Suit Alleges Misuse of Peer Review

A lawsuit, claiming that researchers working for a biotech company used data from a paper one of them reviewed for *Nature* in their own research, is headed for trial in federal court

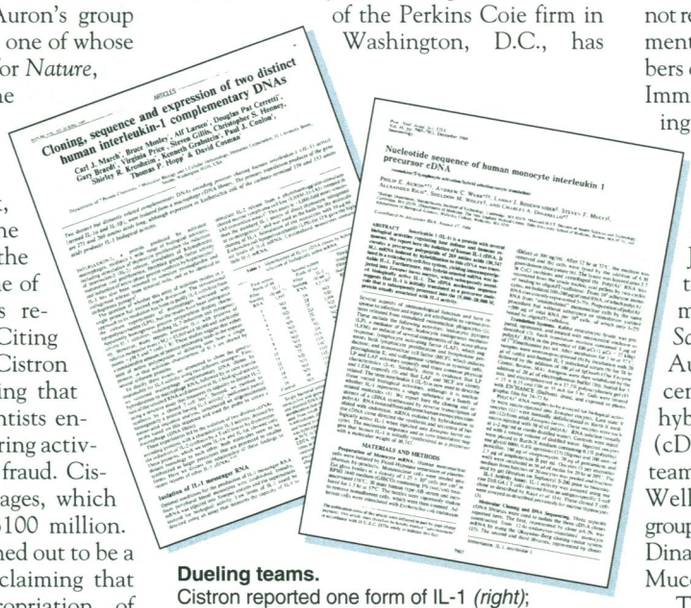
A team of academic researchers headed by biologist Philip Auron, now of Harvard Medical School, believed they had won one of the hottest races in biotechnology in 1983: They had cloned and sequenced the expressed gene for a human immune system molecule called interleukin-1 (IL-1). They sent off a paper to *Nature* describing their results. What happened to that paper over the next several months is now at the center of a lawsuit that is heading toward a trial in federal court in Seattle next year. At issue in the suit is an allegation that's likely to send a chill down the spine of any scientist about to submit a paper for review. Auron's group claims that a competing team, one of whose members reviewed the paper for *Nature*, gained key information from the paper and used it in its own patent application.

The suit pits Cistron Biotechnology Inc. of Pine Brook, New Jersey, which funded the Auron team's work, against the Immunex Corp. of Seattle, one of whose former staff scientists reviewed the *Nature* paper. Citing anti-racketeering statutes, Cistron filed the suit in 1993, charging that Immunex and its former scientists engaged in "a pattern of racketeering activity," including mail and wire fraud. Cistron is asking for treble damages, which could amount to well over $100 million. Although IL-1 has not yet turned out to be a big moneymaker, Cistron is claiming that Immunex's alleged misappropriation of Auron's data helped Immunex raise capital and "resulted in unjust enrichment to Immunex" and severe losses to Cistron.

Immunex has denied Cistron's charges, claiming they are based on a deliberate misreading of the facts. In one court filing, for example, Immunex states flatly that it "has not misappropriated any [IL-1] information from Cistron or the inventors of Cistron patents." And Immunex argues that the molecule claimed in its own patent is genuinely different from the molecule claimed by Cistron, although both are derived from the same human gene, one that was first sequenced by Cistron. Immunex has also made counterclaims of its own, charging in court filings that Cistron has used legal threats to "intimidate" and "undermine the goodwill and reputation of Immunex," issued "false statements," and engaged in "unfair competition." It seeks to recover damages and attorneys' fees from Cistron.

A trial has been set tentatively for 23 April 1996, and, as this long, bitter dispute heads for a denouement, the legal skirmishing is heating up. This month, Immunex is asking the judge to dismiss Cistron's suit on the grounds that the statute of limitations has elapsed.

If this case does go to trial, one line of argument is expected to focus on the scientific community's peer-review procedures. Immunex's lawyer, M. Margaret McKeown of the Perkins Coie firm in Washington, D.C., has questioned witnesses on whether there are written or legal rules that forbid a researcher from using data taken from an unpublished paper he or she is reviewing (see box). And if the court should decide that there are no legal requirements of confidentiality, the implications worry Alexander Rich, a biologist at the Massachusetts Institute of Technology and a co-author of Auron's paper. In a recent interview with *Science*, Rich said: "Anybody who's involved in science would have to say this is a serious threat" to the peer review process.



Dueling teams.
Cistron reported one form of IL-1 *(right)*; Immunex later reported a second form.

Immunex is also making another argument that could affect scientific meetings: It has argued in court filings that Cistron gave up its trade secret claim on IL-1 when Auron briefly flashed DNA sequence data on a screen at a 1984 scientific conference in Germany.

Although much of the evidence in this case has been put under seal by the court, both McKeown and Cistron's attorney—Philip Swain of Kirkland & Ellis in Los Angeles—provided *Science* with copies of some public legal filings. Aside from releasing these documents, however, Immunex isn't discussing the suit. Robin Shapiro, Immunex's spokesperson, said: "We have a policy of not commenting on litigation that is ongoing." Two former Immunex scientists named in the suit—biologists Steven Gillis and Christopher Henney, now at other companies—either did not return telephone messages or declined comment through an attorney. However, members of Cistron's scientific team and a former Immunex scientist discussed the case, speaking mainly on background.

A competitor's "fair" review

According to briefs filed by the two companies and depositions taken in January 1995—from *Nature*'s former editor in chief, John Maddox, and former manuscript editor, Nigel Williams (now *Science*'s European correspondent)—Auron submitted a paper to *Nature* in December 1983 reporting on the isolation by hybridization of a complementary DNA (cDNA) sequence for human IL-1. Auron's team consisted of Rich; Andrew Webb of Wellesley College in Massachusetts; and a group at Tufts University including Charles Dinarello, Lanny Rosenwasser, Steven Mucci, and the late Sheldon Wolff.

Two reviewers advised against publishing the paper, saying the research seemed incomplete, according to Maddox and Williams. The paper was rejected. Rich appealed for a second reading, and *Nature* sent the paper to Gillis in June 1984 for review. Why was Gillis chosen? Because he was "an excellent reviewer ... and this was precisely his area of expertise," Williams stated in his deposition.

After receiving the paper, according to the depositions, Gillis phoned Williams to say that he, like Auron, was trying to purify IL-1. Many journals—including *Nature*—ask scientists to recuse themselves from reviewing a paper if they feel that a conflict of interest would affect their judgment. In this case, however, Maddox and Williams said, Gillis did not bow out, nor did *Nature* suggest that he do so. In retrospect, Maddox said in his deposition, "I think [Gillis] should have

Peer Review: Written and Unwritten Rules

As a bitterly contested lawsuit over the discovery of the genetic sequence for interleukin-1 (IL-1) heads toward a trial in Seattle next year, a key issue is emerging in pretrial questioning of some potential witnesses: Just what rules, if any, govern the confidentiality of information in papers sent out for peer review. Lawyers for the defendant, the Immunex Corp. of Seattle, homed in on this question last January, when they took a deposition from *Nature*'s then–editor in chief, John Maddox. The issue could feature prominently in the case, which centers on a claim by Cistron Biotechnology of Pine Brook, New Jersey, that Immunex scientists improperly used information from a paper they reviewed for *Nature* in their own research (see main text). Immunex has denied the charges.

Margaret McKeown of the Perkins Coie firm in Washington, D.C., pressed Maddox repeatedly to explain what "confidential" means in the context of peer review. "With respect to the word 'confidentiality,' " McKeown asked Maddox, "would you agree that there is nothing [in *Nature*'s boilerplate letter to reviewers] spelled out in terms of definition?" Maddox replied: "Yes." Later, McKeown asked if a possible interpretation of confidentiality is "that one may disclose the document internally at his or her institution, but not hand it out or disclose it publicly?" Maddox responded, "Yes," provided the names of any colleagues consulted are "passed on to us."

"It would be improper for a referee to disclose the content of a manuscript sent by way of review" without the journal's permission, Maddox said. "It would be doubly improper," he added, if a reviewer "used the information in that manuscript to further his own research," and a "flagrant breach of our understanding with referees" if they were to make copies of a paper received for review.

Nature's policy on confidentiality is spelled out in a sentence in the standard letter the journal sends to people who have agreed to referee a paper. It says: "Colleagues may be consulted (and should be identified for us), but please bear in mind that this is a confidential matter." *Nature* does not ask authors or reviewers to identify conflicts of interest, but relies on its editors to do so. In a recent telephone interview with *Science*, Maddox, who retired this month as editor, said "we're in the process" of changing instructions to authors and reviewers to make them more explicit. But he thinks it's "only fair that my successor should determine the policies" for the future.

"If a person makes improper use of information in a manuscript, the first person to know will be the competitor."
—John Maddox

Other journals give similar warnings, some in stronger terms. For example, *Science*'s letter to reviewers explicitly forbids dissemination and exploitation of information in the paper: "We expect reviewers to protect the confidentiality of the material presented. Please ensure that the enclosed manuscript is not disseminated or exploited. If you find it necessary to discuss this paper with a colleague, please specify the particulars in a letter to the editor." The warning issued by the *New England Journal of Medicine* is short but clear: "The manuscript should be considered a privileged communication. You should not show it to another person without calling us, and you should not photocopy it." And the *Journal of the American Medical Association* advises reviewers that "we consider this manuscript and your review of it to be confidential, not to be shared with others. If you need to consult colleagues to help with the review, please inform them that the information is confidential." All three of these journals also explicitly ask reviewers to identify conflicts of interest that might affect the review.

Reflecting on the IL-1 case—which may draw Maddox into court as a witness next year—Maddox told *Science* that the crux of the problem illustrated by the case is: "Can a journal police the understanding we have with referees" that they must "take that confidentiality clause seriously?" In his deposition last January, Maddox mentioned that he had come across few cases of "hanky-panky" in which reviewers had misused papers, perhaps two or three in 15 years. In one instance, he said, "an author discovered, when he went to visit a friend's lab in New York, that not merely did the friend have a copy of his paper, but so did the postdocs in the lab as well, and he was offended." But he said that most people respect confidentiality, and that the number of known violators is so small that "the iceberg must be very small."

The best way to enforce standards of confidentiality, Maddox observed, is to rely on peers to sniff out wrongdoing. "If a person makes improper use of information in a manuscript," Maddox said, "the first person to know will be the competitor ... and he will write to us." The editor might then contact a reviewer's home institution and "complain." As Maddox explained to the Immunex lawyer: "We have, I should say, a fearsome reputation anyway within the academic community, and people do not like being told that *Nature* is angry with them."

–E.M.

disqualified himself as a referee."

On 16 July 1984, Gillis sent *Nature* his review; it was negative but "fair," Maddox said in his deposition. Gillis included a confidential cover letter, now part of the court documents, which stated: "As I mentioned to you on the telephone (in confidence), we have recently purified IL-1 to homogeneity. Fortunately or unfortunately, the amino acid composition generated from this purified protein does not match the amino acid composition called out by the cDNA sequence" in Auron's paper. "I would be most reticent to have this information passed" along, Gillis wrote.

The Auron paper was rejected a second time, according to the depositions. In keeping with standard practice at scientific journals, *Nature* did not tell Auron who had given the negative review, nor that the reviewer was a business competitor, nor that the reviewer claimed to have found a different, "correct" version of IL-1.

About 3 months later, in October 1984, according to news reports in *Nature* and *Lymphokine Research* (*LR*), Cistron and Immunex scientists clashed openly at a meeting of the Fourth International Lymphokine Workshop at Schloss-Elmau, in Germany. Cistron claims that the Alpine encounter provides evidence that Immunex was misusing confidential data from Auron's paper. The flare-up began when Auron, scheduled to speak at the meeting's final session on 20 October, declined to show his data on human IL-1. Auron says he had seen a biotech company staffer in the room with a long-lens camera on a tripod, and objected. The session leader asked people to put down their cameras and pressed Auron to show his data. Auron complied, flashing on the screen a slide listing the more than 1500 nucleotides in Cistron's IL-1 gene.

Immediately—according to *LR* and other

observers who confirmed these details—Immunex staffer Henney leapt from his seat and raced to the microphone. According to *LR*, Henney blurted out that "he was familiar with the sequence Auron presented and that the sequence for IL-1 was known, and was not Auron's sequence." Henney was asked to explain what he knew about Auron's data or other versions of IL-1, but he sat down abruptly and said no more.

In a legal brief, Cistron claims that Henney's remarks are part of "a pattern of behavior" at Immunex in which the company "knowingly [and] fraudulently convinced Cistron, Cistron's partners and funding sources, potential investors ... and the public that Immunex had ownership and inventorship rights in IL-1β, thereby fraudulently bringing about increased investment in Immunex."

Fighting for molecules

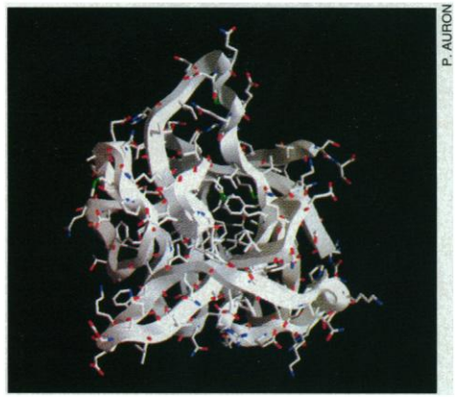
By the time Auron made his presentation at the lymphokine meeting, he and his colleagues had moved to secure their claim on the IL-1 gene. They had submitted a patent application to the U.S. Patent and Trademark Office in May 1984. In December, they published their data in the *Proceedings of the National Academy of Sciences* (*PNAS*), with Auron as lead author. The paper describes the cloning and sequencing of an expressed human IL-1 gene; it is the same gene that's covered by a patent issued in 1988 to Auron *et al.* and licensed to Cistron. One reason Auron and his colleagues rushed the paper into print, they say in court filings, is that they suspected their competitors had somehow seen their data. For example, the page of Auron's submission to *Nature* containing DNA sequence data, according to a sworn statement by Auron, came back from the review "marked up in freehand as if someone had photocopied the figure, analyzed it in detail, and marked certain crucial positions."

In December 1984, Immunex filed for its own patent, covering a smaller, biologically active unit of IL-1. The following June, Gillis co-authored a major scientific article in *Nature*, with Immunex staffer Carl March as lead author. In it, March and other Immunex scientists announced that they had cloned two distinct genes for IL-1. In addition, they sorted out the tangled science that had erupted in recent months. (A Hoffmann-La Roche group had reported on the cloning of a mouse IL-1 gene in November 1984, and two groups in Belgium reported details of the biologically active fraction of IL-1 in March 1985.)

The Immunex team explained that there are at least two human genes for IL-1. One, they wrote, was "very similar to" the gene first reported in *PNAS* by Auron *et al.* They named it IL-1β, giving it secondary status. However, the March paper said, there are "seven nucleotide substitutions"—minor distinctions that could represent natural variations—in the Auron version of this gene that distinguished it from Immunex's version. They also described a second gene for IL-1 with a distinctly different sequence; they called this gene IL-1α.

As the Immunex team explained, each of the two IL-1 genes codes for a large precursor molecule weighing about 31,000 daltons. In the body, these precursors are cut by enzymes to yield small active molecules of about 17,500 daltons. Immunex's patents covered all of IL-1α and, separately, the active portion of IL-1β. The Cistron patent covered all of IL-1β. The lawsuit focuses on the overlap—the active part of IL-1β.

The sheer complexity of the science, says one combatant in the IL-1 wars, created the frustration that has fed this lawsuit. For example, Immunex's choice of nomenclature—still in effect—rankled deeply. Auron says it was "arrogant" of Immunex to have taken alpha status for its own gene. They protested this label in a published letter to *Nature*, grumbling bitterly in a sentence that was edited out but included in a Cistron brief: "The increasing commercialization of molecular biology can cloud both good scientific judgment and publishing practices." Other IL-1 experts, such as Steven Mizel of the Bowman Gray School of Medicine in Winston-Salem, North Carolina, say it's not clear from the science whether IL-1α or β deserved top billing. β is more abundant in humans and has attracted more commercial interest, Mizel says, but α may prove important some day.



Disputed molecule. IL-1β's protein structure, corresponding to sequence published by Cistron group.

It was only in 1992, according to a sworn statement by Cistron's patent attorney—after both companies had obtained patents and the patent files were opened—that Cistron discovered what it labels in its court filings a "fingerprint" in the case. The new information, according to Cistron's patent attorney, Jeff Lloyd of the Saliwanchik & Saliwanchik firm in Gainesville, Florida, was a string of DNA data that had been included in Immunex's patent filing on IL-1 in December 1984. "We were shocked to discover, for the first time," Lloyd's statement says, "evidence that *proved* that Immunex had copied the IL-1β DNA sequence from the Massachusetts inventors" [italics in original]. The alleged proof: Immunex's December 1984 patent filing included Auron's seven supposedly "incorrect" nucleotides in the IL-1 gene. Most of these "Auron errors" are silent: They do not cause a change in an amino acid. But one base—number 95 in the Immunex patent application—was not silent. It did change an amino acid in the nonfunctioning region of the active molecule Immunex wanted to patent. Auron had listed this base as adenine, although later reports, including Immunex's June 1985 paper in *Nature*, listed it as guanine.

In 1988, an Immunex attorney wrote to the Patent Office calling attention to "minor errors" needing correction. One of these, the attorney wrote, was a change of "no functional significance whatever": base number 95 "should be guanine (G), rather than adenine (A)." The Patent Office allowed the change, bringing the patent—which was only issued publicly in 1992—in line with the data in the *Nature* paper.

Immunex dismisses as "a clerical error" the appearance of the incorrect nucleotides in their original patent filing. McKeown, Immunex's attorney, said in court in June 1994: "The evidence will reveal that Immunex had the sequence, that Immunex independently cloned its own sequence, that the errors were included as a result of a clerical error, and ultimately, it was irrelevant, because what Immunex got its patent on had nothing to do with this."

Many details of the litigation, including discussion of this clerical error, remain under seal to protect confidentiality. Because the parties are still bringing new information and arguments to court, surprises could occur before the case comes to a final resolution. The next major issue to be decided by Judge William Dwyer is whether the factual issues in dispute are substantial enough to warrant a jury trial rather than summary judgment. Judge Dwyer has called for arguments on this point and may decide soon. No date has been announced.

For Immunex, which is owned (54%) by the large and successful American Home Products Corp., the objective in this litigation is to avoid a potentially crippling damage award. For Cistron, which has already been through Chapter 11 bankruptcy and has given equity to the Massachusetts institutions that co-sponsored its IL-1 research, the goal is not just to recoup claimed losses but to vindicate old claims of priority.

Those with the most at stake, however, may be scientists who have nothing to do with either of these battling biotech teams. If the case is not settled before it goes to trial, it's possible the trial could drastically redefine the meaning of "confidentiality" in peer review and scientific meetings.

–Eliot Marshall