

## Chapter Five: **Drug Discovery**



During drug discovery, scientists search for molecules—either chemical or biological agents—that could alter a disease pathway. As part of the discovery process, they specifically look for ways to change one or more molecular or cellular processes that occur in the affected cells of a diseased tissue or organ.

## Initiating Drug Discovery Research

An early step in the drug discovery process is to identify an unmet medical need. What is known about the disease? What are the current treatment options, if any? Does the company have the expertise, technology and financial resources to solve the problem? Potential competitors and barriers, such as regulatory constraints, are also taken into consideration.

### BIOFACT



According to the National Center for Health Statistics, the top five diseases causing death in the United States in 2005 were heart disease, cancer, stroke, chronic lower respiratory disease and diabetes.

## Target Discovery

After identifying an unmet medical need and deciding whether it fits within the company's portfolio, scientists look very closely at the biology behind the disease. Where can they intervene, and what options do they have for intervention? Since the human body is an extremely complex system, scientists have to carefully choose the target.

A target is a molecule that plays a critical role in a disease. Scientists estimate that about 8,000 known therapeutic targets exist today. Targets can be secreted factors, cell surface receptors or signaling pathways within a cell. The goal is to develop a drug that affects a target in a way that interferes with the disease process. It's also very important to ensure that the potential benefits of a drug are appropriately weighed against any risks such as possible side effects.

Different targets respond to different therapeutic approaches. To select a target, scientists will

ask, "What are the differences between healthy and diseased cells?"

Ultimately, disease processes take place at the molecular level. There are various causes of diseases. In inherited diseases, a difference in the expression or in the sequence of genes results in abnormal functioning of a person's cells. Sometimes this leads to a target being present in excess; other times it could be deficient or missing. So the scientists will need to decide if the goal will be to block the target or to enhance or replace it in order to restore healthy function. For a disease caused by an external pathogen, such as a virus or bacterium, the pathogen produces molecules that can damage the host organism's cells. Moreover, the pathogen will, itself, display molecules in the infected individual that are not present in a healthy person. The goal in target discovery is to identify those different molecules. This can be done using a variety of technologies such as microarray experiments, protein electrophoresis, **mass spectrometry (MS)**, DNA sequencing and computerized imaging.

### BIOFACT



Researching the genetic and molecular basis of a disease is called studying the mechanism of disease.

While this sounds straightforward, target discovery is often difficult and may take years to complete. Why? Cells and cell-to-cell interactions are very complex. There may be one or more mechanisms of the disease and many points in the mechanism at which to intercede. Moreover, the difference between healthy and diseased cells can be too minute to easily detect, or a method able to detect the difference may not yet have been invented.



## Chemical Libraries

In the 1990s, chemists developed huge libraries of chemical compounds—thousands, even millions, of chemicals with different structures used to screen for new drugs. These libraries are often proprietary and constructed by a company explicitly to support its drug discovery programs.

Initial screening of drug candidates is relatively simple. Once potential drug candidates or leads are identified, more-complex assays are used at subsequent levels of screening. The sources of the compounds found in the drug candidates are often natural products (from microbes, plants and simple marine life) or chemical compounds synthesized by an organic chemist.

Combinatorial chemistry increases the potential of chemical libraries by synthesizing larger, more complex chemicals or chemically related molecules from common chemical structures. Combinatorial chemistry for small-molecule drugs includes the synthesis of large organic molecules by adding together smaller organic molecules, often with improved product results or lessened product side effects.

## Cell Receptors and Ion Channels

The most common drug targets are cell receptors—proteins on or inside a cell to which a specific signaling molecule can attach. These signaling molecules can be hormones, **neurotransmitters**, pharmaceutical drugs, toxins or even infectious agents. When signaling molecules attach to the receptor, a physical change occurs that initiates a specific cellular response.

Other common drug targets are ion channels, proteins that form pores in the membranes that surround cells, and enzymes—proteins that increase the rate of specific chemical reactions.

The complexity of the body's response also means scientists could see a difference in the expression of hundreds of genes without being able to determine which ones were critical to the disease.

### Target Validation

Once scientists identify potential targets, the next step is to validate them. Target validation has two components. The first is to show that the target molecule actually plays a role in the disease. The second is to confirm the target is a candidate for therapeutic intervention: Can a safe and effective drug be made against the target? Scientists complete this second component of target validation before the drug enters human testing.

There are a number of ways to validate a target, and the process must take into consideration time, cost and technology. At the simplest level, the concept of target validation is to use the target to create the disease in a sample of healthy tissues and then block the target to restore the healthy condition. This is done in cell culture or animal models. The trick is to select a model that is representative and will work. Sometimes people who are born without certain functional molecules express a specific disease type. Studying biological samples taken from such human subjects provides another means of validating a target.

Examples of target molecules include receptors, enzymes, **ion channels**, growth factors, cytokines and DNA binding proteins. The common thread among these targets is that they are often involved in **signal transduction** processes in and among cells. Signal transduction pathways control cellular processes

such as division, differentiation, protein synthesis and programmed cell death (**apoptosis**).

Initial studies are often done in cell culture. If cell culture studies are positive, a next step is to use an animal model.

Sometimes a suitable animal model has to be created to validate a target. Sometimes the target doesn't exist in an animal model or may not mimic the human disease state. Sometimes the drug candidate is so specific to humans, it won't recognize the animal model's target or the animal will mount an immune response that blocks any therapeutic effect. For example, Alzheimer's disease occurs only in humans, and only recently have mouse models been developed to mimic the disease.

Scientists also look at what other effects the drug candidate may have within preclinical (both cell culture and animal) models. Sometimes the target is expressed on other cells or tissues besides those directly involved in the disease. What happens to those cells and tissues in the presence of a drug candidate? Does a drug candidate adversely affect other cells or tissues? Does it raise an immune response; stimulate other, similar targets; or otherwise present any concerns about toxicity?

#### BIOFACT



Recently, scientists have begun using computer simulation to model drug-target interactions to guide drug discovery.

Preclinical work helps support later human trials that may occur if the drug candidate continues to show promise. Even if the drug gets marketing approval after successfully completing the necessary phases of human

trials, safety surveillance will continue once the drug has reached the larger patient population. Scientists will continue to answer safety questions throughout the life of a drug.

## Screening

**High-throughput screening** is a process that combines robotics and data processing to rapidly identify the compounds, antibodies or genes that modulate a particular biomolecular pathway. Large batches of potential drugs are tested for binding activity or biological activity against target molecules.

Once a candidate disease is identified, a company's research lab develops a testing method (**assay**) to determine or measure the pharmacological activity of hundreds to hundreds of thousands of molecules.

The assay measures the estimated potential of a molecule to block or stimulate a target. What's being measured could be as simple as the ability of the drug candidate to kill cancer cells in culture or as complex as measuring its ability to inhibit an enzyme involved in a disease. Generally, the more complex the assay, the more relevant the information—but the higher the cost of the assay and the longer it usually takes to get data.

Of the molecules that score a hit—that is, a positive result that appears to have a therapeutic potential—some are identified as lead molecules due to their more druglike properties (solubility, permeability, stability, etc.). Once a drug candidate is identified, scientists may attempt to optimize its ability to fight disease by changing its molecular structure through **combinatorial chemistry** for small molecules or **protein engineering** for large molecules.

## Drug Design

The design approach to drug discovery starts with scientists understanding the genetic and molecular base of a disease and using that information to select a specific therapeutic target. Drugs are then designed to interact with the target. Through rational drug design, scientists seek to develop a drug that is highly specific to a particular target in a disease in hopes of achieving a better therapeutic outcome with potentially fewer side effects.

Scientists can learn more about the structure of the target by using imaging technology such as X-ray crystallography. 3-D structural information about a target enhances drug design strategies.

Considerations in designing a therapeutic agent depend on both the nature of the target and the capabilities of the company. If the target is on the exterior surface of the cell membrane or is secreted, protein therapeutics such as monoclonal antibodies or **peptides** can be used. If the target is on the interior of the cell, only drugs that can cross the cell membrane, such as small molecules, can be used.

When designing a drug candidate, scientists must keep in mind the intended method of drug delivery and determine whether the drug will be a pill swallowed, a liquid injected, a spray inhaled or something else.

## Choosing the Right Tool for the Target

Designing a targeting strategy usually comes down to a choice between a small-molecule drug and a biologic (most often a recombinant protein or antibody). Each has its particular advantages and disadvantages.

Small molecules can usually cross cell membranes and enter cells, allowing them to be used for targets inside cells. Biologics usually cannot cross cell membranes, restricting their use to targets on the surface of, or outside, cells.

Small molecules have good specificity for their targets, but recombinant antibodies generally have extremely high specificity, meaning, fewer adverse reactions for the patient. Small molecules have variable half-lives, which is a measurement of how long a drug stays active in the bloodstream or in its target tissues. Biologics often have much longer half-lives, partly because they are modeled on real biological molecules. This means patients don't have to take as many doses of a biologic, which may result in better patient adherence to therapy.

Biologics usually need to be injected, whereas small molecules can be taken orally. Small molecules can often cross the **blood-brain barrier**, but biologics usually cannot, which to date has limited their usefulness for treating diseases of the brain such as psychiatric disorders and neurodegenerative diseases.