A high-stakes patent trial has seen scientists challenge each other's veracity and reputations potentially tarnished, yet their testimony was not even central to the legal case

No Winners in Patent Shootout

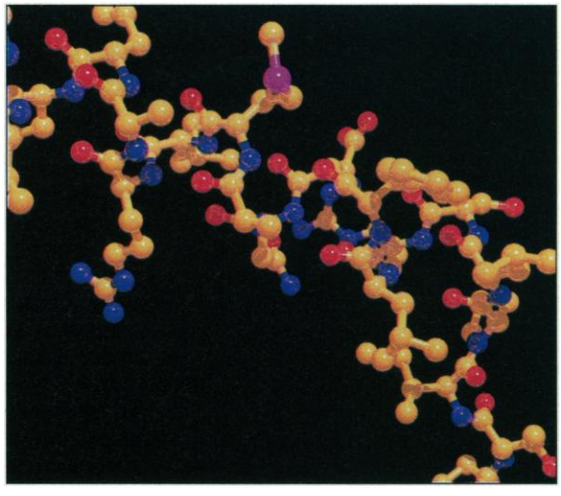
A trial that has made headlines internationally and threatened the reputations of two distinguished scientists ended last week without a verdict. A federal jury deadlocked on a claim by the University of California (UC) that South San Francisco biotech giant Genentech had infringed the university's patent on the gene for human growth hormone. Genentech, whose synthetic version of human growth hormone, Protropin, has racked up sales of more than $2 billion, promptly declared victory. But it was hardly decisive. The nine-member jury upheld the validity of the UC patent, which Genentech had challenged, and split 8 to 1 for UC on infringement. The lone holdout juror saved Genentech from damages that could have been as high as $1.2 billion. At a hearing scheduled for 22 June, UC, which has already invested $20 million and 9 years in the case, is likely to request a new trial.

The scientists who have been drawn into this bruising fight can hardly relish a rematch. The trial took a heavy personal toll on UC witness Peter Seeburg, a former UC San Francisco (UCSF) postdoc and Genentech employee and now a director at the Max Planck Institute for Medical Research in Heidelberg, Germany. Seeburg testified that he and his Genentech colleagues used research materials he had removed from his former UCSF lab during a clandestine New Year's eve visit. And he said they avoided revealing the use of these materials by misrepresenting some data in a 1979 paper in *Nature*. His public admission has prompted the Max Planck Society to open an inquiry into these events of 20 years ago, focusing on possible scientific misconduct. Seeburg's former Genentech colleague, David Goeddel—now president of Tularik Inc. of South San Francisco—has also been bruised by the trial. In his own testimony and subsequent public statements, he has vehemently contested Seeburg's version of events and defended the accuracy of the *Nature* paper.

The sensational revelations and the spectacle of two highly regarded scientists publicly questioning each other's truthfulness created a drama that eclipsed the underlying legal issues. A bitter irony in this case is that Seeburg's testimony was not even central to UC's arguments, and it appears to have had little influence on the jury. UC wasn't suing Genentech for taking or misusing its research materials. The suit was for patent infringement, and the legal reason that Seeburg's testimony could figure in the case at all lay in a loophole created by the way UC's patent was worded.

The scientific dispute

The story began in 1977, when Seeburg was a postdoc with Howard Goodman at UCSF. He was part of a team that pulled off a huge victory in the competitive new field of biotechnology: cloning the cDNA that encodes human growth hormone. UC filed for a patent based on that work, naming Seeburg and Goodman among the co-inventors. In November 1987, Seeburg took a job at Genentech to lead an effort to engineer bacteria to produce human growth hormone. The goal was to create an "expression vector," a ring of DNA containing the growth hormone cDNA spliced to sequences that would allow it to be expressed in bacteria, turning the organisms into growth hormone factories.



Growth market. Genentech's engineered version of human growth hormone has earned more than $2 billion in sales.

Seeburg's career move would be routine for a postdoc today, but at the time he was a pioneer, one of the first postdocs to leave academia to join the brand-new biotech industry. He and his new employer quickly found that the rules governing such transfers were far from clear. Shortly after Seeburg joined Genentech, according to evidence in the trial, company president Robert Swanson wrote to Goodman asking for some of the clones Seeburg had developed at UC. No response from Goodman was admitted as evidence in the trial, but UC attorney Emily Evans of the Palo Alto law firm Morrison & Foerster says the request was not granted.

When that approach failed, Seeburg testified that he went to UCSF with a Genentech colleague, Axel Ullrich, shortly before midnight on New Year's Eve 1978 to retrieve a portion of the DNAs he had worked on. Seeburg bristles at the notion that what has come to be known as the "midnight raid" was a theft. He timed the visit, he says, to avoid an unpleasant confrontation with Goodman, his former adviser, with whom he had had a falling-out. And although he acknowledged in an interview with *Science* that "in a legal sense," his action was wrong, he says he felt at the time that he "had a right to take half the material" that he had worked so hard to create and use it for his future research.

UC took a less charitable view. When university officials learned of the transfer, they fired off a letter to Swanson putting Genentech on notice that the company did not have permission to take the samples or to put them to commercial use. Swanson responded that Seeburg's "entitlement" to continue research with the materials he developed at UC was "in keeping with scientific and university custom of long standing." UC shot back: "[T]here is no 'custom,' 'long-standing' or otherwise, which countenances such conduct for private commercial enrichment." The issue was apparently settled in June 1980, when Genentech agreed to pay UC up to $2 million in royalties for the clones, although UC retained full patent rights.

Just what Seeburg and Goeddel did with those clones is a matter of bitter dispute. Seeburg testified in April that the Genentech team had trouble isolating a growth hormone cDNA complete enough to use in its expression vector, so he says he used DNA from the UC clone. What's more, he testified, Goeddel was in on the alleged scheme. "We agreed that we would use it but not tell anyone," he said.

Goeddel vigorously denies any knowledge that Seeburg used the UC clone. "There was never any agreement," he testified. "I couldn't believe that he could come up with such a sto-

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ry." He testified that Genentech's team independently isolated a growth hormone cDNA that he inserted into the expression vector, which subsequently directed bacteria to make the hormone. That widely hailed accomplishment was reported in *Nature* on 18 October 1979. Genentech received patents for the work and won Food and Drug Administration approval in 1985 for Protropin.

Seeburg testified that the growth hormone cDNA clone described in the *Nature* paper, pHGH31, never existed, and the DNA sequence attributed in the paper to pHGH31 came from the UC clone. The battle over the truth of that testimony focused on Goeddel's and other Genentech employees' lab notebooks. Genentech researchers and expert witnesses saw plenty of evidence in the notebooks of independent cloning of the growth hormone cDNA, and isolation and insertion of the right piece into the expression vector. UC experts found the notebook entries sketchy and incomplete, indicating abandoned cloning efforts followed by the sudden appearance of a DNA fragment "prepared by P. Seeburg," which Goeddel used.

Genentech conceded that the notebooks contain no record of the determination of the DNA sequence of pHGH31. Goeddel says he recalls analyzing a sequence obtained by another employee, but he told *Science* he isn't surprised that a piece of raw data is unaccounted for: "I think if you take any paper after 20 years and ask where is all the primary data, it might be hard to come by."

Goeddel and the other authors of the *Nature* paper wrote letters to the editors of *Science* and *Nature*, denying Seeburg's allegations and inviting *Nature* to examine the notebooks, which Genentech has posted on its Web site at www.genentech.com/labnotebooks. In responses published along with the Genentech letters, Seeburg points out that "the scientific results and conclusions" of the *Nature* paper are "unambiguous and correct," and what he calls the "technical inaccuracy" is limited to one step in the construction of the expression vector. Seeburg told *Science* he does not condone "fudging data" and regrets the flaws in the *Nature* paper, but he considers them a "misdemeanor" rather than fraud. *Nature* seems to share that view, declining in an editorial to investigate the paper. But the Max Planck Society has taken a more stern stance, initiating a formal inquiry into the affair, to be led by an independent legal expert, Walter Odersky.

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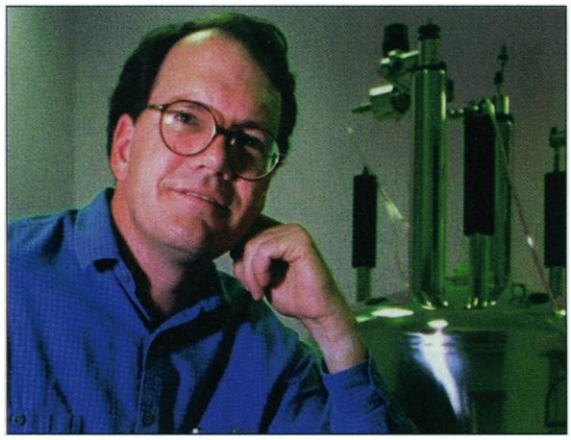
The legal case

Ironically, given the fallout from Seeburg's testimony and the attention it has received, several patent law experts *Science* consulted see it as tangential to the legal issues. And some even suggest it shouldn't have been allowed into the trial at all. UC's accusation of patent infringement did not depend on whether Genentech had directly used UC's cDNA, but only on whether the company's Protropin expression vector had DNA sequences that were claimed in UC's patent. The Seeburg story, in fact, was relevant only because of a quirk in the way that patent was written.

UC's patent covered not only the sequence that encodes growth hormone, but also 48 nucleotides of noncoding sequence that follow it in the UC clone. UC patented this entire sequence as part of a "transfer vector" for introducing DNA into bacteria. To infringe on a patent, a product must contain everything claimed in the patent. Because Seeburg and Goeddel cut off 39 of the 48 noncoding nucleotides when making the expression vector, says UC lead attorney Gerald Dodson of Morrison & Foerster, their vector does not literally infringe UC's patent. If UC had claimed just the coding region, says biotech patent attorney Adriane Antler of the New York patent law firm Pennie & Edmonds, it may have had a case for literal infringement.



Key player. David Goeddel was lead author of the paper announcing Genentech's bacterial production system.

It's unclear why UC's patent included the noncoding sequence. "That was early days on writing applications covering DNA sequences," notes the patent's author, attorney Lorance Greenlee, now of the patent law firm Greenlee, Winner and Sullivan in Boulder, Colorado. "Nobody really knew what the patent office would accept or not accept." Greenlee says he probably just wanted to be complete in claiming the whole sequence.

Whatever the reason for its inclusion, that noncoding sequence meant that UC could only claim infringement under the "doctrine of equivalents," a provision of patent law that says a product may infringe a patent if it has elements that are equivalent to each element of the patent's claims. To make its case, UC had to show that differences between its patented sequence and that used by Genentech were inconsequential, and that Genentech's expression vector is also a transfer vector and so covered by UC's claim. Genentech countered with expert testimony that its vector was significantly different from UC's and that cutting off part of the noncoding sequence was a substantive change, done to improve expression of the hormone in bacteria.

UC introduced Seeburg's scientifically explosive testimony to provide an indirect line of support for its legal arguments. Judge Charles Legge allowed the testimony because, as he said in his jury instructions, if UC could show that Genentech copied UC's invention, that would "suggest that the differences between [UC's claims] and the corresponding features in Genentech's [vector] are insubstantial." As evidence of direct copying, UC lawyers pointed to Seeburg's claim that Genentech used the actual DNA from UC to make its vector.

Several patent experts consulted by *Science* say, however, that the legal basis for Legge's reasoning is shaky. Patent attorney Richard Osman, of the Science & Technology Law Group in San Francisco, notes, for example, that in a 1997 decision, the Supreme Court took a dim view of the relevance of intentional copying to the doctrine of equivalents. "The better view, ..." the court wrote, "is that intent plays no role in the application of the doctrine of equivalents." Martin Adelman, director of intellectual property at George Washington University in Washington, D.C., says he believes the judge made an error in admitting testimony apparently intended "to prejudice the jury."

But it didn't seem to have that effect. "We didn't put major amounts of weight on [Seeburg's testimony]," juror Don Ladue, a supervisor with Pacific Gas and Electric Co. in San Francisco, told *Science*, adding that he and the seven other jurors who found for UC "felt the university proved its case without his testimony." The jury's discussions focused on the patent claims and Genentech's production vector, says Ladue. "If you looked at [UC's claims] versus [Genentech's vector], you could see that under the doctrine of equivalents, it did infringe."

The fact that the scientific testimony had little influence on the jury will be scant consolation to Seeburg, Goeddel, and the other researchers whose activities 20 years ago have been publicly dissected and their motives questioned. And now they face the daunting prospect that, if there is a retrial, they may have to go through it all over again.

–MARCIA BARINAGA

With reporting by Robert Koenig in Bern, Switzerland.