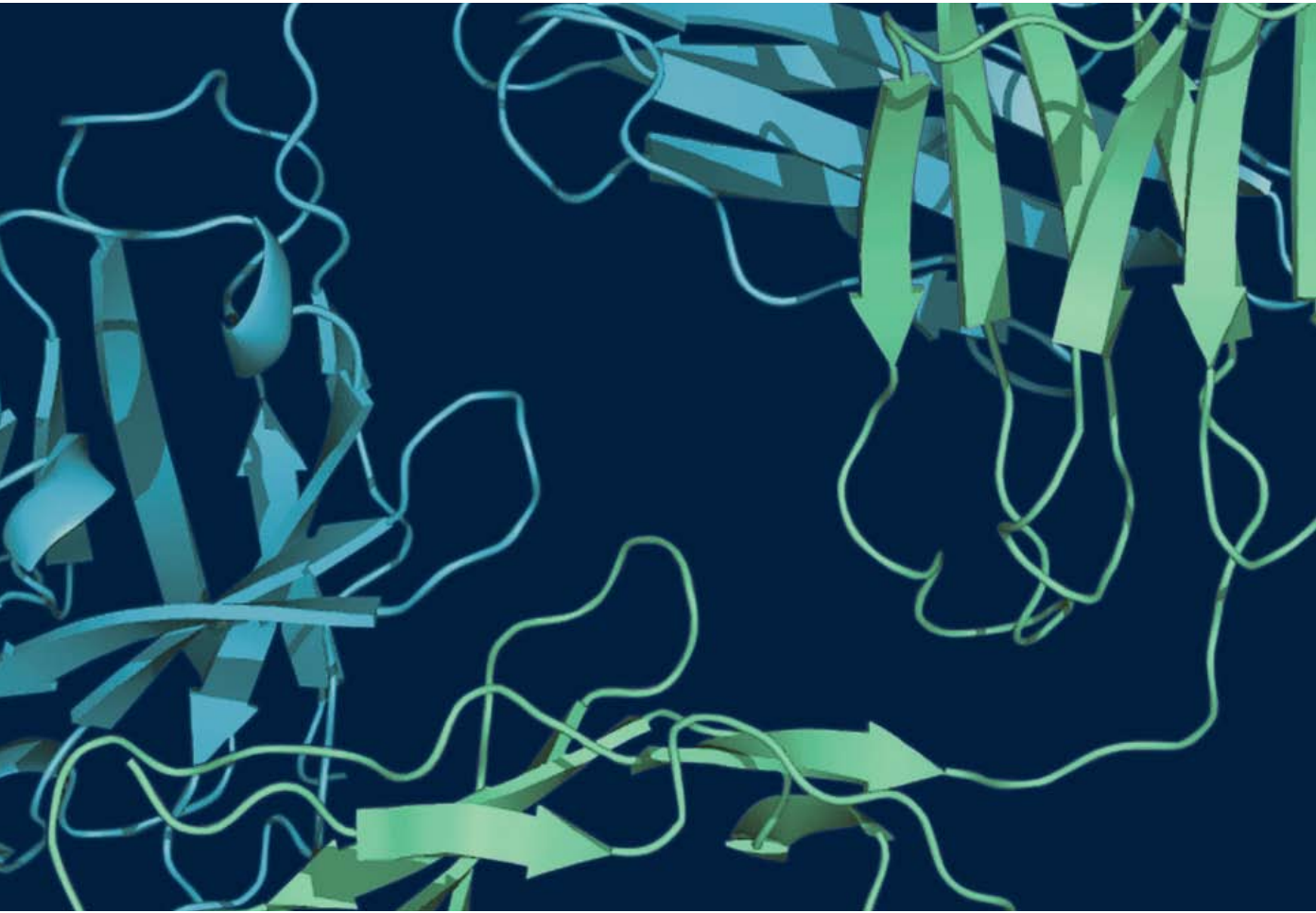


Chapter Three:

How Biology Drives Biotechnology



Biotechnology is based on biology, which is the study of life. The basic unit of life is the cell. Biologists study the structure and functions of cells—what cells do and how they do it. Biotechnologists use this information to develop products.

Biomedical researchers use their understanding of genes, proteins and cell parts to pinpoint the differences between diseased and healthy cells. When researchers know how diseased cells are altered and when they learn how to affect those alterations, they are better able to develop innovative medical diagnostics, devices and therapies.



Autoimmune Diseases

Rheumatoid arthritis is a chronic autoimmune disease that causes inflammation and tissue damage in joints and tendons. It can be a disabling and painful condition and can lead to substantial loss of functionality and mobility.

Psoriasis is a noncontagious disorder that causes red scaly patches to appear on the skin. These patches are areas of inflammation and excessive skin production.

Psoriatic arthritis is a type of inflammatory arthritis that affects up to 30 percent of people suffering from psoriasis.

Juvenile idiopathic arthritis is the most common form of chronic inflammatory arthritis in children.

Ankylosing spondylitis is a chronic, painful, degenerative inflammatory arthritis primarily affecting the spine and causing eventual fusion of the vertebrae.

Lupus is a chronic inflammatory disease that most commonly affects women of childbearing age. Lupus can affect the kidneys, joints, blood and skin, among other organs. Its symptoms can include rash, fever, aches, anemia and hair loss.

Understanding Disease Mechanisms

Early-stage drug research and development (R&D) may begin with understanding the underlying biology of a particular disease. Biotechnology medicines are often created specifically to address a particular disease mechanism.

To design and develop new drugs, researchers must understand the disease mechanisms involved. Some initial questions researchers ask to understand the underlying mechanisms of a disease are: How does a person get the disease? Which cells become diseased? Is this disease caused by genetics, and if so, what genes are turned on or turned off in the diseased cells? What proteins are produced—or not produced—in diseased cells as compared to healthy cells? If the disease is caused by a **pathogen**, what is the interaction between the pathogen and the person?

BIOFACT



The biotechnology industry is one of the most R&D-intensive industries in the world. The United States is recognized as leading the world in biotechnology R&D.

Studying disease mechanisms provides researchers with information that can lead them to identify targets for the early stages of the drug discovery process. An understanding of fundamental biology may lead to effective therapies for patients.

Take treatments available for **autoimmune disorders**, for example. Autoimmune disorders occur when a person's immune system overreacts and attacks proteins, cells and tissues in the body, often leading to inflammation. Biologists have learned that **tumor necrosis**

factor (TNF) plays a major role in regulating inflammation. Researchers know that too much TNF is produced in autoimmune disorders such as rheumatoid arthritis, psoriasis, psoriatic arthritis, juvenile idiopathic arthritis and ankylosing spondylitis. When too much TNF is produced, excessive inflammation occurs—and that can be damaging to joints, skin and other parts of the body. Biotechnology companies have worked to develop medicines that inhibit the activity of TNF.

Models for Studying Disease

Researchers often take several different approaches to creating models for studying a particular disease. One approach is to obtain samples of diseased cells and healthy cells and grow them using a method called **cell culture**. This calls for cells to be incubated and fed with specialized growth **media**. In culture, the cells do what cells do—divide and express genes to produce proteins. By studying how cellular processes differ between healthy and diseased cells, researchers hope to come to understand the mechanism of disease.

Another approach involves studying shared or similar genes and protein equivalents in other species. Since all organisms are made of cells and all cells perform many similar functions, genes and proteins found in humans are also found in other organisms.

BIOFACT



The process of analyzing and interpreting biologic scientific data is called computational biology and involves computer science, applied mathematics and statistics.

The functions of human genes have been revealed by studying parallel genes in

nonhumans. This approach has added to our understanding of how specific genes and proteins direct the functioning of human cells—both healthy and diseased.



Bioinformatics

Bioinformatics combines biology, computer science and information technology into one discipline. The goal of bioinformatics is to capture, organize and index scientific information so researchers can better understand biology. The challenge for computer programmers is to design databases that allow researchers to easily access existing data as well as submit new data.

The scientific community generates volumes of biological data daily. Biotechnology companies use this information to form a comprehensive picture of normal cell activity so researchers can better study diseased cells. This leads to the development of diagnostic tools, therapies and preventive medicines. Because of technological advances in biotechnology, bioinformatics has evolved to focus on nucleotide sequences, genes and amino acid sequences.

Biomarkers

Biomarkers are substances that can be measured and evaluated to indicate (or serve as markers of) normal biologic processes,

disease processes or biologic responses to therapeutic treatment and disease intervention.

Historically, biomarkers were physiological indicators—such as blood pressure or heart rate. Today, disease may also be detected using molecular biomarkers such as prostate-specific **antigen**, a protein that if elevated, may indicate prostate cancer.

BIOFACT



Comparative genomics is the study of genome structure and function among different species. Researchers have obtained complete genomic sequences for the bacterium *Escherichia coli* (*E. coli*), the yeast *Saccharomyces cerevisiae*, the roundworm *Caenorhabditis elegans*, the fruit fly *Drosophila melanogaster*, the laboratory mouse and many other organisms for use in comparative genomic studies with the human genome.

Once a biomarker is validated (meaning all or most patients with the disease test positive for the specific biomarker), it can be used to diagnose disease risk or presence of disease or to help doctors determine patient treatment.

Biomarkers also can be used to predict prognosis—for example, how a disease is likely to progress if left untreated. Identifying biomarkers that indicate specific disease is a crucial step in the R&D process for developing new biotechnology diagnostic tools.

BIOFACT



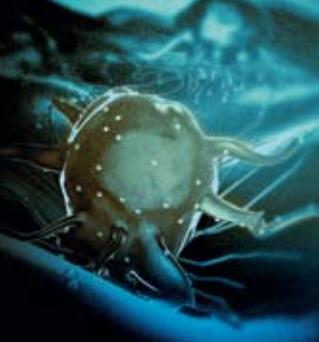
Genetic biomarkers are used in developing diagnostic tests for detecting certain genetic diseases. These tests look for DNA fragments identified as causing disease or associated with susceptibility to a disease.

KRAS: A Biomarker Breakthrough

A biomarker can now help physicians determine which patients will not respond to a certain class of anticancer agents used to treat metastatic colorectal cancer (mCRC). Amgen scientists were the first to show in a phase 3 clinical trial that patients with mCRC carrying specific cancer-promoting mutations in a gene known as *KRAS* are unlikely to benefit from a drug designed to bind to **epidermal growth factor receptor (EGFR)**.

By testing for these mutations, physicians can now eliminate anti-EGFR antibodies as a treatment option for patients with mutated *KRAS* tumors.

KRAS research is regarded internationally as an important step toward personalized medicine for cancer treatment.



Types of Cancer

Cancer is a general term used to describe diseases that occur due to abnormal, uncontrolled and rapid cell growth. There are many types of cancer (carcinoma, lymphoma, leukemia, sarcoma, melanoma, etc.) that affect many types of tissue (prostate, skin, breast, brain, ovaries, lungs, etc.).

Carcinoma is cancer that begins in the skin or in tissues that line or cover internal organs. At least 80 percent of all cancers are carcinomas.

Lymphoma is a cancer of the lymphatic system—a network of thin vessels and nodes throughout the body that helps to fight infection. Lymphoma involves lymphocytes, a type of white blood cell found in the immune system.

Leukemia is cancer that starts in blood-forming tissue—such as bone marrow—and that causes large numbers of abnormal blood cells to be produced and to enter the blood.

Sarcoma is cancer that begins in bone, cartilage, fat, muscle, blood vessels or other connective and supportive tissue.

Melanoma is a cancerous (malignant) tumor that begins in the cells that produce skin coloring (melanocytes). Melanoma is almost always curable in its early stages but can be lethal in later stages.

Researchers study modifications and changes that occur during cellular processes—such as protein synthesis—in various disease states. This can lead to the identification of biomarkers that signal a change in disease progression and can be used as a key development in drug discovery and testing.

Biomarkers are also used in drug discovery to determine whether a drug is effective in animal models and at what doses effectiveness is reached. Finally, biomarkers can be used in disease management to determine whether a drug is having the desired effect and whether the correct dose is being used. This is very important because response to a drug can vary between patients: some require higher or lower doses for the the drug to be effective.

Proteomics

The entire set of proteins produced by an organism is called its proteome. **Proteomics** is the study of protein structure and function. Proteins control all aspects of cellular function. Proteins produced in any specific cell of an organism can vary with a number of factors such as time, hormonal change and stress.

Proteomics researchers identify all proteins involved with protein synthesis and protein folding. Proteins need to fold correctly into

their 3-D shape in order to correctly function. Even small structural defects during the folding process can lead to a number of protein diseases.

Understanding protein structure, function and interaction within and between cells is crucial for drug discovery. Proteins are common drug targets because they are responsible for most normal cell functions—and malfunctions, as in the case of disease. A drug target is the molecule the drug interacts with to bring about the desired change. This is sometimes called hitting the target.

Cancer: From Biology to Treatment

Cancer research is a field that has been at the forefront of utilizing bioinformatics, biomarkers and protein studies to develop new therapies that target specific cellular processes. Cancer biology is a specific field that explores all aspects of the cancer cell. Researchers follow cancer pathways and determine the molecular basis of cancer as they develop diagnostics and treatments.

Cancer starts with changes in one cell or a small group of cells that reproduce uncontrollably. In healthy cells, cell division and growth are tightly regulated. However, cancer cells keep dividing—without normal checks and balances—creating greater opportunity for mutations. A mutation may result from the environment or could have occurred during DNA replication. As the cancer cells replicate and grow, a mass (tumor) is formed. Cells from the tumor can break away (metastasis) and spread through the bloodstream or lymphatic system to other parts of the body, creating new tumors.

Traditionally, cancer has been treated with surgery, radiation and chemotherapy. The biotechnology industry has contributed significant advances in cancer treatment by developing hormone therapies, biologics and targeted therapies such as monoclonal antibodies.

BIOFACT



Biotechnology has created more than 200 new biotherapeutics and vaccines, including products to treat cancer, diabetes, HIV/AIDS and autoimmune disorders. The majority of these products are therapeutic proteins.