AIDS Priority Fight Goes to Court

The Pasteur Institute has charged the U.S. government with breach of contract and in a separate action is seeking to have a U.S. patent declared invalid

A long-simmering dispute between researchers at the Pasteur Institute in Paris and the National Cancer Institute (NCI) in Bethesda, Maryland, over who should be given credit for unraveling the cause of AIDS has erupted into a legal battle that could have a chilling effect on some types of scientific collaboration.

The Pasteur Institute filed suit against the U.S. government on 12 December, claiming that a group headed by Luc Montagnier, rather than a group at NCI headed by Robert C. Gallo, was the first to isolate the virus that causes AIDS and to "recognize the significance thereof in the development of methods of detection of AIDS and pre-AIDS conditions."

At the heart of the suit is a patent, awarded to the U.S. government on 25 May 1985, on a test developed by Gallo's group to detect antibodies to the AIDS virus in blood samples. In essence, the suit charges that, in developing the test, Gallo's group misappropriated materials and information that were supplied by Montagnier on condition that they be used only for research. Gallo has called the charge "outrageous," and claimed that the French group gained far more from collaborating with him than vice versa.

The suit contends that the Pasteur Institute is entitled to all royalties derived from the antibody test, which is now being used to screen every blood donation in the United States, and claims damages of at least $1 million for royalties that have already been paid to the U.S. government. In addition, the institute is seeking, in a separate legal action, to have the U.S. patent overturned.

The dispute rests in part on longstanding disagreements over the relative significance of the research contributions of the NCI and Pasteur groups.* The suit filed last month raises these disagreements to a new level, however, by essentially accusing Gallo of scientific misconduct.

The Pasteur group isolated a retrovirus early in 1983 from a patient with lymphadenopathy. In May of that year, the group, which included Jean-Claude Chermann and Françoise Barré Sinoussi, published a paper in *Science* reporting this isolation. The paper also presented data, derived from reagents supplied by Gallo, indicating that the virus was different from two leukemia viruses, known as human T-cell leukemia virus (HTLV) types I and II, the only other known human retroviruses. Few other researchers were convinced that this new virus was the cause of AIDS, however.

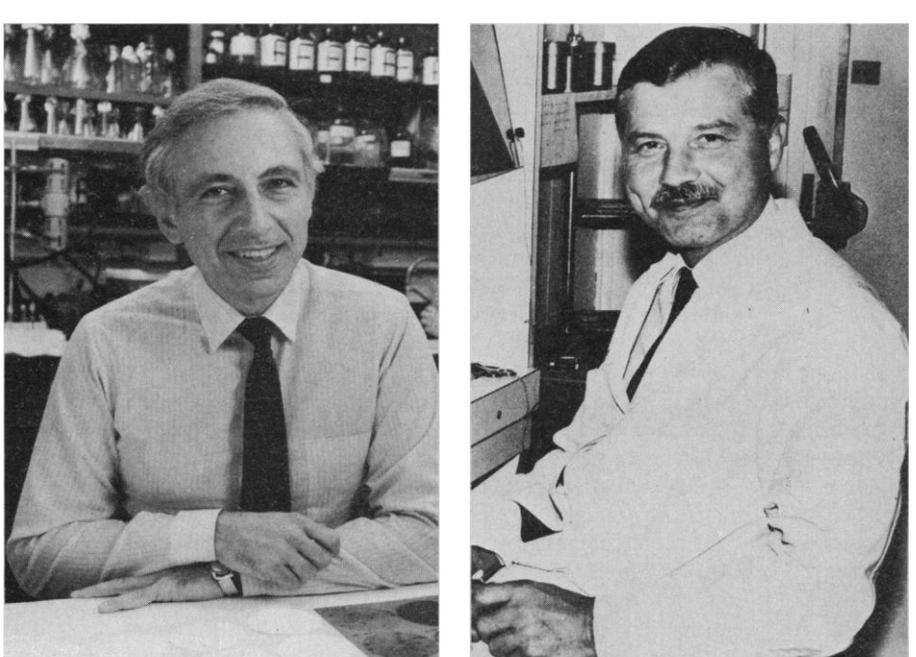
Gallo's group was also attempting to isolate virus from AIDS patients, but although they found signs of retrovirus infection, they could not get any virus to grow in culture. The problem, they subsequently realized, was that the virus killed the cells it infected. Mikulas Popovic, a cell biologist in Gallo's lab, solved this problem in November 1983 by infecting a line of cells that did not die.

This discovery enabled Gallo's group to grow large quantities of virus isolated from AIDS patients and develop a test to detect viral antibodies in blood samples. The antibody test provided convincing evidence that the virus was the cause of the disease. The federal government filed for a patent on the test on 24 April 1984, and Gallo published his results in the 4 May issue of *Science*.

In the meantime, the Pasteur group was growing small quantities of the virus they isolated early in 1983 by propagating it on fresh cells. They used this virus to develop an antibody test in August 1983, and filed for a patent on it in London in September and in the United States in December. Their patent has not yet been awarded in the United States, but the patent based on Gallo's work, which was filed 4 months later, was awarded in May 1985.

Pasteur Institute officials have contended that their patent application has been unfairly dealt with, and they have argued that the work of Montagnier's group has not been accorded due scientific or financial credit. On 6 August last year, a delegation headed by Raymond Dedonder, the head of the Pasteur Institute, met with officials of the U.S. Department of Health and Human Services to try to reach a settlement.

They demanded that the U.S. patent be



The leading combatants

Gallo (left) and Montagnier (right): legal charges stem from early collaboration.

*For a detailed account of the background to the suit, see *Science*, 1 November 1985, p. 518; and 8 November 1985, p. 640.

reissued with the Pasteur Institute as a co-holder, and asked for recognition that Montagnier's group was the first to discover the virus and apply for a patent. The Pasteur officials also demanded that a test kit produced by Genetic Systems Corporation in Seattle, Washington, under license to the institute, be allowed on the U.S. market without infringing the government's patent.

Federal officials have argued that the Pasteur Institute's test would be useless without a method for growing the virus in quantity. They have also maintained that the institute's application was flawed because it states that there is no immune response to the virus's envelope protein. The envelope protein is now known to be the most immunogenic viral antigen.

Negotiations have been proceeding ever since. According to James Swire, an attorney with the New York law firm Townley and Updike, which filed the suit on the Pasteur Institute's behalf, the U.S. government had agreed to recognize the French group as coinventors and said the Genetic Systems kit would be allowed on the U.S. market without the payment of royalties to the federal government.

However, according to Swire, the government was not prepared to share royalties with the Pasteur Institute. Caroline Chaine, a spokesperson for the institute, also says that the government officials imposed other conditions on the settlement that were unacceptable to the Pasteur Institute. She declined to discuss these conditions, however.

Pasteur officials thus decided to press their case with the U.S. Patent Office by requesting an "interference." This would require the government's patent to be withdrawn pending resolution of the institute's claims. In addition, they authorized the filing of the suit charging that Gallo's group broke a contract with the Pasteur Institute.

The charges in the suit center on a sample of the Pasteur Institute's viral isolate, which was sent by Montagnier to Gallo in September 1983. The suit contends that Gallo gained information from this virus that was useful in developing his antibody test, although he accepted the virus on condition that it be used for research only. The suit, in fact, strongly implies that Gallo grew the French virus in the cell line he used to mass-produce virus for the antibody test. The legal complaint states, for example, that the virus described in the U.S. patent "is, or is substantially identical to," the Pasteur Institute's virus.

Gallo has vigorously contested these charges. In a recent interview with *Science*, he said that Montagnier sent a sample of supernatant from his cell culture that contained very little virus. At no time did he receive a virus-producing cell line. Gallo and Popovic both say they could not get the virus to grow, and froze the material.

Gallo also argues that he had several isolates of his own before Montagnier's was sent. The Pasteur Institute's suit contends, however, that "as of December 1983, the scientists at NCI had not successfully isolated such virus." Asked the basis for that charge, Swire would only say "no claim with a specificity of that sort would have been made without a basis for it."

According to published research papers, Gallo's antibody test was developed from virus produced by a cell line infected with supernatant pooled from ten different patients. He later determined the genetic sequence of this virus. However, Gallo's group also infected cell lines with isolates from single patients, and data on some of these were included in the patent application.

Gallo contends that this should be conclusive proof that he did not deliberately grow the French virus. If he already had lines infected with other viruses, why would he do the sequencing and other analyses on virus from the line he is alleged to have infected with the French isolate?

Could the culture have been contaminated accidentally with the French virus? Gallo points out that the genetic sequence of virus growing in the line established from pooled isolates is not identical to that of the French virus, as the suit contends. They differ by about 1.5 percent, a disparity that Gallo says cannot be explained by changes in culture. However, the fact that the line was infected with multiple isolates complicates analyses of the genetics of the virus.

The lawsuit and the patent infringement are unlikely to be resolved for months. In the meantime, unless a settlement is reached quickly, research on both sides will be sidetracked by a convoluted process of legal discovery. One unfortunate result of the suit and the bitter dispute that preceded it is that scientific collaboration in research that is remotely linked to commercial application may be discouraged. ■ COLIN NORMAN

Biotech Market Changing Rapidly

A shakeout looms as investment wanes and cash reserves dip; delays, competition affect all but the fittest biotech ventures

AMID glowing forecasts of miracle drugs, super cows, and hardy high-yielding crops, investment in the infant biotechnology industry in the early 1980's began to mushroom—reaching $2.54 billion by mid-1985. The drive to sculpt new diagnostic tools, drugs, and plants with gene-splicing and cell fusion techniques has been propelled by scores of small companies. These new ventures were seen leading new-product development and spurring upheaval in old-line industries.

In the past 3 years, however, the dynamics of the biotechnology marketplace have changed dramatically. Products are taking longer and costing more to develop, and as a result new venture capital is more difficult to attract. At the same time that biotechnology ventures are striving to become more business-like, they are being battered by mounting domestic and international competitive pressures. Pharmaceutical and chemical companies like Eli Lilly and Monsanto are moving aggressively to position themselves in the biotechnology field.

By setting groups of talented scientists to work on specific problems, these specialized "biotechnology" companies were expected to overtake larger pharmaceutical and chemical houses in the race to produce revolutionary new products for health care and agriculture. The soothsayers have been partly right. Entrepreneurs are creating a host of medical tools to diagnose diseases such as acquired immune deficiency syndrome (AIDS), to treat cancer, and to enable children missing vital growth hormones to attain normal height. Says Stanley T. Crooke, president of research and development at Smith Kline & French Laboratories, "It is impossible to exaggerate the value of biotechnology in the preparation of novel therapeutics."

But what has proved a bit optimistic are predictions for quick exploitation of biotechnology. To date, few of these products