Exploring proteins of the immune system

How might we identify an unknown protein from an amino acid sequence and predict its three-dimensional shape?

The human body must protect itself against environmental threats, including many microorganisms, parasites, and hazardous substances. To accomplish this, the human **immune system** is like a built-in security system that defends our bodies from invaders. The invaders may include pathogens such as bacteria, viruses, or fungi. The act of defense or **immunity** is highly structured, consisting of a complex network of specialized cells, cellular components, and associated proteins. As with much of science, the organization and classification of components within human immunity change as new information is gained by research using the latest tools. The classic view of the human body's defense is that components fall within two categories: *innate* and *acquired immunity.*

In this activity, students will complete the following scenario using various amino acid sequences.

A pharmaceutical company is studying a new immune response triggered by an unknown protein, found in a sample from a patient who recovered quickly from an infection. The company needs your help to figure out what this protein is and what role it might play in immunity.

- Use BLAST to search for matches and identify the likely name or family of the protein.
- Explore UniProt to investigate its known functions, where it's expressed, and any roles it might play in the immune system.
- Use AlphaFold to visualize the protein's 3D shape and think about how its structure might help it carry out its function.

Ohio Standards

- 6.LS.1: Cells are the fundamental unit of life
- 6.LS.3: Cells carry on specific functions that sustain life

Biology

- B.C.1: Cell structure and function
- B.C.2: Cellular processes
- B.H.1: Cellular genetics
- B.H.2: Structure and function of DNA in cells
- B.H.4: Mutations

Human Anatomy and Physiology

- AP.T.1: Blood
- AP.T.3: Lymphatic and Immune Systems

Student prior knowledge

Students should be familiar with immune system components. Use the previous lesson ***Immune system components and response*** or a similar lesson to introduce or review the immune system structures and functions.

Suggested timeline

This activity may take up to two class periods, depending on the research and discussion of the proteins and their functions.

Materials

- Computer with internet connection
- Amino acid sequences:
  - ***ols.plus/uniprot***
  - ***ols.plus/uniprot-key***

Teacher preparation

1. Review activity and run sequences. UniProt may take a few moments to run longer amino acid sequences.
2. Upload links to sequences or the actual sequences to learning management software for easy access by students.
3. Prepare potential discussion to lead while students are waiting for results.
4. Determine wrap-up strategy.

Procedure

1. Review immune system proteins that are included in this scenario.

Receptors	**Signaling molecules**	**Effector molecules**
TLRs, MHC I and II	Chemokines (eotaxins), Interleukins, Interferons	Defensins, Cathelicidins

2. Assign students one or more sequences. Have them follow directions on the student document to run a BLAST on the sequence at the UniProt website.
3. Have students fill in the information about the protein found on UniProt.
4. Have students go to AlphaFold and enter the Entry number from UniProt in the search to see the structure of the protein.
5. Have students grab the axis tool in the lower left corner to rotate the model and see the complete structure.

Suggested wrap-up

Students may take screenshots of the protein structure to compare to structures discovered by other students. Ask students to share the protein structures indicated by their amino acid sequence and describe the 3D structure. Look for patterns within the structures to compare to the function of the protein. Refer to the table to see what the function of the component is.

Category	Function	Innate or adaptive	Examples
Barrier	First line of defense	Innate only	Skin, mucus, tears
Receptors	Molecules on human cells that recognize foreign molecules by invaders	Innate	Toll-like receptors (TLRs – innate)
		Adaptive	MHC class I receptors (all cells) MHC class II receptors (antigen presenting cells) B cell receptors (BCRs – adaptive) T cell receptors (TCRs – adaptive)
Signaling	Peptides that send messages to activate or direct other immune cells	Both	Cytokines, Chemokines, Interleukins
Effectors	Cells or peptides that directly attack pathogens or infected cells	Innate	Microphages, Antimicrobial peptides, Natural killer cells, Natural antibodies (IgA, IgG)
		Adaptive	Antibodies Helper T cells Cytotoxic T cells B cells

Differentiation

There are longer and shorter sequences included in this activity. Teachers may assign sequences to specific students based on complexity.

Extensions

Students may research more information about the proteins. As researchers learn more about various receptors, signaling and effector cells, different treatments and drug therapies may be developed.

Support information

Innate (non-specific) immunity is the body's first and fast response team. It includes the external barriers (skin, mucus membranes) as well as cellular and peptide defenses that quickly act when new invaders get inside the body. Innate immunity can act quickly because cells, like macrophages, have pattern recognition receptors **(PRRs)** called **Toll-like receptors (TLRs)** that detect pathogen-associated molecular patterns **(PAMPs).** For example, macrophages have receptors that detect lipopolysaccharides and flagellin, two proteins found in bacteria (not humans). Once these PAMPs are detected by macrophages, these cells can release signaling molecules **(cytokines and chemokines)** to recruit additional macrophages, as well as release small proteins **(antimicrobial peptides)** that further disrupt bacterial cell membranes, helping to kill invaders.

Adaptive or acquired (specific) immunity is the body's slower response. It must be activated by exposure to the invader. Despite its slow response, acquired immunity is specific to the invader. This

is important for pathogen species or variants that evolved ways to escape detection from the innate immune system. Macrophages can present fragments of the invader called **antigens**, with another series of receptors called the **Major Histocompatibility Complex (MHC)**. These MHC receptors holding antigens are recognized by receptors found on **lymphocytes (T-cell and B-cells),** specialized white blood cells of the adaptive immune system**.** Each lymphocyte cell has receptors that recognize a very specific antigen. If a lymphocyte recognizes its specific antigen displayed by the macrophage, the lymphocyte becomes activated, undergoing multiple rounds of cell division. The outcome of cellular division is a large population of clones that become **effector cells** to carry out the attack to that specific pathogen (e.g. bacteria). Importantly, a population of clones become **memory cells**, providing lasting immunity that is stronger and quicker if exposed to the same pathogen in the future.

Amoeba sisters immune system video: ***youtu.be/fSEFXl2XQpc***

Career connections

- **Immunologist:** study, diagnose, and manage patients with diseases resulting from depressed or ineffective immune systems and the conditions in which immunological treatment forms an important part of therapy and/or prevention.
- **Medical geneticist:** medical doctors with specialized training in medical genetics who evaluate, diagnose, and treat individuals and families with various genetic indications and/or specific genetic conditions.
- **Genomics technician:** characterize and compare DNA and RNA sequences, as well as amino acid sequencing of proteins using various databases and AI technologies.