

## **Genomic and Biotechnology Health-Care Applications**

Biotechnology tools and techniques open new research avenues for discovering how healthy bodies work and what goes wrong when problems arise. Knowing the molecular basis of health and disease leads to improved and novel methods for treating and preventing diseases. In human health care, biotechnology products include quicker and more accurate diagnostic tests, therapies with fewer side effects because they are based on the body's self-healing capabilities, and new and safer vaccines.

### **Diagnostics**

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

Biotechnology has also decreased the costs of diagnostics. A new blood test, developed through biotechnology, measures the amount of low-density lipoprotein (LDL), or "bad" cholesterol, in blood. Conventional methods require separate and expensive tests for total cholesterol, triglycerides and high-density lipoprotein cholesterol. Also, a patient must fast 12 hours before the test. The new biotech test measures LDL in one test, and fasting is not necessary. We now use biotechnology-based tests to diagnose certain cancers, such as prostate and ovarian cancer, by taking a blood sample, eliminating the need for invasive and costly surgery.

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

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

Biotechnology-based diagnostic tests are not only altering disease diagnosis but also improving the way health care is provided. Many tests are portable, so physicians conduct the tests, interpret results and decide on treatment literally at the patient's bedside. In addition, because many of these diagnostic tests are based on color changes similar to a home pregnancy test, the results can be interpreted without technically trained

personnel, expensive lab equipment or costly facilities, making them more available to poorer communities and people in developing countries.

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

## **Therapeutics**

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

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

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

### **Using Natural Products as Therapeutics**

Many living organisms produce compounds that coincidentally have therapeutic value for us. For example, many antibiotics are produced by naturally-occurring microbes, and a number of medicines on the market, such as digitalis, are also made by plants. Plant cell culture, recombinant DNA technology and cellular cloning, now provide us with new ways to tap into natural diversity. As a result, we are investigating many plants and animal as sources of new medicines. Ticks could provide anticoagulants, and poison-arrow frogs might be a source of new painkillers. A fungus produces a novel, antioxidant enzyme that is a particularly efficient at mopping up free radicals known to encourage tumor growth.

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

### **Using Biopolymers as Medical Devices**

Nature has also provided us with biological molecules that can serve as useful medical devices or provide novel methods for drug delivery. Because they are more compatible with our tissues and our bodies absorb them when their job is done, they are superior to most man-made medical devices or delivery mechanisms.

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

### **Replacing Missing Proteins**

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

- factor VIII—a protein involved in the blood-clotting process, lacked by some hemophiliacs.
- insulin—a protein hormone that regulates blood glucose levels. Diabetes results from an inadequate supply of insulin.

### **Using Genes to Treat Diseases**

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

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

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

### **Cell Transplants**

Approximately 10 people die each day waiting for organs to become available for transplantation. To circumvent this problem, scientists are investigating how to use cell culture to increase the number of patients who might benefit from one organ donor. Liver cells grown in culture and implanted into patients kept them alive until a liver became available. In one study of patients with type 1 diabetes, researchers implanted insulin-

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

As is true of patients receiving whole-organ transplant, expensive drugs for suppressing the immune response must be given if the transplanted cells are from someone other than the patient. Researchers are devising ways to keep the immune system from attacking the new cells. Cell encapsulation allows cells to secrete hormones or provide a specific metabolic function without being recognized by the immune system. As such, they can be implanted without rejection. Other researchers are genetically engineering cells to express a naturally occurring protein that disables immune system cells that bind to it.

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

### **Stimulating the Immune System**

We are using biotechnology to enlist the help of our immune systems in fighting a variety of diseases. Like the armed forces that defend countries, the immune system is made up of different branches, each containing different types of "soldiers" that interact with each other and the role players in other branches in complex, multifaceted ways.

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

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

*Cancer vaccines* that help the immune system find and kill tumors have also shown therapeutic potential. Unlike other vaccines, cancer vaccines are given after the patient has contracted the disease, so they are not preventative. They work by intensifying the reactions between the immune system and tumor.

### **Suppressing the Immune System**

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

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

### **Xenotransplantation**

Organ transplantation provides an especially effective, cost-efficient treatment for severe, life-threatening diseases of the heart, kidney and other organs. According to the United Network of Organ Sharing (UNOS), in the United States more than 80,000 people are on organ waiting lists.

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

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

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

### **Regenerative Medicine**

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

### **Tissue Engineering**

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

The most basic forms of tissue engineering use natural biological materials, such as collagen, for scaffolding. For example, two-layer skin is made by infiltrating a collagen gel with connective tissue cells, then creating the outer skin with a layer of tougher protective cells. In other methods, rigid scaffolding, made of a synthetic polymer, is shaped and then placed in the body where new tissue is needed. Other synthetic polymers, made from natural compounds, create flexible scaffolding more appropriate for

soft-tissue structures, like blood vessels and bladders. When the scaffolding is placed in the body, adjacent cells invade it. At other times, the biodegradable implant is spiked with cells grown in the laboratory prior to implantation.

Simple tissues, such as skin and cartilage, were the first to be engineered successfully. Recently, however, physicians have achieved remarkable results with a biohybrid kidney that maintains patients with acute renal failure until the injured kidney repairs itself. A group of patients with only a 10 to 20 percent probability of survival regained normal kidney function and left the hospital in good health because the hybrid kidney prevented the events that typically follow kidney failure: infection, sepsis and multi-organ failure. The hybrid kidney is made of hollow tubes seeded with kidney stem cells that proliferate until they line the tube's inner wall. These cells develop into the type of kidney cell that releases hormones and is involved with filtration and transportation. In addition to carrying out these expected metabolic functions, the cells in the hybrid kidney also responded to signals produced by the patient's other organs and tissues.

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

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

### **Stem Cells**

Stem cell research represents the leading edge of science—a biotechnology method that uses cell culture techniques to grow and maintain stable cell lines. Stem cell therapies could revolutionize approaches for treating many of our most deadly and debilitating diseases and afflictions such as diabetes, Parkinson's Disease, Alzheimer's Disease, stroke and spinal cord injuries.

Development of the remarkable biohybrid kidney described above depended on a supply of kidney stem cells. Doctors used blood stem cells to repair the damaged heart of a 16-year-old boy who had suffered a heart attack following an accident that punctured his heart. They harvested stem cells from his blood, rather than extracting them from bone marrow, and injected them into the coronary arteries that supply blood to the heart muscle.

Most cells in the human body are differentiated—meaning they have a specific shape, size and function. Some cells exist only to carry oxygen through the bloodstream, others to transmit nerve signals to the brain and so forth. Stem cells are cells that have not yet differentiated. Different types of stem cells display varying degrees of plasticity regarding their potential fate.

In adults, some tissues maintain a population of stem cells to replenish cells that have died or been injured; other tissues have no resident stem cell populations. When an *adult stem cell* receives a cue to differentiate, it first divides in two: One daughter cell differentiates, while the other remains undifferentiated, ensuring a continual supply of stem cells. Bone marrow contains stem cells that can differentiate into any of the cell types found in blood, such as red blood cells, T-cells and lymphocytes, and bone. Liver stem cells can become any of the specialized cells of the liver—bile-secreting cells, storage cells or cells that line the bile duct. However, stem cells in the liver do not differentiate into T-cells, and bone marrow stem cells do not become liver cells.

In 1998, researchers reported that they had established human *embryonic stem cell* lines. This breakthrough opened up many avenues for treating diseases and healing injured tissue because embryonic stem cells can become any kind of cell in the body. Embryonic stem cells are derived from a blastocyst, which is the ball of about 150 undifferentiated cells from which an embryo develops. In addition to their total developmental plasticity, embryonic stem cells can produce more of themselves without limit.

By starting with undifferentiated adult and embryonic stem cells, scientists may be able to grow cells to replace tissue damaged from heart disease, spinal cord injuries and burns, and to treat diseases such as Parkinson's Disease, diabetes and Alzheimer's Disease by replacing malfunctioning cells with newly differentiated healthy cells. This process of culturing a line of genetically identical cells to replace defective cells in the body is sometimes referred to as therapeutic cloning.

### **Cell Nuclear Replacement**

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

More information about cell nuclear replacement can be found in "Ethics" and "Biotechnology Tools in Research and Product Development."

### **Vaccines**

Vaccines help the body recognize and fight infectious diseases. Conventional vaccines use weakened or killed forms of a virus or bacteria to stimulate the immune system to create the antibodies that will provide resistance to the disease. Usually only one or a few proteins on the surface of the bacteria or virus, called antigens, trigger the production of

antibodies. Biotechnology is helping us improve existing vaccines and create new vaccines against infectious agents, such as the viruses that cause cervical cancer and genital herpes.

### **Biotechnology Vaccine Production**

Most of the new vaccines consist only of the antigen, not the actual microbe. The vaccine is made by inserting the gene that produces the antigen into a manufacturing cell, such as yeast. During the manufacturing process, which is similar to brewing beer, each yeast cell makes a perfect copy of itself and the antigen gene. The antigen is later purified. By isolating antigens and producing them in the laboratory, it is possible to make vaccines that cannot transmit the virus or bacterium itself. This method also increases the amount of vaccine that can be manufactured because biotechnology vaccines can be made without using live animals.

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

Recently researchers have discovered that injecting small pieces of DNA from microbes is sufficient for triggering antibody production. Such *DNA vaccines* could provide immunization against microbes for which we currently have no vaccines. DNA vaccines against HIV, malaria and the influenza virus are currently in clinical trials.

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

### **Vaccine Delivery Systems**

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

Genetically modified goats have produced a possible malaria vaccine in their milk. Academic researchers have obtained positive results using human volunteers who consumed hepatitis vaccines in bananas, and *E. coli* and cholera vaccines in potatoes. In addition, because these vaccines are genetically incorporated into food plants and need no refrigeration, sterilization equipment or needles, they may prove particularly useful in developing countries (see also "[Plant-Made Pharmaceuticals](#)").

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

### **Genomics and Proteomics**

While biotechnology has already had a significant impact on the diagnosis, treatment and prevention of diseases, the best is yet to come. We are entering a new era in medical research, disease diagnosis and health-care provision.

Revolutionary advances in research, product development and disease management are being driven by the interrelated and rapidly evolving scientific disciplines of genomics and proteomics. These areas of study are elucidating the precise mechanisms that drive and direct biological processes; they're also providing detailed information about the molecular basis of diseases.

Genomics and proteomics will allow us to expand current biotechnology-based approaches to health care, such as therapeutic uses of endogenous proteins and antibodies, discovery of new therapeutic compounds in plants and other organisms, microbe-free vaccines, quick and accurate diagnostics, regenerative medicine and gene therapy to treat certain diseases.

More importantly, however, these advances will bring about radically new approaches to health care. The practice of medicine will be fundamentally changed, becoming more comprehensive and integrated, highly individualized and more preventive rather than simply therapeutic. The expanded knowledge base provided by genomics and proteomics will serve as the foundation for

- predictive tests of impending diseases that can be prevented with targeted interventions.
- fundamental changes in the way drugs are discovered, tested and developed.
- therapies that are tailored to the specific genetic makeup of the patient.
- therapies that address and sometimes correct the biochemical causes of a disease rather than only alleviating the symptoms.