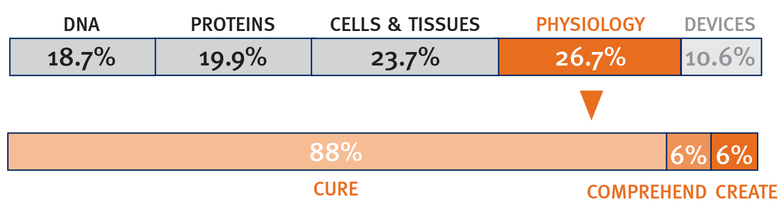
PHYSIOLOGY

Molecules, cells, and tissues interact with and serve as substrates for organs, which are combinations of two or more tissues. The interplay of molecules, cells, tissues, and organs represents both the complexity and the opportunity of physiology, or the study of how living organisms function.

PHYSIOLOGY SECTOR OVERVIEW

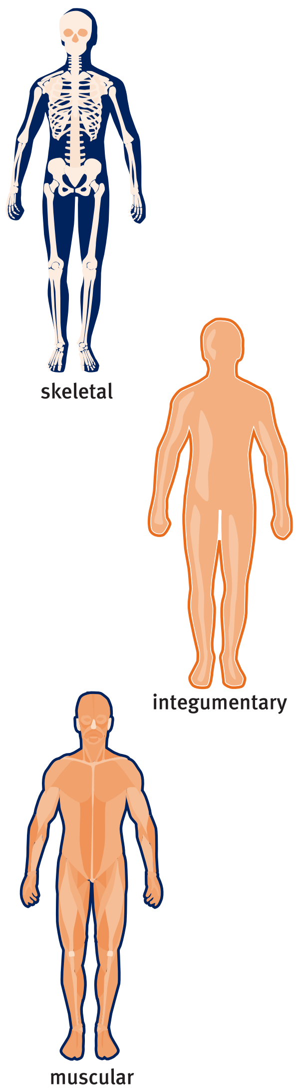
366 companies
26.7% of total industry
1,463,000+ person-years of research, development, manufacturing, sales, marketing activities
28.6% of total person-years



Physiologically focused biotechnology companies provide products and services for the creation of new organs, the comprehension of physiological information, and the cure of human disease. Virtually 90 percent of the companies in the Physiology sector are centered around "Cure"-based drug development efforts. Of the remainder, the central themes are the integration of physiological and clinical data, and the growth of new bone, tissue, and organs for the repair and regeneration of injured tissues and body parts.

Scientific Overview

PHYSIOLOGICAL SYSTEMS IN THE BODY



ORGAN SYSTEMS

Organ systems are composed of two or more different organs that work together to provide a common function. There are ten major organ systems in the human body.

Organ systems that provide form and movement for the human body include the skeletal system (bones), integumentary system (skin), and the muscular system (muscles). Organ systems that transport nutrients, create energy, and eliminate waste include the circulatory system (heart), the respiratory system (lungs), the digestive system (stomach and liver), and the excretory system (kidneys).

The nervous and endocrine systems control and coordinate the physiology of the body over both short- and long-term time scales. Both systems make use of chemical messengers to control the body. The immune system protects the body from foreign invasion by bacteria, viruses, and other microbes.

Skeletal System

The skeletal system provides support for the body, protects the internal organs, and provides specific attachment sites allowing stable positioning of the organs. The organs of the skeletal system include bones, cartilage, tendons, and ligaments.

Integumentary system

The integumentary system protects the body against injury and dehydration, regulates body temperature, and provides a physical barrier against foreign invaders. The major organ of the integumentary system is the skin, which is considered a continuous organ encasing the entire body.

Muscular System

The muscular system drives movement in the body. Specific muscles work in pairs to move limbs as well as control the movement of materials through certain organs, including the stomach, intestine, heart, and circulatory system. The major organs of the muscular system are the skeletal and smooth muscles distributed throughout the body.

Muscles are bundles of cells and fibers that can contract or relax. Pairs of muscles that contract in opposite directions are attached by tendons to the skeletal system and allow for precise movements. There are 630 active muscles in the human body.

Circulatory System

The circulatory system transports nutrients, gases, hormones and wastes through the body via the heart, blood vessels, and blood. Red blood cells carry oxygen from the lungs to all the cells of the body and white blood cells, a key participant in the immune system, protect it from foreign attack.

Arteries are blood vessels that carry blood away from the heart and veins are blood vessels that carry it back. Pumped by the heart's four chambers, one body volume of blood circulates through the entire human body in less than two minutes.

Respiratory System

The respiratory system drives gas exchange between the blood and the environment. Oxygen is absorbed from the atmosphere into the body and carbon dioxide is expelled from the body by way of the nose, mouth, trachea, and lungs.

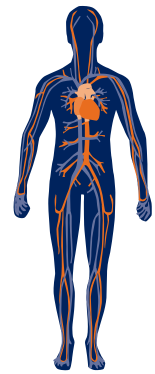
The lungs, two sponge-like organs in the chest, bring air in and out of the body. After entering through the nose or mouth, air travels down the trachea, or windpipe, and then into the bronchi, the major tubes that enter into each lung. Within the lungs, the bronchi divide further into bronchioles, which end in tiny balloon-like sacs called alveoli. These sacs are found throughout the lungs and are where oxygen (from the air) is exchanged for the waste product carbon dioxide (from the blood), which is exhaled. Each lung is composed of sections called lobes. The right lung has three lobes and the left has two, leaving room on the left side for the heart.

Digestive System

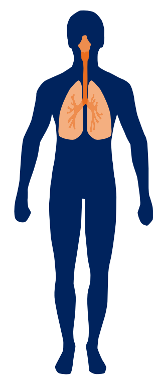
The digestive system breaks down and absorbs nutrients that are necessary for growth and maintenance of the body. The major organs of the digestive system include the mouth, esophagus, stomach, small and large intestines, salivary glands, gallbladder, and liver.

The body digests food at the cellular level to make chemical energy (ATP), which provides the basic fuel for all the body's functions. Cells then use it to make energy. In this process, acids and enzymes eat away at the surface of food. The small intestine breaks the food down further into molecules small enough for the body cells to use. In the "villi" of the small intestine, partially digested food molecules enter the blood vessels. Once these molecules are present in the blood, they can travel all over the body, generating energy in specific areas.

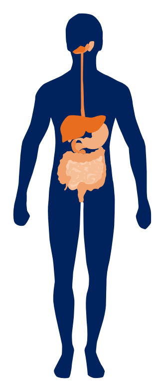
PHYSIOLOGICAL SYSTEMS IN THE BODY



circulatory

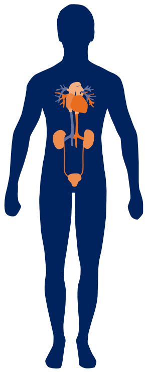


respiratory

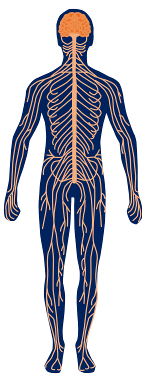


digestive

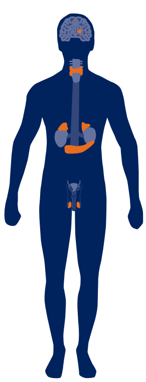
PHYSIOLOGICAL SYSTEMS IN THE BODY



excretory



nervous



endocrine

The liver, the body's largest organ, removes or neutralizes poisons from the blood, produces immune agents to control infection, and filters out bacteria from the blood. It makes proteins that regulate blood clotting and produces bile, a substance which helps absorb fats.

Excretory System

The excretory system filters out cellular wastes, toxins, and excess water or nutrients from the circulatory system. The major organs of the excretory system are the kidneys, ureters, bladder, and urethra. Every human has two kidneys and the total blood volume passes through the kidneys 300 times a day by way of small structures called nephrons. These structures clean all the body's blood in about 45 minutes. Nephrons collect and filter the unwanted materials into the urine, which is sent to the bladder and expelled from the body.

Nervous System

The nervous system coordinates and propagates electrical signals throughout the body and directs behavior, movement, digestion, and circulation. The organs of the nervous system include the brain and spinal cord, which together comprise the central nervous system of a human. There are approximately 30,000 million nerve cells distributed throughout the human body and a nerve cell can transmit about 1,000 nerve impulses each second. In the human brain, there are approximately 1,012 nerve cells with nearly 1,015 interconnections. These nerve cells are fed in the brain by approximately 400 miles of brain capillaries. The surface area of these tubular structures is approximately 100 square feet.

Endocrine System

The endocrine system coordinates long-distance chemical messages through the body. In conjunction with the nervous system, these chemical messages help control such physiological processes as nutrient absorption, body growth, and other physiological responses. The major organs of the endocrine system include a variety of glands that secrete endocrine hormones. A gland is an organ that produces hormones. Among the endocrine organs are the hypothalamus, pituitary, thyroid, and pancreas, as well as the adrenal glands.

The pancreas is an organ of both the digestive and endocrine systems. It is located near the stomach and small intestine and has two major functions. The exocrine pancreas makes enzymes that help in the digestion of food products and the endocrine pancreas produces several hormones that regulate the body in different ways and over long distances.

The thyroid is a small gland inside the neck that produces thyroid hormones, which control the body's metabolism. In particular, the thyroid gland produces two hormones, T3 (called tri-iodothyronine) and T4 (thyroxine). Thyroid hormones regulate the pace at which organs function and coordinate the use of energy in the body. In concert with the thyroid gland, the pituitary gland, located in the brain, produces the thyroid-stimulating hormone, which activates the thyroid to produce more thyroid hormones.

Immune and Lymphatic System

The immune system identifies, destroys, and removes invading microbes and viruses from the body by filtering out organisms that can cause disease, producing certain white blood cells, and generating antibodies to specific foreign attacks. The lymphatic system also removes fat and excess fluids from the blood. The major organs involved in these processes are the lymph, lymph nodes, and vessels, as well as white blood cells, T-cells and B-cells. These are some of the fundamental components of the immune system.

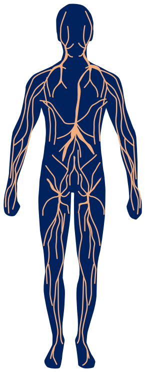
The lymphatic and cardiovascular systems are closely related and are interjoined by a capillary system. Lymph is a milky body fluid that contains a type of white blood cell, called lymphocytes, along with proteins and fats. Lymph serves a central role in the immune system and also absorbs fats from the intestines. It seeps outside the blood vessels in the spaces of body tissues and is stored in the lymphatic system to flow back into the bloodstream. Through the flow of blood in arteries veins and through the lymph nodes, the body is able to eliminate the products of cellular breakdown and bacterial invasion.

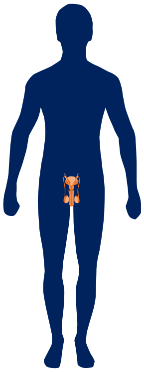
This system, which includes the spleen, the thymus, lymph nodes and lymph ducts, is how the body fights infection and wards off attack from foreign invaders. The lymphatic vessels are present wherever there are blood vessels and transport excess fluid to the end vessels without the assistance of any pumping action. There are more than 100 lymph nodes in the human body, located mainly in the neck, groin, and armpits. These lymph nodes act as barriers to infection by filtering out toxins and microbes. The largest body of lymphoid tissue is the spleen.

Reproductive System

The reproductive system manufactures the cells that allow reproduction. In the male, sperm are created to inseminate the egg cells produced in the female, and the major organs of the male reproductive system include the testes and the seminal vesicles. The major organs of the female reproductive system include the ovaries, oviducts, uterus, vagina and mammary glands.

PHYSIOLOGICAL SYSTEMS IN THE BODY


immune/
lymphatic


reproductive

OVERVIEW OF PHYSIOLOGICAL AND METABOLIC PRINCIPLES

Physiology can be considered the sum of all the chemical and physical processes within a living organism, including metabolism, anabolism, and catabolism. All life must have an unceasing supply of energy and matter. The transformation of this energy and matter within the body is called metabolism. A subset of metabolism is catabolism, essentially "destructive metabolism." In catabolism, large organic molecules are broken down into smaller structures. This process usually occurs with the release of energy (usually ATP), and is used in energy creation. A complimentary subset of metabolism is anabolism, or "constructive metabolism." In anabolism, small molecules are assembled into larger organic molecules. This always requires the input of energy (often ATP).

A properly-functioning organism lives through the interactions of a complex web of chemical and physical processes, each of which is coordinated to optimize the body's overall function. The coordination mechanisms are myriad, and a physiological framework is a scalable "society" of regulatory motifs in the body. It is both present and relevant at all structural and functional levels of the body's organization, including the organization and coordination of genes, proteins, chemical pathways, cells, tissues, organs, and organ systems.

Several features of these physiological regulatory motifs are so common that they represent fundamental design principles for robust physiology. They include:

Homeostasis

The function of components in physiological networks is to maintain a body's internal environment in a relatively constant and stable state. This baseline environment is the focus of physiology and is called homeostasis.

Steady State

When a physiological variable is unchanging but requires the continual introduction of energy to to maintain its constant value it is considered to be at a steady state. The static value for a physiological variable is its operating point. Existing at a steady state is different from equilibrium, where a variable is unchanging but requires no energy to maintain constancy. Systems that exhibit a steady state often do so through adaptation, the ability to effectively cope with change.

Redundancy

Multiple components with similar functions are often present in some physiological systems. These redundant systems back each other up and provide a degree of error tolerance and resistance against system failure.

Modularity

Physiological subsystems and processes are structurally and functionally insulated from one another. That design means failure in one module does not lead to failure in all modules, avoiding the spread of a perturbation and a system-wide catastrophe.

Industry Overview

CURE

Several drug products are in development that target specific components of human physiology even as they attempt to minimize side reactions in the body.

These products range from highly specific radioactive antibodies for anti-cancer applications to protease inhibitors that may partially control virally based infectious diseases like HIV. Common areas of focus include oncology (cancers), infectious diseases (such as hepatitis), neurological disorders (Parkinsons' and Alzheimers'), metabolic disorders (such as obesity and diabetes), and immunological disorders (such as arthritis). Many biotechnology and pharmaceutical companies are concurrently developing several different drugs for several different diseases. The total number of potential drug products being developed by a given company is called a "drug pipeline."

The development of any new drug can cost hundreds of millions of dollars and involve thousands of people in the process. The Food and Drug Administration (FDA) estimates that it takes about eight-and-a-half years to study and test a new drug before it is approved for public use. In the U.S., all drugs must go through the FDA's controlled testing and approval process before they can be sold commercially. With the exception of a few fast-track drugs (e.g., the anti-protease inhibitors developed to treat AIDS patients), most drugs take nearly ten years or more to reach approval and often incur costs as high as $300–500 million to support this testing and approval process. Nearly 90 percent of potential drugs fail to reach the market, making drug development a high-cost, high-stakes gamble.

Preclinical Drug Testing

Before human clinical trials begin, drugs are first tested for effectiveness on human and animal cells in a laboratory setting. Live animals may also be used to ensure that a drug maintains its properties in a whole-body setting and isn't toxic. Animal testing monitors how much of a drug candidate is absorbed into the blood, how and where it is broken down chemically in the body, its toxicity and its breakdown products (metabolites), and how rapidly the drug and its metabolites are excreted out of the body. This extensive testing is necessary because of the complexity of the physiological system; drug candidates very often exhibit unexpected or unanticipated physiological effects. Of 10,000 chemicals tested in this early preclinical stage, only 250 compounds make it to animal testing. Of these, only five enter human clinical trials. And of this group, only one will be eventually approved for human use.

PHYSIOLOGY: CURE

321 companies
23.4% of total industry
1,332,000+ person-years of research

The "Physiology: Cure" sector by itself represents nearly a quarter of the entire biotechnology industry. These companies develop curative drug products for a range of human diseases including oncology, infectious diseases, neurological disorders, metabolic disorders, and immunological disorders.

After extensive laboratory research of a potential new treatment, an investigational new drug application (IND) is filed with the FDA. Following the agency's approval, the three phases of clinical trials may begin. Clinical protocols are designed by experts in various fields and are then reviewed by an independent group called an institutional review board (IRB). Every medical center performing clinical trials must have an IRB to review the protocol and approve its design before a clinical trial may begin.

Phase I

The principal aim of phase I trials is to determine the safety of a drug. Some toxicity may be acceptable, depending on the targeted disease. A small number of healthy volunteers are usually paid to participate in studies, which try to determine what happens to the drug in the healthy body. Phase I trials range in length from six months to one year, with 20 to 80 test subjects. The per-subject cost varies from $8,000 to $15,000, with an additional $500,000 average cost for animal studies. The total cost for a phase I trial averages $900,000. Most drugs fail phase I trials; the odds of success are only 20 percent.

Phase II

The principal aim of phase II trials is to determine the effectiveness ("efficacy") of a potential drug in patients with a specific disease. This testing also determines common short-term side effects resulting from taking the drug candidate. These trials are often larger in scope than phase I trials, with several hundred test patients involved, and the clinical trial data helps to determine the most effective dosages to be used in phase III trials. These trials are usually double-blinded with placebo controls (neither the investigator nor the patient know if the patient is receiving the active drug). This phase can last up to two years. The per-subject cost varies from $8,000 to $15,000, with an additional $1,000,000 average cost for animal studies. The total cost for a single phase II trial averages $3.3 million. Most drugs fail Phase II trials; the odds of success are only 30 percent. A well-designed phase II trial can identify if a drug is unlikely to pass the expensive phase III trial.

Phase III

Phase III studies are expanded studies that can involve several thousands of patients over several years. They are usually double-blinded and placebo-controlled and they are designed to establish effectiveness and side-effect profiles for the candidate drug. Typically, an experimental treatment is compared to a standard treatment, although in some cases two standard treatments or two promising new treatments may be compared. The per-

RENOVIS

South San Francisco, CA
www.renovis.com

Founded:	2000
Employees:	64
Privately held	—

Renovis focuses on drug discovery for neurological and psychiatric diseases and disorders by studying the complexity of the brain through neurogenomics, the comparative analysis of gene expression in the nervous system. In particular, the company is using the mouse brain as an animal model for human nervous system function. The company is performing systematic genomic profiling of identified neurons, providing the gene expression information required to deconstruct brain complexity and understand how specific nerve cells function and interact with one another.

EPIGENESIS PHARMACEUTICALS

Cranbury, NJ
www.epigene.com

Founded:	1995
Employees:	42
Privately held	—

EpiGenesis Pharmaceuticals, Inc., a private company based in Cranbury, NJ, is focused on identifying respiratory disease targets and determining potentially synergistic relationships that may exist between these targets to develop new respiratory medicines. The company is integrating genomic approaches to drug discovery with the use of antisense nucleic acid molecules as potential respiratory drugs, in particular "Respirable Antisense Oligonucleotides" (RASONs), which enable the molecular dissection of respiratory diseases and the identification of validated respiratory drug discovery targets and antisense therapeutics.

ALLECURE

Valencia, CA
www.allecure.com

Founded:	2000
Employees:	38
Privately held	—

Allecure is focused on developing therapies and delivery technologies to treat imbalances in the immune system. The company has a product pipeline focused on treatments for asthma and allergies to insect venom, foods, dust, and pollens. Further, AlleCure is developing drugs that can modulate the immune response. AlleCure has developed a vaccine-based technology platform that can alter the balance of a specific set of immune system helper-T cells, called TH1 and TH2.

subject cost varies from $4,000 to $7,500, with an additional $1,500,000 average cost for animal studies. The total cost for a single phase III trial is $18.8 million. Often, several phase III trials are carried out in parallel, each focusing on a different indication ("label") for the drug candidate.

Most drugs pass phase III trials; the odds of success are about 67 percent. For this reason, the financial impact of clinical trial success is greatest when a drug candidate successfully passes from phase II to phase III trials. A successful phase II trial can significantly increase the valuation of a small biotechnology company, especially if it only has a few drugs in its research and development pipeline.

New Drug Application (NDA)

Since 1938, every new drug has been subject to an approved NDA before U.S. commercialization. The data gathered during the animal studies and human clinical trials of an investigational new drug (IND) become part of the NDA. Submission of an NDA can take one and a half years, and cost between $800,000 and $1.8 million, with an average cost of $1.3 million. The odds of success are about 80 percent for drugs at the NDA stage.

COMPREHEND

Companies and institutions developing a comprehensive understanding of physiology include those that model individual tissues, organs, and organ systems using such interdiciplinary approaches as systems biology and in silico biology.

PHYSIOLOGY: COMPREHEND

23 companies
1.7 % of total industry
48,000+ person-years of research

"Physiology: Comprehend" companies develop tools, software, databases, and data-mining to move towards a more comprehensive understanding of physiology at a molecular level. These companies assess the interrelationship of individual genes, proteins, cells, tissues, and organs, thus providing the framework for ultimately simulating and modeling the function of the whole organism: this sector represents the field of systems biology.

Systems Biology

Systems biology studies the complex interactions of many levels of biological information—gene expression, protein production and modification, and physiology—to understand how they are able to effectively work together in an integrated fashion. Systems biology requires both a systematic and internally consistent set of experimental data from which to model a potentially complex set of interactions and a computer-based environment in which to build interaction models to optimize their predictive power. This latter approach is often termed "in silico biology," since the biological framework is being studied in the silicon-based hardware of a computer.

In Silico Biology

Biologists are now working with mathematicians, physicists, engineers, and computer scientists to develop increasingly rigorous computational models of cells, molecular pathways, and more complex biological systems. Given the exponential increase in available genetic and molecular data, these models will likely continue to improve in predictive power. Many scientists feel that computer-based simulations will eventually serve as a central tool in the study of disease, the evaluation of potential drugs and drug targets, and the evaluation of clinical trial data.

CREATE

The ability to control the interplay of individual genes, proteins, cells, tissues, and organs provides the capacity to create new tissues and organs and to extend the functionality of the body beyond natural constraints.

From artificial bone to the de novo construction of artifical skin and new organs, the ability to replace or augment damaged tissue represents the cutting edge of modern medicine.

Artificial Bone

Human bone is made of a structural backbone of collagen surrounded by a mineral called hydroxyapatite (including calcium and phosphorous) that serves as a kind of cement.

Broken bones are sometimes replaced by synthetic implants. But these implants may not have a long lifespan in the body because they are made of materials that are dissimilar to human bone (e.g., stainless steel and plastic). To solve this, academic and industrial research groups are actively pursuing the development of synthetic bone using more natural materials. Several different approaches are being pursued.

Cambridge University and MIT are sponsoring an interdisciplinary research team that is developing porous "scaffolds" of new bone material that it hopes will permit the rapid growth of new bone.

In the U.K., researchers at Oxford have developed a method of precipitating calcium phosphate in a collagen matrix to produce a bone substitute that mimics the natural product. The precipitation occurs as hydroxyap-

ENTELOS

Menlo Park, CA
www.entelos.com

Founded:	1996
Employees:	85
Privately held	—

Entelos develops dynamic large-scale computer models of human disease that provide a framework for integrating data pertaining to a particular human disease. The data is integrated from a wide variety of experimental sources, including genomic, proteomic, and physiological measurements. The company builds its computer models using thousands of peer-reviewed papers, which then permits the simulation of clinical experiments in silico that would otherwise take months or years to do in the clinic.

PHYSIOLOGY: CREATE

22 companies
1.6% of total industry
83,000+ person-years of research

Companies in the "Physiology: Create" sector develop products for a range of biologically-based materials including artificial skin and bone.

ORTEC INTERNATIONAL, INC.	
New York, NY www.ortecinternational.com	
Founded:	1991
Employees:	95
Public	ORTC
Annual Revenue: (2001)	$0

Ortec International is focused on the repair and regeneration of human tissue. The company has developed a product called "OrCel," a composite cultured skin composed of a bovine collagen matrix in which normal human skin cells are cultured in two layers. Donor skin cells are cultured on and within the porous side of the collagen matrix, and keratinocytes are cultured on its coated, nonporous side. The aseptically processed wound dressing is then applied to grafts. An immediate application of this product is its use in skin grafts for burn patients. Every year, about 100,000 Americans are hospitalized for burn treatment, and almost 6,000 die. By replacing skin injured in burns, patients may have a faster and more effective recovery.

atite forms by the diffusion of ions in sheets of collagen. The collagen/hydroxyapitite sheet can then be used to create a bone-like material through a molding process.

In the U.S., researchers at the University of Texas have discovered and refined a pure calcium phosphate artificial bone material. Bone cells called osteoblasts (cells which aid bone growth) and osteoclasts (cells that actively reabsorb old bone) take this very strong calcium phosphate bioceramic material and convert it into living bone in animals and in humans over a period of time.

Artificial Skin

Artificial skin is useful in the treatment of burn victims, and for patients whose skin becomes damaged due to genetic disorders. But growing skin cells outside of the body, a technique called "culturing," can be a tricky business. No general recipe exists; very different cell types require a unique set of conditions, and some simply will not grow in this way.

In the mid-1980s, Howard Green of Harvard Medical School developed a technique for growing a type of human skin cell called a keratinocyte (which populates the upper epidermal layer of the skin) outside of the body. Dr. Green's keratinocyte culture research created a pathway for the commercialization of artificial skin. His breakthrough occurred when he "seeded" human keratinocytes onto a layer of mouse-derived fibroblast (connective tissue) cells in a plastic culture dish. The resulting product, Epicel, is currently licensed by Genzyme Tissue Repair (Cambridge, Massachusetts), and is used to treat deep wounds that require skin grafting, as occurs with severe burns.

Another product, Integra, was developed for burn victims by engineers at Massachusetts General Hospital and MIT. This product contains no living components and is not actually designed as replacement skin. It instead supplies a protective covering and a pliable scaffold onto which the patient's own skin cells can naturally regrow the lower dermal layer of skin that was destroyed by the burn.

Academic researcher Scott White and his colleagues at the University of Illinois have been developing a prototype for a self-repairing plastic skin. The plastic material contains microcapsules filled with a special agent that promotes the self-healing of the surface when cracked or broken.

Artificial Organs

Artificial organs are being developed by researchers and engineers worldwide to replace the heart, bladder, kidney, blood, and lungs. Since the physical functions of natural organs are relatively well understood, engineers have created functionality in a fairly reproducible way. Major areas of focus include compatibility between the artificial structure and the natural body material surrounding the implant, the longevity of the device within the body, and the interactions between the artificial organ and natural organs, both within the same organ system and between organ systems.