Biogen Pays High Price for Harvard Patent

Harvard University has obtained patents on a potentially powerful gene-splicing technique that stimulates bacteria to make a protein, such as insulin, and then secrete it. An exclusive license to the patents was awarded to Biogen, whose chairman, Walter Gilbert, developed the technique while a professor at Harvard.

If successful, the new process could replace or significantly compete with the gene-splicing methods currently used to manufacture proteins such as human insulin. Eli Lilly & Company, using a process invented by Genentech scientists, makes human insulin by growing bacteria which produce the insulin, cracking open the cells, and then harvesting the insulin. With the Gilbert technique, cells manufacture the desired product, which is then transported out of the cell by a carrier protein into the growth medium. In principle, the Gilbert method permits the continuous production of protein without destroying the cells and also makes the purification of the protein much easier.

Gilbert said in an interview that he believes his process "will be better than the Lilly process." Biogen works cooperatively with Novo Industries, a Lilly competitor in the insulin market. Biogen spent nearly a half million dollars to obtain American and European patents on the technique and about $4 million to $5 million so far on its development.

But others have questioned whether the technique will prove to be commercially valuable. For example, Howard Goodman, chief of Massachusetts General Hospital's department of molecular biology, which is supported by Hoechst, suggests that purification of a protein made by the Gilbert method may be tougher than anticipated because the product must be concentrated from a large volume of growth medium.

Goodman, along with William Rutter and John Baxter of the University of California at San Francisco, were coinventors listed on a patent application that made claims similar to those in the Gilbert application. They filed their application in 1978, 2 months after Gilbert and colleagues. Because the applications were sufficiently alike, the U.S. Trademark and Patent Office declared "an interference." But Goodman and the California researchers withdrew their application a year ago, clearing the way for the approval of the Gilbert patents.

In a separate matter, Biogen announced last week that it intends to begin a joint venture with China to manufacture and market gamma interferon in new treatments for cancer. Each year in China, more than a million new cases each of stomach and liver cancer develop, according to Biogen. The company and the Shaanxi Pharmaceutical Bureau have signed a letter of intent outlining their plans to work together.—**Marjorie Sun**

Wistar Denied Monoclonal Antibody Patent in U.K.

The British Patent Office has rejected an application from the Wistar Institute in Philadelphia for a patent on a method for producing monoclonal viral antibodies. The Patent Office has argued that the technique developed by the institute does not qualify for protection under British law, because it does not appear to involve any sufficiently inventive step beyond the general state of the art in monoclonal antibody research that existed when the patent application was filed.

The decision has generated a certain satisfaction in Britain. The British government has been strongly criticized for failing to secure patent protection on the original techniques when they were developed in the early 1970's by two government-supported scientists, Cesar Milstein and Georges Köhler, at the U.K. Medical Research Council's Laboratory of Molecular Biology in Cambridge, England. At the time, the council encouraged its scientists to make their research methods freely available. "We were influenced by that psychology. We were mainly concerned with the scientific aspects and not giving particular thought to the commercial applications," Milstein later recalled.

The Wistar application was first turned down last year by a senior examiner in the Patent Office. In addition to the lack of "inventiveness," he claimed that the application was "obvious" after the publication of an article in *Lancet* in 1977 suggesting, among the possible uses of monoclonal antibodies, the identification of "the various hepatitis antigens."

The examiner's decision to reject the application has now been supported by the patent court, to which the institute had appealed. In a decision delivered last month in London, the presiding judge declared that the specifications of the Wistar process for which patent protection had been requested "are merely claims to the application of the well known (at the data of application) Milstein process for the production of antibodies generally to the particular field of viral antibodies."

The patent examiner had originally rejected the application on the grounds that the claimed invention was "trite" and thus "devoid of inventive substance," since "all antibodies are immunoglobulins and the specificity of a particular antibody depends simply on the antigen which has given rise to it." He also contended that the applicants had failed to show either that they had overcome specific problems raised by the particular applications that they described, or that they had achieved some surprising results.

The relevance of the *Lancet* article, which predated the patent application and was entitled "Spin Off from Cell Fusion" was challenged by attorneys acting on behalf of the Wistar Institute. They argued that, being an unsigned editorial, the article should be treated as journalistic speculation and should not be taken too seriously.

However, the examiner in the Patent Office rejected this argument, claiming that if read in the context of two earlier papers by Milstein and Köhler, the first appearing in *Nature* in August 1975, the *Lancet* article could be taken as "an informed prediction of what in the passage of two years had come to be seen as inevitable."

The Wistar process for producing viral antibodies from hybrid cells has already been patented in the United States. However, the rejection of the application by the British Patent Office could have significant implications for the patenting of monoclonal antibody techniques elsewhere in Europe, whose countries are signatories to an international convention agreeing to respect common criteria of patentability.—**David Dickson**