M. Sc. Microbiology

Semester – II

Paper – 201 B

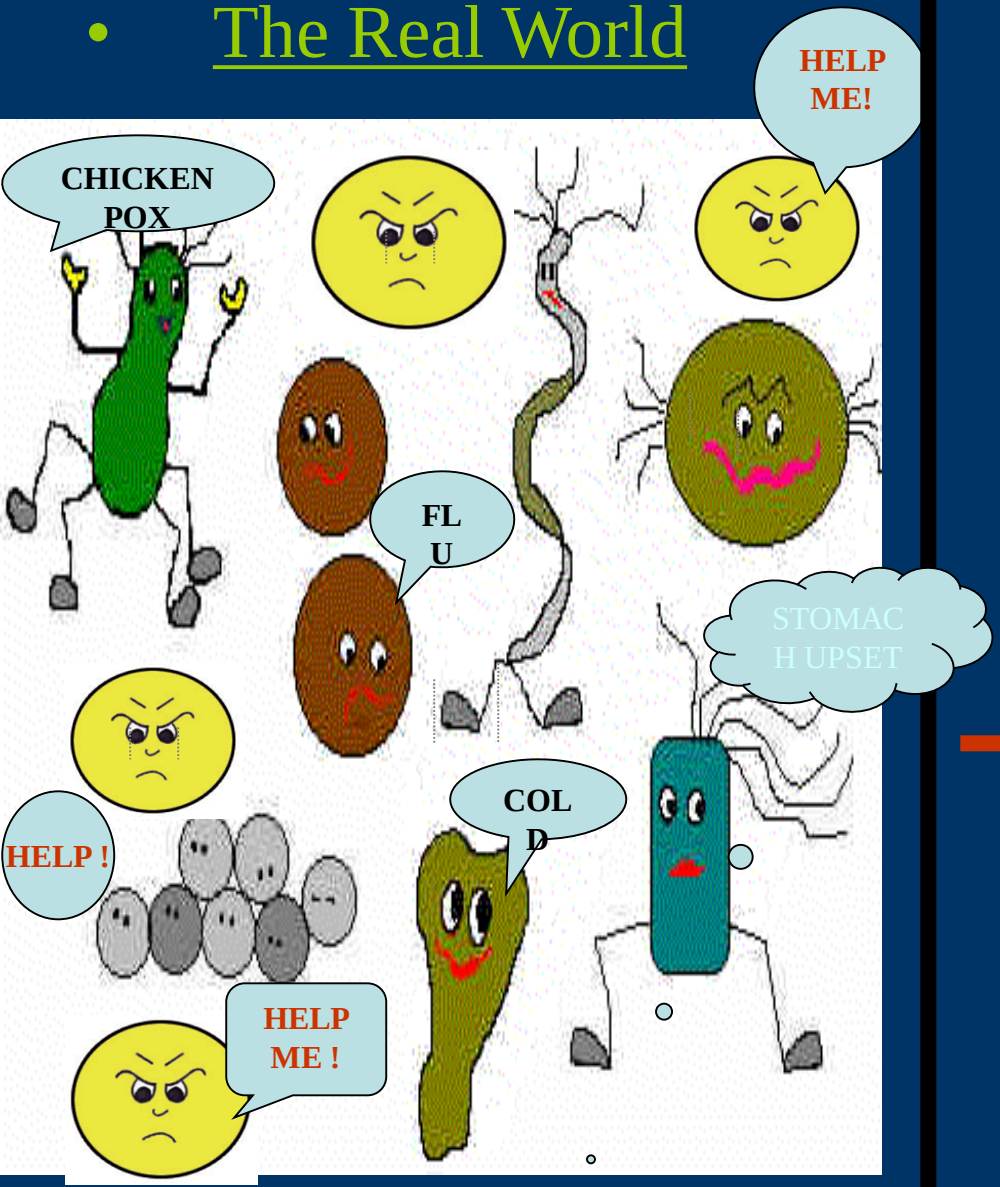
Sub : Immunology

Topic : History of immunology, Lymphoid organs, Cells & Products, Acute phase proteins, Antigen, Antibody, Innate Immunity, TLR: distribution & their roles, Mechanism of Phagocytosis, Complement systems and its role in immunity

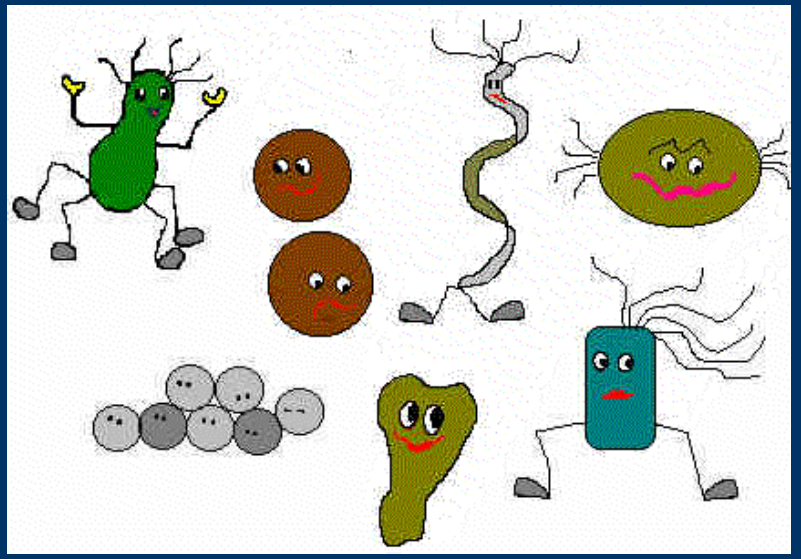
Prof. Keshab Chandra Mondal

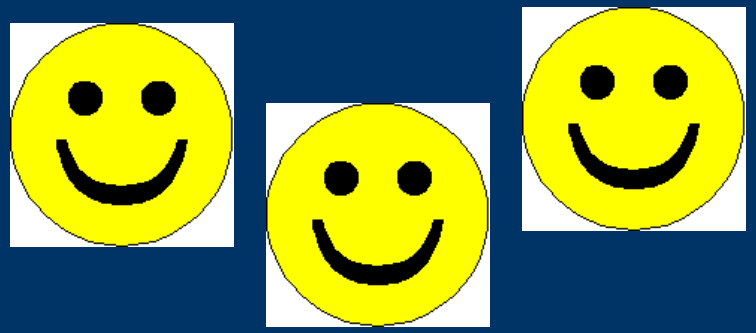

Introduction to Immunology

- The Real World



- The Perfect World

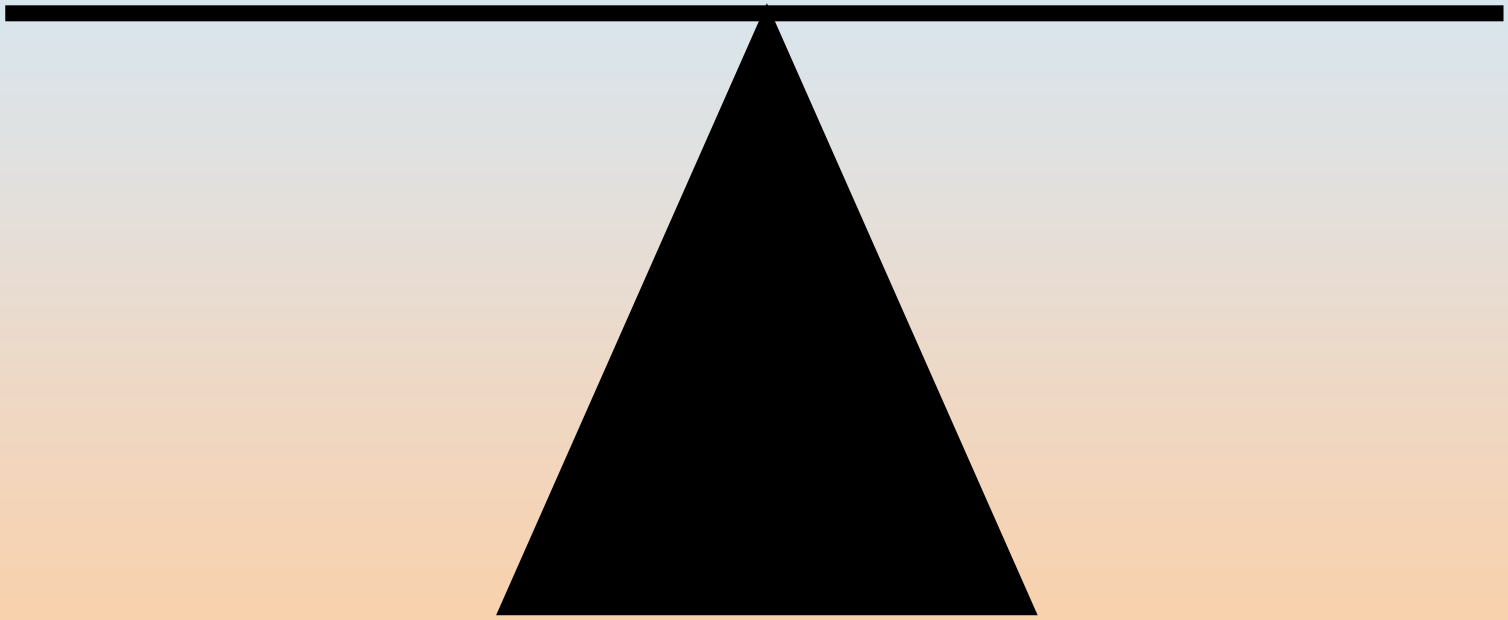




Balance between Infection and Immunity

infection

immunity



$$\text{Disease} = \frac{\text{Bolus of infection x virulence}}{\text{immunity}}$$

What is immunology?

- Immune (Latin- “immunus”)
  - To be free, exempt
  - People survived ravages of epidemic diseases when faced with the same disease again
- The study of physiological mechanisms that humans and other animals use to defend their bodies from invading organisms
  - Bacteria - Viruses
  - Fungi - Parasites - Toxins

The Latin term *"IMMUNIS"* means EXEMPT, referring to protection against foreign agents.

Immunity was defined by Sir Macfarlane Burnet as 'the capacity to recognize the intrusion of material foreign to the body and to mobilise cells and cell products to help remove that particular sort of foreign material with greater speed and effectiveness'.

DEFINITION: - The integrated body system of organs, tissues, cells & cell products that differentiates self from non – self & neutralizes potentially pathogenic organisms.
(The American Heritage Stedman's Medical Dictionary)

HISTORY OF IMMUNOLOGY

•**1798 Edward Jenner, Smallpox vaccination**

•1862 Ernst Haeckel, Recognition of phagocytosis

•1877 Paul Erlich, recognition of mast cells

•1879 Louis Pasteur, Attenuated chicken cholera vaccine development

•1883 Elie Metchnikoff Cellular theory of vaccination

•1885 Louis Pasteur, Rabies vaccination development

•1888 Pierre Roux & Alexandre Yersin, Bacterial toxins

•1888 George Nuttall, Bactericidal action of blood

•1891 Robert Koch, Delayed type hypersensitivity

•1894 Richard Pfeiffer, Bacteriolysis

•1895 Jules Bordet, Complement and antibody activity in bacteriolysis

•1900 Paul Erlich, Antibody formation theory

•1901 Karl Landsteiner, A, B and O blood groupings

•1901-8 Carl Jensen & Leo Loeb, Transplantable tumors

•1902 Paul Portier & Charles Richet, Anaphylaxis

•1903 Almroth Wright & Stewart Douglas, Opsonization reactions

•1906 Clemens von Pirquet, coined the word allergy

•1907 Svante Arrhenius, coined the term immunochemistry

•1910 Emil von Dungern, & Ludwik Hirszfeld, Inheritance of ABO blood groups

•1910 Peyton Rous, Viral immunology theory

•1914 Clarence Little, Genetics theory of tumor transplantation

•1915-20 Leonell Strong & Clarence Little, Inbred mouse strains

•1917 Karl Landsteiner, Haptens

•1921 Carl Prausnitz & Heinz Kustner, Cutaneous reactions

•1924 L Aschoff, Reticuloendothelial system

•1926 Lloyd Felton & GH Bailey, Isolation of pure antibody preparation

•1934-8 John Marrack, Antigen-antibody binding hypothesis

•1936 Peter Gorer, Identification of the H-2 antigen in mice

•1940 Karl Lansteiner & Alexander Weiner, Identification of the Rh antigens

•1941 Albert Coons, Immunofluorescence technique

•1942 Jules Freund & Katherine McDermott, Adjuvants

•1942 Karl Landsteiner & Merrill Chase, Cellular transfer of sensitivity in guinea pigs (anaphylaxis)

•1944 Peter Medwar, Immunological hypothesis of allograft rejection

•1948 Astrid Fagraeus, Demonstration of antibody production in plasma B cells

•1948 George Snell, Congenic mouse lines

•1949 Macfarlane Burnet & Frank Fenner, Immunological tolerance hypothesis

•1950 Richard Gershon and K Kondo, Discovery of suppressor T cells

•1952 Ogden Bruton, discovery of agammaglobulinemia (antibody immunodeficiency)

•1953 Morton Simonsen and W J Dempster, Graft-versus-host reaction

•1953 James Riley & Geoffrey West, Discovery of histamine in mast cells

•1953 Rupert Billingham, Leslie Brent, Peter Medwar & Miriam Hasek, Immunological tolerance hypothesis

•1957 Niels Jerne, David Talmage, Macfarlane Burnet, Clonal selection theory

•1957 Ernest Witebsky et al., Induction of autoimmunity in animals

•1957 Alick Isaacs & Jean Lindemann, Discovery of interferon (cytokine)

•1958-62 Jean Dausset et al., Human leukocyte antigens

•1959-62 Rodney Porter et al., Discovery of antibody structure

•1959 James Gowans, Lymphocyte circulation

•1961-62 Jaques Miller et al., Discovery of thymus involvement in cellular immunity

•1961-62 Noel Warner et al., Distinction of cellular and humoral immune responses

•1963 Jacques Oudin et al., antibody idiotypes

•1964-8 Anthony Davis et al., T and B cell cooperation in immune response

•1965 Thomas Tomasi et al., Secretory immunoglobulin antibodies

•1967 Kimishige Ishizaka et al., Identification of IgE as the reaginic antibody

•1971 Donald Bailey, Recombinent inbred mouse strains

•1974 Rolf Zinkernagel & Peter Doherty, MHC restriction

•**1975 Kohler and Milstein, Monoclonal antibodies used in genetic analysis**

•1984 Robert Good et al., Failed treatment of severe combined immunodeficiency (SCID, David the bubble boy) by bone marrow grafting. 1985 Tonegawa, Hood et al., Identification of immunoglobulin genes

•1985 Leroy Hood et al., Identification of genes for the T cell receptor

•1990 Yamamoto et al., Molecular differences between the genes for blood groups O and A and between those for A and B

•1990 NIH team, Gene therapy for SCID using cultured T cells.

•1993 NIH team, Treatment of SCID using genetically altered umbilical cord cells.

•1985-onwards Rapid identification of genes for immune cells, antibodies, cytokines and other immunological structures.

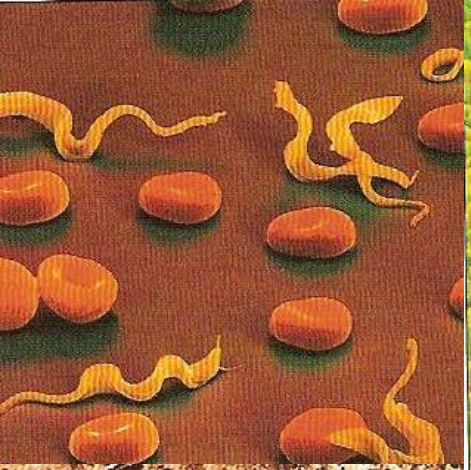
•1798 Edward Jenner, Smallpox vaccination

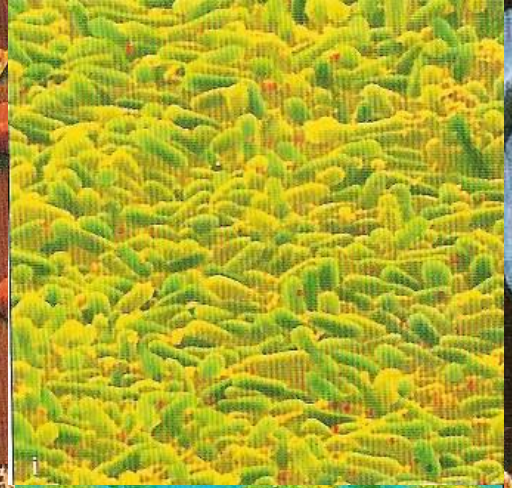
•1975 Kohler and Milstein, Monoclonal antibodies used in genetic analysis

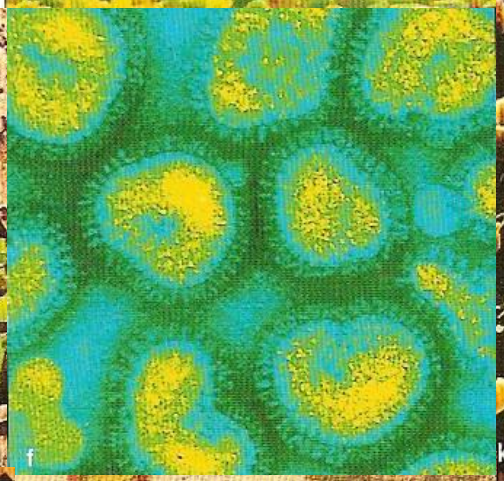
NOBEL LAUREATES IN IMMUNOLOGY

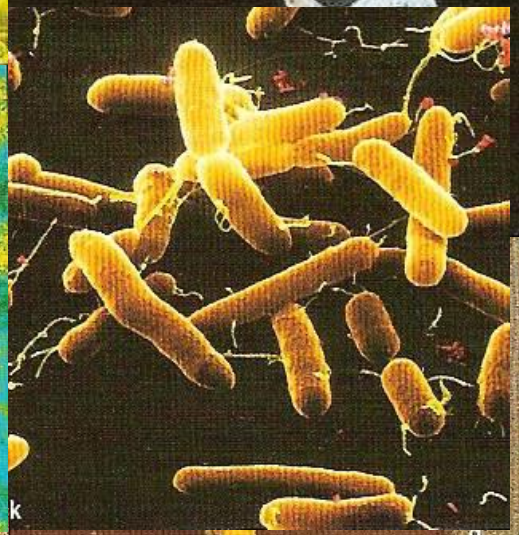
YEAR	RECIPIENT	COUNTRY	RESEARCH
1901	E.A. Von Behring	Germany	Serum antitoxins
1905	Robert Koch	Germany	Cellular immunity to tuberculosis
1908	Elie Metchnikoff Paul Ehrlich	Russia Germany	Role of phagocytosis in immunity Role of antitoxins in immunity
1913	Charles Robert Richet	France	Anaphylaxis
1919	Jules Bordet	Belgium	Complement-mediated bacteriolysis
1930	Karl Landsteiner	United States	Discovery of human blood groups
1951	Max Theiler	South Africa	Development of yellow fever vaccine
1957	Daniel Bovet	Switzerland	Antihistamines
1960	Sir. Macfarlane Burnet Sir. Peter B. Medawar	Australia Great Britain	Discovery of acquired immonological tolerance
1972	Gerald M. Edelman Rodney R. Porter	United States Great Britain	Chemical structure of antibodies
1977	Rosalyn R. Yalow	United States	Development of radioimmunoassay
1980	Baruj Benacerraf Jean Dausset George D. Snell	United States France Sweden	Major histocompatibility complex

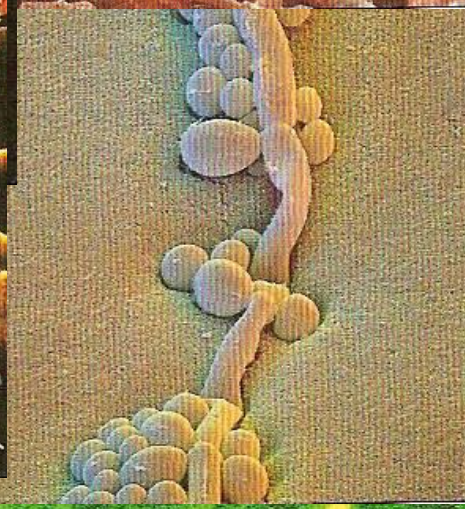
YEAR	RECIPIENT	COUNTRY	RESEARCH
1982	Sune K. Bergstrom Bengt L. Sammelson Sir. John R. Vane	Sweden Sweden United Kingdom	Prostaglandins and related biologically active substances
1984	Cesar Milstein Georges J. F. Kohler Neils K. Jerne	Great Britain Germany Denmark	Monoclonal antibody ,, Immune regulatory theories
1987	Susumu tonegawa	Japan	Gene rearrangement in antibody production
1990	Joseph E. Murray E. Donnall Thomas	United States United States	Transplantation immunology
1996	Peter C. Doherty Rolf M. Zinkernagel	Australia Switzerland	The specificity of the cell-mediated immune response

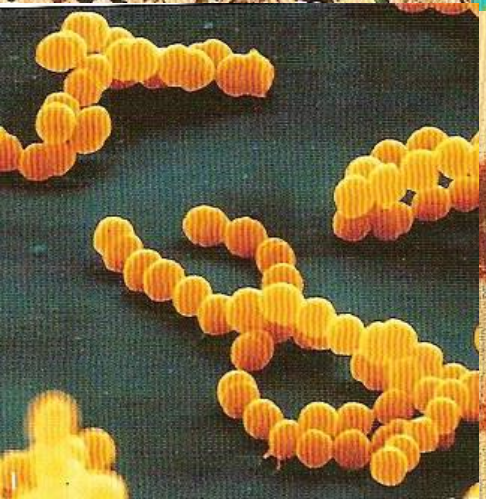


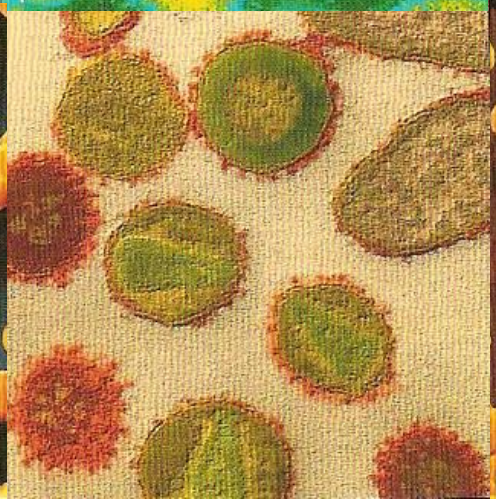


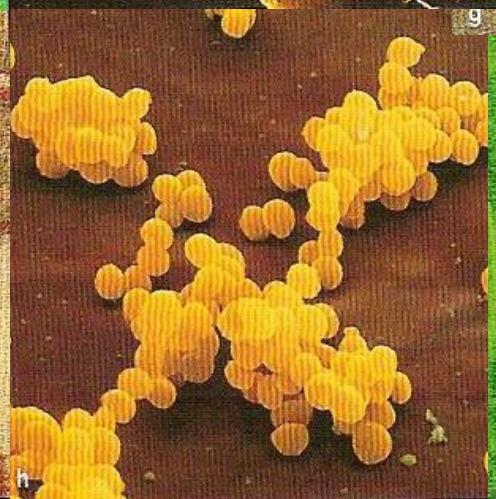












Immunology lingo

- **Antigen**
  - Any molecule that binds to immunoglobulin or T cell receptor
- **Pathogen**
  - Microorganism that can cause disease
- **Antibody (Ab)**
  - Secreted immunoglobulin
- **Immunoglobulin (Ig)**
  - Antigen binding molecules from B cells
- **Vaccination**
  - Deliberate induction of protective immunity to a pathogen
- **Immunization**
  - The ability to resist infection

The immune system is defined as the host’s defense against destructive forces from both outside (e.g., bacteria, viruses, parasites) and within (e.g., malignant and autoreactive cells) the body. Immune responses are generally classified as either innate or acquired.

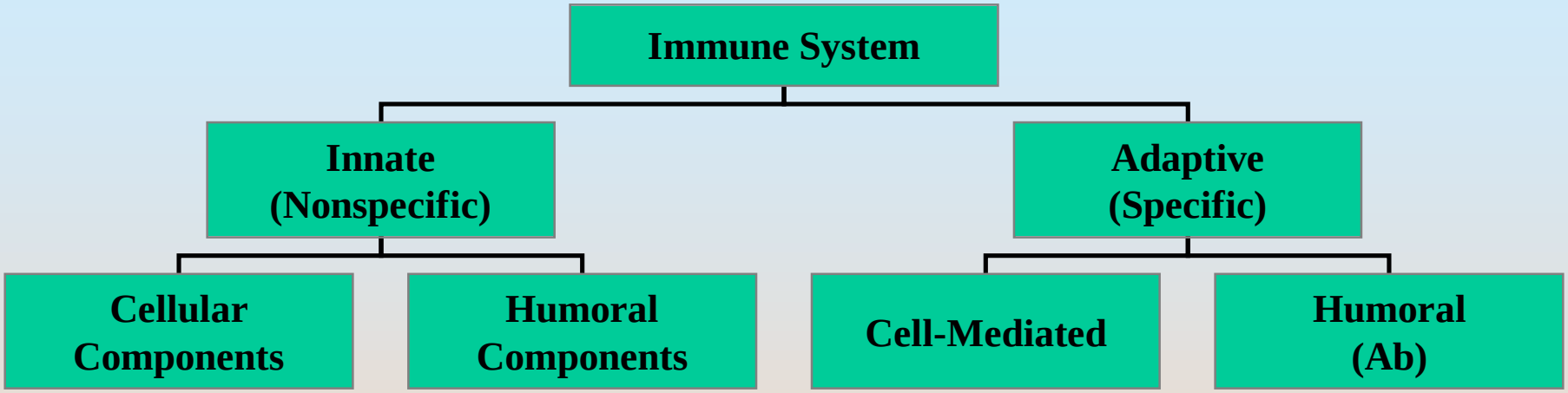
Types of Immunity

- **Innate Immunity**

  The innate immune system provides immunity to invading organisms without the need for prior exposure to these antigens and includes physical barriers, such as the skin and mucous membranes; cell-mediated barriers, including phagocytic cells, inflammatory cells, dendritic cells, and natural killer cells; and soluble mediators, such as cytokines, complement proteins, and acutephase proteins. This arm of the immune system provides the early phases of host defense that protect the organism during the four to five days it takes for lymphocytes to become activated.

- **Adaptive Immunity**

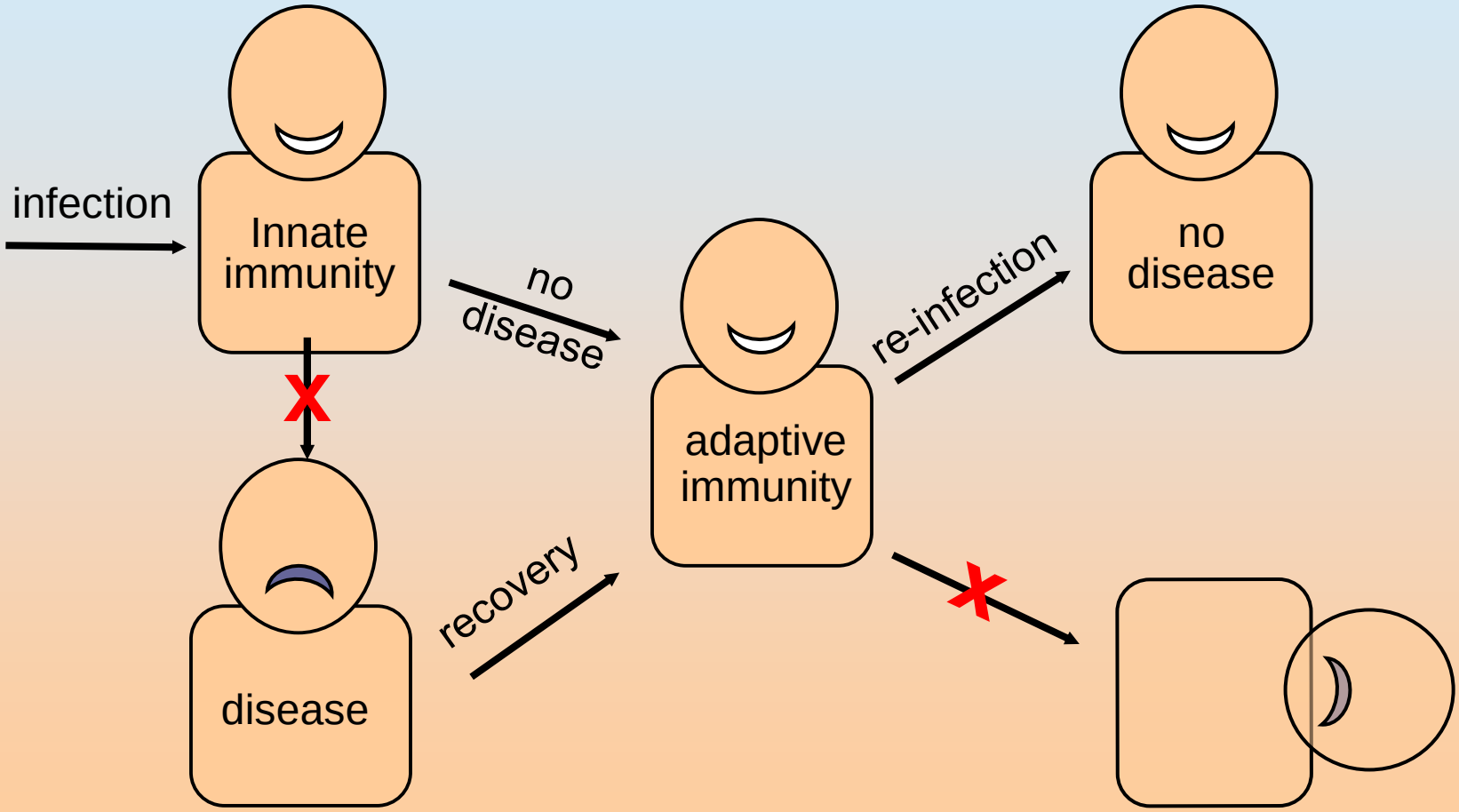
  The acquired, or adaptive, immune system develops over an individual's lifetime. Lymphocytes are an important cellular component of this arm of the immune system that modulate the function of other immune cells or directly destroy cells infected with intracellular pathogens**.** Each developing T or B cell generates a unique receptor, or recognition molecule, such that a set of cells expressing a vast array of diverse receptors is produced, allowing immune cells to selectively eliminate virtually any foreign antigen that enters the body.


Immune System
Innate
(Nonspecific)
Adaptive
(Specific)
Cellular
Components
Humoral
Components
Cell-Mediated
Humoral
(Ab)

Types of Immunity

- **Humoral immunity**
  - Immunity that is mediated by antibodies
  - Can be transferred by to a non-immune recipient by serum
- **Cell Mediated Immunity**
  - Immune response in which antigen specific T cells dominate

Response to Infection



Characteristics of Innate and Adaptive Immunity

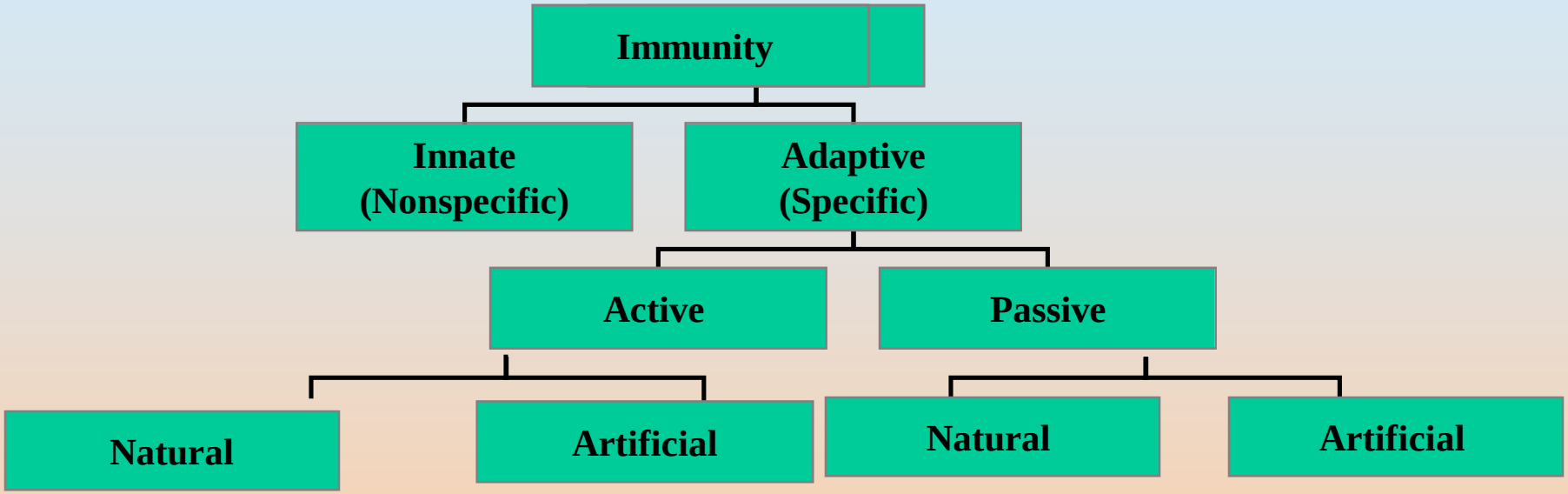
Innate Immunity	Adaptive Immunity
Antigen independent	Antigen dependent
No time lag	A lag period
Not antigen specific	Antigen specific
No Immunologic memory	Development of memory

Components of Innate and Adaptive Immunity

Innate Immunity	Adaptive Immunity
physical barriers	
skin, gut Villi, lung cilia,etc	none
soluble factors	
many protein and non-protein secretions	Immunoglobulins (antibody)
cells	
phagocytes, NK cell eosinophils, K cells	T and B lymphocytes

Arm of immune system	Defenses	Components	Functions
Innate immune system	Physical barriers	Skin Mucous membranes	Prevent the entry of antigens into systemic circulation
	Cell-mediated barriers	Phagocytic cells, e.g., neutrophils, macrophages	Engulf foreign antigens
		Inflammatory cells, e.g., basophils, mast cells Natural killer cells Dendritic cells	Release inflammatory mediators, e.g., histamine, prostaglandins
	Soluble factors	Cytokines Complement proteins Acute-phase proteins	Destroy infected or malignant cells Present antigens to lymphocytes
Acquired immune system	B lymphocytes T lymphocytes	Plasma cells	Activate/recruit other cells Enhance phagocytosis Promote repair of damaged tissue
		$CD4^+$ T-cells Th1 cells Th2 cells Th17 cells Tregs	Secrete antibodies Induce activation of lymphocytes Promote cell-mediated responses Promote humoral (antibody) responses
		$CD8^+$ T-cells Cytotoxic T-cells Suppressor T-cells	Peripheric tolerance Destroy infected or malignant cells Suppress activity of lymphocytes

Different modes of acquiring immunity



Follows clinical or subclinical infection

Induced by vaccination

Transplacental transport of IgG

Blood transfusion

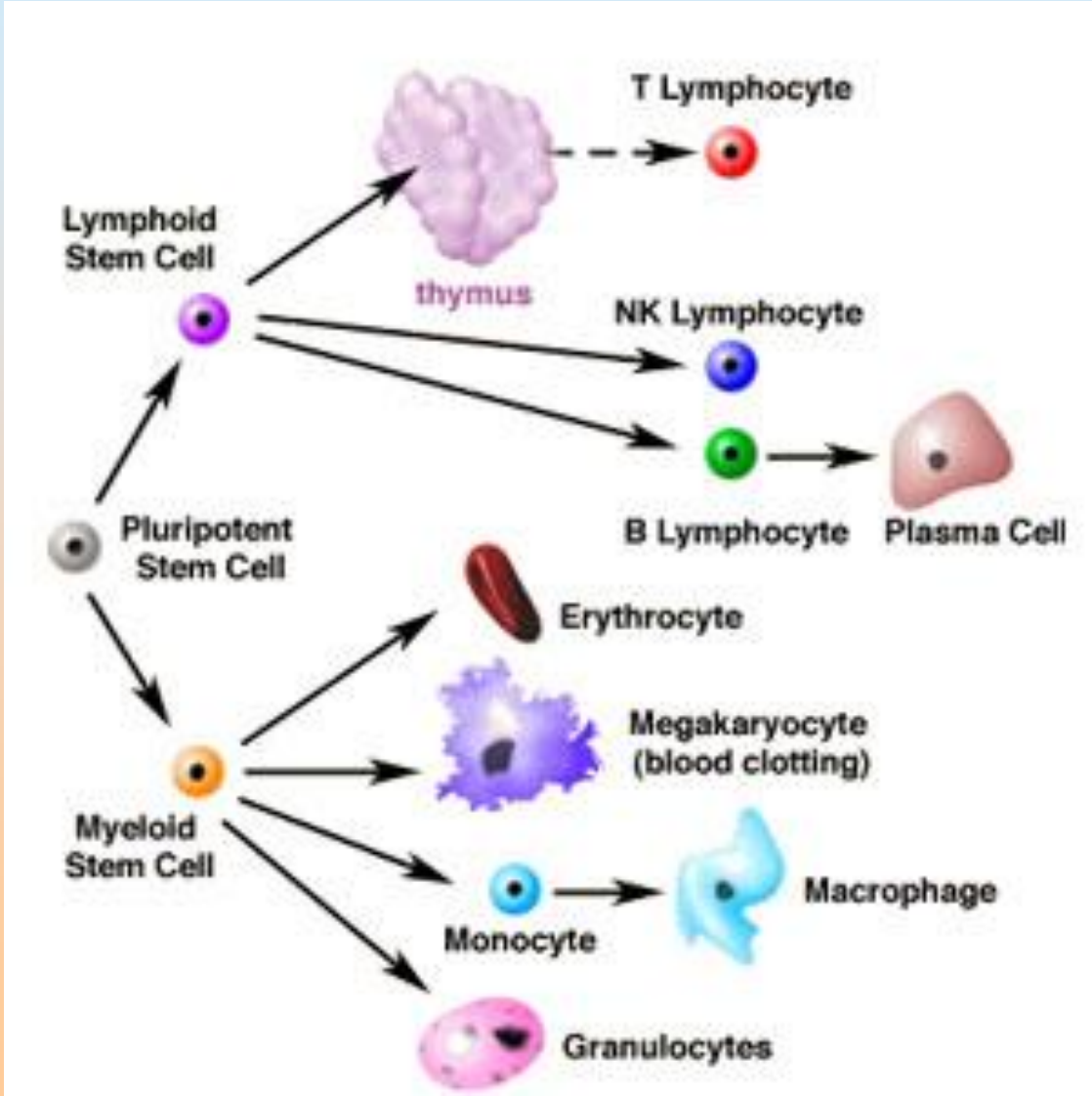
Bonemarrow transplantation

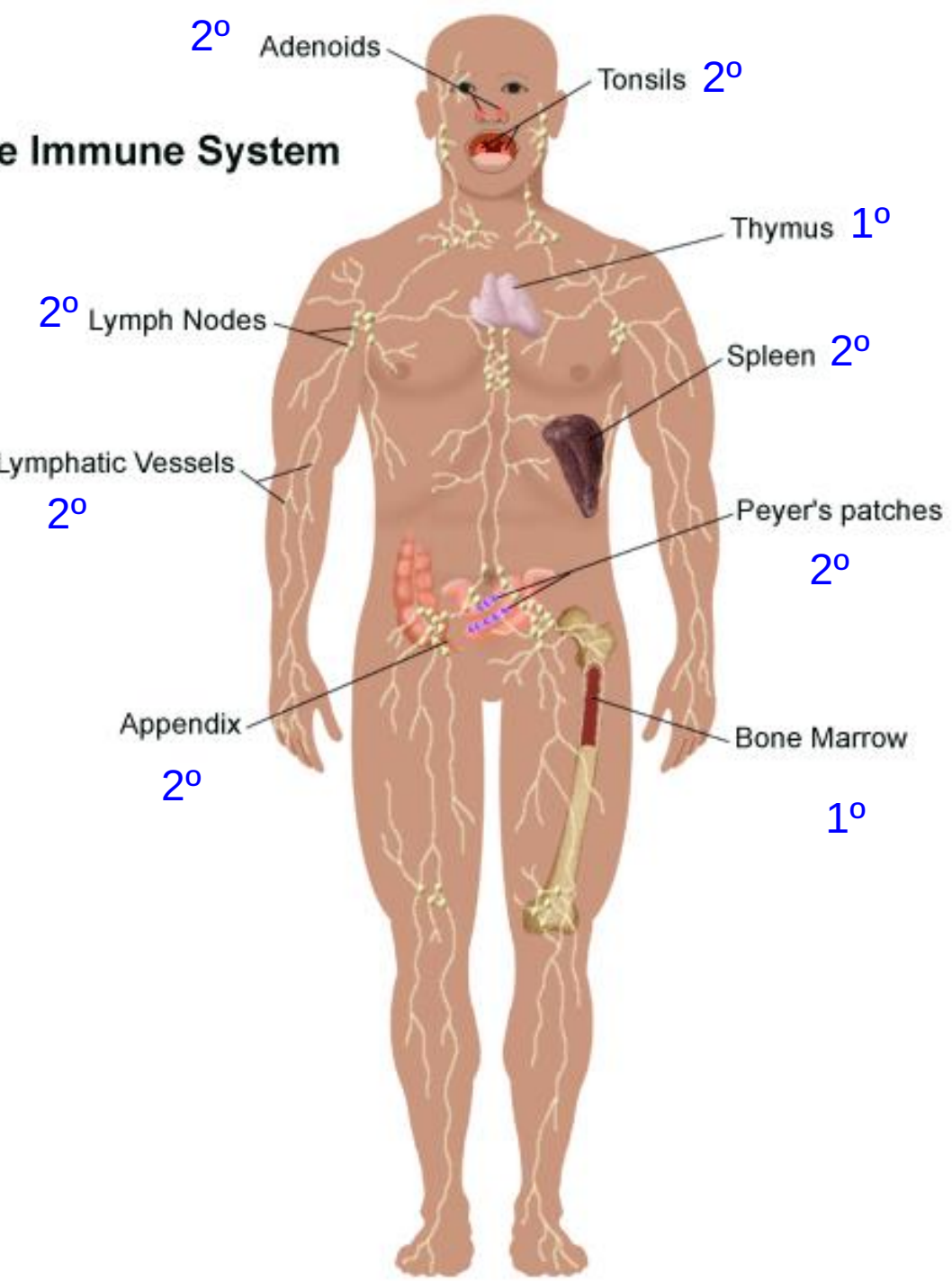
Immuno-responsive cells

- Polymorphonuclear
  - Lobed nucleus
- Mononuclear
  - Non-lobed nucleus
- Granulocyte
  - Many granules seen in cytoplasm
- Neutral
  - Does not stain to acidic or basic compounds
- Acidic (red-pink)
  - Stains to acidic compounds (Eosin)
- Basic (blue-purple)
  - Stains to basic compounds

Cells of the Immune system

- Many cells of the immune system derived from the bone marrow
- Hematopoetic stem cell differentiation

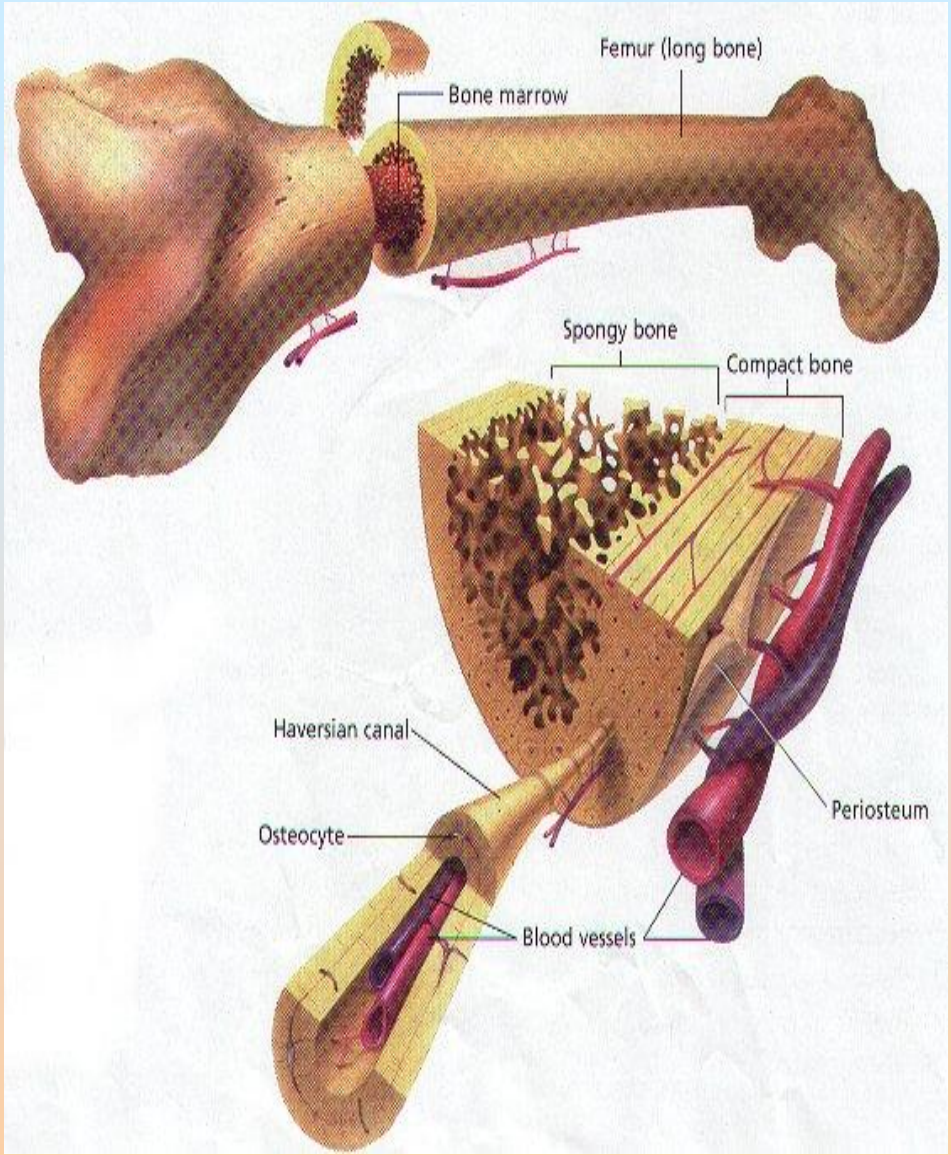


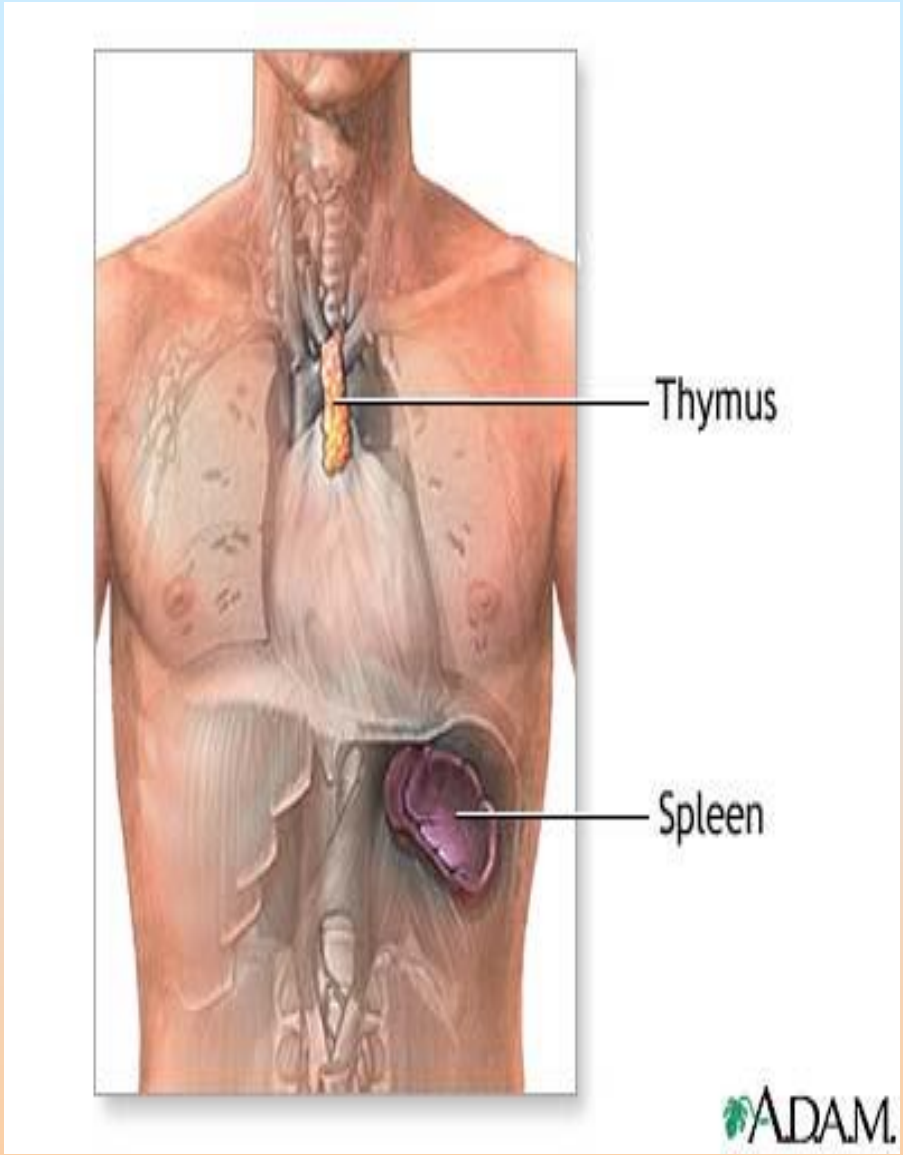


Major Tissues

1 Primary Lymph tissues
  – Cells originate or mature

2 Secondary Lymph Tissues


Femur (long bone)
Bone marrow
Spongy bone
Compact bone
Haversian canal
Osteocyte
Periosteum
Blood vessels


Thymus
Spleen
A.D.A.M.

Primary immune organs and their role in the immune system.

Primary immune organs

- **Bone marrow**
- **Thymus**

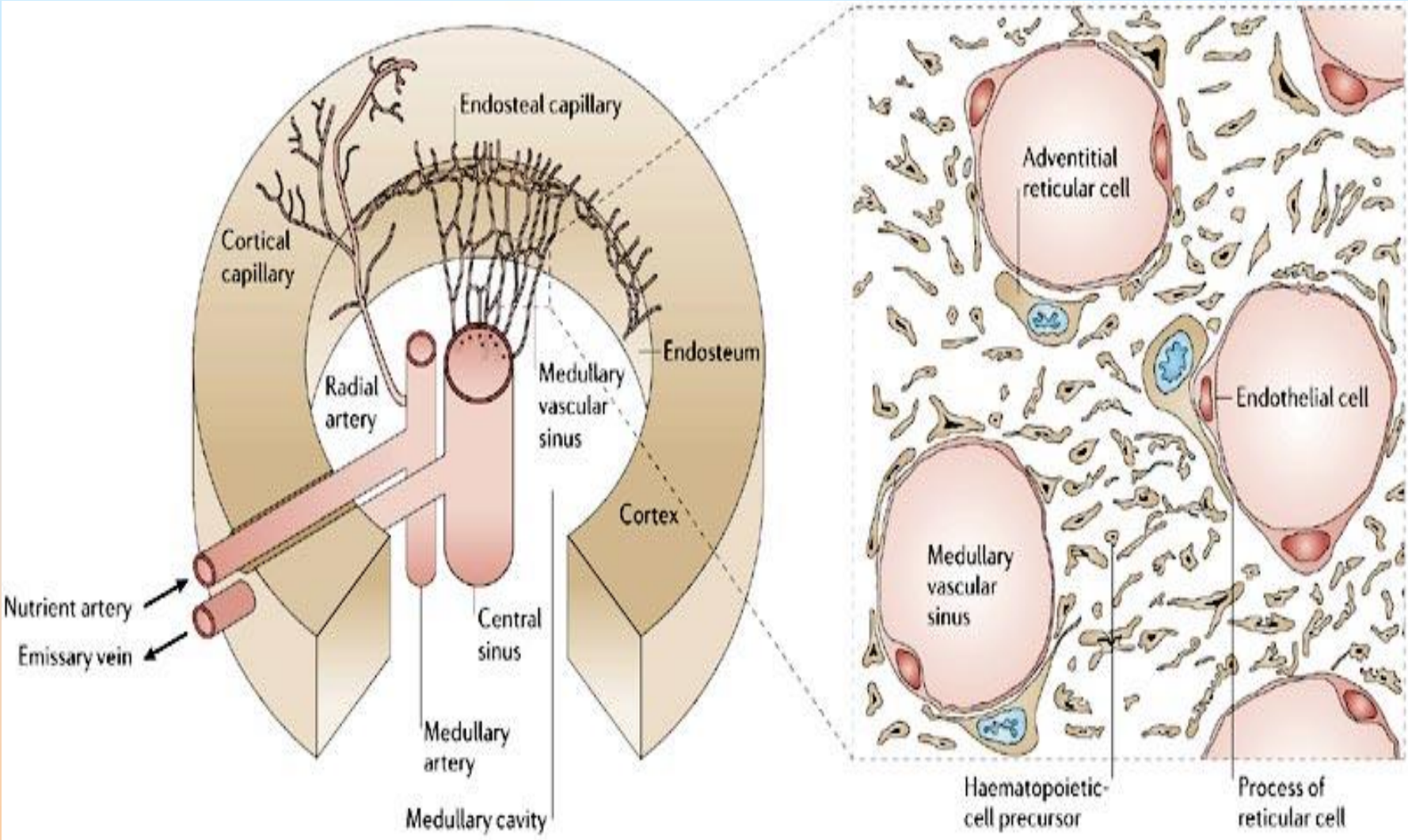
- are places of development, differenciation and maturation of immunocompetent cells and elimination of autoreactive cells

- T and B lymphocytes mature and become competent to respond to antigens in PIOs

Bone marrow

is the central cavity of bone that is the site of generation of all circulating blood cells in the adult, including immature lymphocytes, and the site of B-cell maturation.

- **The pluripotent stem cell gives rise to the progenitor of all immune cells**
- **Production of cells course in the places divided by** vascullar **sinuses**
- Endothelial cells of the sinuses produce **cytokines**
- Sinuses are borded by **reticular cells**



Nature Reviews | Immunology

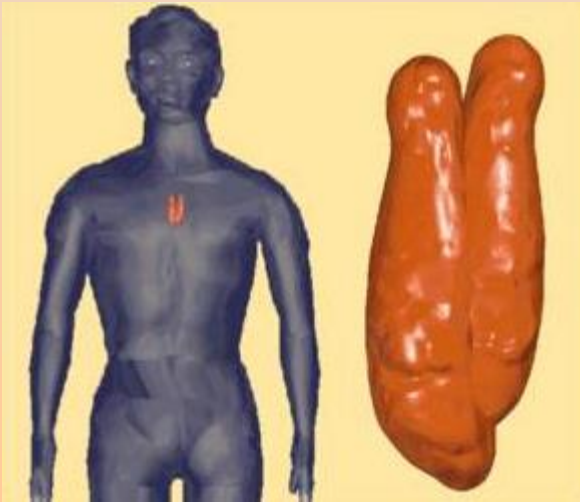
Differentiation in the BM

- Differentiation from the stem cell is influenced by:

- membrane interaction between the stem cells and the stromal cells
- cytokines (**CSF, IL-3, trombopoetin, erytropoetin**)

Thymus

- is located between the sternum and the major vessel trunks
- It consist of two lobes
- Each lobe is surrounded by a capsule and is divided into lobules, which are separated from each other by strands of connective tissue = trabeculae

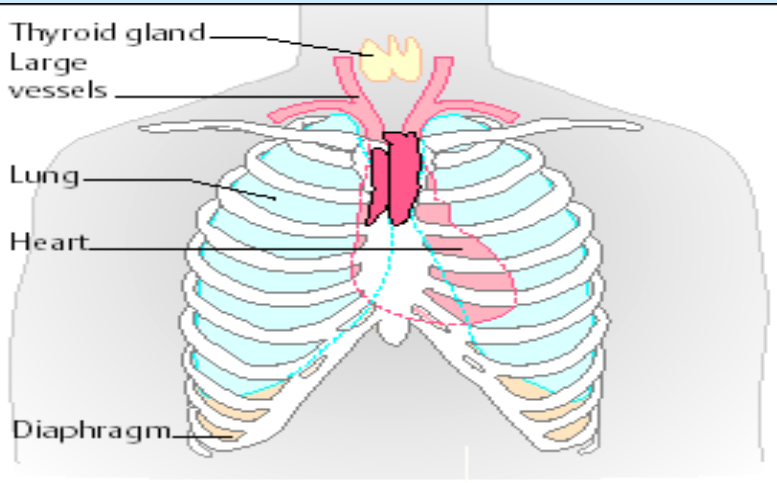


Structure of the thymus

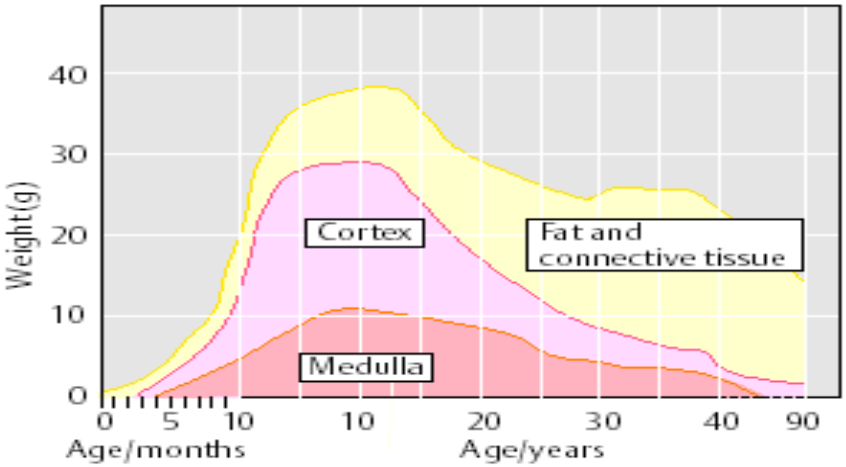
Each lobule is organized into two compartments:

- the cortex (outer compartment) – contains lymphocytes that proliferate

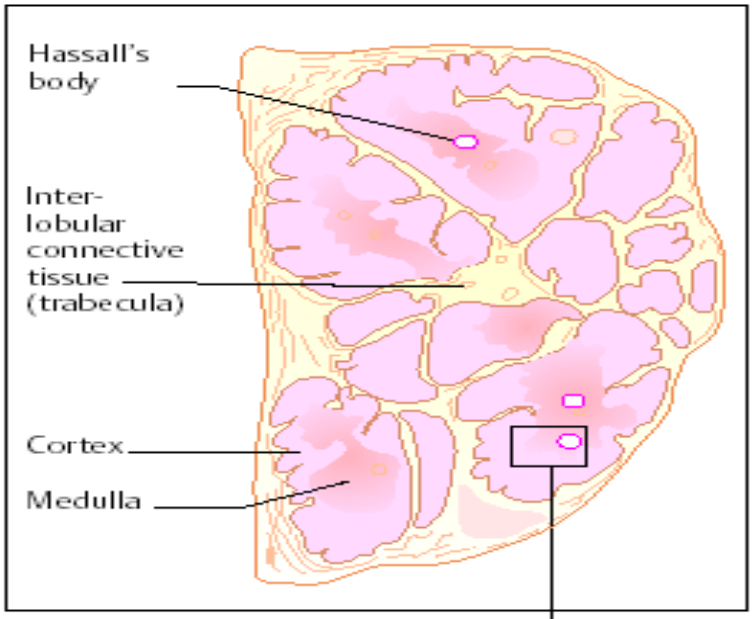
- the medulla (inner compartment)- mature lymphocytes, Hassall´s bodies



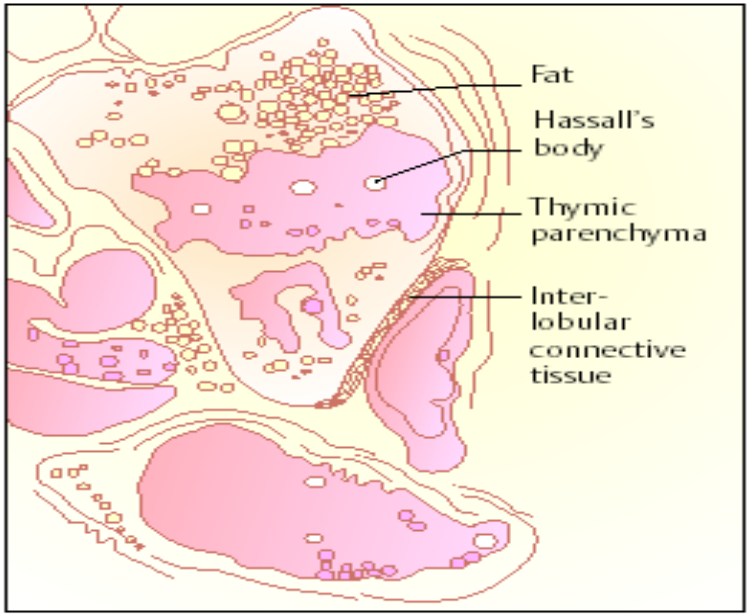
1. Position of the thymus



2. Growth curve



3. Thymus of a newborn



4. Thymus of an adult

Thymus - morphology

stromal cells composed of:

- **thymic epithelial cells** – produce thymulin, thymopoetin, thymosin that influence the maturation of T cells

- **dendritic cells**
- **macrophages**

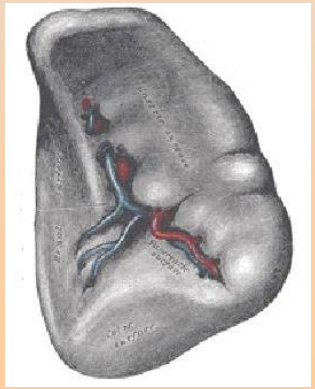
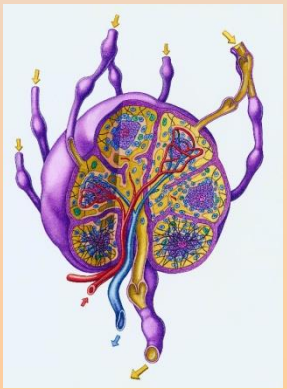
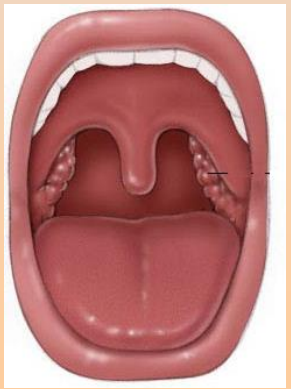
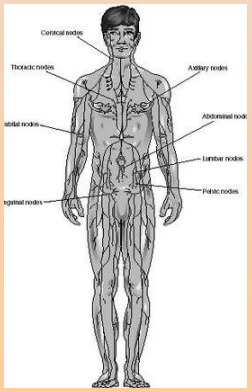
- The thymus contain a large number of blood vessels and efferent lymphoid vessels that drain into the mediastinal lymph nodes

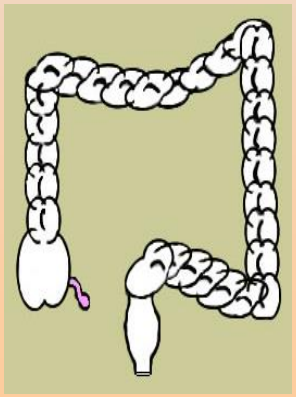
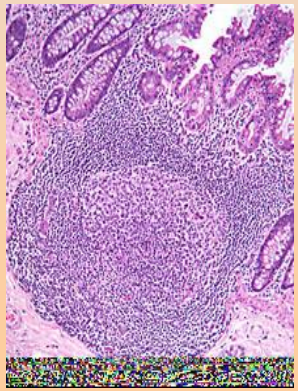
19. Secondary immune organs - structure and function of lymphatic node and spleen.

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

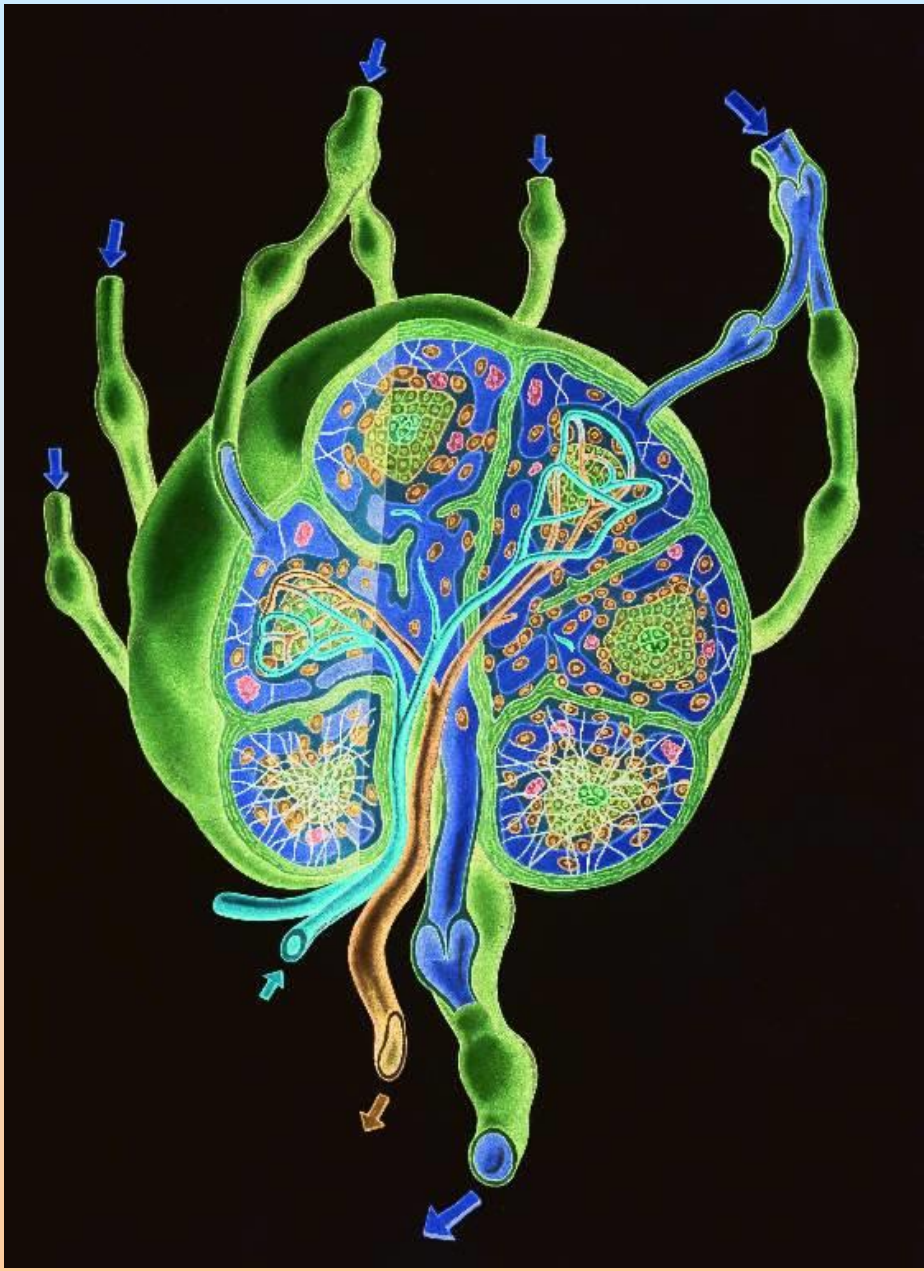
spleen **lymphatic nodes** **tonsils** **MALT** **appendix** **Peyer´s patches**

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



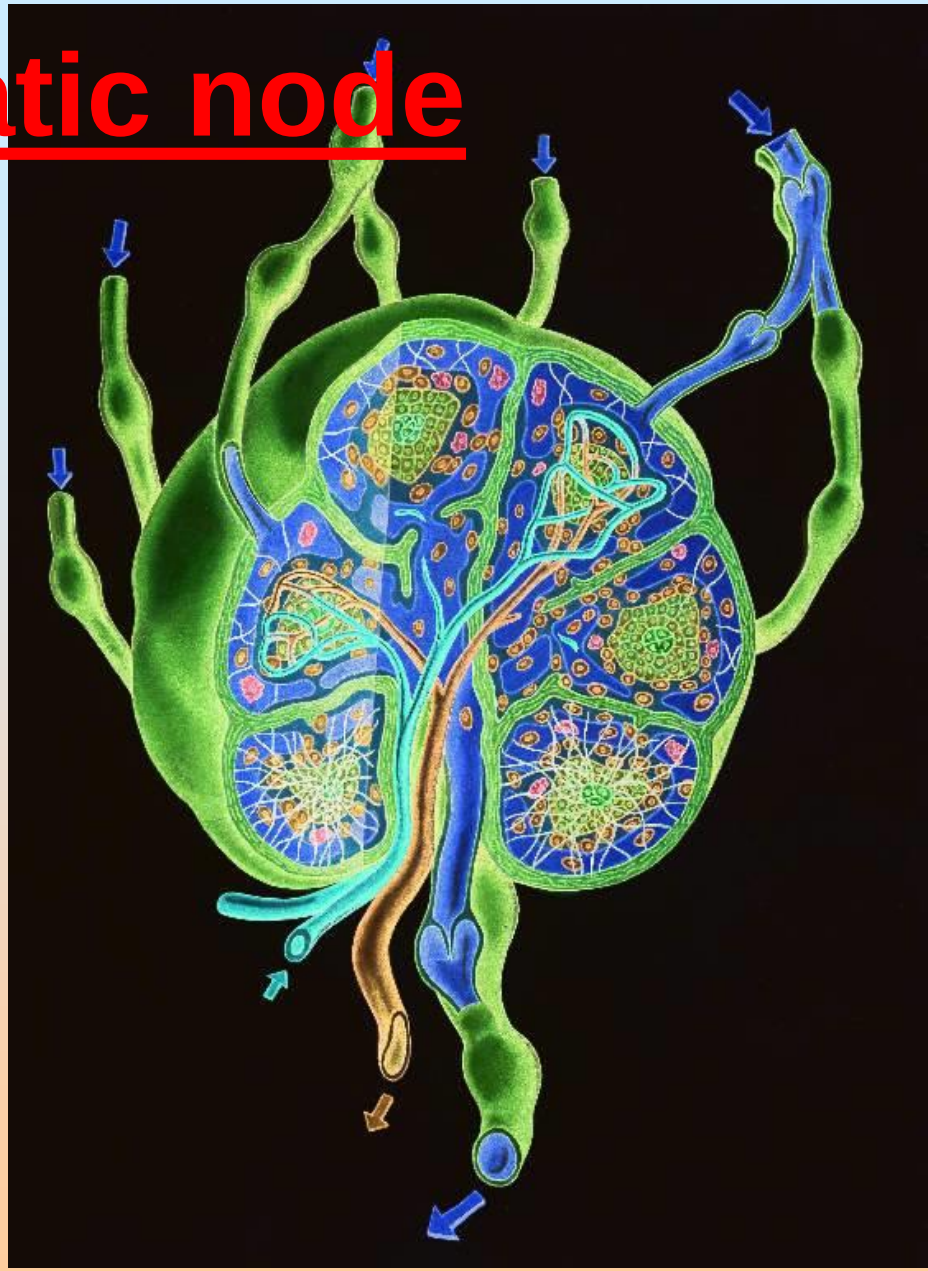
Lymphatic node

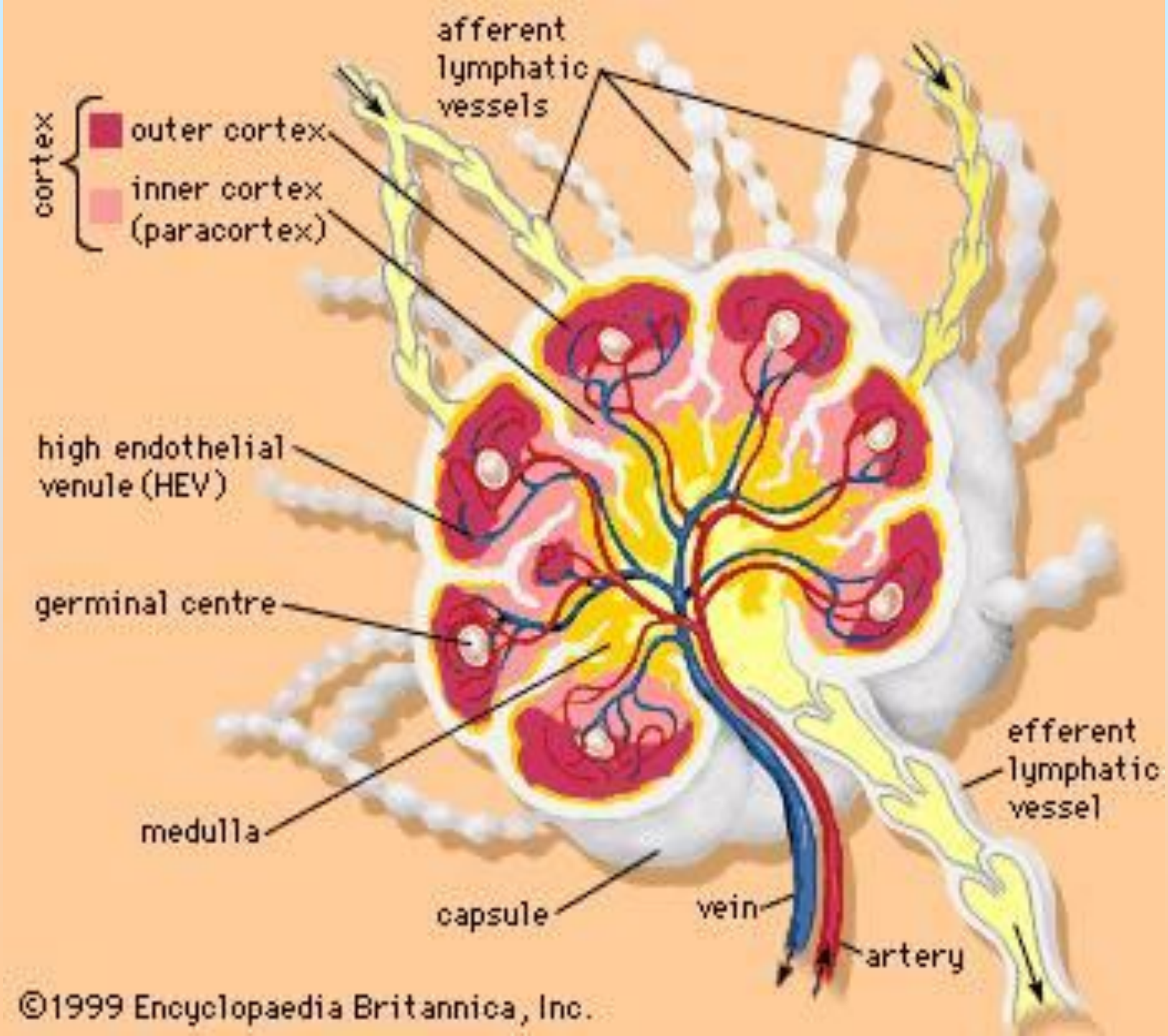
- lymph circulates to the lymph node via afferent lymphatic vessels and drains into the node just beneath the capsule in a space called the subcapsular sinus

- 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




afferent lymphatic vessels
cortex
outer cortex
inner cortex (paracortex)
high endothelial venule (HEV)
germinal centre
medulla
capsule
vein
artery
efferent lymphatic vessel
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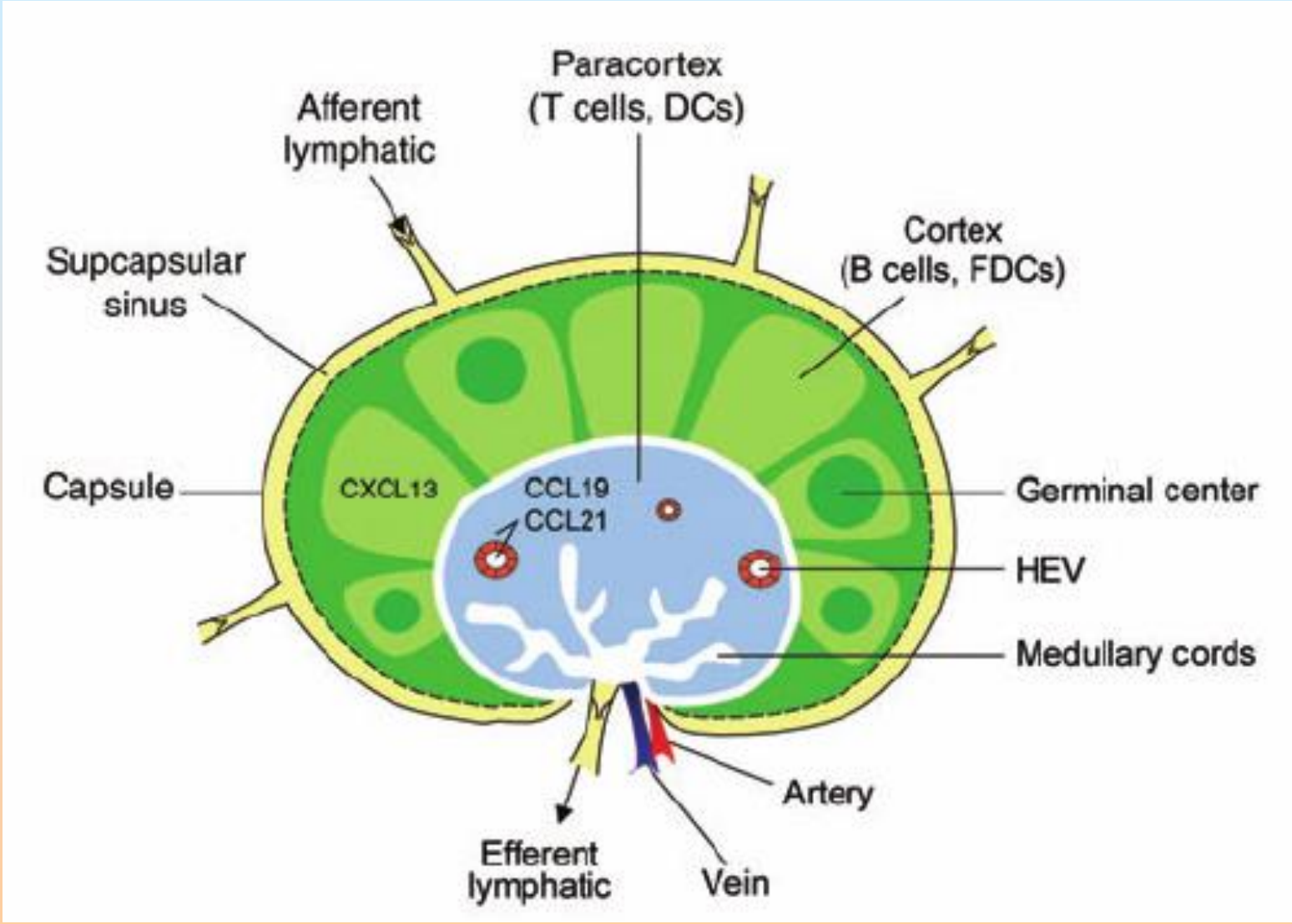

Paracortex
(T cells, DCs)
Afferent
lymphatic
Supcapsular
sinus
Cortex
(B cells, FDCs)
Capsule
CXCL13
CCL19
CCL21
Germinal center
HEV
Medullary cords
Artery
Efferent
lymphatic
Vein

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

Lymphatic node- cortex

Contains **lymphoid folicles** = acumulation of B-lymphocytes and folicular dentritic cells

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

Spleen

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

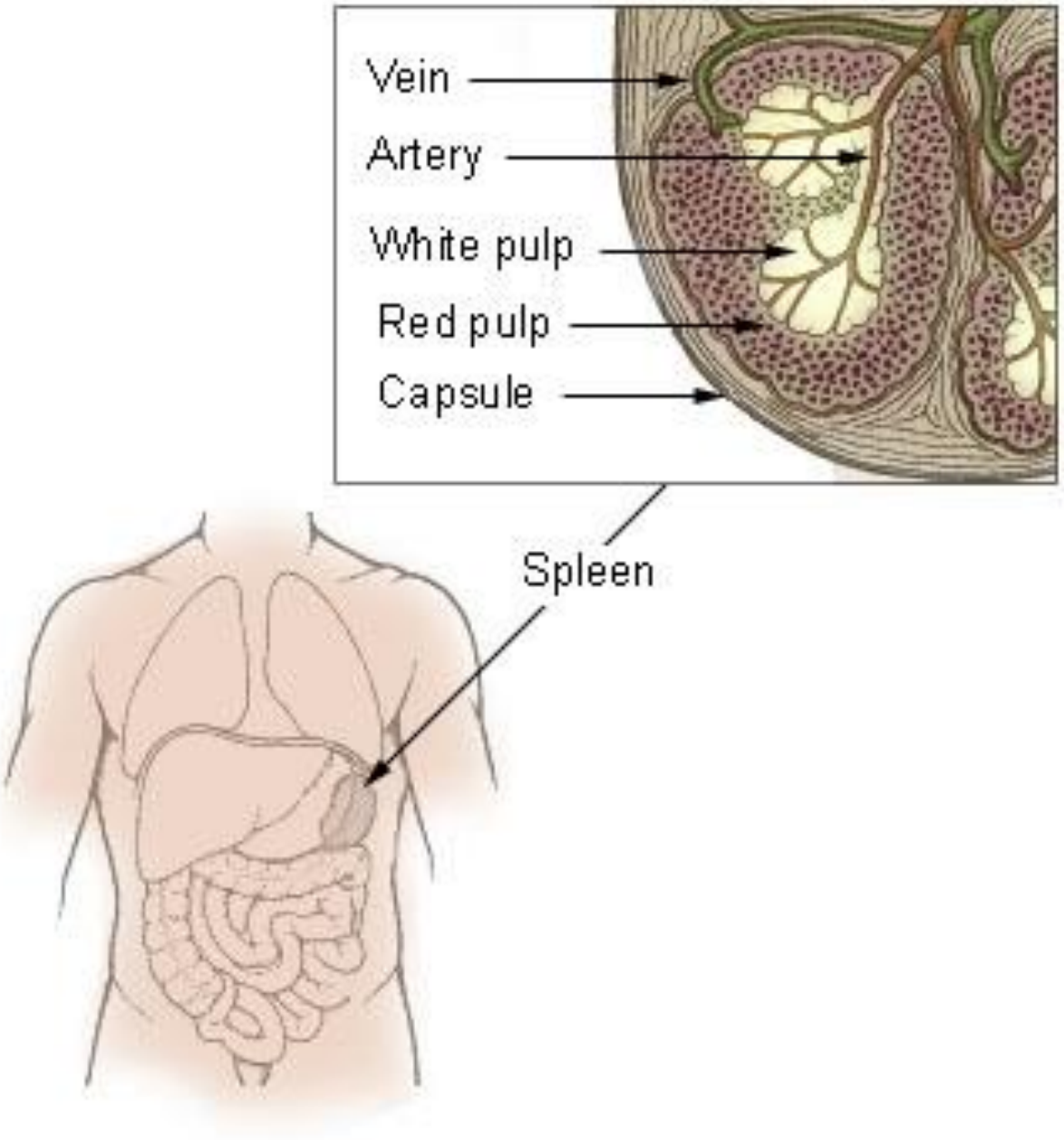
- is surrounded by a capsule, which sends trabeculae into the interior to form a compartmentalized structure
- there are two types of compartments -**red pulp** and **white pulp** with a marginal zone in between
- is NOT supplied by afferent lymphatics

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

Spleen



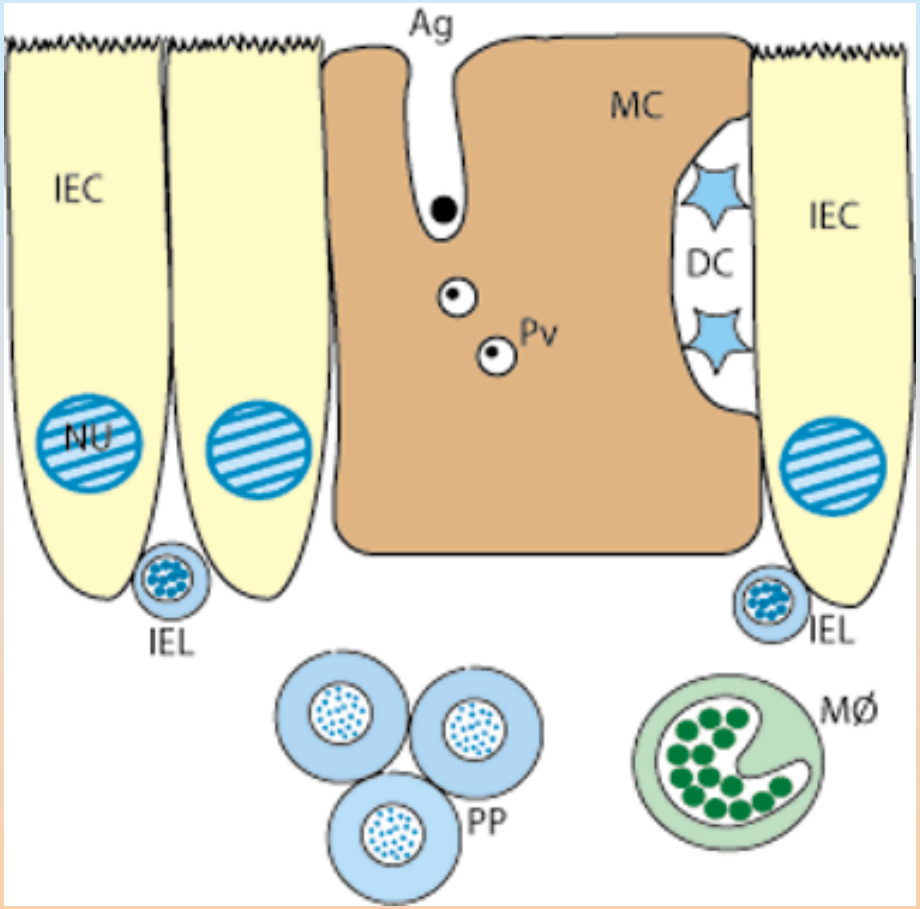
Mucosal immune system

- MALT = mucosal-associated lymphoid tissue
- GALT = gut-associated lymphoid tissue
- BALT = bronchus-associated lymphoid tissue
- digestive, respiratory, and urogenital systems are lined by mucous membranes
- includes loose clusters of lymphoid cells in lamina propria of intestinal villi
- contains a very large population of plasma cells that synthetize IgA antibodies

M cells

- are epithelial cells that are specialized for the transport antigen from the lumen of the respiratory, digestive, 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

DC: dendritic cells, **IEC**: intestinal epithelial cell (Nu-nucleus), **MC**: M cell, **IEL**: intra epithelial lymphocytes, **PP**: Peyer's patches, **MØ**: macrophages



Pv: particulate Ag in pinocytic vesicle of M cell

Secretory IgA

- daily production of secretory IgA into mucous 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

Cutaneous immune system

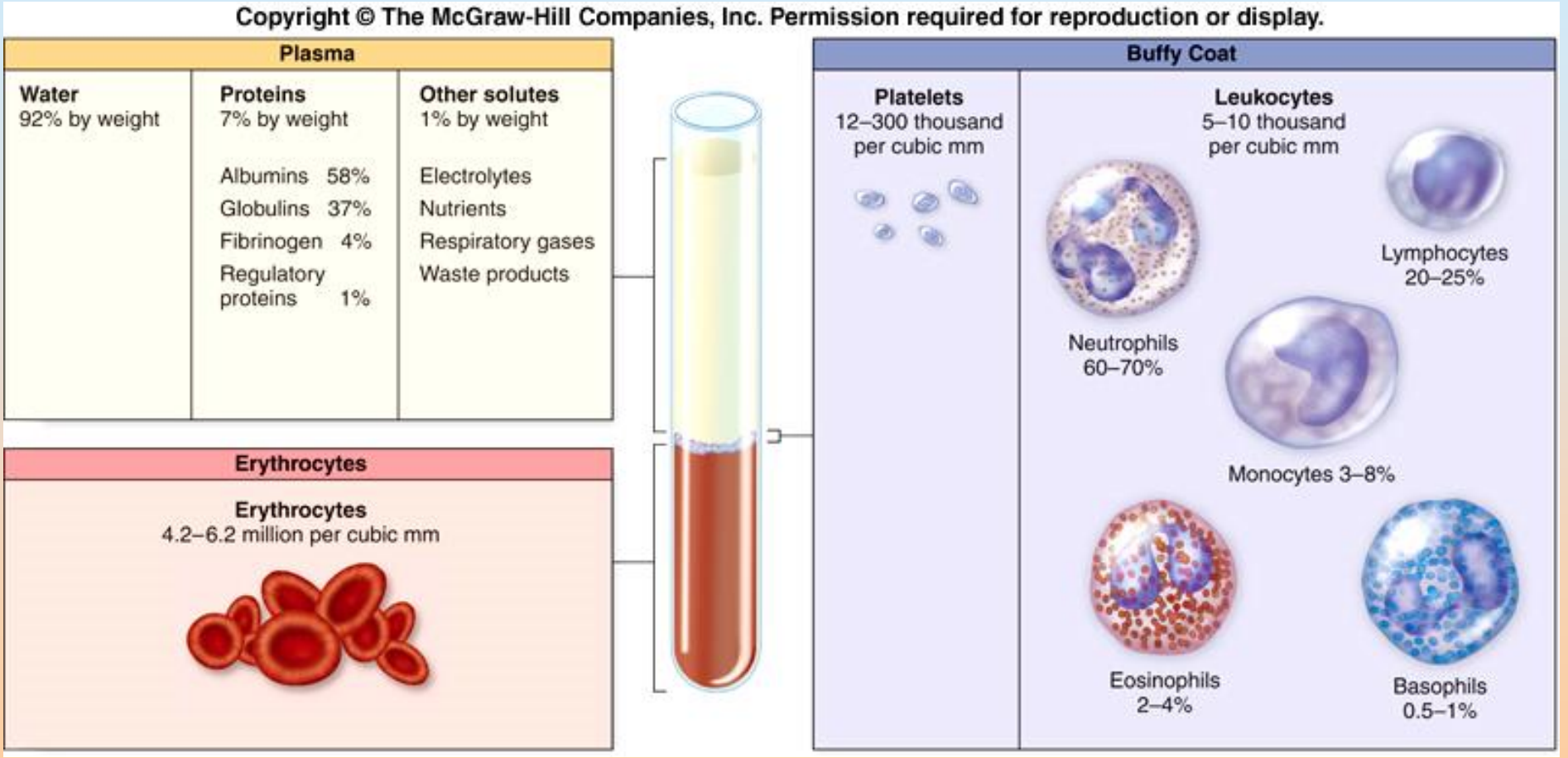
- **Epidermis** contains keratin cells that produce IL-1, 6 and TNF during inflamation; and IL-10, TGF-β during healing
- **Dermis** contains **fibroblasts** that produce collagen, remove apoptotic cells

Components of blood

Serum vs. Plasma

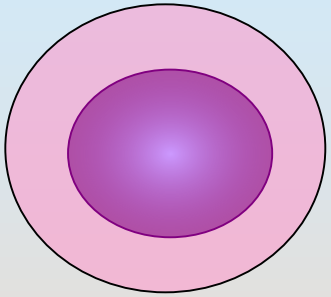
- Serum: cell-free liquid, minus the clotting factors
- Plasma: cell-free liquid with clotting factors in solution (must use an anticoagulant)

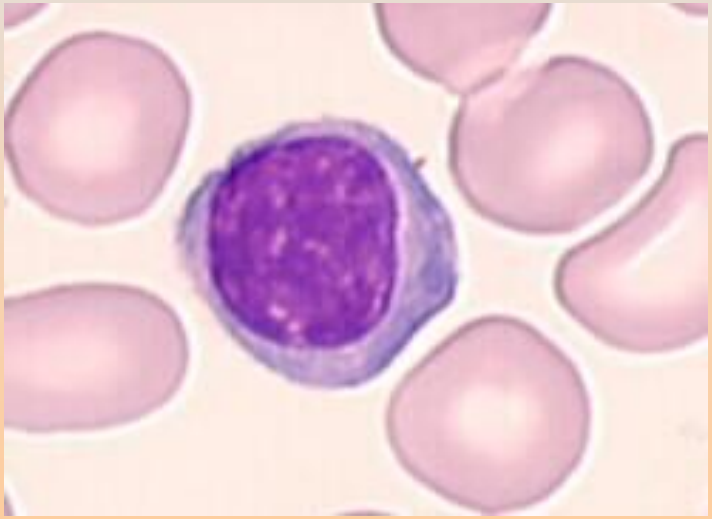
Components of blood



Lymphocytes

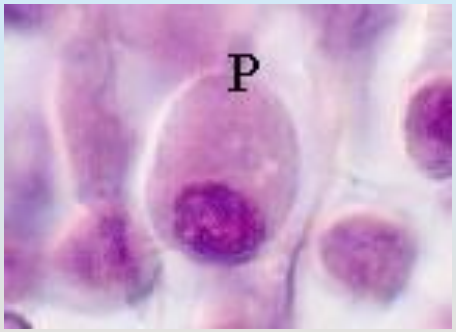
- Many types; important in both humoral and cell-mediated immunity
- B-cells produce antibodies
- T- cells
  - Cytotoxic T cells
  - Helper T cells
- Memory cells

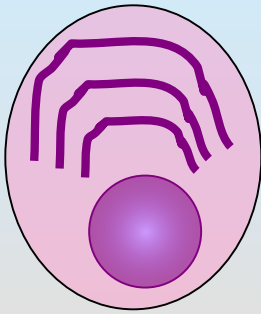


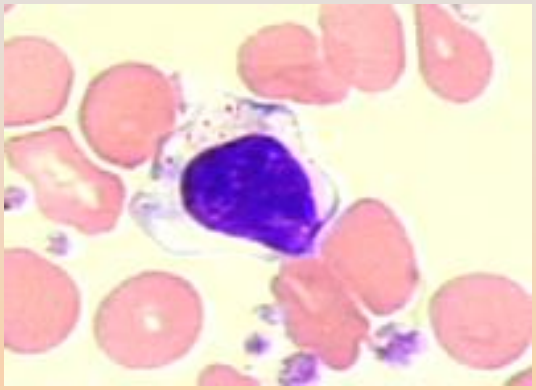


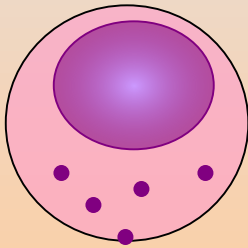
Lymphocytes

- Plasma Cell (in tissue)
  - Fully differentiaited B cells, secretes Ab
- Natural Killer cells
  - Kills cells infected with certain viruses
  - Both innate and adaptive
  - Antigen presentation



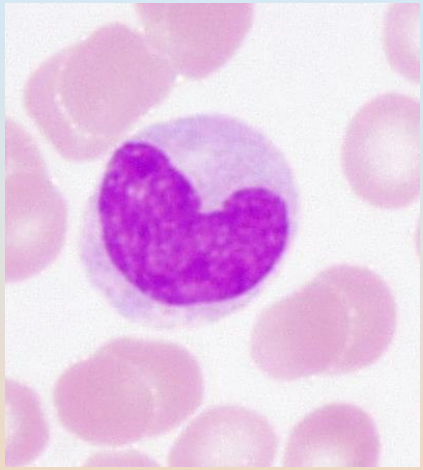


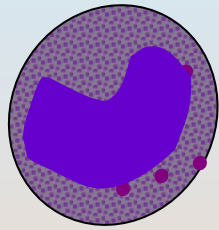


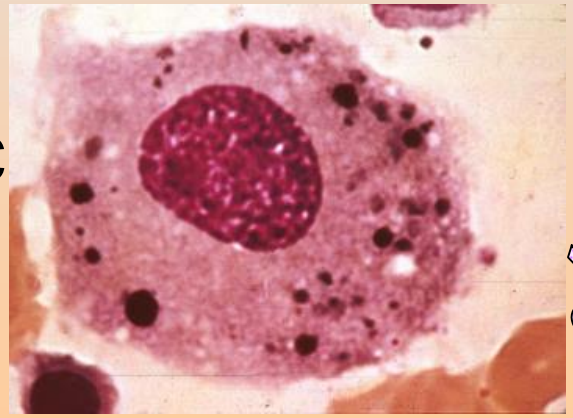


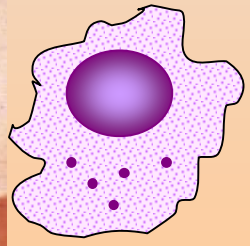
Monocytes/Macrophage

- Phagocytosis and killing of microorganisms
  - Activation of T cells and initation of immune response
- Monocyte is a young macrophage in blood
- There are tissue-specific macrophages
- Antigen Presentation



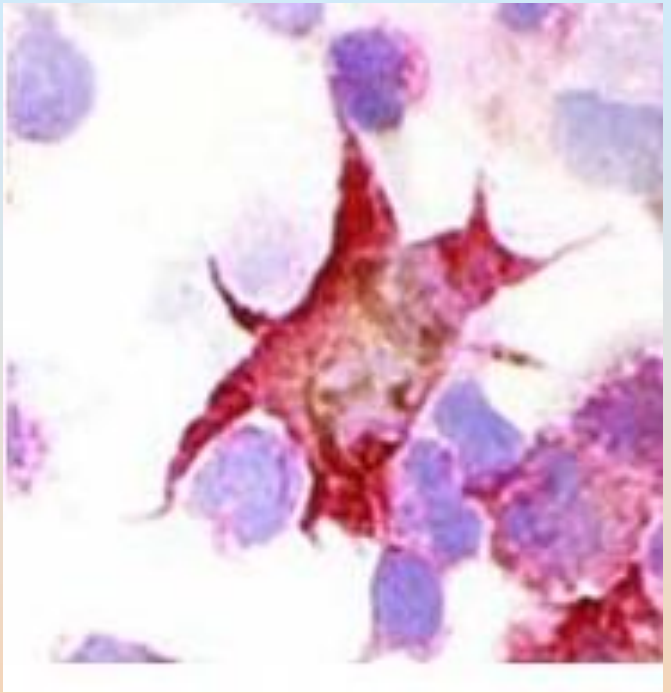


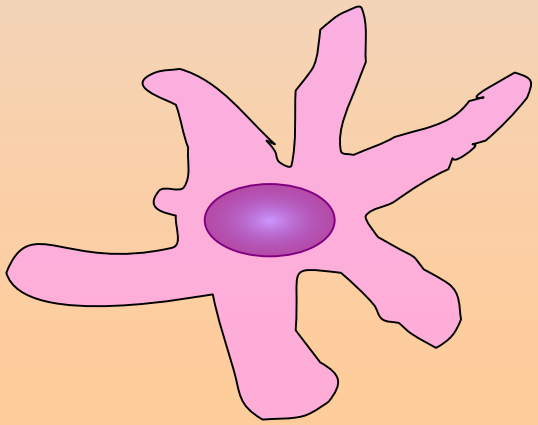




Dendritic Cells

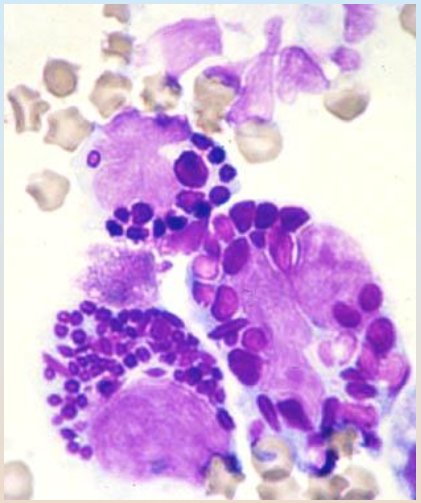
- Activation of T cells and initiate adaptive immunity
- Found mainly in lymphoid tissue
- Function as antigen presenting cells (APC)
- Most potent stimulator of T-cell response

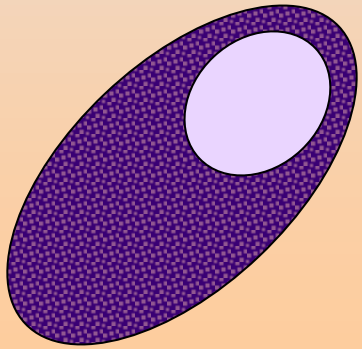




Mast Cells

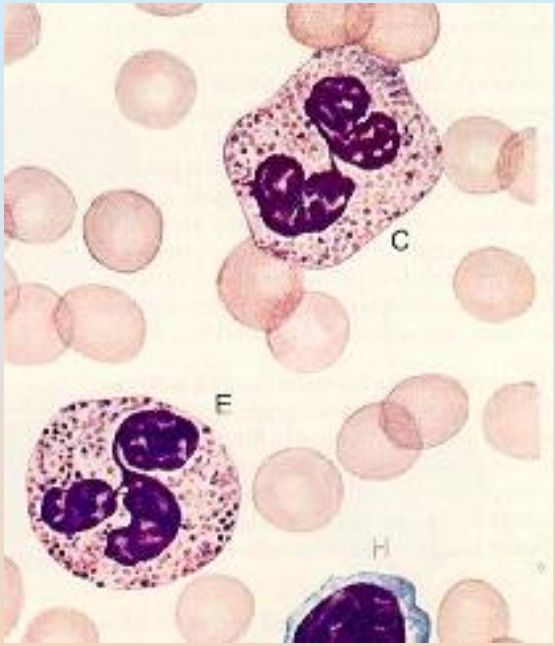
- Expulsion of parasites through release of granules
- Histamine, leukotrienes, chemokines, cytokines
- Also involved in allergic responses

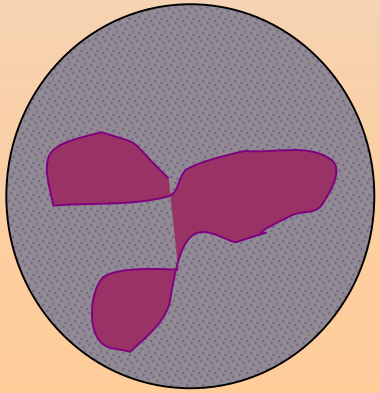




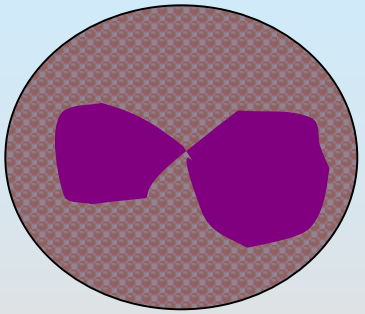
Neutrophil

- Granulocyte
  - Cytoplasmic granules
- Polymorphonuclear
- Phagocytosis
- Short life span (hours)
- Very important at “clearing” bacterial infections
- Innate Immunity

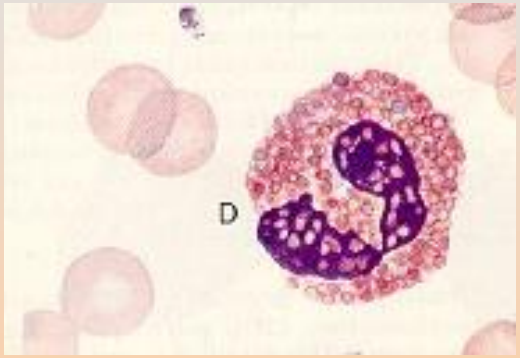




Eosinophils

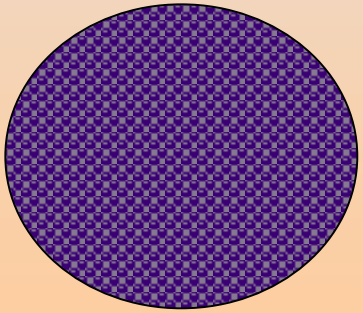


- Kills Ab-coated parasites through degranulation
- Involved in allergic inflammation
- A granulocyte
- Double Lobed nucleus
- Orange granules contain toxic compounds



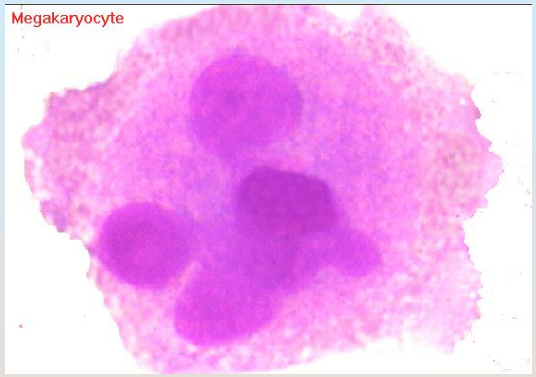
Basophils

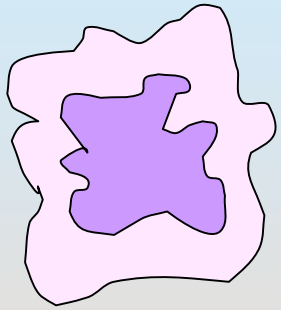
- Might be “blood Mast cells’
- A cell-killing cells
  - Blue granules contain toxic and inflammatory compounds
- Important in allergic reactions

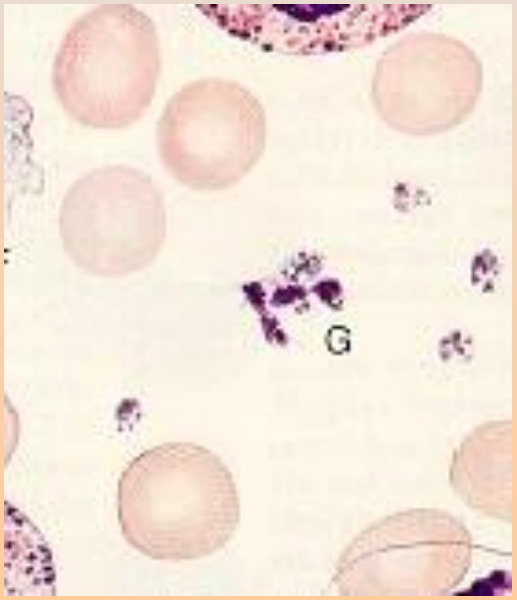


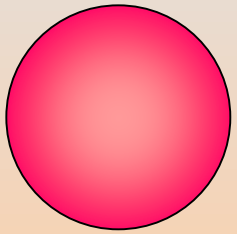
Other Blood Cells

- Megakaryocyte
  - Platelet formation
  - Wound repair
- Erythrocyte
  - Oxygen transport





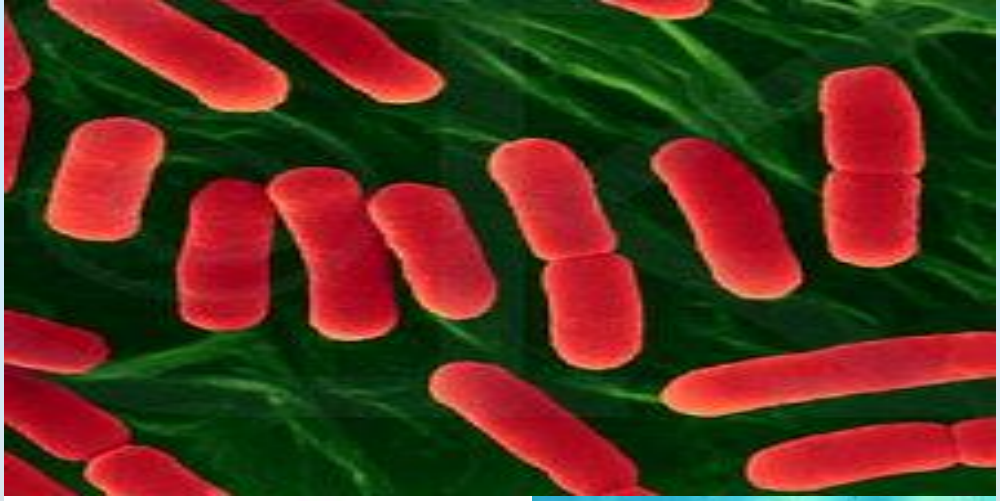


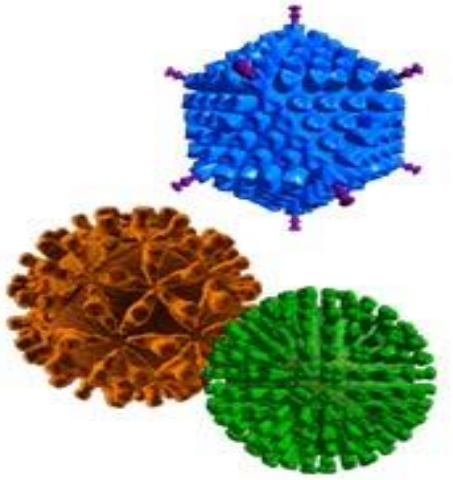


Antigens

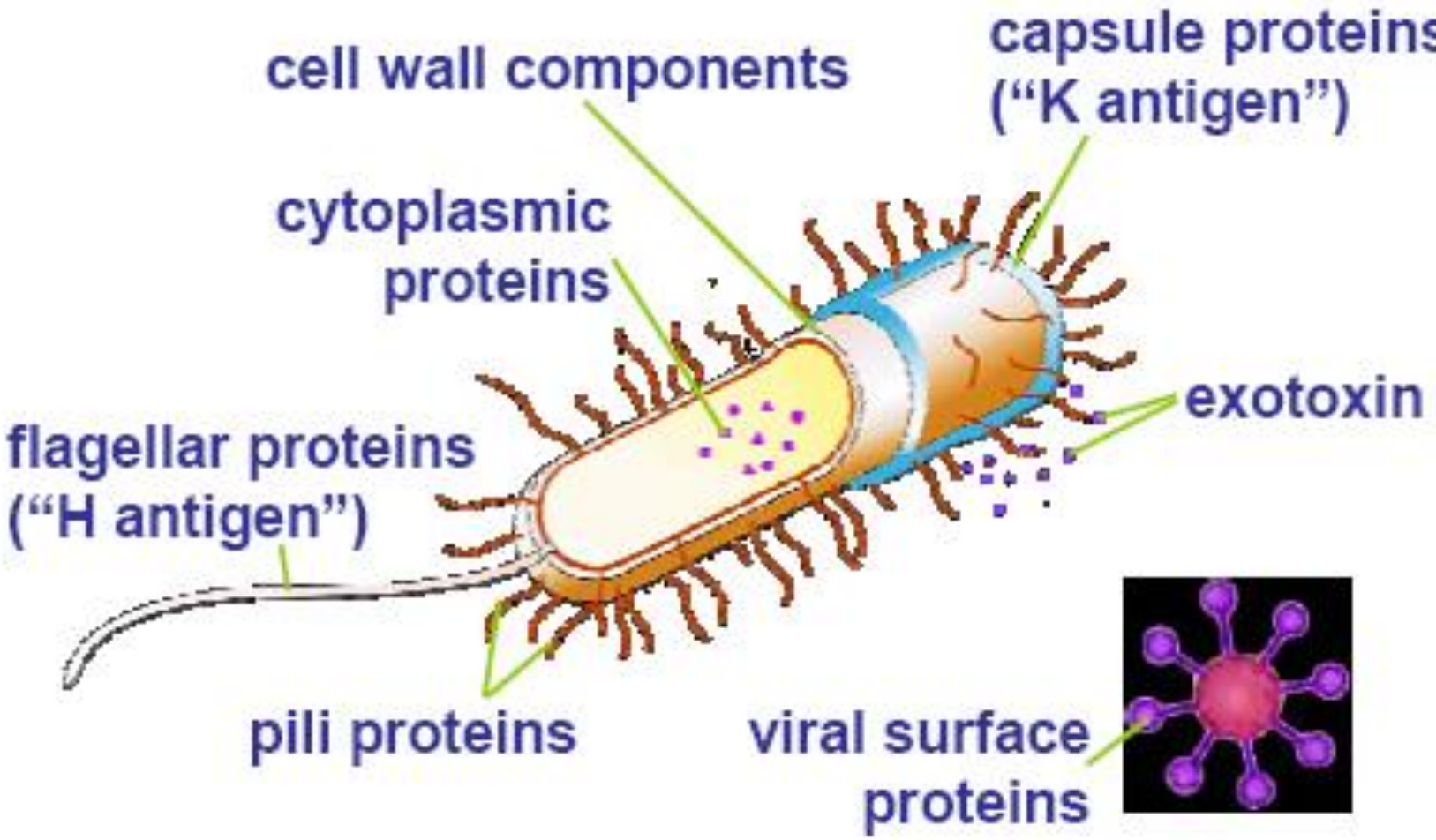
The Invaders . . .

- Bacteria
- Viruses
- parasites such as fungi, protista, & worms





Microbial antigens



DEFINITIONS

A. **Immunogen - A substance that induces a specific immune response.**

B. **Antigen (Ag) - A substance that reacts with the products of a specific immune response.**

C. **Hapten - Haptens are small molecules which could never induce an immune response when administered by themselves but which can when coupled to a carrier molecule. Haptens have the property of antigenicity but not immunogenicity.**

D. **Epitope or Antigenic Determinant - That portion of an antigen that combines with the products of a specific immune response.**

Factors Influencing Immunogenicity
Contribution of the Immunogen

- Foreignness
- Size

- Chemical Composition
  - Primary Structure — **Sequence determinants**
  - Secondary Structure
  - Tertiary Structure
  - Quarternary Structure

  } **Conformational determinants**

Factors Influencing Immunogenicity
Contribution of the Immunogen

- Foreigness
- Size
- Chemical Composition
- Physical Form
  - Particulate > Soluble
  - Denatured > Native

Factors Influencing Immunogenicity
Contribution of the Immunogen

- Foreigness
- Size
- Chemical Composition
- Physical Form
- Degradability
  - Ag processing by Ag Presenting Cells (APC)

Factors Influencing Immunogenicity
Contribution of the Biological System

- Genetics
  - Species
  - Individual
    - Responders vs Non-responders
- Age

Factors Influencing Immunogenicity
Method of Administration

- Dose
- Route
  - Subcutaneous > Intravenous > Intragastric
- Adjuvant
  - Substances that enhance an immune response to an Ag

Chemical Nature of Immunogens

- Proteins
- Polysaccharides
- Nucleic Acids
- Lipids
  - Some glycolipids and phosopholipids can be immunogenic for T cells and illicit a cell mediated immune response

ANTIBODIES

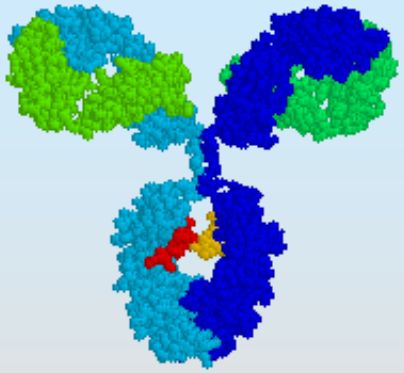
What is antibodies

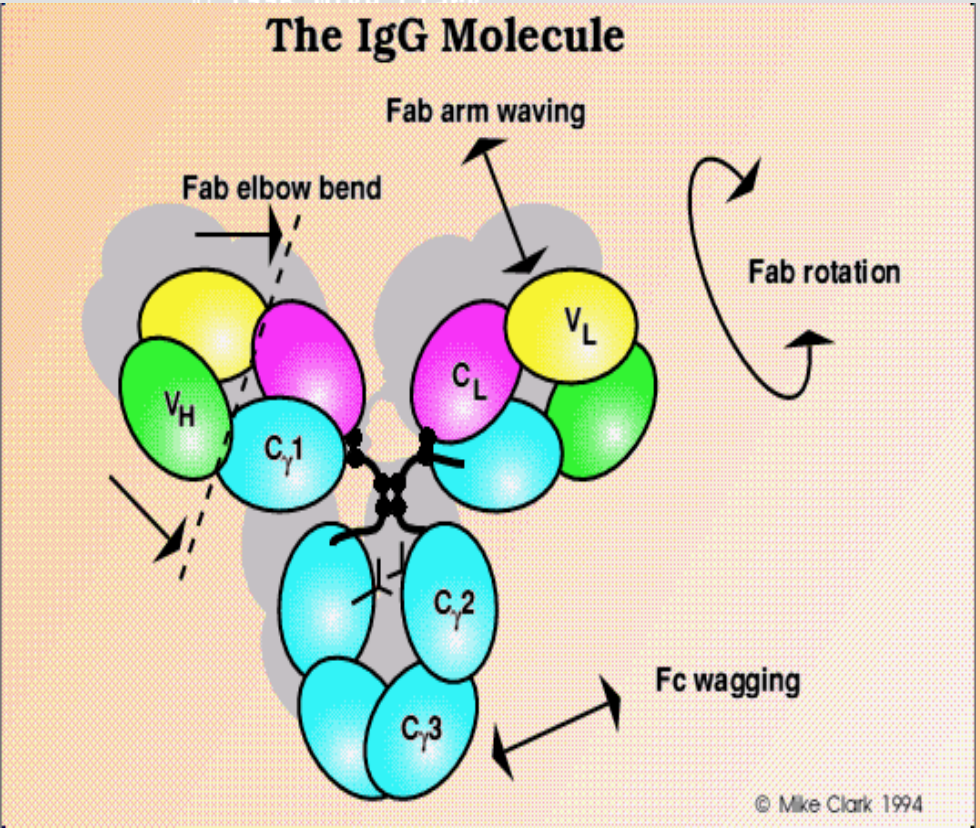
Glycoprotein molecules which are produced by plasma cells in response to an immunogen and which function as antibodies. An antibody is a protein used by the immune system to identify and neutralize foreign objects like bacteria and viruses. Each antibody recognizes a specific antigen unique to its target.

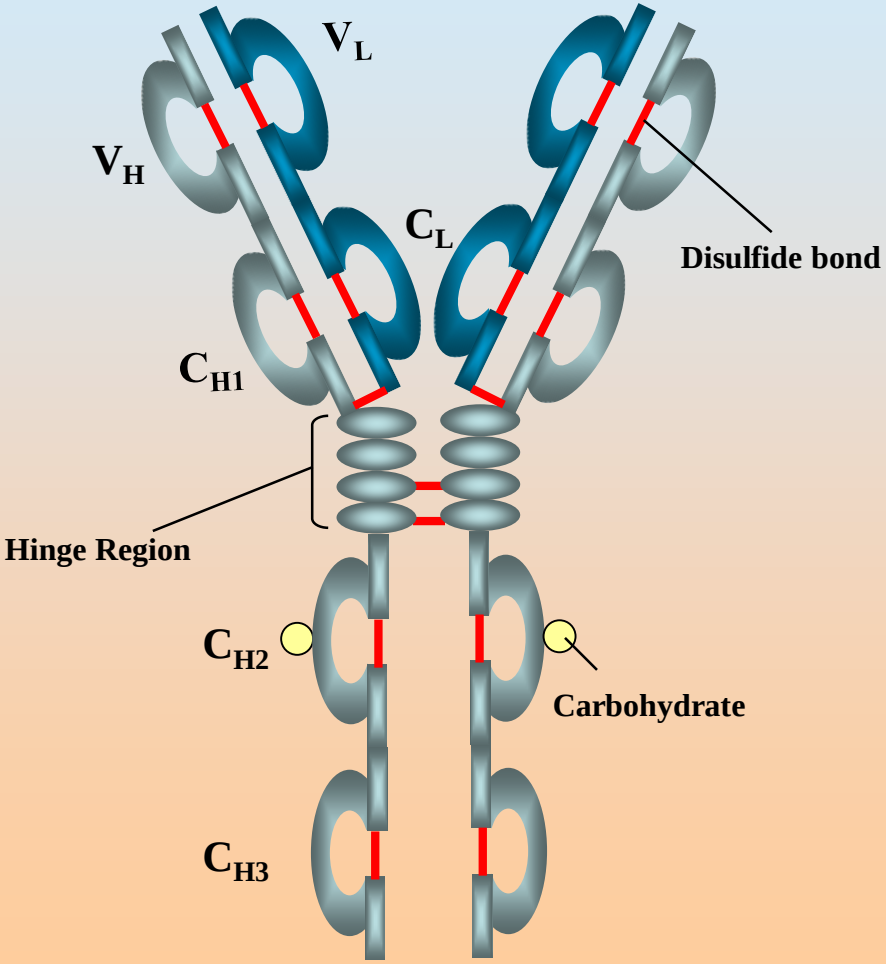
Monoclonal antibodies (mAb) are antibodies that are identical because they were produced by one type of immune cell, all clones of a single parent cell.

Polyclonal antibodies are antibodies that are derived from different cell lines.

The structure of antibodies







Human Immunoglobulin Heavy Chain Types

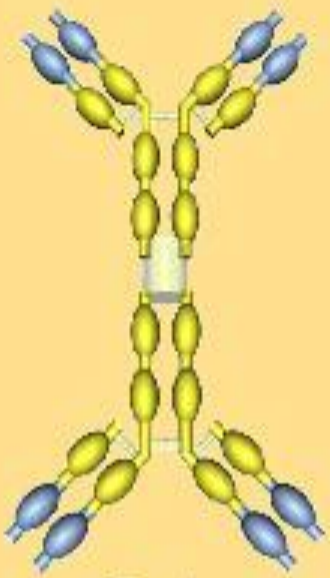
- IgG - Gamma heavy chains
- IgM - Mu heavy chains
- IgA - Alpha heavy chains
- IgD - Delta heavy chains
- IgE - Epsilon heavy chains

Human Immunoglobulin Light Chain Types

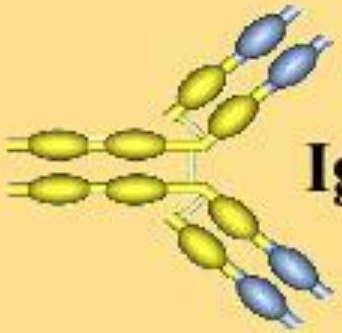
- Kappa
- Lambda

Comparative accounts of Igs

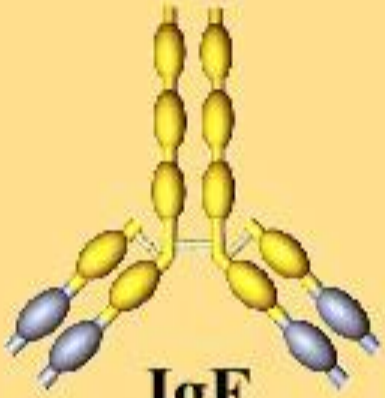
Properties	IgG	IgA	IgM	IgD	IgE
Normal range (mg/ml)	7 -15	1 – 4.5	0.4 -2.1	0.02- 0.03	0.0004
% of total Ig	80	12	7	1	0.001
MW (kd)	150	160- 400	900	185	190
Sedimentation (S)	7	7, 9	19	7	8
Carbohydrate (%)	3	8	12	13	12
Number of monomer	1	1, 2, 3	5	1	1
H chain	γ 1-4	α 1 – 2	μ 1-2	δ	ε
L chain	κ, λ	κ, λ	κ, λ	κ, λ	κ, λ



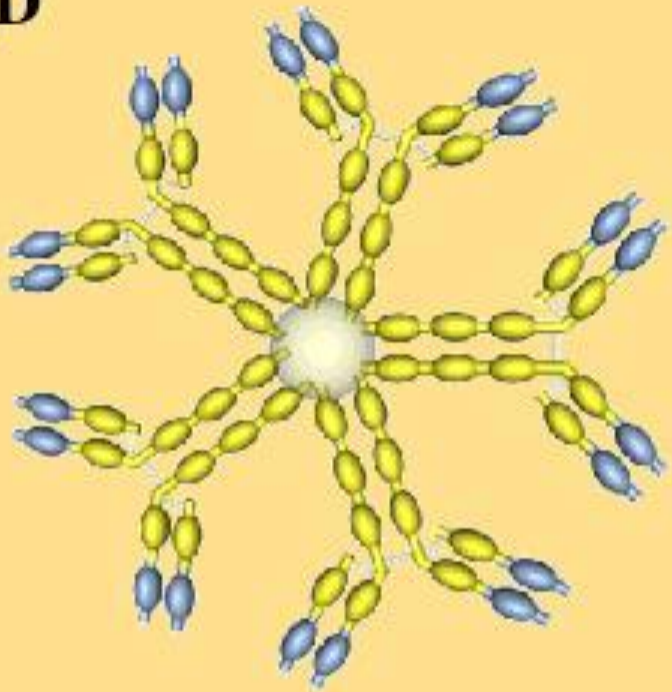
IgA



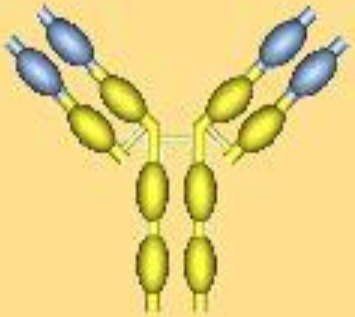
IgD



IgE

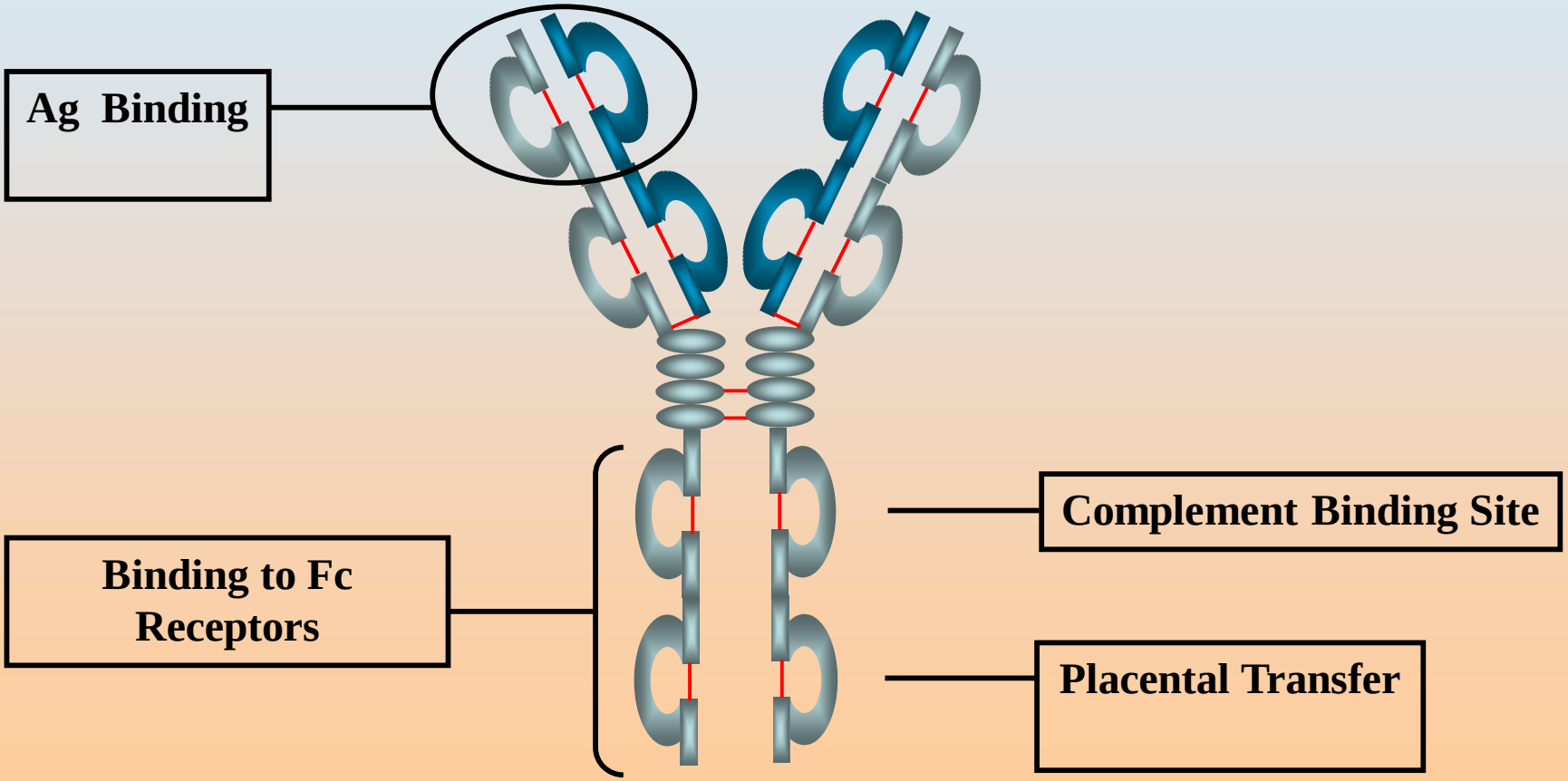


IgM



IgG

Immunoglobulin Fragments: Structure/Function Relationships



Biological function of different classes of immunoglobulin

Class	Accumulation	Function
IgG	Internal body fluids, particularly extravascular	Major line of defense against infection during the first few weeks of a baby; neutralizes bacteria toxins; binds to microorganisms to enhance their phagocytosis and lysis.
IgM	Largely confined to bloodstream	Efficient agglutinating and cytolytic agent; effective first line of defense in cases of bacteremia (bacteria in blood)
IgA	Serum, external body secretions	Protects mucosal surfaces from invasion by pathogenic microbes.
IgD	Serum, on lymphocyte surface of newborn	Regulator for the synthesis of other immunoglobulins; fetal antigen receptor
IgE	Serum	Responsible for severe acute and occasionally fatal allergic reactions; combat parasitic infections

INNATE (NON-SPECIFIC) IMMUNITY

Characteristics of Innate and Adaptive Immunity

Innate Immunity	Adaptive Immunity
Antigen independent	Antigen dependent
No time lag	A lag period
Not antigen specific	Antigen specific
No Immunologic memory	Development of memory

Components of Innate and Adaptive Immunity

Innate Immunity	Adaptive Immunity
physical barriers	
skin, gut Villi, lung cilia,etc	none
soluble factors	
many protein and non-protein secretions	Immunoglobulins (antibody)
cells	
phagocytes, NK cell eosinophils, K cells	T and B lymphocytes

Five main categories of receptors are involved ; non-specific receptors, inflammasomes (Nucleotide-binding domain Leucine-rich Repeats or NLRs),the Retinoic Acid-inducible Gene-1-Like Receptor (RLRs), the C-type Lectin Receptors (CLRs) and Toll-Like Receptors (TLRs)

NON-SPECIFIC RECEPTOR

Include complement receptor, scavenging receptors, mannose-6 phosphate receptor and Fc receptor

- **Complement receptor – recognize complement cleavage product, particularly C3 and use these to opsonize and elicit inflammatory reponses.**
- **Scavenging receptors – helps in receptor mediated endocytosis of foreign particles.**
- **Mannose-6-phosphate receptors – bind with mannose-6-P on the glycoproteins on pathogens and helps in lysosomal degradation.**
- **Fc-receptor - bind with Fc portion of antigen bounded antibody and helps in internalization**

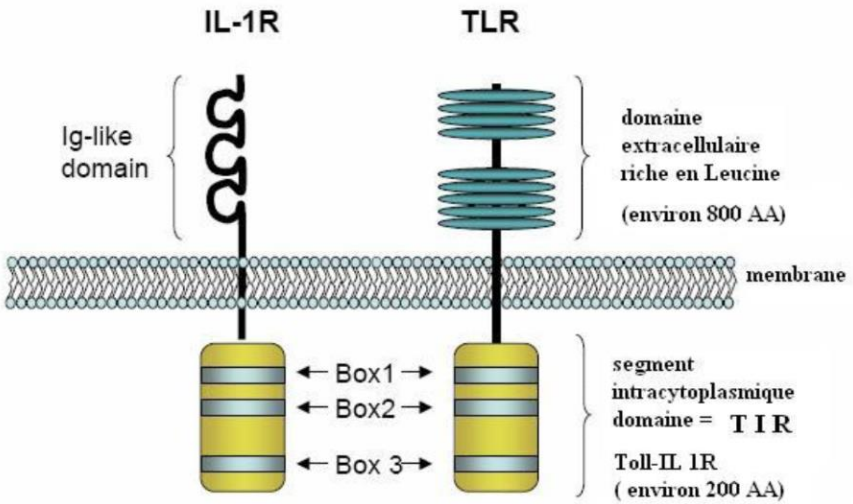
INFLAMMASOMES

The inflammasome is a multiprotein oligomer responsible for the activation of inflammatory responses. The inflammasome promotes the maturation and secretion of pro-inflammatory cytokines Interleukin 1β (IL-1β) and Interleukin 18 (IL-18). The secretion of these cytokines results in pyroptosis, a form of programmed pro-inflammatory cell death distinct from apoptosis. The exact composition of an inflammasome depends on the activator which initiates inflammasome assembly, e.g. dsRNA will trigger one inflammasome composition whereas asbestos will assemble a different variant. Because the pro-inflammatory pathway does not need Toll-like receptors (TLRs), inflammasomes with AIM2 can detect cytoplasmic DNA, a danger signal, that may be threatening and strengthen their innate response.

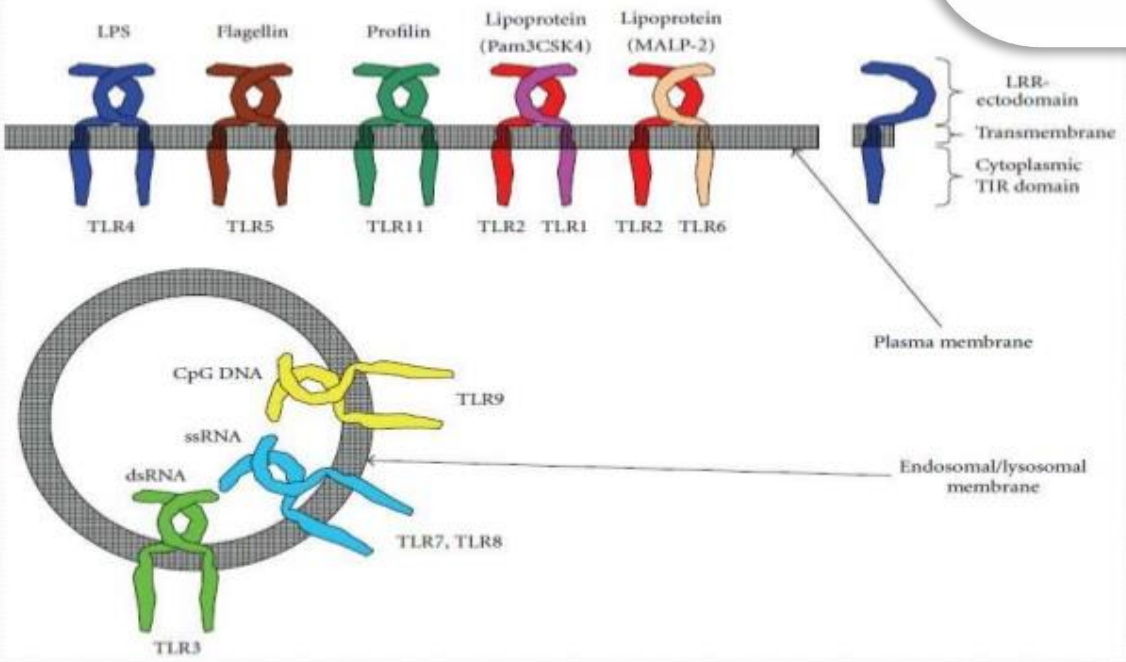
TLR

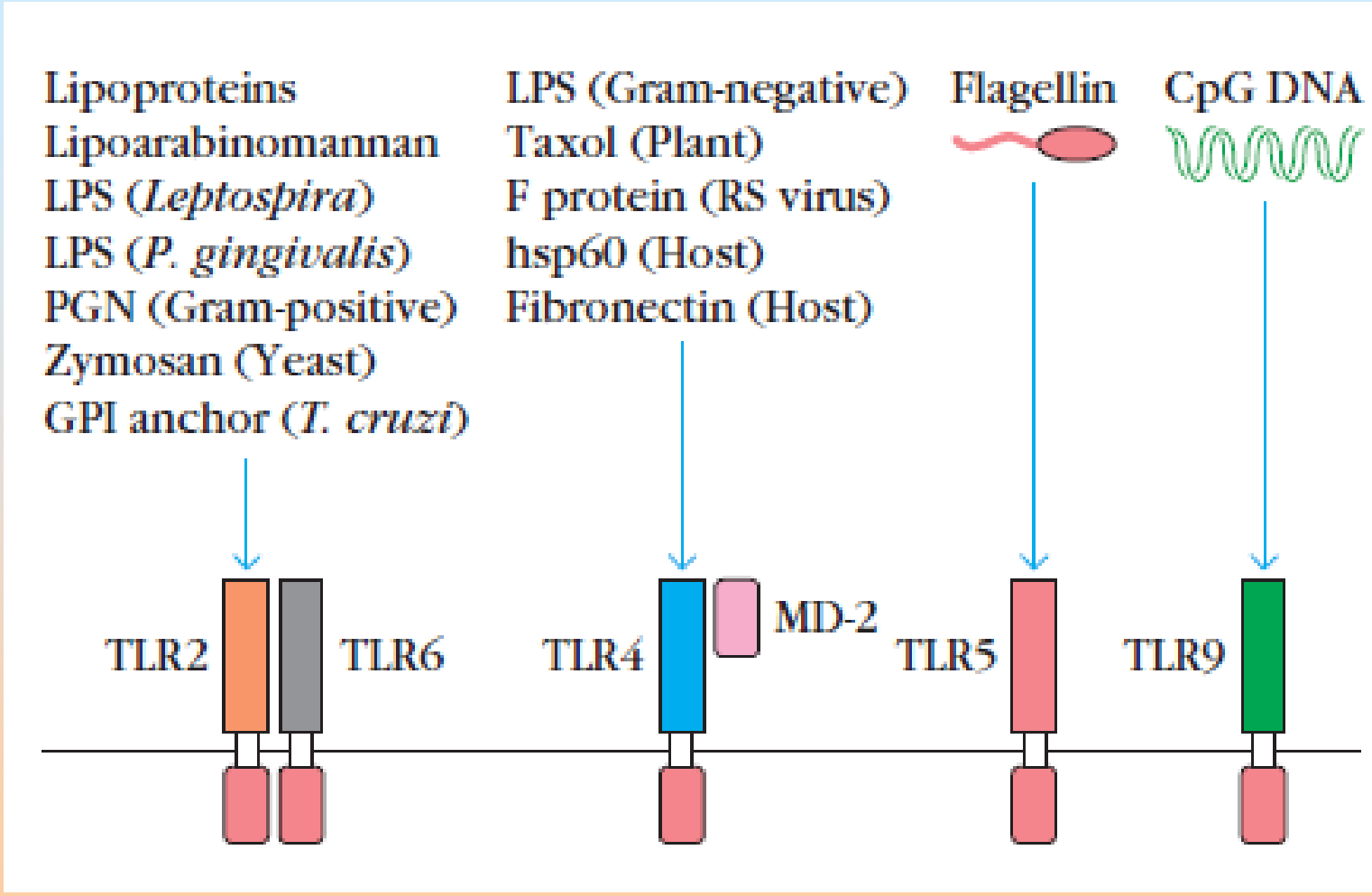
TLRs are categorized into two groups :
cell surface-located (TLR 1, TLR 2, TLR 4, TLR 5, TLR 6, TLR 11) and intracellularly located (TLR 3, TLR 7, TLR 8 & TLR 9).
TLRs sense a plethora (excess) of PMPAs that include peptides, lipopeptides, glycopeptides, glycolipids and nucleic acid. Activated TLRs initiate molecular signaling and results in the release of a lot of pro-inflammatory cytokines.

Structure des TLR

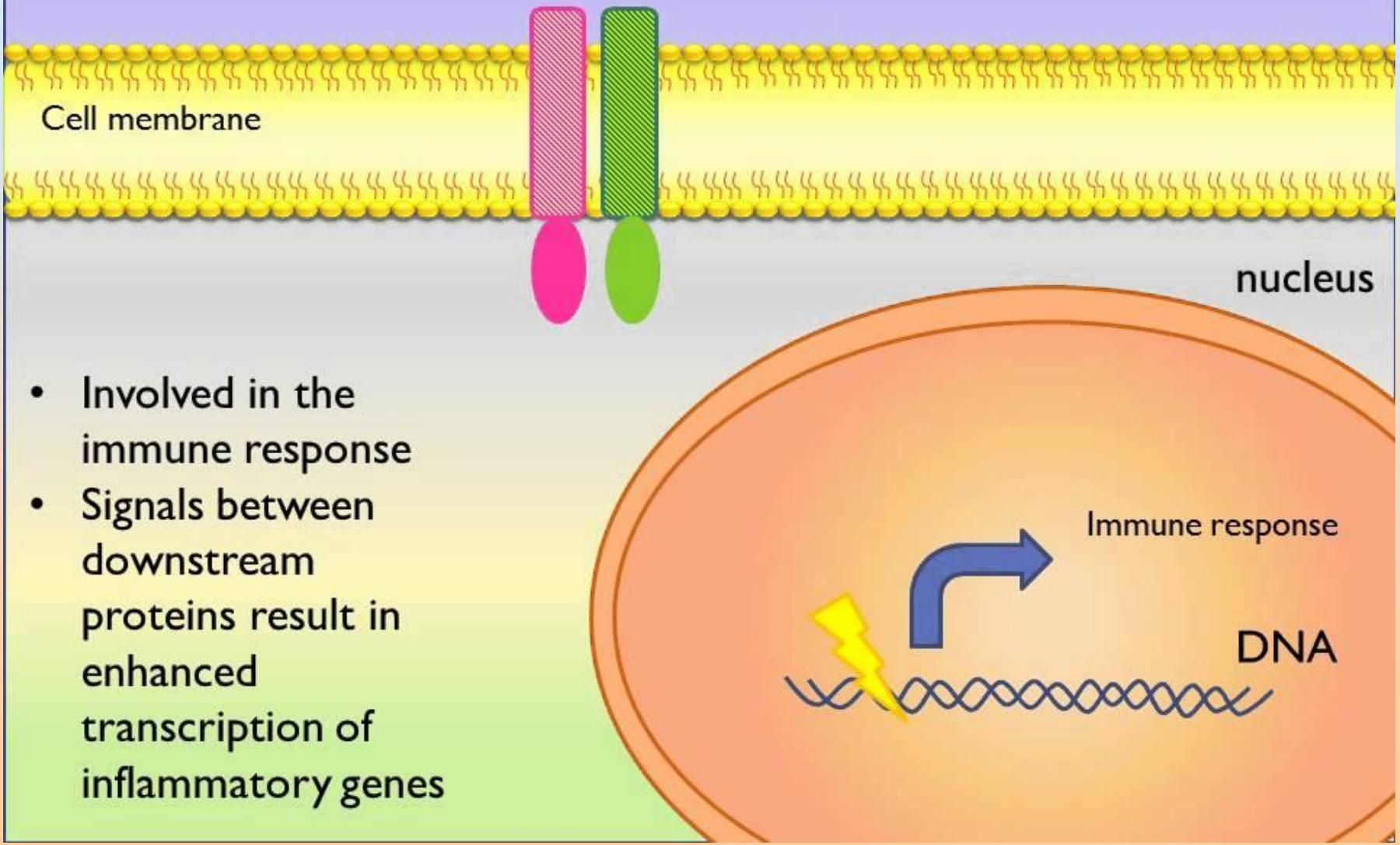


Cellular Localization of TLRs




Lipoproteins
Lipoarabinomannan
LPS (*Leptospira*)
LPS (*P. gingivalis*)
PGN (Gram-positive)
Zymosan (Yeast)
GPI anchor (*T. cruzi*)
LPS (Gram-negative)
Taxol (Plant)
F protein (RS virus)
hsp60 (Host)
Fibronectin (Host)
Flagellin
CpG DNA
TLR2
TLR6
TLR4
MD-2
TLR5
TLR9

Toll-like receptors



- Involved in the immune response
- Signals between downstream proteins result in enhanced transcription of inflammatory genes

Distribution of TLRs in Different Organs

Table 1. *Tissue specificity of the expression of human TLRs by Northern blot analysis**

Organ	TLR1†‡	TLR2†‡§	TLR3†‡	TLR4†‡§	TLR5†‡§	TLR6‖	TLR7**	TLR8**	TLR9**
Brain	−	+	−	−	−ND	+	++	−	
Colon	−	−	−	−	−	ND	−	−	ND
Dendritic cells	+	+	+	+	+	ND	ND	ND	ND
Heart	−	+	−	+	−	−	−	++	−
Kidney	−	−	−	−	−	−	−	−	−
Liver	−	+	+	−	++	−	−	++	+
Lung	−	+	−	+	+	+	+	++	+
Lymphocytes	+	−	−	−	+	ND	ND	ND	ND
Monocytes	+	++	−	+	+	ND	ND	ND	ND
Muscle	−	+	−	−	−	ND	ND	ND	ND
Ovary	+	−	−	−	++	+	ND	ND	ND
Pancreas	−	−	++	−	−	ND	ND	ND	ND
PBL	−	++	−	+	++	ND	ND	ND	ND
Placenta	−	−	++	−	−	ND	ND	ND	ND
PMN	++	++	−	++	−	ND	ND	ND	ND
Prostate	−	−	−	−	+	ND	ND	ND	ND
Small intestine	−	−	−	−	−	ND	+	−	ND
Spleen	+	−	−	−	−	+	+	−	ND
Testis	−	−	−	−	+	ND	ND	ND	ND
Thymus	−	−	−	−	−	+	−	−	ND

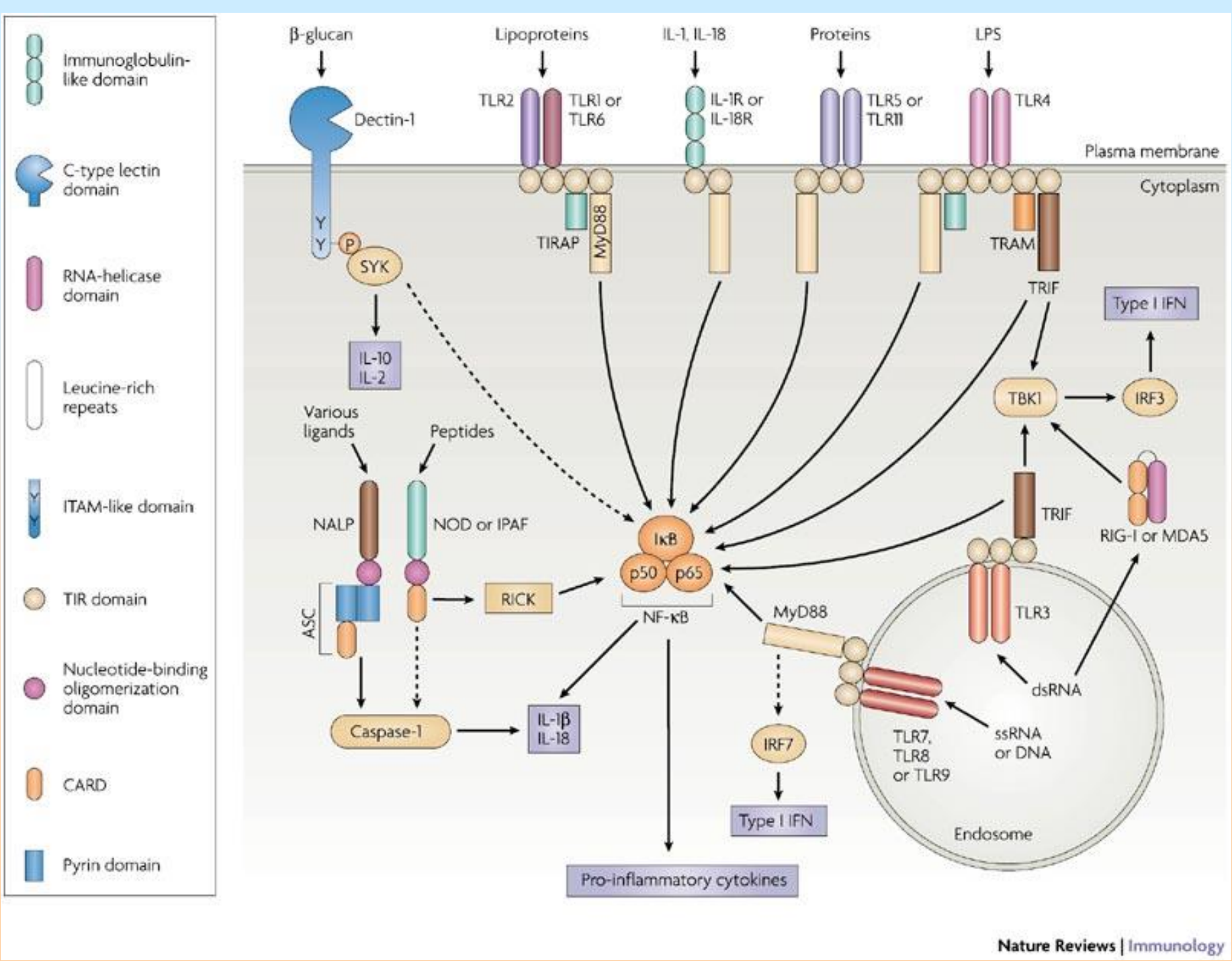
Abbreviations: ND, not done; PBL, peripheral blood lymphocytes; PMN, polymorphonuclear leukocytes.

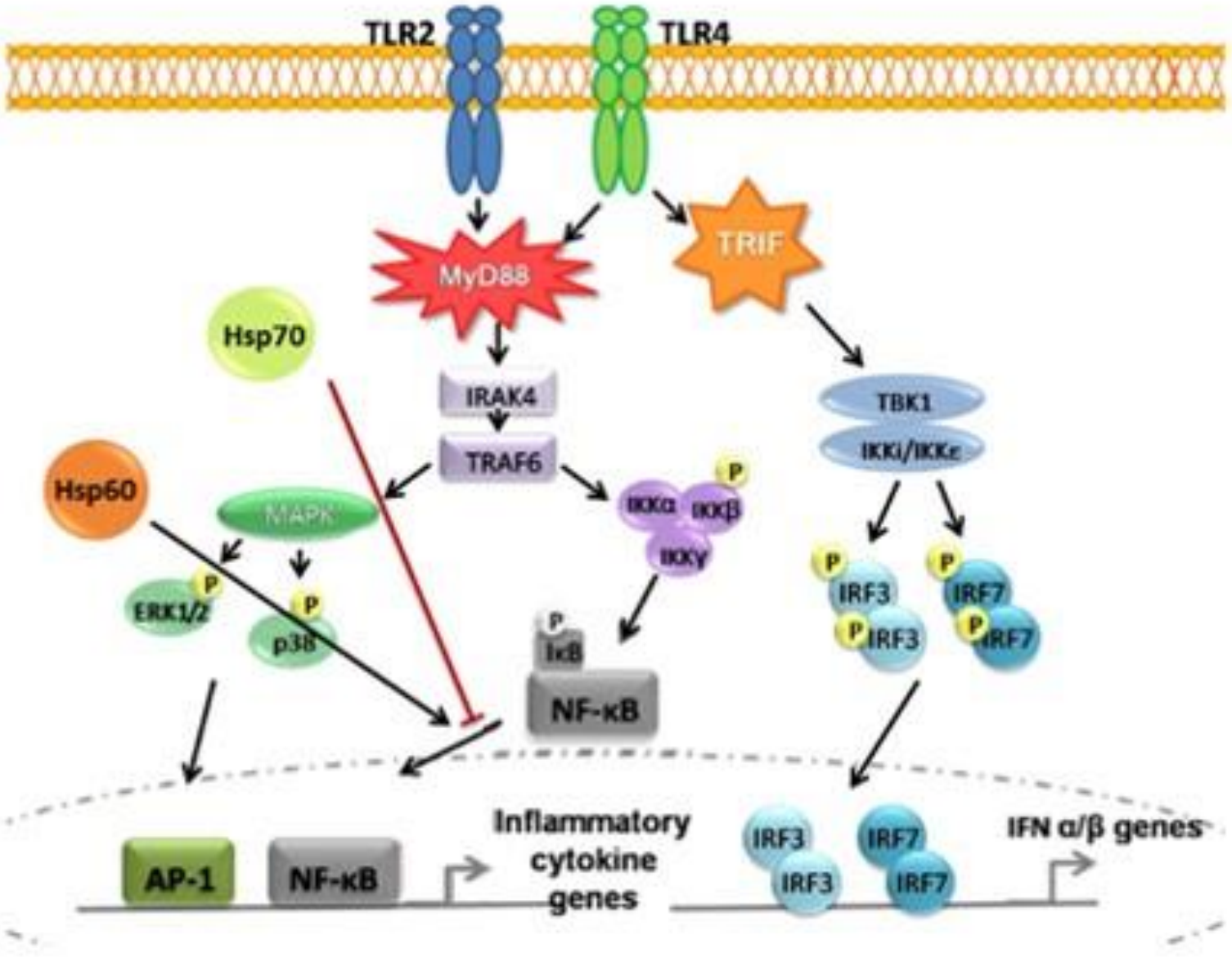
* ++ strong expression, + visible expression, − no visible expression.

TLR in Immuno-competent cells

Table 1 Mammalian pattern-recognition receptors: their major ligands and cell types

Families	Proteins	Major ligands (or activators)	Major cell types[a]
TLRs[c]	TLR1	Triacyl lipopeptides from bacteria and mycobacteria	MΦ, cDC, neutrophil, mast cells
	TLR2	LTA from gram-positive bacteria, yeast zymosan, lipopeptides (Pam_3CSK_4, MALP2), lipoarabinomannan from mycobacteria	MΦ, cDC, neutrophil, mast cell
	TLR3	Viral dsRNA, poly(I:C)	cDC, MΦ (mouse), endo/epithelial cells
	TLR4	LPS from gram-negative bacteria, mannan from *Candida albicans*, GIPLs from *Trypanosoma*, viral envelope proteins from RSV and MMTV	MΦ, cDC, neutrophil, mast cell, eosinophil
	TLR5	Bacterial flagellin	Monocyte, cDC, iEC
	TLR6	Diacyl lipopeptides from *Mycoplasma*, LTA from gram-positive bacteria, yeast zymosan	Monocyte, mast cell, cDC, neutrophil
	TLR7	ssRNA from RNA viruses, imiquimod, resiquimod (R848), synthetic polyU RNA, certain siRNAs	pDC, neutrophil, eosinophil
	TLR8	Resiquimod (R848), viral ssRNA	Monocyte, cDC, mast cell, neutrophil
	TLR9	Bacterial and viral CpG DNA, hemozoin from *Plasmodium*	pDC, NK cell, eosinophil, neutrophil
	TLR10	–	pDC, B cell
	TLR11	Profilin-like molecule from *Toxoplasma gondii*, unknown ligand(s) from uropathogenic bacteria	MΦ, epithelial cell


Immunoglobulin-like domain
C-type lectin domain
RNA-helicase domain
Leucine-rich repeats
ITAM-like domain
TIR domain
Nucleotide-binding oligomerization domain
CARD
Pyrin domain
β-glucan
Lipoproteins
IL-1, IL-18
Proteins
LPS
Dectin-1
TLR2
TLR1 or TLR6
IL-1R or IL-18R
TLR5 or TLR11
TLR4
Plasma membrane
Cytoplasm
Y
Y
P
SYK
TIRAP
MyD88
TRAM
TRIF
Type I IFN
IL-10
IL-2
TBK1
IRF3
Various ligands
Peptides
NALP
NOD or IPAF
IκB
p50
p65
NF-κB
TRIF
RIG-I or MDA5
RICK
ASC
MyD88
TLR3
dsRNA
Caspase-1
IL-1β
IL-18
IRF7
TLR7, TLR8 or TLR9
ssRNA or DNA
Type I IFN
Endosome
Pro-inflammatory cytokines

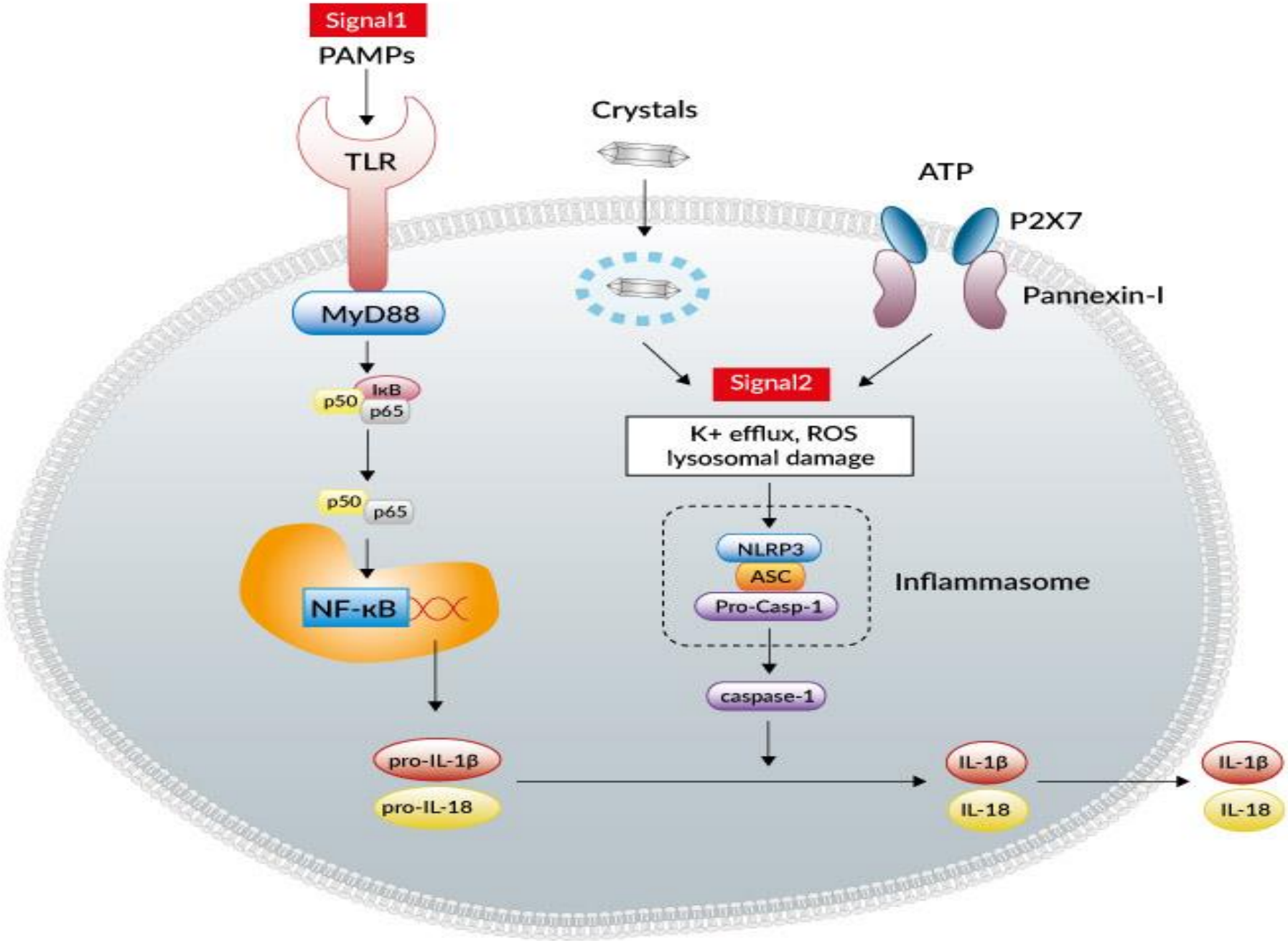

TLR2
TLR4
MyD88
TRIF
Hsp70
IRAK4
TRAF6
TBK1
IKKi/IKKε
Hsp60
MAPK
IKKα
IKKβ
IKKγ
P
ERK1/2
p38
IRF3
IRF7
IκB
NF-κB
AP-1
NF-κB
Inflammatory cytokine genes
IFN α/β genes

MyD88-dependent pathway (Myeloid differentiation primary response 88**)**

The MyD88-dependent response occurs on dimerization of the TLR receptor, and is utilized by every TLR except TLR3. Its primary effect is activation of NFκB (Nuclear factor-κB) and Mitogen-activated protein kinase. Ligand binding and conformational change that occurs in the receptor recruits the adaptor protein MyD88, a member of the TIR family. MyD88 then recruits IRAK (Interleukin-? receptor-associated kinase) 4, IRAK1 and IRAK2. IRAK kinases then phosphorylate and activate the protein TRAF (TNF receptor-associated factor) 6, which in turn polyubiquinates the protein TAK1, as well as itself in order to facilitate binding to IKK-β. On binding, TAK1 (Transforming growth factor beta-activated kinase 1) phosphorylates IKK-β (Inhibitor of Nuclear factor Kappa B Kinase), which then phosphorylates IκB causing its degradation and allowing NFκB to diffuse into the cell nucleus and activate transcription and consequent induction of inflammatory cytokines

TRIF-dependent pathway (TIR-domain-containing adapter-inducing interferon-β**)**

Both TLR3 and TLR4 utilize the TRIF-dependent pathway, which is triggered by dsRNA and LPS, respectively. For TLR3, dsRNA leads to activation of the receptor, recruiting the adaptor TRIF. TRIF activates the kinases TBK1 (TANK-binding kinase 1) and RIPK1, which creates a branch in the signaling pathway. The TRIF/TBK1 signaling complex phosphorylates IRF3 allowing its translocation into the nucleus and production of Interferon type I. [TRAF (tumor necrosis factor receptor-associated factor); TANK (TRAF family member-associated NF-kappa-B activator)]


Signal1
PAMPs
TLR
MyD88
p50
IκB
p65
p50
p65
NF-κB
pro-IL-1β
pro-IL-18
Crystals
ATP
P2X7
Pannexin-I
Signal2
K+ efflux, ROS
lysosomal damage
NLRP3
ASC
Pro-Casp-1
Inflammasome
caspase-1
IL-1β
IL-18
IL-1β
IL-18

The receptors of the innate immune system, called pattern recognition receptors (PRR), are coded in the germ line and recognize conserved molecular structures (PAMPs – Pathogen Associated Molecular Patterns**) shared by a large variety of pathogens (Lipford, Heeg & Wagner 1998; Stahl & Ezekowictz 1998).**

On the other hand, T and B cell antigen-recognition receptors are highly specific, as they undergo gene rearrangements and somatic mutations generating an adapted specificity for the antigen.

However, innate and adaptive immunity, are not two independent mechanisms of defense. It has been shown that receptors of the innate immune system can contribute to signaling that activates the adaptive immune system. Moreover, this activation strongly depends on bacterial (or bacterial product) interactions with PRR on mammalian cells (Kirschning Wesche, Ayres & Rothe 1998).

Determinants Recognized by the Innate Immune System

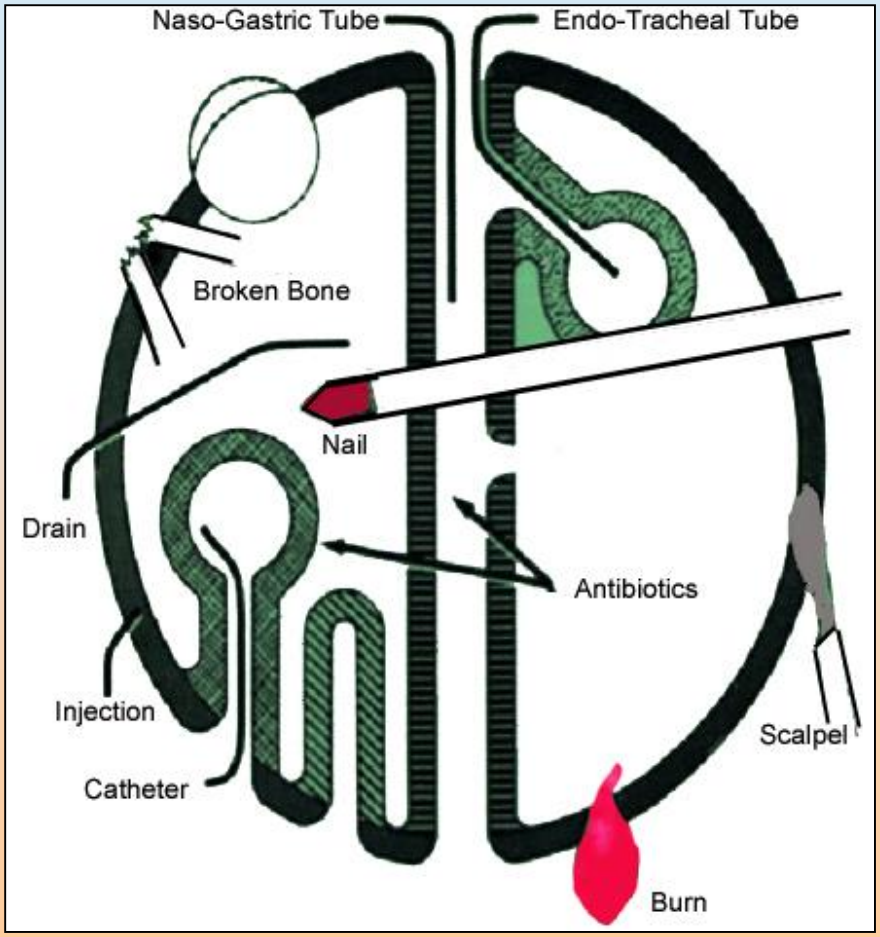
- PAMPs – Pathogen Associated Molecular Patterns
- PRRs – Pattern Recognition Receptors

PAMP	PRR	Biological Consequence of Interaction
Microbial cell wall components	Complement	Opsonization; Complement activation
Mannose-containing carbohydrates	Mannose-binding protein	Opsonization; Complement activation
Polyanions	Scavenger receptors	Phagocytosis
Lipoproteins of Gram + bacteria Yeast cell wall components	TLR-2 (Toll-like receptor 2)	Macrophage activation; Secretion of inflammatory cytokines

PAMP	PRR	Biological Consequence of Interaction
Double stranded RNA	TLR-3	Production of interferon (antiviral)
LPS (lipopolysaccharide of Gram – bacteria	TLR-4	Macrophage activation; Secretion of inflammatory cytokines
Flagellin (bacterial flagella)	TLR-5	Macrophage activation; Secretion of inflammatory cytokines

PAMP	PRR	Biological Consequence of Interaction
U-rich single stranded viral RNA	TLR-7	Production of interferon (antiviral)
CpG containing DNA	TLR-9	Macrophage activation; Secretion of inflammatory cytokines

Physical Barriers to Resistance



Effector mechanisms in Innate Immunity -1

Site	Component	Functions
Skin	squamous cells sweat	desquamation flushing, fatty acids
GI tract	columnar cells	Peristalsis, low pH bile salts, fatty acids
Lung	tracheal cilia	mucociliary elevator surfactants

Effector mechanisms in Innate Immunity -2

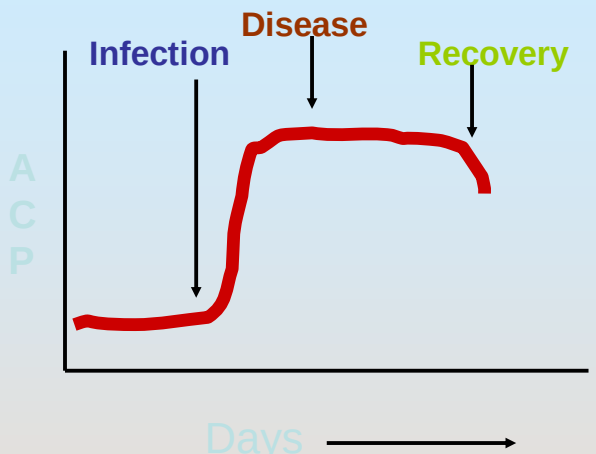
Site	Component	Functions
Nasopharynx and eye	mucus, saliva, tears	flushing, lysozyme
Blood and Lymphiod organs	Phagocytes	phagocytosis and intracellular killing
	K, NK & LAK cells	direct and antibody dependent cytolysis

Effector mechanisms in Innate Immunity -3

Site	Component	Functions
Serum and other serous fluids	lactoferrin, transferrin	iron deprivation
	interferons, TNF-α	antiviral proteins phagocyte activation
	lysozyme	peptidoglycan hydrolysis
	Fibronectin & complement	opsonization, enhanced phagocytosis, inflammation

ACUTE PHASE PROTEINS (ACP)

Serum contain a number of proteins that increases (2 to 200 folds) rapidly during infection – that collectively called ACP

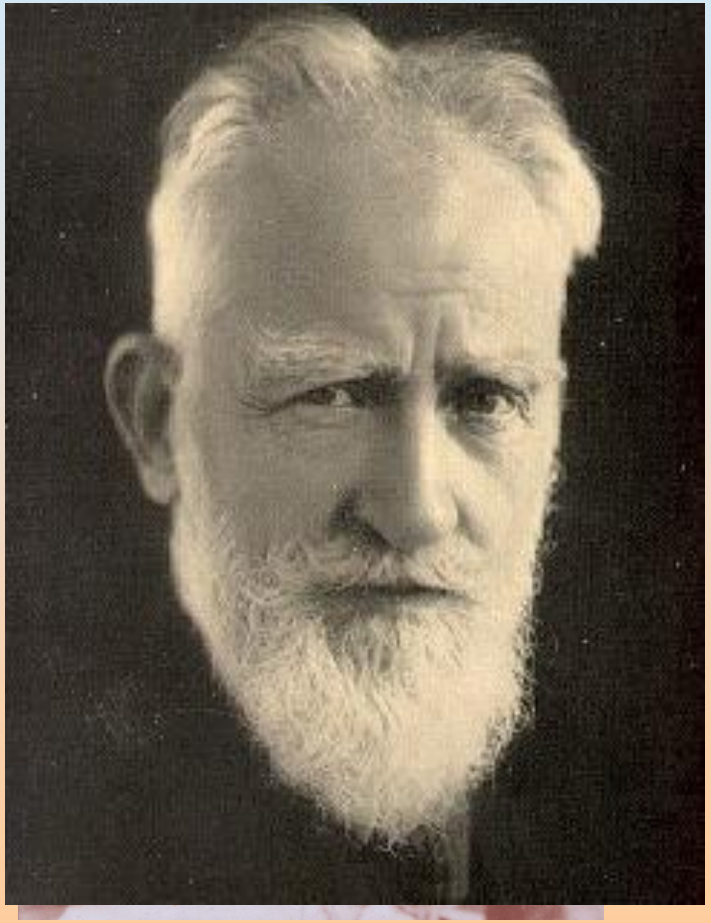


- C-reactive protein (CRP) : These can bind with the C-surface proteins of pneumococci. CRP binds with bacteria to promotes the binding of complement, which facilitate their uptake by phagocytosis.
- Complements : these group of proteins can lysed the live organism, help phagocytosis by opsonization and enhance chemotaxis of immunocompetent cells.
- Interferon : Group of proteins can lysed viral infected cell, tumor cells and blocked viral replications.

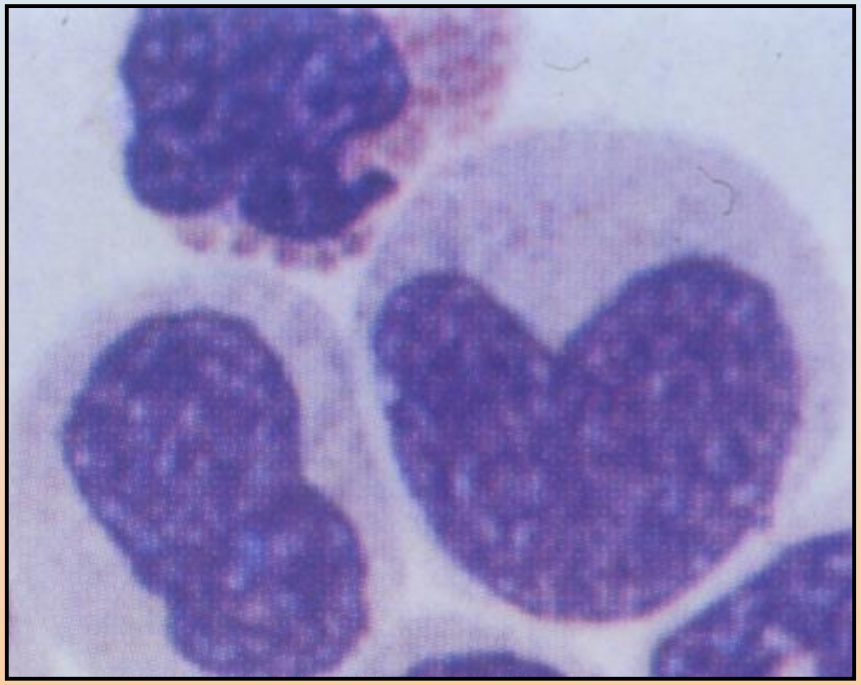
Phagocytes are the Most Important Cells

George Bernard Shaw wrote:

"There is at bottom only one genuine treatment for all diseases,…to stimulate the phagocytes. Drugs are a delusion. …(when) the phagocytes are stimulated; they devour the disease…"



Phagocytes: Macrophages



- phagocytosis, intracellular and extra-cellular killing, tissue repair, antigen presentation for specific immune response
- characteristic nucleus and CD14 membrane marker.

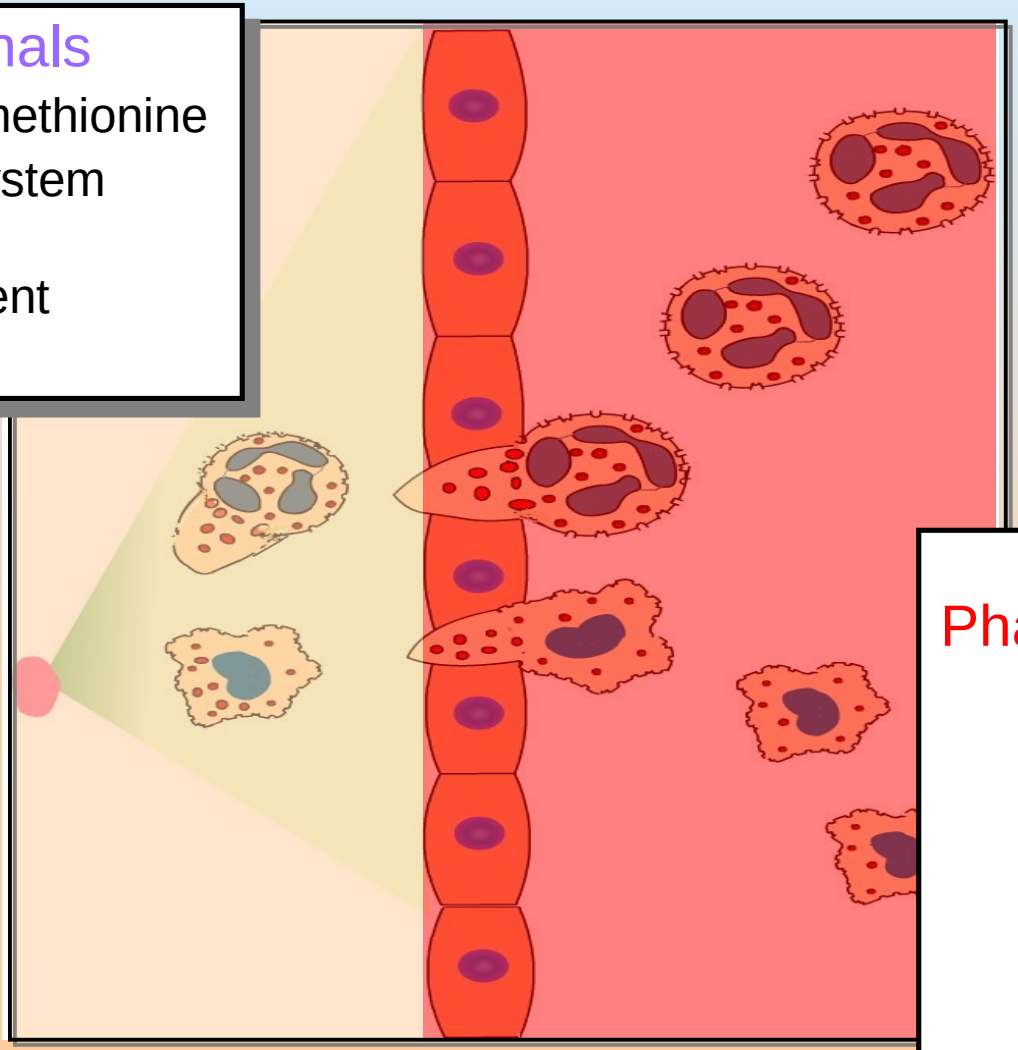
Characteristics of Neutrophil Granules

primary granules	secondary granules
azurophilic; characteristic of young neutrophils;	specific for mature neutrophils
contain cationic proteins, lysozyme, defensins, proteases and **myeloperoxidase**	contain lysozyme, NADPH oxidase, **lactoferrin and B12-binding protein**

Phagocyte Response to Infection

The SOS Signals

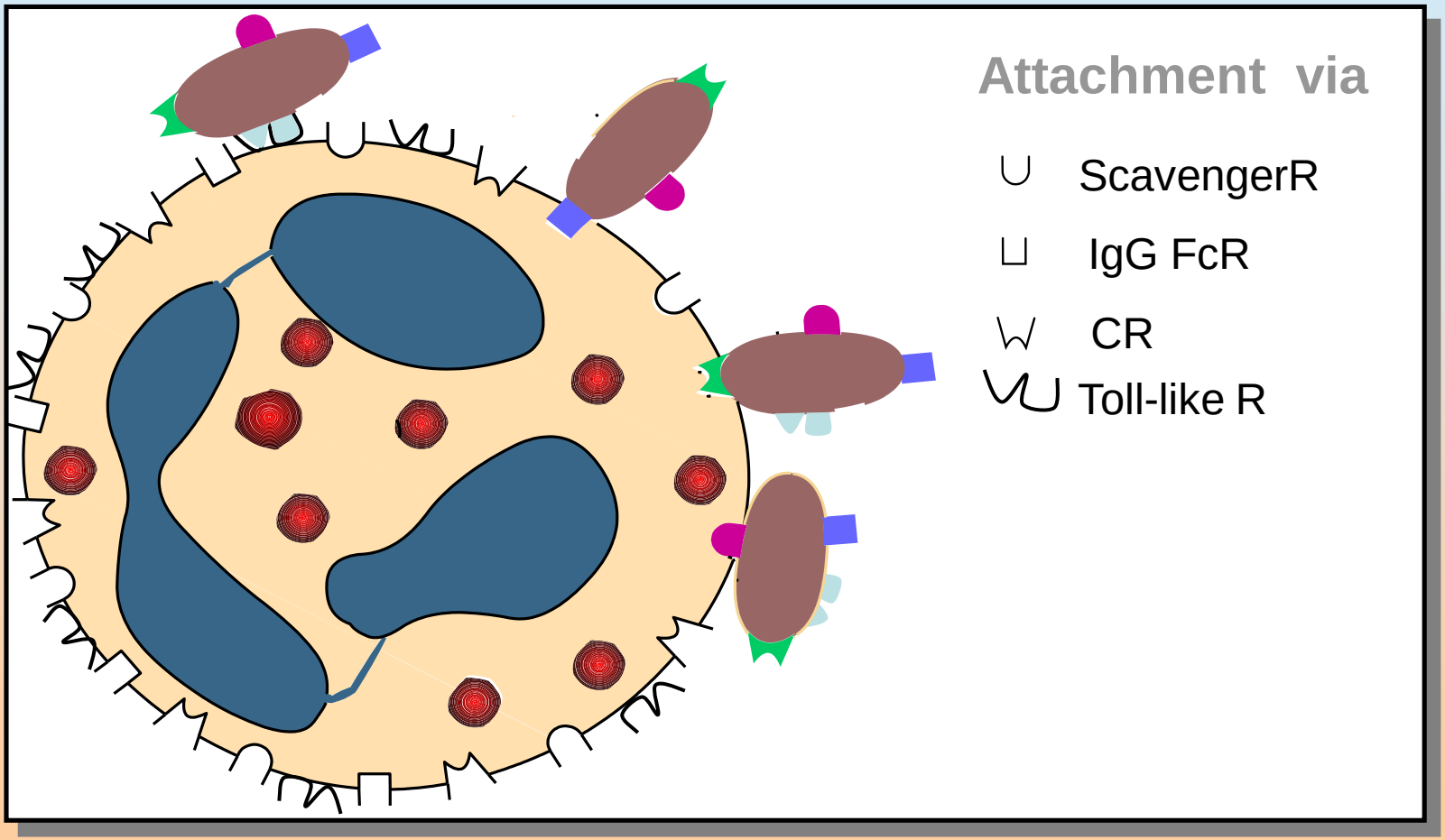
- N-formyl methionine
- Clotting system peptides
- Complement products



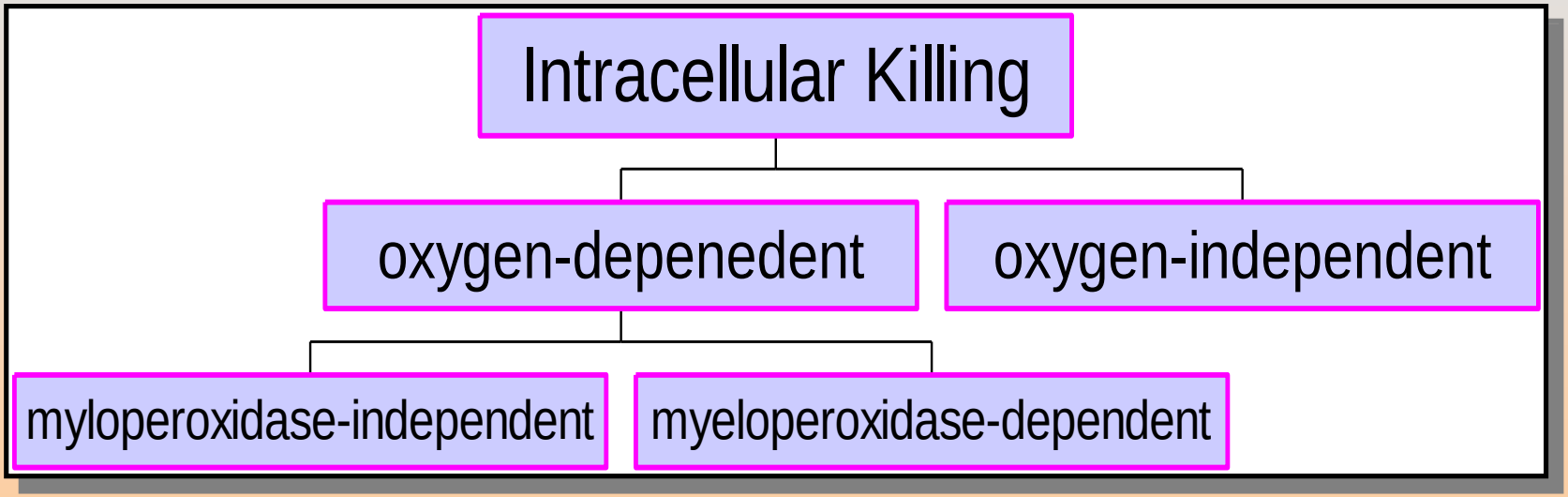
Phagocyte response

- Vascular adherence
- Diapedesis
- Chemotaxis
- Activation
- Phagocytosis and killing

Initiation of Phagocytosis

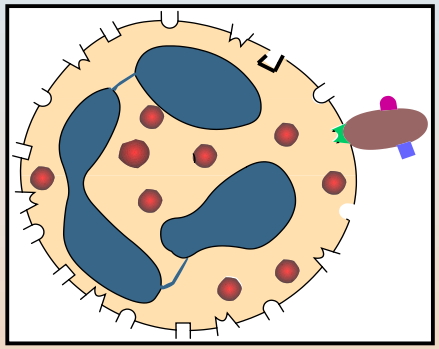


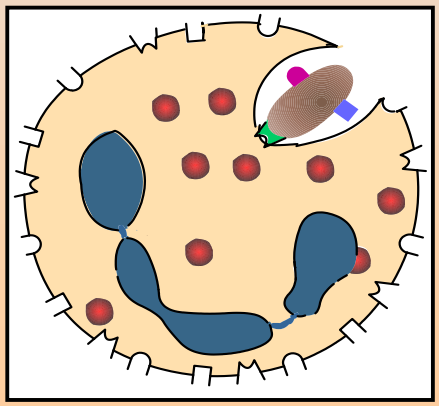
Pathways of Intracellular Killing



Respiratory Burst

Oxygen Dependent Myeloperoxidase Independent Reactions





$$\text{Glucose} + NADP^+ \xrightarrow[\text{G-6-P-dehydrogenase}]{} \text{Pentose-P} + NADPH$$

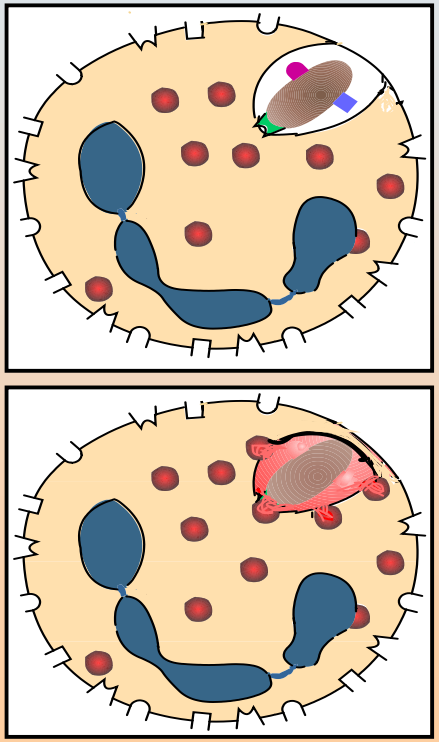
$$NADPH + O_2 \xrightarrow[\text{Cytochrome}_{b558}]{} NADP^+ + O_2^-$$

$$2O_2^- + 2H^+ \xrightarrow[\text{Superoxide dismutase}]{} H_2O_2 + {}^1O_2$$

$$2O_2^- + H_2O_2 \rightarrow .OH + OH^- + {}^1O_2$$

Respiratory Burst

Oxygen Dependent Myeloperoxidase dependent reactions



$$H_2O_2 + Cl^- \xrightarrow[\text{myeloperoxidase}]{} OCl^- + H_2O$$

$$2OCL^- + H_2O \rightarrow {}^1O_2{}^- + Cl^- + H_2O$$

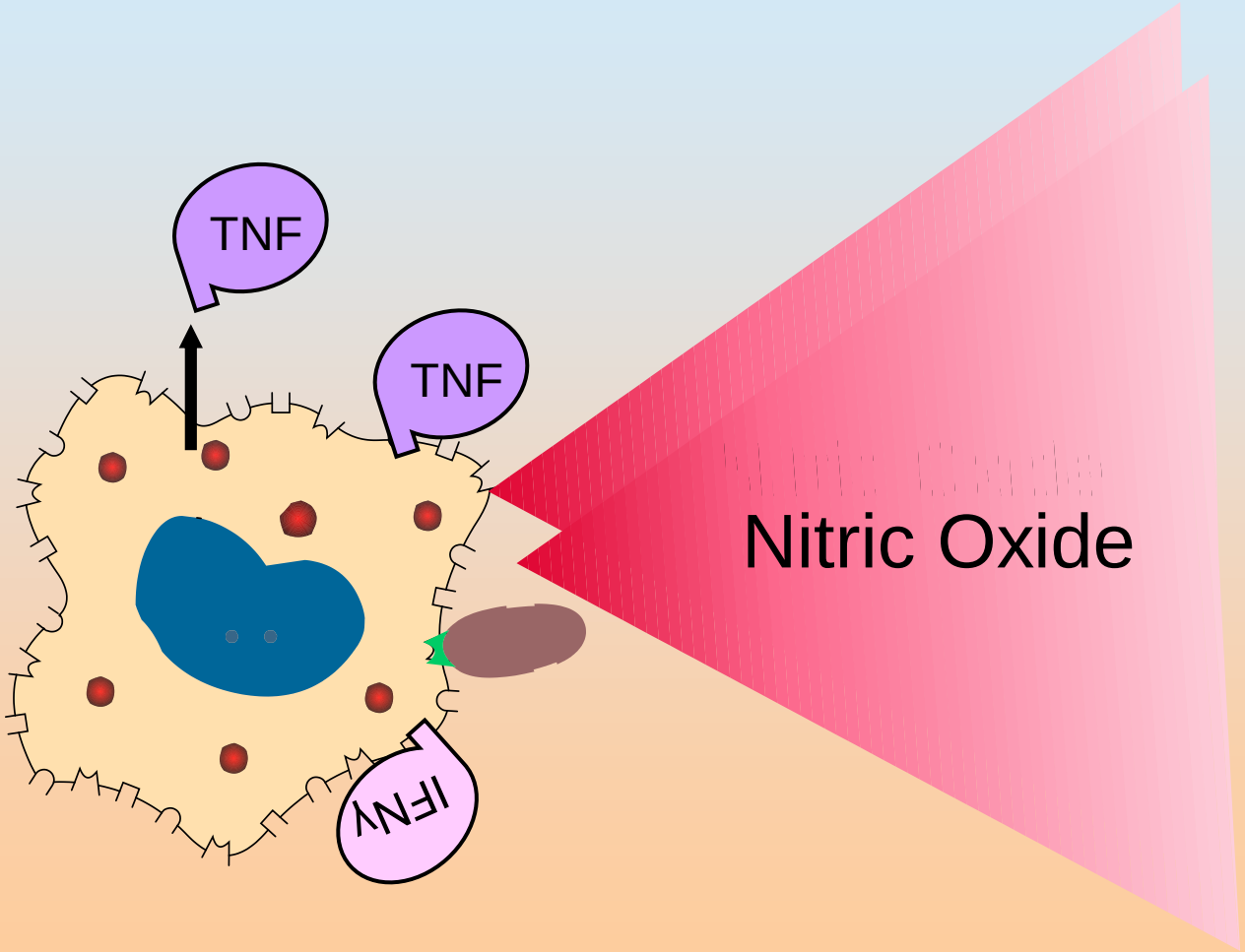
$$2O_2{}^- + 2H^+ \xrightarrow[\text{Superoxide dismutase}]{} H_2O_2 + O_2{}^-$$

$$2\,H_2O_2 \xrightarrow[\text{catalase}]{} H_2O + O_2{}^-$$

Mediators of Oxygen Independent Killing in the Phago-lysosome

Effector Molecule	Function
Cationic proteins (cathepsin)	Damage to microbial membranes
Lysozyme	Hydrolyses mucopeptides in the cell wall
Lactoferrin	Deprives pathogens of iron
Hydrolytic enzymes (proteases)	Digests killed organisms

Nitric Oxide Dependent Killing



Non-specific Killer Cells

NK and LAK cells

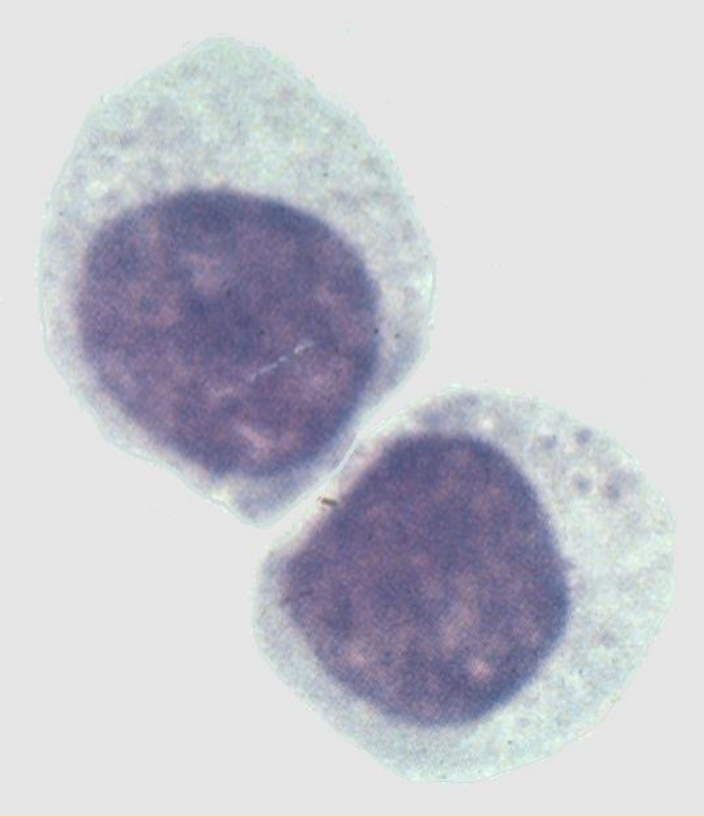
ADCC (K) cell

Activated macrophages

Eosinophils

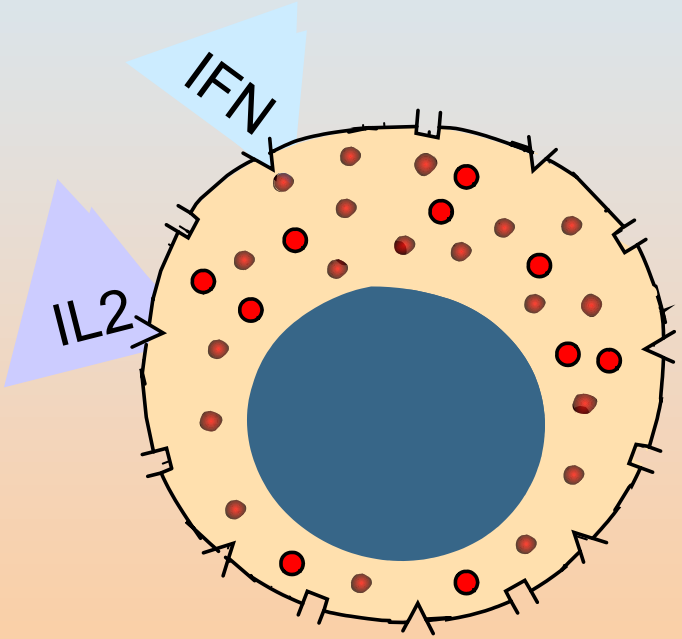
They all kill foreign and altered self targets

Natural Killer (NK) cells



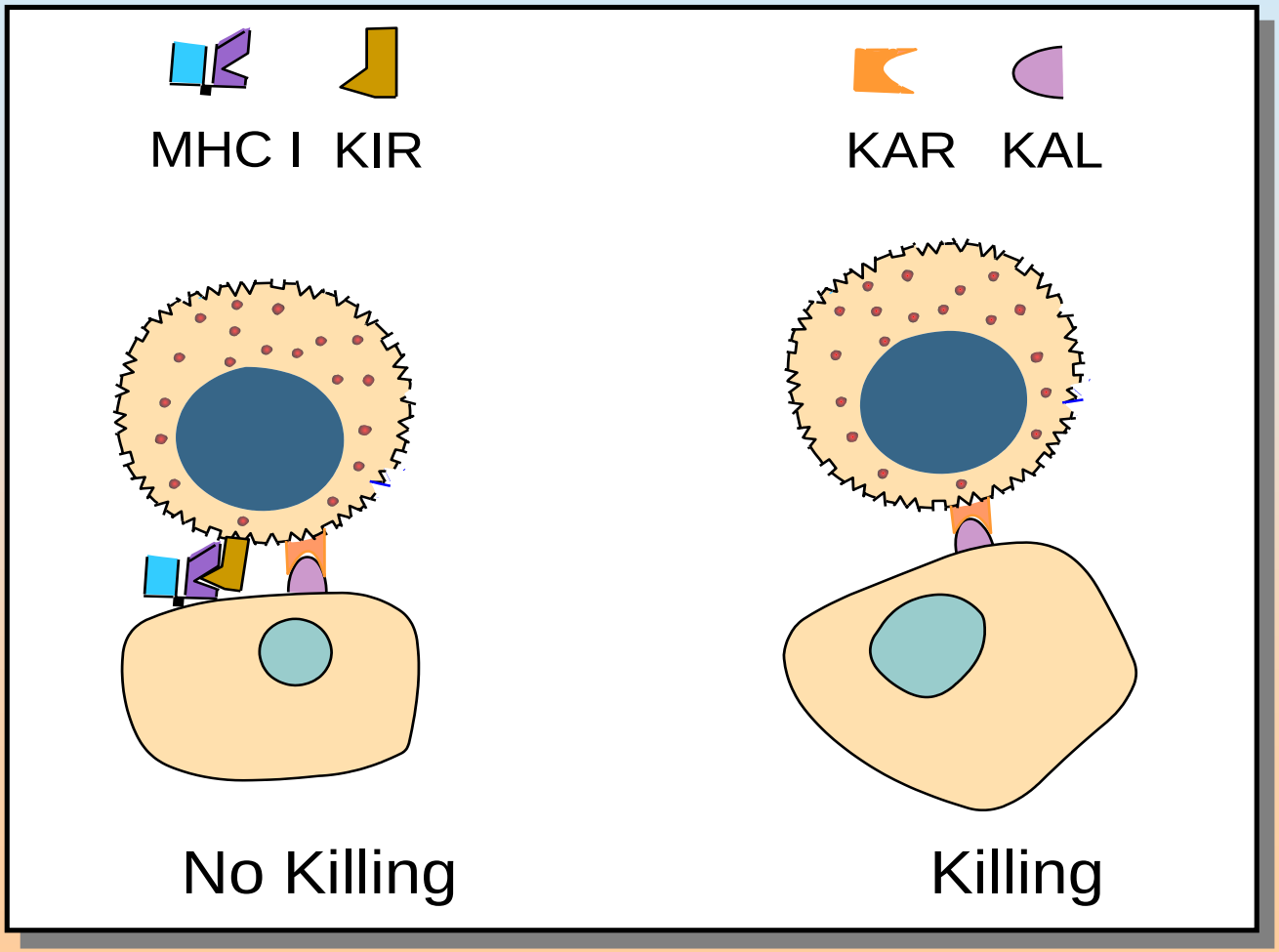
- also known as large granular lymphocytes (LGL)
- kill infected and malignant cells
- are identified by the presence of CD56 & CD16 and absence of CD3
- activated by IL2 and IFN-γ to become LAK cells

Lymphokine Activated Killer (LAK) cell



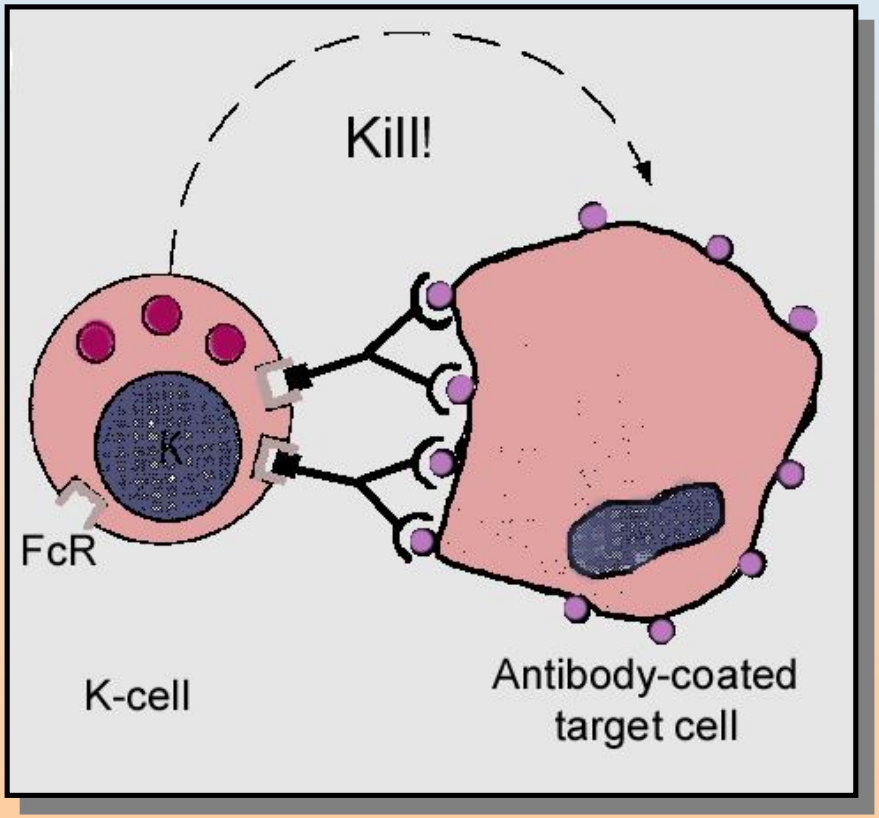
kills transformed and malignant cells

Regulation of NK Cell Function



K Cells

- morphologically undefined
- have IgG Fc receptor
- recognize antibody coated targets
- could be NK cells (IgG), macrophages (IgG), eosinophils (IgE) or other cells (IgG)



Complement

Complement: history

Discovered in 1894 by Bordet

It represents lytic activity of fresh serum

Its lytic activity destroyed when heated at 56C for 30 min

Complement functions

- Host benefit:
  - opsonization to enhance phagocytosis
  - phagocyte attraction and activation
  - lysis of bacteria and infected cells
  - regulation of antibody responses
  - clearance of immune complexes
  - clearance of apoptic cells
- Host detriment:
  - Inflammation, anaphylaxis

Definitions

- C-activation: alteration of C proteins such that they interact with the next component
- C-fixation: utilization of C by Ag-Ab complexes
- Hemolytic units (CH50): dilution of serum which lyses 50% of Ab-coated r.b.c in a suspension
- C-inactivation: denaturation (usually by heat) of an early C-component resulting in loss of hemolytic activity
- Convertase/esterase: altered C-protein which acts as a proteolytic enzyme for another C-component

Proteins of the complement system (nomenclature)

- C1(qrs), C2, C3, C4, C5, C6, C7, C8, C9
- factors B, D, H and I, properdin (P)
- mannose binding lectin (MBL), MBL associated serine proteases (MASP-1 MASP-2)
- C1 inhibitor (C1-INH, serpin), C4-binding protein (C4-BP), decay accelerating factor (DAF),
- C1 receptor (CR1), protein-S (vitronectin)

Molecular Structure of complement proteins

Components	*MW (Kd)*	*No. of Chains*	*Serum conc. (mg/ml)*
Early components			
CLASSIC PATHWAY			
C1q	410	18 (6A+6B+6C)	70
C1r	90	2(identical)	50
C1s	85	2(identical)	50
C4	206	3 ($\alpha + \beta + \gamma$)	300
C2	117	1	25
C3	190	2 ($\alpha + \beta$)	1200
ALTERNATIVE PATHWAY			
C3	190	2 ($\alpha + \beta$)	1200
B	100	1	225
D	25	1	1
P	55	3 or 4 (identical)	25
Late components **(for both)**			
C5	185	2 ($\alpha + \beta$)	85
C6	128	1	60
C7	120	1	55
C8	150	3 ($\alpha + \beta + \gamma$)	55
C9	79	1	60

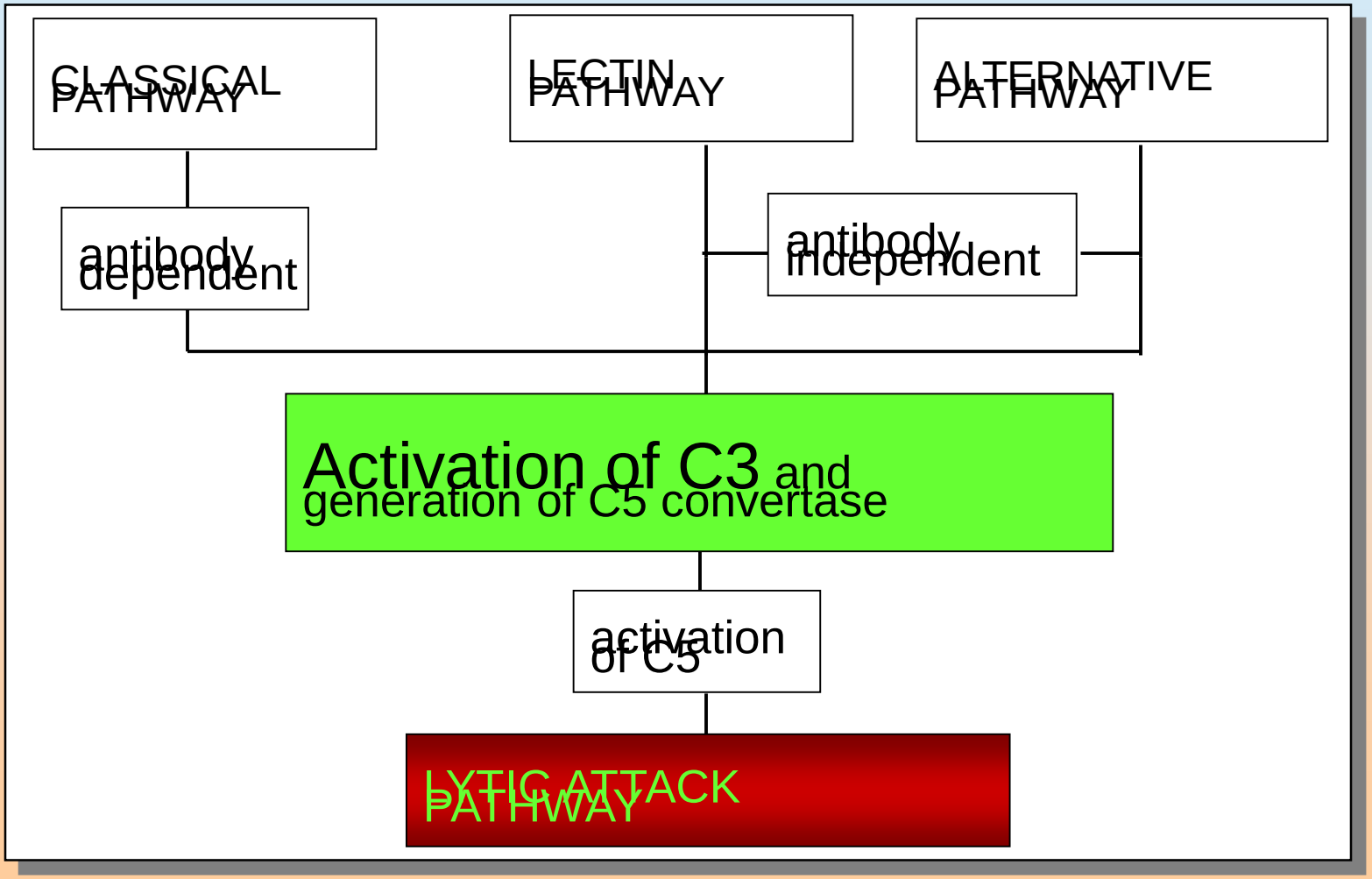
Activation product of complement proteins (nomenclature)

Activated component are usually over-lined: *e.g.* C1$\overline{qrs}$

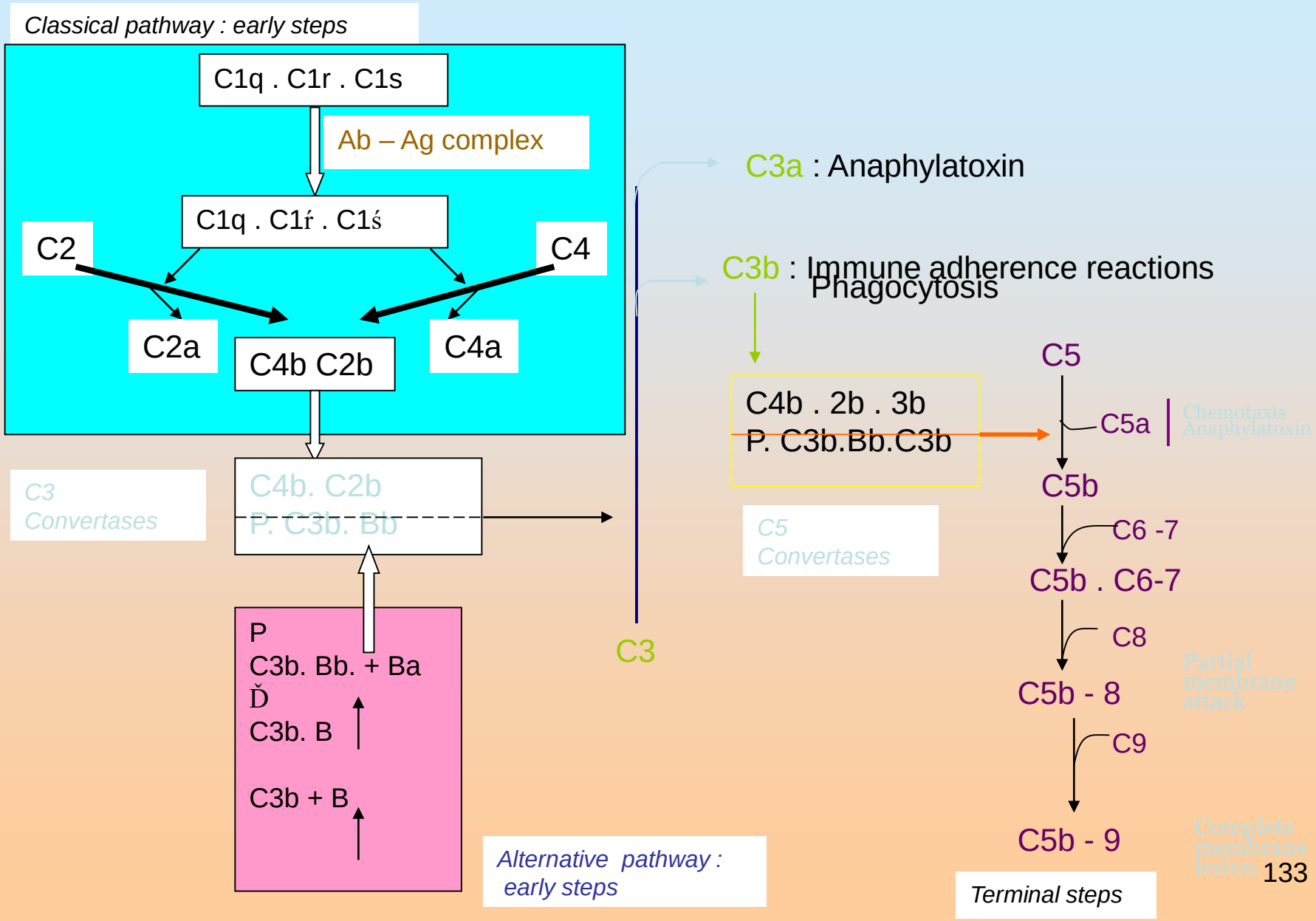
When enzymatically cleaved, the larger moiety, binds to the activation complex or membrane and the smaller peptide is released in the microenvironment

Letter “b” is *usually* added to the larger, membrane-binding, peptide and “a” to the smaller peptide (*e.g.*, C3b/C3a, C4b/C4a, C5b/C5a), *EXCEPT* C2 (the larger, membrane-binding moiety is C2a; the smaller on is C2b)

Pathways of complement activation



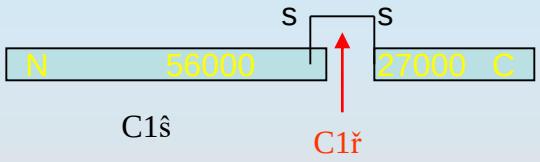
Reaction Sequence



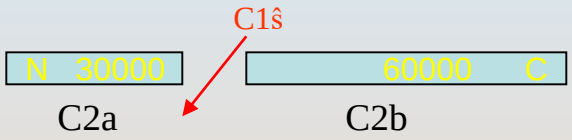
Protease activity

Un activated | *Cleaved*

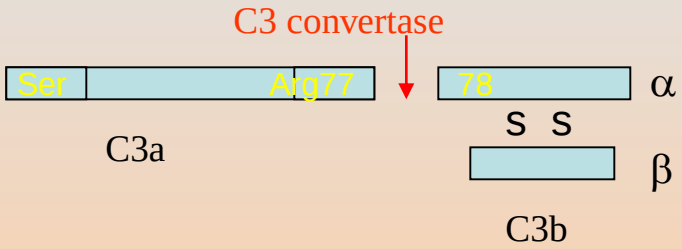
C1s **83000 (d)**



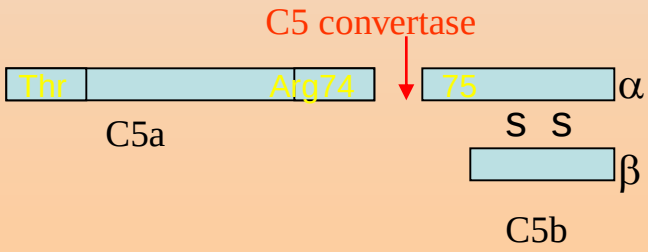
C2 **102000 (d)**



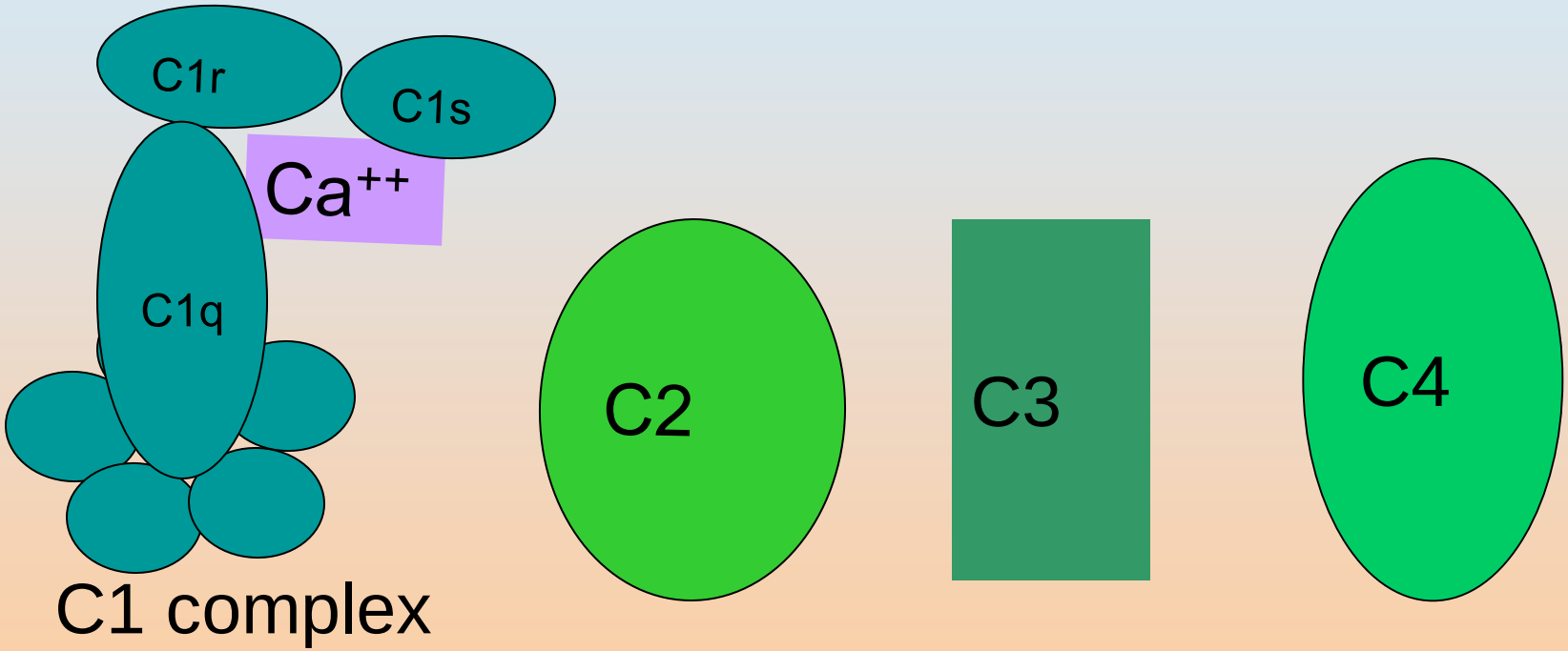
C3 **190000 (d)**



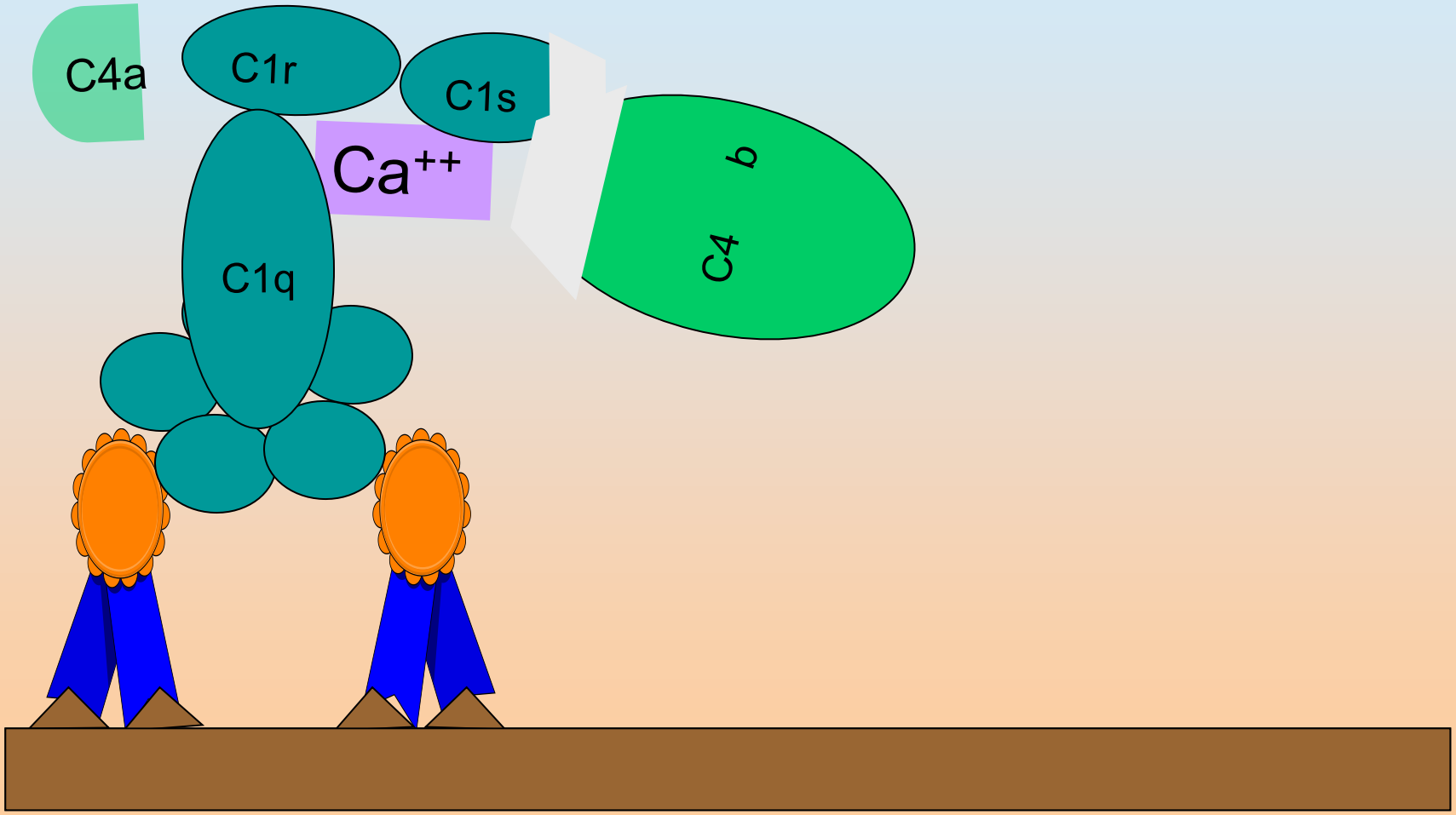
C5 **185000 (d)**



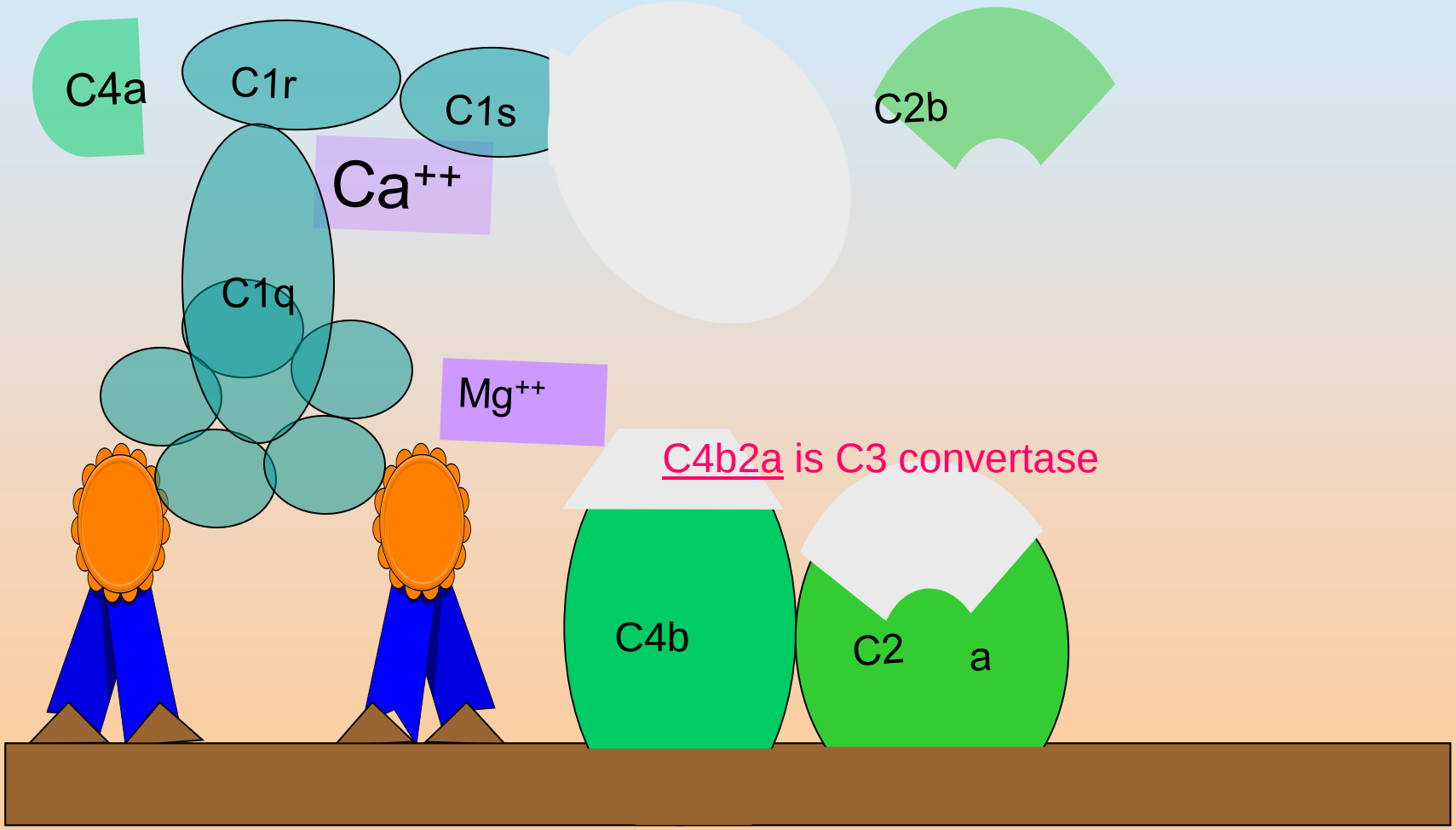
Components of the Classical Pathway



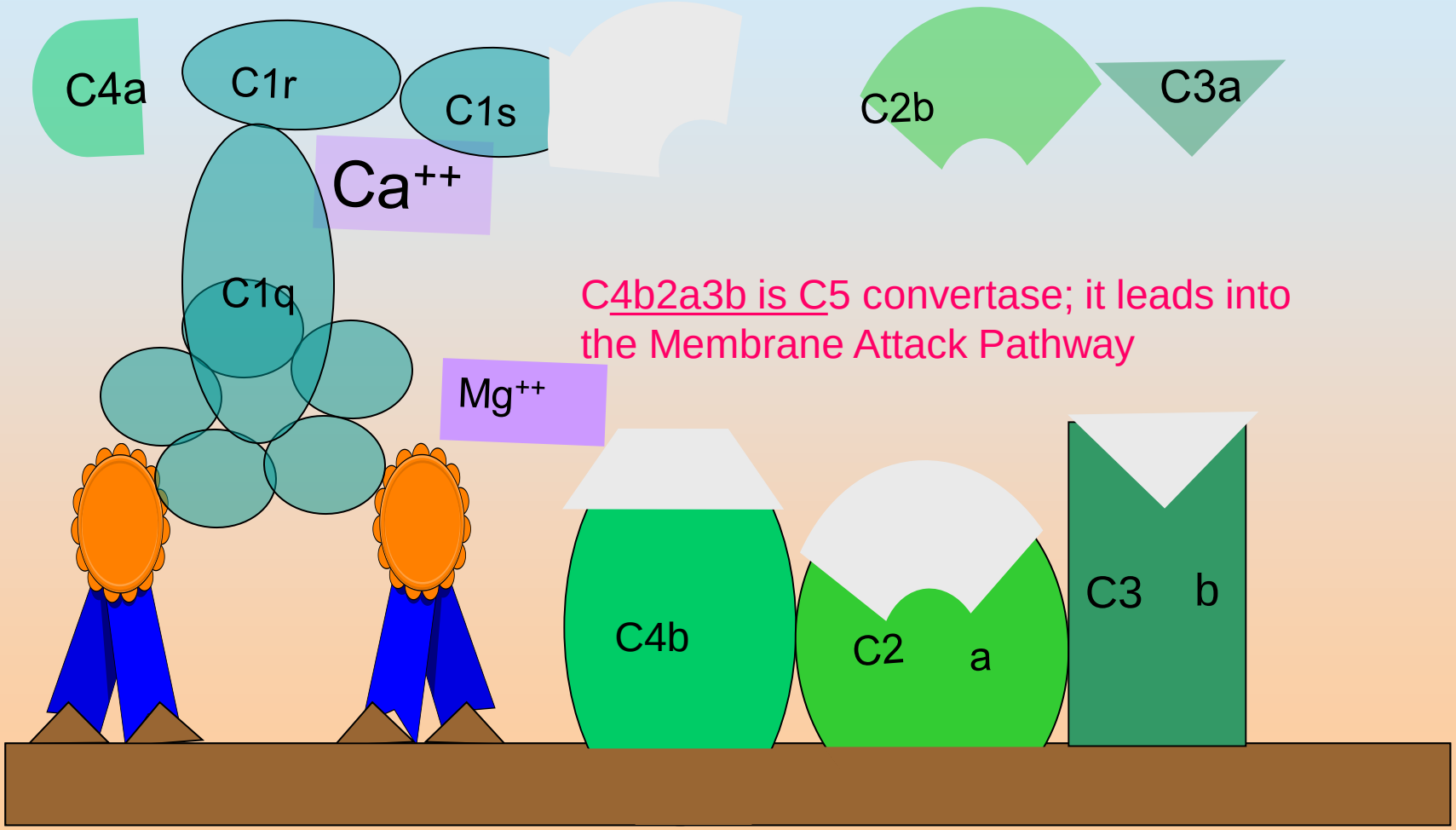
Classical Pathway
Generation of C3-convertase



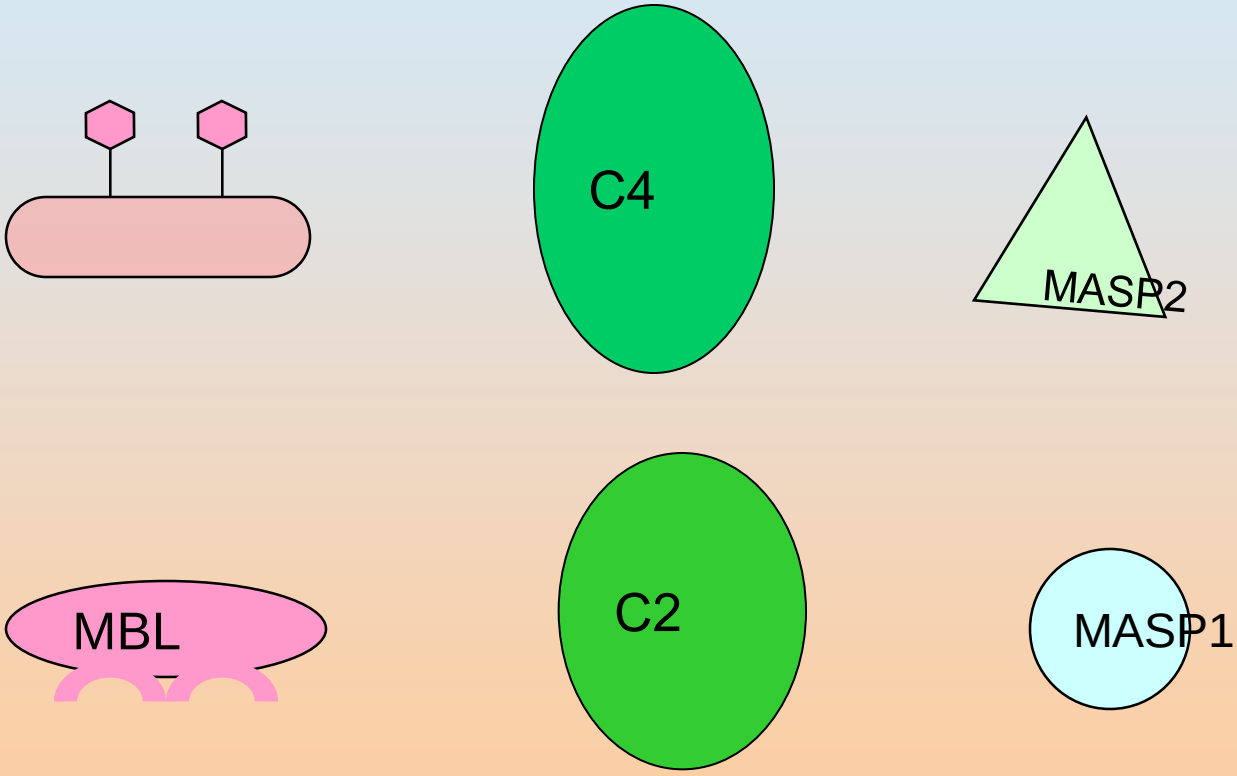
Classical Pathway
Generation of C3-convertase



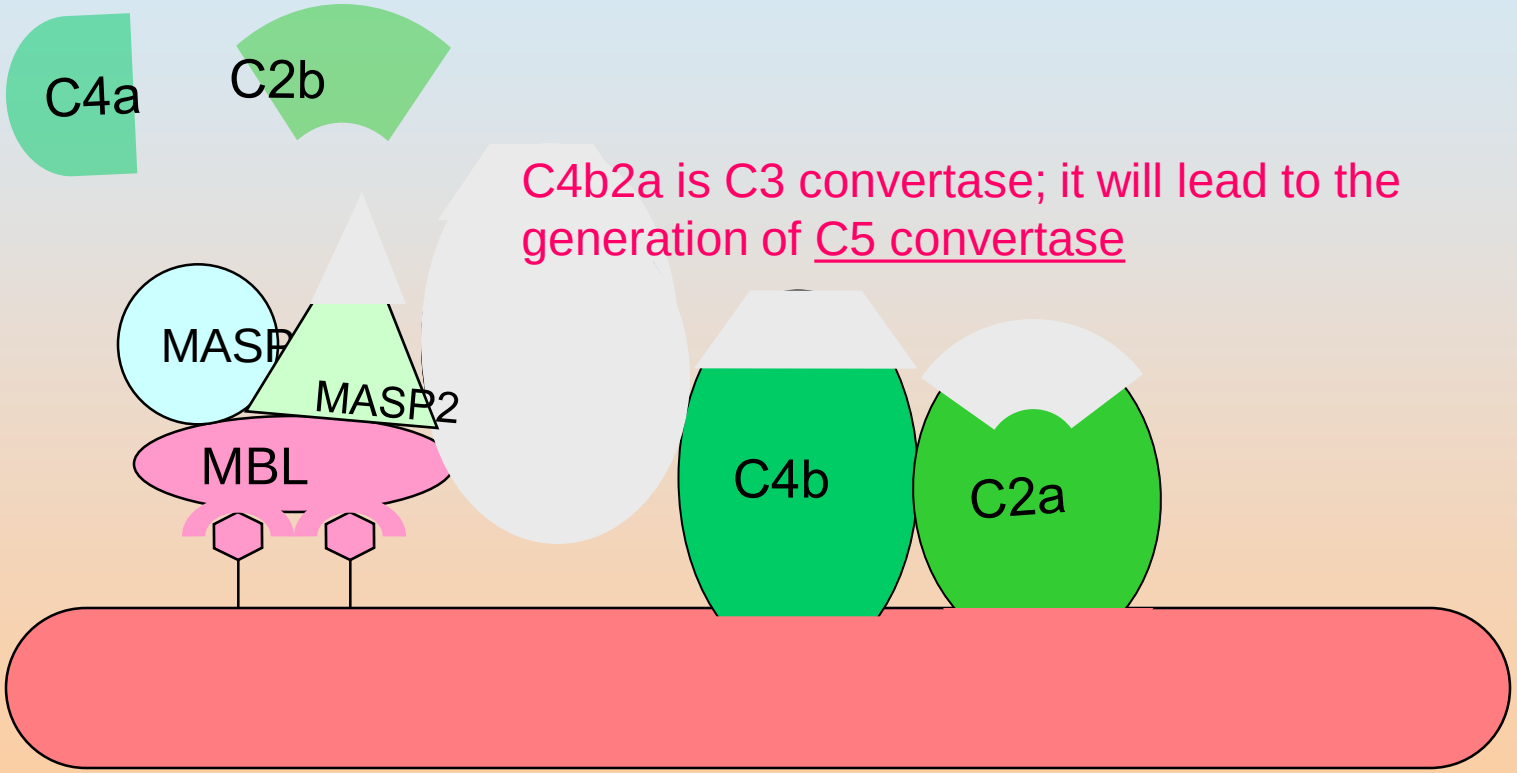
Classical Pathway
Generation of C5-convertase



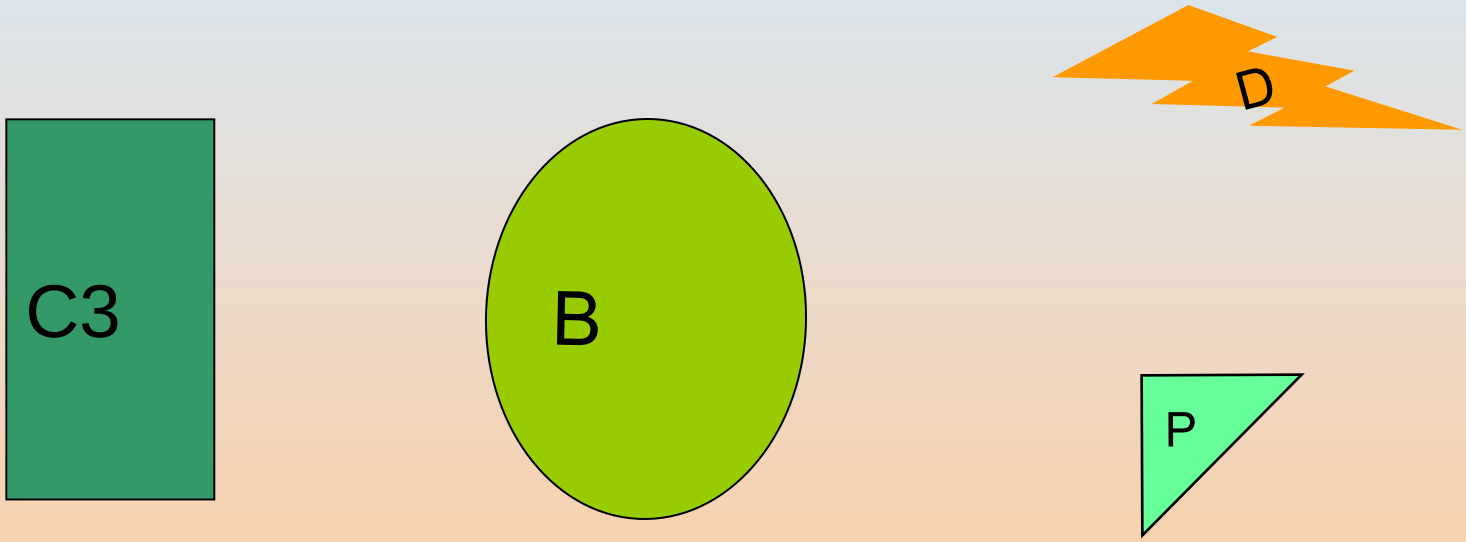
Components of mannose-binding lectin pathway



Mannose-binding lectin pathway



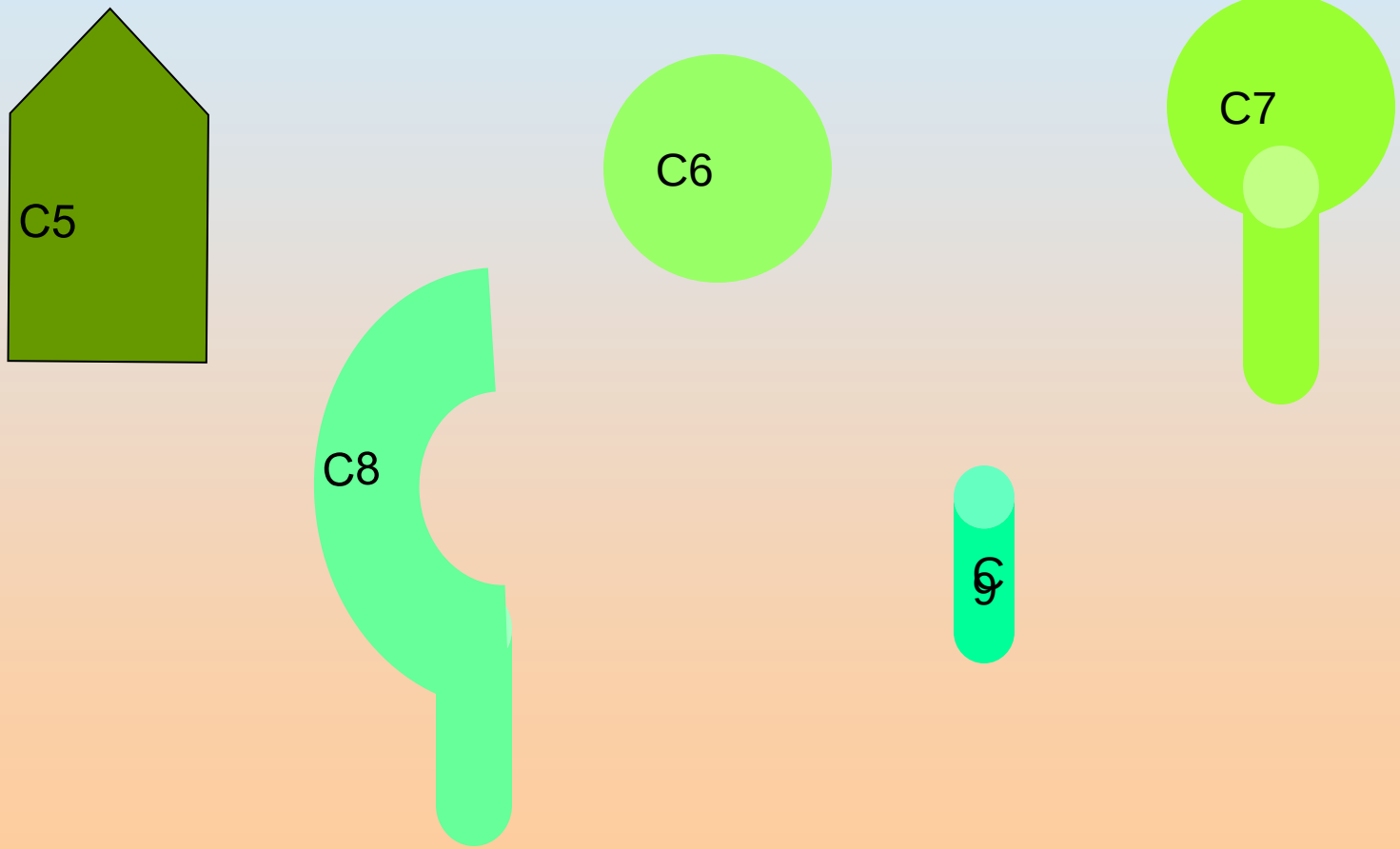
Components of the alternative pathway



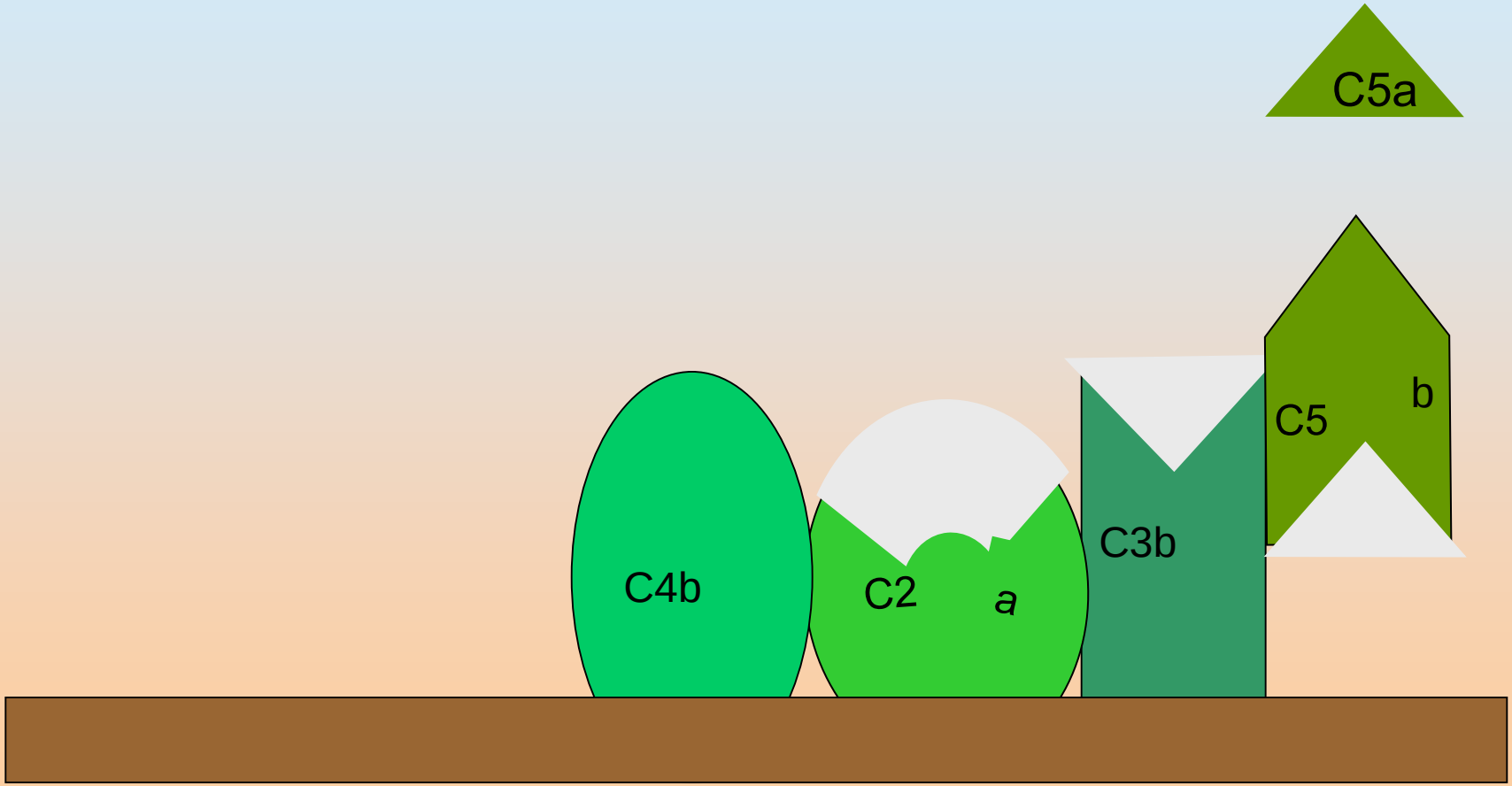
Lytic pathway

Generation of C5 convertase leads to the activation of the Lytic pathway

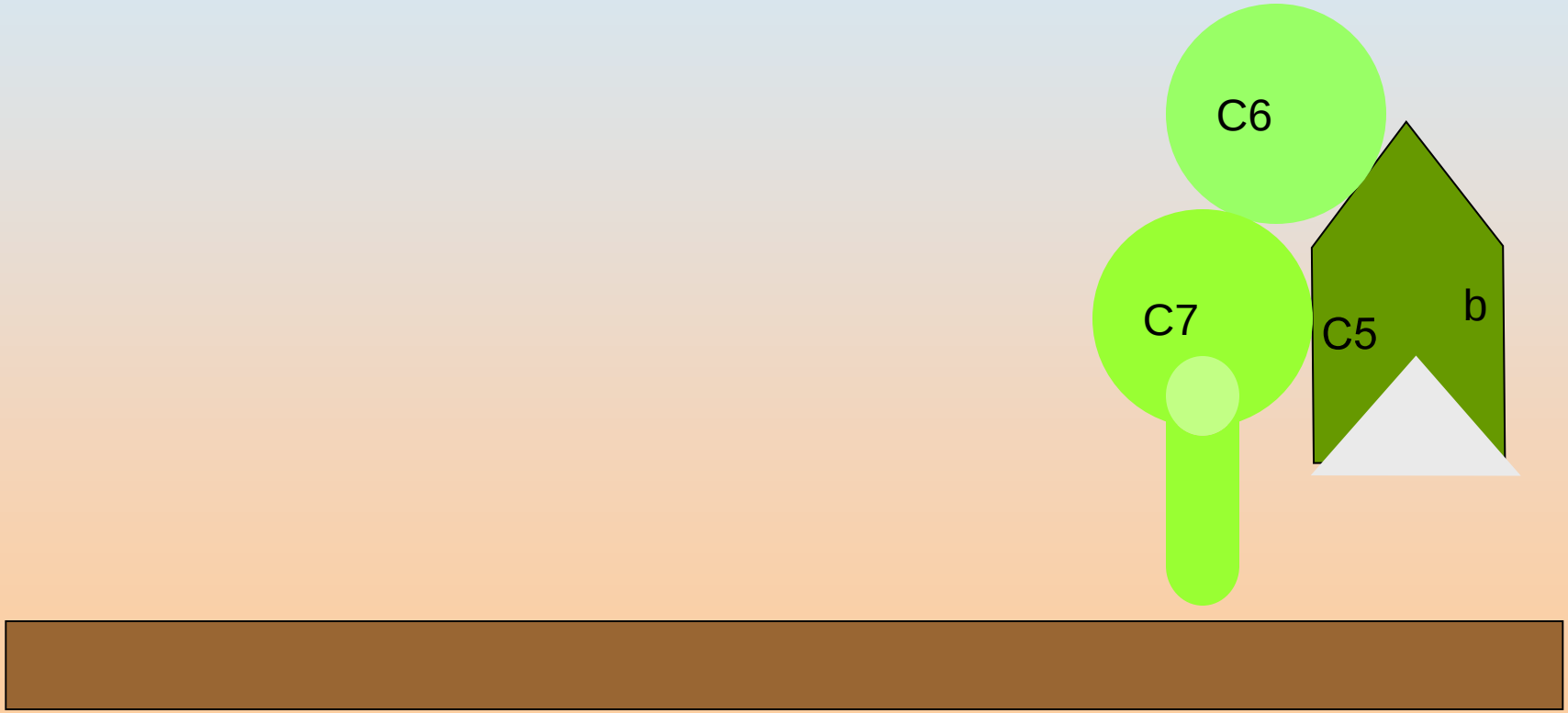
Components of the lytic pathway



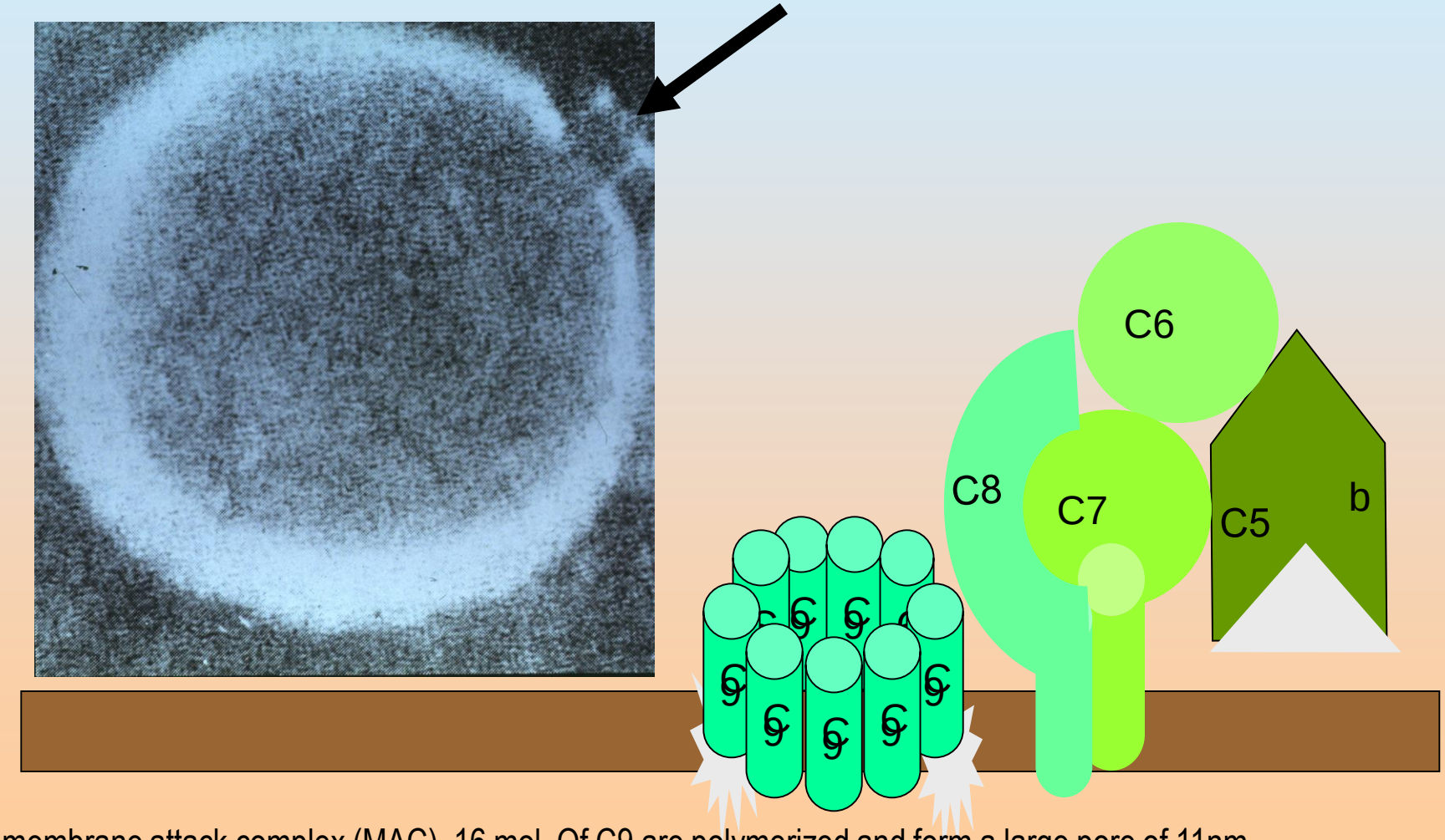
Lytic pathway
C5-activation



Lytic pathway
assembly of the lytic complex



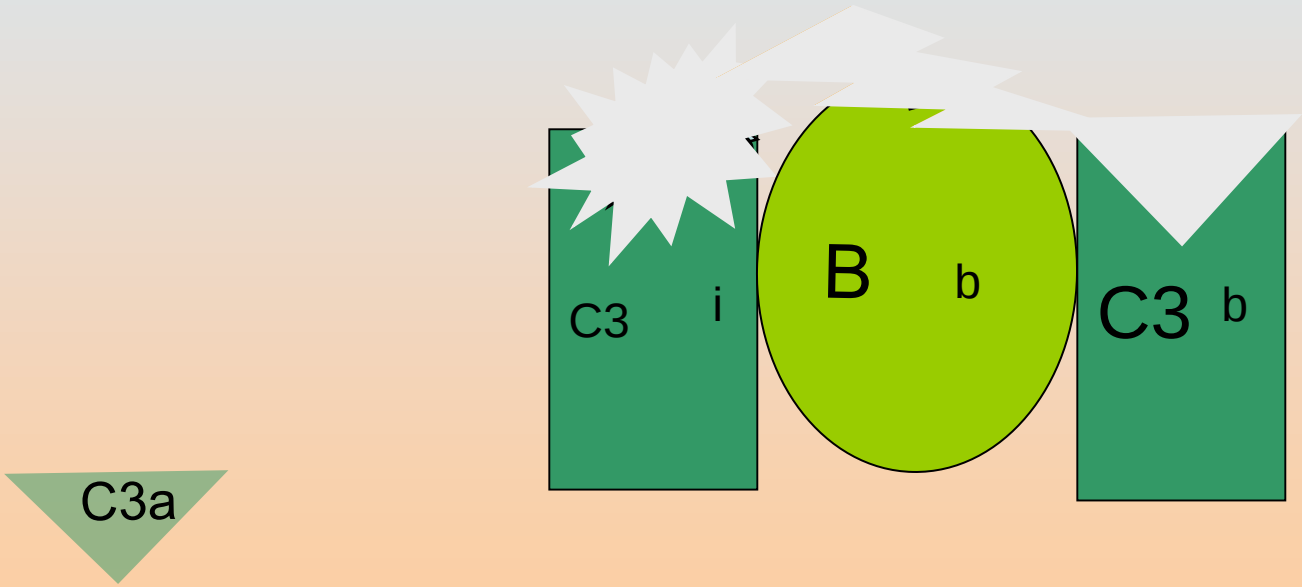
Lytic pathway:
insertion of lytic complex into cell membrane



In membrane attack complex (MAC), 16 mol. Of C9 are polymerized and form a large pore of 11nm

Spontaneous C3 activation

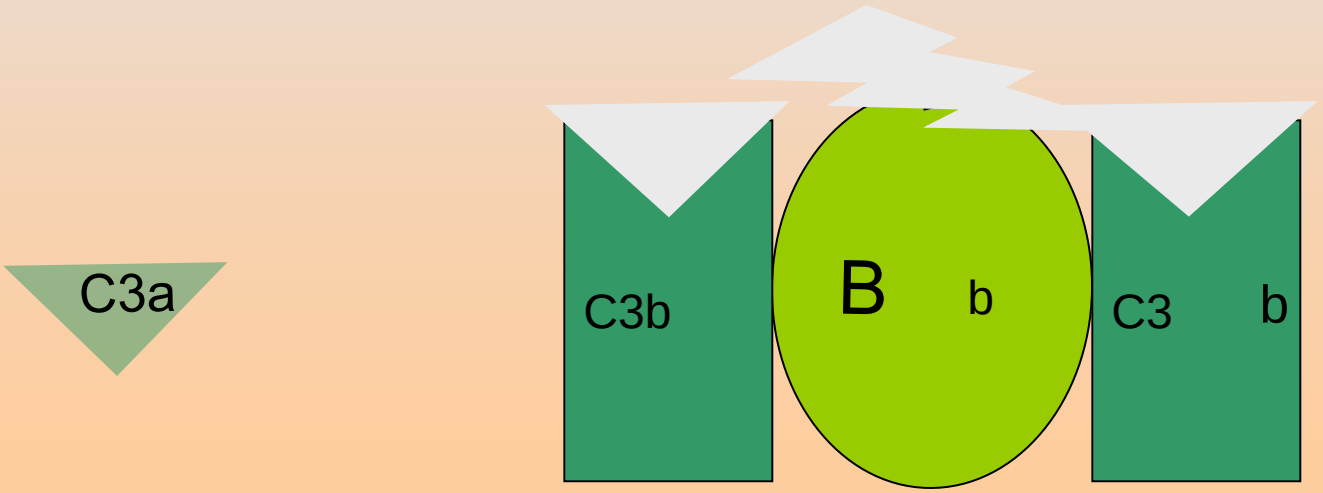
Generation of C3 convertase



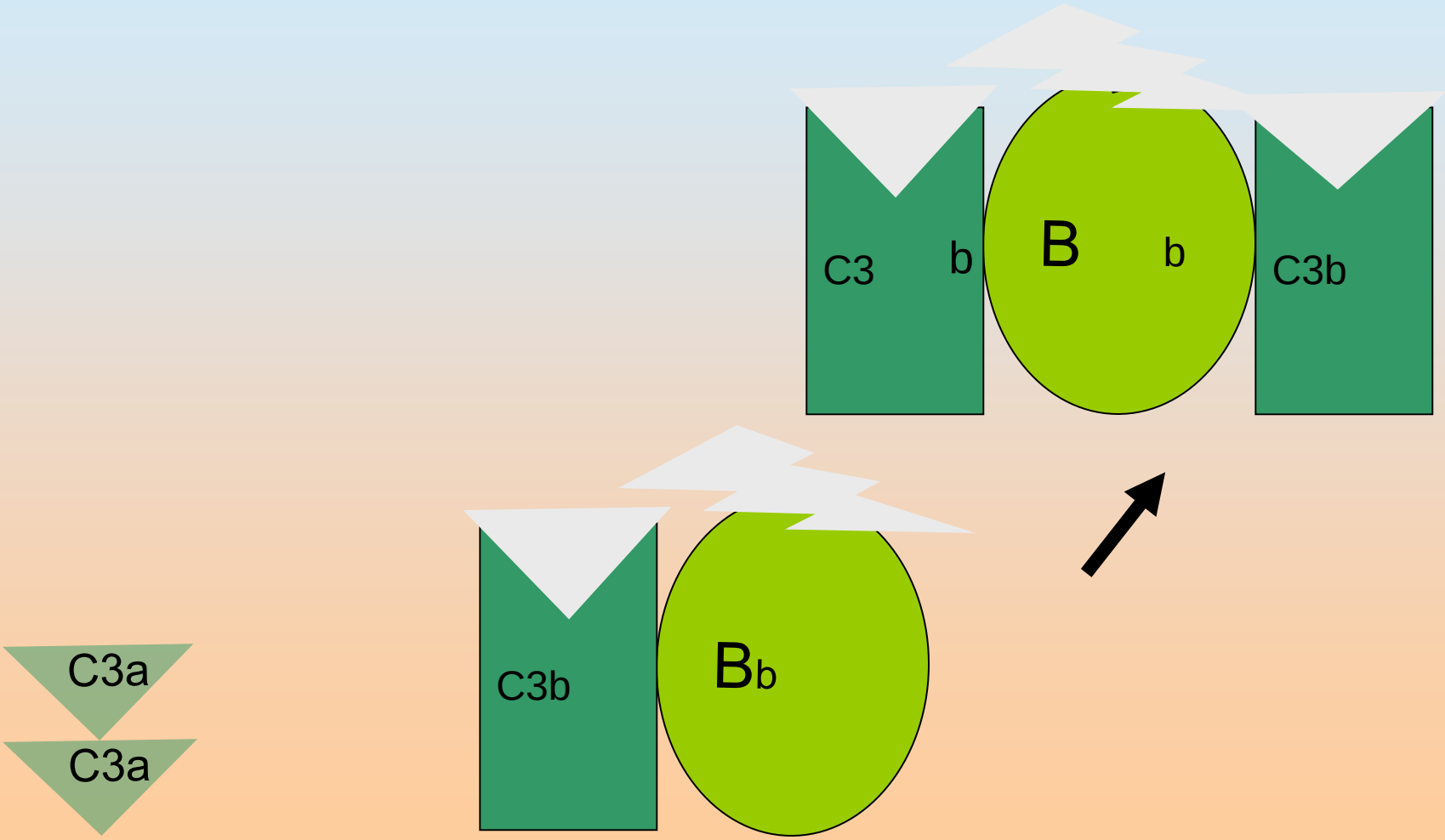
C3iBb complex has a very short half life

C3-activation
the amplification loop

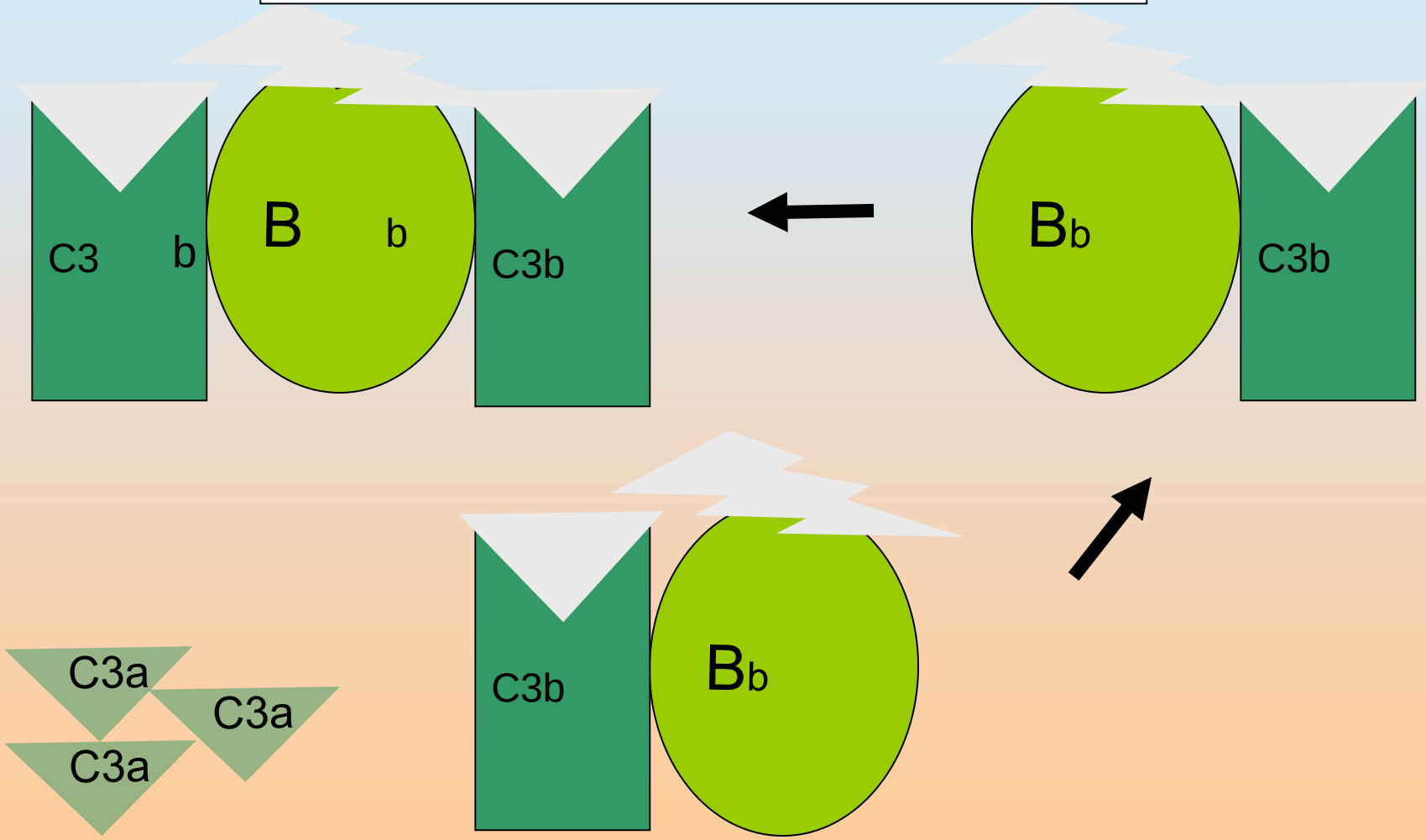
If spontaneously-generated C3b is not degraded



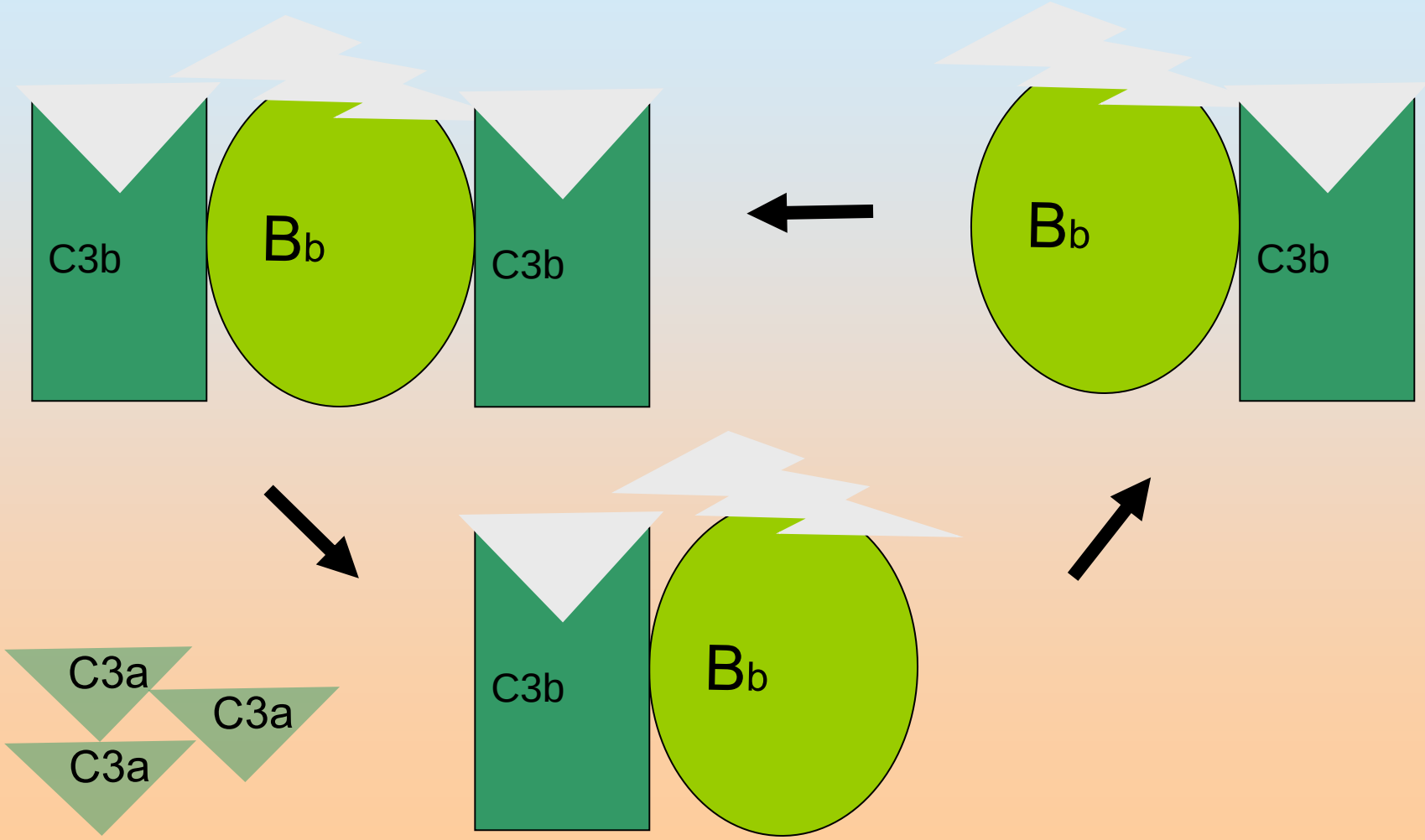
C3-activation
the amplification loop



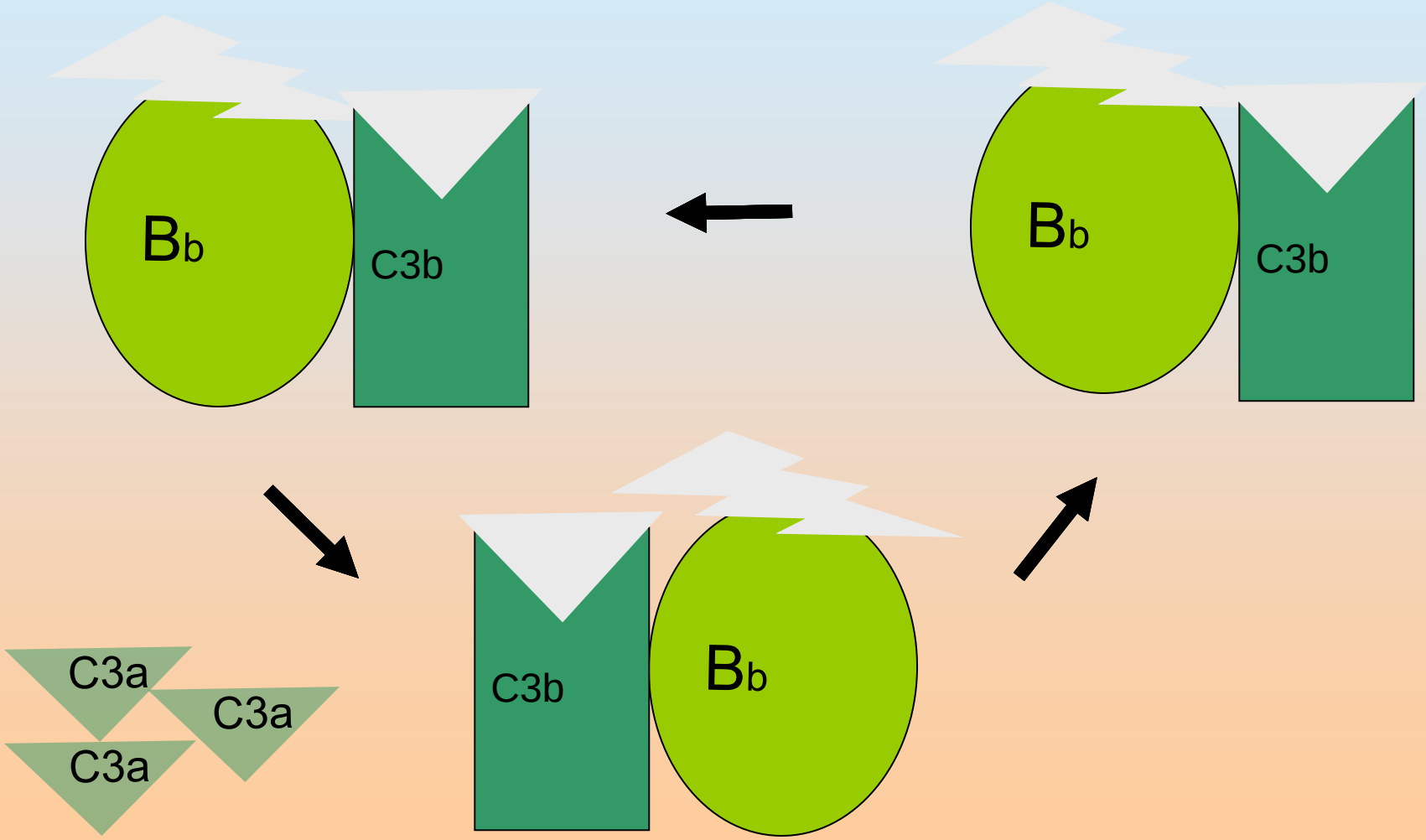
C3-activation
the amplification loop



C3-activation
the amplification loop



C3-activation
the amplification loop

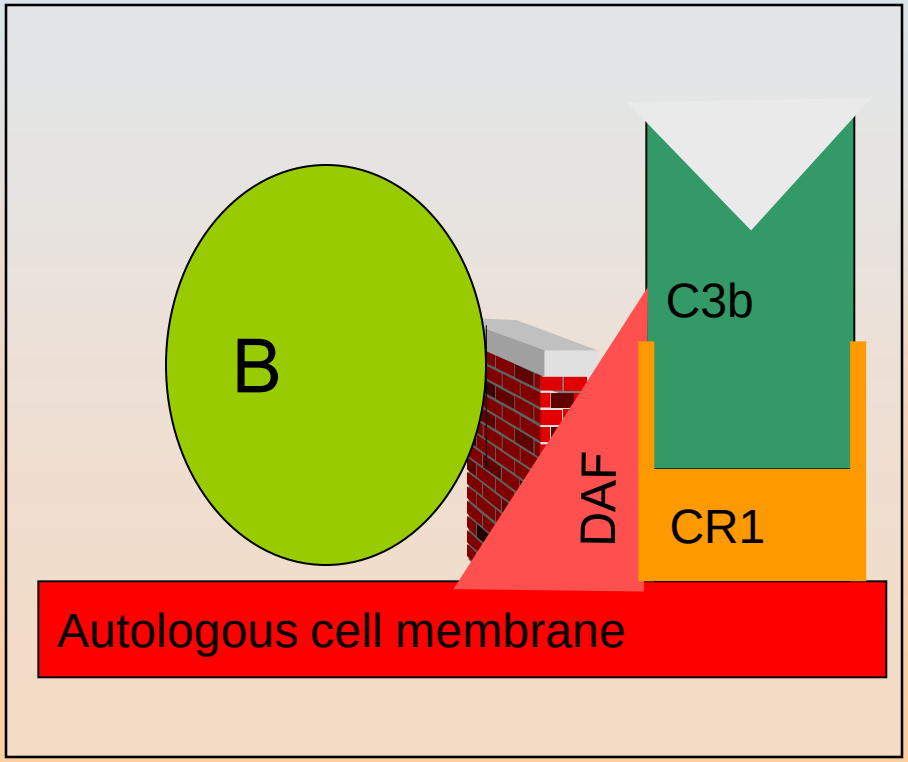


Control of spontaneous C3 activation via DAF

DAF prevents

the binding of

factor B to C3b

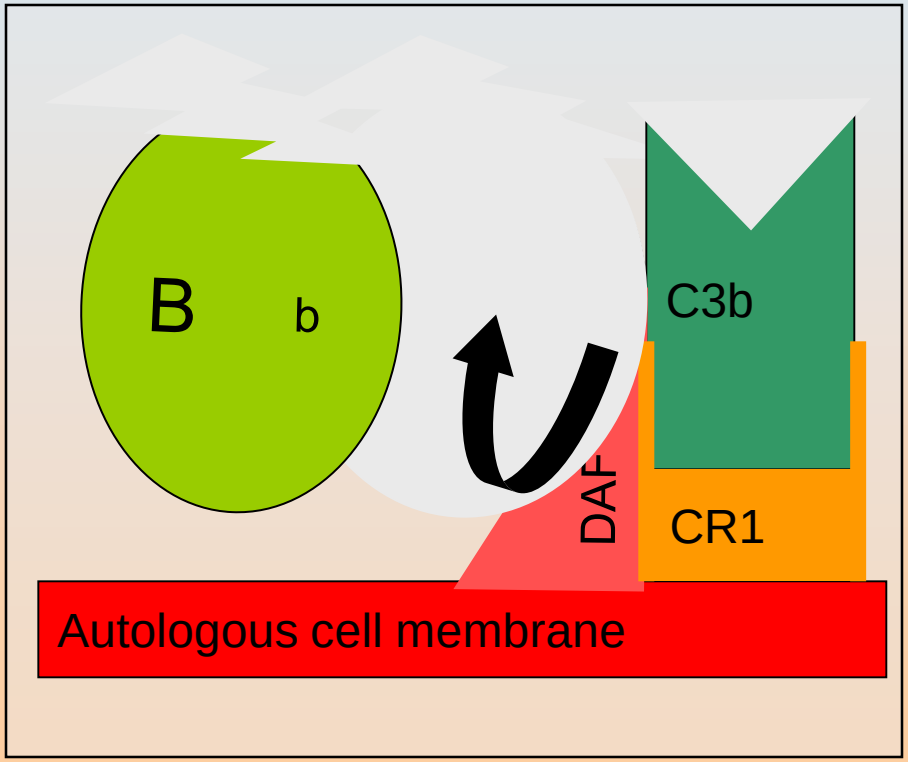


Control of spontaneous C3 activation via DAF

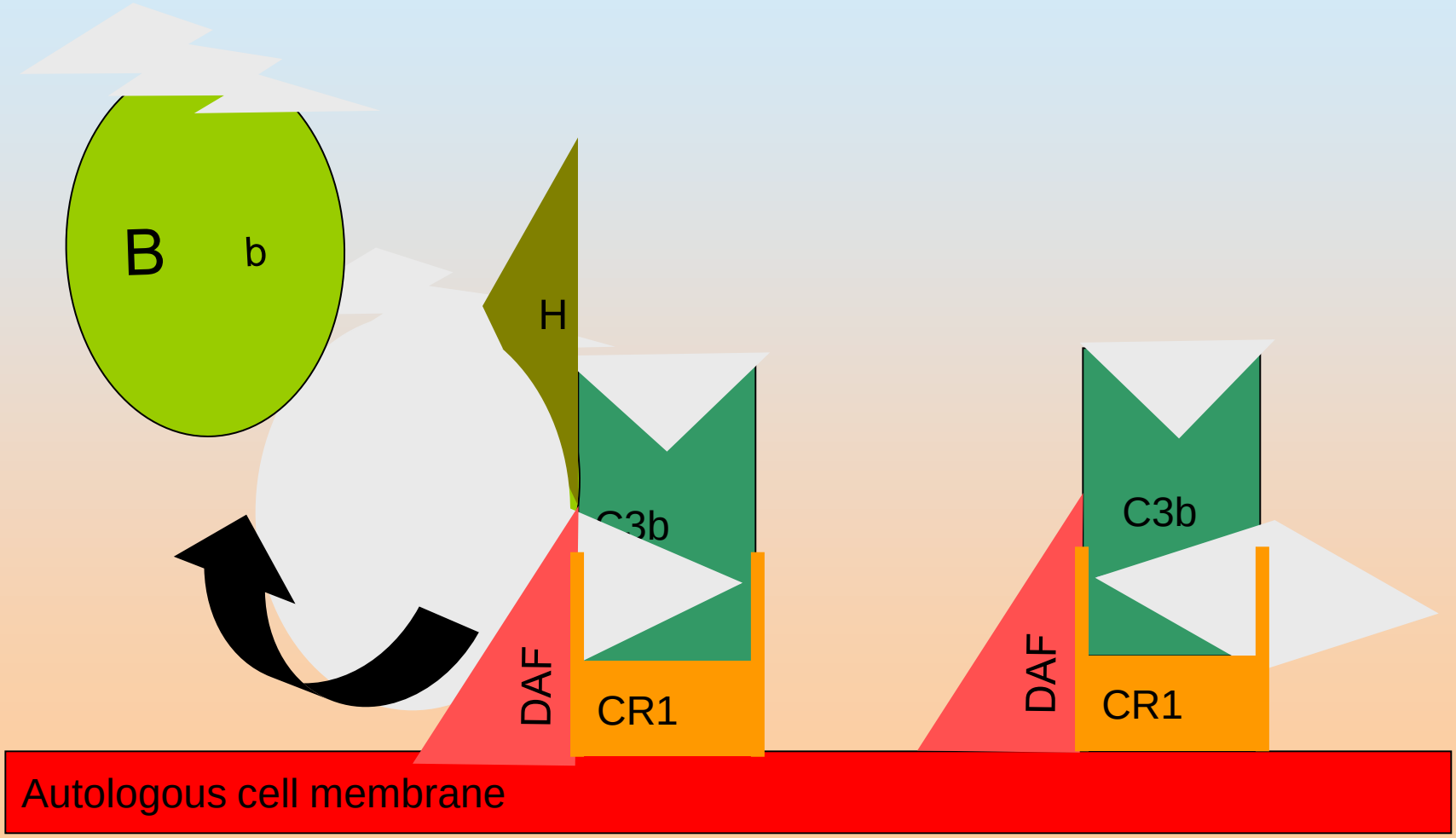
DAF dislodges

C3b-bound

factor Bb



Control of spontaneous C3 activation via CR1

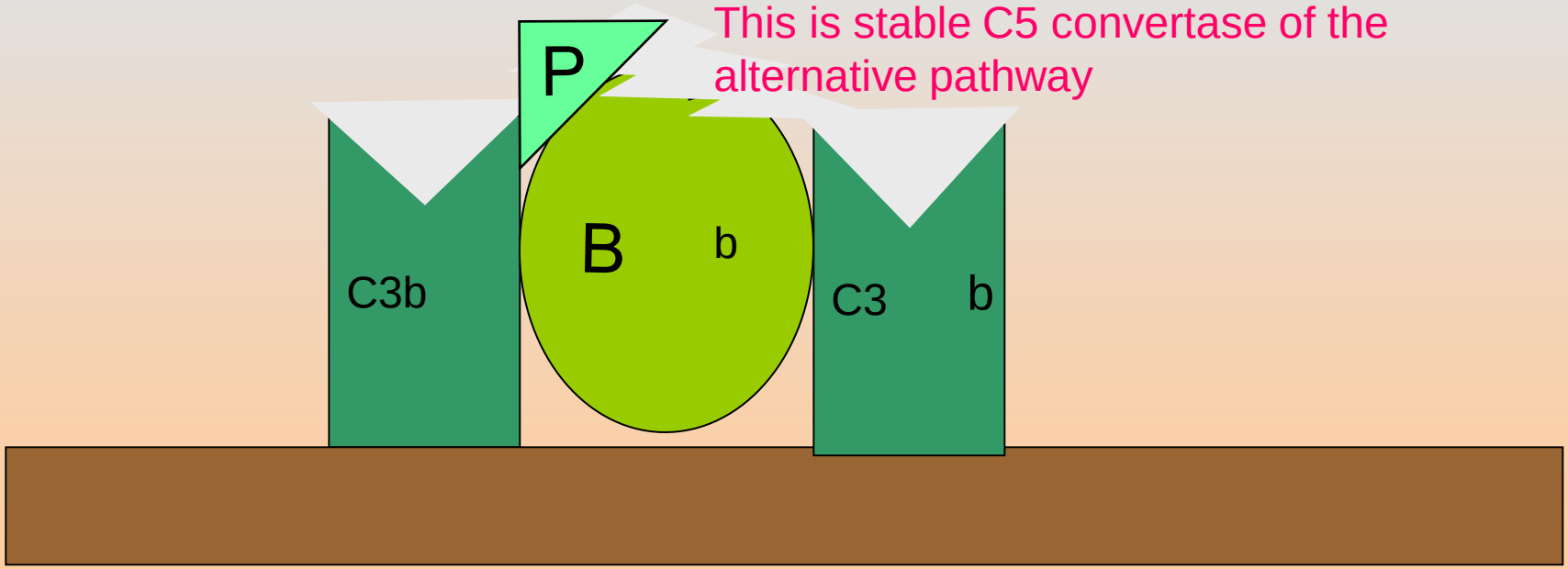


Degradation of spontaneously produced C3b

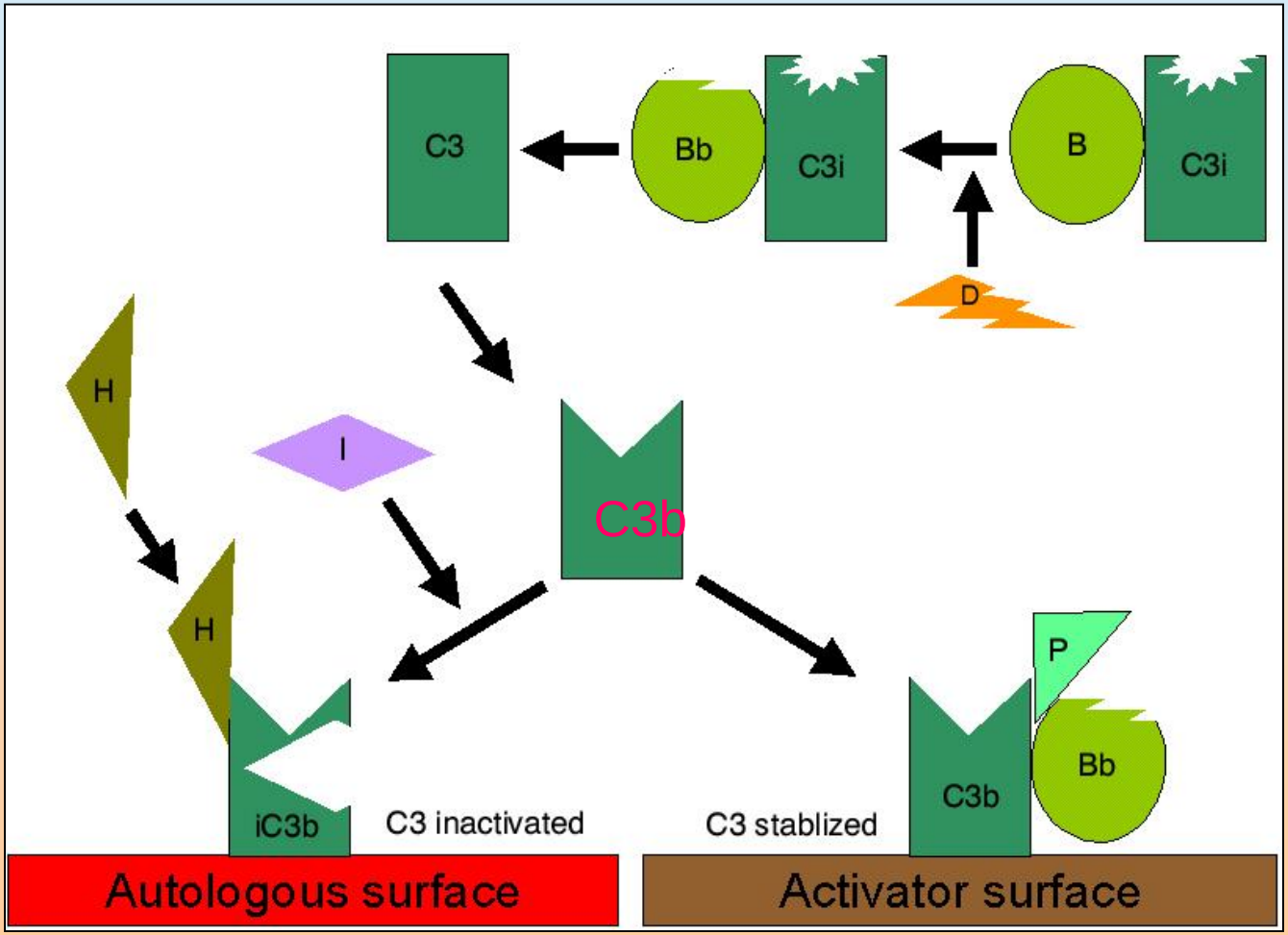
C3b stabilization and C5 activation

C3a

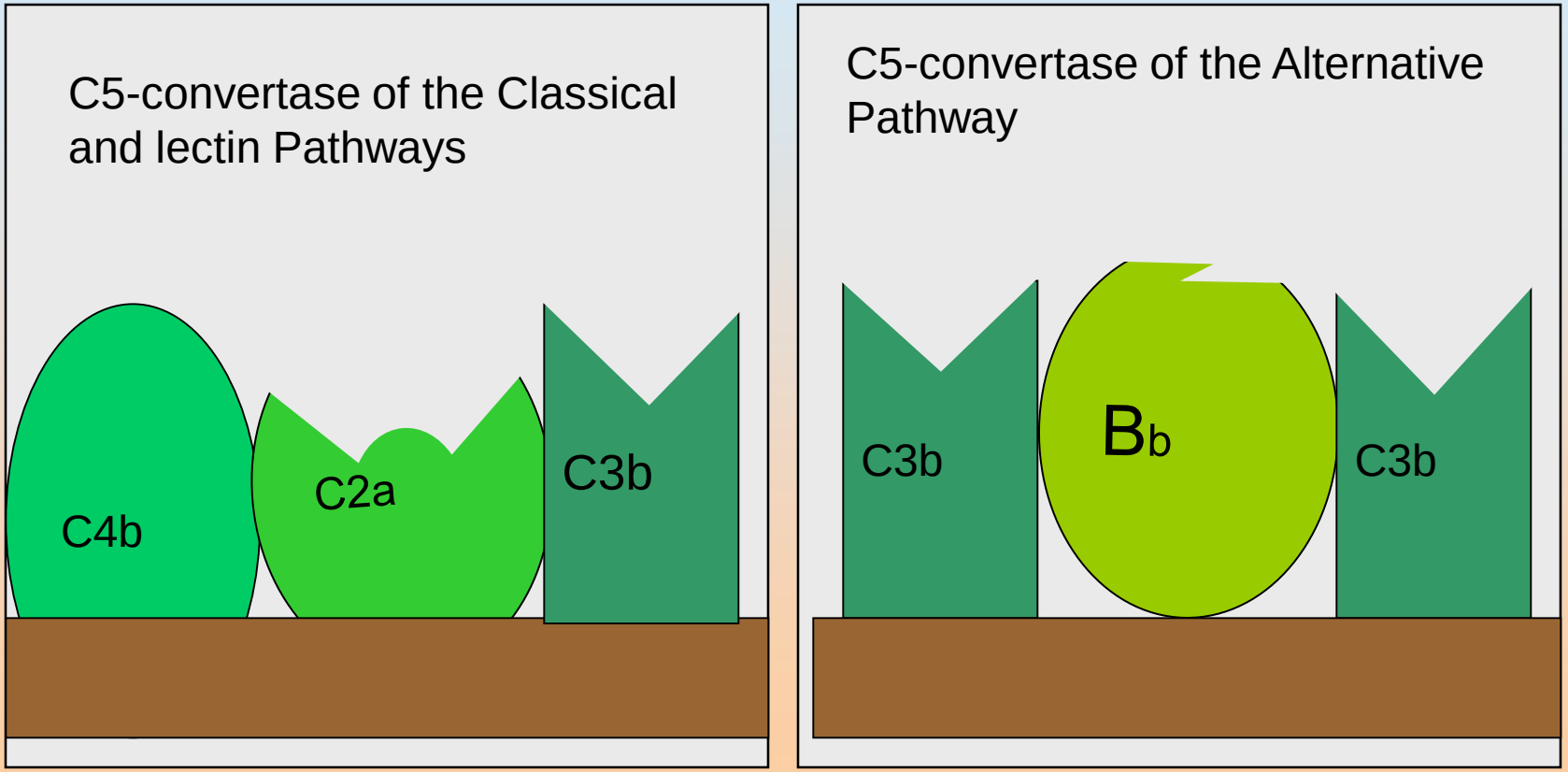
C3b finds an activator (protector) membrane



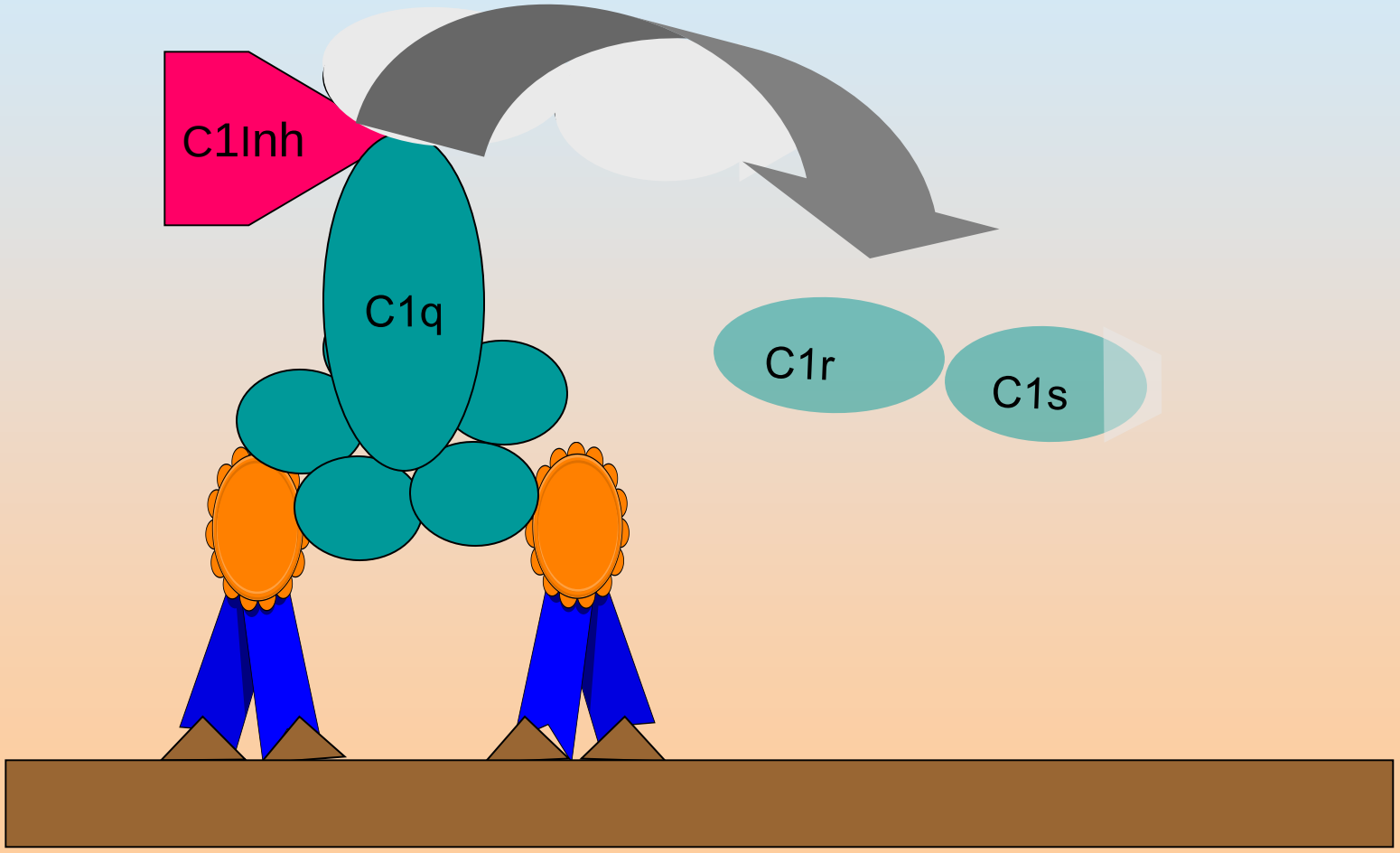
C3b regulation on self and activator surfaces



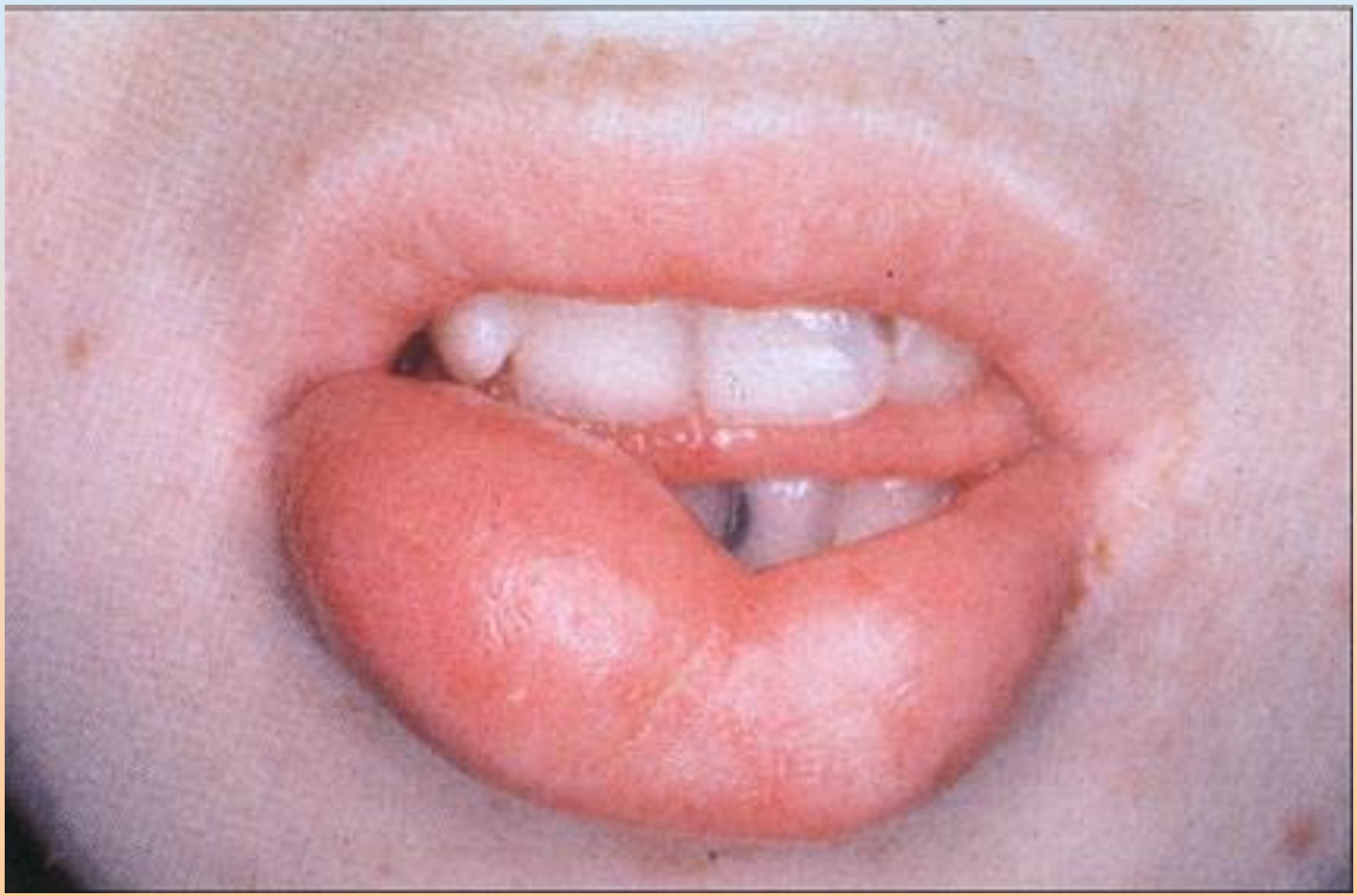
C5-convertase of the two pathways



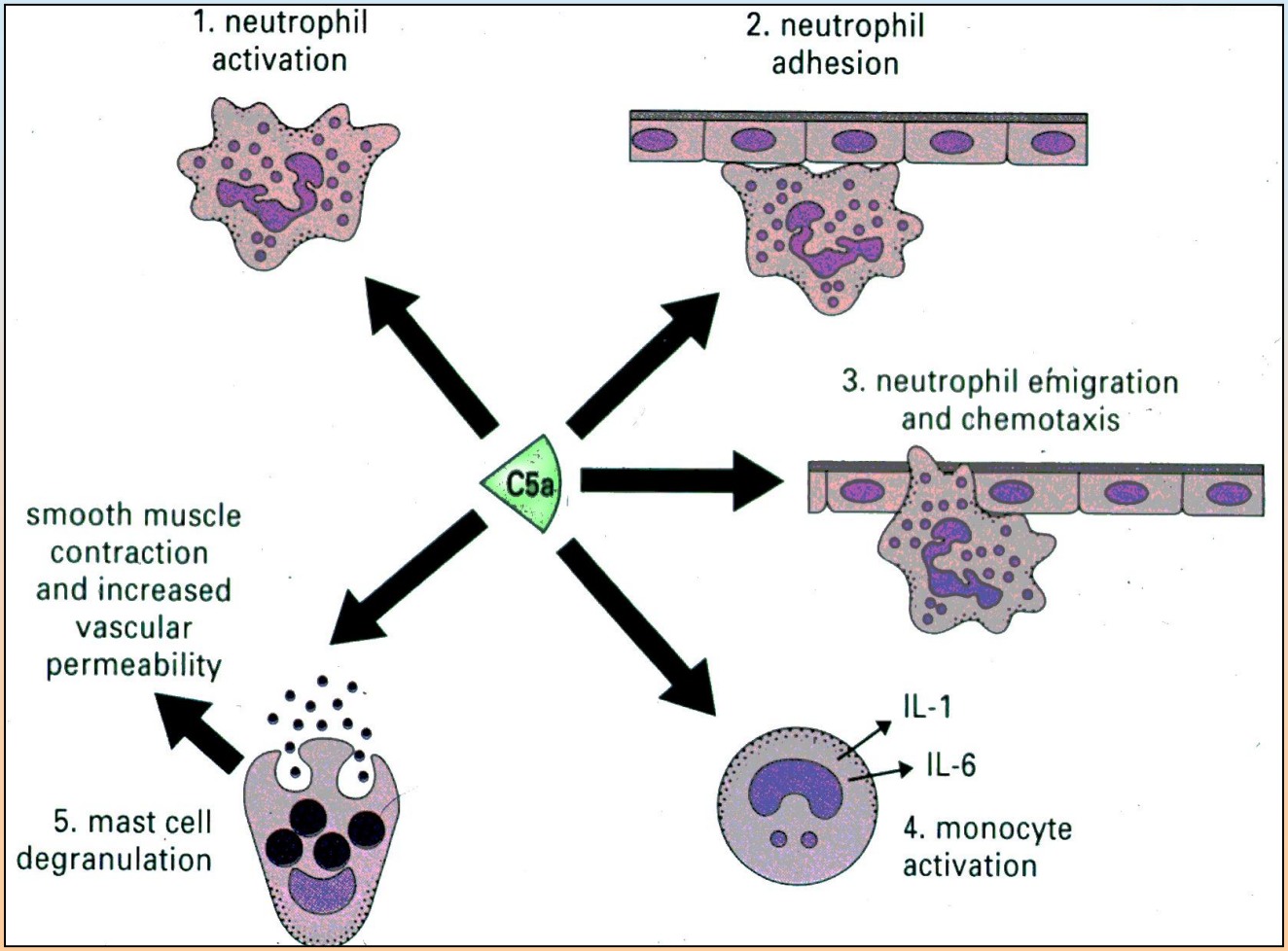
C1qrs breakdown



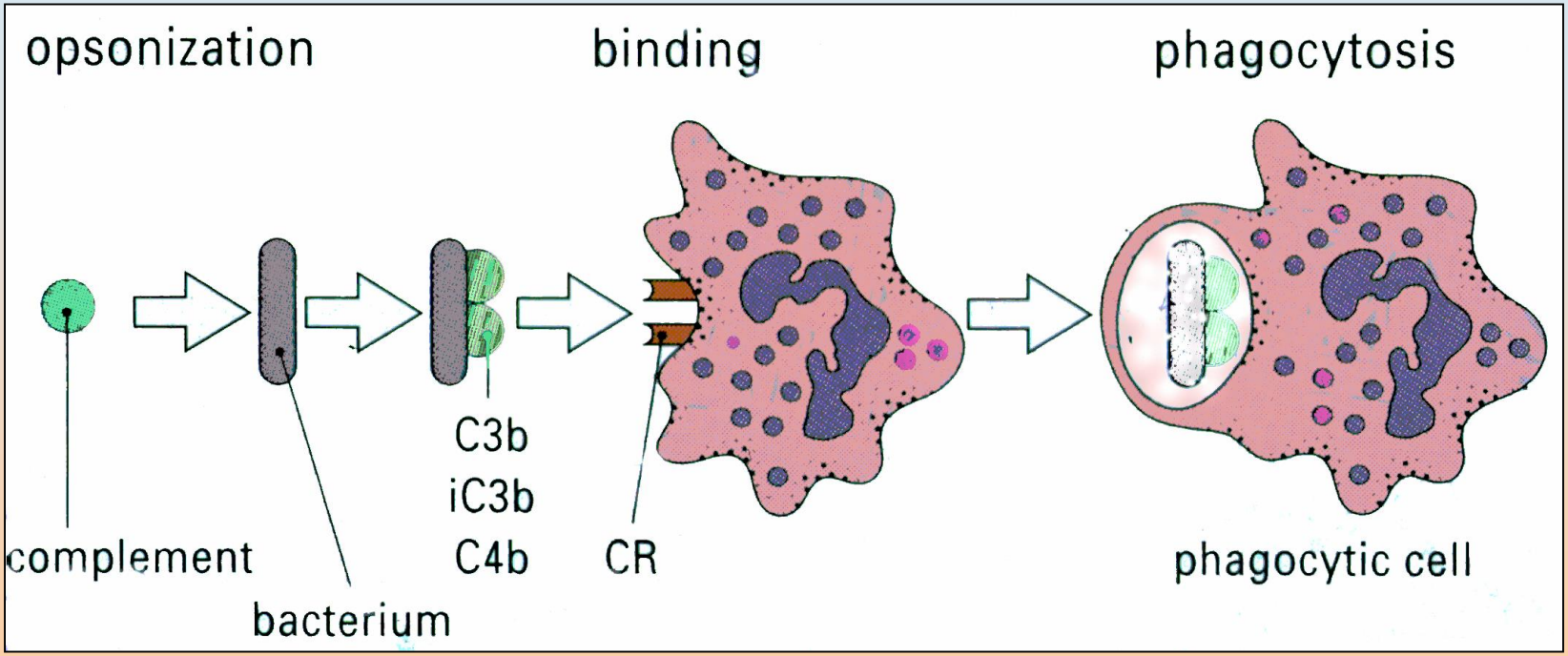
C1-inhibitor deficiency: angioedema



Biological effects of C5a



Opsonization and phagocytosis



Biological properties of C-activation products

Product	Biological Effects	Regulation
C2b (prokinin)	edema	C1-INH
C3a (anaphylatoxin)	mast cell degranulation; enhanced vascular permeability; anaphylaxis	carboxy-peptidase- B (C3-INA)

Biological properties of C-activation products

Product	Biological Effects	Regulation
C3b (opsonin)	opsonization; phagocyte activation	factors H & I
C4a (anaphylatoxin)	as C3, but less potent	(C3-INA)
C4b (opsonin)	opsonization; phagocytosis	C4-BP, factor I

Biological properties of C-activation products

Product	Biological Effects	Regulation
C5a (chemotactic factor)	anaphylactic as C3, but much more potent; attracts & activates PMN causes neutrophil aggregation, stimulation of oxidative metabolism and leukotriene release	carboxy-peptidase-C (C3-INA)
C5b67	chemotaxis, attaches to other membranes	protein-S

Summary of the actions of complement