there are potentialities in the technology, but based on my experiences with other technologies, the gap between a laboratory process and reduction to commercial reality is going to take much longer than the impression created in the numerous articles about the subject," Friedman observes.

"Without the PR, there is no question that the high flying money perceives you as being of little value. But these paper valuations have a way of folding," notes Stephen Turner, president of Bethesda Research Laboratories. Turner raises the analogy of a chain letter, with the man in the street being the ultimate recipient when the gene splicing companies go public.

"That is 100 percent absolutely and completely ridiculous," says E. F. Hutton's Schneider. "None of these companies has any thought of going public and if they were we would tell them not to because there is no guarantee as yet that this technology will produce anything."

There is no guarantee either that the companies now developing particular gene splicing technologies will be able to hold onto their advantage. What if the academic research community should develop a general method for cloning and amply expressing the product of any known gene? With the basic technology available to all, the advantage might move away from the little companies, whose major asset is access to leading molecular biologists, and toward enterprises that either have large sales forces, as do the pharmaceutical companies, or possess advanced expertise in fermentation technology, as do the Japanese.

The cloning gold rush has entered an interesting but unpredictable phase. There is certainly gold to be found, but no one can be quite sure just how soon, or how easy it will be to protect whatever is struck.—NICHOLAS WADE

Hybridomas: A Potent New Biotechnology

A new biotechnology with far-reaching practical applications is about to make a major commercial impact.

Hybridoma technology was invented at about the same time as recombinant DNA but has grown up in its shadow. Yet the technique promises to revolutionize immunology and all the areas of research and medicine which immunology embraces.

Hybridomas are artificially created cells that produce pure or "monoclonal" antibodies. Having a constant and uniform source of pure antibody, instead of the usual mixture produced by the immune system, not only affords a powerful research tool but can be expected to provide quicker and more accurate diagnosis of viruses, bacteria, and cancer cells. The long-range promise of monoclonal anitbodies is that they will be therapeutically useful as vaccine replacements and in the treatment of cancers.

The hybridoma technique was invented in 1975 by Cesar Milstein and Georges Köhler working at the Medical Research Council's Laboratory of Molecular Biology in Cambridge, England. A mouse is injected with antigen and the antibody-making cells of its spleen are then fused in a test tube with a cancerous type of mouse cell known as a plasmacytoma. The hybrid cell so formed produces the single type of antibody molecule of its spleen cell parent and continually grows and divides, like its plasmacytoma cell parent. Once the clone of cells producing the desired antibody has been selected, it can be grown as a continuous cell line from which large amounts of the pure or monoclonal antibody can be harvested. The power of the method is that one or more specific antibodies can be developed against any organism or substance antigenic to the mouse. By contrast, the natural antibodies made against a given antigen are a mixed bag of molecules, with each type targeted against a different feature of the antigen. Monoclonally produced antibodies also have the virtue of consistency—each rabbit produces a different mix of antibodies against a given antigen—and their production costs are cheaper.

The vast promise of hybridoma technology has made it a field of active commercial interest. Industry investment in hybridoma research will amount to some $25 million in 1980 and the potential worldwide market for monoclonal antibodies will grow to more than $500 million by 1987, according to a recent estimate by Boston Biomedical Consultants.*

Pharmaceutical companies such as Eli Lilly and Hoffmann-La Roche have an active interest in hybridoma technology, and five small companies devoted exclusively to monoclonal antibodies have already been founded. Hybritech, of La Jolla, California, was founded in 1978, launched its first hybridoma product in December 1979 and now has three product lines on the market. With $2 million in venture capital, the company expects to expand its present staff of 52 people to 100 by the end of the year.

Another company, Centocor of Philadelphia, has a senior staff of 20, but doesn't expect to launch its first product until the end of next year. Centocor's interest is in applying the hybridoma and other technologies to four areas of diagnostics, those concerning tumors, liver, heart, and viruses. Set up in 1979 by Edwin Allen, formerly of Corning Medical and Instrumentation Laboratories, the company is funded by the Bank of Paris and Venroc, the Rockefeller family's venture capital firm. "We are part of the process of taking basic technology and converting it into useful products. But we are interested in stretching the technologies, so most of our projects are long term in nature," says Allen.

Centocor has ties with leading researchers in the field, particularly the Wistar Institute of Philadelphia. Institute director Hilary Koprowski is chairman of Centocor's board of scientific advisers. The company also has an exclusive license for two important hybridoma patents which were recently granted to the Wistar Institute.

Two other hybridoma ventures are Clonal Research of Newport Beach and Monoclonal Antibodies of Palo Alto, both founded in 1979. A European entry in the field is Sera Laboratories of Crawley Down, England.

Another small company that has entered the field is Bethesda Research Laboratories. Under Sudah Agarwald, ex-NIH, and Richard Farishian, formerly of the Wistar Institute, the company has developed several hybridoma product lines and some 30 more are planned.

Industrial activity in the field is so intense that many researchers have been drawn into it one way or another. According to Henry Weinert of Boston Biomedical Consultants, "Most experi-

*_Monoclonal Antibody Production_. February 1980. 298 p. Boston Biomedical Consultants, 55 William Street, Wellesley, Massachusetts 02181. $8,500.

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enced university-based investigators are almost to a person either directly or indirectly involved in commercial hybridoma ventures." At the same time Weinert has noticed a growing resentment among researchers toward the commercialization of monoclonal antibodies intended for research use.

As with the gene splicing industry, patent protection remains a major uncertainty. The U.S. Supreme Court ruling, expected before mid-June, as to whether forms of life can be patented, is likely to affect certain patent applications. But two significant patents on the hybridoma technique have already been granted.

Monoclonal antibodies at present are sold for research only, with a warning that diagnostic and therapeutic use is not intended. Approval by the Food and Drug Administration for any therapeutic use is likely to be highly problematic because of the agency's wariness of any product of a cancerous cell.

The hybridoma technique at present produces mouse antibodies. These are not the first choice for therapy because of the body's reaction against foreign proteins. Efforts to develop the human equivalent of the mouse plasmacytoma cell should succeed within the next couple of years. An existing method of making human monoclonal antibodies is the lymphoblastoid technique developed at the Karolinska Institute in Stockholm. A human lymphocyte cell producing the desired antibody is transformed into a continuous cell line by being infected with Epstein-Barr virus. Unlike in the hybridoma technique, where antibodies are raised against the antigen of choice, the lymphoblastoid technique requires screening human donors for the antibody needed.

Could monoclonal antibodies prove to be the much derided magic bullet against cancer? Their high specificity makes it reasonable to suppose they might be targeted against cancer cells, if the right antibodies could be obtained. If unable to kill their target cell, antibodies could perhaps be tagged with a standard cytotoxic chemical which would be ingested along with the antibody by the target cell.

It is far too early to say just how monoclonal antibodies may prove useful in therapy, but reports have already appeared of their being used in such applications as curing mice of leukemia and affording protection against malaria (*Science*, 4 January 1980, pp. 68 and 71). Monoclonal antibody production is less fundamentral a technology than gene splicing but its practical ramifications may prove in many ways just as profound.—NICHOLAS WADE

Inventor of Hybridoma Technology Failed to File for Patent

Two patents that between them seem to cover a major fraction of possible hybridoma applications have recently been awarded to the Wistar Institute of Philadelphia in the name of Hilary Koprowski and other Wistar Institute scientists.

The inventor of the technique was not Koprowski but Cesar Milstein, who with Georges Köhler first described how to make hybridomas in 1975.

Milstein did not apply for a patent on his technique. He gave away his plasmacytoma cells in the usual scientific tradition of free exchange, asking only that recipients should not patent any hybridomas made from the cells and that they should not pass them on to third parties.

"We were too green and inexperienced on the matter of patents," Milstein now says. In the past the British Medical Research Council, for which Milstein works, encouraged its scientists to make 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 reflects. His opportunity for patenting his general method, and the mouse cells he developed for it, now seems to have lapsed.

The Wistar Institute seems in a sense to have jumped into the gap which Milstein and Köhler left. A broad patent for monoclonal antibodies raised against tumor cells was granted on 23 October 1979 to Hilary Koprowski and Carlo Croce. A similarly broad patent covering antibodies to viral antigens was issued on 1 April this year to Koprowski, Croce, and Walter Gerhard.

Milstein feels that a patent might be justified for particular clones, even though he asked for all recipients of his mouse plasmacytoma cells not to patent the hybridomas produced from them, but says that he "would feel extremely bad if the rest of the patent is granted, because essentially they are patenting our procedure."

Recipients of Milstein's plasmacytoma cells were asked to sign a letter agreeing to the nonpatenting condition. Milstein has searched through his files but cannot find such a letter from Koprowski. "I would not like to say he had broken an agreement because I have no proof," notes Milstein. Koprowski was unavailable but a Wistar colleague says that Milstein placed no restrictions on the cells he sent Koprowski: "If we had had such a letter we obviously would have honored it," observes Deputy Director Warren Cheston.

Milstein's purpose in not applying for a patent himself and in asking others not to do so is widely attributed to a desire on his part to keep the technique as available as possible. The truth is more complicated. Milstein doesn't remember exactly why he asked people not to patent hybridomas made from his cells: as the flood of requests came in after his first description of the technique was published, he considered this would be a reasonable condition to make and one that would reserve his position.

The fact that neither he nor the Medical Research Council thought to patent a central invention of biotechnology is perhaps not so surprising: the recombinant DNA technique came within a week of being unpatentable. Its inventors, Cohen and Boyer, neglected to mention its commercial significance, which the Stanford University patent officer learned of at the last moment from an article in the *New York Times*. In the long run Milstein and Köhler may not have lost much; they are the acknowledged inventors of the hybridoma technique—the Wistar scientists claim only to have developed a refinement of the basic method—and the Wistar patents are likely to be severely challenged in court.—N.W.

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