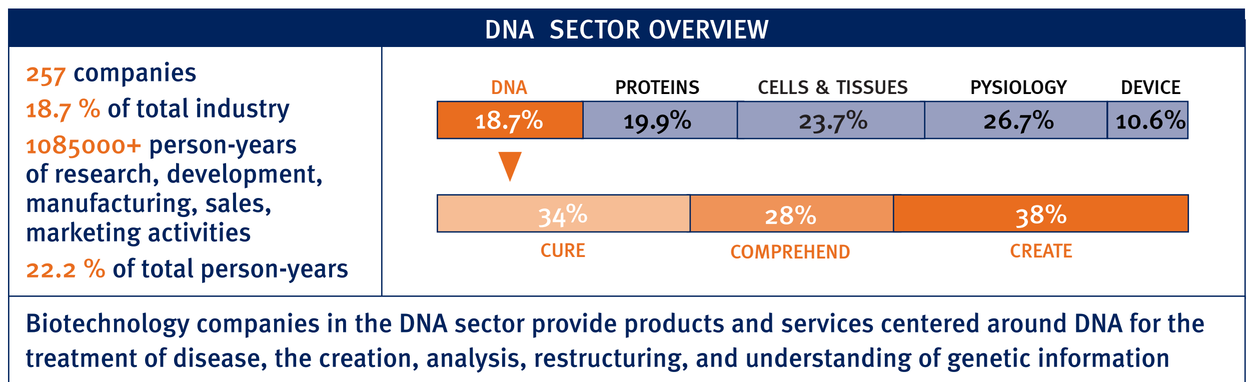
DNA

DNA provides both a universal language for biology and serves as a genetic library that stores the collective experimentation of evolution.

DNA is the genetic material within our bodies that governs transfer of hereditary traits such as eye and hair color, body height, and many other features. This set of molecules is the central repository of information in our cells, and it provides the stability of content that defines all the species on earth. In the past 25 years, the development of techniques to control the structure and function of DNA has led to the emergence of a vibrant market sector within the biotechnology industry.



Scientific Overview

THE DISCOVERY OF GENETICS

Human civilization has been intentionally breeding both animals and plants for more than 10,000 years, yet the cellular and molecular basis of this breeding is fairly recent. Most of the progress in understanding heredity has been made in the past 150 years.

In the seventeenth century, egg cells and sperm cells were discovered, although their proper role in the hereditary process was still misunderstood. Scientists of that day thought that tiny, fully-formed miniature versions of adults were present in either the egg or the sperm. By the eighteenth century, researchers correctly recognized that an egg and a sperm combine to form an embryo. But a clear understanding of heredity had yet to emerge.

Mendel's Experiments

In 1866 an Austrian monk named Gregor Mendel was the first to write about first modern conception of heredity. From his experiments with garden peas, Mendel discovered what he called "discrete hereditary elements," which were responsible for passing traits on to successive generations. In particular, Mendel discovered the plants' respective offspring retained the essential traits of the parents, and therefore were not influenced by the environment. Once he crossed peas of different varieties, Mendel found that specific traits were inherited in particular patterns, where certain traits segregated independent of one another, controlled by what appeared to be "discrete hereditary elements." These elements are now known to be genes.

After seven years spent crossing certain plants with each other, Mendel derived two basic laws of heredity: 1) hereditary factors do not combine, but are passed intact; each member of the parental generation transmits only half of its hereditary factors to each offspring (with certain factors "dominant" over others); and 2) different offspring of the same parents receive different sets of hereditary factors. Though they were ignored for the next 30 years, Mendel's original publications became the foundation of modern genetics.

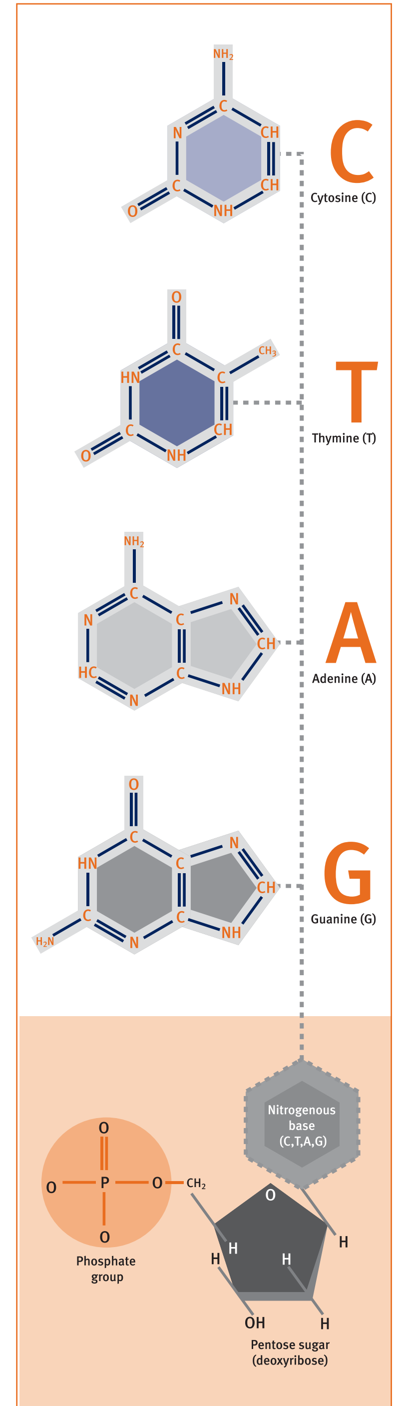
The Debate Surrounding Genetics

The initial discovery of deoxyribonucleic acid (DNA) was made by Friedrich Miescher, a 25-year-old medical scientist. In 1868, Miescher was characterizing proteins within certain cells treated with a digestive substance to isolate the nucleus of the cell. Small amounts of unusual sediments were released as the digestion occurred, and he named these substances "nuclein," which was later termed DNA. Miescher did not appreciate the significance of his discovery: He thought that nuclein was a place for the cell to store phosphorus, and did not suspect a role in the genetics of heredity.

During that same period another scientific pioneer, Albrecht Kossel, published an article that said nuclein was related to the formation of new tissue rather than simply nutritional storage for the cell. He set about to characterize the chemical nature of the nuclein (DNA) material, and in 1885 isolated a chemical unit of DNA, a base called "adenine". In 1893, he isolated another chemical base called "thymine" by using cells extracted from a cow thymus. By 1900 the chemical base "uracil" was discovered. The four chemical bases of nucleic acid were then known to be the molecules adenine, cytosine, thymine, guanine, and uracil (A, C, T, G, and U).

Upon the rediscovery of Mendel's work around 1900, a debate raged regarding the physical substrate of these so-called discrete hereditary units, or genes. Potential candidates included proteins, cell membranes, and DNA. Proteins were thought to be the most likely choice, since they were relatively large molecules, abundant in the cell, and it was thought that a lot of physical material would be needed to hold substantial information.

In the 1920s, a scientist named Phoebus Levene proposed that each segment of DNA contained had a specific structure composed of (a) four nucleotides, each comprising a phosphate group, (b) a sugar molecule, and (c) one of the four chemical bases, A, C, T, or G. These bases seemed to be in exact numerical equivalence, that is, for every A there was a T, and for every C there was a G. He proposed DNA to be composed of four units, a "tetranucleotide," even though such a small molecule seemed unlikely to be the carrier of genetic information. This again raised the debate of protein versus DNA as the source of genetic information.



Around 1910, genes were found to be located on distinct structures located in the nucleus of a cell. These structures were named called chromosomes, and they are composed of both protein and DNA. Scientists knew then the critical role proteins played in many biological functions, so they assumed that chromosomal proteins would carry genetic information within the cell.

This view changed in 1944, when Oswald Theodore Avery, Colin MacLeod, and Maclyn McCarty demonstrated that genes consisted of DNA, not protein. At first this theory was almost ignored because many scientists thought the DNA molecule was too simple to contain the genetic information for most organisms. The definitive proof came from an experiment where the material from one type of bacterium was used to genetically "transform" another bacterial type. When the transforming material was treated with substances that would destroy specific classes of molecules in that material (for example, polysaccharides, lipids, and proteins), the genetic transformation could still occur. However, when the transforming material was treated with a DNA-destroying substance, the genetic transformation could no longer occur. DNA was the only material capable of transforming cells from one type to another. DNA was clearly the substance of genes.

Mendelian genetics presumed that DNA was static, so that the relative position of genes relative to one another remained stable. Barbara McClintock reported a contrary view in 1947 in her studies of changing color patterns in maize kernels over many generations. She determined that the only way the coloration patterns could vary so broadly would be if genes were transposable, e.g., they could move around on the chromosome. This led her to construct a theory of "transposable elements," jumping genes that could move about the maize genome. The scientific community at first failed to appreciate the significance of her discovery. The idea that genes could move did not fit with the perception of a static gene. As the methods of molecular biology improved in the 1980s, several independent groups studying gene structure at the molecular level proved her theory, and she was awarded the Nobel Prize in 1983.

THE STRUCTURE OF DNA

DNA is a double-stranded, twisted ladder-like molecule that serves as the central library of all genetic information for almost all life forms.

DNA appears similar to a spiraling ladder. It consists of just a few kinds of atoms: carbon, hydrogen, oxygen, nitrogen, and phosphorus. Combinations of these atoms form the “sugar-phosphate backbone” of the DNA.

James Watson and Francis Crick discovered the chemical structure of DNA in 1953. Based on Rosalind Franklin’s X-ray diffraction data, which suggested that DNA had a helical structure, Watson and Crick hypothesized that DNA was composed of two chains of threaded, helical coils, with each helix containing matching base pairs (adenosine to thymine, and cytosine to guanine), bound together along the central axis of this double helix to keep the distance between the chains constant. These bases are the rungs of the DNA ladder.

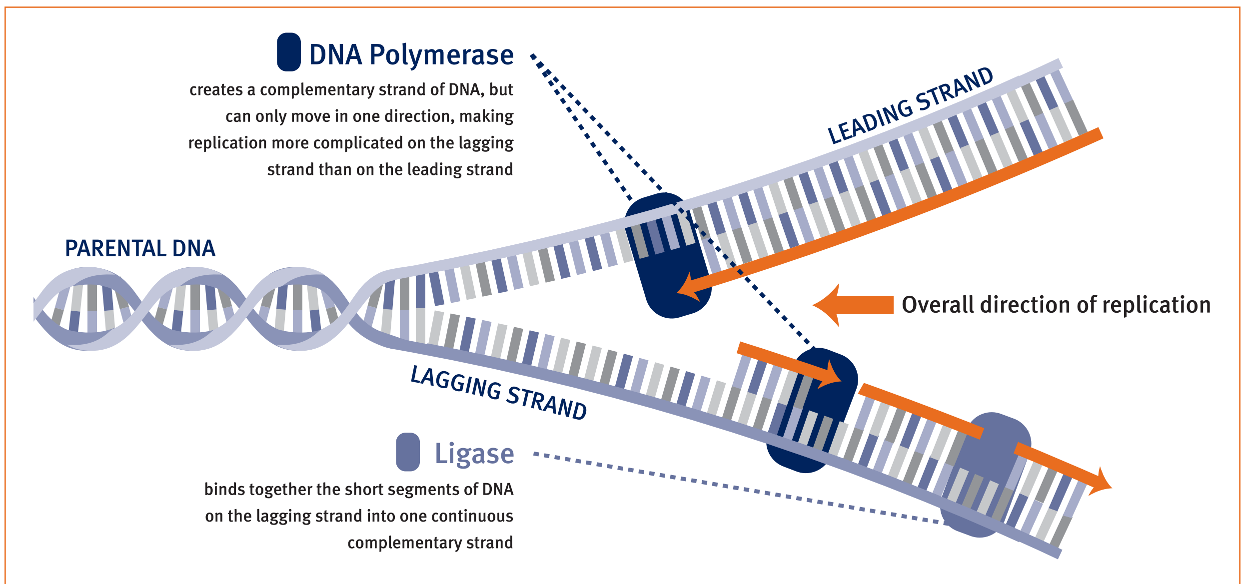
A central question in genetic theory was related to the copying of genetic information: How was genetic material faithfully reproduced as hereditary traits passed down from one generation to another? Based on their proposed DNA structure, Watson and Crick hypothesized that each strand of the DNA molecule is a template for the other when genes are copied. During cell division the two strands separate and on each strand a new “half” is built, permitting faithful replication.

THE FUNCTION OF DNA

If DNA were an information repository for the cell, the duplication of this information would be central if cells were to divide without losing genetic information.

Watson and Crick has proposed that, during DNA replication, special enzymes would move up along the DNA ladder, unzipping the molecule as they moved along. New nucleotides would move in to each side of the unzipped ladder. The bases on these nucleotides would need to be very particular the other bases with which they could connect. That is, cytosine (C) would pair to guanine (G), and adenine (A) would pair to thymine (T). Yet how could this work in practice? What machinery could duplicate DNA?

In 1958, Arthur Kornberg and his colleagues at Stanford University were the first to purify an enzyme with DNA polymerase activity. When this enzyme, termed DNA polymerase, has passed along a single strand of DNA, two identical strands of DNA are left behind. Each contains one side of the original DNA and one side made of "new" nucleotides. Mistakes are rarely made along the way and it is rare when a base pair in one DNA molecule doesn't match the corresponding base pair in the other molecule. The error frequency during DNA strand copying is one mistake in every billion base pairs. That's an error rate akin to a person typing the entire Encyclopedia Britannica five times and hitting only one wrong letter.



THE GENETIC CODE

Scientists had realized that DNA contained genes since the mid-1940s, and the structure of DNA clearly indicated that the sequence of DNA base pairs would somehow serve as a genetic code. Yet what was that code? What was the language of DNA? How could the genes on DNA code for protein structures?

In 1966, this "genetic code" began to be broken by a global group of scientists. The American scientist Marshall Nirenberg collaborated with German scientist Johann Matthaei to prepare an extract from bacterial cells that made protein even when no intact living cells were present. Adding an artificial form of RNA containing only the base uracil (U) to this extract caused it to make an unnatural protein composed entirely of the amino acid phenylalanine. This provided the first clue to the code through which a nucleic acid sequence could control the production of specific types of proteins. That is, "UUU" is the genetic code word, or codon, for the amino acid phenylalanine (correct spelling?). Codons are formed by a sequence of three chemical bases in the nucleic acid strand.

Nirenberg presented his experimental results at the International Congress of Biochemistry in Moscow in 1961. As an unknown scientist with an obscurely titled paper, his initial seminar was very poorly attended. However, a few attendees understood the significant of what they were hearing, and Nirenberg was asked to repeat his talk in the final session of the full Congress. Some audience members recall being electrified by what they heard.

The rest of the genetic code was quickly deciphered through the work of teams of scientists around the world. The fundamentals of the complete genetic code were established and synthesized by Gobind Khorana at the University of Wisconsin at Madison, who showed that the "Rosetta Stone" of genetics is comprised of 64 codons, each unique to a specific amino acid. This is our genetic code.

CIPRO

Cipro, a synthetic antibiotic produced by Bayer, inhibits the bacterial enzyme DNA gyrase, an enzyme that twists the double-helix of bacterial DNA for compact storage when it's not being duplicated during cell division. Without DNA gyrase, bacteria cannot survive as their genetic storage is compromised and breaks down. Cipro is effective against a broad spectrum of pathogens, including many bacterial species, and more than 250 million patients have been treated worldwide.

START (Methionine)	Met	AUG
Leucine	Leu	UUA, UUG, CUU, CUC, CUA, CUG
Serine	Ser	UCU, UCC, UCA, UCG, AGU, AGC
Arginine	Arg	CGU, CGC, CGA, CGG, AGA, AGG
Valine	Val	GUU, GUC, GUA, GUG
Proline	Pro	CCU, CCA, CCC, CCG
Threonine	Thr	ACU, ACC, ACA, ACG
Alanine	Ala	GCU, GCC, GCA, GCG
Glycine	Gly	GGU, GGC, GGA, GGG
Isoleucine	Ile	AUU, AUC, AUA
Phenylalanine	Phe	UUU, UUC
Tyrosine	Tyr	UAU, UAC
Histidine	His	CAU, CAC
Glutamine	Gln	CAA, CAG
Asparagine	Asn	AAU, AAC
Lysine	Lys	AAA, AAG
Aspartic acid	Asp	GAU, GAC
Glutamic acid	Glu	GAA, GAG
Cysteine	Cys	UGU, UGC
Tryptophan	Trp	UGG
STOP		UAA, UAG, UGA

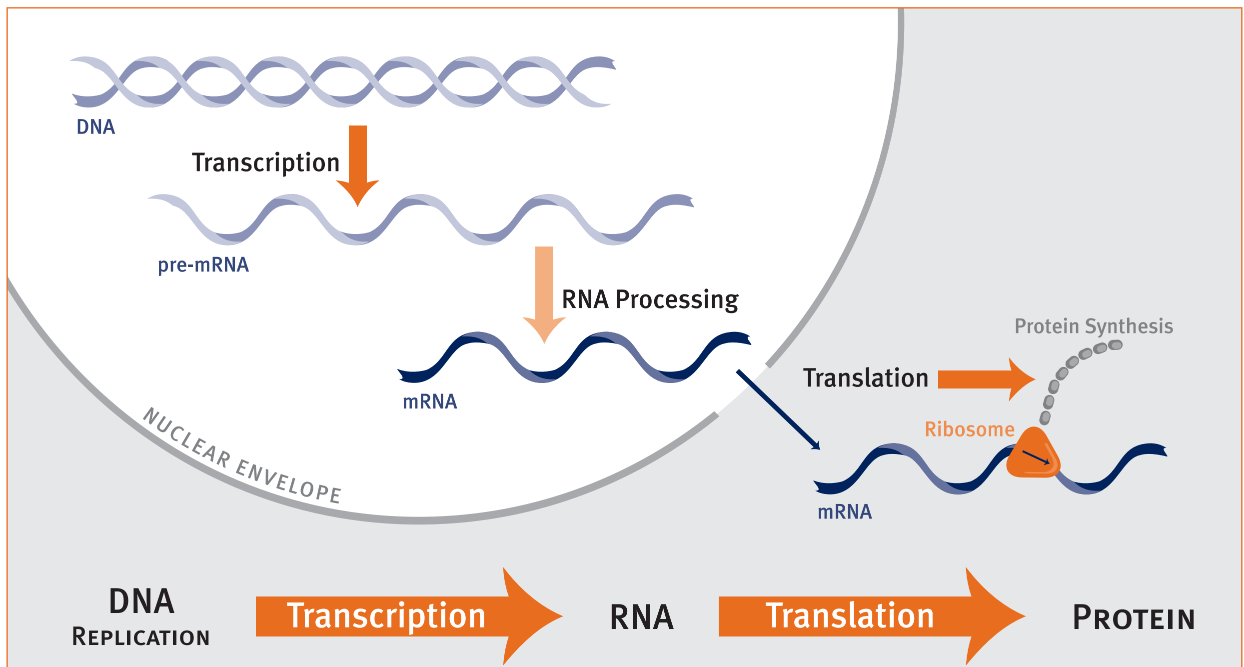
THE "CENTRAL DOGMA"

By the early 1960s enough information had been accumulated about the structure and function of nucleic acids and proteins to build a coherent theory of the information flow within the cell. This theory is referred to as the "central dogma" of modern biology because this information flow is so central to all cellular functions.

Three major events take place as information flows from genes on DNA strands to proteins working within the cell:

(1) DNA strands are replicated so as to preserve the original information contained in the nucleotide sequence while still making the information available to the cell.

(2) DNA is used as a template to create a similar, though slightly different, type of nucleic acid, called messenger RNA. This process is called transcription. RNA has the same primary structure as DNA, but uses a chemical base called uracil in place of thymine. The backbone of the RNA ladder is also slightly more chemically complex, which permits more complex shapes to form in the RNA strand.



(3) Messenger RNA carries genetically-coded information to ribosomes, which read this information and use it for protein synthesis. This process is called translation.

This information flow is mostly in one direction: Proteins do not code for the production of protein, RNA, or DNA. There is no such thing as reverse translation. But in the 1980s it was demonstrated that RNA can be used to create DNA, in a process called reverse transcription.

Why would a nucleic acid structure such as RNA be used as an intermediate between genes on DNA and the proteins encoded by these genes? First, the preservation of the DNA is critical to the long-term health of the cell, and using the original template only sparingly to make working copies limits the potential for damage to this critical information repository. Second, genetic information can be amplified by establishing a one-to-many relationship between DNA and RNA, in which many copies of RNA can be made from a single DNA sequence. These copies can then be processed in different ways by other cellular machinery, permitting regulation and modulation of the working information templates in the cell while still preserving the original information.

A more detailed description of this process is presented in the chapter on proteins.

Industry Overview

Most of the industrial activities in the DNA sector of the biotechnology industry fall into one of three categories: cure, comprehend, and create. The total number of DNA-based "cure" companies is 89, the number of DNA-based "comprehend" companies is 71, and the number of DNA-based "create" companies is 97. The relatively longer history of developing tools and resources for genetic engineering has resulted in the predominance of DNA-based "create" companies.

CURE

Several products in development make use of DNA as a diagnostic and/or therapeutic agent for detection and treatment of disease.

The companies developing, manufacturing, and marketing these tools provide products ranging from screening kits for infectious viral diseases to antiviral and gene therapy products. Two promising approaches for genetic therapy, antisense DNA drugs and DNA vaccines, are described below.

Antisense DNA Drugs

During transcription of genetic information from the DNA strand into an mRNA molecule, the two complementary strands of the DNA strand partly uncoil. One strand is called the "sense" strand, while the other is called the "antisense" strand. They differ functionally in that only the "antisense" strand is used as a template for mRNA transcription.

Antisense drugs are complementary strands of small segments of nucleotides that are designed to bind to a specific mRNA target sequence, inhibiting production of the protein encoded by the target mRNA. By preventing the production of a disease-causing protein, antisense drugs may provide more therapeutic benefit than more traditional drugs, which may not act until the disease-causing protein has already been produced. Antisense drugs also can be much more selective than traditional drugs, and therefore potentially more effective. Several antisense drugs are now in development around the world.

DNA: CURE
89 companies 6.5 % of total industry 264000+ Person-years of research
Companies in the "DNA:Cure" sector provide products and services based on DNA products for the diagnostic and therapeutic treatment of disease.

DNA Vaccines

DNA vaccinations are a branch of gene therapy, a process in which genes are introduced into the body's cells. DNA vaccines are very different in structure from traditional vaccines. DNA vaccines consist of plasmids, small circles of DNA strands that by themselves are unable to produce an infection. The plasmids used for immunization are genetically engineered to carry genes specifying one or more antigenic proteins normally made by a specific pathogenic organism; at the same time, they exclude genes that would enable the pathogen to grow and cause disease.

The DNA vaccine is injected via a needle into the cells of a tissue. The cell begins producing proteins that look like a particular antigen (a substance capable of stimulating the formation of an antibody). If the vaccinated tissue ever encounters the pathogen in which the true antigen is present, it has by then produced antibodies to that antigen, so it can protect itself from that pathogen.

DNA-based vaccines mimic infections in which very small amounts of protein are made but strong immune responses are generated. These immune responses are often stronger than traditional vaccines. Further, DNA vaccines can provide extended protection through long-lasting production of the antigenic protein, maintaining an immune response and subsequent antibody production, so the booster shots of traditional vaccines would not be needed. However, extended stimulation of the immune system could potentially lead to unintended consequences, such as autoimmune disease and chronic inflammation. So clinical trials must be carefully conducted to determine both the safety and the efficacy of the potential DNA vaccine. DNA was first used to trigger an immune response in humans against HIV in 1995. In 1996, independent clinical trials were started for T-cell lymphoma, influenza, and herpes simplex virus.

ISIS PHARMACEUTICALS

Carlsbad, CA
www.isispharm.com

Founded: 1989
Employees: 434
Public (ISIS)
Annual Revenue: $53.3 million (2001)

Isis Pharmaceuticals, Inc. focuses on using antisense technology to treat disease. The company has five drugs in human clinical trials and one marketed product. In 1998, the anti-viral drug Vitravene® (fomivirsen), became the world's first antisense drug to be approved for use in the U.S. It received European regulatory approval in 1999.

DYNAVAX TECHNOLOGIES CORPORATION

Berkeley, CA
www.dynavax.com

Founded: 1997
Employees: 55
Privately held

Dynavax Technologies is a biopharmaceutical company developing innovative products to treat allergy, inflammation-mediated diseases, infectious diseases and cancer. The company's lead products are based on ImmunoStimulatory DNA Sequences (ISS), short DNA sequences that enhance the ability of the immune system to fight disease and prevent inflammation. The company's two most advanced products are AIC, which has provided positive results in recently completed phase II clinical trials for the treatment of ragweed allergy, and a next-generation hepatitis B vaccine that may offer single-dose protection. The company is also investigating ISS-based treatments for cancer and asthma. In addition, Dynavax is developing an oral TNF-alpha synthesis inhibitor initially for the treatment of rheumatoid arthritis.

COMPREHEND

Genomics—the study of genetics—systematically aggregates the collective genetic information of organisms ranging from bacteria and viruses to fish and humans. This information can be used to diagnose disease, predict the future health of an individual, and support the development of cures for diseases.

The ability to sequence individual genes provides a means to understanding the genetic wiring upon which all life is based. In the past 20 years, a revolution has begun through which scientists can analyze the genetic circuits responsible for the diversity of species on the planet, the development plan by which an embryo transforms into an adult, and the genetic basis of human individuality. Several companies produce products centered on sequencing, and on the physical and mathematical analysis of DNA, broadly categorized as genomics and bioinformatics, respectively. Other companies in this market sector specialize in products and services focused on the study of chromosomes, DNA sequencing, genetic fingerprinting, and DNA probes.

Genomics is the study of entire sets of genes sequences within a species, in which all the genes in a particular organism are determined. The first complete viral genome was sequenced in 1977; it was performed on the bacteriophage phi-X-174. While this genome was quite small, it was nevertheless a landmark for genetic knowledge, in that scientists for the first time could study large-scale genetic structure, above the level of individual genes.

The Human Genome Project began in October 1990 as an international 13-year effort to discover all human genes within the complete sequence of the three-billion DNA bases in the human genome and make them accessible for further study. In parallel, the genomes of other, model organisms amenable to biological experimentation were also chosen for complete sequencing. The study was coordinated by the U.S. Department of Energy, the National Institutes of Health, the Human Genome Research Institute as well as private companies in the biotechnology industry, including Celera.

The genomic information from these studies accumulated rapidly in the late 1990s. In 1995, several bacterial genomes were completely sequenced. In 1996, a common yeast genome was sequenced, and in 1998, the genome of the nematode C. elegans was entirely sequenced. The genome of the fruit fly was totally sequenced in 2000. Finally, in 2001, working draft forms of the human genome sequence were published in special issues of Science and Nature.

DNA: COMPREHEND

73 companies
5.2 % of total industry
275487 Person-years of research

Companies in the "DNA:Comprehend" sector provide products and services for the analysis of DNA sequences and patterns of gene expression.

A major surprise came from the cross-species comparisons of these newly-determined genomes. Many scientists were shocked to find that, instead of the predicted 100,000 genes, the human genome contained approximately 31,780 genes. At that size, the human genome is a little larger than the genome of the Arabidopsis plant (approximately 25,000 genes), the worm (approximately 19,099 genes) or the fruit fly (approximately 13,601 genes). To many observers, the size of the human genome seems too small to store so much information. As with the old debate about the substrate of genes (DNA versus protein), scientists are again focused on the issues of genetic storage size versus functional complexity.

Some of these issues can be explored through more detailed analyses of both human and non-human genome sequences. Comparative genomics, the comparison of genomes across and within species, is becoming increasingly feasible. For example, the time and costs associated with DNA sequencing have been rapidly decreasing as improvements in technology are constantly being made. In 1980, sequencing 12,000 bases required one full year. In 1998, it took 20 minutes, and in 2002, 12,000 bases can be easily sequenced in less than one minute. Further, the cost of sequencing per base was about 10 dollars in 1990, and is less than 10 cents today. The human genome draft published last year cost more than 300 million dollars. In contrast, personal genome sequencing should be possible within the next 15 to 20 years at a cost of a few thousand dollars.

CELERA

Norwalk, CT
www.celera.com

Founded:	1998
Employees:	820
Public	(CRA)
Annual Revenue:	$89.4 million (2001)

Celera, a subsidiary of Applera, is well known for its pioneer efforts in sequencing the human genome and publishing a draft genome sequence in early 2001. At that time, the company was engaged in intense competition with public institutions such as the U.S. Department of Energy and the National Institutes of Health Human Genome Research Institute to rapidly complete an accurate draft genome sequence. Today, Celera is focused on discovering and developing new medical products by leveraging its capabilities in proteomics, bioinformatics, and genomics to identify and validate drug targets and diagnostic tests, and to discover new drug candidates.

BD BIOSCIENCES CLONTECH

Palo Alto, CA
www.clontech.com

Founded:	1984
Employees:	300
Public	(BDX)
Annual Revenue:	

Clontech, a division of BD Biosciences, manufactures chemicals, materials, proteins, and tool kits to enable scientists to conduct experiments in the areas of molecular biology, cell biology, and biochemistry. Products sold include restriction enzymes that recognize many different DNA sequences, and enzymes such as DNA polymerases and ligases to modify the structure of DNA.

DNA: CREATE

89 companies
6.5 % of total industry
264000+ person-years of research

Companies in the "DNA:Create" sector provide tools for the creation of new DNA structures, including the sysnthesis of DNA strands and their cutting and pasting into novel structures.

CREATE

Genetic engineering has transformed the modern biologist from an observer to an engineer; by intentionally constructing DNA in specific forms, the molecular basis of genetic diseases can be studied and cured. Many companies are focused on developing products to control the synthesis, manipulation, and inhibition of DNA.

The ability to control the structure of DNA has led to the creation of a thriving industry focused on providing the tools and reagents required for genetic engineering. These companies produce products for a wide variety of tools centered on DNA and gene cloning, nucleic acid separation and purification, gene synthesis, gene transfer, DNA synthesis, and DNA amplification.

The molecular basis for genetic information was borne out of two fundamental drivers: 1) a shift in thinking about DNA, in which scientists began to consider the possibility of actually changing DNA structure instead of simply studying it, and 2) increasing access to the naturally-present cellular proteins (enzymes) that permit restructuring DNA.

If one were to seek to modify a strand of DNA, it would be useful to have several tools: a cutting tool, a pasting tool, and a tool to ensure that the pasted joint was correctly structured. All three of these were developed within three years in the late 1960s.

In 1967 the enzyme called DNA ligase was discovered and isolated by Walter Gilbert at Harvard. This molecule was shown to join together two ends of nucleic acid strands, providing a kind of molecular glue for pasting together DNA.

In 1969, the first gene was sequenced, which provided an effective technique to determine the structure of both native, unchanged genes as well as intentionally-modified gene structures.

In 1970, restriction enzymes were discovered, which serve as a kind of molecular scissors that allows the cutting of DNA at precise positions. Restriction enzymes were used in the cell naturally to fight off foreign invaders; bacteria used restriction enzymes as a primitive “immune system” to detect and destroy foreign, viral DNA invading the cell. Since there are many kinds of viruses and viral DNA sequences, literally hundreds of different restriction enzymes have been discovered, each of which cuts at a different, unique DNA sequence.

Herbert Boyer and Stanley Cohen of Stanford University reported the first genetically-modified organism in 1973. They moved a single gene from

one organism to another. This was done by isolating a plasmid, a circular, self-replicating, independent DNA strand, and inserting a different DNA fragment into the plasmid through a cutting and pasting procedure. The genetically-engineered plasmid replicated in a stable, predictable fashion when placed in bacterial cells, and this tool provided the basis for gene cloning and molecular biology.

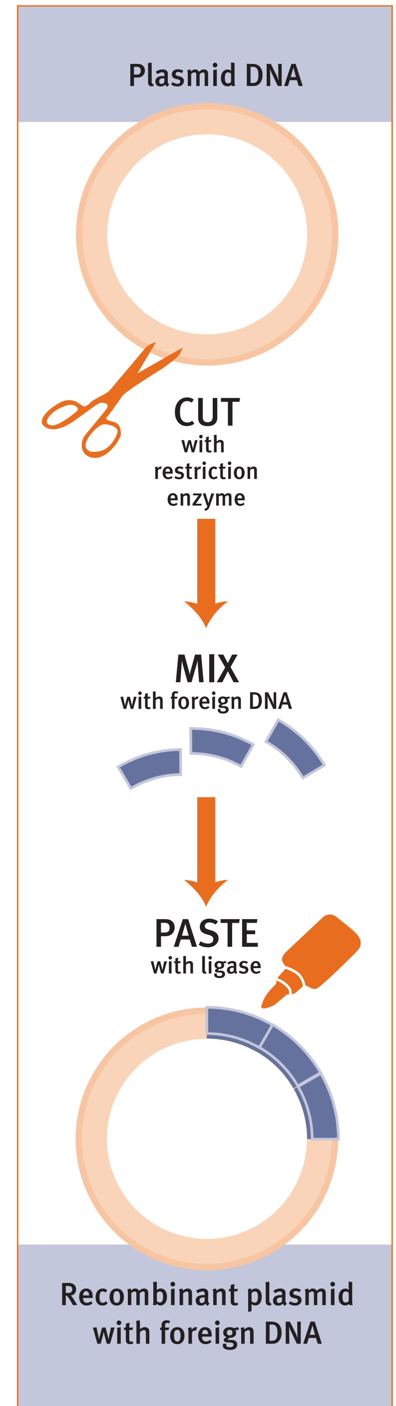
Polymerase Chain Reaction

A new and very powerful approach to genetic engineering was developed in 1983 called polymerase chain reaction (PCR). PCR has been described as finding a needle in a haystack and subsequently producing a pile of needles from the hay. In this process, a short stretch of DNA is selected and amplified about a million-fold. The specific stretch of DNA to be amplified, called the target sequence, is identified by a particular pair of short, synthetic DNA sequences, called primers, which define the end-points of the gene sequence to be amplified.

Since this amplification process is based on a positive feedback loop, it is possible to dramatically increase the amount of target sequence in just a few hours. This amplification can be used to raise the concentration of an unknown DNA sequence above a detection threshold, as would be useful in the detection of viral contaminants in blood, or for forensic investigators or archeologists to determine genetic identity with certainty. For molecular biology, PCR can be used to amplify a rare DNA sequence for synthetic gene construction.

Using DNA for Nanotechnology

Nanometer-scale fabrication processes typically require self-assembly through specific intermolecular interactions. As a well-studied, highly regular molecule, DNA is a good candidate for nano-scale device construction. First, the inter-ladder binding of DNA molecules occurs with high specificity, resulting in the formation of double-helical DNA. In addition, stable, branched DNA molecule can be used in intentional synthetic design. For example, four DNA molecules can be assembled into a quadrilateral. More complex structures have been formed by folding a long DNA strand into a polyhedron that can be ligated to form a periodic structure. This is done by folding the long DNA strand, using restriction enzymes to remove the DNA connecting the intended structure, and, by use of ligases, pasting the remaining pieces into a stable design. Several interesting structures have been fabricated in this manner, including trefoil knots with negative nodes, trefoil knots with positive nodes, figure-eight knots with half-positive and half-negative nodes, and Borromean rings. These structures can also perhaps be viewed as the first examples of nano-scale art.



DNA PRODUCTS AND INTELLECTUAL PROPERTY

Thomas Jefferson introduced the first patent bill to the U.S. Congress in 1790. It became the Patent Act, upon which U.S. patent and trademark law is built. However, this original act was never designed to encompass all the complexities encountered in the development of modern biotechnology products.

To fill in the gaps, U.S. patent law has been repeatedly extended. The U.S. Congress passed the Plant Patent Act (PPA) in 1930. This act extended patent protection to new and distinct asexually-propagated varieties. Since then nearly 7,000 plant patents have been issued. The passage of the PPA marked the first separation of the farmer from control of seed. In that the first "inventors" filing, patents granted under this act were not to farmers but rather nurseries and seed companies. Forty years later, the Plant Variety Protection Act (PVPA) of 1970 extended to plant breeders certain monopoly rights to new varieties of sexually-reproducing plants.

In 1980, a scientist named Chakrabarty (FIRST NAME?) developed a genetically-engineered bacterium capable of breaking down multiple components of crude oil. The patent examiner was unsure as to whether a claim to bacteria was permissible under U.S. patent law. Until this decision, no previous request had come before the patent office wherein a claim had been made for living material. The case made its way to the U.S. Supreme Court and it ruled that that living, genetically-engineered organisms are patentable material. The inherent patentability of life forms or biological material found naturally in life forms is highly controversial to this day.

Can the genes and DNA sequences already present within a person be patented by that person or another person? Who owns our common genetic heritage? Who owns unique variants of that heritage?

Further, when structure and function are dissociated from one another to improve a protein, as is done through molecular breeding, the new gene sequence is both novel and useful. Yet who owns it? Does it belong to the "owner" of the parent gene sequence? Or to the "inventor" who recombined the parental gene sequence in a new way? If the latter case were true, companies could breed each other's products and obviate the original patent protection, dramatically disrupting the competitive landscape of the pharmaceutical industry.