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# The Biochemistry of Drug Development: From Bench to Bedside

Curriculum Unit 14.04.07
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## Rationale

As a high school chemistry teacher at a New Haven magnet school I am always looking for ways to engage my students in the theme of our magnet as it relates to chemistry concepts. I teach at Hyde School of Health Sciences and Sports Medicine and each year work to write units taught through a health science lens and I have found that the Yale New Haven Teacher's Institute is an excellent way to collaborate with colleagues and experts in the field to write engaging and relevant units for my students. This year, as a participant in the "Engineering in Biology, Health and Medicine" seminar, I am focusing on developing a unit for my eleventh grade chemistry students that uses biochemistry concepts to teach how pharmaceutical drugs are developed in industry.

Drug design and development begins with a basic understanding of biochemical principles and enzyme-substrate complexes. With the understanding of characteristics of amino acids and protein folding, engineers are able to design drugs that will interact with the human body. In this unit students will apply the fundamentals of biochemistry to the pharmaceutical industry and learn how drugs are designed, screened and tested. Students will also develop an understanding of how drugs interact with the body.

This unit will begin with biochemistry basics and the concept of enzyme-substrate complexes. Students will understand that enzymes and substrates "fit" together like a lock-and-key in order to create a product. Students will investigate the complexities of protein folding by learning about the 21 different amino acids and their various R-groups. They will learn about the general structure of amino acids and how changing the side group makes an amino acid hydrophilic or hydrophobic, positive or negative. These differences impact how an amino acid behaves and how a protein folds. In turn, protein folding impacts the shape and function of how a protein will behave. Students will discuss the relationship between structure and function and its importance in pharmaceutical development.

After learning about the fundamentals of biochemistry, students will dive into drug development and screening. They will learn about the various ways for drug screening such as top-down and bottom-up methods. Additionally, students will investigate questions such as, what are good drugs? How are drugs developed? And what are scientists looking for when they develop a drug? Students will learn about the different instruments used in drug development and the various types of engineers that can be involved.

Students will be exposed to molecular and chemical engineering, scale up engineering, genetic engineering and biophysics in this truly multi-disciplinary unit.

Finally, students will learn about what happens after a drug is found that will function properly. They will learn about drug scaling and the challenges of creating large batches of product and the process of pharmaceutical testing. Overall, the unit will take students through the entire process of drug design from bench to bedside.

All of the NHPS Inquiry standards will be addressed in this unit through the use of engineering design principles. Students will learn about the experimental process of designing a drug for consumer use and will read complex texts such as journal articles related to drug development. Students will also carry out experiments related to drug development. Additionally, students will investigate enzyme function by designing their own experiment to test which enzyme works best to catalyze a chemical reaction.

## Enzymes: A Fundamental Concept in Biochemistry

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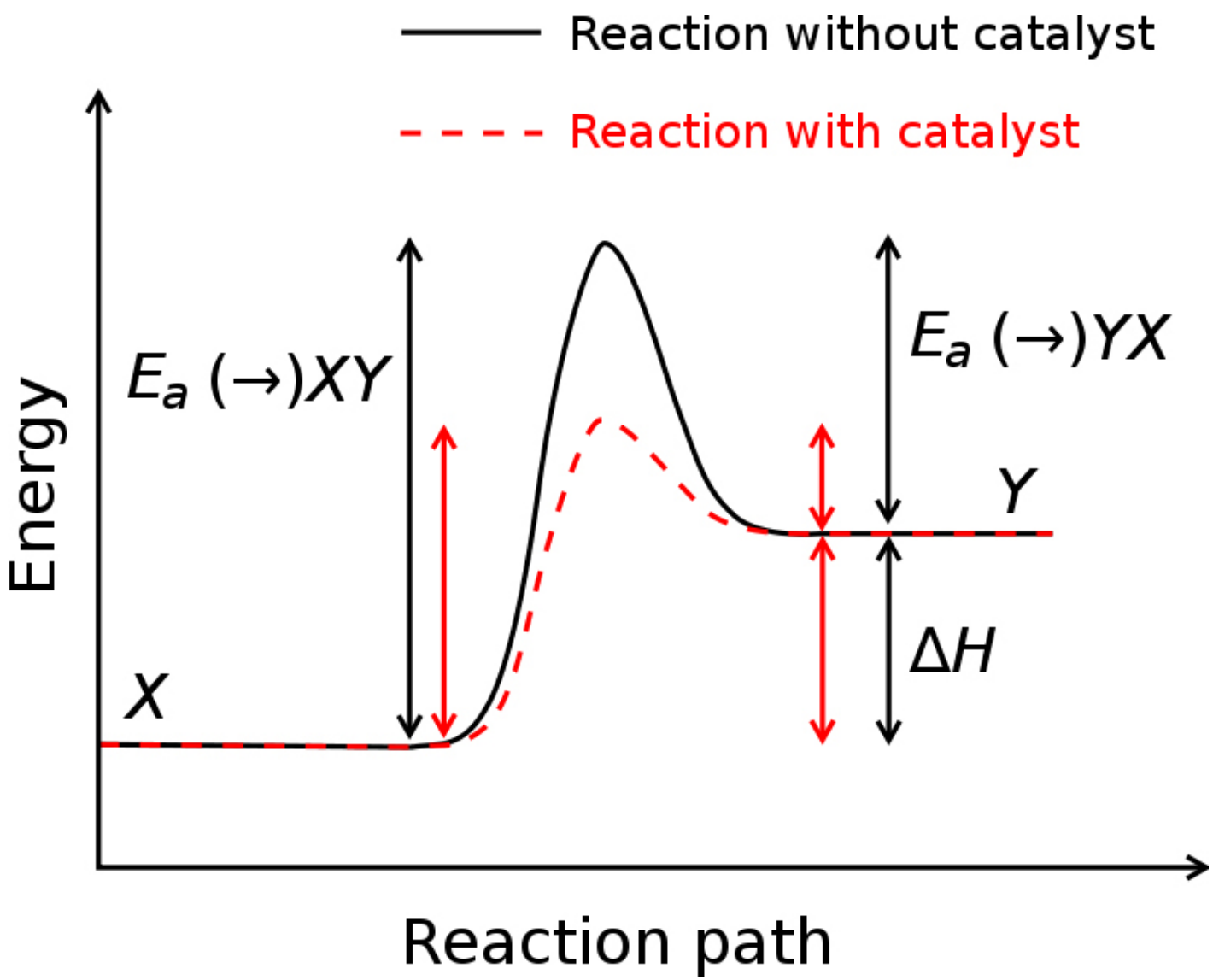
### Chemical Reactions

A chemical reaction is process that changes one set of chemicals into something new with a new set of properties. Chemical reactions can involve putting things together or breaking them apart. Everything that happens in living things is based on chemical reactions that occur in our cells [1]. These chemical reactions involve making and breaking chemical bonds, both of which use energy. All living organisms need energy to carry out the chemical reactions in their cells in order to stay alive. The energy needed to start these reactions is called activation energy [1]. Enzymes are known as "natures catalysts" and help to lower the activation energy needed to start chemical reactions in living things [1]. The image below shows how the energy needed to start a chemical reaction is lowered by the presence of an enzyme catalyst.




http://en.wikipedia.org/wiki/File:Activation_energy.svg

The function of enzymes is explored in greater depth in the following section.

**Enzymes as Catalysts**

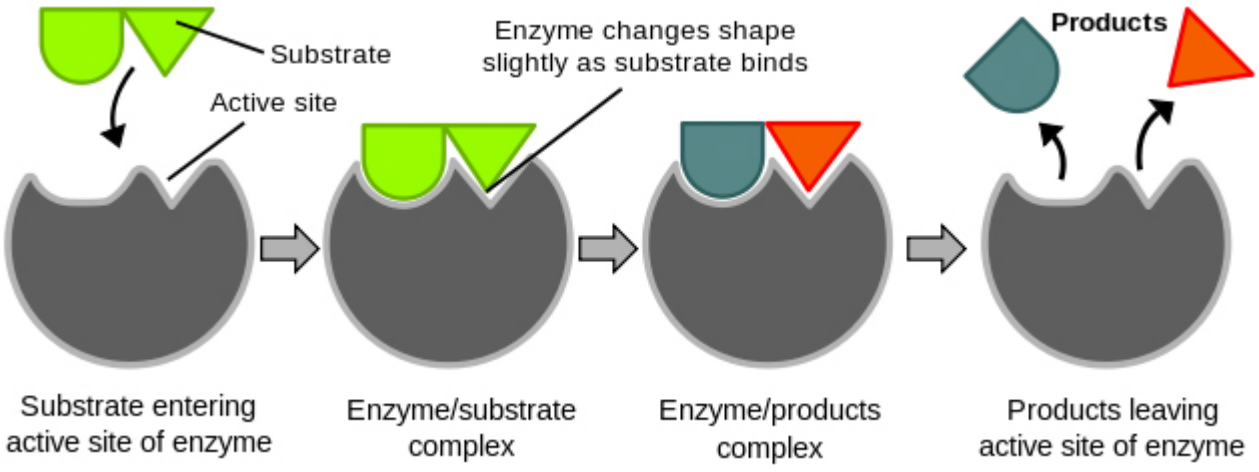
Enzymology is the study of enzymes and is a fundamental concept in biochemistry [2]. The study of enzymes began in the early 19 th century with research on fermentation and digestion [2]. Catalysts are substances that speed up chemical reactions [1]. Enzymes are biological molecules that act as catalysts to speed up chemical reactions in the living organisms; without the presence of enzymes, these chemical reactions would proceed too slowly [1]. In fact, at any given time, all of the work being done in our cells is being catalyzed by enzymatic reactions [3]. Enzymes are created by cells and are necessary for all of the complex reactions that make life possible [4]. It is estimated that cells contain over 3000 different enzymes, each of which catalyze different chemical reactions [5]. Most enzymes are made of protein and can also include other small molecules such as RNA [4] Since enzymes are proteins, they are made up of amino acids, which impact the shape and structure of the enzyme [3]. The impact of the amino acids on enzyme shape will be discussed in more detail later in this paper.

Enzymes function by binding a specific substrate and speeding up the chemical process of creating a product. Their purpose is the speed up the process of putting things together or taking them apart in your cells, allowing them to grow and reproduce [3]. Voet and Voet outline four characteristics of enzymatic reactions that make them different from other chemical reactions: higher reaction rates, milder reaction conditions, greater reaction specificity and capacity for regulation [3].

Reactions that are catalyzed by enzymes are typically $10^4$ to $10^{12}$ times faster than uncatalyzed reactions, allowing for greater product output by several orders of magnitude [2]. Additionally, enzymatic reactions can occur under mild reaction conditions, such as lower temperature and pressure and neutral pH, when compared to uncatalyzed reactions [3].

From the early research of enzymatic reactions, the lock-and-key hypothesis was developed. This hypothesis states that, "the specificity of an enzyme (the lock) for its substrate (the key) arises from their geometrically complementary shape" [2]. Substrates are the reactants in a chemical reaction and enzymes have a great specificity for their substrates [2]. The enzyme and substrate are structurally compatible and fit much like a lock and key or puzzle pieces [5]. Enzymes also have a great specificity for their products, rarely creating side products or errors, making them extremely efficient in catalyzing chemical reactions [2]. Enzymes are also able to self-regulate their catalytic activity based upon the concentration of substrates and products [2].

The basic action of an enzyme is to have the substrate bind to a specific site on the enzyme, known as the active site, where the substrate is then put together or taken apart [3]. This basic action can be broken down into four simple steps: (1) an enzyme and substrate are in the same vicinity in a cell (2) a substrate binds to the enzyme at the active site (3) the substrate is broken down or combined through a process called catalysis (4) the enzyme releases the substrate [6]. When the substrate has bound to the enzyme at the active site this is called the enzyme-substrate complex. The diagram below illustrates the basic action of an enzyme.




http://en.wikipedia.org/wiki/File:Induced_fit_diagram.svg

**General Classes of Enzymes**

There are hundred of enzymes at work in the cell at any given time, but they can be classified generally into groups based on their functions.

There are several classes of enzymes that break down biological materials. Proteases and peptidases are enzymes that break down proteins and peptide chains into their individual amino acids [3]. This class of enzymes can be very specified to only break down certain proteins, while others are generalized and will break down any protein [3]. Amylases are enzymes that break down starch and sugar into smaller molecules [3]. Cellulases also break down cellulose into simple sugars [3]. Another class of enzymes used in the breakdown of materials are lipases, which break down fats [3].

Aside from breaking molecules down, there are other classes of enzymes that perform cellular processes to make energy in the form of ATP [3]. There are 10 enzymes that allow cells to perform glycolysis and another eight enzymes that control the citric acid (Krebs) cycle, both of which work together to create ATP for our cells to use [3].

Additionally, there are groups of enzymes that work on DNA. Restriction enzymes recognize patterns in DNA and cut DNA chains [3]. Other enzymes, such as DNA polymerase and DNA-binding proteins work to reproduce and block access to DNA, respectively [3].

There are even enzymes that produce other enzymes! Virtually all cellular processes require enzymes to make the chemical reactions occur properly.

## Amino Acids and Protein Folding

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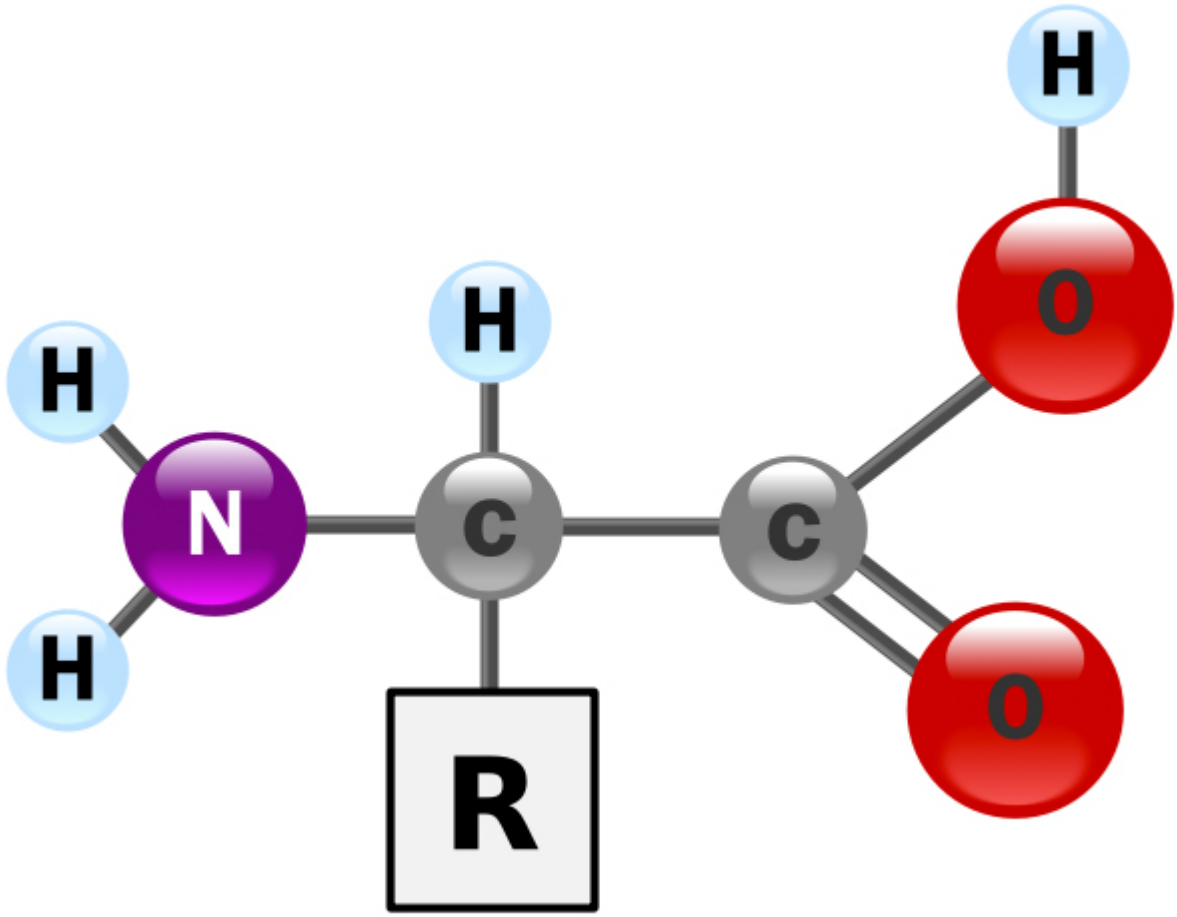
Enzymes are proteins, which are made up of amino acids. It was mentioned previously that the type and order of amino acids in a protein sequence impact the shape and therefore the function of different enzymes.

**Amino Acid Structure**

There are twenty common amino acids used by living organisms [7]. The basic structure of amino acids is a compound consisting of a carboxyl group and amino group, both covalently bonded to a central carbon atom [7]. Amino acids get their name from this amino and carboxyl group attached to the central carbon [3]. Additionally, there is hydrogen and an R group attached to the carbon; the R group is known as a side chain and is what is responsible for the difference in properties of the twenty amino acids [7]. These twenty amino acids are a vital part of all proteins in the human body and are necessary for life [5]. These amino acids can be divided into two groups: essential and non-essential amino acids. Essential amino acids are ones that cannot be created in the body and must be obtained through food; non-essential amino acids can be created from the chemical found in our bodies [3]. Although we focus on the 20 amino acids essential for humans, it is estimated that there are over 100 amino acids present in nature [3]. A diagram below shows the basic structure of amino acids:

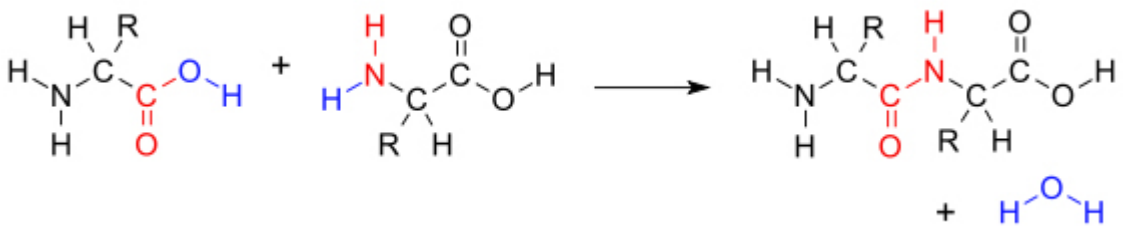



http://en.wikipedia.org/wiki/File:AminoAcidball.svg

Due to the common skeleton structure of all amino acids they have relatively constant percent compositions by mass: 50-55 percent carbon, 7 percent hydrogen, 23 percent oxygen, 16 percent nitrogen and 1 percent sulfur [5]. The molar mass of amino acids ranges from 5000 g to 1 x $10^{7}$ g per mole, depending on the R-group [5].

**Peptide Bonds**

Amino acids are joined together through peptide bonds to create polypeptide chains. Peptide bonds are created through condensation reactions between the amino group on one amino acid and the carboxyl group on another amino acid [5]. This reaction is called a condensation reaction because water is one of the products. The image below shows two amino acids undergoing a condensation reaction to create a dipeptide.



http://en.wikipedia.org/wiki/File:AminoacidCondensation.svg

The dipeptide that is formed in the reaction shown above will then continue to undergo condensation reactions with other amino acids and the final product will be a polymer of amino acids, known as a polypeptide [5]. Polypeptides generally consist of 100 or more amino acids, which is why there are so many different proteins that can be generated from the 20 amino acids that exist in the human body [5].

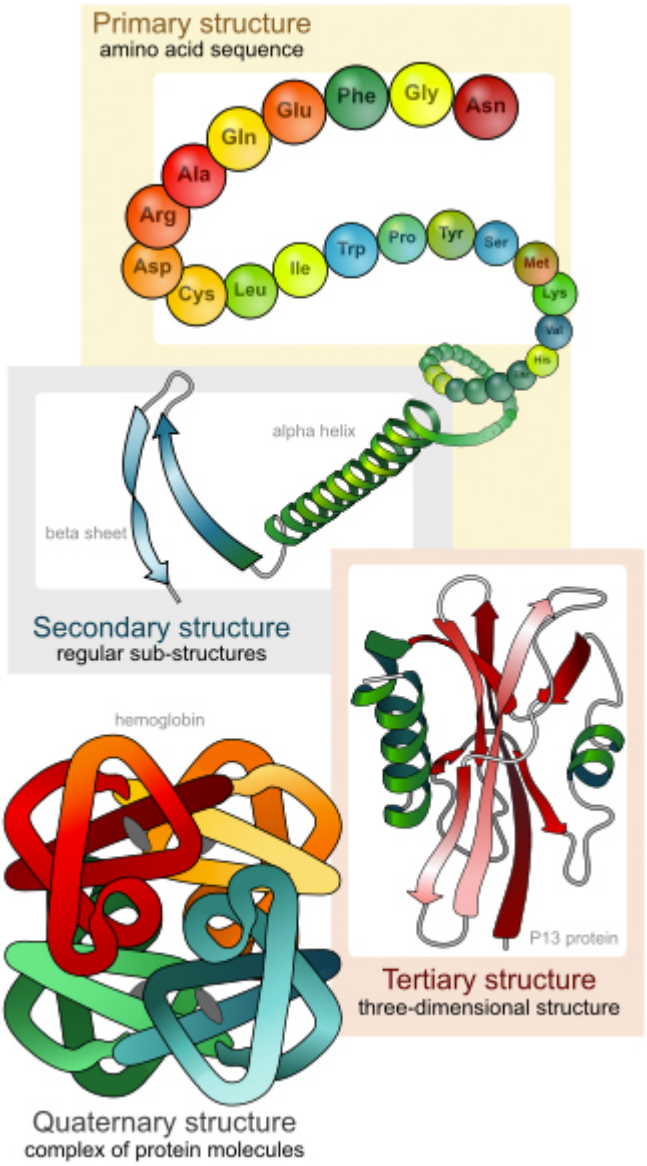
**Protein Folding**

Proteins are polymers of amino acids, meaning they are composed of many amino acids strung together through peptide bonds. The number and sequence of amino acids in a protein molecule determine the protein's structure and function [5]. Protein structure can be divided into four levels of organization: primary, secondary, tertiary and quaternary structure. The primary structure is the unique amino acid sequence of the polypeptide chain [5].

Next, there are two common structures for the secondary structure of protein molecules: the alpha helix and the beta-pleated sheet. The alpha helix structure arises from intramolecular forces, hydrogen bonds, which occur between the groups of amino acids [5]. This forms a rod-like structure known as the alpha helix. The beta-pleated sheet is formed by intermolecular hydrogen bonds that occur between adjacent chains of amino acids [5].

The tertiary structure of protein molecules refers to the three-dimensional structure that is stabilized by dispersion forces, hydrogen bonding, and other intermolecular forces [5]. The tertiary structure differs from the secondary structure in that is can include forces that occur between multiple chains of polypeptides, since proteins can be made up of more than one peptide chain.

The quaternary structure is the overall arrangement of the peptide chains in proteiat [5]. The image below shows a protein sequence at each level of structure.




http://en.wikipedia.org/wiki/File:Main_protein_structure_levels_en.svg

It is the arrangement and sequence of amino acids at the primary structure level that impacts the overall shape and therefore function of proteins. It is the shape of enzymes that impacts how they interact with substrates and catalyze chemical reactions.

## Drug Design and Development

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The process of drug discovery, design and development is lengthy and takes more than fifteen years from bench to bedside. It is also expensive and requires a tremendous level of funding. Researchers spend countless hours working to create drugs that will impact human health and increase our immune system's effectiveness in fighting disease and pathogens. This section will highlight the drug design and development process.

**Drug Discovery**

The first step in the drug discovery process is to understand the disease that is going to be treated or targeted [8]. Researchers begin this pre-discovery process by trying to understand the mechanics of a disease and the impact the disease has on genes and proteins in living cells [8]. Once the disease is understood, researchers begin drug discovery by testing compounds that might interact with the previously identified disease proteins and molecules. Researchers do not work blindly, but instead test "lead compounds" that have been screened and are candidates that are safe and effective [8]. Lead compounds meet several conditions, such as: being absorbed by the bloodstream, distributed to the proper site in the body, being metabolized efficiently, successfully excreted from the body, and non-toxic [8]. Lead compounds can be found in three ways: nature, de novo and high-throughput screening processes [8]. Lead compounds can be found in nature from bacteria, fungi or other sources. De novo research involves creating molecules using computer modeling. High throughput screening is when hundred of compounds are tested to check their compatibility with the target compound [8]. Regardless of the discovery method that is chosen, lead molecules are ones that will interact with the target molecule from the disease and impact its effectiveness.

Once a candidate drug is found, it is optimized in the research lab to make it safer and more effective [8]. This is an early stage of drug development, but researchers begin to think about how they would create the drug for human use, how it would be delivered in the body, and what large-scale manufacturing would look like for the compound. The drug then enters preclinical trials where it is tested in the lab and on animals to determine if it is safe for human testing [8]. The discovery process and preclinical trials can take anywhere from three to six years to find a drug that will be suitable for human testing.

**Drug Development**

Once a drug is approved from preclinical trials it will enter the development process, which has many stages. The first is Phase 1 Clinical Trials, where the drug is tested on a small group of healthy human volunteers to determine if the drug is safe [8]. Then, Phase 2 Clinical Trials are tests on a small group of patients impacted by the disease or condition being targeted in the study. This phase will determine if the drug is working and the risks and side effects it produces [8]. The drug then moves into Phase 3 Clinical Trials where it is tested on a large group of individuals to determine if it is statistically beneficial and working as expected [8]. Phase 3 is the longest part of the clinical trials and drugs that pass this phase apply for approval with the FDA. The clinical trial process can take up to 6 or 7 years to complete.

Once approved, the drug moves into the manufacturing process where it is manufactured on a large scale and distributed. Drugs also enter Phase 4 Trials, where ongoing research continues to determine efficacy and safety [8]. Drug approval and manufacturing can take up to two additional years. The image below reviews the timeline for drug discovery and development.

**Case Study: The HIV Virus**

The drug design process outlined above utilizes structure-based drug design to determine possible candidates. One of the first and most successful structure-based drug design projects was the development of a drug for HIV virus.

HIV, the human immunodeficiency virus, is a virus that attacks human immune cells and causes AID, or

acquired immunodeficiency syndrome. HIV is a major killer worldwide and researchers have spent many years trying to understand this deadly disease. Structural biology and structure-based drug design has been at the forefront of understanding the disease and finding a treatment [9]. HIV is retrovirus, which means that its genetic material is RNA that can enter a cell and be transcribed into DNA [9].

Research has identified an HIV protease, which is a protein that is essential for HIV's life cycle and development [9]. The protease is made up of two equal halves, and has an active site in the center [9]. This protease has become the target of HIV research and structure-based drug design has focused on finding a way to block the enzyme to prevent it from spreading in the body [9]. Researchers used the drug design and discovery process outlined in the previous section to determine what molecule could be used to block this active site and inhibit the molecule. They tested many lead molecules that were found through online chemical libraries and trial-and-error testing. Through the drug design process, scientists found a protease inhibitor that was able to theoretically block the HIV virus from spreading in the body [9]. The process took several years and the drug had to see if it met the requirements for being a viable drug. Unfortunately, the first inhibitor was not able to be absorbed the body so therefore would not be an effective drug for human use [9]. Researchers continued and have found some protease inhibitors that work as antiviral therapy, and although they do not cure HIV/AIDS, they are a breakthrough in structure-based drug development [9]. Researchers continue to look for these structural compounds that could inhibit the action of many viruses that impact humans.

## The World of "Omics"

"Omics" in general aims to study the diverse genes, proteins, metabolic pathways in the body to understand health and disease. The study of genes, proteins and metabolic pathways in the body has helped to develop new technologies for high throughput screening and testing that can be used for drug target discovery.

### Proteomics

The structure and function of proteins was discussed previously in this paper. Proteomics deals with the study of proteins, genes and disease. Currently, researchers are working to develop a map of the human proteome, which would identify novel protein families, protein interactions, and signaling pathways in the human body [10]. Proteomic technology can be applied to medicine because it plays a vital role in drug discovery, diagnostics and molecular medicine [10]. Researchers study proteins that cause diseases and then can create and develop new drugs that mimic protein function or inhibit defective proteins in the body [10]. Advances in proteomics can help scientists create "personalized" medications that are more effective and have fewer side effects. Additionally, research on protein families and classes could help when looking at diseases like cancer, diabetes and heart disease [10]. Researchers are currently identifying unique patterns of protein expression, known as biomarkers, that are associated with specific diseases in order to develop ways to combat and treat these diseases [10].

### Genomics

Genomics is the study of the human genome, which is the complete set of DNA in the human body.

Deoxyribonucleic acid, DNA, is the chemical compound found in the nuclei of cells that contains all of the instructions for the growth, development and activity of living organisms. DNA is made up of four chemical base pairs, adenine (A), thymine (T), guanine (G) and cytosine (C). The sequences of these four nucleotide bases determine the meaning of the information encoded in the DNA as genes. An organism's complete set of DNA is its genome, and is approximately 3 billion DNA base pairs [11]. Researchers that were part of The Human Genome Project, led by the NIH, worked to sequence the entire human genome so that the sequence could be readily and freely available in public databases for use [11]. The project was successfully completed in 2003 and resulted in a sequence of human DNA derived from several individuals [11]. It is a generic sequence of DNA that is used as a research for biomedical studies, specifically related to health and disease. Scientists have been able to use the human genome in their genomic research of complex diseases such as cancer, diabetes, and cardiovascular disease [11]. This research has helped to develop improved diagnostics, more effective therapeutic strategies, approaches for clinical efficacy, and better decision-making tools for patients and providers [11]. New drugs based on genomic research are also currently being developed.

## The Engineering Design Process

The development of pharmaceutical drugs follows many of the steps of the design process. It is important for students to understand the engineering design process in order for them to complete the student activities in this unit. The engineering design process is a series of steps that starts with identifying a problem and ends with developing a solution to that problem [12]. This section will outline the steps of the engineering design process. When using the engineering design process it is not necessary to move in a linear way; researchers and engineers may jump back and forth between steps until they reach a solution [12]. This is important to note for students when they begin using the engineering design process in their research.

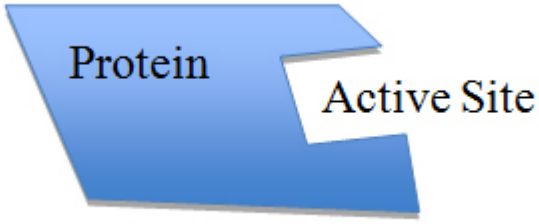
The first step in the engineering design process is to define the problem. The problem is something that needs solved and students should ask themselves questions such as, "what is the problem or need?" "who has the problem or need?" and "why is it important to solve?" [12]. Once the problem has been identified, it is important for engineers to do background research in order to understand the work that has been done before them and to learn from previous researchers [12]. Next, a person must identify the requirements for the solution they are going to create, which can be determined from previous projects or research. Once background research has been conducted, solutions are brainstormed. These are all of the possible solutions that meet the requirements for solving the problem identified in step one. An engineer then chooses the best solution from the list and creates a prototype [12]. A prototype is a model that may or may not be made of the same materials that the final product will use, and does not need to be a refined product. The prototype is then tested to see if it will work to solve the problem. Engineers will then continue to test and redesign their prototype until they have a final product that is a solution to the identified product [12]. When a final design is developed, engineers will communicate their findings and results with the global community and will often move into the manufacturing process [12]. The engineering design process is made up many steps that do not necessarily need to be followed in an exact order. In fact, engineers go back and repeat steps in the process until a final design is created.

## Teaching Strategies

### Enzyme Puzzle Pieces

This is an activity that can be used to teach students the importance of enzyme-substrate recognition and bonding. For a chemical reaction to be catalyzed by an enzyme the substrate must fit precisely in the active site of the enzyme, much like a lock and key. In this activity you can use construction paper to show how the enzyme and substrate fit perfectly together based on their shape.

Begin by cutting out various "protein shapes" from construction paper. They can be any shape you would like and all of them can be different. Next, cut out an "active site" on the construction paper protein. The active site should be a small section of the protein where another piece of paper could easily fit. Please see the diagram below:




Next, use a different color construction paper to cut out a substrate molecule that will fit precisely into the active site on the protein. Please see the diagram below:


Once you have cut out several sets of proteins and active sites pass one piece of construction paper out to each student in your class. They may have a protein or a substrate piece. Then, have the student move around the room to find their "partner." They should know that they must find someone that has the piece that matches theirs, either the protein or the substrate. Once they find their partner, have them discuss why they belong together. Seeing the pieces fit together perfectly and discussing the "lock and key" mechanism of proteins and substrates will help students remember how important the shape of proteins and substrates are to their function.

### Enzyme Lab

This lab activity is used to teach the function of enzymes as catalysts in chemical reactions. They will use various enzymes to speed up the process of making apple juice from applesauce. The procedure is as follows:

1. Place filter paper in a funnel and put funnel in a flask.
2. Set up three flasks with funnels.
3. Pour exactly 20g of apple sauce into each funnel.
4. Add water to the first funnel (8 mL)
5. Add Cellulase enzyme to the second funnel (8 mL)
6. Add Pectinase enzyme to the third funnel (8 mL)
7. Let each flask sit for exactly 20 minutes.
8. After 20 minutes, measure how much juice was produced from each flask using a graduated cylinder.

The students should see that the flasks where an enzyme was added to the applesauce created more juice than the flask that only had water added to it. This will facilitate a discussion about the importance of enzymes catalyzing chemical reactions and can lead to further discussions about chemical reactions in the human body.

**Engineering Pharmaceuticals Research Project**

In this activity students will act as researchers working for a drug development company. They will use the research project found on teachengineering.org to learn about the research phase of drug design and development and learn about biomedical engineers. The lesson outline is described below and the link to the resources for this lesson is located in Appendix B.

Begin by teaching students about biomedical engineering. Review the school required by biomedical engineers and their basic responsibilities in the areas of medicine and biology. Next, review the engineering design process with your students. The engineering design process is discussed in great detail in a previous section of this paper.

Once you have reviewed the necessary background information with your students, give them the biomedical research problem. The research question for this lesson relates to the develop of a new drug, "Outstandix," by a pharmaceutical company. The drug is in the research phase of the engineering design process so the students will act as researchers gathering and prior knowledge that is known about the function of this drug. The drug drastically reduces the levels of the protein Osteopontin in the blood, so students will need to research what others have already learned about Osteopontin in the human body. Students will access scholarly articles in order to gain the information needed to decide if "Outstandix" will be safe for human use and should continue its development.

**Close Reading**

Close Reading is a technique that can be used to teach students how to read and analyze complex texts. It has been shown that the number one predictor of success in college is the ability of a student to read and understand complex texts. In my classroom, I have found that many of my students read below grade-level, so I have implemented a Close Reading Protocol to teach students how to read complex texts that are at or above grade-level. The protocol is outlined below and a sample lesson using a 12 th grade text from Scientific American is included.

1. Choose a complex text that is at or above grade-level from a scholarly journal or scientific writing
2. Select the most important part of the text that is less than 100 lines. It is important in Close Reading that the text is short and concise. You can choose to put various pieces of the text together as long as the entire reading is less than 100 lines in the end.
3. Chunk the text into small parts that are 1-3 sentences long. You students will be reading and re-reading these small sections one at a time in order to dissect and understand the language.
4. For each small chunk, students will read silently as you read aloud.
5. Then, discuss any words that your students might not understand. Write down synonyms for these words.
6. Have students read the section again independently and then have them paraphrase it with a partner.
7. Discuss the paraphrases as a class. At this point all of the students should have an understand of the short passage.
8. Have students read the section again independently and then answer a higher-order thinking question about the small section.
9. You can choose to discuss answers to these questions now or may wait until the entire text has been read.
10. Repeat for each short section until you have gone through the entire text.
11. Finish with a "Big Question" or task for the students that requires them to use all of the information from the text.

The purpose of Close Reading is to have students focus on reading very small, but complex texts. They will read the same couple sentences at least 3 times each in order to make sure they have developed a deep understanding and meaning. A sample text and questions are outlined below. The sample text has been chunked into small sections and there are synonyms for complex terms included that students can fill-in the

blanks with.

The body is protected by a **diverse** (_____) army of cells and molecules that work **in concert** (  ). The ultimate target of all immune **responses** (_____) is an antigen, which is usually a foreign molecule from a **bacterium** (  ) or other invader.

**Synonyms: reactions, together, germ, different**

How is the immune system like an army?

Specialized **antigen-presenting cells** (_____), such as macrophages, **roam** (  ) the body, **ingesting** (  ) the antigens they find and **fragmenting** (  ) them into antigenic peptides that are displayed on the outside of these cells.

**Synonyms: immune cells, breaking, travel, eating**

If the immune system is like an army, what would the **antigen-presenting** cells be? (i.e. what part of the army?)

**T lymphocytes** (_____) have **receptor** (  ) molecules that **enable** (  ) each of them to recognize a different antigenic peptide combination.

Explain how the **T lymphocytes** and **antigen-presenting** cells work together.

T cells **activated** (_____) by that recognition divide and **secrete** (  ) chemical signals that **mobilize** (  ) other **components** (  ) of the immune system, such as B cells.

**Synonyms: release, parts, turned on, organize**

If the immune system is like an army, what are the **T cells**?

When activated, B cells divide and **differentiate** (_____) into plasma cells that secrete antibody proteins. By **binding** (_____) to antigens they find, the antibodies can neutralize them or **precipitate** (  ) their destruction.

**Synonyms: separate, attaching, cause**

What important role to antibodies play in the immune system?

Some T cells and B cells become memory cells that **persist** (_____) in the circulation and **boost** (  ) the immune system's readiness to **eliminate** (  ) the same antigen in the future.

**Synonyms: remove, stay, improve**

Why are memory cells important?

**Using all of the information from the close-reading, write a story demonstrating how the immune system is like an army. Be sure to include all of the parts of the immune system discussed in the reading and explain how they are part of the immune system army.**

## Appendix A: Standards

DINQ.1 Identify questions that can be answered through scientific investigation.

DINQ.2 Read, interpret and examine the credibility and validity of scientific claims in different sources of information.

DINQ.3 Formulate a testable hypothesis and demonstrate logical connections between the scientific concepts guiding the hypothesis and the design of the experiment.

DINQ.4 Design and conduct appropriate types of scientific investigations to answer different questions.

DINQ.5 Identify independent and dependent variables, including those that are kept constant and those used as controls.

DINQ.6 Use appropriate tools and techniques to make observations and gather data.

DINQ.7 Assess the reliability of the data that was generated in the investigation.

DINQ.8 Use mathematical operations to analyze and interpret data, and present relationships between variables in appropriate forms.

DINQ.9 Articulate conclusions and explanations based on research data, and assess results based on the design of the investigation.

DINQ.10 Communicate about science in different formats, using relevant science vocabulary, supporting evidence and clear logic.

## Appendix B: Materials for Students

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Miller, Kenneth R., and Levine, Joseph S. *Biology: Foundation Edition* . New Jersey:

Pearson Education, Inc., 2010.

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