A Bitter Battle Over Insulin Gene

When the University of California sued to uphold its patent rights, little did it expect to come away empty-handed, with $12 million in legal bills and its researchers accused of "inequitable conduct"

The University of California (UC) is learning the hard way that it can be dangerous to charge into court to champion a faculty member's invention. A bruising 7-year patent battle between the university and Eli Lilly and Company resulted last month in a multimillion-dollar setback for the university. Along the way in this high-stakes legal brawl, the scientific integrity of prominent researchers who worked at UC, San Francisco (UCSF) in the 1970s took a battering from Lilly's lawyers, a Nobel Prize–winning scientist advising the company, and a federal judge.

This vicious fight centers on a landmark discovery by UCSF biologists at the dawn of the biotechnology era: the first successful cloning of the rat insulin gene, reported in *Science* 20 years ago (17 June 1977, p. 1313). When Lilly—the nation's biggest insulin maker—refused to honor UC's patents on this and other insulin discoveries, the university sued in 1990. Had UC persuaded or forced Lilly to pay royalties, it might have tapped into an insulin business worth, by Lilly's reckoning, "hundreds of millions of dollars." But last month, the U.S. Court of Appeals for the Federal Circuit ruled that the company had not violated UC's patents. The ruling, written by Judge Alan Lourie, upheld key parts of a decision by U.S. District Court Judge S. Hugh Dillin, who had ruled in Lilly's favor in December 1995. The bottom line for the university: Unless it files and wins another appeal, it has ended up with no royalties and millions of dollars worth of legal bills (see sidebar).

For the former UC researchers in the middle of this case—especially team leaders William Rutter, now chair of Chiron Corp. of Emeryville, California, and Howard Goodman, now at Massachusetts General Hospital in Boston—the appeals court's decision did provide some solace. It set aside a key part of Dillin's finding: that UC had won its patents in part through "inequitable conduct." Dillin had based that ruling on Lilly's contention that the UC scientists had gained an advantage by violating federal gene-splicing rules in force at the time, and that they had "misrepresented the origins" of their insulin data to the public, the National Institutes of Health (NIH), the Senate, and the U.S. Patent and Trademark Office. For this reason, and because Dillin felt that the university had not revealed other adverse information to the patent office, he ruled that UC's patents were "unenforceable."

Rutter and Goodman have consistently denied any wrongdoing, and the appeals court has now declared that this part of Dillin's ruling is not relevant to the central question of whether Lilly had violated UC's patents. As a result, the appeals court did not address the substance of Lilly's charges about what happened 20 years ago.

The UCSF group did its pioneering work in the face of stiff competition from another team, led by Nobelist Walter Gilbert of Harvard, that also was racing to track down the insulin gene. This race unfolded against a turbulent backdrop. The public was just beginning to learn about recombinant DNA technology; some claimed that new organisms might escape from the lab (the risks actually were minuscule), and officials were proposing ill-defined rules to restrict gene splicing. Indeed, fear of engineered organisms was so intense in the 1970s that Cambridge, Massachusetts, banned recombinant DNA work within the city limits for a time, annoying local scientists. During this period, newly published NIH guidelines permitted federally funded researchers to run mammalian gene-cloning experiments only in "vectors"—viruses, DNA loops called plasmids, and other vehicles for replicating DNA—approved by its Recombinant DNA Advisory Committee (RAC) and certified by NIH.

Harsh words. Judge Hugh Dillin slammed UC.

In January 1977, when they were in the early stages of their rat insulin work, the UCSF group used a modified plasmid called pBR 322 to reproduce the rat insulin gene in bacterial cells. While the hugely efficient pBR 322 had been provisionally approved by RAC, it had not been certified as safe by NIH. This breach of the NIH guidelines came to light later that year, when writer Nicholas Wade reported it in *Science* (30 September 1977, p. 1342). That fall, when NIH investigated Wade's report, UC scientists said they had been confused by the new rules, and that they had destroyed all the offending research material on 19 March 1977, a few weeks after realizing that pBR 322 had not been certified. They said they later switched to an approved vector (pMB9), which formed the basis of their published findings. The Senate also held hearings in November 1977; at these, Rutter, then UCSF biochemistry chair and a co-investigator on the insulin project, said that pBR 322 had not been used after March 1977.

Lilly dredged up these events at the patent trial. The company charged that, although the UCSF biologists destroyed some pBR 322 material in March 1977, they retained the DNA for sequencing. The resulting data, Lilly charged, became the basis for the *Science* paper. The same data were also the basis for UC's patent claiming vertebrate genes for insulin,

INSULIN GENE TIMELINE

January 1977 UCSF team begins cloning insulin into pBR 322

4 March Rutter, Goodman learn pBR 322 not certified

19 March NIH official Stetten informally advises UCSF to destroy pBR 322 clones

22/25 March Rutter, Goodman mail certified letters saying they intend to retain cloned pBR 322 DNA for "further sequencing"

18 April NIH certifies vector pMB9 safe

23 April UCSF clones insulin gene into pMB9

9 May UCSF team sends completed insulin manuscript to *Science*

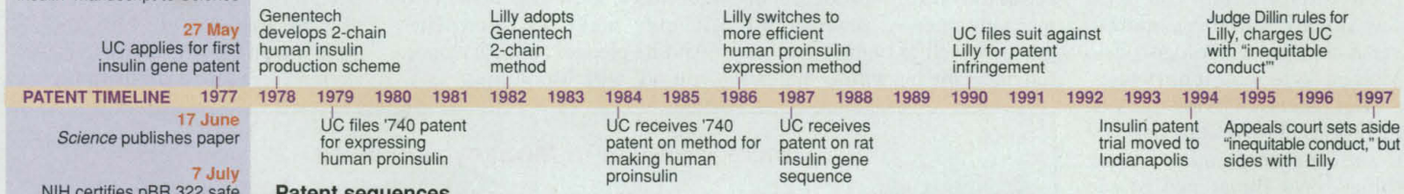
27 May UC applies for first insulin gene patent

17 June *Science* publishes paper

7 July NIH certifies pBR 322 safe

30 September Wade reports UCSF breach of NIH guidelines

8 November Rutter informs Senate pBR 322 not source of *Science* article



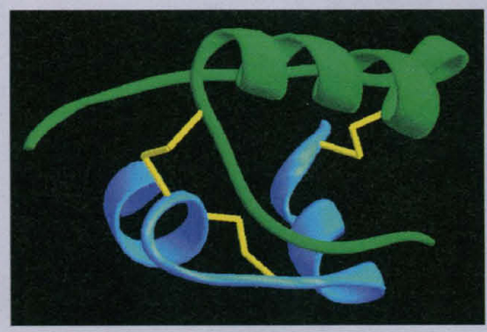
Patent sequences. The cloning of the insulin gene took a few months in 1977 *(vertical timeline)*; the patent issues played out over 20 years *(horizontal timeline)*.

SOURCE: COURT DOCUMENTS

Courts Take a Narrow View of UC's Claims

When a team of biologists at the University of California, San Francisco (UCSF), reported 20 years ago that it had cloned the rat insulin gene, team members thought they had bagged the biggest prize in the new world of biotechnology. But last month, a federal appeals court in Washington, D.C., may have ended any hopes UC had of cashing in on this landmark discovery. It upheld parts of a lower court ruling that two key patents of UC's were flawed, so Eli Lilly and Company—the nation's biggest insulin maker—doesn't have to pay UC potentially tens of millions of dollars in royalties. UC prevailed on one point, though: It persuaded the appeals court to set aside allegations that its researchers and officials had committed "inequitable conduct" (see main story).

Patent experts say the rulings may have implications that extend well beyond UC's balance sheet, making it more difficult for inventors to assert broad claims based on the discovery of a single gene. UC's loss also provides a cautionary tale for universities trying to uphold their intellectual property rights. Universities should do "a good deal of soul-searching" before entering a major patent battle, says UC's director of technology transfer, Terence Feurerborn.



PDB/ABOLA *ET AL.* AND BERNSTEIN *ET AL.*

Focus of the battle. The human insulin molecule.

Former UCSF scientists, including William Rutter—a leader of the group that cloned insulin and now chair of the Chiron Corporation in Emeryville, California—are disappointed, too. Rutter says he's upset that a discovery whose technological value seemed clear 20 years ago has received such poor treatment in the patent system. Finding the rat insulin gene, Rutter suggests, opened the way to modern insulin production. This legal decision, he believes, has failed to protect the "truly innovative discovery ... on which all the rest is based."

Scientists at UCSF under Rutter and co-investigator Howard Goodman, now at the Massachusetts General Hospital in Boston, focused their insulin studies in 1977 on rat DNA, in part because federal guidelines at the time prohibited the use of human DNA. After isolating and cloning a gene for rat insulin and its precursor molecules, they sought patents in May 1977. This was the first time the entire genetic sequence for an insulin gene had been spelled out—making it relatively easy later to "fish out" the human gene. It took two more years of concerted effort at several labs, however, to clone the human gene and coax bacteria to express it.

A decade after applying for a patent on the rat genes, UC received U.S. Patent Number 4,652,525 in 1987, awarding it commercial rights to the use of plasmids containing insulin genes. As soon as federal rules permitted, the UC team zeroed in on human gene experiments, developed data, and applied for a new "methods" patent in 1979. Awarded in 1984, this one (Number 4,431,740) covers the DNA sequence for human insulin, its precursor molecules, and methods of tailoring the human DNA for expression by bacteria.

UCSF scientists did not do all this work in isolation, however. For example, John Shine, the team's "wizard of sequencing," as Rutter calls him, used methods developed in part by a competitor, Harvard's Walter Gilbert. And UC, in turn, had shared technology with Lilly, while Lilly had shared its decades-old expertise in insulin chemistry with the UC team and with a newly formed genetic engineering company in San Francisco, Genentech, Inc.

Genentech played its own major role in insulin manufacturing. Staff scientists, together with Roberto Crea, Keiichi Itakura, and Art Riggs at the City of Hope National Medical Center in Duarte, California, disclosed in November 1977 a method of tailoring a human gene so that bacteria could efficiently express the protein somatostatin. Building on that work, Genentech researchers David Goeddel and Dennis Kleid in 1978 developed with City of Hope a method of independently expressing two elements of the human insulin precursor molecules (the "A" and "B" chains) and using them to build a synthetic form of insulin.

After signing an agreement with Genentech, Lilly in 1982 began marketing synthetic human insulin made by the two-chain process. According to a Lilly legal brief, the company sold about $200 million worth of insulin made this way before switching in 1986 to a more efficient technique. The Itakura-Riggs method is used in this technique to express the entire insulin precursor molecule, which is converted to insulin itself in the body. Lilly claims Genentech developed the process in 1978–1979 in connection with work on human growth hormone. But UC claims that its own scientists were first to get bacteria to express the human insulin precursor gene, on which they filed a patent in 1979.

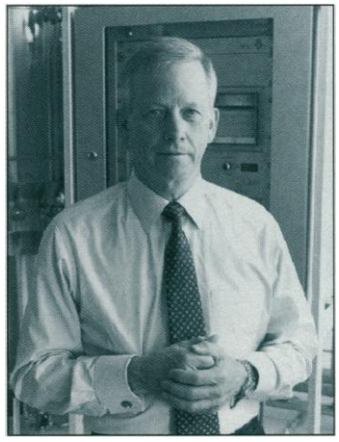
When Lilly refused to pay royalties to UC, the university sued in 1990, claiming that Lilly was infringing on both its patents. To UC's dismay, the trial was shifted to Indianapolis, Lilly's hometown. There, Judge S. Hugh Dillin came down heavily in Lilly's favor in December 1995, rejecting both of UC's patents. He ruled that the rat gene patent was invalid because the gene's sequence differed from the human DNA sequence that Lilly used in manufacturing. And he declared that Lilly's process was different enough from the one UC patented that it did not infringe the patent. UC appealed early this year, and the U.S. Court of Appeals for the Federal Circuit ruled on 22 July that, while Judge Dillin had gone too far in some respects, Lilly would not have to pay royalties.

Some patent experts think the decision could have a broad impact, compelling gene hunters to spell out the exact sequence of all the DNA they hope to claim, rather than just the function of the genes. For example, an attorney for one company says, "we're changing the descriptions in all our patent applications to emphasize the chemistry." And Paul Clark, of Clark and Elbing in Boston, views the decision as "yet another illustration of the poor match between academic research and the patent system." He thinks the ruling will put scientists working with animal models at a disadvantage in the competition for medical-use patents—or encourage them to delay publishing until they have human data.

UC's Fuererborn says he's "leaning strongly in favor" of asking the appeals court for a rehearing. And UC could, in principle, ask for a U.S. Supreme Court review. But attorneys say the Supreme Court accepts few patent cases, and UC officials may not want to push their luck. After all, it could have been worse: The lower court had initially ordered the university to pay Lilly's legal bills, estimated at $18.5 million. That penalty was dropped when the appeals court set aside the "inequitable conduct" allegations. Now, UC is stuck only with its own legal costs: about $12 million. **–E.M.**

applied for on 27 May 1977. Lilly charged that the UC scientists simply labeled the pBR 322 data as coming from the approved pMB9 plasmid. By using pBR 322, Lilly alleged, the UCSF biologists had stolen the march on their competitors, winning an early patent date. (Nobody has charged that the UCSF team's use of pBR 322 endangered safety. Indeed, pBR 322 was certified by NIH on 7 July 1977, 2 months after UC filed its patent.)

Judge Dillin accepted all these arguments when he ruled that the patent had been obtained by "inequitable conduct." But the appeals court dismissed this reasoning, arguing that "a reasonable patent examiner would not have considered noncompliance with the NIH guidelines to be material to patentability." The court added that Dillin had given way to "unfounded speculation" when he theorized that, had the university "complied with the [NIH] guidelines," some other inventor might have beaten UC to the patent office. Within the context of patent law, the appeals court said, there had been no misconduct.



DAVID POWERS

Outraged. William Rutter says Judge Dillin's ruling "demeaned" a key discovery.

Lawyers for UC argue that the ruling nullifies all the facts cited by the lower court. But other patent experts—including Rebecca Eisenberg of the University of Michigan, Ann Arbor—say the "facts" in Dillin's ruling should be taken for what they are: the findings of one well-briefed judge, which have now been ruled legally irrelevant.

Science sought clarification last week from Rutter and Goodman about the origins of the rat insulin data they published in this journal. Attempts to obtain comment from the former postdocs who did the detailed rat DNA analysis were not successful.

Both of the lead researchers dismiss Dillin's judgment as wrongheaded. Rutter calls it "outrageous," adding that it "demeaned the basis of an important scientific discovery." He complains that "it seems like Judge Dillin just copied Lilly's brief." Goodman says the judge's reading of events is "utter nonsense."

Dillin wrote of what he called two "smoking-gun" letters delivered by certified return mail on 22 and 25 March 1977—identical in content, one from Rutter to Goodman, the other from Goodman to Rutter, bearing the names of both scientists. They describe in detail how the two had weighed their options for using or discarding pBR 322 data in 1977, concluding that they felt it best to "keep the cloned DNA since the experiments had already been performed," and "since the hypothetical danger, if any, is not with the DNA itself." The judge was troubled that this version of events appeared in letters postmarked after the date on which the clones were said to have been destroyed (19 March). Dillin interpreted this to mean that Rutter and Goodman had knowingly used pBR 322 sequence data in their publications. Furthermore, he wrote that the certified letters, which sat for years unopened in the two scientists' files, "could have had no purpose but to keep either of the writers from attributing the misuse [of pBR 322 data] to the other."

Rutter dismisses the letters as inconsequential. "They ... reflected our thought processes at the time. ... They were sent to each one as a record, for safekeeping," he says. And Goodman explains: "We tried in that letter to document our thinking as best we could, in anticipation of talking to NIH and deciding what to do." Rutter adds that "our plans changed" after he spoke privately in the spring of 1977 with NIH official DeWitt Stetten, who kept the violation of NIH rules to himself but urged Rutter to destroy the pBR 322 clones. The letters, Rutter says, were "processed and mailed noncontemporaneously." Judge Dillin noted in his opinion, however, that Rutter's conversation with Stetten took place no later than 19 March 1977, several days before the letters were postmarked. He wrote he was "far from convinced" that Rutter and Goodman would revise their decision but not the damaging record they subsequently sent each other for safekeeping.

In reaching his conclusions, Dillin also relied on a set of draft scientific manuscripts written by Goodman. All employ the same language and report essentially the same sequencing data from clones containing the rat insulin gene. But each describes the use of a different type of vector: The first describes the sequencing of pBR 322; the second, pCR1; and the third, pMB9. Testimony during the trial revealed that the UC team never succeeded in cloning the insulin gene into pCR1, which NIH had certified as safe early in 1977. But one manuscript includes a full description of data from a vector described in the underlying text as "pBR 322," amended to "pCR1," with corresponding changes in sequence to reflect different DNA-splicing details. In another draft, "pCR1" in the underlying text is revised to "pMB9."

Lilly also charged that there were anomalies in the genetic information in these manuscripts. Its arguments on this point were presented to the court by Lilly's star witness, Harvard biologist Walter Gilbert. Gilbert charged that all the draft manuscripts contained sequence data on fragments of the insulin gene that are identical to data obtained from pBR 322 clones, as described in Goodman's lab notes—right down to the identical number of nucleotide "A's" in the sequence "tail." In addition, Gilbert pointed to data in the final *Science* manuscript that include typographical sequence errors that appeared in Goodman's lab notes on pBR 322. Citing this evidence, Judge Dillin concluded that "the manuscripts were based on work done with the uncertified vector pBR 322."

Rutter responds that he "firmly believes" that pBR 322 data did not end up in the *Science* paper. He notes that the rat DNA used in the lab's cloning work in 1977 came from a single preparation, and that this might explain why the pBR 322 data were identical to the pMB9 data. He says he cannot be held accountable for sequencing details or errors in "secretarial transcription," which could have caused some confusion.

How did the UC team prepare a manuscript with sequence data from pCR1 clones when pCR1 cloning had failed? Goodman says, "I was up in Seattle at the time, writing manuscripts" based on data supplied by the lab in San Francisco. "There was some mix-up in terms of what vectors were which at that point." He says he wrote "several versions of manuscripts that ... were anticipating which vector might work." Eventually they succeeded with pMB9. (The UC researchers say that after pMB9 was certified as safe on 18 April 1977, they went into high gear, recloning the gene into the new vector, resequencing the DNA, and sending their manuscript to *Science* on 9 May 1977.)

Rutter says that Goodman wrote all the manuscripts. He suggests the pCR1 draft may have been done in anticipation of getting data that were not obtained. "It is not uncommon for scientists to prepare manuscripts concurrently with doing experiments," Rutter says, adding "I know one relatively famous scientist who wrote manuscripts before carrying out the experiments" to sharpen the focus.

He argues that there is also one strong personal indication that Judge Dillin is wrong: The members of the original UC research team—even those who are no longer friends and have gone into competitive projects—remain "absolutely unanimous," Rutter says, that the forbidden vector pBR 322 was not the source of the *Science* data. If anyone doubts that, he adds, the pMB9 clones were deposited "in the bank" at the American Type Culture Collection in Rockville, Maryland, and could be resequenced to see if they yield the data published in the *Science* article.

–Eliot Marshall