

There are more than 400 biotech drug products and **VACCINES** currently in clinical trials targeting more than 200 diseases, including various cancers, Alzheimer's

Guide to

Biotechnology

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 the AIDS virus and detect other conditions early enough to be successfully treated. Home pregnancy tests are also biotechnology **DIAGNOSTIC PRODUCTS**. • Consumers are enjoying

biotechnology foods such as papaya, soybeans and corn. The tools of biotechnology allow plant breeders to select single genes that produce desired traits and move them from one plant to another. • **ENVIRONMENTAL**

biotechnology products make it possible to clean up hazardous waste more efficiently by harnessing pollution-eating microbes without the use of caustic chemicals. • **INDUSTRIAL** biotechnology 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. • **FOOD &**

AGRICULTURE applications are lifting yields and creating hardier crops. • **FORENSIC MEDICINE**, as well

2007


Bio[®]
BIOTECHNOLOGY
INDUSTRY ORGANIZATION

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

Debbie Strickland, BIO, Director of Marketing, Editor

Contributors

Deb Carstou, BIO, Director of State Media Relations and Advocacy

Elinor Van Dyck, Blue House Publishing, Art Director

Barbara Glenn, BIO, Managing Director of Animal Biotechnology

Crispin Littlehales, Writer/Editor

Adrienne Massey, Ph.D., Writer/Editor

Contents

Biotechnology: A Collection of Technologies	I	
What Is Biotechnology?.....	1	
Cells and Biological Molecules.....	1	
Biotechnology Industry Facts	2	
Market Capitalization, 1994–2005.....	3	
U.S. Industry Statistics: 1994–2005.....	3	
New Biotech Drug and Vaccine Approvals/ New Indication Approvals by Year.....	4	
North American Biotech Companies by State and Province.....	4	
Total Financing, 1998–2005.....	5	
Biotech Industry Financing, 2005.....	5	
Time Line	6	
Biotechnology Policy Milestones.....	16	
The Technologies and Their Applications	18	
Bioprocessing Technology.....	18	
Monoclonal Antibodies.....	18	
Cell Culture.....	19	
Recombinant DNA Technology.....	21	
Cloning.....	21	
Protein Engineering.....	22	
Biosensors.....	22	
Nanobiotechnology.....	23	
Microarrays.....	23	
Biotechnology Tools in Research and Development	25	
Research Applications.....	25	
<i>Includes stem cell technology, cloning, microarray technology, antisense and RNA interference, and gene knockouts</i>		
Putting the Pieces Together: ‘Omics’.....	29	<i>Genomics, proteomics and bioinformatics</i>
Product Development Applications.....	31	
Health-Care Applications	34	
Diagnostics.....	34	
Therapeutics.....	34	
Personalized Medicine.....	37	
Regenerative Medicine.....	39	
Vaccines.....	39	
Plant-Made Pharmaceuticals.....	41	
Therapeutic Development Overview	42	
Biotech Drug Development Process.....	44	
Approved Biotechnology Drugs	45	
Agricultural Production Applications	65	
Crop Biotechnology.....	65	<i>Includes production improvement, impact on developing countries, environmental and economic benefits, and regulations</i>
Forest Biotechnology.....	69	
Animal Biotechnology.....	70	<i>Includes companion animals, applications for human medicine, and environmental and conservation efforts</i>
Aquaculture.....	76	
Global Area of Transgenic Crops, 1995 to 2005: Industrial and Developing Countries..	78	
Global Area of Transgenic Crops in 2004 and 2005 by Country.....	78	
Global Area of Transgenic Crops in 2004 and 2005 by Crop.....	79	
Global Area of Transgenic Crops, 1996 to 2005, by Crop.....	79	
Global Area of Transgenic Crops in 2004 and 2005 by Trait.....	80	

Global Area of Transgenic Crops, 1995 to 2005, by Trait	80
Transgenic Crop Area as Percentage of Global Area of Principal Crops.....	81
Global Status of Biotech Crops in 2005.....	81

Agricultural Biotech Products on the Market 82

Food Biotechnology 87

Improving the Raw Materials.....	87
Food Processing.....	88
Food Safety Testing	89

Industrial and Environmental Applications 90

Industrial Sustainability.....	90
Biocatalysts.....	91
Biofuel	92
Green Plastics.....	93
Nanotechnology.....	93
Environmental Biotechnology.....	94
Industries That Benefit.....	95
Some Industrial Biotech Applications by Sector.....	95

Consumer Products Made with Industrial Biotechnology 96

Examples of Industrial Enzymes 98

Preparedness for Pandemics and Biodefense 100

Policy.....	100
A Strategic Asset	100
<i>Vaccines, monoclonal antibodies, DNA- or RNA-based therapeutics, and detection and diagnosis</i>	
Other Approaches	101

Other Uses 102

DNA Fingerprinting.....	102
-------------------------	-----

Ethics 104

BIO Activities.....	104
Ethical Issues.....	105

BIO Statement of Ethical Principles 109

Intellectual Property 111

What Is a Patent?	111
The Purpose of a Patent	111
Patentable Inventions.....	112
Patent Requirements.....	112
The Patent Application.....	113
Patenting Organisms.....	113
Patent Licensing.....	114

Biotechnology Resources 115

Periodicals, Headline Services and Web Sites	115
General Science Journals	116
Biotech Education & Careers.....	116
Selected Recent Reports on Biotechnology.....	116

Glossary 119

Biotechnology: A Collection of Technologies

What Is Biotechnology?

Break *biotechnology* into its roots and you have

bio—the use of biological processes; and
technology—to solve problems or make useful products.

Using biological processes is hardly a noteworthy event. 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. Why is biotechnology suddenly receiving so much attention?

During the 1960s and '70s our understanding of biology reached a point where we could begin to use the smallest parts of organisms—their biological molecules—in addition to using whole organisms.

A more appropriate definition in the new sense of the word is this:

“New” Biotechnology—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 simply changing the singular noun to its plural form, *biotechnologies*.

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 a very specific task.

In spite of the extraordinary diversity of cell types in living things, what is most striking is their remarkable similarity. This unity of life at the cellular level provides the foundation for biotechnology.

All cells have the same basic design, are made of the same construction materials and operate using essentially the same processes. DNA (deoxyribonucleic acid), the genetic material of almost all living things, directs cell construction and operation, while proteins do all the work. Because DNA contains the information for making proteins, it directs cell processes by determining which proteins are produced and when.

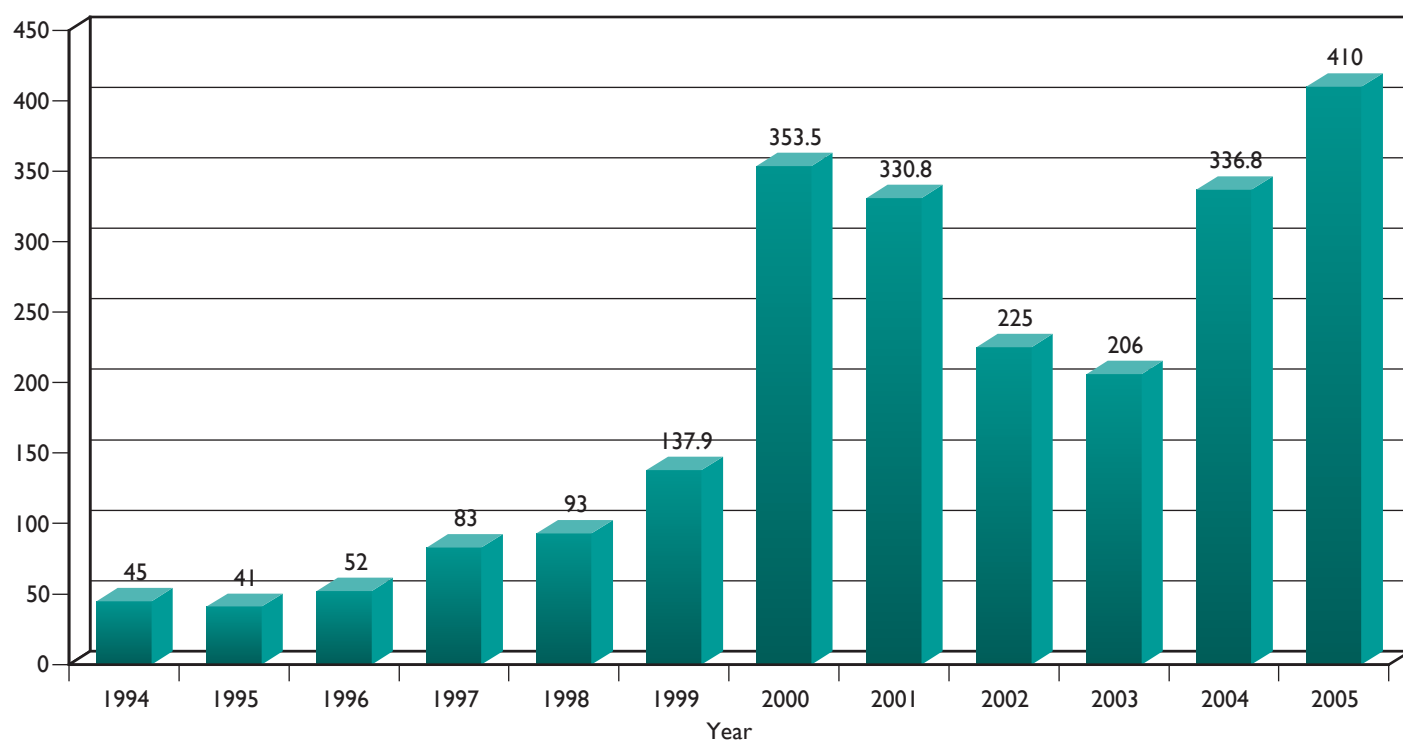
All cells speak the same genetic language. The DNA information manual of one cell can be read and implemented by cells from other living things. Because a genetic instruction to make a certain protein is understood by many different types of cells, technologies based on cells and biological molecules give us great flexibility in using nature's diversity.

In addition, cells and biological molecules are extraordinarily specific in their interactions. As a result, biotechnology products can often solve specific problems, generate gentler or fewer side effects and have fewer unintended consequences. *Specific, precise, predictable.* Those are the words that best describe today's biotechnology.

Biotechnology Industry Facts

- The biotechnology industry originated 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 the AIDS virus and detect other conditions early enough to be successfully treated. Home pregnancy tests are also biotechnology diagnostic products.
- Consumers are enjoying **biotechnology foods** such as papaya, soybeans and corn. Biopesticides and other agricultural products also are being used to improve our food supply and to reduce our dependence on conventional chemical pesticides.
- **Environmental biotechnology** products make it possible to clean up hazardous waste more efficiently by harnessing pollution-eating microbes without the use of caustic chemicals.
- **Industrial biotechnology 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, as well as afforded 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, 2005, there were **1,415 biotechnology companies in the United States**, of which 329 were publicly held.
- **Market capitalization**, the total value of publicly traded biotech companies (U.S.) at market prices, was \$410 billion as of Dec. 31, 2005.
- The biotechnology industry has mushroomed since 1992, with U.S. health-care biotech **revenues** increasing from \$8 billion in 1992 to \$50.7 billion in 2005.
- Biotechnology is one of the most **research-intensive** industries in the world. The U.S. biotech industry spent \$19.8 billion on research and development in 2005.
- The top five biotech companies invested an average of **\$130,000 per employee** in R&D in 2005.
- 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. In 2005, biotech companies signed 564 new agreements with pharmaceutical firms and 354 with fellow biotechs, according to BioWorld.
- Most biotechnology companies are young companies developing their first products and depend on **investor capital** for survival. Biotechnology attracted more than \$20 billion in financing in 2005 and has raised more than \$100 billion since 2000.
- The biosciences—including not just biotechnology but 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.
- **Bioethanol**—made from crop wastes using biotech enzymes—could meet a quarter of U.S. energy needs by 2025.
- The **Biotechnology Industry Organization (BIO)** was founded in 1993 to represent biotechnology companies at the local, state, federal and international levels. As of December 2006, BIO's membership consisted of more than 1,100 biotechnology companies, academic centers, state and local associations and related enterprises.

Market Capitalization, 1994–2005*



*Amounts are U.S. dollars in billions.

Sources:

Ernst & Young LLP

BioWorld

U.S. Biotech Industry Statistics: 1994–2005*

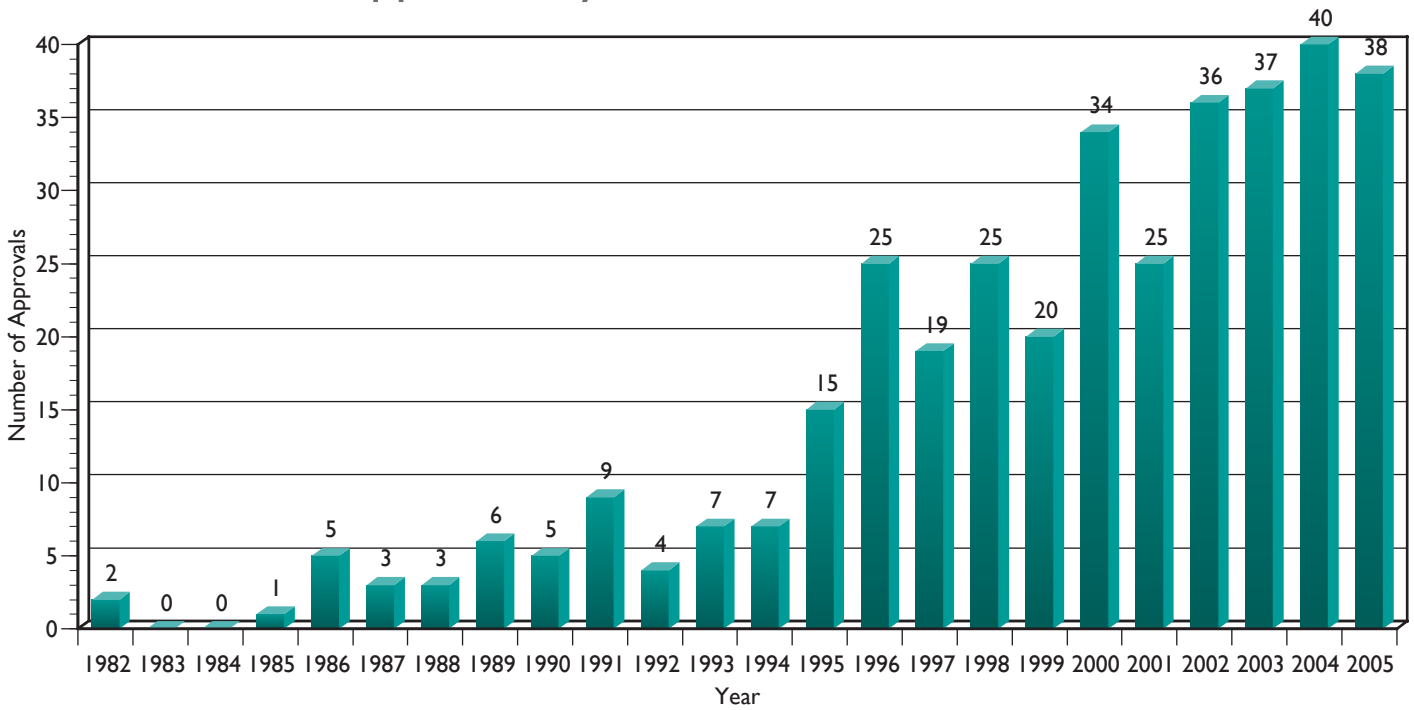
Year	2005	2004	2003	2002	2001	2000	1999	1998	1997	1996	1995	1994
Sales	32.1	28.1	28.4	24.3	21.4	19.3	16.1	14.5	13	10.8	9.3	7.7
Revenues	50.7	43.8	39.2	29.6	29.6	26.7	22.3	20.2	17.4	14.6	12.7	11.2
R&D Expense	19.8	19.6	17.9	20.5	15.7	14.2	10.7	10.6	9.0	7.9	7.7	7.0
Net Loss	4.1	6.8	5.4	9.4	4.6	5.6	4.4	4.1	4.5	4.6	4.1	3.6
No. of Public Companies	329	331	314	318	342	339	300	316	317	294	260	265
No. of Companies	1,415	1,346	1,473	1,466	1,457	1,379	1,273	1,311	1,274	1,287	1,308	1,311

*Amounts are U.S. dollars in billions.

Source:

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

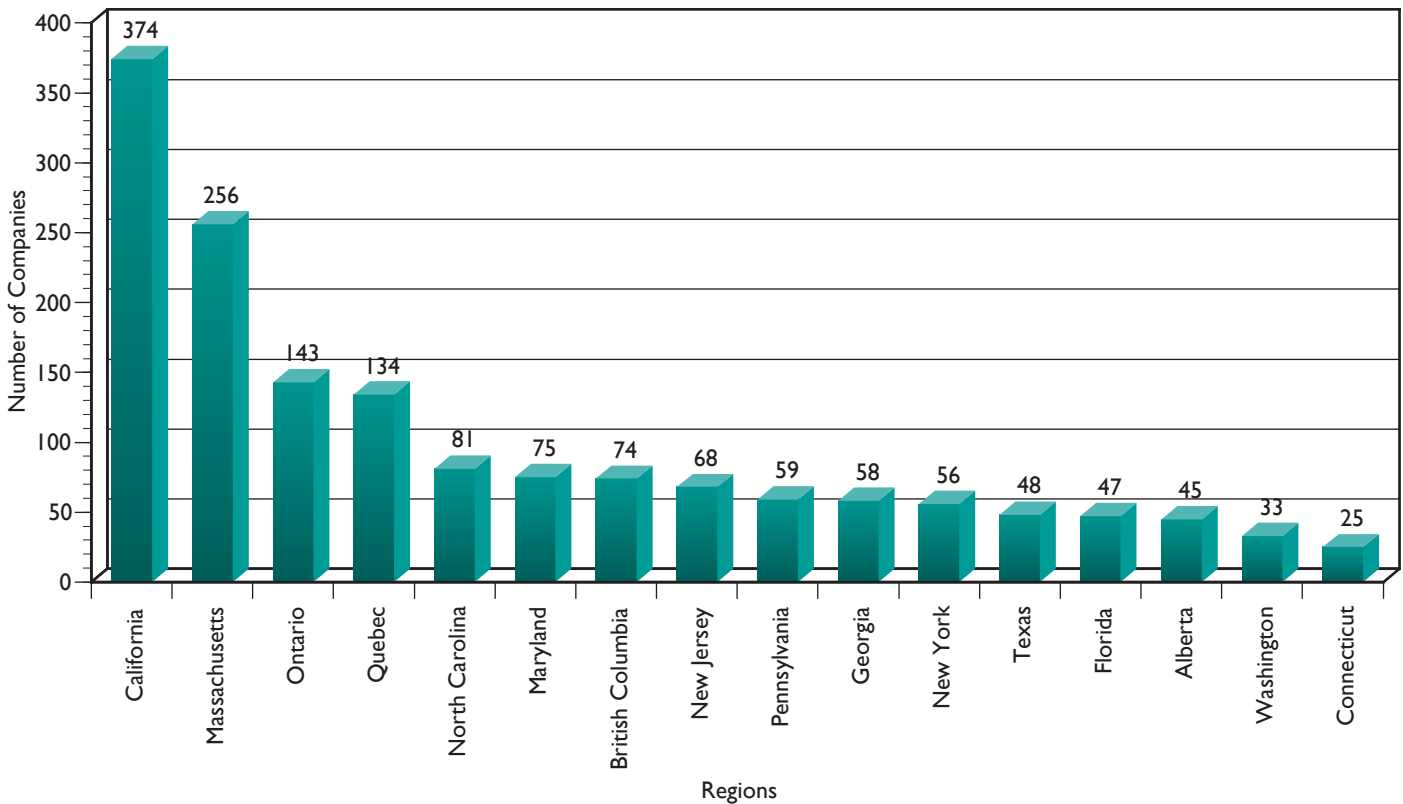
New Biotech Drug and Vaccine Approvals/ New Indication Approvals by Year



Source:
BIO

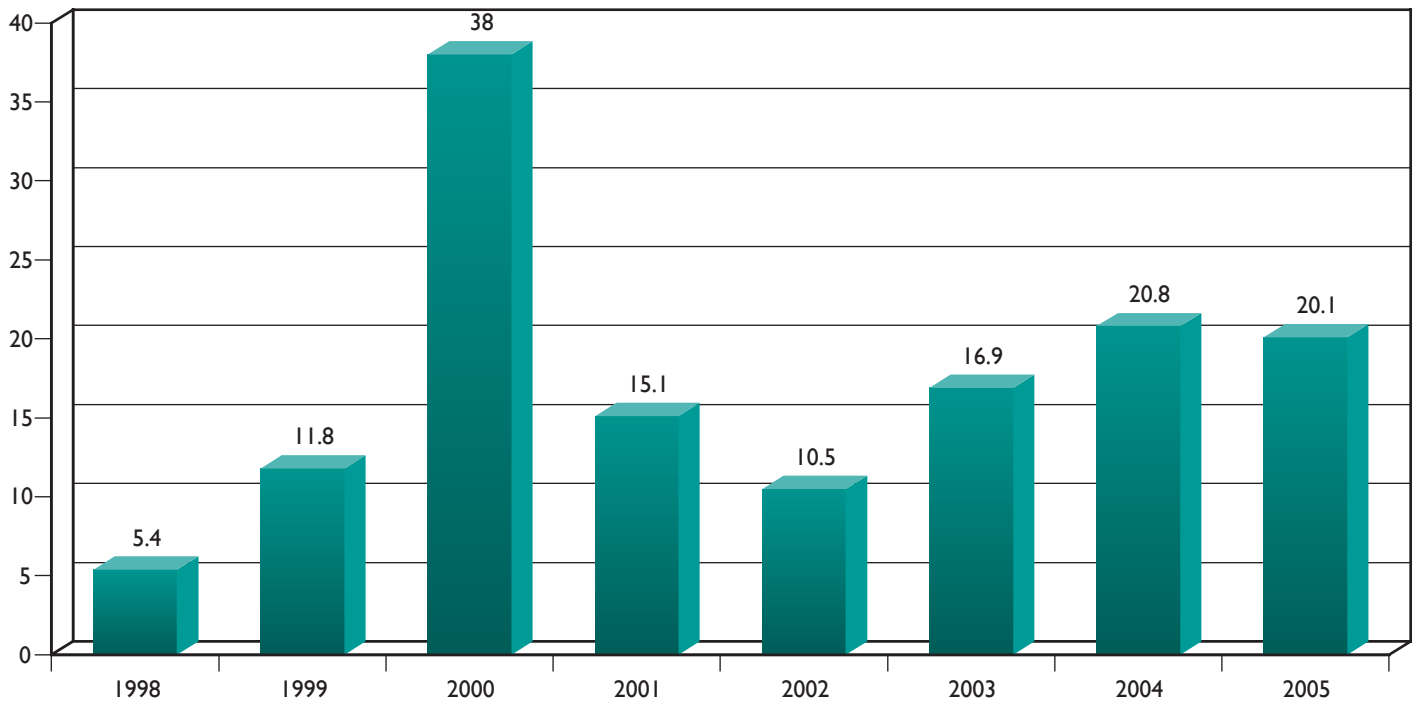
4

North American Biotech Companies by State and Province



Source:
Ernst & Young LLP

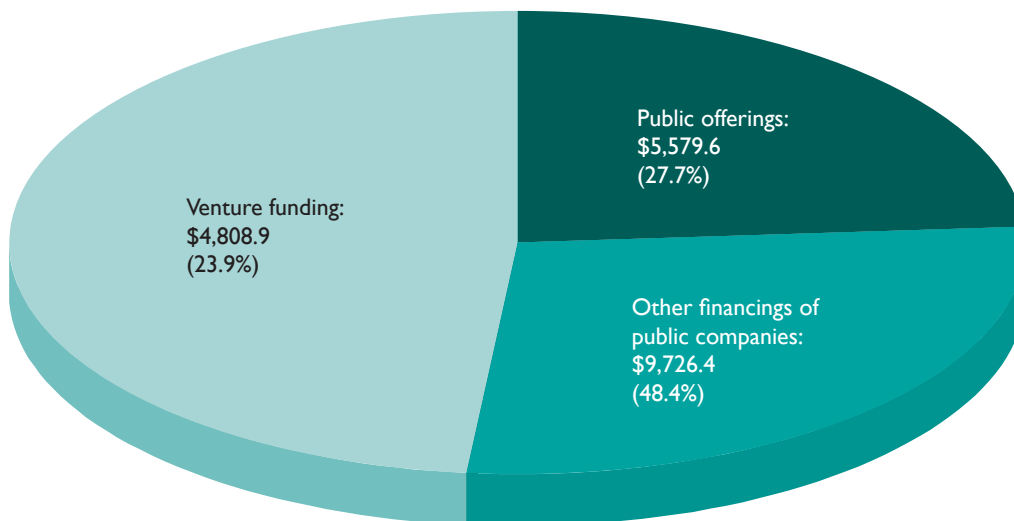
Total Financing, 1998–2005 (in billions of U.S. dollars)



Source:
BioWorld

Biotech Industry Financing, 2005

Total: \$20,114.9 Million
(all figures in millions)



Source:
BioWorld

Time Line

8000 B.C.

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

4000–2000 B.C.

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

500 B.C.

- First antibiotic: moldy soybean curds used to treat boils (China).

A.D. 100

- First insecticide: powdered chrysanthemums (China).

1322

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

1590

- Janssen invents the microscope.

1663

- Hooke discovers existence of the cell.

1675

- Leeuwenhoek discovers bacteria.

1761

- Koelreuter reports successful crossbreeding of crop plants in different species.

1797

- Jenner inoculates a child with a viral vaccine to protect him from smallpox.

1830–1833

- 1830—Proteins discovered.
- 1833—First enzyme discovered and isolated.

1835–1855

- Schleiden and Schwann propose that all organisms are composed of cells, and Virchow declares, “Every cell arises from a cell.”

1857

- Pasteur proposes microbes cause fermentation.

1859

- 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

- 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.

1870–1890

- Using Darwin’s theory, plant breeders crossbreed cotton, developing hundreds of varieties with superior qualities.
- Farmers first inoculate fields with nitrogen-fixing bacteria to improve yields.
- William James Beal produces first experimental corn hybrid in the laboratory.
- 1877—A technique for staining and identifying bacteria is developed by Koch.
- 1878—The first centrifuge is developed by Laval.
- 1879—Fleming discovers chromatin, the rod-like structures inside the cell nucleus that later came to be called chromosomes.

1900

- *Drosophila* (fruit flies) used in early studies of genes.

1902

- The term *immunology* first appears.

1906

- The term *genetics* is introduced.



1911

- The first cancer-causing virus is discovered by Rous.

1914

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

1915

- Phages, or bacterial viruses, are discovered.

1919

- First use of the word *biotechnology* in print.

1920

- The human growth hormone is discovered by Evans and Long.

1928

- Penicillin discovered as an antibiotic: Alexander Fleming.
- 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.
- Karpechenko crosses radishes and cabbages, creating fertile offspring between plants in different genera.
- 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 mass-produced in microbes.

1944

- DNA is proven to carry genetic information—Avery et al.
- Waksman isolates streptomycin, an effective antibiotic for tuberculosis.

**1946**

- Discovery that genetic material from different viruses can be combined to form a new type of virus, an example of genetic recombination.
- Recognizing the threat posed by loss of genetic diversity, the U.S. Congress provides funds for systematic and extensive plant collection, preservation and introduction.

1947

- McClintock discovers transposable elements, or “jumping genes,” in corn.

1949

- 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

- 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

- Discovery of interferons.
- First synthetic antibiotic.

1960

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

1961

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

1963

- New wheat varieties developed by 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

- Harris and Watkins 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).
- Discovery of restriction enzymes that cut and splice genetic material, opening the way for gene cloning.

1971

- First complete synthesis of a gene.

1972

- The DNA composition of humans is discovered to be 99 percent similar to that of chimpanzees and gorillas.
- Initial work with embryo transfer.

1973

- 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 forms a Recombinant DNA Advisory Committee to oversee recombinant genetic research.

1975

- Government first urged to develop guidelines for regulating experiments in recombinant DNA: Asilomar Conference, California.
- The first monoclonal antibodies are produced.

1976

- The tools of recombinant DNA 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.

1977

- First expression of human gene in bacteria.
- Procedures developed for rapidly sequencing long sections of DNA using electrophoresis.

1978

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

1979

- Human growth hormone first synthesized.

ALSO IN THE 1970s

- First commercial company founded to develop genetically engineered products.
- Discovery of polymerases.
- Techniques for rapid sequencing of nucleotides perfected.
- Gene targeting.
- RNA splicing.

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 Cohen and Boyer.
- The first gene-synthesizing machines are developed.
- Researchers successfully introduce a human gene—one that codes for the protein interferon—into a bacterium.
- Nobel Prize in Chemistry awarded for creation of the first recombinant molecule: Berg, Gilbert, Sanger.



1981

- Scientists at Ohio University produce the first transgenic animals by transferring genes from other animals into mice.
- 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.
- First recombinant DNA vaccine for livestock developed.
- First biotech drug approved by FDA: human insulin produced in genetically modified bacteria.
- First genetic transformation of a plant cell: petunia.

1983

- The polymerase chain reaction (PCR) technique is conceived. 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.
- First whole plant grown from biotechnology: petunia.
- First proof that modified plants pass their new traits to offspring: petunia.

1984

- The DNA fingerprinting technique is developed.
- The entire genome of the human immunodeficiency virus is cloned and sequenced.

1985

- Genetic markers found for kidney disease and cystic fibrosis.
- Genetic fingerprinting 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

- First recombinant vaccine for humans: hepatitis B.
- First anticancer drug produced through biotech: interferon.
- The U.S. government publishes the *Coordinated Framework for Regulation of Biotechnology*, establishing more stringent regulations for rDNA organisms than for those produced with traditional genetic modification techniques.
- A University of California–Berkeley chemist describes how to combine antibodies and enzymes (abzymes) to create pharmaceuticals.
- 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.”

1987

- First approval for field test of modified food plants: virus-resistant tomatoes.
- 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.
- Congress funds the Human Genome Project, a massive effort to map and sequence the human genetic code as well as the genomes of other species.

1989

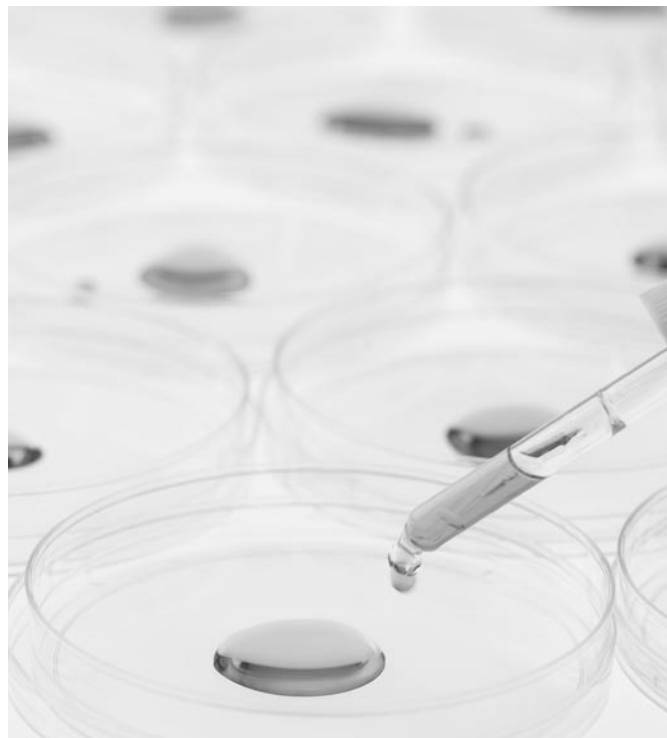
- First approval for field test of modified cotton: insect-protected (Bt) cotton.
- Plant Genome Project begins.

ALSO IN THE 1980s

- Studies of DNA used to determine evolutionary history.
- Recombinant DNA animal vaccine approved for use in Europe.
- Use of microbes in oil spill cleanup: bioremediation technology.
- Ribozymes and retinoblastomas 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.
- First insect-protected corn: Bt corn.
- First food product of biotechnology approved in U.K.: modified yeast.
- First field test of a genetically modified vertebrate: trout.

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 bovine somatotropin (BST) for increased milk production in dairy cows.

1994

- First FDA approval for a whole food produced through biotechnology: FLAVRSAVR™ tomato.
- The first breast cancer gene is discovered.
- Approval of recombinant version of human DNase, which breaks down protein accumulation in the lungs of CF patients.
- BST commercialized as POSILAC® bovine somatotropin.

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 *Hemophilus 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.

1997

- First animal cloned from an adult cell: a sheep named Dolly in Scotland.
- First weed- and insect-resistant biotech crops commercialized: Roundup Ready® soybeans and Bollgard® insect-protected cotton.
- Biotech crops grown commercially on nearly 5 million acres worldwide: Argentina, Australia, Canada, China, Mexico and the United States.
- A group of Oregon researchers claims to have cloned two Rhesus monkeys.

1998

- University of Hawaii scientists clone three generations of mice from nuclei of adult ovarian cumulus cells.
- Human embryonic stem cell lines are established.
- 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* worm, is sequenced.
- A 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.

ALSO IN THE 1990s

- First conviction using genetic fingerprinting in the U.K.
- Discovery that hereditary colon cancer is caused by defective DNA repair gene.
- Recombinant rabies vaccine tested in raccoons.
- Biotechnology-based biopesticide approved for sale in the United States.
- Patents issued for mice with specific transplanted genes.
- First European patent on a transgenic animal issued for transgenic mouse sensitive to carcinogens.

2000

- First complete map of a plant genome developed: *Arabidopsis thaliana*.
- Biotech crops grown on 108.9 million acres in 13 countries.
- "Golden rice" announcement allows the technology to be available to developing countries in hopes of improving the health of undernourished people and preventing some forms of blindness.
- First biotech crop field-tested in Kenya: virus-resistant sweet potato.
- Rough draft of the human genome sequence is announced.

2001

- First complete map of the genome of a food plant completed: rice.
- Researchers with China's National Hybrid Rice Research Center report developing a "super rice" that could produce double the yield of normal rice.
- Complete DNA sequencing of the agriculturally important bacteria *Sinorhizobium meliloti*, a nitro-

gen-fixing species, and *Agrobacterium tumefaciens*, a plant pest.

- A single gene from *Arabidopsis* inserted into tomato plants to create the first crop able to grow in salty water and soil.

2002

- The first draft of a functional map of the yeast proteome, an entire network of protein complexes and their interactions, is completed. A map of the yeast genome was published in 1996.
- International consortia 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, and the first part of the Human Genome Project comes to an end ahead of schedule and under budget.
- Scientists make great progress in elucidating the factors that control the differentiation of stem cells, identifying over 200 genes that are involved in the process.
- Biotech crops grown on 145 million acres in 16 countries, a 12 percent increase in acreage. More than one-quarter (27 percent) of the global acreage was grown in nine developing countries.
- 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. By combining an understanding of the genomes of the fungus and rice, scientists can elucidate the molecular basis of the interactions between the plant and pathogen.
- Scientists are forced to rethink their view of RNA when they discover how important small pieces of RNA are in controlling many cell functions.
- 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. The project raises ethical and security questions.



2003

- Researchers find a vulnerability gene for depression and make strides in detecting genetic links to schizophrenia and bipolar disorder.
- GloFish®, the first biotech pet, hits the North American market. Specially bred to detect water pollutants, the fish glows red under black light thanks to the addition of a natural fluorescence gene.
- Worldwide biotech crop acreage rises 15 percent to hit 167.2 million acres in 18 countries. Brazil and the Philippines grow biotech crops for the first time in 2003. Also, Indonesia allows consumption of imported biotech foods, and China and Uganda accept biotech crop imports.
- The U.K. approves its first commercial biotech crop in eight years. The crop is a biotech herbicide-resistant corn used for cattle feed.
- 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. Dolly was the first successful clone of an adult mammal.
- Japanese researchers develop a biotech coffee bean that is naturally decaffeinated.
- China's State Food and Drug Administration grants the world's first regulatory approval of a gene therapy product, Gendicine, developed by Shenzhen SiBiono GenTech. The product delivers the p53 gene as a therapy for squamous cell head and neck cancer.

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 product for age-related “wet” macular degeneration becomes the first RNAi product to enter a clinical trial.
- The United Nations Food and Agriculture Organization endorses biotech crops and states that biotechnology is a complementary tool to traditional farming methods that can help poor farmers and consumers in developing nations.
- The National Academy of Sciences’ Institute of Medicine finds biotech crops do not pose any more health risks than do crops created by other techniques, and that food safety evaluations should be based on the resulting food product, not the technique used to create it.
- FDA finds biotech wheat safe after a food safety review.
- Monsanto introduces low-linolenic soybeans (produced through conventional breeding methods) that will reduce or eliminate trans fatty acids in processed soybean oil.
- Chicken genome sequenced by the Chicken Genome Sequencing Consortium.
- First cloned pet, a kitten, is delivered to its owner.
- 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.
- California voters pass Proposition 71, which supports embryonic stem cell research with \$3 billion in funding over 10 years.

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, NitroMed’s BiDi1®, treats congestive

heart failure in self-identified black patients. The company hopes a genetic test can be developed to identify patients likely to benefit, regardless of race.

- The Energy Policy Act is passed and signed into law, authorizing numerous incentives for bioethanol development.
- The National Institutes of Health in December 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.
- Using new genome sequence information, 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.
- USDA, Monsanto and Genesee Pharmaceuticals announce a joint soybean genome project.
- The British government approves the Equine Fertility Unit’s research in using nuclear transfer in horse cloning.
- On May 7, the one billionth acre of biotech seed is planted.
- The World Health Organization (WHO) issues the report *Modern Food Biotechnology, Human Health and Development*, which states biotech foods can contribute to enhancing human health and development. According to the report, biotech foods can increase crop yield, food quality, and the diversity of foods which can be grown in a given area. They lead to better health and nutrition and thereby help raise health and living standards.
- The British research firm PG Economics Ltd. finds that the global use of biotech crops has added \$27 billion to farm income, and greatly reduced agriculture’s negative impacts on the environment.
- The National Science Foundation, USDA, and the Department of Energy award \$32 million to a team of university and private laboratory researchers to sequence the corn genome.
- A consortium of scientists led by the National Human Genome Research Institute publishes the dog genome, which belongs to a 12-year-old boxer.

- Global biotech crop acreage reaches 222 million acres.

2006

- A team of researchers headed by the University of Illinois receives a \$10 million federal grant to complete the sequence of the swine genome. The project is expected to be completed within two years.
- In his State of the Union address, President Bush expresses support for bioethanol made from agricultural wastes. “Doesn’t it make sense,” he asked, “to determine whether or not we can use these raw materials to make something out of nothing so that we continue the advance of ethanol and so the market for ethanol expands throughout the United States?”
- The National Institutes of Health begins a 10-year, 10,000-patient study using a genetic test that predicts breast-cancer recurrence and guides treatment. Patients whose cancer is deemed unlikely to recur will be spared chemotherapy. The genetic test, Oncotype DX™ was developed by the biotech company Genomic Health and is already commercially available.
- In January, the American Dietetic Association (ADA) publishes a reaffirmed statement of support on agricultural and food biotechnology. The ADA states that agricultural biotechnology techniques can enhance the quality, safety, nutritional value, and variety of food available for human consumption while increasing the efficiency of food production, food processing, food distribution, and environmental and waste management.
- Dow AgroSciences announces it has received the first regulatory approval for a plant-made vaccine from USDA’s Center for Veterinary Biologics. The vaccine protects poultry from Newcastle disease, and is the first plant-made vaccine to be approved.
- Renessen LLC, a joint venture of Monsanto and Cargill, receives approval from USDA to begin selling the first crop improved through biotechnology with added benefits for use in animal feed. The product, Maveria™ High Value Corn with Lysine, has been improved to grow with increased levels of lysine, an amino acid that is essential for animal diets, especially those of swine and poultry.
- USDA awards \$5 million to a consortium of public wheat breeders and 18 universities for wheat genome research.
- Researchers develop biotech pigs that produce high levels of omega-3 fatty acids. The biotech pigs were developed by inserting the “fat-1” gene that comes from

the roundworm *Caenorhabditis elegans*. The biotech pigs were cloned, and six of the 10 clones produced increased levels of omega-3 fatty acids, which are believed to ward off heart disease.

- 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.
- The French agriculture ministry authorizes 17 new field tests for biotech corn and tobacco crops.

Sources:

Access Excellence

Biotech 90: Into the Next Decade,

G. Steven Burrill with the Ernst & Young High Technology Group

Biotechnology Industry Organization
Genentech, Inc.

Genetic Engineering News

International Food Information Council

ISB News Report

International Service for the
Acquisition of Agri-Biotech
Applications

Texas Society for Biomedical Research
Science

Science News

The Scientist

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 be pluralized as National Institutes of Health).

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 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.

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.

1992

- The FDA clears the way for agricultural biotechnology products with a safety assessment and guidance to industry.
- The Prescription Drug User Fee Act is signed into law, instituting fees for drug approval applicants that provide the FDA with resources to review products faster. The successful program is reauthorized in 1997 and 2002 and is up for reauthorization again in 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.

2000

- The Biomass Research and Development Act is signed into law to promote conversion of biomass into bio-based 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.

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.

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.



The Technologies and Their Applications

Here are a few of the new biotechnologies that use cells and biological molecules and examples of their applications in medicine, agriculture, food processing, industrial manufacturing and environmental management.

Bioprocessing Technology

The oldest of the biotechnologies, bioprocessing technology, uses living cells or the molecular components of their manufacturing machinery to produce desired products. The living cells most commonly used are one-celled microorganisms, such as yeast and bacteria; the biomolecular components we use most often are enzymes, which are proteins that catalyze biochemical reactions.

A form of bioprocessing, *microbial fermentation*, has been used for thousands of years—unwittingly—to brew beer, make wine, leaven bread and pickle foods. In the mid-1800s, when we discovered microorganisms and realized their biochemical machinery was responsible for these useful products, we greatly extended 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, amino acids, vitamins, industrial solvents, pigments, pesticides and food-processing aids.

Today, we are using recombinant DNA technology, coupled with microbial fermentation, to manufacture a wide range of biobased products including human insulin, the hepatitis B vaccine, the calf enzyme used in cheese-making, biodegradable plastics, and laundry detergent enzymes. Bioprocessing technology also encompasses tissue engineering and manufacturing as well as biopharmaceutical formulation and delivery.

Monoclonal Antibodies

Monoclonal antibody technology uses immune-system cells that make proteins called antibodies. We have all experienced the extraordinary specificity of antibodies: Those that attack a flu virus one winter do nothing to protect us from a slightly different flu virus the next year. (Specificity refers to the fact that biological molecules are designed so that they bind to only one molecule.)

The specificity of antibodies also makes them powerful *diagnostic tools*. They can locate substances that occur in minuscule amounts and measure them with great accuracy. For example, we use monoclonal antibodies to

- locate environmental pollutants.
- detect harmful microorganisms 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 joined to a toxin can selectively deliver chemotherapy to a cancer cell while avoiding healthy cells. We are developing monoclonal antibodies to treat organ-transplant rejection and autoimmune diseases by targeting them specifically to the type of immune system cell responsible for these attacks, leaving intact the other branches of the immune system.

MAbs FOR IMMUNE-RELATED CONDITIONS

- **Muromomab-CD3 (OKT3)** is used to prevent acute rejection of organ transplants. A modified version of OKT3 shows promise in inhibiting the autoimmune destruction of beta cells in Type 1 diabetes mellitus.
- **Infliximab (Remicade®)** binds to tumor necrosis factor-alpha and has shown promise against some inflammatory diseases such as rheumatoid arthritis.
- **Omalizumab (Xolair®)** binds to IgE and prevents it from binding to mast cells. The drug is used against allergic asthma.
- **Daclizumab (Zenapax®)** binds to part of the IL-2 receptor and is used to prevent acute rejection of transplanted kidneys. The drug also shows promise against T-cell lymphoma.

MAbs USED TO KILL OR INHIBIT CANCER CELLS

- **Rituximab (Rituxan®)** binds to the CD20 molecule that is found on most B-cells and is used to treat B-cell lymphomas
- **Ibritumomab tiuxetan (Zevalin®)** is used against the CD20 molecule on B-cells (and lymphomas) conjugated to either of two radioactive isotopes in conjunction with Rituxan.

- **Tositumomab (Bexxar®)** is a conjugate of a monoclonal antibody against CD20 and the radioactive isotope iodine-131. It has been approved to treat lymphoma.
- **Trastuzumab (Herceptin®)** binds to HER2, a receptor for epidermal growth factor found on some breast cancers and lymphomas.
- **Cetuximab (Erbix®)** blocks HER1, another epidermal growth factor receptor, and has been approved to treat colorectal cancer.
- **Gemtuzumab ozogamicin (Mylotarg®)** is a conjugate of a monoclonal antibody that binds to CD33, a cell-surface molecule expressed by the cancerous cells in acute myelogenous leukemia, and calicheamicin, a complex oligosaccharide that makes double-stranded breaks in DNA. The drug is the first immunotoxin that shows promise in the fight against cancer.
- **Alemtuzumab (Campath®)** binds to CD52, a molecule found on white blood cells, and has produced complete remission of chronic lymphocytic leukemia (for 18 months and counting).

ANGIOGENESIS INHIBITOR

- **Bevacizumab (Avastin®)** blocks the vascular endothelial growth factor (VEGF) receptor and has been approved for the treatment of colorectal cancer.

OTHER

- **Abciximab (ReoPro®)** inhibits the clumping of platelets by binding the receptors on their surface that normally are linked by fibrinogen. This therapy is helpful in preventing the re-clogging of the coronary arteries in patients who have undergone angioplasty.

Monoclonal antibodies can be created in mice, but mouse antibodies are “seen” by the human immune system and often the human patient mounts an immune response, which not only eliminates the therapeutic MAb administered, but also causes damage to the kidneys. To reduce the problem of human anti-mouse antibodies (HAMA), scientists use chimeric, or humanized, antibodies. To form a chimeric antibody, one must combine the antigen-binding parts (variable regions) of the mouse antibody with the effector parts (constant regions) of a human antibody. Infliximab, rituximab and abciximab are examples. To create human antibodies, one combines only the amino acids responsible for making the antigen binding site (the hypervariable regions) of a mouse antibody and

the rest of a human antibody molecule, thus replacing its own hypervariable regions. Zenapax®, Vitaxin, Mylotarg®, Herceptin®, and Xolair® are examples.

Cell Culture

Cell culture technology is the growing of cells outside of living organisms.

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 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 insects or having pesticides accumulate in the environment. Even though we have recognized the environmen-



tal advantages of biological control for many decades, manufacturing biological control products in marketable amounts has been impossible. Insect cell culture removes these manufacturing constraints. In addition, 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 that utilizes insect cell culture has reached Phase III clinical trials.

MAMMALIAN CELL CULTURE

Livestock breeding has used mammalian cell culture as an essential tool for decades. Eggs and sperm, taken from genetically superior bulls and cows, are united in the lab, and the resulting embryos are grown in culture before being implanted in surrogate cows. 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 to assess the safety and efficacy of medicines. Like plant cell culture and insect cell culture, we are relying on the manufacturing capacity of 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 vaccines. In 2005, the Department of Health and Human Services awarded a \$97 million contract to Sanofi Pasteur to develop mammalian cell culturing techniques to speed the production process for new influenza vaccines and thereby enhance pandemic preparedness.

Therapies based on cultured *adult stem cells*, which are found in certain tissues like the bone marrow and brain, are on the horizon as well. Researchers have found that adult stem cells can be used by the body to replenish tissues. Adult hematopoietic stem cells already are being transplanted into bone marrow to stimulate the generation of the various types of blood cells necessary to rejuvenate an immune system. These stem cells can be harvested in large quantities from umbilical cord blood, but they are difficult to isolate and purify.

Researchers also are working on ways to harvest stem cells from placentas and from fat. Some are looking at cellular reprogramming as a way to get specialized body cells, like skin cells, to revert to a primordial state so that they can be coaxed into various types of tissues.

Embryonic stem cells are also under study as potential therapies. As the name suggests, embryonic stem cells are derived from embryos—specifically those that develop from eggs that have been fertilized *in vitro* (in an *in vitro* fertilization clinic) and then donated by consent for research purposes. The embryos are typically four or five days old and are each a hollow microscopic ball of cells called the blastocyst.

The potential value of stem cell therapy and tissue engineering can best be realized if the therapeutic stem cells and the tissues derived from them are genetically identical to the patient receiving them.

Human embryonic stem cells are isolated by transferring the inner cell mass into a nutrient rich culture medium. There the human stem cells proliferate. Over the course of several days, the cells of the inner cell mass divide and spread all over the dish. Researchers then must remove the growing cells and divide them into fresh culture dishes. This process of replating the cells, called subculturing, is repeated many times over many months. Each cycle of subculturing cells is called a *passage*. Embryonic stem cells that have proliferated in cell culture for six or more months without differentiating (i.e., remain pluripotent) and appear genetically normal are referred to as an *embryonic stem cell line*.

The inner surface of the culture dish may be coated with mouse embryonic skin cells that have been engineered not to divide. This is called the “feeder layer.” It provides a sticky surface to which the human embryonic cells attach. Recently scientists have been figuring out ways to grow embryonic stem cells without using mouse feeder cells—a significant advance because of the risk of viruses and other macromolecules in the mouse cells being transmitted to the human cells.

The potential value of stem cell therapy and tissue engineering can best be realized if the therapeutic stem cells and the tissues derived from them are genetically identical to the patient receiving them. Therefore, unless the patient is the source of the stem cells, the stem cells need to be “customized” by replacing the stem cell’s genetic material with the patient’s before cueing the stem cells to differentiate into a specific cell type. To date, this genetic material replacement and reprogramming can be done effectively only with embryonic stem cells.

Recombinant DNA Technology

Recombinant DNA technology is viewed by many as the cornerstone of biotechnology. The term *recombinant DNA* literally means the joining or recombining of two pieces of DNA from two different species.

Humans began to preferentially combine 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 to combine valuable genetic material from different organisms, we combine genes at the molecular level using the more precise techniques of recombinant DNA technology.

Genetic modification through selective breeding and recombinant DNA techniques fundamentally 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 any other.
- In selective breeding, large sets of genes of unknown function are transferred between related organisms.

By making our manipulations more precise and our outcomes more certain, we decrease the risk of producing organisms with unexpected traits and avoid the time-consuming, trial-and-error approach of selective breeding. By increasing the breadth of species from which we can obtain useful genes, we can access all of nature's genetic diversity.

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.
- treat some genetic diseases.
- enhance biocontrol agents in agriculture.

- increase agricultural yields and decrease production costs.
- decrease allergy-producing characteristics of some foods.
- improve food's nutritional value.
- develop biodegradable plastics.
- decrease water and air pollution.
- slow food spoilage.
- control viral diseases.
- inhibit inflammation.

Cloning

Cloning technology allows us to generate a population of genetically identical molecules, cells, plants or animals. Because cloning technology can be used to produce molecules, cells, plants and some animals, its applications are extraordinarily broad. 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 and essential tool of biotechnology research, development and commercialization. Virtually all applications in biotechnology, from drug discovery and development to the production of transgenic crops, depend on gene cloning.

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 the trait. For a full discussion, see page 27.

ANIMAL CLONING

Animal cloning has helped us to rapidly incorporate improvements into 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, brought animal cloning into the public consciousness, the production of an animal clone was not a new development. Dolly was considered a scientific breakthrough not because she was a clone, but because the source of the genetic material that was used to produce Dolly was an adult cell, not an embryonic one.

Recombinant DNA technologies, in conjunction with animal cloning, are providing us with excellent animal models for studying genetic diseases, aging and cancer and, in the future, will help us discover drugs and evaluate other forms of therapy, such as gene and cell therapy. Animal cloning also provides zoo researchers with a tool for helping to save endangered species.

There are two different ways to make an exact genetic copy of an organism such as a sheep or a laboratory mouse.

Artificial embryo twinning (AET) is the old-fashioned way to clone. AET 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 individual cells and then allow each cell 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) involves 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 and transferred it 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.

Protein Engineering

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

The most pervasive uses of protein engineering to date are applications that 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. The chemical, textile, pharmaceutical, pulp and paper, food and feed, and energy industries are all benefiting from cleaner, more energy-efficient production made possible by incorporating biocatalysts into their production processes.

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, new proteins are being developed 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, which came into its own in 2000 with the birth of the National Nanotechnology Initiative, 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 and its highly specific bonding properties bring atoms together in a predictable pattern to create a nanostructure.

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 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 samples simultaneously.

Researchers currently use microarray technology to study gene structure and function. Thousands of DNA or protein molecules are arrayed on glass slides to create

DNA chips and protein chips, respectively. Recent developments in microarray technology use customized beads in place of glass slides.

DNA MICROARRAYS

DNA microarrays are used to

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

DNA-based arrays will be essential for converting the raw genetic data provided by the Human Genome Project and other genome projects into useful products. Gene sequence and mapping data mean little until we determine what those genes do—which is where protein arrays come in.

PROTEIN MICROARRAYS

While going from DNA arrays to protein arrays is a logical step, it is by no means simple to accomplish. The structures and functions of proteins are much more complicated than that 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 varies with its health, age, and current and past environmental conditions.

Protein microarrays will 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 structure and function.
- assess differential protein expression in order to identify new drug leads.
- evaluate binding interactions between proteins and other molecules.



The fundamental principle underlying microarray technology has inspired 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 glass slide, are being used to detect protein profiles in healthy and diseased tissues and validate potential drug targets. Brain tissue samples arrayed on slides with electrodes allow researchers to measure the electrical activity of nerve cells exposed to certain drugs.

WHOLE-CELL MICROARRAYS

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

SMALL-MOLECULE MICROARRAYS

Small-molecule microarrays allow pharmaceutical companies to screen ten of thousands of potential drug candidates simultaneously.

Biotech Tools in Research and Development

The previous section describes the fundamental scientific and technological advances which together constitute biotechnology. Here we describe some of the many tangible rewards afforded by biotech.

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.

Using the wealth of information this research provides, companies then rely on biotechnology tools and techniques throughout product development and commercialization.

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.

Researchers dissect these processes into the smallest possible bits of useful information. This requires identifying the molecular players involved in each facet of the process, elucidating the nature of their interactions and discovering the molecular control mechanisms that govern these interactions. Once they have teased apart details of the process, they must then reassemble the pieces in a way that provides insight into the inner workings of cells and, ultimately, of whole organisms.

Interestingly, the tools of biotechnology have also become important research tools in many branches of science other than cell and molecular biology, such as chemistry, engineering, materials science, ecology, evolution and computer science. The biotech-driven discoveries in these fields help the biotech industry and others discover and develop products, as well as help industries improve their performance in areas such as environmental stewardship and workplace safety.

UNDERSTANDING CELL PROCESSES

Researchers are making considerable progress in charting the path of a cell from a single, fertilized egg to a whole organism, a feat that has eluded them for decades. 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. The breakthroughs that gave birth to this optimism are 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.

For decades we have known the basic requirements for keeping small numbers of plant and animal cells in culture for many decades. 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. Formerly we assumed all cells

died through an unorganized, passive mechanism as cell parts and processes gradually deteriorated. Now we 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. Scientists also have been able to isolate pluripotent 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 questions and many more will determine the limits of the therapeutic potential of ESCs and ASCs. Only when we understand the precise mix of factors controlling proliferation and development will we 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) when cultured cells are given the proper mix of nutrients and growth factors. However, the stem cells must be touching each other to 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 is believed to be the first clinical trial in the United States of adult mesenchymal stem cells to repair muscle damaged by heart attack.

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. 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.

Scientists had assumed a specialized animal cell could not revert to the unspecialized status it relinquished in the first few days after the fertilized egg began to divide. (Interestingly, specialized plant cells retain the potential to de-specialize.) They assumed a gene turned off during the differentiation process could not simply be activated. The birth of Dolly proved that assumption was incorrect. In a procedure known as *somatic cell nuclear transfer*, 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 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. Because we have learned how to generate ESCs containing undifferentiated genetic material from adult cells for some animals, it is likely we could develop techniques for using human patients' own genetic material to develop replacement cells and tissues.

Others have found that differentiated blood cells, when starved, revert to a stem cell-like condition. With the proper coaxing, scientists 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, which 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. Continued progress in this area of de-differentiation and re-differentiation could some day obviate the need for ESCs in research.

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 of one another. To truly understand gene function, we need to monitor the activity of many genes simultaneously. Microarray technology provides this capability.

Microarray Technology

Researchers can now gain a richer appreciation of gene function because microarray technology allows them to monitor the expression of hundreds or thousands of genes at one time. Recently, 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 that live in environments contaminated with pollutants to that of others that live in pristine environments to identify genes that break down environmental contaminants.

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 chain reaction and consists of a complex cascade of events caused by 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 specific genes in cells, we gain valuable information about the role a given gene plays 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 this 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, developed 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, we should be able to develop animal disease models for many more species.

Putting the Pieces Together: 'Omics'

Biotech's powerful research tools have set the 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 the 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 Pro-

gram 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 that are 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” 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, discovering genes and mapping them 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, but, rather 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 in Arizona 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

Each cell produces 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 Human Proteome Organization estimates that since a human gene is able to code for potentially thousands of proteins, researchers could ultimately establish the genesis of at least one million proteins in the human proteome.

Genes exert their effects through proteins; gene expression is protein production. Ultimately, we must combine structural genomics, functional genomics and proteomics to fully comprehend the relationship between genes, protein production and traits. And yet, proteomics presents researchers with challenges more numerous and more difficult than those encountered in genomics research.

The structure of a protein molecule is much more complicated than the DNA molecule, which is a linear molecule composed of only four randomly repeating

subunits (nucleotides). Proteins, which consist of a chain of up to 22 randomly repeating subunits (amino acids), wind into complicated, intricate shapes, and 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 are not clear on the rules that govern the folding process. Therefore, using the amino acid sequence to predict protein shape and, through this, protein functionality is beyond our current capabilities.

There are thousands of proteins that differ greatly from one another, even within the same individual, but DNA molecules are remarkably similar. In addition, unlike the unvarying genome, an organism's proteome is so dynamic that an almost infinite variety of protein combinations exists. The genome is largely constant, irrespective of cell type and age, but 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.

The genome is largely constant, irrespective of cell type and age, but the proteome varies from one cell type to the next, from one year to the next, and even from moment to moment.

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 waxing and waning protein production.
- discovering how a protein interacts with other proteins within the cell and from outside the cell.

BIOINFORMATICS TECHNOLOGY

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 computational tools provided by 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 of processes and pathways to elucidate the full complexity of the interactions that occur in biological systems. Only with iterative biosimulations generated by computers 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 be increasingly focused on systems and pathways, not single molecules or single genes. Bioinformatics technology will be an essen-

tial component of 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. In 2002, researchers at Stony Brook University synthesized the polio virus. Three years later, the 1918 pandemic flu virus was synthesized at the Armed Forces Institute of Pathology.

On a more positive note, 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.

Product Development Applications

Just understanding biological systems in health and disease is not enough. 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. What is more, biotechnology is creating the tools to pinpoint the winning compounds far earlier in the process.

For example, because we had long known the amino acid sequences of insulin and growth hormone, we began commercial production of recombinant versions relatively soon after we first used recombinant DNA technology to genetically change microbes. 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 prod-

ucts 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

- diagnostic tests 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.
- diagnostics for microbial contaminants in food products or donated blood.
- tests for drug-resistant mutants 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 basis of high blood cholesterol and diabetes, as well as the molecular mechanism of action of the statins, leads many researchers to believe that the statins, which were designed to reduce cholesterol levels, might also help people with diabetes.

The benefits of 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 in the process that is malfunctioning 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 the genes and their protein products involved in diseases makes finding useful molecules more rational than trial and error—hence the phrase *rational drug design*.

Having structure and function information about the genes and their protein products 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 also gives us multiple targets to monitor, modulate or block; every step in a complex sequential process is a possible point of intervention. Knowing the molecular player associated with each step also allows us to focus strategically on the malfunctioning points in a pathway to correct the problem. As a result, we can target products to problems more accurately.

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.

Using our knowledge of genomics and proteomics, we 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 can 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 will provide measures of product efficacy that can be assayed 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 the therapeutic protein target or developing transgenic animal models of human diseases that closely resemble the pathophysiology of human diseases, the results from clinical trials should be more applicable to human systems. As a result, companies can identify safe and effective product candidates much earlier in the product development process.

The biotechnologies can also improve profitability by shortening the product development process because a single technology might be used at many steps in the 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 that therapeutic compound during scale-up.

Targeted Products

We have already described the value detailed information about cell differentiation holds for advances in tissue engineering and regenerative medicine. Without this information, regenerative medicine would have little future. Similar scenarios apply to all cell processes. 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 controlling these problems can be targeted to any of the molecules or cell structures involved in these 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 will not affect a disease that has moved beyond that stage. Some disease processes leave molecular footprints as they go from one stage to the next. Knowing the molecular details allows physicians to diagnose how far the disease has progressed and design an appropriate therapy.

Some diseases also vary in aggressiveness. For example, some forms of breast cancer are more aggressive than others and require different therapeutic approaches. By identifying the unique molecular markers or different types of cancer, we help physicians choose the correct treatment.

Health-Care Applications

B iotechnology 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 treating and preventing diseases. In human health care, biotechnology products include quicker and more accurate diagnostic tests, therapies with fewer side effects and new and safer vaccines.

Diagnostics

W e can now detect many diseases and medical conditions more quickly and with greater accuracy because of new, biotechnology-based diagnostic tools. A familiar example of these benefits 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 almost 1,000 such tests, according to genetests.org. Many of those tests 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 costs of diagnostics in many cases. A blood test developed through biotechnology measures low-density lipoprotein ("bad" cholesterol) in one test, without fasting. We now use biotechnology-based tests to diagnose certain cancers, such as prostate and ovarian cancer, by taking a blood sample, eliminating the need for invasive and costly surgery.

In addition to diagnostics that are cheaper, more accurate and quicker than previous tests, biotechnology is allowing us to diagnose diseases earlier in the disease process, which greatly improves a patient's prognosis. Proteomics researchers are discovering molecular markers that indicate incipient diseases before visible cell changes or disease symptoms appear. Soon physicians will have access to tests for detecting these biomarkers before the disease begins.

The wealth of genomics information now available will greatly assist doctors in early diagnosis of hereditary 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 a predisposition to diseases, such as various cancers, osteoporosis, emphysema, type II diabetes and asthma, giving patients an opportunity to prevent the disease by avoiding triggers such as diet, smoking and other environmental factors.

Biotechnology-based diagnostic tests are not only altering disease diagnosis but also improving the way health care is provided. Many tests are portable, so physicians conduct the tests, interpret results and decide on treatment literally at the patient's bedside. In addition, because many of these diagnostic tests are based on color changes similar to a home pregnancy test, the results can be interpreted without technically trained personnel, expensive lab equipment or costly facilities, making them more available to poorer communities and people in developing countries.

Physicians will someday be able to immediately profile an infection being treated and, based on the results, choose the most effective antibiotics. But the human health benefits of biotechnology detection methodologies go beyond disease diagnosis. For example, biotechnology detection tests screen donated blood for the pathogens that cause AIDS and hepatitis.

Therapeutics

B iotechnology will make possible improved versions of today's therapeutic regimes as well as innovative treatments that would not be possible without these new techniques. Biotechnology therapeutics approved by the U.S. Food and Drug Administration (FDA) to date are used to treat many diseases, including leukemia and other cancers, anemia, cystic fibrosis, growth deficiency, rheumatoid arthritis, hemophilia, hepatitis, genital warts, and transplant rejection.

The therapies discussed below share a common foundation. All make use of biological substances and processes designed by nature. Some use the human body's own tools for fighting infections and correcting problems. Others are natural products of plants and animals. The large-scale manufacturing processes for producing therapeutic bio-

logical substances also rely on nature's molecular production mechanisms.

Here are just a few examples of the types of therapeutic advances biotechnology now makes feasible.

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, we 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 a particularly efficient at mopping up free radicals known to encourage tumor growth. Byetta™ (exenatide), an incretin mimetic, 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.

REPLACING MISSING PROTEINS

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 the missing proteins. Replacement protein therapies include

- factor VIII—a protein involved in the blood-clotting process, lacked by some hemophiliacs.

- insulin—a protein hormone that regulates blood glucose levels. Diabetes results from an inadequate supply of insulin.

USING GENES TO TREAT DISEASES

Gene therapy presents an opportunity using DNA, or related molecules such as RNA, to treat diseases. For example, rather than giving daily injections of missing proteins, 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 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 circumvent this problem, scientists are investigating ways to use cell culture to increase the number of patients who might benefit from one organ donor. Liver cells grown in culture and implanted into patients kept them alive until



a liver became available. In one study of patients with type 1 diabetes, researchers implanted insulin-producing cells from organ donors into the subjects' livers. Eighty percent of the patients required no insulin injections one year after receiving pancreatic cells; after two years, 71 percent had no need for insulin injections. In another study, skeletal muscle cells from the subject repaired damage to cardiac muscle caused by a heart attack.

Drugs for suppressing the immune response must be given if the transplanted cells are from someone other than the patient. Researchers are devising new ways to keep the immune system from attacking the transplanted cells. One method being used 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.

STIMULATING THE IMMUNE SYSTEM

The immune system is made up of different branches, each containing different types of "soldiers" that interact with each other in complex, multifaceted ways.

For example, the *cytokine branch*, which stimulates other immune system branches, includes the interleukins, interferons and colony-stimulating factors—all of which are proteins. Because of biotechnology, these proteins can now be produced in sufficient quantities to be marketed as therapeutics. Small doses of interleukin-2 have been effective in treating various cancers and AIDS, while interleukin-12 has shown promise in treating infectious diseases such as malaria and tuberculosis.

Researchers can also increase the number of a specific type of cell, with a highly specific function, from the *cellular branch* of the immune system. Under certain conditions, the immune system may not produce enough of the cell type a patient needs. Cell culture and natural growth factors that stimulate cell division allow researchers to provide or help the body create the needed cell type.

Cancer vaccines that help the immune system find and kill tumors have also shown therapeutic potential. Unlike other vaccines, cancer vaccines are given after the patient has the disease, so they are not preventative. They work by intensifying the reactions between the immune system and tumor. Despite many years of research, cancer vaccines have not yet emerged as a viable strategy to fight cancer. Nonetheless, researchers are optimistic that this kind of approach to battling cancer would be a major improvement over the therapies used today.

SUPPRESSING THE IMMUNE SYSTEM

In organ-transplant rejections and autoimmune diseases, suppressing our immune system is in our best interest. Currently we are using monoclonal antibodies to suppress, very selectively, the type of cell in the immune system responsible for organ-transplant rejection and autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis. Patients given a biotechnology-based therapeutic often show significantly less transplant rejection than those given cyclosporin, a medicine that suppresses all immune function and leaves organ-transplant patients vulnerable to infection.

Inflammation, another potentially destructive immune system response, can cause diseases, such as ulcerative colitis. Two cytokines, interleukin-1 and tumor necrosis factor, stimulate the inflammatory response, so a number of biotechnology companies are investigating therapeutic compounds that block the actions or decrease production of these cytokines.

XENOTRANSPLANTATION

Organ transplantation provides an especially effective treatment for severe, life-threatening diseases of the heart, kidney and other organs. According to the United Network of Organ Sharing (UNOS), in the United States more than 92,000 people were on organ waiting lists as of May 19, 2006.

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 non-human 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 needs close attention. However, a 1999 study of 160 people who had received pig cells as part of treatments showed no signs of ill health related to this exposure. In addition, scientists have succeeded at deleting the gene that triggers immune activity from a type of pig that cannot be infected with the virus that causes the most concern.

USING BIOPOLYMERS AS MEDICAL DEVICES

Nature has also provided us with biological molecules that can serve as useful medical devices or provide novel methods for 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 man-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 healthcare, making it safer, more cost-effective and, most importantly, more clinically effective.

Pharmacogenomics is a key term, referring to the use of information about the genome to develop drugs. *Pharmacogenetics* 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.

This concept of personalized medicine—also called targeted therapy—is beginning to have a powerful impact on research and treatment, especially in cancer.

CANCER

The biotech breast cancer drug Herceptin® 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®, Tarceva®, Gleevec® and

Campath®, 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 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 900 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 National Institutes of Health 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 from this family that is analyzed by this test, called cytochrome P4502D6, plays an important role in the body's ability to metabolize some commonly prescribed drugs including antidepressants, anti-psychotics, 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®, 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 African Americans. Further testing confirmed those results.

Although BiDil® thus far is the only drug to win a race-based approval, it's far from unique in its differential 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®, 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 non-Hispanic white patients (19 percent vs. 52 percent response rate), according to a recent study in the *New England Journal of Medicine*.

One such 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

Biototechnology permits the use of 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 bio-compatible 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 that maintains patients with acute renal failure until the injured kidney repairs itself. A group of patients with only a 10 to 20 percent probability of survival regained normal kidney function and left the hospital in good health because the hybrid kidney prevented the events that typically follow kidney failure: infection, sepsis and multi-organ failure. 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. In addition to carrying out these expected metabolic functions, the cells in the hybrid kidney also responded to signals produced by the patient's other organs and tissues.



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 production by 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 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 and 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 vac-

cines 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 also increases the amount of vaccine that can be manufactured because biotechnology vaccines can be made without using live animals.

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

Recently 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 and cancer.

Various researchers are developing vaccines against diseases such as diabetes, chronic inflammatory disease, Alzheimer's Disease and cancer.

VACCINE DELIVERY SYSTEMS

Whether the vaccine is a live virus, coat protein or a piece of DNA, vaccine production requires elaborate and costly facilities and procedures. And then there's the issue of injections, which can sometimes be painful and which many patients dislike. Industrial and academic researchers are using biotechnology to circumvent both of these problems with edible vaccines manufactured by plants and animals.

Genetically modified goats have produced a possible malaria vaccine in their milk. 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 (see also "Plant-Made Pharmaceuticals").

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



Plant-Made Pharmaceuticals

The flexibility provided by biotechnology presents many opportunities for using plants in new ways. Advances in biotechnology have made it possible to genetically enhance plants to produce therapeutic proteins essential for the production of a wide range of pharmaceuticals—such as monoclonal antibodies, enzymes and blood proteins.

Plant-made pharmaceutical production is regulated under stringent requirements of the U.S. Department of Agriculture (USDA) and the Food and Drug Administration (FDA). The primary agency that regulates and monitors this technology is USDA's Animal and Plant Health Inspection Service (APHIS). APHIS requires companies to obtain permits for field trials for therapeutic protein production. The agency announced new permit conditions in March 2003. Prior to issuing a test permit, APHIS reviews all plans for seed production, timing of pollination, harvest, crop destruction, shipment, confinement, and the storage and use of equipment. Permits are issued for the importation, interstate movement and field testing of the plants. Field sites are inspected at least five times in a single growing season by APHIS or state officials, with those inspections corresponding to critical times in production, such as preplanting site location evaluation, planting, midseason, harvesting and postharvesting.

In 2004, 16 federal permits for growing plant-made pharmaceuticals were issued in 18 states governing 24 field sites for a total of 277 acres.

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.

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.

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. Using plants to produce therapeutic proteins lowers facility and production costs associated with plant-made pharmaceuticals.

One of the companies developing plant-produced antibodies estimates that this production method is 25 to 100 times less expensive than cell-fermentation methods. Standard fermentation methods can produce 5 to 10 kilograms of a therapeutic antibody per year, while this company reports that it can produce 10,000 kilograms of monoclonal antibodies per year. Using plants as factories to produce therapeutic proteins also enables researchers to develop novel and complex molecular forms that could not normally be grown in 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 healthcare.

BIOLOGICS & DRUGS

Many biotech products 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 (FD&C) Act. Approval of a new drug application (NDA) is required before they can be marketed. (Note: A few biologics, notably insulin and growth hormone, are regulated under the FD&C 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, post-marketing 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 to support 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 109).

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 pre-market 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 (especially those for diseases lacking effective existing treatment), 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 healthcare 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 healthcare 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 healthcare professionals conducting a trial.
- **Institutional review boards**—local oversight groups at hospitals, universities and other healthcare facilities that 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 II diabetes) or it may be narrow (for example, insulin-dependent Type II 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 a 1 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 5 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, the FDA has a goal of acting on a 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

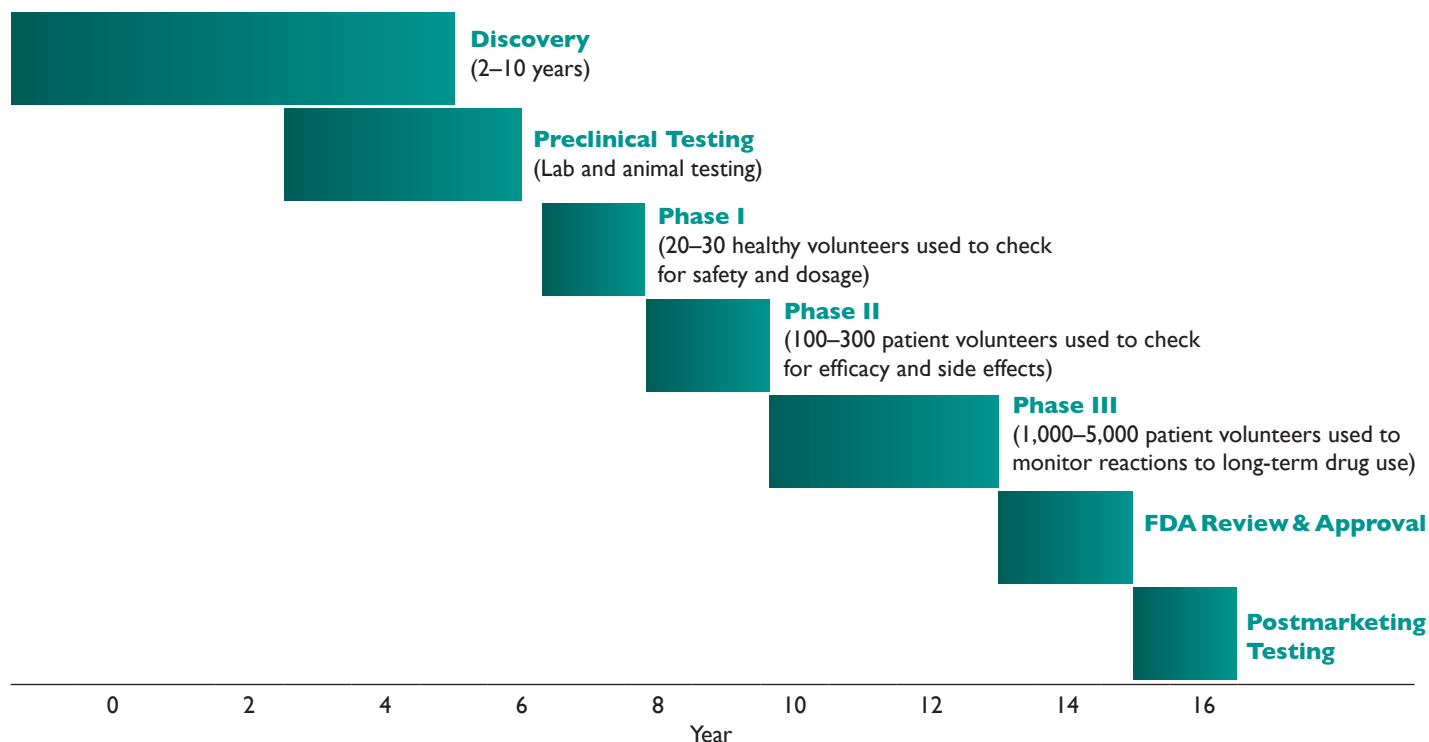
Every approved drug comes with an official product label, in a standardized format, whose contents are

developed by the FDA and the company marketing the drug. The label contents include the approved indication, 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.

The story does not end with approval and labeling. Companies often conduct additional Phase II and III trials in other indications and may apply for approval through a supplemental NDA or BLA. If approved, the new indication is added to the product label.

Companies also conduct Phase IV trials to refine knowledge about the drug. In addition, drug makers are required by law to report adverse events to the FDA, and they are subject to ongoing manufacturing and marketing rules.

Biotech Drug Development Process



Source:
Ernst & Young LLP

Approved Biotechnology Drugs

(Bold text indicates recombinant and monoclonal antibody products.)

Note: This list includes biologics developed by biotechnology companies and pharmaceutical companies, as well as small-molecule products developed by biotechnology companies, and other selected small-molecule or tissue-engineered products. This list covers approvals and new indications from 1982 through 2005. Selected 2006 approvals (through Oct. 31) are also included. Please check bio.org in early 2007 for a complete list of 2006 approvals.

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
Abelcet® (liposomal formulation of amphotericin B)	Enzon	Treatment of invasive fungal infections in patients who are refractory to or intolerant of conventional amphotericin B	Nov 1995
Abraxane™ (paclitaxel, first-in-class protein bound particle)	American Pharmaceutical Partners Inc.	Treats breast cancer after failure of combination therapy for metastatic disease or relapse within six months of adjuvant chemotherapy	Jan 2005
Abreva™ (docosanol)	AVANIR Pharmaceuticals and GlaxoSmithKline, Inc.	Topical treatment of recurrent cold sores (herpes simplex infection)	Jul 2000
Actimmune® (interferon gamma-1b)	InterMune Pharmaceuticals, Inc.	Treatment of chronic granulomatous disease; treatment of severe, malignant osteopetrosis	Dec 1990 Feb 2000
Activase®/Cathflo® Activase® (alteplase; tissue plasminogen activator)	Genentech, Inc.	Treatment of acute myocardial infarction; acute massive pulmonary embolism; acute ischemic stroke within first three hours of symptom onset; dissolution of clots in central venous access devices (Cathflo® Activase®)	Nov 1987 Jun 1990 Jun 1996 Sep 2001
AcuTect™ (technetium Tc-99 apcitide)	Berlex Laboratories	Imaging agent for deep-vein thrombosis	Sept 1998
Adacel™ (tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, absorbed)	Aventis Pasteur Limited	Booster immunization against tetanus, diphtheria and pertussis as a single dose in individuals 11 through 64 years of age	Jun 2005
Adagen® (adenosine deaminase)	Enzon, Inc.	Treatment of severe combined immunodeficiency disease (SCID)	Mar 1990
ADVATE (recombinant clotting factor)	Baxter Healthcare Corp.	Hemophilia A	Jul 2003
Agenerase® (amprenavir)	Vertex Pharmaceuticals and GlaxoSmithKline	HIV	Apr 1999
Albutein® (human albumin)	Alpha Therapeutic Corp.	Treatment of hypovolemic shock; an adjunct in hemodialysis; used in cardiopulmonary bypass procedures	Jan 1986
Aldurazyme® (laronidase)	BioMarin Pharmaceutical Inc. and Genzyme	Mucopolysaccharidosis-I	Apr 2003
Alferon N® (interferon alfa-N3, human leukocyte derived)	Interferon Sciences, Inc.	Treatment of genital warts	Oct 1989
Aloxi (palonosetron HCl)	MGI Pharma Inc. and Helsinn Healthcare SA	Prevention of acute nausea and vomiting in chemotherapy	Jul 2003

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
Alphanate® (human antihemophilic factor)	Alpha Therapeutic Corp.	Treatment of hemophilia A or acquired factor VIII deficiency	Feb 1997
AlphaNine® SD (virus-filtered human coagulation factor IX)	Alpha Therapeutic Corp.	Prevention and control of bleeding in patients with factor IX deficiency due to hemophilia B	Jul 1996
AmBisome® (liposomal amphotericin B)	Gilead Sciences, Inc., and Fujisawa Healthcare	Treatment of fungal infections in patients with depressed immune function and with fever of unknown origin; treatment of cryptococcal meningitis in HIV-infected patients	Aug 1997 Jun 2000
AMEVIVE® (alefacept)	Biogen Idec	Moderate to severe chronic plaque psoriasis	Jan 2003
AMPHOTEC® (lipid-based colloidal dispersion of amphotericin B)	InterMune Pharmaceuticals, Inc.	Second-line treatment of invasive aspergillus infections	Nov 1996
AndroGel™ (testosterone)	Unimed Pharmaceuticals, Inc. (subsidiary of Solvay Pharmaceuticals)	Testosterone-replacement therapy in males with testosterone deficiency	Feb 2000
Angiomax® (bivalirudin)	The Medicines Company	Anticoagulant in conjunction with aspirin in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty; patients undergoing percutaneous intervention	Dec 2000 Jun 2005
Apligraf® (living human skin substitute, from collagen, fibroblasts and keratinocytes)	Organogenesis, Inc., and Novartis Pharmaceuticals Corp.	Treatment of venous leg ulcers; treatment of diabetic foot ulcers	May 1998 Jun 2000
Aranesp™ (darbepoetin alfa)	Amgen	Anemia associated with chronic renal failure; chemotherapy-induced anemia in patients with non-myeloid malignancies	Sep 2001 Jul 2002
Argatroban	Texas Biotechnology Corp. and GlaxoSmithKline	Anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia; anticoagulant for use in patients with or at risk of heparin-induced thrombocytopenia undergoing percutaneous coronary interventions	Jun 2000 Apr 2002
Arranon® (nelarabine injection)	GlaxoSmithKline	A chemotherapy agent for the treatment of patients with T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens	Oct 2005
ATRIPLA™ (efavirenz 600 mg, emtricitabine 200 mg, tenofovir disoproxil fumarate 300 mg)	Gilead Sciences and Bristol-Myers Squibb Co.	Triple-combination treatment for HIV infection in adults	Jul 2006
AVAGE™ (tazarotene; also marketed as Tazorac®)	Allergan, Inc.	Topical treatment of facial fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentiginos	Oct 2002

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
Avastin™ (bevacizumab)	Genentech	First-line treatment, in combination with 5-fluorouracil, of metastatic colorectal cancer; second-line treatment of metastatic colorectal cancer with 5-fluorouracil-based chemotherapy; use in combination with carboplatin and paclitaxel chemotherapy for first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small-cell lung cancer	Feb 2004 Jun 2006 Oct 2006
AVINZA™ (extended-release morphine sulfate)	Ligand Pharmaceuticals and Elan Corp., plc	Once-daily treatment of moderate to severe pain in patients who require continuous opioid therapy for an extended period of time	Mar 2002
AVONEX® (interferon beta 1-alpha)	Biogen Idec	Treatment of relapsing-remitting forms of multiple sclerosis; treatment after initial multiple sclerosis attack if a brain MRI scan shows abnormalities characteristic of the disease	May 1996 Feb 2003
BeneFix™ (coagulation factor IX)	Wyeth	Treatment of hemophilia B	Feb 1997
Betaseron® (interferon beta 1-B)	Berlex Laboratories (subsidiary of Schering-Plough) and Chiron Corp.	Treatment of relapsing-remitting multiple sclerosis; new labeling includes data from studies in patients with secondary progressive multiple sclerosis, and the indications section reflects Betaseron is indicated for treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations	Aug 1993 Mar 2003
BEXXAR® (tositumomab and tositumomab I-131)	Corixa Corp. and GlaxoSmithKline	CD20-positive, follicular non-Hodgkin's lymphoma refractory to rituximab; CD20-positive relapsed or refractory, low grade, follicular or transformed non-Hodgkin's lymphoma	Jun 2003 Jan 2005
BiDil® (isosorbide dinitrate and hydralazine)	NitroMed Inc.	Fixed-dose combination of hydralazine hydrochloride and isosorbide dinitrate for heart failure in self-identified black patients; first drug approved for a specific racial group	Jun 2005
Bioclote™ (antihemophilic factor)	Aventis Behring	Treatment of hemophilia A for the prevention and control of hemorrhagic episodes; perioperative management of patients with hemophilia A	Dec 1993
BioTropin™ (human growth hormone)	Biotech General	Treatment of human growth hormone deficiency in children	May 1995
Boostrix® (tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, absorbed)	GlaxoSmithKline	Booster immunization against tetanus, diphtheria and pertussis as a single dose in adolescents 10-18 years of age	May 2005
BOTOX® COSMETIC (botulinum toxin type A)	Allergan, Inc.	Cervical dystonia in adults; treatment of strabismus and blepharospasm associated with dystonia; temporary improvement in appearance of moderate to severe glabellar lines (frown lines) in adults 65 or younger; primary axillary hyperhidrosis inadequately managed with topical agents	Dec 1989 Dec 2000 Apr 2002 Jul 2004
Byetta® (exenatide injection, first-in-class incretin mimetic)	Amylin Pharmaceuticals	Treatment for Type II diabetes	Apr 2005

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
Campath [®] (alemtuzumab)	Millennium Pharmaceuticals, Inc., and Berlex Laboratories, Inc.	B-cell chronic lymphocytic leukemia in patients who have been treated with alkylating agents and who have failed fludarabine therapy	May 2001 Oct 2004
Captique [™] Injectable Gel (non-animal stabilized hyaluronic acid)	Genzyme Corp. and Inamed Corp.	Facial wrinkle correction	Nov 2004
Carticel [™] (autologous cultured chondrocytes)	Genzyme	Reconstruction of damaged knee cartilage	Aug 1997
CEA-Scan [®] (acritumomab; technetium- 99 labeled)	Immunomedics, Inc.	Imaging agent for metastatic colorectal cancer	Jun 1996
Ceredase [®] (alglucerase; modified form of beta- glucocerebrosidase)	Genzyme	Treatment of type I Gaucher's disease	Apr 1991
Cerezyme [®] (imiglucerase; recombinant form of beta- glucocerebrosidase)	Genzyme	Treatment of type I Gaucher's disease	May 1994
Cialis [®] (tadalafil)	Lilly ICOS LLC (joint venture of Eli Lilly and Co. and ICOS Corp.)	Erectile dysfunction	Nov 2003
CLOLAR [™] (clofarabine)	Genzyme	Refractory or relapsed acute lymphoblastic leukemia in children	Dec 2004
CNJ-016, Vaccinia Globulin Intravenous (purified antibody for specific vaccinia)	Cangene Corp.	Treatment and/or modification of the following conditions, which are complications resulting from smallpox vaccination: eczema vaccinatum, progressive vaccinia; severe generalized vaccinia; vaccinia infections in individuals who have skin conditions such as burns, impetigo, varicella-zoster, or poison ivy; or in individuals who have eczematous skin lesions because of either the activity or extensiveness of such lesions; aberrant infections induced by vaccinia virus that include its accidental implantation in eyes (except in cases of isolated keratitis), mouth or other areas where vaccinia infection would constitute a special hazard	May 2005
Codeprex [™] Extended-Release Suspension CIII (codeine polistirex/ chlorpheniramine polistirex)	UCB	Cough relief; 12-hour dosing	Jun 2004
Comvax [™] (<i>Haemophilus</i> B conjugate [meningococcal conjugate] and hepatitis B [recombinant] vaccine)	Merck & Co., Inc.	Vaccination against <i>Haemophilus influenzae</i> type B and against all known subtypes of hepatitis B in infants born to HbsAg-negative mothers	Oct 1996
CosmoDerm [™] / CosmoPlast [™] (dermal fillers containing human-based collagen)	Advanced Tissue Sciences Inc. and Inamed Corp.	Wrinkles	Mar 2003

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
CroFab™ (crotalidae polyvalent immune Fab, ovine)	Protherics, plc, and Savage Laboratories (unit of Altana, Inc.)	Rattlesnake antivenom	Oct 2000
Cubicin™ (daptomycin)	Cubist Pharmaceuticals Inc.	Complicated skin and skin structure infections caused by susceptible strains of bacteria; <i>S. aureus</i> bacteremia and endocarditis	Sep 2003 May 2006
CytoGam® (CMV immune globulin IV)	MedImmune, Inc.	Prevention of cytomegalovirus (CMV) in kidney transplant patients; prevention of CMV disease associated with kidney, lung, liver, pancreas and heart transplants	Dec 1998 Apr 1990
DACOGEN™ (decitabine for injection)	MGI Pharma and SuperGen	Myelodysplastic syndromes	May 2006
DaunoXome® (liposomal form of the chemotherapeutic agent daunorubicin)	Gilead Sciences	First-line treatment for HIV-related Kaposi's sarcoma	Apr 1996
Depocyt™ (sustained-release formulation of cytarabine)	SkyePharma and Enzon	Treatment of lymphomatous meningitis	Apr 1999
DepoDur® (morphine sulfate; extended-release liposome injection)	Endo Pharmaceuticals, Inc., and SkyePharma plc	Pain following major surgery	May 2004
Dermagraft® (human-based, tissue-engineered living dermal substitute)	Advanced Tissue Sciences, Inc., and Smith & Nephew, plc	Diabetic foot ulcers	Sep 2001
DigiFab™ (digoxin immune fab [ovine])	Protherics, plc	Digoxin toxicity	Sep 2001
Doxil® (liposomal formulation of doxorubicin hydrochloride)	Alza (subsidiary of Johnson & Johnson)	Second-line therapy for Kaposi's sarcoma in AIDS patients; metastatic carcinoma of the ovary in patients with disease that is refractory to both paclitaxel- and platinum-based chemotherapy regimens	Nov 1995 Jun 1999
ELAPRASE™ (idursulfase)	Shire plc	Hunter syndrome (mucopolysaccharidosis II)	Jul 2006
Elestat™ (epinastine)	Inspire Pharmaceuticals Inc., Allergan Inc. and Boehringer Ingelheim	Prevention of itching associated with allergic conjunctivitis	Oct 2003
Eligard™ (slow-release formulation of leuprolide acetate)	Atrix Laboratories and Sanofi-Synthelabo	Advanced prostate cancer; six-month sustained release formulation	Jan 2002 (additional formulation cleared in Jul 2002) Dec 2004
Elitek® (rasburicase)	Sanofi-Synthelabo	Management of plasma uric acid levels in pediatric chemotherapy patients	Jul 2002
Emtriva™ (emtricitabine)	Gilead Sciences	HIV infection in adults	Jul 2003

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
Enbrel® (etanercept)	Amgen and Wyeth	Treatment of moderate to severely active rheumatoid arthritis in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs; treatment of polyarticular course juvenile rheumatoid arthritis; treatment as a first-line therapy for moderate to severe active rheumatoid arthritis; reduction of signs and symptoms of active arthritis in patients with psoriatic arthritis; ankylosing spondylitis; improvement of physical function in patients with moderately to severely active rheumatoid arthritis; expanded psoriatic arthritis label claiming blockage of progression of structural damage; new indication for the treatment of adults with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy; FDA approved new labeling allowing an indication of induction of major clinical response in patients with rheumatoid arthritis; improving physical function in patients with psoriatic arthritis	Nov 1998 May 1999 Jun 2000 Jan 2002 Jul 2003 Jul 2003 Aug 2003 Apr 2004 Sep 2004 Jun 2005
Engerix-B® (hepatitis B vaccine)	GlaxoSmithKline	Hepatitis B vaccine; adults with chronic hepatitis C infection	Sep 1989 Aug 1998
Epogen® (epoietin alfa)	Amgen	Treatment of anemia associated with chronic renal failure and anemia in Retrovir-treated HIV-infected patients; pediatric use	Jun 1989 Jul 1999
Erbix™ (cetuximab)	ImClone Systems Inc. and Bristol-Myers Squibb	Patients with metastatic colorectal cancer who are refractory to or intolerant of irinotecan; use with radiation therapy for treating advanced squamous cell carcinoma of the head and neck, and as a single agent in advanced disease not responsive to platinum-based treatment	Feb 2004 Mar 2006
ESTRASORB™ (estradiol)	Novavax Inc. and King Pharmaceuticals	Moderate to severe vasomotor symptoms in menopausal women	Oct 2003
Evoclin™ Foam (formerly Actiza™) (clindamycin)	Connetics Corp.	Acne vulgaris	Oct 2004
Exjade® (deferasirox, once-daily oral iron chelator)	Novartis AG	Chronic iron overload due to blood transfusions in adults and children age 2 or older	Nov 2005
Fabrazyme® (agalsidase beta)	Genzyme	Fabry's disease	Apr 2003
FACTIVE® (gemifloxacin)	Oscient Pharmaceuticals	Mild to moderate community-acquired pneumonia and acute bacterial exacerbation of chronic bronchitis; community-acquired pneumonia due to multidrug-resistant <i>Streptococcus pneumoniae</i>	Apr 2003 Jul 2003
FENTORA™ (fentanyl buccal tablet)	Cephalon	Management of breakthrough pain in cancer patients already receiving opioid therapy	Sep 2006
Fertinex™ (urofollitropin)	Serono S.A.	Treatment of female infertility to stimulate ovulation in women with ovulatory disorders and in women undergoing assisted reproductive technologies	Aug 1996
FluMist™ (influenza virus vaccine; live, intranasal)	MedImmune Inc.	Prevention of flu	Jun 2003

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
Fluarix™ (influenza virus vaccine)	GlaxoSmithKline Biologicals	For active immunization of adults 18 years and older against influenza disease caused by influenza virus types A and B	Aug 2005
Focalin™ (dexamethylphenidate hydrochloride)	Celgene Corp. and Novartis Pharmaceuticals Corp.	Attention deficit hyperactivity disorder	Nov 2001
Follistim™ (follitropin beta)	Organon (unit of Akzo Nobel)	Recombinant follicle-stimulating hormone for treatment of infertility; induction of spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism in whom the cause of infertility is not due to primary testicular failure	Sep 1997 Feb 2002
FortaFlex™ (bioengineered collagen matrix)	Organogenesis, Inc., and Biomet, Inc.	Rotator cuff repair	Apr 2002
FORTEO® (teriparatide)	Eli Lilly and Company	Treatment of osteoporosis in postmenopausal women at high risk of fracture, and to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk of fracture	Nov 2002
FORTICAL® Nasal Spray (calcitonin salmon)	Unigene Laboratories Inc.	Nasal Spray treats postmenopausal osteoporosis in women with low bone mass	Aug 2005
FOSRENOL® (lanthanum carbonate)	Shire Pharmaceuticals Group	Reduction of blood phosphate levels in patients undergoing kidney dialysis	Oct 2004
Frova™ (frovatriptan succinate)	Vernalis Group, plc, and Elan Corp., plc	Migraine	Nov 2001
FUZEON™ (enfuvirtide)	Trimeris Inc. and Roche	HIV-1 infection; product granted traditional approval	Mar 2003 Oct 2004
GAMMAGARD® (Immune Globulin Intravenous [Human] Solution)	Baxter HealthCare Corp.	Treatment of primary immunodeficiency disorders associated with defects in humoral immunity	May 2005
Ganite™ (gallium nitrate)	Genta Inc.	Cancer-related hypercalcemia resistant to hydration	Sep 2003
GEM 2IS® (purified recombinant growth factor; recombinant human platelet derived growth factor (rhPDGF-BB), and a synthetic calcium phosphate matrix, beta-tricalcium phosphate)	BioMimetic Therapeutics Inc.	Treatment of periodontal bone defects and associated gingival recession	Nov 2005
GenoTropin® (human somatotropin)	Pfizer	Treatment of growth hormone deficiency in children; growth hormone deficiency in adults; long-term treatment of growth failure in children born small for gestational age who fail to catch up by age 2	Aug 1995 Nov 1997 Jul 2001
Geref® (semorelin acetate)	Serono S.A.	Treatment of growth hormone deficiency in children with growth failure	Oct 1997

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
Gleevec™ (imatinib mesylate)	Novartis Pharmaceuticals Corp.	Chronic myeloid leukemia in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy; treatment of Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal tumors; first-line treatment of adult patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia	May 2001 Feb 2002 Dec 2002
Gliadel Wafer (polifeprosan 20 with carmustine implant)	Guilford Pharmaceuticals, Inc.	Newly diagnosed patients with high-grade malignant glioma as an adjunct to surgery and radiation	Feb 2003
GlucaGen ® (glucagon)	Novo Nordisk	Treatment of severe hypoglycemic reactions in insulin-treated diabetics, and for diagnostic use	Jun 1998
Gonal-F ® (follitropin alfa)	Serono S.A.	Treatment of infertility in women not due to primary ovarian failure; treatment of infertility in men and women	Sep 1998 Jun 2000
Hectoro® Capsules (doxercalciferol)	Bone Care International, Inc.	Secondary hyperparathyroidism patients undergoing chronic renal dialysis; additional indication of secondary hyperparathyroidism that develops in earlier stages of chronic kidney disease prior to dialysis	Jun 1999 Apr 2004
Helixate ® (antihemophilic factor)	Aventis Behring	Factor VIII for treatment of hemophilia A; second-generation factor VIII formulated with sucrose for treatment of hemophilia A	Feb 1994 Jun 2000
Hepsera™ (adefovir dipivoxil)	Gilead Sciences, Inc.	Chronic hepatitis B	Sep 2002
Herceptin ® (trastuzumab)	Genentech, Inc.	Treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein	Sep 1998
Hextend® (hetastarch)	BioTime, Inc.	Plasma volume expander for treatment of hypovolemia during surgery	Mar 1999
Humalog ® (insulin)	Eli Lilly and Company	Treatment of diabetes	Jun 1996
Humate-P® (antihemophilic factor/ von Willebrand factor complex-human)	Aventis Behring	Treatment and prevention of bleeding episodes in hemophilia A adult patients; spontaneous and trauma-induced bleeding episodes in severe von Willebrand disease in adult and pediatric patients, and in mild and moderate von Willebrand disease where use of desmopressin is known or suspected to be inadequate	Apr 1999
Humatrope ® (somatotropin)	Eli Lilly and Company	Treatment of growth hormone deficiency in children; somatotropin deficiency syndrome in adults; long-term treatment of children of short stature (unknown cause)	Aug 1996 Mar 1997 Jul 2003
HUMIRA ™ (adalimumab)	Cambridge Antibody Technology and Abbott Laboratories	Patients with moderately to severely active rheumatoid arthritis who have had insufficient response to one or more traditional disease modifying antirheumatic drugs; expanded indication to include improvement in physical function for adult patients with moderately to severely active RA; reducing signs and symptoms of active arthritis in patients with psoriatic arthritis; reducing signs and symptoms of active ankylosing spondylitis	Dec 2002 Jul 2004 Oct 2005 Jul 2006

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
Humulin® (human insulin)	Eli Lilly and Company	Treatment of diabetes	Oct 1982
Hylaform® (Hylan-B gel)	Genzyme and Inamed	Correction of moderate to severe facial wrinkles and folds	Apr 2004
Hylaform® Plus (Hylan-B gel; large-particle size hyaluronic acid-based dermal filler)	Genzyme and Inamed	Correction of moderate to severe facial wrinkles and folds	Oct 2004
Hylenex™ (recombinant human hyaluronidase)	Halozyme Therapeutics Inc.	Adjuvant agent to increase the absorption and dispersion of other injected drugs	Dec 2005
Imagent® (perflexane lipid microspheres)	Alliance Pharmaceutical Corp., Cardinal Health, Inc., and InChord Communications, Inc.	Imaging agent for use in echocardiography	Jun 2002
Increlex™ (mecasermin)	Tercica Inc. and Genentech Inc.	Long-term treatment for growth failure in children with severe primary IGF-I deficiency	Aug 2005
Infergen® (interferon alfacon-1)	InterMune Pharmaceuticals, Inc., and Amgen	Treatment of hepatitis C (HCV) in patients 18 years or older with compensated liver disease who have anti-HCV serum antibodies and/or the presence of HCV RNA; subsequent treatment of HCV-infected patients who have tolerated an initial course of interferon therapy	Oct 1997 Dec 1999
INFUSE™ Bone Graft/LT-CAGE™ (device utilizing recombinant human bone morphogenetic protein [rhBMP-2])	Wyeth and Medtronic Sofamor Danek	For use in spinal fusion surgery to treat certain types of spinal degenerative disease; acute, open tibia shaft fractures in adults	Jul 2002 Apr 2004
INTEGRA® Dermal Regeneration Template (bilayer membrane system for skin replacement)	Integra LifeSciences Holding Corp. and Ethicon, Inc. (a unit of Johnson & Johnson)	Treatment of full-thickness and deep partial-thickness burns; repair of scar contractures	Mar 1996 Apr 2002
Integrilin™ (eptifibatid for injection)	Millennium Pharmaceuticals and Schering-Plough Corp.	Acute coronary syndrome, including both patients managed medically and those undergoing percutaneous coronary intervention; revised prescribing information with new dosing regimen for patients undergoing intracoronary stenting	May 1998 Jun 2001
Intron A® (alpha-interferon)	Schering-Plough Corp.	Treatment of hairy cell leukemia; genital warts; AIDS-related Kaposi's sarcoma; non-A, non-B hepatitis; hepatitis B; chronic malignant melanoma; extended therapy for chronic viral hepatitis C; treatment for follicular lymphoma in conjunction with chemotherapy; treatment of hepatitis B in pediatric patients	Jun 1986 Jun 1988 Nov 1988 Feb 1991 Jul 1992 Dec 1995 Mar 1997 Nov 1997 Aug 1998
IPLEX™ (mecasermin rinfabate [rDNA origin])	Insmad Inc.	Treatment of growth failure in children with severe primary IGF-I deficiency (primary IGF) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH	Dec 2005
ISTOLOL™ (timolol)	ISTA Pharmaceuticals and Senju Pharmaceutical Co.	Glaucoma	Jun 2004

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
Kepivance (palifermin)	Amgen	Severe oral mucositis in cancer patients with hematologic blood cancers undergoing high-dose chemotherapy, with or without radiation, followed by a bone marrow transplant	Dec 2004
Kineret™ (anakinra)	Amgen	Moderately to severely active rheumatoid arthritis in adult patients who have failed disease-modifying antirheumatic drugs	Nov 2001
Kogenate®FS (antihemophilic factor)	Bayer Corp.	Factor VIII for treatment of hemophilia A; second-generation factor VIII formulated with sucrose for treatment of hemophilia A	Sep 1989 Jun 2000
Lantus® (insulin glargine)	Sanofi Aventis	Biosynthetic basal insulin for adult and pediatric patients with type 2 diabetes	Apr 2000
Leukine® (granulocyte macrophage colony-stimulating factor)/ Leukine® Liquid	Berlex Laboratories	Treatment of autologous bone marrow transplantation; treatment of white blood cell toxicities following induction chemotherapy in older patients with acute myelogenous leukemia; for use following allogenic bone marrow transplantation from HLA-matched related donors; for use mobilizing peripheral blood progenitor cells and for use after PBPC transplantation; (Leukine Liquid) ready-to-use formulation in a multidose vial	Mar 1991 Sep 1995 Nov 1995 Dec 1995 Nov 1996
Leustatin™ (cladribine or 2-CDA)	Ortho Biotech, Inc. (subsidiary of Johnson & Johnson)	First-line treatment of hairy cell leukemia	Mar 1993
Levemir® (insulin detemir [rDNA origin] injection)	Novo Nordisk	Treatment of diabetes mellitus (Type I and Type II); for use in children	Jun 2005 Oct 2005
Lexiva™ (fosamprenavir)	Vertex Pharmaceuticals Inc. and GlaxoSmithKline	HIV infection	Oct 2003
LUCENTIS™ (ranibizumab injection)	Genentech	Wet age-related macular degeneration	Jun 2006
LUNESTA™ (formerly Estorra) (eszopiclone)	Sepracor, Inc.	Insomnia	Dec 2004
Luveris® (lutropin alfa for injection)	Serono	For concomitant use with Gonal-f® (follitropin alfa for injection) for stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound luteinizing hormone deficiency	Oct 2004
Luxiq™ (betamethasone)	Connetics Corp.	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses of the scalp	Feb 1999
LYMERix™ (recombinant OspA lipoprotein)	SmithKline Beecham Biologicals (subsidiary of GlaxoSmithKline)	Prevention of Lyme disease	Dec 1998
Macugen® (pegaptanib sodium injection)	Eyeteq Pharmaceuticals, Inc. and Pfizer	Neovascular (wet) age-related macular degeneration	Dec 2004

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
Menactra™ (Meningococcal Polysaccharide [Serogroups A, C, Y and W-135] Diphtheria Toxoid Conjugate Vaccine)	Sanofi Pasteur	For active immunization of adolescents and adults 11-55 years of age for the prevention of invasive meningococcal disease caused by <i>Neisseria meningitidis</i> serogroups A, C, Y and W-135.	Jan 2005
Metadate® CD (bi-phasic release formulation of methylphenidate)	UCB	Attention deficit hyperactivity disorder	Apr 2001
Metvixia (developed under trade name Metvix®) (methyl aminolevulinate)	PhotoCure ASA and Galderma SA	Photodynamic treatment of actinic keratosis	Jul 2004
Mitozytrex (MitoExtra™ proprietary version of mitomycin)	SuperGen, Inc.	Disseminated adenocarcinoma of the stomach or pancreas	Nov 2002
Mylotarg™ (gemtuzumab ozogamicin)	UCB and Wyeth	Human antibody linked to calicheamicin (chemotherapeutic) for treatment of CD33 positive acute myeloid leukemia in patients 60 and older in first relapse who are not considered candidates for cytotoxic chemotherapy	May 2000
Myobloc™ (botulinum toxin type B)	Elan Corp.	Treatment of cervical dystonia	Dec 2000
Myozyme® (alglucosidase alfa)	Genzyme	Pompe disease	Apr 2006
Naglazyme™ (galsulfase)	BioMarin Pharmaceuticals	Enzyme replacement therapy for mucopolysaccharidosis VI (MPS VI)	May 2005
Nabi-HB™ (hepatitis B immune globulin–human)	Nabi Pharmaceuticals	Treatment of acute exposure to HbsAg, perinatal exposure of infants born to HbsAg-positive mothers, sexual exposure to HbsAg-positive persons and household exposure of infants to persons with acute hepatitis B	Mar 1999
NAMENDA™ (memantine)	Neurobiological Technologies Inc. and Forest Laboratories	Moderate to severe Alzheimer's disease	Oct 2003
Natrecor® (nesiritide)	Scios (unit of Johnson & Johnson)	Acutely decompensated congestive heart failure with shortness of breath at rest or with minimal activity	Aug 2001
Neulasta™ (pegfilgrastim)	Amgen	Reduction of incidence of infection as manifested by febrile neutropenia in non-myeloid cancer patients receiving certain chemotherapies	Jan 2002
Neumega® (oprelvekin)	Wyeth	Prevention of severe chemotherapy-induced thrombocytopenia in cancer patients	Nov 1997
Neupogen® (filgrastim)	Amgen	Treatment of chemotherapy-induced neutropenia; bone marrow transplant accompanied by neutropenia; severe chronic neutropenia; autologous bone marrow transplant engraftment or failure; mobilization of autologous PBPCs after chemotherapy	Feb 1991 Jun 1994 Dec 1994 Dec 1995 Apr 1998

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
NeuroSpec™ (formerly LeuTech®) (technetium [^{99m} Tc] fanolesomab)	Palatin Technologies and Mallinckrodt Imaging (Tyco Healthcare)	Diagnosis of appendicitis in patients with equivocal signs	Jul 2004
Nexavar® (sorafenib, tablets)	Onyx Pharmaceuticals Inc. and Bayer Pharmaceuticals Inc.	For patients with advanced renal cell carcinoma	Dec 2005
Norditropin® (somatropin)	Novo Nordisk	Treatment of growth hormone deficiency in children	May 1995
Novantrone® (mitoxantrone)	Amgen	Treatment of acute nonlymphocytic leukemia; hormone refractory prostate cancer; secondary progressive multiple sclerosis	Dec 1987 Nov 1996 Feb 2000
Novolin® (insulin); Novolin L® (insulin; zinc suspension); Novolin R® (insulin, regular); Novolin® 70/30 (70% insulin isophane suspension and 30% regular insulin); Novolin N® (insulin; isophane suspension)	Novo Nordisk	Treatment of diabetes	Oct 1982 Jun 1991 (Novolin® L, R and 70/30) Jul 1991 (Novolin® N)
NovoLog® (insulin aspart)	Novo Nordisk	Insulin analog for adults with diabetes mellitus; for pump therapy in diabetes	May 2000 Dec 2001
NovoSeven® (coagulation factor VIIa)	Novo Nordisk	Treatment of bleeding episodes in hemophilia A or B patients with inhibitors to factor VIII or factor IX; bleeding episodes in patients with factor VII deficiency	Mar 1999 Jul 2005
Nuflexxa™ (1% sodium hyaluronate)	Savient Pharmaceuticals, Inc.	Pain associated with osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics	Dec 2004
Nutropin®/ Nutropin AQ® (somatropin)	Genentech, Inc.	Treatment of growth hormone deficiency in children; growth hormone deficiency in adults; growth failure associated with chronic renal insufficiency prior to kidney transplantation; short stature associated with Turner Syndrome; to improve spine bone mineral density observed in childhood-onset adult growth hormone- deficient patients and to increase serum alkaline phosphatase; long-term treatment of idiopathic short stature	Nov 1993 Jan 1994 Jan 1996 Dec 1996 Dec 1999 Jul 2005
Nutropin Depot™ (sustained-release formulation of somatropin)	Alkermes, Inc., and Genentech, Inc.	Growth hormone deficiency	Dec 1999
OLUX® Foam (clobetasol propionate)	Connetics Corp.	Short-term topical treatment of moderate to severe dermatoses of the scalp; short-term topical treatment of mild to moderate plaque-type psoriasis of non-scalp regions excluding the face and intertriginous areas	May 2000 Dec 2002

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
Oncaspar® (PEG-L-asparaginase)	Enzon, Inc., and Sanofi Aventis	Treatment of acute lymphoblastic leukemia in patients who are hypersensitive to native forms of L-asparaginase; use as part of first-line treatment regimen in acute lymphoblastic leukemia	Feb 1994 Jul 2006
Ontak ® (denileukin diftitox)	Ligand Pharmaceuticals, Inc.	Treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the interleukin-2 receptor	Feb 1999
Oracea™ (capsule formulation of doxycycline)	CollaGenex Pharmaceuticals	Rosacea	May 2006
Orapred ODT™ (prednisolone sodium phosphate tablets)	BioMarin Pharmaceutical and Alliant Pharmaceuticals	Inflammation and asthma indications	Aug 2006
OrCel™ (composite cultured skin; bi-layered cellular matrix)	Ortec International, Inc.	For patients with recessive dystrophic epidermolysis bullosa undergoing hand reconstruction surgery; treatment of donor site wounds in burn victims	Feb 2001 Aug 2001
Orencia ™ (abatacept, fully human soluble fusion protein)	Bristol-Myers Squibb Company	Reducing signs and symptoms of rheumatoid arthritis	Dec 2005
Orfadin® (nitisinone)	Swedish Orphan International AB and Rare Disease Therapeutics, Inc.	Hereditary tyrosinemia type I	Jan 2002
Orthoclone OKT3 ® (muromomab-CD3)	Ortho Biotech, Inc. (subsidiary of Johnson & Johnson)	Reversal of acute kidney transplant rejection	Jun 1986
Orthovisc® (high-molecular-weight hyaluronan)	Anika Therapeutics, Inc., and Ortho Biotech Products LP	Pain associated with osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics	Feb 2004
Ovidrel® (human chorionic gonadotropin)	Serono S.A.	Treatment of infertility in women	Sep 2000
Pacis® (live attenuated <i>Bacillus Calmette-Guerin</i>)	Shire BioChem, Inc., (subsidiary of Shire Pharmaceuticals Group, plc) and UroCor, Inc.	Bladder cancer immunotherapy	Mar 2000
Panretin® (alitretinoin)	Ligand Pharmaceuticals, Inc.	The topical treatment of cutaneous lesions of patients with AIDS-related Kaposi's sarcoma	Feb 1999
Pediarix ™ (diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B [recombinant] and inactivated polio-virus vaccine combined)	GlaxoSmithKline	Prevention of diphtheria, tetanus, pertussis, hepatitis B and polio	Dec 2002
Pegasys ® (peginterferon alfa-2a)	Roche and Nektar Therapeutics, Inc.	Chronic hepatitis C patients with compensated liver disease who have not been previously treated with alpha interferon; combination therapy with Ribavirin in patients with chronic hepatitis C who have compensated liver disease and have not been previously treated with alpha interferon; use in combination with Ribavirin to treat chronic hepatitis C in patients with HIV	Oct 2002 Dec 2002 Feb 2005

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
PEG-Intron™ (pegylated version of interferon alfa-2b)	Enzon, Inc., and Schering-Plough Corp.	Monotherapy for chronic hepatitis C; combination therapy with Rebetol for treatment of hepatitis C in patients with compensated liver disease	Jan 2001 Aug 2001
PHOTOFRIN® PDT (porfimer sodium)	Ligand Pharmaceuticals, Inc.	Palliative treatment of totally and partially obstructing cancers of esophagus; ablation of high-grade dysplasia in Barrett's esophagus patients who do not undergo esophagectomy	Nov 1995 Aug 2003
Plenaxis™ (abarelix)	Praecis Pharmaceuticals Inc.	Palliative treatment of men with advanced symptomatic prostate cancer under certain conditions	Nov 2003
Prandin™ (repaglinide)	Novo Nordisk	Type 2 diabetes	Dec 1997
Prenar® (pneumococcal 7-valent conjugate vaccine [diphtheria CRM-197 protein])	Wyeth	Vaccine for infants and toddlers, 12–15 months, to prevent invasive pneumococcal disease; immunization of infants and toddlers against otitis media caused by vaccine serotypes	Feb 2000 Oct 2002
PRIALT® (ziconotide intrathecal infusion)	Elan Corp. plc	Management of severe chronic pain in patients for whom intrathecal therapy is warranted and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies or IT morphine	Dec 2004
Procrit® (epoietin alfa)	Ortho Biotech, Inc. (subsidiary of Johnson & Johnson)	Treatment of anemia in AZT-treated HIV-infected patients; anemia in cancer patients on chemotherapy; for use in anemic patients scheduled to undergo elective noncardiac, nonvascular surgery	Dec 1990 Apr 1993 Dec 1996
Proleukin, IL-2® (aldesleukin)	Chiron Corp.	Treatment of kidney carcinoma; treatment of metastatic melanoma	May 1992 Jan 1998
ProQuad® (measles, mumps, rubella and varicella virus vaccine live)	Merck & Co. Inc.	Measles, mumps, rubella, and varicella in children 12 months to 12 years	Sep 2005
ProstaScint® (indium In 111 capromab pentetide)	Cytogen Corp.	Imaging agent for newly diagnosed patients with biopsy-proven prostate cancer	Oct 1996
Protropin® (somatrem)	Genentech, Inc.	Treatment of growth hormone deficiency in children	Oct 1985
PROVIGIL® Tablets (modafinil)	Cephalon, Inc.	To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy; excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome and shift-work sleep disorder	Dec 1998 Jan 2004
Pulmozyme® (dornase alfa)	Genentech, Inc.	Treatment of mild to moderate cystic fibrosis; advanced cystic fibrosis; pediatric use in infants 3 months to 2 years and children 2 to 4 years old	Dec 1993 Dec 1996 Mar 1998
Quadramet (samarium SM-153 lexidronam)	Berlex Laboratories (subsidiary of Schering-Plough) and Cytogen Corp.	Pain relief in patients with osteoblastic metastatic bone lesions that enhance on radionuclide bone scan	Mar 1997
RAPTIVA™ (efalizumab)	Xoma Ltd. and Genentech	Chronic moderate to severe psoriasis	Oct 2003

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
Rebetron™ (combination of ribavirin and alpha interferon)	Schering-Plough Corp.	Combination therapy for treatment of chronic hepatitis C in patients with compensated liver disease who have relapsed following alpha-interferon treatment; treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with alpha interferon therapy	Jun 1998 Dec 1998
Rebif® (interferon beta 1-a)	Serono S.A., and Pfizer, Inc.	Relapsing forms of multiple sclerosis	Mar 2002
Recombinate® rAHF/ (antihemophilic factor)	Baxter Healthcare Corp.	Blood-clotting factor VIII for the treatment of hemophilia A	Feb 1992
Recombivax HB®/ Recombivax HB Dialysis Formulation (hepatitis B vaccine)	Merck & Company, Inc.	Vaccination against hepatitis B; hepatitis B vaccine for adolescents and high-risk infants; adults; dialysis; pediatrics	Jul 1986 Jan 1987 Jan 1989 Jun 1993
ReFacto® (antihemophilic factor)	Wyeth	Control and prevention of hemophilia A and short-term prophylaxis to reduce bleeding episodes	Mar 2000
Refludan® (lepirudin)	Berlex Laboratories (subsidiary of Schering-Plough)	For anticoagulation in patients with heparin-induced thrombocytopenia and associated thromboembolic disease in order to prevent further thromboembolic complications	Mar 1998
Regranex® Gel (gel becaplermin)	Ortho-McNeil (subsidiary of Johnson & Johnson) and Chiron Corp.	Platelet-derived growth factor treatment of diabetic foot ulcers	Dec 1997
Remicade® (infliximab)	Centocor, Inc. (subsidiary of Johnson & Johnson)	Short-term management of moderately to severely active Crohn's disease including those patients with fistulae; treatment of patients with rheumatoid arthritis who have had inadequate response to methotrexate alone; improving physical function in patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate; reducing signs and symptoms, and inducing and maintaining clinical remission in patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy; reduction of draining enterocutaneous and rectovaginal fistulae and for maintaining fistula closure in patients with fistulizing Crohn's disease; FDA approved expanded label for Remicade in combination with methotrexate as first-line regimen in patients with moderate to severe rheumatoid arthritis; reducing the signs and symptoms of psoriatic arthritis; expanded label to treat ulcerative colitis; pediatric Crohn's disease; inhibiting progression of structural damage and improving physical function in patients with psoriatic arthritis; chronic severe plaque psoriasis in adults	Aug 1998 Nov 1999 Feb 2002 Jun 2002 Apr 2003 Sep 2004 May 2005 Sep 2005 May 2006 Aug 2006 Sep 2006
Remodulin™ (treprostinil sodium)	United Therapeutics Corp.	Treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms to diminish symptoms associated with exercise	May 2002

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
Renagel® Capsules (sevelamer hydrochloride)	Genzyme	Reduction of serum phosphorus in patients with end-stage renal disease (ESRD); reduction of serum phosphorus in hemodialysis patients with end-stage renal disease; FDA approved new labeling showing the product's phosphorous and calcium-phosphorous control are consistent with the National Kidney Foundation's aggressive guidelines	Nov 1998 Jul 2000 Mar 2004
ReoPro™ (abciximab)	Centocor, Inc. (subsidiary of Johnson & Johnson) and Eli Lilly and Company	Reduction of acute blood clot-related complications for high-risk angioplasty patients; reduction of acute blood clot complications for all patients undergoing any coronary intervention; treatment of unstable angina not responding to conventional medical therapy when percutaneous coronary intervention is planned within 24 hours	Dec 1994 Dec 1997
RespiGam® (immune globulin enriched in antibodies against respiratory syncytial virus [RSV])	MedImmune, Inc.	Prevention of respiratory syncytial virus in infants under 2 with bronchopulmonary dysplasia or history of prematurity	Jan 1996
RESTASIS™ (cyclosporine ophthalmic emulsion)	Allergan, Inc.	Chronic dry eye disease in patients whose tear production is presumed to be suppressed due to ocular inflammation	Dec 2002
Retavase™ (reteplase)	Centocor, Inc. (subsidiary of Johnson & Johnson)	Management of acute myocardial infarction in adults	Oct 1996
Revlimid® (lenalidomide)	Celgene Corp.	For the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities; combination use with dexamethasone for treatment of multiple myeloma patients who have received at least one prior therapy	Dec 2005 Jun 2006
RISPERDAL® CONSTA™ (long-acting formulation of risperidone)	Alkermes Inc. and Johnson & Johnson	Schizophrenia	Oct 2003
Rituxan™ (rituximab)	Biogen Idec and Genentech, Inc.	Treatment of relapsed or refractory, low-grade or follicular, CD20-positive B-cell non-Hodgkin's lymphoma; use with methotrexate to reduce signs and symptoms of moderately to severely active rheumatoid arthritis who have inadequately responded to tumor necrosis factor (TNF) antagonist therapies; first-line treatment of diffuse large B-cell, CD20+, non-Hodgkin's lymphoma in combination with anthracycline-based chemotherapy regimens; first-line treatment of previously untreated patients with follicular CD20+, B-cell non-Hodgkin's lymphoma in combination with CVP (cyclophosphamide, vincristine and prednisolone); low-grade CD20+, B-cell NHL in patients with stable disease or who achieve a partial or complete response following first-line treatment with CVP therapy	Nov 1997 Feb 2006 Feb 2006 Sep 2006 Sep 2006

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
Roferon-A® (interferon alfa-2a)	Hoffmann-La Roche, Inc.	Treatment of hairy cell leukemia; AIDS-related Kaposi's sarcoma; chronic phase Philadelphia chromosome-positive chronic myelogenous leukemia; hepatitis C	Jun 1986 Nov 1988 Oct 1995 Nov 1995
Saizen® (human growth hormone)	Serono S.A.	Treatment of growth hormone deficiency in children; replacement of endogenous growth hormone in adults with growth hormone deficiency	Oct 1996 Aug 2004
SANCTURA™ (tropicium chloride)	Indevus Pharmaceuticals, Inc., and Odyssey Pharmaceuticals, Inc., (subsidiary of PLIVA)	Overactive bladder with symptoms of urge urinary incontinence, urgency and urinary frequency	May 2004
Sarafem™ (fluoxetine hydrochloride)	Indevus Pharmaceuticals, Inc., and Eli Lilly and Company	Treatment of premenstrual dysphoric disorder	Jul 2000
SecreFlo™ (synthetic porcine secretin)	Repligen Corp.	Pancreatic assessment; aid in location and cannulation of pancreatic ducts in patients undergoing endoscopic retrograde cholangiopancreatography	Apr 2002 Nov 2002
Sensipar™ (cinacalcet HCl)	NPS Pharmaceuticals and Amgen, Inc.	Secondary hyperthyroidism in chronic kidney disease patients on dialysis; elevated calcium levels in patients with parathyroid carcinoma	Mar 2004
Simulect® (basiliximab)	Novartis Pharmaceutical Corp.	Prevention of acute rejection episodes in kidney transplant recipients; prevention of rejection in combination with triple immunosuppressive therapy in renal transplant; use in pediatric renal transplant; and use of IV bolus injection	May 1998 Mar 2001
SOMAVERT® (pegvisomant)	Nektar Therapeutics and Pfizer	Acromegaly	Mar 2003
Symlin® (pramlintide acetate injection)	Amylin Pharmaceuticals Inc.	Used in conjunction with insulin at mealtime to treat Type I and Type II diabetes in patients who have failed to achieve desired glucose control despite optimal insulin therapy	Mar 2005
SYNAGIS™ (palivizumab)	MedImmune, Inc.	FDA cleared addition of new safety and efficacy data supporting the drug's use in young children with hemodynamically significant congenital heart disease	Jun 1998
Tamiflu™ (oseltamivir phosphate)	Gilead Sciences, Inc., and Hoffmann-La Roche, Inc.	Treatment of most common strains of influenza in adults; prevention of influenza in adolescents and adults; treatment of acute influenza in children 1 year and older	Oct 1999 Nov 2000 Dec 2000
Tarceva™ (erlotinib)	OSI Pharmaceuticals, Inc. and Genentech	Locally advanced or metastatic non-small-cell lung cancer after failure of at least one prior chemotherapy regimen; for use in combination with gemcitabine chemotherapy in patients with pancreatic cancer who have not received previous chemotherapy	Nov 2004 Nov 2005
Targretin® (bexarotene)/ Targretin Gel® (bexarotene)	Ligand Pharmaceuticals, Inc.	Treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy; topical treatment of cutaneous lesions in patients with early-stage cutaneous T-cell lymphoma	Dec 1999 Jun 2000 (Targretin Gel® Formulation)
Taxus™ Express2™ (paclitaxel-eluting coronary stent)	Angiotech Pharmaceuticals, Inc., and Boston Scientific Corp.	Improving luminal diameter in native coronary arteries for treatment of de novo lesions	Mar 2004

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
Thymoglobulin (antithymocyte globulin; rabbit)	Genzyme	Treatment of acute rejection of kidney transplant in conjunction with immunosuppression	Dec 1998
Thyrogen [®] (thyrotropin alfa)	Genzyme	Adjunctive diagnostic tool for serum thyroglobulin (Tg) testing with or without radioiodine imaging in the follow-up of patients with thyroid cancer	Dec 1998
TNKase [™] (tenecteplase)	Genentech, Inc.	Treatment of acute myocardial infarction	Jun 2000
Tracleer [™] (bosentan)	Actelion Ltd.	Pulmonary arterial hypertension with WHO Class III or IV symptoms	Nov 2001
Trisenox [™] (arsenic trioxide)	Cell Therapeutics, Inc.	Treatment of acute promyelocytic leukemia	Sep 2000
Truvada [™] (emtricitabine and tenofovir disoproxil fumarate)	Gilead Sciences	HIV (as part of combination therapy)	Aug 2004
Twinrix [®] (hepatitis A inactivated and hepatitis B [recombinant] vaccine)	SmithKline Beecham Biologicals (unit of GlaxoSmithKline)	Immunization against hepatitis A and B viruses	May 2001
Tygacil [®] (tigecycline injection)	Wyeth	Treatment of complicated skin structure infections and complicated intra-abdominal infections	Dec 2005
TYSABRI [®] (formerly ANTEGREN [®]) (natalizumab)	Biogen Idec and Elan Corp.	Reduction of clinical relapse frequency in relapsing forms of multiple sclerosis; supplemental BLA approved, allowing market reintroduction (following withdrawal in 2005) as monotherapy for relapsing MS	Nov 2004 Jun 2006
Vectibix [™] (panitumumab)	Amgen	Metastatic colorectal cancer	Sep 2006
VELCADE [™] (bortezomib)	Millennium Pharmaceuticals Inc.	Relapsed and refractory multiple myeloma; treatment of multiple myeloma in patients who have received at least one prior therapy	May 2003 Mar 2005
Velosulin ^{® BR} (insulin; buffered formulation)	Novo Nordisk	Diabetes	Jul 1999
Venoglobulin-S [®] (human immune globulin intravenous 5% and 10% solutions)	Alpha Therapeutic Corp.	Treatment of primary immunodeficiencies; idiopathic thrombocytopenic purpura; Kawasaki disease	Nov 1991 Jan 1995
Ventavis [™] Inhalation Solution (iloprost)	CoTherix Inc. and Schering AG	Pulmonary arterial hypertension in patients with NYHA Class III or IV symptoms	Dec 2004
Vidaza [™] (azacitidine)	Pharmion Corp.	Myelodysplastic syndromes (all five subtypes)	May 2004

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
VIGIV, Vaccinia Immune Globulin Intravenous (intravenous immune globulin)	DynPort Vaccine	For the treatment and modifications of aberrant infections induced by vaccinia virus that include its accidental implantation in eyes (except in cases of isolated keratitis), mouth, or other areas where vaccinia infection would constitute a special hazard; eczema vaccinatum; progressive vaccinia; severe generalized vaccinia, and vaccinia infections in individuals who have skin conditions such as burns, impetigo, varicella-zoster, or poison ivy; or in individuals who have eczematous skin lesions because of either the activity or extensiveness of such lesions.	Feb 2005
Viracept® (nelfinavir)	Agouron Pharmaceuticals Inc. (subsidiary of Pfizer)	HIV	Mar 1997
Viread™ (tenofovir disoproxil fumarate)	Gilead Sciences	For use in combination with other antiretroviral agents for treatment of HIV-1 infection	Oct 2001
VISTIDE® (cidofovir injection)	Gilead Sciences Inc.	Treatment of cytomegalovirus retinitis in AIDS patients	Jun 1996
Visudyne™ (verteporfin for injection)	QLT, Inc., and CIBA Vision	Treatment of wet form of age-related macular degeneration; predominantly classic subfoveal choroidal neovascularization due to pathologic myopia (severe nearsightedness)	Apr 2000 Aug 2001
Vitrace® (hyaluronidase for injection; lyophilized, ovine)	ISTA Pharmaceuticals Ltd.	Spreading agent to facilitate dispersion and absorption of other drugs; FDA approved single-use vial	May 2004 Dec 2004
Vitracem™ (fomivirsen)	Isis Pharmaceuticals, Inc., and CIBA Vision	Treatment of cytomegalovirus retinitis in patients with AIDS	Aug 1998
Vivitrol® (naltrexone for extended release injectable suspension)	Alkermes and Cephalon	Monthly injection to treat alcohol dependence	Apr 2006
WelChol™ (colesevelam)	Genzyme	Reduction of elevated low-density lipoprotein (LDL) cholesterol alone or in combination with HMG-CoA reductase inhibitor (statin) in patients with hypercholesterolemia	May 2000
Wellferon® (interferon alfa-n1, lymphoblastoid)	GlaxoSmithKline	Treatment of chronic hepatitis C in patients 18 years of age or older without decompensated liver disease	Mar 1999
WinRho SDF® (Rho[D] immune globulin)	Nabi Biopharmaceuticals	Prevention of Rh isoimmunization in pregnant women and the treatment of thrombocytopenic purpura	Mar 1995
XIFAXAN™ (rifaximin)	Salix Pharmaceuticals Ltd.	Travelers' diarrhea caused by noninvasive strains of E. coli in patients 12 years of age and older	May 2004
Xigris™ (drotrecogin alfa)	Eli Lilly and Company	Severe, life-threatening sepsis	Nov 2001
Xolair® (omalizumab)	Genentech, Tanox Inc. and Novartis Pharmaceuticals	Moderate to severe persistent asthma in adults and adolescents	Jun 2003
Xyrem® (sodium oxybate)	Orphan Medical, Inc.	Cataplexy associated with narcolepsy	Jul 2002
Zavesca® (miglustat)	UCB and Actelion Ltd.	Mild to moderate Type I Gaucher's disease in patients for whom enzyme replacement therapy is not an option	Aug 2003

PRODUCT	COMPANY	APPLICATION (USE)	APPROVAL DATE (FDA)
ZEGERID™ (omeprazole powder for oral suspension)	Santarus	20 mg dose approved for short-term treatment of active duodenal ulcer; for heartburn and other symptoms associated with gastro-esophageal reflux disease (GERD), for the short-term treatment of erosive esophagitis that has been diagnosed by endoscopy, and for the maintenance of healing of erosive esophagitis; 40 mg formulation subsequently approved for reduction of risk of upper gastrointestinal bleeding in critically ill patients and the short-term treatment of benign gastric ulcers; heartburn and other symptoms associated with gastroesophageal reflux disease, as well as for esophagitis and ulcer indications	Jun 2004 Dec 2004 Feb 2006
Zenapax® (daclizumab)	Hoffmann-La Roche, Inc., and Protein Design Labs	Humanized monoclonal antibody for prevention of kidney transplant rejection	Dec 1997
Zevalin™ (ibritumomab tiuxetan)	IDEC Pharmaceuticals Corp.	Relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma	Feb 2002
Zonegran™ (zonisamide)	Elan Corp	Adjunctive therapy in treatment of partial seizures in adults with epilepsy	Mar 2000
Zorbitive™ (human growth hormone)	Serono S.A.	Short bowel syndrome (product previously approved under the trade name Serostim® for AIDS wasting)	Aug 1996 Dec 2003
Zylet™ (loteprednol etabonate and tobramycin ophthalmic suspension)	Pharmos Corp. and Bausch & Lomb	Steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of infection exists	Dec 2004

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 them to better meet our evolving needs. Society's demand for resources provided by plants and animals will increase as the world's population grows. The global population, which numbered approximately 1.6 billion in 1900, has surged to more than 6 billion and is expected to reach 10 billion by 2030. 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 the anticipated population growth.

Biotechnology can help meet the ever-increasing need by increasing yields, decreasing crop inputs such as water and fertilizer, and providing pest control methods that are more compatible with the environment.

Biotechnology can help meet the ever-increasing need by increasing yields, decreasing crop inputs such as water and fertilizer, and providing pest control methods that are more compatible with the environment.

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 characteristics, the earliest agriculturists performed genetic modification to convert wild plants into domesticated crops long before the science of genetics was understood.

As our knowledge of plant genetics improved, we purposefully crossbred plants with desirable traits (or lacking undesirable characteristics) to produce offspring that combine the best traits of both parents. In today's world, 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 takes 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 our crops.

Biotechnology also removes the technical obstacles to moving genetic traits between plants and other organisms. This opens up a world of genetic traits to benefit food 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

The crop production and protection traits agricultural scientists are incorporating with biotechnology are the same traits they have incorporated through decades of crossbreeding and other genetic modification techniques: 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

Just as biotechnology allows us to make better use of the natural therapeutic compounds our bodies produce, it also provides us with more opportunities to partner with nature in plant agriculture.

Through science, we have discovered that plants, like animals, have built-in defense systems against insects and diseases, and we are searching for environmentally benign chemicals that trigger these natural defense mechanisms so plants can better protect themselves.

Biotechnology will also open 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. Because biopesticides act in unique ways, they can control pest populations that have developed resistance to conventional pesticides.

A biopesticide 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 the United States \$1.2 billion in crop damage each year. Bt bacteria used as a biopesti-

cidal spray can eliminate target insects without relying on chemically based pesticides.

Using the flexibility provided by biotechnology, we can transplant the genetic information that makes the Bt bacterium lethal to certain insects (but not to humans, animals or other insects) into plants on which that insect feeds. The plant that once was a food source for the insect now kills it, lessening the need to spray crops with chemical pesticides to control infestations.

The plant that once was a food source for the insect now kills it, lessening the need to spray crops with chemical pesticides to control infestations.

Herbicide Tolerance

Good planting conditions for crops will also sustain weeds that can reduce crop productivity as they compete for the same nutrients the desired plant needs. To prevent this, herbicides are sprayed over crops to eliminate the undesirable weeds. Often, herbicides must be applied several times during the growing cycle, at great expense to the farmer and possible harm to the environment.

Using biotechnology, it is possible to make crop plants tolerant of specific herbicides. When the herbicide is sprayed, it will kill the weeds but have no effect on the crop plants. This lets farmers reduce the number of times herbicides have to be applied and reduces the cost of producing crops and damage to the environment.

Resistance to Environmental Stresses

In addition to the biological challenges to plant growth and development just described, crop plants must contend with 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.

The crossbreeding limitation posed by reproductive compatibility does not impede crop biotechnology; genes found in any organism can be used to improve crop production. As a result, scientists are making great strides in developing crops that can tolerate difficult growing conditions. For example, researchers have genetically modified tomato and canola plants that tolerate salt levels 300 percent greater than non-genetically modified varieties. Other researchers have identi-

fied many genes involved in cold, heat and drought tolerance found naturally in some plants and bacteria. Scientists in Mexico have produced maize and papaya that are tolerant to the high levels of aluminum that significantly impede crop plant productivity in many developing countries.

Increasing Yields

In addition to increasing crop productivity by using built-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. 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. 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. Continuing population growth, urbanization, poverty, inadequate food distribution systems and high food costs impede universal access to the higher yields provided by technological advances in agriculture. In addition, the crops genetically improved by plant breeders who enabled the Green Revolution were large-volume commodity crops, not crops grown solely by small-scale subsistence farmers.

For many farmers in developing countries, especially those in sub-Saharan Africa, the Green Revolution never materialized because its agricultural practices required upfront investments—irrigation systems, machinery, fuel, chemical fertilizers and pesticides—beyond the financial reach of small-scale farmers.

Today's biological agricultural revolution is knowledge intensive, not capital intensive, because its technological advances are incorporated into the crop seed.

Today's biological agricultural revolution is knowledge intensive, not capital intensive, because its technological advances are incorporated into the crop seed. As a result, small-scale farmers with limited resources should benefit. In addition, because of the remarkable flexibility provided by crop biotechnology, crop improvement through genetic modification need no longer be restricted to the large-volume commodity crops that provide a return on industrial R&D investments. A beneficial gene that is incorporated into maize or rice can also be provided to crops grown by subsistence farmers in developing countries because the requirement for plant reproductive compatibility can be circumvented.

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 institu-

tions 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.
- Seibersdorf 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 and 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 their natural resources, lower food prices for consumers and provide income to their small farmers. Even more important, they understand that biotechnology has the potential to

improve existing exports and create new ones, leading to a more diversified economy and increased independence.

But they also know that many of their agricultural problems are unique and can best be solved by local scientists who are familiar with the intricacies of the problems, 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.
- Taiwan opened an extension of the Hsinchu industrial park devoted exclusively to biotechnology. Companies in the park will have access to \$850 million in government research and development funds and \$4 billion in state and private venture capital, plus a wide range of support services including marketing and global patent applications.
- 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 modified crops to benefit from reduced pesticide applications, lower production costs, higher yields and increased income.

ENVIRONMENTAL AND ECONOMIC BENEFITS

Beyond agricultural benefits, products of crop biotechnology offer many environmental and economic benefits. As described above, biotech crops allow us to increase crop yields by providing natural mechanisms of pest control in place of chemical pesticides. These increased yields can occur without clearing additional land, which is especially important in developing countries. In addition, because biotechnology provides pest-specific control, beneficial insects that assist in pest control will not be affected, facilitating the use of integrated pest management. Herbicide-

tolerant crops decrease soil erosion by permitting farmers to use conservation tillage.

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. In the past few years, a number of independent researchers have produced reports documenting these benefits.

According to the National Center for Food and Agricultural Policy's (NCFAP) 2004 report, in 2003 the 11 biotech crop varieties adopted by U.S. growers increased crop yields by 5.3 billion pounds, saved growers \$1.5 billion by lowering production costs, and reduced pesticide use by 46.4 million pounds. Based on increased yields and reduced production costs, growers realized a net economic impact or savings of \$1.9 billion. Three new traits for corn and cotton were introduced in 2003, and the NCFAP study takes into account six biotech crops—canola, corn, cotton, papaya, soybean and squash.

In its report "Conservation Tillage and Plant Biotechnology," the Conservation Tillage Information Center (CTIC) at Purdue University attributes the recent improvements in tillage reduction to the increased use of the herbicide-tolerant varieties produced through biotechnology. CTIC concludes that the increase in conservation tillage associated with herbicide-tolerant crops decreases soil erosion by 1 billion tons of soil material per year, saves \$3.5 billion per year in sedimentations costs and decreases fuel use by 3.9 gallons per acre.

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

- From 1999 to 2000 in China, insecticide usage decreased by 67 percent and yields increased by 10 percent, leading to income gains of \$500 per hectare.
- Extensive field trials in India from 1998 to 2001 demonstrated a 50 percent reduction in insecticide spraying and a 40 percent increase in yields, which equals an increase in income from \$75 to \$200 per hectare.

Small farmers in South Africa gained through a 25 percent yield increase and decreased number of insecticide sprays from 11 to four, reducing pesticide costs by \$45 per acre. The higher cost of Bt seed (up to \$15 per hectare for small farmers) resulted in an average economic advantage of \$35 per hectare.

REGULATION OF CROP BIOTECHNOLOGY

Since combining specific genes from donor and host plants does not alter the basic nature of the host plant, the result of genetic modification is predictable and can be carefully controlled. As with any new variety of food, the developers test extensively for safety, quality and other factors.

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 [OECD] 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) approves the safety of all 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, any product that uses a gene from a peanut, which is a potential allergen, would be subject to testing and labeling requirements. The FDA also has the authority to order unsafe products off the market.

The 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

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

INCREASING PRODUCTIVITY

We are using biotechnology to create disease- and insect-resistant trees and to increase their growth rates.

We are using biotechnology to create disease- and insect-resistant trees and to increase their growth rates. Scientists 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 decrease the pressure on natural forests.

However, developing trees through the use of biotechnology 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 its 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.

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

I. 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.
- 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 transgenics.

A. 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

1. Disease surveillance and food safety: Using DNA to trace meat and animals through the food chain.
2. Enhanced breeding and selection: Developing animals with desirable traits such as greater muscle mass or milk or egg production.
3. Improved animal production efficiency: Creating management systems based on genetic potential.
4. 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. Research is under way to develop tests that can identify breeds in both purebred and mixed-breed animals and to identify genetic predisposition to disease.

B. 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 (AI) 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.

C. TRANSGENIC ANIMALS

A transgenic animal is one that has had genetic material from another species added to its DNA. This breakthrough technology allows scientists to precisely transfer beneficial genes from one species to another. 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. Transgenic 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 Transgenic Animals

Transgenic animals offer a plethora of benefits that will improve consumer health and nutrition, as well as animal welfare and productivity:

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

Animal Welfare & the Environment

By making animal welfare a priority, transgenic technology (as well as other animal biotechnology) offers tremendous potential benefits for animals. Specifically, it can help cut animal mortality and disease, as well as reduce or eliminate painful standard agricultural practices like castration and de-horning.

Transgenic 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.

D. TRANSGENIC 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.

Transgenic 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 and their products are extremely valuable, often fragile, and animal welfare is a priority for everyone working with these animals. Animal-made pharmaceuticals, for example, cannot be produced in sick animals and so every effort must be made to ensure animal welfare.

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. Moreover, the transgenic animals used to produce pharmaceuticals are expressly excluded from use in the food supply.

What's Next?

Biotechnology is providing the tools to make all these benefits an everyday reality for consumers. In addition to food applications, scientists are attempting to modify animals to produce therapeutic proteins to use in treating cancer, heart attacks, hemophilia, and rheumatoid

arthritis, among other diseases. Some are researching the possibility of using these animals to grow transplant organs that can be used when other options have been exhausted. 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.

II. 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 cloning and transgenic 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.
- And the Environmental Protection Agency regulates pesticides and topical products that kill fleas and other parasites.

The Office of Science and Technology Policy is reviewing the regulatory processes for the products of animal biotechnology, seeking coordination among the federal agencies for a science-based, streamlined approach. Little published regulatory guidance exists for many of the biotechnology products being developed.

In 2003, the U.S. Food and Drug Administration's Center for Veterinary Medicine published the draft executive summary of a 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 finalizing the risk assessment and proposing a risk management process. Additionally, studies conducted by the National Academy of Sciences (NAS) and other new research have determined that cloned animals and their products are safe for human consumption.

III. USING BIOTECHNOLOGY TO IMPROVE ANIMAL HEALTH

Healthy animals provide healthy foods. As of July 2003, there were 105 animal biotech products, including bacterins and killed virus vaccines, used in agricultural and companion animals. The animal health industry invests more than \$400 million a year in research and development.

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 transgenic crops designed to meet the dietary needs of different farm animals.
3. Improved livestock productivity through improved animal breeding and disease resistance.

A. 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, 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 (pleuro-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.

B. BETTER FEED FOR ANIMALS FROM TRANSGENIC 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:

- These products are designed to improve the quality of protein, oils or energy availability in the final animal food 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 on new crops to develop feed with edible vaccines for farm animals. In the near future, pigs could be fed transgenic alfalfa that would stimulate immunity to a serious intestinal virus.

C. IMPROVED LIVESTOCK PRODUCTIVITY THROUGH IMPROVED ANIMAL BREEDING AND DISEASE RESISTANCE

Improved animal breeding. Biotechnology plays a growing role in farm animal breeding programs. 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.

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 transgenic 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 knock-out technology and cloning.
- Researchers in Britain are developing chickens using transgenic technology 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 1950's. Livestock cloning is newest tool in the ART toolbox.

Using biotechnology to increase the productivity of livestock is a variation of selective breeding. We select the best individual animals that possess desirable traits; then, instead of breeding the animals, we 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 also uses somatic cell nuclear transfer. Animals that have been cloned for show ring purposes include cattle, pigs, sheep and horses.

D. ADDITIONAL HEALTH APPLICATIONS OF BIOTECHNOLOGY IN ANIMAL AGRICULTURE

The biotechnology industry has proposed additional unique 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* 0157:H7 shedding in feedlot cattle, a further assist toward improved food safety on the farm.

IV. 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:

- A study published in 2005 by the University of Connecticut and Japan's Kagoshima Prefectural Cattle Breeding Development Institute found meat and milk products from cloned cattle are safe for consumption. The results parallel those of two National Academy of Sciences reports in 2002 and 2004.
- 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 beef cattle genome was created. SNP (single nucleotide polymorphism) 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 affect 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.

V. ENVIRONMENTAL AND CONSERVATION EFFORTS THROUGH ANIMAL BIOTECHNOLOGY

A. ENVIRONMENTAL IMPACTS

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 the chance of manure contributing to groundwater contamination in areas that surround livestock farms.

B. ENDANGERED SPECIES CONSERVATION

Biotechnology is providing new approaches for saving endangered species. Reproductive and cloning technologies, as well as medicines and vaccines developed for use in livestock and poultry, can also 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 guar 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.

VI. ANIMAL BIOTECHNOLOGY TO ENHANCE HUMAN HEALTH

Transgenic animal-made antibodies can be produced from animals that have had human antibody genes transferred to them. These animals can then be vaccinated against human diseases and antibodies can be collected from their blood and used for treating diseases in humans.

Animals are often used as models for research as many of the technologies developed for animals can be trans-

ferred to humans. Some of the work being done with animals that will advance human health:

A. 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.

B. "PHARM" ANIMALS

Researchers are developing transgenic 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 (July 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.

Aquaculture

Aquaculture is the growth of aquatic organisms in a controlled environment. The increased public demand for seafood, combined with the relatively small supply of aquaculture products provided by U.S. companies, has encouraged scientists and industry to study ways that marine biotechnology can increase the production of marine food products. 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 to increase productivity and improve product quality. 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.

A. BIOTECH SALMON

As of September 2006, eight states have passed legislation or have regulations banning various uses of transgenic fish, including Maryland, California, Oregon, and Washington. In 2005, Alaska passed legislation requiring labeling of food from transgenic fish. However, no transgenic fish are approved in the United States, nor in the world, for human consumption at this time.

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 to 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 164 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 \$38.4 billion spent on U.S. pets in 2006. To help companion animals live longer and healthier lives, pet owners spent more than \$7 billion on veterinary care and healthcare products in 2000 (the most recent year for which a statistic is available).

The animal health industry has developed products that contribute to the well-being of companion animals. Pets benefit from 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. Currently researchers are successfully 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. In the United States, an estimated 40,000 people undergo treatment for rabies annually at an average cost of \$1,650.
- 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.

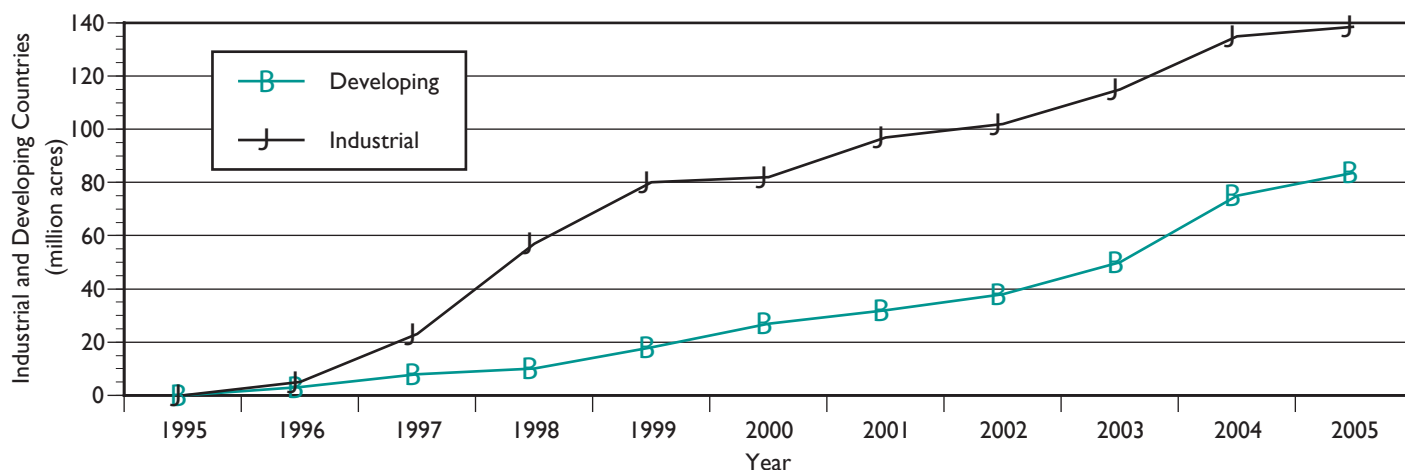


- Other antibody technology is being used to develop diagnostics for feline infectious peritonitis and feline immunodeficiency virus.

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

- An allergen-free cat is being developed.
- 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 2005: Industrial and Developing Countries (million acres)



Source:

Clive James, *Global Status of Commercialized Transgenic Crops: 2005*, ISAAA Briefs No. 34-2005. Ithaca, N.Y. International Service for the Acquisition of Agri-biotech Applications, 2005

Global Area of Transgenic Crops in 2004 and 2005 by Country (million acres)

	2004	%	2005	%	+/-	% Change
USA	117.6	59	123.1	55	+5.5	+4.7
Argentina	40	20	42.2	19	2.2	5.5
Brazil	12.3	6	23.2	10.4	10.9	88.6
Canada	13.3	6	14.3	6.4	1	7.5
China	9.1	5	8.2	3.7	-.9	-9.9
Paraguay	--	--	4.5	2.0	4.5	--
India	1.2	1	3.2	1.4	2	167
South Africa	1.2	1	1.2	<1	0	
Uruguay	.74	<1	.74	<1	0	
Australia	.5	<1	.74	<1	.24	48
Mexico	.24	<1	.25	<1	<.1	
Romania	.24	<1	.25	<1	<.1	
Philippines	.24	<1	.25	<1	<.1	
Spain	.24	<1	.25	<1	<.1	
Colombia	.12	<1	<.25	<1	<.1	
Iran	--	--	<.25	<1	<.1	
Honduras	<.12	<1	<.25	<1	<.1	
Portugal	--	--	<.25	<1	<.1	
Germany	<.12	<1	<.25	<1	<.1	
France	--	--	<.25	<1	<.1	
Czech Republic	--	--	<.25	<1	<.1	

Source:

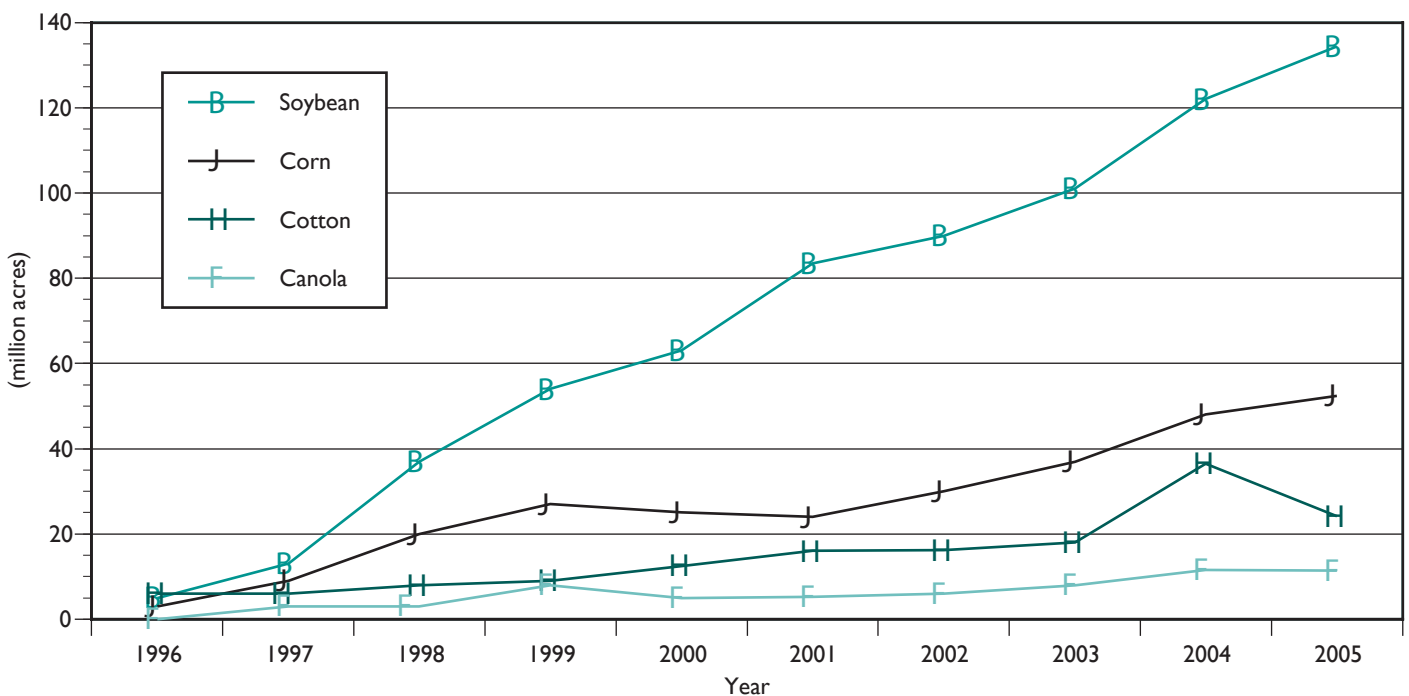
Clive James, *Global Status of Commercialized Transgenic Crops: 2005*, ISAAA Briefs No. 34-2005. Ithaca, N.Y. International Service for the Acquisition of Agri-biotech Applications, 2005

Global Area of Transgenic Crops in 2004 and 2005 by Crop (million acres)

	2004	%	2005	%	+/-	% Change
Soybean	120	+60	134.4	60	14.4	12
Maize	47.7	+23	52.3	24	4.6	9.6
Cotton	22.2	+11	24.2	11	2	9.0
Canola	10.6	+6	11.4	5	0.8	7.5
Total	200.5	100	222.3	100	21.8	11

Source:
Clive James, 2005

Global Area of Transgenic Crops, 1996 to 2005, by Crop (million acres)



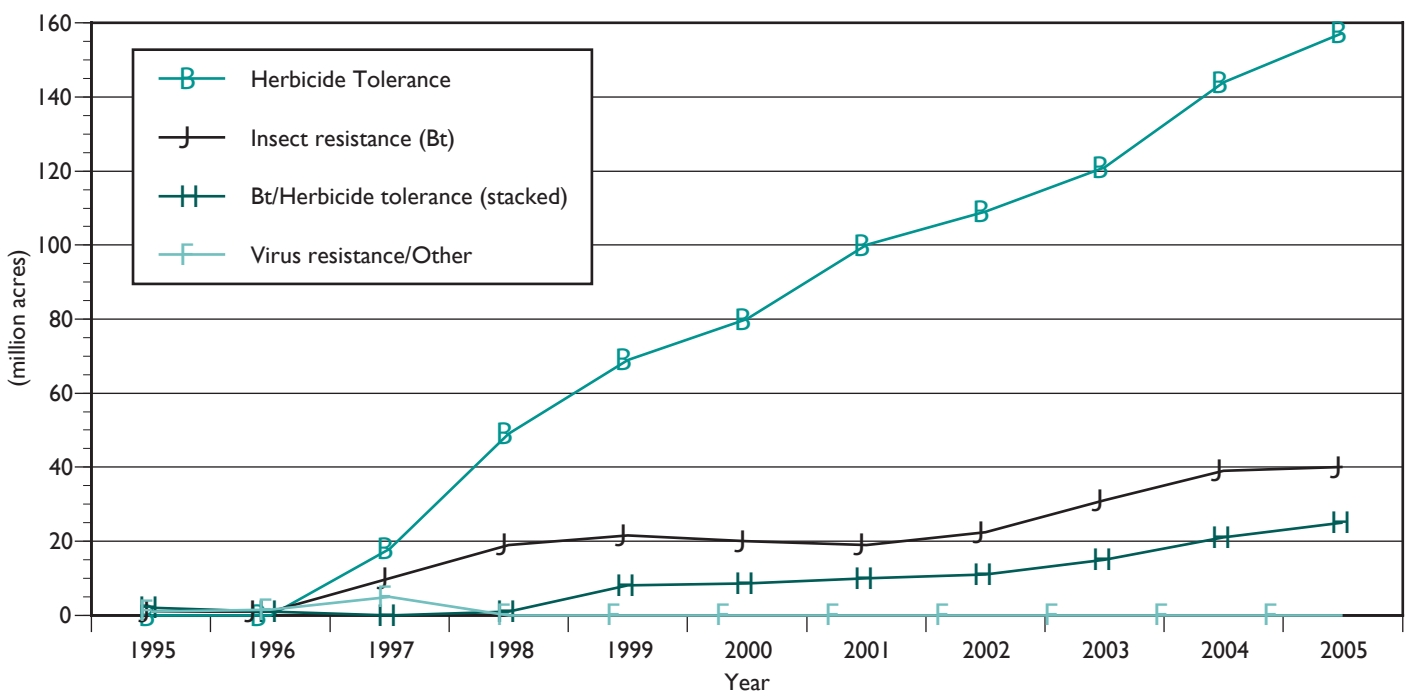
Source:
Clive James, *Global Status of Commercialized Transgenic Crops: 2005*, ISAAA Briefs No. 34-2005. Ithaca, N.Y.
International Service for the Acquisition of Agri-biotech Applications, 2005

Global Area of Transgenic Crops in 2004 and 2005 by Trait (million acres)

	2004	%	2005	%	+/-	% Change
Herbicide tolerance	144.5	72	157.3	71	12.5	9
Insect resistance (Bt)	38.5	19	40	18	1.5	9
Bt/Herbicide tolerance	16.8	9	24.9	11	8.1	49
Total	200	100	222.2	100	22.1	11

Source:
Clive James, 2005

Global Area of Transgenic Crops, 1995 to 2005, by Trait (million acres)

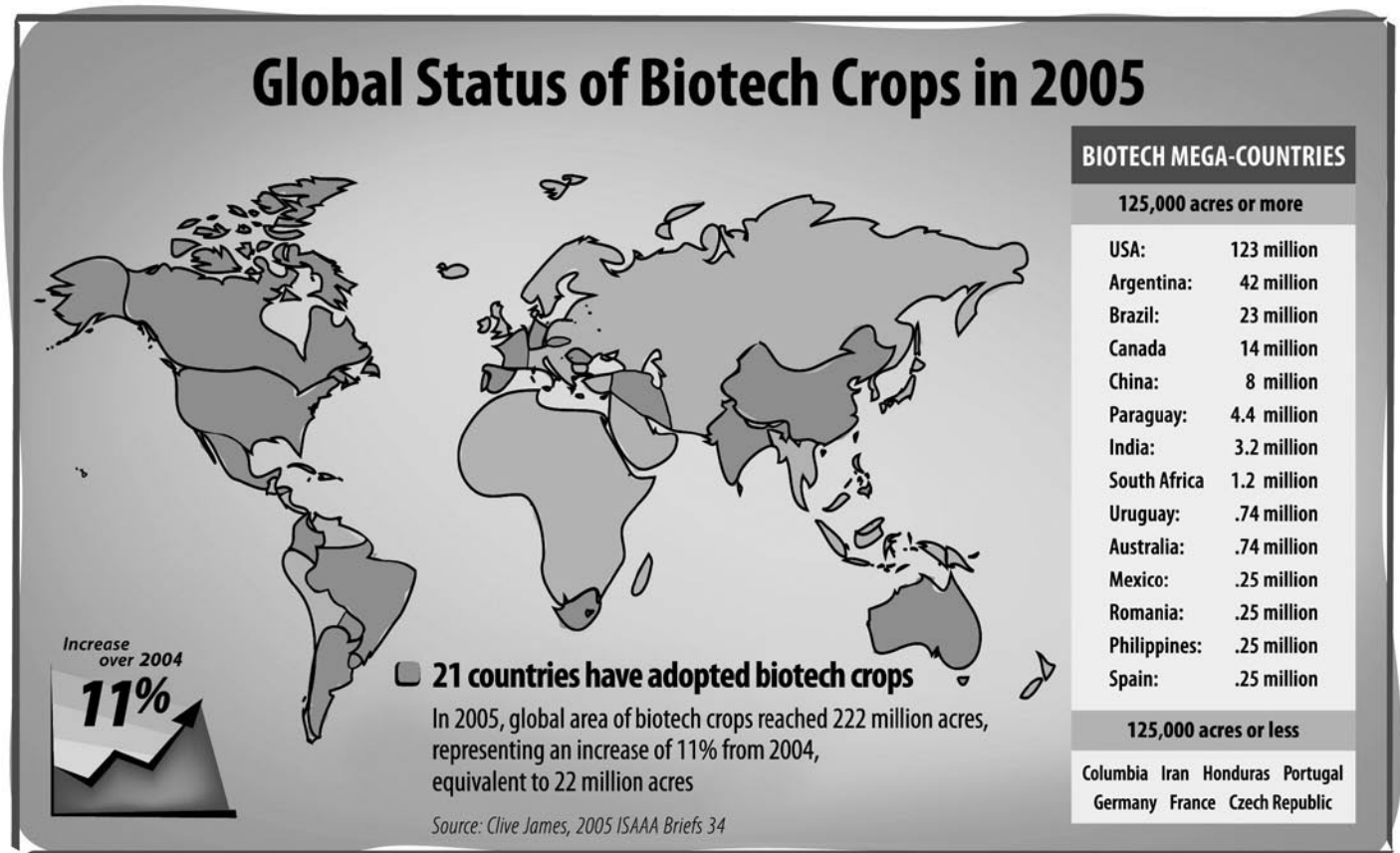


Source:
Clive James, 1997–2005

Transgenic Crop Area as % of Global Area of Principal Crops (million acres)

Crop	Global area	Transgenic crop area	Transgenic area as % of global area
Soybean	224.8	134.9	60
Cotton	86.5	24.2	28
Canola	64.2	11.5	18
Maize	363.1	50.8	14
Total	738.6	221.4	30

Source:
Clive James, 2005



Source:
Council for Biotechnology Information

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. 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.

Cooking oils from NEXERA™ Canola Seed (Developed by Dow AgroSciences, Canada)

This new oil, made from NEXERA™ canola seed, has a unique combination of high oleic (>70 percent) and low linolenic (<3 percent) fatty acids. These oils also have less than 1 percent trans fats and when used as part of a healthy meal can deliver a label claim of trans fat-free (<.5 gram per 100-gram serving).

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 superior 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.

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 Advantage gives farmers another tool for managing weed pests.

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 and Herculex® XTRA Insect Protection Corn (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. 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 RW and 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 kills over 100 grass and broadleaf weeds fast, without crop injury.

NK Knockout™ Corn, NK YieldGard™ Hybrid Corn (developed by Syngenta Seeds) Syngenta Seeds has produced several corn varieties that have been modified to provide natural protection against certain pests

NK® brand YieldGard® (Bt 11) Corn (Developed by Syngenta Seeds) Syngenta Seeds has been producing and selling several corn hybrids since 1997 that have been modified to provide built-in protection against certain insect pests. (YieldGard® is a registered trademark of the Monsanto Company.)

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 superior weed control.

YieldGard® Corn Borer (Developed by Monsanto Company)

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.

CARNATIONS

Moondust Carnation (Introduced in 1996 by Florigene [Formerly Calgene Pacific]) The first mauve carnation followed by Moonshadow (1998), a violet carnation. Carnations are among the species that account for 75 percent of worldwide flower sales. 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 is protected 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 1/2 less 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 Crop-Science) 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. At this time, Monsanto expects that Roundup-Ready® Flex cotton will be in the marketplace in 2006.

WideStrike™ Insect-Protected Cotton (Developed by Dow AgroSciences) This new trait provides a broader spectrum of insect protection than other products currently on the market. This trait protects season long against a broad range of damaging lepidopteran pests, including cotton bollworm, pink bollworm, tobacco budworm, armyworms, and loopers.

MILK PRODUCTION

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, is more plentiful and 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 (PRSV), the deadly disease which almost eliminated the papaya industry in Hawaii during the 1990s.

PEANUTS

Flavr Runner Naturally Stable Peanut (Developed by Mycogen) Peanuts with 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) 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, superior weed control with no effect on crop performance or yield.

SUNFLOWERS

Natreon™ Naturally Stable Sunflower cooking oils (Developed by Mycogen) Sunflowers with modified fatty acid profile to produce sunflower oil that contains virtually no trans-fatty acids. These naturally stable characteristics make this oil very attractive for nutritional drinks, release oils, baking or frying snack foods and other uses.

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 superior weed control.

APPLES

Bt Insect-Protected Apple (Developed with Monsanto technology) These apples will contain built-in insect protection against 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 Sclerotinia.

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.

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

Nutritionally Enhanced Corn (Developed by Dow Agro-Sciences) Corn hybrids that are "nutritionally enhanced" will provide higher energy and more abundant nutrients for a better-balanced ration formulation for livestock.

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 and including amylase expression in processor corn has the potential to reduce the costs of ethanol production up to 10 percent.

Glyphosate-Tolerant Corn (Developed by Syngenta) Developed from a plant-derived glyphosate-resistant gene that is evenly expressed throughout the plant, this new corn hybrid will give farmers another tool for managing weed pests.

Insect-Resistant Corn (Developed by Syngenta) Second-generation Bt control for both European corn borer and corn rootworm stacked to provide growers broader insect management controls.

Insect-Resistant and Glyphosate Tolerance Corn (Developed by Syngenta) Glyphosate tolerance stacked together or separately with second generation Bt control for both European corn borer and corn rootworm to provide growers further options and flexibility to achieve desired effects.

COTTON

Vegetative Insecticidal Protein Cotton (Developed by Syngenta) This second-generation insect control has a broader spectrum and a novel mode of action. VIP Cotton will provide growers an alternative to existing Bt producers 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 superior weed control.

POTATOES

Amflora Potatoes (Developed by BASF) 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

LibertyLink® Soybeans (Developed by Bayer Crop-

Science) Bayer CropScience is obtaining appropriate regulatory clearances in key countries. When used together with glufosinate ammonium herbicide (Liberty®, Ignite® 280), it will allow farmers greater weed control flexibility and important weed resistance management strategies.

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

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 while the crop is growing.

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.

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 affect the food industry by providing new products, lowering costs and improving the microbial processes on which food producers have long relied.

Many of these impacts 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 during the process; 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 consumers. 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, such as aflatoxin, 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 decreased 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 lowering cholesterol levels.

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. The hydrogenation process results in the formation of trans-fatty acids.

Biotechnology companies have given soybean oil these same properties, not through hydrogenation, but by using biotechnology to increase the amount of the naturally occurring fatty acid, stearic acid.

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

Other health and nutritional benefits of crops improved through biotechnology include increased nutritional value of crops, especially those that are food staples in developing countries. 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 the immune response; antioxidants found in green tea; and the glucosinolates in broccoli and cabbage that stimulate anticancer enzymes.

We 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.

PRODUCT QUALITY

We are also using biotechnology to change the characteristics of the raw material inputs so that they are more attractive to consumers and more amenable to processing.

Biotechnology researchers 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.

Japanese scientists have now identified the enzyme that produces the chemical that makes us cry when we slice an onion. Knowing the identity of the enzyme is the first step in finding a way to block the gene to create “tearless” onions.

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. Another important benefit is that starchier potatoes 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 now used biotechnology to increase the amount of the protein casein, which is essential to cheese making, in milk 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 found 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. Any biotechnology product that decreases microbes found on animal products and crop plants will significantly improve the safety of raw materials entering the food supply. Improved food safety through decreased microbial contamination begins on

the farm. Transgenic disease-resistant and insect-resistant crops have less microbial contamination. New biotechnology diagnostics, similar to those described in the chapter on medical applications of biotechnology, detect microbial diseases earlier and more accurately, so farmers can identify and remove diseased plants and animals before others become contaminated.

Biotechnology is improving the safety of raw materials by helping food scientists discover the exact identity of the allergenic protein 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, we are making great progress in identifying these allergens. More importantly, scientists 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 the food-processing industry for decades. 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 conducting a lot of work to improve the microorganisms that carry out food fermentations. 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 have been essential to the food industry not only for their importance as fermentors, but also because they 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 compounds 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.

Food processors use plant starch 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. Scientists are using biotechnology to change the starch in crop plants so that it no longer requires special handling before it can be used.

Enzymes produced by microbial fermentation play essential roles as processing aids in the food industry. 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.

TABLE I

Microbial fermentation is essential to the production of these fermented foods

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

The production of high-fructose corn syrup from corn-starch 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 increase 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.

Food Safety Testing

In addition to the many ways biotechnology is helping us enhance the safety of the food supply, biotechnology is providing us with many tools to detect microorganisms and the toxins they produce. Monoclonal antibody tests, biosensors, polymerase chain reaction (PCR) 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 tests are portable, 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.

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, but 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 carbohydrate feedstocks, such as sugars and starch).
- lower manufacturing cost.

Living systems manage their chemistry more efficiently than man-made chemical plants, and the wastes that are generated are recyclable or biodegradable. Biocatalysts, and particularly enzyme-based processes, operate at lower temperatures and produce less toxic waste, fewer byproducts and less emissions than conventional chemical processes. They may also use less purified raw materials (selectivity). Use of biotechnology can also reduce energy required for industrial processes. Finally, just as biotechnology is providing us with new tools for diagnosing health problems and detecting harmful contaminants in food, it is yielding new methods of monitoring environmental conditions and detecting pollutants.

Biotechnology in industry employs the techniques of modern molecular biology to reduce the environmental impact of manufacturing. Industrial biotechnology also works to make manufacturing processes more efficient for industries such as 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 (OECD), industrial sustainability is the continuous innovation, improvement and use of clean technology to reduce pollution levels and consumption of resources. Modern biotechnology provides avenues for achieving these goals.

In recent years, policy-makers, corporate executives, private citizens and environmentalists have become more concerned about sustainable development. In response to that concern, many leading industrial companies are doing more than meeting their legal minimums. Many 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. Biotechnology provides ways to produce cleaner products and processes by reducing the use of petroleum inputs. Industrial biotechnology instead uses natural sugars as feedstocks.

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 CO₂—one of the greenhouse gases.

Today at least 5 billion kilograms of commodity chemicals are produced annually in the United States using plant biomass as the primary feedstock.

Biotechnology will also have an impact on two sources of energy: fossil fuels and new biomass-based fuels. Innovations wrought by biotechnology can help remove the sulfur from fossil fuels, significantly decreasing their polluting power. Using biomass for energy has the same environmental advantages as using biomass feedstocks, so government labs have devoted significant resources to research on recombinant technology and bioprocess engineering to improve the economic feasibility of biomass-derived energy.

INDUSTRIAL MANUFACTURING PROCESSES

In addition to working toward sustainability by using biomass-based material and energy inputs, biotechnology offers us many options for minimizing the environmental impact of manufacturing processes by decreasing energy use and replacing harsh chemicals with biodegradable molecules produced by living things.

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. Therefore, manufacturing processes that use biological molecules can lower the amount of energy needed to drive reactions.

Manufacturing processes that use biodegradable molecules as biocatalysts, solvents or surfactants are also less polluting. 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 the biocatalysts, which are living organisms or simply their enzymes.

Biocatalysts

Industrial biotechnology companies develop new enzymes, biocatalysts, to be used in manufacturing processes of other industries. Enzymes are proteins

produced by all living organisms. 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 look for biocatalysts with industrial value in the natural environment; 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

Companies involved in industrial biotechnology constantly strive to discover and develop high-value enzymes or other bioactive compounds that will improve current manufacturing processes.

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 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 the great majority 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 biocatalysts that will function optimally at the relatively extreme levels of acidity, salinity, tempera-

ture or pressure found in some industrial manufacturing processes—hence the name *extremophiles*.

Information from genomic studies of microbes is helping researchers capitalize on the wealth of genetic diversity in microbial populations. Researchers use DNA probes to fish, on a molecular level, for genes that express enzymes with specific biocatalytic capabilities. Once snared, such 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 solutions was “research in cutting-edge methods of producing ethanol, not just from corn, but from wood chips and stalks, or switch grass.”

He announced a national goal to make this new kind of ethanol practical and competitive within six years, pledging \$150 million in FY 2007 for biomass research, development and demonstration. Advances in industrial biotechnology and development of new integrated “biorefineries” are at the heart of ethanol production from all sources.

April 2004 saw the first commercial production of ethanol from cellulose, made from wheat straw using biotech enzymes. Some 10 to 15 billion gallons of ethanol could be produced each year from corn stalks and husks and wheat

straw, according to Burrill & Co. Another 50 billion could be made using such raw materials as wood-product manufacturing residues, municipal solid waste and garden waste. Ethanol from dedicated energy crops, like switchgrass, could add even more.

President Bush’s initiative followed passage of the 2005 Energy Policy Act, landmark legislation for industrial biotech, which authorized over \$3 billion in funding for biofuels and biobased products and established a national renewable fuels standard. 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.

Other recent developments in biomass energy include:

- The Department of Energy announced plans to issue up to \$160 million in competitively awarded grants for construction of pioneer biorefineries.
- 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 bio-based 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 2005 joint report from the Departments of Energy and Agriculture found that more than 1 billion tons of biomass are available in the US to produce biofuels and bioproducts, enough to meet over half of US demand for transportation and chemicals.
- 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.
- A growing number of states have implemented their own renewable fuels requirements. Many are also providing incentives for biorefinery construction.

Green Plastics

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

In 2001, the world's first biorefinery opened in Blair, Nebraska, 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, are now using PLA packaging. At the 2006 BIO International Convention in Chicago, professional models in PLA designer gowns put industrial biotech center stage in the world's first biotech fashion show.

Also in 2001, DuPont, and its development partners Genencor and Tate & Lyle, created the high-performance polymer Sorona from the bioprocessing of corn sugar at a biorefinery in Decatur, Illinois. Production of bio-PDO, the renewable raw material for Sorona, is expected to begin in 2006 at a new DuPont/Tate & Lyle biorefinery in Loudon, Tennessee. Production sold out months before the plant was completed.

Early in 2006, agri-food giant Archer Daniels Midland signed an agreement with Metabolix, a small industrial biotech company based in Cambridge, Massachusetts, to produce polyhydroxyalkanoates (PHAs), a versatile family of biobased polymers, at a biorefinery in Clinton, Iowa.

Industrial scientists have also genetically modified both plants and microbes to produce polyhydroxybutyrate, a feedstock for producing biodegradable plastics. Finally, biotechnology provides us with the opportunity to produce abundant amounts of natural protein polymers, such as spider silk and adhesives from barnacles, through microbial fermentation.

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 summary, no matter what stage of industrial production you select—inputs, manufacturing process or final product—biotechnology provides tools, techniques and know-how to move beyond regulatory compliance to proactive pollution prevention and resource conservation strategies that are the hallmarks of industrial sustainability.

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 of carbon and silicon. For example, Genencor International and Dow-Corning have partnered to combine their respective expertise in protein-engineered systems and silicon. Their strategic alliance seeks to apply the biotech business model to a third outlet of creativity where products can be developed for other companies based on specific needs.

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 micro-processing 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 micro-transistors.

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.

New technology allows spider silk to be produced in goats, but in the future it may be possible for scientists to build polymers in the lab that are even stronger and that won't need living expression systems for large-scale production. 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. Biotechnology may hold the key to making carbon nanotubes even more economically attractive.

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.

What does the future market for nanotech look like? The National Science Foundation estimates that by 2015 the market for nanotech products could exceed \$1 trillion.

Industrial biotechnology is poised to merge its applications with carbon and silicon, a merger that could catapult industrial biotech companies from nanospace into financial hyperspace.

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 de-

grading wastes, such as polychlorinated biphenyls (PCBs), to harmless compounds. Marine biotechnologists are studying ways that estuarine bacteria can detoxify materials such as chemical sea brines that cause environmental problems in many industries.

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

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 us with 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 mono-

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 desuphurization
- 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

clonal 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.

- **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 dyeing and finishing processes. 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.

Consumer Goods Made With Industrial Biotech

CONSUMER PRODUCT	OLD PROCESS	NEW INDUSTRIAL BIOTECHPROCESS	BIOTECH ENABLING TECHNOLOGY	CONSUMER BENEFIT
Detergent	Phosphates added as brightening and cleaning agents	Addition of biotechnology enzymes as brightening and cleaning agents: <ul style="list-style-type: none"> ■ Proteases remove protein stains ■ Lipases remove grease stains ■ Amylases remove starch stains 	Genetically enhanced microbes or fungi engineered to make enzymes	<ul style="list-style-type: none"> ■ 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: <ul style="list-style-type: none"> ■ enhance rising ■ strengthen dough ■ prolong freshness 	Microorganisms genetically enhanced to produce baking enzymes (directed evolution and recombinant DNA)	<ul style="list-style-type: none"> ■ 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	<ul style="list-style-type: none"> ■ PLA polyester does not harbor body odor like other fibers ■ Biodegradable ■ Not made from petroleum ■ Does not give off toxic smoke if burned
Vitamin B ₂	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 B ₂ (directed evolution)	<ul style="list-style-type: none"> ■ 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)	<ul style="list-style-type: none"> ■ Less mining ■ Softer fabric ■ Reduced 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)	<ul style="list-style-type: none"> ■ 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)	<ul style="list-style-type: none"> ■ Renewable feedstock ■ Reduces greenhouse gas emissions ■ Increases domestic energy production ■ Is more energy efficient to produce than old process

*any synthetic fiber

CONSUMER PRODUCT	OLD PROCESS	NEW INDUSTRIAL BIOTECHPROCESS	BIOTECH ENABLING TECHNOLOGY	CONSUMER BENEFIT
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)	<ul style="list-style-type: none"> ■ 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)	<ul style="list-style-type: none"> ■ 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., <i>Bacillus subtilis</i>), Fungal α -amylase (e.g., <i>Aspergillus niger</i>), Alkaline α -amylase	Textiles, starch syrups, laundry and dishwashing detergents, paper desizing, fermentation ethanol, animal feed
β -amylase	From a strain of <i>Bacillus</i>	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., <i>Leuconostoc mesenteroides</i>)	Hydrolyzes the polysaccharide dextran
Dextrinase (almost identical to α -glucosidase)		Cleaves dextrin into two molecules of glucose
α -Galactosidase (melibiase)		Could increase yield of sucrose; potential use in the beet sugar industry
Glucoamylase	<i>Aspergillus niger</i> , <i>Rhizopus</i> , <i>Endomyces</i>	Manufacture of dextrose syrup and high-fructose syrup
Hemicellulase/Pentosanase/Xylanase	<i>Thermomyces lanuginosus</i> , <i>Penicillium simplicissimum</i>	Baking, fruit juice manufacture, wood pulp processing
Invertase		Manufacture of invert syrup from cane or beet sugar (use is minor)
Lactase	<i>Kluyveromyces lactis</i> , <i>Aspergillus oryzae</i> , <i>Bacillus</i>	Eliminates lactose from dairy foods
Naringinase		Debitter citrus peel
Pectinase		Fruit processing
Pullulanase	<i>Klebsiella aerogenes</i> , <i>Bacillus acidipullulyticus</i> , <i>Bacillus subtilis</i>	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	<i>Endothia parasitica</i> , <i>Rhizopus</i> , <i>Aspergillus niger</i> , <i>A. oryzae</i>	Baking, improves dough handling
Alkaline protease	<i>Bacillus subtilis</i> , <i>Bacillus licheniformis</i>	Detergents, leather and fur
Bromelain	Pineapple stem	Food industry
Pepsin	Porcine or bovine stomach	Cheese production
Peptidases		
Aminopeptidase	<i>Lactococcus lactis</i>	Food and animal feed

ENZYMES	SOURCE OR TYPE	APPLICATIONS
Endo-peptidase		
Subtilisin	<i>Bacillus subtilis</i> var. Carlsberg, <i>Bacillus licheniformis</i>	Chiral resolution of chemical compounds or pharmaceuticals
Lipases and Esterases	Phospholipases, pregastric esterases, phosphatases	Cleaners, leather and fur, dairy, chemicals
Aminoacylase	Porcine kidney, <i>Aspergillus melleus</i>	Optical resolution of amino acids
Glutaminase	Bacillus, <i>Aspergillus</i>	Conversion of glutamine to glutamate
Lysozyme	Chicken egg white, <i>Saccharomyces cerevisiae</i> , <i>Pichia pastoris</i>	Antibacterial (germicidal in dairy industry)
Penicillin acylase	<i>Bacillus megaterium</i> , <i>Escherichia coli</i>	Chemical synthesis
Isomerase		Converts glucose syrup to high-fructose syrup in food industry
Oxireductases		Chemicals, detergent bleaches, pulp bleaching
Alcohol dehydrogenase	<i>Saccharomyces cerevisiae</i> , <i>Thermoanaerobium brockii</i>	Chiral synthesis of chemicals
Amino acid oxidase	Porcine kidney, snake venom	Chiral resolution of racemic amino acid mixtures
Catalase	<i>Aspergillus niger</i>	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	<i>Achromobacter liquidum</i>	Cosmetics
Transferases		
Cyclodextrin glycosyltransferase		Manufacture of cyclodextrins from starch

Sources:
Diversa & Novo Nordisk

Preparedness for Pandemics and Biodefense

In the wake of the September 11 terrorist attacks, BIO surveyed the industry and found that many biotech 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.

Policy

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. Similarly, the President 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 man-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 even 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 new vaccine technologies, including 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 technol-

ogy 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:

Portable detectors. 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 diagno-

sis and allow it to be performed anywhere, without the need to ship samples to labs.

Portable biosensors have 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, and so on) 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 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, capability 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 or not 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 innocent individuals for crimes they were convicted of before DNA fingerprinting became available.

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 to someday 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.

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 then 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 this, 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.

Scientists 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.

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 the mystery of 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.

Ethics

Biototechnology 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 request for a self-imposed moratorium, 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 members of the press, met at the Asilomar Conference Center to discuss recombinant DNA work, consider whether to lift the voluntary moratorium and, if so, 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* on June 6, 1975.

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 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 their inception.

Over the next few years, the RAC revised the guidelines in the face 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 biotechnology 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, and biotechnology 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 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 improve lives, improve the quality and abundance of food, and protect our environment. Our board of directors has adopted a Statement of Ethical Principles, and we continue to refine a compre-

hensive vision of ways to ensure biotechnology is used for the betterment of humankind and not abused.

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.

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.

We actively encourage discussion of ethical and social implications of scientific developments in biotechnology. In response to a call from U.S. Supreme Court Justice Stephen Breyer and others for an ongoing conversation about the societal impacts of legal and judicial decisions, BIO and Ernst & Young initiated the Biojudiciary Project. The 501(c)(3) organization aims to develop informative, objective educational materials and programs to help judges, law clerks and attorneys learn more about biotechnology.

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, 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.

To further encourage public discussion of the ethical and social aspects of biotechnology, BIO initiated dialogue with leaders of major religious traditions and denominations. We also have met with members of the public who describe themselves as deeply religious.

These activities led to the signing of a memorandum of understanding between BIO and the National Council of Churches in 2003.

BIO and the biotechnology 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.

Ethical Issues

A wide variety of social and ethical issues are associated with biotechnology research, product development and commercialization. Below, we discuss some of these issues. For additional information on these and topics not discussed here, please visit our Web site at www.bio.org.

GENE THERAPY

Gene therapy is subject to greater oversight than virtually all other therapeutic technologies. The 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 clinical trial, started in 1990, more sponsors and academic researchers have moved into the area of gene therapy and are conducting human clinical trials, but the research pace has remained slow and deliberate. Even after a decade of research and clinical testing, many of the gene therapy clinical trials active today are in early-phase stud-

ies (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 regimens, patient populations, indications, combination therapies and novel vectors.

BIO believes that both the FDA and the NIH/RAC play important roles in the oversight process. BIO recommends 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 without hurting 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 gene therapy procedures that would affect the germ-line cells—the egg and sperm—that pass on genetic composition.

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. This protection must be balanced, however, with the need to continue valuable medical research into new diagnostic tests, therapies and cures. 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, and 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. Fewer cell lines than anticipated are available for federal funding. A stem-cell bill calling for the relaxation of the restrictions passed the House in 2005 and the Senate in 2006. President Bush vetoed the legislation, however, and the House failed to override the veto, leaving the 2001 restrictions in place. In the meantime, privately funded research has advanced and use of stem cells in human clinical trials may start soon.

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 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. There are grave moral, ethical and safety concerns surrounding this issue.

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 is also going on 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 is dedicated to open discussion with consumers, farmers, legislators and opinion leaders regarding ethical issues in the use of agricultural biotechnology.

BIO member 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 via market mechanisms.

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. Biotechnology companies have depended on this research to develop more than 200 drugs and vaccines approved by the U.S. Food and Drug Administration, helping 800 million people worldwide and preventing incalculable human suffering.

BIO members are compelled by ethical and legal concerns 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 requirement for many such products. The appropriate and responsible use of animals is therefore 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.

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 the production of meat, milk, and eggs and reducing the environmental impact of agriculture. These technologies are also being used to help preserve endangered species.

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. BIO is 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 biotechnology 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 will actively work 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 by raising awareness of how biotechnology 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.

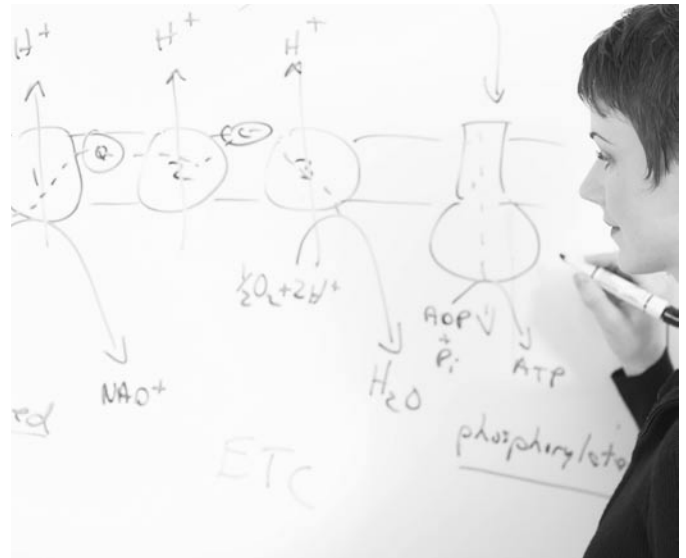
In the United States, biotech products are extensively regulated by federal agencies such as the Food and Drug Administration, the Environmental Protection Agency and the Department of Agriculture. Our industry supports science-based regulation by government agencies to safeguard health, ensure safety 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 ani-



mals—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.

Intellectual Property

B iotechnology is an industry of ideas and invention. That makes intellectual property—typically in the form of patents—the most important asset at most biotech companies. These companies are often small firms—most biotechs have 50 or fewer employees—developing products that can take upwards of 10 years and hundreds of millions of dollars in investment to bring to the marketplace.

In fact, biotech historians credit the resolution of a patent case in 1980 with lifting the industry off the ground. In that case, *Diamond v. Charkrabarty*, the court held that anything touched 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. Note that 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 much shorter depends on how long it 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. For example, if an application is examined in the PTO for four years before it is issued, the enforceable patent term will be 18 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. 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

Three types of patents exist: utility, design and plant patents. Utility patents are granted to those who invent or discover new and useful machines or processes, while 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, 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 time periods seems to have been in Italy in the 15th century. Even before the signing of the Federal Constitution of the United States, most states had their own patent laws. The U.S. 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 (PTO) and are effective only within the United States and its territories. The term of a new patent is 20 years from the date on which the application for the patent was filed in the United States or, in certain cases, from the date an earlier, related application was filed.

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

The patent system provides a process for the disclosure of valuable information that can stimulate research across the globe. 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 whole world.

Moreover, the information disclosed in a patent application is usually available to the public long before a patent issues. If a patent application is filed internationally or (from 2000 onwards) 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. Thus, the patent system greatly stimulates 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. These are:

- *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 two classes:

1. New compositions of matter related to newly discovered isolated genes or proteins or to pharmaceutical inventions based on those genes or proteins. 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 pharmaceutical drug, screening assay or other application.
2. 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.

Patent Requirements

To obtain a patent on a new invention, an inventor must show that these three 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. Also, if the invention has been on sale or in use in the U.S. for a year before the application is filed, a patent will not be awarded to the invention.

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 such a drawing is necessary for understanding the invention.
3. An oath or declaration by the inventor(s) claiming inventorship.
4. A filing fee (about \$400–\$800, or more, depending on the patent application).

Patenting Organisms

Some living things can be patented, but not all. Like any invention, a living thing must be “new” in order to be patented. More importantly, living organisms under consideration for patenting cannot be those that occur or exist in nature. Thus, one cannot obtain a patent on just any living creature, such as 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. Here 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.

ers. 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 does use a patented invention without a license, the patent owner can seek legal remedies for infringement. Such remedies can include damages and an injunction against the infringer to prevent future use.

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 who may not have the resources to fully develop an invention can work with a 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 own-

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 have omitted a useful resource, please 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.

Science.bio.org. Each business morning, BIO shares links to all of the day's significant biotech science stories, including both mainstream press and journal articles.

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 www.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 www.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. All resources are available at www.bvgh.org.

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 biotechnology company, clinical and financial news and data, and offers e-mail headline services. Explore offerings at www.biospace.com.

Biotechnology Healthcare. 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.org.

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 healthcare data and analysis, with articles on issues of access, reimbursement, innovation and quality. Visit www.healthaffairs.org for subscription information.

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.

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 first to publish important breakthroughs, such as the human genome sequence.

Biotech Education & 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.

BioView. BioView has compiled a list of schools offering specialized biotechnology degree and certificate programs. Visit bioview.com/education.html for the list.

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 & HEALTHCARE

Beyond Borders: Global Biotechnology Report 2006.

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 April 2006. See www.ey.com for contact information.

Biotech 2006—Life Sciences: A Changing Prescription.

Each year, the life sciences merchant bank Burrill & Co. publishes a detailed report on the biotech industry, describing new developments in healthcare, agriculture and industrial applications, as well as providing an overview of biotech business activities. See www.burrillandco.com for purchase information. Published April 2006.

BioWorld State of the Industry Report, 2006.

BioWorld's annual report aggregates the biotech industry's financial, partnering and drug approval information for 2005, with analysis explaining what it all means. See www.bioworld.com for purchase information.

Genomics and Global Health. This report from the University of Toronto explores how genomics and related technologies can help achieve the United Nations Millennium Development Goals in global health. The report follows up on the recommendations of *Top 10 Biotechnologies for Improving Health in Developing Countries*. Both reports can be downloaded through www.bvgh.org. Published in September 2002 (*Top 10*) and October 2004 (*Genomics and Global Health*).

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 biosciences. Available for downloading on www.bio.org/local/battelle2006/. Published April 2006.

Innovation or Stagnation: 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 downloading 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.ias.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 downloading on www.oecd.org. Published May 2006.

Outlook 2006. 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 downloading at csdd.tufts.edu. Published 2006.

Parexel's Bio/Pharmaceutical R&D Statistical Sourcebook 2006/2007. 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.

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 downloading on www.pwc.com. Published February 2005.

Personalized Medicine: Hopes and Realities.

This Royal Society report provides a thorough overview of scientific, development and clinical issues in personalized medicine. Available for downloading at www.royalsoc.ac.uk (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 downloading 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.visiongainintelligence.com, www.researchandmarkets.com, www.thefreedoniagroup.com and www.frost.com.

AGRICULTURE

Biotechnology-Derived Crops Planted in 2004—

Impacts on U.S. Agriculture. 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. Published December 2005.

Brief 34: Global Status of Commercialized Biotech/GM Crops: 2005. 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 downloading at www.isaaa.org. Published January 2006.

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 downloading on www.whybiotech.com. Published December 2003.

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 downloading on www.whybiotech.com. Published December 2004.

GM crops: the global socio-economic and environmental impact—the first nine years, 1996-2004. This report from the U.K. firm PG Economics provides cumulative data on the positive environmental and income impact of biotech crops. It is available for downloading at www.pgeconomics.co.uk. Published October 2005.

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 downloading 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 downloading 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 www.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. Published November 2006.

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 by 2025 if action is taken now. 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 downloading on www.ias.unu.edu. Published September 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 downloading on www.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 downloading on www.bio.org/ind/. Published June 2003.

Glossary

A

Acclimatization Adaptation of an organism to a new environment.

Action letter An official FDA communication that informs an NDA or BLA sponsor 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, asparagine, 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 also 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 also 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.

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.

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 (BOD) 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.

Bioprocess A process in which living cells, or components thereof, are used to produce a desired product.

Bioreactor Vessel used for bioprocessing.

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.

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.

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 naturally 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.

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 also 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 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 also 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.

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 also 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 also 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 also 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 also 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 (codons), 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 predisposition 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.

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 (GM-CSF) 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.

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 also 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.

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 also 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 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.

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 also 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 also 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 also 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 also 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

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 also 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. An operon is controlled by an operator gene and a repressor gene.

Organic compound A compound containing carbon.

P

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 also 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 also pharmacogenetics.

Pharmacogenetics The study of inherited differences (variation) in drug metabolism and response. See also 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.

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).

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 protein produced by the bacterium *Staphylococcus aureus* that specifically binds antibodies. It is useful in the purification of monoclonal antibodies.

Proteomics Each cell produces thousands of proteins, each with a specific function. This collection of proteins in a cell is known as the proteome, and, unlike the genome, which is constant irrespective of cell type, the proteome varies from one cell type to the next. The science of proteomics attempts to identify the protein profile of each cell type, 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

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-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.

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.

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 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.

Notes

Notes

Biotechnology Industry Organization

1225 Eye Street, NW

Suite 400

Washington, DC 20005

202-962-9200 (phone)

202-962-9201 (fax)

www.bio.org

