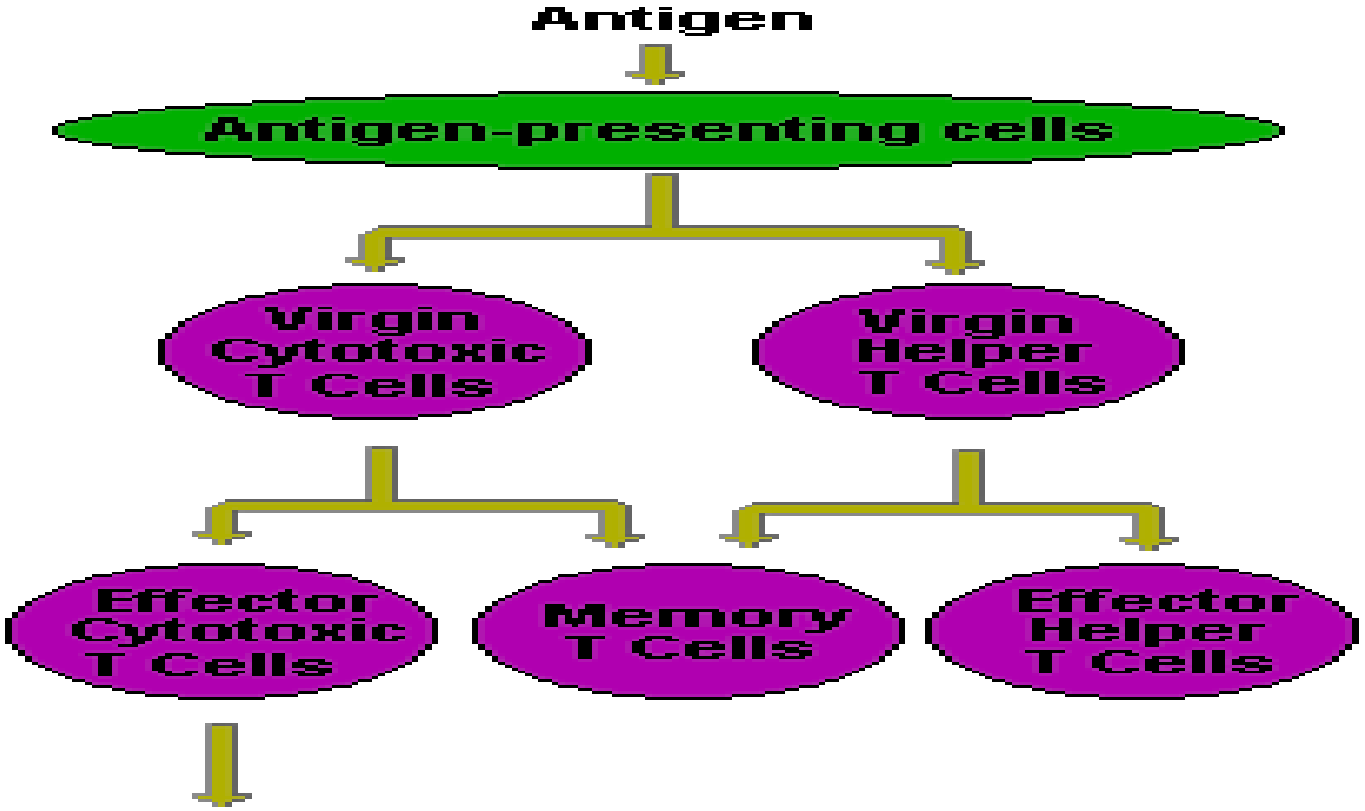
The Immune System

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
The immune system recognizes and responds to tissue grafts and newly introduced proteins	Immune responses are important barriers to transplantation and gene therapy
Defense against tumors	Potential for immunotherapy of cancer
Antibodies are highly specific reagents for detecting any class of molecules	Immunologic approaches for laboratory testing are widely used in clinical medicine and research

Immunity and the Immune Response System

Cell Mediated Response



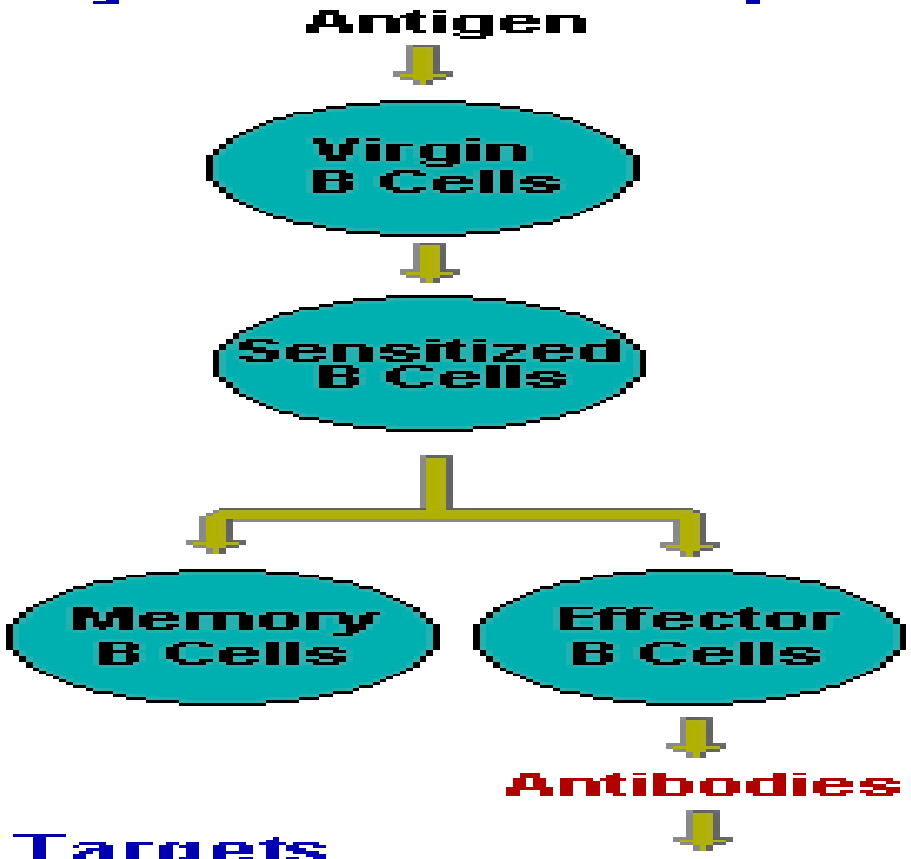
Targets

Cells with antigen on their surface *(intracellular pathogen)*

Outcomes

Cells killed directly

Antibody Mediated Response



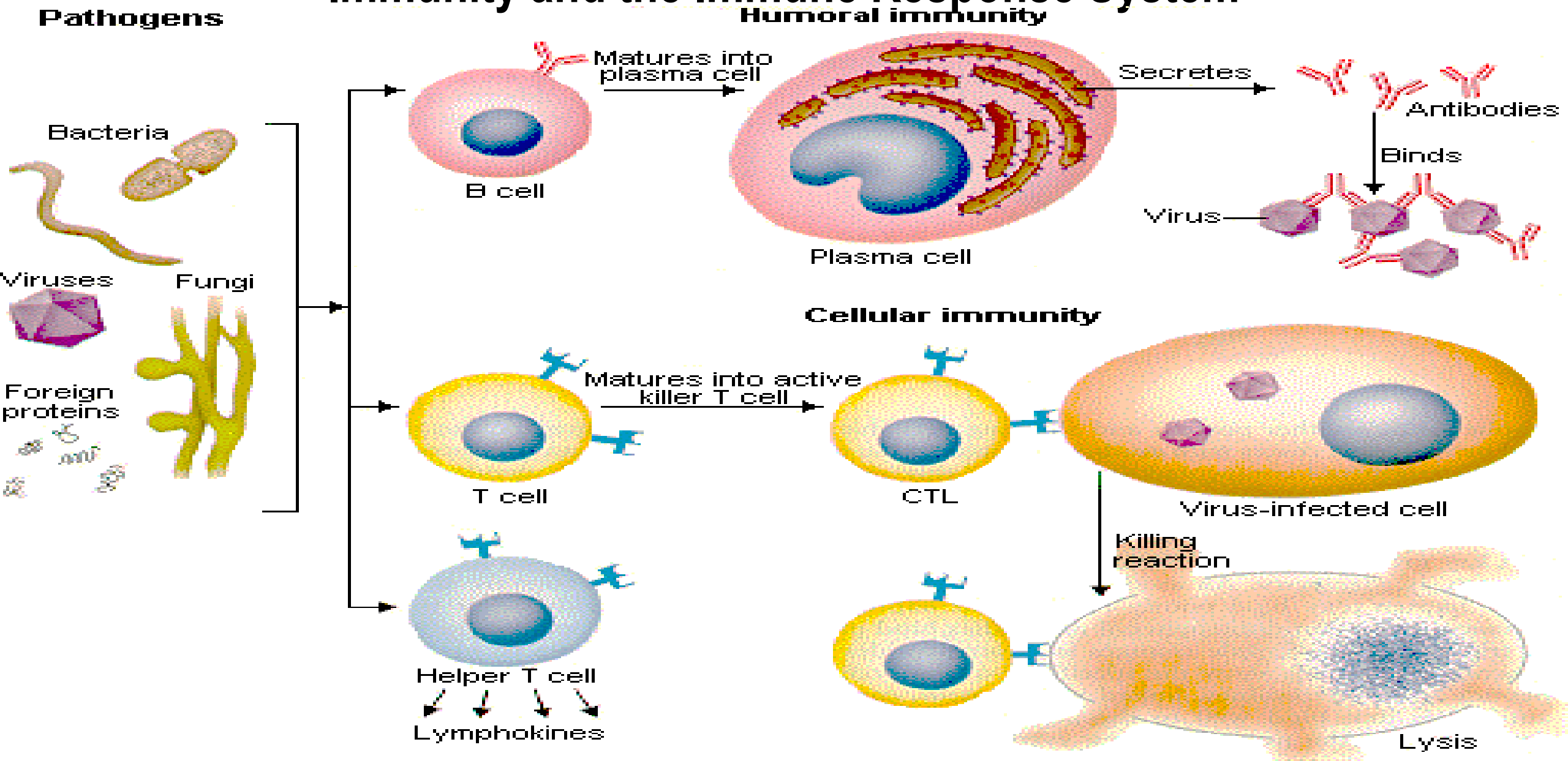
Targets

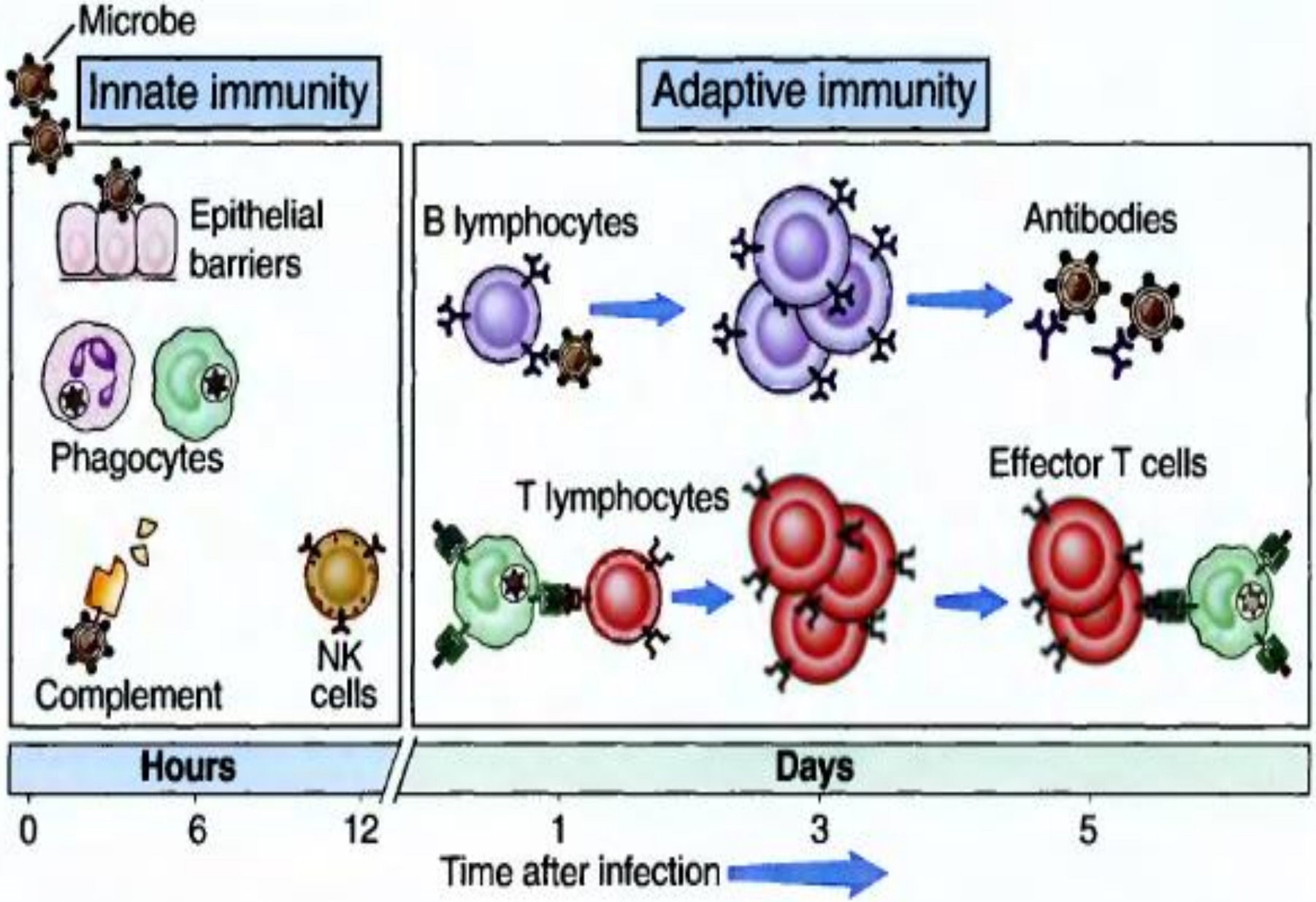
Pathogens or toxins circulating in tissues *(extracellular pathogen)*

Outcomes

Direct inactivation and indirect destruction

Immunity and the Immune Response System




Microbe
Innate immunity
Adaptive immunity
Epithelial barriers
Phagocytes
Complement
NK cells
B lymphocytes
Antibodies
T lymphocytes
Effector T cells
Hours
Days
0
6
12
1
3
5
Time after infection

A Summary of Innate and Acquired Immunity

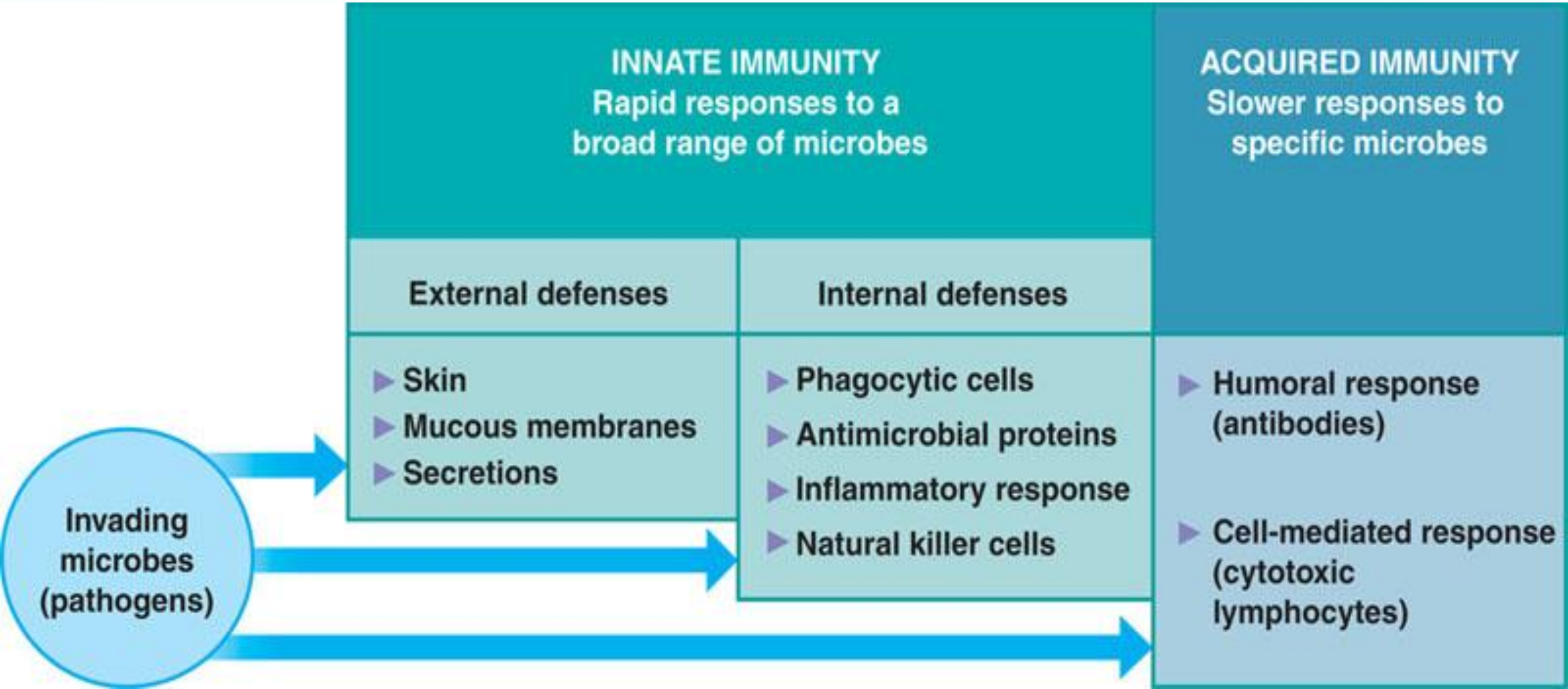
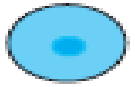


Table 1.1. Characteristics of the innate and the adaptive immune system

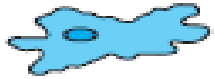
	Immune System	
Characteristic	Innate Immune System	Adaptive Immune System
Immunological Memory	—	+
Specificity	—	+
Response Time Constancy	+	—

Cells of the Immune System

Phagocytes



Monocyte



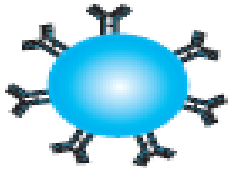
Macrophage

Neutrophil

Antigen Presenting Cells

Dendritic cell

Macrophage



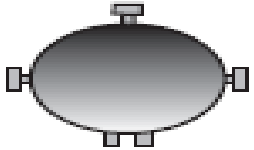
B cell

Inflammatory Cells

Eosinophil

Mast cell or Basphil

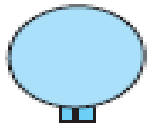
Natural Killer Cell



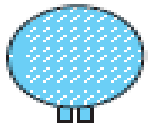
Natural Killer cell

Lymphocytes

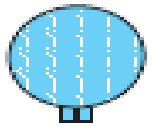
T Cells * (representative sample)



CD4+ T Cell (Th1)



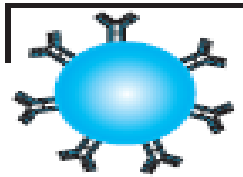
CD4+ T Cell (Th2)



CD8+ T cell (CTL)

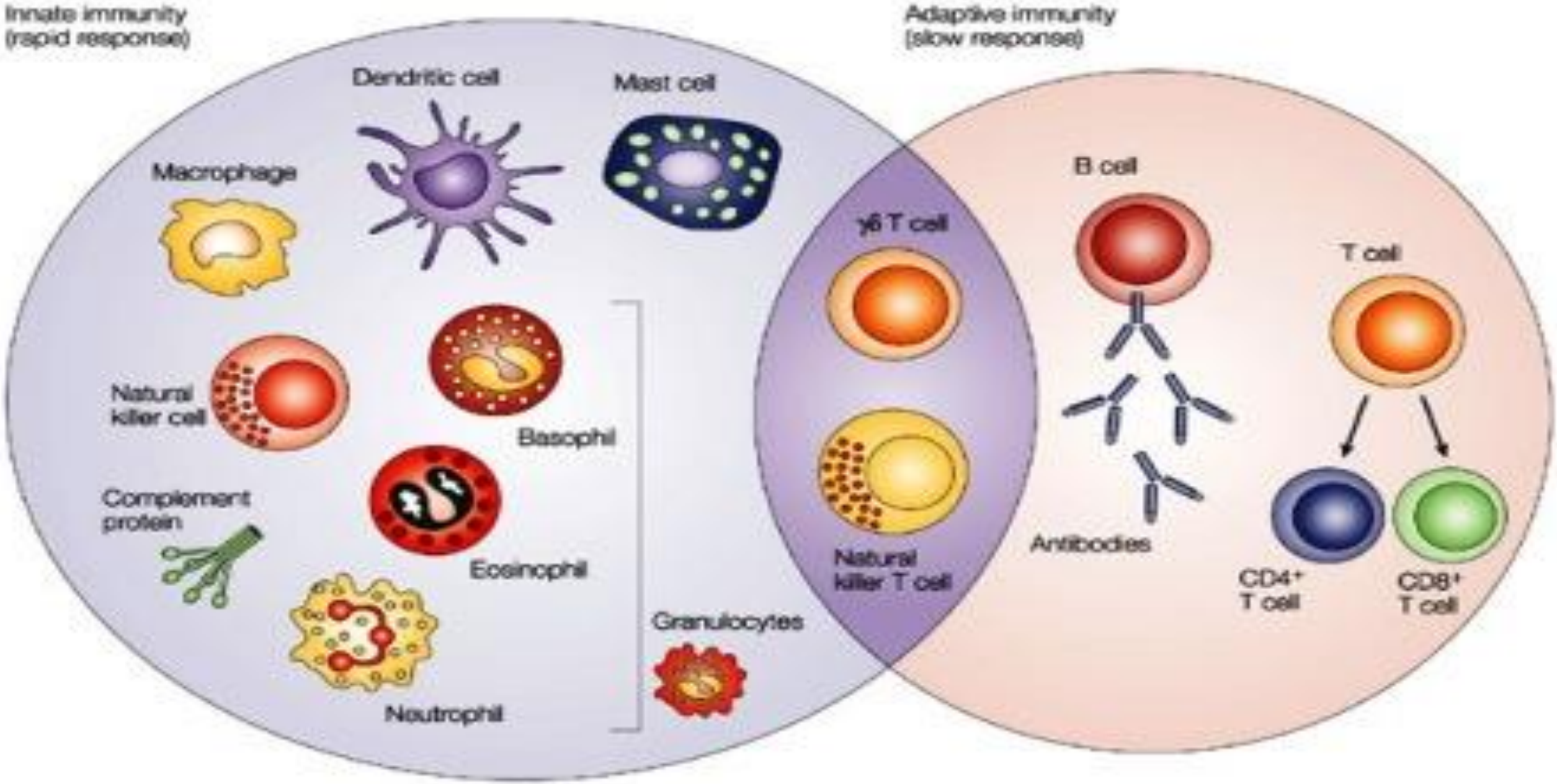
γ/δ T cell

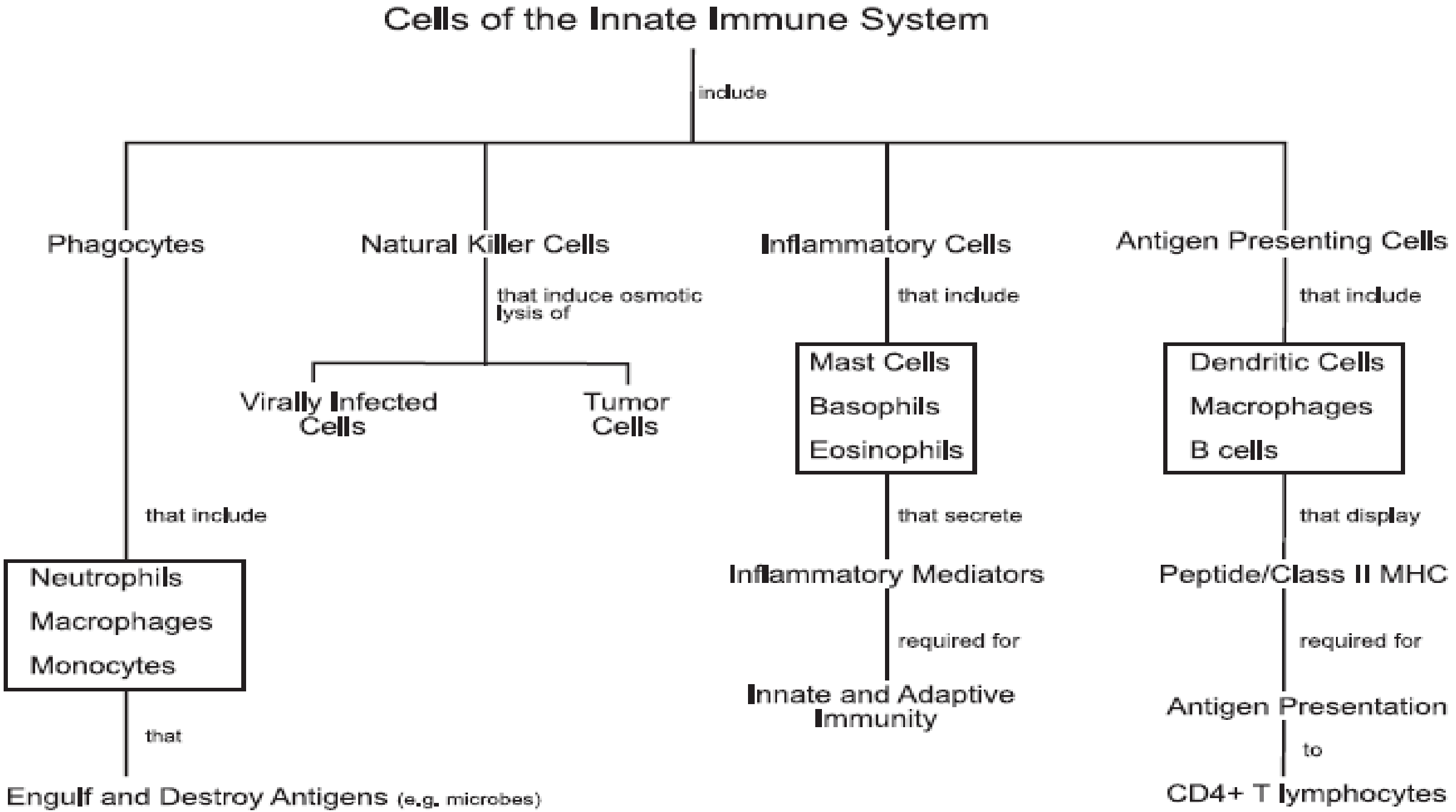
B cells

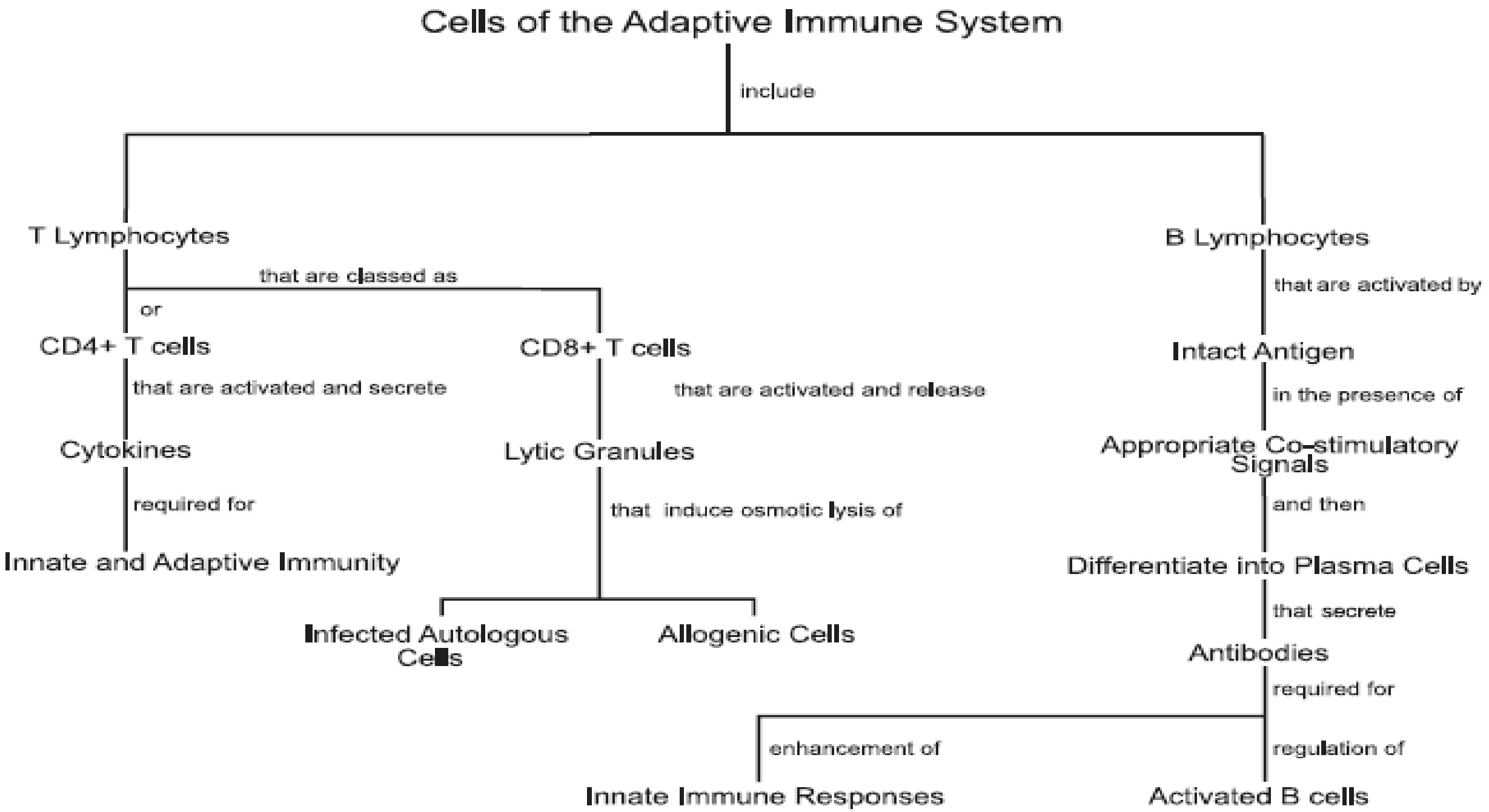


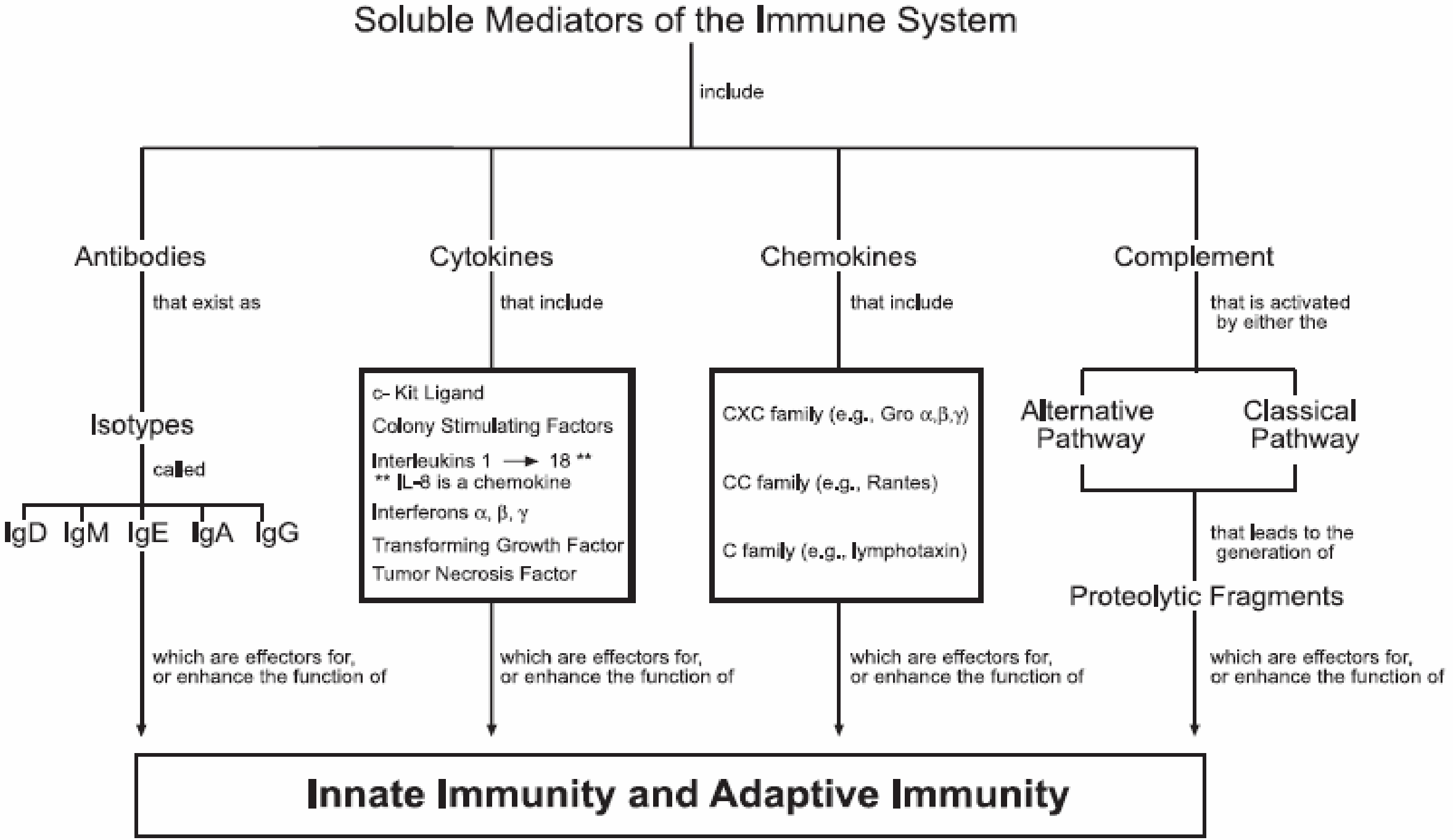
B cell

Plasma cell


Innate immunity
(rapid response)
Adaptive immunity
(slow response)
Dendritic cell
Mast cell
Macrophage
γδ T cell
B cell
T cell
Natural
killer cell
Basophil
Complement
protein
Eosinophil
Natural
killer T cell
Antibodies
CD4+
T cell
CD8+
T cell
Granulocytes
Neutrophil


Cells of the Innate Immune System
include
Phagocytes
Natural Killer Cells
Inflammatory Cells
Antigen Presenting Cells
that induce osmotic lysis of
that include
that include
Virally Infected Cells
Tumor Cells
Mast Cells
Basophils
Eosinophils
Dendritic Cells
Macrophages
B cells
that include
that secrete
that display
Neutrophils
Macrophages
Monocytes
Inflammatory Mediators
Peptide/Class II MHC
that
required for
required for
Innate and Adaptive Immunity
Antigen Presentation
to
Engulf and Destroy Antigens (e.g. microbes)
CD4+ T lymphocytes


Cells of the Adaptive Immune System
include
T Lymphocytes
B Lymphocytes
that are classed as
or
CD4+ T cells
CD8+ T cells
that are activated by
Intact Antigen
that are activated and secrete
that are activated and release
in the presence of
Cytokines
Lytic Granules
Appropriate Co-stimulatory Signals
required for
that induce osmotic lysis of
and then
Innate and Adaptive Immunity
Differentiate into Plasma Cells
that secrete
Infected Autologous Cells
Allogenic Cells
Antibodies
required for
enhancement of
regulation of
Innate Immune Responses
Activated B cells


Soluble Mediators of the Immune System
include
Antibodies
Cytokines
Chemokines
Complement
that exist as
that include
that include
that is activated by either the
Isotypes
called
IgD IgM IgE IgA IgG
c- Kit Ligand
Colony Stimulating Factors
Interleukins 1 → 18 **
** IL-8 is a chemokine
Interferons α, β, γ
Transforming Growth Factor
Tumor Necrosis Factor
CXC family (e.g., Gro α,β,γ)
CC family (e.g., Rantes)
C family (e.g., lymphotaxin)
Alternative Pathway
Classical Pathway
that leads to the generation of
Proteolytic Fragments
which are effectors for, or enhance the function of
which are effectors for, or enhance the function of
which are effectors for, or enhance the function of
which are effectors for, or enhance the function of
Innate Immunity and Adaptive Immunity

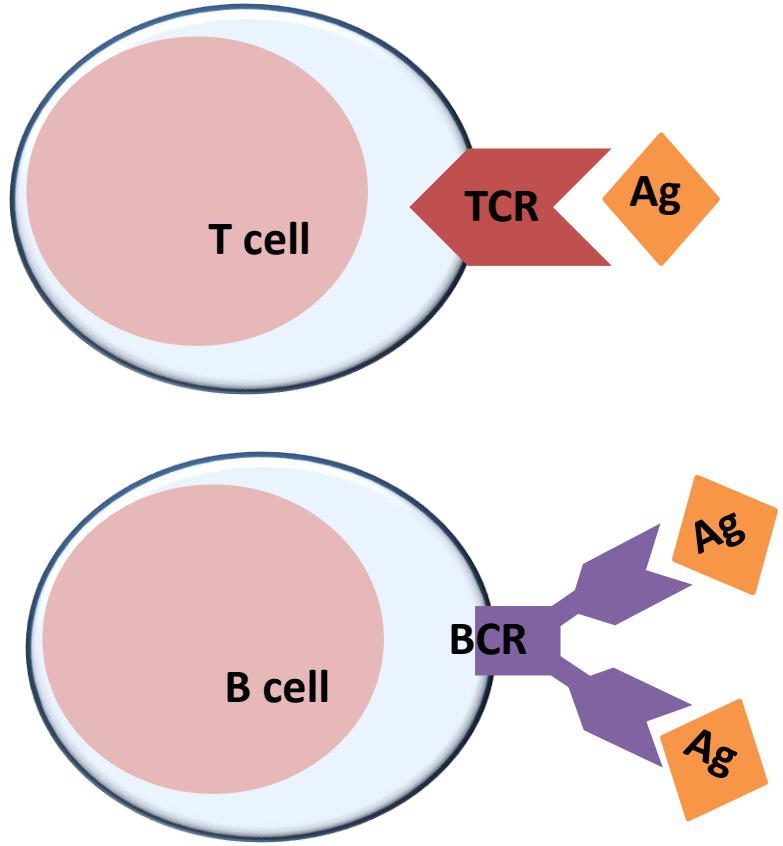
❑ Properties of Adaptive Immune Responses

- **Specificity; definition, what does it implies (lymphocyte repertoire) ? clonal selection hypothesis**
- **Diversity; definition, # of naive cells**
- **Memory; type of response & their mediators , & reasons for the 2nd**

Feature	Functional significance
Specificity	Ensures that distinct antigens elicit responses that target those antigens
Diversity	Enables immune system to respond to a large variety of antigens
Memory	Leads to rapid and 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

Specificity Of Adaptive Immune Response

- Resides with Ag R on T and B cells
- TCR and BCR – both specific for only ONE antigenic determinant
- TCR is monovalent
- BCR is divalent



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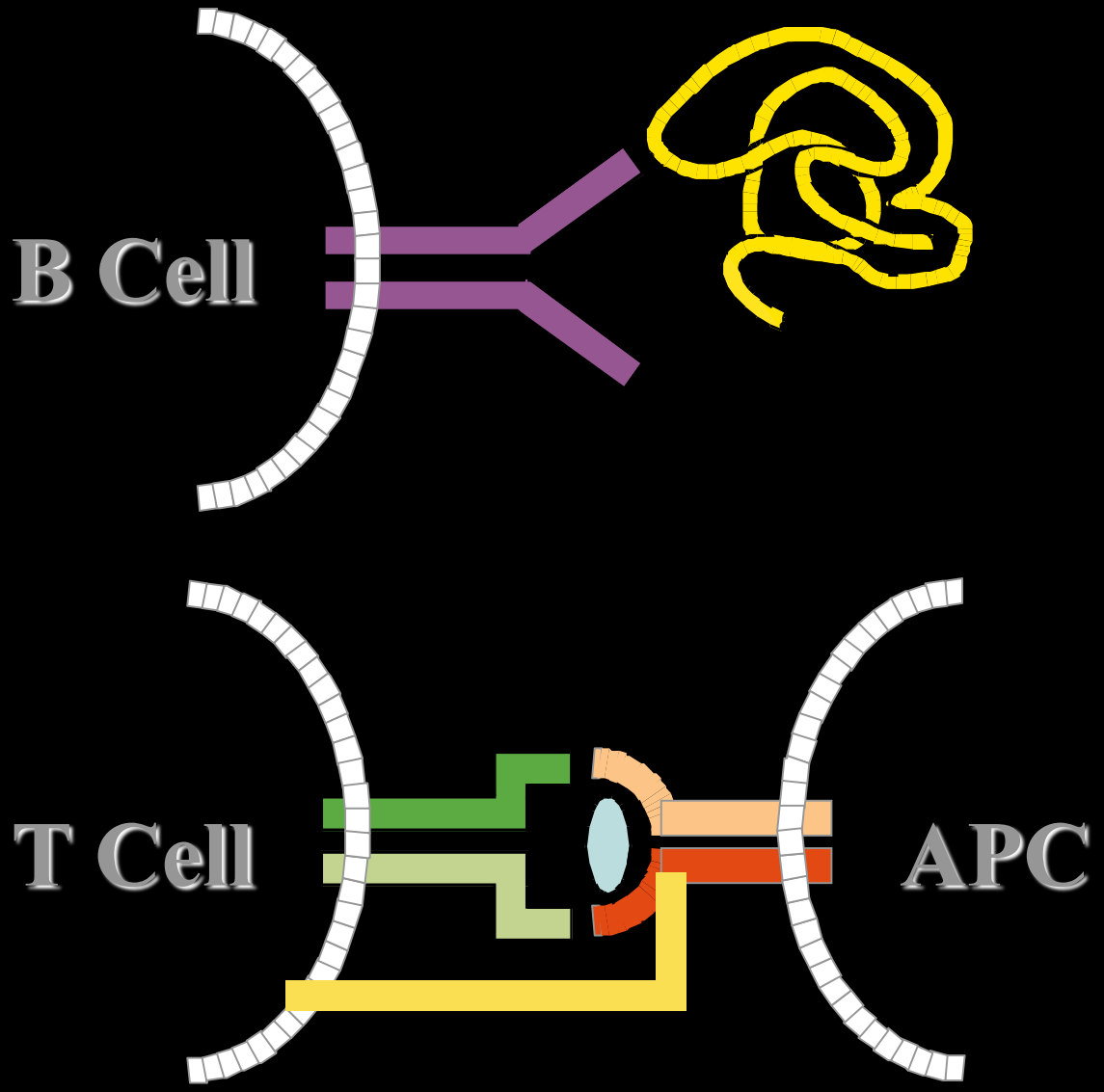
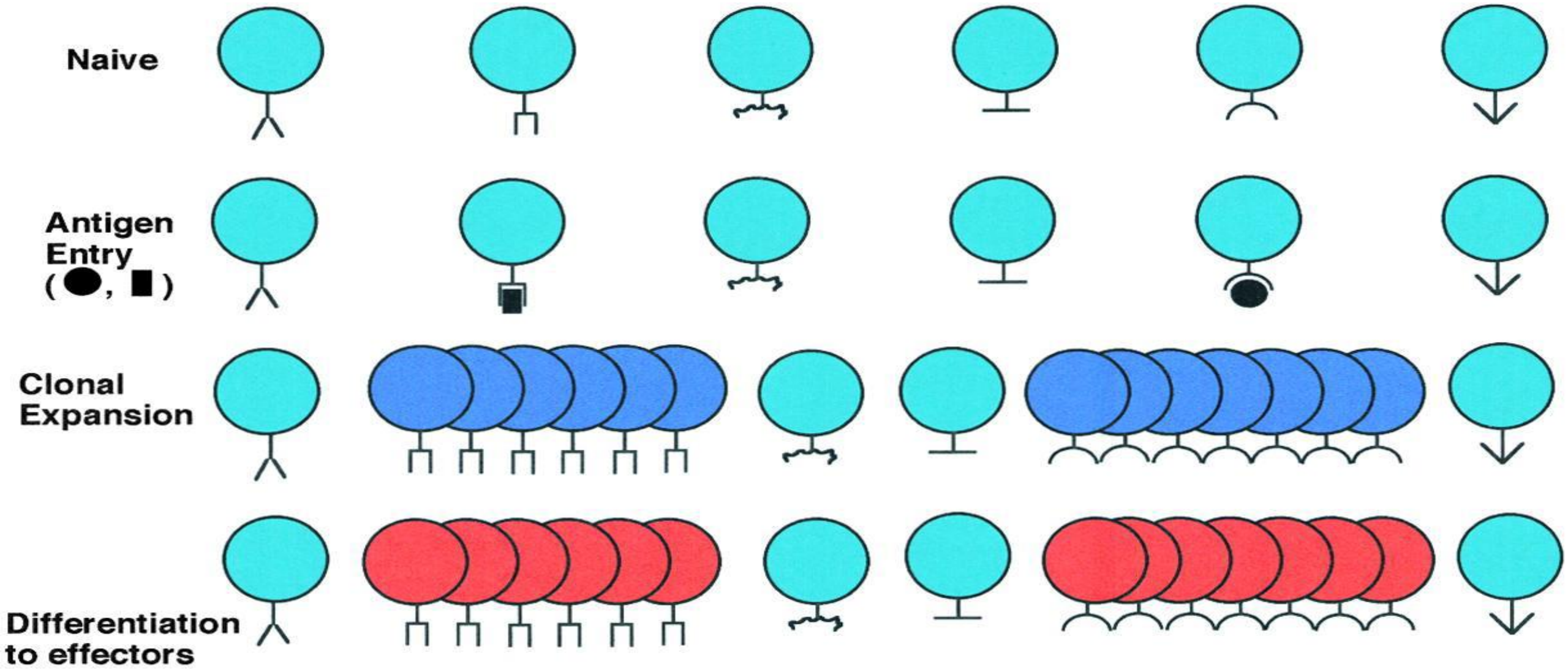
Contrast how B and T cells see antigen



Lymphocyte Repertoire

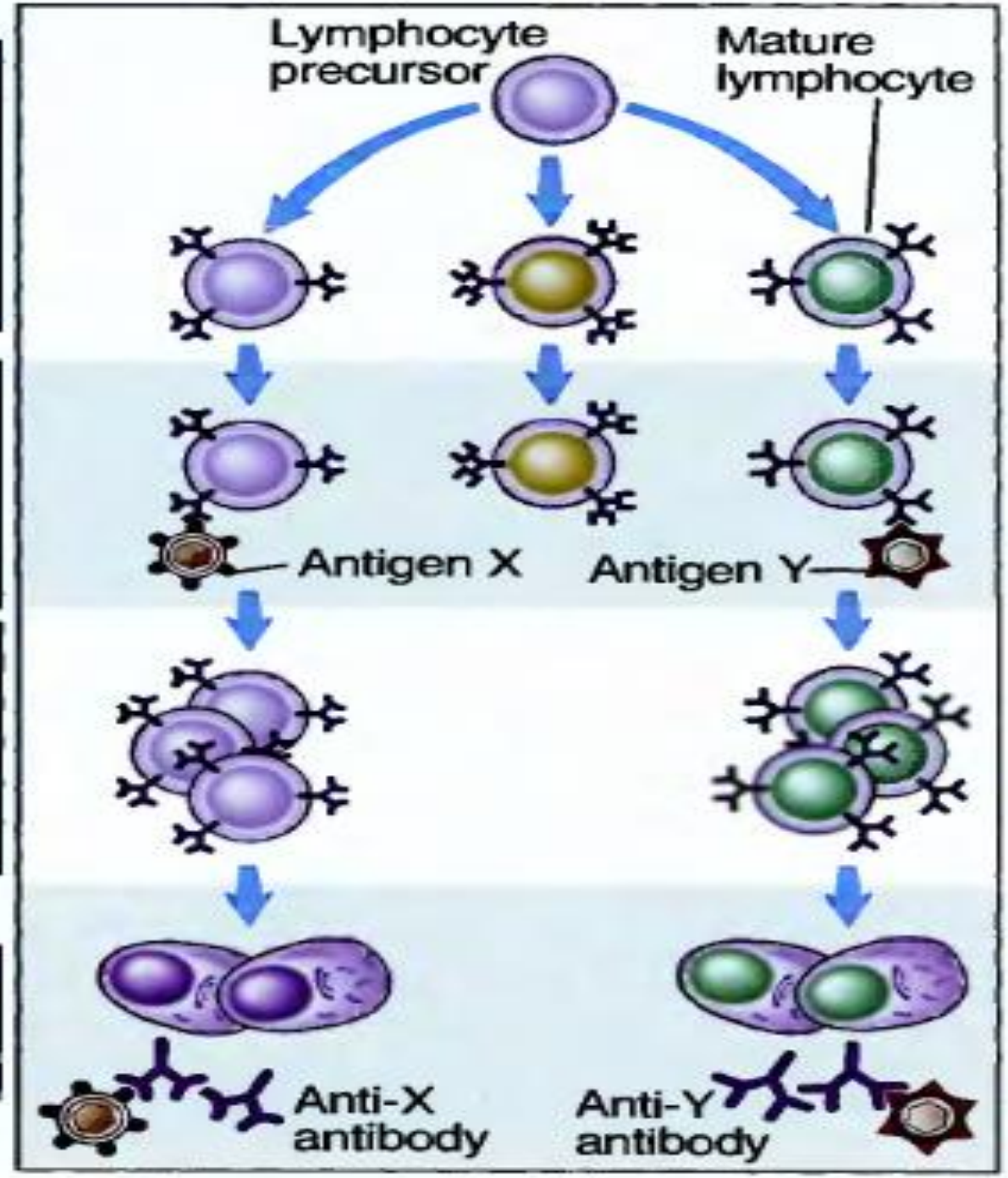


Lymphocyte clones mature in generative lymphoid organs, in the absence of antigens

Clones of mature lymphocytes specific for diverse antigens enter lymphoid tissues

Antigen-specific clones are activated ("selected") by antigens

Antigen-specific immune responses occur

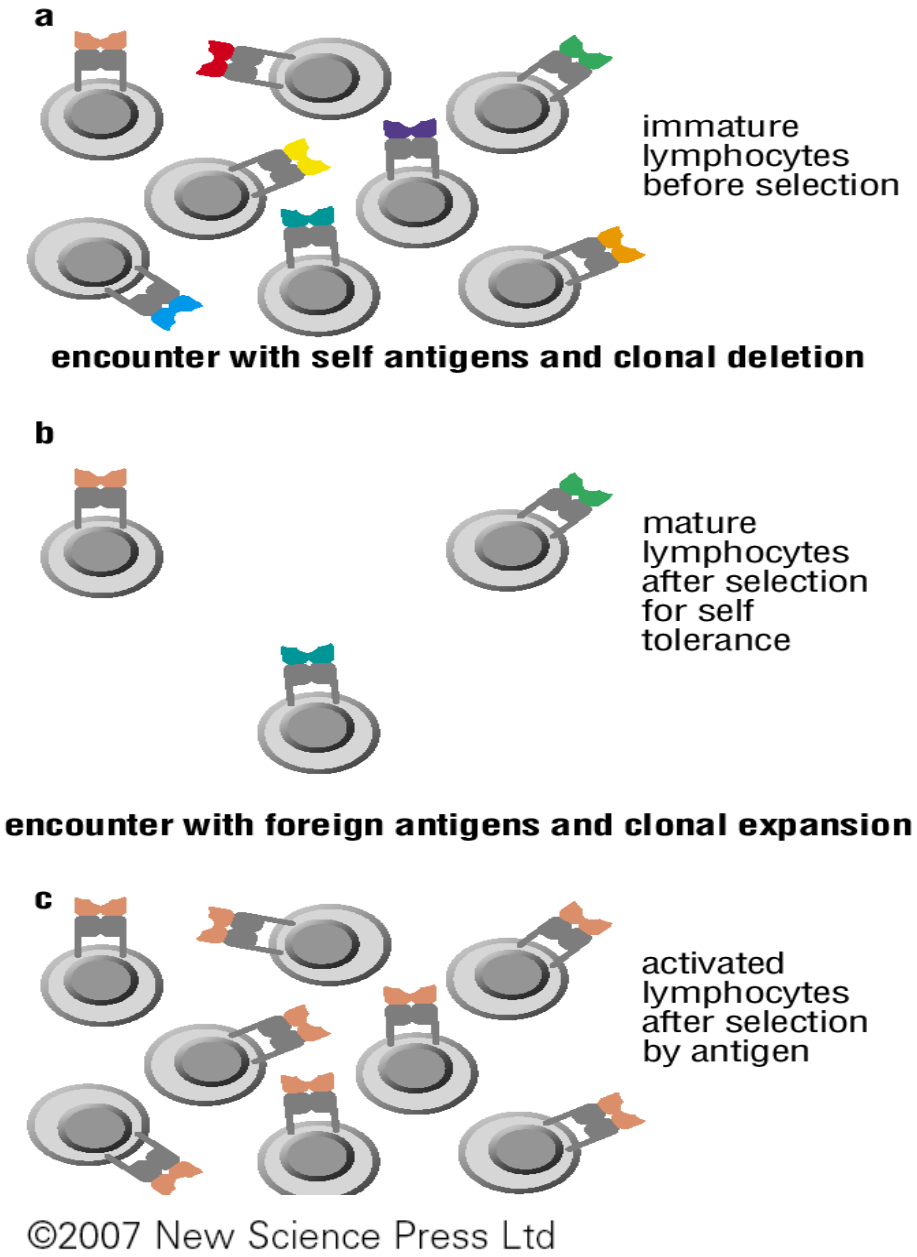


The Clonal Selection Hypothesis

Generation of lymphocytes of many specificities

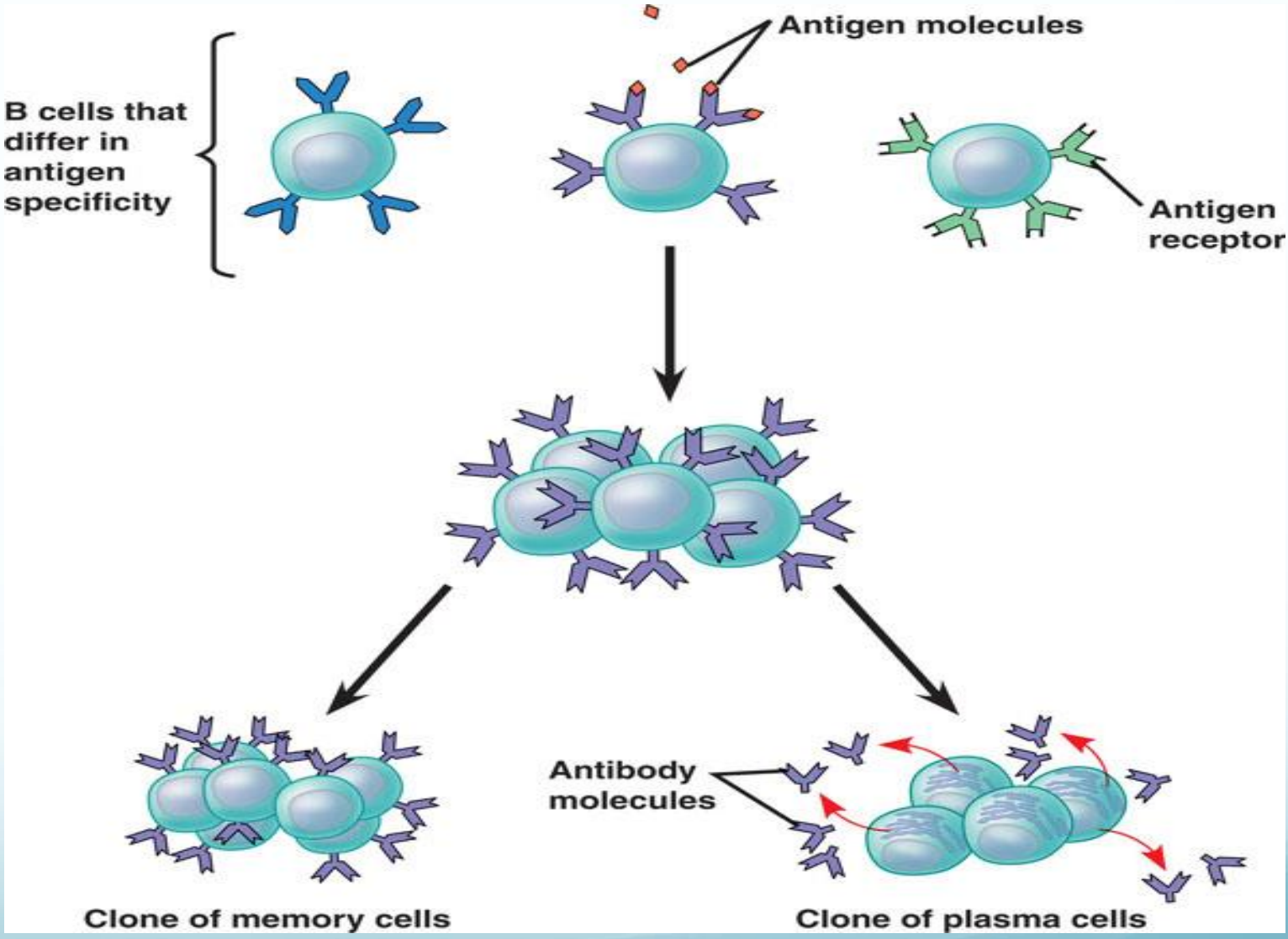
<u>Clonal deletion</u> to remove self-reactive lymphocytes

<u>Clonal selection</u> to expand pathogen-reactive lymphocytes during an immune response

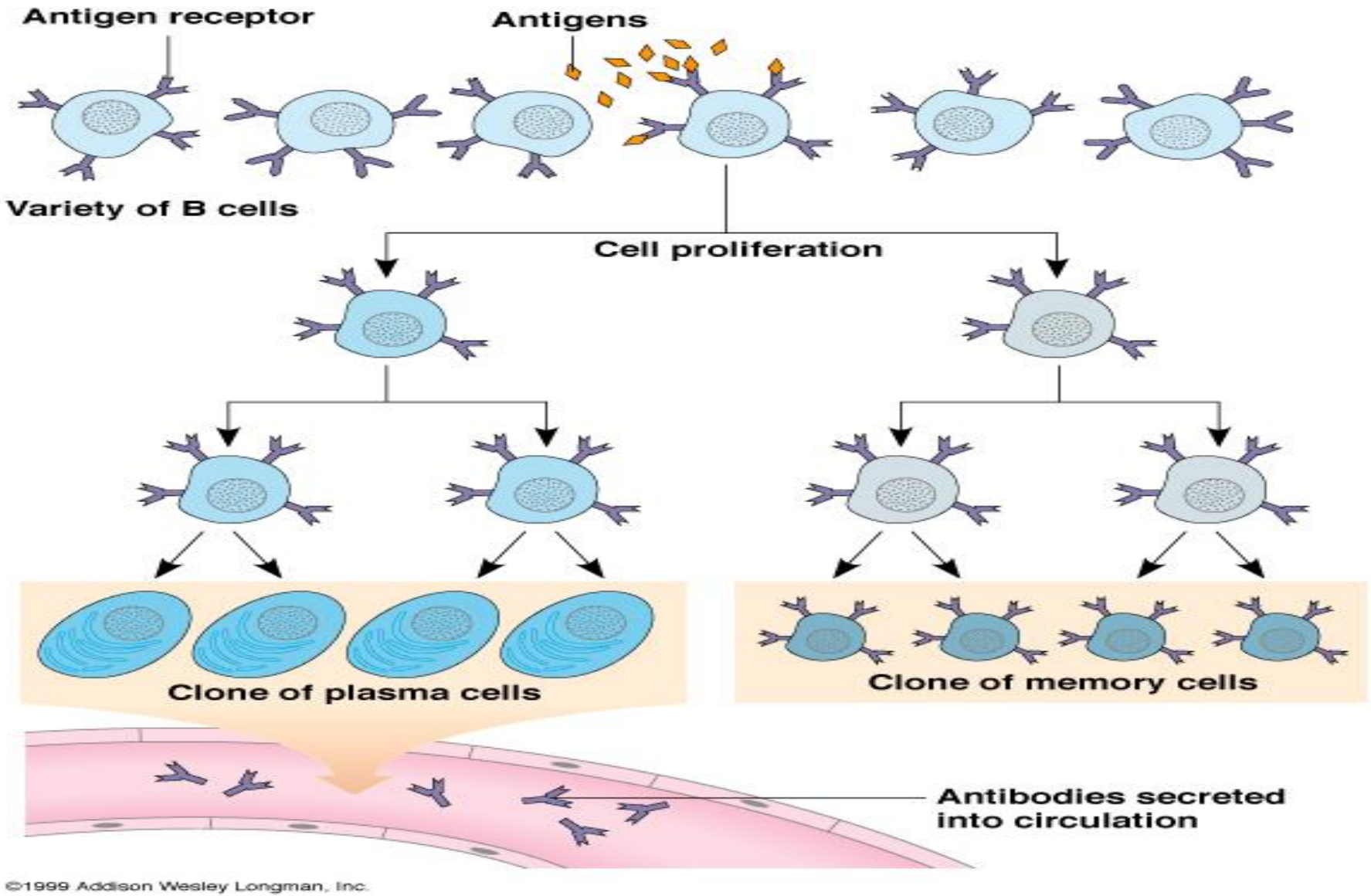


Clonal Selection of Lymphocytes

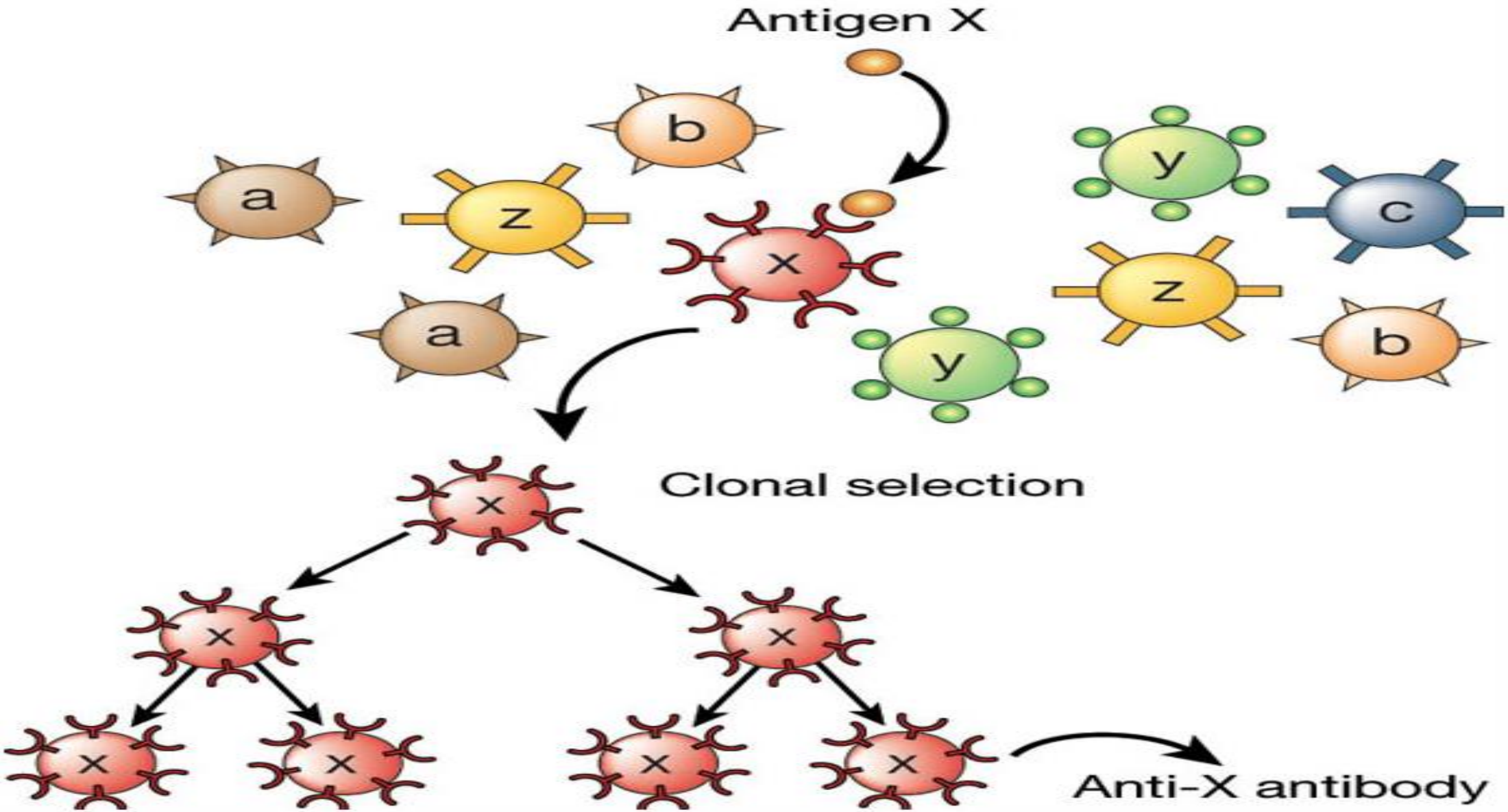
- Clonal selection of B cells generates a clone of short-lived activated **effector cells** and a clone of long-lived **memory cells**.
  - Effector cells produce **antibodies** for a specific antigen.



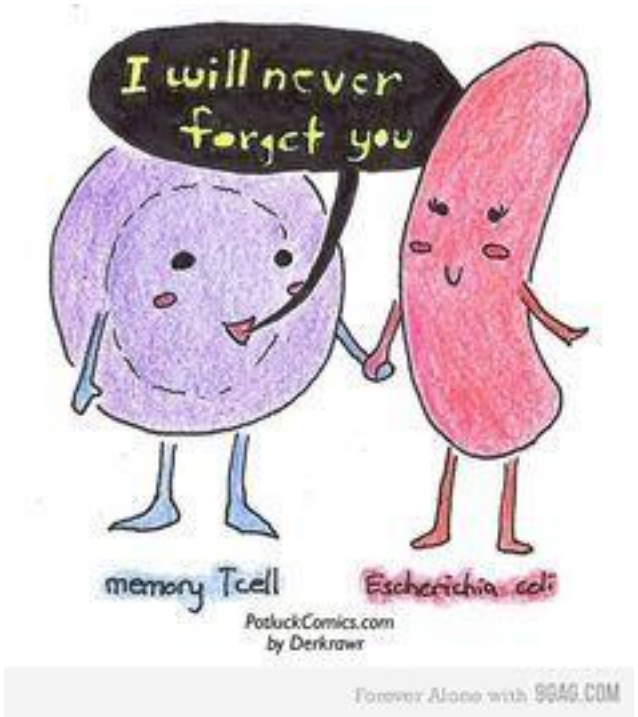
Clonal Selection of B Cells is Due to Antigenic Stimulation

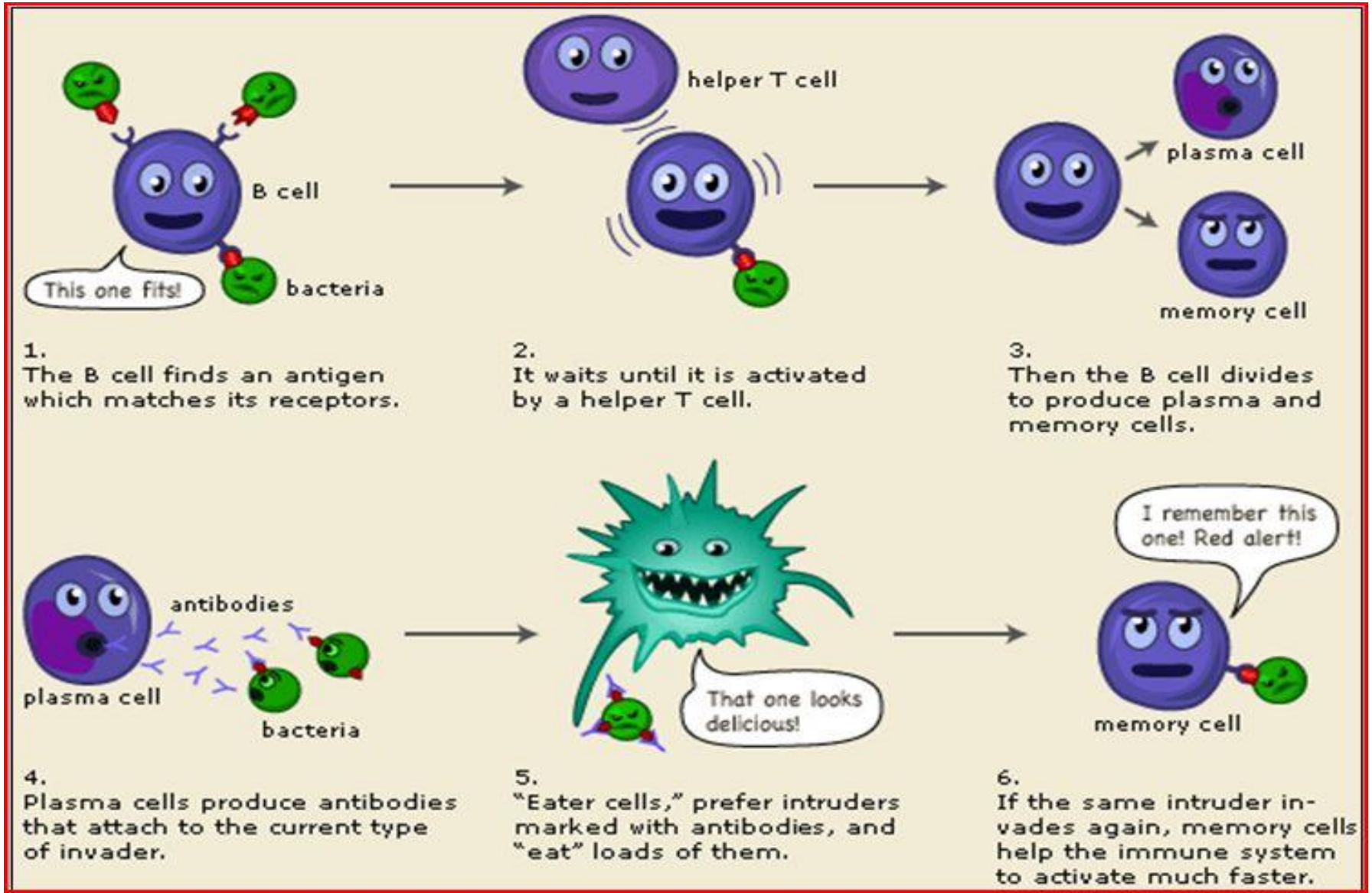


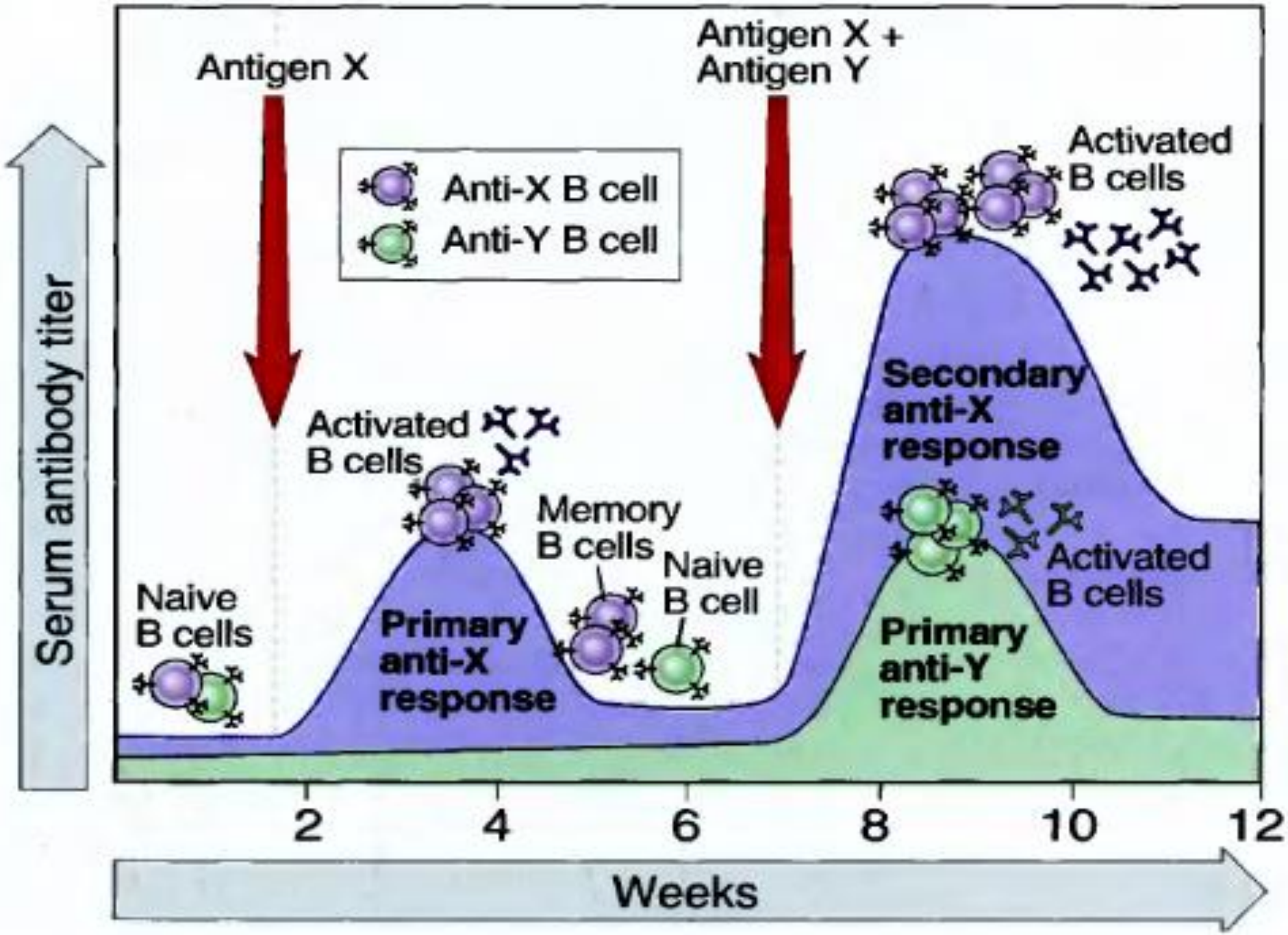
Diversity of Lymphocyte



Memory Of Adaptive Immunity

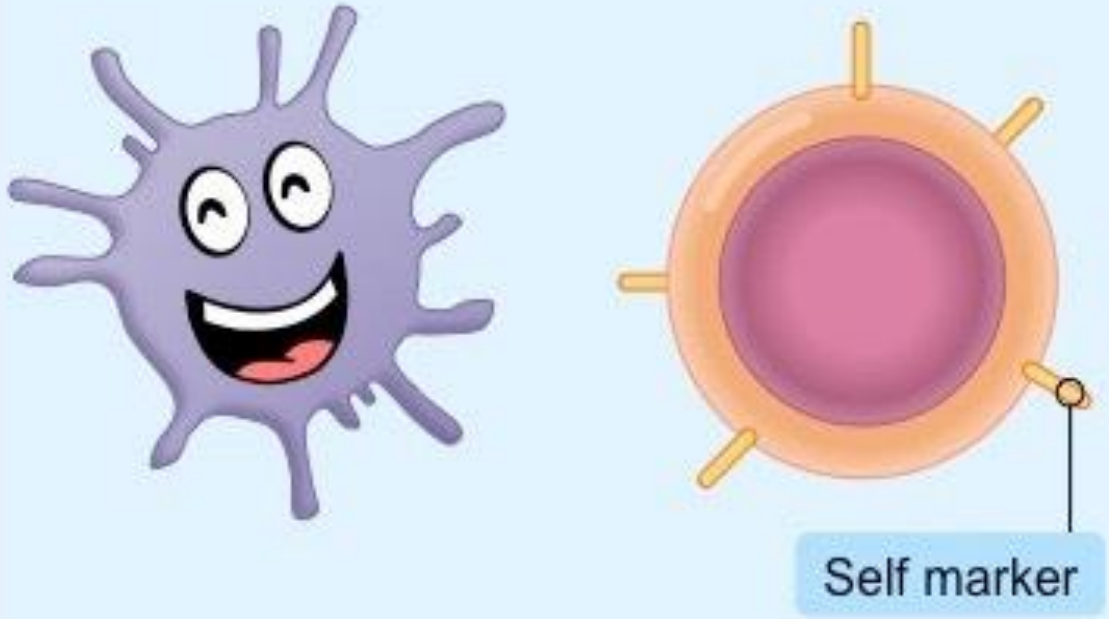





Antigen X
Antigen X +
Antigen Y
Anti-X B cell
Anti-Y B cell
Activated
B cells
Secondary
anti-X
response
Activated
B cells
Memory
B cells
Naive
B cell
Naive
B cells
Primary
anti-X
response
Activated
B cells
Primary
anti-Y
response
Serum antibody titer
2
4
6
8
10
12
Weeks

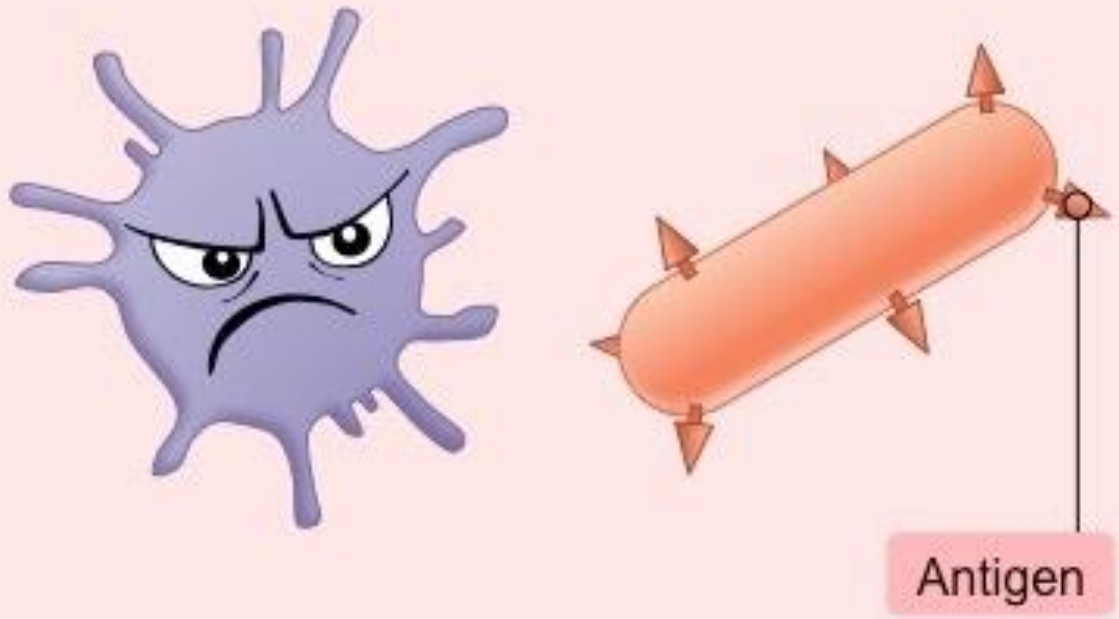
Immunological Tolerance

IDENTIFYING SELF

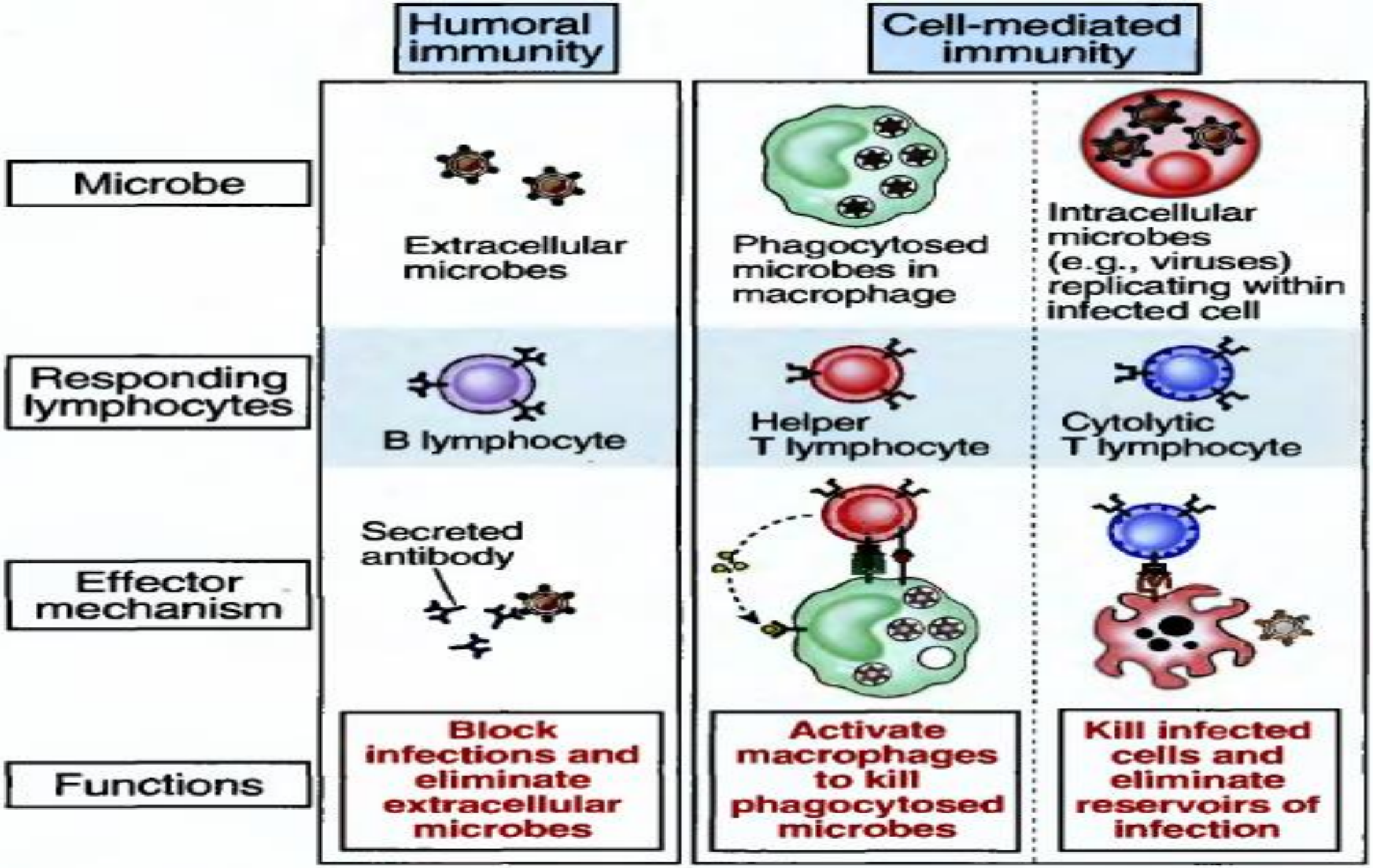


A **self marker** (MHC) labels the body's cells as a *'friend'* and are tolerated by the immune system

IDENTIFYING NON-SELF



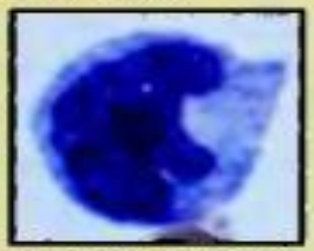
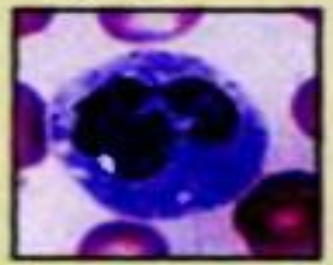
An **antigen** is a molecule that the immune system recognises as foreign (non-self) and treats as a *'foe'*

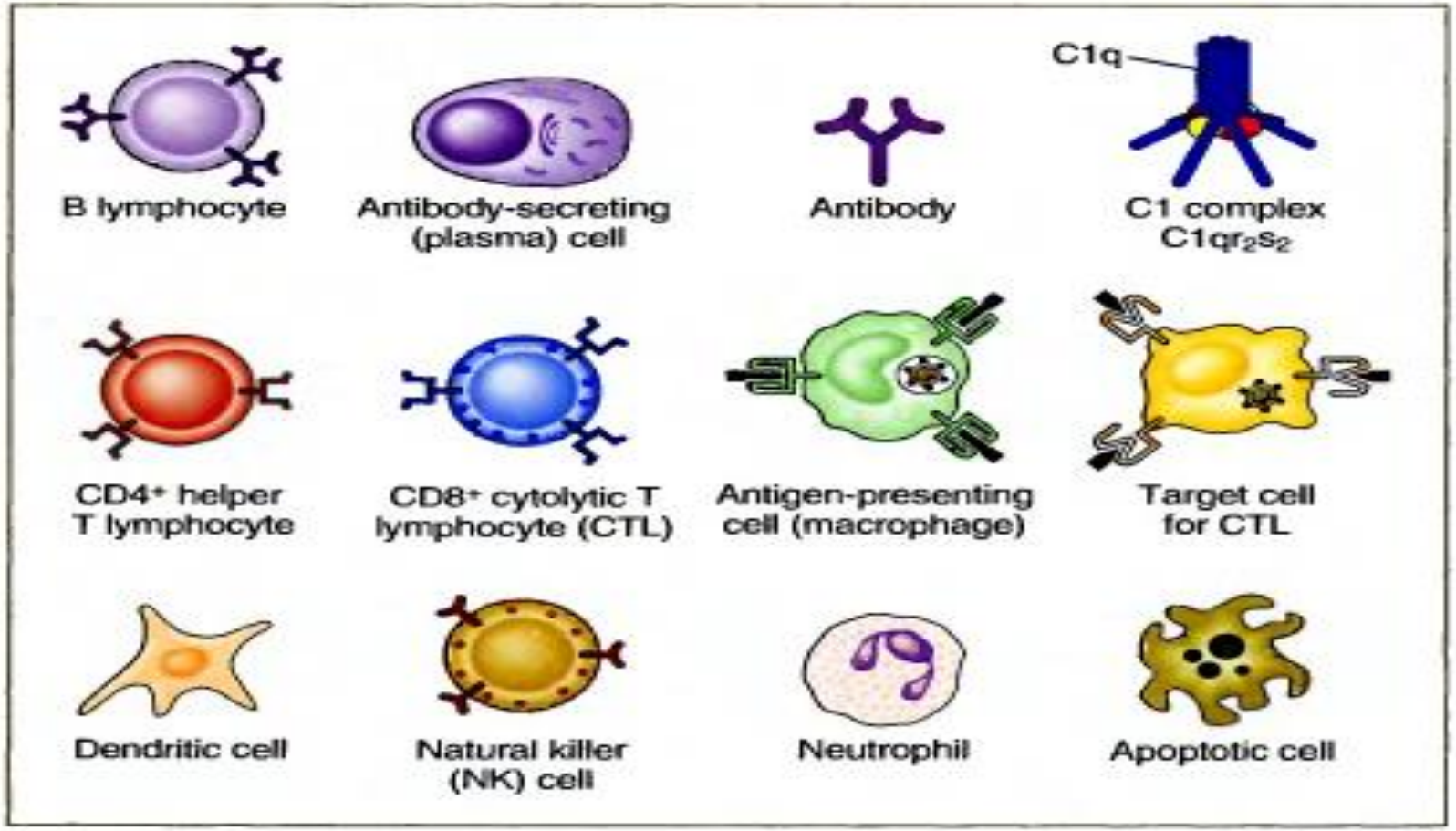

Humoral immunity
Cell-mediated immunity
Microbe
Responding lymphocytes
Effector mechanism
Functions
Extracellular microbes
Phagocytosed microbes in macrophage
Intracellular microbes (e.g., viruses) replicating within infected cell
B lymphocyte
Helper T lymphocyte
Cytolytic T lymphocyte
Secreted antibody
Block infections and eliminate extracellular microbes
Activate macrophages to kill phagocytosed microbes
Kill infected cells and eliminate reservoirs of infection

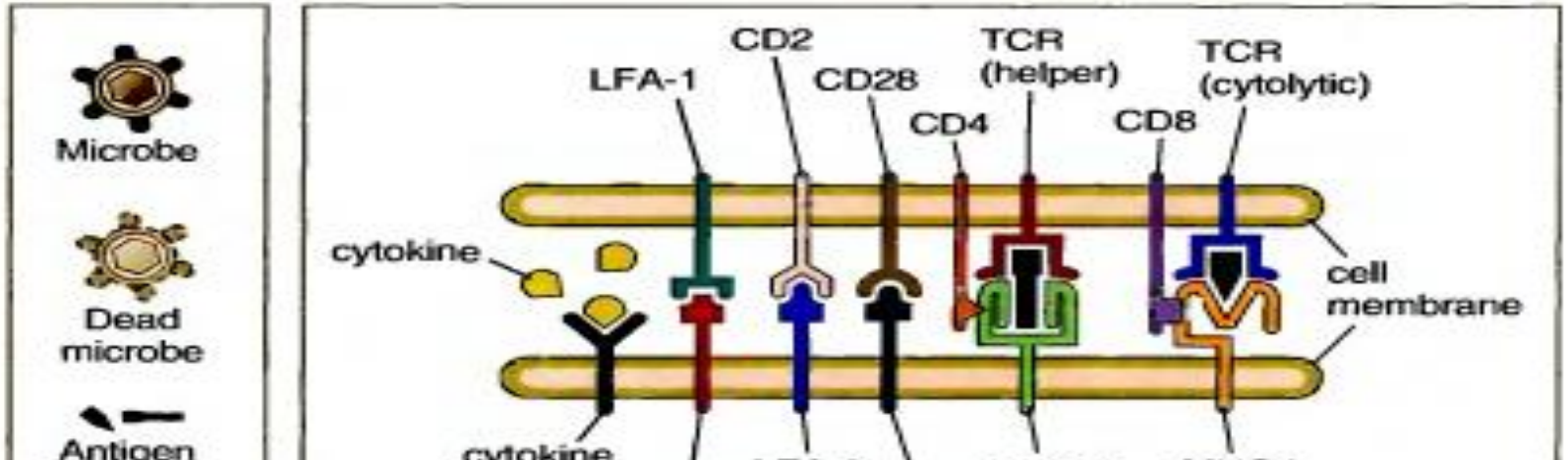
Effector Activity Against Pathogens

	Cell-mediated immunity		Humoral immunity
Typical pathogens	Vaccinia virus Influenza virus Rabies virus *Listeria*	*Mycobacterium tuberculosis* *Mycobacterium leprae* *Leishmania donovani* *Pneumocystis carinii*	*Clostridium tetani* *Staphylococcus aureus* *Streptococcus pneumoniae* Polio virus *Pneumocystis carinii*
Location	Cytosol	Macrophage vesicles	Extracellular fluid
Effector T cell	Cytotoxic CD8 T cell	T_H1 cell	T_H1/T_H2 cell
Antigen recognition	Peptide:MHC class I on infected cell	Peptide:MHC class II on infected macrophage	Peptide:MHC class II on specific B cell
Effector action	Killing of infected cell	Activation of infected macrophages	Activation of specific B cell to make antibody

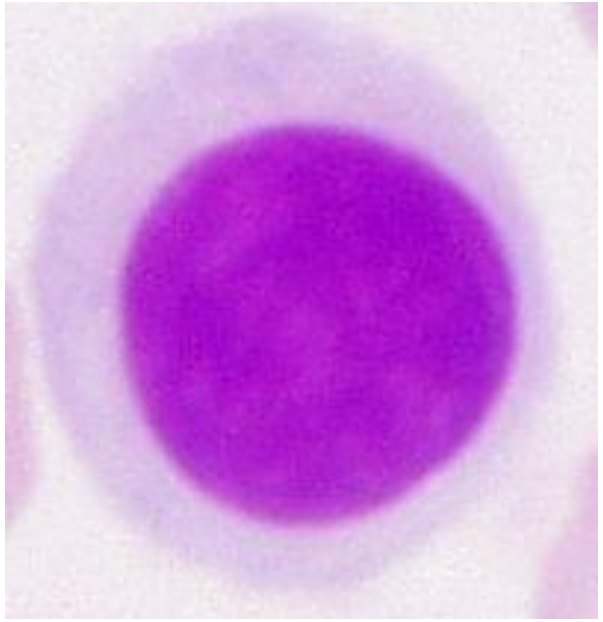
Cells Of Immune System

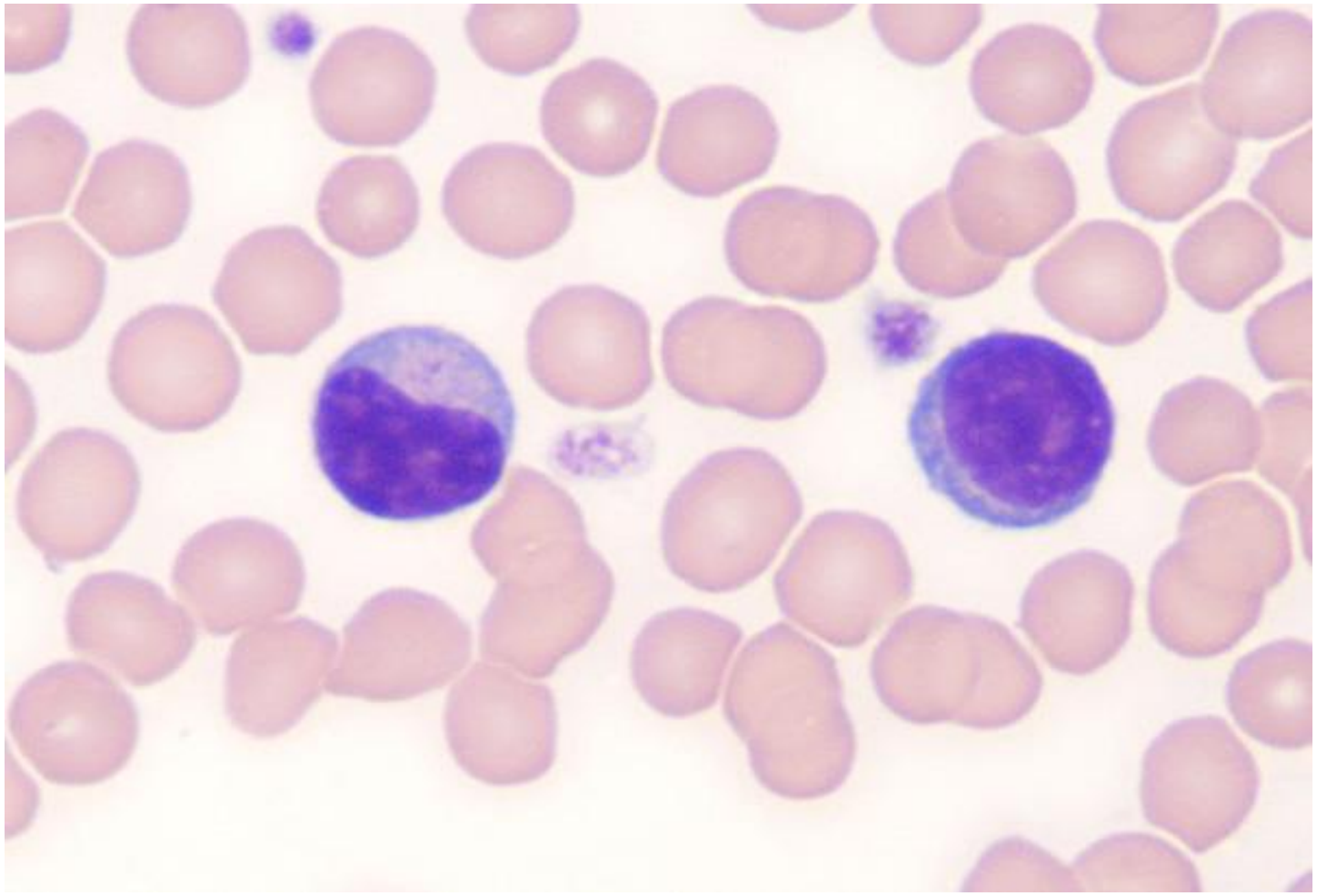
Cell type	Principal function(s)
Lymphocytes: B lymphocytes; T lymphocytes; natural killer cells  *Blood lymphocyte*	Specific recognition of antigens B lymphocytes: mediators of humoral immunity T lymphocytes: mediators of cell-mediated immunity Natural killer cells: cells of innate immunity
Antigen-presenting cells: dendritic cells; macrophages; follicular dendritic cells  *Dendritic cell*  *Blood monocyte*	Capture of antigens for display to lymphocytes: Dendritic cells: initiation of T cell responses Macrophages: initiation and effector phase of cell-mediated immunity Follicular dendritic cells: display of antigens to B lymphocytes in humoral immune responses
Effector cells: T lymphocytes; macrophages; granulocytes  *Neutrophil*	Elimination of antigens: T lymphocytes: helper T cells and cytolytic T lymphocytes Macrophages and monocytes: cells of the mononuclear phagocyte system Granulocytes: neutrophils, eosinophils

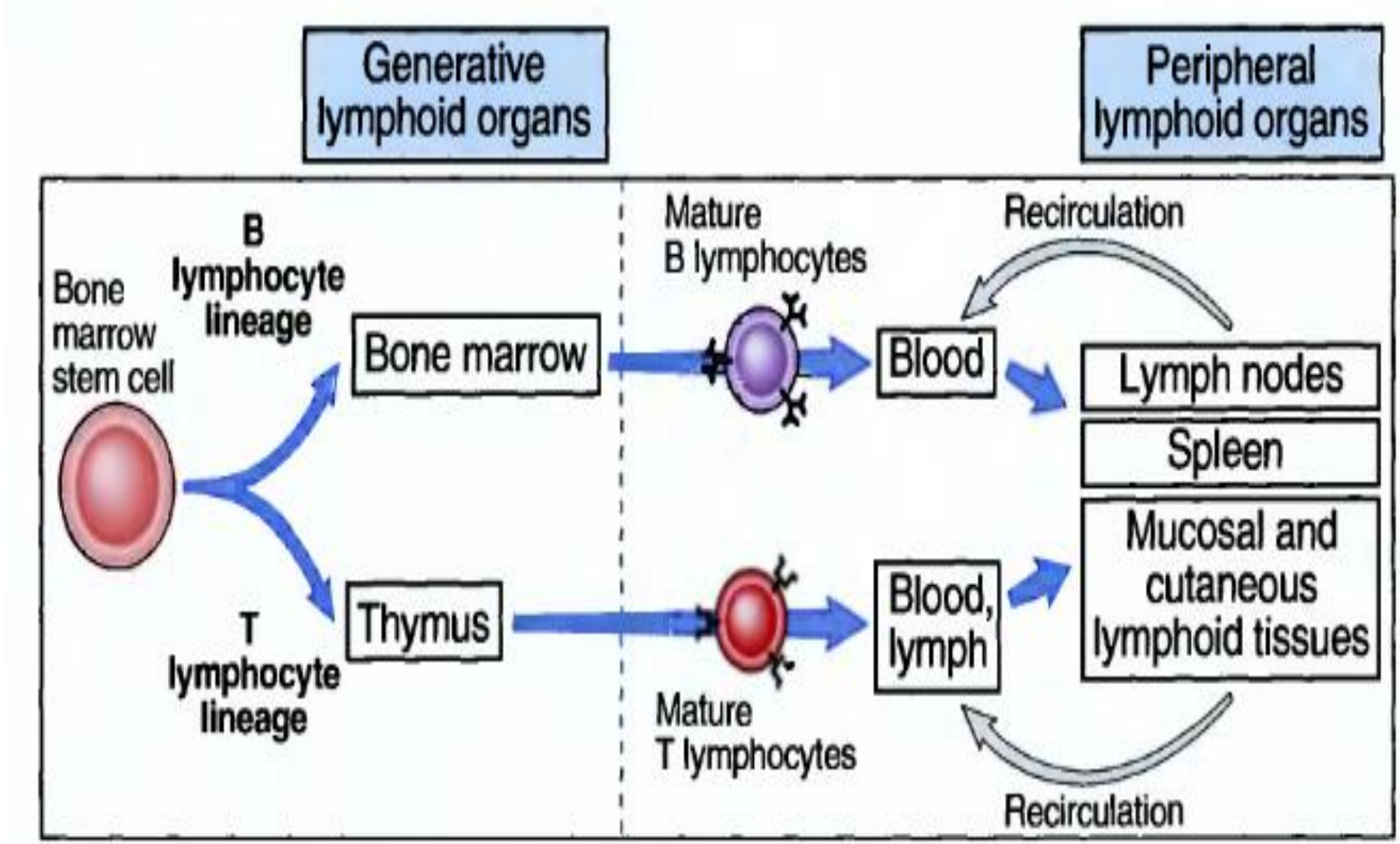

B lymphocyte
Antibody-secreting (plasma) cell
Antibody
C1q
C1 complex $C1qr_2s_2$
$CD4^+$ helper T lymphocyte
$CD8^+$ cytolytic T lymphocyte (CTL)
Antigen-presenting cell (macrophage)
Target cell for CTL
Dendritic cell
Natural killer (NK) cell
Neutrophil
Apoptotic cell


Microbe
Dead microbe
Antigen
LFA-1
CD2
CD28
CD4
TCR (helper)
CD8
TCR (cytolytic)
cytokine
cytokine
cell membrane

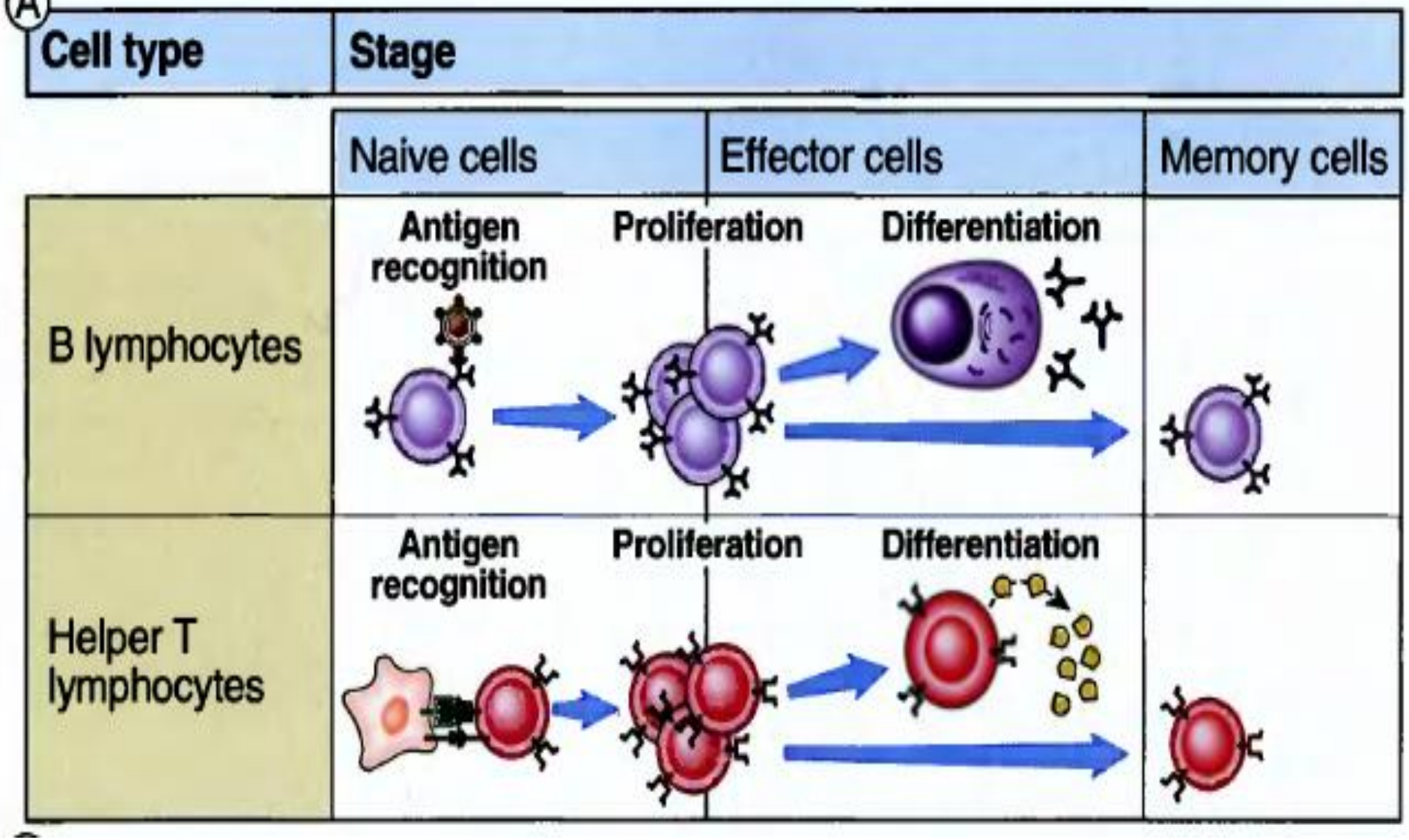
Lymphocyte





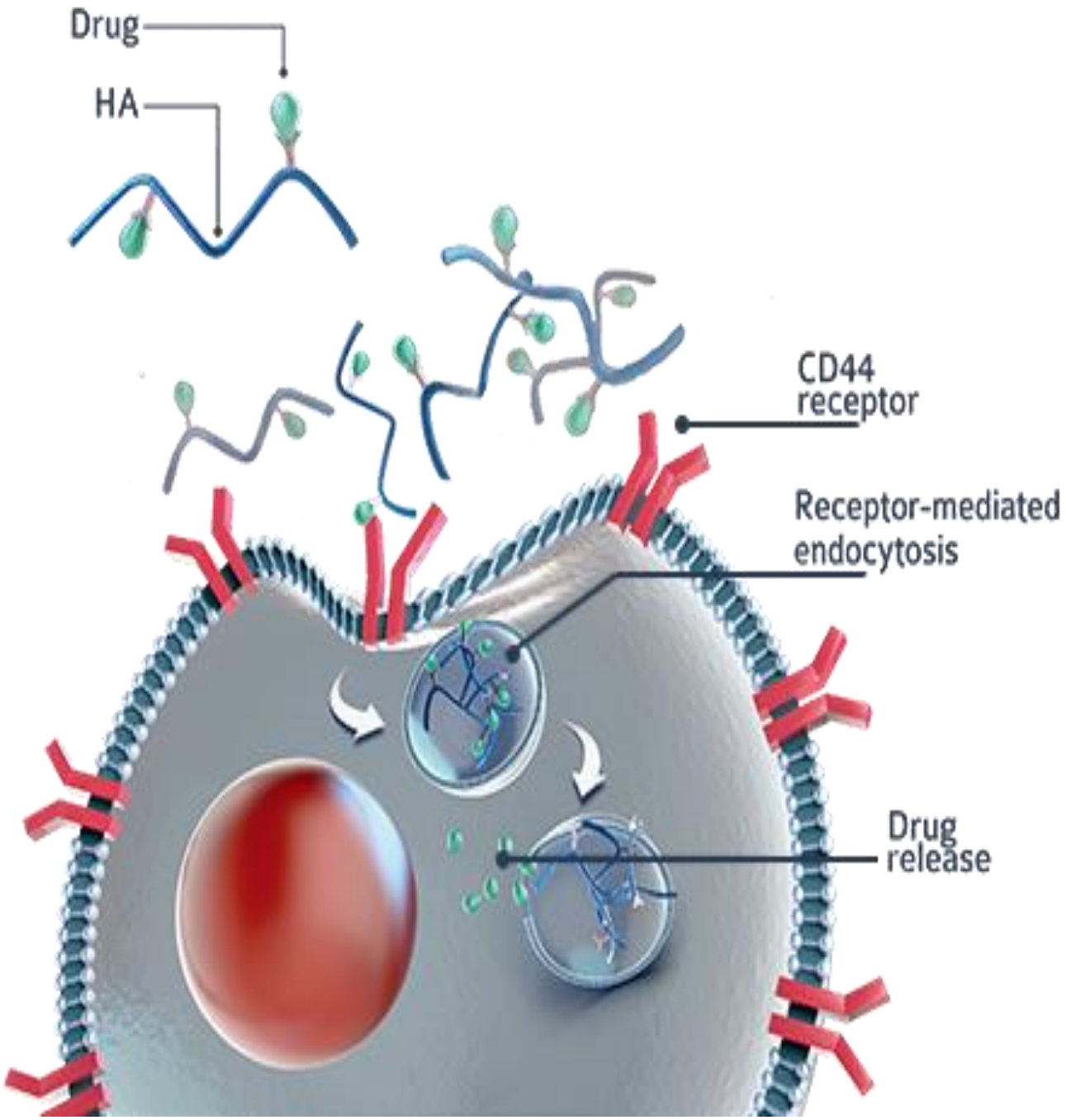

Generative lymphoid organs
Peripheral lymphoid organs
Bone marrow stem cell
B lymphocyte lineage
T lymphocyte lineage
Bone marrow
Thymus
Mature B lymphocytes
Mature T lymphocytes
Blood
Blood, lymph
Recirculation
Lymph nodes
Spleen
Mucosal and cutaneous lymphoid tissues
Recirculation

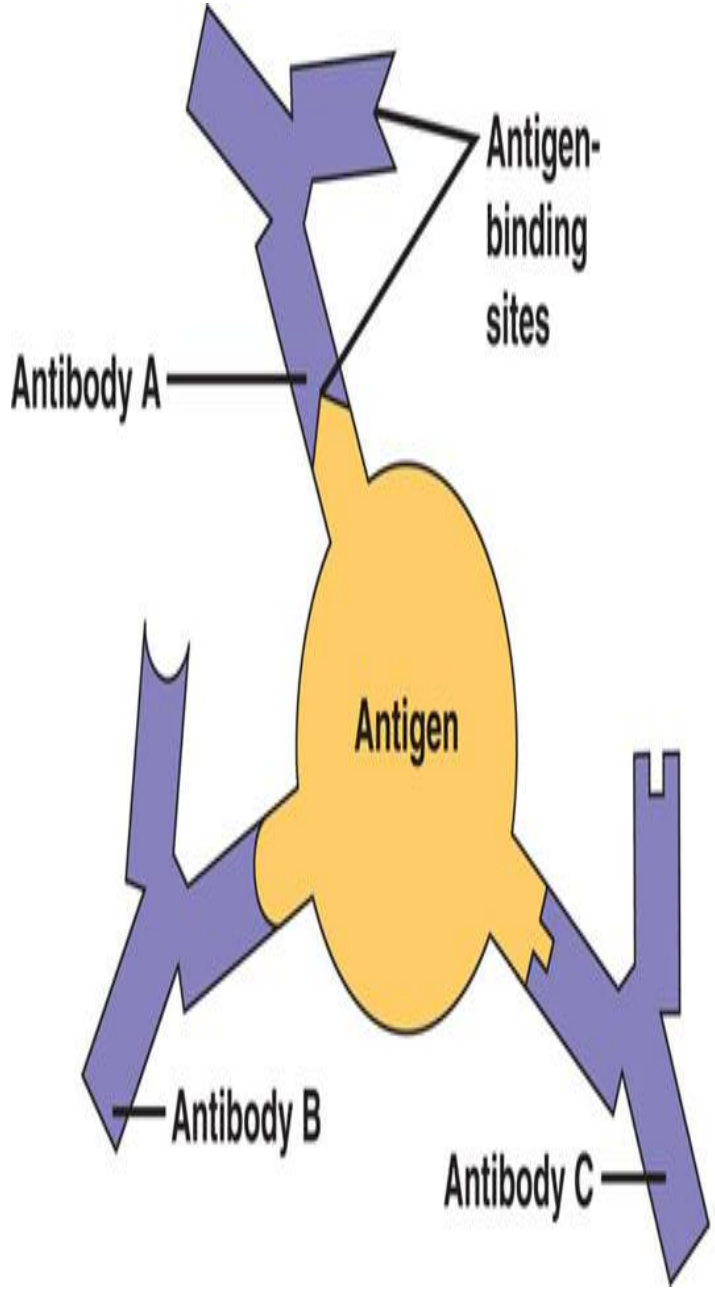
Ⓐ

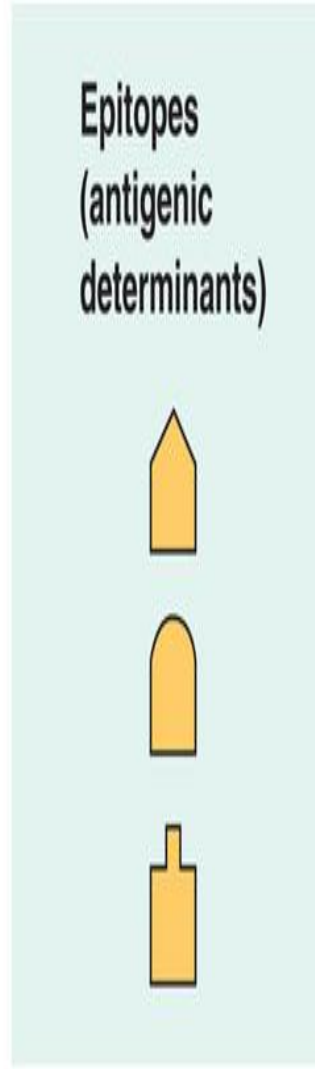

Cell type
Stage
Naive cells
Effector cells
Memory cells
B lymphocytes
Antigen recognition
Proliferation
Differentiation
Helper T lymphocytes
Antigen recognition
Proliferation
Differentiation

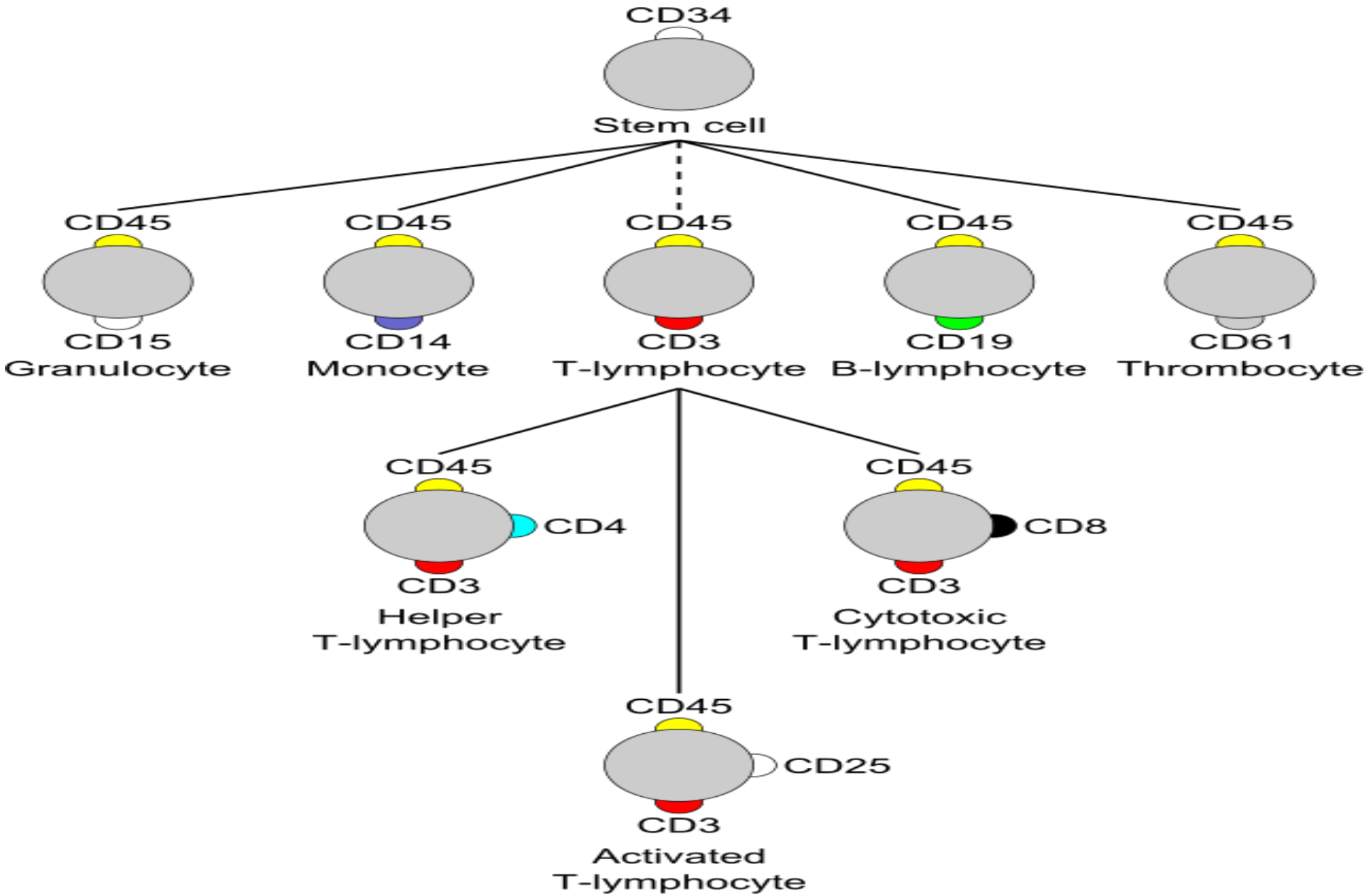
IMMUNO/27

Cluster of Differentiation (CD)


Drug
HA
CD44 receptor
Receptor-mediated endocytosis
Drug release


Antigen-binding sites
Antibody A
Antigen
Antibody B
Antibody C

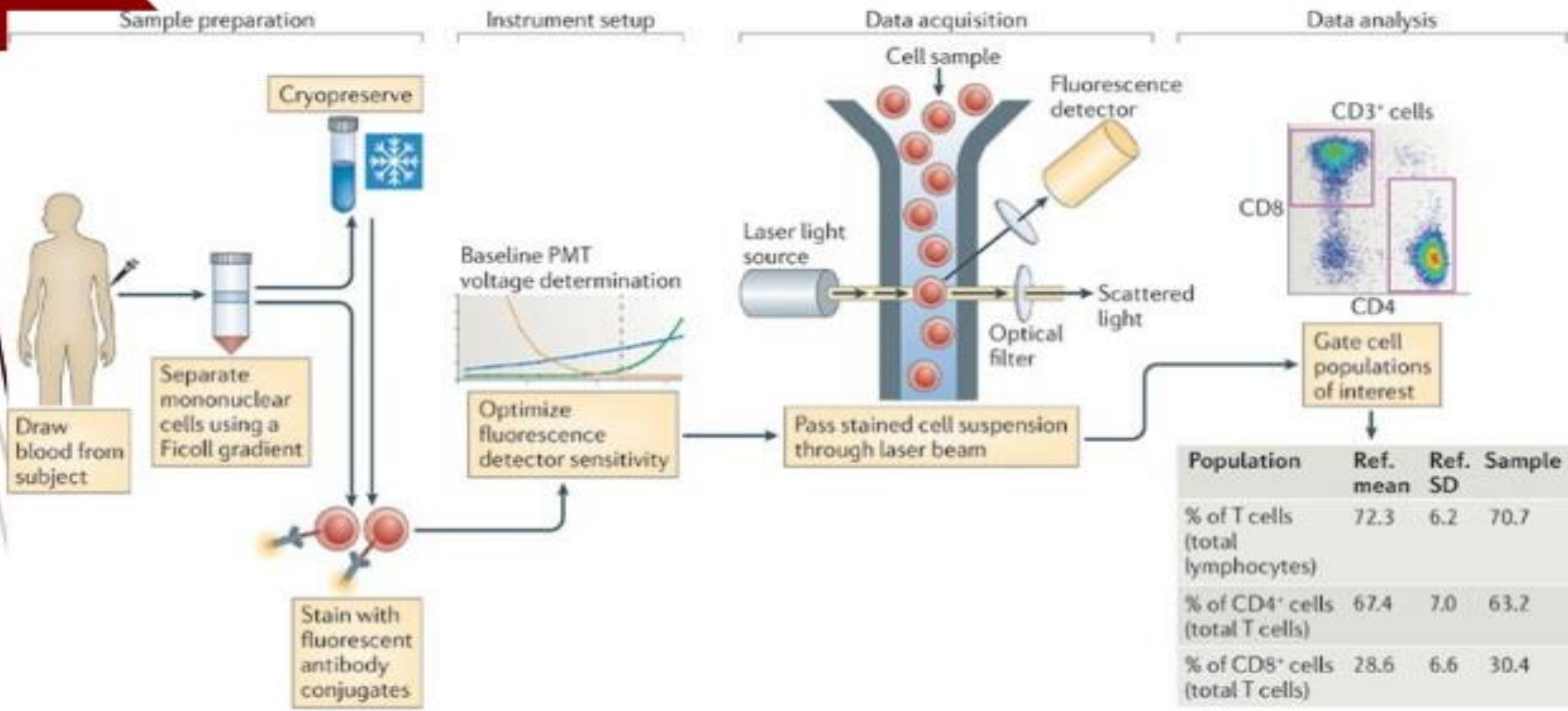

Epitopes (antigenic determinants)


CD34
Stem cell
CD45
CD15
Granulocyte
CD45
CD14
Monocyte
CD45
CD3
T-lymphocyte
CD45
CD19
B-lymphocyte
CD45
CD61
Thrombocyte
CD45
CD4
CD3
Helper
T-lymphocyte
CD45
CD8
CD3
Cytotoxic
T-lymphocyte
CD45
CD25
CD3
Activated
T-lymphocyte

Major distinguishing markers

Marker	B cell	CTL	T-helper
Antigen R	BCR (surface Ig)	TCR	TCR
CD3	--	+	+
CD4	--	--	+
CD8	--	+	--
CD19/ CD20	+	--	--
CD40	+	--	--

Flow cytometry



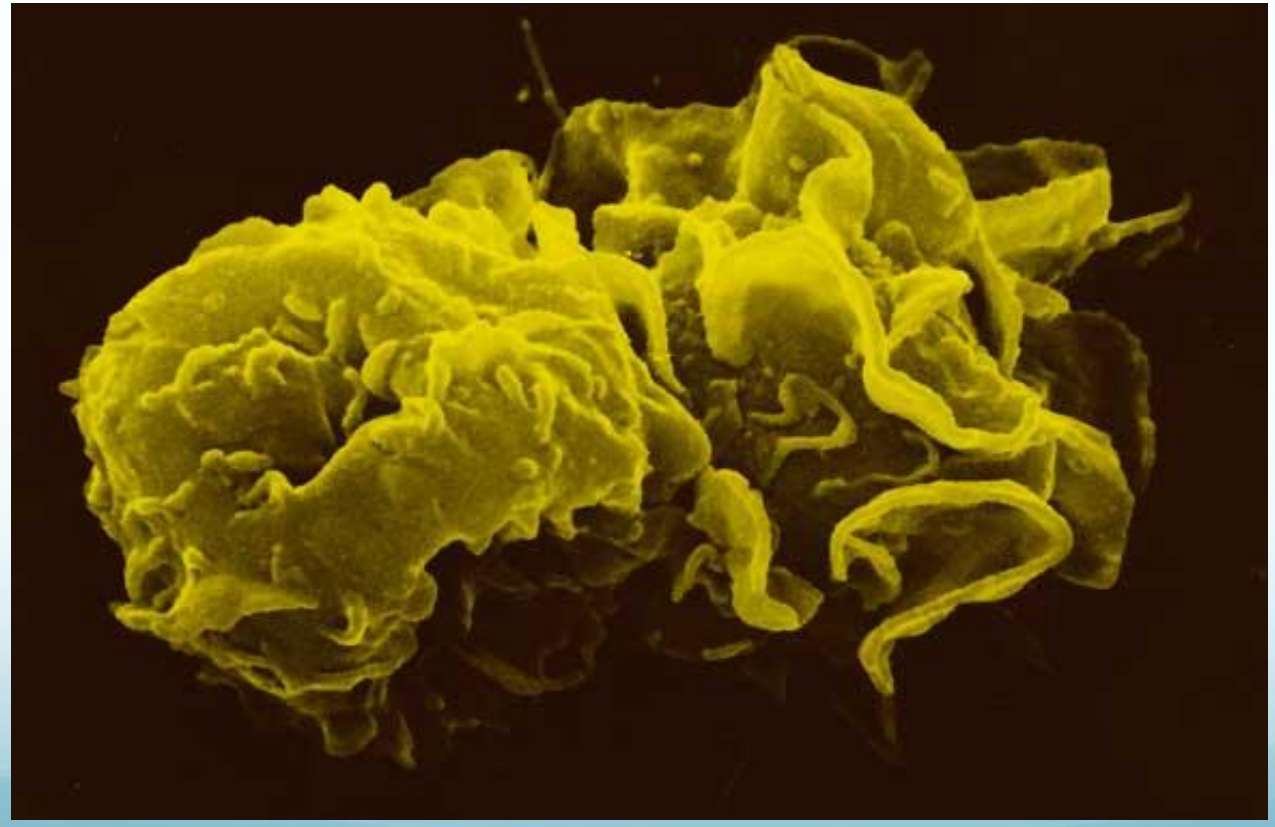
Population	Ref. mean	Ref. SD	Sample
% of T cells (total lymphocytes)	72.3	6.2	70.7
% of CD4⁺ cells (total T cells)	67.4	7.0	63.2
% of CD8⁺ cells (total T cells)	28.6	6.6	30.4

Antigen presenting cells

APCS

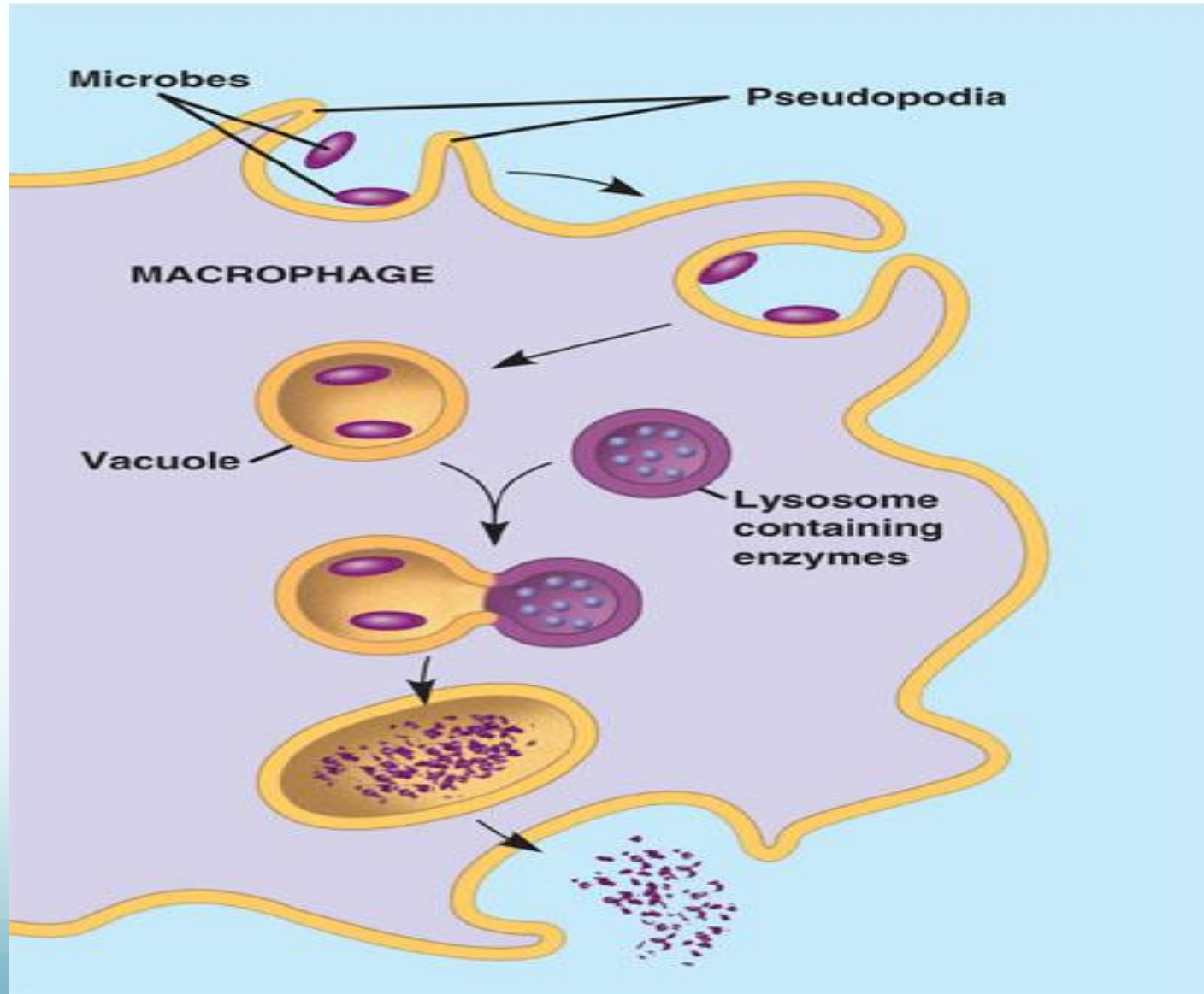
Phagocytic Cells

- Macrophages, a specific type of phagocyte, can be found migrating through the body.
  - Also found in various organs of the lymphatic system.

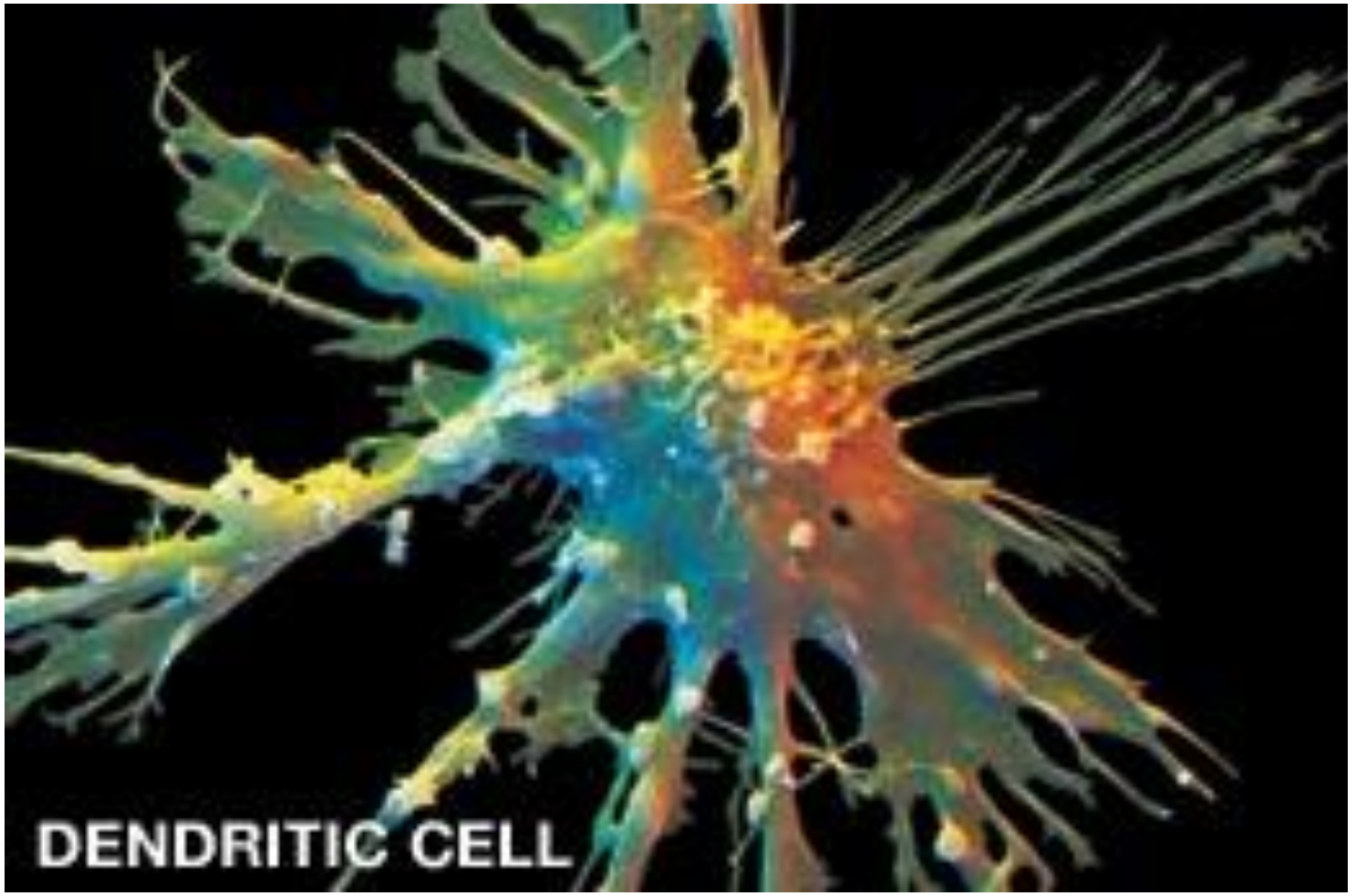


Phagocytic Cells

- Phagocytes attach to their prey via surface receptors and engulf them, forming a **vacuole** that fuses with a **lysosome**.

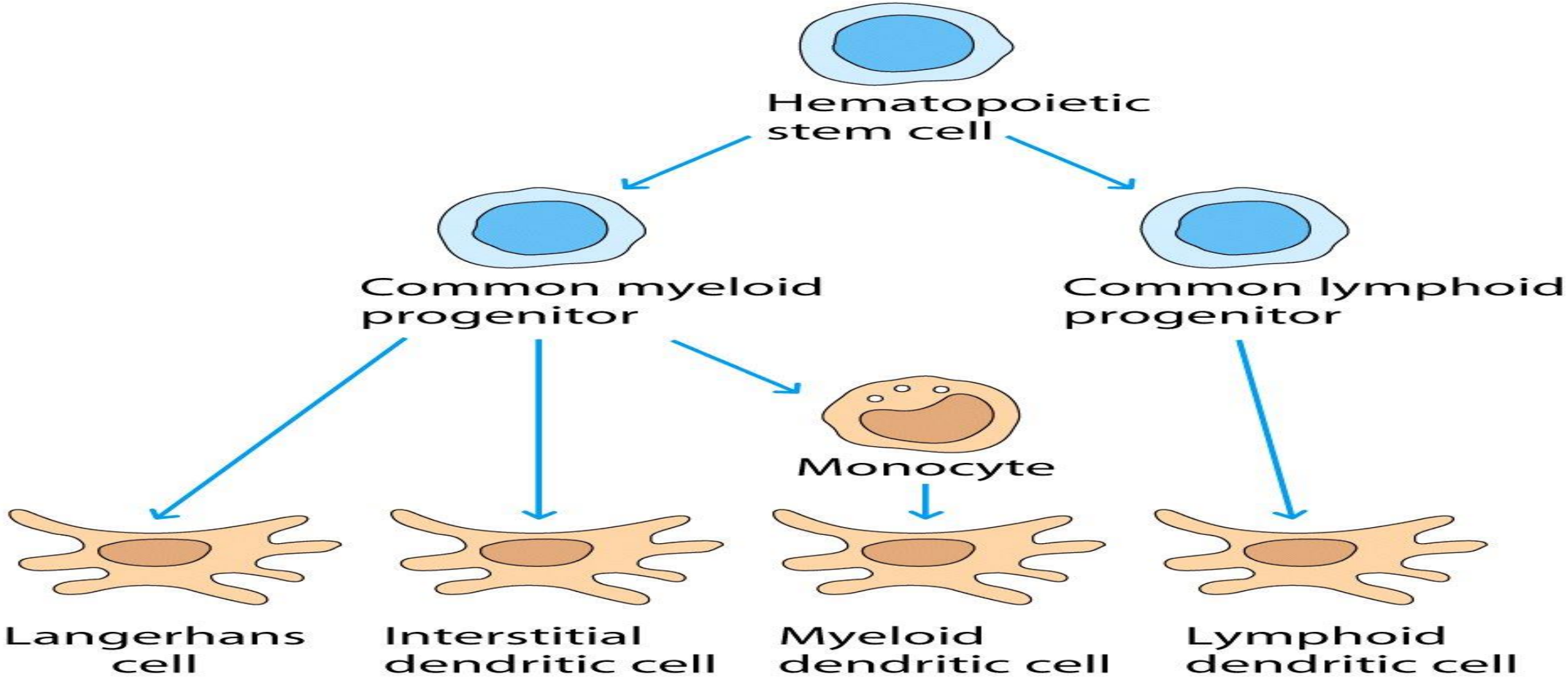


Dendritic Cells



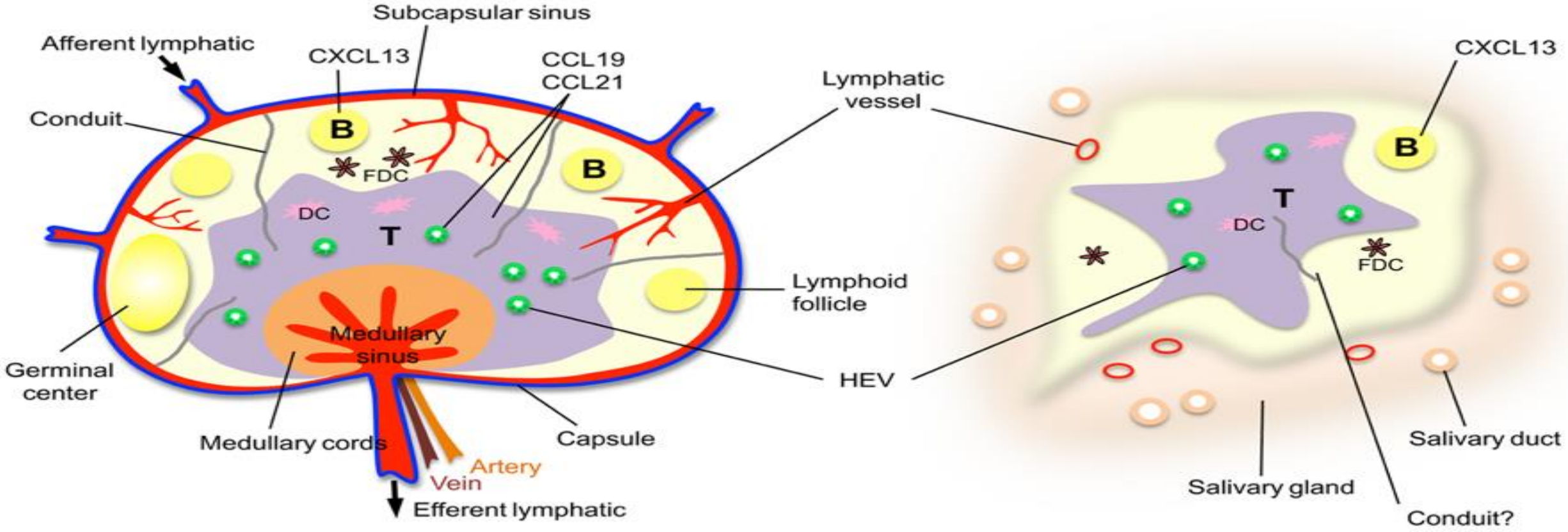
http:www.coleypharma.com

Developmental Pathway of DCs

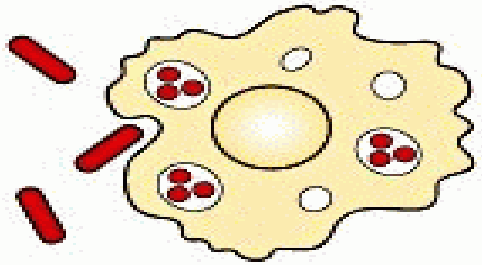
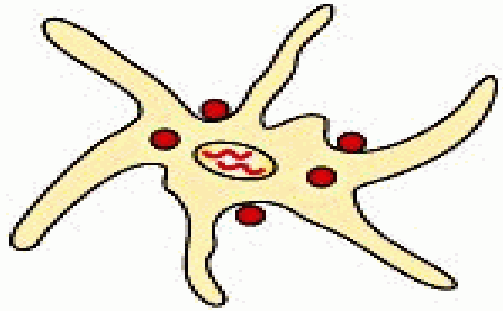
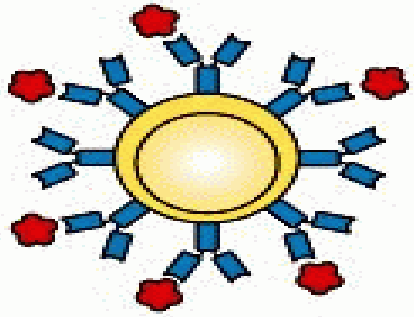


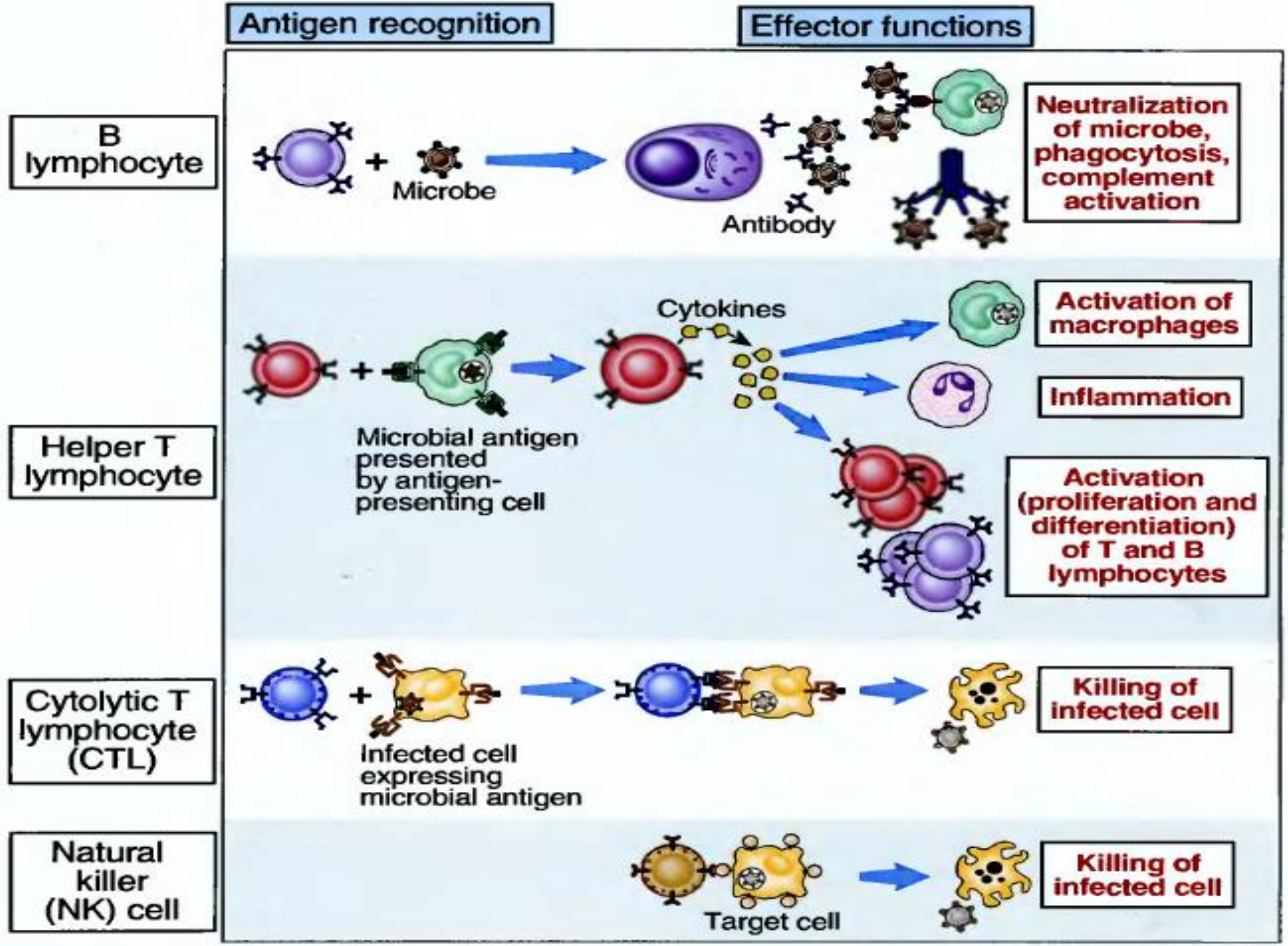
Follicular DCs

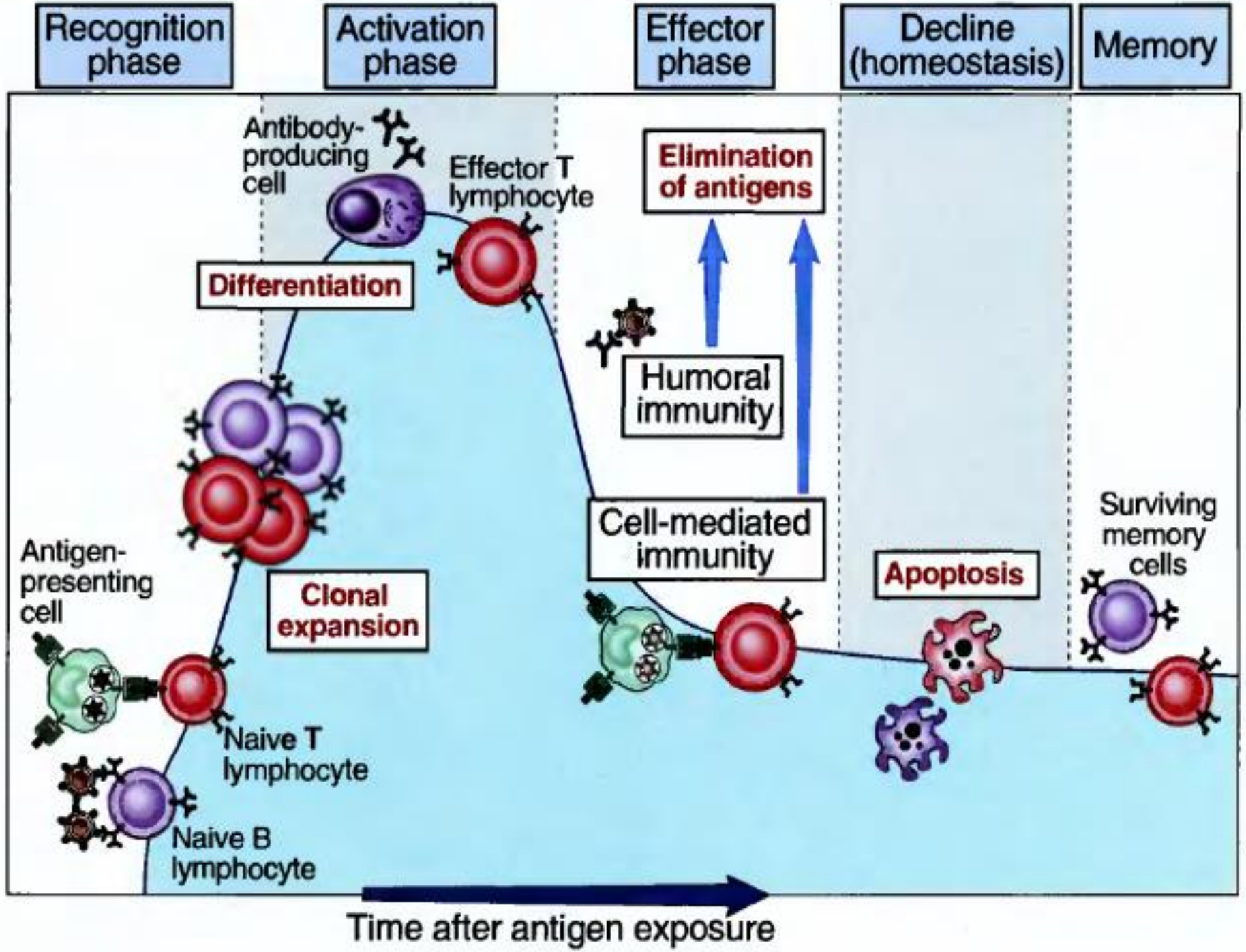
- **Do Not Express MHC II Molecules**
- **Found in Lymph Follicles (Rich in B Cell)**
- **Express FcR For Antibodies and Complement**
- **Ag-Ab Complex Shown To Last Very Long (weeks to months)**



Properties of Antigen-Presenting Cells

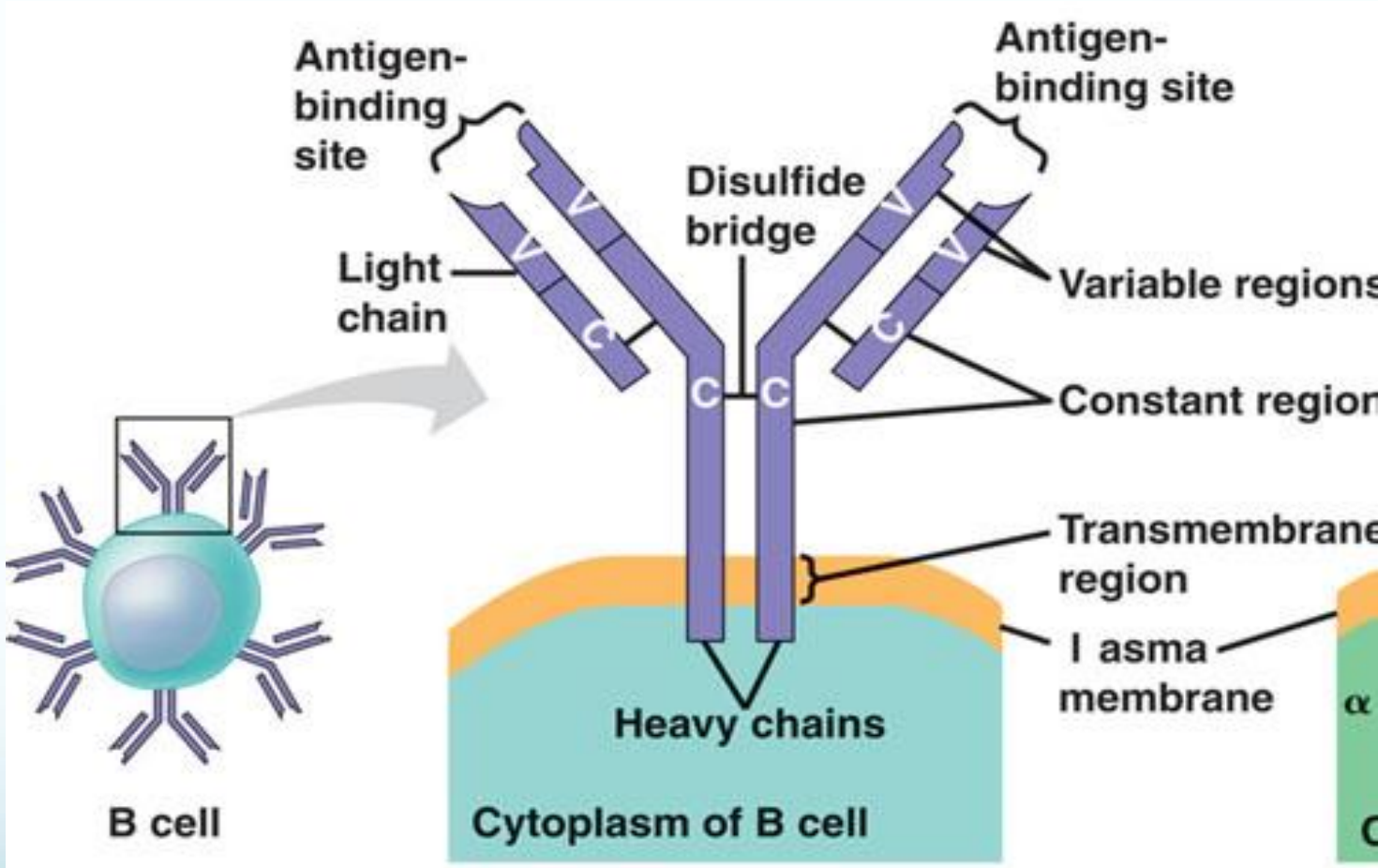
	Macrophages	Dendritic cells	B cells
			
Antigen uptake	Phagocytosis +++	+++ Phagocytosis by tissue dendritic cells. ++++ Viral infection	Antigen-specific receptor (Ig) ++++
MHC expression	Inducible by bacteria and cytokines – to +++	Constitutive ++++	Constitutive. Increases on activation +++ to ++++
Co-stimulator delivery	Inducible – to +++	Constitutive; by mature non-phagocytic lymphoid dendritic cells ++++	Inducible – to +++
Antigen presented	Particulate antigens. Intracellular and extracellular pathogens	Peptides Viral antigens (allergens?)	Soluble antigens. Toxins. Viruses
Location	Lymphoid tissue. Connective tissue. Body cavities	Lymphoid tissue. Connective tissue. Epithelia	Lymphoid tissue. Peripheral blood


Antigen recognition
Effector functions
B lymphocyte
Microbe
Antibody
Neutralization of microbe, phagocytosis, complement activation
Helper T lymphocyte
Cytokines
Activation of macrophages
Inflammation
Microbial antigen presented by antigen-presenting cell
Activation (proliferation and differentiation) of T and B lymphocytes
Cytolytic T lymphocyte (CTL)
Killing of infected cell
Infected cell expressing microbial antigen
Natural killer (NK) cell
Target cell
Killing of infected cell


Recognition phase
Activation phase
Effector phase
Decline (homeostasis)
Memory
Antibody-producing cell
Effector T lymphocyte
Elimination of antigens
Differentiation
Humoral immunity
Cell-mediated immunity
Antigen-presenting cell
Clonal expansion
Apoptosis
Surviving memory cells
Naive T lymphocyte
Naive B lymphocyte
Time after antigen exposure

B Cell Receptors for Antigens

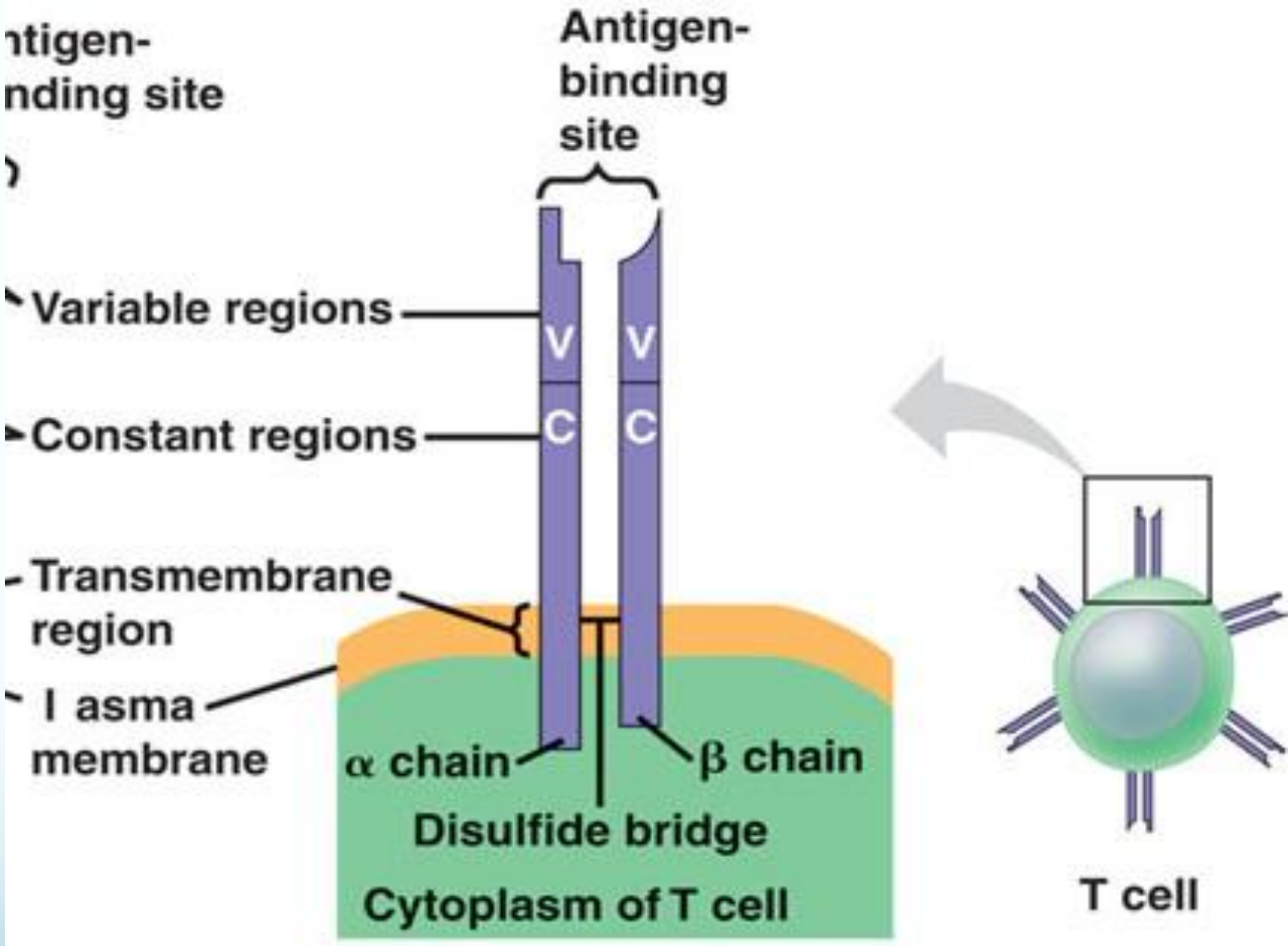
- **B cell receptors** bind to specific, intact antigens.
  - Y-shaped: two identical heavy chains & two identical light chains.
  - Variable regions at the tip provide diversity.



a A B cell receptor consists of t o identical heavy chains and t o identical light chains lin ed by several disulfide bridges

T Cell Receptors for Antigens and the Role of the MHC

- Each T cell receptor consists of two different polypeptide chains.
  - The variable regions form the antigen binding site and provide a diversity of T cells.



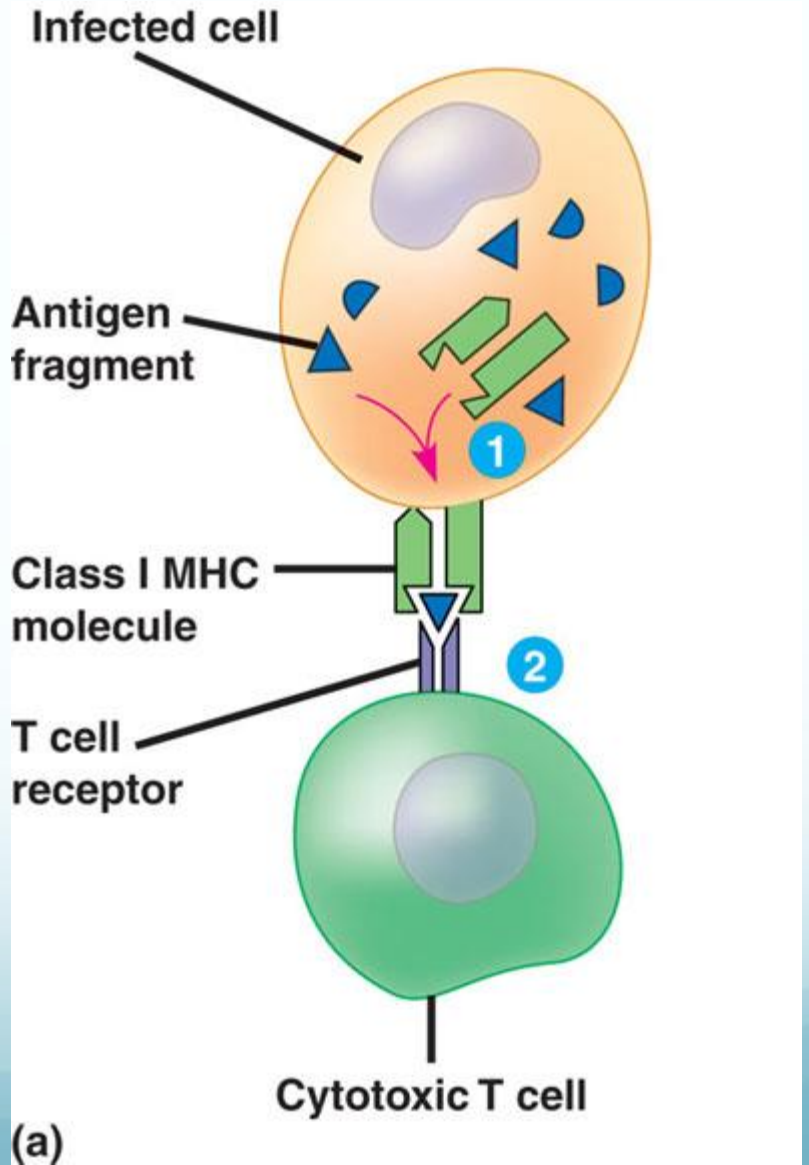
b A T cell receptor consists of one α chain and one β chain lin ed by a disulfide bridge

T Cell Receptors for Antigens and the Role of the MHC

- T cells bind to small fragments of antigens that are bound to normal cell-surface proteins called **MHC molecules**.
- MHC molecules are encoded by a family of genes called the major histocompatibility complex.
- Infected cells produce MHC molecules which bind to antigen fragments and then are transported to the cell surface in a process called **antigen presentation**.
- A nearby T cell can then detect the antigen fragment displayed on the cell's surface
- Depending on their source, peptide antigens are handled by different classes of MHC molecules.

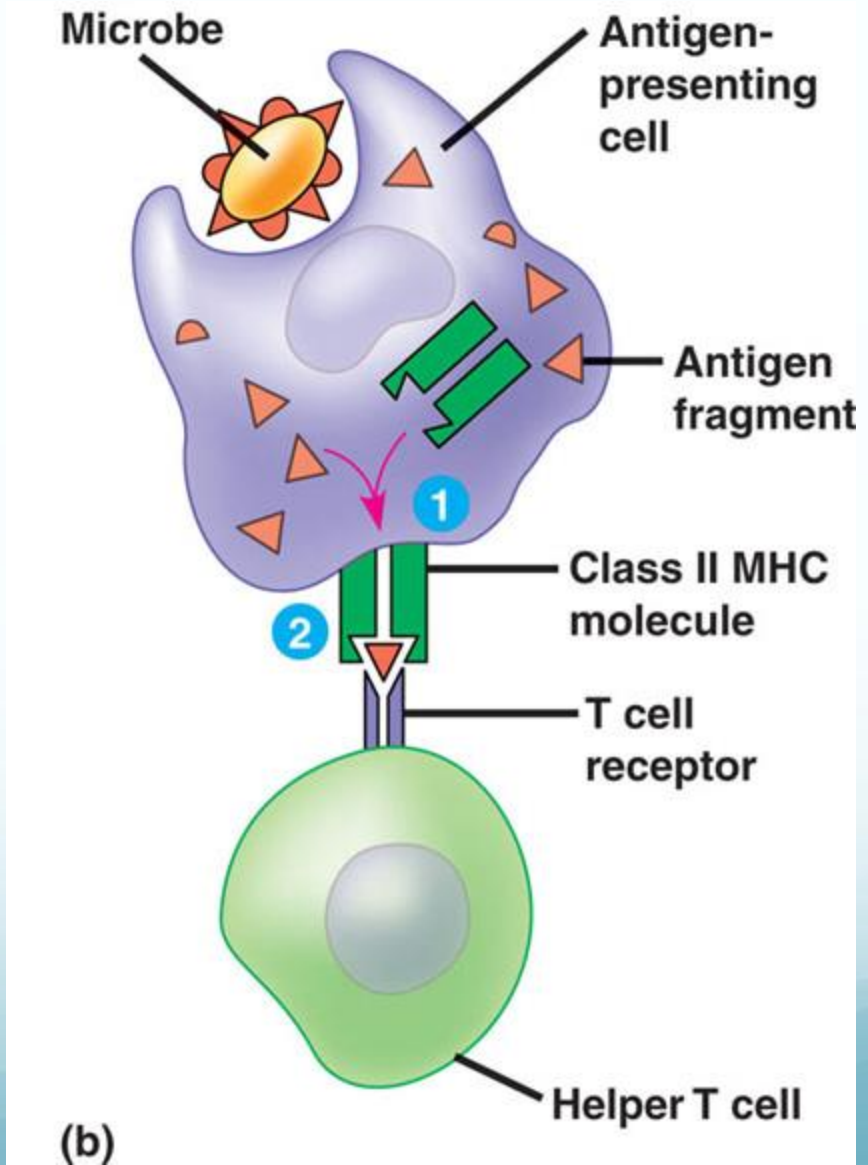
T Cell Receptors for Antigens and the Role of the MHC

- **Class I MHC molecules**, found on almost all nucleated cells of the body, display peptide antigens to **cytotoxic T cells**.

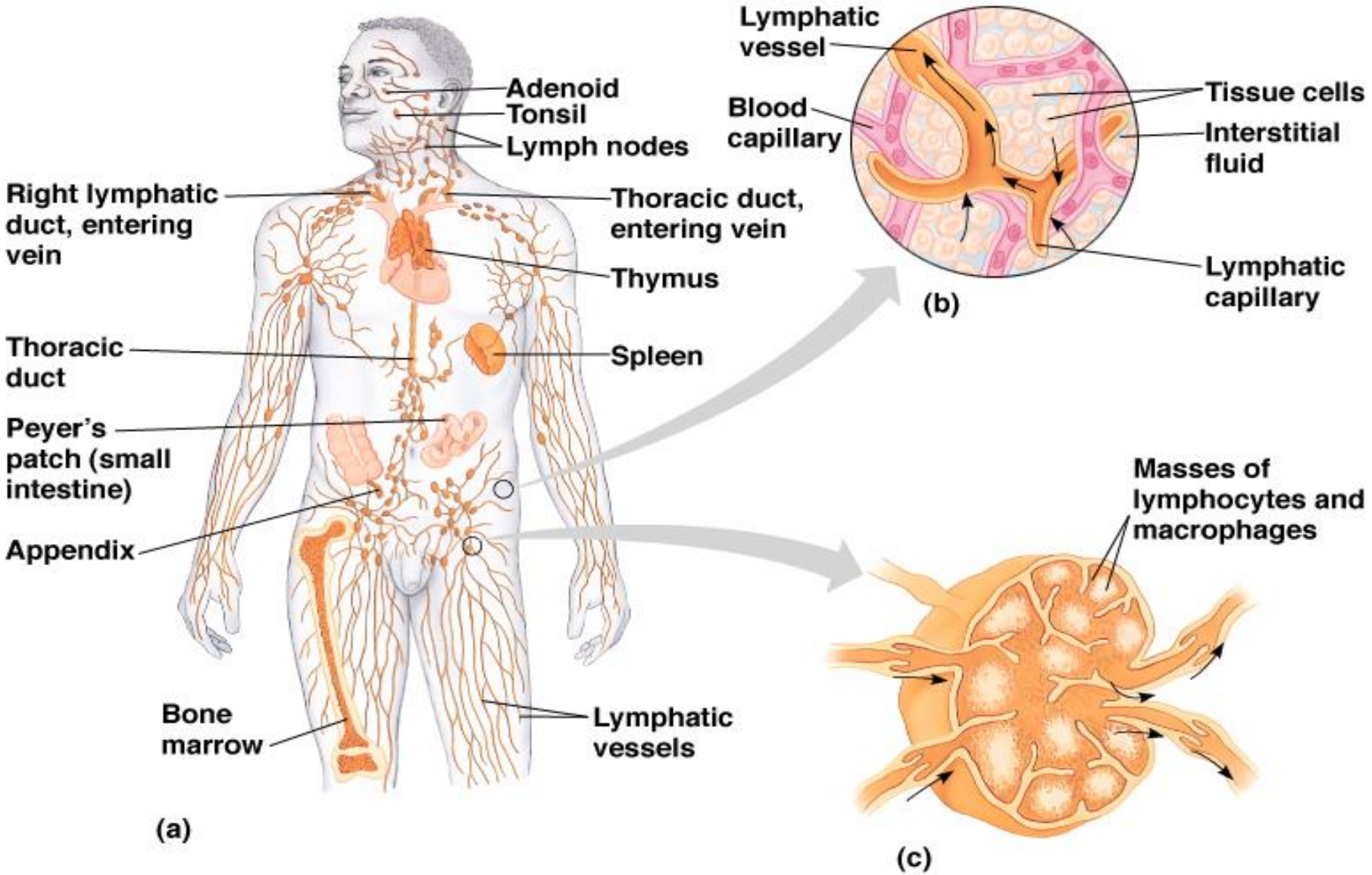


T Cell Receptors for Antigens and the Role of the MHC

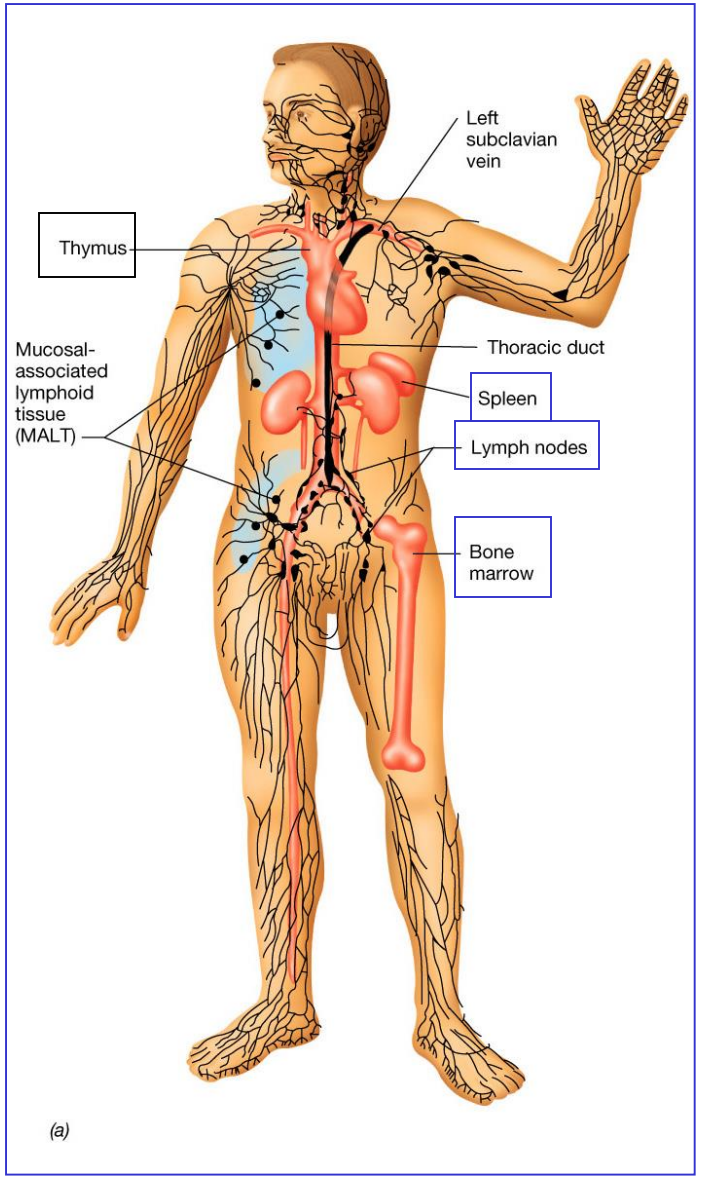
- **Class II MHC molecules**, located mainly on dendritic cells, macrophages, and B cells, display antigens to **helper T cells**.



Components of Human Immune System



The blood and lymph systems



Overall view of the lymph system, showing the locations of major organs

The circulatory system is the means by which cells of the immune system directly or indirectly interact with all of the cells of the body

Lymph nodes: contain high concentrations of leukocytes that filter out microbes and toxins

Spleen of the blood circulatory system has the same function as the lymph nodes

lymph nodes and spleen can sometimes become infected by the organisms that have collected during filtration

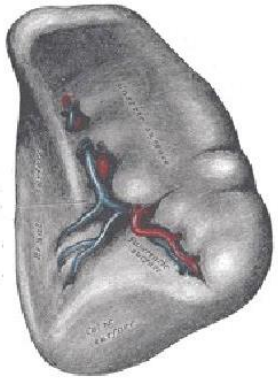
Organs Of Immune System

- Primary Lymphoid Organs
  - Bone Marrow and Thymus
  - Maturation Site
- Secondary Lymphoid Organs
  - Spleen, lymph nodes,
  - MALT (mucosal associated lymph tissue)
  - GALT (gut associated lymph tissue)
  - Trap antigen, APC, Lymphocyte Proliferation

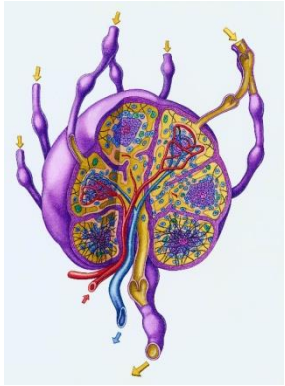
Secondary Immune Organs

- consist of the spleen, the lymph nodes, the mucosal and cutaneous immune system
- are organized to optimize interactions of antigens, APCs and lymphocytes
- are places of the development of adaptive immune responses

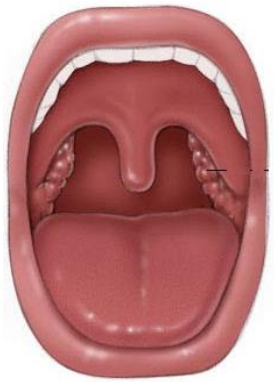
spleen



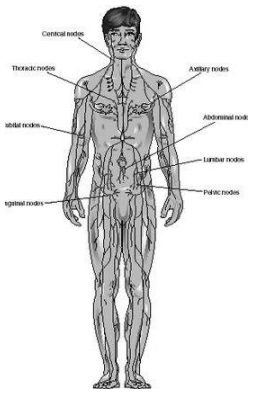
lymphatic nodes



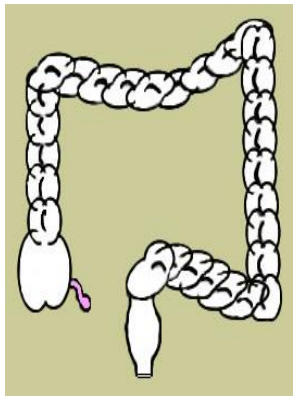
tonsils



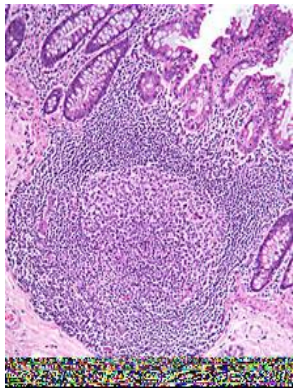
MALT



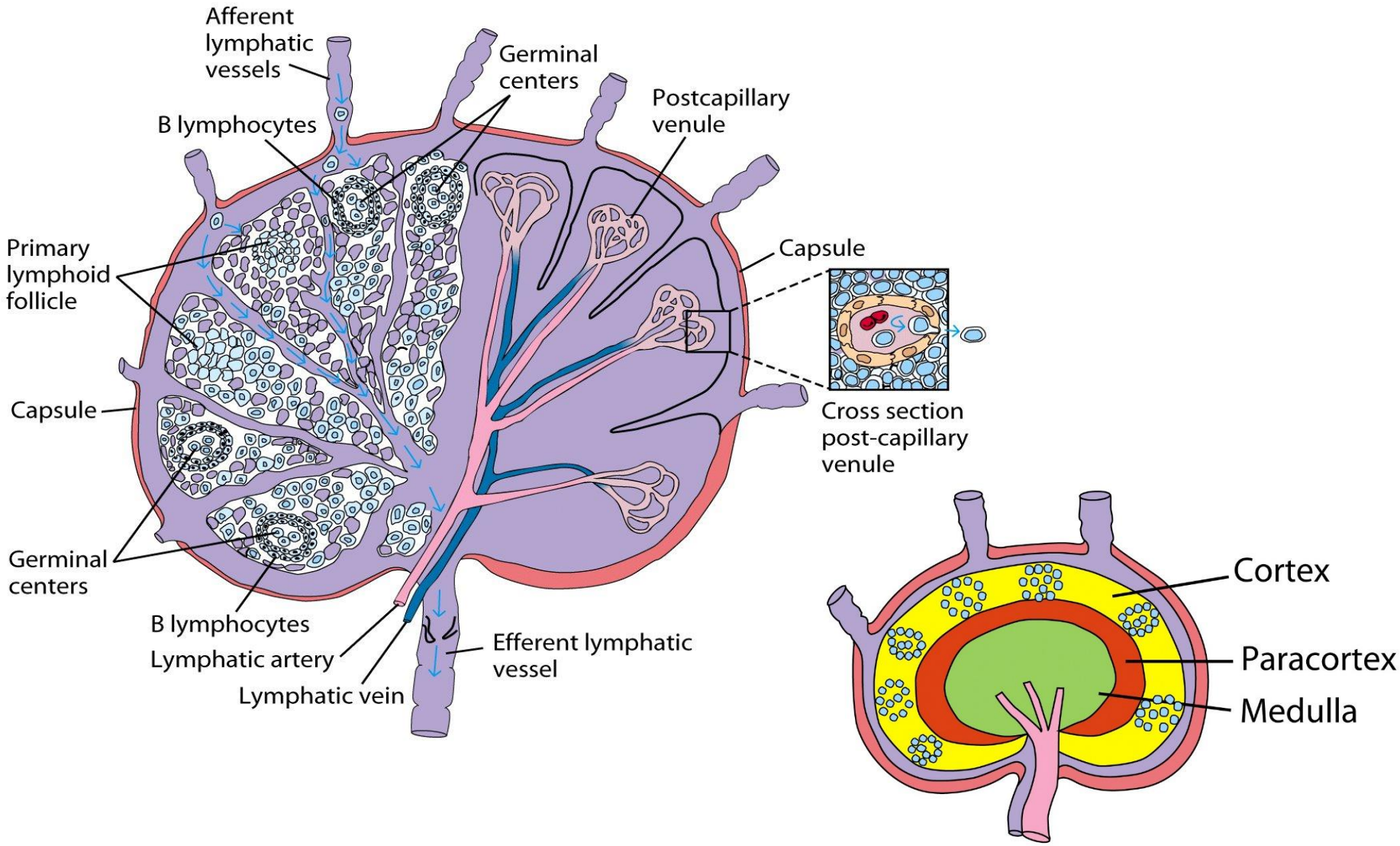
appendix



Peyer´s patches

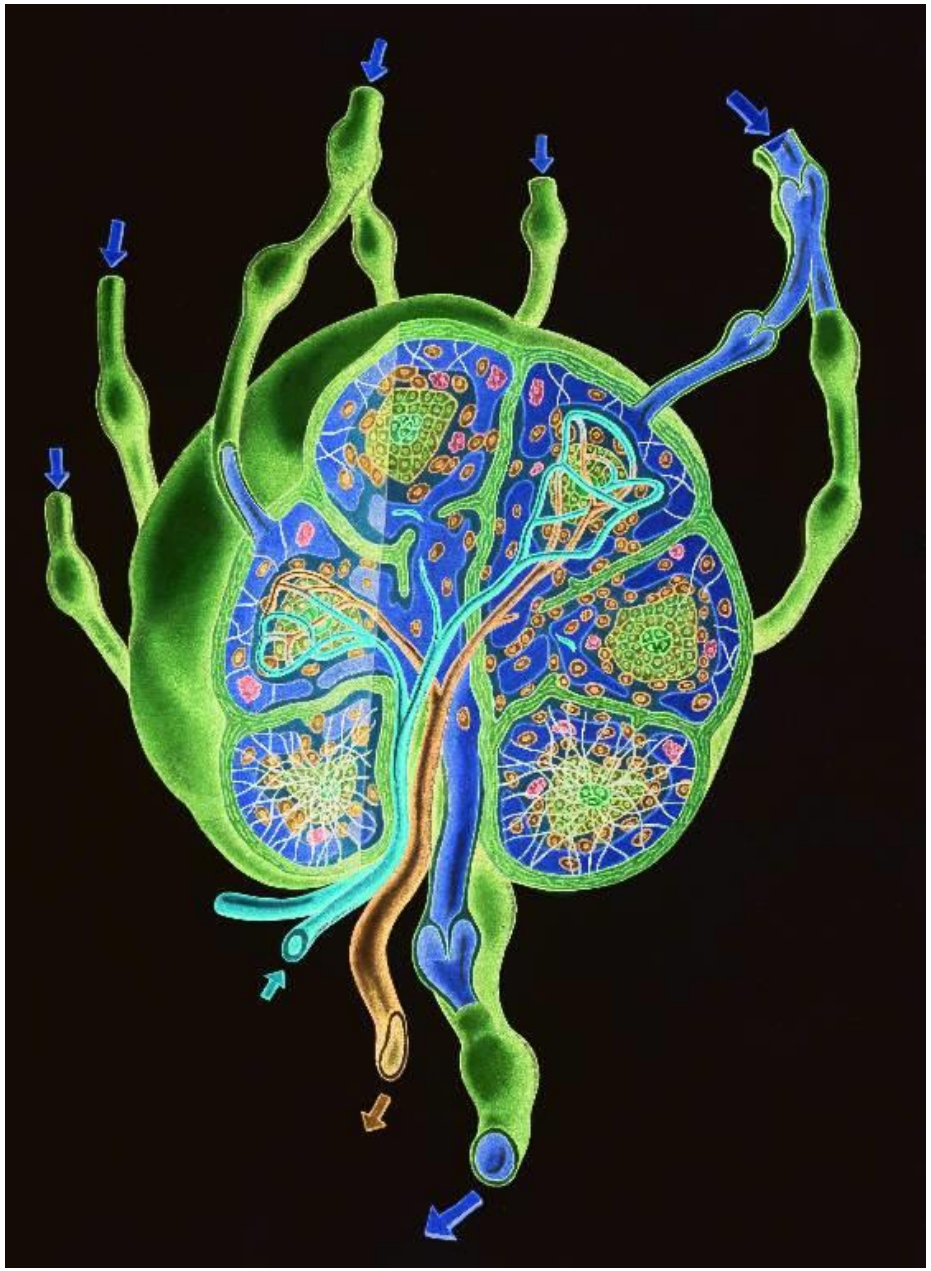


Lymph Node


Afferent lymphatic vessels
Germinal centers
Postcapillary venule
B lymphocytes
Primary lymphoid follicle
Capsule
Capsule
Germinal centers
Cross section post-capillary venule
B lymphocytes
Lymphatic artery
Lymphatic vein
Efferent lymphatic vessel
Cortex
Paracortex
Medulla

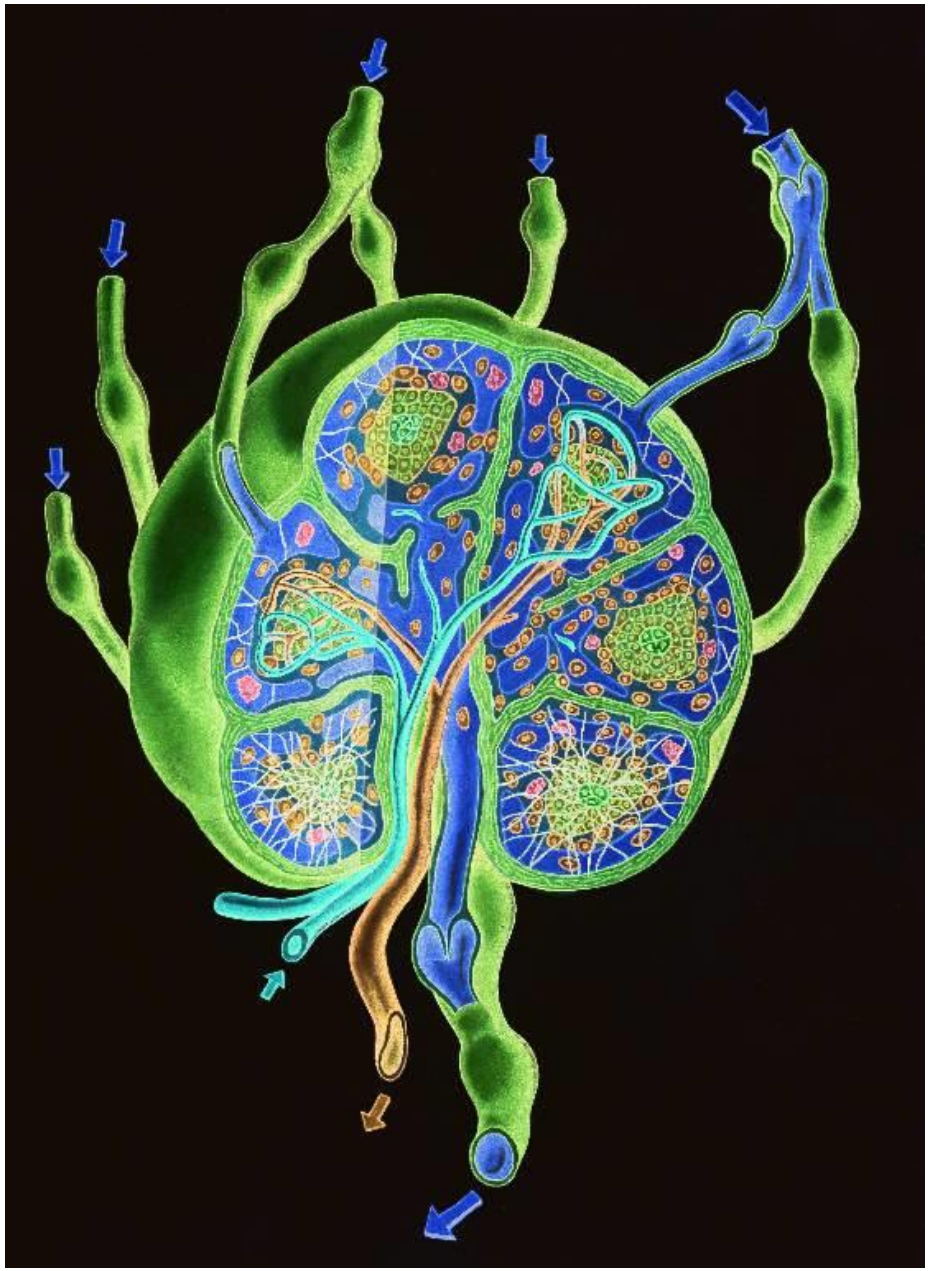
Lymphatic node

- are nodular aggregates of lymphoid tissues located along lymphatic channels throughout the body
- Lymph comes from tissues and most parenchymal organs to the lymph nodes
- Lymph contains a mixture of substances absorbed from epithelia and tissues
- As the lymph passes through lymph nodes, APCs in the LN are able to sample the antigens of microbes that may enter through epithelia into tissues



Lymphatic node

- lymph circulates to the lymph node via afferent lymphatic vessels and drains into the node just beneath the capsule in a space called the subcapsular sinus
- the subcapsular sinus drains into trabecular sinuses and finally into medullary sinuses
- the sinus space is criss-crossed by the pseudopods of macrophages which act to trap foreign particles and filter the lymph
- the medullary sinuses converge at the hilum and lymph then leaves the lymph node via the efferent lymphatic vessel



Lymphatic node - cortex

Contains lymphoid follicles = accumulation of B-lymphocytes and follicular dendritic cells

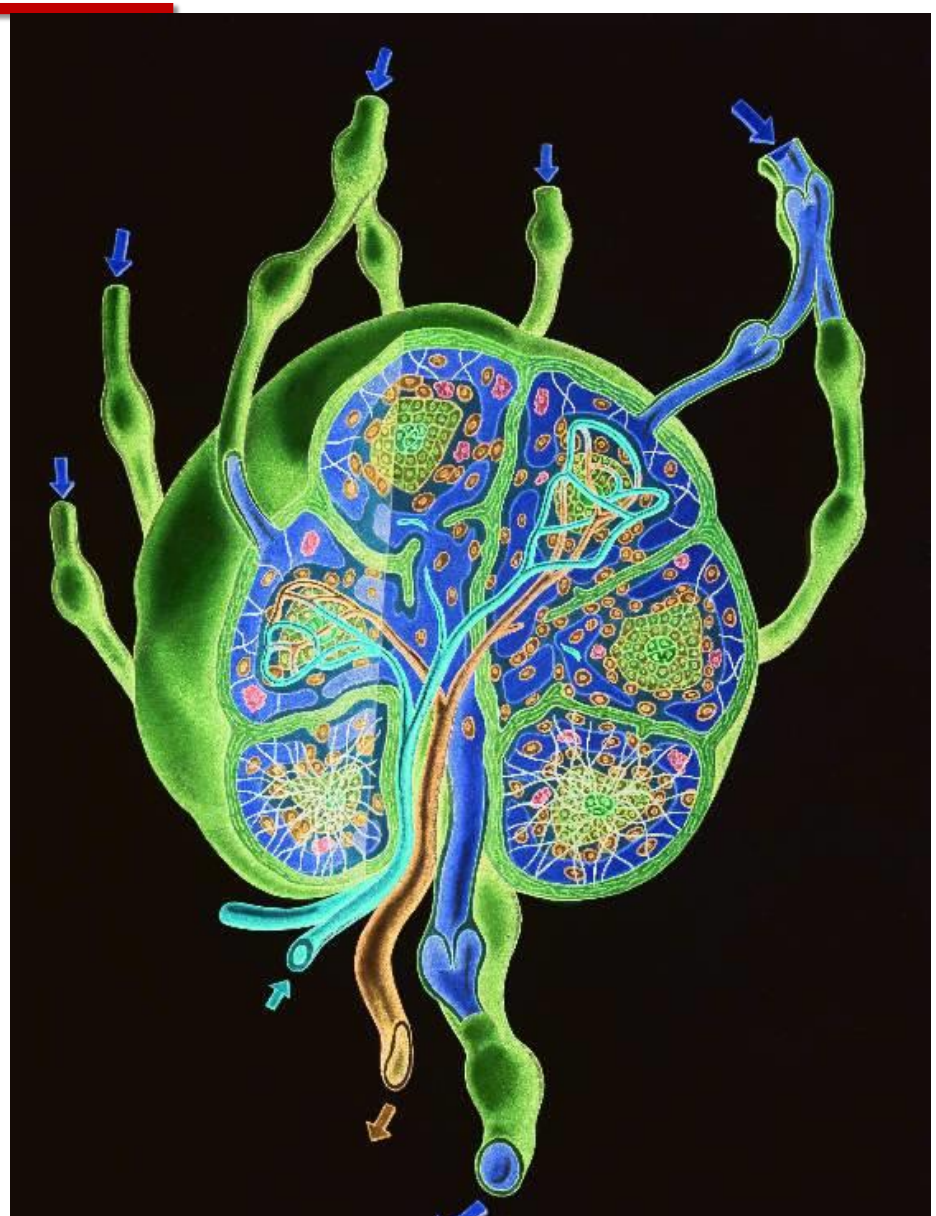
When a lymphocyte recognizes an antigen, B cells become activated and migrate to germinal centers = the secondary nodule

Lymphatic node- medulla

The medullary cords are cords of lymphatic tissue, and include plasma cells and T cells

- **The medullary sinuses are vessel-like spaces separating the medullary cords; contain histiocytes (= immobile macrophages) and reticular cells.**

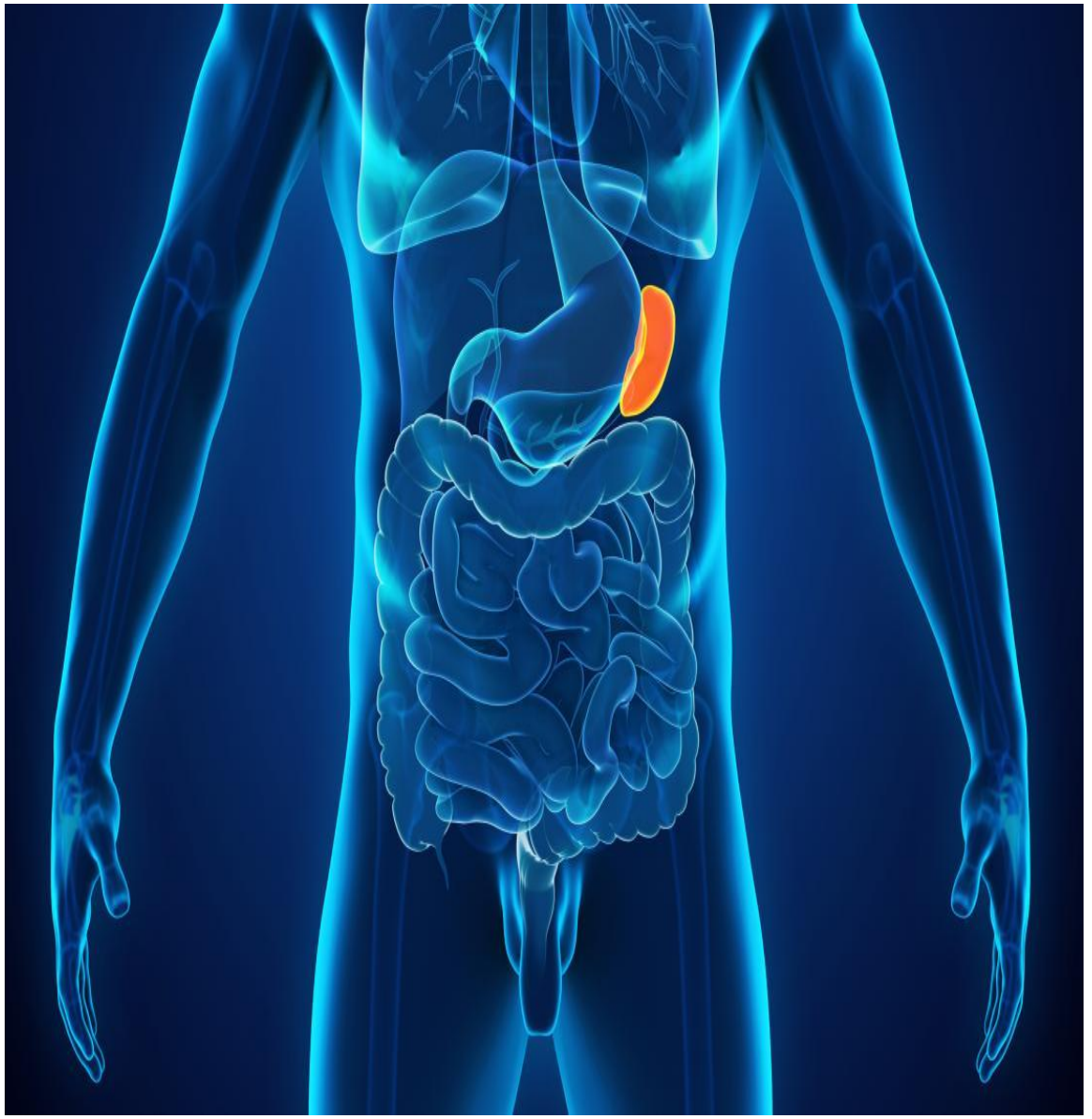
- **Lymph flows to the medullary sinuses from cortical sinuses, and into efferent lymphatic vessels**



Spleen

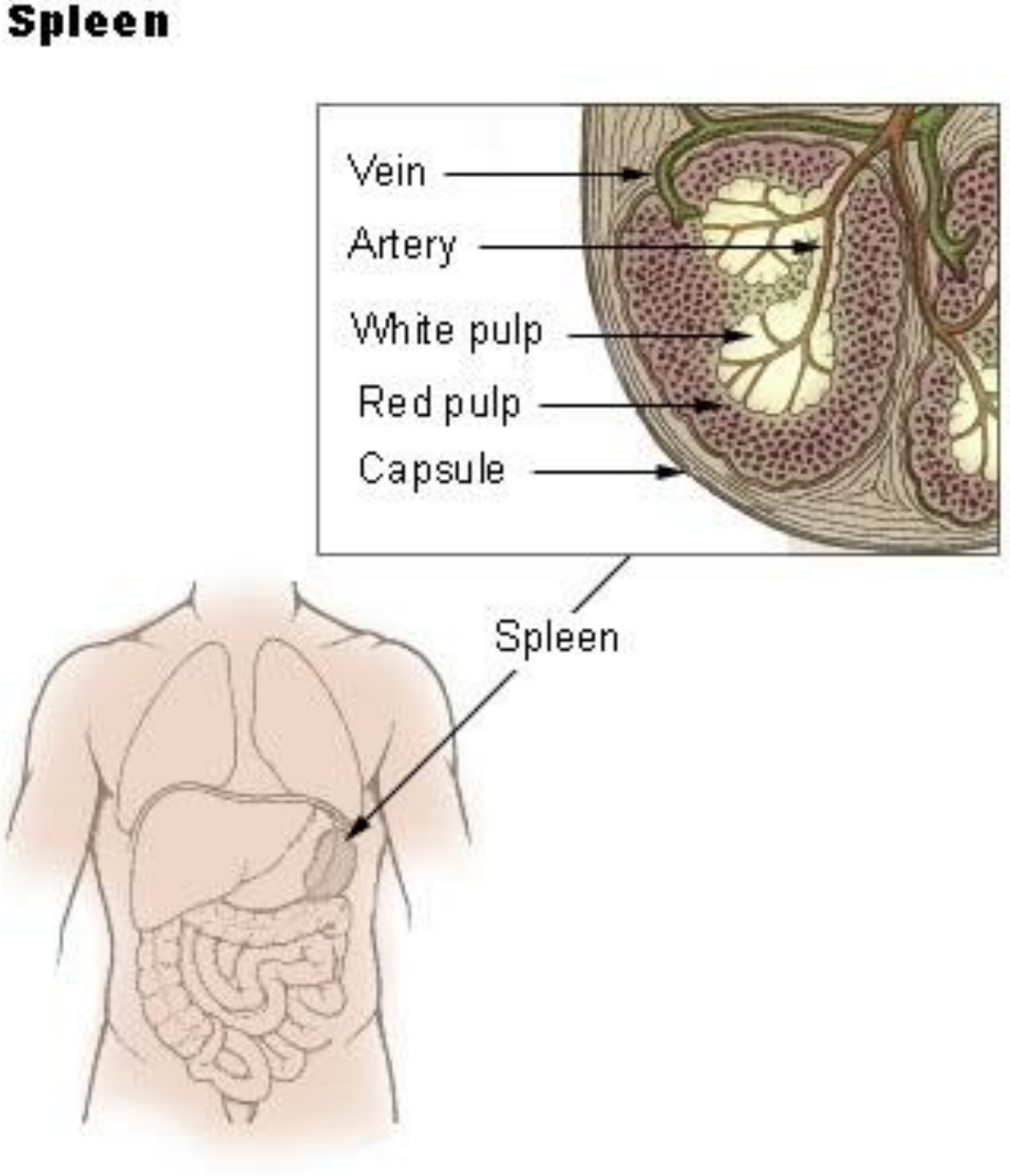
is a secondary lymphoid organ located high in the left abdominal cavity

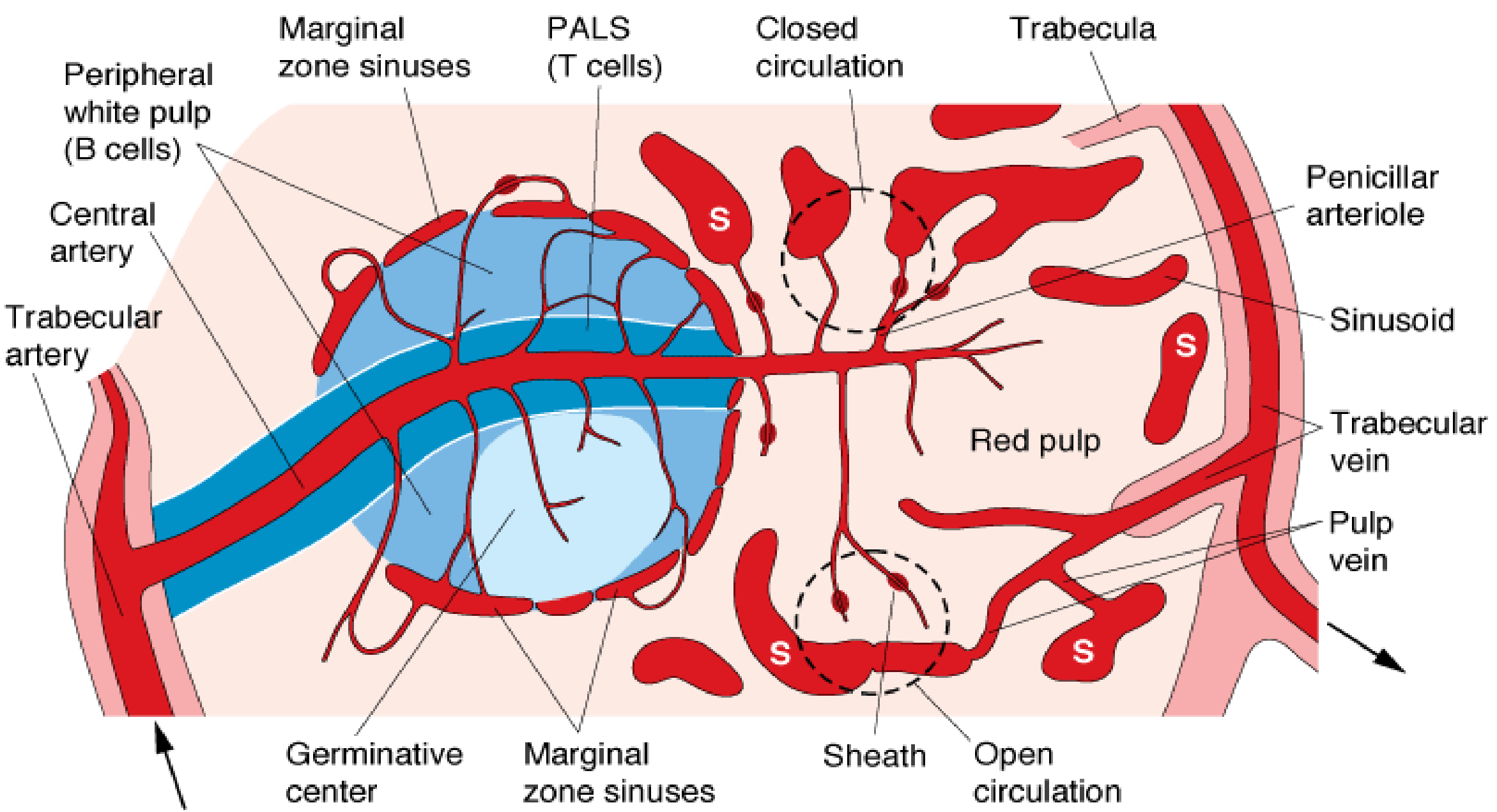
- **is surrounded by a capsule, which sends trabecular into the interior to form a compartmentalized structure**
- **there are two types of compartments -red pulp and white pulp with a marginal zone in between**
- **is NOT supplied by afferent lymphatics**



Spleen

- Red pulp : place of mechanical filtration and elimination of senescent red and white blood cells and microbes
- White pulp : T lymphocytes CD4+,CD8+ are around arterioles (periarteriolar lymphoid sheaths), B lymphocytes are in the folicles; final maturation of B lymphocytes course in germinal center of secondary folicles

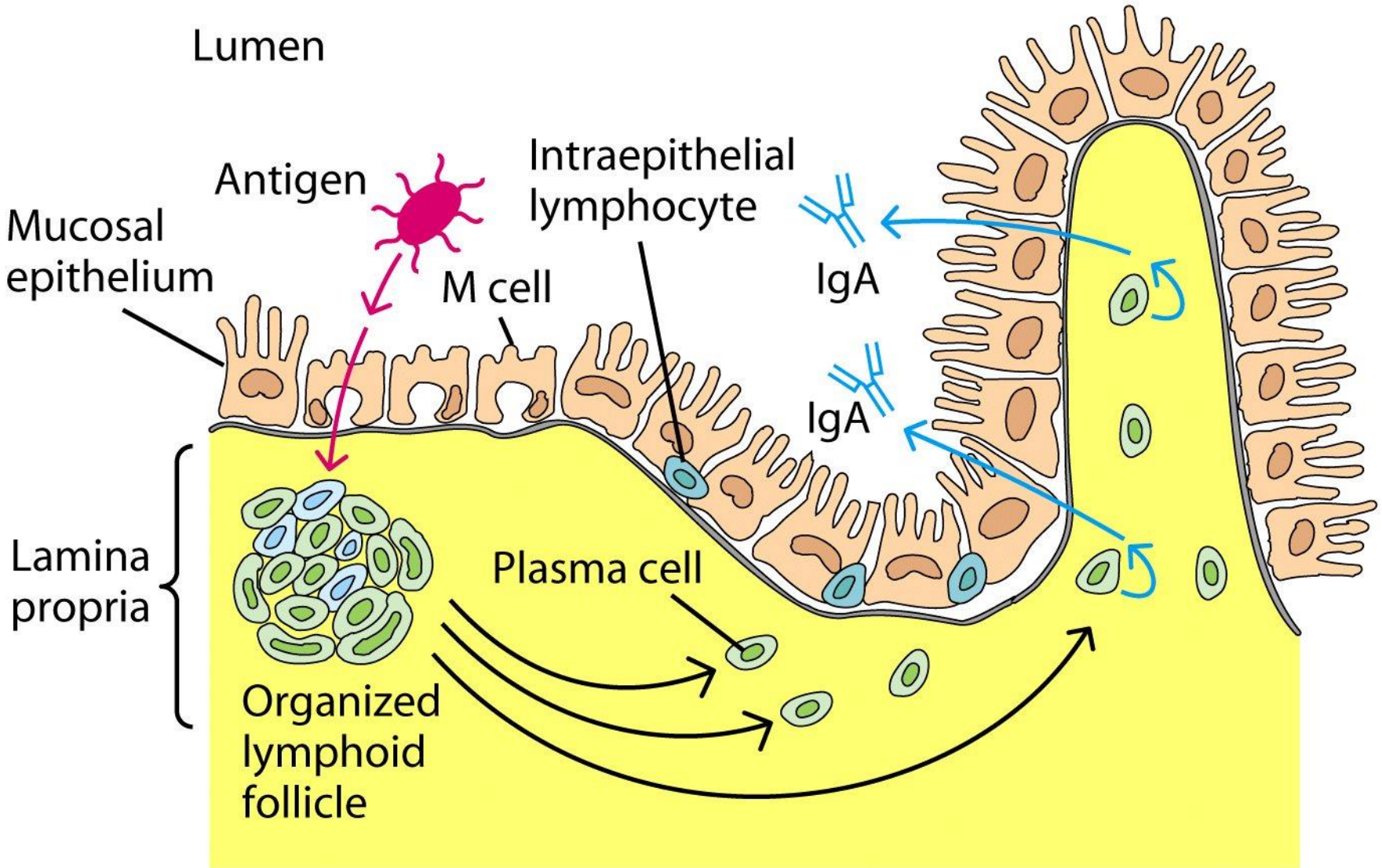




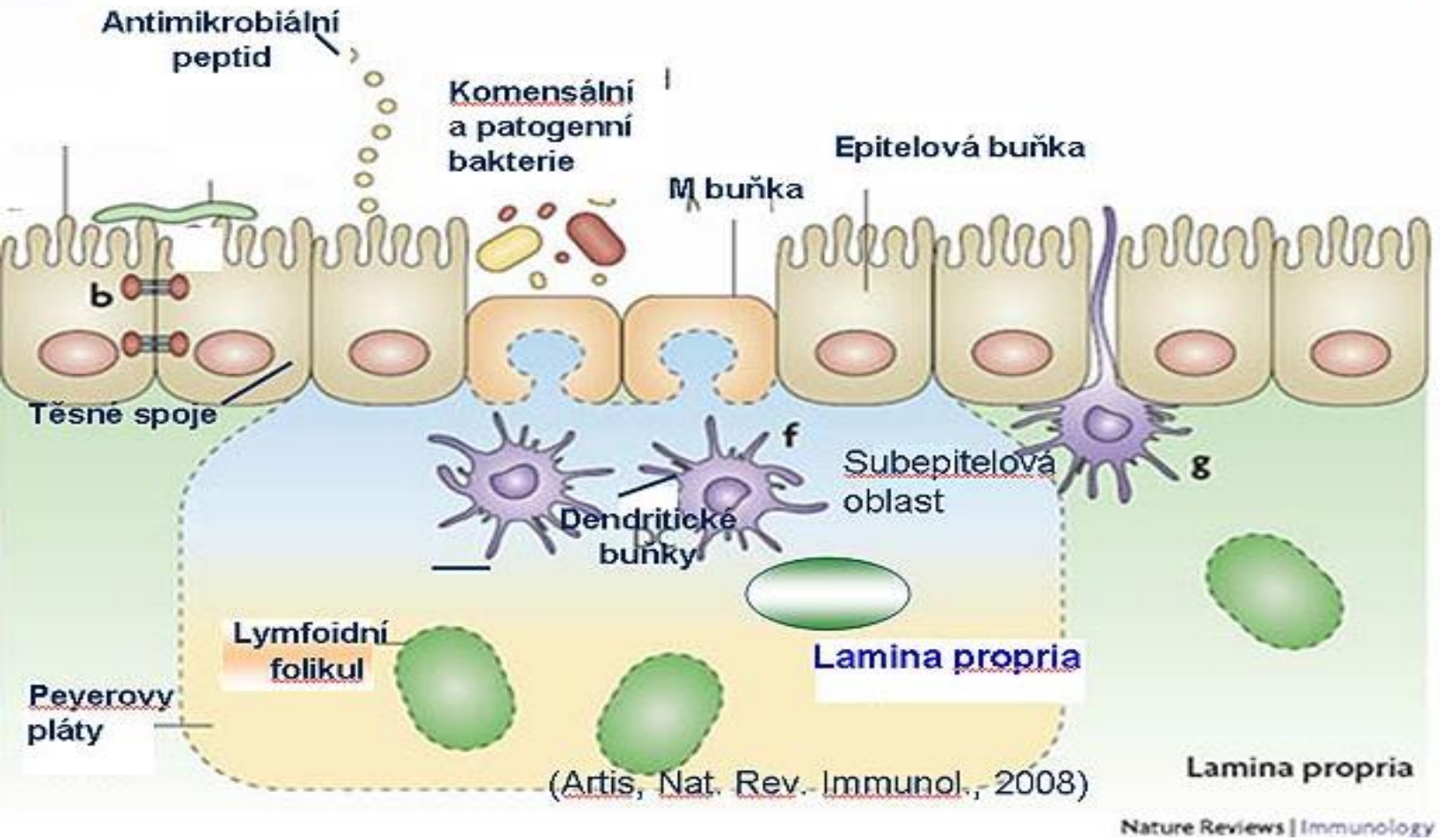
Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com

Mucosal immune system

- **MALT = mucosa-associated lymphoid tissue**
- **GALT = gut-associated lymphoid tissue**
- **BALT = bronchus-associated lymphoid tissue**
- **GIT, respiratory, and urogenital systems are lined by mucous membranes**
- **Includes clusters of lymphoid cells in lamina propria of intestinal villi**
- **contains a very large population of plasma cells that synthesize IgA antibodies**

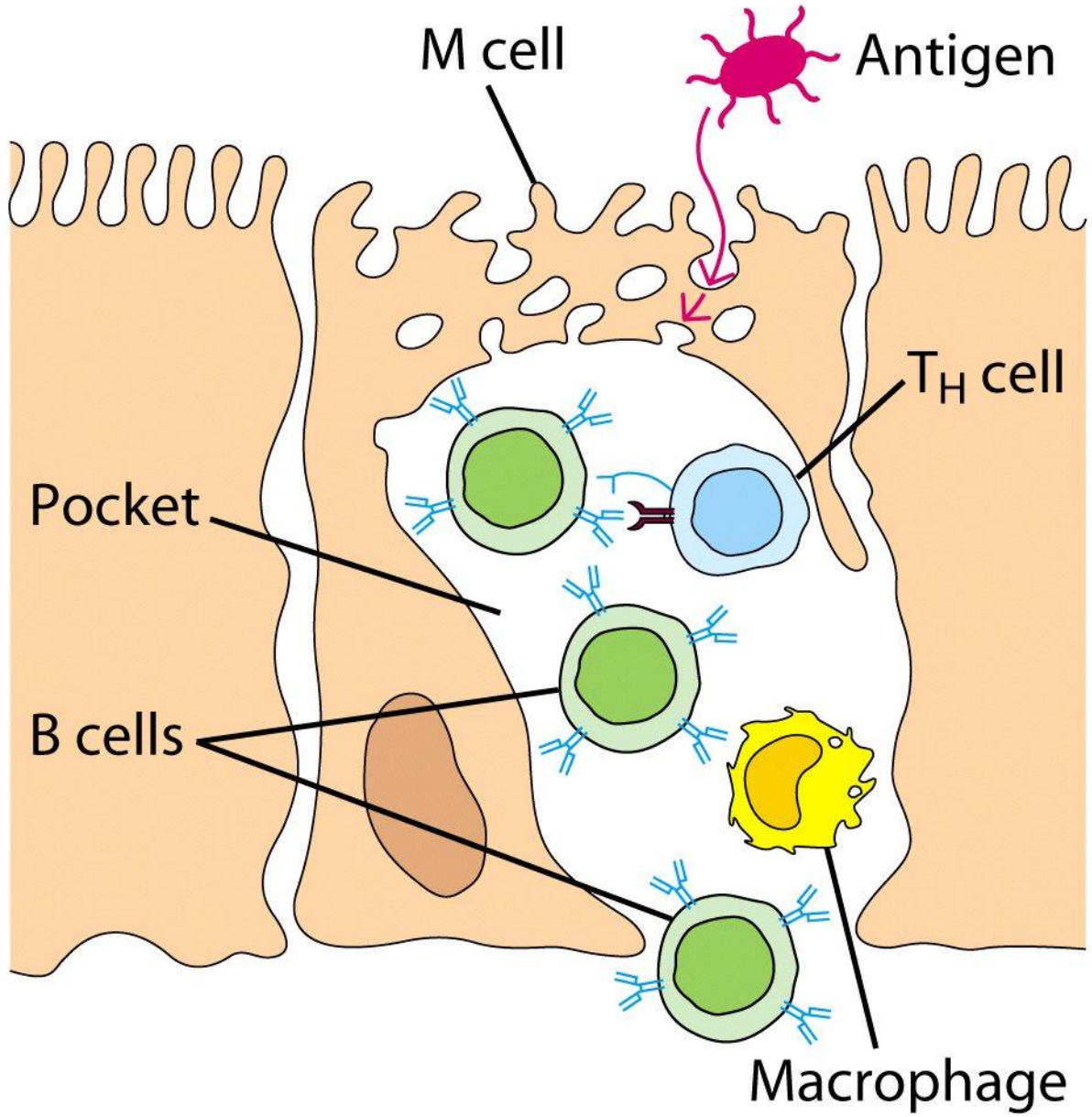

Lumen
Antigen
Intraepithelial lymphocyte
Mucosal epithelium
M cell
IgA
IgA
Lamina propria
Plasma cell
Organized lymphoid follicle

Slizniční bariera střeva



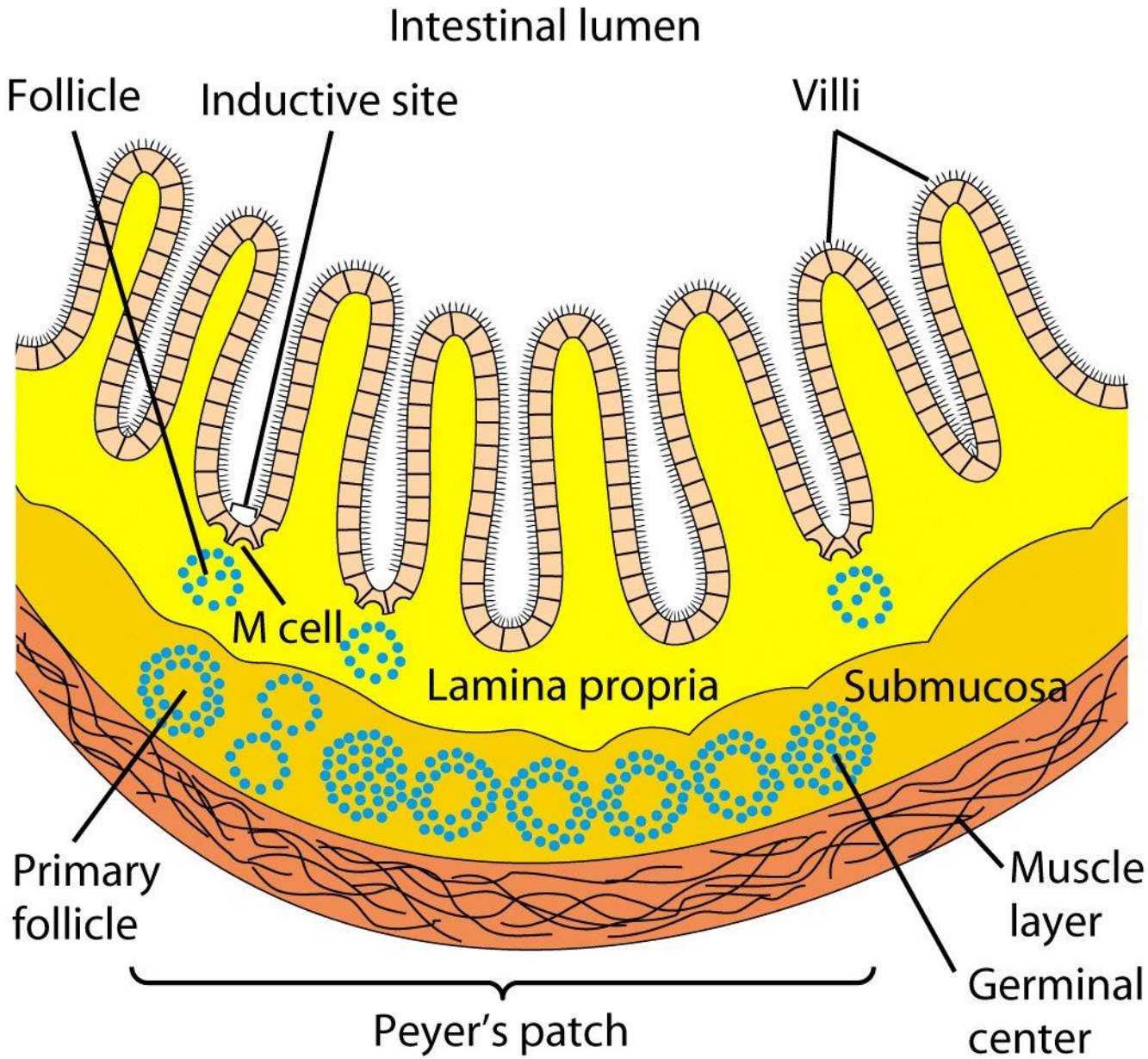
M cells

- **are epithelial cells that are specialized for the transport antigen from the lumen of the respiratory, GIT, and urogenital tracts to the underlying MALT**
- **contain a characteristic pocket filled with B cells, T cells, and macrophages**
- **are found at inductive sites that overlie organized lymphoid follicles in the lamina propria**
- **antigens are endocytosed and transported within vesicles from the luminal membrane to the pocket membrane, where the vesicles fuse and deliver their contents to antigen-presenting cells**


M cell
Antigen
T_H cell
Pocket
B cells
Macrophage

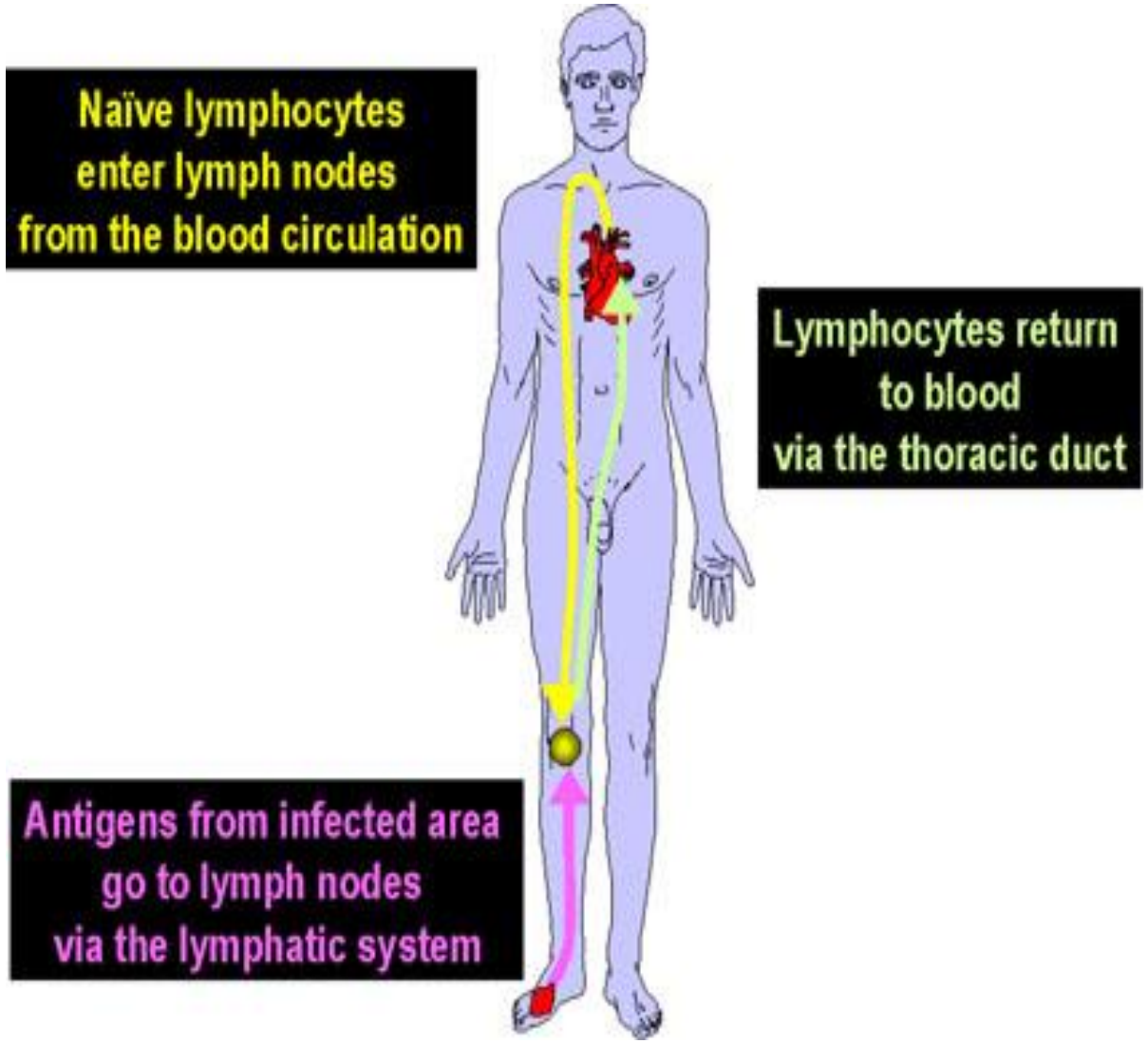
Secretory IgA

- daily production of secretory IgA into mucus secretions exceeds that of any other class of immunoglobulin (5-15 g each day)
- is an important line of defense for mucosal surfaces against bacteria
- binding of secretory IgA to bacteria and viruses also prevents attachment to mucosal epithelial cells, thereby inhibiting infection and colonization

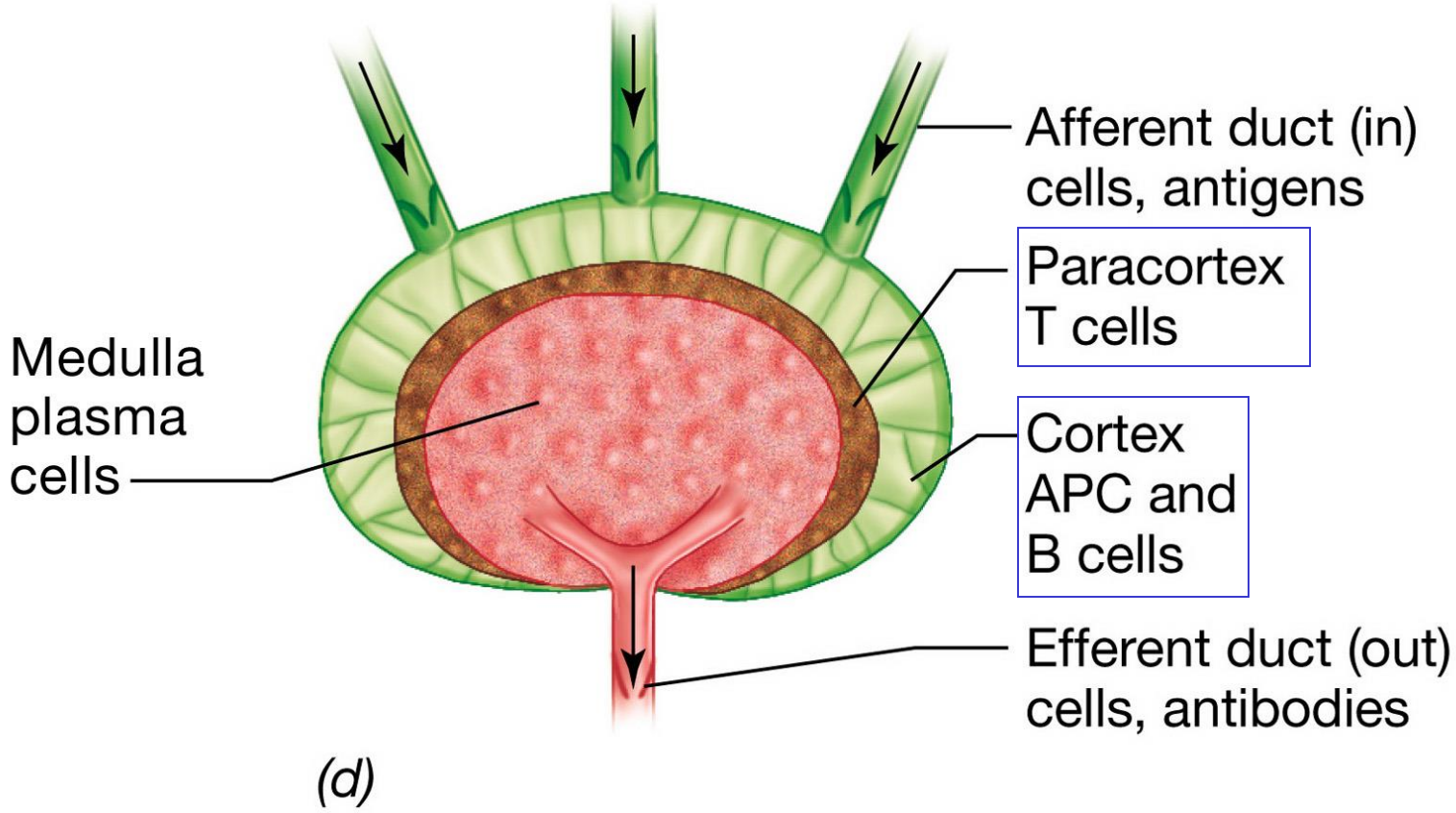

Intestinal lumen
Follicle
Inductive site
Villi
M cell
Lamina propria
Submucosa
Primary follicle
Muscle layer
Germinal center
Peyer's patch

Lymphocyte recirculation

- **Relatively few lymphocytes with a specific AgR**
  - **1/10,000 to 1/100,000**
- **Chances for successful encounter enhanced by circulating lymphocytes**
  - **1-2% recirculate every hour**

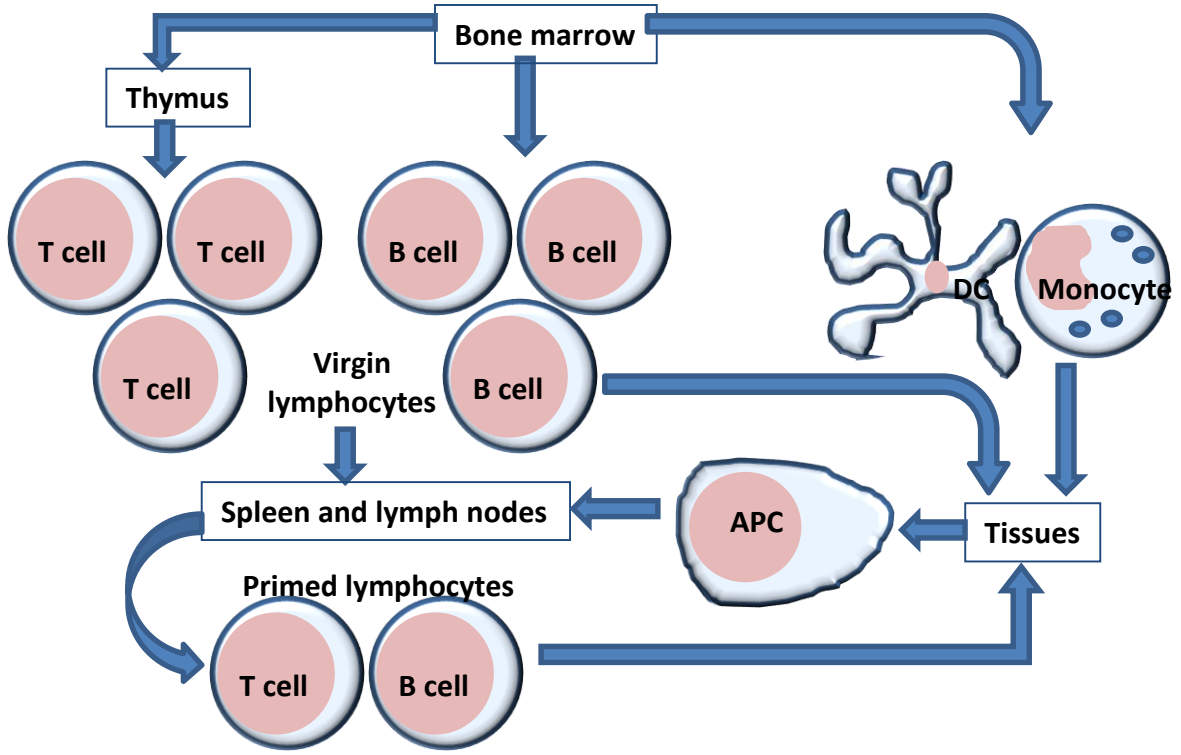


A lymph node: Antigens (proteins produced by pathogens and cells enter through the afferent duct and cells and antibodies to these antigens exit through the efferent duct



Lymphocyte recirculation

- Lymphocytes enter 2° lymphoid organs via high endothelial venules (HEVs)
- Ag is transported to lymph nodes via APC
- Upon activation, lymphocytes travel to tissues



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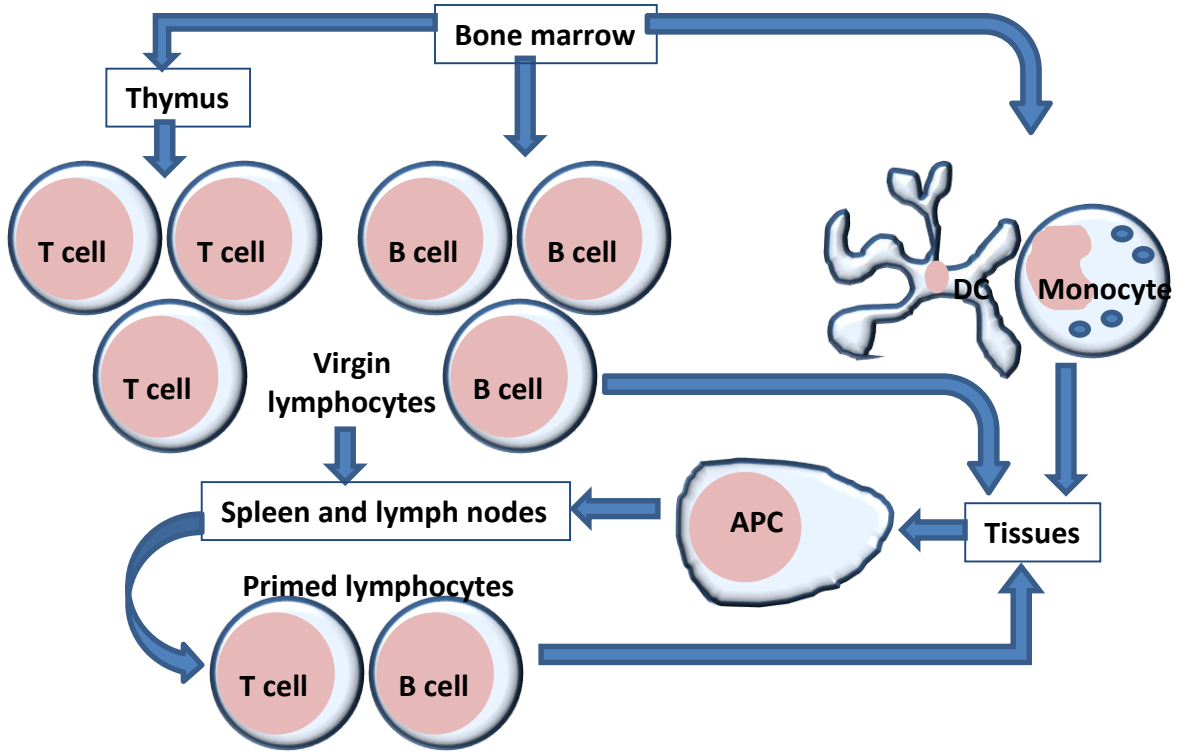
Lymphocyte recirculation

- After activation, new receptors (homing R) are expressed to direct to tissues
- R on lymphocytes recognize CAMs on endothelial cells
- Chemokines at infection help attract activated lymphocytes



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