The Shape of Drugs to Come

Protein engineers are using the building blocks nature provides to design an ever-expanding toolkit of new drug modalities to fight disease.

In the days before biotechnology, the wide range of available medicines obscured the fact that nearly every drug had one thing in common with other drugs. With rare exceptions, medicines were based on chemical compounds that determined their safety and efficacy in patients.

Small molecule compounds remain the most common modality used in medicines, but the fundamental structure of drugs has evolved to include a much wider array of options. The biotech industry opened the door to entirely new modalities that can be made through the marriage of science and the molecular machinery of cells.

The biotech industry got its start by creating genetically engineered versions of human proteins—large molecules far too intricate to assemble through chemical processes. Today, protein engineers can reconfigure nature’s building blocks to design innovative structures that fight disease in a more sophisticated manner.

This ever-growing diversity of modalities has helped Amgen to pioneer a new approach to drug discovery. This approach seeks to gain deep biological insights into disease before selecting the optimal tool to target the key molecular defects.

To increase the likelihood of finding the best tool for the best target, Amgen has built an array of drug modalities that is unsurpassed in the biopharma industry. Our product portfolio and clinical pipeline include nine modalities, and our drug discovery scientists are exploring two additional modalities. This feature provides an overview of these 11 tools and how they can be applied to help patients facing serious illness.

Small molecules

The most common type of medicine has a chemical compound as its active ingredient. These compounds are referred to as small molecules because they are significantly smaller than biological molecules like proteins. They are usually taken by mouth in the form of a tablet, capsule, or liquid, but they can also be injected or infused.
Small-molecule medicines may provide the best or only way to treat certain diseases. Because of their size, these compounds can pass through cell walls to engage targets inside the cell. They can also be designed to cross the blood-brain barrier and engage targets that may contribute to illnesses like dementia and depression.

**Therapeutic proteins**

A protein is a large molecule comprised of a long chain of amino acids that is folded into a three-dimensional shape. The specific amino acid sequence and 3-D shape determines the biological function of the protein. Technically, any protein-based drug is a “therapeutic protein,” but the term was first used to describe medicines that are genetically engineered versions of naturally occurring human proteins.

Therapeutic proteins can be used to replace a protein that is abnormal or deficient in a particular disease. They can also augment the body’s supply of a beneficial protein to help reduce the impact of disease or chemotherapy. Genetically engineered proteins can closely resemble the natural proteins they replace, or they can be enhanced by adding sugars or other molecules that extend the protein’s duration of activity.

**Monoclonal antibodies**

Natural antibodies serve as one of the immune system’s primary sentinels. These large Y-shaped molecules carry two variable domains (the Fab regions), which are designed to recognize and bind to specific antigens that are seen as threats. The targeted antigen might be a protein found on a pathogen or a protein marker found on malignant or infected cells. Antibodies also have an immune-stimulating domain (the Fc region) that helps to mount a broader immune response to threats flagged by antibodies.

Monoclonal antibodies are bioengineered molecules that are designed to target specific proteins involved in disease. Like natural antibodies, they are potent and highly selective in terms of the targets they engage. They also tend to stay in the body longer than most other medicines, so in general, they need to be dosed less frequently. Antibody drugs can be used against targets that are outside cells or on the cell surface, but because of their size, they generally can’t reach targets inside cells.

**Fusion proteins**

The tools of biotechnology can be used to engineer molecules that incorporate genes or portions of genes for two proteins. The resulting fusion protein can offer a combination of attributes that enhance its ability to treat disease.
For example, several fusion proteins have been constructed by combining the binding domain of a cell surface receptor with the tail (Fc) portion of an antibody. The receptor portion functions as a decoy binding site to attract and capture molecules that would otherwise contribute to disease. The antibody portion enables the fusion protein to remain in the body much longer than a circulating receptor would last on its own.

**BiTE® antibody constructs**

BiTE® (Bispecific T cell Engager) antibody constructs are a type of fusion protein that is designed to harness the power of the immune system to treat cancer. These bispecific molecules are created by linking the targeting regions of two antibodies. One arm of the molecule is engineered to bind with a protein found on the surface of cytotoxic T cells, and the other arm is designed to bind to a specific protein found primarily on tumor cells.

When both targets are engaged, the BiTE® molecule forms a bridge between the cytotoxic T cell and the tumor cell, which enables the T cell to recognize the tumor cell and fight it through an infusion of toxic molecules. The tumor-binding arm of the molecule can be altered to create different BiTEs that target different types of cancer.

**Bispecific antibodies**

Standard antibody drugs are designed to specifically target a single antigen. However, many complex diseases are driven by multiple factors, so inhibiting a single target may fail to achieve significant efficacy. For example, in some diseases cells may respond to the inhibition of one receptor by producing more of a second receptor to circumvent the impact of the drug.

Bispecific antibodies aim to treat multifaceted, complex diseases by engaging two disease targets with one molecule. While natural antibodies have two targeting arms that bind to the same target antigen, bispecific antibodies are engineered hybrid molecules with two distinct binding domains that target two distinct antigens.

**Peptides**

Peptide is a term applied to small proteins comprised of short chains of amino acids (roughly 40 or fewer). The body uses a wide variety of peptides as hormones and signaling molecules to stimulate and regulate key biological pathways. Well-known examples of natural peptides include insulin, endorphins, and somatropin (growth hormone).
Peptide medicines can be used to replace or mimic the functions of naturally occurring peptides or to emulate the ability of peptides to engage targets in a highly potent and selective manner. Some peptide therapies can be made using chemical processes, while others are produced inside genetically modified cells.

**Peptibodies**

While peptides have functions and attributes that give them significant therapeutic potential, they also tend to be rapidly cleared from the body. Consequently, peptide medicines may require daily injections, which limit their use to a relatively narrow list of diseases. By fusing a peptide to part or all of an antibody, a peptibody combines the activity of a peptide with the longer duration of activity of an antibody.

**Oncolytic immunotherapy viruses**

Doctors have long observed that certain viruses can slow the progression of cancer. Oncolytic immunotherapy aims to build on this potential by using genetically modified viruses to target tumors in two important and complementary ways.

By deleting certain viral genes, scientists can make viruses that can replicate effectively in tumor cells but not in normal cells. Tumor-selective viral replication can cause tumor cells to lyse, or burst open (oncolysis). The virus can also be modified to produce human signaling proteins that summon immune cells to the site of the lysed tumors, where they encounter tumor antigens. The aim is to generate a broad immunotherapeutic response that can help cytotoxic T cells to recognize and attack distant tumor metastases in the body.

**Antibody-drug conjugates**

Many drugs used to treat cancer have toxicities that lead to serious side effects, which limit the dose and effectiveness of these agents and place a tremendous burden on patients. One potential way to alleviate these problems is through an antibody-drug conjugate (ADC).

An ADC is engineered by linking cytotoxic cancer drug molecules to antibodies or antibody fragments. The antibody portion of the ADC can be designed to target specific proteins found primarily on tumor cells. The goal is to deliver the cytotoxic payload more directly to tumor cells and reduce the collateral damage to healthy tissue. Both parts of an ADC—the targeting region and the payload—can be altered to target different types of tumors with different cancer drugs.
CAR T cells

CAR—chimeric antigen receptors—are genetically engineered protein constructs that can be incorporated into a patient’s own cytotoxic T cells to help them to recognize and fight cancer cells. This protein construct combines DNA from several genes to create a new T cell receptor that binds to antigens found on tumor cells and activates the T cell in response to that binding.

CAR T cell therapy is provided by removing or harvesting T cells from a patient with cancer, transfecting the cells with CAR genes that are directed against the patient’s tumor type, expanding the modified T cell population, and reinfusing the cells back into the patient. CAR T cells are still an investigational therapy, but results from early-stage clinical studies have been encouraging.