for the judge, who has presided over many patent disputes involving pharmaceuticals, but not genetic engineering products.) Genentech brought in Paul Berg of Stanford, George Stark, acting director of the Imperial Cancer Research Fund, and the team of Genentech scientists who cloned the TPA gene. James Watson, director of Cold Spring Harbor Laboratory, has been among the crowd of spectators since the trial began. Watson has collaborated with Genetics Institute on TPA, and Cold Spring Harbor and Genetics Institute will share in any royalties from Wellcome's TPA.

Much of the trial centered on the Genentech's use of hybridization probes to clone the TPA gene. The lead attorney for Genentech, Stephen Gratwick, argued that, in the early 1980s, using a mixed pool of oligonucleotides as probes was novel and that the techniques took "exceptional skill." There is no disagreement that the technique is now widely used, but Berg, in an interview, argues that early on in the project, "Genentech had undertaken the most difficult cloning project to date. They used every trick in the book. The individual techniques were not novel, but the combination of techniques used to clone the TPA gene made their accomplishment a notable achievement."

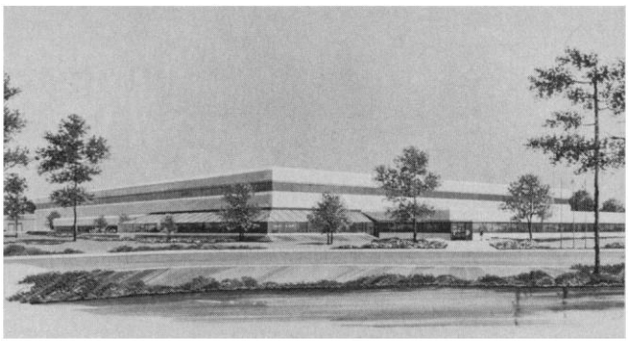
Maniatis counters that "all the technology to clone TPA existed" at the time Genentech was isolating the gene, and that "the technology was common knowledge." At the trial, scientists from the University of Umea in Sweden and the Catholic University of Louvain of Mons in Belgium testified that they have cloned TPA independently of Genentech and that the cloning steps were well known at the time Genentech isolated the TPA gene. Wellcome's lead attorney, Robin Jacob, also argued that the probe techniques had been taught as early as 1980 to students by scientists, including LeRoy Hood of the California Institute of Technology.

Genentech argued at the trial that a laboratory manual on recombinant DNA technology that was coauthored by Maniatis and published in 1981 did not provide instructions about the use of the probes. If the technique was so common, a protocol should have been included in the manual, Genentech argued. Berg notes that the University of Umea scientists only isolated a partial clone, not the complete TPA gene. He says, "There was a lot of discussion at the trial about what *could* be done, but the name of the game in science is getting it done."

Justice Whitford commented on the last day of the trial, "The difficulty in all these cases is being able to secure adequate reward for the work the person has done, because very often if they are not going to get an adequate reward they are not going to spend the money and do the research."

WelGen

A joint venture between Wellcome and Genetics Institute, will be future competition for Genentech.



At press time, it is not clear how the judge ruled on the issue of obviousness. According to Genentech, the court said that company's technology was novel. But Wellcome said that "the judgment is vindication of Wellcome's belief that the Genentech patent failed to fulfill the essential criteria of novelty and inventiveness."

Genentech played down the significance of the ruling. The company said, "This decision relates solely to the United Kingdom." Wellcome said in a statement that it "does not believe that this decision has general implications for patents in the recombinant DNA field."

In the United States, the patent situation is unclear. Genentech has said it has applied for a patent, but other potential applicants are hard to come by because the names of patent applicants are not disclosed until the U.S. Patent and Trademark Office makes a decision on the claims. In Japan, Genentech's patent application faces serious challenges by a crowd of competitors. Unlike the American patent system, the Japanese immediately publish the patent claims submitted by inventors. A comment period follows in which others can contest the application. So far, Kiley says that "more than a dozen companies" have filed in opposition to Genentech's application.

Linda Miller, an analyst at Paine Webber, says that the outcome of the British trial will have an important psychological effect on investors in Genentech, especially in light of the FDA advisory committee's decision not to approve TPA. Peter Drake, an analyst for Kidder Peabody, comments that investors generally believe that the outcome of the British trial will be relevant to the American patent process. Investors, he says, "will draw a straight line from Britain to the U.S."

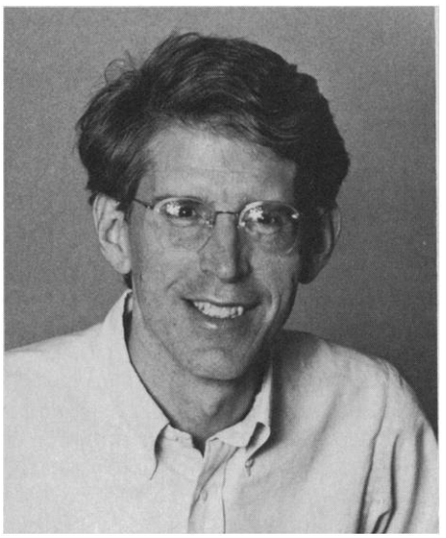
While patent attorneys are busy divining the meaning of the British trial, clinical trials with TPA made by Genentech's competitors are proceeding. Wellcome is conducting clinical trials in Europe, the United States, and Japan; Integrated Genetics started trials in Japan last year; and, in March, Biogen of Cambridge, Massachusetts, applied to the FDA for permission to begin clinical trials with its TPA.

All of the trials conducted so far have tested the "natural" TPA molecule. But scientists at several companies already are designing a new and improved TPA. The companies are modifying the molecular structure by using genetic engineering to enhance certain properties.

Genetics Institute, located in Cambridge, and Integrated Genetics, in Framingham, are considered the top contenders in developing a "second-generation" molecule and are working to extend the half-life of TPA. Genentech also has a research program on second generation TPA but has no comment on its work, says Debra Bannister, a company spokeswoman. Natural TPA has a half-life of only 7 minutes because it is cleared rapidly by the liver. A longer half-life would reduce the dose levels required to lyse a clot, says Alan Smith, scientific director and vice president at Integrated Genetics. A fine balance must be struck: "We want TPA around long enough [in the body] to be useful, but not so long that it sets off bleeding. Large doses can set off bleeding too." Maniatis adds that extending the half-life of TPA will make it easier to administer the drug. TPA is typically given intravenously for an hour and a half, but with a more stable molecule it could be injected with a single shot, which would be more practical for use in medical emergencies, Maniatis says.

To prevent the liver from clearing TPA so quickly, Integrated Genetics has changed one of TPA's carbohydrate groups. Results from rabbit studies indicate that the new TPA is equivalent to the natural TPA at doses four to six times smaller than the normal clot-lysing dose. "But it is difficult yet to extrapolate these data to humans," Smith cautions. A patent on the new molecule was recently published in Europe.

Genetics Institute is not saying much about its second-generation molecule right now. Vice president Robert Kamen will



Tom Maniatis, *a founder of Genetics Institute, says the technology to clone TPA was "common knowledge."*

only comment that the company is trying to extend the half-life too. The company is expected to make a strong bid to produce an alternative TPA because it has retained all the rights to manufacture a modified molecule and is not obligated to license the new technology to Wellcome as it did with its first-generation TPA. (It will be interesting to see what approach Genetics Institute is taking, given that Kamen and Smith conducted research together for 8 years at the Imperial Cancer Research Fund and coauthored scientific papers while there.)

Technical know-how to grow mammalian cells in large volume and sufficient plant capacity are also crucial factors that will help determine which company prevails in the TPA contest. Growing massive quantities of animal cells is still more an art than a science because mammalian cells are finicky creatures. Analysts say that only Genentech and Wellcome currently have the combination of expertise and facilities to grow large quanities of mammalian cells. But Genetics Institute expects to have a substantial capacity to grow these cells in the future. This year, it signed a joint venture with Wellcome to build a mammalian cell culture production plant in Massachusetts. The plant, called WelGen, is expected to be on-line by 1989.

For now the TPA battle is mainly between Genentech and Wellcome. Kamen notes that the decision by the FDA advisory committee "gives competitors a time advantage. We gain whatever time Genentech loses. Before Genentech had a $2\frac{1}{2}$-year time lead. Now the gap could be narrowed by anywhere from 6 months to a year." ■

MARJORIE SUN

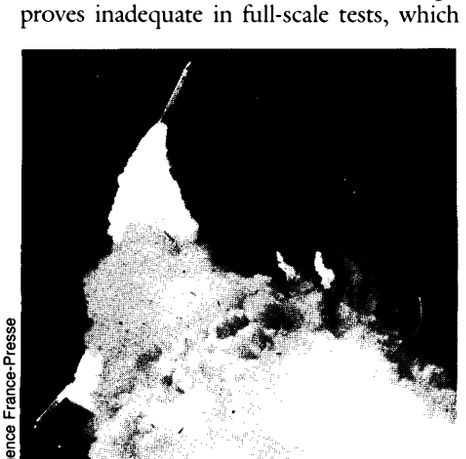
Research Council Critiques NASA's Booster Redesign

The National Aeronautics and Space Administration's (NASA's) recent decision to delay its first post-Challenger space shuttle flight from February to June 1988 has done little to ease the pressure on its solid rocket booster testing program, according to the latest report from an oversight panel convened by the National Research Council.

Indeed, as the agency moves toward full-scale testing of the redesigned boosters it is still operating in a success-oriented mode, writes panel chairman H. Guyford Stever in a 22 June letter to NASA administrator James C. Fletcher. Schedules continue to be based on the presumption that the new "baseline" design for the boosters, which is receiving the lion's share of attention from the engineers at NASA and at prime contractor Morton Thiokol, will work as planned—a situation that the panel has criticized before and still finds troubling.

Stever's letter is the fourth in a series of interim reports by the panel, which was established last year to provide an independent assessment of NASA's efforts to fix the faulty booster joints that burned through and destroyed the Challenger and its crew on 28 January 1986.

The panel did concede that the booster redesign team faces a tough management problem. NASA and Morton Thiokol have only so many test facilities to work with and only so many skilled engineers who understand the boosters; thus, the decision to concentrate resources on the baseline design is understandable. Nonetheless, say the panel members, that strategy is inherently risky, and could backfire if the baseline design proves inadequate in full-scale tests, which are slated to begin this summer. The inevitable result would be more expense and delay.



Agence France-Presse

28 January 1986. *Still firing, the solid rocket boosters go their separate ways as they emerge from the Challenger fireball. Flame can be seen emerging from the ruptured joint in the lower booster.*

The issue of risk is particularly acute right now because the booster redesign is still the most critical element in getting the shuttle ready to fly by June 1988. The decision to delay the first flight gave the redesign team little respite, since the delay is mainly intended to accommodate a full-scale test firing of the shuttle next spring while it is on the launchpad at Cape Canaveral. Yet that test will require using a real set of solid rocket boosters, which means that the first set of flight-ready boosters will have to be delivered by December. The only way that can happen, however, is if all three of the upcoming booster tests go perfectly.

Of the many specific concerns that Stever raises in his letter, perhaps the most urgent relates to the booster team's strategy of "testing with defects." The idea, which Stever and his colleagues endorse in principle, is to measure the margins of safety in the system by introducing deliberate flaws into the joints of the test boosters and seeing what happens. Indeed, since the very act of assembling the booster segments can introduce defects in the joint, and since certain of those defects cannot be detected afterward, this approach is essential.

However, Stever and his colleagues also point out that when using this approach it is critical to identify the "worst credible" flaw in each case, as opposed to the worst imaginable flaw. Otherwise, NASA could end up wasting enormous amounts of time and money protecting against more and more baroque failure modes, while still missing the most threatening of the boosters' real-life problems.

A case in point is the joint between the booster's exhaust nozzle and its main body, where the NASA-Thiokol team is planning to introduce a set of simultaneous failures in the O-rings and in the adhesives of the joint. This combination of flaws is so serious that, in the panel members' judgment, it will cause the joint to fail during the test and will force yet another delay while the connection is redesigned. And yet, the panelists say they are not convinced that the engineers have done enough analysis to prove that the flaw is credible. As the panel's executive director, Myron Newman points out, "We wonder how real this is. We can't say yet whether the test is too stringent, or not stringent enough. What we do say is that they have to do some work on the problem." ■

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