UNIT 2: IMMUNOLOGY

General concepts of Immune system

Function

- The overall function of the immune system is to prevent or limit infection.
- An example of this principle is found in immune-compromised people, including those with genetic immune disorders, immune-debilitating infections like HIV, and even pregnant women.
- The immune system can distinguish between normal, healthy cells and unhealthy cells by recognizing a variety of "danger“.
- Cells may be unhealthy because of infection or because of cellular damage caused by non-infectious agents like sunburn or cancer.
- Infectious microbes such as viruses and bacteria release another set of signals recognized by the immune system.

- The immune system is complex and pervasive.
- There are numerous cell types that either circulate throughout the body or reside in a particular tissue.
- Each cell type plays a unique role, with different ways of recognizing problems, communicating with other cells, and performing their functions.
- By understanding all the details behind this network, researchers may optimize immune responses to confront specific issues, ranging from infections to cancer.
- *Skin*: The skin is usually the first line of defense against microbes.
- Skin cells produce and secrete important antimicrobial proteins, and immune cells can be found in specific layers of skin.
- Immunology is a relatively new science. Its origin is usually attributed to Edward Jenner who discovered in 1796 that cowpox, or vaccinia, induced protection against human smallpox, an often fatal disease.
- Jenner called his procedure vaccination, and this term is still used to describe the inoculation of healthy individuals with weakened or attenuated strains of disease-causing agents to provide protection from disease.

ADAPTIVE & INNATE IMMUNITY

- **Innate immunity** is a type of nonspecific protection against pathogens. It responds quickly to a pathogen, but It doesn't have the ability to remember individual threats and mount a specifically targeted defense if they show up again.

- **Acquired immunity** is the part of immunity that works to identify the difference between individual types of threats.[1] Acquired immunity works more slowly than innate immunity, but it remembers the antigen and responds to it quickly and in a targeted manner if you are exposed again

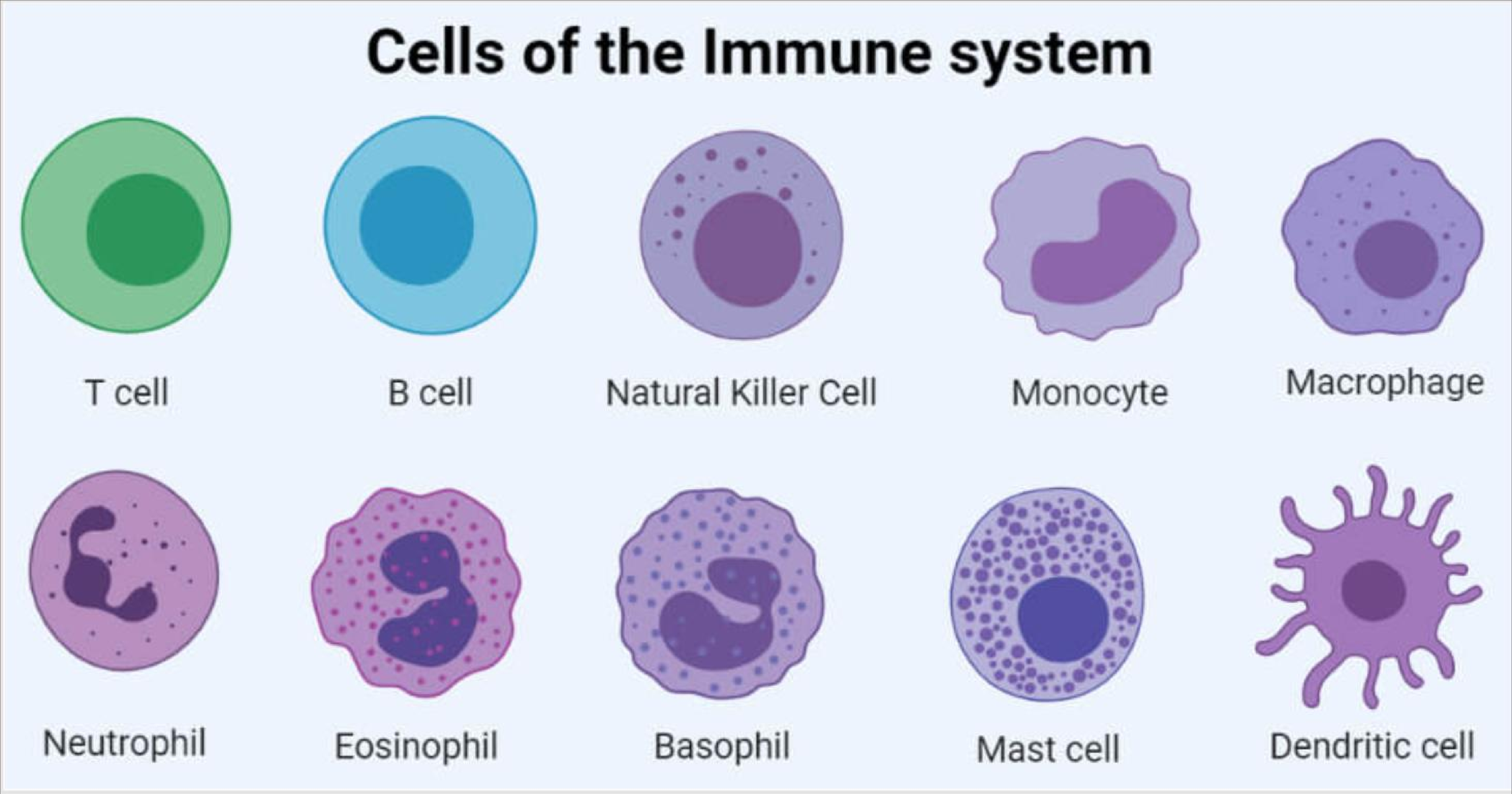
Cells of Immune System- Types and Examples

- The immune system is made up of different immune organs and tissues located all over the body.
- The immune organs are categorized based on their functions and there are two main categories, which include:

1. **Primary lymphoid organs** provide a development and maturation site for lymphocytes, and
2. **Secondary lymphoid organs** whose function includes trapping antigens from the tissues, and the vascular spaces. They are also the site for lymphocyte interaction with the antigens.

- All these organs are connected by the lymphatic system and the blood vessels into a functional unit.
- In the blood and the lymph and populating the lymphoid organs are various types of white blood cells (leukocytes) that play a key role in the body's immune responses.
- Nevertheless, white blood cells are an assemblage of different immune cells. White blood cells provide the defense mechanisms of the body fighting off foreign elements (antigens) from the body.
- Under the White Blood Cells group of cells, they can be categorized into lymphocytes, (including T-lymphocytes, B-lymphocytes, and Natural Killers cells), neutrophils, monocytes, and macrophages.

- All the other cells play additional roles in adaptive immunity such as activation of lymphocytes, increasing the effector mechanisms of antigen clearance by phagocytosis, or secreting various immune-effector molecules.
- Some white blood cells secrete protein molecules known as cytokines which are immunoregulators (regulate the immune responses).
- Other major proteins of the immune system include antibodies produced by B-lymphocytes, and complement proteins (activated by antibodies).



Cells of the immune system

Lymphoid cells (Lymphocytes)

- The lymphocytes make up 20%–40% of the body's white blood cells and 99% of the cells in the lymph.
- There are about 10^{11} lymphocytes in the human body.
- These lymphocytes circulate continuously in the blood and the lymph hence they are able to migrate into the body tissue spaces and lymphoid organs, therefore integrating the immune system to a high degree.
- The lymphocytes are the central cells of the immune system which are responsible for adaptive immunity and immunological features of diversity, specificity, memory, and self/non-self recognition.
- The other immune cells function to engulf and destroy micro-organisms, present antigens and secrete cytokines.

The lymphocytes are broadly divided into three populations based on their functions and cell-membrane components i.e:

1. B-lymphocytes

- B-lymphocytes are also known as B-cells.
- They are the specialized cells of the immune system whose major function is to produce antibodies also known as immunoglobulins or gamma globulins.
- B-lymphocytes are synthesized and mature in the bone marrow from the hematopoietic stem cells, and after which they mature, migrate, and express themselves by forming unique antigen-binding receptors on their membranes, known as B-cell receptors or antibodies.
- Migration of mature B-cells moves to the bone marrow, lymph nodes, spleen, some parts of the intestines, and the bloodstream.

2. T-Lymphocytes

- T-lymphocytes are also known as T-cells, often named in lab reports as CD3 cells.
- They also arise in the bone marrow but migrate to the thymus gland for maturation, where they express a unique antigen-binding molecule on its membrane known as the T-cell receptor.
- The name **T** originated from its site of maturation, the **Thymus.**
- Mature T-cells leave the thymus and populate other organs of the immune system, such as the spleen, lymph nodes, bone marrow, and blood.

Granulocytic Cells

•Granulocytes are white blood cells (leukocytes).

•They are classified based on their cellular morphologies and cytoplasmic staining characteristics and they include **neutrophils, eosinophils, basophils, or mast cells.**

•All granulocytes have multilobed nuclei that make them visually distinctive and easily distinguishable from lymphocytes, whose nuclei are round.

•These granules contain a variety of proteins with distinct functions: Some damage pathogens directly; some regulate trafficking and activity of other white blood cells, including lymphocytes; and some contribute to the remodeling of tissues at the site of infection.

•Neutrophils have a multilobed nucleus and a granulated cytoplasm that stains with both acid and basic dyes; it is often called a **polymorphonuclear leukocyte (PMN)** for its multilobed nucleus.

•The eosinophils have a bilobed nucleus and a granulated cytoplasm that stains with the acid dye eosin red (hence its name).

•The basophil has a lobed nucleus and heavily granulated cytoplasm that stains with the basic dye methylene blue.

•Both neutrophils and eosinophils are phagocytic, whereas basophils are not.

❑ Neutrophils

- Neutrophils are produced by hematopoiesis n the bone marrow.
- They are released into the peripheral blood and circulate for 7–10 h before migrating into the tissues, where they have a life span of only a few days.
- In the bone marrow, a surmountable level of neutrophils is produced in response to the types of infections and they are normally the first cells that arrive at the site of inflammation.

❑ Eosinophils

- They are motile phagocytic cells that can migrate from the blood into the tissue spaces.
- They have a phagocytic mechanism of eliminating antigens but their role as phagocytic cells is much less significant than that of neutrophils.
- They play a role in defense against multicellular parasitic organisms including worms.

❑ Basophils

- Basophils are nonphagocytic granulocytes containing large granules that are filled with basophilic proteins that stain blue in standard H & E staining methodologies.
- Naturally, basophils are in the body’s normal circulation but they can be very potent.
- They function by binding to circulating antibodies and react by the content of their granules which are pharmacologically active substances found in their cytoplasm.
- These substances play a major role in certain allergic responses.
- Just like the eosinophils, basophils are also crucial in response to parasites, and particularly the worms.
- Basophils also secrete cytokines that assist in the modulation of the adaptive immune response.

❖ Mast Cells

- Mast cells are formed in the bone marrow.
- They are released from the bone marrow into the blood as undifferentiated cells, and when they enter the tissues they then mature.
- Mast cells can be found in a wide variety of tissues, including the skin, connective tissues of various organs, and mucosal epithelial tissue of the respiratory, genitourinary, and digestive tracts.

❖ Dendritic Cells

- The dendritic cells acquire their name because they are covered with long membrane extensions resembling the dendrites of the nerve cells.
- Their membranous extension extends and retracts dynamically, increasing the surface area available for browsing lymphocytes.
- They are not easily isolated by conventional methods because the cell isolation damages their long extensions.
- Dendritic cells generally perform the distinct functions of antigen capture in one location and antigen presentation in another.

ANTIGEN

- An antigen is a molecule that stimulates an immune response by activating leukocytes (white blood cells) that fight disease.
- Antigens may be present on invaders, such as bacteria, viruses, parasites, fungi, and transplanted organs, or on abnormal cells, such as cancer cells.
- The body needs to be able to recognize what belongs and what doesn't, and antigens are an important part of that process.
- When the body identifies an antigen, it will initiate an immune response.
- When receptors on white blood cells bind to antigens, this triggers white blood cell multiplication and starts the immune response. Antigens are immune response initiators.
- They can be bound by white blood cells, including leukocytes, which are the cells of the adaptive immune system.
- In a viral infection such as the seasonal flu, the immune system develops a response by creating antibodies that can bind to the specific antigen.

Types of Antigens

Antigens can be divided into two main groups—foreign antigens and autoantigens.

- Foreign Antigens: Otherwise known as heteroantigens, this type comes from outside of the body and are present on bacteria, viruses, snake venom, certain food proteins, and cells from other people.
- Autoantigens: Self-antigens are already present within the body and shouldn't trigger an immune response in healthy individuals because the body should know they’re not harmful. However, sometimes the body erroneously acts against them—leading to autoimmune inflammation

Properties of Antigens

1. Foreign Nature: The prerequisite for immunogenicity is that the substance should be foreign to the body of recipient. As a result the immune system must be able to distinguish between normal body components and foreign substances. Normally the body has no tendency to recognize its own components as antigens, therefore does not initiate an immune response against these.
For example, if serum albumin from a mouse is injected back into the same mouse or into another mouse, no antibody production will occur. On the other hand, if the albumin is infected into an animal of another species, antibody may be produced.

2. Molecular Size: It is not always true that a substance should have to be of foreign origin to make it an antigen. The substance or molecule must have certain physio-chemical properties, where molecular size is an important factor.
Hence small molecules like amino acids or monosaccharides are usually not antigenic. However, low molecular substance can demonstrate immunogenicity, if coupled to a suitable carrier molecule like protein.

3. Antigenic Determinants and Cross-Reactivity:
Only limited parts of the large antigen molecule are involved in the binding to antibodies. These parts are called antigenic determinants. It is established that a molecule must have at least two antigenic determinants in order to stimulate antibody production. For this reason a small molecule does not function as antigen. Because it is not possible for a small molecule to have more than one antigenic determinant.

4. Molecular Rigidity and Complexity:
The rigidity and complexity of the molecule are the important factors for immunogenicity. A rigid molecule is a good antigen, probably because it is easier to raise antibodies to certain structures than to others. The immunogenicity is very much dependent on the complexity of the antigens.
For example, a molecule containing a repeating unit of only one amino acid is generally poor immunogen, even if the molecule is large; while a molecule with two or three repeating amino acids can, however, function well as an immunogen.

ANTIGEN CITY AND IMMUNOGENICITY

- Immunogenicity is the ability of an antigen to produce immunological response in the body leading to antibody production or T-cell activation.
- Antigenicity is characteristic of a foreign substance to be recognised as antigen by the body. Hence every Immunogen is an antigen but not vice-versa.
- For eg. Hapten is an antigen but not Immunogen. It can not induce immunological response alone.
- An immunogen refers to a molecule that is capable of inducing an immune response by an organism’s immune system.
- Antigen refers to a molecule that is capable of binding to the product of that immune response.
- So, an immunogen is necessarily an antigen, but an antigen may not necessarily be an immunogen.

FACTORS AFFECTING ANTIGENICITY

1) molecular weight of antigen. e.g. protein is a good antigen as compare to lipid or nucleic acid.

2) invectiveness (negatives) of antigen, that is due to toxins or chemicals secreted by the antigen

3) degradability: antigen should be degraded in body so that body immune system can react against them.

4) complexity of antigen

ANTIBODY

- **Antibodies, also known as immunoglobulins, are proteins produced by lymphocytes as a result of interaction with antigens.**
- **Antibodies are a part of the humoral immune of the adaptive immune system where each antibody identifies a specific antigen and protects the body against it.**
- Antibodies carry out two principal functions in the immune system. The first function is the recognition and binding to foreign bodies. The second more important function is to trigger the elimination of the attached foreign material.
- Since millions of antibodies are produced during an immune response, some of these remain in circulation in the blood for several months. This provides an extended immunity against the particular antigen.
- Antibodies can be classified into five different classes; IgG, IgM, IgA, IgD, and IgE. All the antibodies have the basic four-chain antibody structure, but they have different heavy chains
- The differences in the immunoglobulins are more pronounced in the Fc regions of the antibody, which leads to the triggering of different effector functions.
- **EPITOPE**: a site on an antigen at which an antibody can bind, the molecular arrangement of the site determining the specific combining antibody. Also called **antigenic determinant .**

Functions of Antibody

- Binds to pathogens
- Activates the immune system in case of bacterial pathogens
- Directly attacks viral pathogens
- Assists in phagocytosis
- Antibody provides long-term protection against pathogens because it persists for years after the presence of the antigen.
- It neutralizes the bacterial toxins and binds the antigen to enhance its efficiency.
- They also act as the first line of defence for mucosal surfaces.
- They ingest cells by phagocytosis.

Types:

1. Immunoglobulin G (IgG)

- Immunoglobulin G (IgG) accounts for around 75% of all antibodies in the human body.
- Depending on the antigen, IgG can either tag a pathogen so other immune cells and proteins will recognize it, or it can promote the release of toxins to directly destroy the microorganism.
- IgG can sometimes trigger an undesirable response in people with autoimmune diseases, in which the immune system inadvertently attacks its own cells and tissues.

2. Immunoglobulin A (IgA)

- Primarily found in mucosal tissues, such as those in the mouth, vagina, and intestines, as well as in saliva, tears, and breast milk.
- It accounts for 15% of all antibodies in the human body and is produced by B cells and secreted from the lamina propria, a thin layer within mucosal tissues.
- IgA is one of the body's first-line defenses against infection.

3. Immunoglobulin M (IgM)

- Is also one of the first antibodies recruited by the immune system to fight infection.
- IgM populations rise very quickly when the body is first confronted with an infectious organism, and then they plummet as IgG antibodies take over.
- IgM is also produced by B cells and, when bound to a pathogen, will spur other antibodies and immune cells into action.
- In addition to activating the immune response, a subset of IgM helps B cells "remember" a pathogen after it has been destroyed.

4. Immunoglobulin E (IgE)

- Immunoglobulin E (IgE) is the antibody responsible for the allergic response that is mostly found in the lungs, skin, and mucosal membranes.
- IgE is produced by B cells secreted by lymph nodes or other lymphoid tissues situated near the site of the allergen (a harmless substance that induces an allergic response).
- IgE also helps to protect the body from parasitic infections, including helminths (parasitic worms)

5. Immunoglobulin D (IgD)

- It is important in the early stages of the immune response.
- It does not actively circulate but instead binds to B cells to instigate the immune response.
- As a signaling antibody, IgD helps incite the release of front-line IgM to fight disease and infection.
- IgD accounts for only around 0.25% of antibodies in the human body.

Polyclonal antibodies

- Polyclonal antibodies are a heterogeneous mix of antibodies.
- Derived from the immune response of multiple B-cells, and each one recognizes a different epitope on the same antigen.
- Because polyclonal antibodies are composed of a mixture of antibodies that represents the natural immune response to an antigen, they are prone to a higher risk of batch-to-batch variability than monoclonal antibodies.

Monoclonal antibodies

- Monoclonal antibodies come from a single B-cell parent clone and therefore only recognize a single epitope per antigen.
- These B-cells are immortalized by fusion with hybridoma cells, allowing for long-term generation of identical monoclonal antibodies.
- Because monoclonal antibodies specifically detect a particular epitope on the antigen, they are less likely than polyclonal antibodies to cross-react with other proteins.

Recombinant antibodies

- Recombinant monoclonal antibodies are developed in vitro using synthetic genes.
- The encoding sequences can be carefully controlled, allowing for optimized binding and improved reproducibility over monoclonal antibodies produced from hybridoma.

Difference Between Antigen And Antibody

Antigen	Antibody
These molecules interact with antibodies or by T-cell receptors when complexed with major histocompatibility complex	Synthesized by plasma cells of B cells that react with antigens who invoked their production
Includes components of viral proteins, cell walls, capsules, and other microbes	Consists of 4 polypeptide chains, two light chains(L chain) and two heavy chains(H chain) forming a Y shape
These are proteins but can be nucleic acids, carbohydrates and lipids	These are glycoproteins made up of carbohydrates and amino acids
Highly complex in structure and composition	Simpler in structure
Causes diseases or allergic reactions	Protects the body against diseases
The pathogen has many epitopes. Epitopes are regions on antigens that interact with antibodies	The region of an antibody that binds with an epitope is called a paratope. Typically, a Y shaped antibody has 2 identical paratopes