

# Biotechnology and Genetic Engineering

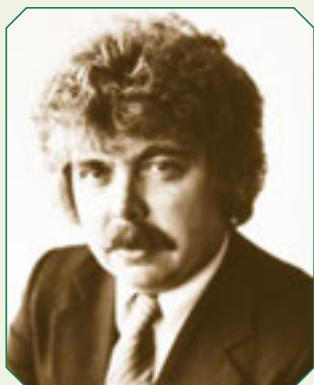
The pharmaceutical industry has embraced the genetic revolution.

CELIA HENRY

Considering just how long people have been using organisms to generate products for them—think thousands of years of beer and wine—the biotechnology industry is remarkably young. The industry as we know it today is not even 30 years old. Yet, even in that short time, it has managed to have a major impact.

In the broadest sense, biotechnology is defined as the use of any technology to manipulate living systems. However, what we call the biotechnology industry is most readily associated with drugs that are produced by bacteria that have been genetically modified to produce a protein they would not have otherwise produced, one that would normally be produced by an entirely different organism.

Before the advent of biotechnology, obtaining adequate quantities of such molecules was an arduous exercise in protein isolation and purification. With the invention of genetic engineering, scientists could harness bacteria to crank out quantities of proteins that made them feasible as drugs.



## Founding Technology

The most important technology for the biotechnology industry got its start when Stanley Cohen, a biologist at Stanford University, and Herb Boyer, a biochemist at the University of California, San Francisco, discussed a research collaboration over late-night deli sandwiches in Hawaii while attending a conference. They would take advantage of their complementary expertise in plasmid biology and restriction enzymes to insert new genes into bacteria. Those new genes didn't have to be from bacteria. Instead, they could be from higher organisms, and the bacteria would produce proteins normally made by other organisms. They started their experiments soon after returning from the conference, and by March 1973, they knew that their method worked, giving researchers the ability to isolate and amplify genes of their choosing.

Recombinant DNA, as it was called, met with initial controversy as people, scientists included, grappled with its implications. Depending on the

perspective, here was a method that could “tinker with” or “improve” life. In response to scientists’ call for a moratorium on recombinant DNA research, the National Institutes of Health (NIH) formed a recombinant DNA advisory committee to oversee research in the field. In February 1975, prominent molecular biologists, along with a few lawyers, physicians, and journalists, met at the Asilomar Conference Center in Pacific Grove, CA, to discuss the issues surrounding such DNA research. The recommendations from the meeting were developed into NIH guidelines that were approved in 1976.

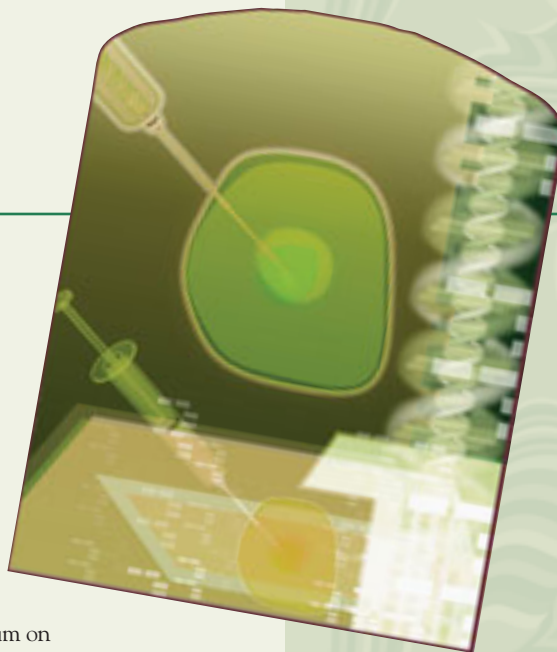
## The Big Boys

In 1976, venture capitalist Robert Swanson approached Boyer about the possibility of starting a company based on recombinant DNA technology. On April 7 of that year, Genentech—the first biotechnology company—and the modern biotech industry were born.

California was the perfect place for the nascent biotech industry because it already had a venture capital community in place from the computer industry. However, money from Kleiner Perkins, the venture capital firm that Swanson worked for, only trickled into Genentech until the company could demonstrate that human proteins could be produced this way.

Swanson served as the CEO of Genentech from 1976 to 1990. In 1990, he was named chairman of the board, a position he held until 1996. Following his retirement from Genentech, he founded K&E Management, an investment management firm that provided funding to start-up biotech companies such as Cytokinetics and AGY Therapeutics.

Within three years of Genentech’s founding, company scientists had produced three human



Top: Biotechnology research, Artville

Center: Herbert Boyer, founder of Genentech, National Library of Medicine



## BIOTECHNOLOGY AND GENETIC ENGINEERING



### TAKING A DIFFERENT TAQ

Kary B. Mullis, a scientist at Cetus Corporation in Emeryville, CA, came up with the idea for the polymerase chain reaction (PCR) in the spring of 1983 while driving. He suggested using a pair of primers to bracket the desired sequence and copying it using DNA polymerase. He quickly realized that such an approach would allow him to double the number of copies of the DNA and that cycling through the reaction several times would result in an exponential amplification of the target DNA. Mullis and his colleagues took close to two years to show that the concept actually worked.

Before PCR could become a viable commercial technique, it was necessary to find a DNA polymerase that could survive temperatures cycling between 37 °C, where annealing and polymerization occur, and 95 °C, where DNA denaturing occurs. The DNA polymerase known as *Taq* polymerase from the thermophilic bacterium *Thermus aquaticus*, found in hot springs in Yellowstone National Park, was chosen.

Because PCR was tangential to Cetus's main focus on cancer therapeutics, the company looked to outside partnerships to commercialize the technique. Cetus signed an agreement with Kodak to develop in vitro diagnostic tests and entered into a joint venture with Perkin-Elmer. Other companies approached Cetus about the possibility of licensing agreements. One of the companies that Cetus negotiated with was Hoffmann-La Roche, which had exclusive rights to the basic patent for interleukin-2, which Cetus was developing as an anticancer drug. Hoffmann-La Roche (Roche) funded diagnostic research at Cetus to the tune of \$6 million per year for five years. In 1991, Roche bought the rights to PCR. Perkin-Elmer formed a strategic alliance with Roche to commercialize PCR.

proteins in bacteria in rapid succession. The first protein to be cloned was somatostatin in 1977. Human insulin followed in 1978, and human growth hormone in 1979.

Although the company still had no products, Genentech went public in 1980. It launched its initial public offering (IPO) on October 14. Shares were offered at \$35 each. Within the first hour, the stock price had jumped to \$89, and it ended that first day at \$71.25, marking one of the most successful public offerings on record.

Genentech's successful IPO demonstrated that biotech companies could raise capital before getting anywhere near the clinic. A wave of new biotech companies was created in the wake of Genentech.

One of those companies was Amgen, which originally stood for Applied Molecular Genetics, in Thousand Oaks, CA.

Amgen was founded in 1980 and began operations in early 1981 with initial funding of approximately \$19 million. Members of the company's original Scientific Advisory Board (SAB) included Leroy C. Hood, then at the California Institute of Technology. Other SAB members were at the University of California, Santa Barbara, and the University of California, Los Angeles. Thousand Oaks was picked as the location for the new company to be near its SAB members. The first CEO of Amgen was George Rathmann, who had been a vice president for research and development at Abbott Laboratories. In 2002, Amgen acquired the Seattle biotech company Immunex.

The first biotech product was marketed in 1982. Genentech's human insulin, called Humulin, was licensed to Eli Lilly and Company, and it remains a major product today, with sales of more than \$1 billion in 2003. Genentech brought its own product to market in 1985—human growth hormone, which was the first biotech product to be manufactured and marketed by a biotech company.

Amgen, which is today the largest biotech

company, went public in 1983. Its first true blockbuster drug was Epogen, a genetically engineered version of erythropoietin, a protein that stimulates the formation of red blood cells. Epogen remains one of the most successful biotechnology drugs, with more than \$2.4 billion in sales in 2003.

Plenty of DNA research was going on outside of California as well. Biogen was founded in 1978 by a group of biologists—many from the Boston area—who gathered in Geneva. Future Nobel Prize winners Phillip Sharp of the Massachusetts Institute of Technology, who won for RNA alternative splicing, and Walter Gilbert of Harvard University, who won for DNA sequencing, were among the founders of Biogen. The company is located in Cambridge, MA.

Genzyme, another Boston area company, was founded in June 1981 by Henry Blair and Sherry Snyder. Genzyme has managed to thrive as a broadly diversified biotech company with divisions working in diagnostics, therapeutics, surgical products, and tissue repair, among other areas.

### The Other Biotech

While work with protein drugs was going on, a parallel branch of the biotech industry was developing—monoclonal antibodies. Antibodies are proteins made by the immune system in response to foreign agents.

Antibodies have excellent recognition properties, but they are difficult to isolate in large quantities. A breakthrough by César Milstein and Georges Köhler at the Medical Research Council Laboratory of Molecular Biology in Cambridge, U.K., in the early 1970s changed that. They found that by fusing an antibody-producing cell with a myeloma cell (an immune system cancer cell) they could get a cell that pumped out large quantities of a single antibody. Such cell fusions are often called hybridomas.

The first company founded to commercialize monoclonal antibodies was San Diego-based Hybritech, started in 1978 by venture capitalist Brook Byers, Ivor Royston, a professor at the University of California, San Diego, and Howard Birndorf, a researcher with Royston. The original idea was to produce monoclonal antibodies as research tools to replace polyclonal antibodies (mixtures of antibodies that target the same antigen), but the company's scope quickly expanded into diagnostic tools and potential therapeutics. It launched its IPO in 1981, raising \$12 million followed by a \$33 million second round in 1982. The company's first product was a test kit for immunoglobulin E. Hybritech was purchased by Eli Lilly in 1985.

Hybritech was just the first in a line of companies seeking to commercialize monoclonal antibodies. However, therapeutic success wasn't achieved until 1998, when the FDA approved Rituxan, a monoclonal antibody developed by IDEC Pharmaceuticals and Genentech to treat non-Hodgkin's lymphoma, a type of cancer. A year

**Above:** PCR instrument, Pharmaceutical Century

later, Genentech won Food and Drug Administration approval for Herceptin, a monoclonal antibody that targets the Her2/neu receptor in patients with metastatic breast cancer.

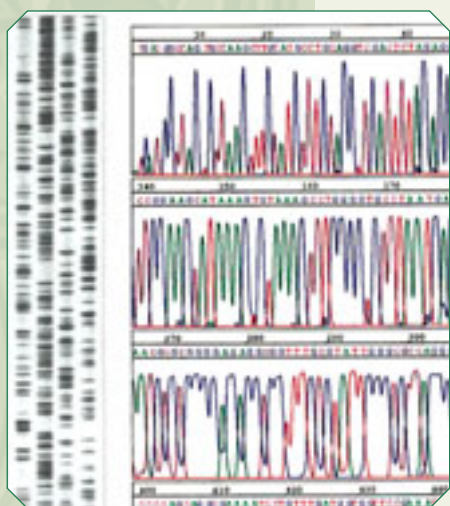
### False Assumptions

In the early days of the biotech industry, companies operated under the false assumption that development of biotech products would be easy. After all, they were making proteins that the body already made. They also assumed that once the technology of cloning the protein was developed, the rest would be easy.

The first-generation biotech products were replacement proteins—things such as insulin for diabetes and interferon and interleukin-2 for cancer. It seemed reasonable to assume that these

drugs would not cause any surprise side effects. The companies forgot that they were delivering large quantities of the proteins systemically when they are usually present locally at fairly low levels. Early clinical trials with interferon and interleukin-2 were plagued by severe side effects.

In addition, the cells being used to produce the proteins made a form that differed slightly from the ones humans make. They had different patterns of carbohydrate modifications, and the bacteria stuck an extra amino acid on the end of the protein that could cause allergic reactions in patients.



### DNA Tools

Advances in methods of analyzing DNA helped to propel the industry forward. Before a gene could be inserted into bacteria, it was necessary to know the sequence of nucleotides in that gene. In 1977, Frederick Sanger of the Medical Research Council's Laboratory of Molecular Biology in Cambridge, U.K., and Walter Gilbert of Harvard University independently devised methods for sequencing DNA.

Sanger's method uses an enzymatic approach in which special versions of the nucleotides serve as chain terminators that prevent further growth of the DNA molecule. The synthesis results in DNA chains of different lengths, and the sequence of the bases in the DNA is revealed by separating the DNA with gel electrophoresis. Gilbert's method uses chemical reagents that selectively cleave the DNA at the different bases, again resulting in DNA strands of varying lengths that are separated by gel electrophoresis.

DNA sequencing became even more useful after Leroy Hood and his coworkers at the California Institute of Technology invented an automated DNA sequencer in 1985. Hood used fluorescently labeled dideoxy reagents in the Sanger sequencing

reaction. The fluorescent dyes eliminated the health hazards of the radioisotopes that were previously used and allowed all four bases to be analyzed in a single gel. The company Applied Biosystems commercialized the technology in 1986. Automated sequencers later became the workhorses of the Human Genome Project.

In 1983, Kary B. Mullis of Cetus Corporation invented the polymerase chain reaction (PCR), which amplifies small amounts of DNA. PCR has particularly revolutionized diagnostics and forensic chemistry by allowing tiny quantities of DNA to be copied and yield enough DNA for analytical analysis (see sidebar).

### Gene Hunting

In the early 1990s, several biotech firms such as Human Genome Sciences (HGS) of Rockville, MD—founded by William A. Haseltine in 1992—concentrated on identifying and patenting genes related to human disease for the purpose of finding drug targets. The business models for these companies called for selling information to larger pharmaceutical companies rather than developing drugs. However, such strategies proved unsustainable, and companies such as HGS, Millennium Pharmaceuticals, and Celera are transforming themselves into full-fledged drug-development companies.

In 1990, the Human Genome Project was launched to obtain the complete blueprint of human DNA. The project was made possible by technologies to automate the sequencing of DNA. The international public effort, which included laboratories from the United States, the United Kingdom, and Japan, was expected to take 15 years.

The appearance of the company Celera Genomics, a joint venture of Perkin-Elmer and Craig Venter, founded in 1998, turned the quest to sequence the human genome into a race between public and private efforts. Celera was using a new approach, called whole-genome shotgun sequencing, in which computer programs were used to reassemble the genome sequence. In June 2000, Francis Collins and Venter unveiled a draft sequence of the human genome, effectively declaring the race a tie.

Public fascination with the Human Genome Project fueled a biotech boom in 2000, based on the mistaken notion that the genome sequence itself would lead directly to cures for disease. More than 60 IPOs were launched that year. According to one estimate, the biotech industry raised more than \$32 billion through all avenues that year.

Today, there are hundreds of biotech companies, ranging from tiny start-ups to the large integrated biotechnology companies. They work in every imaginable therapeutic niche. Some branches of the field have moved beyond therapeutic biotechnology to agriculture and even industrial chemicals. ♦

**Above:** DNA sequencing, 2003, Analytical Chemistry