

AIDS RESEARCH

U.S.-French Patent Dispute Heads for a Showdown

Until the past few weeks, a bitter and protracted dispute between France and the United States over who should receive credit—and commercial reward—for discovering the AIDS virus seemed to have died down to a few embers. But now it has flared up again, as representatives from the two countries prepare for a crucial meeting on 11 July during which France's Pasteur Institute will demand a bigger share of the royalties from the HIV blood test that it now splits with the U.S. Department of Health and Human Services (HHS).

Fanning the flames is a campaign by Pasteur director Maxime Schwartz to convince his counterpart at the National Institutes of Health (NIH), Harold Varmus, that the dispute "will not die" until Pasteur scientists receive more money and more recognition for their role in discovering HIV. Adding gasoline to the fire is a report from the HHS's Office of Inspector General (OIG) which implies that Robert Gallo and Mikulas Popovic misappropriated a virus sample given to them by Pasteur's Luc Montagnier in 1983 and used it to make a blood test.

Until this document was made public in a 19 June article by the *Chicago Tribune's* John Crewdson, the troubles that have dogged Gallo and Popovic for a decade seemed to be coming to an end. In November, Popovic won an appeal against HHS's Office of Research Integrity (ORI), which had charged him with scientific misconduct for errors in a key 1984 *Science* paper that laid out evidence proving HIV is the cause of AIDS. ORI had also charged Gallo with scientific misconduct for allegedly making false statements in the same *Science* paper, statements that downplayed the Pasteur Institute's contributions. When Popovic won his appeal, ORI promptly dropped the case against Gallo.

Then, in January, a criminal investigation of Gallo and Popovic ended with no charges filed. Since November 1991, the HHS OIG had been investigating whether the two scientists had made false statements to government officials about their discovery of HIV and in their patent application for the blood test. The OIG forwarded its findings to the U.S. Attorney in Maryland for possible criminal prosecution.

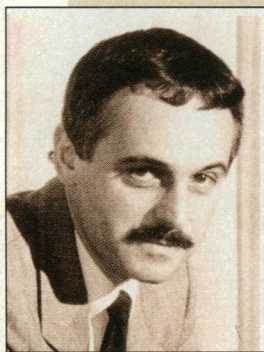
But after considering several potential charges—including perjury, obstruction of justice, mail fraud, and conspiracy to defraud the government—the U.S. Attorney's office wrote the OIG on 10 January that it had

decided not to prosecute because it didn't have a winnable case. As the U.S. Attorney explained, in addition to jurisdictional problems and a 5-year statute of limitations on many of the alleged offenses, it would be difficult to convince a jury beyond a reasonable doubt that either Gallo or Popovic "acted with the requisite criminal intent."

This notice closed the OIG's own investigation and led to the new report. Dated 10 June, the report is a "closing investigative memorandum" for the OIG's own files that summarizes the evidence it had turned over to the U.S. Attorney. Although the 35-page

"The cooperation which has existed between our two institutions...will be greatly damaged."

—Maxime Schwartz



report offers no new evidence, it questions key assertions made by Gallo and Popovic, including their evidence that they independently discovered the AIDS virus (see box on p. 24). Gallo's attorney, Joseph Onek, brands the report "nonsensical," calling

it part of the government's "endless harassment" of his client.

The OIG's report was meant to be nothing more than a cover sheet to a closed file, but it may already be influencing the 11 July U.S.-French meeting on royalties from the HIV blood test. Before the report surfaced, Varmus maintained in correspondence with Schwartz that there were no grounds for redistributing royalties from the HIV blood-test patent. But in a 23 June letter to Schwartz, Varmus suggested he may be willing to give "an acknowledgement" that the Pasteur virus was used by NIH scientists to develop the American HIV blood test. To Pasteur attorney Michael Epstein, such an acknowledgement should be followed by more patent royalties. "We are prepared to interpret it in the most favorable way and see how it develops," says Epstein. "It's a positive step." Varmus

has declined to discuss the matter with *Science*.

At the center of this dispute is work done by Gallo, Popovic, and their co-workers at the National Cancer Institute (NCI) that was published in four landmark papers in *Science* on 4 May 1984. The papers detailed how Gallo's group grew large quantities of a retrovirus, which they dubbed HTLV-III, and proved convincingly that it causes AIDS. A few months later, however, it became clear that the main HTLV-III isolate they were using—HTLV-IIIIB—closely resembled the "Bru" isolate of "LAV," the virus Montagnier had sent Gallo's group in 1983.

Because the NCI researchers had signed a contract promising not to use the French virus for commercial purposes, there were immediate charges—and conflicting interpretations. One possible explanation for the similarity between the viruses was that LAV-Bru had contaminated the U.S. group's cultures, but Gallo discounted this notion at the time and insisted IIIIB and LAV-Bru might be distinct. The Pasteur quickly accused Gallo's lab of "misappropriating" LAV-Bru.

On 29 May 1985, the U.S. Patent and Trademark Office awarded HHS a patent for the HIV blood test resulting from the work in Gallo's lab. Pasteur, which had filed for a patent on its own HIV blood test in December 1983, went on the offensive. Pasteur officials tried to convince their counterparts at NIH that a misappropriation had occurred. When talks broke down, they filed a lawsuit. In 1987, the two countries agreed to settle the suit and share credit and royalties for the discovery of HIV; a U.S. patent was issued to the French. That settlement, signed by President Ronald Reagan and Prime Minister Jacques Chirac, seemed to end the dispute.

The rapprochement was short-lived. In 1989, the *Chicago Tribune* ran a lengthy article by Crewdson detailing alleged wrongdoing in Gallo's lab, which ultimately triggered investigations by NIH, HHS, and Representative John Dingell (D-MI), and the evidence uncovered by these probes has inflamed the Pasteur officials' sense that they got a raw deal in the patent settlement.

Some of the evidence, ironically, came straight from Gallo's lab. In 1991, the Gallo and Montagnier labs analyzed old samples of LAV-Bru, which led to the finding of a contaminant, LAV-Lai, in one of the samples Montagnier had sent Gallo in 1983. Gallo concluded that LAV-Lai had also contaminated IIIIB. Pasteur attorneys took this as fresh evidence that Gallo had simply "rediscovered" LAV in 1984, and they demanded a bigger share of the royalties. The Bush Administration turned them down.

Pasteur officials hoped the Clinton Administration would be more receptive, and on 14 February 1994, Pasteur director Schwartz sent Varmus a fat package detailing the Pasteur's case. *Science* has obtained this

A Parting Shot From a Closed Case

The latest headline-grabbing investigatory report in the case of Robert Gallo and the discovery of the AIDS virus reads like a brief for the prosecution in a scientific fraud case against the National Cancer Institute researcher. And perhaps that should come as no surprise, since the 10 June report summarizes files the Office of Inspector General (OIG) of the U.S. Department of Health and Human Services (HHS) turned over to the U.S. Attorney in Maryland to support a possible criminal prosecution of Gallo and his former chief virologist, Mikulas Popovic, for allegedly making false statements on a patent application for an HIV blood test.

The U.S. Attorney decided in January not to prosecute, citing legal obstacles and difficulties in proving intent (see main text). The OIG's report, which was leaked to the press within days of being completed, is a "closing investigative memorandum" for the files. It rarely balances charges against rebuttals—and reaches no conclusions.

The 35-page report goes over much of the ground covered by HHS's Office of Research Integrity (ORI) and its predecessor, the Office of Scientific Integrity (OSI), which found Gallo and Popovic guilty of making false statements in papers they published on the discovery of the AIDS virus. The charges against Popovic were thrown out by an appeals board; ORI subsequently dropped the charges against Gallo.

Gallo, who would not comment publicly about the details of the OIG report, says there "obviously is not anything new" in it. "What I've read are misunderstandings, mistakes, and things taken out of context," he contends. Joseph Onek, Gallo's attorney, went further. On 23 June Onek sent the OIG a six-page critique of the memo, which he called "a disgrace" and said "should be withdrawn immediately." Onek said the memo was "filled with an extraordinary number of errors reflecting deliberate factual distortions, scientific illiteracy and obvious bias."

The report reviews an investigation conducted by OIG between October 1991 and January 1994. The investigation centered on events dating back to 1983, when France's Pasteur Institute sent Gallo's lab a presumed AIDS virus, which they called LAV. Shortly after Gallo published evidence in May 1984 showing that the cause of AIDS was a virus he called HTLV-III, which he said his lab independently isolated and grew, it was discovered that LAV and HTLV-III appeared to be identical.

In a sworn declaration Gallo gave to the Patent and Trademark Office in 1986 defending a 1985 patent awarded for a blood test based on HTLV-III, he stated that when the patent was filed, "my colleagues and I did not consider LAV and HTLV-III to be the same or even substantially the same virus." He also said he saw "no evidence" that LAV was the cause of AIDS at that time, and he claimed that Popovic had only "temporarily" transmitted LAV to a cell line, suggesting that they had not grown it in sufficient quantities to characterize it or to have had LAV contaminate HTLV-III.

The memo attacks on several fronts the claim that Gallo believed LAV and HTLV-III were different. It points out that on 17 March 1984, Gallo asserted during a lecture in France that he believed HTLV-III was "very similar" to LAV. On 6 April, he met

in Paris with scientists from the Pasteur and the U.S. Centers for Disease Control (CDC) and reviewed data that showed the similarity between the two viruses. He also told OSI that "the same virus type was suspected, I would say, by...the early part of 1984."

Onek's critique of the report notes, however, that in April 1984 there "were many apparent differences between LAV and HTLV-III." For example, the French did not believe LAV included the surface protein, gp41, that was the basis for Gallo's initial blood test. In light of this, Onek contends, Gallo believed that LAV and HTLV-III, "though being of the same general virus type, might be different subtypes." As for the CDC data, Onek dismisses it as "inherently unreliable" because the French, unlike Gallo, did not use a confirmatory assay.

The OIG details several instances in which Gallo said LAV only grew transiently in his lab and contrasts them with statements he later made to the contrary. As the report noted, Gallo has said his early statements referred only to growing LAV in quantities large enough for a commercial blood test.

Perhaps the most explosive charge in the OIG report involves the "pool" experiment, in which Popovic says he combined several suspected HIV isolates to try to jump-start the growth of one of them.

The virus that came out of the pool; Gallo has always maintained, is the isolate IIIB, which was used to develop his blood test. But the OIG memo states

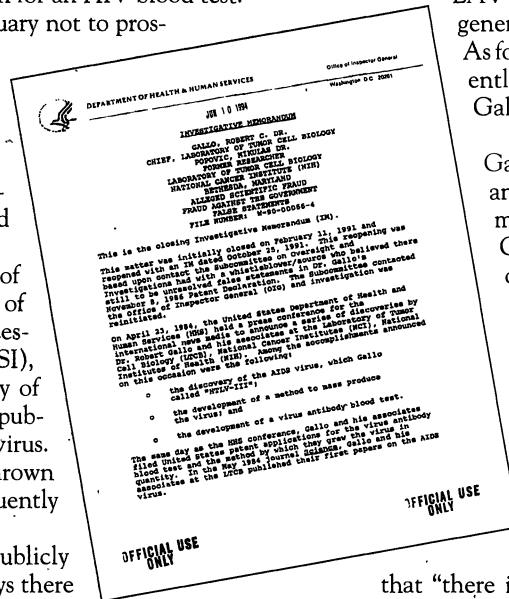
that "there is reason to doubt that pool experiment... really was done." Specifically, the report notes that no IIIB isolate independent of LAV was ever found, and recent analyses of 10 samples Popovic said he put into the pool revealed that four of them did not contain any HIV. Though the report doesn't state it, the implication is that the pool was a fiction used to hide the fact that Gallo's lab stole LAV.

Onek counters that this point "makes no sense" and stresses that six of the 10 samples did contain virus that was neither IIIB nor LAV, implying, according to Onek, that the pool clearly did exist. What is more, he attacks the implication that Gallo and Popovic stole LAV, pointing out that they had an isolate, RF, that could have been used for the blood test. "The existence of RF removes any motive for Dr. Popovic or Dr. Gallo to misappropriate the French virus and strongly supports the contention...of an accidental contamination."

Finally, the OIG's memo asserts that a patent examiner who evaluated HHS's application was unaware of the extent of the French work and notes that Gallo had a duty to disclose it. Indeed, the examiner told the OIG that had she known more about work with LAV, she would have declared an "interference," putting the two patent applications on hold. An interference was in fact declared only after the Gallo patent was issued. Onek, who did not address this point in his critique, noted to *Science* that a May 1984 Gallo paper cites the French work as being "in press."

In a parting shot, the memo's conclusion notes that although the U.S. Attorney's office declined to prosecute, it said the decision "does not mean that we believe [Gallo and Popovic] should continue to receive their annual royalty payments" from the patent. Gallo has so far received a total of \$688,237.

—J.C.



package through the Freedom of Information Act (FOIA). One of the documents Schwartz sent was a 26-page memo from the Pasteur's New York attorneys that read, in part, "the Clinton Administration need not perpetuate a lie." The memo further warned that if the Pasteur didn't receive a bigger share of the blood-test royalties, the United States would be sending "a frightful message to the international scientific community: Don't cooperate and don't collaborate."

Varmus did not reply. On 24 March, Schwartz wrote again, including an affidavit given by Pasteur researcher Françoise Barré-Sinoussi to ORI investigators on 13 November 1993. In her affidavit, Barré-Sinoussi recounted a conversation she had with Popovic during a bus ride at Gallo's annual lab meeting in 1992. Barré-Sinoussi, who played a key role in the Pasteur's isolation of LAV, said she and Popovic discussed the famous "pool" experiment Popovic did to develop the IIIB isolate. In this experiment, alluded to in one of the *Science* papers, Popovic says he pooled culture fluids from several AIDS patients, hoping this would increase the chances he could get the AIDS virus (which had proved extremely difficult to culture) to grow. According to Barré-Sinoussi, Popovic told her he had mixed LAV with his independent isolates. If this were true, it would be an admission that Popovic had knowingly used the French virus to create IIIB—in short, that he had stolen LAV.

In addition to this explosive document, Schwartz included a new affidavit from Barré-Sinoussi, dated 17 March, in which she not only reaffirmed her recollection of what Popovic said during the bus ride but also charged that Gallo had been "pressuring" her—in writing and in phone calls—to "clarify and alter" her original affidavit. "I believe Dr. Gallo's behavior in this regard is improper," she wrote.

Yet 3 days before signing this second affidavit, Barré-Sinoussi responded to questions from *Science* with a letter stating that her initial affidavit had "apparently led to some misunderstandings." In particular, she wrote, "in my mind it was obvious that LAV had been put in the pool when I spoke with Mika Popovic." Therefore, she continued, "our discussions about the 'pooling procedure' did not concern whether he stole the virus or not, but about the fact that LAV grew out of the pool and why." She said she did not, in fact, believe that she was "giving new information to ORI" and indeed "never mentioned this talk" to anyone before ORI contacted her.

Popovic, who now works at Sweden's Karolinska Institute, told *Science* last week that he was "shocked" by Barré-Sinoussi's memory of their conversation. "It's ridiculous," says Popovic. "We didn't discuss the pool at all." Instead, he says, they discussed the no-

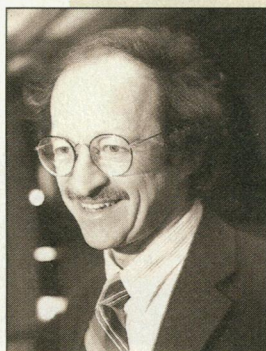
menclature of the various HIV isolates.

These enclosures in the correspondence from Schwartz to Varmus apparently didn't produce the desired effect, and so, in April, Schwartz stepped up the pressure with a letter that included a 1992 memo from Michael Astrue, then the top lawyer at HHS, to then-HHS Secretary Louis Sullivan. In this "Eyes Only" memo—which HHS would not release under FOIA but *Science* has obtained from other sources—Astrue contends the Pasteur doesn't have a valid legal argument to receive more royalties because "there is no showing that Dr. Gallo or other officials of the Department deliberately sought to mislead the French to entice them to enter into [the 1987] settlement agreement."

In spite of this lack of a legal case, Astrue recommended that the U.S. voluntarily relinquish its share of future royalties to the French. The \$2 million in royalties HHS was receiving annually were "buying more negatives than positives," wrote Astrue. And the dispute, he argued, was a "considerable dis-

"The acknowledgement of the role of the Institut Pasteur in isolating the AIDS-causing virus was very slow to occur."

—Harold Varmus



traction" for key AIDS researchers and officials that was putting "a strain" on relations with the French and discouraging international scientific cooperation. Astrue, now general counsel at Biogen Inc. in Massachusetts, stresses he

was not saying Gallo did wrong.

Varmus finally replied to Schwartz on 8 June. In his "considered judgment," the NIH director wrote, the royalty arrangement should stand. "I share your sense that the acknowledgement of the role of the Institut Pasteur in isolating the AIDS-causing virus was very slow to occur, causing much frustrating litigation and other unproductive activity," wrote Varmus. "I am deeply sorry that those events occurred." But, Varmus continued, the contribution of NIH scientists should also be recognized. "Both hands, as it were, were necessary to grip the problem." Varmus also noted that the NIH was giving up much more than the French in the 50–50 split, since royalties from the U.S. test cur-

rently total \$36.8 million, while the French test has earned only \$5.7 million.

Schwartz fired back on 13 June that he was "deeply shocked and greatly troubled by your response." Schwartz further urged Varmus to relent, writing, "I am afraid that the cooperation which has existed between our two institutions, and more generally between scientists, will be greatly damaged."

Then came the OIG's 10 June report. Two weeks later, Varmus wrote Schwartz a letter with a different tone. Although Varmus noted that neither the U.S. Attorney nor HHS's OIG ever found "deliberate misconduct by the Government," he wrote, "Were I to be persuaded that a change in our current arrangement for distribution of royalties is warranted, I would surely take steps to see that a change is made." He added: "When we last spoke you reiterated your wish for an acknowledgment from me appropriate to the current state of knowledge: that the French virus was used by [NIH] scientists in developing the American test kit. I am entirely open to taking steps that appropriately accomplish that goal, which you and I share." He suggested that Schwartz send "a concrete proposal setting forth the elements of such an acknowledgment" to HHS's general counsel.

Pasteur attorney Epstein says in light of the OIG report, "any foot-dragging" on HHS's part might lead the Pasteur to sue. But according to an independent analysis done for HHS in 1992 by the Chicago law firm Allegrretti & Witcoff Ltd., the U.S. patent rests on firm legal ground. The Allegrretti report, which was obtained by *Science*, spells out how the original French patent application was inferior to the U.S. one, and it concludes that even if Gallo made false statements during the patent dispute, the patent would only be invalid if it could be proven that the statements were intended to deceive. Gallo's disputed statements "might be subject to variable interpretations but they are not *prima facie* false," the report said.

The debate over the patent royalties should come to a head when Varmus and Schwartz meet on 11 July. The occasion will be the annual meeting of the board of the French and American AIDS Foundation, which was established by the Reagan-Chirac agreement to oversee royalties from the two blood tests. If the board—which includes Gallo, Varmus, Montagnier, Schwartz, and two additional representatives from each side—decides to reallocate royalty money by giving more to the French, some observers, like former HHS general counsel Astrue, believe this decade-old feud would be settled. "My guess is absent new information, this is petering out." Then again, like trick birthday candles, this case has proven time and again that just when you think the flame is out, it suddenly flares up again.

—Jon Cohen