Immunology

Course 1: Introduction to Immunology

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What is Immunity?

Immunity:

- Is a biological term that describes a state of having sufficient **biological defenses** to avoid infection, disease, or other unwanted biological invasion.
- In other words, it is nothing but the **capability of the body to resist harmful microbes from entering the body.**

Immunology:

The study of all aspects of the immune system in all organisms.

Definition

- Immunology is defined as the study of the molecules, cells, organs, and systems responsible for the recognition and disposal of foreign material.
- Immunology began as a branch of microbiology. The study of infectious disease and the body's response to them has a major role for the development of immunology.

Immune system

The immune system is a network of cells, tissues, and organs that work together to defend the body against attacks by “foreign” invaders such as *bacteria*, *viruses*, *parasites*, and *fungi.*

Immunity:

Immunity can be defined as the way in which the body can protect itself from invasion by pathogenic microorganism and provide a defense against their harmful effect. Immunity is classified in to two major groups:

Nonspecific immunity (Innate Immunity).

Specific immunity (Acquired Immunity).

Antigen

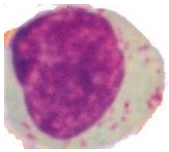
A live (e.g., viruses and bacteria) or inactivated substance capable of producing an immune response .

Antibody

Protein molecules (immunoglobulins) produced by B lymphocytes to help eliminate an antigen.

Characteristics of the immune system

- Broad range:
  - Bacteria
  - Toxins
  - Viruses
  - Parasites
  - Tumor cells
  - Fungi
  - Foreign cells
  - Particulates
- Highly specific
  - Pathogen species and strains
  - Self vs non-self
  - Memory
- Widespread
  - Every organ and system
- Extremely fluid
  - It moves!!!!

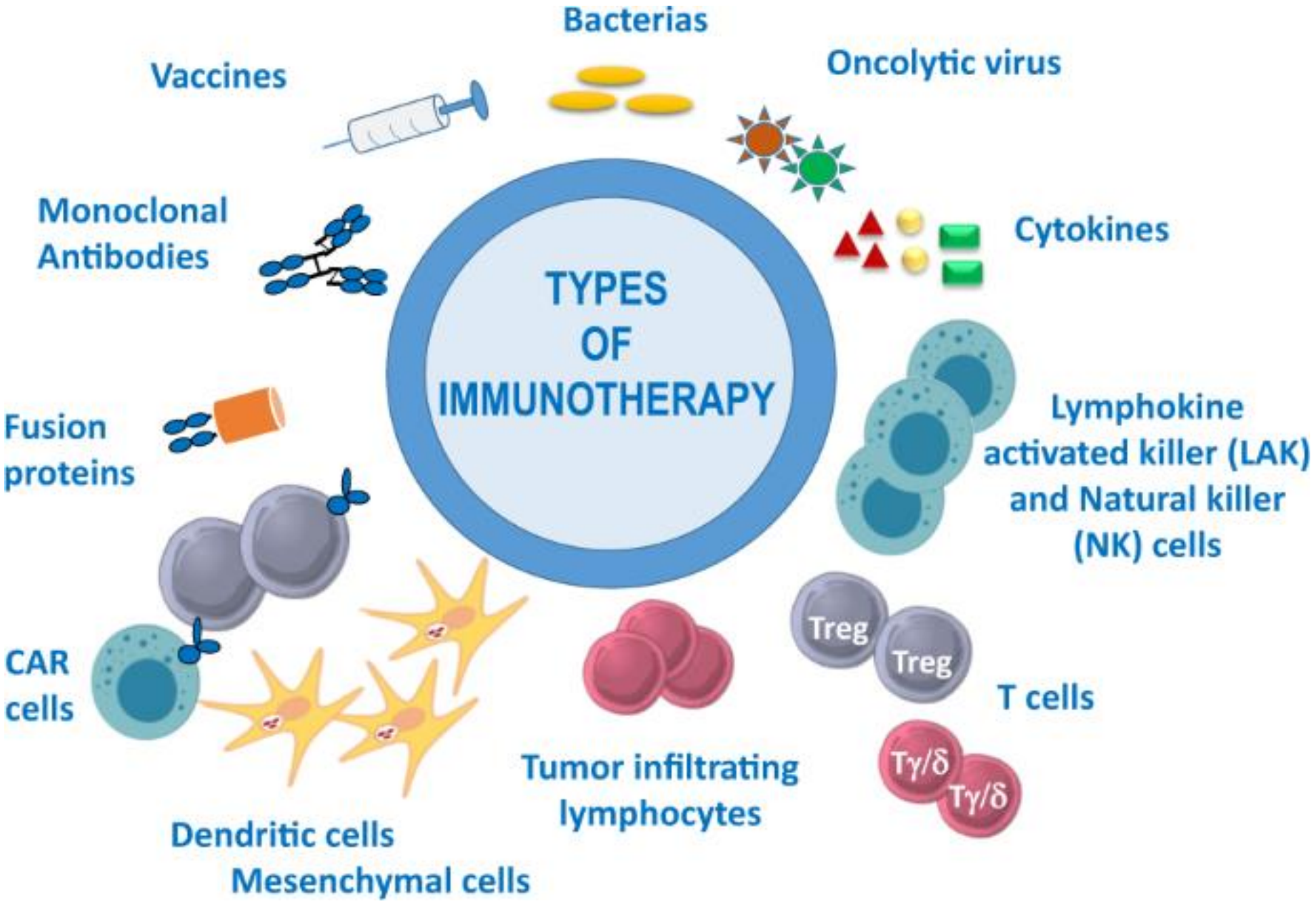


The functional importance of the immune system

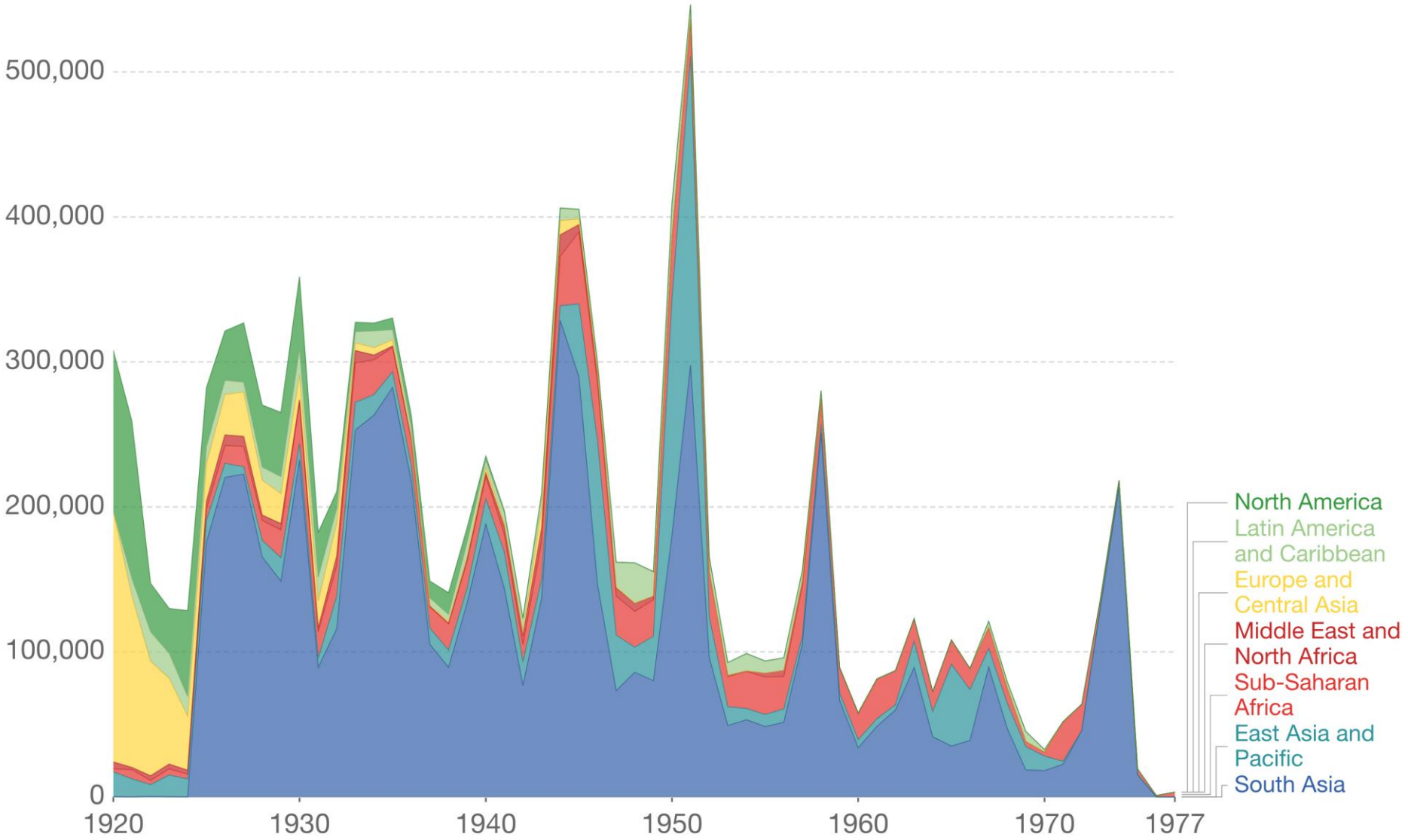
Role of the immune system	Implications
Defense against infections	Deficient immunity results in increased susceptibility to infections; exemplified by AIDS Vaccination boosts immune defenses and protects against infections
Defense against tumors	Potential for immunotherapy of cancer
Clearance of dead cells and tissue repair	Deficient immunity can lead to secondary infections after injury, and excessive immune reposnes can lead to fibrosis and organ dysfunction
The immune system can injure cells and induce pathologic inflammation	Immune responses are the cause of allergic, autoimmune, and other inflammatory diseases
The immune system recognizes and responds to tissue grafts and newly introduced proteins	Immune responses are barriers to transplantation and gene therapy

Subjects In Immunology

- Cell mediated host defense functions
- Antibody related defense mechanisms
- Hypersensitivity reactions (Including Allergy)
- Auto Immunity
- Immunodeficiency
- Transplantation


TYPES
OF
IMMUNOTHERAPY
Bacterias
Vaccines
Oncolytic virus
Monoclonal
Antibodies
Cytokines
Fusion
proteins
Lymphokine
activated killer (LAK)
and Natural killer
(NK) cells
CAR
cells
Treg
Treg
T cells
Tγ/δ
Tγ/δ
Tumor infiltrating
lymphocytes
Dendritic cells
Mesenchymal cells

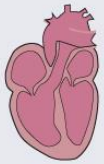
Reported number of smallpox infections by world region, 1920 to 1977

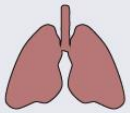


Source: World Health Organization (1969-1988)

The Many Components of Organ Transplantation

Organ, Tissue, or Cell:


Heart


Lungs


Kidneys

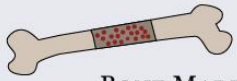

Liver

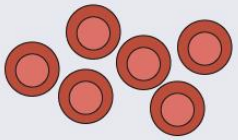

Intestines


Pancreas


Cornea


Heart Valves


Bone Marrow

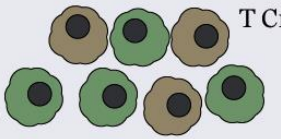

Stem Cells

Transplant:

Nonself — foreign antigens

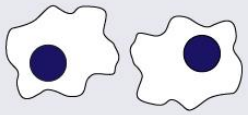
Recognition? Tolerance? Acceptance?

Self (Host Immune System)


T Cells

B Cells


Natural Killer Cells


Macrophages


Dendritic Cells

Adaptive Immunity — *Innate Immunity*

Rejection:

Hyperacute, acute, or Chronic

Graft vs Host
Donor cells reject recipient cells

Host vs Graft
Recipient cells reject donor cells

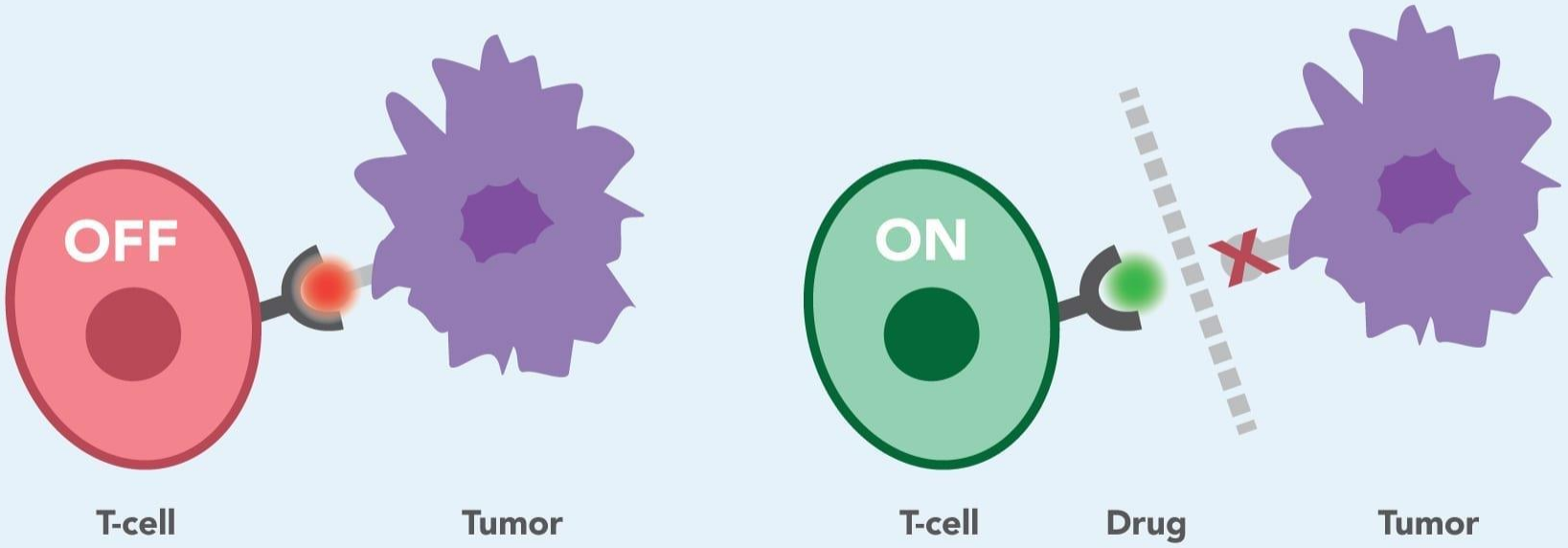
Science Immunology | AAAS

https://medlineplus.gov/organtransplantation.html
https://medlineplus.gov/ency/article/000815.htm
http://www.who.int/transplantation/cell_tissue/en/
https://www.lls.org/treatment/types-of-treatment/stem-cell-transplantation/allogeneic-stem-cell-transplantation

How Does Immunotherapy Work?

Tumor cells bind to T-cells to deactivate them

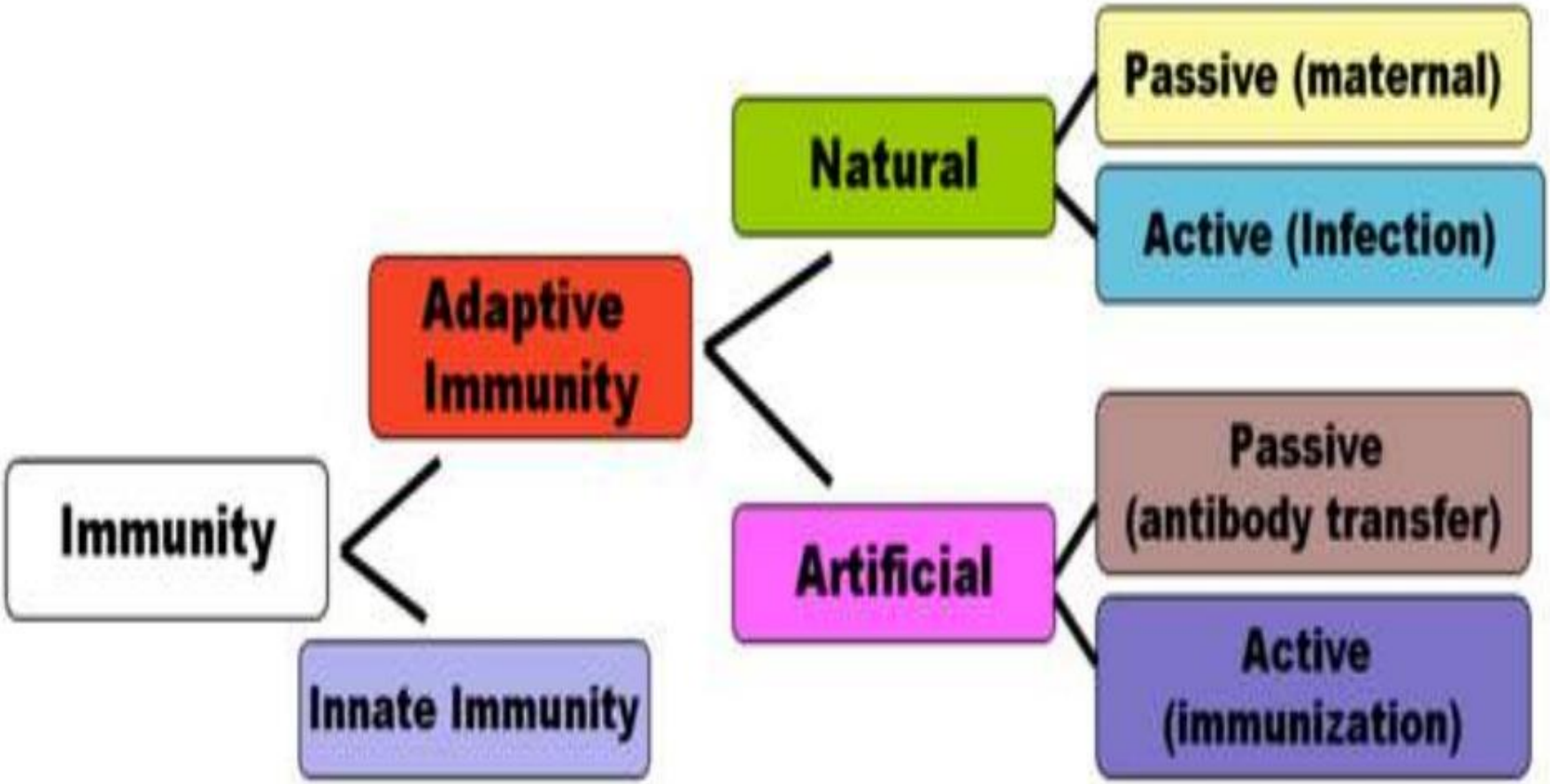
Immunotherapy drugs can block tumor cells from deactivating T-cells

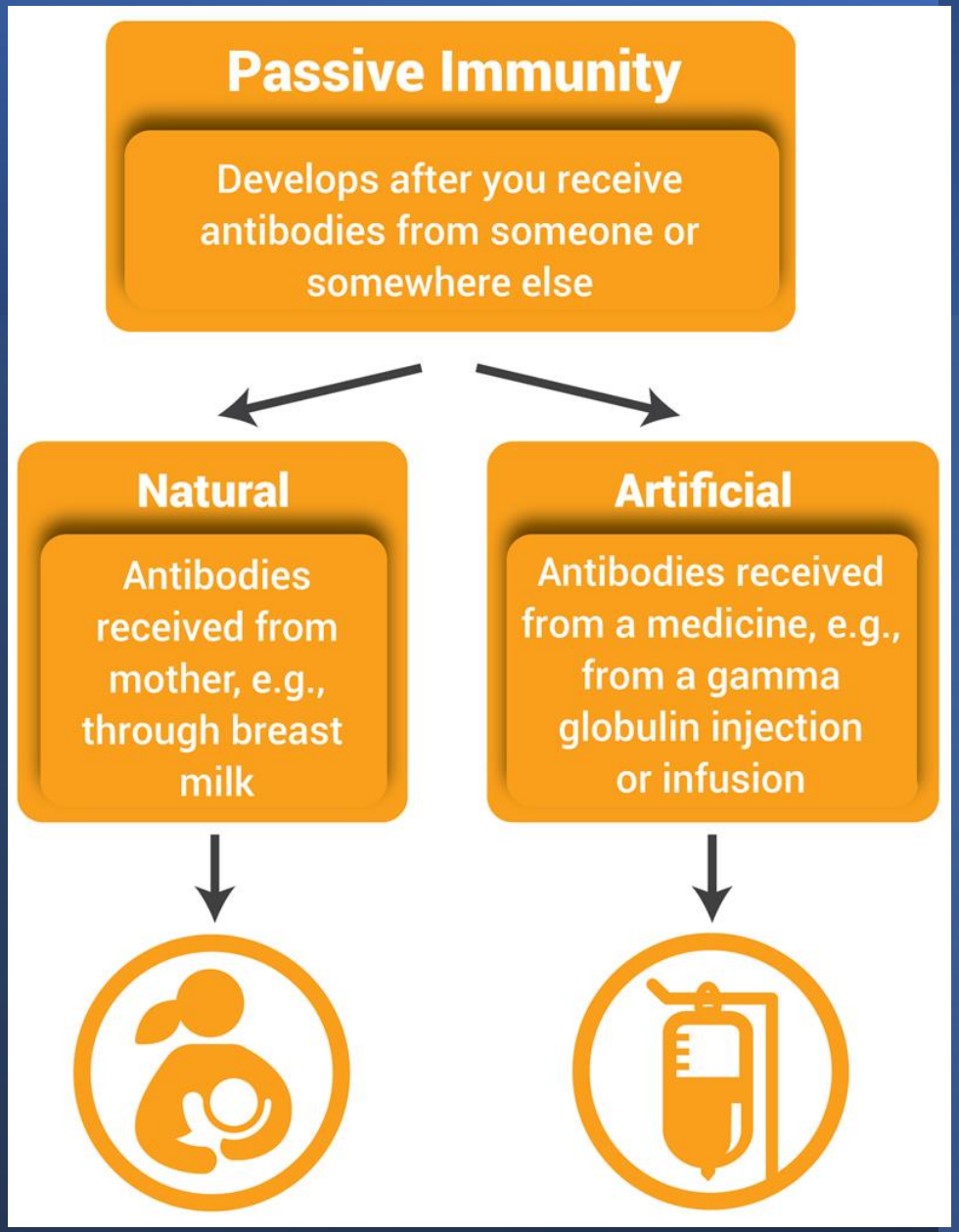


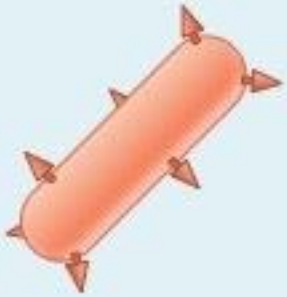
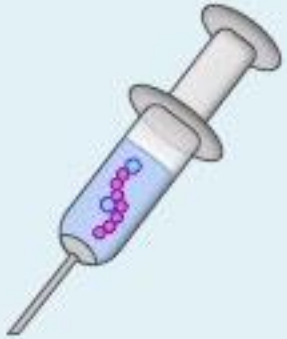
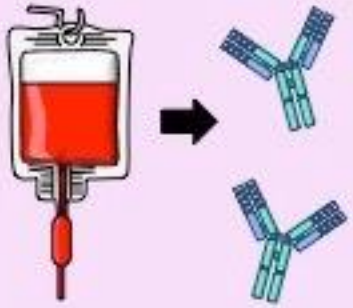
Columbia University Medical Center

Immunotherapy - New form of Cancer Treatment
Now available for patients in India

Basic classification of Immunity




Passive Immunity
Develops after you receive antibodies from someone or somewhere else
Natural
Antibodies received from mother, e.g., through breast milk
Artificial
Antibodies received from a medicine, e.g., from a gamma globulin injection or infusion

ACTIVE IMMUNITY		PASSIVE IMMUNITY	
Natural	**Artificial**	**Natural**	**Artificial**
			
Infection	Vaccination	Maternal antibodies	Monoclonal antibodies

The human immune system

Immune system

acquired

White blood cells tackle certain pathogens or mutated body cells

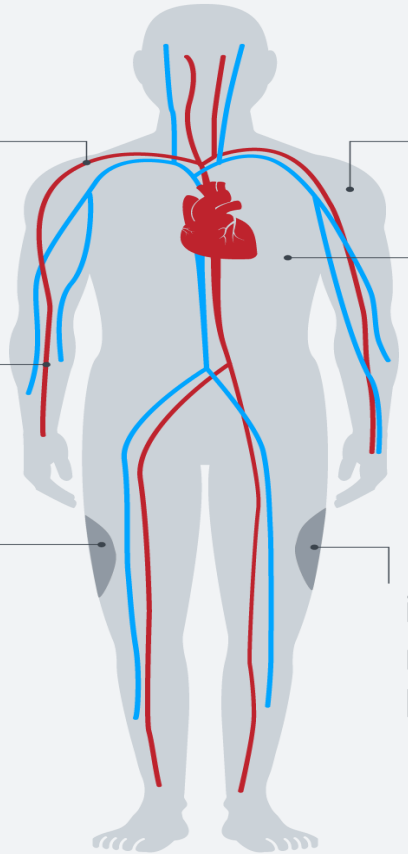
Defense cells in the blood: B lymphocytes

Antibodies

Defense cells in lymphoid tissue: T lymphocytes

innate

Initial immune response



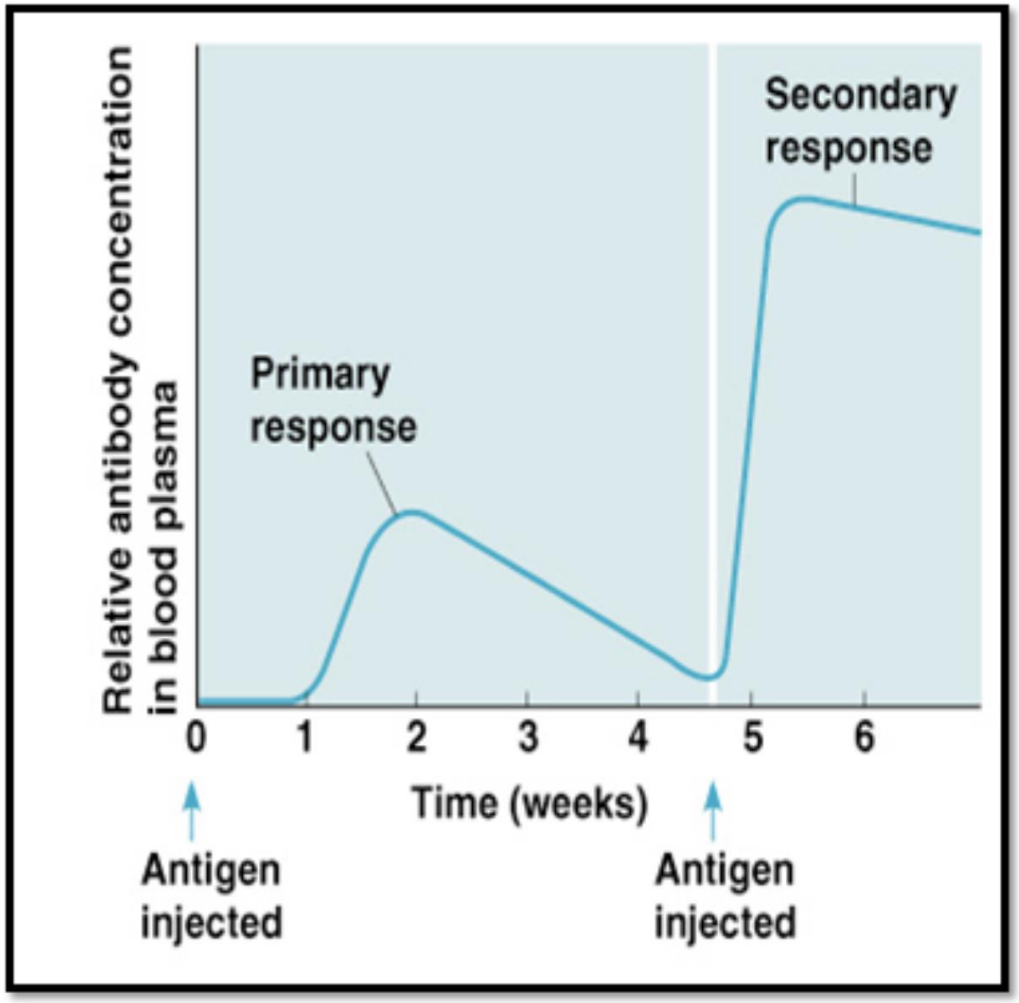
Protection from the inside: bacteria-killing substances

First order of attack in lymphoid tissue: macrophages and killer cells

DW Source: DW

Primary vs. Secondary Immune Response

The initial immune response to a particular antigen is called **Primary Response,**
It takes approximately 10 to 14 days for antibodies to be produced.
Primary response result in the production of memory cells
The second immune response to the same antigen is called **Secondary Response,** it is characterized by large quantities of antibodies which take less time to be developed than primary immune response.

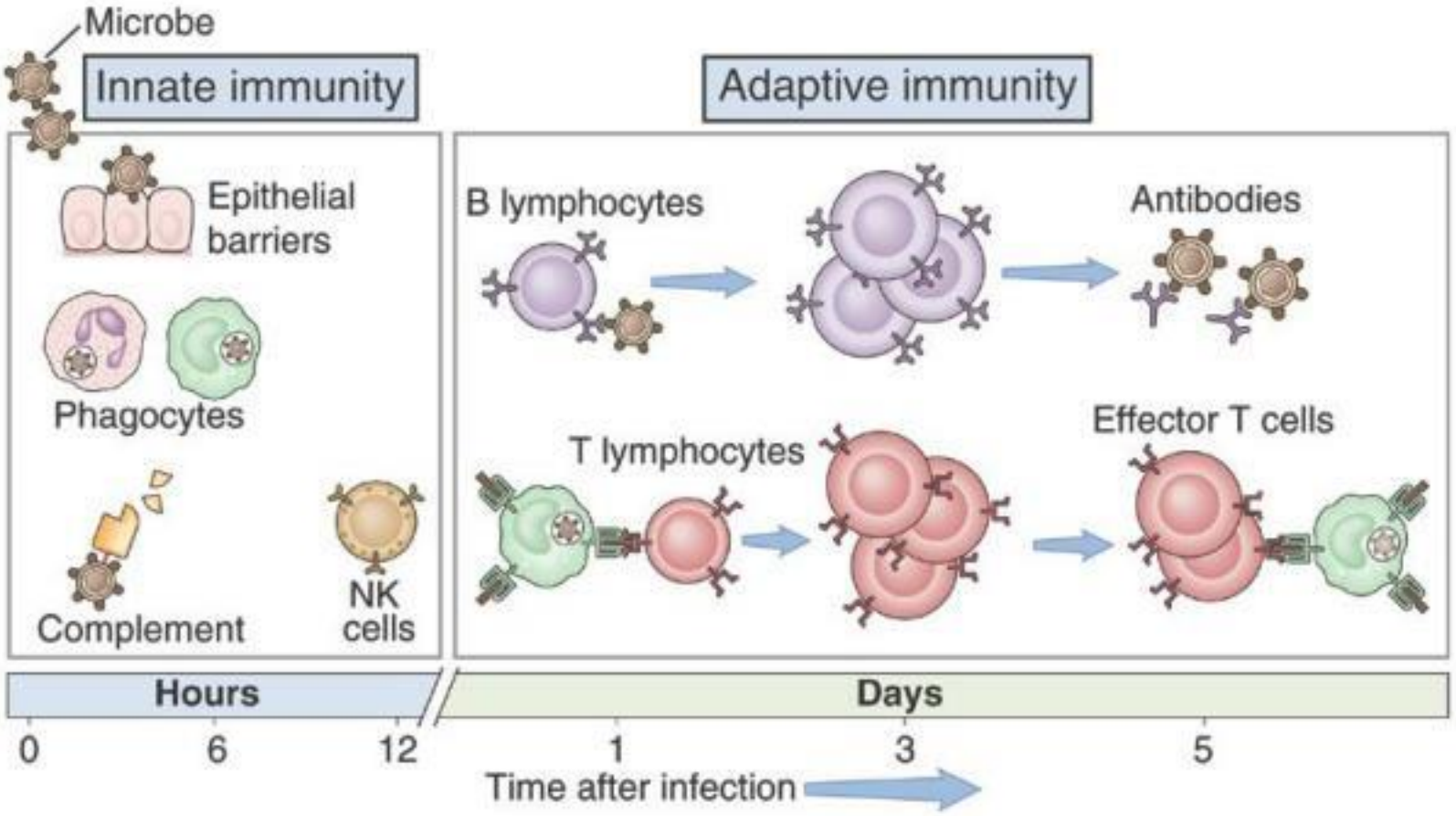


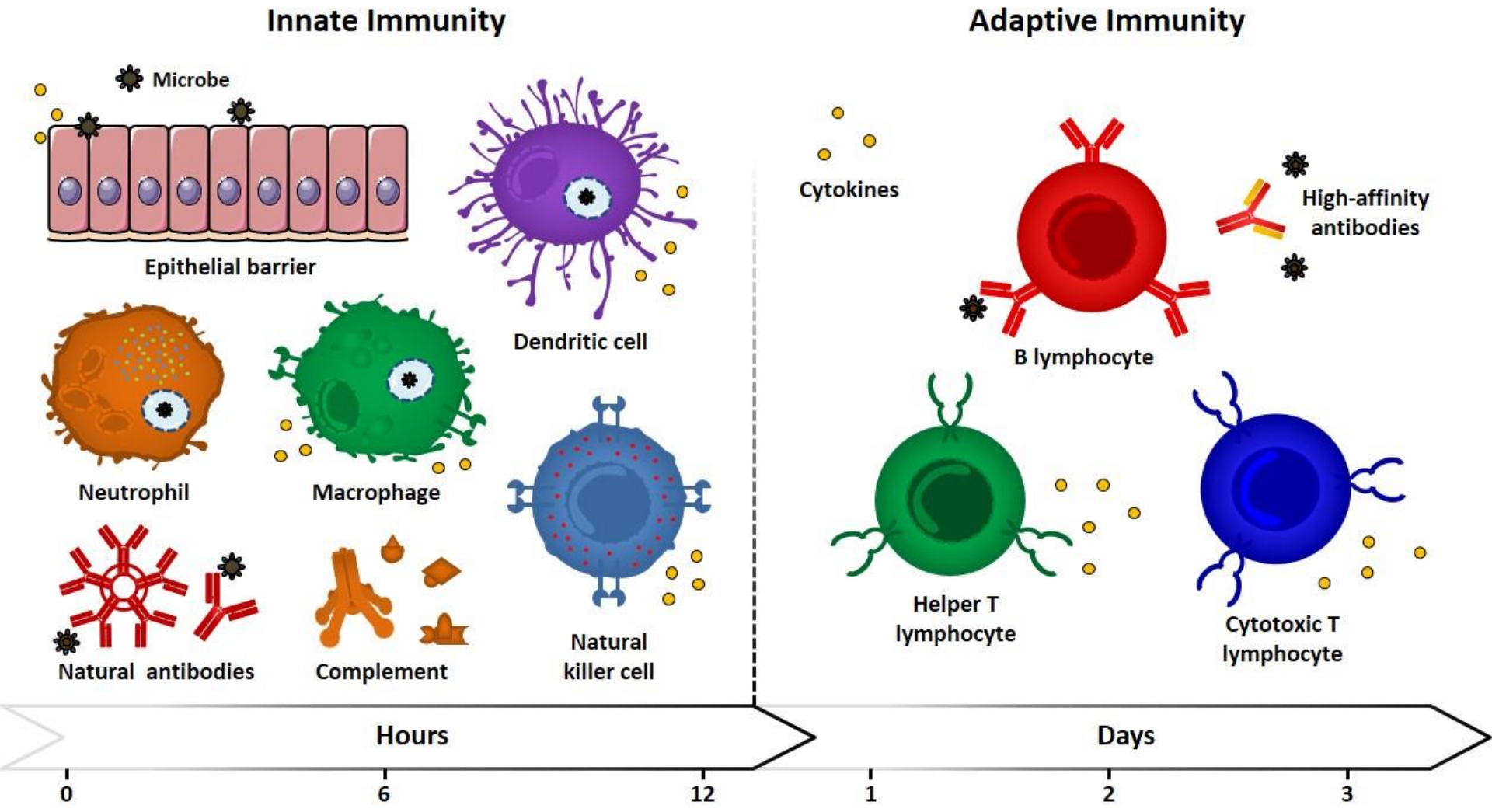
Innate and Adaptive Immunity

- Innate immunity is the first protective barrier against infections.

- Immune response that comes into play slowly after infection but provides more effective defense against infections is called adaptive immunity.

Innate and Adaptive Immunity




Innate Immunity
Adaptive Immunity
Microbe
Epithelial barrier
Dendritic cell
Cytokines
High-affinity antibodies
B lymphocyte
Neutrophil
Macrophage
Natural killer cell
Helper T lymphocyte
Cytotoxic T lymphocyte
Natural antibodies
Complement
Hours
Days
0
6
12
1
2
3

Innate and Adaptive Immunity

- **Antibodies capture infectious agents in serum and destroy microorganisms**
- **T lymphocytes neutralize microbes inside the cell**
- The kinetics of natural and acquired immune responses are similar and may vary according to different infections.

Innate Immunity

- **The term innate immunity is the host defense that prevents the entry of microbes and destroys the microbes that manage to enter the host tissues.**
- **This defense is always present in healthy individuals.**

Innate Immunity

- The first lines of defense of innate immunity to prevent germs from entrance;
- **Epithelial barrier,**
- **Specialized cells in the epithelium**
- **Natural antibiotics**

Innate Immunity

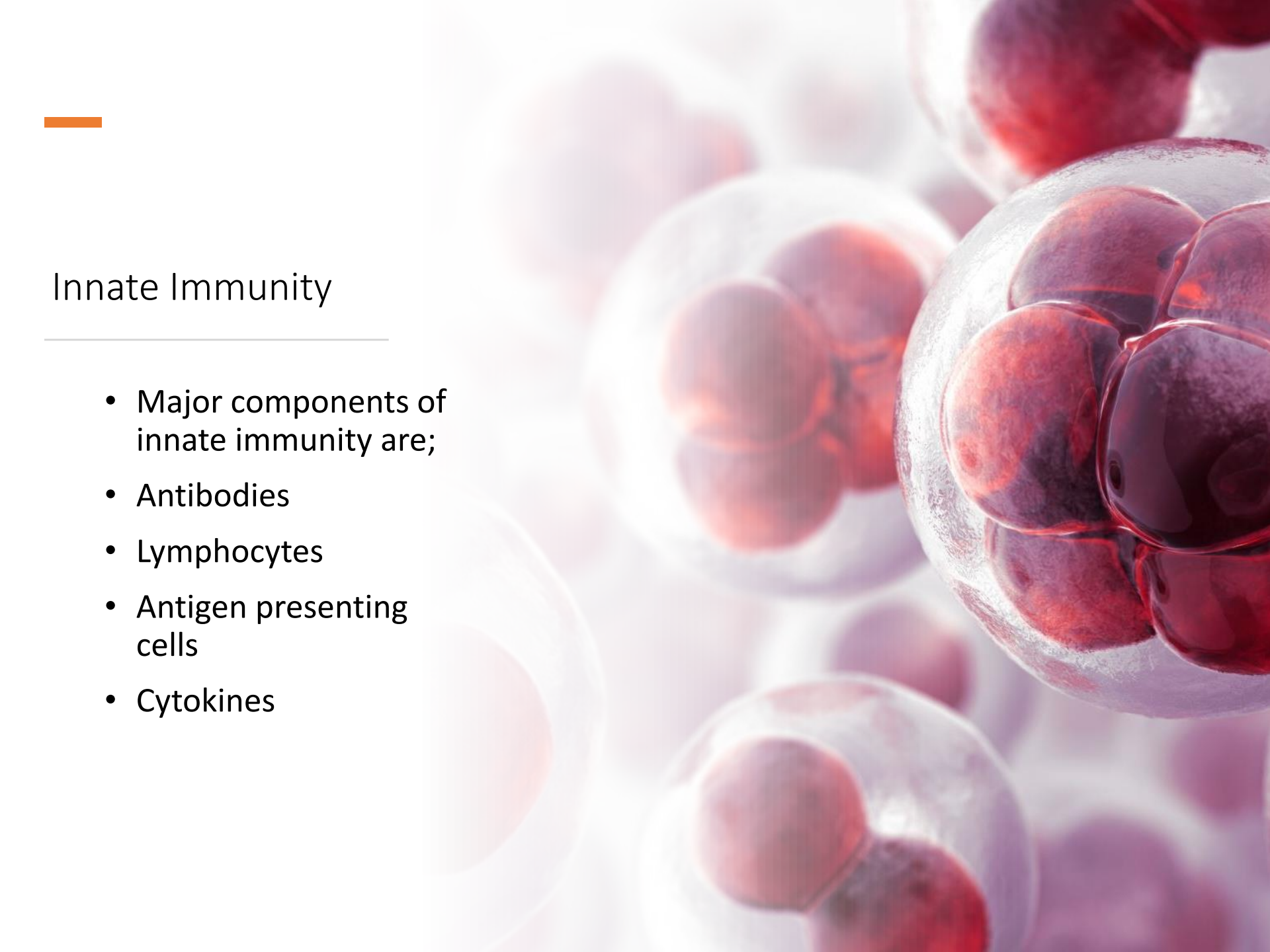
- **If microbes cross the epithelium and enter the circulation, they are attacked by phagocytes, specialized lymphocytes called natural killer (NK) cells and proteins of the complement system**

Innate Immunity

- Although innate immunity fights as effectors against many infections, **microbes that are pathogenic to humans evolve to resist the innate immune response.**
- It is the task of the acquired immune response to defend against infectious substances.
- **Therefore, disorders in the acquired immune system result in increased susceptibility to infections.**

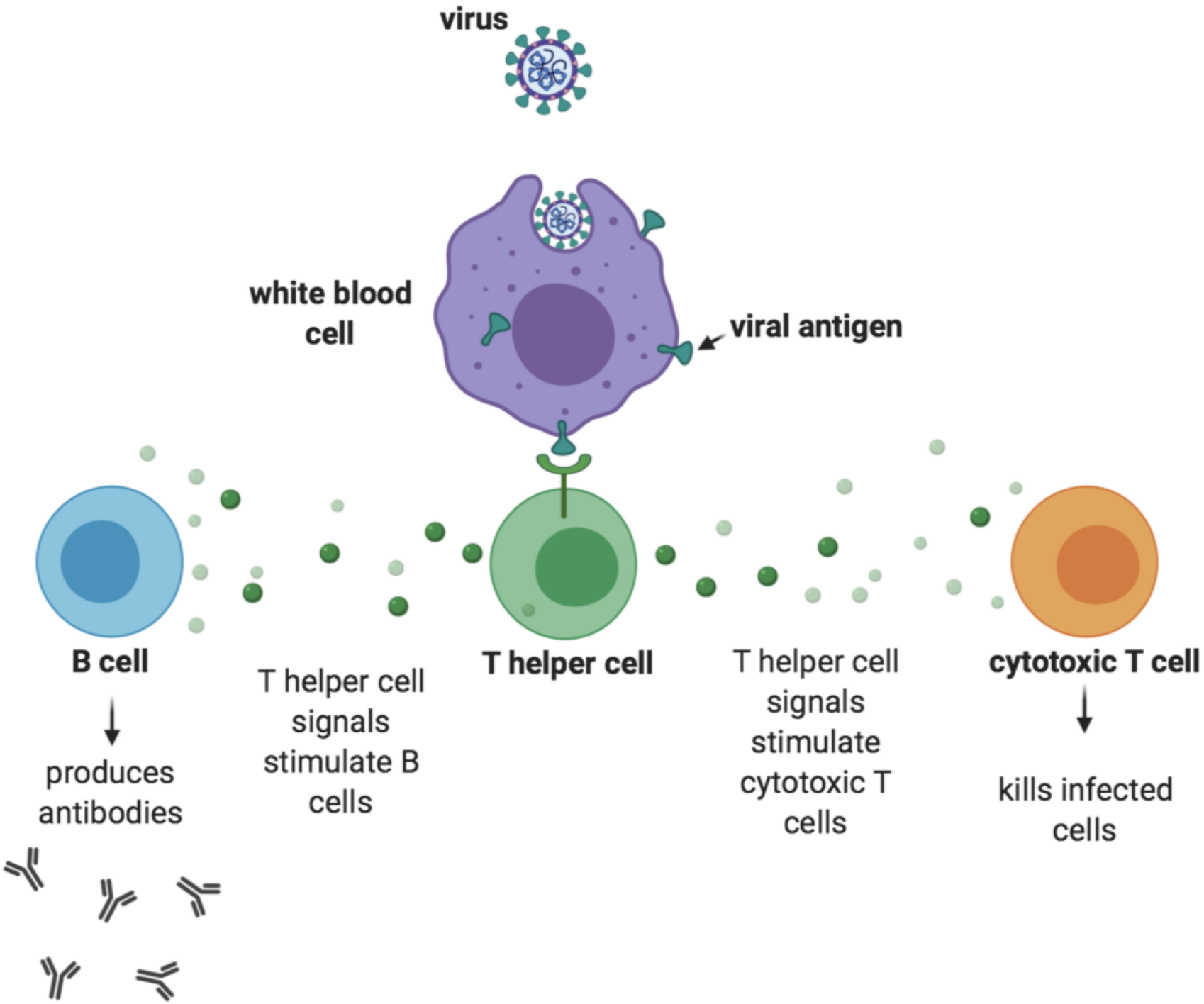
Innate Immunity

- Major components of innate immunity are;
- Antibodies
- Lymphocytes
- Antigen presenting cells
- Cytokines

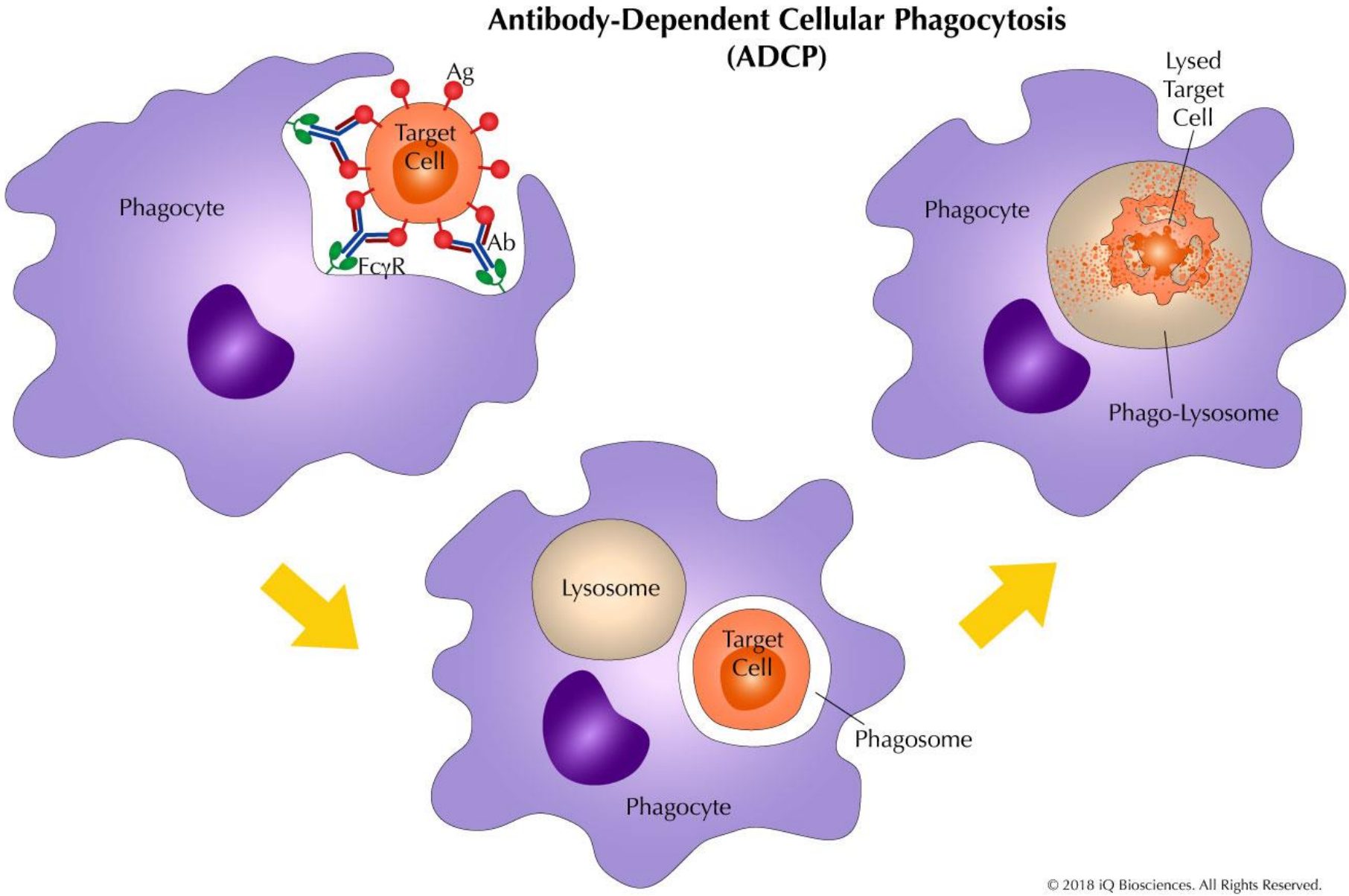


Acquired Immunity

- Acquired immune responses are triggered **only if microbes or their antigens cross the epithelial barrier and are transported to lymphoid organs where they are recognized by lymphocytes.**
- Acquired immune responses create special mechanisms to combat different types of microbes
- **For example, antibodies destroy microbes living outside the cell, T lymphocytes inside the cell.**


virus
white blood cell
viral antigen
B cell
produces antibodies
T helper cell signals stimulate B cells
T helper cell
T helper cell signals stimulate cytotoxic T cells
cytotoxic T cell
kills infected cells

Innate and Adaptive Immunity Interactions



Innate and Adaptive Immunity Interactions

- For example, antibodies (a component of acquired immunity) bind to microbes.
- **The microbe coated with antibody binds easily to phagocytes (cell of innate immunity) and activates them so that microbes are digested and destroyed by phagocytes.**

Active Adaptive Immunity

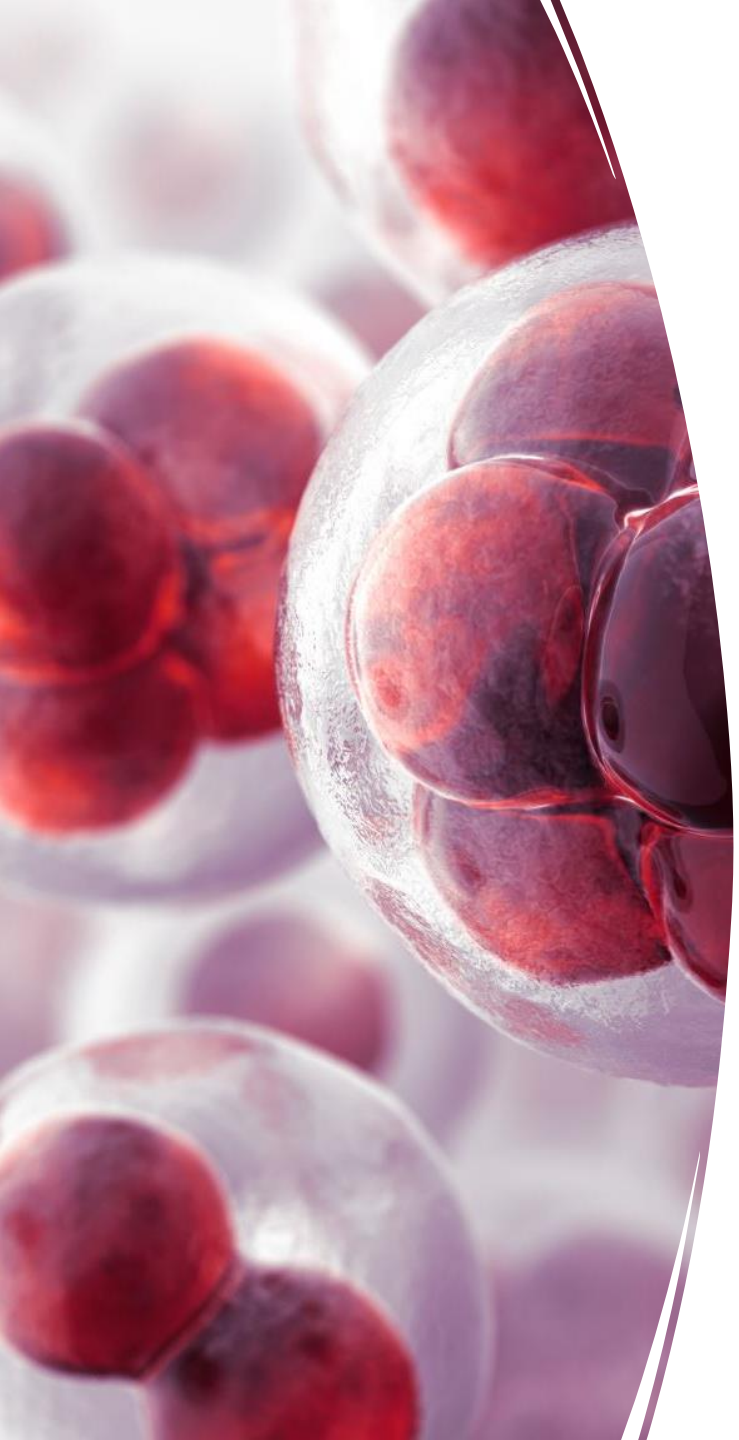
- **Humoral Immunity**
- **Cellular Immunity**

Humoral Immunity

- Humoral immunity is created by proteins called antibodies produced by **B lymphocytes.**
- **Antibodies neutralize microbes and microbial toxins present in the blood,** mucous fluids and in the lumens of mucous organs such as the gastrointestinal and respiratory tract.

Humoral Immunity

- One of the important properties of antibodies is to **prevent microbes on the mucosal surface and blood from reaching and evading in host cells and related tissues.**
- In this way, antibodies prevent infections before they invade.



Cellular Immunity

- Antibodies cannot reach the microorganisms that live and divide inside the infected cell.
- Cellular immunity ensures the defense against such intracellular microbes.
- **Cellular immunity is generated by T lymphocyte cells**

Cellular Immunity

- **Some T lymphocytes activate phagocytes to destroy germs.**
- **Other T lymphocytes kill all host cells that contain infectious microbes in their cytoplasm.**
- Antibodies produced by B lymphocytes are specifically designed to recognize **extracellular microbial antigens**, while T lymphocytes recognize antigens produced by **microbes within the cell.**

B versus T Lymphocytes

Characteristic	B Lymphocytes	T Lymphocytes
Ancestral Origin	Bone marrow	Bone marrow
Site of Maturational Processing	Bone marrow	Thymus
Receptors for Antigen	B-cell receptors are antibodies inserted in the plasma membrane; highly specific	T-cell receptors present in the plasma membrane are not the same as antibodies; highly specific
Bind with	Extracellular antigens such as bacteria, free viruses, and other circulating foreign material	Foreign antigen in association with self-antigen, such as virus-infected cells
Types of Active Cells	Plasma cells	Cytotoxic T cells, helper T cells, regulatory T cells
Formation of Memory Cells	Yes	Yes
Type of Immunity	Antibody-mediated immunity	Cell-mediated immunity
Secretory Product	Antibodies	Cytokines
Functions	Help eliminate free foreign invaders by enhancing innate immune responses against them; provide immunity against most bacteria and a few viruses	Lyse virus-infected cells and cancer cells; provide immunity against most viruses and a few bacteria; aid B cells in antibody production; modulate immune responses
Life Span	Short	Long

- Another important difference between T and B lymphocytes is that although most T lymphocytes only recognize microbial protein antigens, **antibodies; recognize many different types of microbial molecules including protein, carbohydrate and lipid**

Features of Adaptive Immunity

Most important features:

specificity

memory

Features of Innate and Adaptive immunity

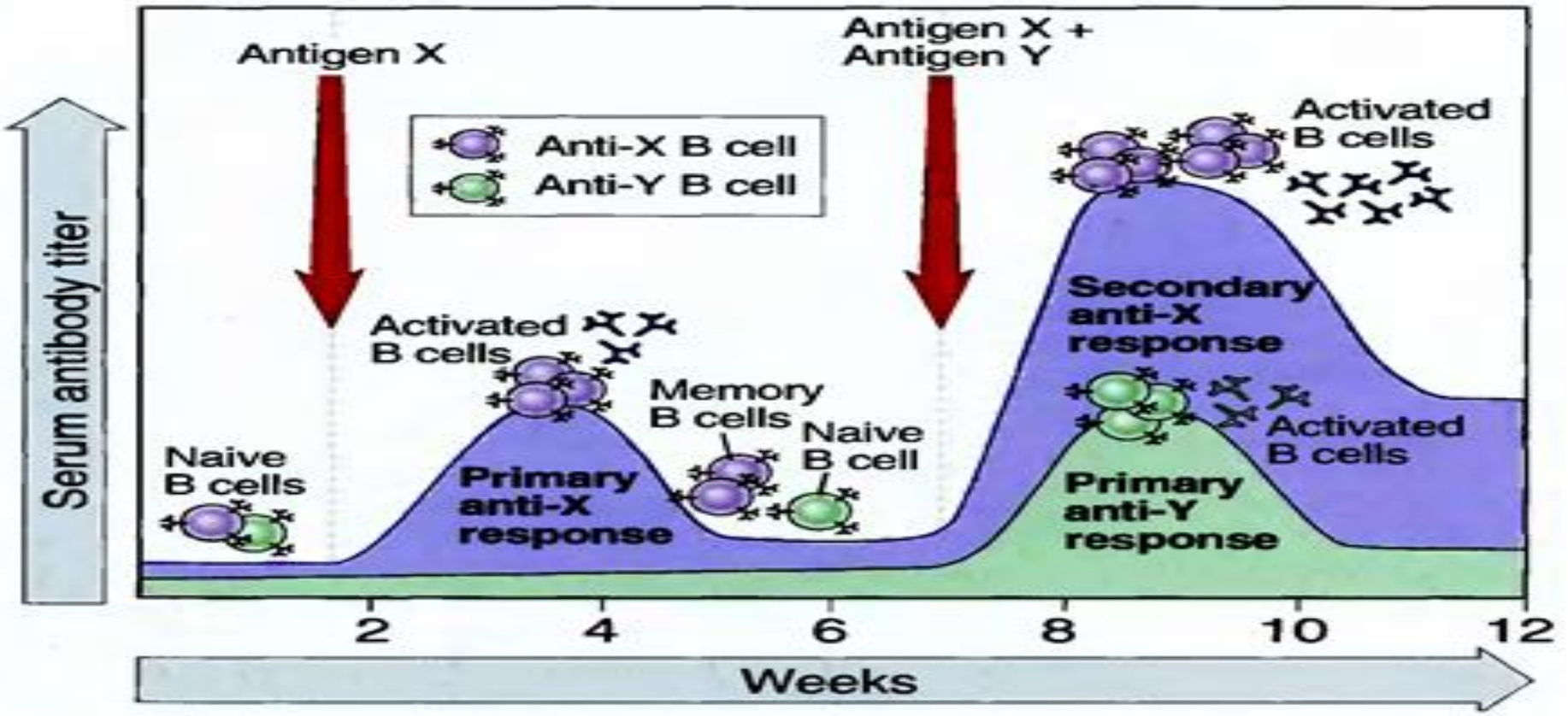
Characteristics	Innate	Adaptive
Specificity	Microbes and products of damaged host cells	Microbial and non microbial antigens
Diversity	Limited; germline encoded	Very large; receptors are produced by somatic recombination of gene segments
Memory	None	yes
Non-reactivity to self	Yes	Yes
Components		
Cellular and chemical barriers	Skin, mucosal epithelia; antimicrobial molecules	Lymphocytes in epithelia; antibodies secreted at epithelial surfaces.
Blood Proteins	Complements, others	Antibodies
Cells	Phagocytes, natural killer cells	Lymphocytes

Properties of adaptive immune responses

Feature	Functional significance
Specificity	Ensures that distinct antigens elicit specific responses
Diversity	Enables immune system to respond to a large variety of antigens
Memory	Leads to enhanced responses to repeated exposures to the same antigens
Clonal expansion	Increases number of antigen-specific lymphocytes to keep pace with microbes
Specialization	Generates responses that are optimal for defense against different types of microbes
Contraction and homeostasis	Allows immune system to respond to newly encountered antigens
Nonreactivity to self	Prevents injury to the host during responses to foreign antigens

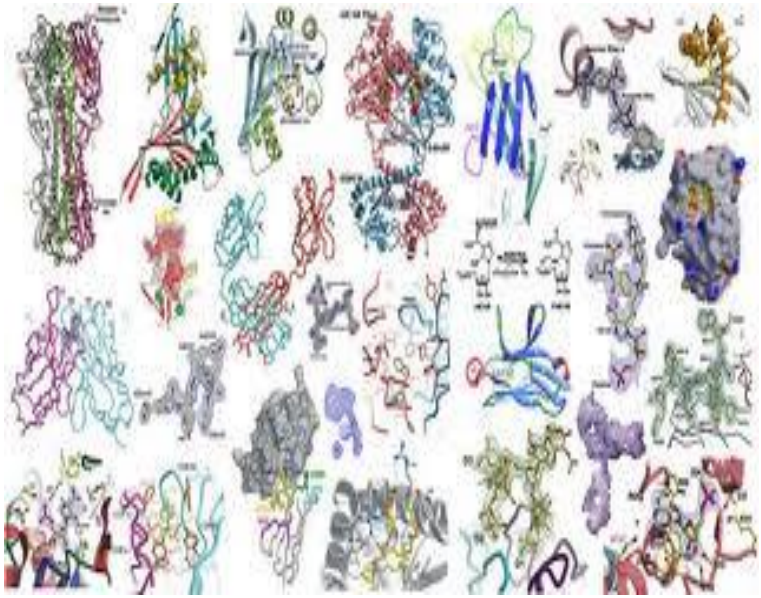
The two features that best distinguish adaptive and innate immunity are specificity and memory

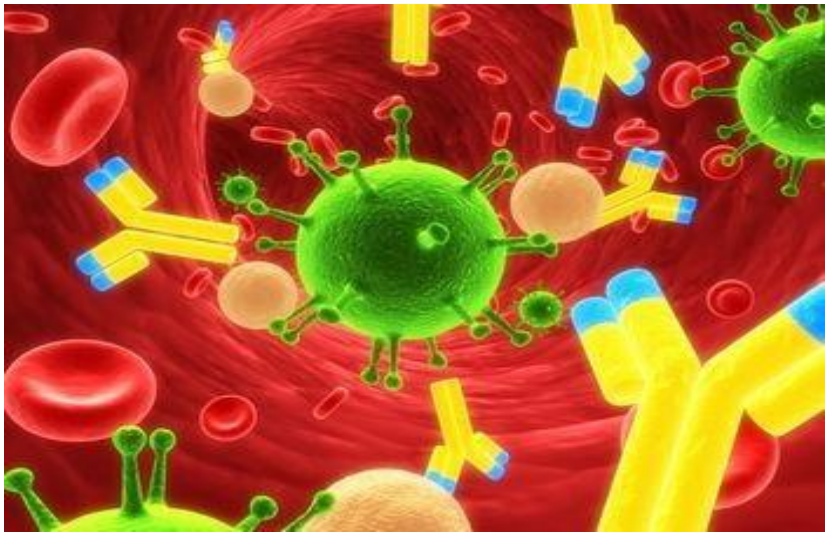
Specificity and Memory in Adaptive Immunity



Specificity

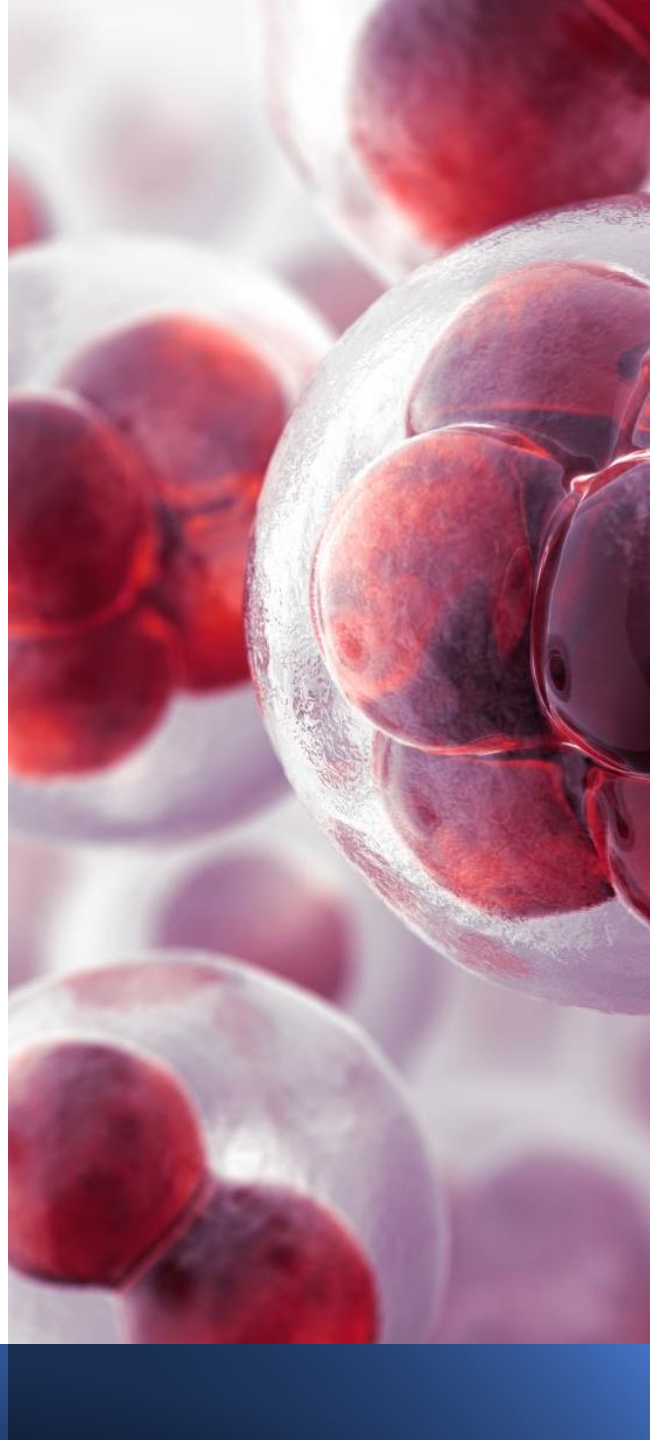
- The immune system has the ability to distinguish between at least **one billion different antigens and antigen fragments.**



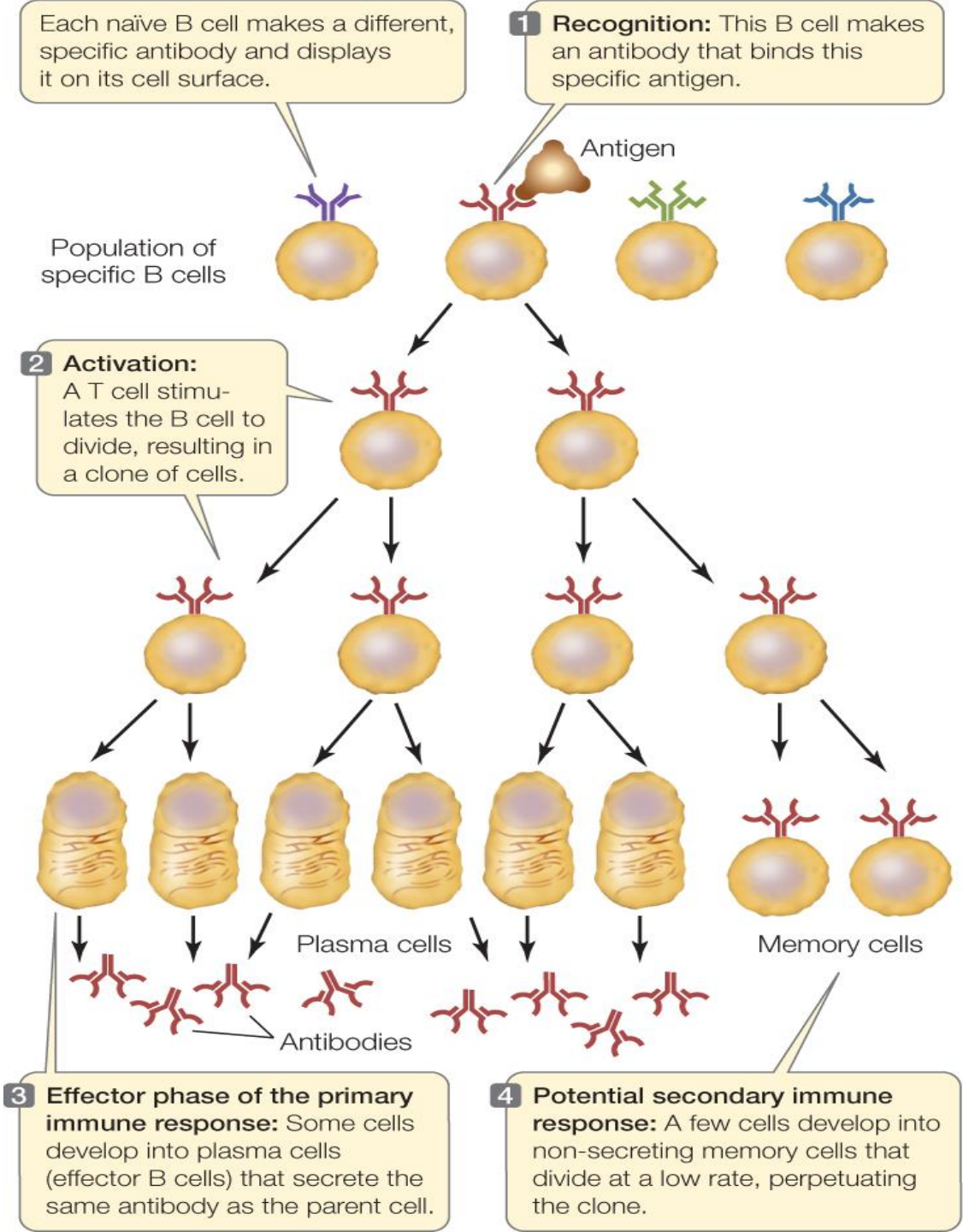


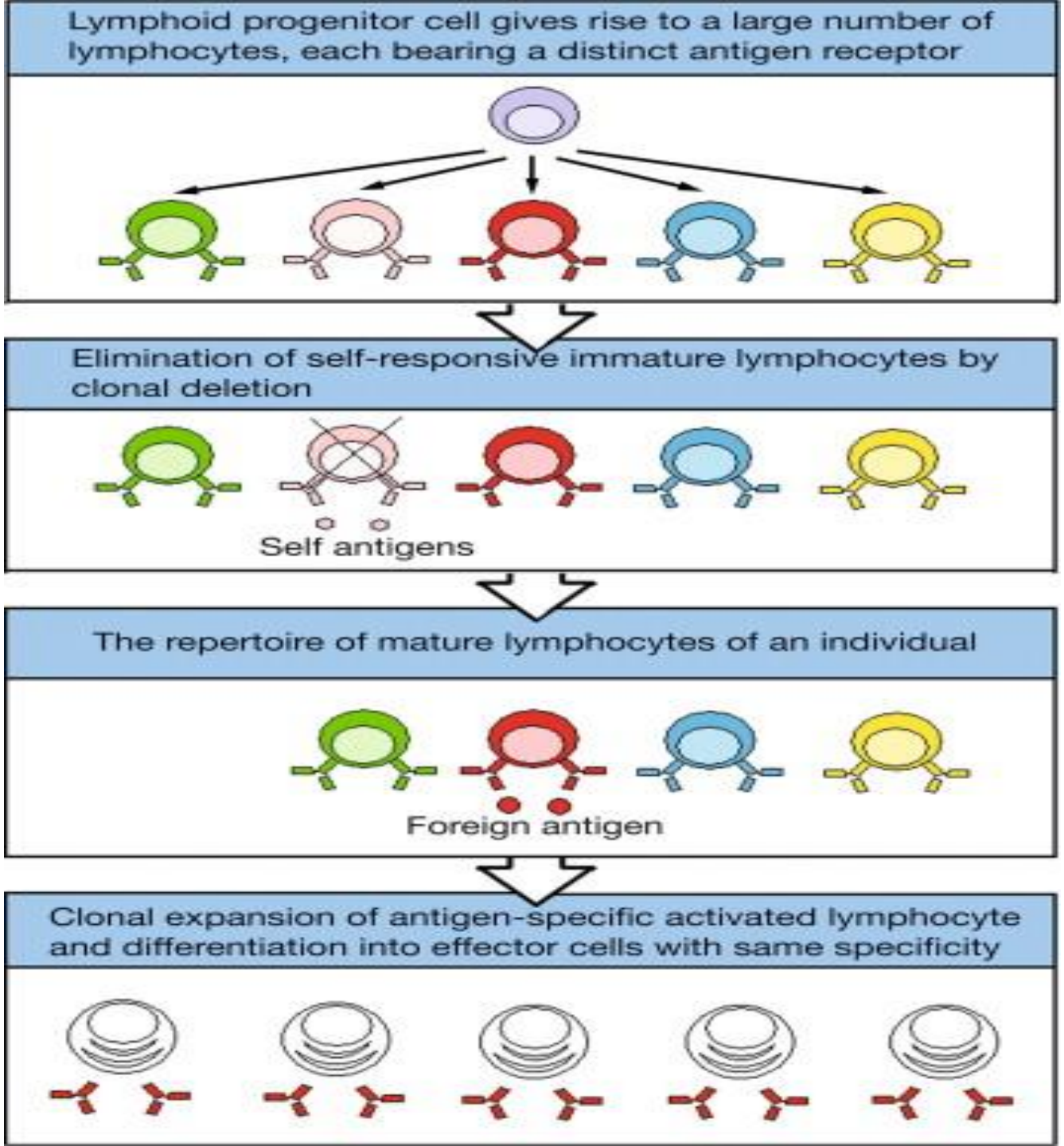
Causes of specificity and diversity

- **Lymphocytes made up of many different clones**
- **Each clone has a different antigen receptor distribution from the lymphocytes in the other clone.**



Clonal Selection Theory




Lymphoid progenitor cell gives rise to a large number of lymphocytes, each bearing a distinct antigen receptor
Elimination of self-responsive immature lymphocytes by clonal deletion
Self antigens
The repertoire of mature lymphocytes of an individual
Foreign antigen
Clonal expansion of antigen-specific activated lymphocyte and differentiation into effector cells with same specificity

Memory

- **When the immune system encounters the same antigen over and over again, it creates a greater and more effective response.**
- In the first encounter with the antigen, the immune response is generated by naive lymphocytes and this is called the primary (primary) immune response.

Naive Lymphocytes

- The term naive lymphocyte refers to

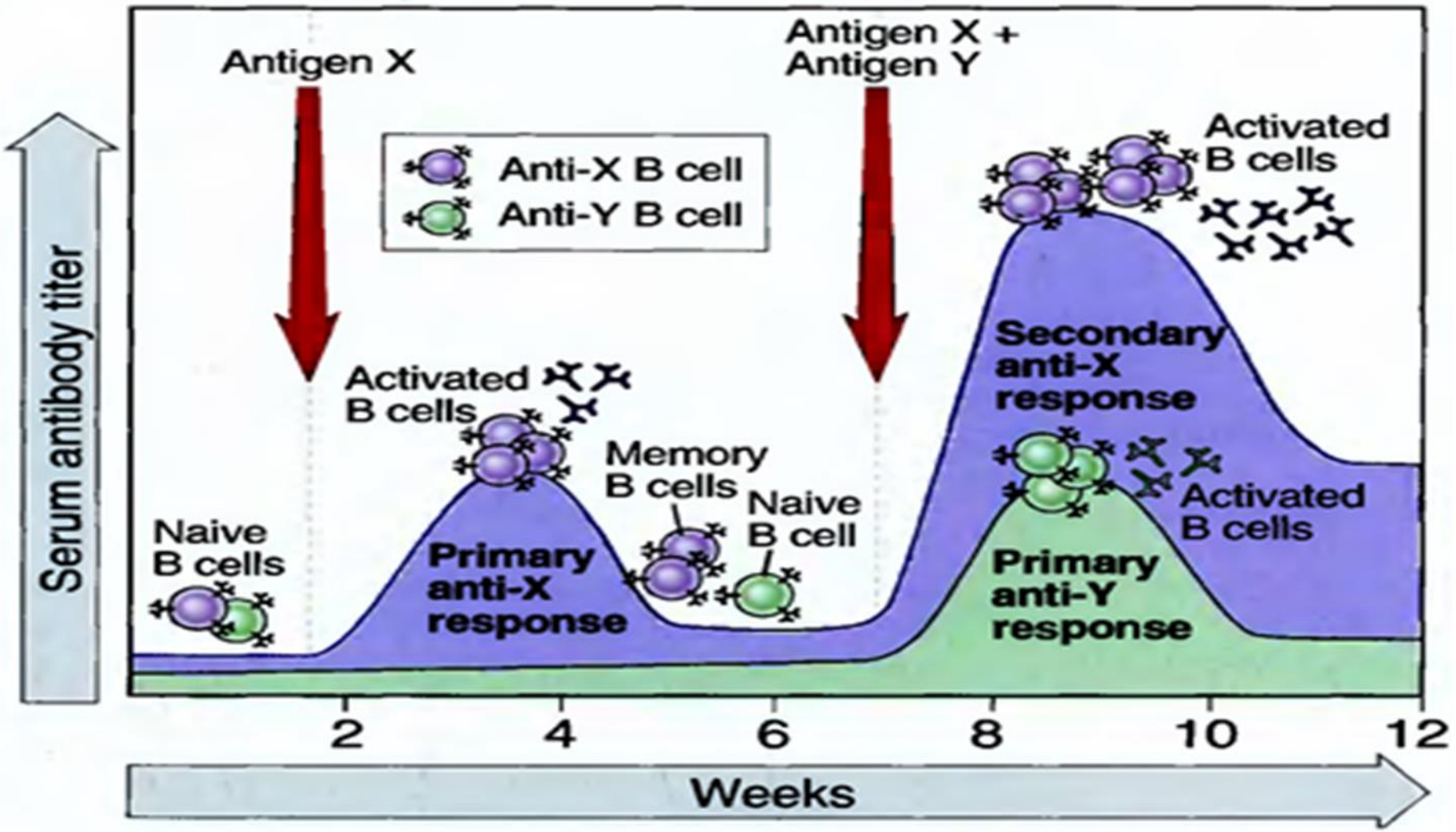
1. they are immunologically inexperienced,
2. they have not encountered antigens before
3. they do not produce an immune response

Stages of lymphocyte activation

- **Naïve lymphocytes**
  - Mature lymphocytes that have not previously encountered antigen; function -- antigen recognition
  - Preferential migration to peripheral lymphoid organs (lymph nodes), the sites where immune responses start
- **Effector lymphocytes**
  - Activated lymphocytes capable of performing the functions required to eliminate microbes ('effector functions")
  - Effector T lymphocytes: cytokine secretion (helper cells), killing of infected cells (CTLs)
  - B lymphocytes: antibody-secreting cells (e.g. plasma cells)
- **Memory lymphocytes**
  - Long-lived, functionally silent cells; mount rapid responses to antigen challenge (recall, or secondary, responses)

Secondary Immnue Response

- When the same antigen is encountered again, it creates an immune response that is faster, larger and better able to eliminate the antigen than the primary response called **secondary immune response.**

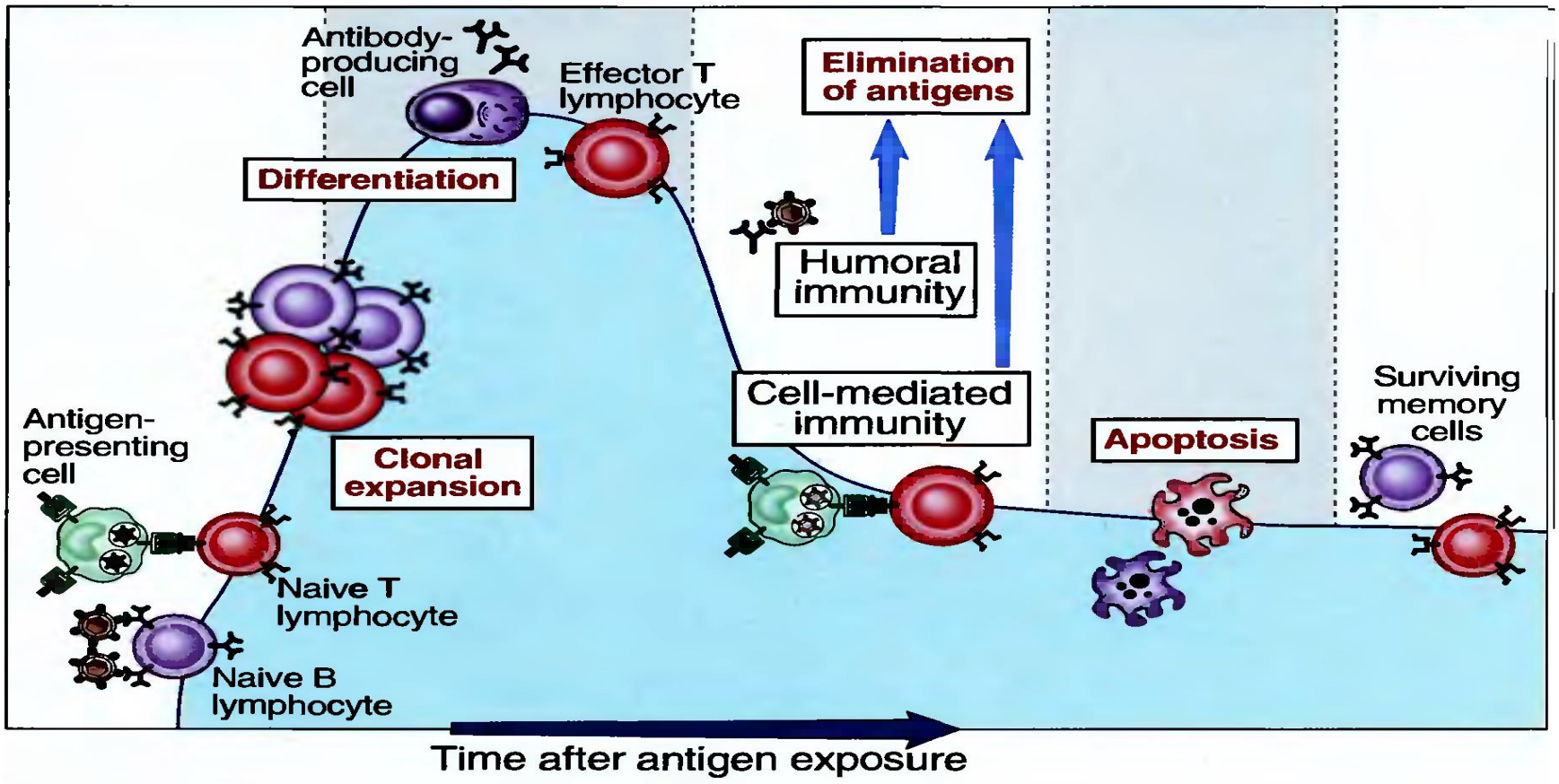


Secondary response occurs as a result of the transformation of long-lasting memory lymphocytes into effector lymphocytes

Phases of Immune Responses

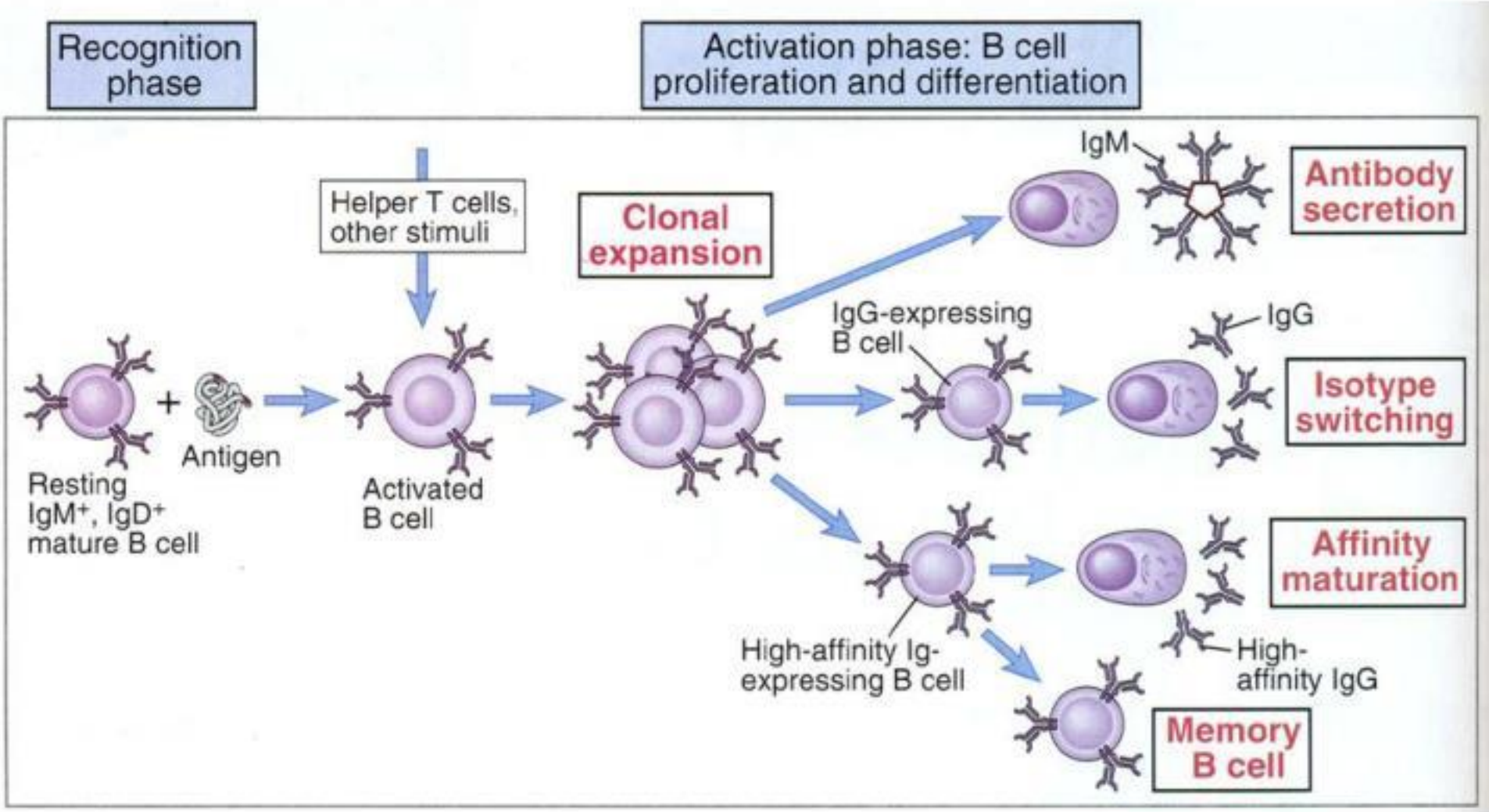
1. Antigen recognition,
2. Lymphocyte activation,
3. Elimination of antigens,
4. Termination of the immune response,
5. Memory

Phases of Adaptive Immunity



(review)

Phases of the humoral immune response

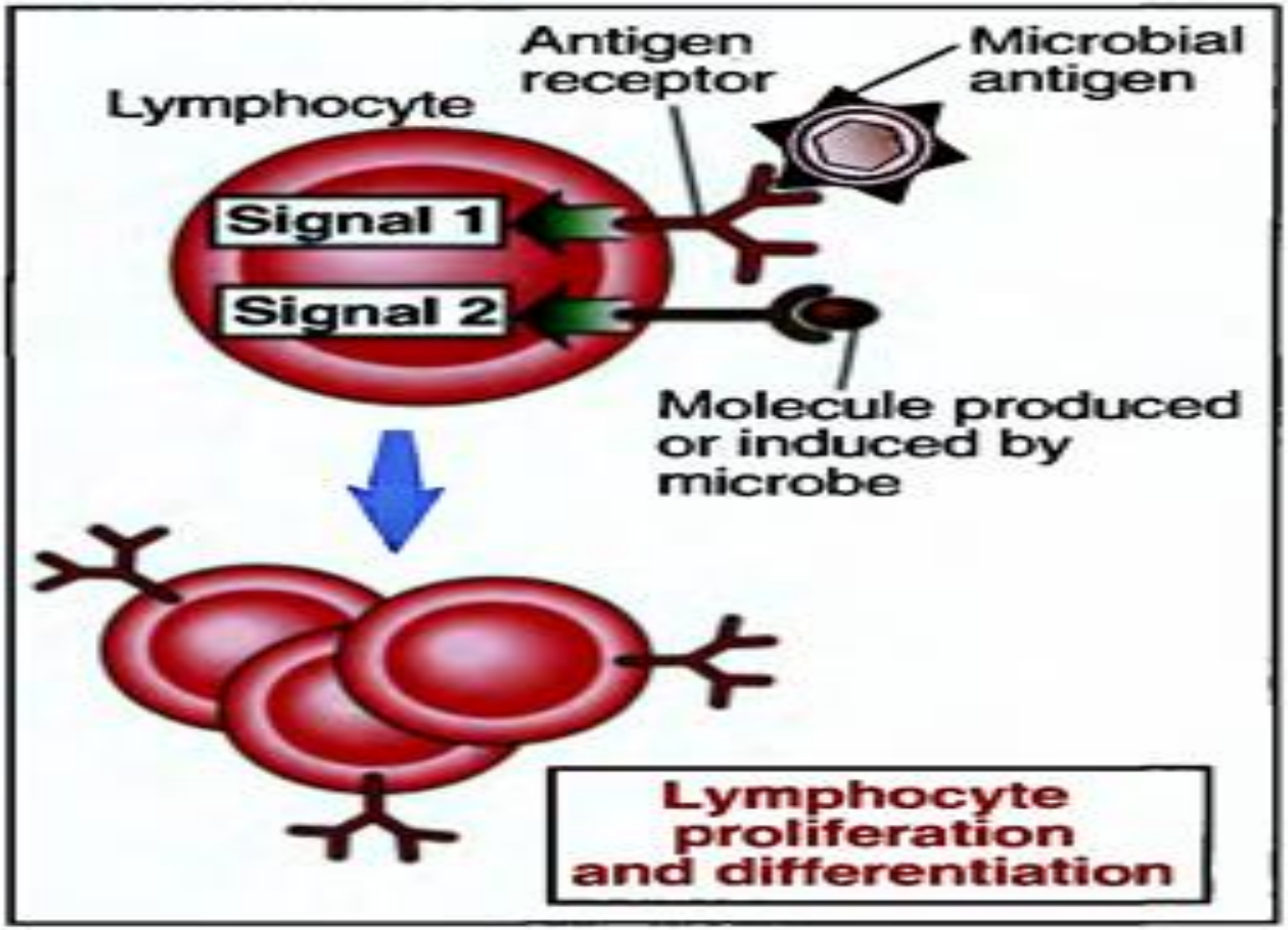


Co-stimulation

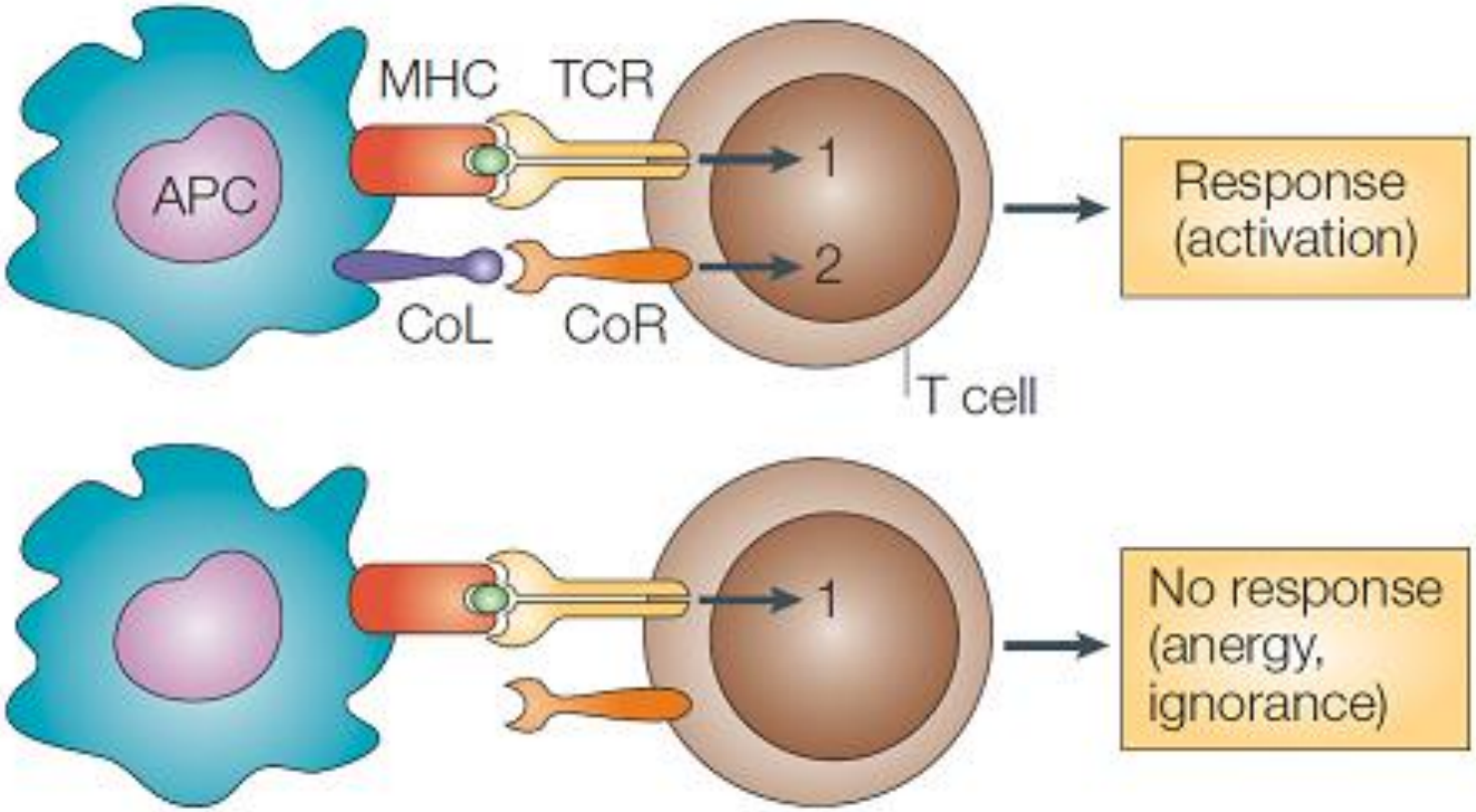
- At least two kinds of signals are required for activation of lymphocytes:

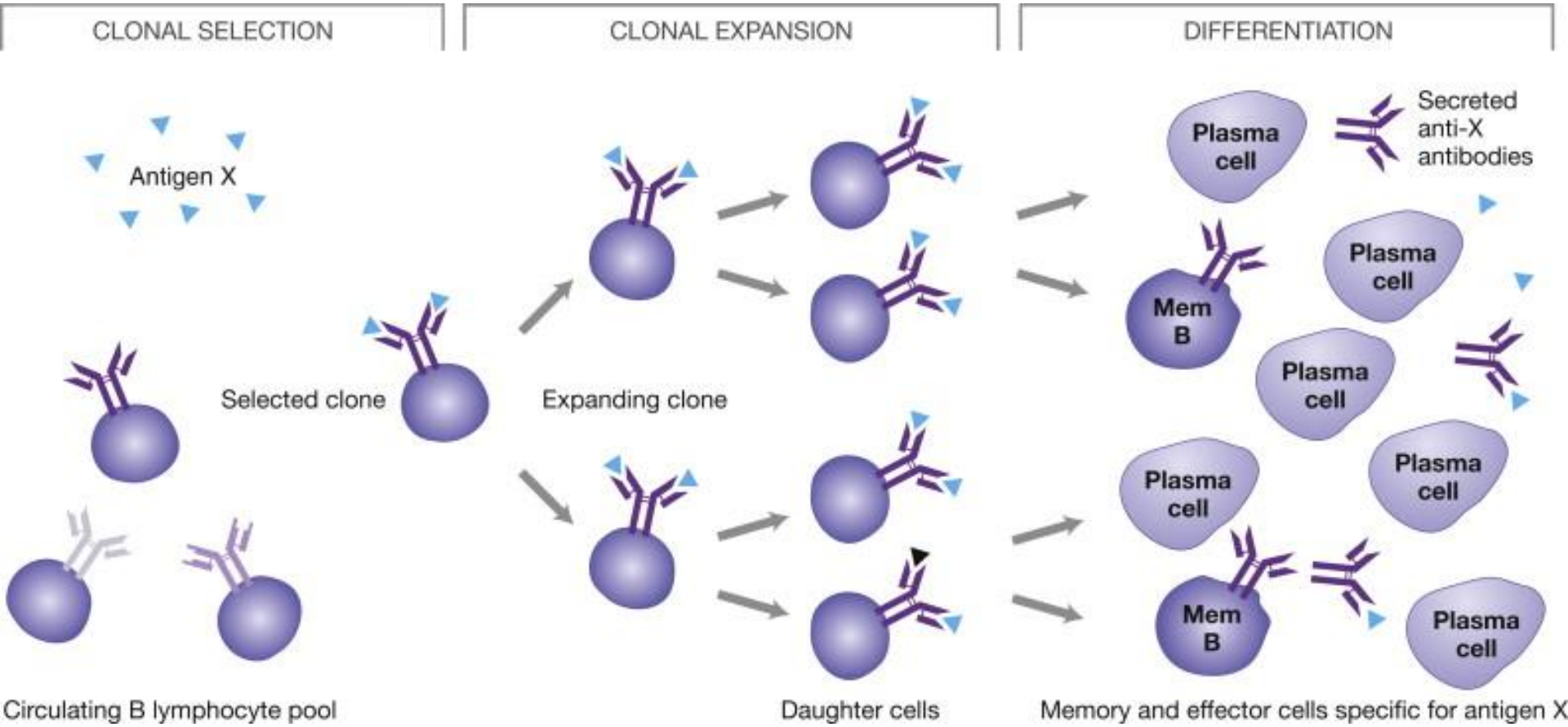
1. Binding of antigens to the receptors of lymphocytes **(signal 1)**
2. Binding of products produced by during the immune response against the microbe to lymphocytes **(signal 2)**

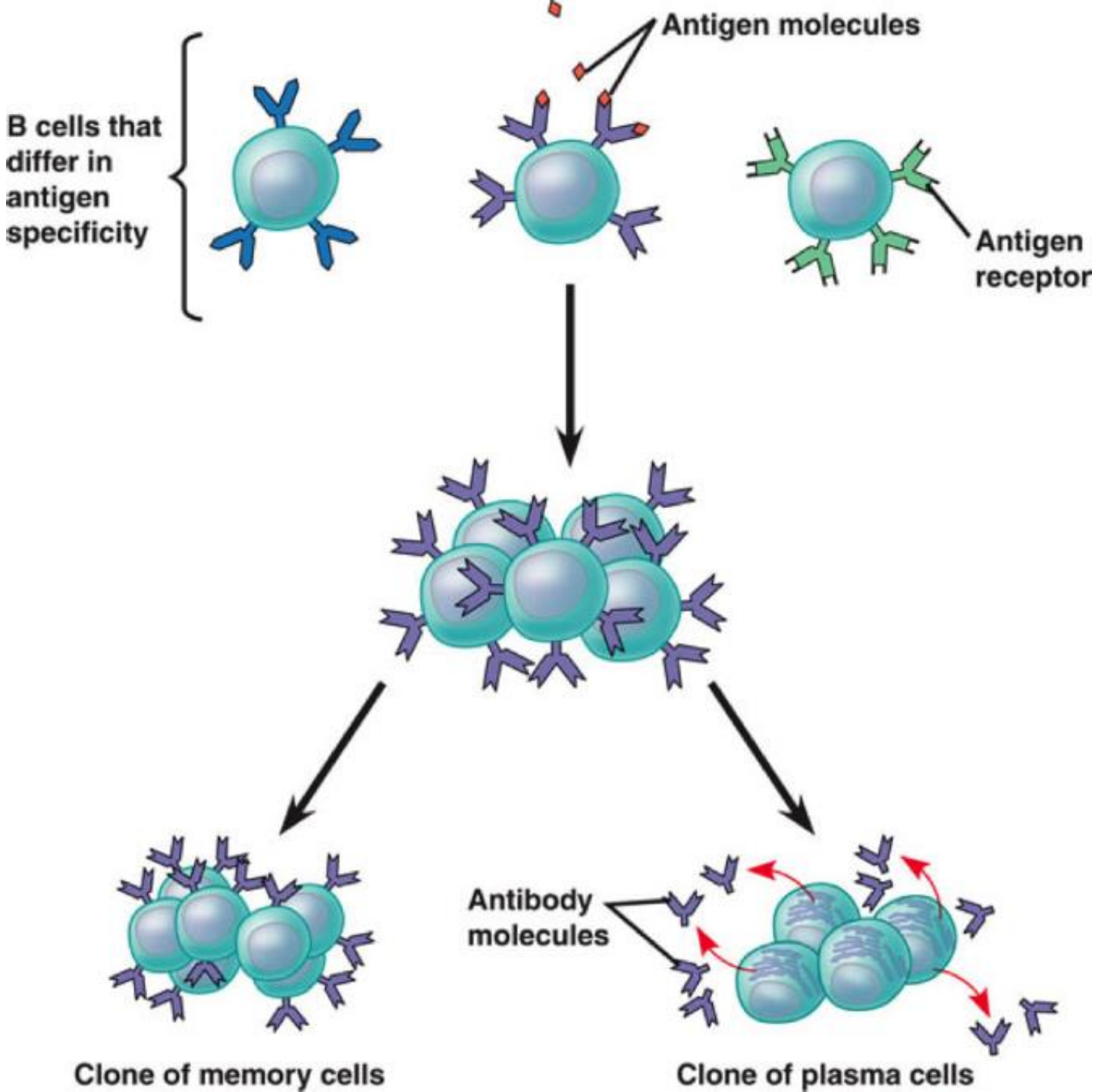
Lymphocyte activation



- The second signals are also called **'co-stimulatory molecules'.** Because they work together with antigens to activate cells.
- This need for second signals ensures that the acquired immune response is generated only against microbes and not against other harmless non-infectious antigens.

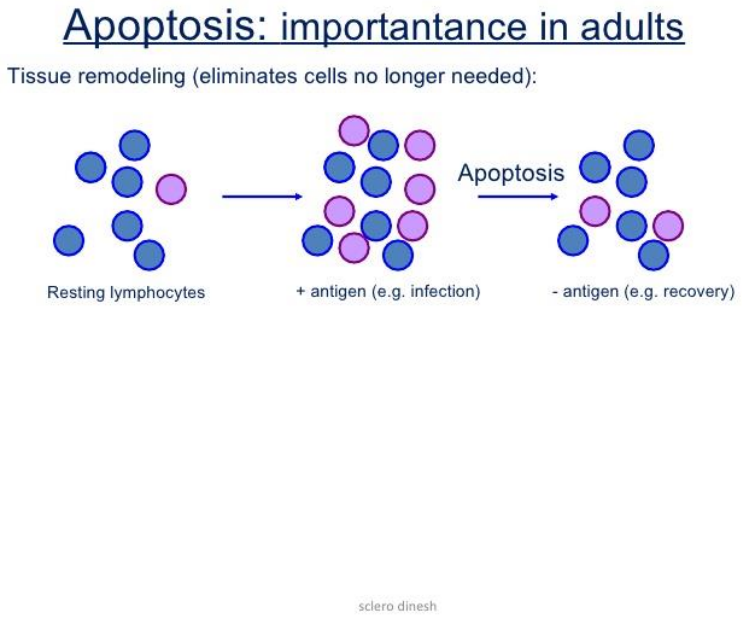

MHC
TCR
APC
1
2
CoL
CoR
T cell
Response (activation)
1
No response (anergy, ignorance)


CLONAL SELECTION
CLONAL EXPANSION
DIFFERENTIATION
Antigen X
Selected clone
Expanding clone
Plasma cell
Secreted anti-X antibodies
Mem B
Plasma cell
Plasma cell
Plasma cell
Plasma cell
Mem B
Plasma cell
Circulating B lymphocyte pool
Daughter cells
Memory and effector cells specific for antigen X


Antigen molecules
B cells that differ in antigen specificity
Antigen receptor
Antibody molecules
Clone of memory cells
Clone of plasma cells

Apoptosis

- After the infection is cleared, the stimulation that leads to lymphocyte activation ends
- As a result, most of the cells activated by antigens are eliminated by apoptosis.
- Dead cells are cleared by phagocytes before they initiate a harmful reaction



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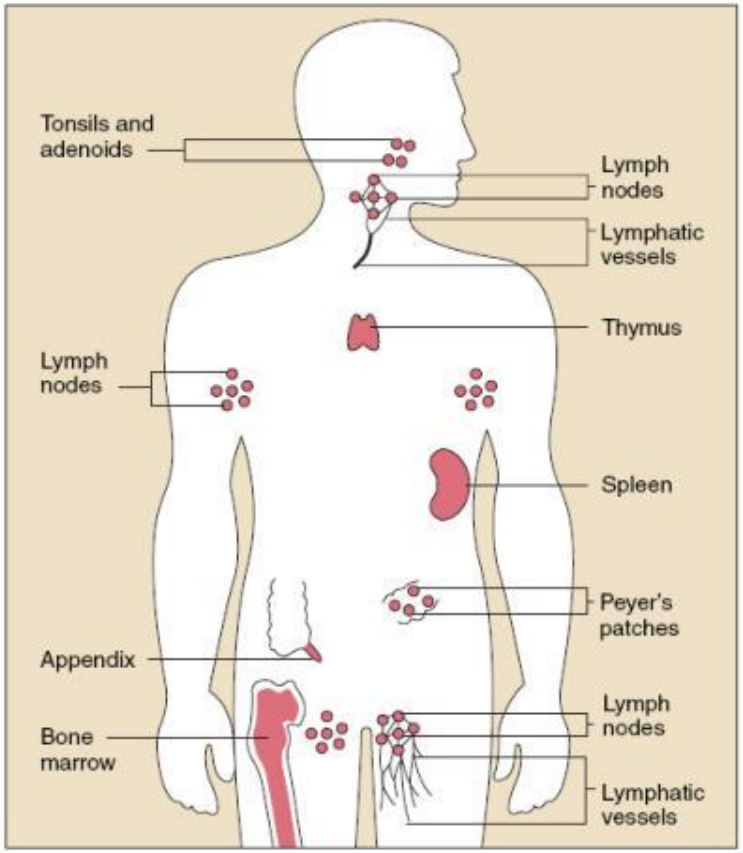
LYMPHOID ORGANS

Primary lymphoid organs:

- Bone marrow
- Thymus

the cells of the immune system originate in and mature here

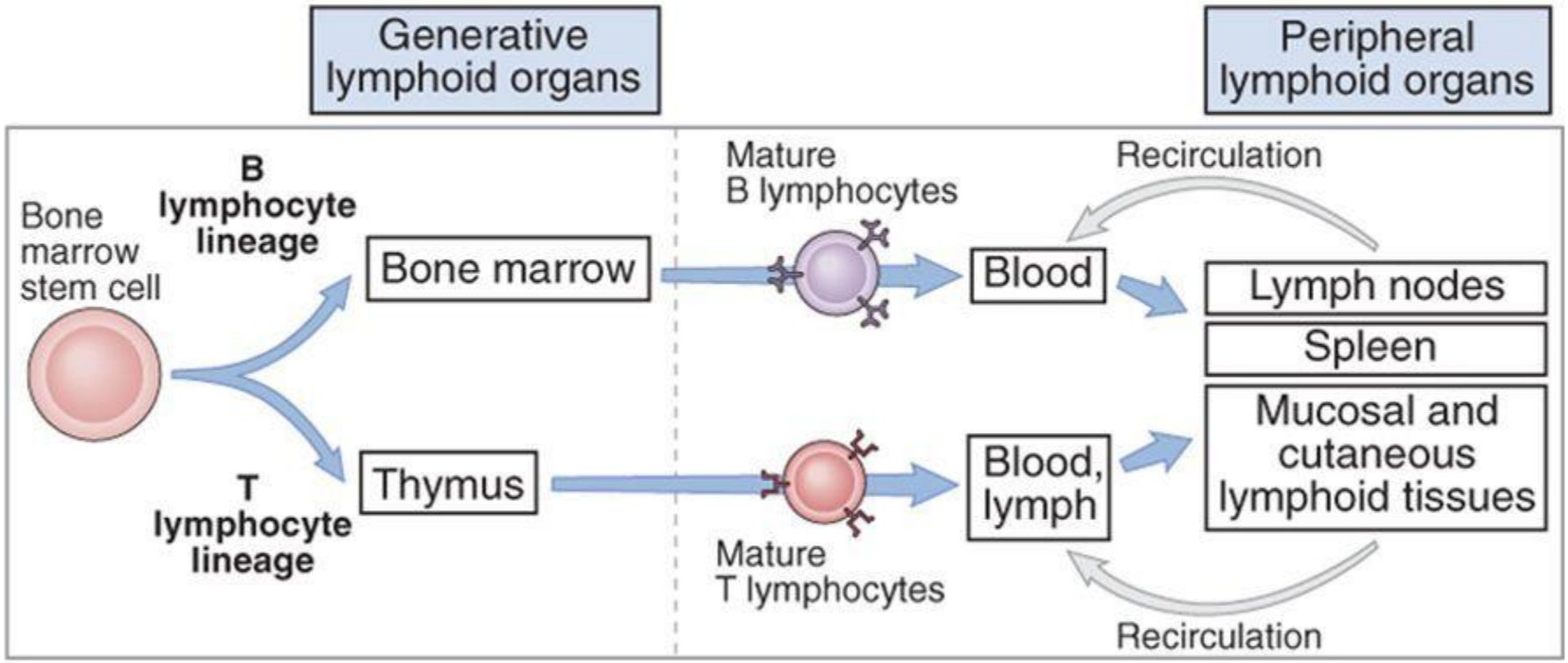


Secondary lymphoid organs:

- Spleen
- Lymphatic vessels
- Lymph nodes
  - Adenoids and tonsils
  - MALT (Mucosal Associated Lymphoid Tissue)
    - GALT (Gut Associated Lymphoid Tissue)
    - BALT (Bronchus Associated Lymphoid Tissue)
    - SALT (Skin Associated Lymphoid Tissue)
    - NALT (Nasal Associated Lymphoid Tissue)

not for cell development. (final differentiation, activation may be performed) The cells of the adaptive immune system recognize here the pathogens

Lymphocyte maturation



Primary lymphoid organs:

1- Thymus:

-T Lymphocytes develop within this lymphoid organ.

-**Function**: The clonal selection of T lymphocytes.

(Lymphocyte educational Center)

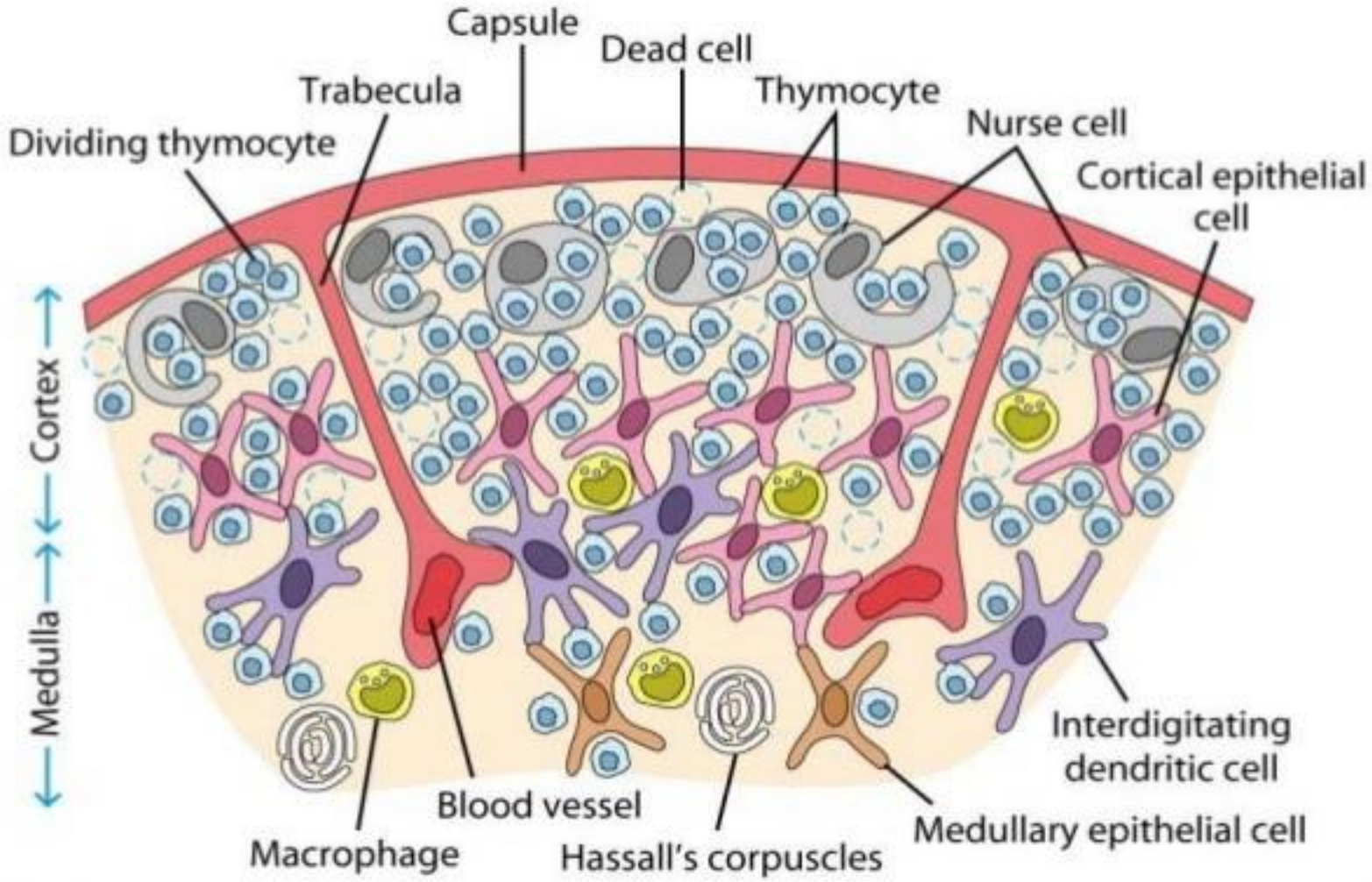
-It increases in size during fetal and neonatal life.

-It is progressively inactivated (curved spirally) following puberty.

-Two important parts:

1-Thymic Cortex.

2-Thymic Medulla.


Capsule
Dead cell
Trabecula
Thymocyte
Dividing thymocyte
Nurse cell
Cortical epithelial cell
Cortex
Medulla
Interdigitating dendritic cell
Blood vessel
Medullary epithelial cell
Macrophage
Hassall's corpuscles

2-Bone marrow:

-B lymphocytes are “home schooled” within this organs.

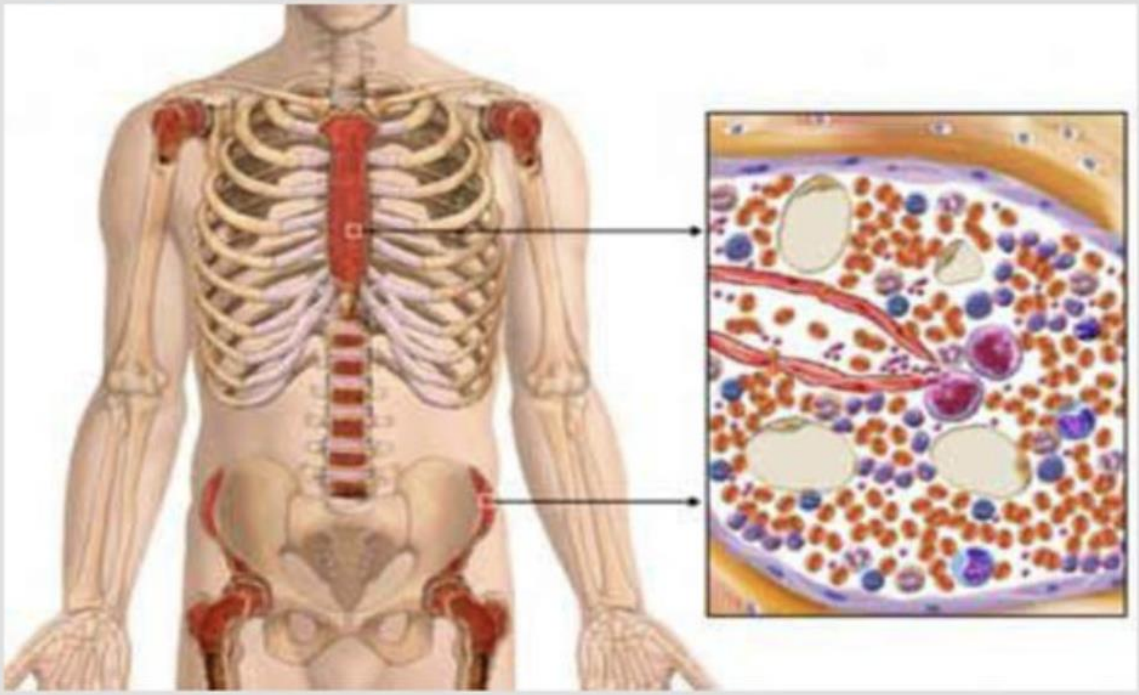
-**Function:**

Primary differentiation of B lymphocytes.

B lymphocytes begin to display IgM on their surfaces.

-The primary site for cytokines-Immune cell interactions.

-Bone marrow removes the B cells that show self-reactivity by apoptosis.



Secondary Lymphoid Organs:

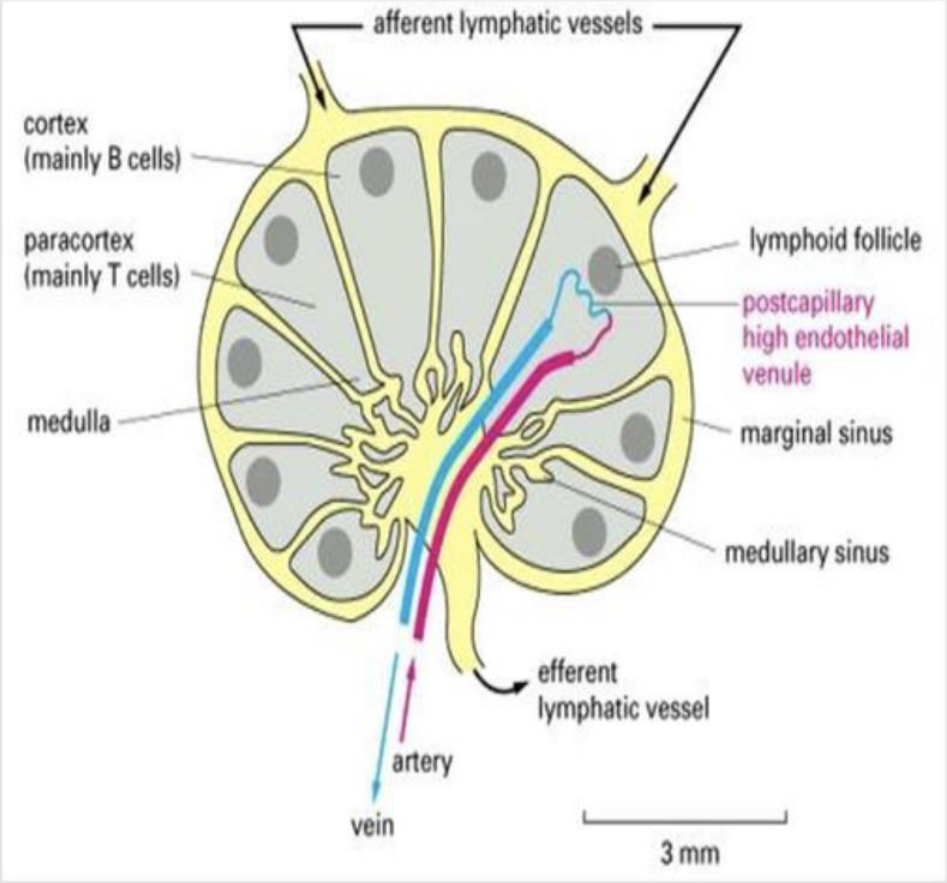
1-Lymph nodes:

-It acts as filters to purify lymph.

-Divided into the cortex and medulla.

-The **superficial cortex** contains lymphocyte-rich nodules (follicles) (mainly B cells).

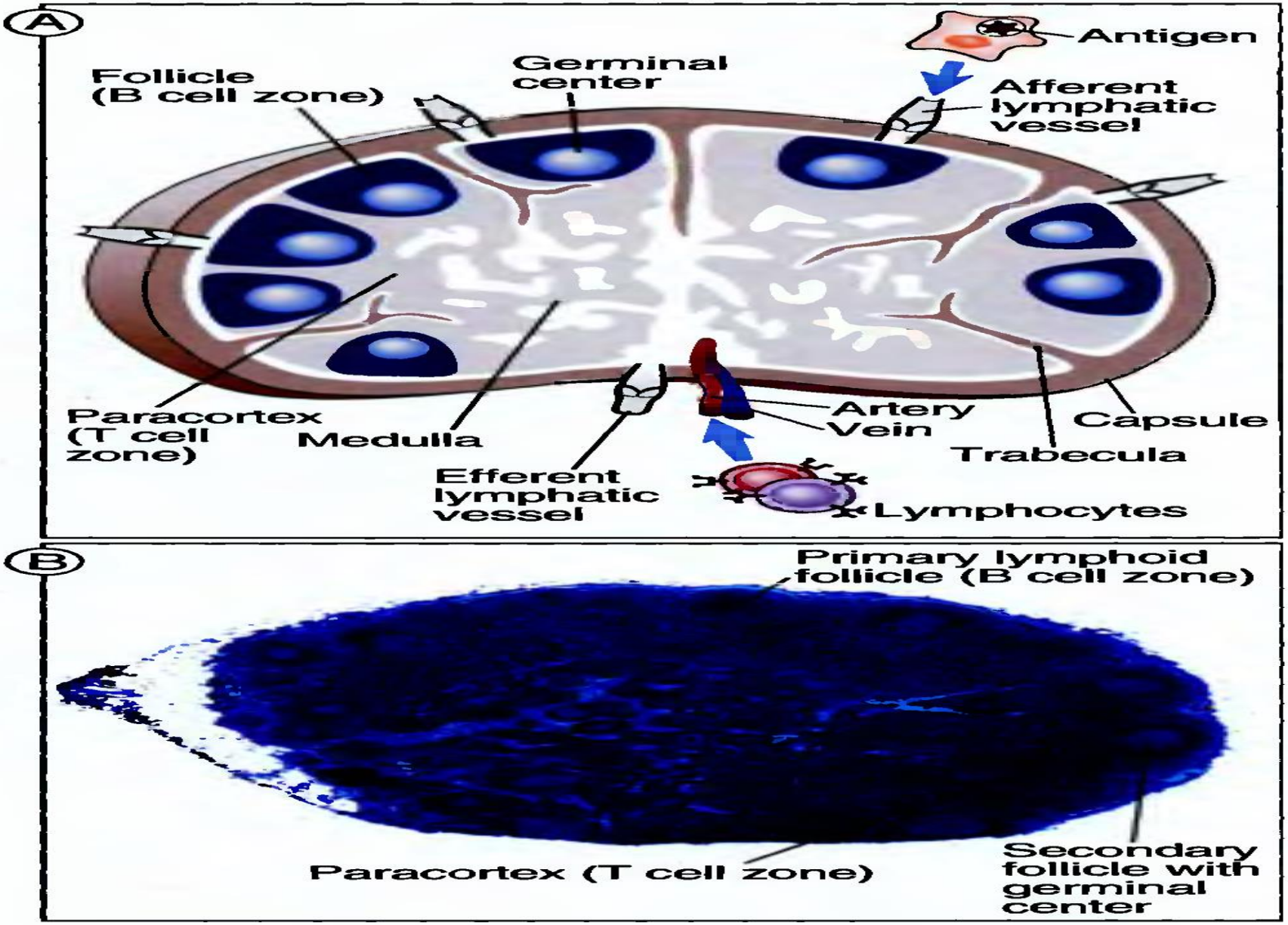
-The **deep cortex** is the T-cell-rich area.



Lymph nodules

- Lymph nodes are nodular structures that are formed by the gathering of lymphoid tissues located around lymphatic ducts that spread throughout the body.
- Fluids from all epithelium, connective tissue and most parenchymal organs are drained by lymphatics.
- This fluid that is drained from the tissues to the lymph node is called lymph.

Lymph node morphology



2-The Spleen:

-The largest lymphoid organ.

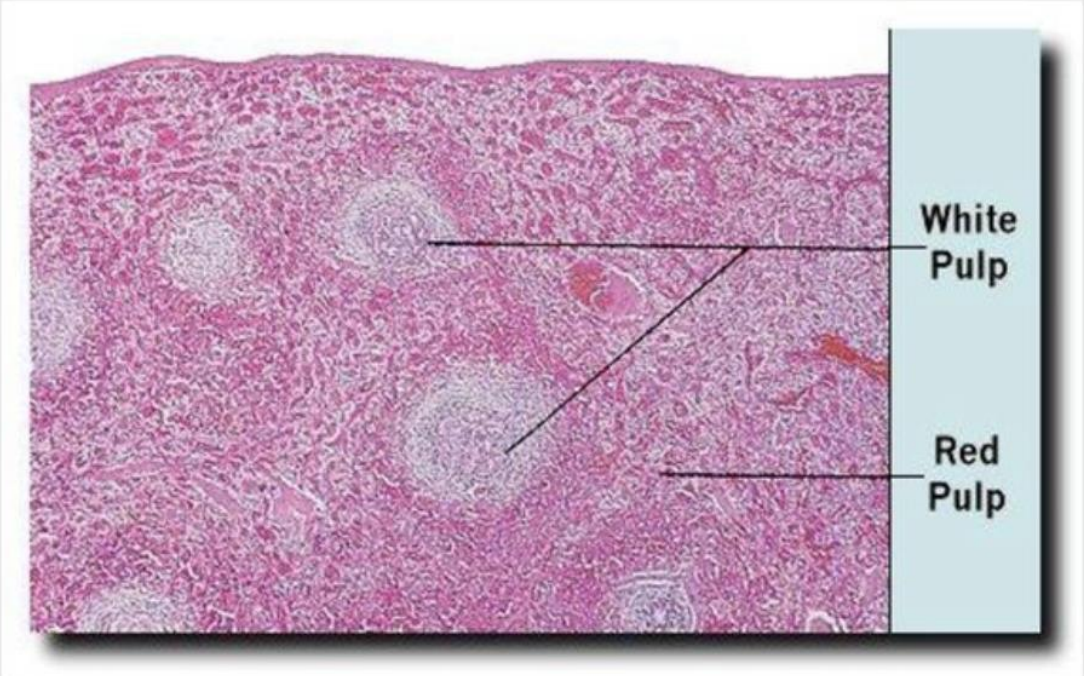
-Concentrates blood-borne antigens and microbes.

-Contains T cells, B cells, and Large numbers of **plasma** cells (secreting immunoglobulins into the circulation).

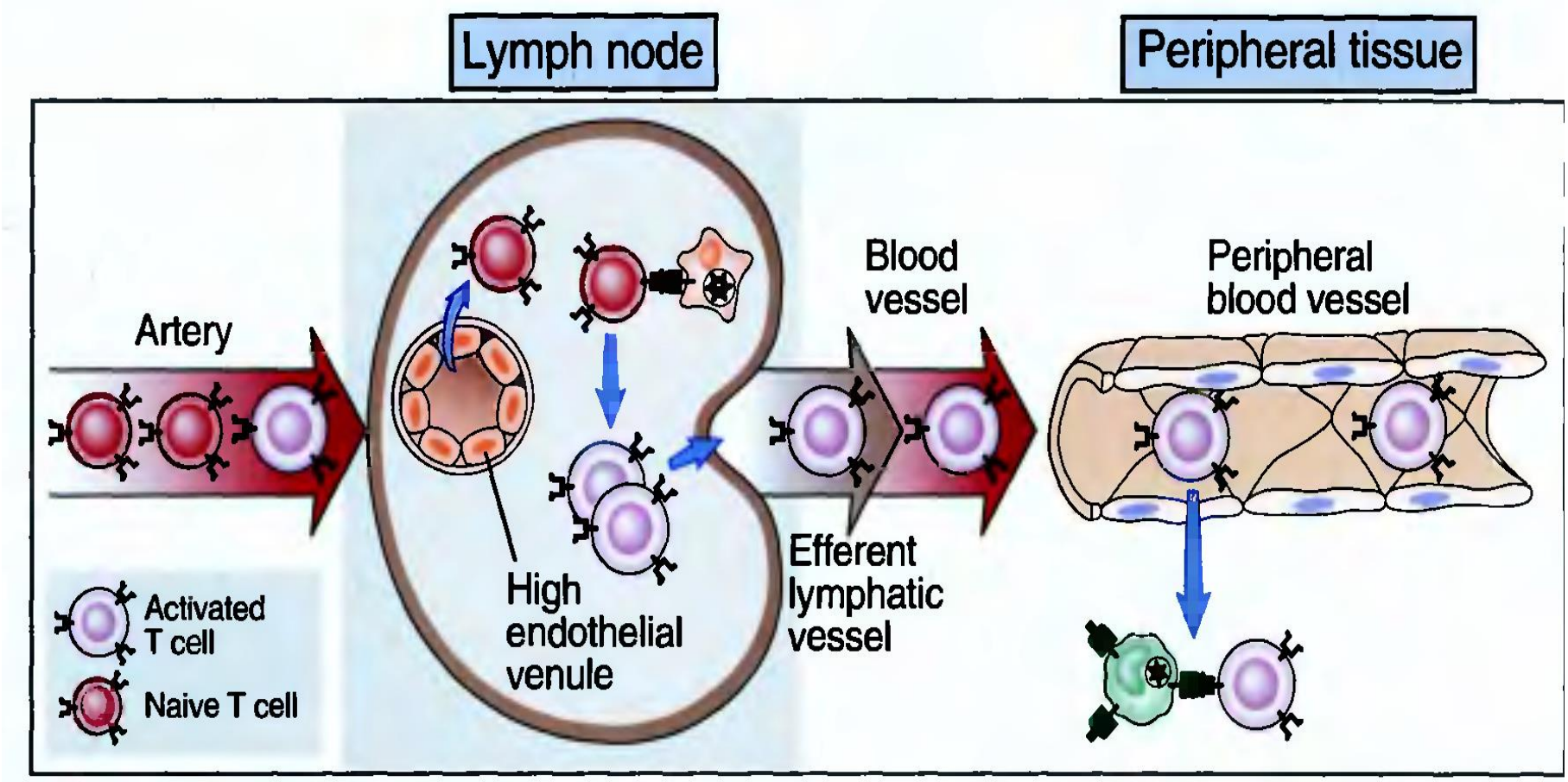
-**Divided into**:

1-Lymphocyte-rich **white pulp**.

2-Erythrocyte-rich **red pulp** (also contains macrophages).



Circulation of T lymphocytes



- Blood is mostly associated with T lymphocytes, as effector T cells locate and destroy the microbe at any infection site.
- In contrast, B lymphocytes remain in lymphoid organs and do not need to migrate to the site of infection.
- Instead, B lymphocytes produce antibodies and these antibodies enter the bloodstream to find microbes and microbial toxins in the circulation or in distant areas