Innate (Nonspecific) Immunity

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3rd class/1st lecture

Definitions

❖ ***Immunity***(*Latin "immunitas"*) **:**

– Universal biological phenomenon that develops many programs based on the unique genotype of the body ("self") in foreign surroundings.

–There are two major types of immunity, *innate immunity*, which is phylogenetic and polyspecific, and *adaptivei mmunity*, which is acquired during an ongoing individual life.

–Innate immunity is an immediate response to a pathogen that does not confer long-lasting protective immunity. It is a nonspecific defense system .

–Adaptive immunity is highly specific, has immunologic memory, and can respond rapidly and vigorously to a second antigen exposure. The adaptive immune response involves antibody-mediated and cellmediated

- ***Immunology:*** **is a life science that studies the immune system,immunological mechanisms, and immunopathology in humans, animals, and other living beings.**

- ***Aantigen:*** **is a substance containing such information about "non-self," "self," and/ or "former self," which can trigger immune responses in the body to induce a very long and even lifelong memory.**

- ***Immunoglobulin*** **or** ***antibody*** **:is an effector molecule of the B-cell-mediated responses, which is secreted by plasma cells and interacts to appropriate antigen specific to this antibody.**

- ***Molecular patterns:*** **are low-molecular substances evoking the reactions of innate immunity with no memory.**

- ***Pattern recognition receptors*** **(*PRRs*) :are molecules expressed by cells of the innate immunity, which are capable of sensing“patterns,” triggering the reactions of innate immunity**

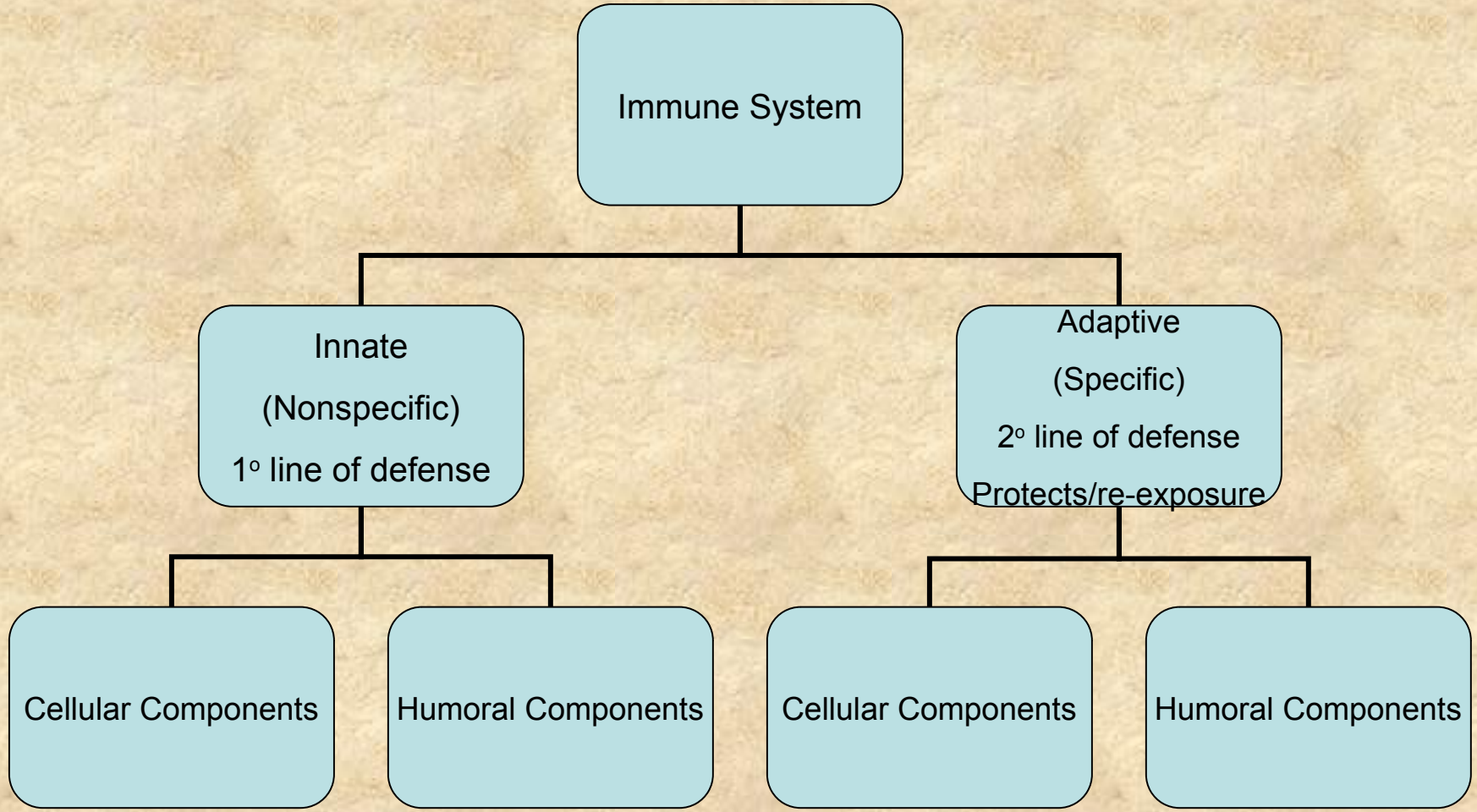
- ***Antigenicity*****: is the quality of an antigen to serve *ligand* for a *receptor*. The receptors for antigens are TCR and BCR.**

- ***Specificity*: is the antigen quality to be a unique molecule for only one receptor.**

- ***Cytokines* :are specialized regulatory molecules, which mainly act on cells in a short distance manner.**

- ***Chemokines:* are cytokines, which drive the migration of immune system's cells for homing and/or inflammation. Chemokines are divided into *homeostatic* and *inflammatory* chemokines**

Overview of the Immune System

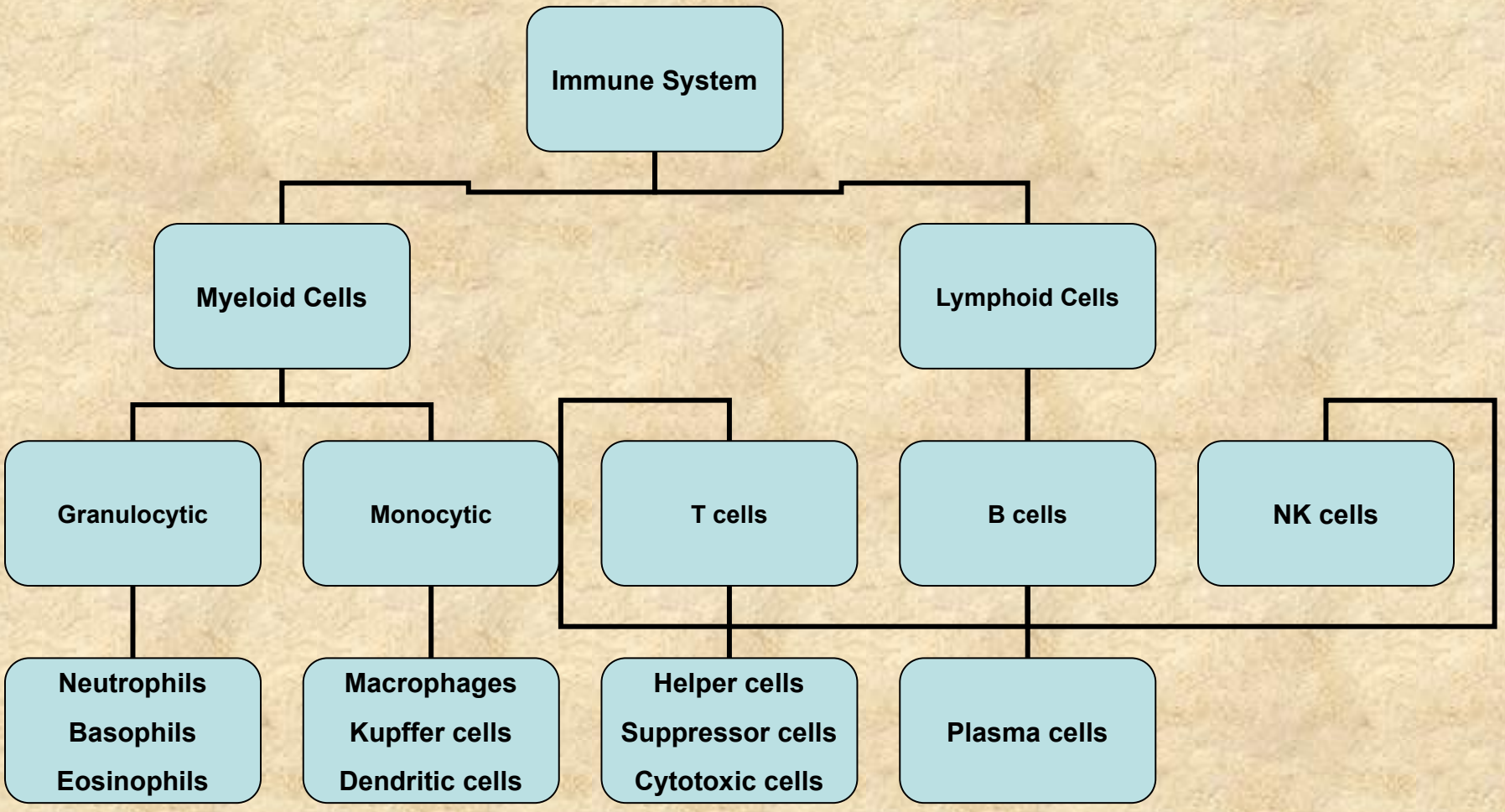


Interactions between the two systems

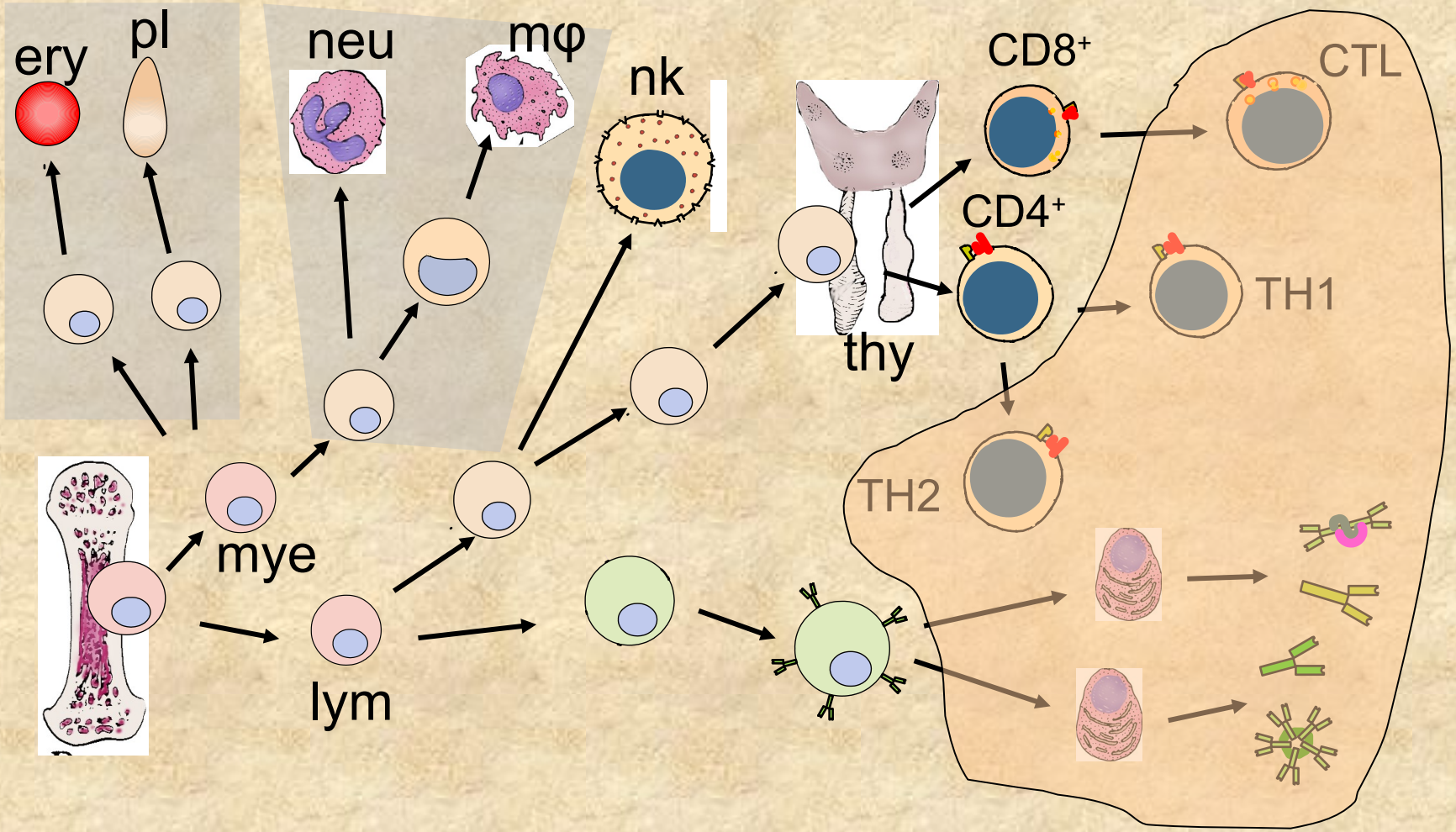
Comparison of Innate and Adaptive Immunity

Innate Immunity	Adaptive Immunity
• No time lag	• A lag period
• Not antigen specific	• Antigen specific
• No memory	• Development of memory

Cells of the Immune System



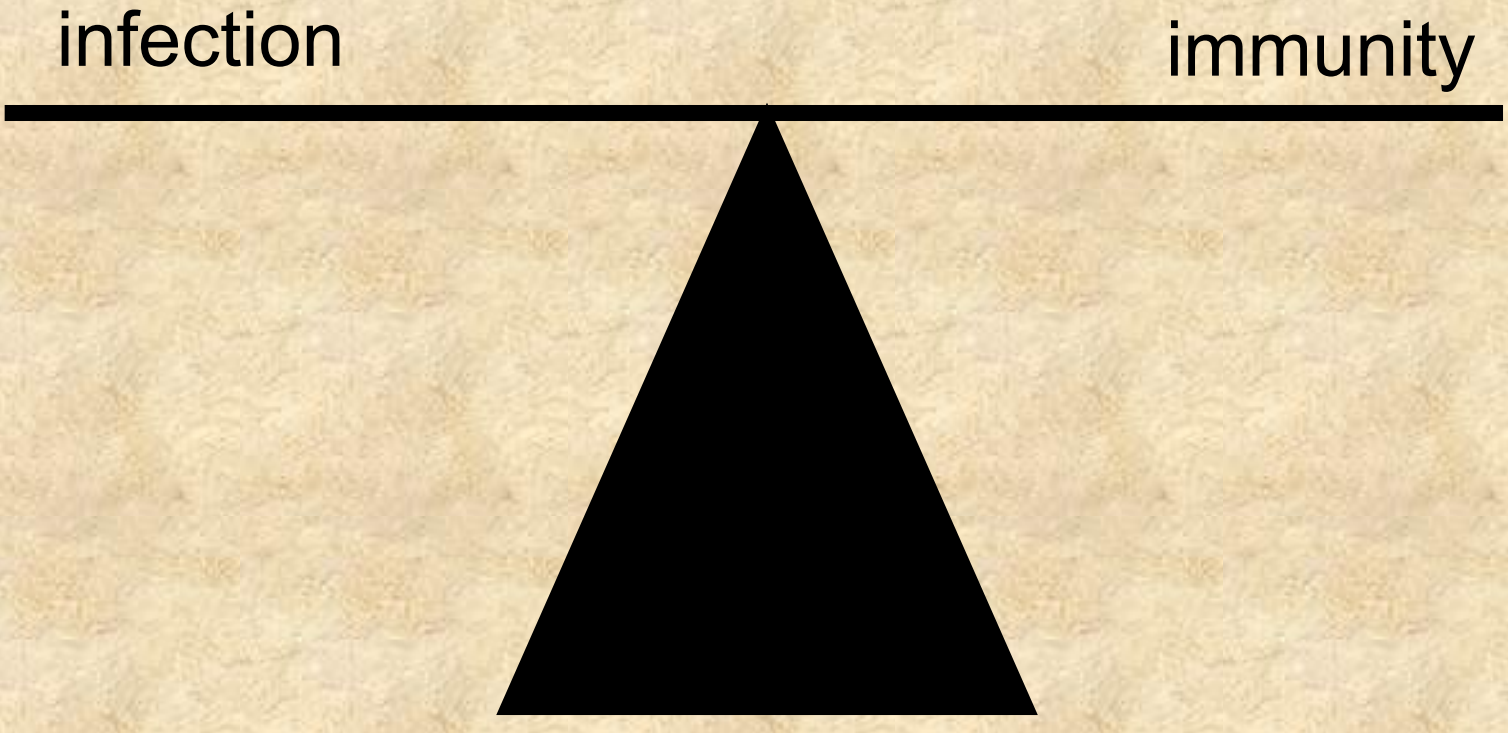
Development of the Immune System



Function of the Immune System (Self/Non-self Discrimination)

- To protect from pathogens
  - Intracellular (*e.g.* viruses and some bacteria and parasites)
  - Extracellular (*e.g.* most bacteria, fungi and parasites)
- To eliminate modified or altered self

Infection and Immunity Balance

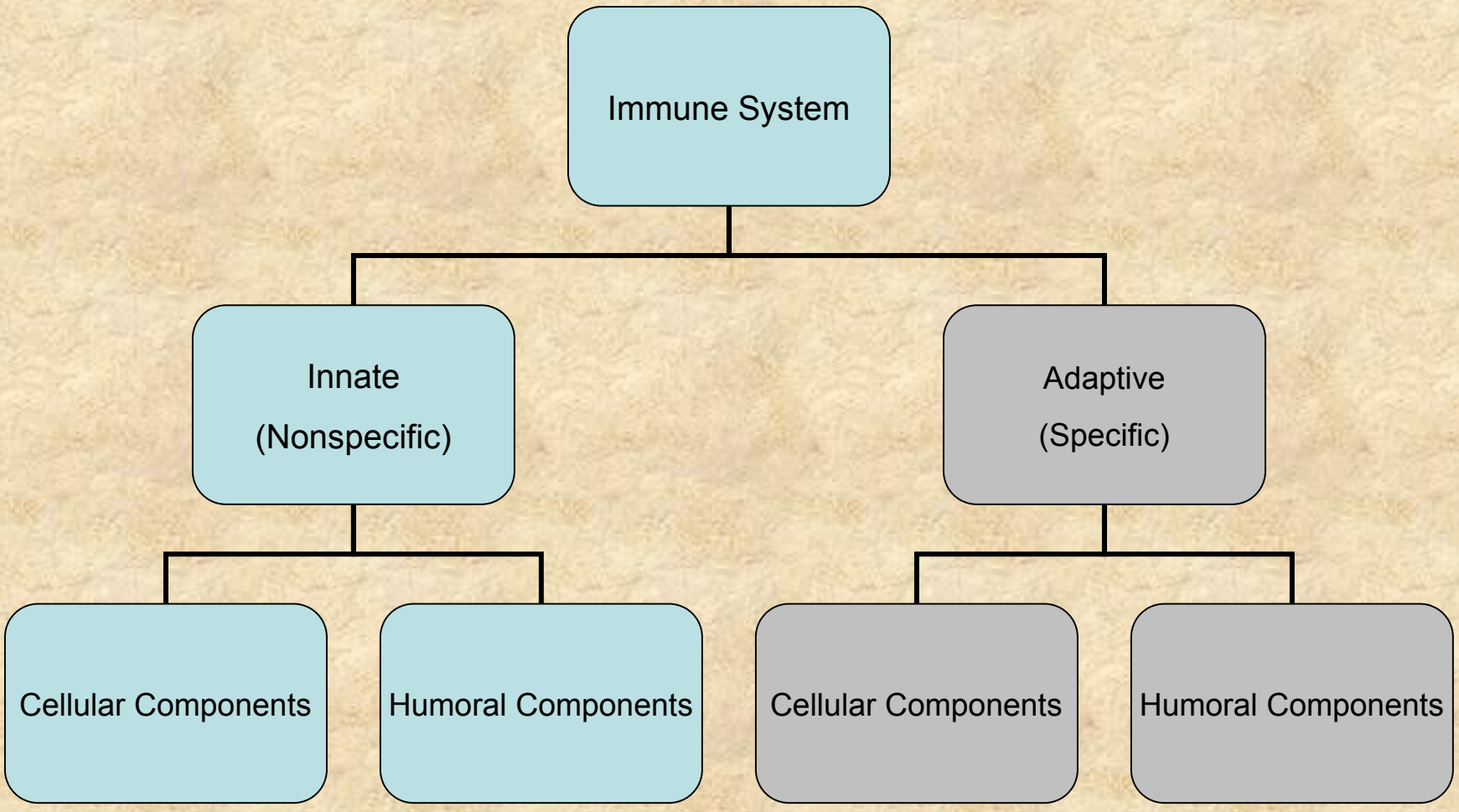


$$\text{Disease} = \frac{\text{Bolus of infection x virulence}}{\text{immunity}}$$

Effects of the Immune System

- Beneficial:
  - Protection from Invaders
  - Elimination of Altered Self
- Detrimental:
  - Discomfort and collateral damage (inflammation)
  - Damage to self (hypersensitivity or autoimmunity)

Overview of the Immune System



Innate Host Defenses Against Infection

- Anatomical barriers
  - Mechanical factors
  - Chemical factors
  - Biological factors
- Humoral components
  - Complement
  - Coagulation system
  - Cytokines
- Cellular components
  - Neutrophils
  - Monocytes and macrophages
  - NK cells
  - Eosinophils

Anatomical Barriers - Mechanical Factors

System or Organ	Cell type	Mechanism
Skin	Squamous epithelium	Physical barrier Desquamation
Mucous Membranes	Non-ciliated epithelium (*e.g.* GI tract)	Peristalsis
	Ciliated epithelium (*e.g.* respiratory tract)	Mucociliary elevator
	Epithelium (*e.g.* nasopharynx)	Flushing action of tears, saliva, mucus, urine

Anatomical Barriers - Chemical Factors

System or Organ	Component	Mechanism
Skin	Sweat	Anti-microbial fatty acids
Mucous Membranes	HCl (parietal cells) Tears and saliva	Low pH Lysozyme and phospholipase A
	Defensins (respiratory & GI tract)	Antimicrobial
	Sufactants (lung)	Opsonin

Anatomical Barriers - Biological Factors

System or Organ	Component	Mechanism
Skin and mucous membranes	Normal flora	Antimicrobial substances Competition for nutrients and colonization

Humoral Components

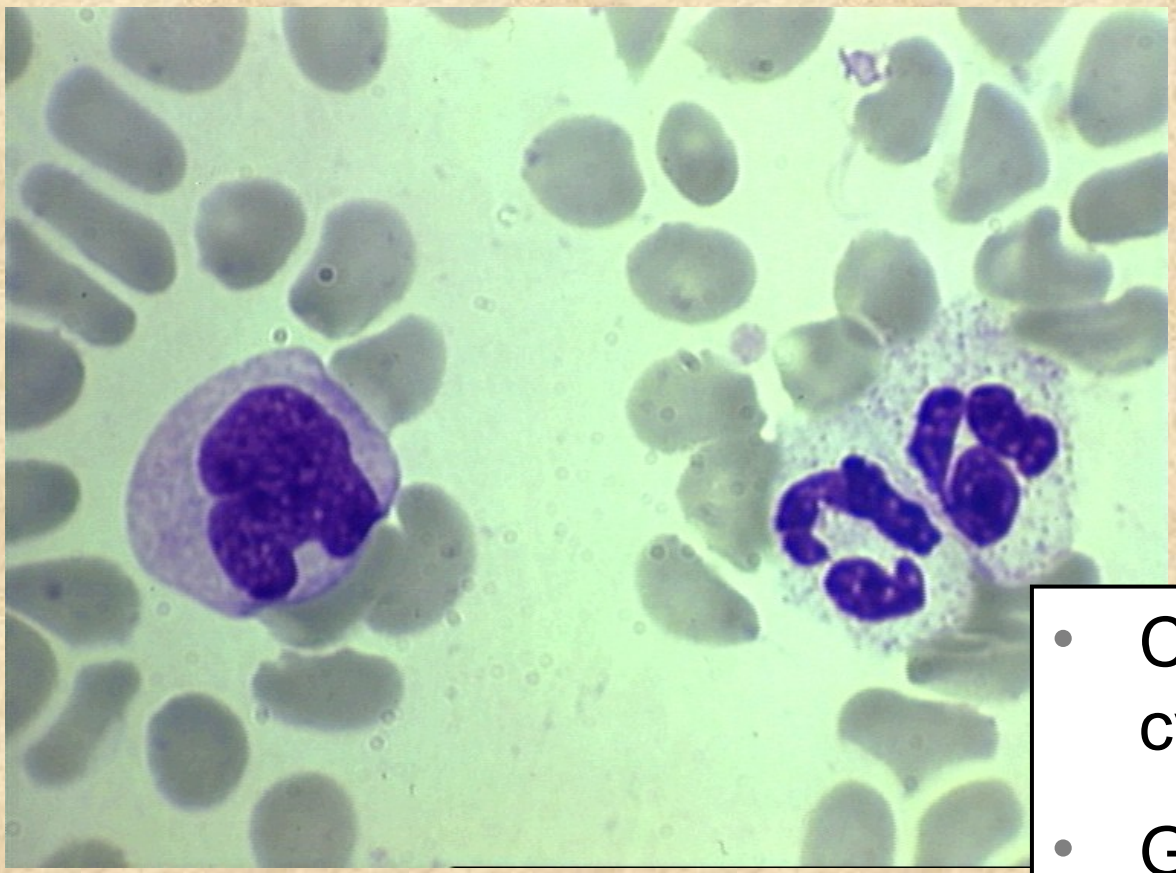
Component	Mechanism
Complement	Lysis of bacteria and some viruses Opsonin Increase in vascular permeability Recruitment and activation of phagocytic cells
Coagulation system	Increase vascular permeability Recruitment of phagocytic cells B-lysin from platelets – a cationic detergent
Lactoferrin and transferrin	Compete with bacteria for iron
Lysozyme	Breaks down bacterial cell walls
Cytokines	Various effects

Cellular Components

Cell	Functions
Neutrophils	Phagocytosis and intracellular killing Inflammation and tissue damage
Macrophages	Phagocytosis and intracellular killing Extracellular killing of infected or altered self targets Tissue repair Antigen presentation for specific immune response
NK and LAK cells	Killing of virus-infected and altered self targets
Eosinophils	Killing of certain parasites

Phagocytosis
and
Intracellular Killing

Phagocytes - Neutrophils (PNMs)



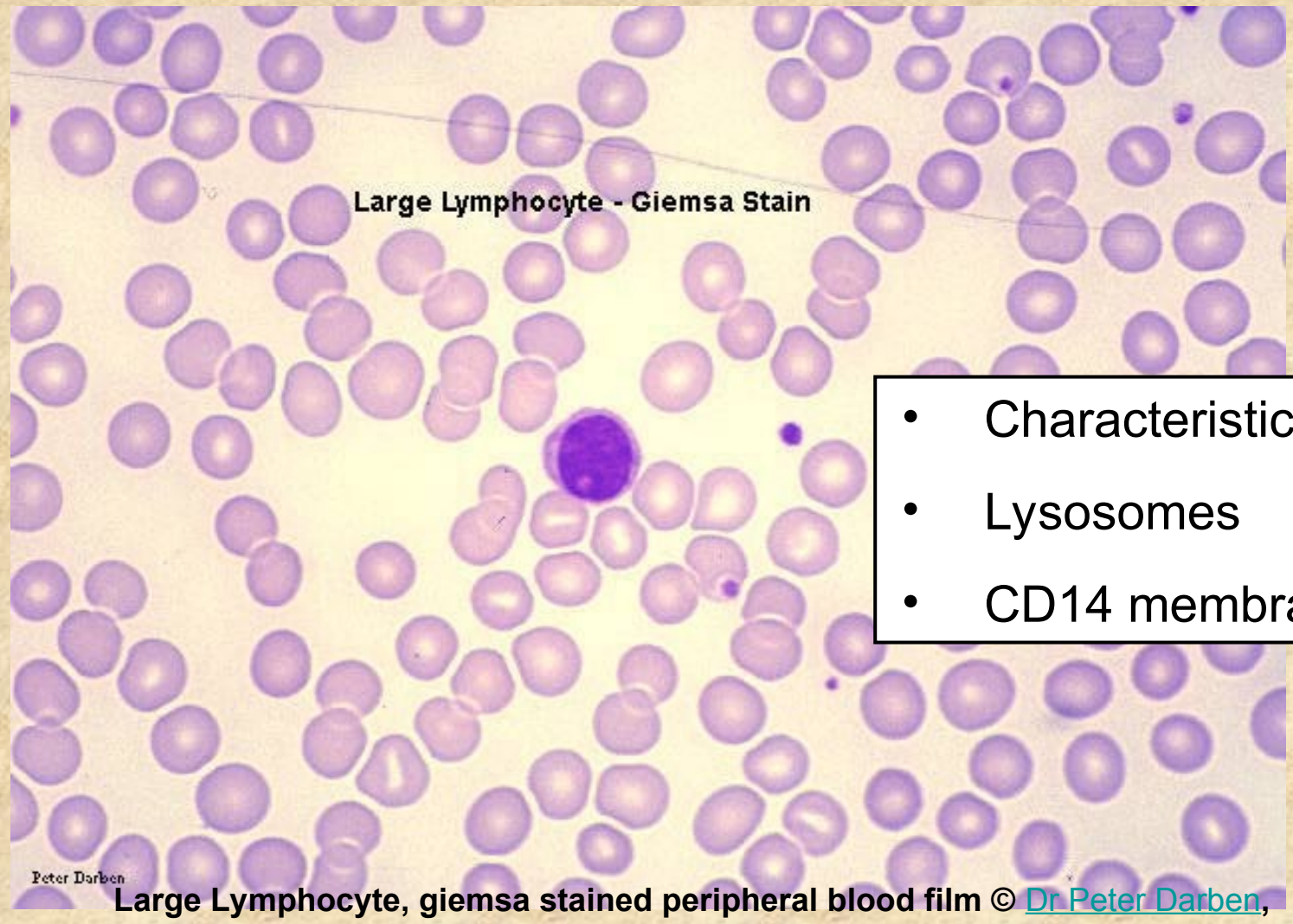
Blood film showing a monocyte (left) and two neutrophils © Bristol Biomedical Image Archive Used with permission

- Characteristic nucleus, cytoplasm
- Granules
- CD 66 membrane marker

Characteristics of Neutrophil Granules

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

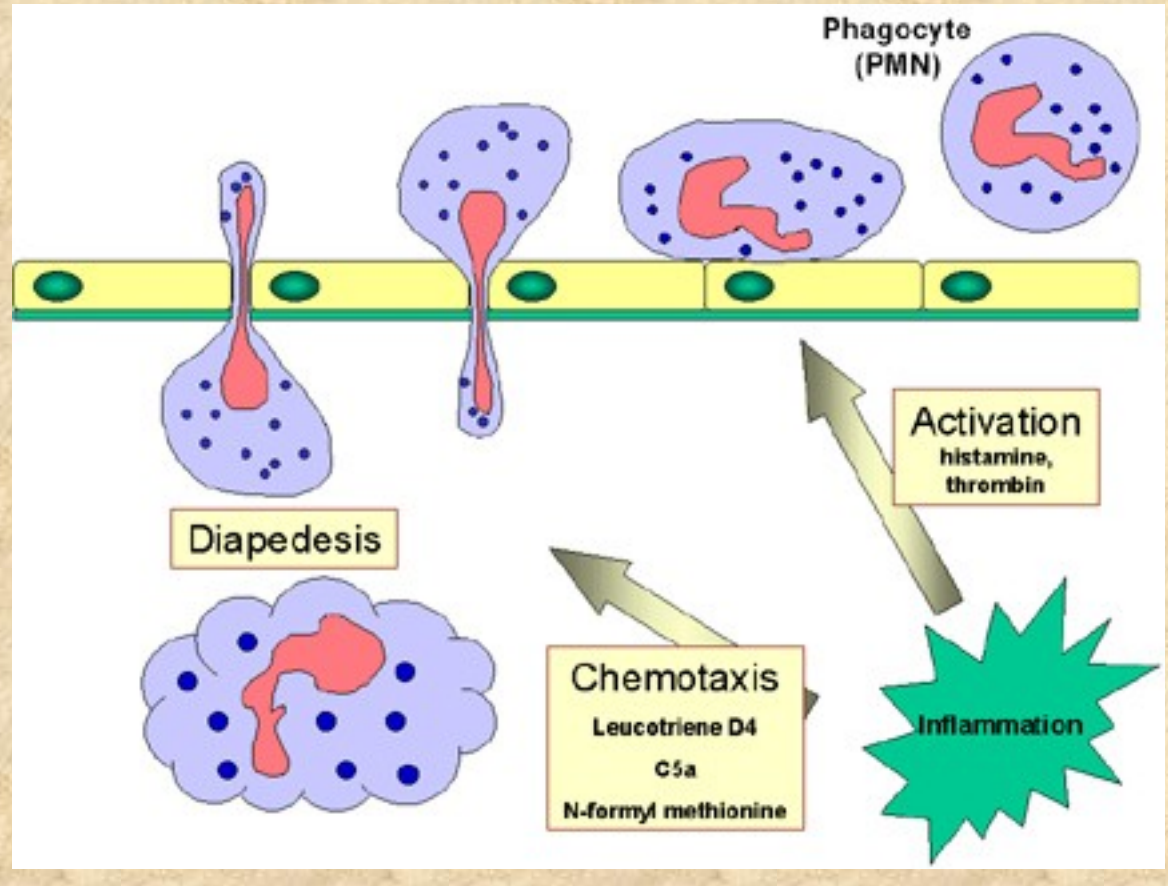
Phagocytes - Macrophages



- Characteristic nucleus
- Lysosomes
- CD14 membrane marker

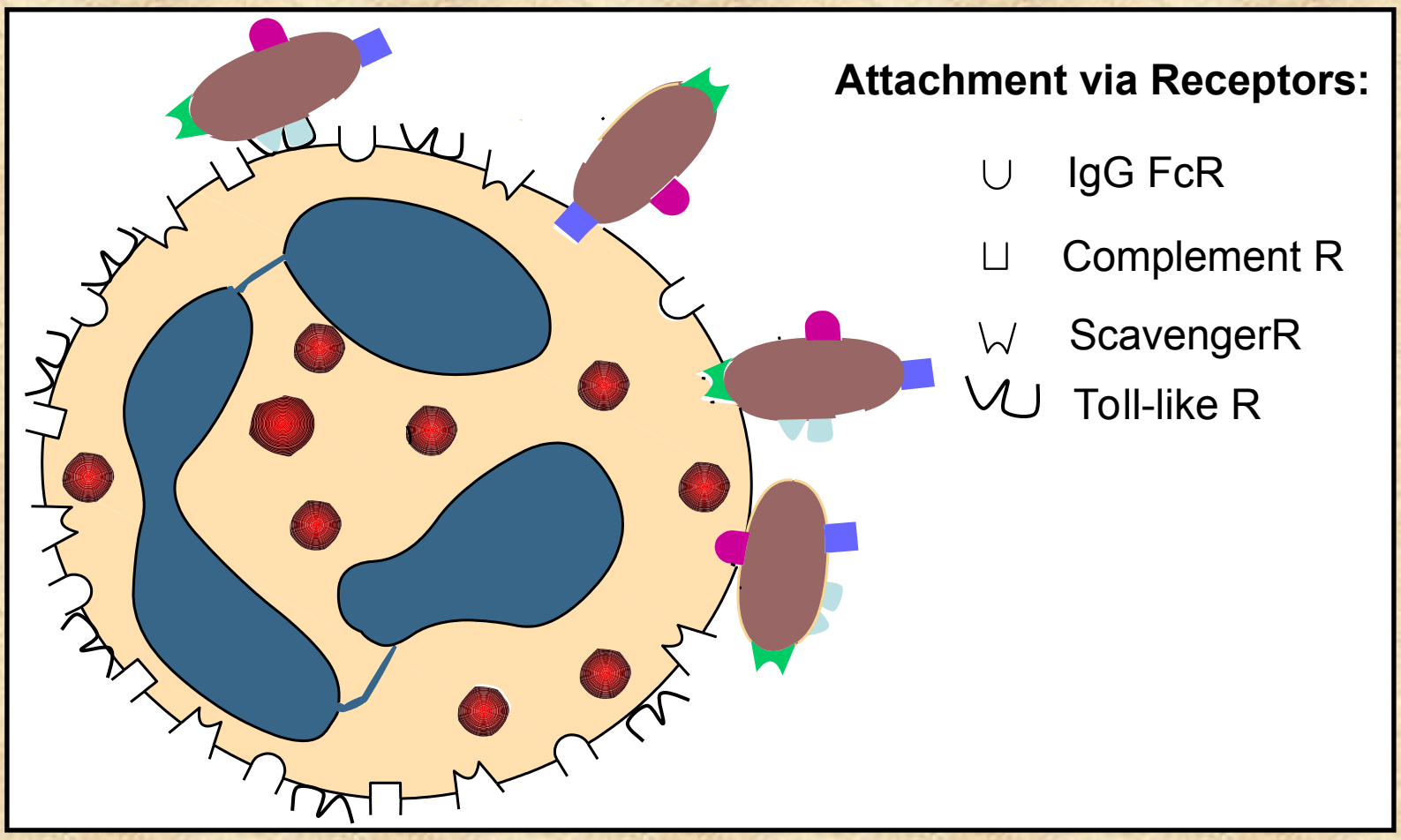
Large Lymphocyte, giemsa stained peripheral blood film © Dr Peter Darben, Queensland University of Technology clinical parasitology collection. Used with permission

Phagocyte Response to Infection

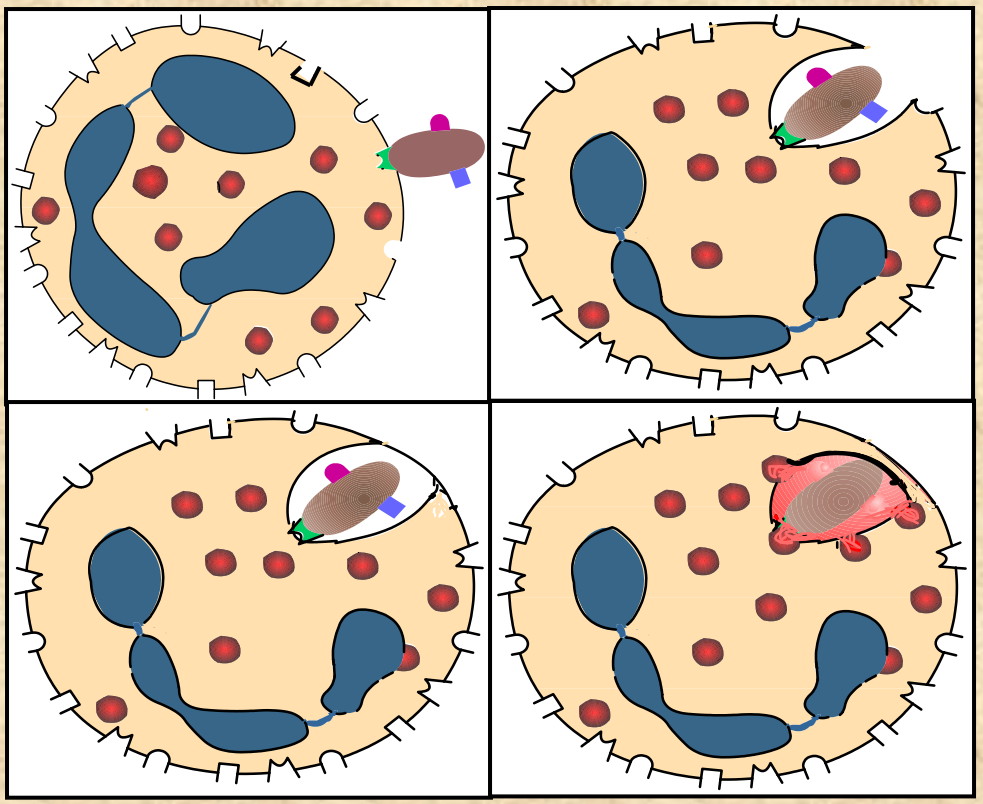


- The SOS Signals
  - N-formyl methionine-containing peptides
  - Clotting system peptides
  - Complement products
  - Cytokines released by tissue macrophages
- Phagocyte response
  - Vascular adherence
  - Diapedesis
  - Chemotaxis
  - Activation
  - Phagocytosis and killing

Initiation of Phagocytosis



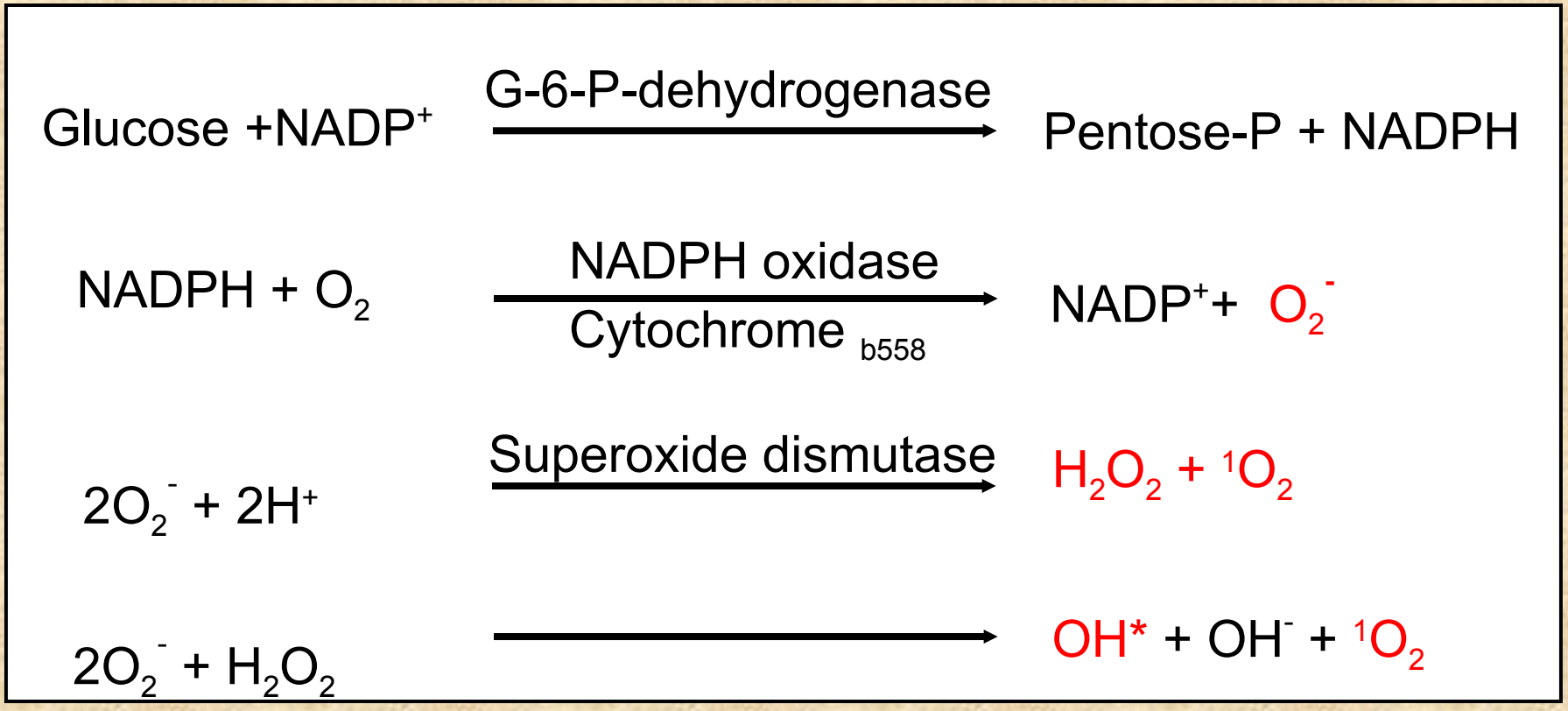
Phagocytosis



- Attachment
- Pseudopod extension
- Phagosome formation
- Granule fusion
- Phagolysosome formation

Respiratory Burst

Oxygen-Dependent Myeloperoxidase-Independent Reactions



Toxic compounds – Superoxide anion (O_2^-), Hydrogen peroxide (H_2O_2), Singlet oxygen ($^1O_2$) and Hydroxyl radical (OH*)

Respiratory Burst

Oxygen-Dependent Myeloperoxidase-Dependent Reactions

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

$$2OCl^- + H_2O \longrightarrow {}^1O_2 + Cl^- + H_2O$$

Toxic compounds – Hypochlorous acid (OCl^-), and Singlet oxygen ($^1O_2$)

Respiratory Burst

Detoxification Reactions

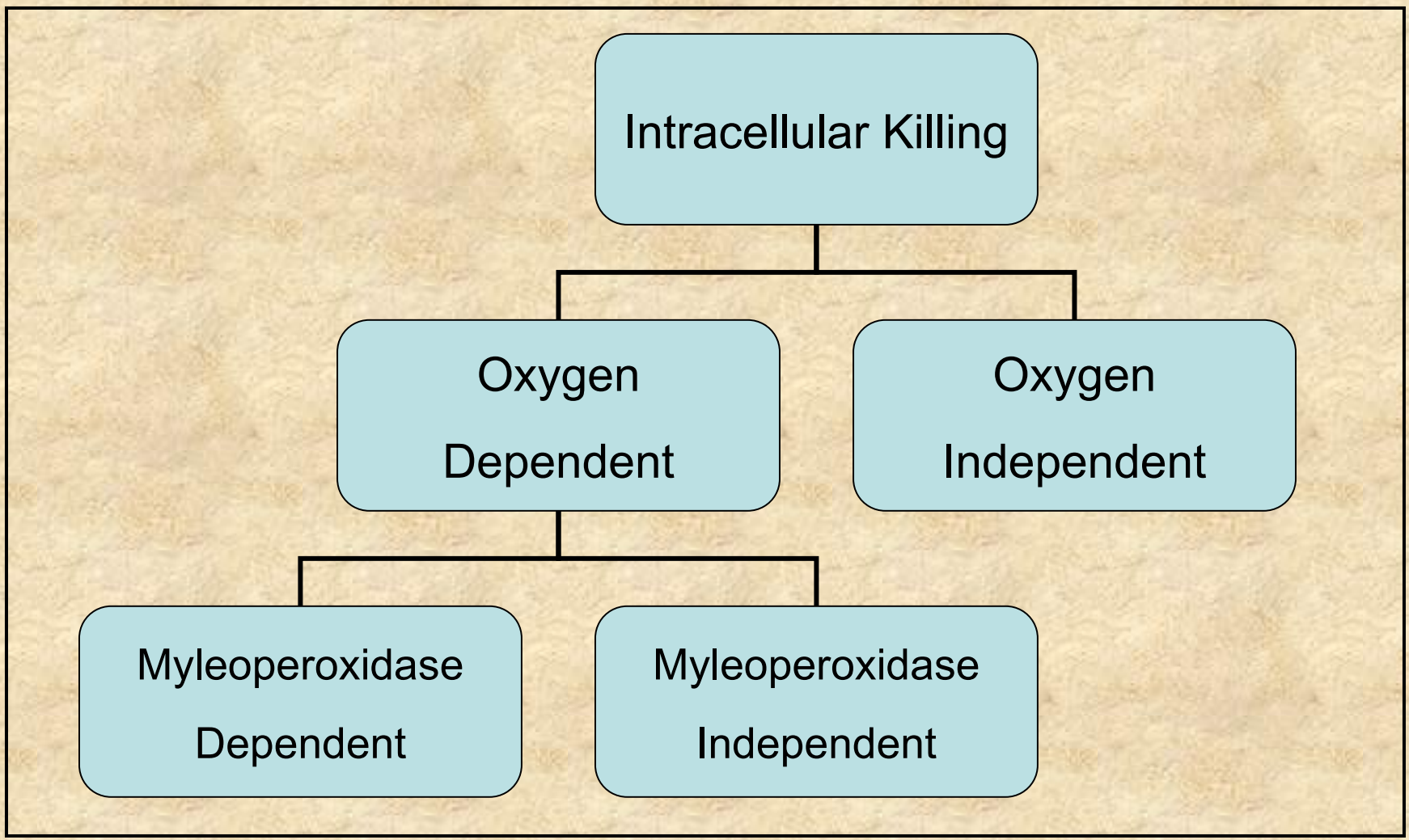
$2O_2^- + 2H^+ \xrightarrow{\text{Superoxide dismutase}} H_2O_2 + O_2$

$2\ H_2O_2 \xrightarrow{\text{Catalase}} H_2O + O_2$

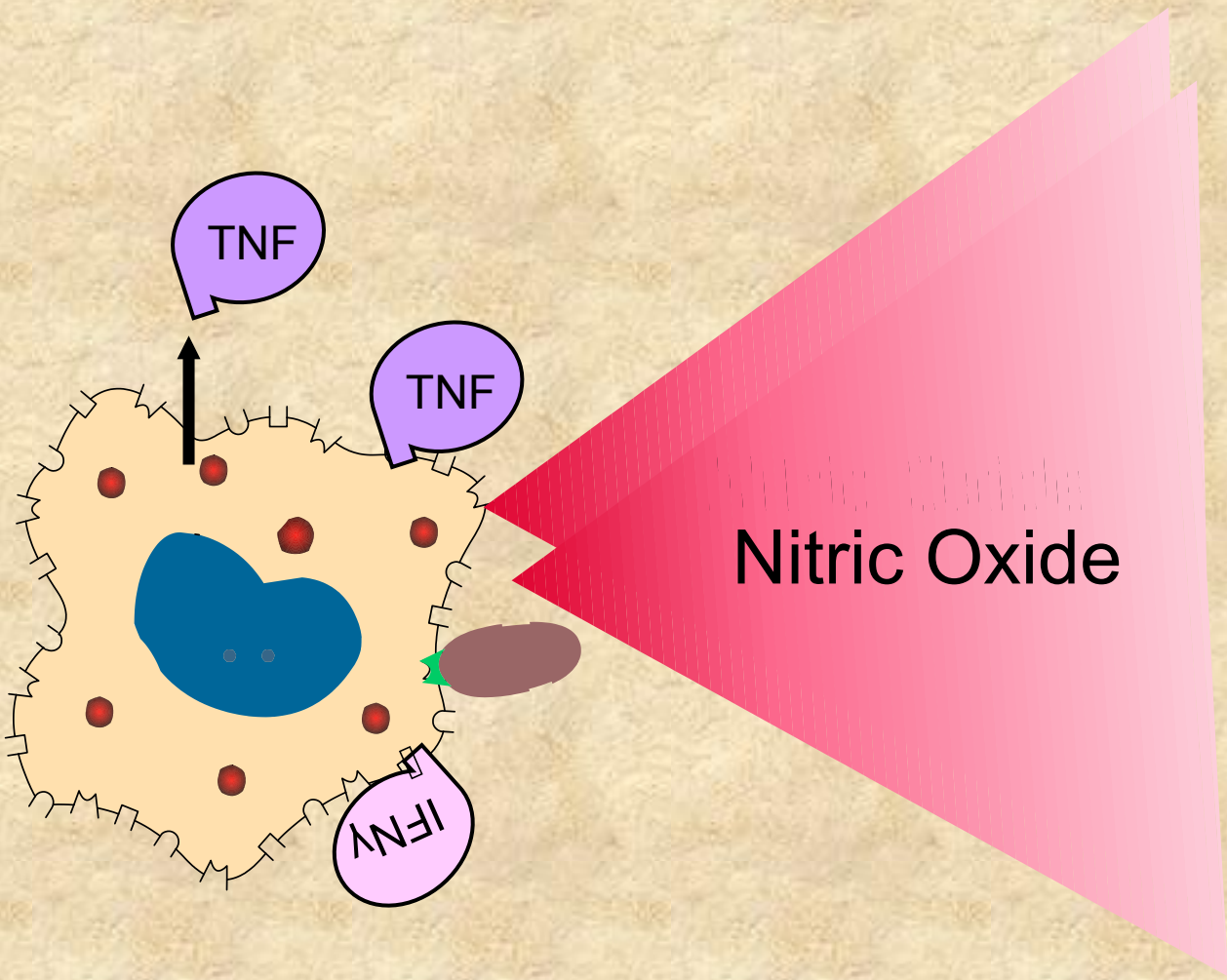
Oxygen-Independent Killing in the Phagolysosome

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

Summary of Intracellular Killing Pathways



Nitric Oxide Dependent Killing



Non-specific Killer Cells

NK and LAK cells

ADCC (K) cell

Activated macrophages

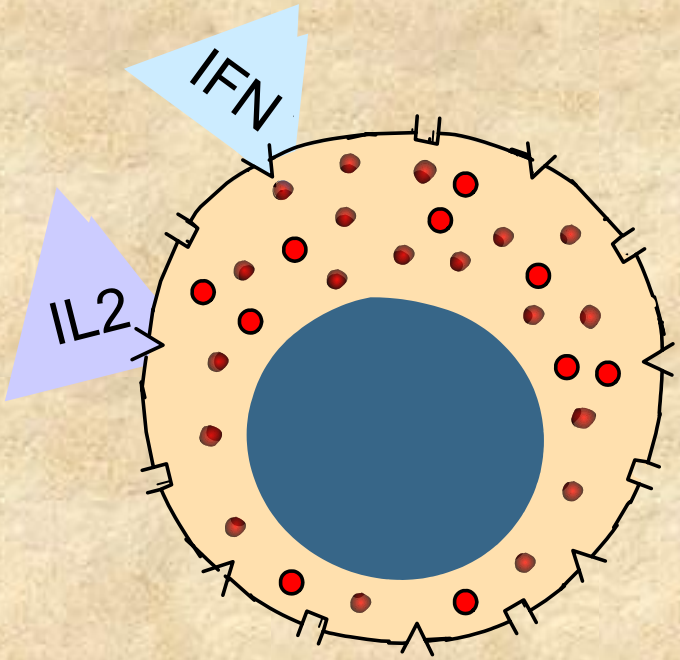
Eosinophils

They all kill foreign and altered self targets

Natural Killer (NK) cells

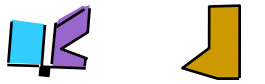
- also known as large granular lymphocytes (LGL)
- kill virus-infected or malignant cells
- identified by the presence of CD56 & CD16 and absence of CD3
- activated by IL2 and IFN-γ to become LAK cells

Lymphokine Activated Killer (LAK) cell



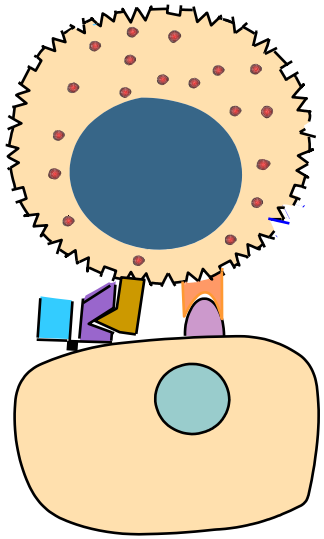
kills transformed and malignant cells

Regulation of NK Cell Function

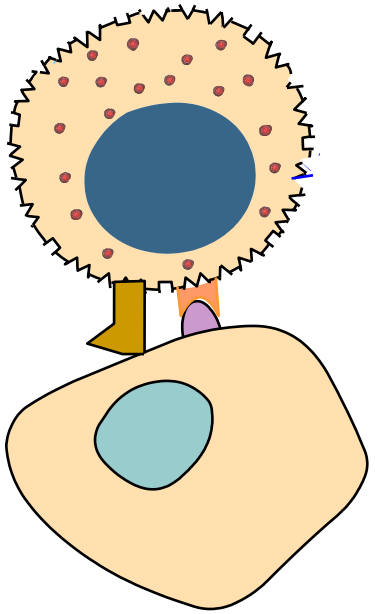


•MHC I •KIR

•KAR •KAL



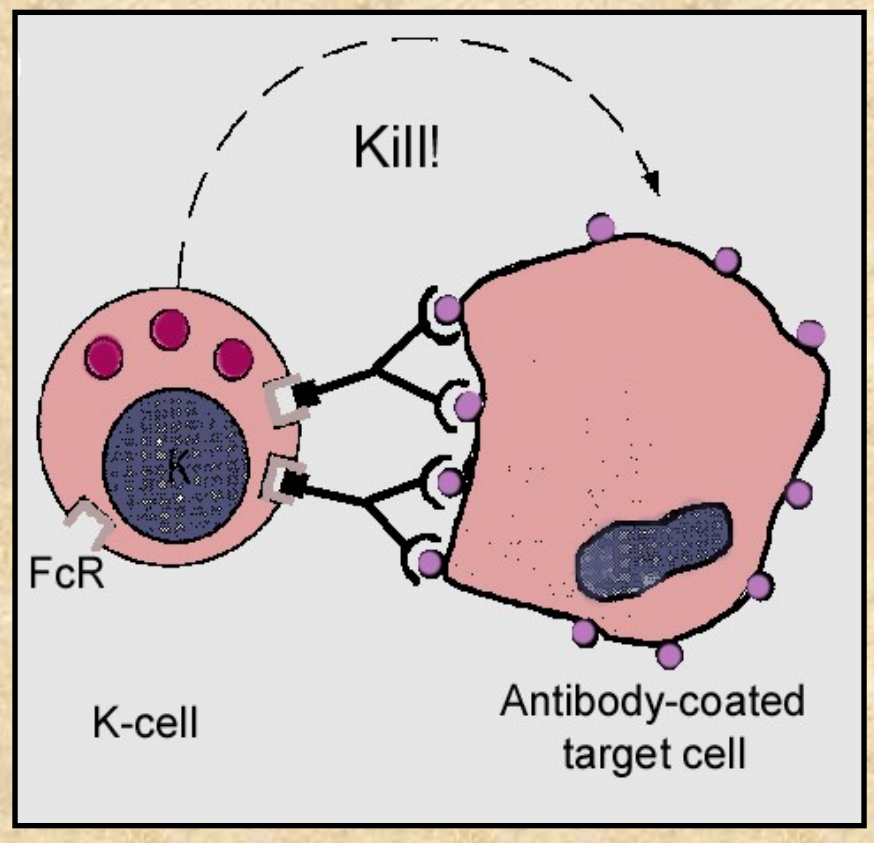
•No Killing



•Killing

K Cells

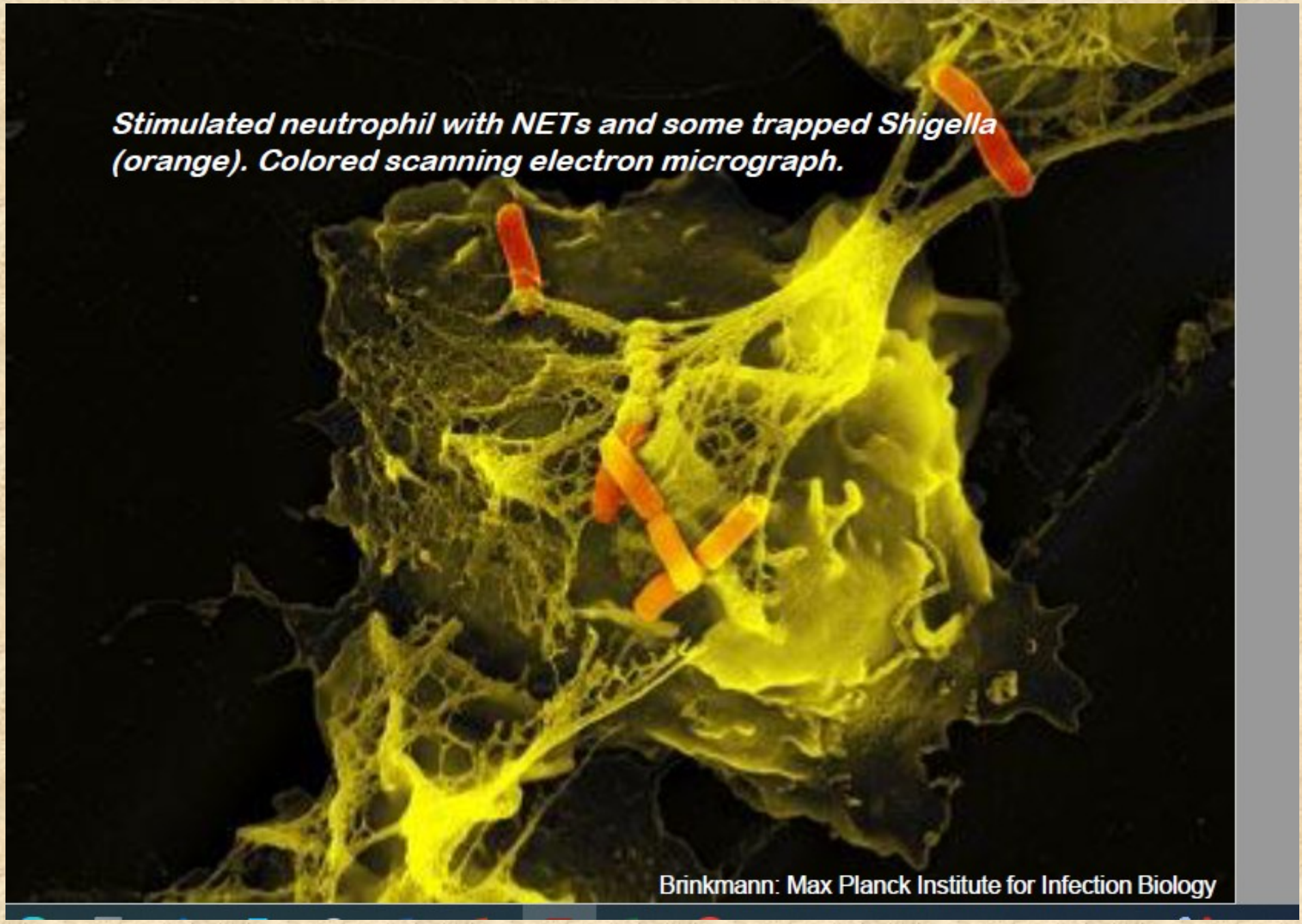
- morphologically undefined
- mediate ADCC
- have Fc receptor
- recognize antibody coated targets
- could be NK cells (IgG), macrophages (IgG), eosinophils (IgE) or other cells (IgG)

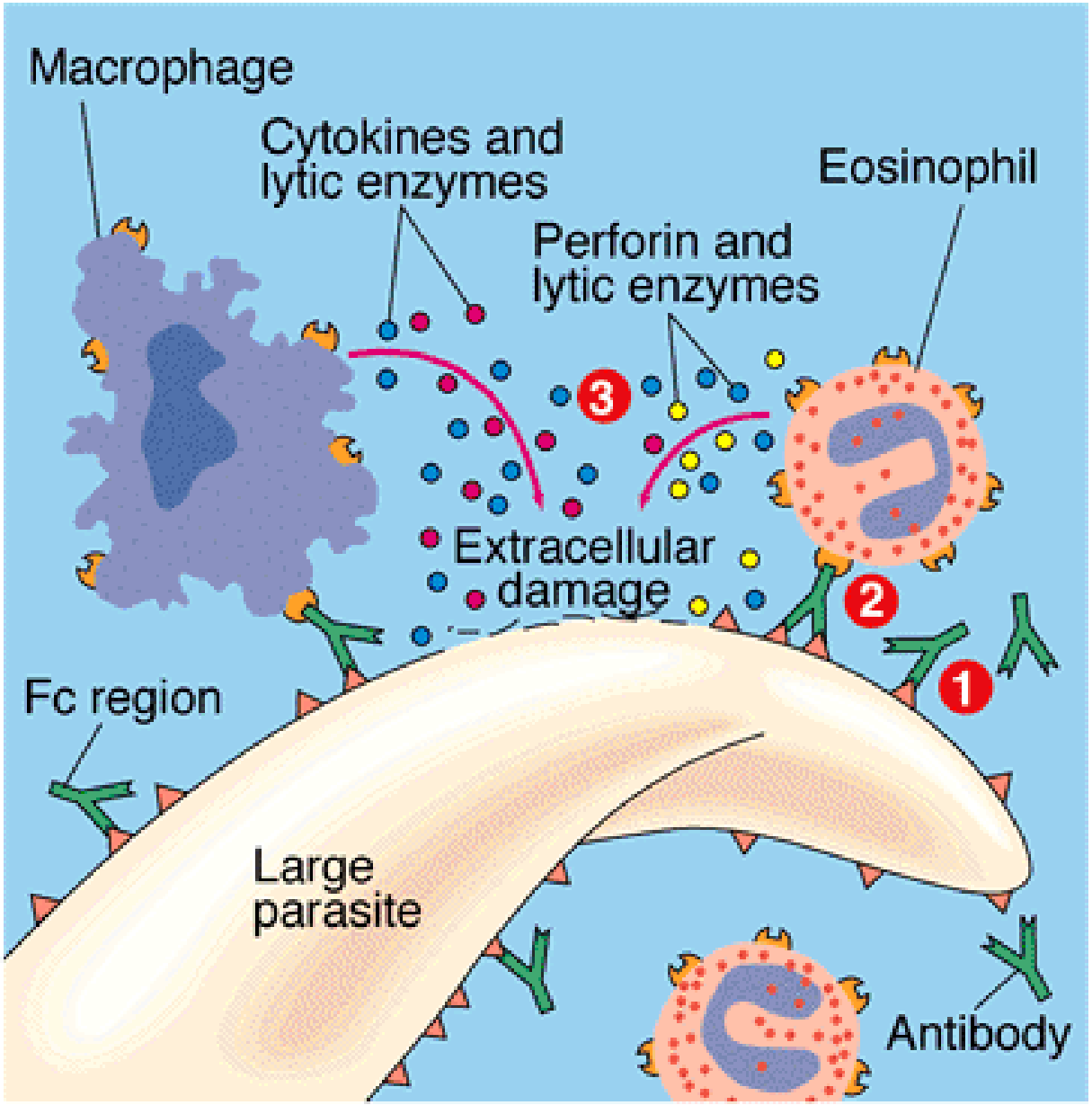


Extracellular killing - NETosis

- Neutrophils have the ability to mix and extrude their DNA and bactericidal molecules creating NET-like structures in a unique type of cell death called NETosis.

- This process is important in order to control extracellular infections limiting collateral damage. Its aberrant function has been implicated in sepsis and autoimmune disease


Stimulated neutrophil with NETs and some trapped Shigella (orange). Colored scanning electron micrograph.
Brinkmann: Max Planck Institute for Infection Biology



Cells of the Immune System

1-Lymphocytes

❖***Lymphocytes*** **and** ***monocytes*****, or agranulocytes, and** ***polymorphonuclear leukocytes*** **(*PMN*) or granulocytes complete white blood cells (WBCs) in the bloodstream.**

❖**T lymphocytes (T cells) and B lymphocytes (B cells) are the main cells of adaptive responses, whereas innate lymphoid cells (ILCs) are important for innate immunity**

.

T-cell (left) and B-cell

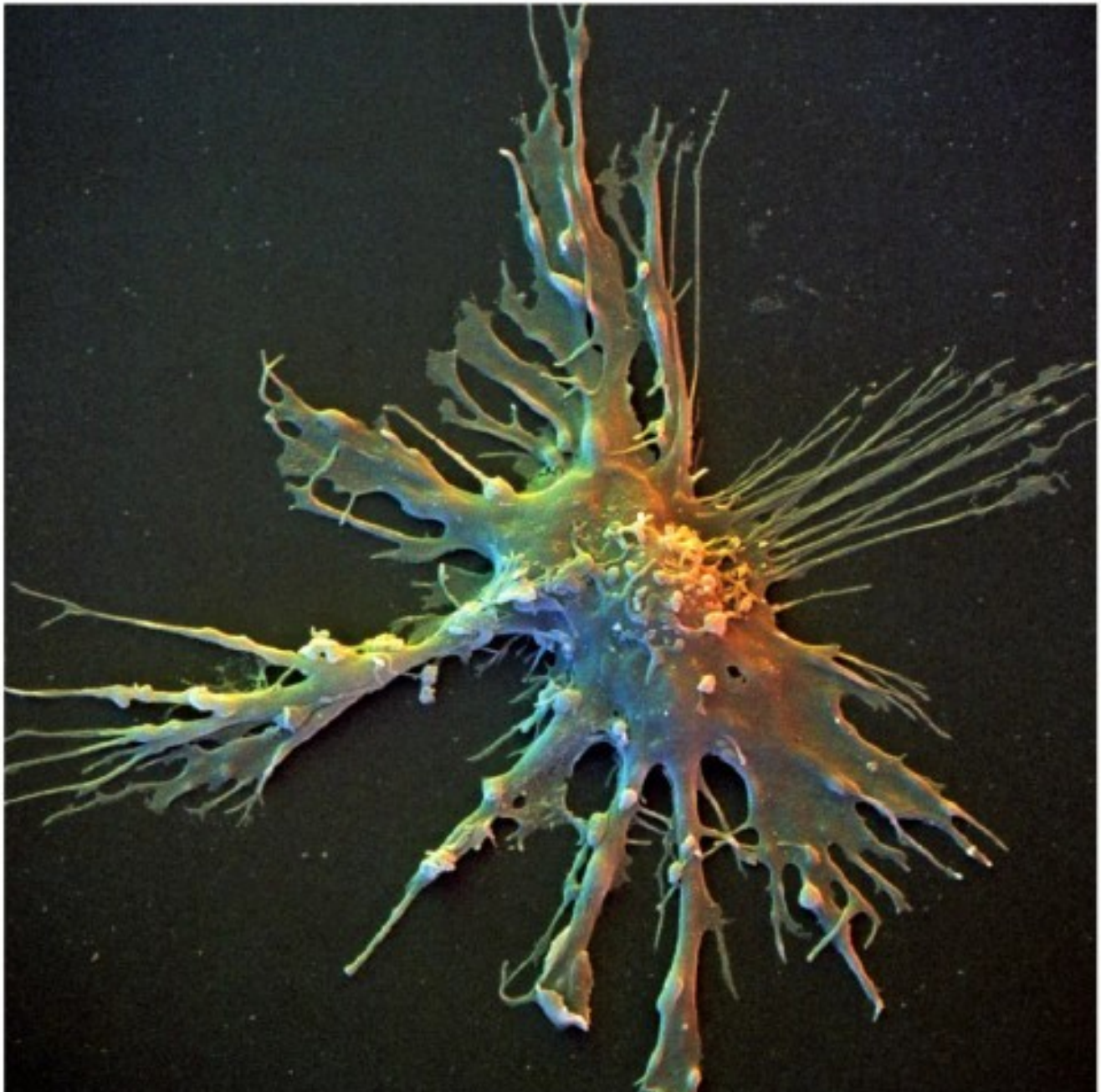
2-*Innate lymphoid cells* (*ILCs*)

- ILCs are involved in the innate immunity, inflammation, lymphoid tissue development in fetal life, and immunoregulation .
- Among recently described ILCs, one ILC subgroup,*NK cells*, has been characterized many years ago.

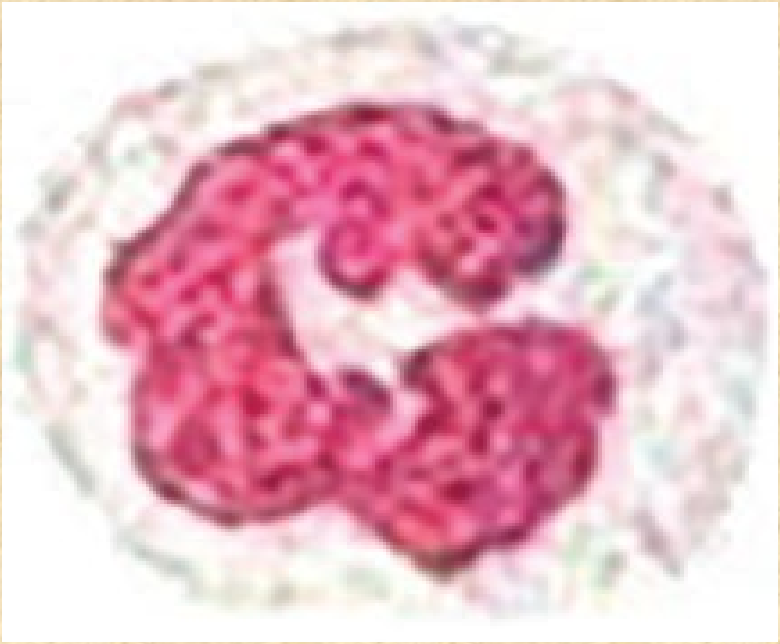
3-*Dendritic cells* (*DCs*)

- Are a heterogeneous cell population characterized by outgrowth (dendrite) morphology.
- high levels of Class I and Class II HLA molecule antigen Presentation and activation of naive lymphocytes.

Dendritic cell



4- Monocytes and Macrophages



Monocytes :

- are related to WBC and have a bean-shaped nucleus.
- Monocytes are precursors of some macrophages, dermal DCs, and Langerhans DCs.

Macrophages

1.are large mononuclear cells important for both innate and adaptive immunity.

2-They are able to *phagocyte* large objects like protozoans and infected cells, *secrete* a lot of active substances like cytokines, fulfill the *presentation* of antigen/Class II HLA molecules complexes to CD4+ T lymphocytes, and take part in *type IV hypersensitivity*.

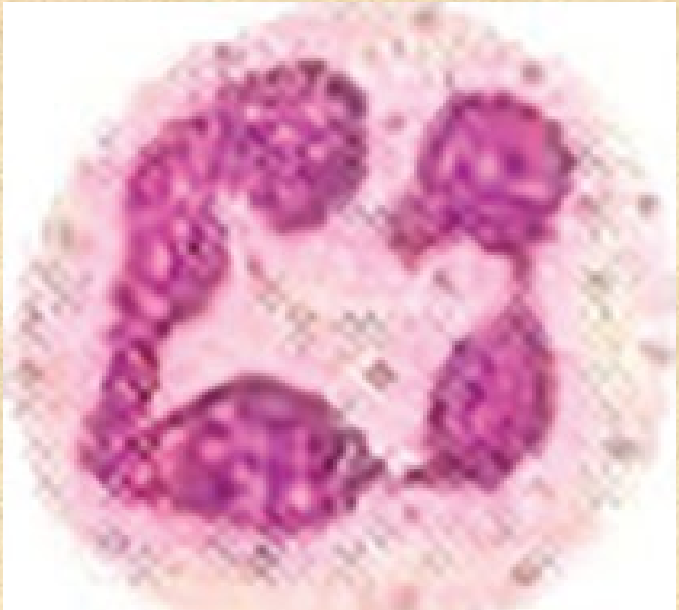
3-There are two distinct types, *inflammatory* (*M1*) and *anti-inflammatory* (*M2*).While *tumor-associated macrophages* (*TAMs*) characterized by variable patterns of activity.

5-Neutrophils

- **They have a segmented nucleus and three types of granules containing microbicidal factors.**

- **There are two pools of neutrophils, *a circulating pool* and *marginal pool*.**

- **Neutrophils are capable of *phagocyting* and destroying extracellular pathogens like bacteria and molds. Also, neutrophils can fulfill *NETosis* to attack pathogens in a specific manner.**



6-Eosinophils

- **These cell are important for defense against parasitic invasions.**
- **They take part in *type I hypersensitivity* and so-called eosinophil inflammation. Analogous to neutrophils, eosinophils are able to *phagocytosis* and *NETosis*.**

7-Basophils and Mast Cells

Basophils

- **These cells containing lots of large basophilic granules and function similar to mast cells**

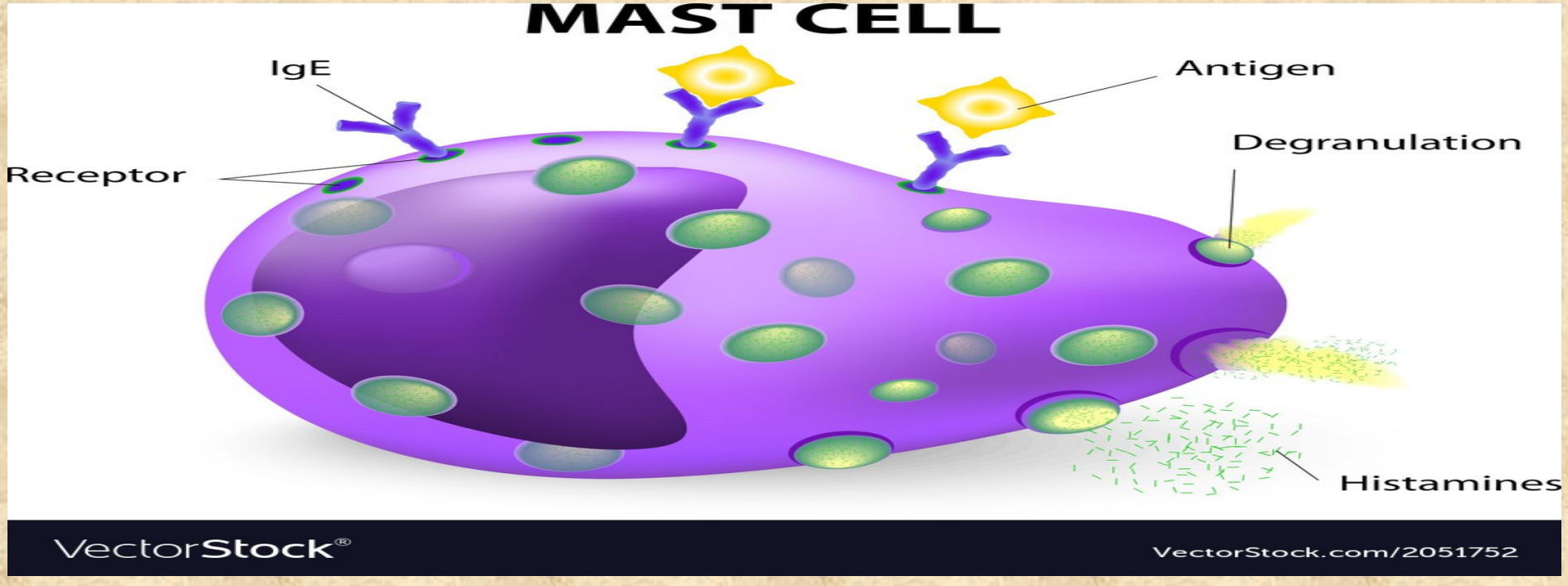
Mast cells

- ***Mast cells* are large cells found in connective tissues throughout the body, most abundantly in the skin, submucosa (a connective tissue phenotype), and mucosa (a mucosal or atypical phenotype).**

- **Mast cells contain many large granules rich in histamine, chemotactic peptides, arachidonates, proteoglycans, etc.**

- **High-affinity Fcε receptors (FcεRI) allow mast cells to bind IgE molecules that leads to their degranulation and activation at early phase of *type 1 hypersensitivity*.**

- **Analogous to neutrophils and eosinophils, mast cells are able to develop *phagocytosis* and *NETosis*.**



Antigen-presenting cells (APCs),

Antigen-presenting cells (APCs), including dendritic cells, macrophages, and B cells,have crucial roles in the adaptive immune responses.

They encounter a native antigen or several native antigens in the site of infection, endocyte them, then accumulate, and carry to the secondary organs of the immune system.

Macrophages phagocyte large intracellularly located antigenic objects, e.g., infected cells, fungi, protozoans, etc.