University and Drug Firm Battle Over Billion-Dollar Gene

A lawsuit over interferon may change the informal ways by which researchers exchange materials

A human gene potentially worth billions of dollars has become the subject of an extraordinary dispute between the University of California and the pharmaceutical house of Hoffmann-La Roche.

The gene in question contains the genetic information for the synthesis of interferon, the body's natural antiviral protein. Cloned by the gene splicing company Genentech under contract to Roche, it is the basis for an interferon manufacturing process that could well capture a large slice of the future market. Should interferon prove effective against cancer—a question still unresolved because of the minute quantities so far available for study—the worldwide sales of the substance could reach $3 billion a year by 1987, according to one estimate.

The dispute centers around the terms under which Roche obtained the interferon gene. Should it come to trial, it could effect a major change in the free and informal ways in which researchers are accustomed to exchange biological materials, as well as raising unprecedented issues about the patentability of the human genome.

The University of California considers itself the aggrieved party, but Roche on 12 September initiated court proceedings by asking for a determination of the issues.

The chief issue is the university's claim that Roche has made "unauthorized use" of material developed by two of the university's researchers. Roche officials will so far make no comment other than that they have acted properly.

The free and easy basis on which researchers exchange materials has been violated by Roche, claims Bertram Rowland, attorney for the University of California. "The academic relationship is now being subverted by industry. I don't mind if Roche enjoys the benefits of this relationship as long as they pay for it," says Rowland, who is trying to secure the promise of a royalty payment from the company.

Roche declines comment, but the company's position could be that the cells containing the gene were common scientific property; and even if not, that Roche took no physical part of the cells but only a copy of part of their genetic information.

There is no quarrel about the provenance of the disputed gene. In 1977, a 59-year-old patient lay dying in a Los Angeles hospital from acute myelogenous leukemia. For the sake of scientific research, he agreed to a painful procedure of no medical benefit to himself, the sampling by suction from his bone marrow of the cancerous blood-forming cells. Two months later he died.

The cells, however, attained immortality through the skillful care of two research hematologists at the School of Medicine of the University of California, Los Angeles, Phillip Koeffler and David Golde. Koeffler and Golde succeeded in making the cells grow and divide in the test tube, a feat of considerable importance to those seeking to study and devise treatments for this particularly intractable form of leukemia. Koeffler and Golde christened the cell line in their own honor with the acronym KG-1.

Golde sent a sample of the cells to a longtime friend and research colleague, Robert Gallo of the National Cancer Institute, who wanted to test them for the presence of viruses. On 9 June 1978, the establishment of the cell line was announced in *Science*. Some months later, as part of a routine screening procedure, Gallo noted an additional fact about the cells: they produced interferon.

The discovery was no great surprise, but Gallo mentioned it to Golde, who was not previously aware of the fact, and to a long-standing research colleague with a keen interest in interferon, Sidney Pestka. Pestka works at the Roche Institute of Molecular Biology, an establishment wholly funded by, but generally regarded as scientifically independent from, the drug firm of Hoffmann-La Roche.

Pestka, who had tested all Gallo's other cell lines for interferon, asked if he could test KG-1 as well. After conversations with Golde which are now differently interpreted, Gallo passed a sample of the cells on to Pestka. In essence, Gallo believes Golde implied the cells could be given out; Golde denies it.

Pestka's only reason for wanting to work with the cells, he told Gallo, was to see if he could improve their production of interferon. After several months of hard work, in which he manipulated the cell cycle and studied the optimum medium for growth, Pestka succeeded in making KG-1 a superproducer of interferon, the best by a certain margin of any cell in his possession.

Up to this point the handling of KG-1 differed scarcely from any other exchange of materials among academic scientists. But the instant that Pestka made the cells the top interferon producer in his laboratory, they became very hot property. It was around the same time, in January 1980, that the gene splicing company Biogen, under contract to Schering-Plough, held a splashy press conference to announce the cloning of the interferon gene, news that added $50 million to Biogen's paper value and $426 million to Schering-Plough's.

The existence of the rival partnership between Roche and Genentech was at that stage not publicly known. The partners had conceived a highly ingenious method for cloning interferon genes which was to put them a jump ahead of Biogen and Schering-Plough. It would also provide a launching pad for Genentech to go public and for some of its directors and shareholders to make themselves millionaires. In this plan KG-1 played a leading role.

Cloning a gene is no problem compared with the difficulty of obtaining the gene in the first place. To fish out the interferon gene from the 100,000 or so others in the human cell, Roche contracted with Charles Todd of the City of Hope National Medical Center to determine the amino acid sequence of part of the interferon molecule. Under another contract to Roche, Genentech then synthesized segments of DNA that corresponded, via the genetic code, to the relevant regions of the interferon molecule as determined by Todd and others.

The segments of synthetic DNA were designed to identify the full interferon gene by virtue of the fact that they would chemically combine with that part of the

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gene to which they corresponded. But instead of trying to match up the synthetic probes with the full gene set of a cell, Genentech and Roche had a better idea. They would take a cell that produced high quantities of interferon, extract all its messenger RNA (a relatively large part of which would be copies of the interferon gene), and, with the aid of enzymes, make DNA copies of the RNA. This library of complementary DNA molecules would contain a near priceless volume, the genetic information for how to make interferon. But vital to the scheme was that the library contain enough copies for the synthetic DNA probe to find one.

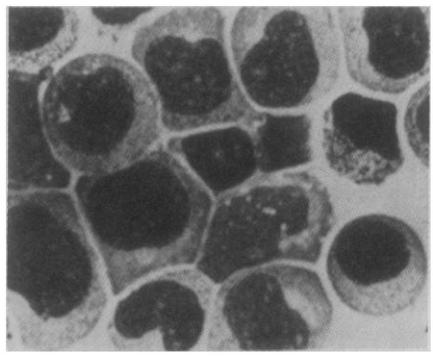
This is where KG-1 came in. There is no reason to suppose that the KG-1 leukocyte interferon gene differs in any important way from any other individual's equivalent gene. What was important was that—as a result of Pestka's manipulations—KG-1 produced interferon messenger RNA in copious quantities.

Dead KG-1 cells were sent by Roche to Genentech. Genentech constructed a library of complementary DNA sequences, cloned them in bacteria, and with the synthetic probe identified the clones having an interferon gene. Genentech soon had enough of the precious substance to show that the bacterially made variety, even though it lacks the sugar groups of natural interferon, still possesses its antiviral properties.

After announcing this advance in June, Genentech revealed plans last month to offer one million of its shares (13 percent of the equity) to the public, at a price of $25 to $30 a share. The creation of a public market for Genentech's shares will enable its stockholders to convert their paper holdings to hard cash, and some of the directors, should they sell all their shares, would presumably become millionaires. Genentech's current profits are miniscule: the value of its shares will rest heavily on its chief potential money-spinner—interferon made to the instructions of the KG-1 gene.

The transfer of knowledge to the private sector for the public good is generally described as a socially desirable objective, and the case of the KG-1 interferon gene might seem to afford an eminent case in point. But because certain ground rules have yet to be worked out, it has also raised the vexatious problem of the ownership of the interferon gene.

Mightn't the gene be regarded as the unalienable property of the individual to whom it belonged, or, since he is dead, to his heirs? Neither Roche nor the University of California seem to think so since each is claiming the gene for itself.



KG-1 cells, home to a billion dollar gene.

Roche and Genentech are said to have filed a joint patent application covering both the interferon made from the gene and the gene splicing manufacturing process itself. The University of California has not filed a patent application for the KG-1 cells, and since the paper describing them was published more than a year ago, the opportunity for patenting would ordinarily be considered to have lapsed. But the university's attorney, Bertram Rowland, contends that the cells could still be patented since, though published, they were not made generally available.

The university in any case is claiming a royalty on the grounds that it was its researchers who "created" the gene. "Is it fair that this property, created in a university environment, should be taken by industry and utilized without making some reasonable compensation to the university?" asks Rowland.

Whatever the justice of this claim, it is only fair also to take into account the contributions of others in developing the KG-1 cells into a valuable property. It was Gallo who discovered they produced interferon. It was Pestka who worked out ways to make them superproducers. It was Genentech's scientists who made the probe and who, because of Pestka's manipulations, were able to extract the interferon gene.

The university claims that Roche "subverted" for profit the academic relationship in which the cells passed freely from Golde to Gallo to Pestka. The claim touches upon the scientific etiquette regarding properties such as cell lines. By and large, a researcher is expected to make any special materials he has developed freely available to colleagues. In return, by an unspoken gentleman's agreement, his colleagues will treat the material like property borrowed from a friend—in other words as something not to be passed on to third parties, or used for private gain, without specific permission from the owner.

Two issues are raised in the case of KG-1: Under what circumstances did Gallo pass the cells on to Pestka? And, if the cells were not common property, should Pestka, or someone else on behalf of Roche, have asked permission from Golde to clone material from the cells and to file patent applications?

Gallo gave Pestka samples of KG-1 because he believed he had Golde's assent. According to Gallo, Golde said in conversation that he was not interested in interferon and that in any case the cells were now out, because a hundred labs had them. On this basis Gallo passed the line on to Pestka, whom he regarded as a friend and researcher working at a nonprofit institution, not as a corporation scientist. Golde denies telling Gallo that the cells had been given to a hundred laboratories. "I want to make it clear that I never authorized a transfer of cells from Bob Gallo's laboratory and that the transfer of cells to Roche was against my wishes and violated my understanding with Bob Gallo," he wrote in a letter of 18 July 1980 to National Cancer Institute director Vincent DeVita.

On present showing, the transfer of cells from Gallo to Pestka was at worst a misunderstanding between Gallo and Golde as to Golde's intent. Gallo had nothing to gain by passing on the cells, and the transfer was in accord with his well-known policy of making cells freely available to other researchers.

Harder to explain, not least because Pestka declines comment, is why he—or someone on Roche's behalf—apparently neglected to observe the scientific courtesy of asking permission to clone the cells and to file for patents on the clones. According to Gallo, Pestka did not mention he planned to clone the KG-1 DNA; if he had, Gallo would have told him to ask Golde's permission. Roche may have considered that the cells had become common property; even so, there would have been no harm in checking with Golde. Had the company sought Golde's permission, though, the university would certainly have asked for a royalty, says Rowland, a circumstance Roche may perhaps have considered. In any event, the handling of the cells by Roche and Genentech after they had come into Pestka's possession was a secret process, allowing Roche alone to benefit at the expense of others, such as its rival Schering-Plough, says Rowland.

On 12 September Roche filed suit in a California court for a judge to determine all these issues and to establish what duty—Roche suggests none—is owed by the firm to Golde, Koeffler, and the University of California. If the issue comes to trial, it may resolve or open up some novel legal ground. There is the issue of

researchers' rights in the cells and other materials which at present are exchanged under the protection only of mutual trust and gentleman's agreements, forces apparently too fragile to withstand the stresses of commercialization. There is the issue of whether Roche, in taking only genetic information from the KG-1 cells, was infringing upon even theoretically patentable material. Computer programs cannot be patented, nor can scientific theories: Is genetic information some different category? Another conceivable issue, also apparently novel, is that of a patient's rights in his own genes.

That the KG-1 case has surfaced at all is a tribute to the ingenuity of researchers and entrepreneurs in putting the new biotechnology so rapidly into practice. Yet the powerful forces of the profit motive clearly have the capacity to strain and rupture the informal traditions of scientific exchange.—NICHOLAS WADE

UCSD Gene Splicing Incident Ends Unresolved

After an episode commingling the trivial and the tragic, researcher quits post

The gene splicing incident at the University of California, San Diego, which began as a matter of a trivial infraction of the NIH rules, has ended in what researcher Ian Kennedy calls "irreconcilable differences" between himself and the university's biosafety committee. Kennedy, in whose laboratory the infraction occurred, resigned from the university on 12 September.

His decision followed the submission on 28 August of a report to the NIH from the chairman of the university's biosafety committee, Gordon Gill. The report makes plain that Kennedy and the committee could not agree on the sequence of events that led up to the infraction, a virus cloning experiment which, though now permitted, was barred by the then prevailing NIH rules.

By both Kennedy's version and the committee's, the infraction was of a somewhat trivial nature and, since the experiment is now permitted, clearly raised no issue of public health. It is overshadowed by the situation surrounding the differences between Kennedy and the committee, a situation which caused anguish to his colleagues and has now led to the resignation of an able researcher.

The episode began earlier this year when students in Kennedy's laboratory told the chairman of the biology department of their concern that Kennedy had cloned part of the genetic material of the then prohibited Semliki forest virus instead of the Sindbis virus that was planned for the experiment. A sample of the presumed Sindbis virus was sent for testing to the California State Department of Health, which reported that it contained *Semliki* forest virus.

Kennedy attributed the result to an accident that occurred when shipping the viruses to San Diego from the University of Warwick, England, where he used to work: Semliki forest virus must have contaminated a vial of Sindbis virus and overgrown it in culture, he suggested. The biosafety committee concluded that, for whatever reason, the wrong virus had been cloned. Kennedy's permission to clone was rescinded, and the committee so informed the NIH in a preliminary report of 31 July.

A four-person subcommittee appointed to make a further study has now examined Kennedy's laboratory records and talked with his technicians and former students. Some troubling differences have emerged between Kennedy's account of what was done and when, and the version arrived at by the subcommittee.

In brief, Kennedy's position, as described in the committee's latest report, is that he cloned what he assumed to be Sindbis virus during a period from December 1979 to January 1980. DNA prepared from these clones was used in January to perform an important experiment, the infection of mouse cells to produce entities that protect the cell from further attack. Kennedy described the experiment at a seminar but has not yet published it. From January onward, Kennedy states, he worked on developing cloning methods for Semliki forest virus—in anticipation of the experiment becoming legal—up to but not beyond the point of cloning it. Cloning experiments by his technician in March and April were undertaken with the presumed Sindbis material to instruct her in cloning techniques.

The biosafety committee's version, in essence, is that from June 1979, Kennedy began a logical, clear-cut sequence of experiments directed toward the cloning of Semliki forest virus, and that the cloning of that virus occurred in March and April of this year. The committee does not believe that there is conclusive evidence of any earlier cloning of either virus.

A comparison of the two accounts would suggest that the infraction of the NIH rules was only one among several questions confronting the biosafety committee. For one thing, the committee's own reconstruction of events was in severe conflict with Kennedy's account. For another, the January mouse cell experiment depended on the existence of cloned material.

Kennedy, having read the committee's report, still stands on his version of events. In an hour-long conversation, he offered a firm, articulate, and plausible defense of his position. He believes that through procedural defects the four conducting the inquiry misinterpreted the evidence in his notebooks and failed to allow him sufficient time to explain his position, in part because of pressure from the NIH to submit a report quickly. The inquiry was opened with very little notice, he says, and he got off on the wrong foot by a dispute as to the date at which the P3 lab was supposed to start keeping records. From that point on, in Kennedy's view, it was hard for him to recover ground in explaining the complicated chronology and sometimes personal shorthand of his notebooks. Not being allowed to be present when his technician and others were questioned, he was unable to correct several simple misunderstandings created in the committee's minds.

Members of the subcommittee decline in general to comment on the situation, though one member states that Kennedy was given ample time to present his case and that there was no pressure from the NIH.

The task of deciding between Ken-

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