Recombinant DNA: Warming Up for Big Payoff

The recombinant DNA technique has already helped engender a multimillion dollar industry, even though the first commercial application is at least a year away from market

The first products of recombinant DNA technology have yet to reach the marketplace, but that prospect has already made millionaires—at least on paper—out of a handful of scientists and entrepreneurs who have founded companies to exploit the technique.

Spearheading the gene-splicing industry are four small companies backed by venture capital and with leading molecular biologists among their founders and advisers. Next in the field were the large pharmaceutical companies. The latest arrivals on the scene are the giants of the oil and chemical industries, such as Dupont and Standard Oil of Indiana, which are either recruiting in-house teams or establishing links with the small companies.

Already much in evidence is the enjoyable hoopla that surrounds large sums of money being put at risk. The birth of the new genetic technology is likened, particularly by those who hold stock in it, to the rise of the semiconductor industry. "In our opinion," states Nelson Schneider, an investment analyst with E. F. Hutton, "Wall Street is not yet fully aware of the range of applications of DNA research, namely, that it can be brought to bear in energy, food processing, agriculture, and organic chemicals as well as health care and pharmaceuticals."

While recombinant DNA techniques assuredly have a bright commercial future, there is a wide range of estimates as to how close that future is. The prime candidate for the first recombinant DNA product to reach the consumer market is human insulin. Genentech Corporation of San Francisco, under contract to Eli Lilly, has succeeded in programming bacteria to produce the A and B chains of human insulin from synthetically made genes. According to E. F. Hutton's Schneider, Lilly's human insulin "could be on the marketplace within a year barring a roadblock from the FDA," and production costs may prove 30 to 50 percent cheaper than the present method of extracting insulin from pig and cattle glands. Officials at Lilly are more cautious. "Production costs are impossible to estimate until a great deal more development work has been done," says Irving Johnson, Lilly's vice president of research, who oversees the Genentech contract. Prices based on published yields of expressed protein would not be economical. Johnson believes the development problems can be solved reasonably quickly but declines to speculate when human insulin will be ready for marketing or what the attitude of the FDA might be.

Johnson nonetheless is enthusiastic about the general commercial promise of gene splicing. "Potential applications of recombinant DNA techniques are limited only by the imagination of the people using them," he says. The applications now contemplated fall into three broad categories. First is the idea of programming bacteria to produce complex biological molecules of therapeutic importance, such as insulin, growth hormone, and interferon. A second use, less spectacular but of immediate economic significance, is to improve existing fermentation processes for making substances such as antibiotics. A third class of applications includes those which impinge directly on the chemical and energy industries: one project is to tailor bacteria to convert ethylene to ethylene glycol; another is to ferment biomass into ethyl alcohol.

Most of the running in commercial gene-splicing developments—at least in public—has been made by four small companies, Cetus, Genentech, Genex, and Biogen. Cetus, the eldest of the four, was founded in 1971 with the intent of producing better microorganisms for industry, using standard genetic techniques. Recombinant DNA has been a natural addition to its tools. Microbiologist Joshua Lederberg, president of the Rockefeller Institute, is chairman of the board of scientific advisers. Three founders of the company, Ronald Cape, Donald Glazer, and Peter Farley, between them own 20 percent of the stock. Since the paper value of the company—computed from recent stock transactions—is now about $100 million, they are all rich men, on paper or otherwise.

Socal (Chevron) owns 25 percent of Cetus, Standard Oil of Indiana has 22 percent, National Distillers 16 percent, and the remaining stock is owned by 200 smaller shareholders. Situated in Berkeley, California, Cetus now has about 200 staff, including some 35 Ph.D.'s.

One of Cetus's major projects is a venture with Socal to convert ethylene and propylene into their oxides and glycols by means of immobilized enzymes and cells. The biological catalysts are expected to perform the task more cheaply than the conventional process, which requires high temperatures and pressures and metallic catalysts. Another project, in conjunction with National Distillers, is to convert sugar to alcohol with a particularly efficient yeast strain developed by Cetus. "The alcohol process is going great guns at our bench; ditto the ethylene glycol," says Cetus chairman Ronald Cape. Cetus has some 15 projects in all and has diversified into four industries, those of oil and energy, pharmaceuticals, chemicals, and single-cell protein. "With this selection of projects we may be wrong in some of our predictions but if with all 15, then we're very unlucky gamblers," says Cape.

Across the bay from Cetus, in San Francisco, is Genentech, the most publicly renowned practitioner of gene splicing. Its two most spectacular public successes to date are ingenious methods for making human insulin and human growth hormone. The insulin work is being performed under contract to Eli Lilly, the growth hormone project for the Swedish drug firm A. B. Kabi, the largest conventional producer of growth hormone. Genentech's growth hormone is quasi-synthetic; 80 percent of the gene was copied off messenger RNA and the rest was synthesized. (There is no restriction enzyme site at the right place on the gene and it was judged better to synthesize a new segment of gene than have a stretch of extra material on the hormone.)

Genentech's work on growth hormone pits it in rivalry against researchers at the University of California, San Francisco, who are developing a different growth hormone process under contract to Eli

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Supreme Court to Say if Life Is Patentable

The U.S. Supreme Court announced on 29 October that it would review the issue of whether living organisms can be patented.

This weighty legal question has been moving through the courts with all deliberate speed since 1976. Upon it hangs an important part of the commercial future of recombinant DNA technology: The Patent and Trademark Office has been holding all such patent claims in abeyance until the issue before the Supreme Court has been resolved.

The two test cases at issue do not, as it happens, involve recombinant DNA. One is a claim by Upjohn for patenting a strain of bacteria that produces the antibiotic lincomycin. The other is an application by General Electric on behalf of the oil-slick-digesting *Pseudomonas* bacterium developed by Ananda Chakrabarty.

The two claims are the shuttlecocks in an elaborate legal game that has pitted the Patent Office against the Court of Customs and Patent Appeals, with the Supreme Court as referee.

In both the General Electric application, filed in 1972, and the Upjohn case, submitted in 1974, the Patent Office examiner denied those parts of the claim that sought to patent the bacterium itself, as distinct from the process in which it was used. The examiner's position was upheld by the Patent Office's Board of Appeals, and the cases went separately to the Court of Customs and Patent Appeals.

The thrust of the Patent Office's position is that the patent law doesn't specifically say that life forms are patentable. The statute provides: "Whoever invents or discovers any new and useful process, machine, manufacture or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor. . . ." Plant varieties enjoy the protection of the patent law but that, the Patent Office contends, is only because Congress passed legislation, in 1930 and again in 1970, for this specific purpose. The 1970 law specifically excludes fungi and bacteria.

> ". . . the fact that microorganisms . . . are alive, is a distinction without legal significance."

The Court of Customs and Patents Appeals batted both cases back to the Patent Office with the ruling that the claims should be allowed. It could not be the intent of the existing patent law to deny patentability to something just because it is alive, the court opined. Provided that a bacterium fulfills the usual legal criteria for patentability, "We do not see any reason to deprive it or its creator or owner of the protection and advantages of the patent system by excluding it from the [statute's] categories of patentable invention on the sole ground that it is alive. It is because it is alive that it is useful."

The bedrock of the appeals court's position was that "In short, we think the fact that microorganisms, as distinguished from chemical compounds, are alive, is a distinction without legal significance."

Detectable in the court's opinion was a touch of irritation at the fuddy-duddy timidity of the Patent Office. New technologies, said one judge, "have historically encountered resistance. But if our patent laws are to achieve their objective, extra-legal efforts to restrict wholly new technologies to the technological parameters of the past must be eschewed."

The ruling was bold and crisp, but also split. In both the Upjohn and General Electric cases, three of the appeals court judges ruled that the claims should be upheld, two dissented. Perhaps encouraged by the division, the Patent Office appealed both cases up to the Supreme Court. The Supreme Court accepted the Upjohn case for review in June 1978 but did not issue a decisive verdict. It bucked the issue back to the Court of Customs and Patents Appeals with an order that the court reconsider its opinion in the light of another Supreme Court patent ruling, known as Parker *v.* Flook, which concerned the patentability of computer programs.

The appeals court evidently thought that the Supreme Court must be joking: "To conclude on the light *Flook* sheds on these cases, very simply . . . we find none." It reaffirmed its rulings that bacteria are patentable. The Patent Office then appealed both cases back to the Supreme Court, charging that the appeals court, in saying living things are patentable, had significantly extended the coverage of the patent laws without legislative authorization. "The economic implications of that holding are very significant, given the vast area that it opens to patentability," the government claims in its brief. The Supreme Court has now agreed to review the issue for a second time. If it upholds the appeals court, the backlog of recombinant DNA claims can presumably be processed by the Patent Office in the usual way. If appeals court rulings are vacated, an act of Congress may be required to give the new technology the full benefit of patent protection.

The master patent application on recombinant DNA is that filed by the technique's inventors, Stanley Cohen of Stanford University and Herbert Boyer of the University of California, San Francisco. But the application was nearly never filed because the inventors neglected to mention the commercial significance to their university patent offices. The Stanford patent officer, Niels Reimers, learned of the technique by reading an article in the *New York Times* and managed to file an application 1 week before deadline, which in the United States is a year after the first published description of the process.

Stanford plans to adopt a liberal licensing policy if the patent is granted. "Our plan is to license non-exclusively and for a very low royalty. It appears that our patent will underlie most work in the field," Reimers says. The patent would not apply to researchers, only to those using the technique for commercial purposes.

The Stanford application is so broad that it is likely to be appealed by users interested in testing the limits of its scope.—N.W.

Lilly. The rivalry is the closer because individuals such as Herbert Boyer have connections with both Genentech and UCSF.

Genentech was founded in 1976 by Boyer and Robert Swanson. From a two-man, $1-million-dollar outfit it has now grown into an enterprise with a paper value of some $65 million and more than 50 staff, including 25 Ph.D.'s and a similar number of outside consultants. About half the stock is owned by the two founders and by the scientific and management staff, none of whom has yet sold any shares. The rest of the company is owned by providers of venture capital, such as the International Nickel Company (Inco) of Toronto. Inco was an early backer of Genentech, invested briefly in Cetus and helped found Biogen. Other backers include Kleiner and Perkins, Monsanto, the Hillman Company of Pittsburgh, the Mayfield Fund of San Francisco, the French firm Soffinova, and the Lubrizol Corp. of Cleveland.

Making improved bacteria to produce expensive amino acids is a leading project of Genex, a Bethesda-based firm with 12 in-house scientists and a scientific board chaired by David Jackson of the University of Michigan. The company was founded in 1977 by Robert Johnston and Leslie Glick. The founders and scientific members own more than a third of the stock. Innoven, a joint venture of Monsanto and Emerson Electric, owns less than a third, and the Koppers Company recently paid $3 million for a share of the company that Glick describes as "less than a third," which puts its paper value at more than $9 million.

Partly because the other three companies were already established in the United States, the founders of Biogen decided in 1978 to incorporate in Luxembourg, with a research facility in Geneva. Its scientific board, mostly Europeans, includes Walter Gilbert of Harvard and Philip Sharp of MIT. The company was set up on the initiative of Dan Adams, then head of the venture capital division of Inco. Inco still owns 23 percent of the stock. The drug company Schering-Plough recently purchased a 16 percent interest for $8 million, setting the paper value of the company at $50 million. Vaccines are one of Biogen's principal ventures. Kenneth Murray of Edinburgh University, a scientific board member, has succeeded in cloning the coat protein of hepatitis B virus, which could form the basis of an antihepatitis vaccine.

Several pharmaceutical companies have started to build up competence in recombinant DNA techniques, including Eli Lilly, Upjohn, Pfizer, G. D. Searle, Merck, and Hoffmann-La Roche. The big companies have been slower to move on recombinant DNA, but are also more secretive about their plans. "The small companies are gambling on a quick success and they all have common lists of what they are trying to do. Our group has a broader data base, and might have a different type of list," says Lilly's Irving Johnson. Lilly has in-house programs on fermentation technology, medical research, and agriculture, to which recombinant DNA techniques are seen as generally applicable. Upjohn has "half a dozen scientists" working on better fermentation methods and production of new antibiotics. An Upjohn researcher, Thomas Fraser, recently accomplished the technically interesting feat of getting chicken ovalbumin expressed by *E. coli*. G. D. Searle conducts recombinant DNA research at its laboratories in High Wycombe, England, where company scientists recently persuaded a bacterium to produce the flu virus antigen hemagglutinin. Pfizer and Hoffmann-La Roche hope to use gene splicing to produce the antiviral substance interferon.

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The oil and chemical corporations have demonstrated their interest mostly by buying into the specialist companies. But Dupont is recruiting five to ten scientists to work on molecular genetics, including recombinant DNA. Subjects of interest include diagnostic products, pharmaceuticals, and agrochemicals.

The development of the industrial potential of genetic engineering seems at first sight to bear out the old claim that small companies tend to be more innovative than large companies. The small gene splicers and some observers certainly see it that way. "The large pharmaceutical and chemical companies simply didn't see the potential for commercial opportunities—they were caught flat-footed but now appear to be trying to catch up," remarks Schneider. "When we were getting started," says Ronald Cape of Cetus, "we ran around the drug industry shouting our heads off for 2 or 3 years and were met with absolutely glassy stares from almost all the professionals." Managers in large companies contend that their slower approach to gene splicing is more prudent, that the benefits are still far off or uncertain, and that there are many other promising ventures besides recombinant DNA competing for their resources. "All the little companies have to survive by making themselves highly visible for contract work, so they try to exploit their activities as much as possible to get support," notes one industry observer. "I think our timing is appropriate. The field has moved more rapidly than I anticipated but there is still an awfully long way to go before the benefits can be achieved," says Ralph Hardy, associate research director at Dupont.

A conference held last month at the National Institutes of Health suggested that at least one of the proposed applications of recombinant DNA, production of pure vaccines, may be considerably further off than predicted. Although virologists reported great strides in manipulating viral genes, old-hand vaccine makers were skeptical that the new techniques had anything immediate to offer. "I don't see any short-term payoff from recombinant DNA technology—it is going to be a long haul," said John Seal, deputy director of the National Institute of Allergy and Infectious Diseases.

The combined paper value of the four small gene-splicing companies now amounts to more than $225 million, an argument that they are at least on the track of something that investors consider valuable. On the other hand, the first recombinant DNA product, if it be human insulin, is probably at least a year away from the market, and even longer if the Food and Drug Administration classifies it as a new drug, requiring clinical trials, rather than a new manufacture. Nor is any fermentation process yet known to be proceeding with the help of gene-spliced microorganisms. Another uncertainty is the patent situation. No patents on recombinant DNA have yet been granted. The Patent and Trademark Office wants an act of Congress passed before it will issue any patent on a living microorganism, and has twice fought an appeals court direction to the contrary up to the Supreme Court (see box). At present, the commercial applications of recombinant DNA remain as much shouting as substance, but the field has progressed with great rapidity and is clearly headed for interesting places.

—NICHOLAS WADE