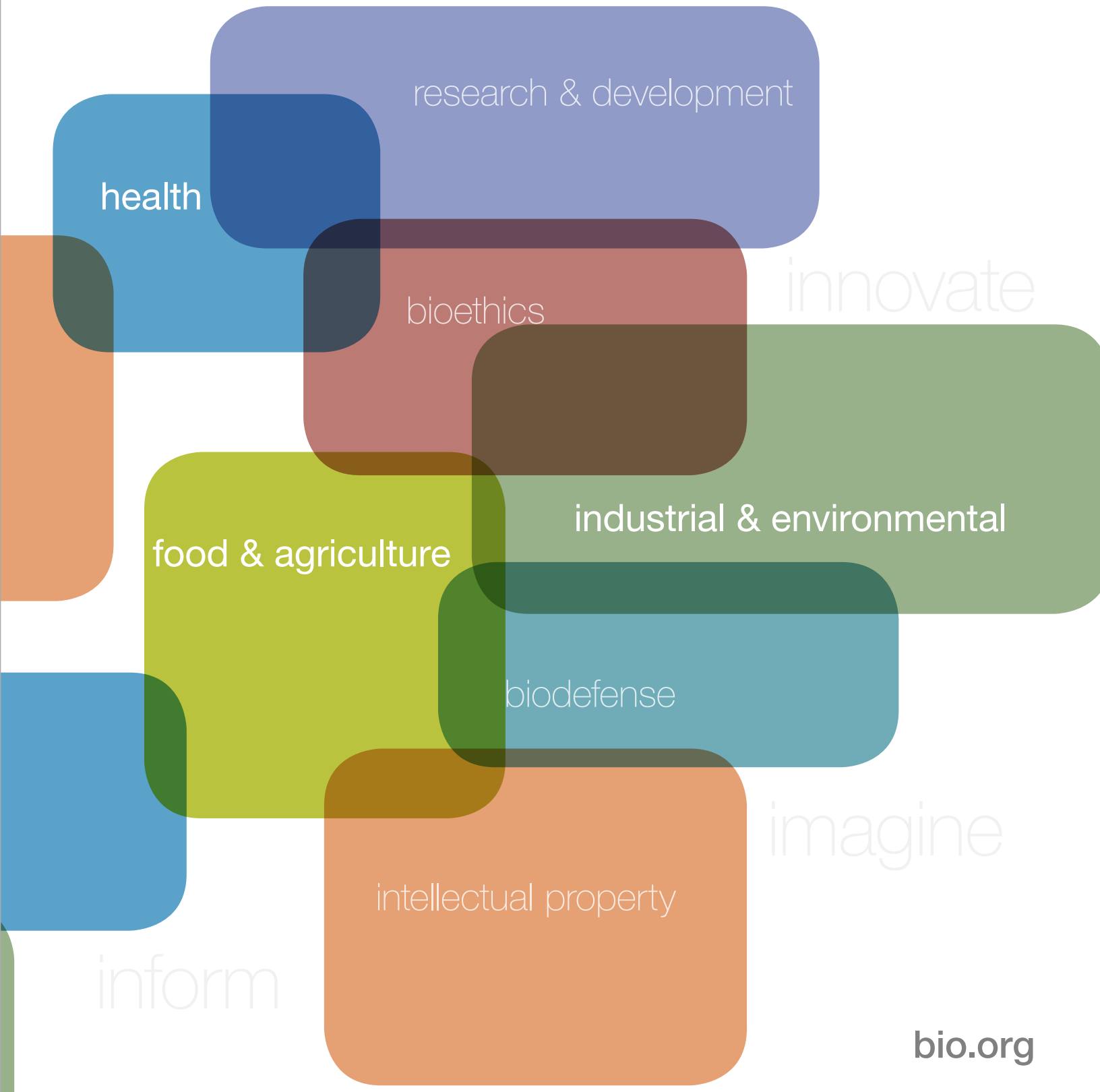
guide to biotechnology 2008

Bio
BIOTECHNOLOGY
INDUSTRY ORGANIZATION



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The *Guide to Biotechnology* is compiled by the
Biotechnology Industry Organization (BIO)

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biotechnology: A Collection of Technologies

What Is Biotechnology?

At its simplest, biotechnology is technology based on biology. From that perspective, the use of biological processes is hardly noteworthy. We began growing crops and raising animals 10,000 years ago to provide a stable supply of food and clothing. We have used the biological processes of microorganisms for 6,000 years to make useful food products, such as bread and cheese, and to preserve dairy products.

Crops? Cheese? That doesn't sound very exciting. So why does biotechnology receive so much attention?

The answer is that in the last 40 years we've gone from practicing biotechnology at a macro level—breeding animals and crops, for example—to working with it at a micro level. It was during the 1960s and '70s that our understanding of biology reached a point where we could begin to use the smallest parts of organisms—the biological molecules of which they are composed—in addition to using whole organisms.

An appropriate modern definition of biotechnology would be "the use of cellular and biomolecular processes to solve problems or make useful products."

We can get a better handle on the meaning of the word *biotechnology* by thinking of it in its plural form, *biotechnologies*. That's because biotechnology is a *collection* of technologies that capitalize on the attributes of cells, such as their manufacturing capabilities, and put biological molecules, such as DNA and proteins, to work for us.

Cells and Biological Molecules

Cells are the basic building blocks of all living things. The simplest living things, such as yeast, consist of a single, self-sufficient cell. Complex creatures more familiar to us, such as plants, animals and humans, are made of many different cell types, each of which performs very specific tasks.

In spite of the extraordinary diversity of cell types in living things, what is most striking is their remarkable similarity.

It turns out that all cells have the same basic design, are made of the same materials and operate using essentially the same processes. Almost all cells have a nucleus, which contains DNA that directs cell construction and operation. Cells share other structures as well, including those that manufacture proteins. This unity of life at the cellular level provides the foundation for biotechnology.

WHAT IS DNA?

DNA, or deoxyribonucleic acid, is the hereditary material in humans and almost all other organisms. Nearly every cell in a person's body has the same DNA. Most DNA is located in the cell nucleus (where it is called nuclear DNA), but a small amount of DNA can also be found in another part of the cell called the mitochondria (mitochondrial DNA or mtDNA).

The information in DNA is stored as a code made up of four chemical bases: adenine (A), guanine (G), cytosine (C) and thymine (T). Human DNA consists of about 3 billion bases, and more than 99 percent of those bases are the same in all people. The order, or sequence, of these bases determines the information available for building and maintaining an organism, similar to the way in which letters of the alphabet appear in a certain order to form words and sentences. No two people, except for identical twins, share the exact same DNA sequences.

DNA bases pair up with each other, A with T and C with G, to form units called base pairs. Each base is also attached to a sugar molecule and a phosphate molecule. Together, a base, sugar, and phosphate are called a nucleotide. Nucleotides are arranged in two long strands that form a spiral called a double helix. Long, continuous strands of DNA are organized into chromosomes. Human cells (except for the sex, or germ, cells) have 46 chromosomes, arranged in 23 pairs. Half come from the mother, half from the father.

Specific sections of DNA that carry the code for particular proteins are called genes. When a particular protein is needed, the DNA base pairs split, and RNA (ribonucleic acid) bases attach to the open DNA bases, forming a strand of mRNA (messenger RNA). The mRNA travels to other parts of the cell where the sequence of the mRNA is "read" by other cell structures that make the protein.

The NIH provides a well-illustrated primer on DNA and genetics, Help Me Understand Genetics. You can download it at http://ghr.nlm.nih.gov/.

WHY IS DNA THE CORNERSTONE OF BIOTECHNOLOGY?

Because virtually all cells speak the same genetic language, DNA from one cell can be read and acted on in another one—even a different cell type from a different species. This feature is what makes DNA the cornerstone of modern biotechnology. Scientists can,for example, use a yeast cell to make human insulin by inserting the human insulin gene into the yeast.

DNA is also the foundation for hundreds of diagnostic tests for genetic diseases and predisposition to disease. Some new tests can even identify which treatment, and what dosage, is best for a particular patient.

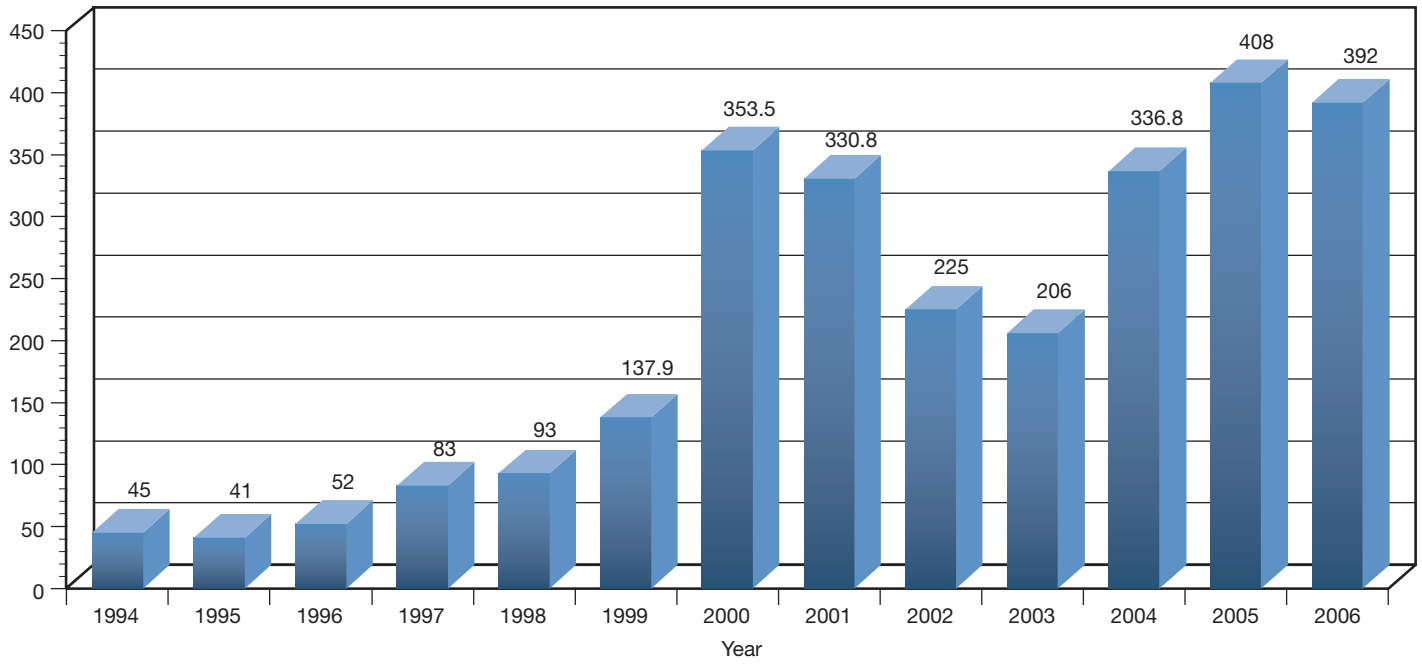
Because DNA and related cellular processes are so specific, biotechnology products can often solve problems with fewer unintended consequences than other approaches. In fact, the best words to describe today's biotechnology are *specific, precise* and *predictable*.

biotechnology
Industry Facts

- The biotechnology industry emerged in the 1970s, based largely on a **new recombinant DNA technique** whose details were published in 1973 by Stanley Cohen of Stanford University and Herbert Boyer of the University of California, San Francisco. Recombinant DNA is a method of making proteins—such as human insulin and other therapies—in cultured cells under controlled manufacturing conditions. Boyer went on to co-found Genentech, which today is biotechnology's largest company by market capitalization.
- Biotechnology has created **more than 200 new therapies and vaccines**, including products to treat cancer, diabetes, HIV/AIDS and autoimmune disorders.
- There are more than **400 biotech drug products and vaccines currently in clinical trials** targeting more than 200 diseases, including various cancers, Alzheimer's disease, heart disease, diabetes, multiple sclerosis, AIDS and arthritis.
- Biotechnology is responsible for hundreds of **medical diagnostic tests** that keep the blood supply safe from HIV and detect other conditions early enough to be successfully treated. Home pregnancy tests are also biotechnology diagnostic products.
- **Agricultural biotechnology** benefits farmers, consumers and the environment—by increasing yields and farm income, decreasing pesticide applications and improving soil and water quality, and providing healthful foods for consumers.
- **Environmental biotech** products make it possible to clean up hazardous waste more efficiently by harnessing pollution-eating microbes.
- **Industrial biotech applications** have led to cleaner processes that produce less waste and use less energy and water in such industrial sectors as chemicals, pulp and paper, textiles, food, energy, and metals and minerals. For example, most laundry detergents produced in the United States contain biotechnology-based enzymes.
- **DNA fingerprinting**, a biotech process, has dramatically improved criminal investigation and forensic medicine. It has also led to significant advances in anthropology and wildlife management.
- The biotech **industry** is regulated by the U.S. Food and Drug Administration (FDA), the Environmental Protection Agency (EPA) and the Department of Agriculture (USDA).
- As of Dec. 31, 2006, there were **1,452 biotechnology companies in the United States**, of which 336 were publicly held.*
- **Market capitalization**, the total value of publicly traded biotech companies (U.S.) at market prices, was $360 billion as of late April 2008 (based on stocks tracked by *BioWorld*).
- The biotechnology industry has mushroomed since 1992, with U.S. health care biotech **revenues** from publicly traded companies rising from $8 billion in 1992 to $58.8 billion in 2006.*
- Biotechnology is one of the most research-intensive industries in the world. U.S. publicly traded biotech companies spent $27.1 billion on **research and development** in 2006.*
- There were 180,000 employed in U.S. biotech companies in 2006.*
- The top five biotech companies invested an average of **$170,000 per employee** in R&D in 2007.
- In 1982, **recombinant human insulin** became the first biotech therapy to earn FDA approval. The product was developed by Genentech and Eli Lilly and Co.
- **Corporate partnering** has been critical to biotech success. According to *BioWorld*, in 2007 biotechnology companies struck 417 new partnerships with pharmaceutical companies and 473 deals with fellow biotech companies. The industry also saw 126 mergers and acquisitions.
- Most biotechnology companies are young companies developing their first products and depend on **investor capital** for survival. According to *BioWorld*, biotechnology attracted more than $24.8 billion in financing in 2007 and raised more than $100 billion in the five-year span of 2003–2007.
- The biosciences—including all life-sciences activities—**employed 1.2 million people** in the United States in 2004 and generated an additional 5.8 million related jobs.**
- The **average annual wage** of U.S. bioscience workers was $65,775 in 2004, more than $26,000 greater than the average private-sector annual wage.**
- The **Biotechnology Industry Organization** (BIO) was founded in 1993 to represent biotechnology companies at the local, state, federal and international levels. BIO comprises more than 1,200 members, including biotech companies, academic centers, state and local associations, and related enterprises.

* New data are expected in mid-2008 from Ernst & Young, which publishes an annual global overview of the biotechnology industry.
** The data are from a BIO-sponsored Battelle Memorial Institute report, *Growing the Nation's Biotech Sector: State Bioscience Initiatives 2006.* A new, updated report is expected to be released in 2008.

Market Capitalization, 1994–2006*



Sources:
Ernst & Young LLP**

U.S. Biotech Industry Statistics: 1994–2006*

Year	2006	2005	2004	2003	2002	2001	2000	1999	1998	1997	1996	1995	1994
Sales	45.3	39.7	28.1	28.4	24.3	21.4	19.3	16.1	14.5	13	10.8	9.3	7.7
Revenues	53.5	48.5	43.8	39.2	29.6	29.6	26.7	22.3	20.2	17.4	14.6	12.7	11.2
R&D Expense	22.9	16.6	19.6	17.9	20.5	15.7	14.2	10.7	10.6	9.0	7.9	7.7	7.0
Net Loss	3.5	1.4	6.8	5.4	9.4	4.6	5.6	4.4	4.1	4.5	4.6	4.1	3.6
No. of Public Companies	336	331	331	314	318	342	339	300	316	317	294	260	265
No. of Companies	1,452	1,475	1,346	1,473	1,466	1,457	1,379	1,273	1,311	1,274	1,287	1,308	1,311

Source:
Ernst & Young LLP, annual biotechnology industry reports, 1995–2006. Financial data based primarily on fiscal-year financial statements of publicly traded companies.**

*Amounts are U.S. dollars in billions.

** New data are expected in mid-2008 from Ernst & Young, which publishes an annual global overview of the biotechnology industry.

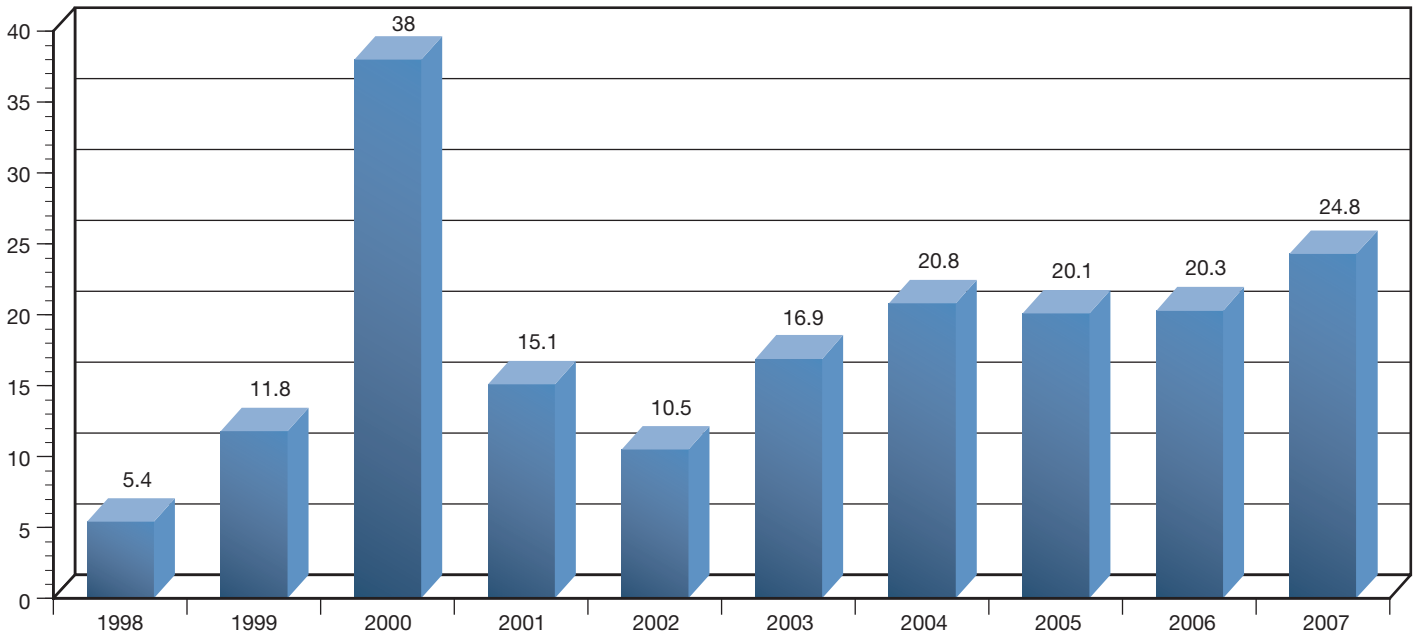
U.S. Public Companies by Region, 2006

REGION	NO. PUBLIC COS.	MARKET CAP.*	REVENUE*	R&D*
San Francisco Bay Area	69	$145,553	$17,668	$7,485
New England	60	$62,936	$10,384	$3,919
San Diego	38	$20,916	$3,252	$1,432
New Jersey	28	$28,556	$1,747	$802
Mid-Atlantic	23	$17,111	$2,061	$1,270
Southeast	19	$5,301	$544	$271
New York State	17	$8,893	$1,373	$685
Mid-West	8	$1,161	$121	$90
Pacific Northwest	15	$4,928	$196	$521
Los Angeles/Orange County	11	$81,585	$14,692	$4,898
North Carolina	9	$2,017	$328	$191
Pennsylvania/Delaware Valley	12	$7,140	$2,078	$603
Texas	11	$1,495	$160	$170
Colorado	6	$1,847	$296	$195
Utah	2	$1,454	$160	$170
Other	8	$1,526	$384	$107

* Amounts are in millions of U.S. dollars.

Source:
Ernst & Young LLP

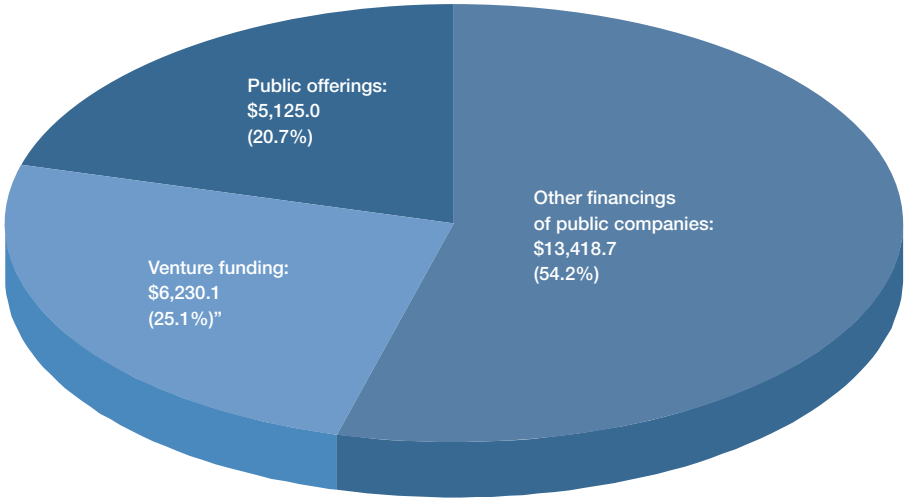
Total Financing, 1998–2007 (in billions of U.S. dollars)



Source:
BioWorld

Biotech Industry Financing

Total: $24,773.8 Million
(all figures in millions)



Source:
BioWorld

time line

8000 B.C.

- Humans domesticate crops and livestock.
- Potatoes are first cultivated for food.

4000–2000 B.C.

- Biotechnology is first used to leaven bread and ferment beer with yeast (Egypt).
- Production of cheese and fermentation of wine begin (Sumeria, China and Egypt).
- Babylonians control date palm breeding by selectively pollinating female trees with pollen from certain male trees.

500 B.C.

- The first antibiotic is put to use: moldy soybean curds used to treat boils (China).

A.D. 100

- Powdered chrysanthemums are the first insecticide (China).

1322

- An Arab chieftain first uses artificial insemination to produce superior horses.

1590–1608

- The compound microscope is invented in the Netherlands. There is some dispute about who exactly should be credited with the invention; Hans Jansen, his son Zacharias Jansen and Hans Lippershey has each been credited with the breakthrough.

1663

- English physicist Robert Hooke discovers existence of the cell.

1675

- Dutch scientist Antonie van Leeuwenhoek discovers bacteria.

1761

- German botanist Joseph Koelreuter (also spelled Josef Kölreuter and Kohlreuter) reports successful crossbreeding of crop plants in different species.

1797

- English surgeon Edward Jenner pioneers vaccination by inoculating a child with a viral vaccine to protect him from smallpox.

1830–1833

- 1830—Proteins are discovered.
- 1833—The first enzyme is discovered and isolated.

1835–1855

- German scientists Mathias Schleiden and Theodor Schwann propose that all organisms are composed of cells, and German pathologist Rudolf Virchow declares, "Every cell arises from a cell."

1857

- French chemist and microbiologist Louis Pasteur proposes microbes cause fermentation.

1859

- English naturalist Charles Darwin publishes the theory of evolution by natural selection. The concept of carefully selecting parents and culling the variable progeny greatly influences plant and animal breeders in the late 1800s despite their ignorance of genetics.

1865

- The science of genetics begins: Austrian monk Gregor Mendel studies garden peas and discovers that genetic traits are passed from parents to offspring in a predictable way—the laws of heredity. Mendel's discoveries were largely ignored until the early 20th century.

1870–1890

- Using Darwin's theory, plant breeders crossbreed cotton, developing hundreds of varieties with superior qualities.
- Farmers first add nitrogen-fixing bacteria to fields to improve yields.
- American botanist William James Beal produces first experimental corn hybrid in the laboratory. Beal also started the world's longest-running (and still ongoing) study of seed viability.
- 1877—A technique for staining and identifying bacteria is developed by German physician and early bacteriologist Robert Koch.
- 1878—The first centrifuge is developed by Swedish engineer and inventor Gustaf de Laval.
- 1879—Walther Flemming, a physician and one of the founders of the study of cytogenetics, discovers chromatin, the

rod-like structures inside the cell nucleus that later came to be called chromosomes.

1897

- German biochemist Eduard Buchner discovers that specialized proteins (enzymes) are responsible for converting sugar to alcohol.

1900

- Fruit flies (*Drosophila melanogaster*) are used in early studies of genes. The fruit fly remains an important model organism today.
- American agronomist and inventor George Washington Carver seeks new industrial uses for agricultural feedstocks such as peanuts and soybeans.

1902

- The term *immunology* first appears.

1906

- The term *genetics* is introduced.

1911

- American pathologist Peyton Rous discovers the first cancer-causing virus.

1914

- Bacteria are used to treat sewage for the first time in Manchester, England.

1915

- Phages, or bacterial viruses, are discovered.

1919

- The word *biotechnology* is first used in print.

1920

- American scientists Herbert McLean Evans and Joseph Long isolate human growth hormone.

1928

- Scottish scientist Alexander Fleming discovers penicillin.
- A small-scale test of formulated *Bacillus thuringiensis* (Bt) for corn borer control begins in Europe. Commercial production of this biopesticide begins in France in 1938.

- Russian scientist Georgii Karpechenko crosses radishes and cabbages, creating fertile offspring between plants in different genera.
- German botanist Friedrich Laibach first uses embryo rescue to obtain hybrids from wide crosses in crop plants—known today as hybridization.

1930

- U.S. Congress passes the Plant Patent Act, enabling the products of plant breeding to be patented.

1933

- Hybrid corn, developed by Henry Wallace in the 1920s, is commercialized. Growing hybrid corn eliminates the option of saving seeds. The remarkable yields outweigh the increased costs of annual seed purchases, and by 1945, hybrid corn accounts for 78 percent of U.S.-grown corn.

1938

- The term *molecular biology* is coined.

1941

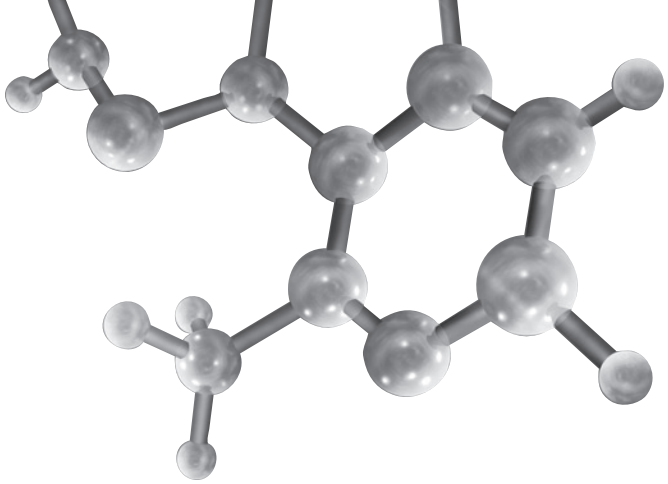
- The term *genetic engineering* is first used, by Danish microbiologist A. Jost in a lecture on reproduction in yeast at the technical institute in Lwow, Poland.

1942

- The electron microscope is used to identify and characterize a bacteriophage—a virus that infects bacteria.
- Penicillin is mass-produced in microbes.

1943

- German botanist Friedrich Laibach proposes *Arabidopsis thaliana* as a model organism for plant genetic research.



1944
- Canadian-born American bacteriologist Oswald Avery and colleagues discover that DNA carries genetic information.
- Ukranian-born American biochemist Selman Waksman isolates streptomycin, an effective antibiotic for tuberculosis.

1946
- Scientists discover that genetic material from different viruses can be combined to form a new type of virus, an example of genetic recombination.

1947
- American plant cytogeneticist Barbara McClintock discovers transposable elements, or "jumping genes," in corn.

1949
- American chemist Linus Pauling shows that sickle cell anemia is a "molecular disease" resulting from a mutation in the protein molecule hemoglobin.

1951
- Artificial insemination of livestock using frozen semen is accomplished.

1953
- The scientific journal *Nature* publishes James Watson and Francis Crick's manuscript describing the double helical structure of DNA, which marks the beginning of the modern era of genetics.

1955
- An enzyme involved in the synthesis of a nucleic acid is isolated for the first time.

1956
- American biochemist and physician Arthur Kornberg discovers the enzyme DNA polymerase I, leading to an understanding of how DNA is replicated.

1958
- Sickle cell anemia is shown to occur due to a change of a single amino acid.
- DNA is made in a test tube for the first time.

1959
- Systemic fungicides are developed. The steps in protein biosynthesis are delineated.

ALSO IN THE 1950s
- Interferons are discovered.
- The first synthetic antibiotic is created.

1960
- Exploiting base pairing, hybrid DNA-RNA molecules are created.
- Messenger RNA is discovered.

1961
- USDA registers the first biopesticide: *Bacillus thuringiensis*, or Bt.

1963
- New wheat varieties developed by American agricultural scientist Norman Borlaug increase yields by 70 percent.

1964
- The International Rice Research Institute in the Philippines starts the Green Revolution with new strains of rice that double the yield of previous strains if given sufficient fertilizer.

1965
- Henry Harris and John Watkins at the University of Oxford successfully fuse mouse and human cells.

1966
- The genetic code is cracked, demonstrating that a sequence of three nucleotide bases (a codon) determines each of 20 amino acids. (Two more amino acids have since been discovered.)

1967
- The first automatic protein sequencer is perfected.

1969
- An enzyme is synthesized *in vitro* for the first time.

1970
- Norman Borlaug receives the Nobel Peace Prize (see 1963).
- Scientists discover restriction enzymes that cut and splice genetic material, opening the way for gene cloning.

1971
- The first complete synthesis of a gene is completed.

1972
- American biochemist Paul Berg publishes the results of his work creating the first DNA molecules that combine genes from different organisms.
- The DNA composition of humans is discovered to be 99 percent similar to that of chimpanzees and gorillas.
- Initial work is done with embryo transfer.

1973
- American biochemists Stanley Cohen and Herbert Boyer perfect techniques to cut and paste DNA (using restriction enzymes and ligases) and reproduce the new DNA in bacteria.

1974
- The National Institutes of Health (NIH) forms a Recombinant DNA Advisory Committee to oversee recombinant genetic research.
- Research using genetically enhanced microbes for industrial applications begins.

1975
- The first monoclonal antibodies are produced.

1976
- The tools of recombinant DNA (rDNA) are first applied to a human inherited disorder.
- Molecular hybridization is used for the prenatal diagnosis of alpha thalassemia.
- Yeast genes are expressed in *E. coli* bacteria.
- The sequence of DNA base pairs for a specific gene is determined.
- First guidelines for recombinant DNA experiments released: National Institutes of Health–Recombinant DNA Advisory Committee.
- Recombinant DNA pioneer Herbert Boyer co-founds Genentech, the first company based on the technology.

1977
- A human gene is expressed in bacteria for the first time.
- Procedures are developed for rapidly sequencing long sections of DNA using electrophoresis.

1978
- The high-level structure of a virus is first identified.
- Recombinant human insulin is first produced.
- North Carolina scientists show it is possible to introduce specific mutations at specific sites in a DNA molecule.

1979
- Human growth hormone is first synthesized.

ALSO IN THE 1970s
- Techniques for rapid sequencing of nucleotides are perfected.

1980
- The U.S. Supreme Court, in the landmark case *Diamond v. Chakrabarty*, approves the principle of patenting organisms, which allows the Exxon oil company to patent an oil-eating microorganism.
- The U.S. patent for gene cloning is awarded to American biochemists Stanley Cohen and Herbert Boyer.
- The first gene-synthesizing machines are developed.
- Researchers successfully introduce the human gene for interferon into a bacterium.
- Paul Berg, Walter Gilbert and Frederick Sanger receive the Nobel Prize in Chemistry for creation of the first recombinant molecule.

1981
- Scientists at Ohio University produce the first transgenic animals by transferring genes from other animals into mice.
- A Chinese scientist becomes the first to clone a fish—a golden carp.

1982
- Applied Biosystems, Inc., introduces the first commercial gas phase protein sequencer, dramatically reducing the amount of protein sample needed for sequencing.
- The first recombinant DNA vaccine for livestock is developed.
- The first biotech drug is approved by FDA: human insulin produced in genetically modified bacteria. Genentech and Eli Lilly developed the product.
- The first genetic transformation of a plant cell occurs, using the petunia.

1983

- American biochemist Kary Mullis invents the polymerase chain reaction (PCR) technique. PCR, which uses heat and enzymes to make unlimited copies of genes and gene fragments, later becomes a major tool in biotech research and product development worldwide.
- The first genetic transformation of plant cells by TI plasmids is performed.
- The first artificial chromosome is synthesized.
- The first genetic markers for specific inherited diseases are found.
- Biotechnology is used to grow a whole plant, the petunia. The petunia passes its new traits to offspring.

1984

- The DNA fingerprinting technique (using PCR) is developed.
- The entire genome of the human immunodeficiency virus (HIV) is cloned and sequenced.

1985

- Genetic markers are found for kidney disease and cystic fibrosis.
- Genetic fingerprinting is entered as evidence in a courtroom.
- Transgenic plants resistant to insects, viruses and bacteria are field-tested for the first time.
- The NIH approves guidelines for performing gene-therapy experiments in humans.

1986

- The first recombinant vaccine for humans is approved, a vaccine for hepatitis B.
- Interferon becomes the first anticancer drug produced through biotech.
- Scientists at the Scripps Institute and the University of California–Berkeley describe how to combine antibodies and enzymes (abzymes). Abzymes show potential to break chemical bonds, including protein peptide bonds, with great precision.
- The first field tests of transgenic plants (tobacco) are conducted.
- The Environmental Protection Agency approves the release of the first transgenic crop—gene-altered tobacco plants.
- The Organization of Economic Cooperation and Development (OECD) Group of National Experts on Safety in Biotechnology states: "Genetic changes from rDNA techniques will often have inherently greater predictability compared to traditional techniques" and "risks associated with rDNA organisms may be assessed in generally the same way as those associated with non-rDNA organisms."
- Microbes are first used to clean up an oil spill. (The first industrial biotech patent ever issued was for a microbe to clean up oil spills; see 1980.)

1987

- The first field test for a biotech crop—virus-resistant tomatoes—is approved.
- Frostban, a genetically altered bacterium that inhibits frost formation on crop plants, is field-tested on strawberry and potato plants in California, the first authorized outdoor tests of a recombinant bacterium.

1988

- Harvard molecular geneticists are awarded the first U.S. patent for a genetically altered animal—a transgenic mouse.
- A patent for a process to make bleach-resistant protease enzymes to use in detergents is awarded.
- Juries in the U.S. and the U.K. deliver the first murder convictions based on DNA evidence.

1989

- The first field test for biotech cotton—an insect-protected (Bt) variety—is approved.
- The Plant Genome Project begins.
- The first DNA fingerprinting–based exoneration occurs. As of April 2008, 216 people had been exonerated through DNA, according to The Innocence Project.

ALSO IN THE 1980s

- Studies of DNA are used to determine evolutionary history.
- A recombinant DNA animal vaccine is approved for use in Europe.
- Ribozymes and retinoblastomas are identified.

1990

- Chy-Max™, an artificially produced form of the chymosin enzyme for cheese-making, is introduced. It is the first product of recombinant DNA technology in the U.S. food supply.
- The Human Genome Project—an international effort to map all the genes in the human body—is launched.
- The first experimental gene therapy treatment is performed successfully on a 4-year-old girl suffering from an immune disorder.
- The first transgenic dairy cow—used to produce human milk proteins for infant formula—is created.
- The first insect-protected biotech corn is produced: Bt corn.
- The first food product of biotechnology is approved in U.K.: modified yeast.
- The first field test of a genetically modified vertebrate—trout—is initiated.

1992

- American and British scientists unveil a technique for testing embryos *in vitro* for genetic abnormalities such as cystic fibrosis and hemophilia.
- The FDA declares that transgenic foods are "not inherently dangerous" and do not require special regulation.

1993

- Merging two smaller trade associations creates the Biotechnology Industry Organization (BIO).
- FDA approves recombinant bovine somatotropin (rBST) for increased milk production in dairy cows. The product (rBST) is commercialized as POSILAC®.
- FDA approves Betaseron® (interferon beta-1a), the first of several biotech products that have had a major impact on multiple sclerosis treatment.

1994

- FDA approves the first whole food produced through biotechnology: FLAVRSAVR™ tomato.
- The first breast-cancer gene is discovered.
- Pulmozyme® (dornase alfa), a recombinant version of human DNase, is approved. The drug breaks down protein accumulation in the lungs of cystic fibrosis patients.

1995

- The first baboon-to-human bone marrow transplant is performed on an AIDS patient.
- The first full gene sequence of a living organism other than a virus is completed, for the bacterium *Haemophilus influenzae*.
- Gene therapy, immune-system modulation and recombinantly produced antibodies enter the clinic in the war against cancer.

1996

- The discovery of a gene associated with Parkinson's disease provides an important new avenue of research into the cause and potential treatment of the debilitating neurological ailment.
- Farmers plant biotech staple crops—corn, soybeans and cotton—for the first time.
- The genome sequence of the microorganism *Methanococcus jannaschii* confirms that there is a third main branch of life on Earth, along with bacteria and eukaryotes (fungi, protists, plants and animals). The third branch is called Archaea.

1997

- Dolly the sheep is unveiled in Scotland as the first animal cloned from an adult cell.
- The first weed- and insect-resistant biotech crops are commercialized: Roundup Ready® soybeans and Bollgard® insect-protected cotton.
- Biotech crops are grown commercially on nearly 5 million acres worldwide. The crops are grown in Argentina, Australia, Canada, China, Mexico and the United States.
- Rituxan® (rituximab) is the first anticancer monoclonal antibody to win FDA approval.
- A group of Oregon researchers claims to have cloned two Rhesus monkeys.
- The first industrially relevant gram-positive microorganism (*Bacillus subtilis*) genome is sequenced.
- DHA and ALA oil produced from biotech-enhanced microalgae are introduced into worldwide markets.

1998

- Human embryonic stem cell lines are established.
- The FDA approves the breast cancer drug Herceptin® (trastuzumab) for patients whose cancer overexpresses the HER2

receptor. It is widely considered the first pharmacogenomic (or personalized) medicine.

- The Perkin-Elmer Corp. enlists American biologist Craig Venter to a head a new company called Celera Genomics whose goal is to sequence the human genome faster than the Human Genome Project. (Celera has since been absorbed by Applera Corp.)
- University of Hawaii scientists clone three generations of mice from nuclei of adult ovarian cumulus cells.
- Scientists at Japan's Kinki University clone eight identical calves using cells taken from a single adult cow.
- The first complete animal genome, for the *C. elegans* roundworm, is sequenced.
- An early rough draft of the human genome map is produced, showing the locations of thousands of genes.
- Five Southeast Asian countries form a consortium to develop disease-resistant papayas.
- The first gene chip for transcriptional profiling of an industrial organism is designed.

1999

- The U.K.'s Wellcome Trust joins forces with 10 large pharmaceutical companies to create The SNP Consortium, whose goal is to find and map 300,000 common single nucleotide polymorphisms (SNPs) in the human genome.
- The Human Genome Project completes the first finished, full-length sequence of a human chromosome, chromosome 22. The HGP moves up the date for a complete human genome draft to 2000.
- For the first time, investors put more than $10 billion into the biotech industry. Investment has never since dipped below that level.
- A new diagnostic test allows quick identification of Bovine Spongiform Encephalopathy (BSE, also known as "mad cow" disease) and Creutzfeldt-Jakob Disease (CJD).
- Jessie Gelsinger's death in a human gene-therapy experiment triggers increased scrutiny of the technology.

ALSO IN THE 1990s

- A defective DNA repair gene is discovered and linked to hereditary colon cancer.
- A recombinant rabies vaccine is tested in raccoons.
- A biotechnology-based biopesticide is approved for sale in the United States.
- The first European patent on a transgenic animal is issued for a transgenic mouse sensitive to carcinogens.

2000

- A rough draft of the human genome sequence is announced.
- The first complete map of a plant genome is developed: *Arabidopsis thaliana*.
- Biotech crops are grown on 108.9 million acres in 13 countries.
- Developers of transgenic rice enhanced with beta carotene—"Golden Rice"—announce they will make the technology available to developing countries in hopes of improving the health of undernourished people and preventing some forms of blindness.
- Kenya field tests its first biotech crop: virus-resistant sweet potato.

2001

- Researchers with China's National Hybrid Rice Research Center report developing a "super rice" that could produce double the yield of normal rice.
- Genome sequences are completed of the agriculturally important bacteria *Sinorhizobium meliloti*, a nitrogen-fixing species, and *Agrobacterium tumefaciens*, a plant pest.
- A single gene from *Arabidopsis* is inserted into tomato plants to create the first crop able to grow in salty water and soil.
- The world's first biorefinery opens in Blair, Neb., to convert sugars from field corn into polylactic acid (PLA)—a composite biopolymer that can be used to produce packaging materials, clothing and bedding products.
- The FDA approves an gene-targeted drug called Gleevec® (imatinib) to treat patients with chronic myeloid leukemia. It is hailed as the first of what is hoped will be a series of new cancer drugs based directly on genetic discoveries.

2002

- A draft sequence of the rice genome is completed, marking the first genome sequence of a major food crop.
- The first draft of a functional map of the yeast proteome, an entire network of protein complexes and their interactions, is completed.

- International consortiums sequence the genomes of the parasite that causes malaria and the species of mosquito that transmits the parasite.
- The draft version of the complete map of the human genome is published.
- Scientists are forced to rethink their view of RNA when they discover how important small pieces of RNA are in controlling many cell functions.
- Scientists make great progress in elucidating the factors that control the differentiation of stem cells, identifying more than 200 genes that are involved in the process.
- Researchers announce successful results for a vaccine against cervical cancer, the first demonstration of a preventative vaccine for a type of cancer.
- Scientists complete the draft sequence of the most important pathogen of rice, a fungus that destroys enough rice to feed 60 million people annually.
- The Japanese pufferfish genome is sequenced. The pufferfish sequence is the smallest known genome of any vertebrate.
- Scientists at Stony Brook University in New York assemble a synthetic virus, polio, using genome sequence information.

2003

- Brazil and the Philippines grow biotech crops for the first time.
- The U.S. Environmental Protection Agency approves the first transgenic rootworm-resistant corn, which may save farmers $1 billion annually in crop losses and pesticide use.
- An endangered species (the banteng) is cloned for the first time. 2003 also brought several other cloning firsts, including mules, horses and deer.
- Dolly, the cloned sheep that made headlines in 1997, is euthanized after developing progressive lung disease.
- Japanese researchers develop a biotech coffee bean that is naturally decaffeinated.
- China grants the world's first regulatory approval of a gene therapy product. Gendicine, developed by Shenzhen SiBiono GenTech, delivers the p53 gene as a therapy for squamous cell head and neck cancer.
- McKinsey & Co. projects industrial biotechnology could reach $160 billion in value by 2010.
- FDA approves the first nasal-mist influenza vaccine, FluMist®.

2004

- The FDA approves the first anti-angiogenic drug for cancer, Avastin® (bevacizumab).
- The FDA clears a DNA microarray test system, the AmpliChip® Cytochrome P450 Genotyping Test, to aid in selecting medications for a wide variety of common conditions.
- An RNA-interference (RNAi) product for age-related "wet" macular degeneration becomes the first RNAi product to enter a clinical trial.
- GloFish®, the first biotech pet, hits the North American market.
- The United Nations Food and Agriculture Organization endorses biotech crops.
- The National Academy of Sciences' Institute of Medicine (IOM) finds biotech crops pose no more health risks than do crops created by other techniques. The IOM recommends basing food-safety evaluations on the resulting food product, not the technique used to create it.
- FDA finds a type of biotech wheat safe after a food safety review.
- The chicken genome is sequenced by the Chicken Genome Sequencing Consortium.
- The first cloned pet, a kitten, is delivered to its owner.
- The laboratory-rat genome is sequenced.
- Researchers complete the sequence of the chimpanzee—humanity's closest primate relative.
- The Canadian biotech company Iogen achieves the first commercial production and delivery of bioethanol, producing the fuel with biotech enzymes and wheat straw.

2005

- Researchers at the University of Georgia successfully produce a cow cloned from the cells of a carcass.
- FDA for the first time approves a drug for a specific race. The drug, BiDil®, treats congestive heart failure in self-identified black patients.
- The Energy Policy Act is passed and signed into law, authorizing numerous incentives for bioethanol development.

- The National Institutes of Health launches a pilot project to determine the feasibility of The Cancer Genome Atlas. The ultimate goal would be a complete map of the genomic changes involved in all types of human cancer.
- Scientists at the Centers for Disease Control & Prevention partially synthesize the flu virus that killed at least 20 million people worldwide in 1918–1919.
- Scientists at Harvard University report success in converting skin cells into embryonic stem cells through fusion with existing embryonic stem cells.
- On May 7, the one billionth acre of biotech seed is planted.
- The World Health Organization (WHO) issues *Modern Food Biotechnology, Human Health and Development*, which concludes biotech foods can enhance human health and economic development.
- The British research firm PG Economics Ltd. finds that the global use of biotech crops has added $27 billion to farm income and reduced agriculture's environmental impact.
- A consortium of scientists led by the National Human Genome Research Institute publishes the dog genome. It belongs to a 12-year-old boxer.
- The first enzymes for low-energy (cold) ethanol production are commercialized as corn-derived ethanol production hits 4 billion gallons per year.

2006

- The American Dietetic Association publishes a reaffirmed statement of support for agricultural and food biotechnology.
- Dow AgroSciences wins the first regulatory approval for a plant-made vaccine. The vaccine protects poultry from Newcastle disease.
- Renessen LLC receives approval to begin selling animal feed made from high-lysine biotech corn. Lysine is essential in animal diets, especially those of swine and poultry.
- Researchers develop biotech pigs that produce high levels of omega-3 fatty acids with the help of a gene from the roundworm *C. elegans*.
- FDA approves the recombinant vaccine Gardasil®, the first vaccine developed against human papillomavirus (HPV), an infection implicated in cervical and throat cancers.

2007

- Researchers at the University of Wisconsin, Madison, and Kyoto University in Japan announce successful reprogramming of human skin cells to create cells indistinguishable from embryonic stem cells.
- Researchers at Children's Hospital Boston and the Harvard Stem Cell Institute determine that discredited Korean scientist Hwang Woo-Suk created the world's first embryonic stem cell line derived from parthenogenesis.
- The FDA approves the H5N1 vaccine, the first vaccine approved for avian flu.
- University of Buffalo researchers describe the central mechanism of action for enzymes.
- Taiwanese researchers develop a biotech eucalyptus tree that ingests up to three times more carbon dioxide than conventional varieties. The biotech eucalyptus also produces less lignin and more cellulose.
- Korean researchers unveil the first-ever poodle clone.
- U.S. researchers announce the production of biotech cattle that cannot develop prion proteins. Prions have been implicated in the degenerative neurological disease bovine spongiform encephalopathy.

2008

- The draft corn genome sequence is completed. It is only the third plant genome to be completed, after *Arabidopsis* and rice.

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Biotechnology Policy Milestones

1902

- The Biologics Control Act passes to ensure purity and safety of serums, vaccines and similar products.

1906

- The Food and Drugs Act is signed into law, prohibiting interstate commerce in misbranded and adulterated food, drinks and drugs. (Note: For a detailed FDA timeline, visit http://www.fda.gov/opacom/backgrounders/miles.html.)

1930

- The National Institute of Health is created (later to become the National Institutes of Health as new research institutes in specific disease or research areas are added).

1938

- Congress passes The Federal Food, Drug, and Cosmetic (FDC) Act of 1938, one of a handful of core laws governing the FDA. Among other provisions, the FDC Act requires new drugs to be shown safe before marketing. Thus begins a new system of drug regulation.

1946

- Recognizing the threat posed by loss of genetic diversity, the U.S. Congress provides funds for systematic and extensive plant collection, preservation and introduction.

1962

- Thalidomide, a new sleeping pill, is found to have caused birth defects in thousands of babies born in Western Europe. The Kefauver-Harris Drug Amendments are passed to require drug makers to demonstrate efficacy and greater drug safety. The biggest change is that, for the first time, drug manufacturers are required to prove to FDA the effectiveness of their products before marketing them.

1965

- President Johnson signs H.R. 6675 to establish Medicare health insurance for the elderly (coverage for the disabled was added in 1972) and Medicaid for the indigent. Although Medicare covers drugs used in clinics and hospitals, it omits outpatient prescriptions—a gap that will grow in significance as pharmaceuticals, including many biotech drugs, become a more important component of care. (See the Kaiser Family Foundation's complete Medicare timeline at http://www.kff.org/medicare/timeline/pf_entire.htm for more details.)

1971

- President Nixon calls for a War on Cancer and signs the National Cancer Act into law, stimulating new research.

1974

- Leading biologists call for a voluntary moratorium on recombinant DNA experiments while safety standards are set.

1975

- Some 150 scientists, attorneys, government officials and journalists meet at the Asilomar Conference Center near Monterey, Calif., to discuss recombinant DNA research and develop strict safety protocols.

1976

- The NIH adopts guidelines for federally funded recombinant DNA research, with oversight provided by the Recombinant DNA Advisory Committee.

1980

- The Supreme Court decides in *Diamond vs. Chakrabarty* that "anything under the sun that is made by the hand of man," including biotechnology-modified organisms, is patentable. The decision helps open the floodgates to a wave of investment that includes the first biotech IPOs.
- The Patent and Trademark Act Amendments of 1980—commonly known as the Bayh-Dole Act—lay the ground rules for technology transfer from academia to industry. The act creates a uniform patent policy among federal agencies that

fund research and specifies that federal grant recipients—such as universities and small businesses—own federally funded inventions.

1983

- The Orphan Drug Act is signed into law, creating new incentives to conduct R&D on therapies for rare diseases. More than 250 orphan drugs have reached the U.S. market in the years since.
- Congress creates the Small Business Innovation Research (SBIR) grant program, a boon to cutting-edge biotech research at small companies.

1986

- The U.S. government publishes the *Coordinated Framework for Regulation of Biotechnology*, establishing more stringent regulations for rDNA organisms used in agriculture than for those produced with traditional genetic modification techniques. The framework clarifies the agricultural biotech responsibilities of the Food & Drug Administration, the U.S. Department of Agriculture and the Environmental Protection Agency.

1988

- The U.S. Patent and Trademark Office grants Harvard University a patent for a mouse used for cancer research (the OncoMouse®).
- The United States launches the Human Genome Project when Congress appropriates funds for the Department of Energy and the National Institutes of Health to support research to determine the structure of complex genomes. The project is fully underway by 1990.

1992

- The FDA clears the way for agricultural biotechnology products with a safety assessment and guidance to industry.
- The Prescription Drug User Fee Act (PDUFA) is signed into law, instituting drug and biologic application review fees that provide the FDA with resources to review products faster. The successful program is reauthorized in 1997, 2002 and 2007.

1993

- The Biotechnology Industry Organization (BIO) is created out of the merger of two predecessor organizations, the Industrial Biotechnology Association and the Association of Biotechnology Companies. (A history of BIO is posted on BIO.org in the "About BIO" section.)

1997

- The Food and Drug Administration Modernization Act (FDAMA) is signed into law, codifying administrative changes begun in 1995 and introducing new reforms. Provisions include criteria for fast-track drug development, easier patient access to experimental drugs and medical devices, and an online database of clinical trials.

1998

- Congress undertakes a doubling of the National Institutes of Health budget in five years, raising it to $27 billion by 2003. Since then the agency's budget has stagnated.

1999

- President Clinton signs an executive order to promote development of biobased products and bioenergy.

2000

- The Biomass Research and Development Act is signed into law to promote conversion of biomass into biobased industrial products.

2001

- President Bush announces that federal funding will be made available to support research using embryonic stem cell lines created as of Aug. 9, 2001.

2002

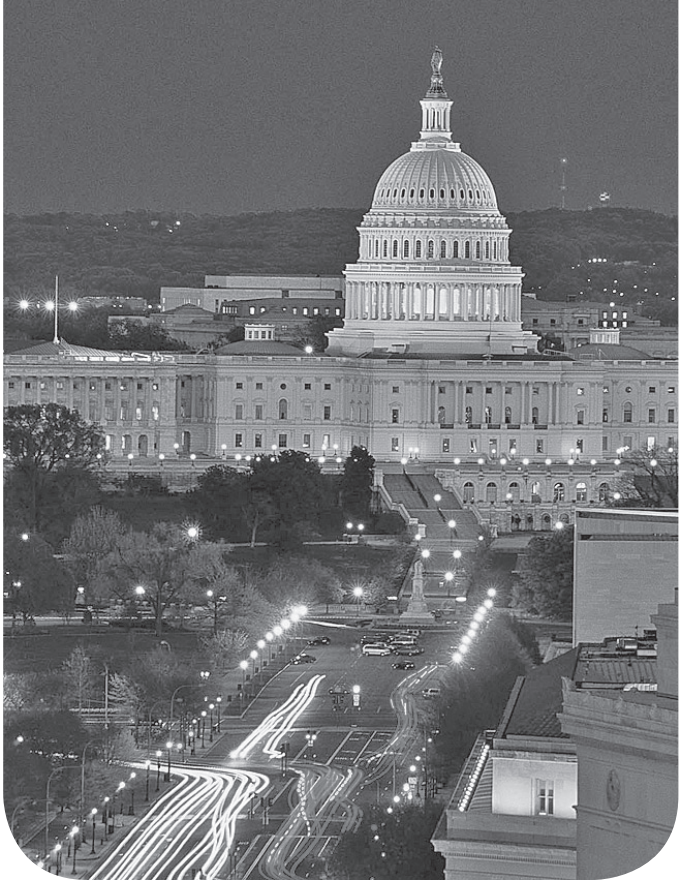
- The Farm Security and Rural Investment Act includes biotech measures such as significantly increased funding for research and risk assessment and new programs for promoting biotechnology in developing countries. The legislation also supports industrial biotechnology with a new requirement for federal agencies to buy biobased products, such as plant-made plastics and biofuels, whenever feasible.

2003

- The Medicare Modernization Act becomes law, providing prescription drug coverage for senior citizens and the disabled beginning Jan. 1, 2006.

2004

- The FDA publishes a white paper outlining the Critical Path Initiative, which seeks to expedite drug development by promoting the use of technologies such as computer-based predictive models, biomarkers, imaging technologies and improved clinical trial design.



- The Project BioShield Act is signed into law, providing $5.6 billion over 10 years for the federal government to procure diagnostics, therapies and vaccines to protect Americans from chemical, nuclear and biological warfare agents.
- California voters pass Proposition 71, which supports embryonic stem cell research with $3 billion in funding over 10 years.

2005

- The Energy Policy Act of 2005 passes, authorizing $3.6 billion in funding for bioenergy and biobased products.
- Pandemic legislation signed into law provides $3.8 billion for preparedness, including $3 billion for medical countermeasures. The legislation also includes liability protection for manufacturers of these products.

2006

- The World Trade Organization issues a confidential final ruling on the U.S./Canada/Argentine challenge against the European Union (EU) on approval of new biotech crops. According to news reports, the ruling concludes that the EU breached its trade commitments with respect to 21 agricultural biotechnology products—including types of oilseed, rape, maize and cotton.
- In his State of the Union address, U.S. President George W. Bush expresses support for bioethanol made from agricultural wastes and switchgrass.

2007

- Congress passes The Food and Drug Administration Amendments Act (FDAAA), which provides FDA with substantial resources for enhancing and modernizing the FDA Drug Safety System. Legislation to reauthorize the Prescription Drug User Fee Act also passes in conjunction with FDAAA. FDAAA is widely considered the most sweeping FDA overhaul in decades. Previous landmark FDA legislation focused on premarket testing of safety (the FDC Act) and efficacy (the Kefauver-Harris amendments); this legislation focuses on *postmarket* safety. Among its many provisions, FDAAA requires greater collaboration between the FDA and drug manufacturers to develop risk-evaluation and mitigation strategies prior to approval, gives the FDA new labeling authority, and calls for an enhanced clinical trials registry and a results databank.
- The U.S. Department of Energy (DOE) invests more than $1 billion in biorefinery projects and bioenergy research centers in 2007.
- The Energy Independence and Security Act of 2007 becomes law, establishing a new Renewable Fuel Standard that calls for nationwide use of 36 billion gallons of biofuels by 2022, including 21 billion gallons of advanced biofuels and cellulosic ethanol.

2008

- The FDA publishes a favorable risk assessment for food derived from cloned animals and their offspring. The assessment reflects FDA's review of more than 700 scientific research studies, conducted over the past 30 years. The agency concludes that foods from animal clones and their offspring are equivalent to foods from other livestock.
- At press time, the House and Senate had both passed the Genetic Information Nondiscrimination Act, and President Bush was expected to sign it into law. The law will protect against job or health insurance discrimination based on genetic testing results.
- At press time, Congress is considering sweeping patent reform. Visit the Intellectual Property section of BIO.org for information.

technologies and Tools

Here is an overview of the major technologies and tools used in biotech.

Bioprocessing Technology

The oldest of the biotechnologies, bioprocessing, uses living cells or the molecular components of cells' manufacturing machinery to produce desired products. The living cells most commonly used are one-celled microorganisms, such as yeast and bacteria; the biomolecular components used include DNA (which encodes the cells' genetic information) and enzymes (proteins that catalyze biochemical reactions).

A form of bioprocessing, *microbial fermentation*, has been used for thousands of years to brew beer, make wine, leaven bread and pickle foods. In the mid-1800s, when we discovered microorganisms and realized they were responsible for these useful products, we greatly expanded our use of microbial fermentation. We now rely on the remarkably diverse manufacturing capability of naturally occurring microorganisms to provide us with products such as antibiotics, birth control pills, vaccines, amino acids, vitamins, industrial solvents, pigments, pesticides, biodegradable plastics, laundry-detergent enzymes and food-processing aids.

CELL CULTURE

Cell-culture technology is the growing of cells outside of living organisms (*ex vivo*).

PLANT CELL CULTURE

An essential step in creating transgenic crops, plant cell culture also provides us with an environmentally sound and economically feasible option for obtaining naturally occurring products with therapeutic value, such as the chemotherapeutic agent paclitaxel, a compound found in yew trees and marketed under the name Taxol®. Plant cell culture is also under study as a manufacturing tool for therapeutic proteins, and is an important source of compounds used as flavors, colors and aromas by the food-processing industry.

INSECT CELL CULTURE

Insect cell culture can broaden our use of biological-control agents that kill insect pests without harming beneficial ones or having pesticides accumulate in the environment. Even though we have recognized the environmental advantages of biological control for decades, the manufacture of such products in marketable amounts has been impossible. Insect cell culture removes these manufacturing constraints.

Like plant cell culture, insect cell culture is being investigated as a production method of therapeutic proteins. Insect cell culture is also being investigated for the production of VLP (virus-like particle) vaccines against infectious diseases such as SARS and influenza, which could lower costs and eliminate the safety concerns associated with the traditional egg-based process. A patient-specific cancer vaccine, Provenge, that utilizes insect cell culture is up for FDA approval, along with a second vaccine for Human Papilloma Virus (HPV), Cervarix.

MAMMALIAN CELL CULTURE

Livestock breeding has used mammalian cell culture for decades. Eggs and sperm, taken from genetically superior cows and bulls, are united in the lab, and the resulting embryos are grown in culture before being implanted. A similar form of mammalian cell culture has also been an essential component of the human *in vitro* fertilization process.

Our use of mammalian cell culture now extends well beyond the brief maintenance of cells in culture for reproductive purposes. Mammalian cell culture can supplement—and may one day replace—animal testing of medicines. As with plant cell culture and insect cell culture, we are relying on mammalian cells to synthesize therapeutic compounds, in particular, certain mammalian proteins too complex to be manufactured by genetically modified microorganisms. For example, monoclonal antibodies are produced through mammalian cell culture.

Scientists are also investigating the use of mammalian cell culture as a production technology for influenza vaccines. In 2006, the Department of Health and Human Services awarded contracts totaling approximately $1 billion to several vaccine manufacturers to develop new cell-culture technologies for manufacturing influenza vaccine. Cell-culture technology has been used for other vaccines, but each vaccine process is unique and influenza vaccine manufacturing has traditionally been performed using large quantities of eggs. New manufacturing technologies are an essential part of pandemic influenza preparedness and require extensive research and development. Cell-culture techniques could enhance the manufacturing capabilities and capacity.

Recombinant DNA Technology

Recombinant DNA is the foundation of modern biotechnology. The term *recombinant* DNA literally means the joining—or *recombining*—of two pieces of DNA from different sources, such as from two different organisms.

Humans began to change the genetic material of domesticated plants and animals thousands of years ago by selecting which individuals would reproduce. By breeding individuals with valuable genetic traits while excluding others from reproduction, we changed the genetic makeup of the plants and animals we domesticated. Now, in addition to using selective breeding, we recombine genes at the molecular level using the more precise techniques of recombinant DNA technology. Making manipulations more precise and outcomes more certain, biotechnology decreases the risk of producing organisms with unexpected traits and avoids the time-consuming, trial-and-error approach of selective breeding.

Genetic modification through selective breeding and recombinant DNA techniques resemble each other, but there are important differences:

- Genetic modification using recombinant DNA techniques allows us to move single genes whose functions we know from one organism to another.
- In selective breeding, large sets of genes of unknown function are transferred between related organisms.

Techniques for making selective breeding more predictable and precise have been evolving over the years. In the early 1900s, Hugo DeVries, Karl Correns and Eric Tshermark rediscovered Mendel's laws of heredity. In 1953, James Watson and Francis Crick deduced DNA's structure from experimental clues and model building. In 1972, Paul Berg and colleagues created the first recombinant DNA molecules, using restriction enzymes. Ten years later, the first recombinant DNA-based drug (recombinant human insulin) was introduced to the market. By 2000 the human genome had been sequenced and today we use recombinant DNA techniques, in conjunction with molecular cloning to:

- produce new medicines and safer vaccines.
- enhance biocontrol agents in agriculture.
- increase agricultural yields and decrease production costs.
- reduce allergy-producing characteristics of some foods.
- improve food's nutritional value.
- develop biodegradable plastics and other biobased products.
- decrease water and air pollution.
- slow food spoilage.

Monoclonal Antibodies

Monoclonal antibody technology uses immune-system cells to make proteins called *antibodies*, which help the body to destroy foreign invaders such as viruses or bacteria. We have all experienced the extraordinary specificity of antibodies (specificity refers to the ability of antibodies to bind to only one type of molecule). For example, the antibodies that attack a flu virus one winter may do little to protect us from a slightly different flu virus the next year.

The method of making monoclonal antibodies involves fusing a human myeloma cell (a cancerous immune B cell) that can no longer secrete antibodies to a normal B cell from a mouse that has been immunized to secrete a particular antibody. The myeloma component helps the hybrid cell multiply indefinitely, and the fused cell—called a hybridoma—can be cultured. The cells all produce exactly the same antibody—hence the term *monoclonal antibody*. As with the antibodies our bodies make to fight disease, monoclonal antibodies bind with specificity to their targets, making them tempting candidates for fighting cancer, infections and other diseases.

The specificity of antibodies also makes them powerful diagnostic tools. They can locate substances that are present in minuscule amounts and measure them with great accuracy. For example, monoclonal antibodies can be used to:

- locate environmental pollutants.
- detect harmful miroorganisms in food.
- distinguish cancer cells from normal cells.
- diagnose infectious diseases in humans, animals and plants more quickly and more accurately than ever before.

In addition to their value as detection devices, monoclonal antibodies (MAbs) can provide us with highly specific *therapeutic compounds*. Monoclonal antibodies can treat cancer, for example, by binding to and disabling a crucial receptor or other protein associated with cancerous cells. Joined to a toxin, a monoclonal antibody can selectively deliver chemotherapy to a cancer cell while avoiding healthy cells. Monoclonal antibodies have also been developed to treat organ-transplant rejection and autoimmune diseases by specifically targeting the type of immune system cell responsible for these attacks.

Monoclonal antibodies can be created in mouse cells, but often the human patient mounts an immune response to mouse antibodies. This immune response not only eliminates the therapeutic MAb administered, but is also dangerous for patients and may cause lasting damage. To reduce this problem scientists create *chimeric,* or humanized, antibodies in which some parts of mouse origin are replaced with parts of human origin. Such antibodies are less likely to trigger an unwanted immune response.

Cloning

Cloning technology allows us to generate a population of genetically identical molecules, cells, plants or animals. Its applications are extraordinarily broad and extend into many research and product areas. Any legislative or regulatory action directed at "cloning" must take great care in defining the term precisely so that the intended activities and products are covered while others are not inadvertently captured.

MOLECULAR OR GENE CLONING

Molecular or gene cloning, the process of creating genetically identical DNA molecules, provides the foundation of the molecular biology revolution and is a fundamental tool of biotechnology. Virtually all applications in biotechnology, from drug discovery and development to the production of transgenic crops, depend on gene cloning.

The research findings made possible through molecular cloning include identifying, localizing and characterizing genes; creating genetic maps and sequencing entire genomes; associating genes with traits and determining the molecular basis of these traits. For a full discussion, see page 25.

ANIMAL CLONING

Animal cloning has been rapidly improving livestock herds for more than two decades and has been an important tool for scientific researchers since the 1950s. Although the 1997 debut of Dolly the cloned sheep was a worldwide media event, animal cloning was not altogether new. Dolly was considered a scientific breakthrough *not* because she was a clone, but because the source of the genetic material used to produce Dolly was an adult cell, not an embryonic one.

There are, in fact, two ways to make an exact genetic copy of an organism such as a sheep or a laboratory mouse:

- **Embryo Splitting** is the old-fashioned way to clone. Embryo splitting mimics the natural process of creating identical twins, only in a Petri dish rather than the mother's womb. Researchers manually separate a very early embryo into two parts and then allow each part to divide and develop on its own. The resulting embryos are placed into a surrogate mother, where they are carried to term and delivered. Since all the embryos come from the same zygote, they are genetically identical.
- **Somatic cell nuclear transfer** (SCNT) starts with the isolation of a somatic (body) cell, which is any cell other than those used for reproduction (sperm and egg, known as the germ cells). In mammals, every somatic cell has two complete sets of chromosomes, whereas the germ cells have only one complete set. To make Dolly, scientists transferred the nucleus of a somatic cell taken from an adult female sheep to an egg cell from which the nucleus had been removed. After some chemical manipulation, the egg cell, with the new nucleus, behaved like a freshly fertilized zygote. It developed into an embryo, which was implanted into a surrogate mother and carried to term.

Animal cloning provides many benefits. The technology can help farmers produce animals with superior characteristics, and it provides a tool for zoo researchers to save endangered species. Also, in conjunction with recombinant DNA technologies, cloning can provide excellent animal models for studying genetic diseases and other conditions such as aging and cancer. In the future, these technologies will help us discover drugs and evaluate other forms of therapy, such as gene and cell therapy.

Protein Engineering

Protein engineering technology is used, often in conjunction with recombinant DNA techniques, to improve existing proteins (e.g., enzymes, antibodies and cell receptors) and create proteins not found in nature. These proteins may be used in drug development, food processing and industrial manufacturing.

Protein engineering has most commonly been used to alter the catalytic properties of enzymes to develop ecologically sustainable industrial processes. Enzymes are environmentally superior to most other catalysts used in industrial manufacturing because, as biocatalysts, they dissolve in water and work best at neutral pH and comparatively low temperatures. In addition, because biocatalysts are more specific than chemical catalysts, they also produce fewer unwanted byproducts. Makers of chemicals, textiles, pharmaceuticals, pulp and paper, food and feed, and energy are all benefiting from cleaner, more energy-efficient production made possible with biocatalysts.

The characteristics that make biocatalysts environmentally advantageous may, however, limit their usefulness in certain industrial processes. For example, most enzymes fall apart at

high temperatures. Scientists are circumventing these limitations by using protein engineering to increase enzyme stability under harsh manufacturing conditions.

In addition to industrial applications, medical researchers have used protein engineering to design novel proteins that can bind to and deactivate viruses and tumor-causing genes; create especially effective vaccines; and study the membrane receptor proteins that are so often the targets of pharmaceutical compounds. Food scientists are using protein engineering to improve the functionality of plant storage proteins and develop new proteins as gelling agents.

In addition, researchers are developing new proteins to respond to chemical and biological attacks. For example, hydrolases detoxify a variety of nerve agents as well as commonly used pesticides. Enzymes are safe to produce, store and use, making them an effective and sustainable approach to toxic materials decontamination.

Biosensors

Biosensor technology couples our knowledge of biology with advances in microelectronics. A biosensor is composed of a biological component, such as a cell, enzyme or antibody, linked to a tiny transducer—a device powered by one system that then supplies power (usually in another form) to a second system. Biosensors are detecting devices that rely on the specificity of cells and molecules to identify and measure substances at extremely low concentrations.

When the substance of interest binds with the biological component, the transducer produces an electrical or optical signal proportional to the concentration of the substance. Biosensors can, for example:

- measure the nutritional value, freshness and safety of food.
- provide emergency room physicians with bedside measures of vital blood components.
- locate and measure environmental pollutants.
- detect and quantify explosives, toxins and biowarfare agents.

Nanobiotechnology

Nanotechnology is the next stop in the miniaturization path that gave us microelectronics, microchips and microcircuits. The word *nanotechnology* derives from *nanometer*, which is one-thousandth of a micrometer (micron), or the approximate size of a single molecule. Nanotechnology—the study, manipulation and manufacture of ultra-small structures and machines made of as few as one molecule—was made possible by the development of microscopic tools for imaging and manipulating single molecules and measuring the electromagnetic forces between them.

Nanobiotechnology joins the breakthroughs in nanotechnology to those in molecular biology. Molecular biologists help nanotechnologists understand and access the nanostructures and nanomachines designed by 4 billion years of evolutionary engineering—cell machinery and biological molecules. Exploiting the extraordinary properties of biological molecules and cell processes, nanotechnologists can accomplish many goals that are difficult or impossible to achieve by other means.

For example, rather than build silicon scaffolding for nanostructures, DNA's ladder structure provides nanotechnologists with a natural framework for assembling nanostructures. That's because DNA is a nanostructure; its highly specific bonding properties bring atoms together in a predictable pattern on a nano scale.

Nanotechnologists also rely on the self-assembling properties of biological molecules to create nanostructures, such as lipids that spontaneously form liquid crystals.

> Most appropriately, DNA, the information storage molecule, may serve as the basis of the next generation of computers.

DNA has been used not only to build nanostructures but also as an essential component of nanomachines. Most appropriately, DNA—the information storage molecule—may serve as the basis of the next generation of computers. As microprocessors and microcircuits shrink to nanoprocessors and nanocircuits, DNA molecules mounted onto silicon chips may replace microchips with electron flow-channels etched in silicon. Such biochips are DNA-based processors that use DNA's extraordinary information storage capacity. (Conceptually, they are very different from the DNA microarray chips discussed below.) Biochips exploit the properties of DNA to solve computational problems; in essence, they use DNA to do math. Scientists have shown that 1,000 DNA molecules can solve in four months computational problems that would require a century for a computer to solve.

Other biological molecules are assisting in our continual quest to store and transmit more information in smaller places. For example, some researchers are using light-absorbing molecules, such as those found in our retinas, to increase the storage capacity of CDs a thousand-fold.

Some applications of nanobiotechnology include:

- increasing the speed and power of disease diagnostics.
- creating bio-nanostructures for getting functional molecules into cells.
- improving the specificity and timing of drug delivery.
- miniaturizing biosensors by integrating the biological and electronic components into a single, minute component.
- encouraging the development of green manufacturing practices.

Microarrays

Microarray technology is transforming laboratory research because it allows us to analyze tens of thousands of data points simultaneously.

Thousands of DNA or protein molecules, or tissue samples, can be analyzed on a single "chip"—a small glass surface that carries an array of microscopic points that indicate each molecule or sample that is being studied.

DNA MICROARRAYS

DNA microarrays can be used to analyze an entire genome on one chip. This provides a whole picture of genetic function for a cell or organism, rather than a gene-by-gene approach.

Scientists can use DNA microarrays to:

- detect mutations in disease-related genes.
- monitor gene expression.
- diagnose infectious diseases and identify the best antibiotic treatment.
- identify genes important to crop productivity.
- improve screening for microbes used in environmental cleanup.

DNA-based arrays are essential for using the raw genetic data provided by the Human Genome Project and other genome projects to create useful products. However, gene sequence and mapping data mean little until we determine what those genes do—which is where protein microarrays can help.

PROTEIN MICROARRAYS

The structures and functions of proteins are often much more complicated than those of DNA, and proteins are less stable than DNA. Each cell type contains thousands of different proteins,

some of which are unique to that cell's job. In addition, a cell's protein profile—its proteome—varies with its health, age, and current and past environmental conditions.

Protein microarrays may be used to:

- discover protein biomarkers that indicate disease stages.
- assess potential efficacy and toxicity of drugs before clinical trials.
- measure differential protein production across cell types and developmental stages, and in both healthy and diseased states.
- study the relationship between protein interactions and function.
- evaluate binding interactions between proteins and other molecules.

The availability of microarray technology has enabled researchers to create many types of microarrays to answer scientific questions and discover new products.

TISSUE MICROARRAYS

Tissue microarrays, which allow the analysis of thousands of tissue samples on a single slide, are being used to detect molecular profiles in healthy and diseased tissues and validate potential drug targets. For example, brain tissue samples arrayed on slides connected to electrodes allow researchers to measure the electrical activity of nerve cells exposed to certain drugs.

WHOLE-CELL MICROARRAYS

Whole-cell microarrays alleviate the problem of protein instability in microarrays and permit a more accurate analysis of protein interactions within a cell.

from biotechnology to biology:
Using Biotech Tools to Understand Life

Both academic and industrial scientists have come to depend on various biotechnologies to study the workings of biological systems in remarkably precise detail. These biotech research tools have allowed them to answer long-standing scientific questions and have changed the questions they ask, the problems they tackle and the methods they use to get answers.

Research Applications of Biotechnology

Researchers use biotechnology to gain insight into the precise details of cell processes: the specific tasks assigned to various cell types; the mechanics of cell division; the flow of materials in and out of cells; the path by which an undifferentiated cell becomes specialized; and the methods cells use to communicate with each other, coordinate their activities and respond to environmental changes.

Once they have teased apart details of a process, researchers must then reassemble the pieces in a way that provides insight into the inner workings of cells and, ultimately, of whole organisms.

UNDERSTANDING CELL PROCESSES

Researchers have made tremendous progress toward charting the path of a cell from a single, fertilized egg to a whole organism. The development of a multicelled organism from a single cell involves cell proliferation and *cell differentiation*—groups of cells becoming specialized, or differentiated, to perform specific tasks. Cell differentiation is the process of turning off certain genes within a group of cells while turning on others. Scientists are optimistic about elucidating the many steps in the differentiation pathway and identifying the external and internal factors regulating the process. Two important breakthroughs have fueled this optimism: the development of a protocol for maintaining human stem cells in culture and the birth of the cloned sheep Dolly.

> A delicate balance exists between factors that stimulate cell division and those that inhibit it. Any disruption of this balance leads to uncontrolled cell proliferation—cancer—or cell death.

We have known for decades the basic requirements for keeping small numbers of plant and animal cells in culture. We maintained these cultures primarily to collect products that cells produce naturally. For example, plant-cell culture gives us flavors, colors, thickeners and emulsifiers for food processing.

Researchers now are keeping cells in culture to investigate the molecular basis of many cell processes, especially cell growth, proliferation, differentiation and death.

All cells progress through essentially the same cycle: They increase in size up to a certain point, the genetic material replicates, and the cell divides in two. Understanding what controls *the cell cycle* is essential to understanding the cause of many human and animal diseases, the basis of increasing crop plant yields, and a means for quickly increasing the cells used to manufacture products as diverse as fermented foods and medicines.

Improvements in cell-culture technology have allowed us to better understand the molecular basis of the cell cycle. The rigorously controlled sequence of steps in the cell cycle depends on both genetic and nutritional factors. A delicate balance exists between factors that stimulate cell division and those that inhibit it. Any disruption of this balance leads to uncontrolled cell proliferation—cancer—or cell death.

Studying cells in culture has led to a radical revision of our view of cell death. We once thought cells died in an unorganized, passive way, as cell parts and processes gradually deteriorated. But we now know that much cell death is a highly organized, well-planned sequence of events programmed into the genome. Prolonged cell stress and other factors trigger programmed cell death, or *apoptosis*, in which the cell dismantles itself in an orderly way, breaks down its genome and sends a signal to the immune system to dispatch white blood cells that will remove it.

Programmed cell death eliminates cells with damaged DNA, removes immune system cells that attack healthy cells and shapes tissue formation during development. A better understanding of cell death can also help us figure out why only some cells with environmentally damaged DNA turn cancerous; what breaks down in autoimmune diseases; and how to create better tissues for replacement therapies.

STEM CELL TECHNOLOGY

After animal cells differentiate into tissues and organs, some tissues retain a group of undifferentiated cells to replace that tissue's damaged cells or replenish its supply of certain cells, such as red and white blood cells. When needed, these *adult stem cells* (ASCs) divide in two. One cell differentiates into the cell type the tissue needs for replenishment or replacement, and the other remains undifferentiated.

Embryonic stem cells (ESCs) have much greater plasticity than ASCs because they can differentiate into any cell type. Mouse embryonic stem cells were discovered and cultured in the late 1950s. The ESCs came from 12-day-old mouse embryo cells

that were destined to become egg or sperm (germ cells) when the mouse matured. In 1981, researchers found another source of mouse ESCs with total developmental plasticity—cells taken from a 4-day-old mouse embryo.

In the late 1990s researchers found that human ESCs could be derived from the same two sources in humans: primordial germ cells and the inner cell mass of 5-day-old embryos. These human embryonic stem cells were found to have the same pluripotent properties. Consequently, scientists believe ESCs have enormous potential to lead to treatments and cures for a variety of diseases.

Scientists also have been able to isolate stem cells from human placentas donated following normal, full-term pregnancies. Under certain culture conditions, these cells were transformed into cartilage-like and fat-like tissue.

Maintaining cultures of ESCs and ASCs can provide answers to critical questions about cell differentiation: What factors determine the ultimate fate of unspecialized stem cells? How plastic are adult stem cells? Could we convert an ASC into an ESC with the right combination of factors? Why do stem cells retain the potential to replicate indefinitely? Is the factor that allows continual proliferation of ESCs the same factor that causes uncontrolled proliferation of cancer cells? If so, will transplanted ESCs cause cancer?

The answers to these and many other questions will determine the limits of the therapeutic potential of ESCs and ASCs. Only when they understand the precise mix of factors controlling proliferation and development will scientists be able to reprogram cells for therapeutic purposes.

Using stem cell cultures, researchers have begun to elaborate the intricate and unique combination of environmental factors, molecular signals and internal genetic programming that decides a cell's fate. Israeli scientists directed ESCs down specific developmental pathways by providing different growth factors. Others discovered that nerve stem cells require a dose of vitamin A to trigger differentiation into one specific type of nerve cell, but not another.

> What factors wipe out a differentiated cell's identity and take it back to its embryonic state of complete plasticity? Before Dolly's birth, we did not know we could ask that question, much less answer it.

Another type of ASC, *mesenchymal stem cells*, can differentiate into at least three different cell types (fat cells, bone cells and cartilage cells) depending in part on the mix of nutrients and growth factors. Their destiny also depends on their physical proximity to one another. If mesenchymal stem cells are touching each other, they may become fat cells; if the cell density is too high, they will not differentiate into bone cells even when provided the appropriate nutrients and chemical signals.

Researchers have recently demonstrated that some types of mesenchymal stem cells might have even more developmental flexibility *in vivo*. When injected into mouse embryos, these cells differentiate into most of the cell types found in mice. In 2005, researchers at Johns Hopkins University began what was believed to be the first clinical trial in the United States of adult mesenchymal stem cells to repair muscle damaged by heart attack. Results of the trial, which used an Osiris Therapeutics experimental technology, were promising, even thought it was only a Phase I study for safety. Forty-two percent of patients who received the therapy experienced improvement in their condition at six months, versus only 11 percent of placebo patients.

Another approach to developing therapies based on cells takes a different tack. Rather than determining the molecular events that turn a stem cell into a specific cell type, scientists are studying the de-differentiation process.

THE LESSON OF CLONING: DE-DIFFERENTIATION IS POSSIBLE

Scientists had assumed a specialized animal cell could not revert to the unspecialized status of an embryonic stem cell. (Interestingly, specialized plant cells retain the potential to de-specialize.) They assumed a gene turned off during the differentiation process could not be activated. The birth of Dolly proved that assumption was incorrect. In a procedure known as *somatic cell nuclear transfer (SCNT)*, a nucleus from a fully differentiated body (somatic) cell was placed in an egg, and its identity—adult sheep mammary gland cell nucleus—was erased. That egg developed into Dolly.

The birth of Dolly via SCNT showed that the genetic programming of a nucleus from a specialized somatic cell can be erased and reprogrammed, *in vitro*, by placing it in an egg cell. The egg develops into a 5- or 6-day-old embryo that is genetically identical to the animal that provided the nucleus, and cells taken from the embryo can develop into any cell type found in the animal.

After SCNT showed we could generate ESCs containing undifferentiated genetic material from adult cells for some animals, it seemed likely we could develop similar techniques for using human patients' own genetic material to develop replacement cells and tissues for therapeutic purposes. This idea is called *therapeutic cloning*.

Other possibilities are now emerging for cellular de-differentiation and re-differentiation. For example, differentiated blood cells, when starved, revert to a stem cell-like condition. With

the proper coaxing, scientists have converted those cells into nerve and liver cells and even into blood vessels, which consist of two cell types with very different functions: muscle cells for contraction and cells lining the inner surface for movement of substances into and out of the blood. In addition, scientists have established conditions for de-differentiating a highly specialized type of nerve cell into a type of neural stem cell. The neural stem cells were then reprogrammed into many other types of cells found in the nervous system.

In 2005, Harvard University scientists succeeded in creating cells similar to ESCs by fusing a human skin cell with an ESC. The resulting hybrid cell was de-differentiated and ESC-like. Two years later, researchers at the University of Wisconsin, Madison, and Japan's Kyoto University succeeded in reprogramming skin cells into cells indistinguishable from embryonic stem cells—without using egg cells or ESCs as starting material. Instead, they used different combinations of genes to trigger de-differentiation.

The researchers noted that work with embryonic stem cells remains critical. It is simply too early in this young scientific field to know which techniques will prove most effective in medical applications.

UNDERSTANDING GENE FUNCTION

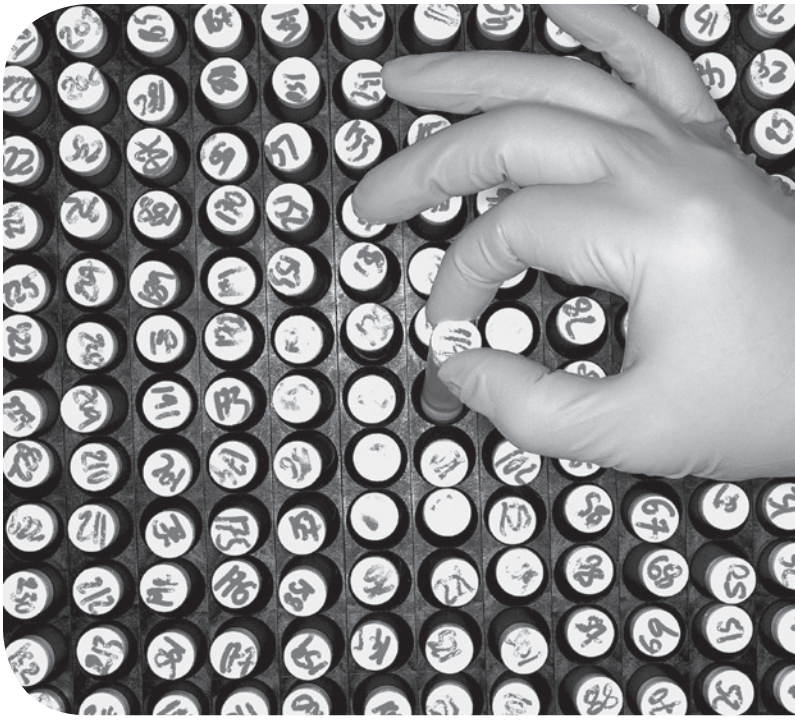
The cell processes described above—growth, proliferation, differentiation, apoptosis—and many more are carried out and controlled by proteins. Proteins are the molecular players that regulate and drive each minute step of the overall process.

Understanding the details of cell processes in health and disease means understanding proteins. Because genes contain the information for making proteins, understanding proteins means understanding gene function. The tools of biotechnology give scientists myriad opportunities to study gene function. Here are only a few of the ways biotechnology allows investigators to probe the genetic basis of cell functions.

Molecular Cloning

> If scientists voted for the most essential biotechnology research tool, molecular cloning would likely win.

If scientists voted for the most essential biotechnology research tool, molecular cloning would likely win. Either directly or indirectly, molecular cloning has been the primary driving force of the biotechnology revolution and has made remarkable discoveries routine. The research findings made possible through molecular cloning include identifying, localizing and characterizing genes; creating genetic maps and sequencing

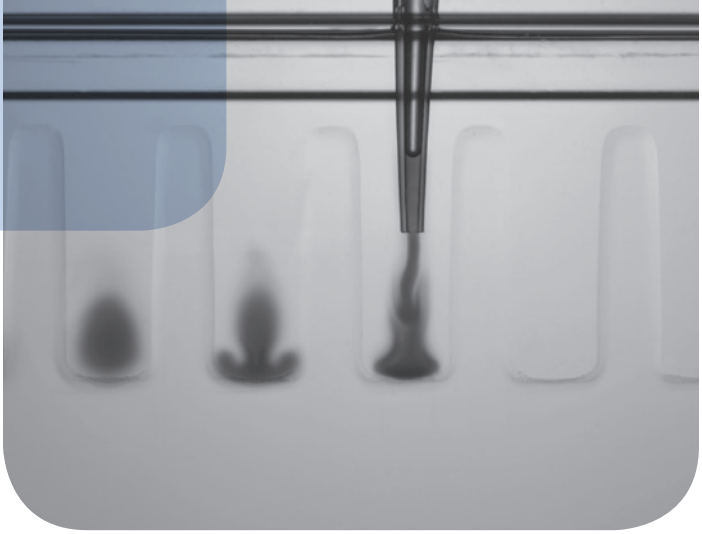


entire genomes; associating genes with traits and determining the molecular basis of the trait.

Molecular cloning involves inserting a new piece of DNA into a cell in such a way that it can be maintained, replicated and studied. To maintain the new DNA fragment, scientists insert it into a circular piece of DNA called a plasmid that protects the new fragment from the DNA-degrading enzymes found in all cells. Because a piece of DNA is inserted, or recombined with, plasmid DNA, molecular cloning is a type of recombinant DNA technology.

The new DNA, now part of a recombinant molecule, replicates every time the cell divides. In molecular cloning, the word *clone* can refer to the new piece of DNA, the plasmid containing the new DNA and the collection of cells or organisms, such as bacteria, containing the new piece of DNA. Because cell division increases, or "amplifies," the amount of available DNA, molecular cloning provides researchers with an unlimited amount of a specific piece of genetic material to manipulate and study.

In addition to generating many copies of identical bits of genetic material, molecular cloning also enables scientists to divide genomes into manageable sizes. Even the simplest genome—the total genetic material in an organism—is too cumbersome for investigations of single genes. To create packages of genetic material of sizes that are more amenable to studies such as gene sequencing and mapping, scientists divide genomes into thousands of pieces and insert each piece into different cells. This collection of cells containing an organism's entire genome is known as a *DNA library*. Because identifying and mapping genes relies on DNA libraries created with molecular cloning, "to clone" can also mean to identify and map a gene.



One of the primary applications of molecular cloning is to identify the protein product of a particular gene and to associate that protein with the appearance of a certain trait. While this is useful for answering certain questions, genes do not act in isolation from one another. To fully understand gene function, we need to monitor the activity of many genes simultaneously. Microarray technology provides this capability.

Microarray Technology

With microarray technology, researchers can learn about gene function by monitoring the expression of hundreds or thousands of genes at one time. For example, a 12,000-gene microarray allowed researchers to identify the 200 or so genes that, based on their gene expression profiles, distinguish stem cells from differentiated cells.

Monitoring simultaneous changes in gene function will shed light on many basic biological functions. For example, scientists are using microarrays to observe the changes in gene activity that occur as normal cells turn cancerous and begin to proliferate. In addition to providing information on possible causes of cancer, this type of information can shed light on the genes that let a cell know that it is time to divide.

Microarrays that display various tissue types allow us to determine the different genes that are active in different tissues. Simply being able to link an active gene to a tissue type can clue researchers in on its function. For example, a plant gene active in leaves but not roots or seeds may be involved in photosynthesis.

Different environmental conditions also affect gene expression. Researchers subject plants to stresses such as cold and drought, and then they use microarray technology to identify the genes that respond by initiating protein production. Researchers are also comparing gene activities of microbes in polluted environments to those of microbes in pristine environments to identify genes that break down environmental contaminants. (For more on microarrays, see page 22.)

Antisense and RNA Interference

Another approach to understanding the relationship of genes, proteins and traits involves blocking gene expression and measuring resulting biochemical or visible changes. Scientists use antisense technology to block genes selectively. Antisense molecules are small pieces of DNA (or, more often, its close relative, RNA) that prevent production of the protein encoded in the blocked DNA.

A related, but mechanistically different, method of silencing genes is known as RNA interference (RNAi). Antisense technology works by using a single strand of DNA or RNA to physically block protein production from the RNA template. In RNA interference, adding small, double-stranded pieces of RNA to a cell triggers a process that ends with the enzymatic degradation of the RNA template. RNA interference, which was discovered serendipitously in plants in the 1990s, appears to be a natural mechanism that virtually all organisms use to defend their genomes from invasion by viruses. RNAi therapies are now in clinical testing.

> Precisely blocking the functions of single genes to assess gene function can provide important insights into cell processes.

Precisely blocking the functions of single genes to assess gene function can provide important insights into cell processes. Most cell processes are structured as pathways that consist of small biochemical steps. Sometimes the pathway resembles a complex chain reaction that starts with one protein causing changes in another protein. At other times, the pathway is a sequence of enzyme-catalyzed reactions in which each enzyme (protein) changes a molecule slightly and then hands it off to the next enzyme. The physical manifestation of a certain trait or disease is the culmination of many or all of these steps.

Gene Knockouts

One of biotech's most powerful research tools for elucidating gene function is targeted mutations, or gene knockouts. By deleting or disrupting a specific gene, we gain valuable information about that gene's role in the expression of a certain protein. When gene-knockout technology is combined with our ability to derive genetically identical animals from cultured cells, we can determine how the absence of a protein affects the whole organism. Scientists have created a wide variety of genetically identical colonies of mice with very specific genes knocked out to study the processes of gene regulation, DNA repair and tumor development.

For years scientists have used animal models of disease to understand the pathophysiology of disease in humans. Our research capabilities in disease pathology broadened greatly as we coincidentally learned more about the genetic causes of diseases, de-

veloped methods of knocking out specific genes and learned how to maintain cultures of embryonic stem cells. Using this suite of technologies, researchers have created animal disease models for Alzheimer's disease, aging, cancer, diabetes, obesity, cardiovascular disease and autoimmune diseases. Using nuclear transfer and embryonic stem cell culture, scientists should be able to develop animal disease models for many more species.

Putting the Pieces Together: 'Omics' and Related Tools

Biotech's powerful research tools have set a fast pace for basic scientific discovery. They have enabled researchers to tease apart cellular and genetic processes so thoroughly that we are beginning to understand biological systems at their most fundamental level—the molecular level. But biological organisms do not operate as molecular bits and pieces. The only way to truly understand organisms is to reassemble these bits and pieces into systems and networks that interact with each other.

This need to assemble separate findings into a complete picture has given birth to a rash of "omics": *genomics, proteomics, metabolomics, immunomics* and *transcriptomics*. These research avenues attempt to integrate information into whole systems rather than focus on the individual components in isolation from each other. The biotechnologies are important tools in these endeavors, but information technologies are also essential for integrating molecular data into a coherent whole.

The fields of research described below bridge scientific discoveries in cellular and molecular biology with their commercial applications.

GENOMICS

Genomics is the scientific study of the genome and the role genes play, individually and collectively, in determining structure, directing growth and development, and controlling biological functions. It consists of two branches: structural genomics and functional genomics.

Structural Genomics

The field of structural genomics includes the construction and comparison of various types of genome maps and large-scale DNA sequencing. The Human Genome Project and the less well-publicized Plant Genome Research Program are structural genomics research on a grand scale. In addition to genome mapping and sequencing, the objective of structural genomics research is gene discovery, localization and characterization.

Private and public structural genomics projects have generated genome maps and complete DNA sequences for many organisms, including crop plants and their pathogens, disease-causing bacteria and viruses, yeast essential to the food processing and brewing industries, nitrogen-fixing bacteria, the malaria parasite and the mosquito that transmits it, and the microbes we use to produce a wide variety of industrial products. In addition, in the spring of 2003, the Human Genome Project was completed ("rough drafts" of the genome were completed in 2000). Because all living organisms share a common heritage and can translate genetic information from many other organisms into biological function, the different genome projects inform each other, and any gene discovered through these projects could have wide applicability in many industrial sectors.

Knowing the complete or partial DNA sequences of certain genes or markers can provide researchers with useful information, even if the precise details of gene function remain unknown. For example, sequence data alone can:

- help plant breeders follow specific traits in a breeding program and test for inheritance without having to rear the plants to reproductive maturity.
- be used to isolate specific recombinant molecules or microbes with unique biochemistry.
- identify the genes involved in complex traits that are controlled by many genes and those that have an environmental component.
- detect microbial contaminants in cell cultures.

Functional Genomics

While sequencing entire genomes and discovering and mapping genes are truly remarkable achievements, they represent only the first milestone in the genomics revolution. Gene sequence and mapping data mean little until we determine what those genes do, how they are regulated, and how the activity of one affects others. This field of study, known as functional genomics, enables researchers to navigate the complex structure of the human genome and to make sense of its content.

Studies show that mammalian genomes have roughly the same number of genes and, in some cases, species less complex than mammals have a higher number of genes. It is not, however, the number of genes that is important to our understanding of the various species; rather, it is the compositional, functional, chemical and structural differences that dictate differentiation.

Evolutionary analysis is emerging as a critical tool for elucidating the function and interactions of genes within a genome.

Molecular evolutionists use comparative genomics techniques and bioinformatics technologies to analyze the number of changes that DNA sequences undergo through the course of evolution. Using this data, researchers can recognize functionally important regions within genes and even construct a molecular timescale of species evolution.

The fruit fly (*Drosophila melanogaster*) has proven to be an invaluable model in the study of inherited genes. The humble fly's desirable attributes include hardiness, availability and short generation time. As a result, a wealth of research and data produced from the study of the fruit fly are publicly available. Researchers at the Center for Evolutionary Functional Genomics at the Arizona Biodesign Institute have developed "FlyExpress," a web-based informatics tool that uses advanced image processing and database techniques. Using this system, researchers can rapidly analyze gene expression patterns in embryonic image data.

PROTEOMICS

Genes exert their effects through proteins; gene expression is protein production. And there's an incredible amount of it going on, around the clock, in living cells. A cell may produce thousands of proteins, each with a specific function. This collection of proteins in a cell is known as its *proteome*, and *proteomics* is the study of the structure, function, location and interaction of proteins within and between cells. The collection of proteins in an entire organism is also referred as its *proteome* (e.g., *the human proteome*).

The structure of a protein molecule is much more complicated than that of DNA, which is a linear molecule composed of only four nucleotides. DNA's nucleotides—in sequences of three called codons—code for 20 amino acids, which are the building blocks of proteins. Like DNA, proteins are built in a linear chain, but the amino acids form complex bonds that make the chain fold into complicated, intricate shapes. Those shapes are essential to each protein's function.

We know that the sequence of amino acids affects the shape a protein assumes, but we do not yet understand all the rules that govern the folding process. This means that protein shape or function generally can't be predicted from the amino acid sequence.

Adding to the complexity, proteins undergo modifications after they are built (called *post-translational modifications*). These affect a protein's form and function as well, helping to explain how the 25,000 human genes in the genome can make the hundreds of thousands of proteins that comprise the human proteome.

Unlike the unvarying genome, an organism's proteome is so dynamic that an almost infinite variety of protein combinations exists. The proteome varies from one cell type to the next, from one year to the next, and even from moment to moment. The cellular proteome changes in response to other cells in the body and external environmental conditions. A single gene can code for different versions of a protein, each with a different function.

When the Human Genome Project began, the first task researchers took on was developing the necessary tools for completing the project's goals and objectives. Proteomics researchers likewise are developing tools to address many proteomics objectives, such as:

- cataloging all of the proteins produced by different cell types.
- determining how age, environmental conditions and disease affect the proteins a cell produces.
- discovering the functions of these proteins.
- charting the progression of a process—such as disease development, the steps in the infection process or the biochemical response of a crop plant to insect feeding—by measuring changes in protein production.
- discovering how a protein interacts with other proteins within the cell and from outside the cell.

BIOINFORMATICS AND SYSTEMS BIOLOGY

Biotechnology as we know it today would be impossible without computers and the Internet. The common language of computers allows researchers all over the world to contribute and access biological data; the universal language of life enables collaborations among scientists studying any plant, animal or microbe.

One of the most formidable challenges facing researchers today remains in informatics: how to make sense of the massive amount of data provided by biotechnology's powerful research tools and techniques. The primary problems are how to collect, store and retrieve information; manage data so that access is unhindered by location or compatibility; provide an integrated form of data analysis; and develop methods for visually representing molecular and cellular data.

Bioinformatics technology uses the computational tools of the information technology revolution—such as statistical software, graphics simulation, algorithms and database management—for consistently organizing, accessing, processing and integrating data from different sources.

Bioinformatics consists, in general, of two branches. The first concerns data gathering, storing, accessing and visualization; the

second branch focuses more on data integration, analysis and modeling and is often referred to as *computational biology*.

> *Systems biology* is the branch of biology that attempts to use biological data to create predictive models of cell processes, biochemical pathways and, ultimately, whole organisms.

Systems biology is the branch of biology that attempts to use biological data to create predictive models of cell processes, biochemical pathways and, ultimately, whole organisms. Systems biologists develop a series of mathematical models to elucidate the full complexity of interactions in biological systems. Only with iterative computer biosimulations will we be able to develop a complete picture of the system we are studying. As an indicator of how essential computers have become to biotechnology labs, the phrase *in silico* has joined *in vivo* and *in vitro* as a descriptor of experimental conditions.

Over time, biotechnology products will increasingly focus on systems and pathways, not single molecules or single genes. Bioinformatics technology will be essential to every step in product research, development and commercialization.

SYNTHETIC BIOLOGY

Now that scientists have broken genomes apart, can they put them together? Synthetic biology, sometimes described as the inverse of systems biology, seeks to do just that and assemble genomes and whole organisms. Synthetic biologists are working to:

- develop a set of "standard parts" that can be used (and re-used) to build biological systems.
- reverse engineer and redesign biological parts.
- reverse engineer and redesign a "simple" natural bacterium.

The research is advancing fast. In 2002, researchers at Stony Brook University in New York synthesized the polio virus. Three years later, the 1918 pandemic flu virus was synthesized at the Armed Forces Institute of Pathology.

Synthetic biologists also are seeking to build organisms that can create energy and medicines. A project to develop a bacterial strain that can produce a malaria drug precursor attracted more than $40 million in funding from the Gates Foundation.

Early in 2006, Dr. Jay Keasling, director of the Berkeley Center for Synthetic Biology, engineered a yeast containing bacterial and wormwood genes into a chemical factory to produce a precursor to artemisinin, the most effective and expensive antimalarial drug.

Researchers at the Howard Hughes Medical Institute and Yale University have used synthetic biology techniques to build proteins that don't exist in the natural world. They've constructed these proteins from beta-amino acids, which are distinct from the alpha-amino acids that compose natural proteins. Their synthetic proteins are as stable as natural ones, but provide a distinct advantage: As they will not be degraded by enzymes or targeted by the immune system as natural ones are, these beta-proteins could be used as the basis for future drugs that would be more effective than natural protein drugs.

The Next Step: Using New Knowledge to Develop Products

Merely understanding biological systems is not enough, and this is especially true in medicine. Companies must turn the information gleaned from basic research, genomics and proteomics into useful products. The tools and techniques of biotechnology are helpful not only in product discovery but also are useful throughout the development process.

PRODUCT DISCOVERY

A fundamental challenge facing many sectors of the biotechnology industry is how to improve the rate of product discovery. Many believe that current technology can vastly reduce the time it takes to discover a drug. Moreover, biotechnology is creating the tools to pinpoint the winning compounds far earlier in the process.

For example, because scientists had long known the amino acid sequences of insulin and growth hormone, it was possible to commercially produce recombinant versions relatively soon after the advent of the technology. Discovering endogenous proteins that stimulate the immune system and red blood cell production led rapidly to their use as therapeutics. Other basic research has led to new products such as enzymes for food processing or industrial manufacturing and microbes with novel biochemistry for breaking down or synthesizing molecules.

In addition, knowing only portions of the DNA sequence of certain genes can provide useful products, even without knowing

about the gene's function or the protein it encodes. For example, new product discoveries based solely on DNA sequence data acquired through structural genomics include:

- diagnostics for plant, animal and human diseases.
- tests to identify the presence of genetically modified food products.
- antisense molecules to block gene expression.
- tests to identify genetic susceptibilities to certain diseases.
- tests for microbial contaminants in food products or donated blood.
- tests for drug-resistant strains of HIV and other pathogens.
- gene-based therapeutics, such as DNA vaccines and gene therapies.

In general, however, the information accumulating from studies of structural and functional genomics, proteomics and basic biology bolsters new product discovery by helping us understand the basic biology of the process we want to control or change. Understanding the process leads to new and better products, and sometimes provides new uses for old products. For example, understanding the molecular bases of high blood cholesterol and diabetes, as well as the molecular mechanism of action of statin drugs, leads many researchers to believe that statins (designed to reduce cholesterol levels) might also help people with diabetes.

The benefits of this deeper understanding to new product discovery apply to all industrial sectors that use biotechnology: pharmaceuticals, diagnostics, agriculture, food processing, forestry and industrial manufacturing. Medical applications of biotechnology illustrate how understanding molecular details encourages product discovery.

New Targets

The deconstruction of disease pathways and processes into their molecular and genetic components illuminates the exact point of malfunction and, therefore, the point in need of therapeutic intervention. Often, the biotechnology-derived therapeutic compound will not be a gene, protein or any type of biological molecule, but the therapeutic target will *always* be a gene or protein.

> Having structure and function information about genes and proteins involved in diseases makes finding useful molecules more rational than trial and error—hence the phrase *rational drug design*.

Having the complete roster of the molecular players gives us multiple targets to monitor, modulate or block; every step in a complex sequential process is a possible point of intervention.

For example, we have elaborated the cascade of events that typifies programmed cell death (apoptosis), and we now know chemotherapy and radiation induce apoptosis. Therefore, tumors that resist chemotherapy and radiation treatments have changes in their apoptosis mechanism. Targeting the molecules involved in apoptosis should lead to new therapies for resistant tumors.

With this knowledge of genomics and proteomics, scientists can identify not only the molecular target, but also the location of its bull's-eye, which is usually one or a few locations within a protein molecule. The new field of *chemical genomics* allows us to identify small inorganic molecules that bind to those sites. These small molecules may be drawn from a collection of molecules built painstakingly by chemists over decades, or they might be the products of a relatively new technology that uses robotics to generate millions of chemical compounds in parallel processes, *combinatorial chemistry*.

PRODUCT DEVELOPMENT

Genomics, proteomics, microarray technology, cell culture, monoclonal antibody technology and protein engineering are just a few of the biotechnologies that are being brought to bear at various stages of product development. Understanding the molecular basis of a process of interest allows many products to be tested in cells, which can save companies time and money *and* lead to better products. For example, agricultural biotechnology companies developing insect-resistant plants can measure the amount of protective protein that a plant cell produces and avoid having to raise plants to maturity. Pharmaceutical companies can use cell-culture and microarray technology to test the safety and efficacy of drugs and observe adverse side effects early in the drug development process.

In addition, by genetically modifying animals to produce therapeutic protein targets or developing advanced transgenic animal models of human diseases, we can learn more about drug candidates' *in vivo* effects before they enter human clinical trials. These technologies can help companies identify the best potential drug compounds quickly.

Often, a single technology can be used at many steps in the development process. For example, a small piece of DNA that the research lab uses to locate a gene in the genome of a plant pathogen may eventually become a component of a diagnostic test for that pathogen. A monoclonal antibody developed to

identify therapeutic leads might be used to recover and purify a therapeutic compound during scale-up.

Targeted Products

Knowing molecular biology intimately leads to development of highly targeted products. For example, because we now understand the cell cycle and apoptosis, we are better able to develop products to treat diseases rooted in these processes. All cancers stem from uncontrolled cell multiplication and autoimmune diseases from a failure of apoptosis. Drugs for these ailments can be targeted to any of the molecules or cell structures involved in awry cell processes. Functional genomics has provided information on the molecular changes that occur in precancerous cells. Knowing this, we can develop detection tests for molecular markers that indicate the onset of cancer before visible cell changes or symptoms appear.

Many chemotherapeutic agents target proteins active during cell division, making no distinction between healthy cells that divide frequently (such as those that produce hair or blood cells) and cancerous cells. To protect those healthy cells, some companies are developing medicines that would stop the cell cycle of healthy cells before delivering a dose of a chemotherapeutic agent.

Products Tailored to Individuals

We are entering the age of *personalized medicine* in which genetic differences among patients are acknowledged and used to design more effective treatments. A medicine's effectiveness and safety often varies from one person to the next. Using data acquired in functional genomics, we will be able to identify genetic differences that predispose patients to adverse reactions to certain drugs or make them good subjects for other drugs. This tailoring of therapeutics to the genetic makeup of the patient is known as *pharmacogenomics*.

Just as people do not respond to a drug the same way, not all stages or types of a disease are the same. Medicines targeted to earlier stages of a disease may not affect a disease that has moved beyond that stage. Some diseases leave molecular footprints as they go from one stage to the next. Others vary in aggressiveness from patient to patient. Knowing the molecular profile allows physicians to diagnose how far the disease has progressed, or how aggressive it is, and choose the most appropriate therapy.

health care
Applications

Biotechnology tools and techniques open new research avenues for discovering how healthy bodies work and what goes wrong when problems arise. Knowing the molecular basis of health and disease leads to improved methods for diagnosing, treating and preventing illness. In human health care, biotechnology products include quicker and more accurate diagnostic tests, therapies with fewer side effects and new and safer vaccines.

Diagnostics

We can now detect many diseases and medical conditions more quickly and with greater accuracy because of new, biotechnology-based diagnostic tools. A familiar example is the new generation of home pregnancy tests that provide more accurate results much earlier than previous tests. Tests for strep throat and many other infectious diseases provide results in minutes, enabling treatment to begin immediately, in contrast to the two- or three-day delay of previous tests.

> A familiar example of biotechnology's benefits is the new generation of home pregnancy tests that provide more accurate results much earlier than previous tests.

Biotechnology also has created a wave of new genetic tests. Today there are more than 1,200 such tests in clinical use, according to genetests.org, a site sponsored by the University of Washington. Many are for genetic diseases, while others test *predisposition* to disease. Emerging applications include tests to predict response to medicines and assist with nutritional planning.

Biotechnology has lowered the cost of diagnostics in many cases. A blood test developed through biotechnology measures low-density lipoprotein ("bad" cholesterol) in one test, without fasting. Biotech-based tests to diagnose certain cancers, such as prostate and ovarian cancer, by taking a blood sample, eliminate the need for invasive and costly surgery.

In addition to diagnostics that are cheaper, more accurate and quicker than previous tests, biotechnology is allowing physicians to diagnose diseases earlier, which greatly improves prognosis. Proteomics researchers are taking this progress a step further by identifying molecular markers for incipient disease before visible cell changes or symptoms appear.

The wealth of genomics information now available will greatly assist doctors in early diagnosis of diseases such as type I diabetes, cystic fibrosis, early-onset Alzheimer's disease and Parkinson's disease—ailments that previously were detectable only after clinical symptoms appeared. Genetic tests will also identify patients with predisposition to diseases such as various cancers, osteoporosis, emphysema, type 2 diabetes and asthma, giving patients an opportunity to prevent the disease by avoiding triggers such as poor diet, smoking and other environmental factors.

Some biotechnology tests even act as barriers to disease—these are the tests used to screen donated blood for the pathogens that cause AIDS, hepatitis and other infections.

Biotech-based tests also are improving the way health care is provided. Many diagnostic tests are portable, so physicians conduct the tests, interpret results and decide on treatment at the point of care. In addition, because many of these tests give results in the form of color changes (similar to a home pregnancy test), results can be interpreted without technically trained personnel, expensive lab equipment or costly facilities, expanding access to poorer communities and developing countries.

Therapeutics

Biotechnology will make possible improved versions of today's therapeutic regimes as well as tomorrow's innovative treatments. Biotech therapeutics approved by the U.S. Food and Drug Administration (FDA) are used to treat many diseases and conditions, including leukemia and other cancers, anemia, cystic fibrosis, growth deficiency, rheumatoid arthritis, hemophilia, hepatitis, genital warts and transplant rejection.

Some biotech companies are using emerging biological knowledge, the skills of rational drug design, and high-throughput screening of chemical libraries to find and develop small-molecule therapies, which are often formulated as pills. Others focus on biological therapies, such as proteins, genes, cells and tissues—all of which are made in living systems. These therapies are what people often first think of when they hear the term *biotechnology*.

The therapies discussed below all make use of biological substances and processes designed by nature. Some use the human body's own tools for fighting disease. Others are natural products of plants and animals. The large-scale manufacturing processes for producing therapeutic biological substances also rely on nature's molecular production mechanisms.

USING NATURAL PRODUCTS AS THERAPEUTICS

Many living organisms produce compounds that have therapeutic value for us. For example, many antibiotics are produced by naturally occurring microbes, and a number of medicines on the market, such as digitalis, are made by plants. Plant cell culture, recombinant DNA technology and cellular cloning now provide us with new ways to tap into natural diversity.

As a result, scientists are investigating many plants and animals as sources of new medicines. Ticks and bat saliva could provide anticoagulants, and poison-arrow frogs might be a source of new painkillers. A fungus produces a novel antioxidant enzyme that is particularly efficient at "mopping up" free radicals known to encourage tumor growth. Byetta™ (exenatide) was chemically copied from the venom of the gila monster and approved in early 2005 for the treatment of diabetes. PRIALT® (ziconotide), a recently approved drug for pain relief, is a synthetic version of the toxin from a South Pacific marine snail.

The ocean presents a particularly rich habitat for potential new medicines. Marine biotechnologists have discovered organisms containing compounds that could heal wounds, destroy tumors, prevent inflammation, relieve pain and kill microorganisms. Shells from marine crustaceans, such as shrimp and crabs, are made of chitin, a carbohydrate that is proving to be an effective drug-delivery vehicle.

Marine biotechnologists have discovered organisms containing compounds that could heal wounds, destroy tumors, prevent inflammation, relieve pain and kill microorganisms.

RECOMBINANT PROTEIN THERAPEUTICS

Some diseases are caused when defective genes don't produce the proteins (or enough of the proteins) the body requires. Today we are using recombinant DNA and cell culture to produce these proteins. Replacement protein therapies include:

- factor VIII—a blood-clotting protein missing in some hemophiliacs. Marketed by several companies under various brand names.
- insulin—a hormone that regulates blood glucose levels. Diabetes results when the body can no longer make insulin (or can no longer respond to it). Marketed by several companies under various brand names.
- human growth hormone—a hormone essential to achieving normal height. Children with growth disorders may be prescribed a recombinant version of this protein. Marketed by several companies under various brand names.
- betaglucocerebrosidase—a protein whose absence results in Gaucher's disease, a rare genetic disorder. Marketed as Cerezyme®.

Other protein therapies do not treat a protein deficiency per se. Instead, they introduce or boost levels of a protein in order to fight a symptom or disease process. For example, anemia patients may be treated with recombinant erythropoietin (Epogen® and Procrit®), which stimulates the formation of red blood cells. Heart attack and some stroke patients are often given a bolus of recombinant tissue plasminogen activator to break up blood clots. Protein drugs can be life-savers for acute conditions, but they are also used to treat chronic diseases, such as rheumatoid arthritis, Crohn's disease and multiple sclerosis.

MONOCLONAL ANTIBODIES

Because monoclonal antibodies (MAbs) offer highly specific darts to throw at disease targets, they are attractive as therapies, especially for cancer. The first anticancer MAb, Rituxan™ (rituximab), was approved in 1997 for the treatment of non-Hodgkin's lymphoma. Since then, many other MAb-based therapies have followed, including:

- Avastin® (bevacizumab), which binds to vascular endothelial growth factor (VEGF) and prevents its interaction with the VEGF receptor, which helps stimulate blood vessel formation, including the blood vessels in tumors. Avastin has been approved for the treatment of metastatic colorectal cancer, non-small cell lung cancer and metastatic breast cancer.
- Bexxar® (tositumomab), a conjugate of a monoclonal antibody against CD20 and the radioactive isotope iodine I-131. It has been approved to treat non-Hodgkin's lymphoma.
- Campath® (alemtuzumab), which binds to CD52, a molecule found on white blood cells, and treats B-cell chronic lymphocytic leukemia.
- Erbitux® (cetuximab), which blocks epidermal growth factor receptor (EGFR), has been approved to treat colorectal cancer and squamous cell head and neck cancer.
- Herceptin® (trastuzumab), which binds to the HER2 receptor to treat breast cancer.
- Mylotarg™ (gemtuzumab ozogamicin), which uses a monoclonal antibody to deliver a chemotherapy agent to treat some leukemia patients.
- Zevalin® (ibritumomab tiuexetan), which, like Bexxar, is a conjugate of a monoclonal antibody and a radioactive isotope. It is approved for non-Hodgkin's lymphoma.

Monoclonal antibodies are also used to treat immune-related disorders, infectious diseases and other conditions that are best treated by blocking a molecule or process.

USING GENES TO TREAT DISEASES

Gene therapy presents an opportunity to use DNA, or related molecules such as RNA, to treat diseases. For example, rather than giving daily injections of a missing protein, physicians could supply the patient's body with an accurate "instruction manual"—a nondefective gene—correcting the genetic defect so the body itself makes the proteins. Other genetic diseases could be treated by using small pieces of RNA to block mutated genes.

Only certain genetic diseases are amenable to correction via *replacement gene therapy*. These are diseases caused by the lack of a protein, such as hemophilia and severe combined immunodeficiency disease (SCID), commonly known as the "bubble boy disease." Some children with SCID are being treated with gene therapy and enjoying relatively normal lives, although the therapy has also been linked to developing leukemia. Hereditary disorders that can be traced to the production of a defective protein, such as Huntington's disease, may be best treated with RNA that interferes with protein production.

Medical researchers also have discovered that gene therapy can treat diseases other than hereditary genetic disorders. They have used briefly introduced genes, or *transient gene therapy*, as therapeutics for a variety of cancers, autoimmune disease, chronic heart failure, disorders of the nervous system and AIDS.

In late 2003, China licensed for marketing the first commercial gene therapy product, Gendicine, which delivers the P53 tumor suppressor gene. The product treats squamous cell carcinoma of the head and neck, a particularly lethal form of cancer. Clinical trial results were impressive: Sixty-four percent of patients who received the gene therapy drug, in weekly injections for two months, showed a complete regression and 32 percent attained partial regression. With the addition of chemotherapy and radiation, results were improved greatly, with no relapses after three years.

CELL TRANSPLANTS

Approximately 18 people die each day waiting for organs to become available for transplantation in the United States. To address this problem, scientists are investigating ways to use cell culture to increase the number of patients who might benefit from one organ donor. In one study, liver cells grown in culture and implanted into patients kept them alive until a liver became available. In other studies, patients with type 1 diabetes have received transplants of insulin-producing cells; the procedure works well briefly, but medium-term results have been disappointing.

A patient receiving cells from a donor must take powerful drugs every day to prevent the immune system from attacking the transplanted cells. These drugs have many side effects, prompting researchers to seek new ways to keep the immune system at bay. One method being tested is *cell encapsulation*, which allows cells to secrete hormones or provide a specific metabolic function without being recognized by the immune system. As such, they can be implanted without rejection. Other researchers are genetically engineering cells to express a naturally occurring protein that selectively disables immune system cells that bind to it.

Other conditions that could potentially be treated with cell transplants are cirrhosis, epilepsy and Parkinson's disease.

XENOTRANSPLANTATION

Organ transplantation provides an especially effective treatment for severe, life-threatening diseases of the heart, kidney and other organs. However, the need greatly exceeds the availability of donor organs. According to the United Network of Organ Sharing (UNOS), in the United States almost 100,000 people were on organ waiting lists as of April 2008.

Organs and cells from other species—pigs and other animals—may be promising sources of donor organs and therapeutic cells. This concept is called *xenotransplantation*.

Organs and cells from other species—pigs and other animals—may be promising sources of donor organs and therapeutic cells. This concept is called *xenotransplantation.*

The most significant obstacle to xenotransplantation is the immune system's self-protective response. When nonhuman tissue is introduced into the body, the body cuts off blood flow to the donated organ. The most promising method for overcoming this rejection may be various types of genetic modification. One approach deletes the pig gene for the enzyme that is the main cause of rejection; another adds human genetic material to disguise the pig cells as human cells.

The potential spread of infectious disease from other species to humans through xenotransplantation is also a major obstacle to this technology.

USING BIOPOLYMERS AS MEDICAL DEVICES

Nature has also provided us with biological molecules that can serve as useful medical devices or provide novel methods of drug

delivery. Because they are more compatible with our tissues and our bodies absorb them when their job is done, they are superior to most human-made medical devices or delivery mechanisms.

For example, hyaluronate, a carbohydrate produced by a number of organisms, is an elastic, water-soluble biomolecule that is being used to prevent postsurgical scarring in cataract surgery; alleviate pain and improve joint mobility in patients with osteoarthritis; and inhibit adherence of platelets and cells to medical devices, such as stents and catheters. A gel made of a polymer found in the matrix connecting our cells promotes healing in burn victims. Gauze-like mats made of long threads of fibrinogen, the protein that triggers blood clotting, can be used to stop bleeding in emergency situations. Adhesive proteins from living organisms are replacing sutures and staples for closing wounds. They set quickly, produce strong bonds, and are absorbed.

Personalized Medicine

In the future, our individual genetic information will be used to prevent disease, choose medicines and make other critical decisions about health. This is personalized medicine, and it could revolutionize health care, making it safer, more cost-effective and, most importantly, more clinically effective.

Pharmacogenomics, which refers to the use of information about the genome to develop drugs, is also used to describe the study of the ways genomic variations affect drug responses.

The variations affecting treatment response may involve a single gene (and the protein it encodes) or multiple genes/proteins. For example, some painkillers work only when body proteins convert them from an inactive form to an active one. How well these proteins do their jobs varies considerably between people. As another example, tiny genetic differences can change how statin drugs work to lower blood cholesterol levels.

Biotechnology researchers are interested in the use of gene-based tests to match patients with optimal drugs and drug dosages. This concept of personalized medicine—also called targeted therapy—is beginning to have a powerful impact on research and treatment, especially in cancer.

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CANCER

The biotech breast cancer drug Herceptin® (trastuzumab) is an example of a pharmacogenomic drug. Initially approved in 1998, Herceptin targets and blocks the HER2 protein receptor, which is overexpressed in some aggressive cases of breast cancer. A test can identify which patients are overexpressing the receptor and can benefit from the drug.

New tests have been launched recently that identify patients likely to respond to Iressa® (gefitinib), Tarceva® (erlotinib), Gleevec® (imatinib) and Campath® (alemtuzumab), and patients developing resistance to Gleevec. Tests are available to choose the correct dosage of a powerful chemotherapy drug for pediatric leukemia; the tests have saved lives by preventing overdose fatalities.

One of the most exciting new tests is Genomic Health's Oncotype DX™, which examines expression of 21 genes to quantify risk of breast cancer recurrence and predict the likelihood that chemotherapy will benefit the patient. Impressed with the product's results in recent studies, the National Institutes of Health (NIH) in May 2006 launched a large new study called TAILORx (Trial Assigning Individualized Options for Treatment [Rx]) that will utilize Oncotype DX™ to predict recurrence and assign treatment to more than 10,000 women at over 1,000 sites in the United States and Canada.

Many more pharmacogenomic cancer products—both medicines and tests—are in development. In fact, oncology may be entering an era when cancer treatment will be determined as much or more by genetic signature than by location in the body.

The idea is simple, but the project is monumental, given the variety of genetic tools cancer cells use to grow, spread and resist treatment. The NIH in December 2005 announced it was taking on this challenge through The Cancer Genome Atlas. The project aims to map all gene variations linked to some 250 forms of cancer, not only the variations that help cause cancer, but also those that spur growth, metastasis and therapeutic resistance.

OTHER APPLICATIONS

In December 2004, the FDA approved Roche and Affymetrix's AmpliChip® CYP450 Genotyping Test, a blood test that allows physicians to consider unique genetic information from patients in selecting medications and doses of medications for a wide variety of common conditions such as cardiac disease, psychiatric disease and cancer.

The test analyzes one of the genes from the family of cytochrome P450 genes, which are active in the liver to break down certain drugs and other compounds. Variations in this gene can cause a patient to metabolize certain drugs more quickly or more slowly than average, or, in some cases, not at all. The specific enzyme ana-

lyzed by this test, called cytochrome P4502D6, plays an important role in the body's ability to metabolize some commonly prescribed drugs, including antidepressants, antipsychotics, beta-blockers and some chemotherapy drugs.

AmpliChip was the first DNA microarray test to be cleared by the FDA. A microarray is similar to a computer microchip, but instead of tiny circuits, the chip contains tiny pieces of DNA, called probes.

RACE- AND GENDER-BASED MEDICINE

In 2005, the FDA for the first time approved a drug for use in a specific race: BiDil® (isosorbide and hydralazine), a life-saving drug for heart failure in black patients. In the 1990s, the drug had failed to beat placebo in a broad population but showed promise in black patients. Further testing confirmed those results.

Although BiDil thus far is the only drug to win a race-specific approval, it's far from unique in its varied effects across populations. Many drugs, including common blood-pressure medicines and antidepressants, exhibit significant racially correlated safety and efficacy differences.

For example, in a large study of one of the most common blood pressure medications, Cozaar® (losartan), researchers found a reduced effect in black patients—a fact that has been added to the prescribing information for the drug. Interferon, likewise, appears to be less effective in blacks with hepatitis than in non-Hispanic white patients (19 percent vs. 52 percent response rate), according to a study in the *New England Journal of Medicine*.

Another study found Japanese cancer patients are three times more likely to respond to Iressa, apparently because of a mutation in a gene for the drug's target, epidermal growth factor receptor.

Genetic variations—mutations that affect drug receptors, pathways and metabolizing enzymes—are thought to underlie most of the racial, ethnic and geographic differences in drug response, making the field ripe for biotech-style personalized medicine. NitroMed, for example, is collecting genetic material with the hope of developing a test to identify all patients—irrespective of race—likely to respond to BiDil.

> Some companies are exploring the concept of gender-based medicine to take into account the differences in male and female response to medicine.

Some companies are exploring the concept of gender-based medicine to take into account the differences in male and female response to medicine. Aspirin, for example, prevents heart attacks in men but not in women. At least one biotech company is developing a lung cancer drug that shows greater promise in women.

Regenerative Medicine

Biotechnology is showing us new ways to use the human body's natural capacity to repair and maintain itself. The body's toolbox for self-repair and maintenance includes many different proteins and various populations of stem cells that have the capacity to cure diseases, repair injuries and reverse age-related wear and tear.

TISSUE ENGINEERING

Tissue engineering combines advances in cell biology and materials science, allowing us to create semi-synthetic tissues and organs in the lab. These tissues consist of biocompatible scaffolding material, which eventually degrades and is absorbed, plus living cells grown using cell-culture techniques. Ultimately the goal is to create whole organs consisting of different tissue types to replace diseased or injured organs.

The most basic forms of tissue engineering use natural biological materials, such as collagen, for scaffolding. For example, two-layer skin is made by infiltrating a collagen gel with connective tissue cells, then creating the outer skin with a layer of tougher protective cells. In other methods, rigid scaffolding, made of a synthetic polymer, is shaped and then placed in the body where new tissue is needed. Other synthetic polymers, made from natural compounds, create flexible scaffolding more appropriate for soft-tissue structures, like blood vessels and bladders. When the scaffolding is placed in the body, adjacent cells invade it. At other times, the biodegradable implant is seeded with cells grown in the laboratory prior to implantation.

Simple tissues, such as skin and cartilage, were the first to be engineered successfully. Recently, however, physicians have achieved remarkable results with a biohybrid kidney (renal-assist device, or RAD) that maintains patients with acute renal failure until the injured kidney repairs itself. In a clinical trial of the RAD in patients with acute kidney injury, patients receiving the RAD were 50 percent less likely to die. The hybrid kidney is made of hollow tubes seeded with kidney stem cells that proliferate until they line the tube's inner wall. These cells develop into the type of kidney cell that releases hormones and is involved with filtration and transportation.

The human body produces an array of small proteins known as *growth factors* that promote cell growth, stimulate cell division and, in some cases, guide cell differentiation. These natural regenerative proteins can be used to help wounds heal, regenerate injured tissue and advance the development of tissue engineering described in earlier sections. As proteins, they are prime candidates for large-scale recombinant production in transgenic organisms, which would enable their use as therapeutic agents.

Some of the most common growth factors are:

- *epidermal growth factor*, which stimulates skin cell division and could be used to encourage wound healing;
- *erythropoietin*, which stimulates the formation of red blood cells and was one of the first biotechnology products;
- *fibroblast growth factor*, which stimulates cell growth and has been effective in healing burns, ulcers and bone, and in growing new blood vessels in patients with blocked coronary arteries;
- *transforming growth factor-beta*, which helps fetal cells differentiate into different tissue types and triggers the formation of new tissue in adults; and
- *nerve growth factors*, which encourage nerve cells to grow, repair damage; they could be used in patients with head and spinal cord injuries or degenerative diseases such as Alzheimer's disease.

Vaccines

Vaccines help the body recognize and fight infectious diseases. Conventional vaccines use weakened or killed forms of a virus or bacteria to stimulate the immune system to create the antibodies that will provide resistance to the disease. Usually only one or a few proteins on the surface of the bacteria or virus, called antigens, trigger the production of antibodies. Biotechnology is helping us improve existing vaccines and create new vaccines against infectious agents, such as the viruses that cause cervical cancer and genital herpes.

BIOTECHNOLOGY VACCINE PRODUCTION

Most of the new vaccines consist only of the antigen, not the actual microbe. The vaccine is made by inserting the gene that produces the antigen into a manufacturing cell, such as yeast. During the manufacturing process, which is similar to brewing beer, each yeast cell makes a perfect copy of itself and the antigen gene. The antigen is later purified from the yeast cell culture. By isolating antigens and producing them in the laboratory, it is possible to make vaccines that cannot transmit the virus or bacterium itself. This method can also increase the amount of vaccine that can be manufactured because each manufacturing cell can produce many antigens for purification.

Using these techniques of biotechnology, scientists have developed antigen-only vaccines against life-threatening diseases such as hepatitis B and meningitis.

Researchers have discovered that injecting small pieces of DNA from microbes is sufficient for triggering antibody production.

Such *DNA vaccines* could provide immunization against microbes for which we currently have no vaccines.

Biotechnology is also broadening the vaccine concept beyond protection against infectious organisms. Various researchers are developing vaccines against diseases such as diabetes, chronic inflammatory disease, Alzheimer's disease, cancer and autoimmune disorders.

VACCINE DELIVERY SYSTEMS

Most vaccines require special handling—many require refrigeration during shipping and storage—syringes and skilled professionals to administer them. Some researchers are working to create new vaccine delivery technologies that simplify distribution and use. Technologies under study include oral vaccines, vaccines administered via patch, and even edible vaccines manufactured by plants and animals.

Academic researchers have obtained positive results using human volunteers who consumed hepatitis vaccines in bananas, and *E. coli* and cholera vaccines in potatoes. In addition, because these vaccines are genetically incorporated into food plants and need no refrigeration, sterilization equipment or needles, they may prove particularly useful in developing countries.

Researchers are also developing skin patch vaccines for tetanus, anthrax, influenza and *E. coli.*

Plant-Made Pharmaceuticals

Advances in biotechnology have made it possible to genetically enhance plants to produce therapeutic proteins essential for the production of a wide range of protein pharmaceuticals—such as monoclonal antibodies, enzymes and blood proteins.

Plant-made pharmaceutical production is regulated under stringent rules of the U.S. Department of Agriculture (USDA) and the FDA. The primary agency that regulates and monitors this technology is USDA's Animal and Plant Health Inspection Service (APHIS).

Therapeutic proteins produced by transgenic plants to date include antibodies, antigens, growth factors, hormones, enzymes, blood proteins and collagen. These proteins have been grown in field trials in a wide variety of plants, including alfalfa, corn, duckweed, potatoes, rice, safflower, soybeans and tobacco.

> Field trials with protein-producing plants are providing the essential building blocks for innovative treatments for diseases such as cancer, HIV, heart disease, diabetes, Alzheimer's disease, kidney disease, Crohn's disease, cystic fibrosis, multiple sclerosis, spinal cord injuries, hepatitis C, chronic obstructive pulmonary disease, obesity and arthritis.

In addition, scientists have made excellent progress in using plants as vaccine-manufacturing and -delivery systems. They have used tobacco, potatoes, tomatoes and bananas to produce experimental vaccines against infectious diseases, including cholera, a number of microbes that cause food poisoning and diarrhea (e.g., *E. coli* and the Norwalk virus), hepatitis B and the bacterium that causes dental cavities. A cancer "vaccine" (which is therapeutic and not preventative) to non-Hodgkin's lymphoma has also been produced in plants.

ECONOMIC AND ACCESS BENEFITS

Since most proteins cannot be chemically synthesized, there are very few options for protein production for pharmaceutical purposes: mammalian and microbial cell cultures and plants. More than $500 million and five years are required to build a facility for mammalian cell cultures.

Because protein-producing plants require relatively little capital investment, and the costs of production and maintenance are minimal, they may provide the only economically viable option for independent production of therapeutic proteins in underdeveloped countries.

Therapeutic Development Overview

In the United States, the Food & Drug Administration regulates the development, manufacturing and marketing of most biotechnology therapeutics used in health care.

BIOLOGICS & DRUGS

Many biotech therapies are *biologics*, meaning they are derived from living sources such as cells. Biologics are complex mixtures whose active ingredients—usually proteins—are hundreds of times larger than the compounds found in most pills. These products usually must be injected or infused directly into the bloodstream to be effective.

Biologics include blood and blood-derived products and vaccines, as well as biotechnology-based recombinant proteins and monoclonal antibodies. Most biologics are regulated by the FDA under the Public Health Service Act and require approval of a biologic license application (BLA) prior to marketing.

Through the late 1990s, biotechnology was closely associated with recombinant and antibody-based biologics, but increasingly biotech companies are using genetic and other biological discoveries to develop so-called small-molecule drugs. These are the chemically simple compounds that are so familiar on pharmacy shelves. They are often formulated as pills (although small-molecule products may also be injected or infused) and most are easily duplicated by generic manufacturers through well-understood chemical processes.

The FDA regulates small-molecule drugs under the Food, Drug and Cosmetic (FDC) Act. Approval of a new drug application (NDA) is required before such a drug can be marketed. (Note: A few biologics, notably insulin and growth hormone, are regulated under the FDC Act as well.)

Although drugs and biologics are subject to different laws and regulations, drugs and most therapeutic biologics both fall under the purview of the FDA's Center for Drug Evaluation and Research (CDER, usually pronounced "cedar"). Vaccines, blood products, and cell and gene therapies are regulated by the FDA's Center for Biologics Evaluation and Research (CBER, usually pronounced "seeber").

PRODUCT DEVELOPMENT

It typically takes 10 to 15 years and an average of more than $800 million (including the cost of failures) to develop a new therapy. The process is rigorous and conducted in multiple stages, beginning with lab and animal testing, followed by clinical trials in humans, regulatory review and, if a product is approved, postmarketing studies and surveillance.

ANIMAL TESTING

Once a potential drug has been identified, animal testing is usually the first step, typically in two or more species, since drug effects vary across species. Many of these studies are ADME (absorption, distribution, metabolism and excretion) and toxicity studies. They document absorption of the drug, how the body breaks it down chemically, the toxicity and activity of the breakdown products (called metabolites), and the speed at which the drug and its metabolites are cleared from the body.

Scientists also use animal models of particular diseases to test for efficacy signals that can guide further refinement of a drug or clinical testing. Although animal efficacy results are important to drug development, they may be used for efficacy evidence in support of FDA approval for human use only for biodefense products. Biodefense products can be tested for safety in humans, but not for efficacy, because it would be unethical to expose volunteers to chemical warfare agents, anthrax and the like in order to test whether a medicine or vaccine works.

Scientists hope someday to supplement or replace some animal testing with advanced technologies such as computer models of human biological pathways. But some animal testing is likely to remain necessary for maximizing safety before products are tested in humans.

BIO members abide by BIO's Ethical Principles for the Care and Use of Animals in Biotechnology Research. (See page X.)

CLINICAL TRIALS

A drug that passes animal safety studies may move into human testing following the submission of an investigational new drug (IND) application to the FDA. Most studies, or trials, of new products may begin 30 days after the agency receives the IND.

Almost every new drug goes through multiple clinical trials, beginning with early studies (Phase I) in small groups of patients to test safety. Larger mid-stage trials (Phase II) examine safety and obtain preliminary efficacy data. The final stage of premarket testing (Phase III) seeks to gather convincing efficacy data in the specific patient population the drug's developer hopes to treat.

The design, or *protocol*, of clinical trials varies tremendously, depending on the nature of the product, the patient population and efficacy of existing treatments. Some drugs, for very rare and devastating diseases, have been approved after studies in only a handful of patients; others, often products for milder conditions and/or for which therapies are already available, must be tested in thousands of patients to win approval.

In many trials, one group of patients (or arm of the study) receives the drug being tested, while another group (the control group) receives a placebo that looks just like the drug and is administered the same way. Patients are randomized—that is, randomly assigned—to one or the other arm.

A trial in which the health care provider knows whether the patient is receiving the placebo or active drug, but the patient does not, is a single-blind trial. One in which neither the patient nor the health care provider knows whether the drug or placebo is being administered is called double-blind. Especially for trials measuring efficacy, double-blinded, randomized trials are considered the gold standard.

Other key terms for clinical trials:

- *Investigators*—the doctors or other health care professionals conducting a trial.
- *Institutional review boards*—local oversight groups at hospitals, universities and other health care facilities who ensure trials are conducted ethically and as safely as possible.
- *Endpoints*—a clinical trial's outcome measures (such as tumor shrinkage, viral clearance, or survival).
- *Indication*—the specific condition a drug aims to treat. An indication may be broad (for example, Type 2 diabetes) or it may be narrower (for example, insulin-dependent Type 2 diabetes).

Clinical trials must be sufficiently powered—that is, must enroll enough patients with appropriately selected endpoints—to deliver meaningful conclusions.

Once data from a well-designed trial are recorded and analyzed, researchers convey how confident they are that their conclusions are meaningful through a statistic called the *p-value*. This is a calculated measure of the likelihood that a trial's conclusion resulted from chance. For example a p-value of 0.01 means there is only a one percent likelihood the outcome resulted from chance. For a clinical trial to be counted as a success, it must typically meet its endpoints with a p-value of 0.05 or less—meaning there is no more than a five percent probability the outcome resulted from chance.

PHASE I

Usually, the first study a drug or biologic enters is a Phase I trial enrolling a small number (fewer than 100) of healthy volunteers to test safety and obtain data on dosing, metabolism and excretion. Some Phase I trials are conducted in patients with a condition the drug might someday treat. Interesting signs of efficacy may be noted at this stage, but have little or no statistical weight.

A new type of early human testing, called Phase 0, or microdosing, is popular with some who hope to lower preclinical development time and cost. Conducted under an exploratory investigational new drug application, these tests may involve fewer than 10 patients who receive less than 1 percent of a standard drug dose. Using cutting-edge technologies such as accelerated mass spectrometry, Phase 0 studies seek to characterize drug metabolism and toxicity.

PHASE II

In Phase II, testing expands to include (usually) 100 to 300 participants who have a disease or condition the product may treat. Additional safety data are gathered, along with evidence of efficacy. Researchers may conduct Phase II trials of a drug in several related conditions—for example, testing a cancer drug in a variety of cancers—in order to define the best patient population(s) for Phase III trials.

PHASE III

Phase III brings one or more even larger trials (often about 1,000 to 5,000 patients) in the specific patient population for which the drug developer hopes to win FDA approval. Phase III trials test efficacy and monitor for side effects, and multiple Phase III trials in one or more indications may be conducted for a single product.

APPROVAL PROCESS

If a therapy succeeds in clinical trials, the next step is applying for approval with the FDA by filing either a new drug application (NDA) or biologics license application (BLA). These applications can run hundreds of thousands of pages and include details on the product's structure, manufacturing, lab testing and clinical trials.

As part of the Prescription Drug User Fee Act (PDUFA), the FDA has a goal of acting on priority-review products (those addressing unmet medical needs) by six months after the application receipt. For a standard-review product, the agency's goal is a 10-month review. The term *PDUFA date* is the date by which the FDA must act to meet this goal for a particular product.

In weighing an NDA or BLA, particularly for a novel product, the FDA may seek the guidance of one of its independent advisory committees. Each committee has 10–15 members and includes experts and representatives of the public. The committees host public meetings, often attracting media coverage, at which the pros and cons of the products in question are presented and debated, culminating with a recommendation either for or against approval.

Advisory committee recommendations are non-binding, however. The final regulatory decision rests with the agency.

POST-APPROVAL

Every approved drug comes with an official product label, in a standardized format, whose contents are developed by the FDA and the company marketing the drug. The label contents include the approved indication(s), as well as a description of the drug, its side effects, dosage, clinical trial summaries and other information useful to physicians. Although doctors may prescribe a therapy "off-label" for indications not expressly approved by the FDA, manufacturers are prohibited from marketing off-label indications, and insurance does not always cover such uses.

Because clinical trials are not large enough to detect rare side effects, new drugs must be monitored once they enter the market. Drug makers are required by law to report adverse events to the FDA, and patients and physicians may also report problems to the agency through its MedWatch Web site (www.fda.gov/medwatch/).

To cast a wider net and pick up adverse events physicians and patients may not even realize are related to a drug, the Food & Drug Administration Amendments Act of 2007 (FDAAA) mandates a private-public partnership to conduct active postmarket surveillance through the analysis of large patient databases (such as those maintained by major insurers and the Centers for Medicare and Medical Services).

Additionally, for some new drugs, the FDA and a company may create a Risk Evaluation and Mitigation Strategy (REMS) to ensure the drug's benefits outweigh the risks. A Phase IV clinical trial may be designed to refine knowledge about the drug.

Initial drug approvals usually cover only a single indication, often a narrow one. Although drugs may be prescribed off-label for other indications, companies often conduct additional Phase II and III trials to confirm the drug works in those indications. If successful, they submit the new data to the FDA for approval through a supplemental NDA or BLA. If approved, a new indication is added to the product label, allowing the company to market the drug for that indication.

agricultural
Production Applications

Humans have always relied on plants and animals for food, shelter, clothing and fuel, and for thousands of years farmers have been changing plants and animals to better meet our evolving needs. Those needs will grow significantly in the next few decades as population climbs. The global population, approximately 1.6 billion in 1900, has surged to 6.7 billion and is expected to reach 9 billion by 2050. The United Nations Food and Agriculture Organization estimates world food production will have to double on existing farmland if it is to keep pace with population growth.

Biotechnology can help by increasing yields, reducing the use of resources such as water and fertilizer, and controlling pests in environmentally compatible ways.

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Crop Biotechnology

Farmers and plant breeders have relied for centuries on crossbreeding, hybridization and other genetic modification techniques to improve the yield and quality of food and fiber crops and to provide crops with built-in protection against insect pests, disease-causing organisms and harsh environmental conditions. Stone Age farmers selected plants with the best characteristics and saved their seeds for the next year's crops. By selectively sowing seeds from plants with preferred traits, the earliest agriculturists performed genetic modification to convert wild plants into domesticated crops.

As knowledge of plant genetics improved, farmers crossbred plants with desirable traits (or lacking undesirable ones) to produce offspring that combined the best traits of both parents. Today, virtually every crop plant grown commercially for food or fiber is a product of crossbreeding, hybridization or both. Unfortunately, these processes are often costly, time consuming, inefficient and subject to significant practical limitations. For example, producing corn with higher yields or natural resistance to certain insects would take dozens of generations of traditional crossbreeding, if it is possible at all.

The tools of biotechnology allow plant breeders to select single genes that produce desired traits and move them from one plant to another. The process is far more precise and selective than traditional breeding in which thousands of genes of unknown function are moved into crops.

Biotechnology also overcomes the technical obstacles to moving genetic traits between plants and other organisms. This opens up a world of genetic traits to benefit food, fuel and fiber production. We can, for example, take a bacterium gene that yields a protein toxic to a disease-causing fungus and transfer it to a plant. The plant then produces the protein and is protected from the disease without the help of externally applied fungicides.

IMPROVING CROP PRODUCTION

Today's technology may be different, but the goals of agricultural scientists remain the same: increased yields; resistance to diseases caused by bacteria, fungi and viruses; the ability to withstand harsh environmental conditions such as freezes and droughts; and resistance to pests such as insects, weeds and nematodes.

Natural Protection for Plants

Scientists have discovered that plants, like animals, have built-in defense systems against insects and diseases, and they are searching for environmentally benign chemicals that trigger those natural defense mechanisms.

Biotechnology also opens up new avenues for working with nature by providing new *biopesticides*, such as microorganisms and fatty acid compounds, that are toxic to targeted crop pests but do not harm humans, animals, fish, birds or beneficial insects. Biopesticides can also control pest populations that have developed resistance to conventional pesticides.

A biopesticide that farmers (including organic farmers) have used since the 1930s is the microorganism *Bacillus thuringiensis*, or Bt, which occurs naturally in soil. Several of the proteins the Bt bacterium produces are lethal to certain insects, such as the European corn borer, a prevalent pest that costs U.S. farmers more than $1 billion in crop damage and control costs each year. Bt bacteria used as a biopesticidal spray can eliminate target insects without chemical pesticides.

Using the flexibility provided by biotechnology, we can transplant the genetic information for Bt proteins into plants. The plant that once was a food source for an insect now kills it, lessening the need to spray crops with chemical pesticides to control infestations.

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Herbicide Tolerance

When growing conditions are good for crops, they are also good for weeds. Biotechnology offers a way to kill the weeds with

herbicides—without damaging the crop plants. Many biotech crops are tolerant of specific herbicides, allowing farmers to spray herbicide over their fields and destroy the weeds without damaging the crops. The method saves labor and promotes no-till farming, which can cut soil erosion up to 90 percent.

Resistance to Environmental Stresses

In addition to biological, or biotic, challenges such as insects and weeds, crop plants must contend with the abiotic stresses nature dispenses regularly: drought, cold, heat and soils that are too acidic or salty to support plant growth. While plant breeders have successfully incorporated genetic resistance to biotic stresses into many crop plants through crossbreeding, their success at creating crops resistant to abiotic stresses has been more limited, largely because few crops have close relatives with genes for resistance to these stresses.

Biotechnology jumps over this hurdle by allowing scientists to import useful genes from other species. For example, researchers have genetically modified tomato and canola plants to tolerate salt levels 300 percent greater than non-genetically modified varieties. Other researchers have identified genes involved in cold, heat and drought tolerance in some plants and bacteria, and are working on introducing those genes to crops. Scientists in Mexico have used gene transfer to produce maize and papaya that are tolerant to the high levels of aluminum that significantly limit crop plant productivity in many developing countries.

Increasing Yields

In addition to building in protection against diseases, pests, environmental stresses and weeds to minimize losses, scientists use biotechnology to improve crop yields directly. Researchers at Japan's National Institute of Agrobiological Resources added maize photosynthesis genes to rice to increase its efficiency at converting sunlight to plant starch and increased yields by 30 percent. Other scientists are altering plant metabolism by blocking gene action in order to shunt nutrients to certain plant parts. For example, yields increase as starch accumulates in potato tubers and not leaves, or as oil-seed crops, such as canola, allocate most fatty acids to the seeds.

Biotechnology also allows scientists to develop crops that are better at accessing the micronutrients they need. For example, Mexican scientists have genetically modified plants to secrete citric acid, a naturally occurring compound, from their roots. In response to the slight increase in acidity, minerals bound to soil particles, such as calcium, phosphorous and potassium, are released and made available to the plant.

Nitrogen is the critical limiting element for plant growth and, step-by-step, researchers from many scientific disciplines are teasing apart the details of the symbiotic relationship that allows nitrogen-fixing bacteria to capture atmospheric nitrogen and provide it to the plants that harbor them in root nodules:

- Plant geneticists in Hungary and England have identified the plant gene and protein that enable the plant to establish a relationship with nitrogen-fixing bacteria in the surrounding soil.
- Microbial geneticists at the University of Queensland have identified the bacterial gene that stimulates root nodule formation.
- Collaboration among molecular biologists in the European Union, United States and Canada yielded the complete genome sequence of one of the nitrogen-fixing bacteria species.
- Protein chemists have documented the precise structure of the bacterial enzyme that converts atmospheric nitrogen into a form the plant can use.

CROP BIOTECHNOLOGY IN DEVELOPING COUNTRIES

Today, 70 percent of the people on the planet grow what they eat, and, despite the remarkable successes of the Green Revolution in the 1960s, millions of them suffer from hunger and malnutrition. Feeding the world's poorest is complicated by many factors, including population growth and urbanization, climate change, poverty, inadequate food distribution systems, and high food and energy costs. Moreover, investment in agriculture in many poor countries has declined precipitously in recent decades.

In fact, the Green Revolution never reached many small-holder farmers, especially those in sub-Saharan Africa, because the new agricultural practices required upfront investments—in irrigation systems, machinery, fuel, chemical fertilizers and pesticides—beyond the financial reach of small-holder farmers.

The good news is that the biotech agricultural revolution is taking hold in poor countries faster than the Green Revolution because this new technology is knowledge intensive, not capital intensive: Biotech advances are incorporated into the crop seed itself. Moreover, because of the remarkable flexibility provided by crop biotechnology, an improvement can be duplicated across multiple staple crops.

Realizing biotechnology's extraordinary capacity for improving the health, economies and living conditions of people in developing countries, many universities, research institutions, government agencies and companies in the industrialized world have developed relationships for transferring various biotechnologies to developing countries. The nature of the

relationship varies, depending on the needs and resources of the partners involved. For example:

- Cornell University donated transgenic technology for controlling the papaya ring spot virus to research institutions in Brazil, Thailand and Venezuela and provided their scientists with training in transgenic techniques.
- Japan's International Cooperation Agency built tissue culture facilities at an Indonesian research institution so that scientists there could develop disease-free potato materials for planting. The Indonesian researchers are also working with scientists at Michigan State University to develop insect-resistant potatoes and sweet potatoes.
- An Australian agricultural research center collaborated with Indonesian researchers on studies of nitrogen fixation and development of disease-resistant peanuts.
- Seiberdorf Laboratories (Austria) worked with the Kenyan Agricultural Research Institute to transfer technology for cassava mutagenesis and breeding.
- Monsanto has donated virus resistance technologies to Kenya for sweet potatoes, Mexico for potatoes and Southeast Asia for papaya. The company has also donated technology for pro-vitamin A production in oilseed crops to India.
- Pioneer Hi-Bred and the Egyptian Agricultural Genetic Engineering Research Institute (AGERI) collaborated to discover potentially novel strains of Bt in Egypt. Pioneer trained AGERI scientists in methods for characterizing Bt strains and transgenic techniques. Patents are owned by AGERI and licensed to Pioneer.
- AstraZeneca trained scientists from Indonesia's Central Research Institute for Food Crops in the use of proprietary technologies for creating insect-resistant maize.
- The Malaysian palm oil research institute has collaborated with Unilever and universities in England, the United States and the Netherlands on research to change the nutritional value of palm oil and find new uses for it, such as lubricants, fuels, a vitamin E precursor, natural polyester and biodegradable plastics.

While technology transfer has been and, no doubt, will continue to be an essential mechanism for sharing the benefits of crop biotechnology, many developing countries are taking the next step: investing resources to build their own capacity for biotechnology research, development and commercialization. The leaders in these countries recognize the potential of crop biotechnology to provide agricultural self-sufficiency, preserve natural resources, lower food prices for consumers and provide income to small-

holder farmers. Plus, they understand that biotechnology has the potential to improve existing exports and create new ones, leading to a more diversified economy and increased independence.

These leaders also know that many of their agricultural problems can best be solved by local scientists who are familiar with the intricacies of the regional farmland and climate, local traditions, and applicability—or lack of it—of technologies that were developed to solve agricultural problems in industrialized countries. To move their countries forward, they are investing human and financial resources in developing local strength in crop biotechnology. For example:

- The Malacca government in Malaysia formed a unit in the Chief Minister's Office to promote research and development in biotechnology and established the Sarawak Biodiversity Center to ensure sustainable use of genetic resources and to build a strong database for bioresources.
- Pakistan's Ministry of Science and Technology prepared a biotechnology action plan and funded a three-year program to promote biotechnology research and development.
- Uganda's National Council of Science and Technology established its first commercial agricultural biotechnology lab to produce disease-free coffee and banana plantlets.
- Egypt's government, a longtime supporter of agricultural biotechnology, released a report encouraging farmers to plant genetically engineered crops to benefit from reduced pesticide applications, lower production costs, higher yields and increased income.

ENVIRONMENTAL AND ECONOMIC BENEFITS

Because farmers in many countries have grown biotech crops for years, data are now available for assessing the magnitude of the

environmental and economic benefits provided by biotechnology. A number of independent researchers have produced reports documenting these benefits.

According to the National Center for Food and Agricultural Policy's (NCFAP) 2006 report, in 2005 biotech crops adopted by U.S. growers increased yields by 8.3 billion pounds, saved growers $1.4 billion by lowering production costs, and reduced pesticide use by 69.7 million pounds. Based on increased yields and reduced production costs, growers realized a net economic impact or savings of $2.0 billion. The NCFAP study takes into account eight biotech crops—alfalfa, canola, corn, cotton, papaya, soybean, squash and sweet corn.

The Conservation Tillage Information Center (CTIC) at Purdue University attributes recent improvements in tillage reduction—which reduces soil erosion—to the increased use of the herbicide-tolerant crop varieties produced through biotechnology. CTIC concludes that this increase in conservation tillage prevents 1 billion tons of soil erosion per year, saves $3.5 billion per year in sedimentations costs and lowers fuel use by 3.9 gallons per acre.

In developing countries, a single biotech crop, Bt cotton, has led to substantial environmental and economic benefits for farmers, according to the International Service for the Acquisition of Agri-Biotech Applications:

- Bt cotton increased yields by up to 50 percent for Indian farmers and 10 percent for Chinese farmers, and reduced insecticide use in both countries up to 50 percent.
- In India, farmer income from cotton has increased as much as $1.7 billion, thanks to biotechnology. Chinese farmers have experienced similar gains, with incomes growing more than $800 million nationally.
- A study of 9,300 cotton-growing households in India found that those in households growing Bt cotton have slightly more access to social benefits such as prenatal visits, assistance with at-home births, school enrollment for children and childhood vaccinations.

REGULATION OF CROP BIOTECHNOLOGY

U.S. regulatory policy for biotechnology products was established in 1986 with the publication by the White House Office of Science and Technology Policy of the "Coordinated Framework." This framework builds on the work of international expert bodies (such as the Organization for Economic Cooperation and Development and the U.S. National Academy of Sciences). The responsibilities of regulatory agencies are clarified, linked to the laws they administer and coordinated with other agencies that have potentially overlapping responsibilities.

The U.S. Food and Drug Administration (FDA) reviews the safety of foods and new food ingredients. In addition, all producers are required to ensure the safety and quality of anything they introduce into the food supply.

The FDA requires strict premarket testing and regulatory oversight of genetic modifications that significantly alter the nutritional value of the host food, use genetic material from outside the traditional food supply or use known allergens.

The FDA also requires labeling of any food product produced through biotechnology that significantly alters the host food's nutritional value or uses material from a known allergen. For example, if a product used a gene from a peanut, which is a potential allergen, it would be subject to testing and labeling requirements. The FDA also has the authority to order unsafe products off the market.

The U.S. Department of Agriculture (USDA) and the U.S. Environmental Protection Agency (EPA) impose safety requirements and/or performance standards on the development of pesticides, herbicides and genetically enhanced test crops. The USDA regulates to ensure that crop varieties improved through biotechnology are safe for the agricultural environment. Rigorous assessments are conducted concerning the derivation of the new varieties and their performance under contained and controlled field trials.

The EPA also coordinates with the USDA and FDA, using its own statutes to regulate the growing of plants with pest-protection characteristics. The EPA sets allowable food residue tolerance levels for any novel compounds that might be used.

Forest Biotechnology

Wood provides us with fuel, construction materials and paper, and its supplies are dwindling rapidly. Wood products are a $400 billion global industry, employing 3 million people, and demand is rising, even as major economies, such as Europe and Japan, are unable to grow enough trees to meet their current demand.

INCREASING PRODUCTIVITY

Scientists are using biotechnology to create cold tolerant trees, disease- and insect-resistant trees and to increase their growth rates. They are also learning how to use biotechnology to improve the efficiency with which trees convert solar energy into plant material and to shunt more of that energy into wood production and less into pollen, flowers or seeds. All of these methods of increasing productivity should lighten the pressure on natural forests.

However, developing biotech trees is a lengthy undertaking because trees take a long time to grow. So researchers are looking to other methods for increasing productivity. For example, they are using a biotechnology process in a fungus to fight diseases that infect trees and are working on improving the microorganisms that live on tree roots and provide trees with nutrients, much as nitrogen-fixing bacteria increase the nutrients available to soybeans and alfalfa. In addition, biopesticides have also been used extensively to control forest pests, and we expect progress in insect cell culture to boost the number of biocontrol agents available for forest insect control.

ENVIRONMENTAL BENEFITS

Perhaps a more important economic role for biotechnology in this industry will be found in changing the way we convert trees to useful products. Extensive research is being conducted to increase a tree's amount of cellulose, the raw material for papermaking, and to decrease the amount of lignin, a tough molecule that must be removed in papermaking. These improvements would also ease conversion of sawdust, woodchips and other wood-processing waste into ethanol, bioplastics and other biobased products that can be made from cellulose.

Traditionally, removing lignin from trees has required harsh chemicals and high energy costs, so changing the cellulose:lignin ratio genetically has important environmental implications, as does increasing the growth rate of trees. Because trees absorb carbon dioxide, any advance that allows us to increase tree yields without cutting down forest could have significant positive effects on global warming. Other environmental benefits that biotechnology is providing to the forestry industry include enzymes for:

- Pretreating and softening wood chips prior to pulping.
- Removing pine pitch from pulp to improve the efficiency of paper-making.
- Enzymatically bleaching pulp rather than using chlorine.
- De-inking of recycled paper.
- Using wood-processing wastes for energy production and as raw materials for manufacturing high-value organic compounds.
- Remediating soils contaminated with wood preservatives and coal tar.

Animal Biotechnology

WHAT IS ANIMAL BIOTECHNOLOGY?

Animals are helping to advance biotechnology, and biotechnology is improving animal health in return. Combining animals and biotechnology can lead to progress in four areas:

- Improved animal health and welfare.
- Enhancements to animal products.
- Environmental and conservation benefits.
- Advances in human health.

Animal biotechnology includes all animals—livestock, poultry, fish, insects, companion animals and laboratory animals—and covers three primary technologies: genomics, cloning and genetic engineering.

Animal Genomics

Having access to the genome of a livestock species makes it possible to identify individual genes and proteins that can control a host of commercially and economically crucial functions—everything from muscle growth and tenderness to disease resistance and reproduction. Even subtle differences in the genetic makeup of an individual animal can greatly affect its value for breeding, feedlot or branding purposes.

The diagnostic tools developed through the use of genomics are improving management practices, animal health and food quality. Traditionally, decisions regarding breeding or feedlot selection were made by human observation. But genomic-based diagnostic and selection tools replace "eyeballing" with scientific precision and efficiency, leading to more consistent and cost-effective results.

Benefits of DNA-based Products

- Disease surveillance and food safety: Using DNA to trace meat and animals through the food chain.
- Enhanced breeding and selection: Developing animals with desirable traits such as greater muscle mass or milk or egg production.
- Improved animal production efficiency: Creating management systems based on genetic potential.
- Enhanced end product quality and consistency: Certifying branded meat (such as Angus beef) to meet consumer demand.

Genomic technology extends beyond the farm. The major pet registries use diagnostic tests to verify parentage. New tests that can help identify breeds in both purebred and mix-breed animals are available commercially. Research is underway to identify genetic predisposition to disease.

Animal Cloning

Livestock cloning is the most recent evolution of selective assisted breeding in the ancient practice of animal husbandry. Arab sheikhs

first used artificial insemination in horses as early as the 14th century. In the last 50 years, techniques such as embryo transfer, in vitro fertilization, embryo splitting and blastomere transfer have become commonplace—providing farmers, ranchers and pet enthusiasts powerful tools for breeding the best animals.

Cloning does not change an animal's genetic makeup: it is simply another form of sophisticated assisted reproduction. Cloning allows livestock breeders to create an exact genetic copy of an existing animal—essentially an identical twin.

Livestock Cloning Benefits

Cloning animals is a reliable way of maintaining high-quality livestock to meet our nutritional needs. Identifying and reproducing superior livestock genetics ensures herds are maintained at the highest quality possible.

Animal cloning offers benefits to consumers, farmers and endangered species:

- Cloning accelerates the birth of the best possible stock and provides farmers with certainty of the genetic makeup of a particular animal.
- Cloning reproduces the strongest, healthiest animals, thus optimizing animal well-being and minimizing the need for veterinary intervention.
- Cloning can be used to protect endangered species. For example, in China, panda cells are kept on reserve as insurance against extinction.

For more information on animal cloning, visit CloneSafety.org.

Genetically Engineered or "Biotech" Animals

A genetically engineered animal is one that has had its genome deliberately modified using techniques of modern biotechnology. A transgenic animal has genetic material from another species added to its DNA. Transgenic technology can improve the nutritional value of animal products through enhanced genes. In addition, the technology promises improved animal welfare and productivity—a critical capability in meeting the food demands of a growing global population. Genetically engineered animals currently under development include pigs, cattle, fish and poultry, each of which will be thoroughly reviewed by the appropriate federal agencies before entering the marketplace.

Benefits of Genetically Engineered Animals

Genetically engineered animals have potential to improve consumer health and nutrition, as well as animal welfare and productivity. Benefits include:

- Increased nutritional value.
- Quality assurance.
- Higher-efficiency production.
- Stronger disease resistance.
- Improved animal welfare—less disease and longer lifespan.

Animal Welfare & the Environment

Genetic engineering technology can help cut animal mortality and disease, and thereby minimize the need for animal care interventions.

The technology can also be used to mitigate environmental impacts of livestock production. The EnviroPig™, for example, dramatically lowers levels of phosphorus pollution. Such applications underscore the industry's commitment to environmental protection.

Genetically Engineered Animals for Advancing Human Health

For decades, animals have been used to produce human pharmaceuticals. Horses, pigs, rabbits and other species have been enlisted to produce such products as anti-venoms, biologics to prevent organ transplant rejection, and the blood thinner heparin. Biotechnology now allows us to modify genes in these animals so that the drug proteins are more compatible with human biochemistry.

Animal production also offers the most efficient, practical way to produce certain drugs that are difficult to make in sufficient quantities using other methods. For example, animals can make human antibodies to deadly infectious diseases if they are modified with human immune genes.

Genetic engineering technology can also be used to make animal organs more compatible for transplant into humans, a process called xenotransplantation. Heart valves from pigs are already

used to replace damaged valves in human hearts. If xenotransplantation could be perfected with the help of transgenics, hundreds of thousands of lives could be saved each year.

Animal Welfare & the Environment

Biotechnology animals that produce biomedical products are extremely valuable, and animal welfare is a priority for everyone working with these animals.

Most of these technologies are being developed in domesticated animal species. Since these animals live on farms and do not mate with wildlife, the risk to the environment is miniscule.

What's Next?

Biotechnology is providing the tools to make all these benefits an everyday reality for consumers. In many cases, the largest impediment to successfully implementing these technologies is the absence of a clear regulatory pathway leading to commercialization. Another important challenge is educating the public, scientific and regulatory communities about the safety, effectiveness and benefits of these products.

HOW ARE PRODUCTS OF ANIMAL BIOTECHNOLOGY REGULATED?

Animal biotechnology is making incredible progress. If proven safe for animals, humans and the environment, it holds vast promise for improving our quality of life. Use of animal genomics, an extension of traditional animal breeding, is accepted as safe and is largely unregulated. However, scientists and industry leaders are awaiting final publication of a federal regulatory framework for genetically engineered animals.

Three government agencies regulate the animal health industry:

- The U.S. Department of Agriculture regulates veterinary biologics, vaccines and diagnostic test kits.
- The Food and Drug Administration reviews and approves new pharmaceuticals and feed additives.
- The Environmental Protection Agency regulates pesticides and topical products that kill fleas and other parasites.

The Department of Health and Human Services has developed a framework for the regulatory processes for the products of animal biotechnology from gentic engineering. Coordination among the federal agencies will be important for a science-based, streamline approach. Little published regulatory guidance exists for many emerging biotech products.

In early 2008, the U.S. Food and Drug Administration's Center for Veterinary Medicine published a long-awaited food safety risk assessment regarding cloning of farm livestock and their offspring, including the safety of food products for human consumption. The FDA concluded that meat and milk from animal clones and their offspring were safe to eat. Next steps include developing a risk-management process. Additionally, studies conducted by the National Academy of Sciences and other experts have determined that cloned animals and their products are safe for human consumption.

USING BIOTECHNOLOGY TO IMPROVE ANIMAL HEALTH

More than 100 animal biotech products, including bacterins and killed virus vaccines, are used in agricultural and companion animals. In 2006, the animal health industry invested $618 million in research and development, approximately 12 percent of its $5.8 billion in sales.

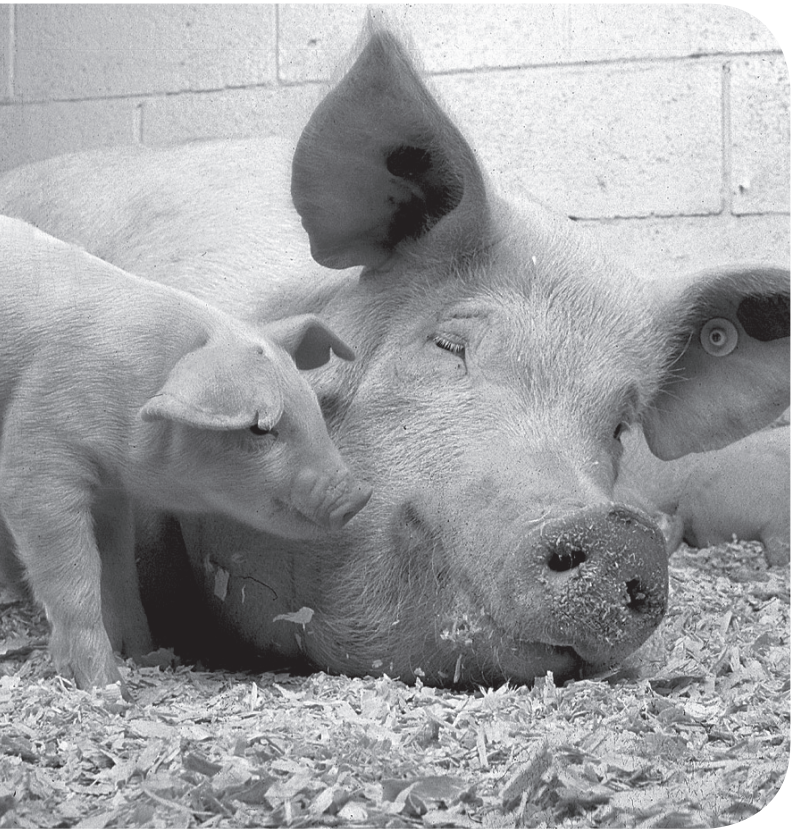
Biotechnology provides new tools for improving animal health and increasing livestock and poultry productivity. These improvements come from:

1. An enhanced ability to detect, treat and prevent diseases and other problems.
2. Better feed derived from biotech crops designed to meet the dietary needs of different farm animals.
3. Improved livestock productivity through improved animal breeding and disease resistance.

Enhancing Detection, Treatment and Prevention of Animal Diseases

The animal health industry has developed many effective treatments that can prevent and treat dangerous livestock and poultry diseases. Quick diagnosis and treatment, coupled with strong preventative measures, help lower production costs and improve overall animal well-being. Additionally, healthier farm animals result in safer foods for consumers.

- Biotechnology allows farmers to quickly diagnose the following infectious diseases through DNA and antibody-based tests: brucellosis, pseudorabies, scours, foot-and-mouth disease, bluetongue, avian leucosis, bovine spongiform encephalopathy (mad cow disease) and trichinosis.
- Farmers may soon be able to manage several farm animal diseases through biotechnology-based pharmaceuticals, including foot-and-mouth disease, classical swine fever and bovine spongiform encephalopathy.
- New biological vaccines protect farm animals from a wider range of diseases, including foot-and-mouth disease, scours, brucellosis, shipping fever, lung infections affecting pigs (pleu-



ro-pneumonia, pneumonic pasteurellosis, enzootic pneumonia), hemorrhagic septicemia, fowl cholera, Newcastle disease of poultry, rabies and infections that affect cultivated fish.

- Molecular-based typing of pathogens, such as genetic fingerprinting, allows for the monitoring of the spread of disease within and between herds and can identify the source of an outbreak.
- Genetic analysis of animal pathogens is leading to an improved understanding of the factors that cause disease and how best to control them.

Better feed for animals from biotech crops

Crops improved through biotechnology may provide nutritionally enhanced feed for farm animals. Improved feeds will raise animal size, productivity and growth rates. Biotech versions of several animal-feed crops are under study:

- Some products are designed to improve the quality of protein, oils or energy availability in the final animal feed product.
- One crop is designed to improve shelf life of beef by improving the antioxidant properties of the meat's fats.
- Through biotechnology, increased digestibility of the low-quality roughages will allow crops to be more useful in feeding livestock.
- Scientists are working to develop feed with edible vaccines for farm animals. For example, in the future, pigs could be fed transgenic alfalfa that would stimulate immunity to a serious intestinal virus.

Improved livestock productivity through improved animal breeding and disease resistance

Improved animal breeding. The goal of livestock producers is to select the best animals for their breeding programs to obtain the same output (milk, eggs, meat, wool) with less input (food), or increased output with the same input. Improving animal health as well as increasing muscle mass and decreasing fat in cattle and pigs have long been goals of livestock breeders.

Biotechnology is helping them reach those goals. For example, with genetic mapping techniques, animals that are naturally disease-resistant can be identified and used for breeding programs, resulting in naturally healthier offspring. Conversely, animals with genetic weaknesses and defective genes can be identified and removed from breeding programs. Examples of this work include the following:

- New DNA tests can identify pigs with the genetic condition porcine stress syndrome, which causes tremors and death under stressful conditions.
- Inherited weaknesses of cattle can be identified with DNA tests, which are currently being used in national breeding herds in Japan. Tests can identify leukocyte adhesion deficiency, which causes repeated bacterial infections, stunted growth and death within the first year of life. Other DNA tests can identify a hereditary condition that produces anemia and retards growth in Japanese black cattle.
- Genetic mapping and the development of DNA markers are being used to identify genes in chickens that have developed a resistance to Marek's disease, a virus-induced disease similar to cancer.
- USDA biotech researchers announced a breakthrough using Genetic engineering technology that will help cows resist mastitis, a bacterial infection of milk glands that causes inflammation, swelling and lower milk production. Mastitis results in losses of up to $2 billion annually for U.S. dairy farmers.
- Experimental cattle resistant to bovine spongiform encephalopathy are being produced using biotechnology techniques such as knockout technology and cloning.
- Using genetic engineering technology, researchers in Britain are developing chickens that are resistant to avian influenza. If the birds are approved by regulators, it would take only four to

five years to breed enough to replace the entire world population of chickens.

Assisted reproductive technologies (ART). Livestock producers are always interested in improving the productivity of agricultural animals and have used assisted reproductive technologies since the first use of artificial insemination in the 1950s. Livestock cloning is the newest tool in the ART toolbox.

Using biotechnology to increase the productivity of livestock is a variation of selective breeding. Breeders select the best individual animals that possess desirable traits; then, instead of breeding the animals, they collect eggs and sperm and allow fertilization to occur in a laboratory dish. This *in vitro* fertilization is followed by embryo culture, a form of mammalian cell culture in which the fertilized egg develops into an embryo. When the embryo is a few days old, it is taken from the laboratory dish and implanted into a female of the same species—but not necessarily of the same breed. This is known as embryo transfer.

Sometimes the embryo, which is a clump of cells at this stage in development, is divided into several parts, and each cell cluster is implanted. This is a form of cloning that has been used for a few decades to improve the genetic makeup of the herd more quickly than by simply relying on a single female that produces one calf per year.

The industry that is commercially cloning farm livestock is also using somatic cell nuclear transfer (SCNT). Animals that have been cloned with SCNT for show ring purposes include cattle, pigs, sheep and horses.

As yet, no SCNT-cloned animals or their offspring have been introduced into the food supply. However, in early 2008, the FDA published a final risk assessment concluding that food products from these animals are safe, so cloning technology is now being slowly adopted in the United States.

Additional health applications of biotechnology in animal agriculture

The biotechnology industry has proposed additional solutions for animal health and food safety.

- DNA sequencing of individual animals could serve as the ultimate animal identification, allowing for tracking of meat from farm to table.
- A biotech vaccine for Newcastle disease in chickens was approved by the USDA. This vaccine is a plant-made pharmaceutical developed to improve animal health.
- A cattle vaccine produced in plants could reduce *Escherichia coli (E. Coli)* 0157:H7 shedding in feedlot cattle, a further assist toward improved food safety on the farm.

ENHANCING ANIMAL PRODUCTS

Biotechnology can dramatically improve animal products that humans consume and use. Some of these improvements result from vaccines, medicines and diagnostic tests that make animals healthier. However, biotechnology has also made great strides in enhancing animal products at a cellular level through genomics, cloning and transgenic technologies. Recent breakthroughs include the following:

- Researchers can produce biotech cows, pigs and lamb with reduced fat and increased lean muscle.
- Recent research showed that pigs could be produced with higher heart healthy omega-3 fatty acids, using transgenic technology.
- Genetic mapping projects allow farmers to identify highly productive animals for breeding programs. Genomics technology is being applied to improving the conventional breeding of superior animals in order to produce desirable traits.
  - Genetic technologies are finding a place in the beef industry.
    - In 2003, the first validated SNP (single nucleotide polymorphism) beef cattle genome was created. SNP technology is being used to identify clusters of genes that contribute to a trait—for example, leaner beef cattle. Then, through conventional breeding, lines of cattle are being developed that express the increased muscling.
    - A DNA test has been approved to verify Angus beef.
  - Worldwide, research teams are working to sequence the genomes of a wide variety of animals. In October 2004, the Bovine Genome Sequencing Project announced it had successfully sequenced the cow genome. In December 2004, the Chicken Genome Sequencing Consortium announced it had sequenced the chicken genome. In late 2005, a new Consortium for Swine Genome Sequencing was launched.
- Biotech cows can now produce "designer milks" with increased levels of protein that can improve the diet of children or improve production of cheese and yogurt.
- Scientists are now working to remove from milk the proteins that cause lactose intolerance. It is estimated that 90 percent of the Asian population is lactose intolerant.

- Australian scientists have increased wool production by feeding sheep biotech lupin, a mainstay of sheep's summer diet.
- Scientists are working to develop biotech shrimp that lack the protein responsible for 80 percent of shrimp allergies.

ENVIRONMENTAL AND CONSERVATION EFFORTS THROUGH ANIMAL BIOTECHNOLOGY

Environmental Impact

Livestock producers are challenged with disposing of more than 160 million metric tons of manure annually. Animal manure, especially that of swine and poultry, is high in nitrogen and phosphorus, which can contribute to surface and groundwater pollution.

- Several crops improved with biotechnology may offer animal feed that decreases phosphorus and nitrogen excretion, total manure excretion and offensive odors.
- Further, the EnviroPig is a biotech pig that is environmentally friendly. This pig has a gene added to enhance salivary phytase, thereby improving phosphorus digestibility and retention of phosphorus, with reduced excretion of phosphorus in the manure of the animal. The goal is to lower groundwater phosphorus contamination in areas that surround livestock farms.

Endangered Species Conservation

Reproductive and cloning technologies, as well as medicines and vaccines developed for use in livestock and poultry, can help save endangered mammals and birds.

Borrowing biotechnology techniques used by livestock breeders, veterinarians at the Omaha Zoo recently used hormonal injections, artificial insemination, embryo culture and embryo transfer to produce three Bengal tiger cubs. A Siberian tigress served as the surrogate mother for these embryos.

Worldwide, researchers have used cloning technologies to conserve endangered species. In September 2001, researchers at the University of Teramo, Italy, created a clone of the European mouflon, the world's smallest wild sheep. There are thought to be fewer than 1,000 adult mouflons in Sardinia, Corsica and Cyprus.

In January 2001, the world's first cloned endangered species, an ox-like guar, was born in the United States, though it succumbed to a common dysentery infection. There are estimated to be fewer than 36,000 guars in India and Southeast Asia due to human development of their natural habitat.

Researchers also have worked to clone the argali, the largest wild sheep, but have been unable to produce live offspring.

In December 2003, the first cloned whitetail deer was reported in the United States. Though not an endangered species, researchers believe the successful clone will provide valuable insight into cloning other wild animals, including endangered species.

In April 2003, the San Diego Zoo reported the birth of a cloned banteng, a wild cow native to the island of Java. Since January 2004, the banteng has been on public view at the San Diego Zoo; it is the first cloned species to be on display to the public at any zoo.

Researchers at the San Diego Zoo also employ other biotech and reproductive technologies in their conservation efforts. In 1975, they created the Frozen Zoo, a genetic bank that currently houses frozen cells from more than 7,000 endangered or threatened mammals, birds and reptiles. Other animal conservation organizations, including the Zoological Society of London and the Cincinnati Zoo, have created genetic databases to store cryogenically frozen samples of DNA, gametes and cell tissues for later use.

Recently, Chinese scientists announced that they are close to cloning the giant panda using trans-species cloning technology. The giant panda is a highly endangered species.

Furthermore, in 2005, an endangered species of Mongolian gazelle was cloned for the first time. The year also marked several other animal cloning firsts, including water buffalo and an Arab endurance champion horse.

Early in 2006, the first commercially cloned horses were born; champion cutting horses were cloned and healthy foals have been born.

Biotechnology techniques for working with endangered species have not been limited to cloning. Some researchers are using genetic samples to study the distribution of species and track the relationships between different groups of animals. These studies may help to prevent excessive interbreeding among small groups of animals.

Genetic studies also can help produce a healthier population of endangered species through increased genetic diversity. Conservationists studying the endangered Florida panther realized that, as the population shrank, inbreeding became more common. Through genetic testing, researchers found that the panthers were closely related to Texas cougars and had previously interbred. By introducing some cougars in the Florida panther breeding pool, scientists increased the genetic diversity of the species, resulting in a healthier panther population.

ANIMAL BIOTECHNOLOGY TO ENHANCE HUMAN HEALTH

Animals are often used as models for research, as many of the technologies developed for animals can be transferred to hu-

mans. They are also used more directly as sources of drugs and other therapies. Some of the work being done with animals that will advance human health:

Xenotransplantation

Extensive research has been done on the potential for using biotech animals as blood or organ donors for humans. The primary barriers to successful xenotransplantation include the immune reactions of the recipient to the graft, the possibility that animal tissues or organs might not function well in a human recipient, and the possibility that the xenotransplant might carry infection. Biotechnology has been used to address the problem of immunorejection, and biotech pigs have been developed with organs that may resist rapid rejection by the human immune system.

"Pharm" Animals

Researchers are developing genetically engineered animals, including cows, goats and sheep, that produce milk containing therapeutic proteins. These proteins may be used to nourish premature infants or to treat emphysema, cystic fibrosis, burns, gastrointestinal infections and immunodeficiency diseases such as AIDS. Some interesting ongoing projects include:

- The first drug product for humans produced by a transgenic animal was recently (August 2006) approved by the European Commission. This protein is human anti-thrombin, a naturally occurring plasma protein that has both anti-coagulant and anti-inflammatory properties. The protein is produced by transgenic goats whose milk contains human anti-thrombin.
- In 2005 in Argentina, cows were improved with biotechnology to produce human growth hormone. Scientists estimate that just 15 of these Jersey cows could produce enough human growth hormone to meet the current world demand.
- Dutch researchers are working with biotech rabbits that secrete a potential drug for Pompe's disease in their milk. Pompe's disease is an extremely rare genetic disorder that can result in crippled muscles, breathing problems and sometimes death.
- Scientists are working with biotech goats that produce an experimental anticancer medication.
- Biotech cows can now produce the human milk protein lactoferrin, which is an antibacterial protein that can be used to treat immunosuppressed patients or incorporated into infant formula.

Animals can also generate antibody therapeutics with the insertion of genes for creating human antibodies. These animals can then be vaccinated against human diseases, and antibodies can be collected from their blood and used for treating diseases in humans.

Biotechnology in Aquaculture

Aquaculture is the growth of aquatic organisms in a controlled environment. The increased public demand for seafood has encouraged scientists and industry to study ways that marine biotechnology can increase production. By using biotechnology techniques, including molecular and recombinant technology, aquaculture scientists study the growth and development of fish and other aquatic organisms to understand the biological basis of traits such as growth rate, disease resistance or resistance to destructive environmental conditions.

Researchers are using marine biotechnology to identify and combine valuable traits in parental fish and shellfish. The traits scientists and companies are investigating for possible incorporation into several marine organisms include increased production of natural fish growth factors and the natural defense compounds marine organisms use to fight microbial infections. Biotechnology is also improving productivity through the development of feed additives, vaccines and other pharmaceutical agents.

Some of the biotech improvements being made with fish include:

- Some biotech salmon reach maturity quickly and do not hibernate, which enables year-round availability of salmon.
- Researchers are trying to develop fish that are more resistant to disease, tolerant of low oxygen levels in the water and tolerant of freezing temperatures.
- Some species of fish naturally produce a protein that allows them to survive in the Arctic. This "anti-freeze" gene has been transplanted to other species of fish so they can survive in very cold waters.

COMPANION ANIMALS

Approximately 163 million dogs and cats are companion animals in the United States (in more than 60 percent of all American households). America's emotional attachment to its pets is evidenced by the estimated $43 billion that will be spent on U.S. pets in 2008, according to the American Pet Products Manufacturers Association. That total includes $10.9 billion for veterinary care.

That care increasingly includes preventive medicines and disease treatments that have been improved through biotechnology. Animal vaccines are critical to preventing diseases such as rabies, distemper, feline leukemia and hepatitis. In addition, researchers have developed biotechnology-based products to treat heartworm, arthritis, parasites, allergies, dental problems, heart disease, kidney failure, separation anxiety, cognitive dysfunction syndrome and other problems.

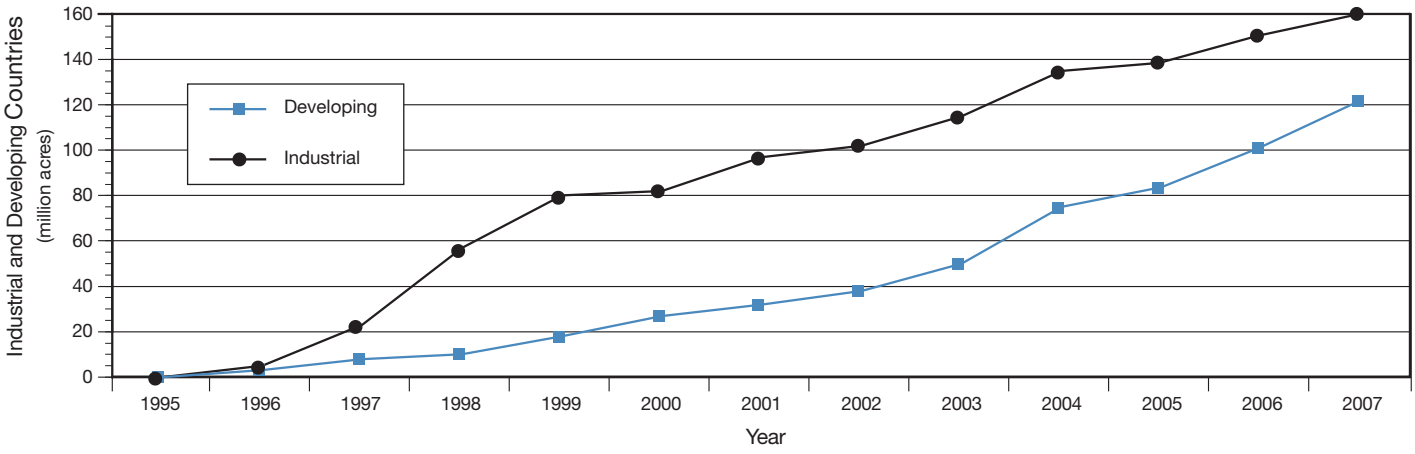
Recent biotechnology-driven developments in companion animal health care include the following:

- Immunologists have developed a vaccine for feline immunodeficiency virus (FIV), an organism carried by as many as 25 percent of cats. In addition to saving cats' lives, the research for creating the FIV vaccine provides many clues in the development of an HIV/AIDS vaccine.
- Gene therapy has restored the vision of dogs afflicted by Leber congenital amaurosis, an untreatable condition that causes almost complete blindness. Researchers are also testing gene therapy for melanoma, canine lymphoma and bone cancer. Canine lymphoma accounts for 20 percent of all canine tumors and usually kills within a month of diagnosis. Gene therapy treatment may prolong life by a year.
- A rabies vaccine has been widely used with wild raccoon populations to limit transmission to companion animals.
- Projects for mapping the genetic code of fleas may someday result in products that rid dogs and cats of the insect.
- Monoclonal antibody technology is being used to develop treatments for canine lymphoma.
- Other antibody technology is being used to develop diagnostics for feline infectious peritonitis and feline immunodeficiency virus.

Other recent biotechnology-driven developments in companion animals are listed below:

- The first biotech animal to be sold to the public reached the market in January 2004; GloFish are biotech ornamental fish that contain a gene from a sea anemone. Under black light, the GloFish fluoresce in a brilliant red color. The U.S. Food and Drug Administration conducted a complete scientific and technical review of the biotech fish, including assessing target animal safety, human safety and environmental safety, and found them safe and environmentally harmless.

Global Area of Transgenic Crops, 1995 to 2007: Industrial and Developing Countries (million acres)



Source:
Clive James, *Global Status of Commercialized Transgenic Crops: 2007*, ISAAA Briefs No. 37-2007. Ithaca, N.Y. International Service for the Acquisition of Agri-biotech Applications, 2007

Global Area of Transgenic Crops in 2006 and 2007 by Country (million acres)

COUNTRY	2006	%	2007	%	+/-	% CHANGE
USA	134.9	53.5	142.5	50.5	7.6	5.6
Argentina	44.5	17.7	47.2	16.7	2.7	6.0
Brazil	28.4	11.3	37.1	13.2	8.7	30.6
Canada	15.1	6.0	17.3	6.1	2.2	14.6
India	9.4	3.7	15.3	5.4	5.9	62.7
China	8.6	3.4	9.4	3.3	0.8	9.3
Paraguay	4.9	1.9	6.4	2.3	1.5	30.6
South Africa	3.5	1.4	4.4	1.6	0.9	25.7
Uruguay	1.0	0.4	1.2	0.4	0.2	20
Philippines	0.5	0.2	0.7	0.2	0.2	40
Australia	0.5	0.2	0.25	<0.1	0.25	-50
Spain	0.25	0.1	0.25	<0.1	–	–
Mexico	0.25	0.1	0.25	<0.1	–	–
Colombia	<0.25	<0.1	<0.25	<0.1	–	–
Chile	0	–	<0.25	<0.1	–	–
France	<0.25	<0.1	<0.25	<0.1	–	–
Honduras	<0.25	<0.1	<0.25	<0.1	–	–
Czech Republic	<0.25	<0.1	<0.25	<0.1	–	–
Portugal	<0.25	<0.1	<0.25	<0.1	–	–
Germany	<0.25	<0.1	<0.25	<0.1	–	–
Slovakia	<0.25	<0.1	<0.25	<0.1	–	–
Romania	<0.25	<0.1	<0.25	<0.1	–	–
Poland	0	–	<0.25	<0.01	–	–

Source:
Clive James, *Global Status of Commercialized Transgenic Crops: 2007,* ISAAA Briefs No. 37-2007. Ithaca, N.Y. International Service for the Acquisition of Agri-biotech Applications, 2007

agricultural biotech
Products on the Market

CANOLA

LibertyLink® Canola (developed by Bayer CropScience) Introduced in 1995, LibertyLink Canola allows growers a wide application window to apply Liberty® herbicide over-the-top during the growing season. Liberty herbicide controls over 100 grass and broadleaf weeds, with no crop injury. This results in effective weed control while maintaining excellent crop performance and yield.

InVigor® Hybrid Canola (developed by Bayer CropScience) **InVigor Hybrid Canola** are high-yielding hybrid canola varieties that are also tolerant to Liberty® herbicide. InVigor hybrid seed was first sold in Canada in 1996 and in the United States in 2000.

Roundup Ready® Canola (developed by Monsanto) Roundup Ready Canola allows growers to apply Roundup® herbicide over-the-top of the crop during the growing season, for weed control with enhanced crop safety.

CORN

NutriDense® Corn (developed by BASF) This nutritionally enhanced corn contains a stacked set of output traits designed to enhance animal feed performance. Traits include higher concentrations of amino acids, oil and certain minerals.

Rogers® brand Attribute® Bt Sweet Corn (developed by Syngenta Seeds) Attribute insect-protected sweet corn varieties from Syngenta provide a high level of built-in protection against European corn borer and corn earworm, protecting crops from ear damage and yield loss.

Agrisure® GT Glyphosate-Tolerant Corn (developed by Syngenta) Developed from a plant-derived glyphosate-resistant gene that is evenly expressed throughout the plant, corn hybrids with **Agrisure GT** provide tolerance to in-crop applications of glyphosate-based herbicides.

Agrisure® CB/LL Agrisure (developed by Syngenta) features the Bt11 event, which has been protecting cornfields since it was introduced in 1997. The Bt11 event utilizes the naturally occurring soil bacterium *Bacillus thuringiensis* and produces a protein that is toxic to lepidopteran insects. In addition, all hybrids with Agrisure CB/LL are tolerant to Liberty® herbicide. The LibertyLink® benefit gives growers another option for weed control.

Agrisure® RW (developed by Syngenta) features a modified full-length Cry3Aa gene from *Bacillus thuringiensis*, offers excellent built-in control of northern, western and Mexican corn rootworms with outstanding yield results. An innovative trait conversion process allows hybrids with Agrisure RW to reach their full yield potential while delivering outstanding protection from corn rootworm.

Agrisure® GT3000 (developed by Syngenta) is the stacked corn product that combines Agrisure glyphosate-tolerant corn with corn borer and rootworm resistance to provide growers with the experience of full advantage of all traits in a single elite genetic hybrid.

Herculex® I Insect Protection (developed by Dow AgroSciences and Pioneer Hi-Bred International, Inc.) These corn hybrids provide the broadest spectrum above-ground in-plant insect protection currently available, including first- and second-generation European corn borer, southwestern corn borer, black cutworm, western bean cutworm, fall armyworm, sugarcane borer, southern corn stalk borer and lesser corn stalk borer. All Herculex I hybrids also contain LibertyLink®, making them tolerant to over-the-top applications of Liberty® herbicide, and some are available stacked with Roundup Ready® Corn 2.

Herculex® RW Rootworm Protection (co-developed by Dow AgroSciences and Pioneer Hi-Bred International, Inc.) Corn hybrids containing Herculex RW rootworm protection provide below ground in-plant corn rootworm protection against western, northern and Mexican corn rootworm. All Herculex RW hybrids also contain LibertyLink®, making them tolerant to over-the-top applications of Liberty® herbicide, and some are available stacked with Roundup Ready® Corn 2.

Herculex® XTRA Insect Protection Corn (co-developed by Dow AgroSciences and Pioneer Hi-Bred International, Inc.) Corn hybrids containing the Herculex XTRA insect protection, a combined trait product of both Herculex I and Herculex RW, provide the broadest spectrum above and below ground in-plant insect protection available on the corn market. All Herculex XTRA hybrids also contain LibertyLink®, making them tolerant to over-the-top applications of Liberty® herbicide, and some are available stacked with Roundup Ready® Corn 2.

LibertyLink® Corn (developed by Bayer CropScience) Introduced in 1997 in the United States and 1998 in Canada, LibertyLink Corn allows growers a wide application window to apply Liberty® herbicide over the top during the growing season. Liberty herbicide controls over 100 grass and broadleaf weeds fast, without crop injury.

Roundup Ready® Corn (developed by Monsanto) Approved in 1997, Roundup Ready Corn allows over-the-top applications of Roundup® herbicide during the growing season for weed control.

YieldGard® Corn Borer (developed by Monsanto) Introduced in 1997 in the United States, YieldGard Corn Borer hybrids offer season-long, whole-plant protection from the European corn borer and also controls the Southwestern corn borer.

YieldGard® Rootworm-Protected Corn (developed by Monsanto) YieldGard corn carries built-in protection against corn rootworm. Current products include YieldGard Rootworm stacked with Roundup Ready® technology.

YieldGard® Plus Corn (developed by Monsanto) YieldGard Plus Corn is the first stack of two insect-protection traits in a single seed, combining the built-in protection against European corn borer and corn rootworm.

YieldGard® Plus with Roundup Ready® Corn (developed by Monsanto) YieldGard Plus with Roundup Ready Corn is the first seed to contain three separate biotech traits, with insect protection against European corn borer and corn rootworm and tolerance to over-the-top applications of Roundup herbicide.

YieldGard® VT™ Triple Corn (developed by Monsanto) hybrids are created using a process called VecTran technology, which stands for Vector-Stack Transformation. The vector combines two traits, Roundup Ready® and YieldGard Rootworm, using a single DNA-insertion process and is stacked with YieldGard Corn Borer.

CARNATIONS

Moondust Carnation (introduced in 1996 by Florigene [formerly Calgene Pacific]) The first mauve carnation, followed by Moonshadow (1998), a violet carnation. Conventional breeding failed to produce these flowers with hues in the mauve-blue-violet range because of a genetic gap; they lack the ability to produce the blue pigment, delphinidin. Florigene also has an active research and development program to extend the vase life of flowers.

COTTON

Bollgard® Insect-Protected Cotton (developed by Monsanto) Introduced in 1996, cotton with Monsanto's Bollgard gene protects against cotton bollworms, pink bollworms and tobacco budworms. Bollgard cotton is a great example of how biotechnology can reduce the amount of pesticide applications on a specific crop. According to the technology provider, growers using Bollgard technology sprayed an average of 2.5 fewer applications per acre than conventional cotton growers. This data is further underscored by EPA research. In just one year, 1999, EPA estimated that growers who planted Bollgard cotton reduced their insecticide application by 1.6 million pounds.

Bollgard® II Insect-Protected Cotton (developed by Monsanto) Bollgard II is Monsanto's second generation of insect-protected cotton technology. This new cotton technology is designed to offer new benefits to cotton growers, including a broader spectrum of control of damaging insects and better defense against the development of resistance in target insects. Research indicates that Bollgard II will provide greater control of cotton bollworm, beet and fall armyworm, and soybean loopers compared with Bollgard.

LibertyLink® Cotton (developed by Bayer CropScience) LibertyLink cotton allows growers a wide application window to apply Liberty® herbicide over the top during the growing season. Liberty herbicide controls over 100 grass and broadleaf weeds, with no crop injury. LibertyLink cotton is offered in top FiberMax® varieties.

Roundup Ready® Cotton (developed by Monsanto) Approved in 1996, Roundup Ready® cotton tolerates both over-the-top and postdirected applications of Roundup® herbicide. Roundup Ready cotton provides growers with an excellent resource for practicing conservation tillage in their fields.

Roundup-Ready® Flex Cotton (developed by Monsanto) Next Generation Roundup Ready cotton is expected to provide growers with an expanded window of application of Roundup® herbicide.

WideStrike® Insect Protection for Cotton (developed by Dow AgroSciences) is a two-gene trait that provides a very wide spectrum of insect protection. This trait protects season long against a broad range of damaging lepidopteran pests, including cotton bollworm, pink bollworm, tobacco budworm, armyworms and loopers.

MILK AND DAIRY

Chymogen® (developed by Genencor International and marketed by Chr. Hansen's) Chymogen is the biotechnology-produced version of an enzyme (chymosin) found in calves that makes milk curdle to produce cheese. Because it is produced through biotechnology, it is purer and more plentiful; it also eliminates variability in the quality and availability of the enzyme in calves' stomachs. It is used in approximately 60 percent of all hard-cheese products made today.

Posilac® Bovine Somatotropin (BST) (developed by Monsanto) BST is a naturally occurring protein hormone in cows that

induces them to produce milk. BST improves milk production by as much as 10 to 15 percent and is now used by farmers whose herds represent over 30 percent of the nation's cows. The FDA approved it in 1993.

ChyMax® (fermentation-derived) (developed by Pfizer, marketed by Chr. Hansen's) ChyMax is another version of chymosin, an enzyme that causes milk to coagulate. It is an advanced fermentation ingredient that is of higher purity, quality and activity than natural rennet.

PAPAYA

Rainbow and SunUp (developed by Cornell Research Foundation and the Papaya Administrative Committee) Rainbow (a yellow-fleshed hybrid between a conventional papaya and a genetically enhanced one) and SunUp (a red-fleshed transgenic papaya) have been enhanced to resist papaya ringspot virus, the deadly disease that almost eliminated the papaya industry in Hawaii during the 1990s.

PEANUTS

Flavr Runner Naturally Stable Peanut (developed by Mycogen) these peanuts have a modified fatty acid profile to produce nuts high in oleic acid. The benefit to the industry is longer shelf life for nuts, candy and peanut butter.

RAPESEED

Laurical® (developed by Calgene, LLC) Laurical is a less expensive source of high-quality raw materials for soaps, detergents and cocoa butter replacement fats. Rapeseed plants with more than 45 percent laurate in oil have been produced.

SOYBEANS

Roundup Ready® Soybeans (developed by Monsanto) Introduced in 1996, Roundup Ready Soybeans allow growers to apply Roundup® herbicide over-the-top during growing season. The result is dependable weed control with no effect on crop performance or yield.

MISCELLANEOUS

Messenger® (developed by EDEN Bioscience) This is the first of a series of products based on naturally occurring harpin protein technology. Approved by the EPA in April 2000, Messenger stimulates growth and defense pathways inherent within each plant without altering the plant's DNA. Messenger treatments promote healthier plants and increased yields, as well as increased disease resistance and deterrence of insects such as nematodes. Messenger is a labeled product, currently being sold in cotton, citrus, apples, strawberries, rice, tomatoes, peppers, cucurbit vegetables, cane berries, grass seed, potatoes and many other crops.

In Development

ALFALFA

Roundup Ready® Alfalfa (developed with Monsanto technology) allows over-the-top applications of Roundup® herbicide during the growing season for weed control.

APPLES

Bt Insect-Protected Apple (developed with Monsanto technology) These apples will contain built-in insect protection against the codling moth.

BANANAS

Disease-Resistant Bananas (developed by DNA Plant Technology Corporation) These bananas will be resistant to the fungal disease black sigatoka.

CANOLA

Disease-Resistant Canola (developed by DuPont) Canola that can resist yield-robbing diseases such as *Sclerotina*.

CORN

Improved Drought Response Corn (developed by DuPont) Hybrid corn that can mine the existing moisture in the soil more efficiently or survive drought periods and still produce high yields.

EXTRAX™ Corn (developed by Monsanto), a new corn-processing system developed by Renessen, bolts on to the front of a conventional dry-grind ethanol plant, allowing the plant to produce a greater array of high-value products. In addition to ethanol, a mill using the EXTRAX corn processing system will produce food grade vegetable oil and improved animal feed products.

Drought Tolerant Corn (developed by Monsanto) First-generation drought tolerant corn is targeted to minimize uncertainty in farming by buffering against the effects of water limitation, primarily in areas of annual water stress. In the U.S. this area has historically been the dryland farms of the western Great Plains.

Drought Tolerant Corn—Second Generation (developed by Monsanto) The second generation of drought tolerant corn is aimed at boosting yield stability for broad-acre applications and reducing water input required in water-limited environments.

Higher-yielding corn (developed by Monsanto) is aimed at boosting the intrinsic yield potential of corn hybrids through insertion of key genes.

Mavera™ Corn (developed by Monsanto) The Mavera family of high-value corn products have more than 50% more oil than conventional corn products. Mavera high-oil corn products offer exceptional value when used in Renessen's new EXTRAX™ processing system. Mavera high-value corn is a family of products with increasing oil levels being added over time from both advanced breeding and biotechnology approaches.

Nitrogen Utilization Corn (developed by Monsanto) Nitrogen utilization targets ways that corn plants can use nitrogen more efficiently, exploring the potential to boost yield under normal nitrogen conditions or to stabilize yield in low nitrogen environments.

SmartStax™ Corn (developed by Monsanto), a system that combines eight different herbicide-tolerance and insect-protection genes, will include above- and below-ground insect-protection systems, including Dow AgroSciences' Herculex® I and Herculex RW technologies; Monsanto's YieldGard® VT Rootworm/RR2™ and YieldGard® VT PRO™ technologies; and the two established weed control systems, Roundup Ready® and LibertyLink®.

YieldGard® Rootworm III (developed by Monsanto) is designed to offer increased control and durability against the corn rootworm by using two distinct modes of action providing two different approaches to insect control.

YieldGard® VT™ PRO (developed by Monsanto) is the second generation of YieldGard® Corn Borer and broadens the spectrum of insect control to include corn earworm and fall armyworm and increases the durability of the trait with the use of two proteins for dual mode of actions for resistance.

Increased-Energy-Availability Corn (developed by DuPont) is corn that livestock can more readily digest and more efficiently use nutrients in the grain.

Second-Generation YieldGard® Corn Borer (developed by Monsanto) The second-generation corn–borer protected product in the YieldGard family is expected to provide an even broader spectrum of insect control than today's YieldGard. In addition to the control of the European and southwestern corn borer, field trials indicate it will provide enhanced control of the corn earworm, fall armyworm and black cutworm. The next-generation corn borer-protected corn will contain a new gene with a unique mode of action compared with YieldGard Corn Borer or other products on the market, thus providing a defense against insect resistance and ensuring that insect-protected products will remain effective and continue to deliver benefits for many years to come.

Corn Amylase for Enhanced Ethanol Production (developed by Syngenta) Amylase breaks starch down to sugar; including amylase expression in processor corn has the potential to reduce the costs of ethanol production up to 10 percent.

Corn Broad Spectrum Lepidoptera Control (developed by Syngenta) will protect corn above the ground by delivering high-level control of a broad spectrum of lepidopteran insects including fall army worm, corn ear worm, western bean and black cutworm and sugar cane borer, which are key pests in the United States, Brazil and Argentina. The gene contained in the product has a distinct mode of action that is structurally and functionally different from the genes contained in insect control technologies currently in the marketplace

Corn Broad Spectrum Lepidoptera Control stacked with Corn Borer Control (developed by Syngenta) A stack of two corn traits, Agrisure® CB/LL product (Bt11) and the Broad Spectrum Lepidoptera Control, which contains a novel insecticidal protein called Vegetative Insecticidal Protein 3A. The combination of these traits targets in-crop control of a broad range of lepidopteran pest larvae. This stack technology will unite two unique genes—the first new approach to Lepidoptera control in corn since transgenic technology was first introduced in 1995.

Drought tolerance (developed by Syngenta) This will bring together a combination of leading genes to improve plants' ability to perform under drought stress. These combinations will deliver around 10 percent more yield in drought conditions, or allow growers to maintain existing yields while using 50 percent less water.

Nitrogen Use Efficiency Trait (developed by DuPont) The Nitrogen Use Efficiency trait will allow farmers to apply reduced quantities of nitrogen to their corn crop while maintaining overall yields or alternatively increase yields at existing levels of nitrogen use.

Optimum® GAT® trait (developed by DuPont) The Optimum GAT (Glyphosate ALS Tolerance) trait offers corn growers a new and better choice in herbicide tolerance that maximizes yield and productivity, improves crop safety and expands weed control options. DuPont plans to launch Optimum GAT in corn in 2010.

Dow AgroSciences Herbicide Tolerance Corn (DHT1) (developed by Dow AgroSciences) will provide tolerance to broadleaf and grass herbicides including phenoxy auxins and the "fop" family of herbicides. DHT1 will improve the performance of glyphosate and glufosinate herbicides and further enhances the herbicide-tolerant cropping systems and will be stacked with Herculex® Insect Protection in-plant traits.

COTTON

Bollgard® III cotton (developed by Monsanto) third-generation of insect control further broadens the control

spectrum of lepidopteran insects, by incorporating a new Bt protein. The goal will be broad control of multiple pests with enhanced, season-long protection.

Cotton Lygus Control (developed by Monsanto) extends the spectrum of cotton insect control to lygus bugs, piercing-sucking insects that damage bolls and reduce overall plant health and yield.

Dicamba- and glufosinate-tolerant stacked with Roundup Ready® Flex cotton (developed by Monsanto) represents the industry's first three-way stack of herbicide-tolerant technologies including Roundup Ready® Flex, dicamba tolerance and glufosinate tolerance. This product will provide two new, unique modes of action combined with Roundup Ready Flex to provide cotton growers with the most effective weed management system available.

Drought-tolerant cotton (developed by Monsanto) is designed to minimize risk in cotton farming by providing yield stability in environments experiencing sporadic or consistent water stress and by reducing water needs on irrigated acres.

GlyTol® Cotton (developd by Bayer CropScience) GlyTol cotton is a weed-management solution that will provide farmers a flexible and effective alternative system for weed management in cotton. GlyTol cotton will offer tolerance to numerous formulations of glyphosate herbicide.

GlyTol® + LibertyLink® Cotton (developd by Bayer CropScience) GlyTol + LibertyLink cotton will have built-in stacked herbicide tolerance to both glyphosate and glufosinate ammonium. This product will be an effective new weed management solution that will provide additional options and flexibility to cotton growers.

Vegetative Insecticidal Protein Cotton (VipCot) (developed by Syngenta) This second-generation insect control has a broader spectrum and a novel mode of action. VipCot will provide growers an alternative to existing Bt products and will improve grower flexibility in managing insect resistance.

LETTUCE

Roundup Ready® Lettuce (developed with Monsanto technology) Allows over-the-top applications of Roundup® herbicide during the growing season for weed control.

POTATOES

Amflora Potatoes (developed by BASF) These potatoes with genetically enhanced starches offer considerable benefits as raw materials in many industries. Paper, textile and adhesives industries, for example, will soon be able to take advantage of BASF's Amflora potato, which provides pure amylopectin starch directly from the potato tuber.

RICE

LibertyLink® Rice (developed by Bayer CropScience) Bayer CropScience is obtaining appropriate regulatory clearances in key countries. When LibertyLink Rice is used together with Liberty® herbicide, it will allow farmers greater weed control flexibility and may promote water conservation.

SOYBEANS

Dicamba-tolerant Soybeans (developed by Monsanto) provide a new, unique mode of action for weed control. It is designed to provide soybean growers with the most effective and highest yielding weed-management system available when stacked with Monsanto's Roundup Ready® 2 Yield® trait.

First- and Second-Generation High-Oil Soybeans (developed by Monsanto) are targeted to increased oil content in soybean to improve oil crushing yield, thus helping processors meet the growing demand for vegetable oil for food and bio-fuel.

High-Stearate Soybeans (developed by Monsanto) are designed with elevated levels of stearate to enhance the texture and reduce the levels of linolenic acid for increased stability for many types of foods that require solid fat functionality.

First- and Second-Generation Higher-Yielding Soybeans (developed by Monsanto) are aimed at boosting the intrinsic yield potential of the soybean through insertion of key genes.

Improved-Protein Soybeans (developed by Monsanto) will provide soybeans with improved taste, texture and health properties to help meet consumer demand for healthier foods.

Insect-Protected + Roundup Ready 2 Yield® Soybeans (developed by Monsanto) use the same Bt technology widely adopted in corn and cotton to control lepidopteran insect pests that are economically important for South American farmers. Insect-protected soybeans are targeted to be introduced together with Roundup Ready 2 Yield® soybeans for effective control of both insects and weeds.

Omega-3 Enriched Soybeans (developed by Monsanto) represent a land-based source of essential omega-3 fatty acids. This product is targeted to produce 20 percent stearidonic acid omega-3 fatty acid with the taste, shelf life and oil stability of soybean oil.

Roundup Ready 2 Yield Soybeans® (developed by Monsanto) are the second-generation Roundup Ready® soybean product designed to provide farmers with soybeans that are tolerant to the Roundup® family of agricultural herbicide and have enhanced yields, with a target of 7 to 11 percent yield increase compared with Roundup Ready® soybeans.

Soybean Disease Resistance (developed by Monsanto) is aimed at reducing the impact of Asian Soybean Rust on soybean production.

Soybean Nematode Resistance (developed by Monsanto) is aimed at providing superior control of Soybean Cyst Nematode compared with current genetic sources of resistance that are available in commercial germplasm.

Vistive® III Soybeans (developed by Monsanto) are designed by combining breeding and biotechnology to lower linolenic and saturate content of soybean oil while boosting oleic content to produce oil with the monounsaturated fat content of olive oil and the low saturated fat content of canola oil.

LibertyLink® Soybeans (developed by Bayer CropScience) When used together with glufosinate ammonium herbicide (Liberty®, Ignite® 280), these soybeans will allow farmers greater weed control flexibility and important weed resistance management strategies.

Soybeans with Improved Protein Functionality (developed by Dupont) is a food soy ingredient that does a better job of improving quality and consistency of food products.

Optimum® GAT® trait (developed by DuPont) The Optimum GAT (Glyphosate ALS Tolerance) trait offers soybean growers a new and better choice in herbicide tolerance that maximizes yield and productivity, improves crop safety and expands weed control options. DuPont plans an initial introduction in 2009.

High Oleic Soybeans (developed by DuPont and Bunge) High oleic soybeans will be the first transgenic product that provides direct consumer benefits. They are a low trans fat, low saturate product with high heat stability for improved frying performance. The oil's high heat stability in industrial and transportation settings also enables the development of renewable, environmentally friendly options to petroleum-based products. The high oleic soybean oil trait is on track for commercial introduction in 2009.

Dow AgroSciences Herbicide Tolerance Soybeans (DHT2) (developed by Dow AgroSciences) will provide tolerance to broadleaf and grass herbicides, including phenoxy auxins, and the "fop" family of herbicides. DHT2 will improve the performance of glyphosate herbicides and further enhances the herbicide tolerant cropping system.

STRAWBERRIES

Strawberry (developed by DNA Plant Technology Corporation) The company is adding genes to confer resistance to glyphosate herbicide and fungal diseases.

SUGAR BEETS

Roundup Ready® Sugar Beets (developed by Monsanto) Roundup Ready® sugar beets are tolerant of Roundup® herbicide and provide growers with a new weed-control option.

TURF GRASS

Roundup Ready® Creeping Bentgrass (developed with Monsanto technology) allows over-the-top applications of Roundup® herbicide to control Poa Annua, Poa Trivialis and other weeds of turf on golf course fairways and greens allowing more flexible weed control and reduced turf-management inputs.

ENERGY CROPS

Blade™ Switchgrass (developed by Ceres) Coming in the spring of 2009, these are the first switchgrass cultivars developed specifically for biofuels.

Blade™ Sorghum (developed by Ceres) Coming in the spring of 2009, this is a high-biomass sorghum developed specifically for biofuels.

MISCELLANEOUS

AquaAdvantage® Salmon, Tilapia, Trout and Flounder (developed by Aqua Bounty Farms) The AquaAdvantage® salmon have the capability of growing from egg to market size (6 to 10 lb.) in one to one-and-a-half years. Conventional fish-breeding techniques require two to three years to bring a fish to market. This new salmon could make fish farming more environmentally sustainable, decrease over-fishing of wild salmon and lower consumer costs. Aqua Bounty expects to introduce the AquaAdvantage® salmon within two to three years to a public for whom salmon is an increasingly popular food.

Genetically Modified Fruits and Vegetables with Longer Postharvest Shelf Life (developed by Agritope, Inc., a wholly owned subsidiary of Epitope, Inc.) Using ethylene-control technology, Agritope, Inc., has created delayed-ripening, longer-lasting tomatoes and raspberries.

Phytase for Animal Feed (developed by Syngenta and Zymetrics) The phytase enzyme releases phosphorous-based nutrients in animal feed in a form that can be easily digested by single-stomach animals such as pigs, chickens and turkeys. A phytase supplement can enhance the nutritional value of the feed and reduce phosphorus levels in animal manure, which can help improve environmental quality. The new microbial (Zymetrics) and corn phytase (Syngenta) supplements are designed with enhanced thermostability, which provides livestock producers more options in developing feed rations.

food Biotechnology

We have used biotechnology to manufacture food products for more than 8,000 years. Bread, alcoholic beverages, vinegar, cheese and yogurt, and many other foods owe their existence to enzymes found in various microorganisms. Today's biotechnology will continue to help the food industry by providing new products, lowering costs and improving the microbial processes on which food producers have long relied.

Many of these developments will improve the quality, nutritional value and safety of the crop plants and animal products that are the basis of the food industry. In addition, biotechnology offers many ways to improve the processing of those raw materials into final products: natural flavors and colors; new production aids, such as enzymes and emulsifiers; improved starter cultures; more waste treatment options; "greener" manufacturing processes; more options for assessing food safety; and even biodegradable plastic wrap that kills bacteria.

Improving the Raw Materials

The first generation of transgenic crops primarily benefited farmers. Although there are consumer benefits in growing these crops, the benefits are largely invisible to the public. For example, studies have shown that because insect-resistant corn (Bt corn) sustains relatively little insect damage, fungi and molds cannot infect those plants as easily as non-insect-resistant crops. Therefore, the level of toxins produced by these pathogens, some of which are fatal to livestock, is much lower in Bt corn than non-Bt corn.

The benefits of the next wave of biotechnology crops will be more obvious to consumers. Some of those benefits will involve improvements in food quality and safety, while others will provide consumers with foods designed specifically to be healthier and more nutritious.

HEALTH AND NUTRITIONAL BENEFITS

A variety of healthier cooking oils derived from biotechnology are already on the market. Using biotechnology, plant scientists have lowered the total amount of saturated fatty acids in certain vegetable oils. They have also increased the conversion of linoleic acid to the fatty acid found mainly in fish that is associated with cardiovascular health.

Another nutritional concern related to edible oils is the negative health effects produced when vegetable oils are hydrogenated to increase their heat stability for cooking or to solidify oils used in making margarine, baked goods and other products. The hydrogenation process results in the formation of harmful trans-fatty acids.

Biotechnology companies have given soybean oil desirable properties, not through hydrogenation, but by increasing the amount of a naturally occurring fatty acid called stearic acid.

Biotechnology can also increase the nutritional value of crops, especially those that are food staples in developing countries. For example, scientists at Nehru University in New Delhi used a gene found in the South American plant amaranth to increase the protein content of potatoes by 30 percent. These transgenic potatoes also contain large amounts of essential amino acids not found in unmodified potatoes. Other examples include golden rice and canola oil, both of which are high in vitamin A. The golden rice developers further improved rice with two other genes that increase the amount and digestibility of iron.

Biotechnology also promises to improve the health benefits of *functional foods*. Functional foods are foods containing significant levels of biologically active components that impart health benefits beyond our basic needs for sufficient calories, essential amino acids, vitamins and minerals. Familiar examples of functional foods include compounds in garlic and onions that lower cholesterol and improve immune response; antioxidants found in green tea; and the glucosinolates in broccoli and cabbage that stimulate anticancer enzymes.

Scientists are using biotechnology to increase the production of these compounds in functional foods. For example, researchers at Purdue University and the U.S. Department of Agriculture created a tomato variety that contains three times as much of the antioxidant lycopene as the unmodified variety. Lycopene consumption is associated with a lower risk of prostate and breast cancer and decreased blood levels of "bad cholesterol." Other USDA researchers are using biotechnology to increase the amount of ellagic acid, a cancer protective agent, in strawberries.

Animal scientists are also using biotechnology to create healthier meat products, such as beef with lower fat content and pigs with a higher lean-to-fat ratio.

PRODUCT QUALITY

Researchers are using biotechnology to change the characteristics of fresh foods so that they are more attractive to consumers and more amenable to processing. They are increasing the shelf life of fresh fruits and vegetables; improving the crispness of carrots, peppers and celery; creating seedless varieties of grapes and melons; extending the seasonal geographic availability of tomatoes, strawberries and raspberries; improving the flavor of tomatoes, lettuce, peppers, peas and potatoes; and creating caffeine-free coffee and tea.

Much of the work on improving how well crops endure food processing involves changing the ratio of water to starch. Potatoes with higher starch content are healthier because they absorb less oil when they are fried, for example. Starchier potatoes also require less energy to process and therefore cost less to handle.

Many tomato processors now use tomatoes derived from a biotechnology technique, somaclonal variant selection. The new tomatoes, used in soup, ketchup and tomato paste, contain 30 percent less water and are processed with greater efficiency. A 1/2 percent increase in the solid content is worth $35 million to the U.S. processed-tomato industry.

Another food-processing sector that will benefit economically from better quality raw materials is the dairy products industry. Scientists in New Zealand have used biotechnology to increase milk levels of the protein casein, which is essential to cheese making, by 13 percent.

Biotechnology also allows the economically viable production of valuable, naturally occurring compounds that cannot be manufactured by other means. For example, commercial-scale production of the natural and highly marketable sweetener known as fructans has long eluded food-processing engineers. Fructans, which are short chains of the sugar molecule fructose, taste like sugar but have no calories. Scientists found a gene that converts 90 percent of the sugar in beets to fructans. Because 40 percent of the transgenic beet dry weight is fructans, this crop can serve as a manufacturing facility for fructans.

SAFETY OF THE RAW MATERIALS

The most significant food-safety issue food producers face is microbial contamination, which can occur at any point from farm to table. Biotechnology reduces contamination with transgenic disease-resistant and insect-resistant crops. In addition, new biotechnology diagnostics, similar to those described in the chapter on medical applications, detect microbial diseases earlier and more accurately, so farmers can identify and remove diseased plants and animals before others become contaminated.

Biotechnology is also improving the safety of raw materials by helping food scientists discover the exact identities of allergenic proteins in foods such as peanuts, soybeans and milk, so they can then remove them. Although 95 percent of food allergies can be traced to a group of eight foods, in most cases we do not know which of the thousands of proteins in a food triggered the reaction. With biotechnology techniques, scientists are making great progress in identifying these allergens. More importantly, they have succeeded in using biotechnology to block or remove allergenicity genes in peanuts, soybeans and shrimp.

Finally, biotechnology is helping us improve the safety of raw agricultural products by decreasing the amount of natural plant toxins found in foods such as potato and cassava.

Food Processing

Microorganisms have been essential to food-processing for centuries. They play a role in the production of the fermented foods listed in Table 1. They also serve as a rich source of food additives, enzymes and other substances used in food processing.

IMPROVING FOOD FERMENTORS

Because of the importance of fermented foods to so many cultures, scientists are working to improve the microorganisms that carry out food fermentation. The bacterium responsible for many of our fermented dairy products, such as cheese and yogurt, is susceptible to infection by a virus that causes substantial economic losses to the food industry. Through recombinant technology, researchers have made some strains of this bacterium and other important fermentors resistant to viral infection.

We have known for years that some bacteria used in food fermentation produce compounds that kill other, contaminating bacteria that cause food poisoning and food spoilage. Using biotechnology we are equipping many of our microbial fermentors with this self-defense mechanism to decrease microbial contamination of fermented foods.

FOOD ADDITIVES AND PROCESSING AIDS

Microorganisms are the source of many of the additives and processing aids used in food processing. Biotechnology advances will enhance their value to the food industry even further.

Food additives are substances used to increase nutritional value, retard spoilage, change consistency and enhance flavor. The com-

pounds food processors use as food additives are substances nature has provided and are usually of plant or microbial origin, such as xanthan gum and guar gum, which are produced by microbes. Many of the amino acid supplements, flavors, flavor enhancers and vitamins added to breakfast cereals are produced by microbial fermentation. Through biotechnology, food processors will be able to produce many compounds that could serve as food additives but that now are in scant supply or that are found in microorganisms or plants difficult to maintain in fermentation systems.

Microorganisms also produce enzymes that are essential food-processing aids. The first commercial food product produced by biotechnology was an enzyme used in cheese making. Prior to biotech techniques, this enzyme had to be extracted from the stomach of calves, lambs and baby goats, but it is now produced by microorganisms that were given the gene for this enzyme.

The production of high-fructose corn syrup from cornstarch requires three enzymes, and those same enzymes are important in making baked goods and beer. Other enzymes are essential to the production of fruit juices, candies with soft centers and cheeses. The food industry uses more than 55 different enzyme products in food processing. This number will rise as we discover how to capitalize on the extraordinary diversity of the microbial world and obtain new enzymes that will prove important in food processing.

Scientists are also using biotechnology to change crops themselves to be easier to process. For example, some are working to change the starch in crop plants so that it no longer requires special handling before it can be used as a thickener and fat substitute in low-fat products. Currently, the starch is extracted from plants and modified using chemicals or energy-consuming mechanical processes.

Food Safety Testing

Biotechnology is providing us with many tools to detect microorganisms and the toxins they produce. Monoclonal antibody tests, biosensors, polymerase chain reaction methods and DNA probes are being developed that will be used to determine the presence of harmful bacteria that cause food poisoning and food spoilage, such as *Listeria* and *Clostridium botulinum*.

We can now distinguish *E. coli* 0157:H7, the strain of *E. coli* responsible for several deaths in recent years, from the many other harmless *E. coli* strains. These portable tests are quicker and more sensitive to low levels of microbial contamination than previous tests because of the increased specificity of molecular technique. For example, the new diagnostic tests for *Salmonella* yield results in 36 hours, compared with the three or four days the older detection methods required.

Biotechnology-based diagnostics have also been developed that allow us to detect toxins, such as aflatoxin, produced by fungi and molds that grow on crops, and to determine whether food products have inadvertently been contaminated with peanuts, a potent allergen.

TABLE 1

Microbial fermentation is essential to the production of these fermented foods

beer	cottage cheese	soy sauce
bologna	distilled liquors	tamari
bread/baked goods	kefir	tea
buttermilk	miso	tempeh
cheeses	olives	tofu
cider	pickles	vinegar
cocoa	salami	wine
coffee	sauerkraut	yogurt
	sour cream	

industrial and environmental Applications

The contributions that biotechnology has made to health care and agriculture have received much attention from the press and the public, and now society is beginning to see the benefits of biotechnology's "third wave"—industrial and environmental biotech.

This third wave of biotechnology is already successfully competing with traditional manufacturing processes and has shown promise for achieving industrial sustainability.

To industry, sustainable development means continuous innovation, improvement and use of "clean" technologies to make fundamental changes in pollution levels and resource consumption. An industrially sustainable process should, in principle, be characterized by

- reduction or elimination of toxic waste.
- lower greenhouse gases.
- low consumption of energy and nonrenewable raw materials (and high use of plant-based carbohydrate feedstocks, such as sugars and starch).
- lower manufacturing cost.

Living systems manage their chemistry efficiently, and their wastes are recyclable or biodegradable. Biocatalysts, and particularly enzyme-based processes, operate at lower temperatures and produce less toxic waste, fewer byproducts and lower emissions than conventional chemical processes. They may also use less purified raw materials (selectivity). Biotechnology can also reduce energy required for industrial processes. And it is providing new methods of monitoring environmental conditions and detecting pollutants.

Industrial biotechnology is making manufacturing processes more efficient in many industries, including textiles, paper and pulp, and specialty chemicals. Some observers predict biotechnology will transform the industrial manufacturing sector in much the same way that it has changed the pharmaceutical, agricultural and food sectors. Industrial biotechnology will be a key to achieving industrial and environmental sustainability.

Industrial Sustainability

According to the Organization for Economic Cooperation and Development, industrial sustainability is the continuous innovation, improvement and use of clean technology to reduce pollution levels and consumption of resources. Modern biotechnology provides tools for achieving these goals.

In recent years, people across the political and economic spectrum have become more concerned about sustainable development. In response to those concerns, many leading industrial companies are developing policies and implementation plans for sustainability that include guidelines for environmental health and safety as well as product stewardship.

The key words to achieving sustainability are "clean" and "efficient." Any change in production processes, practices or products that makes production cleaner and more efficient per unit of production or consumption is a move toward sustainability.

In practical terms, industrial sustainability means employing technologies and know-how to lessen material and energy inputs, maximize renewable resources and biodegradable substances as inputs, minimize the generation of pollutants or harmful waste during product manufacture and use, and produce recyclable or biodegradable products.

MATERIAL AND ENERGY INPUTS

Manufacturing processes have long relied on petroleum, a nonrenewable resource that generates pollution and solid waste, as a source of material and energy. With biotechnology, manufacturers can reduce petroleum inputs and use natural sugars as feedstocks instead.

Through biotechnology, the use of renewable, biomass-based feedstocks will increase. Bio-feedstocks offer two environmental advantages over petroleum-based production: Production will be cleaner, in most cases, and less waste will be generated. When the biomass source is agricultural refuse, our gains double: We will enjoy all the advantages of bio-feedstocks while reducing wastes generated from another human endeavor—agriculture. A final advantage of using plant biomass as feedstock is that as our crop of feedstock grows, it consumes CO_2—one of the greenhouse gases.

Today at least 17.6 billion pounds of commodity chemicals are produced annually in the United States using plant biomass as the primary feedstock.

Biotechnology will also have an impact on energy production. With enzymes called cellulases, it is possible to break down plant cellulose and make new sugars that can be turned into fuel (usually ethanol). Biomass is renewable—and it is plentiful—so government labs have devoted significant resources to research on recombinant technology and bioprocess engineering to improve the economic feasibility of biomass-derived energy. Innovations wrought by biotechnology can improve conventional, petroleum-based fuel production by removing the pollutant sulfur.

INDUSTRIAL MANUFACTURING PROCESSES

Biotechnology can also minimize the environmental impact of manufacturing by decreasing energy use and replacing

harsh chemicals with biodegradable molecules produced by living things.

Manufacturing processes that use biological molecules can lower the amount of energy needed to drive reactions. That's because, unlike many chemical reactions that require very high temperatures and pressures, reactions using biological molecules work best under conditions that are compatible with life—that is, temperatures under 100° F, atmospheric pressure and water-based solutions.

Microbial fermentation systems have provided us with some very important industrial solvents, such as ethanol and acetic acid, for decades. Many surfactants used in chemical manufacturing processes are biological molecules that microorganisms produce naturally, such as emulsan and sophorolipids. Marine biotechnologists have recently discovered a surfactant produced by marine microorganisms that may replace chemical solvents. However, the biological products that offer us the greatest potential for decreasing the environmental impact of industrial manufacturing processes are biocatalysts.

Biocatalysts

In chemistry, a catalyst is a molecule that fosters a chemical reaction and comes out of the reaction unchanged. Living organisms manufacture protein catalysts called enzymes—these are biocatalysts.

In humans, enzymes help digest food, turn the information in DNA into proteins, and perform other complex functions. Enzymes are characterized according to the compounds they act upon. Some of the most common enzymes are proteases, which break down protein; cellulases, which break down cellulose; lipases, which act on fatty acids and oils; and amylases, which break starch down into simple sugars.

Industrial biotechnology companies develop new enzymes to be used in manufacturing processes of other industries. These companies search the natural environment for biocatalysts with industrial value; improve the biocatalysts to meet very specific needs, using the techniques described below; and manufacture them in commercial quantities using fermentation systems similar to those that produce human therapeutic proteins or bulk yeast for the brewing and baking industries. In some cases, genetically altered microbes (bacteria, yeast, etc.) carry out the fermentation. In other cases, either naturally occurring microbes or microbes genetically modified with other techniques are the production organism.

DISCOVERING NOVEL BIOCATALYSTS

Chemical processes, including paper manufacturing, textile processing and specialty chemical synthesis, sometimes require very high or very low temperatures or very acidic or alkaline conditions. Incorporating biocatalysts into manufacturing processes carried out under such extreme conditions requires finding organisms that can survive there. The best place to begin the search for such an organism is in natural environments that mimic the extreme manufacturing conditions, and the best organisms to look for in those environments are microorganisms.

Since the dawn of life, microbes have adapted to every imaginable environment. No matter how harsh the environment, some microbe has found a way to make a living there. Life in unusual habitats makes for unique biocatalysts, and most of that biochemical potential remains untapped. Fewer than 1 percent of the microorganisms in the world have been cultured and characterized. Through bioprospecting, scientists are discovering novel organisms with biocatalysts that will function optimally at the relatively extreme levels of acidity, salinity, temperature or pressure found in some industrial manufacturing processes. These organisms are called *extremophiles.*

Researchers use DNA probes in microorganisms to fish, on a molecular level, for genes that express enzymes with specific biocatalytic capabilities. Once snared, the enzymes can be identified and characterized for their ability to function in industrial processes, and if necessary, they can be improved with biotechnology techniques.

IMPROVING EXISTING BIOCATALYSTS

To improve the productivity-to-cost ratio, scientists are modifying genes to increase enzyme productivity in microorganisms currently used in enzyme production. They also give new manufacturing capabilities to these microbial workhorses by genetically altering them to make enzymes that come from microbes that are too expensive or too finicky to cultivate in the lab.

The biotechnology techniques of protein engineering and directed protein evolution maximize the effectiveness and efficiency of enzymes. They have been used to modify the specificity of enzymes, improve catalytic properties or broaden the conditions under which enzymes can function so that they are more compatible with existing industrial processes.

Biofuel

In his January 2006 State of the Union address, President Bush declared: "America is addicted to oil, which is often imported from unstable parts of the world. The best way to break this addiction is through technology." One of his key technological proposals was "research in cutting-edge methods of producing ethanol, not just from corn, but from wood chips and stalks, or switchgrass."

He announced a national goal to make this new kind of ethanol practical and competitive within six years. Advances in industrial biotechnology and development of new integrated "biorefineries" are at the heart of ethanol production from all sources, including cellulosic biomass.

Found in plant cell walls, cellulose is the world's most common organic compound and, when broken down into small sugars in a biorefinery, can serve as the raw material to make ethanol, biodegradable plastics and other chemicals and materials. Biomass refers to biological material, and in industrial biotech contexts, usually refers to cellulosic plant matter that can be used as feedstock in a biorefinery.

April 2004 saw the first commercial production of ethanol from cellulose, made from wheat straw using biotech enzymes. Since then, a number of breakthroughs have occurred, including the commercial launch of cellulases (enzymes to break down cellulose for ethanol production) and of biotechnology-designed energy crops. As of May 2008, at least 30 cellulosic ethanol biorefineries were planned or operating across the United States.

The potential impact of this technology is tremendous. A 2005 joint report from the Departments of Energy and Agriculture found that more than 1 billion tons of biomass could be available in the U.S. to produce biofuels and bioproducts, enough to meet 30 percent of U.S. demand for transportation fuels and 25 percent of demand for chemicals.

President Bush's bioenergy initiative followed passage of the 2005 Energy Policy Act, landmark legislation for industrial biotech, which authorized more than $3 billion in funding for biofuels and biobased products and established a national renewable fuels standard (RFS). The bill established a goal of displacing 30 percent of today's gasoline consumption with ethanol or other biofuels by 2030. A recent Natural Resources Defense Council report suggests that that potential could be even higher.

A second round of energy legislation passed in 2007, the Energy Independence and Security Act, which dramatically scaled up the RFS to 36 billion gallons of biofuels by 2022. More than 60 percent of the total—2 billion gallons—must be made from non-grain feedstocks (i.e., cellulosic materials, such as crop and wood wastes and energy crops such as switchgrass).

McKinsey & Company analysts project that the new RFS will bring the potential for tens of billions of dollars for biotech companies, farmers, suppliers and fuel producers and necessitate the investment of more than $100 billion for building some 300 new biorefineries. The new RFS provisions in the federal energy bill already have induced an unprecedented level of venture capital investment in the biofuel industry.

Other recent developments in biomass energy include:

- A growing number of states have implemented their own renewable fuels requirements. Many are also providing incentives for biorefinery construction.
- A 2006 report from the Worldwatch Institute found that "development of biofuels and biobased co-products has the potential to increase energy security for many nations; to create new economic opportunities for people in rural, agricultural areas the world over; to protect and enhance the environment on local, regional and global scales; and to provide new and improved products to millions of consumers."
- A 2004 Natural Resources Defense Council report projects biofuels could add $5 billion to farmer profits by 2025.
- Also in 2004, the Ag Energy Working Group of the Energy Future Coalition published a report showing how America's farmers can contribute 25 percent of the total energy consumed in the United States by 2025, without affecting food and feed production.
- The U.S. Department of Energy (DOE) is investing up to $385 million on six biorefinery projects over the next four years. The projects selected include: Iogen Biorefinery Partners, LLC; BlueFire Ethanol, Inc.; Range Fuels; POET (Broin Companies); ALICO, Inc.; and Abengoa Bioenergy.
- DOE is also investing up to $375 million in three new Bioenergy Research Centers, located in Oak Ridge, Tenn.; Madison, Wisc.; and near Berkeley, Calif. The centers focus on reducing the cost of cellulosic ethanol.
- DOE announced $200 million in grant funding to support the development of small-scale (10 percent of commercial scale) cellulosic biorefineries that produce liquid transportation fuels such as ethanol as well as biobased chemicals and bioproducts used in industrial applications.
- DOE selected five projects to receive $23 million in grants to further development of highly efficient fermentative organisms to convert biomass material to ethanol.

Modern biorefineries to produce cellulosic ethanol from a wide variety of biomass resources are currently being constructed throughout the United States, Canada and Europe. Included in the map below are existing, planned and under construction facilities to produce cellulosic biofuels.

Existing and Planned U.S. Cellulosic Ethanol Biorefineries

Planned Commercial-Scale Plant

Planned Pilot/Demonstration Plant

Abengoa Bioenergy Hugoton, KS	30m/yr	**Mascoma** Lansing, MI	40m/yr	**Abengoa Bioenergy** York, NE	10m/yr	**Ecofin, LLC** Washington County, KY	1m/yr	**Pure Vision Technology** Ft. Lupton, CO	2m/yr
ALICO, Inc. LaBelle, FL	13.9m/yr	**Poet** Emmetsburg, IA	25m/yr	**AE Biofuels** Butte, MT		**ICM** St. Joseph, MO	1.5m/yr	**RSE Pulp & Chemical** Old Towne, ME	2.2m/yr
BlueFire Ethanol Irvine, CA	17m/yr	**Range Fuels** Treutlen County, GA	20m/yr	**BioFuels Energy Corp.** Raymondville, TX	4m/yr	**Lignol Innovations, Inc.** Commerce City, CO	2m/yr	**Stora Enso** Wisconsin Rapids, WI	5.5m/yr
Colusa Biomass Colusa, CA	20m/yr	**SunOpta Bioprocess LLC/ Central Minnesota Ethanol Co-Op** Little Falls, MN	10m/yr	**Catalyst Renewables Corp.** Lyonsdale, NY		**Mascoma** Rome, NY	0.5m/yr	**Verenium** Jennings, LA	1.4m/yr
Gulf Coast Energy Moss Head, FL	70m/yr	**University of Florida** Okeelanta, FL	2m/yr	**Clemson University Restoration Institute** North Charleston, SC	10m/yr	**Mascoma** Vonore, TN	5m/yr	**Western Biomass*** Upton, WY	1.5m/yr
Gulf Ethanol Corp. Houston, TX		**Xethanol Corp./Southeast Biofuels** Auburndale, FL	8m/yr	**DOE Bioethanol Plant** Golden, CO		**Pacific Ethanol** Boardman, OR	2.7m/yr	*In Operation	
Iogen Biorefinery Partners Shelly, ID	18m/yr								

Bio® BIOTECHNOLOGY INDUSTRY ORGANIZATION

May 2008

Green Plastics

Biotechnology also offers the prospect of replacing petroleum-derived polymers with biological polymers derived from grain or agricultural biomass.

Like cellulosic ethanol, green plastics are made in biorefineries. There, in place of petroleum-based chemicals to create plastics and polyesters, biotechnology uses sugar from plant material. Almost all the giant chemical companies are building partnerships with biotech companies to develop enzymes that can break down plant sugars.

In 2001, the world's first biorefinery opened in Blair, Neb., to convert sugars from field corn into polylactic acid (PLA)—a compostable biopolymer that can be used to produce packaging materials, clothing and bedding products. Price and performance are competitive with petroleum-based plastics and polyesters. Several national retailers, including Whole Foods and Wal-Mart, now use PLA packaging.

PLA-based fabrics made their media debut at the 2006 BIO International Convention in Chicago, where a fashion show featured the PLA-based Ingeo™ fabric in dresses from Oscar de la Renta, Halston and other leading designers. Ingeo is made by NatureWorks LLC, a joint venture between Cargill and Teijin Limited of Japan.

DuPont and development partners Genencor and Tate & Lyle have created a similar product, the high-performance polymer Sorona® made from the bioprocessing of corn sugar.

Early in 2006, agri-food giant Archer Daniels Midland entered this growing market by signing an agreement with Metabolix, a small industrial biotech company based in Cambridge, Mass., to produce polyhydroxyalkanoates (PHAs), a versatile family of biobased polymers branded as Mirel™, at a biorefinery in Clinton, Iowa. The plant is expected to begin operations in late 2008 and is designed to produce 110 million pounds of Mirel™, annually.

Industrial scientists have also genetically modified both plants and microbes to produce polyhydroxybutyrate, a feedstock for producing biodegradable plastics.

Biotechnology also provides the opportunity to make entirely new products based on natural protein polymers, such as spider silk and adhesives from barnacles. Researchers are developing techniques to make these materials through microbial fermentation.

ENVIRONMENTAL AND ECONOMIC BENEFITS

Petroleum—whether processed into gasoline, plastics, plant fertilizer or other chemicals—is a major environmental problem. When burned it releases massive amounts of carbon dioxide, the principal greenhouse gas driving global warming. Biorefining can reduce these emissions significantly, because the plant matter used to make ethanol, bioplastics and other products absorbs as much carbon dioxide when it is growing as it releases when it burns (as ethanol) or biodegrades (as plastic and other products).

Biobased plastics are already clearly cost competitive with petroleum-based materials. And plastics and chemicals made with industrial biotechnology meet the most important environmental goals, including reducing use of petroleum and other non-renewable resources; using less energy and other natural resources in production; reducing waste in landfills; reducing hazardous waste; and lowering greenhouse gas emissions throughout the lifecycle of consumer products.

A 2007 study by the Environmental Protection Agency, *Bioengineering for Pollution Prevention*, noted the following: "Given the inherent problems associated with persistent plastics in the environment—increasing pressure on landfill space, concerns over climate change, and the economic reality that biobased plastics are already competing in the market without subsidies—applying the tools of industrial biotechnology to the production of environmentally benign plastics is a particularly vibrant area of scientific and commercial activity."

Compared to most traditional hydrocarbon-based polymers, PLA biobased plastic uses 30 to 50 percent less fossil-fuel energy and results in lower CO2 emissions by 50 to 70 percent.

The production of biobased propanediol (a key ingredient for polymers and other materials and chemicals) consumes 40 percent less energy and reduces greenhouse gas emissions by 20 percent versus petroleum-based propanediol, according to manufacturer DuPont Tate & Lyle BioProducts. Production of 100 million pounds of biobased propanediol will save the energy equivalent of 10 million gallons of gasoline per year, or enough to fuel 22,000 cars annually.

Nanotechnology

Remember the movie *Fantastic Voyage,* in which technology existed to shrink a full-size submarine and its human passengers to microscopic size? Today, industrial biotech companies are embarking on their own fantastic voyage into the submicroscopic worlds of biotechnology and nanotechnology. There, they are exploiting the physio-chemical activities of cells to accomplish tasks at nano (10^{-9} meters) scale.

Some are taking genomics and proteomics one step further and exploring how to apply this knowledge gained in the organic world to the inorganic world. For example, Genencor International and Dow-Corning have partnered to combine their respective expertise in protein-engineered systems and silicon.

Such convergence of biotech and nanotech promises to yield many exciting and diverse materials and products. In the area of photonics lies the potential for developing new micro-optical switches and optical microprocessing platforms. In the field of catalysis, the use of inorganic carbon or silicon substrates embedded with biocatalysts has high commercial potential.

BUILDING NANOSTRUCTURES

One of the more exciting research-stage nano-biotech applications uses knowledge about protein engineering to "build" pre-engineered nanostructures for specific tasks. For instance, we know that certain genes in aquatic microorganisms code for proteins that govern the construction of inorganic exoskeletons. In theory, it should be possible to elucidate these gene functions and re-engineer them to code for nanostructures that could be commercially important, such as specific silicon chips or microtransistors.

Researchers at the University of Illinois recently discovered a first-of-its-kind carbon-silicon compound in freshwater diatoms. This discovery promises to open the door to understanding the molecular process of biosilicification, or the ways plants and animals build natural structures. This understanding may lead to applications ranging from low-cost synthesis of advanced biomaterials to new treatments for osteoporosis. NASA and some companies are also looking at bioactive ceramics found to have unanticipated bio-adhesive properties. These properties could provide new ways to purify water since bacteria and viruses adhere to these ceramic fibers.

Protein polymer structures are another area ripe for research and development. Industrial biotech companies have years of experience with genetic platform technologies that can be applied to repeating amino acid sequences. These five to six repeat segments can govern the physical structure of a host of biopolymers.

In the future it may be possible for scientists to build stronger polymers in the lab based on biological materials such as spider silk. It is not difficult to imagine completely new, commercially attractive polymers being developed using recombinant DNA technology.

Carbon nanotube technology is another exciting area of research and development in the nanoworld. Their great tensile strength makes nanotubes perfect for use in new high-tech composites, for switching in computers and for the storage of hydrogen energy for transportation or power-generation applications. Carbon nanotubes can be coated with reaction-specific biocatalysts and other proteins for specialized applications.

Looking further into the future, we may see the use of DNA fragments for electronic switching come into play, along with the materials just discussed. The number of possible new nano-bio combinations is amazingly large. The National Science Foundation estimates that by 2015 the market for nanotech products could exceed $1 trillion.

Environmental Biotechnology

Environmental biotechnology is the use of living organisms for a wide variety of applications in hazardous waste treatment and pollution control. For example, a fungus is being used to clean up a noxious substance discharged by the paper-making industry. Other naturally occurring microbes that live on toxic waste dumps are degrading wastes, such as polychlorinated biphenyls, to harmless compounds. Marine biotechnologists are studying ways that estuarine bacteria can detoxify materials such as chemical sea brines that cause environmental problems.

Environmental biotechnology can more efficiently clean up many hazardous wastes than conventional methods and greatly reduce our dependence on methods such as incineration or hazardous waste dumps.

HOW DOES IT WORK?

Using biotechnology to treat pollution problems is not a new idea. Communities have depended on complex populations of naturally occurring microbes for sewage treatment for over a century. Every living organism—animals, plants, bacteria and so forth—ingests nutrients to live and produces a waste byproduct as a result. Different organisms need different types of nutrients. Certain bacteria thrive on the chemical components of waste products. Some microorganisms, for example, feed on toxic materials such as methylene chloride, detergents and creosote.

Environmental engineers use bioremediation in two basic ways. They introduce nutrients to stimulate the activity of bacteria already present in the soil at a hazardous waste site, or they add new bacteria to the soil. The bacteria then "eat" the hazardous waste at the site and turn it into harmless byproducts. After the bacteria consume the waste materials, they die off or return to their normal population levels in the environment.

The vast majority of bioremediation applications use naturally occurring microorganisms to identify and filter manufacturing waste before it is introduced into the environment or to clean up existing pollution problems. Some more advanced systems using genetically modified microorganisms are being tested in waste treatment and pollution control to remove difficult-to-degrade materials.

In some cases, the byproducts of the pollution-fighting microorganisms are themselves useful. Methane, for example, can be derived from a form of bacteria that degrades sulfur liquor, a waste product of paper manufacturing.

ENVIRONMENTAL MONITORING

The techniques of biotechnology are providing novel methods for diagnosing environmental problems and assessing normal environmental conditions so that we can be better-informed environmental stewards. Companies have developed methods for detecting harmful organic pollutants in the soil using monoclonal antibodies and the polymerase chain reaction, while scientists in government labs have produced antibody-based biosensors that detect explosives at old munitions sites. Not only are these methods cheaper and faster than laboratory methods that require large and expensive instruments, but they are also portable. Rather than gathering soil samples and sending them to a laboratory for analysis, scientists can measure the level of contamination on site and know the results immediately.

Industries That Benefit

- ***The chemical industry:*** using biocatalysts to produce novel compounds, reduce waste byproducts and improve chemical purity.
- ***The plastics industry:*** decreasing the use of petroleum for plastic production by making "green plastics" from renewable crops such as corn or soybeans and, in the future, cellulosic biomass.
- ***The paper industry:*** improving manufacturing processes, including the use of enzymes to lower toxic byproducts from pulp processes.
- ***The textiles industry:*** lessening toxic byproducts of fabric dying and finishing processes. Plus, fabric detergents are becoming more effective with the addition of enzymes to their active ingredients.
- ***The food industry:*** improving baking processes, fermentation-derived preservatives and analysis techniques for food safety.
- ***The livestock industry:*** adding enzymes to increase nutrient uptake and decrease phosphate byproducts.
- ***The energy industry:*** using enzymes to manufacture cleaner biofuels from agricultural wastes.

SOME INDUSTRIAL BIOTECH APPLICATIONS BY SECTORS

- Biological fuel cells
- Fine and bulk chemicals
- Chiral compound synthesis
- Synthetic fibers for clothing
- Pharmaceuticals
- Food flavoring compounds
- Biobased plastics
- Biopolymers for automobile parts
- Bioethanol for transportation
- Nutritional oils
- Oil and gas desulfurization
- Leather degreasing
- Biohydrogen
- Biopolymers for plastic packaging
- Coal bed methane water treatment
- Chem/bio warfare agent decontamination
- Pulp and paper bleaching
- Biopulping (paper industry)
- Specialty textile treatment
- Enzyme food processing aids
- Metal ore heap leaching
- Electroplating/metal cleaning
- Rayon and other synthetic fibers
- Metal refining
- Vitamin production
- Sweetener production (high-fructose corn syrup)
- Oil-well drill-hole completion (non-toxic cake breakers)
- Road surface treatment for dust control
- Textile dewatering
- Vegetable oil degumming

consumer goods
Made With Industrial Biotech

CONSUMER PRODUCT	OLD PROCESS	NEW INDUSTRIAL BIOTECH PROCESS	BIOTECH ENABLING TECHNOLOGY	CONSUMER BENEFIT
Detergent	Phosphates added as brightening and cleaning agents	Addition of biotechnology enzymes as brightening and cleaning agents: • Proteases remove protein stains • Lipases remove grease stains • Amylases remove starch stains	Genetically enhanced microbes or fungi engineered to make enzymes	• Elimination of water pollution from phosphates • Brighter, cleaner clothes with lower-temperature wash water • Energy savings
Bread	Potassium bromate, a suspected cancer-causing agent at certain levels, added as a preservative and a dough strengthening agent	Addition of biotechnology enzymes to: • enhance rising • strengthen dough • prolong freshness	Microorganisms genetically enhanced to produce baking enzymes (directed evolution and recombinant DNA)	• High-quality bread • Longer shelf life • No potassium bromate
Polyester Bedding	Polyester produced chemically from petroleum feedstock	Biotech polyester (PLA) produced from corn sugar feedstock	Existing bacillus microbe used to ferment corn sugar to lactic acid; lactic acid converted to a biodegradable polymer by heating; polymer made into plastic products and polyester	• PLA polyester does not harbor body odor like other fibers • Biodegradable • Not made from petroleum • Does not give off toxic smoke if burned
Vitamin B2	Toxic chemicals, such as aniline, used in a nine-step chemical synthesis process	One-step fermentation process uses vegetable oil as a feedstock	Genetically enhanced microbe developed to produce vitamin B2 (directed evolution)	• Biologically produced without chemicals • Greatly reduces hazardous waste generation and disposal
Stonewashed Jeans	Open-pit mining of pumice; fabric washed with crushed pumice stone and/or acid	Fabric washed with biotechnology enzyme (cellulase) to fade and soften jeans or khakis	Textile enzymes produced by genetically enhanced microbe (extremophiles and recombinant DNA)	• Less mining • Softer fabric • Reduces energy consumption • Lower cost
Paper Bleaching	Wood chips boiled in a harsh chemical solution to yield pulp for paper making	Enzymes selectively degrade lignin and break down wood cell walls during pulping	Wood-bleaching enzymes produced by genetically enhanced microbes (recombinant DNA)	• Reduces use of chlorine bleach and reduces toxic dioxin in the environment • Cost savings due to lower energy and chemical costs
Ethanol Fuel	Food and feed grains fermented into ethanol (a technology that is thousands of years old)	Cellulase enzyme technology allows conversion of crop residues (stems, leaves, straw and hulls) to sugars that are then converted to ethanol	Genetically enhanced organism developed to produce enzymes that convert agricultural wastes into fermentable sugars (directed evolution, gene shuffling)	• Renewable feedstock • Reduces greenhouse gas emissions • Increases domestic energy production • Is more energy efficient to produce than old process
Antibiotics	Chlorinated solvents and hazardous chemicals used to produce antibiotics through chemical synthesis	One-step biological process uses direct fermentation to produce antibiotic intermediate	Genetically enhanced organism developed to produce the key intermediate of certain antibiotics (recombinant DNA)	• 65% reduction in energy consumption • Overall cost savings
Contact Lens Solution	Surfactants and/or saline solutions (do not remove protein deposits) used to clean lenses	Protease enzymes remove protein deposits from the contact lens	Genetically enhanced microbes engineered to make protease enzymes (directed evolution)	• More effective contact lens cleaning • Less eye irritation

examples of Industrial Enzymes

ENZYMES	SOURCE OR TYPE	APPLICATIONS
Carbohydrases		Laundry and dishwashing detergents, industrial pipe/tank cleaners, textiles, pulp and paper, fermentation ethanol
Alpha-amylase	Bacterial α-amylase (e.g., *Bacillus subtilis*), Fungal α-amylase (e.g., *Aspergillus niger*), Alkaline α-amylase	Textiles, starch syrups, laundry and dishwashing detergents, paper desizing, fermentation ethanol, animal feed
β-amylase	From a strain of *Bacillus*	Brewing, maltose syrup
Cellulase		Dishwashing detergents, animal feed, textiles, bioenergy production
β-Glucanase	exo-β-1,4-glucanase, endo-β-1,4-glucanase	Brewing industry
β-Glucosidase		Transforms isoflavone phytoestrogens in soymilk
Dextranase	Made by various microorganisms (e.g., *Leuconostoc mesenteriodes*)	Hydrolyzes the polysaccharide dextran
Dextrinase		Cleaves dextrin into two molecules of glucose
α-Galactosidase (melibiase)		Could increase yield of sucrose; potential use in the beet sugar industry
Glucoamylase	*Aspergillus niger*, Rhizopus, Endomyces	Manufacture of dextrose syrup and high-fructose syrup
Hemmicellulase/Pentosanase/Xylanase	*Thermomyces lanuginosus, Penicillium simplicissimum*	Baking, fruit juice manufacture, wood pulp processing
Invertase		Manufacture of invert syrup from cane or beet sugar (use is minor)
Lactase	*Kluyveromyces lactis, Asperigillus oryzae, Bacillus*	Eliminates lactose from dairy foods
Naringinase		Debitter citrus peel
Pectinase		Fruit processing
Pullulanase	*Klebsiella aerogenes, Bacillus acidipullulyticus, Bacillus subtilis*	Antistaling agent in baked goods
Proteases		Brewing, baking goods, protein processing, distilled spirits, laundry and dishwashing detergents, lens cleaners, leather and fur, chemicals
Acid proteinase	*Endothia parasitica*, Rhizopus, *Aspergillus niger, A. oryzae*	Baking, improves dough handling
Alkaline protease	*Bacillus subtilis, Bacillus licheniformis*	Detergents, leather and fur
Bromelain	Pineapple stem	Food industry
Pepsin	Porcine or bovine stomach	Cheese production
Peptidases		
Aminopeptidase	*Lactococcus lactis*	Food and animal feed
Endo-peptidase		
Subtilisin	*Bacillus subtilis* var. Carlsberg, *Bacillus lichenformis*	Chiral resolution of chemical compounds or pharmaceuticals
Lipases and Esterases	Phospholidases, pregastric esterases, phosphatases	Cleaners, leather and fur, dairy, chemicals
Aminoacylase	Porcine kidney, *Aspergillus melleus*	Optical resolution of amino acids
Glutaminase	*Bacillus, Aspergillus*	Conversion of glutamine to glutamate
Lysozyme	Chicken egg white, *Saccharomyces cerevisiae, Pichia pastoris*	Antibacterial (germicidal in dairy industry)
Penicillin acylase	*Bacillus megaterium, Escherichia coli*	Chemical synthesis

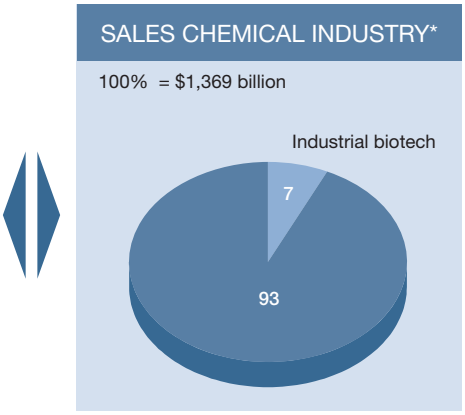
ENZYMES	SOURCE OR TYPE	APPLICATIONS
Isomerase		Converts glucose syrup to high-fructose syrup in food industry
Oxireductases		Chemicals, detergent bleaches, pulp bleaching
Alcohol dehydrogenase	*Saccharomyces cerevisiae, Thermoanarobium brockii*	Chiral synthesis of chemicals
Amino acid oxidase	Porcine kidney, snake venom	Chiral resolution of racemic amino acid mixtures
Catalase	*Aspergillus niger*	Desugaring of eggs
Chloroperoxidase	Algae, bacteria, fungi, mammalian tissues	Steroid synthesis
Peroxidase	Horseradish	Laundry and wood pulp bleaches
Lyases		
Acetolactate decarboxylase		Brewing industry
Aspartic β-decarboxylase		Manufacture of L-alanine from L-aspartic acid
Histidase	*Achromobacter liquidum*	Cosmetics
Transferases		
Cyclodextrin glycosyltransferase		Manufacture of cyclodextrins from starch

Sources:
Diversa and Novo Nordisk

Industrial Biotech–Related Sales in Chemicals, 2005: $95.5 Billion

Billions of dollars

SEGMENT	BIO-DEPENDENT SALES 2008	PRODUCT EXAMPLES/COMMENTS
Biofuels	26	Ethanol, Biodiesel
Plant extracts	24	Hydrocolloids (gums, industrial starches...), essential oils, botanicals
Pharmaceutical ingredients	12	Biocatalytically produced APIs, antibiotics, therapeutic proteins**
Bulk/polymers	12	Natural rubber, biopolymer PLA, biobased polyols
Food/feed ingredients	9	Citric acid, lysine, glutamic acid, Vitamin B12, polyunsaturated fatty acids
Oleochemicals	9	Fatty acids, fatty alcohols, surfactants, gylcerol
Enzymes	2.5	Detergent enzymes, textile processing aids, grain processing enzymes
Others	1	Other specialties, R&D services
Total BIO	**95.5**	



* Current chemical industry sales excluding B2C sales in pharma and personal care: $1,369 billion
** Top-down estimate based on industry interviews; assumes 25% share of total intermediate and active pharmaceutical ingredient sales.

Source:
McKinsey & Co.

preparedness for
Pandemics and Biodefense

In the wake of the September 11, 2001, terrorist attacks, BIO surveyed the biotech industry and found that many companies were already working on defense projects or developing technologies useful for both conventional health care and for defense against biological, chemical and radiological/nuclear agents. Biotechnology companies are also developing novel approaches to prepare for a pandemic, including the development of new vaccines, antivirals and diagnostic and detection tools.

BIO POLICY: BIODEFENSE AND PANDEMICS

BIO has a long-standing policy of opposing the use of biotechnology to develop weapons of any sort that contain pathogens or toxins aimed at killing or injuring humans, crops or livestock.

Appropriate uses of biotechnology include products and services to inoculate citizens against infectious agents that may be used in an attack; to detect biological, chemical or radiological/nuclear attacks; and to diagnose and treat those who may have been exposed to such attacks.

A Strategic Asset

Many U.S. biotechnology companies are actively developing medical countermeasure technologies. Some companies are working on defense-specific technologies under contracts with the federal government. Many more are working on technologies that can be used for conventional health care, pandemics and biological defense, such as antivirals, antibiotics and diagnostic tools.

Recognizing the important value that the biotechnology industry has in developing bioterror countermeasures, President Bush announced in January 2003 the Project BioShield initiative, which would fund new programs at the National Institutes of Health designed to spur countermeasure development. The Project Bioshield Act was signed into law in July 2004 and authorizes $5.6 billion in procurement funding for medical countermeasures against chemical, biological, radiological or nuclear attacks. The President also approved $3.3 billion in FY 2006 and an additional $2.3 billion in FY 2007 for the Department of Health and Human Services for development and procurement of medical countermeasures against a potential influenza pandemic.

Biotechnology companies have products and platforms, including vaccines, therapeutics and diagnostics, that can be enlisted to prepare our nation for human-made and natural emergencies. In addition, drug-delivery technology can make urgently needed medications easier to administer on the battlefield or during a civilian crisis. Medications could even be stored in a soldier's backpack.

VACCINES AGAINST WEAPONIZED PATHOGENS

Vaccines of varying efficacy and convenience exist for anthrax, smallpox, plague and tularemia, and vaccines are in development for other infectious agents that may be used in biological assaults.

The major challenges in vaccine technology are to develop vaccines against a variety of infectious agents (including new strains), to shorten the time needed to establish immunity (some vaccines require multiple boosters to be effective), to be able to produce them in large quantities, improve ease of administration and make them safer. Biotechnology companies are working to solve these problems with new vaccines based on improved delivery technologies and discoveries made through genetic research.

Examples:

- Researchers are exploring vector technology to induce rapid protection. Applications include a third-generation anthrax vaccine. This strategy has the flexibility to address a number of different bioterrorism agents and may elicit a long-lasting immune response after a single oral dose.
- By manipulating an immunotoxin-hybrid molecule used to kill tumor cells in lymphoma patients, researchers have created a vaccine that has been shown to protect mice against ricin, an extremely potent toxin, without significant side effects.
- Agricultural biotechnology researchers are working on fruits and vegetables genetically modified to contain vaccines. Such foods could protect large populations in a very short period of time.

MONOCLONAL ANTIBODIES

Monoclonal antibodies can be used like antibiotics or antivirals, as a way to treat viral and bacterial infections; they can also be used to detect the presence of infectious agents or to clear bacterial toxins from the bloodstream. And, like vaccines, they can confer immunity against biological agents.

Example:

An antibody combination that attaches to anthrax toxin and clears it from the body is under study. The technology could be applied to other biowarfare threats, such as dengue fever, Ebola and Marburg viruses, and plague.

DNA- OR RNA-BASED THERAPEUTICS

Researchers are applying genomics and proteomics technologies to discover weaknesses in viruses and bacteria that can be targeted with a new generation of antibiotics and antivirals. Such weaknesses include proteins or segments of RNA essential to an infectious organism's survival or replication. Projects are under way targeting both.

RNAi, or RNA interference, is another exciting technology. RNAi technologies aim to "silence" targeted genes to prevent the manufacture of disease-causing proteins. RNAi could apply to a number of infectious diseases related to national preparedness.

In a similar vein, the Defense Advanced Research Projects Agency (DARPA) has funded projects that entail rapid DNA analysis, followed by the rapid synthesis of drugs that can bind, or disable, segments of DNA crucial to an infectious organism's survival.

Researchers have completed genome sequences for numerous infectious agents, including the bacteria that cause malaria, stomach ulcers and food poisoning, as well as organisms responsible for hospital-acquired infections, cholera, pneumonia and chlamydia, and for potential biowarfare agents, such as the organism responsible for bubonic plague *(Yersinia pestis)*.

BATTLEFIELD EPIDEMICS

Under battlefield conditions, soldiers are vulnerable to naturally occurring infections such as influenza. The biotechnology industry is addressing such illnesses with vaccines (including some under development that could be taken orally), antivirals and antibiotics.

DETECTION AND DIAGNOSIS

As we saw in the anthrax scare of 2001, we need to be able to rapidly determine whether a person has been exposed to an infectious agent, and we also need capabilities for detecting these agents in the environment. Some devices have been developed already for these purposes, and others are in the pipeline.

Example:
DARPA provided funding for a portable detection device that can analyze DNA from a sample to detect the presence of a preselected infectious agent in 30 minutes. Such devices speed detection and allow it to be performed anywhere, without the need to ship samples to labs.

Portable biosensors have also been developed to detect the exact DNA sequences of pathogens in the atmosphere. Such rapid-detection systems provide the precious time necessary for evacuation, vaccination or other prophylactic measures necessary to save lives.

Other Approaches

REMEDIATION TECHNOLOGIES

Specialized industrial enzymes can be sprayed over contaminated areas, rendering infectious agents harmless.

BARRIER STRATEGIES

These strategies center on the creation of molecular barriers to infection. One company, for example, is developing molecules that adhere to entry sites on mucosal membranes to prevent the absorption of viruses and bacteria into the bloodstream.

NONBIOLOGICAL ATTACKS AND EMERGENCIES

Although the spotlight is on bioterrorism, the biotechnology industry is developing products that may have utility in treating injuries and illness resulting from conventional attacks as well. Artificial skin products, for example, were deployed to treat burn victims of the September 11 attacks. Other biotechnology products with potential applications in an emergency include blood products (such as blood replacement and purification products now in development) and surgical products.

other uses

DNA Fingerprinting

DNA fingerprinting, which is also known as DNA typing, is a DNA-based identification system that relies on genetic differences among individuals or organisms. Every living thing (except identical twins, triplets, etc.) is genetically unique. DNA typing techniques focus on the smallest possible genetic differences that can occur: differences in the sequence of the four building blocks of DNA. These building block molecules, or nucleotides, are commonly designated A, T, C and G.

Some uses of DNA typing compare the nucleotide sequence of two individuals to see how similar they are. At other times, the scientist is interested in assessing sequence similarity between a DNA sample and the known sequence of a reference sample. DNA typing has become one of the most powerful and widely known applications of biotechnology today. It is used for any task where minute differences in DNA matter, such as determining the compatibility of tissue types in organ transplants, detecting the presence of a specific microorganism, tracking desirable genes in plant breeding, establishing paternity, identifying individual remains and directing captive breeding programs in zoos.

DNA fingerprinting is, of course, also used to solve crimes by comparing samples gathered at a crime scene to a suspect's DNA. The technology has also exonerated more than 200 people who were wrongly convicted of crimes.

DNA TYPING TECHNIQUES

Scientists have developed two main techniques to look directly at minute differences in genes. Each technique has advantages and disadvantages, and both are used in basic and applied research, by clinicians, public health officials, forensic scientists and commercial labs. The technique of choice depends upon the question being asked, amount of DNA available, ability to minimize contamination, cost and urgency. Sometimes both techniques are used in combination.

One technique, known as *restriction analysis*, uses naturally occurring enzymes that cut DNA at very precise locations. Because of differences in the sequence of nucleotides, the enzymes cut DNA samples from different individuals in different places. The cut fragments of DNA are different sizes and compose a DNA pattern, or "fingerprint," unique to each individual. Comparing the different-sized DNA fragments of two samples provides very strong evidence about whether the two samples came from a single source or individual.

Another DNA typing technique, the polymerase chain reaction (PCR), makes use of the process by which cells duplicate their DNA before they divide into two cells. PCR makes thousands of copies of a specific DNA sequence in a matter of hours. PCR, like restriction analysis, allows us to compare two DNA samples to see if they come from the same individual, but it also allows us to detect the presence or absence of particular bits of DNA in a sample. Used in this way, PCR can quickly and accurately diagnose infections such as HIV and chlamydia and detect genes that may predispose an individual to many forms of cancer and cystic fibrosis, or help protect an individual from HIV-AIDS.

To successfully identify minute differences in DNA molecules, scientists must focus DNA-typing techniques on regions of the DNA molecule that are highly variable between two individuals. This is one of the reasons they often use DNA from mitochondria instead of nuclear DNA, which does not tend to vary as much from one individual to the next. Another reason for using mitochondrial DNA is its unique inheritance pattern; virtually all is inherited from the female parent.

FORENSIC USES

In criminal investigations, DNA from samples of hair, bodily fluids or skin at a crime scene are compared with those obtained from suspected perpetrators. DNA typing was first used in Great Britain for law enforcement purposes in the mid-1980s and was first employed in the United States in 1987. Today, the Federal Bureau of Investigation performs most DNA typing for local and state law enforcement agencies, and private biotechnology companies also perform DNA fingerprinting tests.

DNA typing has reaped positive return in many states, where the genetic records of prisoners were matched with samples recovered from murders and sexual assaults. DNA typing has exonerated more than 200 innocent individuals for crimes they were convicted of before DNA fingerprinting became available. Sixteen of those prisoners were on death row.

The widespread acceptance of DNA typing by court systems around the country has led many states to pass laws requiring people convicted of sex offenses and other crimes to be DNA typed and included in statewide offender databases. Law enforcement officials hope someday to integrate the FBI and various state DNA offender records into a single national database that would allow for the rapid comparison and matching of known offenders with genetic material recovered from crime scenes.

DNA typing is also used to identify the remains of unknown individuals, as in the recent identification of the Unknown Soldier, or to identify the bodies of people slain in political upheavals. American soldiers now deposit samples in a DNA data bank as a backup for the metal dog tags they wear in combat.

Scientists even used DNA fingerprinting to identify the remains of Czar Nicholas Romanov II of Russia and his family, executed by the Bolsheviks in 1918. They compared DNA from bones with DNA from blood samples of living descendants of Nicholas II, including Prince Philip of Great Britain. The results of DNA typing disproved one woman's claim that she was the Russian Grand Duchess Anastasia and had survived the Romanov massacre.

PATERNITY

Paternity determination is possible with DNA typing because half of the father's DNA is contained in the child's genetic material. Using restriction analysis, DNA fingerprints of the mother, child and alleged father are compared. The DNA fragments from the mother that match the child's are ignored in the analysis. To establish paternity, the remaining DNA fragments in the child's DNA fingerprint, which have been inherited from the biological father, are compared to the DNA sequences of the alleged father.

ANTHROPOLOGY

Scientists are using DNA typing to help piece together the thousands of fragments gathered from the Dead Sea Scrolls. With DNA typing they can separate scrolls written on sheepskin from those on goatskin. From there, scientists are reconstructing the pieces as they were originally assembled.

DNA typing can determine the degree of relatedness among human fossils from different geographic locations and geologic eras. The results shed light on the history of human evolution and migration.

WILDLIFE MANAGEMENT

The more we understand about the genetic makeup of natural populations, the better our conservation and management plans will be. Scientists use DNA typing to measure the amount of genetic variation between different populations of a species, determine the geographic distributions of species, help preserve endangered or threatened species, and determine the genetic resilience of wild populations of endangered species. For example, we now know that cheetahs are at risk of extinction largely because there is virtually no genetic variation in the species.

DNA typing recently helped scientists solve a mystery involving the Mexican group of Pacific loggerhead turtles. Pacific loggerheads nest in Japan and Australia, not in Mexico, yet very young loggerheads are often found off the Mexican coast. Biologists assumed the young loggerheads could not have swum the 10,000 miles from Japan to Mexico, and even farther from Australia, so the origin of the Mexican loggerheads was a mystery. Using DNA typing, however, biologists established that the young loggerheads in Mexico are, in fact, born in Australia or Japan, are carried to Mexico by ocean currents, and then swim back to Australia or Japan when they are ready to breed.

DNA fingerprinting has also been used to monitor illegal trade in protected species. For example, scientists determined that fish products on sale in Japan included whale meat that had been illegally imported, as well as other species that had been hunted illegally. Similar studies conducted on ivory uncovered elephant poaching in countries where it is illegal. Finally, some countries, including the United States, are using DNA typing to prevent the importation of caviar from endangered sturgeon species.

intellectual Property

Biotechnology is an industry of ideas and invention. That makes intellectual property, typically in the form of patents, often the most important asset a biotech company has. These companies are often small firms—most biotechs have 50 or fewer employees—developing products that can take upwards of 15 years and hundreds of millions of dollars in investment to bring to the marketplace.

Intellectual property protection is so critical that a 1980 case is credited with helping launch the biotech industry. In *Diamond v. Chakrabarty*, the court held that "anything under the sun that is made by the hand of man"—including modified cells and other biological materials—may be patented.

What Is a Patent?

A patent is an agreement between the government and an inventor whereby, in exchange for the inventor's complete disclosure of the invention, the government gives the inventor the right to exclude others from making, using, selling or importing the invention for a limited time. The property right provided in a patent is quite different from what we typically think of when we own property. What is granted is not the right to make, use, offer for sale, sell or import, but the right to *stop others* from making, using, offering for sale, selling or importing the invention.

The United States Patent & Trademark Office (PTO) evaluates patent applications and issues patents. Patents usually last 20 years from the date on which the patent application is filed (*not* when it is *issued*). Thus, the enforceable term of a patent is between 17 and 20 years; exactly how long depends on how long the application is under PTO review. The PTO provides a three-year period for the agency to issue a patent. Anything beyond three years will be added to the end of the patent term, to ensure a 17-year minimum. So even if an application is examined in the PTO for, say, four years before it is issued, the enforceable patent term will be 17 years.

In highly regulated industries such as biotechnology, the "effective" period of patent protection may be much less than 17–20 years. Why? As an example, consider a drug whose patent is issued during Phase I trials. Before it can enter the market, the drug still has to undergo at least two more rounds of clinical testing and an evaluation period at the FDA, all of which may take five to 10 years. Its patent may be granted years before FDA approval, thus starting the clock before the product can be sold. By the time the drug reaches patients, it may have less than 10 years of patent protection left. (The Hatch-Waxman Act partially offsets the time lost in development of drugs, but the period of "effective patent protection" is still much shorter than for other products.)

Once a patent has expired, anyone may make, use, offer for sale, sell or import the invention without permission of the patentee.

TYPES OF PATENTS

Patents fall into three categories: utility, design and plant patents:

- Utility patents are granted to those who invent or discover new and useful machines or processes.
- Design patents are issued to inventors of new, original and ornamental design for an article of manufacture.
- Plant patents are given to those who invent or discover—and then asexually reproduce—a new plant type.

PATENT PROTECTION IN THE CONSTITUTION

A patent grants exclusive rights to inventors for limited periods. The first law providing exclusive rights to the makers of inventions for limited periods seems to have been in Italy in the 15th century. Even before the signing of the U.S. Constitution, most states had their own patent laws. The Constitution entrusted Congress to provide protection for inventions. The basis for the federal patent and copyright systems is found in the Constitution of the United States, Article 1, Section 8, Clause 8, which states:

> Congress shall have power…to promote the Progress of Science and useful Arts by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.

Congress has enacted various laws relating to patents. The first U.S. patent law was enacted in 1790. Today, in the United States, patents are granted by the U.S. Patent and Trademark Office and are effective only within the United States and its territories.

The Purpose of a Patent

The rationale for a patent system is to provide an advantage to society as a whole by rewarding the development of new inventions. Thus, the patent system has two basic purposes: to promote the advancement of technology and to protect the inventor.

PROMOTING TECHNOLOGICAL ADVANCEMENT

To obtain a patent, an inventor must "teach" the public how to make and use the invention in the best way the inventor knows. Thus, the patent system rewards only those inventors who are willing to share their inventions with the world.

Moreover, the information disclosed in a patent application is usually available to the public long before a patent is issued. If a patent application is filed internationally or (starting in 2000) in the United States, it is published 18 months after its initial filing. The exception to this rule is that an applicant who has filed only in the U.S. and not abroad may request that the U.S. application not be published. If however, the applicant files in a foreign country, then the U.S. patent application will be published.

Once published, a patent application and all its information are available to anyone, stimulating the flow of scientific and technological knowledge. That's why societies that protect inventors with patents are the world's most advanced, scientifically and technologically.

Patentable Inventions

Under U.S. law, various types of invention can be patented:

- *A process*—for example, a process of making a chemical by combining chemical X with chemical Y, or a method of treating a cancer patient by administering a specific drug.
- *A machine*—for example, a flat-screen, high-definition television set or an X-ray machine.
- *An article of manufacture*—for example, a silicon computer chip or a specially molded piece of plastic for an automobile bumper.
- *A composition of matter*—for example, a new pharmaceutical drug or a new plastic for use in kitchen counters.
- Any new and useful improvement to an invention that falls under any of these categories.

Other types of inventions or discoveries cannot be patented; these include naturally occurring organisms, laws of nature, natural or physical phenomena and abstract ideas.

BIOTECHNOLOGY PATENTS

Biotechnology inventions generally fall into one of the following classes:

1. New compositions of matter related to:
   - newly discovered isolated nucleic acids
   - proteins
   - pharmaceutical inventions based on these nucleic acids or proteins or cell lines transformed by nucleic acids
   - One cannot patent a naturally occurring gene or protein as it exists in the body, but one can patent a gene or protein that has been isolated from the body and is useful in that form as a drug, screening assay or other application.
2. Methods of making the above products through, for example, transformation technology or cell culture technology.
3. Methods of treating patients with a given disease through the use of a particular gene or protein. Even if someone has a patent on a gene or protein, a second inventor can obtain a patent on a new use of that gene or protein, if the second inventor discovers a new use for the substance. Such methods of treatment can also include delivery mechanisms.
4. Methods of detecting or monitoring disease states such as through detection assays.

Patent Requirements

Patents are territorial. To obtain a patent on a new invention, an inventor must show that the following criteria are met:

1. The invention is novel and nonobvious: that is, the invention is really new. The invention must not have been described or discovered by another before the inventor filed a patent application. The invention must also not be obvious from the prior work of others. In patenting a gene or a protein, the requirement for novelty and nonobviousness usually means that the inventor must know the chemical structure of the new gene or protein. If that structure already is known, the inventor can't meet this requirement.

2. The invention is useful. The inventor must show that the invention has a real-world use. It isn't enough just to find a new gene or protein. The inventor must specify what the uses are; for example, whether the gene or protein is useful as a drug for disease X or as a target for disease Y or as a diagnostic marker for disease Z.
3. The application describes the invention in sufficient detail to allow the public to make and use the invention. The inventor must teach or "enable" other persons that are skilled in the technological area of the invention to use the invention described by the inventor.

In addition to the above criteria, a description of the material or tool for which a patent is sought cannot have been published in print, either in the United States or abroad. Moreover, if the invention has been on sale or in use in the U.S. for a year before the application is filed, it is not patentable.

The Patent Application

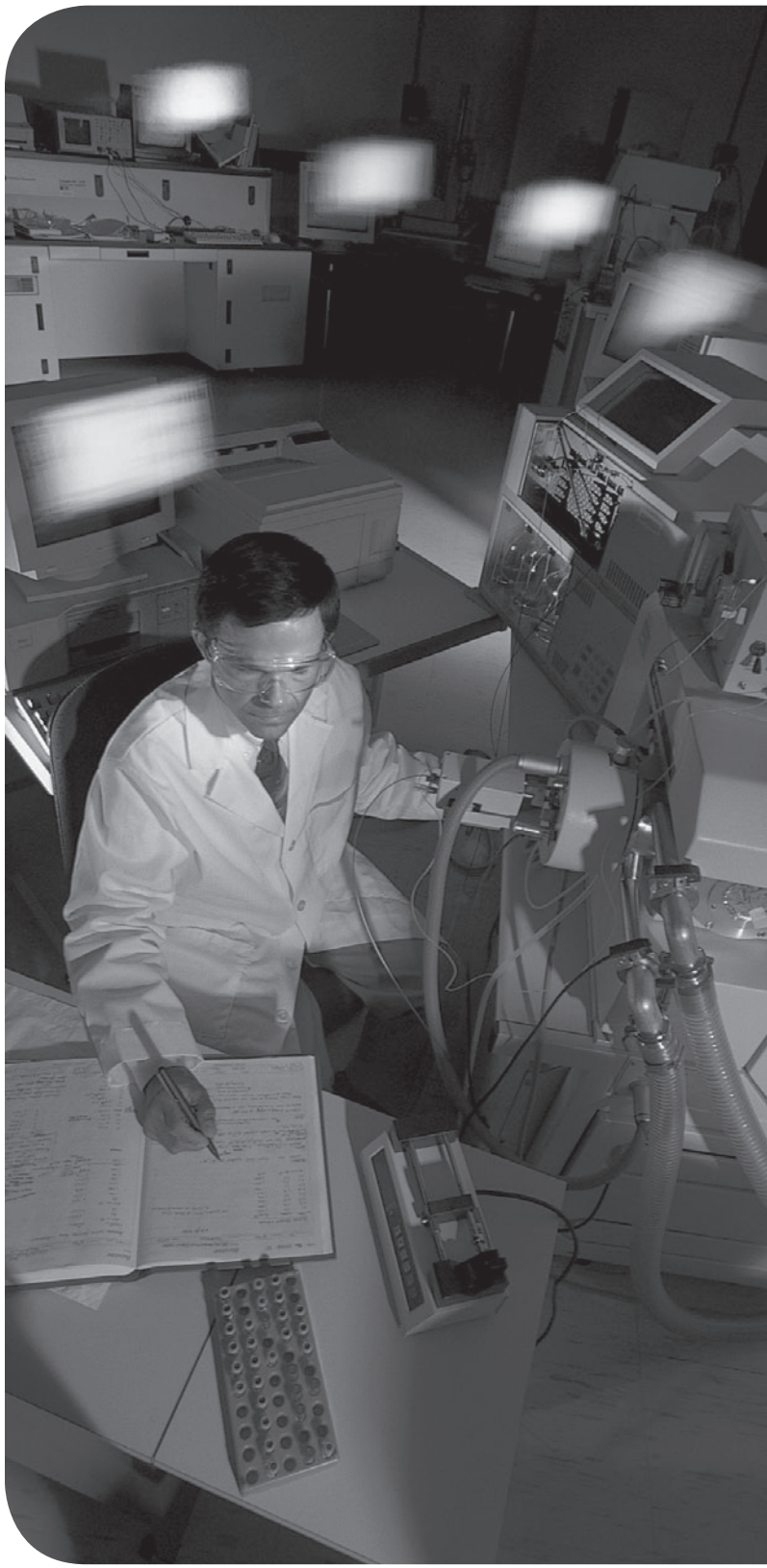
To obtain a patent, the inventor is required to submit a patent application to each country in which he or she desires to obtain patent protection. In the United States, a complete patent application must contain the following components:

1. A written English-language document (called the specification) that clearly describes and explains the invention. Attached to the specification must be at least one "claim" that sets forth the desired legal parameters of the claimed invention.
2. A drawing illustrating the invention (if needed to understand the invention).
3. An oath or declaration by the inventor(s) claiming inventorship.
4. A filing fee (amount varies depending on the patent application).

Patenting Organisms

Some living things can be patented, but not all. As with any invention, a living thing must be "new" in order to be patented. Accordingly, living organisms that occur or exist in nature are not patentable. For instance, one can't patent a mouse, because mice have been around for a long time. If someone makes a kind of mouse that never existed before, however, then that kind of mouse might be patented. Below are a few examples of patentable organisms.

- **Microbes:** As long ago as 1873, Louis Pasteur received a U.S. patent for yeast "free from organic germs or disease." With the



growth of genetic engineering in the late 1970s, the patentability of living organisms was re-examined, and confirmed. A landmark case involved Ananda Chakrabarty's invention of a new bacterium genetically engineered to degrade crude oil. In 1980, the Supreme Court clearly stated that new microorganisms not found in nature, such as Chakrabarty's bacterium, were patentable. Chakrabarty received a patent in 1981 (U.S. Pat. No. 4,259,444). In the Chakrabarty decision, the Supreme Court stated that "anything under the sun that is made by the hand of man" is patentable subject matter. Therefore, if a product of nature is new, useful and nonobvious, it can be patented if it has been fashioned by humans.

- **Plants:** In 1930, the U.S. Congress passed the Plant Patent Act, which specifically provided patent protection for newly invented plants that are asexually reproduced. In 1970, Congress provided similar protection for newly invented sexually reproduced plants.
- **Animals:** In the 1980s, the question of whether multicellular animals could be patented was examined. The key case involved a new kind of "polyploid" oyster that had an extra set of chromosomes. This new, sterile oyster was edible all year round because it did not devote body weight to reproduction during the breeding season. The PTO found that such organisms were in fact new and therefore eligible for patenting. It found this particular type of oyster to be obvious, however, and thus did not allow a patent for it. Nonetheless, the polyploid oyster paved the way for the patenting of other nonnaturally occurring animals. In 1988, Philip Leder and Timothy Stewart were granted a patent on transgenic nonhuman mammals (U.S. Pat. No. 4,736,866) that covered the so-called Harvard mouse, which was genetically engineered to be a model for the study of cancer.
- **Natural Compounds:** Natural compounds, such as a human protein or the chemical that gives strawberries their distinctive flavor, are not themselves living, but occur in nature. Thus, they are new and can be patented only if they are somehow removed from nature. Therefore, a compound that is *purified* away from a strawberry, or a protein that is *purified* away from the human body can be patented *in its purified state*. Such a patent would not cover the strawberry or the person. The U.S. PTO does not allow anyone to patent a human being under any circumstances.

Patent Licensing

A patent license is a contract between the owner of a patent and an independent party who wishes to make, use or sell the invention claimed in the patent. Such a contract is in essence a promise by the patent owner that the owner will not sue the independent party, called the licensee, for patent infringement, provided that he or she complies with the terms of the contract. Typically, the licensee agrees to pay the patent owner a percentage of the revenue the licensee receives from sale of the invention and/or other license fees.

Many inventions require significant capital investment before they can be used commercially. By licensing a patented invention to a third party, a patent owner without the resources to fully develop an invention can work with the third party to commercialize it.

In some cases, a license from more than one person may be necessary to use an invention effectively. For example, one party could obtain a patent on a new protein, while a second party obtains a patent on a new use of that same protein. In order to sell that protein for the new use, a third party would require a license from both patent owners. If the two patent owners want to sell the protein for the new use, they would need to grant a license to each other. Such licenses are often called cross-licenses. In rapidly developing fields of technology, cross-licenses are very common.

If a third party uses a patented invention without a license, the patent owner can seek legal remedies for infringement, including damages and an injunction against the infringer to prevent future use.

Recent Patent Developments

In April 2007, the U.S. Supreme Court handed down what may be the patent ruling of the decade. The *KSR International v. Teleflex, Inc.* decision made it more difficult to obtain or protect patents on products combining elements of pre-existing inventions. Some fear this decision could hamper biotech innovation. However, we really don't know the ultimate impact—that will be determined by future litigation. At stake is the ability of biotech companies to obtain appropriate patent protection on their inventions.

Meanwhile, new rules from the U.S. Patent & Trademark Office were scheduled to go into effect in November 2007. However, GlaxoSmithKline won a permanent injunction.

The new rules would have limited the number of continuing applications that an applicant could file. (A *continuation application* is filed by an inventor who wants to add additional claims to an existing patent application.) The rule changes would also have limited the number of claims that could be filed and pursued, and increased disclosure requirements if these limits were exceeded. Many in the biotech industry were concerned about these changes, since it can take 10 to 15 years develop a patented biotechnology product. Strong patent protection is critical in allowing biotech companies to attract the investment needed during that time.

ethics

Modern biotechnology was born under unique social and political circumstances, establishing a precedent that shaped the development of the industry and continues to influence its character even today.

In 1973, a few days after Drs. Herbert Boyer and Stanley Cohen described their successful attempt to recombine DNA from one organism with that of another, a group of scientists responsible for some of the seminal breakthroughs in molecular biology sent a letter to the National Academy of Sciences (NAS) and the widely read journal *Science* calling for a self-imposed moratorium on certain scientific experiments using recombinant DNA technology. The scientists temporarily halted their research and publicly asked others to do the same. Even though they had a clear view of their work's extraordinary potential for good and no evidence of any harm, they were uncertain of the risks some types of experiments posed. They suggested that an international group of scientists from various disciplines meet, share up-to-date information and decide how the global scientific community should proceed. International scientists in this exceptionally competitive field complied with this request to halt certain research.

A few months after the moratorium request, the scientists sent a second letter, endorsed by the NAS, to the National Institutes of Health (NIH), asking it to establish an advisory committee for evaluating the risks of recombinant DNA, develop procedures to minimize those risks and devise guidelines for research using recombinant DNA. In response to the request, the NIH formed the Recombinant DNA Advisory Committee (RAC), which received its official charter in October 1974.

In February 1975, 150 scientists from 13 countries, along with attorneys, government officials and 16 journalists, met at the Asilomar Conference Center in Monterey, Calif., to discuss recombinant DNA work, consider whether to lift the voluntary moratorium and, if so, to establish strict conditions under which the research could proceed safely. The conference attendees replaced the moratorium with a complicated set of rules for conducting certain kinds of laboratory work with recombinant DNA, but disallowed other experiments until more was known. The final report of the Asilomar Conference was submitted to the NAS in April 1975, and a conference summary was published in *Science* and the Academy *Proceedings*.

At no other time has the international scientific community voluntarily ceased the pursuit of knowledge *before* any problems occurred, imposed regulations on itself and been so open with the public.

The NIH-RAC met for the first time just hours after the Asilomar conference ended. The committee adopted the conference consensus as interim rules for federally supported laboratories in the United States. It spent the next year developing an initial set of guidelines for recombinant DNA molecule research. After public review of the draft guidelines, the RAC published the final version in July 1976. Comparable organizations in other countries promulgated similar guidelines overseeing laboratory research with recombinant DNA. BIO member companies have voluntarily adhered to these guidelines since its inception.

Over the next few years, the RAC revised the guidelines in light of accumulating data that supported the safety of recombinant DNA laboratory research. Oversight policies of laboratory research in many other countries relaxed as well. During the early 1980s, as the biotech industry moved from basic research into product development, the RAC assumed the responsibility of formulating safety standards for industrial manufacturing using recombinant organisms and reviewed proposals voluntarily submitted by companies such as Genentech and Eli Lilly.

As data supporting the safety of recombinant DNA research and product development grew, biotech products moved toward commercialization under the regulatory oversight of the Food and Drug Administration, Environmental Protection Agency and U.S. Department of Agriculture. The RAC then began to focus more on social and ethical issues, precipitated primarily by the use of recombinant DNA in humans for therapeutic purposes.

Thus, from its inception, the biotech industry has supported public discussion and appropriate regulation of its work.

BIO values the important role the academic scientific community and the RAC have played in the early stages of recombinant DNA research, biotechnology manufacturing and human gene-transfer trials. Their approach, supported voluntarily by private and public researchers, ensured the thoughtful, responsible and very public introduction of and discussion about this new technology.

BIO ACTIVITIES

BIO is committed to the socially responsible use of biotechnology to save or enhance lives, improve the quality and abundance of food, and protect the environment. As our companies develop technologies that promise to benefit humankind, these technologies also may bring ethical questions. To help us examine bioethics issues as they arise, BIO several years ago formed a committee on bioethics. This committee formulated ethical principles that were adopted by our board of directors as a Statement of Ethical Principles in 1997 (see below). We continue to refine a comprehensive vision of ways to ensure biotechnology is used for the betterment of humankind and not abused.

BIO and the biotech industry respect the power of the technology we are developing, and we accept the need for appropriate regulation. We work with state, federal and international regulatory bodies to shape the development of regulatory policies that foster safe, effective and beneficial products.

We must continue to address ethical questions that arise as science progresses. While biotechnology can greatly improve the quality of life, we recognize that this new technology should be approached with an appropriate mixture of enthusiasm, caution and humility. To that end, in June 2006, BIO's Board of Directors approved the establishment of a Board Standing Committee on Bioethics to enable industry executives to participate in policy, strategy and planning discussions regarding bioethics issues that confront all sectors of the industry: human health, food and agriculture, and industrial and environmental biotechnology.

Ethical Issues

Myriad social and ethical issues are associated with biotech research, product development and commercialization. Below, we discuss some of these issues. For additional information on these and other topics, please visit bio.org.

GLOBAL HEALTH

Biotechnology has extraordinary potential to improve the health and well-being of people in the developing world, but significant impediments exist to the development and dissemination of diagnostics, therapeutics and vaccines for the infectious diseases prevalent in developing countries. To explore the obstacles and devise mechanisms for circumventing them, BIO and the Bill and Melinda Gates Foundation joined forces in 2004 to establish BIO Ventures for Global Health (BVGH), a new non-profit organization. BVGH works with companies, donors and investors to bring new vaccines, therapies, diagnostics and delivery tools to market in developing nations.

GENE THERAPY

Gene therapy is subject to greater oversight than virtually any other therapeutic technology. NIH guidelines require federally funded institutions and their collaborators to submit detailed information about proposed and ongoing clinical trials of gene therapy products. Much of this information must be disclosed to the public. The FDA, which has statutory authority to regulate gene therapy products (including clinical trials), collects detailed information about investigational products and clinical trials, reviews adverse-event reports,

and requires annual reports of all ongoing trials. The combined activities and responsibilities of the FDA, through its statutory role as the regulator of drug development, and the NIH/Recombinant DNA Advisory Committee (RAC), as the forum for public discussion, have served to protect patients while ensuring that important research moves ahead.

The field of gene therapy continues to focus on patients with severe and life-threatening diseases who usually have few treatment options or who have failed all available therapies. Thousands of patients have now received somatic cell (nonreproductive cell) gene therapies targeted at life-threatening genetic diseases, cancer and AIDS.

Since the first gene-therapy clinical trial launched in 1990, more sponsors and academic researchers have moved into the area and are conducting human clinical trials, but the research pace has remained slow and deliberate. Even after more than a decade of research and clinical testing, many of the gene therapy clinical trials active today are in early-phase studies (Phase I/II) that evaluate the safety of the gene therapy vector (the agent used to carry new DNA into a cell). Gene therapies continue to be in early stages of development because researchers are methodically exploring options for routes of administration, dosing regimes, patient populations, indications, combination therapies and novel vectors.

BIO POLICY: GENE THERAPY

BIO believes that both the FDA and the NIH/RAC play important roles in the oversight process. We recommend that any system of oversight for gene therapy provide the agencies with safety data while ensuring patient confidentiality and protection of trade secrets. BIO is always ready to work with the NIH/RAC and the FDA to develop a system that protects patients and the integrity of the product development process.

GERM-LINE GENE THERAPY MORATORIUM

For more than a decade, the academic and industrial research communities have observed a voluntary moratorium on human gene therapy procedures that would affect the germ-line cells—the egg and sperm—that pass on genetic composition.

BIO POLICY: MEDICAL PRIVACY AND GENETIC DISCRIMINATION

BIO recognizes the need for confidentiality of all individually identifiable medical information. We support national policy—legislation or regulations—to protect the confidentiality of all personal medical information, including data derived from genetic tests. The industry believes that an individual's medical information must be respected, treated confidentially and safeguarded from discriminatory misuse. BIO believes that protecting patient privacy and promoting medical research are mutually attainable goals.

In September 1996, BIO's Board of Directors called for strong controls on the use of all confidential medical information, including genetic information. At BIO's urging, 11 national biotechnology industry groups from around the world have also endorsed the call for strong protections against the misuse of personal medical information.

BIO supports legislation that prohibits insurers from denying individuals insurance based on their genetic information. People should have the option of using diagnostic or predictive tests that can help them recognize early warning signs of disease and seek proper treatment. This option could be jeopardized if genetic information were used to discriminate.

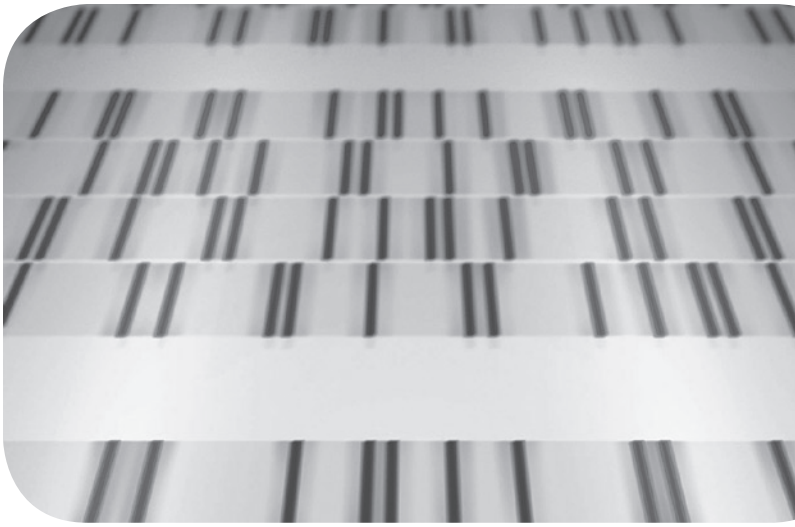
STEM CELLS

Researchers can now separate early, undifferentiated stem cells from blastocysts—the 5-day-old ball of cells that eventually develops into an embryo. Such embryonic stem cells can differentiate into any cell type found in the human body; they also have the capacity to reproduce themselves. The ability to maintain stem cell lines in culture and direct their development into specific cell types holds the potential to save many lives by controlling cancer, re-establishing function in stroke victims, curing diabetes, regenerating damaged spinal cord or brain tissue and successfully treating many diseases associated with aging.

These undifferentiated cells lines are also powerful research tools. By studying these cells, we will begin to understand the mechanisms that guide cell differentiation and de-differentiation.

Scientists have also learned that undifferentiated cells from other tissue (for example, "adult" stem cells) have value. BIO supports research on these cells. However, according to the NIH and the NAS, only the embryonic stem cell can be turned into any cell type.

On August 9, 2001, President Bush announced federal funding would be allowed for research on embryonic stem cell lines that were derived from blastocysts prior to 9:00 p.m. that day. At the time, the Administration believed that more than 60 embryonic stem cell lines were available for research. Today, estimates from the National Institutes of Health (NIH) show the number of available lines at 21, well short of the number the policy intended to make available. These 21 cell lines are not genetically diverse enough to meet research needs, and it is likely that many or all of them cannot be used to develop therapies for humans because they were exposed to mouse-derived "feeder" cells. Without federal funding, embryonic stem cell research in the United States may fall behind that in other countries, and American citizens may have to wait even longer for therapies for unmet medical needs.



BIO POLICY: STEM CELL RESEARCH

BIO strongly supports the enactment of federal legislation that provides for innovative stem cell research, such as the Stem Cell Research Enhancement Act of 2007 (S. 5). This bill would have amended the Public Health Service Act to allow federal funding of research on stem cell lines derived from discarded human embryos created for fertility treatments, but it was not enacted.

In 2007 and early 2008 there were several major scientific breakthroughs in stem cell research: Researchers announced that they had created human embryonic stem cell lines without destroying human embryos; other researchers announced that they had reprogrammed adult stem cells to behave like embryonic stem cells. These discoveries, made possible because of previous research on embryonic stem cells, are still in the early stages, and it is not yet clear whether they will yield cell lines useful for the development of new treatments and cures. As long as new treatments and cures are not available for the millions of patients awaiting them, we believe scientists should be able to continue to pursue promising routes to finding them.

CLONING

Cloning is a generic term for the replication in a laboratory of genes, cells or organisms from a single original entity. As a result of this process, exact genetic copies of the original gene, cell or organism can be produced.

BIO POLICY: HUMAN CLONING

BIO is opposed to human reproductive cloning—using cloning technology to create a human being. BIO was one of the first national organizations to offer public support for voluntary moratorium on research into cloning a whole human being. Human reproductive cloning would involve taking the nucleus of a somatic cell (a body cell that is neither an egg nor a sperm) of a person and inserting it into an unfertilized egg from which the nucleus has been removed. The egg containing the somatic cell nucleus is then implanted into a woman's uterus. In theory, this would lead to the development of a human being after a gestation period. Reproductive cloning is too dangerous and raises far too many ethical and social questions to be undertaken.

Another type of cloning involves somatic cell nuclear transfer to an egg, as described above. However, as the egg divides, the undifferentiated cells are kept in culture and never implanted. A few days after cell division begins, stem cells are separated from the rest of the cells. The stem cells continue to divide, creating a cell line that is genetically identical to the somatic cell from which the nucleus was removed.

Undifferentiated cells that are genetically identical to the patient have remarkable therapeutic potential. Given the proper environments, these cells could develop into new tissues that could replace diseased tissues and cure diseases such as diabetes, Parkinson's, Alzheimer's and various types of cancer and heart disease. This avenue of study could produce replacement skin, cartilage and bone tissue for burn victims and nerve tissue for those with spinal cord or brain injuries. Research also continues regarding the environmental cues, genes and structures that direct cell differentiation into whole organs composed of different tissue types. This application of cloning technology is often referred to as therapeutic cloning, or somatic cell nuclear transfer (SCNT).

One reason for doing SCNT is to understand the process of reprogramming—how the egg cell takes genetic material from a fully differentiated cell and turns it back into an undifferentiated cell. Once that process is understood, egg cells would not be needed and this process could be replicated in a lab.

Because of the remarkable potential of cellular cloning to cure diseases and restore function to diseased tissues, in 2002 the National Academy of Sciences released a report supporting the use of cloning for therapeutic purposes, but opposing its use for reproductive cloning. BIO agrees with Academy's conclusions and positions.

FOOD AND AGRICULTURE

Agriculture is fundamental to the economies and environments of the entire world. Agricultural biotechnology is used to modify plants and animals to meet consumer demand for more healthful, nutritious foods, and to produce foods in more environmentally sustainable ways. Crops and animals are also being modified to provide new, more plentiful and safer sources of medicine to treat human diseases.

BIO POLICY: AGRICULTURAL BIOTECHNOLOGY

BIO is dedicated to open discussion with consumers, farmers, legislators and opinion leaders regarding ethical issues in the use of agricultural biotechnology.

Our companies affirm and uphold the science-based regulation and government oversight of agricultural biotechnology by the Food and Drug Administration, the U.S. Department of Agriculture and the Environmental Protection Agency. This oversight ensures the safety and quality of the food supply and has established effective performance standards for developing safe techniques to reduce agricultural losses to plant disease, insect pests and weeds.

We believe the public should fully participate in the introduction of these new products both through an open, accessible and accountable regulatory system and through exercise of free market choice.

We encourage increased awareness and understanding of how agricultural biotechnology is being applied and its impact on farming practices, the environment and biological diversity.

USE OF ANIMALS IN RESEARCH

Research involving animals has been critical to understanding the fundamental processes of human biology that are so integral to modern medicine. Biotech companies have depended on this research to develop more than 200 drugs and vaccines approved by the U.S. Food and Drug Administration, helping more than 800 million people worldwide and preventing incalculable human suffering.

In addition to human therapeutics, animal research has also been critical to the development of biotechnology-derived veterinary biologics and vaccines approved by the USDA to improve the health of livestock, poultry and companion animals. Genomics, transgenics and cloning technologies provide new approaches for advancing the quality and efficiency of meat, milk and egg production—and in reducing the environmental impact of agriculture. These technologies are also being used to help preserve endangered species.

BIO POLICY: ANIMALS IN RESEARCH

BIO members are legally and ethically compelled to evaluate the safety and efficacy of potential medicines and food products before they are given to humans and animals; the use of

animals in research is a necessity for many such products. The appropriate and responsible use of animals is an indispensable part of biomedical and agricultural research. BIO members are committed to act ethically and to apply high standards of care when using animals in scientific procedures.

BIO members are committed to reducing the number of animals used for research when it is possible to develop, validate and use alternative methodologies consistent with regulatory requirements for testing, while maintaining the scientific integrity of the research.

BIO affirms and upholds the science-based regulation and oversight of animal research by the U.S. government agencies. Furthermore, BIO members abide by the regulatory requirements of all other countries in which they conduct animal research. In addition, many BIO members welcome external unbiased agencies, such as the Association for Assessment and Accreditation of Laboratory Animal Care, to evaluate their facilities, provide feedback on programs, and accredit their work.

The ability to conduct humane and responsible animal-based research must be preserved to help conquer disease, alleviate suffering, and improve quality of life. BIO believes that such use is a privilege, imposing a responsibility to provide proper care and humane treatment in accordance with the following principles:

- **Humane Treatment of Animals.** BIO members are committed to improving the quality of human and animal life with biotechnology, while taking responsibility for respecting the animals that support their research and for treating those animals humanely.
- **Judicious Use of Animals.** BIO is committed to the judicious use of animals in biotechnology research for experimental purposes. Alternative methodologies that reduce the number of animals used for research, replace animal experiments with non-animal methods when possible, and refine the use of animals in research (such as using cell and tissue cultures and computer modeling in early screening of the toxic potential of a substance) should be used whenever possible. Biotechnology offers great promise for further reducing use of animals in research.
- **High Standards of Care.** High standards of care should be maintained for animals used in biotechnology research as published by the Institute for Laboratory Animal Research, Commission on Life Sciences, National Research Council *(The Guide for the Care and Use of Laboratory Animals, 7th ed.,1996)* and the Federation of Animal Science Societies *(The Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching, 1999)*. Animals must be properly housed, fed and kept in surroundings appropriate to their species. We are committed to the minimization of discomfort, distress and pain consistent with sound scientific practices. Investigators and personnel shall be appropriately qualified for and experienced in conducting procedures on animals and in the husbandry and handling of the species being studied.
- **Regulatory Oversight.** Animal biotech research (including products from transgenic animals) is subject to science-based regulatory oversight by the U.S. Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), the U.S. Environmental Protection Agency (EPA), the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), the U.S. Fish and Wildlife Service (FWS) and other local agencies. BIO actively works with these agencies to ensure high standards of care and use for all animals involved in biotechnology research.
- **Increased Public Awareness.** BIO encourages increased public awareness and understanding of how biotech research involving animals is being applied in human health, animal health, agricultural, industrial and environmental areas.
- **Open Discussion of Ethical Considerations.** BIO seeks to actively and thoroughly study the ethical considerations involved in the use of animals in biotechnology, and to openly discuss these issues with ethicists, consumers, medical professionals, farmers, legislators, scientists, opinion leaders and other interested groups.

BIO statement of Ethical Principles

We respect the power of biotechnology and apply it for the benefit of humankind.

We will pursue applications of biotechnology that promise to save lives or improve the quality of life. We will avoid applications of our technology that do not respect human rights or carry risks that outweigh the potential benefits.

We listen carefully to those who are concerned about the implications of biotechnology and respond to their concerns.

The resolution of bioethical issues requires broad public discourse. We acknowledge our responsibility to consider the interests and ideas of all segments of society and to be sensitive to cultural and religious differences. We will seek dialogue with patients, ethicists, religious leaders, health-care providers, environmentalists, consumers, legislators and other groups who share an interest in bioethical issues.

We help educate the public about biotechnology, its benefits and implications.

For informed debate to occur, the public and our elected representatives need greater knowledge and a better understanding about biotechnology and its applications. BIO and its members pledge to advance public awareness and understanding.

We place our highest priority on health, safety and environmental protection in the use of our products.

In the United States, biotech products are extensively regulated by federal agencies such as the Food and Drug Administration, the Environmental Protection Agency and the Department of Agriculture. Our industry supports science-based regulation by government agencies to safeguard health, ensure safety and protect the environment.

We support strong protection of the confidentiality of medical information, including genetic information.

Individually identifiable medical information must be treated confidentially and safeguarded from misuse. We oppose the use of medical information to promote intolerance, to discriminate against or to stigmatize people.

We respect the animals involved in our research and treat them humanely.

Laboratory animals are essential to research on new therapies and cures. We test new treatments on laboratory animals to assess product safety before administering them to humans. We develop transgenic animals—those with genes from another species, usually humans—to test treatments for life-threatening diseases. We also develop transgenic sheep, goats and cattle by inserting a gene that allows them to produce human pharmaceuticals in their milk. We breed animals that may provide tissues and organs for transplantation to humans. We will follow rigorously all government regulations and professional standards in the United States, such as the Animal Welfare Act and the federal guidelines for animal care and use promulgated by the National Institutes of Health.

We are sensitive to and considerate of the ethical and social issues regarding genetic research.

We will not, for example, treat genetic disorders by altering the genes of human sperm or eggs until the medical, ethical and social issues that will arise from this kind of therapy have been more broadly discussed and clarified. Also, we support continuation of the voluntary moratorium on the potential cloning of entire human beings, with the understanding that research should continue on the cloning of genes and cells to benefit humankind.

We adhere to strict informed-consent procedures.

For clinical research conducted in the United States, the National Institutes of Health and the Food and Drug Administration require informed consent from all participants and approval by a national or local review board. We adhere to these requirements in our medical research, except in situations in which obtaining consent is not necessary (e.g., research on anonymous information) or not possible (e.g., emergency care of unconscious patients).

We will abide by the ethical standards of the American Medical Association and, where appropriate, other health-care professional societies to ensure that our products are appropriately prescribed, dispensed and used.

These ethical standards are designed to ensure that health-care professionals do not receive monetary or other compensation that might adversely affect how they care for their patients.

We develop our agricultural products to enhance the world's food supply and to promote sustainable agriculture with attendant environmental benefits.

There are significant advantages to increasing the yield of crops. Farmers must produce increasing amounts of food per acre to feed a growing global population. We will strive to make this possible while reducing the amount of external supplements (fertilizers, pesticides, etc.) necessary. We will develop our products with an eye toward good stewardship of our agricultural and environmental resources and the sustainability of such development. With regard to the development of new agriculture crops, we pledge to abide by established standards of environmental safety at home and abroad.

We develop environmental biotechnology to clean up hazardous waste more efficiently with less disruption to the environment and to prevent pollution by treating waste before it is released.

Many environmental engineering firms, industry and governments are using biotechnology to harness the power of naturally occurring organisms to degrade contaminants at hazardous waste sites. We will strive to optimize the cost-efficiencies and environmental advantages associated with using biotechnology while protecting human health and the environment. We also will continue to develop and implement more environmentally safe and cost-effective means of treating hazardous waste streams in industrial processes.

We oppose the use of biotechnology to develop weapons.

We support the Biological Weapons Convention, a treaty signed by the United States and many other nations banning development and use of biological weapons. We will not undertake any research intended for use in developing, testing or producing such weapons.

We continue to support the conservation of biological diversity.

The genetic variation of animals, plants and other organisms is a valuable natural resource. The environment is constantly changing, and without an adequate store of genetic diversity, organisms will not be able to adapt. Genetic diversity decreases every time a species, breed or crop variety becomes extinct. Working with governments and other organizations, we will help to catalog and conserve these precious resources.

biotechnology Resources

BIO has compiled a list of publications, Web sites, e-mail services and other resources that we believe are especially useful in learning about biotechnology and monitoring progress. A few notes about the list:

- It includes both free sources and those that charge fees.
- Most items on the list are non-BIO resources. BIO staff are not responsible for and cannot assist with access to non-BIO resources.
- Biotechnology is a fluid industry. When using any biotech resource (including this book), it is a good idea to note the publication date and check other sources for the most complete and current information.
- This list is not intended to be comprehensive, but if we've left out a resource you've found particularly useful, let us know by e-mailing info@bio.org.

Periodicals, Headline Services and Web Sites

FROM BIO

BIO.org. BIO's award-winning Web site offers a wealth of information on biotechnology applications as well as archives of speeches, policy papers, special reports and comments on issues of interest to the biotech community.

BIO SmartBrief. This popular e-mail service provides headlines and brief summaries of all the important biotech news of the day, from sources around the world. Visit www.smartbrief.com/bio/ to sign up.

Food & Ag Weekly News. This e-mail publication covers BIO activities, policy news and mainstream news coverage of agricultural biotechnology. It is available only to BIO members. For information on joining BIO, visit bio.org/join.

BIO News. The Biotechnology Industry Organization's members-only magazine covers BIO activities as well as selected biotechnology financial, legislative and regulatory news. Information on joining BIO is available at bio.org/join.

BIO Health Policy Newsletters. *Economic Week in Review, International Week in Review, IP News, Bioethics News, BIO Science & Regulatory News* (Except for *Economic Week in Review*, these newsletters are available only to BIO members. For information on joining BIO, visit bio.org/join.)

OTHER SOURCES

BIO Ventures for Global Health. The BVGH Web site includes an interactive pipeline database on diseases affecting developing countries, as well as news, features and policy reports on the biotechnology industry's work in global health. It also provides a primer on global health issues. All resources are available at www.bvgh.org.

BiobasedNews.com. The Biobased Information System provides business-related information on biofuels, new crops, biobased products, and industrial biotechnology The site offers a free biweekly e-mail newsletter, a list of industry conferences and links to other resources. All resources are available at www.biobasednews.com.

BioCentury. BioCentury's weekly flagship publication features analysis and news summaries on the biotech industry. BioCentury also provides a daily news summary, published each weekday evening. Subscription information and full product listings are available at www.biocentury.com.

BioSpace. BioSpace tracks a wide range of biotech-company, clinical and financial news and data; it also offers an e-mail headline services. Explore offerings at www.biospace.com.

Biotechnology Health Care. This monthly magazine delivers selected industry news and includes features on science, product development, financial issues, and reimbursement. Subscription information and selected articles are available at www.biotechnologyhealthcare.com.

BioWorld. BioWorld's offerings include a daily biotech newspaper, as well as weekly publications on financial and international news. Subscription information and full product listings are available at www.bioworld.com.

FierceBiotech. This business-focused summary of the day's biotech news highlights is delivered via e-mail. Learn more or sign up at www.fiercebiotech.com.

Genetic Engineering News. This tabloid-sized trade magazine is published twice monthly and includes news and features on the industry. GEN is free to qualified industry subscribers. Apply for a subscription at www.genengnews.com.

Health Affairs. Published every other month, this is one of the definitive sources for health care data and analysis, with articles on issues of access, reimbursement, innovation and quality. Visit www.healthaffairs.org for subscription information.

Help Me Understand Genetics. *Help Me Understand Genetics*, (http://ghr.nlm.nih.gov/handbook) a handbook from the NIH, presents basic information about genetics in clear, easy-

to understand language. It also includes links to additional online resources. It is part of a larger, equally helpful NIH site, Genetics Home Reference.

Industrial Biotech Innovation Report. This weekly e-mail newsletter is a digest of business and research news about industrial biotechnology from around the world, offering headlines and summaries of top news stories. The subscription-only report is a service of the American Chemical Society and BIO. Subscription information is available at www.allisinfo.com.

Industrial Biotechnology. This quarterly journal covers industrial and environmental biotechnology applications in chemicals, energy and manufacturing. Subscription information is available at www.liebertpub.com.

In Vivo. Windhover Information publishes this monthly magazine of commentary and analysis on biotechnology, pharmaceuticals and other industries. The emphasis is on business strategies and industry trends. Windhover offers a suite of additional publications and data as well. Visit www.windhover.com for subscription information.

Nature Biotechnology. This specialty publication from the Nature Publishing Group is published monthly and includes news, features and journal articles. Subscription information is available on www.nature.com.

Science.bio.org. The science-oriented site links to all of the day's significant biotech science stories, including both mainstream press and journal articles.

Signals Magazine. Recombinant Capital publishes this online magazine of biotech industry trends and analysis. The magazine and archives are free, with no registration required. Visit www.signalsmag.com.

Tufts CSDD Impact Report. The Tufts Center for the Study of Drug Development publishes a single-topic report every other month covering original research on product development issues affecting pharmaceutical and biotech companies. For a list of topics covered and subscription information, visit csdd.tufts.edu.

Why Biotech. Operated by the Council for Biotechnology Information, this media- and consumer-friendly Web site includes feature stories, links to reports and extensive data on agricultural biotechnology. Access is free, with no registration required. Visit www.whybiotech.com.

Your World. The Biotechnology Institute's magazine is published twice a year and targets grades 7 through 12. Each issue combines in-depth features on a single topic with supplemental educational activities and materials. See www.biotechinstitute.org for a list of topics covered, subscription information and free pdf downloads of every issue.

General Science Journals

The following science journals, while not biotech-exclusive, provide extensive biotechnology coverage: *Nature, Science, Scientific American, The New Scientist* and *The Scientist*. *Nature* and *Science* are often are first to publish important breakthroughs, such as the human genome sequence.

Biotech Education and Careers

Note: Many job-listing Web sites and services cover the biotech industry. Below are resources that offer added content of interest.

Biotechnology Institute. The Biotechnology Institute focuses on K-12 biotechnology education, offering teacher-student resources and programs. Publications include *Genome: The Secret of How Life Works*; *Your World* magazine; and *Shoestring Biotechnology*, a laboratory guide for teachers with a shoestring budget. Visit the Biotechnology Institute at www.BiotechInstitute.org.

ScienceCareers. Science magazine has compiled extensive career resources and articles for science students and job seekers at ScienceCareers.Sciencemag.org.

Selected Recent Reports on Biotechnology

GENERAL AND HEALTH CARE

Beyond Borders: Global Biotechnology Report 2008. Ernst & Young's annual survey of the biotechnology industry tracks company data and industry trends, compares U.S. biotech performance to that of the rest of the world, and ranks top U.S. and Canadian biotech regions. Published Spring 2008. See www.ey.com for contact information.

Biotech 2008—Life Sciences: A 20/20 Vision to 2020. Each year, the life sciences merchant bank Burrill & Co. publishes a detailed report on the biotech industry, describing new developments in health care, agriculture and industrial applications, as well as providing an overview of biotech business activities. See www.burrillandco.com for purchase information. Published Spring 2008.

BioWorld State of the Industry Report, 2008. BioWorld's annual report aggregates the biotech industry's financial, partnering and drug approval information for 2007, with analysis explaining what it all means. See www.bioworld.com for purchase information.

Closing the Global Health Innovation Gap: A Role for the Biotechnology Industry in Drug Discovery for Neglected Diseases. In this study, BIO Ventures for Global Health examines the core capabilities of the biotechnology industry, academia and the nonprofit entities that focus on clinical development of new drugs for neglected diseases. It focuses on three classes of diseases—malaria, tuberculosis and trypanosomal diseases (human African trypanosomiasis, Chagas disease and leishmaniasis). Available for download at www.bvgh.org. Published in November 2007.

Growing the Nation's Biotech Sector: State Bioscience Initiatives 2006. This report from BIO and the Battelle Memorial Institute presents updated data, examines growth trends and identifies cities with the largest and most concentrated employment in several bioscience subsectors. The report also identifies key trends in state and regional initiatives to support the biosicences. Available for download at bio.org/local/battelle2006/. Published April 2006.

Challenge and Opportunity on the Critical Path to New Medical Products. This report from FDA explains why drug development is so slow and offers ideas for accelerating the process. This landmark report initiated the Critical Path Initiative. Available for download at www.fda.gov/oc/initiatives/criticalpath/. Published March 2004.

Medical Biotechnology: Achievements, Prospects and Perceptions. Published by the United Nations Institute for Advanced Studies, this book examines the drivers of medical and pharmaceutical biotechnology development in the United States, Europe and Japan and provides case studies for several developing countries. Available for purchase through www.unu.edu. Published September 2005.

OECD Biotech Statistics 2006. This publication of the Organization of Economic Cooperation and Development includes data for 23 OECD countries and two observer countries, plus China (Shanghai), and takes a major step forward in improving the comparability of biotechnology indicators among countries. Available for download on www.oecd.org. Published May 2006.

Outlook 2008. The Tufts Center for Drug Development's annual report offers a brief synopsis of the year's major regulatory and R&D issues. Available for download at csdd.tufts.edu. Published 2008.

Parexel's Bio/Pharmaceutical R&D Statistical Sourcebook 2007/2008. This book contains studies, analysis, articles and extensive data sets on R&D/regulatory activity and spending across the pharmaceutical and biotech sectors. See www.parexel.com for purchase information. Published May 2007

Personalized Medicine: The Emerging Pharmacogenomics Revolution. PriceWaterhouseCoopers explains how personalized medicine can remake the pharmaceutical industry and the challenges to realizing that vision. Available for download at www.pwc.com. Published February 2005.

Personalised Medicines: Hopes and Realities. This Royal Society report provides a thorough overview of scientific, development and clinical issues in personalized medicine. Available for download at royalsociety.org/ (select Adobe Acrobat Reader to open). Published September 2005.

A Survey of the Use of Biotechnology in U.S. Industry. In 2003, the U.S. Commerce Department published data from the most comprehensive survey ever conducted of companies using biotechnology. The book includes data on jobs, financial performance and technological applications, and is available for download at www.technology.gov/reports. Published October 2003.

MARKET REPORTS

A number of publishers, consultants and analysts publish detailed reports on specialized biotechnology sectors (anything from microarrays to diabetes drugs). Sites offering such reports for sale include www.datamonitor.com, www.marketresearch.com, www.visiongain.com, www.researchandmarkets.com, www.freedoniagroup.com and www.frost.com.

AGRICULTURE

The benefits of adopting genetically modified, insect resistant (Bt) maize in the European Union (EU): first results from 1998-2006 plantings. This paper, from PG Economics, examines the impact of the use of Bt maize resistant to the European corn borer and the Mediterranean stem borers in the EU. Available for download at www.pgeconomics.co.uk. Published March 2007.

A 2006 Update of Impacts on US Agriculture of Biotechnology-Derived Crops Planted in 2005. This report from the National Center for Food and Agricultural Policy explores the impact of six biotech crops on U.S. farmers' yields and incomes. The report includes data for individual states. Available for download at www.ncfap.org. Published November 2006.

Brief 37-2007: Global Status of Commercialized Biotech/GM Crops: 2007. Each year, the International Service for the Acquisition of Agri-Biotech Applications publishes a global survey of biotech crops plantings. Data are provided by crop and by country. Available for download at www.isaaa.org. Published January 2008.

The Economic Status and Performance of Plant Biotechnology in 2003: Adoption, Research and Development in the United States. This study explores the economic impact of agricultural biotechnology and includes data from companies, states and academic institutions. The author, C. Ford Runge, Ph.D., is the director of the Center for International Food and Agricultural Policy at the University of Minnesota. Available for download at www.whybiotech.com. Published December 2003.

Animal Cloning: A Risk Assessment—FINAL. In a report written by FDA scientists, the agency has concluded that meat and milk from cow, pig and goat clones, as well as the offspring of any animal clones, are as safe as food we eat every day. Available for download at www.fda.gov/cvm/cloning.htm. Published January 2008.

The Global Diffusion of Plant Biotechnology: International Adoption and Research in 2004. This study of plant biotech R&D and adoption offers both a comprehensive overview and individual country profiles from around the world. Available for download at www.whybiotech.com. Published December 2004.

Global Impact of Biotech Crops: Socio-Economic and Environmental Effects in the First Ten Years of Commercial Use. This report from the U.K. firm PG Economics provides cumulative data on the positive economic and environmental impact of biotech crops. It was published in the journal *Agbio Forum*. Available for download at www.agbioforum.org. Published October 2006.

Modern Food Biotechnology, Human Health and Development: An Evidence-Based Study. This World Health Organization report describes health and quality-of-life benefits that biotech foods can deliver. Available for download at www.who.int/foodsafety. Published 2005.

Quantification of the Impacts on U.S. Agriculture of Biotechnology Derived Crops Planted in 2005. This study from the National Center for Food and Agricultural Policy suggests biotech is helping meet increased demand for corn to manufacture ethanol. According to the author, U.S. farmers produced an additional 7.6 billion pounds of corn thanks to biotech—a 29 percent increase over 2004 production. Available for download at www.ncfap.org. Published November 2006.

INDUSTRIAL & ENVIRONMENTAL

25 by 25: Agriculture's Role in Ensuring U.S. Energy Independence. This report by the Ag Energy Working Group of the Energy Future Coalition shows how farmers can contribute 25 percent of U.S. total energy consumption. Available at bio.org/ind/25x25.pdf. Published August 2004.

Achieving Sustainable Production of Agricultural Biomass for Biorefinery Feedstock. This BIO report details how American farmers can feed the growing biofuel industry by harnessing cellulosic biomass. It also proposes guidelines and incentives to encourage farmers to produce sufficient raw materials for the growing biorefinery and biofuels industry in a sustainable way. Available at bio.org/ind/biofuel/SustainableBiomassReport.pdf. Published November 2006.

Bioengineering for Pollution Prevention through Development of Biobased Energy and Materials, State of the Science Report. This report from the Environmental Protection Agency's National Center for Environmental Research provides a comprehensive assessment of the pollution prevention attributes of industrial biotechnology. Available for download at es.epa.gov/ncer/publications/statesci/bioengineering.pdf. Published July 2007.

Biofuels for Transport: Global Potential and Implications for Sustainable Agriculture and Energy in the 21st Century. This report, sponsored by the German Federal Ministry of Food, Agriculture and Consumer Protection is a comprehensive assessment of the opportunities and risks associated with the large-scale international development of biofuels. Information about purchasing the report can be found at www.worldwatch.org/node/5303. Published August 2007.

Growing Energy: How Biofuels Can Help End America's Oil Dependence. This Natural Resources Defense Council report describes how biofuels can cut U.S. dependence on foreign oil while lifting farm profits. The NRDC published a follow-up issue paper, *Bringing Biofuels to the Pump: An Aggressive Plan for Ending America's Oil Dependence*. Both are available for downloading at www.nrdc.org. Published December 2004, July 2005.

Industrial and Environmental Biotechnology: Current Achievements, Prospects and Perceptions. This report by the United Nations Institute of Advanced Studies provides an overview of I&E biotechnology. Available for download at www.ias.unu.edu. Published 2005.

New Biotech Tools for a Cleaner Environment: Industrial Biotechnology for Pollution Prevention, Resource Conservation and Cost Reduction. Produced by BIO, this report applies case-study data from the Organization for Economic Cooperation and Development to whole industries, describing the potential for biotech processes to cut raw material consumption and pollution. Available for download at bio.org/ind/. Published June 2004.

Policy Recommendations and Report of the Bioenergy and Agriculture Working Group. This report, by a working group of the Energy Future Coalition, recommends that government take aggressive steps to shift to renewable, agriculture-based fuels, such as bioethanol. Available for download at bio.org/ind/. Published June 2003.

Synthetic Genomics: Options for Governance. Released by the J. Craig Venter Institute, the Center for Strategic and International Studies, and the Massachusetts Institute of Technology, the report assesses the current state of synthetic biology and formulates policies that can support continued research and development of beneficial applications and prevent possible misuses of the technology. Available for download at www.csis.org/component/option,com_csis_pubs/task,view/id,4119/type,1/ or www.jcvi.org/cms/research/projects/syngen-options/overview/. Published October 2007.

glossary of Biotech-related Terms

Editor's Note: The glossary includes terms used in this book as well as other biotechnology terms that may be useful.

1,3-Propanediol (PDO) a naturally occurring polymer (glycol) or "green plastic" that can be formulated into a variety of industrial products including composites, adhesives, laminates, coatings, moldings, novel aliphatic polyesters, copolyesters, solvents, antifreeze and other end uses.

A

ADME An acronym for absorption, distribution, metabolism and excretion; refers to how a drug travels through the body.

Acclimatization Adaptation of an organism to a new environment.

Action letter An official FDA communication that informs a company seeking a drug approval of a decision by the agency. An approval letter allows commercial marketing of the product.

Active immunity A type of acquired immunity whereby resistance to a disease is built up by either having the disease or receiving a vaccine to it.

Adjuvant Insoluble material that increases the formation and persistence of antibodies when injected with an antigen.

Aerobic Needing oxygen for growth.

Agrobacterium tumefaciens A common soil bacterium used as a vector to create transgenic plants.

Allele Any of several alternative forms of a gene.

Allogenic Of the same species, but with a different genotype. Also allogeneic.

Alzheimer's disease A disease characterized by, among other things, progressive loss of memory. The development of Alzheimer's disease is thought to be associated, in part, with possessing certain alleles of the gene that encodes apolipoprotein E.

Amino acids Building blocks of proteins. There are 20 common amino acids: alanine, arginine, aspargine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine. Two more amino acids have been discovered in microbes: selenocysteine and pyrrolysine.

Amplification The process of increasing the number of copies of a particular gene or chromosomal sequence.

Anaerobic Growing in the absence of oxygen.

Antibiotic Chemical substance formed as a metabolic byproduct in bacteria or fungi and used to treat bacterial infections. Antibiotics can be produced naturally, using microorganisms, or synthetically.

Antibody Protein produced by humans and higher animals in response to the presence of a specific antigen.

Anticodon Triplet of nucleotide bases (codon) in transfer RNA that pairs with (is complementary to) a triplet in messenger RNA. For example, if the codon is UCG, the anticodon is AGC. See Base; Base pair; Complementarity.

Antigen A substance that, when introduced into the body, induces an immune response by a specific antibody.

Antigenic determinant See Hapten.

Antihemophilic factors A family of whole-blood proteins that initiate blood clotting. Some of these proteins, such as factor VIII, can be used to treat hemophilia. See Factor VIII; Kidney plasminogen activator.

Antisense A piece of DNA producing a mirror image ("antisense") messenger RNA that is opposite in sequence to one directing protein synthesis. Antisense technology is used to selectively turn off production of certain proteins.

Antiserum Blood serum containing specific antibodies against an antigen. Antisera are used to confer passive immunity to many diseases.

Apolipoprotein E (Apo E) Certain alleles of the gene that encodes the protein apolipoprotein E have been associated with the development of heart disease and Alzheimer's disease.

Assay Technique for measuring a biological response.

Attenuated Weakened; with reference to vaccines, made from pathogenic organisms that have been treated so as to render them avirulent.

Autoimmune disease A disease in which the body produces antibodies against its own tissues.

Autoimmunity A condition in which the body mounts an immune response against one of its own organs or tissues.

Autosome Any chromosome other than a sex chromosome.

Avirulent Unable to cause disease.

B

Bacillus subtilis A bacterium commonly used as a host in recombinant DNA experiments. Important because of its ability to secrete proteins.

Bacillus thuringiensis (Bt) Naturally occurring soil bacterium that generates a protein toxic to a variety of lepidoptera, such as corn borers, but is harmless to people and animals.

Bacteriophage Virus that lives in and kills bacteria. Also called phage.

Bacterium Any of a large group of microscopic organisms with a very simple cell structure. Some manufacture their own food, some live as parasites on other organisms, and some live on decaying matter.

Bagasse The residue after the extraction of juice from crushed sugarcane stalks.

Base A key component of DNA and RNA molecules. Four different bases are found in DNA: adenine (A), cytosine (C), guanine (G) and thymine (T). In RNA, uracil (U) substitutes for thymine. Also known as nitrogenous bases. A base, a phosphate molecule and a sugar joined together constitute a nucleotide.

Base pair Two nucleotide bases on different strands of the nucleic acid molecule that bond together. The bases can pair in only one way: adenine with thymine (DNA), or uracil (RNA) and guanine with cytosine.

Bioassay Determination of the effectiveness of a compound by measuring its effect on animals, tissues or organisms in comparison with a standard preparation.

Bioaugmentation Increasing the activity of bacteria that break down pollutants by adding more of their kind. A technique used in bioremediation.

Biocatalyst In bioprocessing, an enzyme that activates or speeds up a biochemical reaction.

Biochemical The product of a chemical reaction in a living organism.

Biochip An electronic device that uses organic molecules to form a semiconductor.

Bioconversion Chemical restructuring of raw materials by using a biocatalyst.

Biodegradable Capable of being reduced to water and carbon dioxide by the action of microorganisms.

Bioenrichment A bioremediation strategy that involves adding nutrients or oxygen, thereby bolstering the activity of microbes as they break down pollutants.

Biofuel Transportation fuel derived from renewable resources such as grain, plant biomass and treated municipal and industrial waste.

Bioinformatics The science of informatics as applied to biological research. Informatics is the management and analysis of data using advanced computing techniques. Bioinformatics is particularly important as an adjunct to genomics research, because of the large amount of complex data this research generates.

Biolistic device A device that shoots microscopic DNA-coated particles into target cells.

Biological oxygen demand The amount of oxygen used for growth by organisms in water that contains organic matter.

Biologic A therapeutic or prophylactic derived from a living source (human, animal or unicellular). Most biologics are complex mixtures that are not easily identified or characterized, and many are manufactured using biotechnology. Biological products often represent the cutting-edge of biomedical research and are sometimes the most effective way to prevent or treat a disease.

Biologic response modifier A substance that alters the growth or functioning of a cell. Includes hormones and compounds that affect the nervous and immune systems.

Biomass The totality of biological matter in a given area. As commonly used in biotechnology, refers to the use of cellulose, a renewable resource, for the production of chemicals that can be used to generate energy or as alternative feedstocks for the chemical industry to reduce dependence on nonrenewable fossil fuels.

Biomaterials Biological molecules, such as proteins and complex sugars, used to make medical devices, including structural elements used in reconstructive surgery.

Bioplastics "Green" plastics manufactured using biopolymers; they are usually biodegradable. Bioplastics are derived from plant sources such as hemp oil, soybean oil and corn starch (unlike traditional plastics that are derived from petroleum).

Biopolymers Special class of polymers, such as starch, proteins and peptides, produced by living organisms in which the monomer units, respectively, are sugars, amino acids and nucleic acids. Often synonymous with bioplastics.

Biological control The human use of living organisms or viruses to control pest (plant or animal) populations.

Bioprocess A process in which living cells, or components thereof, are used to produce a desired product.

Bioreactor Vessel used for bioprocessing.

Biorefinery A facility that integrates biomass conversion processes and equipment to produce fuels, power, value-added chemicals and bioplastics.

Bioremediation The use of microorganisms to remedy environmental problems, rendering hazardous wastes nonhazardous.

Biosynthesis Production of a chemical by a living organism.

Biotechnology The use of biological processes to solve problems or make useful products.

Biotransformation The use of enzymes in chemical synthesis to produce chemical compounds of a desired stereochemistry.

Blastocyst (Blastula) The 4- to 5-day-old ball of undifferentiated cells from which a prospective embryo develops. In mammals it consists of two distinct parts: the inner cell mass and the trophoblast.

B lymphocytes (B-cells) A class of lymphocytes, released from the bone marrow, that produce antibodies.

Bovine somatotropin (BST) A hormone secreted by the bovine pituitary gland. It is used to increase milk production by improving the feed efficiency in dairy cattle milk. Also called bovine growth hormone.

BRCA1 and BRCA2 (BReast CAncer genes 1 and 2) Two genes that normally help to restrain cell growth, but which can contain certain genetic mutations associated with the development of breast and ovarian cancer. Note, however, that inherited BRCA1 and BRCA2 mutations are thought to account for less than 10 percent of all breast and ovarian cancers. Recent evidence suggests that somatic cell genetic mutations (i.e., noninherited genetic mutations) in these two genes may also play a role in the development of cancer.

C

Callus A cluster of undifferentiated plant cells that can, in some species, be induced to form the whole plant.

Carbohydrate A type of biological molecule composed of simple sugars such as glucose. Common examples include starch and cellulose.

Carcinogen Cancer-causing agent.

Catalyst An agent (such as an enzyme or a metallic complex) that facilitates a reaction but is not itself changed during the reaction.

Cell The smallest structural unit of a living organism that can grow and reproduce independently.

Cell culture Growth of cells under laboratory conditions.

Cell differentiation The process by which descendants of a common parental cell achieve specialized structure and function.

Cell fusion See **Fusion**.

Cell line Cells that grow and replicate continuously outside the living organism.

Cell-mediated immunity Acquired immunity in which T lymphocytes play a predominant role. Development of the thymus in early life is critical to the proper development and functioning of cell-mediated immunity.

Cellulase A class of enzymes produced by fungi, bacteria, plants and animals that converts cellulose to sugar.

Cellulose A complex carbohydrate that is composed of glucose units and forms the primary structural component of green plants.

Cellulosic ethanol Ethanol fuel produced through enzymatic hydrolysis from a wide variety of cellulosic biomass feedstocks including agricultural plant wastes (corn stover, cereal straws, sugarcane bagasse), plant wastes from industrial processes (sawdust, paper pulp) and energy crops grown specifically for fuel production (switchgrass).

Chemical genomics Using structural and functional genomic information about biological molecules, especially proteins, to identify useful small molecules and alter their structure to improve their efficacy.

Chemical synthesis Purposeful physical and chemical manipulations, usually involving one or more reactions, in order to get a product or products.

Chimera The individual (animal or lower organism) produced by grafting an embryonic part of one individual onto an embryo of either the same or a different species.

Chromosomes Threadlike components in the cell that contain DNA and proteins. Genes are carried on the chromosomes.

Clinical studies Human studies that are designed to measure the efficacy of a new drug or biologic. Clinical studies routinely involve the use of a control group of patients that is given an inactive substance (placebo) that looks like the test product.

Clone A term that is applied to genes, cells or entire organisms that are derived from—and are genetically identical to—a single common ancestor gene, cell or organism, respectively. Cloning of genes and cells to create many copies in the laboratory is a common procedure essential for biomedical research. Note that several processes commonly described as cell "cloning" give rise to cells that are almost but not completely genetically identical to the ancestor cell. Cloning of organisms from embryonic cells occurs in nature (e.g., identical twins). Researchers have achieved laboratory cloning using genetic material from adult animals of several species, including mice, pigs and sheep.

Codon A sequence of three nucleotide bases that specifies an amino acid or represents a signal to stop or start a function.

Co-enzyme An organic compound that is necessary for the functioning of an enzyme. Co-enzymes are smaller than the enzymes themselves and sometimes separable from them.

Co-factor A nonprotein substance required for certain enzymes to function. Co-factors can be co-enzymes or metallic ions.

Colony-stimulating factors (CSFs) A group of lymphokines that induce the maturation and proliferation of white blood cells from the primitive cell types present in bone marrow.

Combinatorial chemistry A product discovery technique that uses robotics and parallel synthesis to generate and screen quickly as many as several million molecules with similar structure in order to find chemical molecules with desired properties.

Co-metabolism A microbe oxidizing not only its main energy source but also another organic compound.

Complementarity The relationship of the nucleotide bases on two different strands of DNA or RNA. When the bases are paired properly (adenine with thymine [DNA] or uracil [RNA]; guanine with cytosine), the strands are complementary.

Complementary DNA (cDNA) DNA synthesized from a messenger RNA rather than from a DNA template. This type of DNA is used for cloning or as a DNA probe for locating specific genes in DNA hybridization studies.

Computational biology A subdiscipline within bioinformatics concerned with computation-based research devoted to understanding basic biological processes.

Conjugation Sexual reproduction of bacterial cells in which there is a one-way exchange of genetic material between the cells in contact.

Corn stover The leaves and stalks of maize plants usually left in a field after harvest.

Crossing over Exchange of genes between two paired chromosomes.

Cross-licensing Legal, contractual procedure in which two or more firms with competing, similar technologies and possible conflicting patent claims strike a deal to reduce the need for legal actions to clarify who is to profit from applications of the technology.

Culture As a noun, cultivation of living organisms in prepared medium; as a verb, to grow in prepared medium.

Culture medium Any nutrient system for the artificial cultivation of bacteria or other cells; usually a complex mixture of organic and inorganic materials.

Cyto- Referring to cell.

Cytogenetics Study of the cell and its heredity-related components, especially chromosomes.

Cytoplasm Cellular material that is within the cell membrane and surrounds the nucleus.

Cytotoxic Able to cause cell death.

D

Deoxyribonucleic acid (DNA) The molecule that carries the genetic information for most living systems. The DNA molecule consists of four bases (adenine, cytosine, guanine and thymine) and a sugar-phosphate backbone, arranged in two connected strands to form a double helix. See Complementary DNA; Double helix; Recombinant DNA.

Differentiation The process of biochemical and structural changes by which cells become specialized in form and function.

Diploid A cell with two complete sets of chromosomes. Compare Haploid.

DNA See Deoxyribonucleic acid.

DNA chip A small piece of glass or silicon that has small pieces of DNA arrayed on its surface.

DNA fingerprinting The use of restriction enzymes to measure the genetic variation of individuals. This technology is often used as a forensic tool to detect differences or similarities in blood and tissue samples at crime scenes.

DNA hybridization The formation of a double-stranded nucleic acid molecule from two separate strands. The term also applies to a molecular technique that uses one nucleic acid strand to locate another.

DNA library A collection of cloned DNA fragments that collectively represent the genome of an organism.

DNA polymerase An enzyme that replicates DNA. DNA polymerase is the basis of PCR—the polymerase chain reaction.

DNA probe A small piece of nucleic acid that has been labeled with a radioactive isotope, dye or enzyme and is used to locate a particular nucleotide sequence or gene on a DNA molecule.

DNA repair enzymes Proteins that recognize and repair certain abnormalities in DNA.

DNA sequence The order of nucleotide bases in the DNA molecule.

DNA vaccines Pieces of foreign DNA that are injected into an organism to trigger an immune response.

Double-blind trial A clinical trial in which neither the patient nor the health care provider knows whether the drug or placebo is being administered.

Double helix A term often used to describe the configuration of the DNA molecule. The helix consists of two spiraling strands of nucleotides (a sugar, phosphate and base) joined crosswise by specific pairing of the bases. See Deoxyribonucleic acid; Base; Base pair.

Diagnostic A product used for the diagnosis of disease or medical condition. Both monoclonal antibodies and DNA probes are useful diagnostic products.

Drug delivery The process by which a formulated drug is administered to the patient. Traditional routes have been oral or intravenous perfusion. New methods deliver through the skin with a transdermal patch or across the nasal membrane with an aerosol spray.

E

Electrophoresis A technique for separating different types of molecules based on their patterns of movement in an electrical field.

Electroporation The creation of reversible small holes in a cell wall or membrane through which foreign DNA can pass. This DNA can then integrate into the cell's genome.

Enzyme-linked immunosorbent assay (ELISA) A technique for detecting specific proteins by using antibodies linked to enzymes.

Embryonic stem cells Cells that can give rise to any type of differentiated cell. They can be derived from two sources: the inner cell mass from a blastocyst or the primordial germ cells (eggs and sperm) of an older embryo.

Endostatin An endogenous protein that blocks the proliferation of blood vessels.

Endpoints A clinical trial's outcome measures (such as tumor shrinkage viral clearance, or survival).

Environmental biotechnology The process of using cells or cell components to prevent or clean up pollution.

Enzymatic hydrolysis The process by which enzymes are used to catalytically convert starch or cellulose into sugar.

Enzyme A protein catalyst that facilitates specific chemical or metabolic reactions necessary for cell growth and reproduction.

Erythropoietin (EPO) A protein that boosts production of red blood cells. It is clinically useful in treating certain types of anemia.

Escherichia coli (E. coli) A bacterium that inhabits the intestinal tract of most vertebrates. Much of the work using recombinant DNA techniques has been carried out with this organism because it has been genetically well characterized.

Eukaryote A cell or organism containing a true nucleus, with a well-defined membrane surrounding the nucleus. All organisms except bacteria, viruses and cyanobacteria are eukaryotic. Compare Prokaryote.

Exon In eukaryotic cells, that part of the gene that is transcribed into messenger RNA and encodes a protein. See Intron; Splicing.

Expression In genetics, manifestation of a characteristic that is specified by a gene. With hereditary disease, for example, a person can carry the gene for the disease but not actually have the disease. In this case, the gene is present but not expressed. In industrial biotechnology, the term is often used to mean the production of a protein by a gene that has been inserted into a new host organism.

Extremophiles Microorganisms that live at extreme levels of pH, temperature, pressure and salinity.

F

Factor VIII A large, complex protein that aids in blood clotting and is used to treat hemophilia. See Antihemophilic factors.

Feedstock The raw material used for chemical or biological processes.

Fermentation The process of growing microorganisms for the production of various chemical or pharmaceutical compounds. Microbes are normally incubated under specific conditions in the presence of nutrients in large tanks called fermentors.

Functional foods Foods containing compounds with beneficial health effects beyond those provided by the basic nutrients, minerals and vitamins. Also called nutraceuticals.

Functional genomics A field of research that aims to understand what each gene does, how it is regulated and how it interacts with other genes.

Fusion Joining of the membrane of two cells, thus creating a daughter cell that contains some of the same properties from each parent cells. Used in making hybridomas.

G

Gel electrophoresis A process for separating molecules by forcing them to migrate through a gel under the influence of an electric field.

Gene A segment of chromosome. Some genes direct the syntheses of proteins, while others have regulatory functions. See Operator gene; Structural gene; Suppressor gene.

Gene amplification The increase, within a cell, of the number of copies of a given gene.

Gene knockout The replacement of a normal gene with a mutated form of the gene by using homologous recombination. Used to study gene function.

Gene machine A computerized device for synthesizing genes by combing nucleotides (bases) in the proper order.

Gene mapping Determination of the relative locations of genes on a chromosome.

Gene sequencing Determination of the sequence of nucleotide bases in a strand of DNA. See Sequencing.

Gene therapy The replacement of a defective gene in an organism suffering from a genetic disease. Recombinant DNA techniques are used to isolate the functioning gene and insert it into cells. More than 300 single-gene genetic disorders have been identified in humans. A significant percentage of these may be amenable to gene therapy.

Genetic code The code by which genetic information in DNA is translated into biological function. A set of three nucleotides (codon), the building blocks of DNA, signifies one amino acid, the building blocks of proteins.

Genetic modification A number of techniques, such as selective breeding, mutagenesis, transposon insertions and recombinant DNA technology, that are used to alter the genetic material of cells in order to make them capable of producing new substances, performing new functions or blocking the production of substances.

Genetic predisposition Susceptibility to disease that is related to a genetic mutation, which may or may not result in actual development of the disease.

Genetic screening The use of a specific biological test to screen for inherited diseases or medical conditions. Testing can be conducted prenatally to check for metabolic defects and congenital disorders in the developing fetus as well as postnatally to screen for carriers of heritable diseases.

Genetic testing The analysis of an individual's genetic material. Genetic testing can be used to gather information on an individual's genetic predisposition to a particular health condition, or to confirm a diagnosis of genetic disease.

Genetically enhanced microbes (GEMs) Organisms changed through selective breeding, mutagenesis, transposon insertions or recombinant DNA technology so they can make new substances or perform new functions.

Genome The total hereditary material of a cell, comprising the entire chromosomal set found in each nucleus of a given species.

Genomics The study of genes and their function. Recent advances in genomics are bringing about a revolution in our understanding of the molecular mechanisms of disease, including the complex interplay of genetic and environmental factors. Genomics is also stimulating the discovery of breakthrough health-care products by revealing thousands of new biological targets for the development of drugs and by giving scientists innovative ways to design new drugs, vaccines and DNA diagnostics. Genomic-based therapeutics may include "traditional" small chemical drugs, as well as protein drugs and gene therapy.

Genotype Genetic makeup of an individual or group. Compare Phenotype.

Germ cell Reproductive cell (sperm or egg). Also called gamete or sex cell.

Germplasm The total genetic variability, represented by germ cells or seeds, available to a particular population of organisms.

Glycoprotein A protein conjugated with a carbohydrate group.

Granulocyte One of three types of white blood cells. Granulocytes digest bacteria and other parasites.

Granulocyte-macrophage colony stimulating factor (GMCSF) A natural hormone that stimulates white blood cell production, particularly that of granulocytes and monocytes (the precursors of macrophages).

Growth factors Naturally occurring proteins that stimulate the growth and reproduction of specific cell types. Growth factors are essential to regenerative medicine and tissue engineering.

Growth hormone A protein produced by the pituitary gland that is involved in cell growth. Human growth hormone is used clinically to treat dwarfism. Various animal growth hormones can be used to improve milk production as well as produce a leaner variety of meat.

H

Haploid A cell with half the usual number of chromosomes, or only one chromosome set. Sex cells are haploid. Compare Diploid.

Hapten The portion of an antigen that determines its immunological specificity. When coupled to a large protein, a hapten stimulates the formation of antibodies to the two-molecule complex. Also called antigenic determinant.

Hemagglutination Clumping (agglutination) of red blood cells.

Heredity Transfer of genetic information from parent cells to progeny.

Histocompatibility Immunologic similarity of tissues such that grafting can be done without tissue rejection.

Histocompatibility antigen An antigen that causes the rejection of grafted material from an animal different in genotype from the host animal.

Homeobox Family of genes that regulate activities of other genes (turns genes on and off).

Homologous Corresponding or alike in structure, position or origin.

Hormone A chemical or protein that acts as a messenger or stimulatory signal, relaying instructions to stop or start certain physiological activities. Hormones are synthesized in one type of cell and then released to direct the function of other cell types.

Host A cell or organism used for growth of a virus, plasmid or other form of foreign DNA, or for the production of cloned substances.

Host-vector system Combination of DNA-receiving cells (host) and DNA-transporting substance (vector) used for introducing foreign DNA into a cell.

Human Genome Project An international research effort aimed at discovering the full sequence of bases in the human genome. Led in the United States by the National Institutes of Health and the Department of Energy.

Human immunodeficiency virus (HIV) The virus that causes acquired immune deficiency syndrome (AIDS).

Hybridization Production of offspring, or hybrids, from genetically dissimilar parents. The process can be used to produce hybrid plants (by crossbreeding two different varieties) or hybridomas (hybrid cells formed by fusing two unlike cells, used in producing monoclonal antibodies). See DNA hybridization.

Hybridoma The cell produced by fusing two cells of different origin. In monoclonal antibody technology, hybridomas are formed by fusing an immortal cell (one that divides continuously) and an antibody-producing cell. See also Monoclonal antibody; Myeloma.

Hydrolysis Decomposition of a chemical compound through reaction with water.

Immune response The response of the immune system to challenge by a foreign antigen.

Immune serum Blood serum containing antibodies.

Immune system The combination of cells, biological substances (such as antibodies) and cellular activities that work together to provide resistance to disease.

Immunity Nonsusceptibility to a disease or to the toxic effects of antigenic material. See Active immunity; Cell-mediated immunity; Natural active immunity; Natural passive immunity; Passive immunity.

Immunoassay Technique for identifying substances based on the use of antibodies.

Immunodiagnostic The use of specific antibodies to measure a substance. This tool is useful in diagnosing infectious diseases and the presence of foreign substances in a variety of human and animal fluids (blood, urine, etc.). The approach is currently being investigated as a way of locating tumor cells in the body.

Immunofluorescence Technique for identifying antigenic material that uses an antibody labeled with fluorescent material. Specific binding of the antibody and antigen can be seen under a microscope by applying ultraviolet light rays and noting the visible light that is produced.

Immunogen Any substance that can elicit an immune response.

Immunoglobulin General name for proteins that function as antibodies. These proteins differ somewhat in structure and are grouped into five categories on the basis of these differences; immunoglobulin G (IgG), IgM, IgA, IgE and IgD.

Immunology Study of all phenomena related to the body's response to antigenic challenge (i.e., immunity, sensitivity and allergy).

Immunomodulators A diverse class of proteins that boost the immune system. Many are cell growth factors that accelerate the production of specific cells that are important in mounting an immune response in the body. These proteins are being investigated for use in possible treatments for cancer.

Immunotoxins Specific monoclonal antibodies that have a protein toxin molecule attached. The monoclonal antibody is targeted against a tumor cell, and the toxin is designed to kill that cell when the antibody binds to it.

Inducer A molecule or substance that increases the rate of enzyme synthesis, usually by blocking the action of the corresponding repressor.

In situ In its original or natural place or position.

Industrial biotechnology The process of using the life sciences, enzymes or microbes in industrial processes or in producing commercial products.

Indication The specific condition a drug aims to treat. An indication may be broad (for example, type 2 diabetes) or it may be narrower (for example, insulin-dependent type 2 diabetes).

Institutional review board (IRB) Local oversight group at a hospital, university or other health care facility who ensure trials are conducted ethically and as safely as possible.

Interferon A class of lymphokine proteins important in the immune response. There are three major types of interferon: alpha (leukocyte), beta (fibroblast) and gamma (immune). Interferons inhibit viral infections and may have anticancer properties.

Interleukin A type of lymphokine that regulates the growth and development of white blood cells. Twelve interleukins (IL-1 through IL-12) have been identified to date.

Intron In eukaryotic cells, a sequence of DNA that is contained in the gene but does not encode for protein. The presence of introns "splits" the coding region of the gene into segments called exons. See Exon; Splicing.

Investigational New Drug Application (IND) An application to begin studies of a new drug or biologic on humans. The IND gives the plan for the study and contains formulation, manufacturing and animal test result information.

In vitro Literally, "in glass." Performed in a test tube or other laboratory apparatus.

In vivo Literally, "in the living." Performed in a living organism.

Islet cells Pancreatic cells that are the source of insulin and two other hormones involved in regulating glucose metabolism and absorption.

Isoenzyme One of the several forms that a given enzyme can take. The forms may differ in certain physical properties, but function similarly as biocatalysts.

Isogenic Of the same genotype.

K

Kidney plasminogen activator A precursor to the enzyme urokinase, which has blood-clotting properties.

L

Leukocyte A colorless cell in the blood, lymph and tissues that is an important component of the body's immune system. Also called white blood cell.

Life cycle assessment (LCA) A systematic technique for identifying and evaluating the potential environmental benefit and impact of products or processes.

Library A set of cloned DNA fragments that taken collectively contain the entire genome of an organism. Also called a DNA library.

Ligase An enzyme used to join DNA or RNA segments together.

Linkage The tendency for certain genes to be inherited together due to their physical proximity on the chromosome.

Linker A fragment of DNA with a restriction site that can be used to join DNA strands.

Lipoproteins A class of serum proteins that transport lipids and cholesterol in the bloodstream. Abnormalities in lipoprotein metabolism have been implicated in certain heart diseases.

Lymphocyte A type of leukocyte found in lymphatic tissue in the blood, lymph nodes and organs. Lymphocytes are continuously made in the bone marrow and mature into antibody-forming cells. See B lymphocytes; T lymphocytes.

Lymphokine A class of soluble proteins produced by white blood cells that play a role, as yet not fully understood, in the immune response. See Interferon; Interleukin.

Lymphoma Form of cancer that affects the lymph tissue.

M

Macrophage A type of white blood cell produced in blood vessels and loose connective tissues that can ingest dead tissues and cells and is involved in producing interleukin-1. When exposed to the lymphokine macrophage-activating factor, macrophages also kill tumor cells. See Phagocyte.

Macrophage colony stimulating factor (M-CSF) A natural hormone that stimulates the production of white blood cells, particularly monocytes (the precursors of macrophages).

Medium A substance containing nutrients needed for cell growth.

Meiosis Process of cell reproduction whereby the daughter cells have half the chromosome number of the parent cells. Sex cells are formed by meiosis. Compare Mitosis.

Messenger RNA (mRNA) Nucleic acid that carries instructions to a ribosome for the synthesis of a particular protein.

Metabolism All biochemical activities carried out by an organism to maintain life.

Microbial herbicides and pesticides Microorganisms that are toxic to specific plants or insects. Because of their narrow host range and limited toxicity, these microorganisms may be preferable to their chemical counterparts for certain pest-control applications.

Microbiology Study of living organisms that can be seen only under a microscope.

Microinjection The injection of DNA using a very fine needle into a cell.

Microorganism Any organism that can be seen only with the aid of a microscope. Also called microbe.

Mitosis Process of cell reproduction whereby the daughter cells are identical in chromosome number to the parent cells. Compare Meiosis.

Molecular genetics Study of how genes function to control cellular activities.

Monoclonal antibody (MAb) Highly specific, purified antibody that is derived from only one clone of cells and recognizes only one antigen. See Hybridoma; Myeloma.

Monocytes One of three types of white blood cells. Monocytes are precursors to macrophages.

Multigenic Of hereditary characteristics, one that is specified by several genes.

Mutagen A substance that induces mutations.

Mutant A cell that manifests new characteristics due to a change in its DNA.

Mutation A change in the genetic material of a cell.

Myeloma A type of cancer cell (plasma cell) that is used in monoclonal antibody technology to form hybridomas.

N

Nanobiotechnology The merger of biotechnology and nanotechnology to build or manipulate matter at a molecular level.

Nanotechnology The engineering of functional systems at the molecular scale; also, a branch of science that proposes the manipulation of single atoms.

Natural active immunity Immunity that is established after the occurrence of a disease.

Natural killer (NK) cell A type of leukocyte that attacks cancerous or virus-infected cells without previous exposure to the antigen. NK cell activity is stimulated by interferon.

Natural passive immunity Immunity conferred by the mother on the fetus or newborn.

Nitrogen fixation A biological process (usually associated with plants) whereby certain bacteria convert nitrogen in the air to ammonia, thus forming a nutrient essential for plant growth.

Nitrogenous base See Base.

Noncoding DNA DNA that does not encode any product (RNA or protein). The majority of the DNA in plants and animals is noncoding.

Nuclease An enzyme that, by cleaving chemical bonds, breaks down nucleic acids into their constituent nucleotides.

Nucleic acids Large molecules, generally found in the cell's nucleus and/or cytoplasm, that are made up of nucleotides. The two most common nucleic acids are DNA and RNA.

Nucleotides The building blocks of nucleic acids. Each nucleotide is composed of sugar, phosphate and one of four nitrogen bases. The sugar in DNA is deoxyribose and RNA's sugar is ribose. The sequence of the bases within the nucleic acid determines the sequence of amino acids in a protein. See Base.

Nucleus The structure within eukaryotic cells that contains chromosomal DNA.

O

Oligonucleotide A polymer consisting of a small number (about two to 10) of nucleotides.

Oncogene Gene thought to be capable of producing cancer.

Oncogenic Cancer causing.

Oncology Study of cancer.

Operator gene A region of the chromosome, adjacent to the operon, where a repressor protein binds to prevent transcription of the operon.

Operon Sequence of genes responsible for synthesizing the enzymes needed for biosynthesis of a molecule.

Organic compound A compound containing carbon.

P

Parthenogenesis Asexual reproduction achieved with only a female gamete; this form of reproduction is more common in plants and invertebrate animals.

Passive immunity Immunity acquired from receiving preformed antibodies.

Pathogen Disease-causing organism.

Peptide Two or more amino acids joined by a linkage called a peptide bond.

Personalized medicine The use of individual molecular (often genetic) information to prevent disease, choose medicines and make other critical decisions about health.

Phagocyte A type of white blood cell that can ingest invading microorganisms and other foreign material. See Macrophage.

Pharmacogenomics The science that examines the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict whether a patient will have a good response to a drug, a bad response to a drug, or no response at all. See Pharmacogenetics.

Pharmacogenetics The study of inherited differences (variation) in drug metabolism and response. See Pharmacogenomics.

Phenotype Observable characteristics resulting from interaction between an organism's genetic makeup and the environment. Compare Genotype.

Photosynthesis Conversion by plants of light energy into chemical energy, which is then used to support the plants' biological processes.

Phytoremediation The use of plants to clean up pollution.

Plasma The fluid (noncellular) fraction of blood.

Plasmapheresis A technique used to separate useful factors from blood.

Plasmid A small circular form of DNA that carries certain genes and is capable of replicating independently in a host cell.

Pluripotent cells Having the capacity to become any kind of cell or tissue in the body. Embryonic stem cells and cells of the inner cell mass are pluripotent. Adult stem cells are multipotent. The mammalian embryo (blastocyst trophoblast plus inner cell mass) is totipotent because it can become an entire organism. Fully differentiated cells from many plants are totipotent.

Polyclonal Derived from different types of cells.

Polyhydroxyalkanoates (PHAs) Linear polyesters (plastics) produced in nature by bacterial fermentation of sugar or lipids.

Polylactide (PLA) A biodegradable, thermoplastic, aliphatic polyester derived from renewable resources, with corn starch or sugarcane serving as common feedstocks.

Polymer A long molecule of repeated subunits.

Polymerase General term for enzymes that carry out the synthesis of nucleic acids.

Polymerase chain reaction (PCR) A technique to amplify a target DNA sequence of nucleotides by several hundred thousandfold.

Polypeptide Long chain of amino acids joined by peptide bonds.

Preclinical studies Studies that test a drug on animals and in other nonhuman test systems. Safety information from such studies is used to support an investigational new drug application (IND).

Pretreatment A process that renders plant matter more susceptible to enzyme breakdown.

Prokaryote An organism (e.g., bacterium, virus, cyanobacterium) whose DNA is not enclosed within a nuclear membrane. Compare Eukaryote.

Promoter A DNA sequence that is located in front of a gene and controls gene expression. Promoters are required for binding of RNA polymerase to initiate transcription.

Prophage Phage nucleic acid that is incorporated into the host's chromosome but does not cause cell lysis.

Protein A molecule composed of amino acids. There are many types of proteins, all carrying out different functions essential for cell growth.

Protein A A protein produced by the bacterium *Staphylococcus aureus* that specifically binds antibodies. It is useful in the purification of monoclonal antibodies.

Protein production A process that covers all aspects of protein formation from gene expression to the production of the final product.

Proteome The entire complement of proteins expressed by a genome, cell, tissue or organism; the protein complement of an organism coded for by its genome. Each cell produces thousands of proteins, each with a specific function. This collection of proteins in a cell is known as the proteome (from protein and genome). Unlike the genome, which is constant irrespective of cell type, the proteome varies from one cell type to the next.

Proteomics The science of proteomics attempts to identify the protein profile of various cell types, assess protein differences between healthy and diseased cells, and uncover not only each protein's specific function but also how it interacts with other proteins.

Protoplast The cellular material that remains after the cell wall has been removed from plant and fungal cells.

Pure culture In vitro growth of only one type of microorganism.

R

Radioimmunoassay (RIA) A test combining radioisotopes and immunology to detect trace substances. Such tests are useful for studying antibody interactions with cell receptors, and can be developed into clinical diagnostics.

Rational drug design Using the known three-dimensional structure of a molecule, usually a protein, to design a drug molecule that will bind to it. Usually viewed as an alternative to drug discovery through screening many molecules for biological activity.

Reagent Substance used in a chemical reaction.

Recombinant DNA (rDNA) The DNA formed by combining segments of DNA from two different sources.

Regeneration Laboratory technique for forming a new plant from a clump of plant cells.

Regulatory gene A gene that acts to control the protein-synthesizing activity of other genes.

Replication Reproduction or duplication, as of an exact copy of a strand of DNA.

Replicon A segment of DNA (e.g., chromosome or plasmid) that can replicate independently.

Repressor A protein that binds to an operator adjacent to a structural gene, inhibiting transcription of that gene.

Restriction enzyme An enzyme that breaks DNA in highly specific locations, creating gaps into which new genes can be inserted.

Restriction fragment length polymorphism (RFLP) The variation in the length of DNA fragments produced by a restriction endonuclease that cuts at a polymorphic locus. This is a key tool in DNA fingerprinting and is based on the presence of different alleles in an individual. RFLP mapping is also used in plant breeding to see if a key trait such as disease resistance is inherited.

Reticuloendothelial system The system of macrophages, which serves as an important defense system against disease.

Retrovirus A virus that contains the enzyme reverse transcriptase. This enzyme converts the viral RNA into DNA, which can combine with the DNA of the host cell and produce more viral particles.

Rheology Study of the flow of matter such as fermentation liquids.

Rhizobium A class of microorganisms that converts atmospheric nitrogen into a form that plants can utilize for growth. Species of this microorganism grow symbiotically on the roots of certain legumes, such as peas, beans and alfalfa.

Ribonucleic acid (RNA) A molecule similar to DNA that delivers DNA's genetic message to the cytoplasm of a cell where proteins are made.

Ribosome A cellular component, containing protein and RNA, that is involved in protein synthesis.

RNA interference A natural process used by organisms to block protein production.

S

Saccharification The hydrolysis of cellulose or starch into glucose.

Scale-up Transition from small-scale production to production of large industrial quantities.

Selective medium Nutrient material constituted such that it will support the growth of specific organisms while inhibiting the growth of others.

Sepsis The presence in the blood or other tissues of pathogenic microorganisms or their toxins; the condition associated with such presence.

Sequencing Decoding a strand of DNA or gene into the specific order of its nucleotides: adenine, cytosine, guanine and thymine. This analysis can be done manually or with automated equipment. Sequencing a gene requires analyzing an average of 40,000 nucleotides.

Serology Study of blood serum and reactions between the antibodies and antigens therein.

Single-blind trial A clinical trial in which the health care provider knows whether the patient is receiving the placebo or active drug, but the patient does not.

Single-cell protein Cells or protein extracts from microorganisms, grown in large quantities for use as protein supplements.

Somatic cells Cells other than sex or germ cells.

Somatic cell gene therapy Somatic cell gene therapy involves the insertion of genes into cells for therapeutic purposes; for example, to induce the treated cells to produce a protein that the body is missing. It does not affect genetic makeup of a patient's offspring and generally does not change all, or even most, cells in the recipient. Somatic cell gene therapy is only one way of applying the science of genomics to improve health care.

Somatic cell nuclear transfer The transfer of a nucleus from a fully differentiated cell into an egg that has had its nucleus removed.

Splicing The removal of introns and joining of exons to form a continuous coding sequence in RNA.

Starch ethanol Ethanol produced from the starch in fruit and seeds.

Stop codon One of three codons in messenger RNA that signal the end of the amino acid chain in protein synthesis.

Structural gene A gene that codes for a protein, such as an enzyme.

Substrate Material acted on by an enzyme.

Suicide gene A gene that codes for an antibiotic that can kill the host bacterial cell. It is genetically modified into the bacterium along with a molecular switch that is controlled by a nutrient in the environment. When the nutrient disappears, the suicide gene is switched on and the bacterium dies.

Suppressor gene A gene that can reverse the effect of a mutation in other genes.

Systems biology A hypothesis-driven field of research that creates predictive mathematical models of complex biological processes or organ systems.

Switchgrass A bunch grass that is a good candidate for biofuel due to its hardiness, rapid growth and low fertilization and herbicide requirements.

T

Technology transfer The process of transferring discoveries made by basic research institutions, such as universities and government laboratories, to the commercial sector for development into useful products and services.

Template A molecule that serves as the pattern for synthesizing another molecule.

Terminator Sequence of DNA bases that tells the RNA polymerase to stop synthesizing RNA.

Tertiary structure The total three-dimensional shape of a protein that is essential to protein function.

Therapeutics Compounds that are used to treat specific diseases or medical conditions.

Thymus A lymphoid organ in the lower neck, the proper functioning of which in early life is necessary for development of the immune system.

Tissue culture In vitro growth in nutrient medium of cells isolated from tissue.

Tissue plasminogen activator (tPA) A protein produced in small amounts in the body that aids in dissolving blood clots.

T lymphocytes (T-cells) White blood cells that are produced in the bone marrow but mature in the thymus. They are important in the body's defense against certain bacteria and fungi, help B lymphocytes make antibodies and help in the recognition and rejection of foreign tissues. T lymphocytes may also be important in the body's defense against cancers.

Toxin A poisonous substance produced by certain microorganisms or plants.

Transcription Synthesis of messenger (or any other) RNA on a DNA template.

Transdifferentiation The process whereby a specialized cell de-differentiates and re-differentiates into a different cell type; or the process whereby an adult stem cell from a specific tissue type becomes a cell type from a very different tissue (for example, a nerve stem cell differentiates into a kidney cell).

Transduction Transfer of genetic material from one cell to another by means of a virus or phage vector.

Transfection Infection of a cell with nucleic acid from a virus, resulting in replication of the complete virus.

Transfer RNA (tRNA) RNA molecules that carry amino acids to sites on ribosomes where proteins are synthesized.

Transformation Change in the genetic structure of an organism by the incorporation of foreign DNA.

Transgenic organism An organism formed by the insertion of foreign genetic material into the germ line cells of organisms. Recombinant DNA techniques are commonly used to produce transgenic organisms.

Translation Process by which the information on a messenger RNA molecule is used to direct the synthesis of a protein.

Transposon A segment of DNA that can move around and be inserted at several sites in bacterial DNA or in a phage, thus alerting the host's DNA.

Tumor necrosis factors (TNFs) Rare proteins of the immune system that appear to destroy some types of tumor cells without affecting healthy cells.

V

Vaccine A preparation that contains an antigen, consisting of whole disease-causing organisms (killed or weakened) or parts of such organisms, that is used to confer immunity against the disease that the organisms cause. Vaccine preparations can be natural, synthetic or derived by recombinant DNA technology.

Vector The agent (e.g., plasmid or virus) used to carry new DNA into a cell.

Virion An elementary viral particle consisting of genetic material and a protein covering.

Virology Study of viruses.

Virulence Ability to infect or cause disease.

Virus A submicroscopic organism that contains genetic information but cannot reproduce itself. To replicate, it must invade another cell and use parts of that cell's reproductive machinery.

W

White biotechnology European term for industrial biotechnology.

White blood cells Leukocytes.

Wild type The form of an organism that occurs most frequently in nature.

X

X-ray crystallography An essential technique for determining the three-dimensional structure of biological molecules. This information aids in the discovery of products that will interact with the biological molecule.

Xenobiotics Synthetic chemicals believed to be resistant to environmental degradation. A branch of biotechnology called bioremediation is seeking to develop biological methods to degrade such compounds.

Xenotransplantation The transplantation of living organs, cells or tissues from animals into humans.

Y

Yeast A general term for single-celled fungi that reproduce by budding. Some yeasts can ferment carbohydrates (starches and sugars) and thus are important in brewing and baking.

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