THE BIRTH OF BIOTECHNOLOGY: Harnessing the Power of DNA

Dinesh Ramde

The ascent of biotechnology from the discovery of the DNA structure to experimental gene therapy has been marked by revolutionary discoveries and fascinating technical advances. These developments have created a sense that we can make dramatic improvements in health care, agriculture, energy production, and other areas. But the speed at which the biotech industry took off, the magnitude of its success, and the scope of its impact have surprised even its pioneers. These considerations, industry experts say, give them even more confidence that biotechnology will deliver on its early promise in the not-so-distant future.

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The discoverers of the DNA structure, James Watson, at left, and Francis Crick, look at their model of a DNA molecule.

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Focusing on the history of biotechnology is like writing an autobiography as a teenager—it seems odd to focus on the past when so much more is yet to come.

Still, the biotech industry has taken a wild ride from its humble beginnings in austere laboratories a quarter of a century ago. The industry's growth has been marked by innovative scientific techniques and breakthrough discoveries around the globe.

Biotech intrigues not because of how far it has come but because of the new frontiers it has yet to explore. Scientists foresee revolutionary changes in how we feed the world, how we vaccinate our children, and how we clean our air and water.

As biotechnology grows up, we take a look back at its birth and infancy, in part through the eyes of the scientists and entrepreneurs who fathered it.

The Birth of Biotech

In 1863, Austrian botanist Gregor Mendel discovered that pea plants passed on traits from parent to progeny in discrete biological units that would be later known as genes. Six years later, Swiss biochemist Johann Friedrich Miescher isolated from white blood cells the substance that would be called deoxyribonucleic acid, or DNA.

It would be another 75 years before the two discoveries were linked. In 1944, Canadian biologist Oswald Avery suggested that DNA was the mechanism by which bacteria passed on their hereditary material. However, Avery's explanation was met with skepticism by those who believed that the genetic information of an organism was far too complex to be contained in DNA.

Then in 1953, American biologist James Watson and British molecular biologist Francis Crick determined the double-helix structure of DNA, which, in turn, led to a cascade of new discoveries of how DNA works at a molecular level.

These discoveries were advancements only in the field of biochemistry. It was not until 1972 that scientists pioneered a way to combine biochemistry with a technique that led to the birth of biotechnology. That was the year that American biochemists Herbert Boyer, Paul Berg, and Stanley Cohen developed recombinant DNA, a modified DNA molecule created by combining DNA from two unrelated organisms.

Every cell in a living organism, from a bacterium to a human, contains DNA. In turn, DNA is made up of four building blocks called bases, the names of which are abbreviated A, T, G, and C. In the same way the 26 letters of the English alphabet can be arranged, repeated, and strung together to make meaningful sentences, so too are series of the four DNA bases strung together in an order unique to every living creature.

DNA is a permanent blueprint that gives rise to temporary analogs of itself called ribonucleic acid, or RNA, that ultimately instructs cellular machinery to create unique

proteins. Each string of DNA bases that codes for one protein is called a gene.

One can think of a gene as a set of instructions that tells a cell's machinery how to put amino acids together to form a protein. The machinery of any cell, bacterial or human, will use that set of instructions to create exactly the same sequence of amino acids, and hence create exactly the same protein.

If that is the case, reasoned Boyer and his colleagues, what if we take a human gene that creates a vital protein, insert that gene into bacterial DNA, and compel the bacteria to pump out continuous supplies of that protein? When his team did just that, creating recombinant DNA that combined human and bacterial DNA, biotechnology was born. The scientists had figured out a way to turn organisms as simple as bacteria into factories, tiny assembly lines that manufacture essential human proteins such as insulin and human growth hormone.

The Business World Responds

The fledgling technology and the genetically modified organisms it yielded inspired fear as much as it did excitement. "We had to be terribly cautious—you can't put these things back in a bottle," says George Rathmann, the first chief executive officer (CEO) of the biotech firm Amgen based in Thousand Oaks, California. "You might end up with a new infective agent that is more lethal than smallpox or strep, and it would be even worse if it were combined into a viral organism."

Concerns like these led scientists in 1975 to convene the Asilomar Conference in Pacific Grove, California. At the conference, about 140 scholars created strict rules to dictate the limits to which recombinant DNA research must be restricted. It mandated, for example, that the technology could be applied only to organisms that cannot live outside a laboratory on their own, and it could not be used in genes that might be active in humans.

"It was a concern, to be sure, throughout the industry," Rathmann says. "In Abbott Labs, they were so concerned about recombinant DNA that their workers had to wear suits, helmets, almost literally a whole spacesuit. Some companies were so cautious—to the point of overkill—that they never got off the ground."

Other companies embraced the new technology. Boyer teamed up with venture capitalist Bob Swanson to found Genentech in South San Francisco in 1976. From the beginning, Boyer saw the potential of the new technology. "This was very exciting, a challenging opportunity to take this academic endeavor that I was a part of and turn it into something meaningful in the way of providing medicines and drugs to benefit people," Boyer says.

AP/WWP/Paul Sakuma

A bioprocess in a cell development room at Genentech.

Genentech did not take long to make its mark with the development of a human insulin drug produced by genetically engineered bacteria. The Food and Drug Administration, a U.S. government regulatory agency, approved the drug in 1982. In the ensuing years, other companies followed suit with drugs similarly derived from modified bacteria, drugs that fought kidney transplant rejection, replenished white blood cells in chemotherapy patients, and treated hemophilia.

Plants were also the beneficiaries of recombinant DNA technology. In 1987, Advanced Genetic Sciences created a genetically modified bacterium that prevented frost from developing on strawberry and potato plants. This technology has enabled the production of more hardy and nutritious foods. For example, rice has been genetically modified to be high in vitamin A, and tomatoes have been modified to produce less of the substance that causes them to rot. These were changes that could not be brought about by simple selective breeding.

Critics of the technology say that genetically modified foods carry health risks that do not exist in crops produced through traditional breeding techniques, a claim that has never been scientifically proven. Some also argue that companies that create modified crops may ultimately claim intellectual, and by the same token financial, rights to those crops to the detriment of the poor in developing nations. So far, the opposite has been happening, with farmers in developing countries benefiting with increased yield from biotech crops.

Spawning New Science

Techniques that have enabled the manipulation of DNA have allowed scientists to pursue revolutionary technologies. In the 1980s, PPL Therapeutics in Edinburgh,

Scotland, used genetic engineering to create Rosie, a cow whose milk contained the human protein alpha-lactalbumin. This milk can be administered to premature babies who are too small to nurse, and the protein enhancement provides amino acids essential to the infants' development.

Gusto/ Photo Researchers, Inc.

Ian Wilmut and his creation, Dolly, the first sheep cloned from an adult sheep cell.

Rosie's embryos have been used to create clones of the cow, clones that will be allowed to reproduce normally to create a herd of enhanced dairy cows. The cloning process involved removing DNA from one of Rosie's cells and using it to replace the DNA of a separate cow embryo. The resulting calf is then genetically identical to Rosie. Such experiments had been performed for years on frogs, mice, and sheep.

In 1997, researchers at the Roslin Institute in Scotland made an even more dramatic announcement: They had cloned a sheep by taking DNA from a sheep cell and putting it in a mammary cell, not an embryo, proving for the first time that even "adult" cells can change into different cells. Until then, the process was mostly thought limited to immature stem cells.

A year later, American developmental biologist James Thompson first cultivated human embryonic stem cells—cells that are prized for their ability to grow into specific cells. Scientists are studying whether stem cells can be used to replace dead or injured cells, thereby giving patients with brain or organ failure hope for a cure.

In addition to cloning technology, another revolutionary DNA project was under way in the 1990s. Ever since Watson and Crick deduced the molecular structure of DNA, scientists hoped to identify every single gene in human DNA, a daunting task considering a human has between 20,000 and 25,000 genes. By 1990, technology was sufficiently advanced for a worldwide consortium to undertake this bold venture, called the Human Genome Project.

The goals of the project were threefold: to identify every human gene; to determine the order of the three billion pairs of bases—that is, the building blocks A, T, G, and C—that comprise human DNA; and to make the sequence available to researchers. The project was completed in 2003, two years ahead of schedule, and scientists are currently studying the data for medical gene therapy.

Exceeding All Expectations

The biotechnology industry grew and evolved with a speed that neither Boyer nor Rathmann could possibly envision.

"Seeing what's happening today, it staggers the mind," Boyer says. "We certainly had great expectations, and when we started we were like kids in a candy shop with any number of directions to go in. I remember thinking in the early days when we developed recombinant DNA techniques, that this technology is unlimited. But we still couldn't foresee all of this."

Rathmann left a comfortable career in medical diagnostics to become Amgen's CEO and third employee, a move he says testifies to his tremendous confidence in the technology. "The decision was easy for me because the science was so powerful," he says. "But it's absolutely wrong to suggest the industry evolved the way we thought it would. It's not surprising it was so successful, but the magnitude of its success, its importance to human medicine, it's really quite unbelievable."

Rathmann recalls seeing government figures in the 1980s suggesting that the biotech industry could one day grow into a $4 billion industry. "That shows you how poorly we imagined," he says. "Amgen alone turned into a $95 billion company."

To Rathmann, however, the money is a secondary concern. At 77, the former Amgen CEO takes Epogen, one of Amgen's genetically engineered drugs, almost every day in his battle against kidney disease. He believes the industry's first 25 years are only the beginning of something grand.

"The future was terribly bright in 1980, and it's even more exciting today because there's been such a great track record of success across the board," he says. "I think we'll see a continuing blossoming of the effects of biotechnology. This is a beautiful, beautiful science." ■

The opinions expressed in this article do not necessarily reflect the views or policies of the U.S. government.

BIOTECHNOLOGY'S FIRST 142 YEARS

1863	Gregor Mendel discovers that pea plants pass on hereditary information in distinct units that will be later called genes.
1869	Johann Friedrich Miescher isolates DNA from human white blood cells.
1944	Studying pneumococcus bacteria, Oswald Avery et al. determine that DNA is the hereditary material.
1953	James Watson and Francis Crick discover the molecular double-helix structure of DNA.
1955	Fred Sanger determines the amino acid sequence of insulin.
1972-73	Paul Berg, Herbert Boyer, and Stanley Cohen develop recombinant DNA techniques.
1975	Scientists express concern that recombinant DNA can lead to the development of dangerous organisms. At the Asilomar Conference, a group of scientists draw up strict restrictions around the use of recombinant DNA techniques.
1976	Herbert Boyer and Bob Swanson found biotech pioneer firm Genentech.
1978	Somatostatin becomes the first human protein developed using recombinant technology.
1984	Chiron Corporation announces it has cloned and sequenced the entire HIV genome.
1985	Plants genetically engineered to be resistant to insects and viruses are field-tested for the first time.
1990	GenPharm International, a biopharmaceutical company, creates the first transgenic dairy cow, which produces human milk proteins for infant formula.
1990	The Human Genome Project is launched.
1993	The U.S. Food and Drug Administration concludes that genetically engineered foods are not inherently dangerous.
1997	Researchers at Scotland's Roslin Institute report they have cloned a sheep.
1998	Two research teams succeed in growing embryonic stem cells.
2003	The Human Genome Project is completed.
2004	Korean researchers announce the successful cloning of a human embryonic cell.