Trial Set to Focus on Peer Review

Two biotech companies, aided by scientific experts, are planning to fight it out in court over the right of academics to keep manuscripts secret while they are undergoing peer review

More than a decade after it first began, a race to patent a biological molecule is about to be decided in a Seattle courtroom. But this will be no ordinary legal contest over patent law. After years of pretrial skirmishing, the contestants and their teams of experts have recently been homing in on an explosive issue that is likely to resonate widely throughout the scientific community. At stake, according to some scientists, is an ominous question: Does the academic notion of confidential peer review—that reviewers are forbidden to disclose or use information they see in an unpublished manuscript—have any legal validity?

Facing each other across the U.S. District courtroom in Seattle when the trial opens on 24 September—barring any last-minute delays—will be Cistron Biotechnology of Pine Brook, New Jersey, and the Immunex Corp. of Seattle, each backed by a phalanx of lawyers and scientific experts. Cistron is contending that in 1984, an Immunex scientist took data on an immune-system protein from a paper he reviewed for possible publication in *Nature* and shared it with his colleagues, who then used the unpublished information in their own research and patent applications. The paper had been written by an academic consortium funded by Cistron, which was then in a scientific race with Immunex and was trying to raise capital to support its research (*Science*, 22 December 1995, p. 1912).

Immunex has denied any wrongdoing. The company has declined to discuss the case on grounds that the judge has discouraged any communication with the press. Cistron officials have also declined to comment. But voluminous transcripts of pretrial depositions and reports of expert witnesses give an account of the issues at stake. They show, for example, that Immunex is planning to argue that its patents derive from its own discoveries and were obtained independently. But they also indicate that Immunex is likely to concede that its scientists compared their data with information in the unpublished manuscript. Immunex lawyers, in fact, have been laying the groundwork for a categorical defense: that there is no rule—legal or otherwise—that prevents a reviewer from using data in an academic paper he or she reviews. Furthermore, Immunex argues in its filings that scientific data obtained by publicly funded scientists, like those on Cistron's team, are not protected by trade secrecy laws. The confidentiality of peer review is therefore shaping up to be the main issue on trial.

Both sides have lined up an impressive list of witnesses who may be called to testify. Cistron's roster, for example, includes Sir John Maddox, the former editor of *Nature*; Lawrence Bogorad, professor emeritus of biology at Harvard University and recently retired editor of the *Proceedings of the National Academy of Sciences*; Richard Flavell, chair of immunology at the Yale University School of Medicine; Edmond Fischer, professor emeritus of biochemistry at the University of Washington and a winner of the 1992 Nobel Prize for work on cellular regulation and signal transduction; and Harry Manbeck Jr., the former commissioner of U.S. Patents and Trademarks. Immunex's experts include Robert Armitage, a Washington, D.C., patent attorney formerly in charge of intellectual property at the Upjohn Co.; Gregory Siskind, a professor of medicine and associate dean for research and sponsored programs at Cornell University Medical College; biochemistry professor Kenneth Walsh of the University of Washington, Seattle; and Joost Oppenheim, chief of the lab of immunoregulation at the National Cancer Institute's facility in Frederick, Maryland.

CISTRON BIOTECHNOLOGY

"If one could gain a material advantage from knowing what is in a manuscript, one has a potential conflict of interest and should not review the paper."
—Lawrence Bogorad

IMMUNEX

The Auron paper "clearly stopped being confidential ... at the point at which [the authors] began steps to get it to the entire scientific community by submitting it for publication."
—Robert Armitage

These armies are circling a narrow battleground, focusing on the right of academic scientists to keep commercial secrets. Initially, Cistron had blasted Immunex with a volatile mix of charges, including allegations of "racketeering" and fraud. But in April, the judge presiding over the case, William Dwyer, limited the scope to questions of trade secrecy and "unfair competition." After that, Cistron reduced its damage claims against Immunex from well over $100 million to between $67 million and about $90 million. Immunex, meanwhile, had filed a counterclaim accusing Cistron of engaging in unfair competition. Specifically, Immunex claims in legal papers that Cistron—which failed to market any successful products and went bankrupt—is trying to win through legal gimmicks what it could not win in the lab or the marketplace. According to experts close to Immunex who spoke on condition of anonymity, this counterclaim may be dropped, but it will remain the theme of Immunex's defense.

IL-1β MOLECULE: P. AURON

The 10-year interleukin war

Cistron filed its lawsuit about 3 years ago, but the dispute behind it goes back to the 1980s, when Cistron and Immunex scientists were racing to isolate and patent a protein called human interleukin-1 (IL-1)—an immune factor once touted as a hot prospect for controlling immune responses, but now a commercial dud. The Cistron team consisted of researchers at three universities in New England, led by Philip Auron, then at the Massachusetts Institute of Technology. The Immunex team, entirely composed of staff researchers, was led by Immunex's top scientists at the time, Steven Gillis and Christopher Henney. They have since moved to other companies.

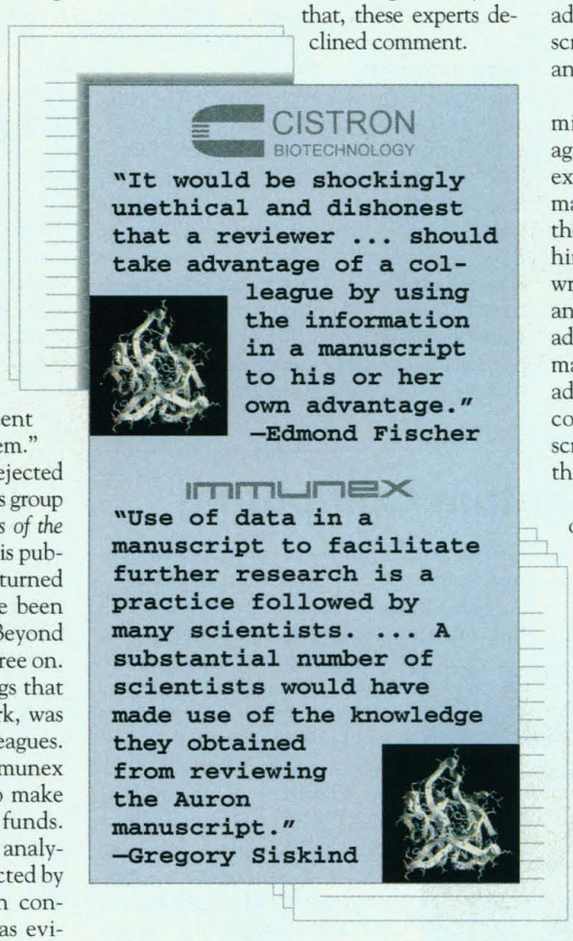
While many aspects of the case are disputed, a few are not: Auron and his team were the first to submit a paper claiming to have isolated the human DNA coding for IL-1. They sent the paper to *Nature* in December

1983, but it received two negative reviews from outside scientists. *Nature* then asked Gillis to be a third reviewer, even though he was a direct competitor, and he also turned in a negative review. Along with his comments on the manuscript, which *Nature* passed along to Auron without revealing their source—standard practice for virtually all academic journals—Gillis sent a confidential note saying that his team had independently isolated IL-1, and that his data proved Auron wrong. "As I mentioned ..." Gillis wrote to *Nature* on 16 July 1984, "we have recently purified human IL-1 to homogeneity. Fortunately, or unfortunately, the amino acid composition generated from this purified protein does not match" the one given in Auron's paper. Gillis continued: "I purposely left this comment out of my comments for the authors, as I would be most reticent to have this information passed to them."

Nature kept Gillis's secret. Then it rejected the Auron manuscript. In 1985, Auron's group published its report in the *Proceedings of the National Academy of Sciences*, while Gillis published one of his own in *Nature*. (As it turned out, Gillis and Auron appear to have been analyzing different forms of IL-1.) Beyond these facts, there is little the parties agree on.

Cistron claims in many court filings that Gillis, while disparaging Auron's work, was actually sharing it with Immunex colleagues. Furthermore, Cistron claims that Immunex used Auron's data as a "road map" to make discoveries, get patents, and raise funds. Cistron's argument rests in part on an analysis of Immunex's lab notebooks conducted by Yale immunologist Flavell, a Cistron consultant. In a 29-page report entered as evidence, Flavell writes that Immunex "extensively relied in its IL-1 research program ... on information derived from the Auron manuscript." In addition, Flavell says, Immunex copied a DNA sequence from Auron's manuscript into its computer, then into U.S. and European patent applications. Flavell says there is clear evidence of this copying, including a set of errors in a DNA sequence that appeared first in the Auron manuscript, then in Immunex's patent applications.

In its initial response to this lawsuit, Immunex told the court that these DNA errors—which came to be known as the Auron "fingerprint"—had been included in patent applications through a "clerical error." *Science*'s request for information about the clerical error did not elicit a clarification from Immunex's attorneys or its spokesperson, Robin Shapiro. Nor do reports prepared for the trial by Immunex's experts say anything about the clerical error. Indeed, the two reports that deal with sequence data—prepared by Walsh and Oppenheim—remain confidential, at Immunex's request. Oppenheim says that he has provided "an alternative interpretation" to Flavell's account of how Immunex might have obtained its IL-1 data. And Walsh says that he is "not in entire agreement with the conclusions" of the Flavell report. Beyond that, these experts declined comment.



The battle over peer review

While neither side is devoting much time to the "clerical error," both are investing heavily in exploring what is and is not permissible in peer review. Cistron claims in its court filings that, at a minimum, Gillis behaved unethically by using data from an unpublished manuscript. In addition, Cistron alleges that Gillis and Immunex "misappropriated" a trade secret when they filed a patent containing Auron's data. In making these arguments, Cistron has found no shortage of experts to shore up its claims. For example, Maddox said in a deposition taken in London in July that he now views it as "outrageous" that Gillis requested—and got—secrecy for his own IL-1 data. He added that if Immunex did indeed use information from the Auron manuscript in its research, that "certainly would have been improper."

Bogorad, the Harvard biologist, filed an 18-page report with the court on Cistron's behalf in which he says that after reading Flavell's report, he concluded that Immunex had used data from the Auron manuscript "as a road map." He strongly denounces that alleged conduct as "improper," adding that, "In my opinion, the Immunex employees were stealing." The accepted standard, Bogorad claims, is that "if one could gain a material advantage from knowing what is in a manuscript, one has a potential conflict of interest and should not review the paper."

In a report written for Cistron and submitted to the court, biochemist Fischer agrees that "if the reviewer is doing work in exactly the same area [as the author of a manuscript], or is doing overlapping work, the reviewer has an obligation to disqualify himself and return the manuscript." Fischer writes that "it would be shockingly unethical and dishonest that a reviewer ... should take advantage of a colleague by using the information in a manuscript to his or her own advantage." A reviewer must protect the confidentiality of an unpublished manuscript, Fischer claims, "regardless of whether the manuscript is stamped 'confidential.' "

Immunex has responded to this barrage of high-toned outrage with several arguments. Company consultants have said in briefs filed with the court that academics who receive public grants are categorically excluded from holding trade secrets under provisions of the Bayh-Dole Act, a law that aims to promote the transfer of technology to private hands. Second, Immunex argues through expert-witness statements that anyone who sends a manuscript to a journal has automatically surrendered trade secrecy protection through the act of submitting for publication. In this case, Auron revealed some IL-1 data at a scientific conference in October 1984, proof, according to Immunex, that he was not protecting a trade secret. Third, Immunex claims that the guidelines for handling manuscripts under review are so variable and vague that there is no clear-cut, uniform rule about what a reviewer is or is not supposed to do.

The lead witness on Immunex's trade secrecy position is patent attorney Armitage, who said in a deposition in March that Auron's paper "clearly stopped being confidential ... at the point at which [the authors] began steps to get it to the entire scientific community by submitting it for publication." Trade secrets can only be maintained, Armitage writes, in outfits that work hard to prevent the release of information. Cistron had signed an agreement with its university partners to control information, but Armitage argues that it was not rigid enough, because "Cistron had no right to prevent publication" by university-based researchers, who are free to publish their work.

Cornell's Siskind agrees in his expert report for Immunex that Auron and his col-

leagues—as university-based, publicly funded scientists—could not keep secrets. "A decision to accept public funding and the use of nonprofit university facilities is inconsistent with efforts to keep data secret," Siskind argues. The only way to protect intellectual property in these circumstances, according to Siskind, is to file a patent. (Cistron did, but the patent wasn't issued until 1988.) Even if an academic discovery is awaiting a patent, Siskind argues, "it would be unreasonable to extend protection to the review process."

As for the complaints of unethical conduct raised by Cistron, Siskind argues that standards vary from journal to journal, making it hard to label anyone as being out of line. "There are no codes, standards, or rules governing journal peer review which are generally accepted by all groups in the biomedical community," Siskind argues, adding that "Immunex, Dr. Gillis, and Dr. Henney acted within the range of commonly accepted norms of behavior in their use of the Auron manuscript. Their conduct was ethical and violated no rules and no uniformly accepted standard of conduct at the time."

Indeed, Siskind continues, the "use of data in a manuscript to facilitate further research is a practice followed by many scientists," and "some scientists believe it is unrealistic and even unethical not to use whatever information is available to them." Siskind believes that "a substantial number of scientists would have made use of the knowledge they obtained from reviewing the Auron manuscript." And he notes that Bogorad and Fischer conceded, when questioned by an Immunex attorney, that it would be all right for a reviewer to drop a project after reading a manuscript claiming to have completed the same work.

Many of the witnesses in this case—including Maddox—have conceded that there are no uniform standards governing peer review. But they argue passionately that the standards of conduct are genuine and that all scientists know what they are. Cistron's attorneys go further, arguing that these standards are so widely understood that the alleged violation of them by the Immunex staffers was a violation of fair business practices. This argument could be worth a lot to Cistron, should it hold up in court. But Immunex's lawyers are confident that it will not.

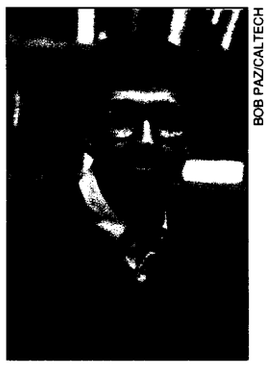
If there is no further delay in the trial or a pretrial settlement—which sources close to the case say is unlikely—a Seattle jury will soon cast its vote on Cistron's allegations and, by extension, on the sanctity of peer review. Its verdict will be extensively peer-reviewed throughout the scientific community.

–Eliot Marshall

INFORMATION SCIENCE

All Together for Quantum Computing

More than 10 years ago, the late physicist Richard Feynman planted a dream: harnessing the weird ambivalence of quantum-mechanical states to compute at a pace that would outstrip the fastest possible classical computer. Since then physicists have made great strides in the theory of quantum computers and even in their hardware, going as far as making simple quantum logic gates (*Science*, 7 July 1995, p. 28). What they haven't done is show that quantum computers will ever really work. "When you go from the mathematics to the engineering," says Caltech physicist Hideo Mabuchi, "the prospects don't look so great."



BOB PAZ/CALTECH

QUIC mover. Caltech's Jeff Kimble.

Now a consortium of researchers from Caltech, the Massachusetts Institute of Technology (MIT), and the University of Southern California (USC) has founded an institute for Quantum Information and Computing (QUIC) at Caltech to test the promise of quantum computing and see how, short of a full-fledged computer, quantum mechanics might be harnessed to manipulate information. Starting this month with a 5-year, $5 million grant from the Defense Advanced Research Projects Agency (DARPA), the institute-without-walls will unite researchers who will work on different pieces of the quantum-computing puzzle. The aim is to answer a few simple but profound questions about quantum information processing, says Caltech theorist and provost Steve Koonin: "What good is it? What class of problems might it be good for if it existed? And how perfect does a [quantum computer] have to be for it to work?"

The phenomenon at the heart of a potential quantum computer is the ability of a microscopic system, say an atom or a single photon, to be in more than one quantum mechanical state at the same time—a superposition of states. As USC computer scientist and QUIC researcher Alvin Despain explains, a laser can excite an atom into a superposition of both its ground and its excited states. If those two states represent a binary 1 and 0, then calculations on the superposition act on both values at once. A quantum computer containing n atoms in superposed states, says Despain, could do a calculation on 2^n numbers at once—a degree of parallelism that is inconceivable for classical computers.

Quantum computing suffers two handicaps, however. First, says Mabuchi, the laws of quantum physics and the subtleties of a quantum-mechanical measurement limit the amount of information that can be extracted from a quantum computer. As a result, researchers have so far figured out only two applications for which they might use a quantum computer: factoring large numbers, and simulating other quantum systems such as high-temperature superconductors. Second, quantum superpositions are extraordinarily fragile: Any contact with the environment sets off a process known as decoherence, and the quantum superposition collapses to a mundane classical one. "It appears the main advantages of quantum computation are lost if you really have any significant degree of uncontrolled interaction with the environment, and if you're not able to perform manipulations of the computer with a high degree of accuracy," says Mabuchi.

DARPA put out a call for proposals to study quantum computing and its limits last year, after the agency decided to look at research somewhat beyond the cutting edge of technology, says Despain. The QUIC researchers, led by Caltech's Jeff Kimble, responded with a proposal for a many-faceted research program. Seth Lloyd of MIT will work on algorithms for quantum calculations, while Kimble and his colleagues, who have already built a primitive logic gate, will develop data storage registers and better logic gates. Despain's own group will simulate various quantum architectures to see which have the most tolerance to errors and decoherence, and Caltech theoretical physicist John Preskill will develop means of correcting those errors to see, as he puts it, "how long you can do a quantum computation in a noisy environment before your quantum computer crashes." Finally, Koonin will study the quantum-mechanical theory on which all these dreams are founded.

With much to be gained from studying quantum information processing, even without achieving a working quantum computer, all of the research will be exploratory as well, says Kimble: "in the spirit of a 'bold new frontier' and not so much just a better widget." Then again, the widget is a pretty appealing prospect, says Despain: "Quantum computing isn't something one would do unless we thought the payoff would be incredible."

–Gary Taubes