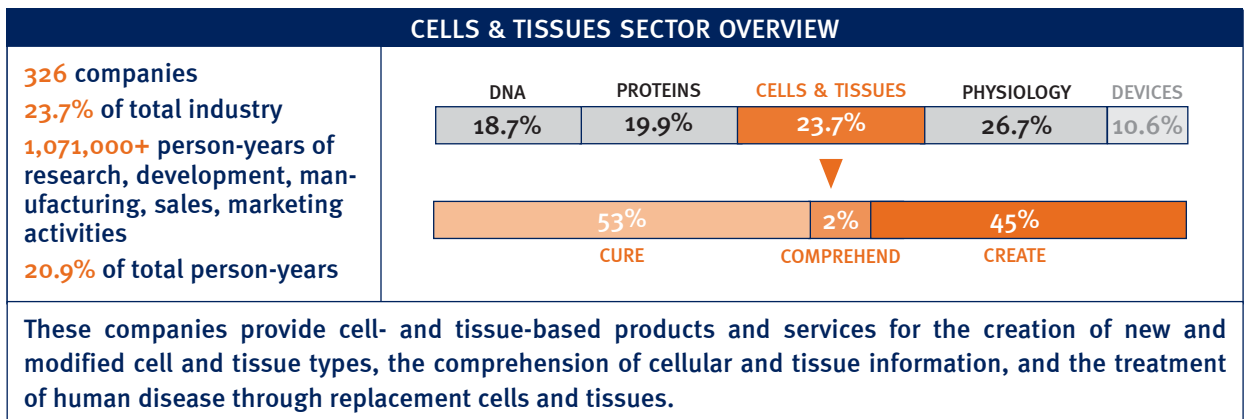


# CELLS AND TISSUES

Cells are the fundamental organizational unit of living beings. A tissue is a group of similarly functioning cells and is essential for all types of physiological functioning.

The next two levels of biological organization—cells and tissues—are treated together in this chapter for several reasons. First, they are functionally intertwined, in that tissues are composed of two or more different cell types, and so changing the structure or function of a tissue is closely related to changes in cellular function within that tissue. Likewise, their commercial potential in the Cure, Comprehend, and Create arenas is closely linked. This is most evident when considering stem cells, from which entire tissues can be created. Thus an understanding of cellular functions is critical to the understanding of tissue-based products.



# Scientific Overview

## Cells

Cells are one of the most fundamental organizing motifs of living beings, as membrane-enclosed, DNA-containing, metabolizing, and self-replicating structures.

### CELL STRUCTURE

Cells types fall into two broad, structurally distinct classes: prokaryotic and eukaryotic.

Prokaryotic organisms are typically one-celled organisms whose cells lack nuclei, such as bacteria. Eukaryotes are more complex than prokaryotes, in that eukaryotic cells contain nuclei, membrane-bound organelles (differentiated structures within cells that perform specific functions) and are often somewhat larger than individual prokaryotic cells. Eukaryotes may consist of one cell (such as protozoa) or may be multicellular (such as plants, fungi, animals, and humans). The discussion here will focus mainly on eukaryotic organisms.

### CELL SIZE

Cells are small so that their surface area-to-volume ratio is as high as possible.

High surface areas permit the rapid intake of food and the effective release of waste. As a cell's volume increases, the ratio of its surface area to its interior volume decreases. If a cell has more interior volume, then more membrane is needed to carry off wastes and obtain nutrients (since these functions depend on the membrane of a cell). Thus, larger cells have greater challenges with waste removal and nutrient feeding than smaller cells. This geometric constraint ultimately limits the useful size that cells may obtain.

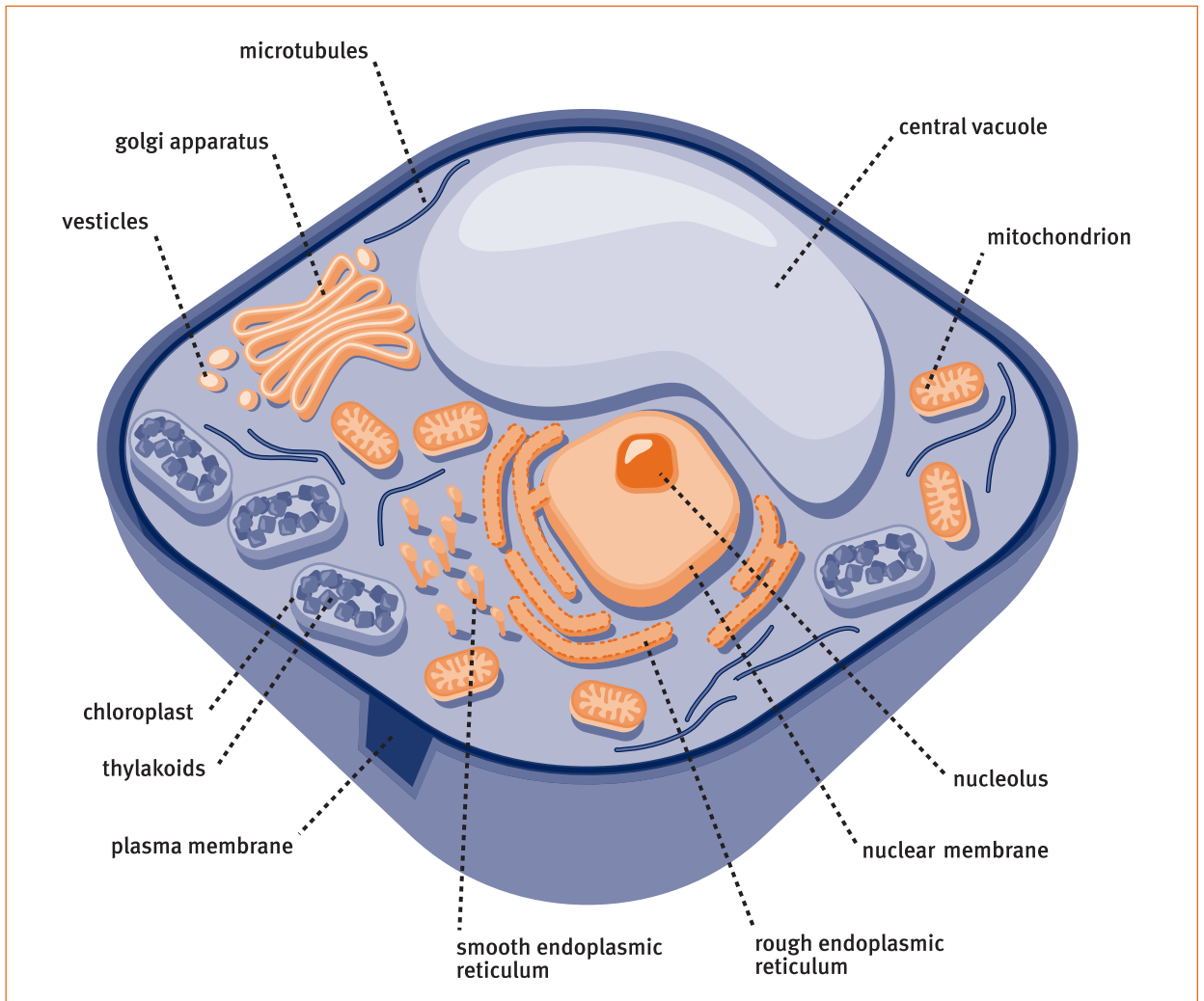
One way around this surface-area constraint on cell size is the formation of various structures that serve either to increase the area of the plasma membrane without significantly increasing internal volume (such as folding the membrane into pockets) or to develop specialized cellular components that increase the membrane's area without actually increasing the surface area of a cell's plasma membrane (e.g., the membrane-based organelles of eukaryotic cells).

# CELL COMPONENTS

The components of the cell work in synergy to process food, create energy, and eliminate waste.

These components fall into several broad classes, including membranes, cytoskeletal elements, and organelles (discrete bodies found in the cytoplasm of a cell, defined by a surrounding membrane, and performing a specific function). Together, these structures carry out the mechanical processes required for life.

ILLUSTRATION OF A PLANT CELL



# COMPARTMENTALIZATION

The size and structure of cells are designed to permit mutually incompatible chemical reactions to occur in parallel. The cell does this by building separate compartments to allow these reactions to occur at the same time but in different places.

Chemical complexity is required for the proper functioning of the more sophisticated cellular functions in a cell. However, complex chemical reactions can be incompatible with one another. Two or more otherwise incompatible chemical reactions can nevertheless occur within the same cell as long as the reacting chemicals or materials do not come into contact with each other. Thus the compartmentalization of mutually incompatible reactions provides a means to increase the potential chemical complexity of a cell. Reactions can be separated in space by placing a membrane between the respective substrates and products of each reaction.

In prokaryotes the plasma membrane is further employed as an anchor for specific enzymes. Since the internal membranes of prokaryotes have no membrane-bound organelles, they have only a limited membrane area in which to anchor certain enzymes. Prokaryotes also have only a limited capacity to separate mutually incompatible chemical processes spatially since these may occur in the same cell at the same time. These fundamental restrictions limit the potential complexity of prokaryotic life.

In contrast, eukaryotic cells have many internal membrane-enclosed compartments such as numerous organelles that harbor spatially discrete locations in which sophisticated intracellular chemistry can occur.

## Membranes

Cells contain cytoplasm and cytoskeletal components surrounded by membranes. The plasma membrane is the structural boundary surrounding and defining the limits of individual cells. It forms a selective barrier that only lets certain molecules into or out of the cell under very specific conditions. Within the plasma membrane barrier is the cytoplasm, a water-based solution of macromolecules, salts, and a number of structural components important for cellular functions. The cytosol is the water solution that makes up the cytoplasm. Other components of the cytoplasm include the cytoskeletal elements, a network of protein-based fibers that fall into three classes: the microtubules, microfilaments, and intermediate filaments.

Microtubules such as tubulin are the largest-diameter cytoskeleton components, and these structures can be very long (as long as the cell). The microtubules are composed of individual protein subunits, and in their

aggregate structure the microtubules serve to shape and support the cell. Microtubules are easily made smaller by removing tubulin subunits; they are also easily expanded by adding tubulin subunits. Within the cells, extensive cellular machinery permits the controlled coordination of microtubule length. The microtubulin network functions as the tracks for movement of the organelles, much like an interstate highway system of transport.

Microtubules also make up cilia and flagella, hair-like structures that project from the cytoplasm to an area just outside of the cell. Flagella are long, whip-like structures that are typically few in number per cell, while cilia are shorter, oar-like structures that typically number many per cell. Both cilia and flagella are involved in cell movement, as well as in moving external material over surfaces of a cell. For example, ciliated cells line the respiratory system and push foreign material out of the lungs.

As the smallest of the cytoskeleton components, microfilaments such as actin consist of two interwoven chains of actin-protein subunits. Together with the protein myosin, microfilaments comprise the contractile organelles within muscle cells, which both move the cell and components within the cells (such as chromosomes during cell division).

As their name implies, intermediate filaments have a diameter that is intermediate between that of microtubules and microfilaments, and these structures are often used to reinforce the shape of a cell as well as anchor various organelles in a typically static fashion.

## The Organelles

Organelles are specialized, sub-cellular organic machines, often surrounded by membranes, that perform specific functions in the cell. These organelles include the nucleus, the rough and smooth endoplasmic reticulum, the Golgi apparatus, mitochondria, chloroplasts, thylakoids, lysosomes, vacuoles, and transport vesicles. Each of these organelles is described in greater detail below.

### Nucleus

In eukaryotic cells, most of the DNA is physically separated from the cytoplasm, through containment in the cell's nucleus. Within the nucleus, DNA is harbored and supported by protein structures called histones, and the chromosomal complex is stable in this form. The structure that functions as the boundary between the interior of the nucleus from the bulk of the cells' cytoplasm is the nuclear membrane, a double membrane that contains numerous pores. These pores permit molecules to move into and out of the nucleus.

Within the nuclear areas, a small structure called the nucleolus is present. This substructure is made up of protein and RNA but contains very little DNA. Among the many functions of the nucleus is the assembly of ribosomes, which, after assembly, are transported out of the nucleus via pores in the nuclear membrane. As was discussed in the section on protein and RNA, ribosomes are nonmembrane-bound organelles that are responsible for catalyzing protein synthesis. In the cell, ribosomes may be either free (suspended in the cytoplasm) or bound (attached to organelles such as the endoplasmic reticulum).

### Endoplasmic Reticulum

The endoplasmic reticulum (ER) is continuous with and connected to the outer nuclear membrane. The ER is a network of membranous tubules and sacs called cisternae. The ER may be divided functionally and structurally into two types: rough endoplasmic reticulum and smooth endoplasmic reticulum.

Rough endoplasmic reticulum derives its name from its bumpy appearance in electron micrographs. The rough ER is responsible for protein synthesis, modification, and assembly, and it is bumpy because it is bound with ribosomes building proteins.

Smooth endoplasmic reticulum lacks bound ribosomes. This area localizes and coordinates specific chemical reactions such as lipid synthesis (particularly steroid synthesis) and carries out particular metabolic reactions like carbohydrate metabolism.

### The Golgi Apparatus

In 1897, Camillo Golgi discovered a structure within cells that was subsequently named after him: the Golgi apparatus. The discovery of this organelle was a breakthrough in cell biology; however, the existence of the Golgi apparatus was debated for decades, as scientists believed that it only represented an artifact of the staining process. In the mid-1950s, the existence of Golgi apparatus was confirmed with an electron microscope.

The Golgi apparatus is a coordination center for the transport of materials among the various organelles in the cell and is a central intermediary connecting the contents of several organelles with one another. In addition to vesicle transport functions, the Golgi is also a site of protein modification and storage. Significant intracellular packaging occurs in the Golgi apparatus.

### Mitochondria

Mitochondria have been called the most successful life form on the planet, in large measure because nearly all animal and plant cells contain

numerous mitochondria. These organelles serve as the energy center of the cell, and are responsible for cellular respiration, the mechanism by which most eukaryotes generate the majority of their energy.

The evolutionary origins of mitochondria are parasitic bacteria that long ago entered eukaryotic cells and proceeded to evolve into a mutually beneficial (symbiotic) role with the eukaryotic cell, providing cellular energy in exchange for a buffered, nutrient-rich environment in which to live. During evolution, an ancestral cell formed a working relationship with a free-living, bacterial organism. This co-dependent relationship allowed these ancient cells to produce energy in the form of high-energy phosphate bonds of adenosine triphosphate (ATP), more efficiently than other cells. This selective advantage fostered the development of multicellular organisms, and as a remnant of its past life, each mitochondrion contains a “private” set of genes for the production of proteins that are critical to the process of cellular energy production.

### Chloroplasts

Chloroplasts are energy-producing organelles found in plants and algae that are responsible for photosynthesis (the conversion of energy and carbon dioxide into energy-rich sugar molecules). Analogous to mitochondria, chloroplast substructures are similar to those also found in cyanobacteria, and include (from the outside in): the outer membrane, the intermembrane space, the inner membrane, the stroma (the cytoplasm equivalent), and an independent set of DNA.

Chloroplasts, like mitochondria and their bacterial ancestors, divide by binary fission, and are essentially parasitic bacteria that long ago entered the plant cell and evolved into a mutually beneficial, symbiotic energy production role. Both plant and animal cells have bacterial cells inside them that serve as energy centers.

### Thylakoids

Thylakoids are membrane-bound organelles found within chloroplasts that look like flattened disks arrayed in stacks to optimize the potential surface area exposed to the sun. The original disks are called grana. Thylakoids are derived from the inner membrane of chloroplasts, and function as the physical site of photosynthesis within chloroplasts.

### Vesicles

Most organelles in a cell communicate via transport vesicles, which are membrane-enclosed, spherical structures that transport their contents and membranes to organelles by fusing their vesicle membranes with the target

### IN SEARCH OF EVE?

The DNA in mitochondria is independent of the DNA in the nucleus and passes down from mother to daughter without any paternal influence. All the mitochondria inherited by humans come from their mothers' eggs. Because of this inheritance pattern, several research groups have attempted to define the original biblical “Eve,” though this research is extremely controversial. Certain geneticists believe that human beings may be descended from one female who lived about 200,000 years ago. These researchers found a high correlation between the nature of mitochondrial DNA mutations, ethnic groups, and geographic locations, suggesting that all humans are descended from a small group of proto-humans originating in either south Asia or sub-Saharan Africa. It's a shocking statement to most paleoanthropologists, who insist that the fossil record shows the human species to be far more ancient and diverse.

organelle. Vesicles differ according to their contents and targets. One function of the Golgi apparatus is to properly coordinate vesicles and their organelle targets with the proper contents for particular vesicles—in essence, shipping the right materials to the right locations at the right time.

### Lysosomes

Primarily found in animal cells and created by the Golgi apparatus, lysosomes are organelles containing digestive enzymes which provide a region separate from the cytoplasm where cellular components are digested back to their component parts. This compartmentalization protects the cell from uncontrolled auto-digestion.

The lysosomes collect large molecules inside and outside the cell in order to break them down into smaller pieces that can be better used by the cell. The degradation pathway in the lysosomes is a very regimented, step-wise process.

### Vacuoles

Vacuoles are a set of specialized, membrane-enclosed structures that are connected with the Golgi apparatus via transport vesicles. The functions of vacuoles range from digestion (via food vacuoles), contractions (via contractile vacuoles, which pump water out of the cytoplasm), and the central vacuole in plant cells, a storage area within the plant cell. Vacuoles allow cells to have a relatively large volume while simultaneously having a relatively small cytoplasmic volume, minimizing the distribution of cellular machinery and conserving the production of cellular materials.

### Extracellular Matrix

The extracellular matrix is the glue between and surrounding animal cells, and consists of protein collagen and high carbohydrate-content fibers and the gluey matrix in which these fibers are embedded.

Within the extracellular matrix, protein tubes called “gap junctions” provide for intercellular transport of relatively small molecules, allowing cells to readily communicate with one another to coordinate responses to physiological events. There are also “tight junctions,” water-tight connections between cells.

# Tissues

There are four primary tissue types in the human body: epithelial tissue, connective tissue, muscle tissue, and nerve tissue. Each of these is described briefly below.

## EPITHELIAL TISSUE

Epithelial tissue is the fundamental tissue that covers the spaces and surfaces of the body.

The cells of epithelial tissue are tightly packed and, in aggregate, form continuous sheets that serve as linings for different regions of the body. Epithelial tissue serves to keep the body's organs separate, in place, and protected. Some examples of epithelial tissue are the outer layer of the skin, the inside of the mouth and stomach, and the tissue surrounding virtually all the body's organs.

There are three types of epithelial tissues: 1) coverings and linings; 2) glandular; and 3) sensory. The covering and lining epithelia are associated with several structures, including the skin, the gastro-intestinal tract, and the respiratory tract. The cells in these tissues have functions which vary according to their location: the skin cells protect, the gland cells secrete, the gastrointestinal tract cells absorb, and the alveoli of the lungs have cells which promote the diffusion of gases such as oxygen.

## CONNECTIVE TISSUE

A wide variety of connective tissues in the body provide support and structure.

Most connective tissue contains fibrous strands of the protein collagen that add support. Examples of connective tissues include tendons and ligaments, cartilage, bone, and fat. Blood is also a form of connective tissue.

### CONNECTIVE TISSUE DISORDERS

The strength of connective tissues in the body comes from fibers of collagen, a protein. Some types of connective tissues are firm to give support, others are elastic to allow movement and strength, and still others bind other body components together. Consequently, if collagen is defective in connective tissues, many problems can arise in the body. In particular, disorders of connective tissue can lead to any of several debilitating diseases, such as Ehlers-Danlos syndrome and Alport syndrome.

Ehlers-Danlos syndrome is a group of heritable disorders of connective tissue, characterized by easy bruising, fragility of the skin, and poor wound healing. EDS is caused by a defect in a type of collagen protein that serves as a building block in the body. EDS is known to affect both males and females of all races and ethnic backgrounds, and occurs at a rate of one in 5,000 people.

Different mutations in the collagen proteins can cause different diseases. Alport syndrome, a hereditary disease of the kidneys, is often caused by a mutation in one of several genes that code for the protein chains of Type IV collagen. This disease primarily and most severely affects men, causing blood in the urine, hearing loss, and eye problems. Eventually, kidney dialysis or transplant may be necessary. Alport syndrome affects about one in 5,000 Americans. There are several varieties of the syndrome, some occurring in childhood and others that affect men in their 20s or 30s. All varieties of the syndrome are characterized by kidney disease that usually progresses to chronic kidney failure.

## MUSCLE TISSUE

**Muscle tissue is a specialized type of tissue that can contract.**

This tissue harbors the specialized proteins actin and myosin, which, when acting together, slide past one another and allow the movement of muscles in the body.

## NERVE TISSUE

**Nerve tissues send electronic signals throughout the body, thereby causing behavioral responses.**

Most nerve tissue contains two primary types of cells: neurons and glial cells. Neurons can create and conduct electrical signals called “action potentials.” These electrical signals propagate along nerve cells in the brain, the spinal cord, and the neuro-muscular regions of the body. Glial cells can also electrically signal other cells in the nervous system, although by a different mechanism than that typically used by neurons. Together, the cells in these nerve tissues transduce external sensory perceptions into internally coded information, process the information, and coordinate the responses of a body to the information. Behavioral responses can be as varied as conscious thought, body movement, or secretion.

# Industry Overview

## CURE

Disorders of cellular organelles can trigger disease throughout the body, whether caused by physiological or genetic factors. A number of companies are manufacturing drugs that target many such disorders, from emphysema to Tay-Sachs disease.

### Mitochondrial Disease

Heavy reliance on mitochondrial energy production within eukaryotic cells has associated costs. As we age, mitochondrial function degrades, resulting in diminished energy production and accelerated free radical production that may initiate some diseases. Severe defects in mitochondrial function undermine cellular integrity, especially in highly energy demanding tissues such as the brain, the eye, the heart, and other muscles. In addition to physiological stress, genetic mutations in mitochondrial DNA can cause dozens of rare, but very debilitating human diseases.

Many of these mitochondrial diseases are known best by their acronyms, such as MELAS, which stands for mitochondrial encephalomyopathy lactic acidosis and stroke-like symptoms. All MELAS patients have a mutation in the DNA stored in their mitochondrial genome. While this disease is caused by a specific defect in mitochondria, and thus has an organelle origin, the disease can nevertheless cause a wide range of symptoms throughout the body, from diabetes mellitus to progressive neurodegenerative disorders. MELAS is often characterized by stroke-like episodes, and the organ systems included in the multisystemic involvement are the central nervous system, skeletal muscle, eye, cardiac muscle, and more rarely the gastrointestinal system. The prevalence of MELAS is estimated at 16.3 per 100,000 people. This high prevalence suggests that mitochondrial disorders may constitute one of the largest diagnostic categories of neurogenetic diseases among adults.

### Endoplasmic Reticulum Disease

Even very subtle malfunctioning of proteins within organelles can create disease. For example, a genetic deficiency of a protein called 1-antitrypsin ( $\alpha 1$ -AT) results in an abnormally-folded protein, which is unable to be secreted and instead accumulates within the endoplasmic reticulum (ER). This deficiency is the most common metabolic cause of emphysema.

Emphysema is a chronic, obstructive pulmonary disease (COPD) and is characterized by a gradual loss of lung function. Its symptoms range from chronic cough and sputum production to severe disabling shortness of

#### CELLS & TISSUES: CURE

172 companies  
12.5% of total industry  
662,000+ person-years of research

“Cell: Cure” companies provide products and services useful for the cellular treatment of disease, including the development and application of replacement cells and tissues for damaged or diseased tissues.

## MITOKOR

San Diego, CA  
www.mitokor.com

Founded: 1991  
Employees: 130  
Privately held: —

MitoKor is pioneering therapeutic solutions for diseases based on mitochondrial research. Mitochondrial dysfunction is a significant contributing factor in major diseases such as Alzheimer's, Parkinson's, osteoarthritis, and Type 2 diabetes mellitus. MitoKor has established a program to determine how changes in mitochondrial DNA might be associated with these different diseases. By characterizing mutations in the genes of mitochondrial DNA, and by identifying the proteins found within the mitochondria, the company hopes to compare the mitochondrial profiles of normal and ill patients. In doing so, the company seeks to develop potential interventional strategies for mitochondrial disease.

breath. The prevalence of emphysema is one in 1,000 people, and it is consistently higher in males than females, as well as in Caucasians relative to other races.

## Lysosomal Disease

Within each organelle are many potential sites for malfunction. Lysosome disorders can be manifested during membrane transport or during the storage of specific compounds.

### Lysosomal Membrane Transport Disorders

Cystinosis is a rare genetic metabolic disease primarily affecting children. It causes an amino acid, cystine, to accumulate in the kidneys, eyes, liver, muscles, pancreas, brain and white blood cells and slowly destroy them. Without specific treatment, children with cystinosis develop end-stage kidney failure at about age nine.

Cystinosis also causes complications in other organs. Complications include muscle wasting, difficulty swallowing, diabetes, blindness, and hypothyroidism. It is estimated that at least 2,000 individuals worldwide have cystinosis, though exact numbers are difficult to obtain because the disease often goes undiagnosed. One of the major complications of cystinosis is a failure of the kidneys to reabsorb nutrients and minerals. In adolescent cystinosis, kidney and eye symptoms typically become apparent during the teenage years or early adulthood. Cysteamine (Cystagon) has been approved by the FDA for standard treatment of cystinosis. Cysteamine is a cystine-depleting agent that lowers its levels within the cells. Cysteamine has proven effective in delaying or preventing renal failure and improves growth of children with the disease.

Sialic acid storage disease (SSD), or Salla disease is a relatively rare lysosomal storage disorder that is named after the area in Finland where the first patients originated. It is caused by a defective sialic acid transporter in the lysosome membrane that normally ensures the efflux of free sialic acid outside the lysosomes. Patients with this disease often show retarded motor skills within the first two years of life; most survive to adulthood, but suffer from severe mental retardation. The global prevalence of this disease is one in 500,000, although in Finland, genetic inbreeding has resulted in a rate of one in 3,000.

### Lysosomal Enzyme Transport Disorders

Lysosomal enzyme transport disorders include mucopolipidosis II (also called I-cell disease), and mucopolipidosis III (also called pseudo-Hurler polydystrophy). There are similar biochemical abnormalities in both diseases but each differs in clinical severity. I-cell and Hurler disease cause similar restriction of joint movement and skeletal changes. Death usually occurs by five years of age. Pseudo-Hurler polydystrophy patients usually show symptoms at two-to-four years of age, with a stiffness of the shoulder and hands that leads to claw-hand deformity, mild facial coarsening, carpal tunnel syndrome, and cardiac disease. Intelligence is usually, but not always, reduced. These diseases are rare, occurring at a rate of one in 325,000 people.

### Lysosomal Storage Disorders

Individually, lysosomal storage disorders are rare genetic diseases. But as a group they are relatively common and represent an important and complex health problem. Lysosomal storage disorders include acid maltase deficiency (lysosomal glycogen storage disease), an accumulation of glycogen in muscle tissue. One of the enzymes (acid maltase) needed to break down glycogen in the muscle cells lacks proper function. Without acid maltase, glycogen continues to enter into the muscle cell, but can't get out. The glycogen accumulates and finally destroys the muscles. Glycogen storage disease type II is also called GSD II, acid maltase deficiency, or Pompe's disease, and is rare. A recent study of carrier frequency in the U.S. indicated a frequency of one in 40,000 people.

Another relatively common lysosomal storage disorder is Tay-Sachs disease, a deficiency in one of the enzymes responsible for breaking down a fat (lipid) called hexosaminidase A. This deficiency causes a great amount of lipids to be deposited in neuronal (nerve) tissue and leads to severe brain damage and nervous degeneration. The disease is progressive and terminal, resulting in early death around three years of age. This disease is mostly found in the Ashkenazi Jewish population. Tay-Sachs has a reported prevalence of one in 3,900 Ashkenazi Jews, compared to one in 200,000 in the overall population.

Gaucher's disease is a deficiency in the lysosomal enzyme glucocerebrosidase. The disease results in liver and spleen enlargement and erosion of long bones like the femur. If the disease occurs in infancy, brain damage results and can cause learning disabilities. This disease is also mostly found in the Ashkenazi Jewish population. Gaucher has a reported prevalence of one in 855 Ashkenazi Jews, compared to one in 57,000 in the overall population.

## CELLOMICS

Pittsburgh, PA  
www.cellomics.com

Founded: 1996  
Employees: 125  
Privately held: —

Cellomics' products and services enable drug discovery by combining automated intracellular and intercellular measurements with searchable databases of cellular information to build on existing genomic and proteomic data. The company provides information on multiple interacting or independent components within or between living cells. Intracellular and intercellular measurements are carried out by high-throughput cellular screening, the creation of specific cell lines, and the development of automated cell analysis instrumentation. Cellular bioinformatics services continuously monitor the research literature of molecular and cellular biology, automatically extracting and storing scientific and clinical information regarding intercellular relationships.

Given the cellular and organelle-specific nature of these diseases, it is useful to be able to treat them at the organelle level of biological organization. Companies are developing products that allow the mass production, discrete identification, and physical manipulation of cells for both research and diagnostic purposes. Another promising approach to cellular-scale medicine makes use of gene transfer to introduce therapeutic genes into specific cells and organelles. Companies are also now investigating how to optimize cellular gene transfer methods into cells to produce transgenic tissues or whole transgenic animals. This research is at a relatively early stage when compared with small molecule or protein-based therapeutic drugs.

## COMPREHEND

**The ability to track and follow individual cells and organelles within a living organism enable scientists to study a wide range of cellular and sub-cellular structure and function.**

Companies involved in this market segment focus on providing products for the tracking of cells, such as specific cell markers, the physical screening and separation of cells based on their different markers, and a variety of dyes, reagents, and imaging compounds that permit the analyses of specific cells and organelles. Several companies such as Cellomics (see box) are now developing tools and techniques to map cellular behavior in an attempt to model the physiology and biochemistry of both the healthy and the diseased cell.

In particular, signaling pathways are the means by which cells communicate with their environment and with each other. Understanding cellular signaling networks is a major challenge in post-genomic molecular biology. Research and development is now focused on the development of databases, simulations, and modeling techniques to understand and predict the behavior of cells. Visualization of intercellular behavior is possible with interactive software tools, and the relevant levels of cellular behavior are being modeled even with partial knowledge. The constraints are explicitly represented in these models, which over time can be refined and extended in different ways. Cellular models are also being linked to experimental data where possible. Further, simulations are being developed that will help predict the potential effects of genetic alterations such as gene mutations, and the effects of specific drugs. This cellular informatics work is at a relatively early stage.

## CELLS & TISSUES: COMPREHEND

8 companies  
0.6% of total industry  
9,000+ person-years of research

Companies in the Cell: Comprehend sector provide products and services for the analysis of cellular and organelle structure and function and their interrelationship.

# CREATE

The ability to genetically engineer cells, biochemically alter their function, and mass produce cells at high volume offers a variety of potential uses. Of particular interest is the use of stem cells for therapeutic functions and customizing cells for bio-degradative purposes in environmental remediation.

## Stem Cells and Regenerative Medicine

In 1998, the state of the art in regenerative medicines involved the controlled cultivation and manipulation of embryonic stem cells. These are very versatile (pluripotent) cells derived from an early mouse embryo that can be propagated stably, in vitro, in the undifferentiated state. By early 1998 researchers had developed the ability to differentiate these cells into all types found in an embryonic and adult mouse in vivo, and could induce these cells to differentiate into many cell types in vitro. However, many researchers thought equivalent work with human cells was several years, perhaps several decades, away.

By late 1998, two independent research groups had successfully cultivated human embryonic stem cells, and, by 2001, researchers had also showed that adult stem cells could differentiate into developmentally unrelated cell types, such as nerve cells into blood cells.

### Embryonic Stem Cells:

Stem cells found in the early embryo (blastocyst) are used to create a stem cell colony in a plate culture. These cells can produce almost every kind of cell, and can replicate in culture almost indefinitely. They are also highly controversial, as their use requires initial cultivation from human tissues.

### Embryonic Germ Cells:

Fetal tissue is transformed into a germ cell line. These cells were destined to be part of the reproductive system (e.g., sperm and eggs). Embryonic germ cells may be able to produce most cells.

### Umbilical Cord Stem Cells:

Using the umbilical cord as a source of germ cells, these cells may be an abundant source from which to differentiate both blood and immune cells.

## STEM CELLS INC.

Palo Alto, CA  
www.stemcellsinc.com

Founded: 1988  
Employees: 33  
Public: STEM  
Annual Revenue: (2001) \$0.8 million

StemCells, Inc. develops therapies that use stem and progenitor cells (rather than embryonic stem cells) to treat human diseases and injuries such as Parkinson's disease, hepatitis, diabetes, and spinal cord injuries. Progenitor cells have already developed from stem cells, but can still produce one or more types of mature cells within an organ. StemCells, Inc. currently has active research and development programs for three classes of cell types: neural, liver, and pancreatic cells. The neural cell program is developing therapies to treat neurological diseases such as Parkinson's, Huntington's, Alzheimer's, epilepsy, and multiple sclerosis. The liver stem cell program is developing replacement cells to repair livers that have been damaged due to disease or injury. The pancreatic cell program is focused on creating pancreatic islet stem cells, which may be useful for treating Type I diabetes.

## CELLS & TISSUES: CREATE

146 companies  
10.6% of total industry  
400000+ person-years of research

Companies in the "Cell: Create" sector are mainly focused on creating products and services for the production and control of stem cells and the synthesis of new tissues for the replacement of damaged and diseased tissues.

## GENENCOR

Palo Alto, CA  
www.genencor.com

Founded: 1982  
Employees: 1144  
Public GCOR  
Annual Revenue: (2001) \$326 million

Genencor is focused on engineering enzymes and cells that drive chemical reactions for applications ranging from health care and agriculture to the industrial chemicals markets. The company engineers biocatalysts for a wide variety of applications such as treating textiles, cleaning contact lenses, processing paper, brewing low-calorie beer, and efficiently converting plants such as corn to chemicals such as ethanol. The company sells more than 250 products to customers in 80 countries around the world.

### Adult Stem Cells:

Found in the brain, bone marrow, blood, skeletal muscle, skin and elsewhere, these cells are more difficult to identify, isolate, and grow in cultures, and they may not be as versatile as embryonic stem cells. However, they are also the least controversial, as their use does not require cultivation from embryonic tissue.

Using stem cells, two types of cloning can be performed in regenerative medical procedures. In therapeutic cloning, stem cells are harvested from the blastocyst and used as replacement cells. This practice is permitted in several countries. In contrast, reproductive cloning relies on the early embryo (blastocyst) to breed a clone of the original patient. This practice is prohibited in most countries.

### Cellular Machines for Environmental Control

Biotechnology can be used to precisely target and reverse environmental damage ranging from oil spills to contaminated air.

Ever since the Industrial Revolution, the unregulated use of technology has contributed to a variety of environmental problems, including contaminated soil, air, and water. Biotechnology's solutions to these problems involve products and processes that cleanse such contamination, industrial effluents and petrochemical spills.

For each of these environmental challenges, the cleansing function of biotechnology arises through highly controlled and localized biodegradation processes, in which a genetically engineered microbe consumes the target waste over a discrete time window, after which the microbe expires. This can be designed into a cleaning process by having a microbial cleaner organism depend on a complex combination of extraordinarily scarce nutritional inputs not found in nature. When this small supply of artificially-created nutrients is fully consumed, nothing is available to sustain the microbe beyond the cleaning period. This solution both resolves environmental issues and anticipates potential problems without creating an environmental impact greater than the original problem.

Companies producing products and services for environmental bioremediation include those focused on soil decontamination, industrial and agricultural waste treatment, and biofuel products (e.g., the use of biomass as a fuel source).

Ethanol, a chemical distilled from corn, is fuel-efficient and pollutes less than gasoline, yet it is now too expensive to manufacture on a scale large because the technology has only been able to use the edible part of plants. Genencor, an industrial biotech company in California, is now developing

a more cost-effective way to make ethanol from biomass—unused crops, trees, grasses, and other agricultural waste products—by engineering and manufacturing genetically modified cellulases enzymes. These enzymes can process all the parts of the plants, not just the edible parts, leading to the low-cost conversion of biomass into ethanol.

## REGENERATIVE MEDICINE AND QUESTIONS FOR THE ETHICS OF A GLOBAL SOCIETY

Regenerative medicine is the replacement of damaged cells by genetically similar yet functional cells. This could be achieved by using embryonic stem cells from cloned human embryos or from highly versatile, “pluripotent” adult stem cells. Potential uses of stem cells vary from discrete transplantation of specific cells to the activation of internally grown (endogenous) cells to provide “self-repair.”

The potential uses for stem cells are significant: replacing damaged cardiac muscle cells and arteries to treat heart disease; adding healthy pancreatic cells that produce insulin to treat type 1 diabetes; replacing damaged nerve cells to treat Alzheimer’s or Parkinson’s Disease; repairing spinal cord injuries; and providing healthy new skin tissue for burn victims. The many potential benefits of stem cell technology in regenerative medicine are clear.

But the use of embryonic stem cells for therapeutic purposes raises some fundamental, ethical questions about the position of the embryo in the context of society’s medical needs. Do we have a right to manipulate living matter at will, especially when the source tissue comes from a human embryo? Is there a fundamental value set to which all of us must conform? How can we justly and compassionately treat individuals who disagree with a particular decision? Since this technology treats the embryo as raw material, productive discourse requires identifying the conceptual ambiguities that exist between science and religion, and seeking a common framework in which to carry out a respectful dialog.

