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THE PROMISE OF BIOTECHNOLOGY

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ECONOMIC PERSPECTIVES

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ABOUT THIS ISSUE

New technologies, whether they are in medicine, industry, or agriculture, often initially generate public skepticism. Nowhere is this currently more evident than in biotechnology, where issues of health and environment are hotly debated.

"Bioconservative intellectuals are fully cognizant of the tendency for our species to be suspicious of the new and the strange, and they clearly want to harness that suspicion as a strategy to restrain biotechnological progress," writes author Ronald Bailey in his 2005 book *Liberation Biology*.

But as Bailey points out, public opinion is highly changeable, and the benefits from technological progress are not always well understood. He cites in vitro fertilization and optical laser technologies as just two examples where the public had fears and/or doubts but now broadly supports the technologies and appreciates the huge gains from them.

This issue of *Economic Perspectives* explores some of the most promising applications of biotechnology, from microorganisms engineered to produce hydrogen gas from organic waste and bacteria engineered to break down environmental pollutants to crops that add vitamins to what we eat and novel drugs for treating human diseases such as Alzheimer's and diabetes.

As National Science Adviser John Marburger writes in the introduction to this publication: "Our aim is not simply to understand disease, but to cure it; not only to consume whatever edible we find, but to make it safer, more nutritious; not just to harvest nature's random products for our manufacturers, but to make them stronger, safer, and more adapted to our needs."

We hope that readers will take the time to review each of the articles and gain from them a greater understanding of the tremendous potential that biotechnology offers for improving the quality of life for all people throughout the world.

The Editors

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THE PROMISE OF BIOTECHNOLOGY

INTRODUCTION

Biotechnology is the most recent step in humankind's long endeavor to use nature's own processes to advance the human condition. The word itself joins knowledge to practice, science to technology. We might have used it to describe the emergence of agriculture, or of pharmacology, or even the training of athletes—activities that have grown from ancient roots into exotic and very contemporary forms. In each case, accumulating knowledge of nature has suggested ways of making life safer, healthier, and more productive. While biotechnology is a relatively new word with narrower connotations, it is good to keep in mind its link to the past, especially when speaking of its benefits for cultures separated from the traditions of modern science.

Biotechnology begins with the study of plants and animals, intricate and beautiful even in their smallest features. Great artists have struggled to capture the details of birds, flowers, and insects that underlie their wonderful variety. Each advance in our ability to see things at a smaller scale has brought new wonders into view, new patterns and behaviors that explain the mysteries of the larger parts. During the past quarter-century, these advances have brought us to one of nature's major milestones: We can now "see" the elemental atoms of which all normal matter is constructed. Below this level is a yawning gap to the dense kernels of atomic nuclei, a hundred thousand times smaller than the smallest atom, where a new world—an equally beautiful but lifeless world—is being explored by physicists.

Life, in other words, can be surveyed today for the first time in history throughout its entire spectrum, from the smallest to the largest scales. The tools that made this possible draw heavily from other fields of science and require large investments that normally only governments can make. The insights revealed by these tools, however, can be analyzed and exploited with relatively modest resources. That is just as well because small-scale nature is stunningly complex. We are nowhere near understanding all that we can see, and even with powerful new tools, exploring the terrain of life will consume the energies of entire communities of scientists. The territory is vast, and the mapping and developing of it are international enterprises.

This vastness of the universe of living things extends not only in numbers of species and types of organisms and the varieties of chemicals that make them function, but also to the processes of life. From the numerous systems of chemical reactions, material transport, information flow, and mechanical support at the smallest scale to the functions of organs and the behavior of organisms at the largest, the sheer volume of information required to understand even simple life-forms is staggering. It is not enough to see these things. To comprehend them requires storing a huge amount of information, retrieving it efficiently, and processing it to test ideas about causes and effects. Biology can only now produce its own technology because the technology of information has matured in our era.

Seeing small with X-ray diffraction, magnetic resonance, and electron microscopes, and *thinking big* with fast computers, gigantic databases, and wide-band transfer, are two of three ingredients that permit a "bio" technology. The third ingredient is the ability to make things happen at the smallest scale. The means of doing so are varied, and they often recruit life's own processes to execute our direction. This is an old idea, not unlike the use of bees for pollination. Today we use bacteria and viruses to carry out our microscopic husbandry. But we also use lasers and tiny probes and activated molecules whose effectiveness we learned from laborious experiment. The manipulation of matter at this scale is part of what nanotechnology is all about, and it is no accident that nanotechnology, information technology, and biotechnology are growing up together. They are convergent technologies, and they feed each other in a complex ecology of discovery, innovation, and increased human effectiveness.

Biotechnology is the application of the three ingredients to accomplish human goals. Our aim is not simply to understand disease, but to cure it; not only to consume whatever edible we find, but to make it safer, more nutritious; not just to harvest nature's random products for our manufactures, but to make them stronger, safer, and more adapted to our needs. Nature's complexity, once a barrier to these aims, is now revealed to us as a rich source of opportunities to achieve them. How we seize these opportunities for the good of humankind is what we call biotechnology. ■

John Marburger
Director
Office of Science and
Technology Policy
Executive Office of the President

GLOBAL CHALLENGES AND BIOTECHNOLOGY

Jennifer Kuzma

AP/WWP/NREL

A bus runs on diesel fuel made from soybeans.

Biotechnology, if used appropriately, has the potential to provide more and healthier foods, reduce dependence on fossil fuels, and offer more effective cures for diseases. Enzymes that can break down plant material into biofuels such as ethanol will eventually lead to the more cost-effective production of sustainable bioenergy products. A new bioengineered form of rice bolstered with vitamin A may help reduce blindness stemming from vitamin deficiency in developing countries.

But these and other applications carry risks that need to be addressed through regulatory and safety regimes. Governments and other organizations also need to step in and invest in biotech research and development tailored toward products that can help developing countries and assist these nations in building the capacity to benefit from bio-innovation.

***Jennifer Kuzma** is associate director of the Center for Science, Technology, and Public Policy at the University of Minnesota.*

Science can only ascertain what is, but not what should be, and outside of its domain, value judgments of all kinds remain necessary.

— Albert Einstein

For centuries, humans have harnessed the power of biological systems to improve their lives and the world. Some argue that biotechnology began thousands of years ago, when crops were first bred for specific traits and microorganisms were used to brew beer. Others define the beginning of biotechnology as the emergence of techniques allowing researchers to precisely manipulate and transfer genes from one organism to another. The discovery of the structure of deoxyribonucleic acid (DNA) in the 1950s marks the start of this era. Genes are made up of DNA and are expressed into proteins, which do chemical work and form structures to give us specific traits. In the 1970s, scientists discovered and used the power of natural "scissors"—proteins called restriction enzymes—to specifically remove a gene from one kind of organism and put it into related or unrelated organisms. Thus, recombinant DNA technology, or what most experts now label as modern biotechnology, was born.

The pioneers of biotechnology could not have envisioned our current abilities to engineer plants to resist disease, animals to produce drugs in their milk, and small

particles to target and destroy cancer cells. However, biotechnology is more than engineering—it is also a set of tools for understanding biological systems. Genomics is based on these tools and is the study of genes and their functions. We have determined the composition of, or "sequenced," the entire set of genes for humans and several other organisms using biotechnology. Genomic information is helping us better to evaluate the commonalities and diversity among organisms and human beings and to understand and cure disease, even tailoring treatments to individuals.

Biotechnology, or really any technology, does not exist in a vacuum. It is derived from human efforts and affected by social, cultural, and political climates. Society drives and regulates technology, attempting to minimize the downsides and maximize the benefits. Many natural and physical scientists would prefer that the separation between social and ethical concerns and science and technology be well defined. Recent controversies over the use of genetically engineered organisms in food and agriculture have illustrated that this boundary is not so clear. Not only are there safety concerns about genetically engineered organisms, but there are also cultural differences in acceptance of the products.

International contexts for technologies are important and should be considered. Biotechnology is not a panacea for global problems, but it is a tool that holds a great deal of promise if used appropriately. On the other hand, there are social systems that are affected by new technologies and fears of creating greater divides between rich and poor if technology is not accessible to all sectors of society. With this context in mind, this article outlines several global challenges and considers how biotechnology can be harnessed to meet them in sustainable and equitable ways.

Nati Harnik/AP/WWP

Pellets of plastic made of maize are poured into a dish.

The Energy Challenge, Climate Change, and the Environment

Fossil fuels are a finite energy resource, and we are expending them more quickly than nature can replenish them. Biotechnology has a role to play in the use of more renewable sources of energy. Biomass energy, for example, is a carbon-neutral energy source, as plants eventually take as much carbon from the atmosphere as they release. Researchers are engineering better cellulases—enzymes that can break down plant material into biofuels such as ethanol. Better cellulases will eventually lead to the more cost-effective production of sustainable bioenergy products.

Some believe that climate change will have the greatest impacts on the poor, who do not have the resources to move or adapt when natural disasters strike or their surroundings change. Not only would a transition to biomass energy have positive environmental effects; it could also lead to economic development in rural communities all over the world. Farmers could grow crops for their food, feed, and energy needs. However, they must have access to the technology that makes biomass conversion possible. Getting technologies to rural areas and building capacity to operate such systems will be challenging.

Other examples of the energy and environmental applications of biotechnology include microorganisms engineered to produce hydrogen gas from organic waste, plants engineered to make biodegradable polymers, molecular machines based on plant photosynthetic proteins to harness energy from the sun, bacteria engineered to break down environmental pollutants, and biosensors developed to rapidly detect harmful environmental contaminants. The environmental applications of biotechnology are often overlooked and underfunded, yet the sustainability of our planet in the face of an increasing population is an issue of utmost importance.

Agriculture, Food Quality, and Security

Biotechnology has taken off in areas of food and agriculture. For example, cotton, soybeans, maize, and other crops have been engineered to contain proteins from the bacterium *Bacillus thuringiensis* (Bt) that protect them from insect pests. Bt crops are grown widely in many countries. The cultivation of Bt cotton in China has significantly reduced the use of chemical pesticides that are dangerous to human health, benefiting rural farmers.

On the other hand, there have been concerns associat-

ed with Bt crops. Starlink was a Bt maize variety approved only for animal feed in the United States, given questions about its potential to be a human allergen. However, it eventually contaminated some maize-based products in the human food supply. Also, the genes for Bt proteins have been discovered in Mexican maize varieties, although Mexico has a moratorium on planting Bt maize. This contamination has caused concern because Mexico is the geographic center of diversity for maize, and many want to preserve native varieties for cultural and agronomic reasons. Therefore, in order to reap the benefits of genetically engineered crops, it is important that good international biosafety regimes be developed to avoid future mishaps and enhance confidence in the use of these crops.

Healthier and more nutritious foods are also being developed via biotechnology. For example, more than 100 million people are affected by vitamin A deficiency, which is responsible for hundreds of thousands of cases of blindness annually. Researchers have engineered a variety of rice to supply the metabolic precursor to vitamin A. This "golden rice" is being bred with local varieties to enhance its properties for growth in developing countries. Intellectual property hurdles have been overcome to distribute the rice for free to subsistence farmers—this is especially important because the cost of seed could otherwise be prohibitive. Researchers are developing other crops that have increased quantities of iron, vitamin E, essential amino acids, and healthier oils.

For the future, additional applications of biotechnology to food and agriculture could prove useful. The United Nations Environment Program ranks freshwater shortages as the second greatest environmental problem, behind climate change, for the 21st century. Drought- and salinity-tolerant crops tailored to developing countries could greatly enhance food security in areas where a combination of natural disasters and marginal land are sure to lead to famine in a given year. Through genomics and modern biotechnology, we are getting closer to understanding, identifying, and engineering the many traits that control water use and salt utilization in plants.

Health and Medicine

Medical applications of biotechnology are better known in the public's eye. Stem cells and cloning have gained unusual prominence in national and international politics. Stem cells are the early-stage cells in an organism that have been shown to give rise to different kinds of tissues. They have successfully replaced or repaired damaged tissue in animal models, and they hold great promise for treating human diseases such as Alzheimer's and diabetes. Although the vast majority of people agree that cloning to produce humans (reproductive cloning) is unacceptable, therapeutic cloning, in which the cloning process is used only to harvest stem cells, is hotly debated. Therapeutic cloning could supply stem cells that exactly match a patient, minimizing the serious risks associated with tissue rejection. These methods hold great promise. However, the ethical, cultural, and policy issues associated with them will continue to occupy scientists and politicians in the foreseeable future.

A fundamental application of biotechnology to medicine is in drug discovery. Humans have discovered drugs from natural sources by trial and error since the beginning of history. Now genomics and its companion field for proteins—proteomics—have allowed us to discover drugs more systematically. The automation of biochemical binding assays in small chips called microarrays enables scientists to screen thousands of chemical compounds for their effectiveness against disease-causing proteins in a very short time. This high-throughput screening, as it is called, would not have been possible without years of serious investment in basic biotechnology research.

With microarray analysis, the activity of thousands of genes can be quickly measured. Many researchers are harnessing this tool to determine early gene activity when

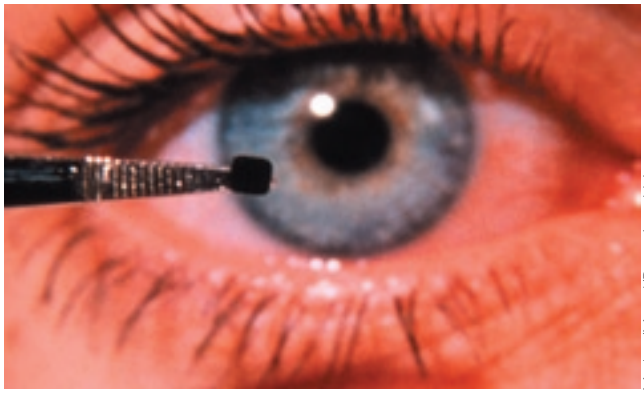
Jay Laprete/AP/WWP

A patient undergoes gene therapy.

humans are infected with pathogens. Rapid, noninvasive screens are envisioned for the future, and they will be especially important for infections that require immediate treatment in order to reduce spread and save lives, such as infections resulting from a bioterrorist attack. Nanosensors are being developed from particles that are about 50,000 times smaller than the diameter of human hair to detect protein and gene expression in individual cells

in the body, thus allowing the assessment of the health of cells at early stages of disease. The U.S. government is spending millions of dollars on nanosensors that can be placed in the blood of astronauts to monitor continuously for space radiation exposure.

Gene therapy, in which genes are delivered to specific diseased organs or tissues in the body to overcome metabolic deficiencies or other disease, is another area of great promise. The use of viruses to deliver genes has shown risks to human health, making trials with these viruses



Markus/Matzel/Peter Arnold, Inc.

A micro device for a retina implant.

controversial. The convergence of nanotechnology with biotechnology will allow for safer gene delivery methods that are not based on viruses. Chemically synthesized nanoparticles that carry genes or therapeutics specifically to diseased cells are currently being tested in animals.

Biotechnology also plays an important role in preventing disease. Vaccines produced by recombinant DNA methods are generally safer than traditional vaccines because they contain isolated viral or bacterial proteins, as opposed to killed or weakened disease-causing agents. However, many citizens in developing nations do not have access to any vaccines, let alone ones derived from biotechnology. Currently, most vaccines require cold storage and professional administration through injection. Therefore, researchers are working on genetically engineered plants to deliver vaccines through food. The cost of plant-derived, orally administered hepatitis B vaccine is estimated to be one-sixth that of current hepatitis B vaccines. Enough antigen to immunize all babies in the world each year could be grown on approximately 80 hectares of land. However, as with Bt crops, there are general concerns about pharmaceutical crops because they may cross-pollinate with food crops in the field. It will be especially important to develop biosafety regimes that either use crops that do not cross-pollinate (for example, male sterile) or isolate the pharmaceutical crops (for example, in greenhouses).

The Challenges

It is striking that a number of the above examples relate to the Millennium Declaration, an agreement reached in 2000 by more than 170 countries to address poverty, economic development, and environmental preservation. Yet science and technology are seldom integrated with international programs focused on social and economic development. There has been significant progress in meeting some of the goals of the Millennium Declaration, such as reducing poverty, increasing primary education and gender equality, and lowering child mortality. However, less progress has been made in fighting global disease and improving environmental sustainability. These are challenges in which biotechnology can play a role.

Investments in science and technology by any nation will eventually bear economic fruit. However, investments to address the social, political, cultural, and ethical issues surrounding applications of biotechnology are equally important. There are good ways to foster open dialogue on such issues. We may never agree on some applications of biotechnology, such as therapeutic cloning, but dialogue leads to better understanding of each other's views and respect for our differences.

We should not minimize the potential health and environmental risks of biotechnology. We need to fund studies of these effects by independent organizations. Regulatory systems should be streamlined to be effective, efficient, and transparent. Currently, there are few incentives for the independent study of regulatory systems and policy.

Finally, we need to invest in technologies that are tailored toward helping developing countries and building capacity in their communities, for example, through education, training, and assistance with intellectual property issues. Biotechnology investments have primarily been made in developed countries and on products that will offer financial returns. This focus is natural for the private sector, but a broader agenda is needed. Governments and other organizations should step in and invest in research and development in developing countries and in products that can benefit those countries. Through increased awareness of the social context of biotechnology and commitments to resolve existing issues, one can envision a future in which biotechnology is harnessed responsibly to help all nations and all people. ■

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

A CHEMICAL REACTION FOR BIOTECHNOLOGY: The 2005 Nobel Prize

Cheryl Pellerin

A chemical reaction with great commercial potential in the pharmaceutical, biotechnology, and food industries caught the eyes of the Royal Swedish Academy of Sciences this year. The academy awarded the 2005 Nobel Prize in Chemistry to three scientists—Americans Robert Grubbs and Richard Schrock, and Frenchman Yves Chauvin—for developing a reaction that streamlines the development and industrial production of bioengineered drugs, plastics, and other materials in a way that makes such production less expensive and more environmentally friendly.

"Metathesis is ... an important weapon in the hunt for new pharmaceuticals for treating many of the world's major diseases," the Royal Swedish Academy of Sciences said in announcing the prize. The work by the Nobel Prize winners, it said, will aid researchers in their efforts to develop biotech medicines to address such illnesses as bacterial infections, hepatitis C, cancer, Alzheimer's disease, Down's syndrome, osteoporosis, arthritis, inflammation, fibrosis, and HIV/AIDS.

The reaction that Grubbs, Schrock, and Chauvin developed is called "olefin" metathesis. Olefin metathesis starts with a carbon chain that has a carbon-carbon double bond, which is ordinarily hard to break. A special catalyst—a substance that increases the reaction rate without being consumed in the process—that has a carbon-metal double bond is added. During the reaction, all the elements of the carbon chain and the catalyst combine to form a single ring. The ring then breaks apart, and a carbon atom from the carbon-metal double bond has changed places with a carbon atom from the carbon-carbon double bond. The resulting two substances are a new chemical compound and a modified catalyst. Synthesizing this new compound in any other way would have been very complicated and required many more reaction steps.

"The discovery of metathesis involved finding ways to break [the carbon-carbon] bonds and reform them very easily under very mild conditions," according to Charles Casey, professor of chemistry at the University of Wisconsin and past president of the American Chemical Society.

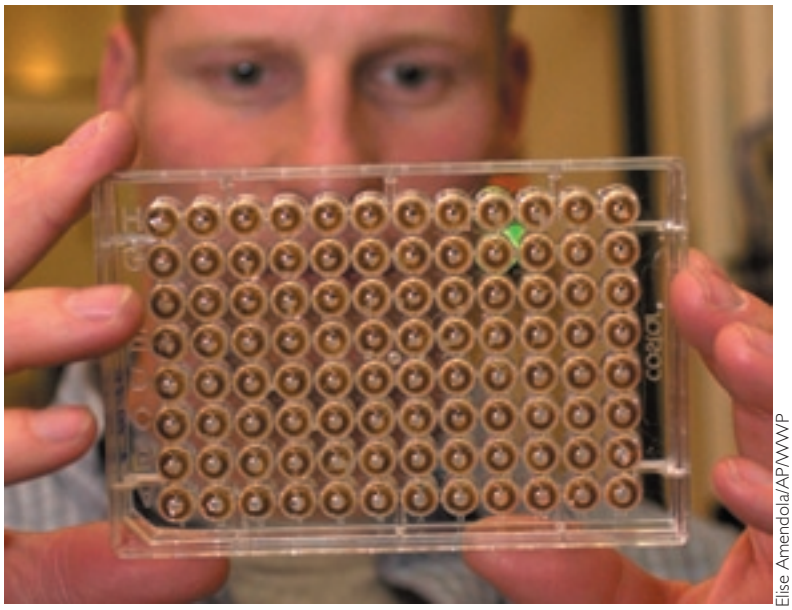
Many industrial biotechnology companies use olefin metathesis to produce candidates for drugs and other compounds. Metathesis can also be used to synthesize a naturally occurring substance, such as an insect hormone, and produce it in large quantity for use as a natural insecticide.

"There are all kinds of complex organic molecules that we'd love to synthesize," Casey said, "and these [metathesis reactions] are some of the most efficient ways to do it." ■

Cheryl Pellerin is a State Department science writer.

THE TRANSFORMING POWER OF MEDICAL BIOTECHNOLOGY

Bill Snyder



Elise Amendola/AP/WWP

Samples of purified DNA are being prepared for sequencing; a part of the Human Genome Project.

Tremendous progress has been made since the early gene splicing experiments from which the biotechnology industry emerged. New drugs and vaccines, improved and accelerated drug discovery, better diagnostic capabilities, and other medical uses attest to it. But the progress so far is viewed by many scientists as only a beginning. They believe that, in the not-so-distant future, the refinement of "targeted therapies" aimed at the biological underpinnings of disease should dramatically improve drug safety and efficacy, and the development of predictive technologies may lead to a new era in disease prevention, particularly in some of the world's rapidly developing economies. Yet the risks cannot be disregarded as new developments and discoveries bring new questions, particularly in such areas as gene therapy, the ethics of stem cell research, and the use of genomic information.

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Thirty years ago, more than 100 of the world's leading scientists gathered at the Asilomar Conference Center in Pacific Grove, California, to debate the potential risks of genetic engineering. Concerned that the technology of DNA (deoxyribonucleic acid) recombination could transform harmless microbes into dangerous human pathogens, the scientists agreed to a voluntary moratorium on certain experiments.

The dire predictions proved unfounded. On the contrary, gene splicing has fomented multiple revolutions in medicine: quick methods for detecting an infection or monitoring cholesterol levels, development of new vaccines and completely novel classes of therapeutics, and breakthroughs in understanding diseases as diverse as cystic fibrosis and cancer.

Out of the early gene-splicing experiments, the lively—and highly profitable—biotechnology industry emerged. DNA recombination made possible the sequencing of the human genome and laid the foundation for the nascent fields of bioinformatics, nanomedicine, and individualized therapy. Within the next two decades, many scientists

believe, the refinement of "targeted therapies" aimed at the biological underpinnings of disease should dramatically improve drug safety and efficacy, while development of predictive technologies such as proteomics may lead to a new era in disease prevention.

Yet concerns remain about the risks of gene therapy, the ethics of stem cell research, and the potential misuse of genomic information. Depending on one's point of view, biotechnology brims with promise or peril or a combination of the two.

The Initial Steps

The first "bioengineered" drug, a recombinant form of human insulin, was approved by the U.S. Food and Drug Administration (FDA) in 1982. Until then, insulin was obtained from a limited supply of beef or pork pancreas tissue. By inserting the human gene for insulin into bacteria, scientists were able to achieve bacterial production of large quantities of the life-saving protein. In the near future, patients with diabetes may be able to inhale insulin, eliminating the need for injections.

The first recombinant vaccine, approved in 1986, was produced by slipping a gene fragment from the hepatitis B virus into yeast. The fragment was translated by the yeast's genetic machinery into an antigen, a protein found on the surface of the virus that stimulates the immune response. This avoided the need to extract the antigen from the serum of people infected with hepatitis B.

Today there are more than 100 recombinant drugs and vaccines. Because of their efficiency, safety, and relatively low cost, molecular diagnostic tests and recombinant vaccines may have particular relevance for combating long-standing diseases of developing countries, including leishmaniasis (a tropical infection causing fever and lesions) and malaria.

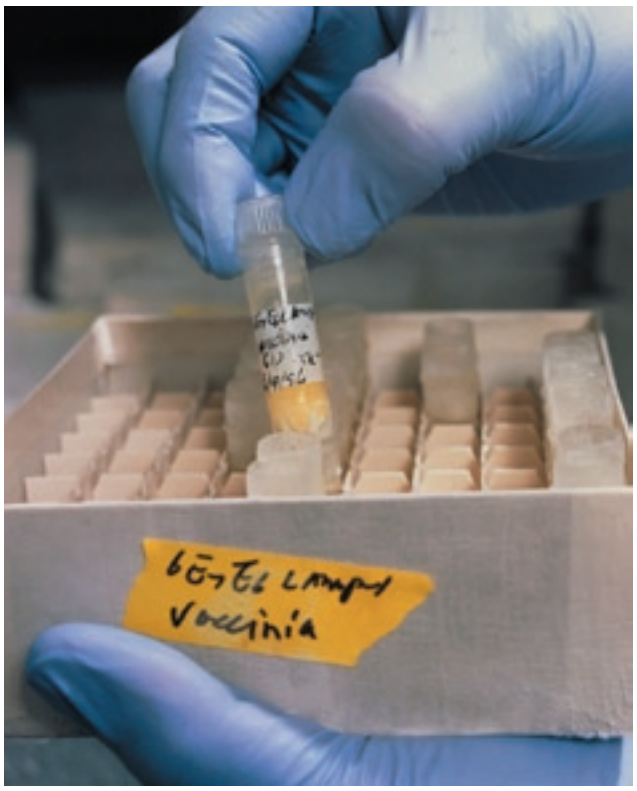
Improved Diagnostic Capabilities

Biotechnology also has dramatically improved diagnostic capabilities. The polymerase chain reaction, a method for amplifying tiny bits of DNA first described in the mid-1980s, has been crucial to the development of blood tests that can quickly determine exposure to the human immunodeficiency virus (HIV), for example.

The development of monoclonal antibodies in 1975 led to a similar medical revolution. The body normally produces a wide range of antibodies—immune system proteins—that root out microorganisms and other foreign invaders. By fusing antibody-producing cells with myeloma cells, scientists were able to generate antibodies that would, like "magic bullets," hone in on specific targets including unique markers, called antigens, on the surfaces of inflammatory cells.

Early examples include monoclonal antibodies that can prevent the body's immune system from rejecting organ transplants, and the much-heralded Herceptin, approved for treatment of advanced breast cancer in 1998. Other monoclonal antibodies have been approved for the treatment of multiple sclerosis and rheumatoid arthritis, and they currently are being tested in patients as potential treatments for asthma, Crohn's disease, and muscular dystrophy.

When tagged with radioisotopes or other contrast agents, monoclonal antibodies can help pinpoint the location of cancer cells, thereby improving the precision of surgery and radiation therapy, and showing—within 48 hours—whether a tumor is responding to chemotherapy. The proteins also can deliver a lethal dose of toxic drug to cancer cells, avoiding collateral damage to normal tissues nearby.



David Parker/Photo Researchers, Inc.

A cervical cancer vaccine based on a genetically engineered virus.

Transgenic Animals

Genetic testing currently is available for many rare disorders, such as hemophilia, which is caused by a mutation in a single gene. Little can be done to prevent or slow some of these diseases, however, and the underpinnings of more complex illnesses such as cancer, heart disease, and mental illness are as yet not well understood.

That situation is changing, thanks in part to the ability, achieved in the early 1980s, to insert DNA from humans into mice and other animals.

Because they now express human genes, "transgenic" animals can be studied as models for the development of diabetes, atherosclerosis, and Alzheimer's disease. They also can generate large quantities of potentially therapeutic human proteins. For example, a recombinant "clot-buster," expressed in the milk of transgenic goats, currently is being tested in patients.

The sequencing of the human genome, completed just two years ago, also has given scientists an incredibly rich "parts list" with which to better understand why and how disease happens. It has given added power to gene expression profiling, a method of monitoring expression of thousands of genes simultaneously on a glass slide called a microarray. This technique can predict the aggressiveness of breast cancer in certain instances.

Another rapidly developing field is proteomics—the use of technologies such as mass spectrometry to detect protein biomarkers in the blood that may indicate early signs of disease, even before symptoms appear. One such marker is C-reactive protein, an indicator of inflammatory changes in blood vessel walls that presage atherosclerosis.

High-throughput screening, conducted with sophisticated robotic and computer technologies, enables scientists to test tens of thousands of small molecules in a single day for their ability to bind to or modulate the activity of a "target," such as a receptor for a neurotransmitter in the brain. The goal is to improve the speed and accuracy of drug discovery while lowering the cost and improving the safety of pharmaceuticals that make it to market.

Response to Antibiotic Resistance

Biotechnology also is solving the urgent and growing problem of antibiotic resistance.

With the help of bioinformatics—powerful computer programs capable of analyzing billions of bits of genomic sequence data—scientists are cracking the genetic codes of bacteria and discovering "weak spots" vulnerable to attack by compounds identified via high-throughput screening. This kind of work led in 2000 to the approval of Zyvox, the first entirely new antibiotic to reach the market in 35 years.

Lytic bacteriophages, viruses that infect and kill bacteria, may be another way to counter resistance. First used to treat infection in the 1920s, "phage therapy" was largely eclipsed by the development of antibiotics. Earlier this year, however, researchers in the former Soviet republic of Georgia reported that a biodegradable polymer impregnated with bacteriophages and the antibiotic Cipro successfully healed wounds infected with a drug-resistant bacterium.

Nanomedicine is another rapidly moving field. Scientists are developing a wide variety of nanoparticles and nanodevices, scarcely a millionth of an inch in diameter, to improve detection of cancer, boost immune responses, repair damaged tissue, and thwart atherosclerosis. Earlier this year, the FDA approved a nanoparticle bound to the cancer drug Taxol for treatment of advanced breast cancer. Another nanoparticle is being tested in heart patients in the United States as a way to keep their heart arteries open following angioplasty.

Studies of human embryonic stem cells aimed at replacing cells damaged by diabetes, cancer, or Alzheimer's disease have been controversial in the United States because of concerns that such research requires the destruction of potential human life. Research, however, is progressing rapidly in privately funded labs in the United States and throughout the world.

The Challenge of Gene Transfer

Some biotech approaches to better health have proven to be more challenging than others. An example is gene transfer, the replacement of a defective gene with a normally functioning one. The normal gene is delivered to target tissues in most cases by an adenovirus that has been genetically altered to render it harmless.

The first gene transfer experiment, conducted in 1990 at the National Institutes of Health (NIH), successfully corrected an enzyme deficiency in a four-year-old girl. Nine years later, however, the death of a different patient, apparently from an overwhelming immune reaction to the gene-carrying virus, led to stricter safety requirements in clinical trials.

Progress has been slow since then, although gene transfer currently is being studied in patients in the United States and other countries as a potential treatment

Lawrence Jackson/AP/WWP

Howard University researchers are building a genetic database on African-Americans.

for peripheral arterial disease, Parkinson's disease, and certain forms of cancer. The Chinese government recently approved the first marketed gene transfer for treatment of head and neck cancer.

Scientists do not believe they will find a single gene for every disease. As a result, they are studying relationships between genes and probing populations for variations in the genetic code, called single nucleotide polymorphisms, or SNPs, that may increase one's risk for a particular disease or determine one's response to a given medication.

This powerful ability to assign risk and response to genetic variations is fueling the movement toward "individualized medicine." The goal is nothing short of prevention, earlier diagnosis, and more effective therapy by prescribing interventions that match patients' particular genetic characteristics.

Pursuing New Possibilities

In response to concerns that information about disease risk could be used to deny people health insurance or employment, a raft of legislation at both the state and federal levels has been passed in recent years in the United States to prohibit genetic discrimination.

Meanwhile, the NIH, a major supporter of medical research in the United States, is encouraging academic institutions to pursue the new science and new possibilities. Vanderbilt University Medical Center in Nashville, Tennessee, for example, is revising its research enterprise strategic plan to emphasize personalized medicine, drug discovery, and population health care—how best to deliver health care to populations.

The pursuit of cutting-edge research "brings us closer to our ultimate goal of eliminating disability and disease through the best care modern medicine can provide," says Dr. Harry R. Jacobson, Vanderbilt's vice chancellor for health affairs.

Biotechnology is a neutral tool; nevertheless, its capabilities raise troubling ethical questions. Should prospective parents be allowed to "engineer" the physical characteristics of their embryos? Should science tinker with the human germline, or would that alter in profound and irrevocable ways what it means to be human?

More immediately, shouldn't researchers apply biotechnology—if they can—to eliminating health disparities among racial and ethnic groups? While genetic variation is one of many factors contributing to differences in health outcome (others include environment, socioeconomic status, health care access, stress, and behavior), the growing ability to mine DNA databases from diverse populations should enable scientists to parse the roles these and other factors play.

"Understanding the genetic underpinnings of heart disease and cancer will aid the development of screening tools and interventions that can help prevent the spread of these devastating disorders into the world's most rapidly developing economies, including the Far East," says Dr. Jeffrey R. Balser, associate vice chancellor for research at Vanderbilt.

Biotechnology cannot solve complicated health problems alone. Supportive health care infrastructures must be put in place to guarantee access to the new screening tests, vaccines, and medications, and cultural, economic, and political barriers to change must be overcome. Research must include more people from disadvantaged groups, which will require overcoming long-held concerns some of them have had about medical science.

"It will also be critical to make sure that new knowledge and technologies are not used to discriminate inappropriately against individuals and groups," says Dr. Ellen Wright Clayton, co-director of the Vanderbilt Center for Biomedical Ethics and Society. "The laws that have already been passed are a step in the right direction, but more work remains to be done to ensure the kind of inclusive and healthy society to which we aspire." ■

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

THE RACE AGAINST GENE DOPING

Huntington F. Willard

U.S. baseball player Rafael Palmeiro dives to grab a ball. Roberto Borea/AP/WWP

In the last few years, public discussion of performance-enhancing drug usage in sports has reached a fever pitch. After swearing to the U.S. Congress in March 2005 that he had never used steroids, Baltimore Oriole baseball player Rafael Palmeiro, a one-time certainty for the Baseball Hall of Fame, was given a 10-game suspension in August. His transgression? A positive test for steroids. Earlier leaked grand jury testimony in an investigation into a San Francisco laboratory appeared to implicate several other high-profile ballplayers and track and field stars in steroid usage. Elsewhere, anti-doping officials regularly test competitive cyclists and sanction those who test positive for drug use. A recent retrospective test of 70 urine samples from the 1998 Tour de France found 40 to be positive for EPO, a hormone that promotes the formation of red blood cells and can increase stamina. No reliable test for EPO was available in 1998.

For all of the recent headlines about anabolic steroid usage in American football and synthetic hormone usage in European cycling, high-tech gene doping may soon have the dubious honor of rendering them obsolete. Commissioner of the National Football League Paul Tagliabue, appearing before Congress barely a month after Palmeiro issued his denial, said as much: "When [gene doping] happens, the [drug doping] issues that our society is discussing today ... will be as irrelevant as the blacksmith in the automobile age."

Gene doping, the nontherapeutic use of DNA and/or cells to enhance athletic performance, has the potential to offer the cheater a "souped-up," or supercharged, body that can run faster and jump higher but whose modifications are virtually undetectable. If an athlete injects himself with additional copies of a gene already present in his body, how is one to distinguish the original from the copy? Only an expensive and invasive muscle biopsy could detect the presence of a slightly altered synthetic gene.

We know that a high proportion of our physical prowess is hardwired in our genomes. A recent study of young adult males undergoing cycle training suggested that as many as 500 genes and DNA markers scattered across the genome may be associated with athletic performance and health-related fitness. Mice lacking the myostatin gene, for example, tend to develop huge muscles, the result of more and bigger muscle fibers—these rodents have been nicknamed "Schwarzenegger mice." How many body builders could resist that?

As with other doping methods, the safety issues surrounding gene doping should be enough to give athletes pause. Abuse of EPO, for example, can have devastating consequences. EPO can thicken the blood to such an extent that it will cause heart failure, especially in elite athletes whose resting heart rates tend to be extraordinarily slow. Not long after the arrival of EPO in cycling, 18 Belgian and Dutch cyclists died

suddenly of heart attacks. So it is fair to ask: What will the risks of EPO gene doping be once the EPO gene can be administered without fear of detection?

Some have argued that the best way to control gene doping is to legalize it. After all, they say, if Tiger Woods can have Lasik eye surgery to improve his vision to 20/10 and thereby help his golf game, why shouldn't a cyclist be able to modify his genes? Moreover, this argument goes, by making gene doping legal and regulating it, safety standards could be imposed.

Cyclists ride in Paris during a Tour de France race. Michel Spingler/AP/WWP

But would gene doping violate the spirit of sports? So far the official response is yes. In recent years, both the International Olympic Committee and the World Anti-Doping Agency have added gene doping to their lists of banned substances (the International Cyclists' Union has been strangely quiet on the subject). Whether a practical means of enforcing those bans can be developed remains to be seen.

In our competitive culture, the desire to win is ever present. In early 2005, after U.S. Major League Baseball was shamed into imposing a somewhat stricter steroid-testing regimen, the Office of the Commissioner of Baseball released the names of 41 minor league players who had failed spring-training drug tests. Remarkably, these players stayed on the "juice" (banned drugs), even though they knew they were likely going to be tested, caught, and publicly identified. And what of Palmeiro? If he knowingly took steroids, could he somehow not have known he would be instantly transformed from hero to pariah if he were caught? Conventional doping may be going the way of the blacksmith, but there appears to be little doubt that gene doping will soon be here to stay. What will that mean for the games we play? ■

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PLANT BIOTECHNOLOGY: Advances in Food, Energy, and Health

Richard Hamilton, Richard B. Flavell, and Robert B. Goldberg

The world will need to produce more food, feed, and fiber during the next 50 years than in the entire history of humankind. The technological revolution created by genomics provides a unique opportunity to achieve this goal. Genetically engineered herbicide- and insect-resistant crops are delivering benefits through more affordable food, feed, and fiber that require fewer pesticides, conserve more soil, and provide for a more sustainable environment. And contrary to criticism, biotech crops have proven to be as safe as, or safer than, those produced by conventional methods. In the future, advances in agricultural biotechnology will result in crops that have improved tolerance to drought, heat, and cold; require fewer fertilizer and pesticide applications; produce vaccines to prevent major communicable diseases; and have other desirable traits.

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Plants and agriculture have played an important role in the development and advancement of civilization. Plants provide sustainable supplies of food for humans, feed for animals, fiber for construction and clothing, medicines and drugs, perfumes, chemicals for industrial processes, energy for cooking and heating, and, most recently, biomass to meet the increasing demand for transportation fuels. Plants also play a major environmental role by preventing soil erosion, boosting levels of oxygen in the atmosphere, reducing carbon dioxide emissions from burning fossil fuels, and enriching soils with nitrogen, which they cycle between soil and the atmosphere.

AGRICULTURE IN THE 21ST CENTURY

If population growth continues as predicted, we will need to produce more food, feed, and fiber during the next 50 years than in the entire history of humankind. And we will need to do this on a decreasing amount of land that is suitable for agriculture and crop production.

This presents several major challenges for 21st-century agriculture:

- Crop yields need to be increased beyond the spectacular gains of the 20th century in order to meet increasing demand and save open space.
- Inputs required for intensive agriculture, such as water and fertilizers, need to be reduced.
- Crops need to be developed that can flourish in harsh conditions so that substandard land can be used to grow important crops, growing seasons can be extended, and yields are not decreased by drought, heat, cold, and other stresses.
- The environmental impacts of agriculture resulting from the use of pesticides, herbicides, and fertilizers need to be reduced. For example, crops need to be engineered that are resistant to pests, that take up nutrients more effectively from the soil, and that can out-compete weeds for water and sunlight.
- Food crops need to be optimized for human health and nutrition, providing essential vitamins, amino acids, and proteins to help eliminate malnutrition and disease.
- Novel energy crops need to be developed that are high yielding and that can be used as a renewable source of biomass for fuels to limit our dependence on a petroleum-based energy system.
- We need to go "back to the future" and engineer specialty crops that can be used as factories to produce chemicals and proteins for industrial and medical applications—for example, plastic precursors and vaccines to combat human and animal pathogens.

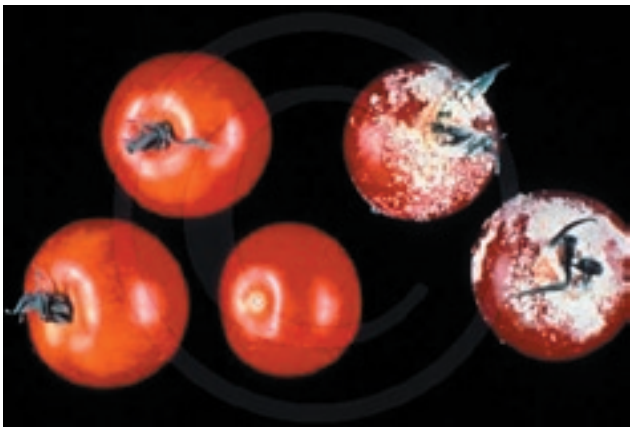
These challenges will require application of the most sophisticated breeding and molecular techniques available today, as well as the development of new ones. Nevertheless, there has never been a more exciting time for plant biology and agriculture, and the technological revolution created by the genomics era provides a unique opportunity to achieve these goals over the next two decades or sooner.

Using Biotechnology to Develop New Crops

Most of the crops that we grow today did not spring forth from a mythical Garden of Eden and do not grow "naturally." To the contrary, most major crops were engineered by our ancestors thousands of years ago from wild relatives by selecting and breeding for traits that optimized crops for human use. These early genetic engineers learned how to recognize random mutations that appeared in wild plant populations and to use this genetic variability to create the food crops that we use today. For example, maize was bred from teosinte grass 10,000 years ago by selecting for a few genes that control cob size, seed structure and number, and plant architecture. Almost all of the crops that we use today, such as wheat, soybean, rice, potato, cabbage, broccoli, and tomato, were engineered in an analogous manner; that is by use of breeding technologies to create new gene combinations within a crop species and then selecting for better traits in the progeny.

The most significant innovations that are transforming agriculture are genetic engineering technologies that allow novel genes to be isolated, manipulated, and re-inserted into crop plants; the ability to regenerate almost any plant species from tissue culture into a fertile plant; and the development of high-throughput genomic technologies. The latter permits the mapping and sequencing of entire plant genomes and the identification of genes that control all plant processes, including those that can contribute to meeting the challenges of agriculture in the future, such as genes for disease resistance, drought resistance, seed size, and number.

At the genetic level, crop breeding depends on randomly introducing mutations, or genetic variability, into a plant's genome and then selecting from a large population the small subset of changes that result in a positive change. In the vast majority of cases, the genetic changes that are made are unknown. By contrast, genetic engineering affords a more precise alternative to breeding, and, because of its precision, it can be used to develop new, valuable traits in a small fraction of the time required to pursue the relatively imprecise techniques of breeding. Genes that have been characterized extensively can be introduced into crop plants in a precise and directed way in order to generate novel, genetically enhanced crops with traits that would not be possible to achieve using classical breeding procedures.



Volker Steger/Peter Arnold, Inc.

Mold-resistant bioengineered tomatoes and regular tomatoes over time.

The Growth and Benefits of Biotech Crops

The first genetically engineered crops developed in the early 1980s were resistant to herbicides and insects. Today, these two traits—herbicide and insect resistance—account for the majority of biotech crops. Over the past 20 years, there has been a worldwide effort to isolate genes that will provide a long list of traits that breeders, farmers, consumers, and industrialists have nominated for improvement in a variety of crops. Plant biotechnology and genetic engineering is now a major activity in the public and private sectors and is becoming a significant part of plant breeding on all continents. In fact, there has never been a more exciting time for agriculture because powerful genomic technologies make it possible to identify genes that have the potential for revolutionizing crop production over the next 50 years.

In 2005, we celebrate 10 years of biotech crop cultivation. During that period, 400 million hectares of genetically enhanced biotech crops have been grown. Biotech crops have been adopted by farmers all over the globe at a rate faster than any crop varieties in the history of agriculture—even faster than high-yielding hybrid maize during the last century. Since their introduction in 1996, the use of genetically enhanced biotech crops has grown at a rate of more than 10 percent per year, and in 2004, according to a report of the International Service for the Acquisition of Agri-biotech Applications, their adoption increased 20 percent. The main crops carrying new biotech genes are soybean, maize, cotton, and canola, accounting, respectively, for 56 percent, 14 percent, 28 percent, and 19 percent of the worldwide acreage for these crops. Together, they occupy nearly 30 percent of the global area devoted to these crops. In the United States, biotech soybean (herbicide resistant), maize (herbicide and insect resistant), and cotton (herbicide and insect resistant) account for

Betsy Blaney/AP/WWP

A cotton field.

approximately 85 percent, 75 percent, and 45 percent of the total acreage for these crops.

The United States is the leading grower of biotech crops, with more than 48 million hectares, followed by Argentina (16 million hectares), Canada (6 million hectares), Brazil (4.8 million hectares), and China (4 million hectares). The value of biotech crops is nearly $5 billion, representing 15 percent and 16 percent of the global crop production and seed markets, respectively. Biotech crops are delivering benefits through more affordable food, feed, and fiber that require fewer pesticides, conserve more soil, and provide for a more sustainable environment. In addition, the annual income of poor farmers in the developing world has increased significantly from the use of biotech crops, according to recent data from the United Nations Food and Agriculture Organization. Most of the value added has gone to those farmers rather than to the technology providers.

Concerns Limiting the Growth of Biotech Crops

Although crops produced by using biotechnology and genetic engineering have been adopted at warp speed and are the most tested and studied crops in human history, agricultural biotechnology is not without controversy. Opposition to the use of biotechnology and genetically engineered organisms derived from it is largely confined to Europe, where a small but vocal group of activists have fomented public opinion against the technology.

In an environment where non-biotechnology-related food scares over mad cow disease and dioxin have eroded the European public's confidence in the regulatory oversight of their food supply, activist groups have been able to generate substantial distrust of agricultural biotechnology. This distrust is misplaced: The hypothetical fears have failed to materialize after more than 10 years of safe use and more than 400 million hectares of cropland planted with genetically enhanced varieties. There are no known examples of ill effects of these crops in humans, and there are demonstrable environmental benefits. In fact, major studies, which have been published in peer-reviewed journals over the past five years, indicate that biotech crops are substantially equivalent to their non-biotech counterparts, that yields have been increased, that pesticide applications have been reduced, that large amounts of soil have been conserved, and that management practices have been successful in preventing or minimizing the resistance to

Joerg Boethling

Genetically modified rice plants.

insect-resistant crops. Although no technology is without zero risk, biotech crops have proven to be as safe as, or safer than, those produced by conventional methods.

What About the Future?

In the next decade, further advances in agricultural biotechnology will result in crops that have improved tolerance to drought, heat, and cold; require fewer fertilizer and pesticide applications; produce vaccines to prevent major communicable diseases; have increases in seed size,

Scott Olson/Getty Images

Various corn hybrids are grown for use in ethanol production.

number, and nutritional content; and are able to regenerate in the absence of fertilization—fixing hybrid vigor. Crops will also be generated that are enhanced nutritionally to help alleviate malnutrition in the developing world. Currently, "golden rice 2" cultivars undergoing field testing are capable of delivering as much as 30 micrograms of beta-carotene, a precursor to vitamin A, according to a recent article by Jacqueline Paine and others. The authors estimate that this amount of beta-carotene should provide at least 50 percent of the recommended daily allowance for vitamin A in a typical child's portion of 60 grams of rice.

Beyond applications to increase production of food, feed, and fiber, biotechnology is making a substantial contribution to the energy area. Advances in biotechnology have enabled the production of large amounts of inexpensive cellulases that can be used to convert cellulose to simple sugars that can, in turn, be fermented into fuels such as ethanol. Recent estimates from the U.S. Department of Energy indicate that the United States could obtain 30 percent or more of its transportation fuels from biomass sources by 2020. Agricultural biotechnology has the potential to increase this number even further by enhancing biomass yield density, improving the processing characteristics of the biomass feedstock, and decreasing the need for agronomic inputs such as water, fertilizer, and pesticides.

Several key countries, notably the United States and China, are pushing ahead in agricultural biotechnology, making the necessary investments in research and development and providing a viable regulatory system for the introduction and commercialization of new bio-enhanced crops.

If we are going to create a new kind of agriculture in the 21st century that is both sustainable and productive with respect to food security and energy self-sufficiency, we will need to use all of the scientific tools and discoveries at our disposal, including biotechnology and genetic engineering, and to follow the continuous path of agricultural breakthroughs that have advanced human progress for thousands of years. ■

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BIOTECH BUGS

Following miracle cures and miracle foods, genetically modified (GM) bugs are generating a buzz in the scientific community as possibly the next "miracle" in the field of biotechnology. The successful application of GM insects could dramatically improve public health, particularly in developing countries, enhance agricultural production, and improve the natural environment, according to some scientists. It also could make one hesitate whether to hit a mosquito on one's neck because it can fight rather than carry a disease.

There are two types of GM insects under research: paratransgenic and transgenic. Paratransgenic insects are created by integrating a piece of DNA manipulated in the laboratory (referred to as the transgene) into the microbes that naturally inhabit their alimentary canal. Genes expressed in these microbes can alter the characteristics of the host insect. Transgenic insects are the product of the physical integration of transgenes into the chromosomes of an insect.

Genetically altering an insect so that all of its descendants will also be genetically altered requires that the initial integration of the transgene occur in the chromosomes of cells that will produce sperm or eggs (most insect reproduction is sexual). GM insects must have characteristics readily visible so scientists or other stakeholders can have a way of controlling them during research, for example, in order to separate male from female insects.

Scientists are working to develop a broad array of insects with new characteristics that could make them useful in fighting the spread of infectious diseases, controlling noxious weeds and insect pests, and producing pharmaceuticals. For example, honeybees can be genetically altered in a way that makes them resistant to diseases and parasites, and genetically engineered silkworms can produce industrial proteins for application in the creation of novel materials.

But no matter how productive those GM honeybees and silkworms can be, the greatest interest lies in GM bugs that may be able to save lives. Mosquitoes spread malaria, which infects 300 million to 500 million people and kills over 1 million annually, according to the World Health Organization. Chemical pesticides currently being used have negative effects on human health and the environment. And the emergence of insects resistant to many pesticides has undermined the efficacy of these pesticides.

AP/WWP/USDA

GM mosquitoes carry a promise of a clean and radical solution to the malaria problem. Scientists want to genetically modify male insects, which then could be bred, sterilized, and released into the wild to mate with females. Such skewed reproducing would lead to the eradication, or at least a dramatic reduction, of the natural mosquito population.

Another approach is to infiltrate genes for malaria resistance into the existing population of these insects. Introduced at high enough frequencies, such infiltration could decrease transmission of the disease, according to Anthony James, professor of biology and biochemistry at the University of California, Irvine.

The first confined field trials with different GM insects have already been conducted, and some projects are expected to reach full environmental release within three to five years. But a swarm of GM insects is nowhere near on the horizon. Technological and other obstacles will prevent scientists and businesses from wide-scale releases of transgenic bugs for at least 5 to 10 years or more, according to Luke Alphey of Oxford University's Department of Zoology.

Scientists and regulators also need to deal with uncertainty about the lasting effects these insects could have on ecosystems, public health, and food safety. What is more, the fact that insects do not respect borders creates international regulatory challenges that the world has never faced with GM crops. The United States and many other governments currently have no comprehensive policies on how transgenic insects will be reviewed, and international organizations are not involved yet in the relevant regulatory process. As a result, a 2004 report by the Pew Initiative on Food and Biotechnology concludes that the research threatens to outpace regulatory preparedness. The report says that if regulators and scientists want to have a clear set of rules in place before unconfined field testing is ready to occur, they will need to start discussions now. ■

Source: Adapted from materials produced by the Pew Initiative on Food and Biotechnology, including September 2004 conference papers on biotech bugs.

DESIGNING NOVEL MATERIALS AND MOLECULAR MACHINES

Shuguang Zhang

By imitating nature, scientists are designing completely new molecular patterns that can serve as a blueprint of new materials and sophisticated molecular machines. In the emerging field of nanotechnology, basic natural building blocks such as amino acids are used to create structures such as peptides and proteins for applications in medicine and energy. Nanobiotechnologists have begun to exploit molecular self-assembly as a fabrication tool for building new nanobiostructures such as nanotubes for metal casting, nanovesicles for drug encapsulations, and nanofiber scaffolds for growing new tissues. They also have constructed an extremely high-density nanoscale photosystem and ultra-lightweight solar-energy-harvesting molecular machines. With better understanding of these seemingly intractable phenomena, one day mankind may be able to use nano devices to repair body parts or to rejuvenate the skin, enhance human capabilities, harness the unlimited solar energy, and achieve other feats that seem impossible today.

Shuguang Zhang *is associate director of the Center for Biomedical Engineering at the Massachusetts Institute of Technology.*

About 10,000 years ago, humans began to domesticate plants and animals. Now it's time to domesticate molecules.

— Susan Lindquist, Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology

Biotechnology, which is known primarily by its medical and agricultural applications, is increasingly being focused on the building of new biological materials and machines in an astonishing diversity of structures, functions, and uses. The advent of nanotechnology has accelerated this trend. Learning from nature, which over billions of years has honed and fashioned molecular architectural motifs to perform a myriad of specific tasks, nanobiotechnologists are now designing completely new molecular patterns—bit by bit, from the bottom up—to build novel materials and sophisticated molecular machines. Over the next generation, advances such as new materials to repair damaged tissues and molecular machines to harness solar energy from the smallest molecular amino acids and lipids will likely have an enormous impact on our society and the world's economy.

Modern biotechnology has already produced a wide array of useful products, such as humanized insulin and new vaccines. But what lies ahead can be even more revolutionary. That is why governments small and large, and industries local and global, are increasingly seeking to attract biotechnology talent and investment. There is no doubt that biotechnology, helped by the tools of nanotechnology, is expanding at an accelerating rate, and that the best is yet to come.

IMITATING NATURE

Nature itself is the grandmaster when it comes to building extraordinary materials and molecular machines atom by atom and molecule by molecule. Shells, pearls, corals, bones, teeth, wood, silk, horn, collagen, muscle fibers, and extra-cellular matrices are just a few examples of natural materials. Multifunctional macromolecular assemblies, such as hemoglobin, polymerases, and membrane channels, are all essentially exquisitely designed molecular machines.

Through billions of years of molecular selection and evolution, nature has produced a basic set of molecular building blocks that includes 20 amino acids, a few nucleotides—the structural units of nucleic acids such as ribonucleic acid (RNA) and deoxyribonucleic acid (DNA)—a dozen or so lipid molecules, and two dozen sugars. From these seemingly simple building blocks, natural processes are capable of fashioning an enormously diverse range of fabrication units that can further self-organize into refined structures, materials, and molecular machines that not only have high precision, flexibility, and error-correction capacity, but also are self-sustaining and evolving. For example, the photosynthesis systems in some bacteria and all green plants take sunlight and convert it into chemical energy. When there is less sunlight, as, for example, in deep water, the photosystems must evolve to become more efficient to collect the sunlight.

In the early 1990s, biotechnologists began to learn how to manipulate natural building blocks with at least one relevant dimension being between one nanometer (one billionth of a meter) and 100 nanometers to fabricate new molecular structures, thus ushering science and technology into the age of designed molecular materials. Much like clay and water can be combined to make bricks with multiple uses that, in turn, can be used to build walls such as the Great Wall of China, houses, or roads, basic natural building blocks such as amino acids can be used to create structures such as peptides and proteins that can be used for a variety of purposes. For example, animals grow hair or wool to keep themselves warm, shellfish grow shells to protect their tissue from harm, spiders spin silk to capture insects, and our cells make a lot of collagens to keep cells together to form tissues and organs.

If we shrink the construction units one billion times to the nanoscale, we can construct molecular materials and machines from prefabricated units in a way similar to that in which a house is assembled from prefabricated parts.

Peptides formed from amino acids are molecular architectural units that are proving very useful in the development of new nanobiological materials. In water and in the body fluids, these peptides form well-ordered nanofiber scaffolds useful for growing three-dimensional (3-D) tissue and for regenerative medicine. For example, scientists have fabricated artificial cartilage and bones to replace damaged tissue using the biological scaffolds and cells.

CGhim Wei Ho/Mark Welland, Nanostructure Center, University of Cambridge

A 3-D nanomaterial grown from tiny droplets of a liquid metal on a silicon surface.

Furthermore, scientists have also shown that the designer self-assembling peptide nanofibers can stop bleeding instantly, a characteristic useful in surgeries. New peptides are proving to be remarkably useful in drug, protein, and gene deliveries, because they can encapsulate some water-insoluble drugs and ferry them into cells and other areas of the body. They also are essential to fabricating bio-solar, energy-harvesting molecular machines that use the photosystem from spinach and tree leaves.

Molecular Self-assembly

All biomolecules, including peptides and proteins, naturally interact and self-organize to form well-defined structures with specific functions. By observing the processes by which these biological molecular structures are assembled in nature, nanobiotechnologists have begun to exploit self-assembly as a fabrication tool for building new nanobiostructures such as nanotubes for metal casting, nanovesicles for drug encapsulations, and nanofiber scaffolds for growing new tissues.

Molecular self-assembly involves mostly weak bonds—as does human handholding—that can be joined and disjoined quickly. This is in sharp contrast to the very strong bonds that join our arms to our body. Individually, weak molecular forces are quite insignificant. Collectively, weak interactions such as the hydrogen bond and the ionic bond play an indispensable role in all biological structures and their interactions. The water-mediated hydrogen bond, in which numerous water molecules work as a bridge to connect two separate parts, is especially important for biological systems, since all biological materials interact with water. The bond, found in all collagens, works to increase the moisture for an extended time.

As to molecular building blocks, the designed peptides resemble the toy Lego bricks that have both pegs and holes arranged in a precisely determined manner and can be assembled into well-formed structures. Often referred to as "peptide Legos," these new molecular bricks under certain environmental conditions spontaneously assemble into well-formed nanostructures.

In water, peptide Lego molecules self-assemble to form well-ordered nanofibers that further associate to form scaffolds. One such nanofiber scaffolding material that has been commercially realized is PuraMatrix, so called because of its purity as a biotechnologically designed biological scaffold. Biomedical researchers currently use it worldwide to study cancer and stem cells, as well as to repair bone tissue.

Since these nanofiber scaffolds contain 5 to 200 nanometer pores and have extremely high water content, they are of potential utility in the preparation of 3-D cell and tissue growth and in regenerative medicine. In addition, the small pore size of these scaffolds may allow drugs to be released slowly so people do not have to take their medicine several times a day but rather once over a longer period. A slow-release nanoscaffold device can be implanted on the skin with medicine supplies sufficient for months or years.

Creating More Building Blocks

Using nature's lipids as a guide, a new class of lipid-like peptide detergents has been designed. These peptides have seven to eight amino acids, giving them a length similar to naturally occurring lipids, which make up cell walls 20,000 times thinner than the diameter of a piece of human hair.

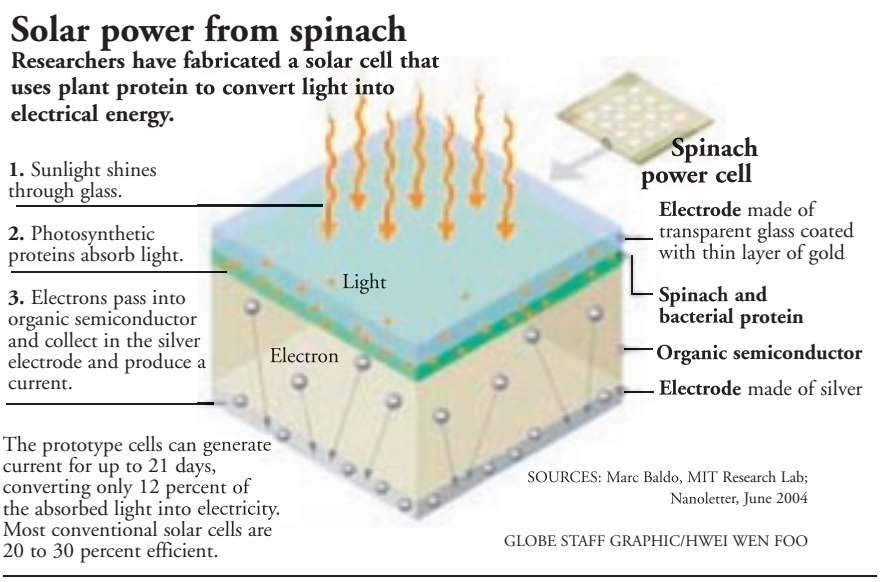
Simple lipid-like peptide detergents produce remarkably complex and dynamic structures in the same way that the assembly of numerous simple bricks can make many different and distinctive architectural structures.

Some peptide detergents have been found to be excellent materials for stabilizing notoriously hard-to-stabilize membrane proteins—protein molecules attached to or associated with the membrane of a cell—thus opening a new avenue for overcoming one of the biggest challenges in biology: obtaining clear pictures of the ubiquitous and vital membrane proteins.

Numerous drugs exert their effect through membrane proteins. But how these drugs interact with vital membrane proteins at the finest molecular level remains largely unknown. The designed peptide detergents promise to change this. If we can fully understand the interactions of these proteins, we may be able to produce more effective and efficient drugs with few or no side effects.

Harnessing Solar Energy

Detailed molecular study of how membrane proteins function is just an exercise in understanding them. By deepening our knowledge of how cells communicate with their surroundings, we learn how all living systems respond to their environments. With this know-how, modern nanobiologists have begun to fabricate advanced molecular machines able to develop extremely sensitive sensors for medical detection or to harness bio-solar energy. For example, ancient Chinese doctors smelled a patient to diagnose a medical problem because they believed that an illness can change a patient's body odor or secretion. In modern medical science, a number of instruments are used to make an accurate diagnosis. In the future, a smell sensor as sophisticated as a dog's nose could help distinguish people with medical problems from healthy ones. In the United Kingdom, dogs have already demonstrated their ability to identify people suffering from cancer by sniffing their odors.



Courtesy of *The Boston Globe*

Figure 1. The spinach chip and bio-solar energy-harvesting molecular machine. The photons (either from the sun or any other light) can be directly converted into electric energy using the combination of a natural green plant photosynthetic system and semiconducting material carbon C_{60} and conducting materials—gold and silver electrodes.

No one would argue that affordable, sustainable, and environmentally sound energy is requisite for the welfare of modern civilization. With environmental damages caused by fossil fuel pollution and the demand for energy burgeoning worldwide, the world's energy problems are now more urgent than ever. Alternative solutions, long debated but rarely seriously pursued, are now being pursued with a sense of urgency.

Further, the increasingly mobile nature of computing and communication, and the nanonization of materials and molecular machines, demand that smaller, lightweight, self-sustaining energy sources be developed. An obvious

source of infinite energy is the sun. Nature has produced an efficient system to directly convert photons into electrons and further into chemical energy; green plants and other biological organisms have been using this system for billions of years.

Most energy on earth is obtained from photosynthesis through photosystems, the most efficient energy-harvesting system. If a way to harness the energy produced by natural photosystems can be developed, we will have a clean and nearly inexhaustible energy source.

Borrowing from the bacterial and green plant energy-harvesting photosystem, nanobiotechnologists have demonstrated that photons can be converted directly into electrons by newly designed bio-solar molecular machines. Through a combination of precision engineering and biological engineering of the photosystem, they have constructed an extremely high-density nanoscale photosystem and ultra-lightweight solar-energy-harvesting molecular machines.

Two key components are required to fabricate a bio-solar energy-harvesting molecular machine—a bio-solar energy production system (photosystem) from leaves of green plants, and the designed peptide detergents. For bio-solar energy production, a simpler photosystem was used. Scientists originally purified the photosynthesis system from spinach, and they have recently reported successfully purifying photosynthetic systems from maple, pine, and oak trees and from bamboo leaves. The entire photosystem complex—only about 20 nanometers in height—was anchored onto a gold surface with an upright orientation.

Experimentation is continuing to devise ways to increase the amount and duration of energy produced by this exciting new molecular-energy-harvesting machine (figure 1).

What Lies Ahead?

The continued development of nanobiotechnology materials and molecular machines will deepen our understanding of seemingly intractable phenomena. Nanoscale engineering through molecular design of self-assembling peptides is an enabling technology that will likely play an increasingly important role in the future of biotechnology and will change our lives in the coming decades. For example, aging and damaged tissues can be replaced with the scaffolds that stimulate cells to repair body parts or to rejuvenate the skin. We also might be able to swim and dive like dolphins or to climb mountains with a nanoscaffold lung device that can carry an extra supply of oxygen. It is not impossible to anticipate painting cars and houses with photosynthesis molecular machines that can harness the unlimited solar energy for all populations on every corner of the planet, not just for the wealthy few.

We are just at the beginning of a great journey and will make many unexpected discoveries. Although nanotechnologists face many challenges, they will actively pursue many issues related to the molecular fabrication of composite materials and molecular machines. Biotech self-assembling peptides can be considered the building blocks for emerging materials and for fabricating future man-made molecular machines. These peptides can also be designed in combination to incorporate other building blocks such as sugars, lipids, nucleic acids, and a large number of metal crystals. Nature has inspired us and opened the door to its secrets. It is up to our imagination to expand upon its materials and molecular machines. ■

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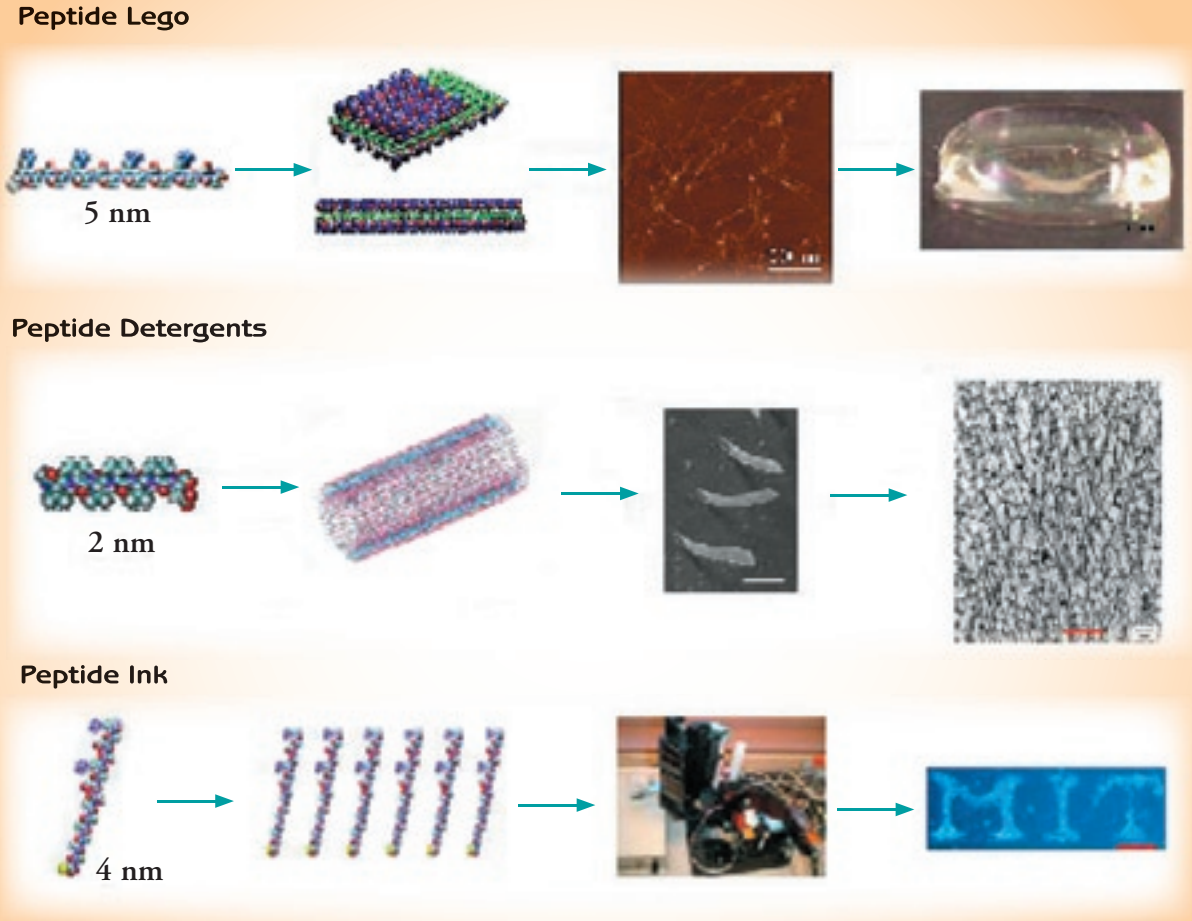
Examples of New Nanobiotechnological Materials



Peptide Lego, also called ionic self-complementary peptide, has 16 amino acids, about five nanometers in size. Peptide Lego molecules form nanofiber scaffolds that can be used in studies of cancer cells and stem cells, as well as for bone tissue repair in medicine. **Peptide detergents**, about two nanometers in size, can self-assemble into nanotubes and nanovesicles with a diameter of about 30 to 50 nanometers. These nanotubes go on to form an interconnected network that can be used in the development of more effective and more efficient drugs with fewer side effects. **Peptide ink**, about four nanometers in size, can be used as ink for an inkjet printer to directly print on a surface, instantly creating any pattern. The peptide ink, like blue and red inks, is useful to instantly alter the surface property so that cells can directly attach on to it. It can be used for developing cell-based sensors and coating for medical implants. When the peptide ink is applied along a certain pattern or shape on the surface, rat neural cells can spell, for example, M.I.T., as shown here.

WHITHER NANOTECHNOLOGY?

Akhlesh Lakhtakia

"Think small, dream big" is a typical slogan about the promise of nanotechnology within the scientific research community. Once relegated to pure fiction, nanotechnology is becoming increasingly linked with advances in biotechnology and information technology. With annual expenditure for nanotechnology research in the United States estimated to be in excess of $2.6 billion in 2004, the word "nano" is even finding its way into popular culture, from daily horoscopes to newspaper cartoons.

Yet the relatively small number of applications that have made it through to industrial uses represent "evolutionary rather than revolutionary advances," according to a 2004 panel report from the Royal Society of London and the Royal Academy of Engineering.

Nanotechnology is not a single process; neither does it involve a specific type of material. Instead, the term nanotechnology covers all aspects of the production of devices and systems by manipulating matter at the nanoscale.

Take an inch-long piece of thread and chop it into 25 pieces, and then chop one of those pieces into a million smaller pieces. Those itty-bitty pieces are about one nanometer long. The ability to manipulate matter and processes at the nanoscale undoubtedly exists in many academic and industrial laboratories. At least one relevant dimension must lie between 1 and 100 nanometers, according to the definition of nanoscale by the U.S. National Research Council. Ultra-thin coatings have one nanoscale dimension, and nanowires and nanotubes have two such dimensions, whereas all three dimensions of nanoparticles are at the nanoscale.

Nanotechnology is being classified into three types. The industrial use of nanoparticles in automobile paints and cosmetics exemplifies incremental nanotechnology. Nanoscale sensors exploiting the fluorescent properties of disks called quantum dots (which are 2 to 10 nanometers in diameter) and electrical properties of carbon nanotubes (which are 1 to 100 nanometers in diameter) represent evolutionary nanotechnology, but their development is still in the embryonic stage. Radical nanotechnology, the stuff of science-fiction thrillers, is nowhere on the technological horizon.

Material properties at the nanoscale differ from those in bulk because of extremely large surface areas per unit volume at the nanoscale. Quantum effects also come into play at the nanoscale. Nanoscale properties and effects should transform current practices in integrated electronics, optoelectronics, and medicine. But the translation from the laboratory to mass manufacturing is fraught with significant challenges, and reliable manipulation of matter at the nanoscale in a desirable manner remains very difficult to implement economically. And very little data exist on the health hazards of nanotechnology.

Nanotechnology is emerging at a crucial stage of our civilization. A remarkable convergence of nanotechnology, biotechnology, and information technology is occurring. Some of the extremely pleasant prospects of their symbiosis, among others, are new medical treatments, both preventive and curative; monitoring systems for buildings, dams, ships, aircraft, and other structures vulnerable to natural calamities and terrorist acts; and energy-efficient production systems that produce very little waste.

The convergence of the three technologies is to be expected. Protein molecules such as kinesin are being developed to transport cargo molecules over distances on the order of a millimeter on silicon wafers for eventual use in smart nanosensor systems and

molecular manufacturing systems. Cells, bacteria, and viruses are being used to manufacture complex templates to precipitate medically useful molecules without producing medically harmful molecules in pharmaceutical factories. Nanotechnology also is being used to fabricate laboratories-on-a-chip to carry out tests of biological fluids, with the data being optically accessed and electronically stored and processed. Nano drug delivery systems are expected to be used inside living organisms to modify specific biological functions, for example, to develop or boost immunities against specific pathogens.

The convergence also makes urgent the need for better regulation and oversight. With most of the work being conducted under governmental auspices, citizen watchdog groups and nongovernmental organizations, as well as private-sector scientific panels, must be given greater authority to oversee this research. At the same time, laws must be formulated to guide the conduct of individuals in charge of government programs and private contractors on nanotechnology.

Nanotechnology today is probably like Mozart when he was five years old: bursting with promise, with the best yet to come after a few years of nurturance. ■

Akhlesh Lakhtakia is distinguished professor of engineering science and mechanics at Pennsylvania State University.

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THE INTERNATIONAL RICE GENOME SEQUENCING PROJECT: A Case Study

C. Robin Buell

Peter Beyer/University of Freiburg

Golden and regular white rice.

What started as a Japanese research project evolved into an international research venture that delivered a key tool for advancing a second "green revolution." By involving researchers and resources from many countries, the International Rice Genome Sequencing Project (IRGSP) in 2005 produced a "map" of rice's genetic makeup. This map will enable breeders to accelerate their breeding programs and develop more hearty rice varieties, and farmers to improve their growing methods and extend their growing seasons. Also, scientists have been able to utilize the complete rice genome to further their studies on other cereals.

***C. Robin Buell** is an associate investigator with the Institute for Genomic Research and was a participant in the IRGSP.*

An ancient Chinese proverb states that "precious things are not pearls and jade but the five grains, of which rice is the finest." Indeed, based on daily worldwide consumption, rice is more precious than pearls: Some 50 percent of the inhabitants of the planet consume rice every day. For a large percentage of these people, rice is the major, and possibly the only, caloric source.

Being able to provide sufficient and nutrient-rich rice is essential to meet the needs of the world's population. While conventional plant breeding has significantly increased rice output, international collaborative efforts have resulted in a better understanding of the rice genome that promises the development of rice varieties with even greater yields and disease resistance.

A Second Green Revolution

Over the past 40 to 50 years, scientists were able to make major improvements in the yield, pest resistance, and nutritional content of rice as well as of other crops. They achieved these results through the implementation of conventional breeding involving genetic crosses between varieties of plants and selection by the breeder for the most desirable progeny. This phase of improvements in agricultural output was termed the Green Revolution, and Norman Borlaug, a key geneticist, was awarded the Nobel Peace Prize in 1970 for his achievements in enhancing agricultural production.

However, in the 21st century, the growing worldwide population, coupled with reduced acreage for agricultural production, will present serious challenges to the world's ability to feed itself. Thus, a second "green revolution" is needed.

Takuji Sasaki

IRGSP participants; the author is third from the left in the front row.

One tool now in use that can advance this second green revolution is genomics, which involves understanding the genes within an organism and how they function in the growth and development of the organism. The science of genomics took a major step forward about 10 years ago when researchers at the Institute for Genomic Research in the United States were able to determine the complete sequence (a map of the genetic makeup) of a free-living microorganism, *Haemophilus influenzae*, a bacterium that causes the flu. The techniques developed at the institute are now widely used to determine the genetic makeup in all types of organisms, including animals, plants, and fungi.

The Rice Genome Project

In the early 1990s, Japanese scientists began research on sequencing the rice genome. In 1998, in an effort to accelerate this work and utilize international expertise, a group of scientists from several countries, led by Japanese researchers, initiated the International Rice Genome Sequencing Project. With funding from many countries—including Japan, China, Korea, Thailand, India, France, Brazil, and the United States—and from Taiwan, hundreds of scientists from around the world contributed to sequencing the rice genome. The international collaboration enabled the division of labor and distribution of costs among the participants. It also allowed participating countries to have a defined stake in the project and get recognition for completing a part of or an entire chromosome. The project was completed in December 2004, and the results were published in August 2005.

The IRGSP was able to identify in excess of 37,000 genes in the rice genome, more than the number of genes in the human genome. Analysis of other rice genome sequences with the IRGSP sequence resulted in the identification of more than 80,000 new genetic markers—genes that produce a recognizable trait—that will enable breeders to accelerate their breeding programs and develop more hearty rice varieties.

Even before the IRGSP had completed its task, the project's investigators were making their findings publicly available to scientists around the world for use in a broad range of plant biology research. One finding was the critical gene involved in controlling flowering time in rice. Day length—the hours of daylight versus darkness that change throughout the seasons—controls when a plant such as rice flowers and consequently when it sets seed. By identifying the mechanism of flowering time, scientists can now attempt to develop rice varieties that flower earlier in the planting season, thus expanding the growing season for farmers.

Broader Implications

Although rice has a substantial role in worldwide agriculture, it has another role for scientists. It is well known that primates such as humans and chimpanzees have similar genes and genomes. The same relationship occurs with rice and its close relatives—cereals such as wheat, maize, barley, oats, sorghum, and millet. For technical and financial reasons, a complete genome sequence is available only for rice. But with the close relationship between the cereals, scientists who work on other cereals have been able to utilize the rice genome to further their studies. Indeed, researchers were able to use the rice genome sequence to identify a key barley gene involved in resistance to a fungal pathogen responsible for a disease known as powdery mildew.

The benefits of the rice genome project are clear:

• As new crop and hardier crop species are developed, and as the understanding of basic plant biology accelerates, countries will be better positioned to meet the needs of a growing population in the 21st century.

• The IRGSP's collaborative format demonstrates the scientific leaps that can be accomplished when experts from around the world have access to each other's research.

• The IRGSP has shown that state-of-the-art scientific endeavors do not have to involve only highly developed countries, and that collaborative international efforts can serve to enable less developed nations to acquire cutting-edge technologies.

• The IRGSP experience will likely yield new efforts with stronger collaborative features. This has already begun

with the International Rice Functional Genomics Consortium—a collaboration among international scientists to expand understanding of rice's 37,000+ gene functions so as to meet increasing production needs.

Public-Private Partnerships

Clearly, completing the mission of the IRGSP was a challenge, and there were bumps in the road. The largest issue that the IRGSP had to address involved the parallel efforts to sequence the rice genome by Monsanto and Syngenta, two large, international agribusinesses, and the Beijing Genomics Institute, a research center in China. The IRGSP subsequently collaborated with Syngenta and Monsanto, establishing a highly productive public-private partnership. This partnership incorporated private sector data into the public research results.

The benefits have far outweighed any challenges. In addition to providing an invaluable resource for the world's scientists and farmers, the successful completion of the IRGSP demonstrates that international scientific collaborations are productive and serve purposes greater than their initial goals. Certainly for other large scientific endeavors, international collaborative efforts should be considered as a viable strategy. ■

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THE BIRTH OF BIOTECHNOLOGY: Harnessing the Power of DNA

Dinesh Ramde

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

A. Barrington Brown/Photo Researchers, Inc.

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

Dinesh Ramde *is a writer with The Associated Press.*

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

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

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

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

The Birth of Biotech

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

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

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

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

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

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

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

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

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

The Business World Responds

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

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

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

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

AP/WWP/Paul Sakuma

A bioprocess in a cell development room at Genentech.

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

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

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

Spawning New Science

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

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

Gusto/ Photo Researchers, Inc.

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

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

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

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

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

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

Exceeding All Expectations

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

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

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

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

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

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

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BIOTECHNOLOGY'S FIRST 142 YEARS

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

U.S. REGULATION OF AGRICULTURAL BIOTECHNOLOGY

Three U.S. government agencies—the U.S. Department of Agriculture (USDA), the Environmental Protection Agency (EPA), and the Food and Drug Administration (FDA)—are responsible for oversight of genetically engineered plants and products. Their responsibilities are complementary, and in some cases overlapping. USDA's Animal and Plant Health Inspection Service has jurisdiction over the planting of genetically engineered plants. EPA has jurisdiction over the testing, distribution, and use of pesticides engineered into plants, and FDA has jurisdiction over the food and feed uses of all foods from plants. The following excerpt is a brief overview of the role these agencies play in regulating genetically modified organisms.

U.S. Department of Agriculture
Animal and Plant Health Inspection Service

Within USDA, the Animal and Plant Health Inspection Service (APHIS) is responsible for protecting agriculture from pests and diseases. Under the Plant Protection Act, USDA-APHIS has regulatory oversight of products of modern biotechnology that could pose such a risk. Accordingly, USDA-APHIS regulates organisms and products that are known or suspected to be plant pests or to pose a plant pest risk, including those that have been altered or produced through genetic engineering. These are called "regulated articles." USDA-APHIS regulates the import, handling, interstate movement, and release into the environment of regulated organisms that are products of biotechnology, including organisms undergoing confined experimental use or field trials. Regulated articles are reviewed to ensure that, under the proposed conditions of use, they do not present a plant pest risk through ensuring appropriate handling, confinement, and disposal.

USDA-APHIS regulations provide a petition process for the determination of nonregulated status. If a petition is granted, that organism will no longer be considered a regulated article and will no longer be subject to oversight by USDA-APHIS. The petitioner must supply information such as the biology of the recipient plant, experimental data and publications, genotypic and phenotypic descriptions of the genetically engineered organism, and field test reports. The agency evaluates a variety of issues, including the potential for plant pest risk; disease and pest susceptibilities; the expression of gene products, new enzymes, or changes to plant metabolism; weediness and impact on sexually compatible plants; agricultural or cultivation practices; effects on non-target organisms; and the potential for gene transfer to other types of organisms. A notice is filed in the [government-published] *Federal Register*, and public comments are considered on the environmental assessment and determination written for the decision on granting the petition. Copies of the USDA-APHIS documents are available to the public.

For further information, visit
http://www.aphis.usda.gov/brs/.

Under the Virus, Serum, Toxin Act, USDA-APHIS Veterinary Services inspects biologics production establishments and licenses veterinary biological substances, including animal vaccines that are products of biotechnology.

For further information, visit
http://www.aphis.usda.gov/vs/.

U.S. Environmental Protection Agency

The EPA, through a registration process, regulates the sale, distribution, and use of pesticides in order to protect health and the environment, regardless of how the pesticide was made or its mode of action. This includes regulation of those pesticides that are produced by an organism through techniques of modern biotechnology. The Biopesticides and Pollution Prevention Division of the Office of Pesticide Programs, under the Federal Insecticide, Fungicide, and Rodenticide Act, regulates the distribution, sale, use, and testing of pesticidal substances produced in plants and microbes. Generally, experimental use permits are issued for field testing. Applicants must register pesticidal products prior to their sale and distribution, and the EPA may establish conditions for use as part of the registration. The EPA also sets tolerance limits for residues of pesticides on and in food and animal feed, or

establishes an exemption from the requirement for a tolerance, under the Federal Food, Drug, and Cosmetic Act.

For further information, visit
http://www.epa.gov/pesticides/biopesticides.

The EPA's Toxic Substance Control Act Biotechnology Program of the Office of Prevention and Toxic Substances currently regulates microorganisms intended for general industrial uses. The program conducts a pre-market review of "new" microorganisms, that is those microorganisms formed by deliberate combinations of genetic material from organisms classified in different taxonomic genera.

For further information, visit
http://www.epa.gov/oppt/biotech/.

U.S. Food and Drug Administration

The FDA is responsible for ensuring the safety and proper labeling of all plant-derived foods and feeds, including those developed through bioengineering. All foods and feeds, whether imported or domestic and whether derived from crops modified by conventional breeding techniques or by genetic engineering techniques, must meet the same rigorous safety standards. Under the Federal Food, Drug, and Cosmetic Act, it is the responsibility of food and feed manufacturers to ensure that the products they market are safe and properly labeled. In addition, any food additive, including one introduced into food or feed by way of plant breeding, must receive FDA approval before marketing. (The term "food additive" refers to substances introduced into food that are not pesticides and are not generally recognized as safe by qualified scientific experts.)

The FDA ensures that food and feed manufacturers meet their obligations through its enforcement authority under the Federal Food, Drug, and Cosmetic Act. To help sponsors of foods and feeds derived from genetically engineered crops comply with their obligations, the FDA encourages them to participate in its voluntary consultation process. All foods and feeds from genetically engineered crops currently on the market in the United States have gone through this consultation process. With one exception, none of these foods and feeds was considered to contain a food additive, and so did not require approval prior to marketing.

For further information, visit
http://www.cfsan.fda.gov/~lrd/biotechm.html

Source: United States Regulatory Agencies Unified Biotechnology Web Site: http://usbiotechreg.nbii.gov/roles.asp

GLOSSARY OF BIOTECHNOLOGY TERMS

Alpha helix: A common protein structure, found especially in hair, wool, fingernails, and animal horns, characterized by a single, spiral chain of amino acids stabilized by hydrogen bonds.

Amino acids: The most basic building blocks of all life. Amino acids are molecules that contain both amino and carboxylic acid functional groups.

Antigen: Usually a protein found on the surface of the virus that stimulates the immune response, especially the production of antibodies.

Biobased products: Fuels, chemicals, building materials, electric power, or heat produced from biological materials. The term may include any energy, commercial, or industrial products, other than food or feed, that utilize biological material or renewable domestic agricultural (plant, animal, and marine) or forestry materials.

Bioinformatics: The use of applied mathematics, informatics, statistics, and computer science to study biological systems. Major research areas include sequence alignment, gene finding, genome assembly, protein structure alignment, protein structure prediction, prediction of gene expression, and protein-protein interactions.

Biopesticides: Certain types of pesticides derived from such natural materials as animals, plants, bacteria, and certain minerals. For example, canola oil and baking soda are considered biopesticides.

Biotechnology: A set of biological techniques developed through basic research and applied to research and product development. Biotechnology refers to the use of recombinant DNA, cell fusion, and new bioprocessing techniques.

Biotechnology-derived: The use of molecular biology and/or recombinant DNA technology, or in vitro gene transfer, to develop products or to impart specific capabilities in plants or other living organisms.

Bt corn: A maize plant that has been developed though biotechnology so that the plant tissues express a protein that is toxic to some insects but nontoxic to humans and other mammals.

Cell: The basic structural and functional unit of all organisms. Cells contain DNA and many other elements to enable the cell to function.

Cellulase: An enzyme complex that breaks down cellulose to beta-glucose. It is produced mainly by symbiotic bacteria in the ruminating chambers of herbivores. Aside from ruminants, most animals (including humans) do not produce cellulase and are therefore unable to use most of the energy contained in plant material.

Chromosomes: The self-replicating genetic structure of cells containing the cellular DNA. Humans have 23 pairs of chromosomes.

Collagen: The main protein of connective tissue and the most abundant protein in mammals. It is the main component of ligaments and tendons.

Cry1A: A protein derived from the bacterium *Bacillus thuringiensis* that is toxic to some insects when ingested. This bacterium occurs widely in nature and has been used for decades as an insecticide, although it constitutes less than two percent of the overall insecticides used.

Cultivar: In botany, a plant that has been created or selected intentionally and maintained through cultivation.

Double helix: The twisted-ladder shape that two linear strands of DNA assume when complementary nucleotides on opposing strands bond together.

DNA (deoxyribonucleic acid): The genetic material of all cells and many viruses; the molecule that encodes genetic information. DNA is a double-stranded molecule held together by weak bonds between base pairs of nucleotides. The four nucleotides in DNA contain the bases adenine (A), guanine (G), cytosine (C), and thymine (T). In

nature, base pairs form only between A and T and between G and C; thus the base sequence of each single strand can be deduced from that of its partner.

Gene: The fundamental physical and functional unit of heredity. A gene is an ordered sequence of nucleotides located in a particular position on a particular chromosome that encodes a specific functional product such as a protein or an RNA molecule.

Gene expression: The process by which a gene's information is converted into the structures and functions of a cell.

Gene expression profiling: A method of monitoring expression of thousands of genes simultaneously on a glass slide called a microarray.

Gene flow: The transfer of genes from one population to another of the same species, as by migration or the dispersal of seeds and pollen.

Gene mapping: The process of determining where genes are located on individual chromosomes.

Gene splicing: The isolation of a gene from one organism, and then the introduction of that gene into another organism using techniques of biotechnology.

Gene therapy: An experimental medical technique that relies on the insertion of genes into an individual's cells and tissues to treat a disease. Typically, a defective gene is replaced by a normally functioning one. The normal gene is delivered to target tissues in most cases by an adenovirus that has been genetically altered to render it harmless.

Gene transfer: A common technique in molecular biology that refers to a genetic change brought about by taking up and recombining DNA.

Genetic engineering: The technique of removing, modifying, or adding genes to a DNA molecule in order to change the information it contains. By changing this information, genetic engineering changes the type or amount of proteins an organism is capable of producing, thus enabling it to make new substances or perform new functions.

Genetically modified organism (GMO): Often, the label GMO and the term "transgenic" are used to refer to organisms that have acquired novel genes from other organisms by laboratory gene transfer methods.

Genetics: The study of the patterns of inheritance of specific traits.

Genome: All the genetic material in the chromosomes of a particular organism.

Germline: The line (sequence) of germ cells that have genetic material that may be passed to a child.

Herbicide-tolerant crop: Crop plants that have been developed to survive application(s) of one or more commercially available herbicides by the incorporation of certain gene(s) via biotechnology methods such as genetic engineering, or via traditional breeding methods such as natural, chemical, or radiation mutation.

Hybrid: Seed or plant produced as the result of controlled cross-pollination as opposed to seed produced as the result of natural pollination. Hybrid seeds are selected to have higher quality traits (for example, yield or pest tolerance).

Membrane protein: A protein molecule that is attached to or associated with the membrane of a cell.

Microbial pesticides: Pesticides that consist of a microorganism, for example, a bacterium, fungus, virus, or protozoan, as the active ingredient. Microbial pesticides can control many different kinds of pests, although each separate active ingredient is relatively specific to its target pest or pests. For example, some fungi control certain weeds, and other fungi kill specific insects. The most widely used microbial pesticides are subspecies and strains of *Bacillus thuringiensis*, or Bt.

Molecular machine: An assemblage of a discrete number of molecular components designed to achieve a specific function. Each molecular component performs a single act, while the entire supramolecular structure performs a more complex function that results from the cooperation of the various molecular components.

Molecular self-assembly: The assembly of molecules without guidance or management from an outside source. Self-assembly can occur spontaneously in nature,

for example in cells (such as the self-assembly of the lipid bilayer membrane) and other biological systems, as well as in human engineered systems. Many biological systems use self-assembly to assemble various molecules and structures. Imitating these strategies and creating novel molecules with the ability to self-assemble into supramolecular assemblies is an important technique in nanotechnology.

Monoclonal antibody: An antibody that is mass produced in the laboratory from a single clone and that recognizes only one antigen. Monoclonal antibodies are typically made by fusing a normally short-lived, antibody-producing B cell to a fast-growing cell, such as a cancer cell. The resulting hybrid cell, or hybridoma, multiplies rapidly, creating a clone that produces large quantities of the antibody.

Mutation: Any inheritable change in DNA sequence.

Nanomedicine: A rapidly moving scientific field in which scientists are developing a wide variety of nanoparticles and nanodevices, scarcely a millionth of an inch in diameter, to improve detection of cancer, boost immune responses, repair damaged tissue, and thwart atherosclerosis. Earlier in 2005, the U.S. Food and Drug Administration approved a nanoparticle bound to the cancer drug Taxol for treatment of advanced breast cancer. Another nanoparticle is being tested in heart patients in the United States as a way to keep their heart arteries open following angioplasty.

Nanometer: One billionth of a meter.

Nanotechnology: Systems for transforming matter, energy, and information that are based on nanometer-scale components with precisely defined molecular features. Also, techniques that produce or measure features less than 100 nanometers in size.

Natural selection: The concept developed by Charles Darwin that genes that produce characteristics that are more favorable in a particular environment will be more abundant in the next generation.

Nucleotide: A cellular constituent that is one of the building blocks of ribonucleic acids (RNA) and deoxyribonucleic acid (DNA). In biological systems, nucleotides are linked by enzymes in order to make long, chainlike polynucleotides of defined sequence.

Pathogen: An agent that causes disease, especially a living microorganism such as a bacterium or fungus.

Peptide: Fragments of a protein, from two or more amino acids in a chain, much like beaded chain bracelets. When animal meat proteins are digested, they break down first into peptides and then into their amino acid constituents.

Pesticide resistance: A genetic change in response to selection by a pesticide resulting in the development of strains capable of surviving a dose lethal to a majority of individuals in a normal population. Resistance may develop in insects, weeds, and pathogens.

Plant-incorporated protectants (PIPs): Formerly referred to as plant pesticides, substances that act like pesticides that are produced and used by a plant to protect it from pests such as insects, viruses, and fungi.

Pollen: The cells that carry the male DNA of a seed plant.

Polymerase chain reaction (PCR): A technique for copying and amplifying the complementary strands of a target DNA molecule. It is an in vitro method that greatly amplifies, or makes millions of copies of, DNA sequences that otherwise could not be detected or studied.

Protein: A large molecule composed of one or more chains of amino acids in a specific order. The order is determined by the base sequence of nucleotides in the gene that codes for the protein. Proteins are required for the structure, function, and regulation of the body's cells, tissues, and organs, and each protein has unique functions. Examples are hormones, enzymes, and antibodies.

Proteomics: The use of technologies such as mass spectrometry to detect protein biomarkers in the blood that may indicate early signs of disease, even before symptoms appear. One such marker is C-reactive protein, an indicator of inflammatory changes in blood vessel walls that presage atherosclerosis.

Recombinant DNA molecules (rDNA): A combination of DNA molecules of different origin that are joined using recombinant DNA technologies.

Recombinant DNA technology: A procedure used to join together DNA segments in a cell-free system (an environment outside a cell or organism). Under appropriate conditions, a recombinant DNA molecule can enter a cell and replicate there, either autonomously or after it has become integrated into a cellular chromosome.

Recombination: The process by which progeny derive a combination of genes different from that of either parent.

Resistance management: Strategies that can be employed to delay the onset of resistance. For insect resistance management, this includes the use of a "refuge" in which the insect will not be challenged by the pesticide used in the rest of the field.

Selective breeding: Making deliberate crosses or matings of organisms so that the offspring will have a desired characteristic derived from one of the parents.

Single nucleotide polymorphisms (SNPs): Relationships between genes and probing populations for variations in the genetic code that may increase one's risk for a particular disease or determine one's response to a given medication.

Splicing: See Gene splicing.

Stem cell: A "generic" cell that can make exact copies of itself indefinitely. In addition, a stem cell has the ability to produce specialized cells for various tissues in the body, such as heart muscle, brain tissue, and liver tissue. Scientists are able to maintain stem cells forever, developing them into specialized cells as needed. There are two basic types of stem cells. The first type is the embryonic stem cell, which is obtained from either aborted fetuses or fertilized eggs that are left over from in vitro fertilization. Embryonic stem cells are useful for medical and research purposes because they can produce cells for almost every tissue in the body. The second type is the adult stem cell, which is not as versatile for research purposes because it is specific to certain cell types, such as blood, intestines, skin, and muscle.

Tissue culture: A process of growing a plant in the laboratory from cells rather than seeds. This technique is used in traditional plant breeding, as well as when using techniques of agricultural biotechnology.

Traditional breeding: The modification of plants and animals through selective breeding. Practices used in traditional plant breeding may include aspects of biotechnology such as tissue culture and mutation breeding.

Transgenic: Containing genes altered by insertion of DNA from an unrelated organism; taking genes from one species and inserting them into another species in order to get a certain trait expressed in the offspring.

Variety: Subdivision of a species for taxonomic classification. Used interchangeably with the term "cultivar" to denote a group of individuals that is distinct genetically from other groups of individuals in the species. An agricultural variety is a group of similar plants that, by structural features and performance, can be identified from other varieties within the same species.

Virus: A noncellular biological entity that can reproduce only within a host cell. Viruses consist of nucleic acid covered by protein; some animal viruses are also surrounded by a membrane. Inside the infected cell, the virus uses the synthetic capability of the host to produce a progeny virus. ■

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INTERNET RESOURCES

Online sources for information about biotechnology

U.S. GOVERNMENT

National Library of Medicine
National Center for Biotechnology Information
http://www.ncbi.nlm.nih.gov/

National Nanotechnology Initiative
http://www.nano.gov/

U.S. Department of Agriculture

Animal Plant and Health Inspection Service
Biotechnology Regulatory Services
http://www.aphis.usda.gov/brs/index.html

Economic Research Service
Economic Issues in Agricultural Biotechnology
http://www.ers.usda.gov/publications/aib762/

United States Regulatory Oversight in Biotechnology Responsible Agencies
http://www.aphis.usda.gov/brs/usregs.html#usda

U.S. Department of State
Bureau of International Information Programs
http://www.usinfo.state.gov/ei/economic_issues/biotechnology.html

U.S. Environmental Protection Agency
Toxic Substances Control Act Biotechnology Program
http://www.epa.gov/opptintr/biotech/index.html

U.S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
http://www.cfsan.fda.gov/~lrd/biotechm.html

U.S. Regulatory Agencies Unified Biotechnology Web Site
http://usbiotechreg.nbii.gov

ACADEMIC AND RESEARCH INSTITUTIONS

AgBioWorld
http://www.agbioworld.org

Agricultural Biology Communicators
U.S. Land Grant Colleges and Universities
http://agribiotech.info/

American Institute of Biological Sciences
http://www.actionbioscience.org/index.html

American Phytopathological Society
http://www.apsnet.org/media/ps/

Center for Global Food Issues
http://www.cgfi.com

Cornell University
http://www.nysaes.cornell.edu/agbiotech

Council for Agricultural Science and Technology
http://www.cast-science.org

Donald Danforth Plant Science Center
http://www.danforthcenter.org/

Foresight Nanotech Institute
http://www.foresight.org/

Information Systems for Biotechnology
http://www.isb.vt.edu

International Service for the Acquisition of Agri-biotech Applications
http://www.isaaa.org/

Iowa State University
http://www.biotech.iastate.edu/

National Agricultural Biotechnology Council
http://www.cals.cornell.edu/extension/nabc

Pew Initiative on Food and Biotechnology
http://www.pewagbiotech.org

University of California Biotechnology Program
http://ucbiotech.org/

University of Maryland

Medical Biotechnology Center
http://www.umbi.umd.edu/~mbc/

Agricultural Biotechnology
http://agnic.umd.edu/

INDUSTRY

AGBIOS
http://www.agbios.com/main.php

Biotech Knowledge Center
http://www.biotechknowledge.com

Biotechnology Industry Organization
http://www.bio.org/

Council for Biotechnology Information
http://www.whybiotech.com/

CropLife America
http://www.croplifeamerica.org

INTERNATIONAL ORGANIZATIONS

Consultative Group on International Agricultural Research
http://www.cgiar.org

EUROPA
(European Commission)
http://www.europa.eu.int/comm/food/food/biotechnology/index_en.htm

European Food Safety Authority
http://www.efsa.eu.int/science/gmo/catindex_en.html

Food and Agriculture Organization
http://www.fao.org/biotech

International Food Policy Research Institute
http://www.ifpri.org/themes/biotech/biotech.htm

International Rice Research Institute
http://www.irri.cgiar.org

International Service for National Agricultural Research
http://www.isnar.cgiar.org/kb/Bio-index.htm

Organization for Economic Cooperation and Development
http://www.oecd.org/topic/0,2686,en_2649_37437_1_1_1_1_37437,00.html

World Health Organization
http://www.who.int/foodsafety/biotech/en/

World Intellectual Property Organization
http://www.wipo.int/tk/en/genetic/index.html

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