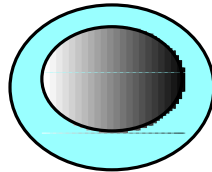

Advanced 11 Medical Applications - I - ~ Immunology ~

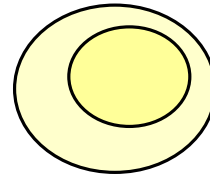
Prof. K. Isobe
Dept. of Program in Integrated
Molecular Medicine
Nagoya University



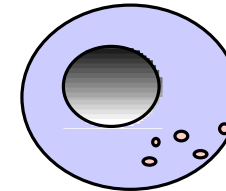
T cell



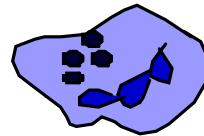
B cell



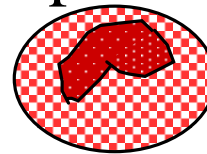
NK cell



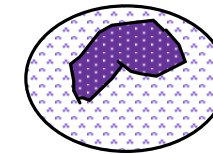
Neutrophil



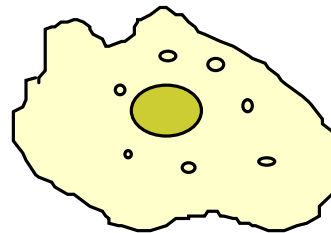
Eosinophil



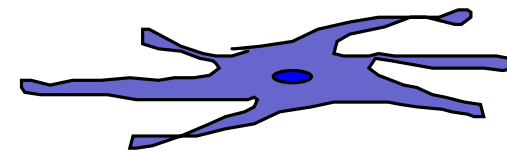
Basophil



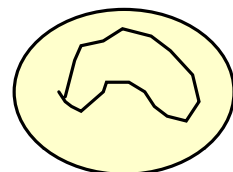
Macrophage



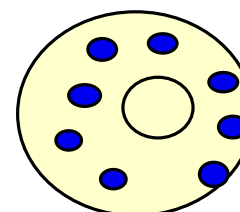
Dendritic cell

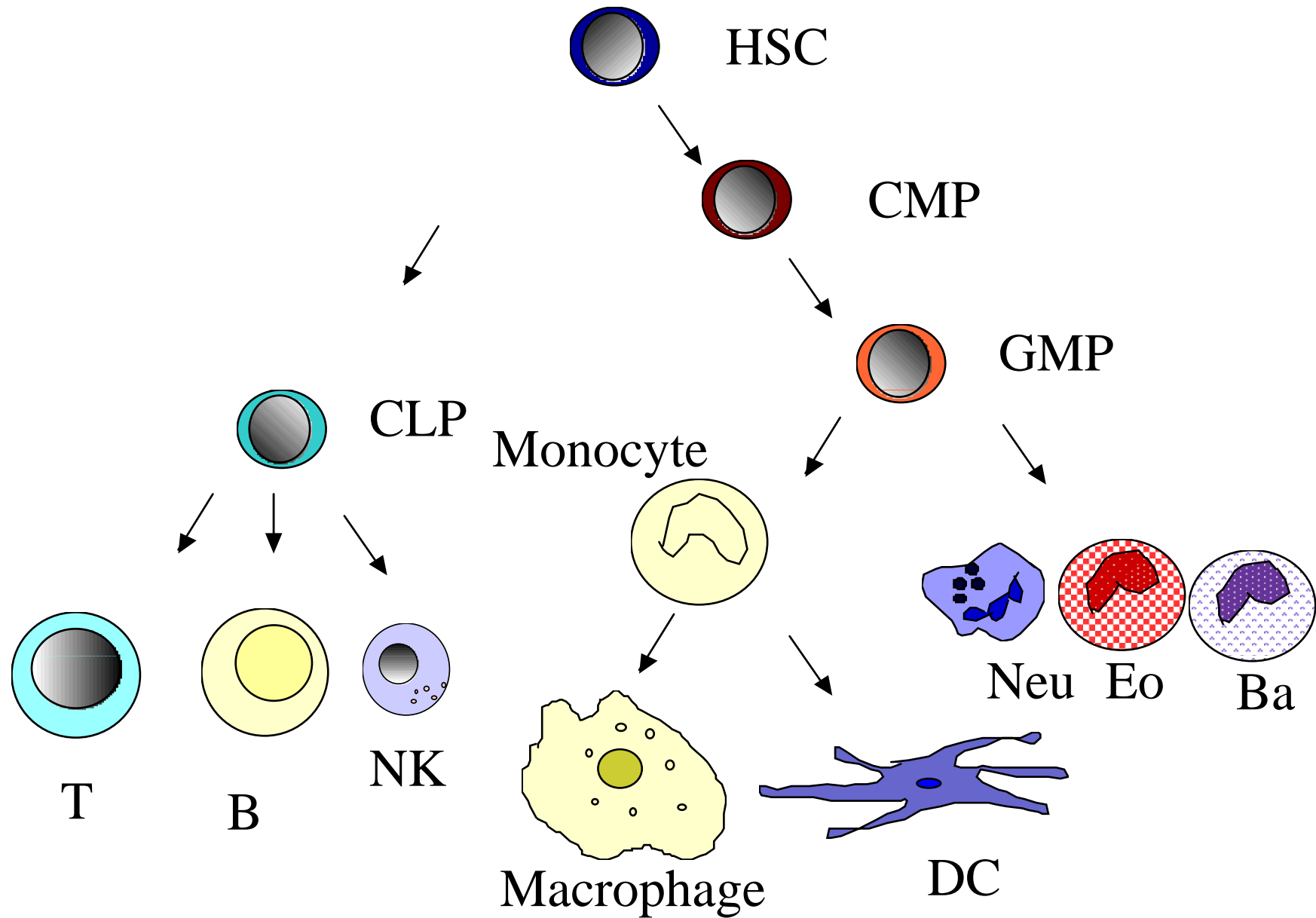


Monocyte



Mast cell





Innate immunity

Microorganism

Other stimuli



Bacterial infection and innate immunity

Myeloid-lineage cells



Innate immune responses

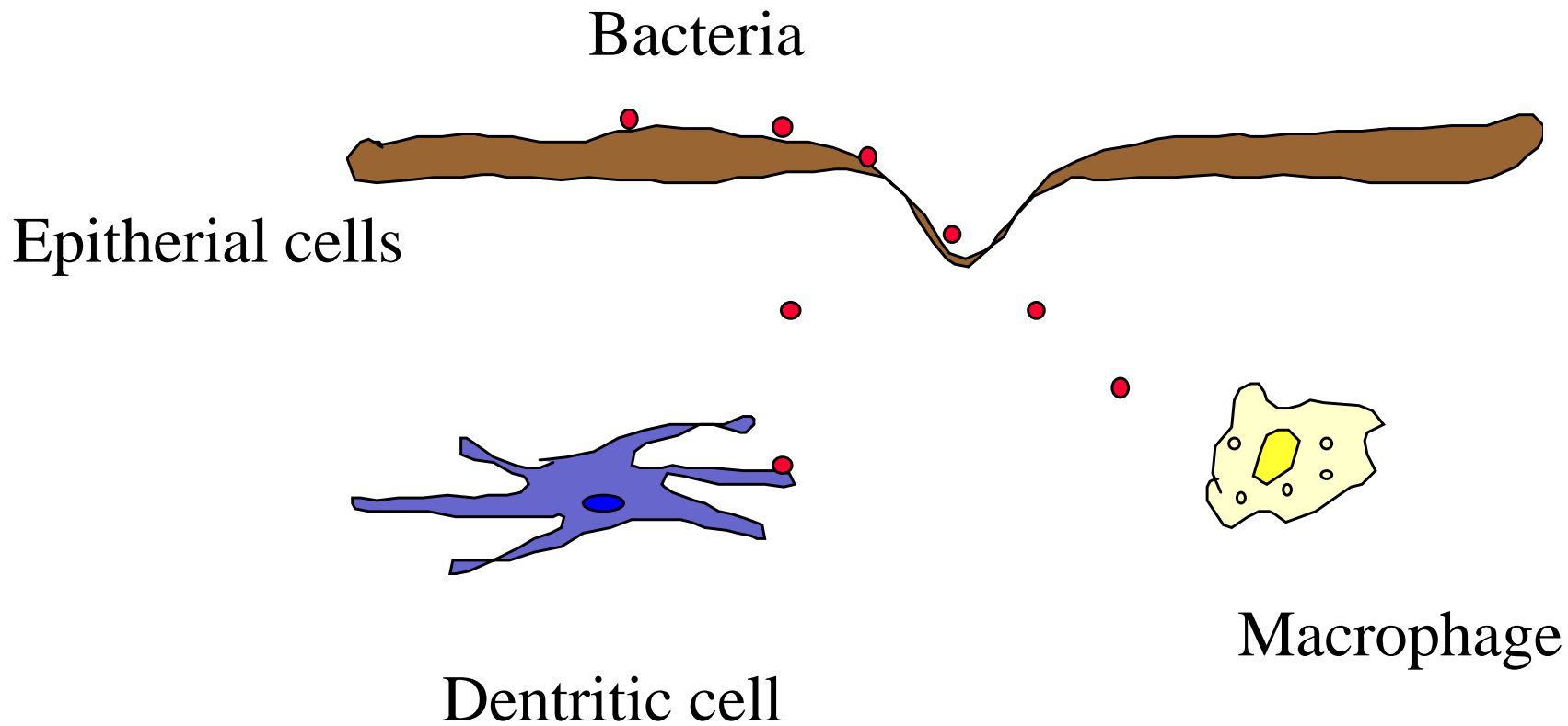
- Immune system works to eliminate invading microorganisms. Once tissues are damaged, immune system also works to repair damaged tissue.
- First, small number of tissue macrophages and dendritic cells phagocytose the microorganism or damaged tissues and produce inflammatory cytokines (IL-1 β , TNF α and IL-6) and chemokines, which induce migration of neutrophils from blood vessel within 1 hour. Neutrophils engulf the microorganism and damaged tissues and die.
- Then monocytes in blood vessel migrate to the site of inflammation and become macrophages. These macrophages engulf dead neutrophils and also damaged tissues.



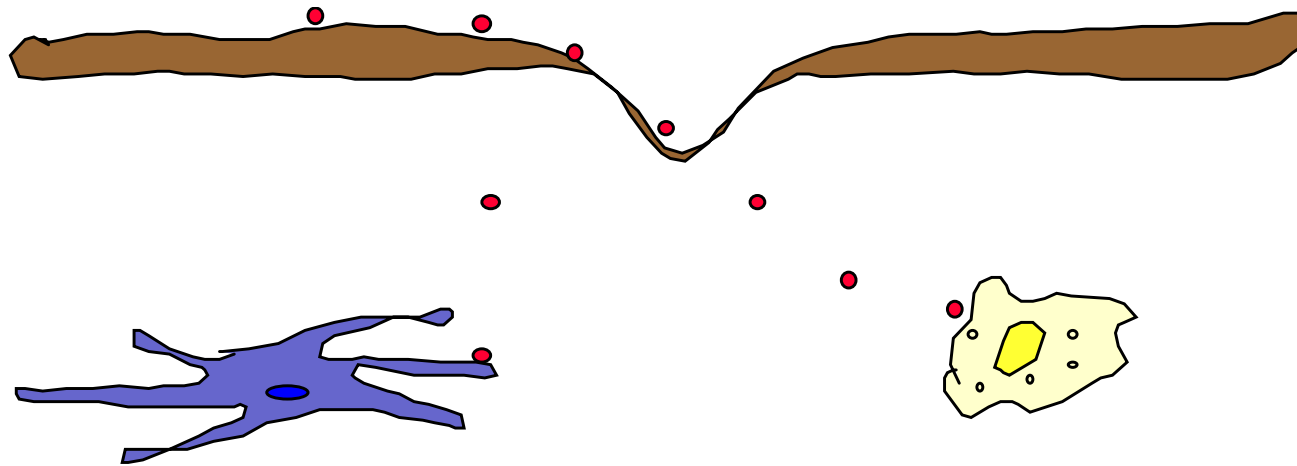
Infection of Bacteria to skin lesion

Neutrophil, macrophages



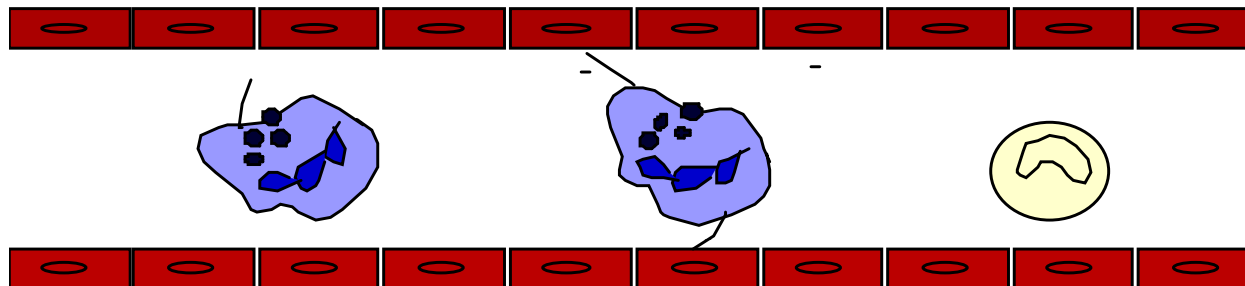


Production cytokines and chemokines



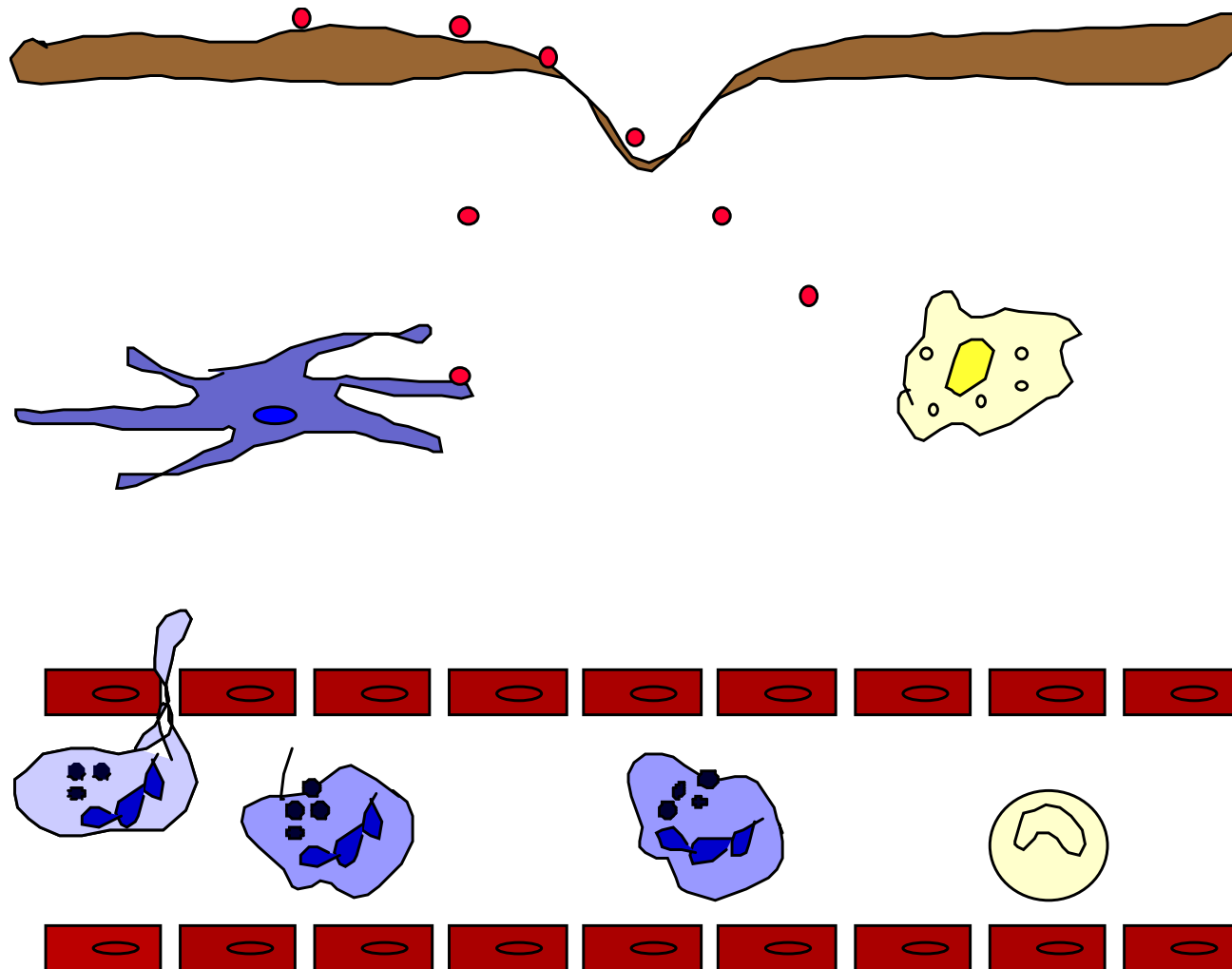
IL-1 β , TNF- α , IL-6

CXCL8, IL-12

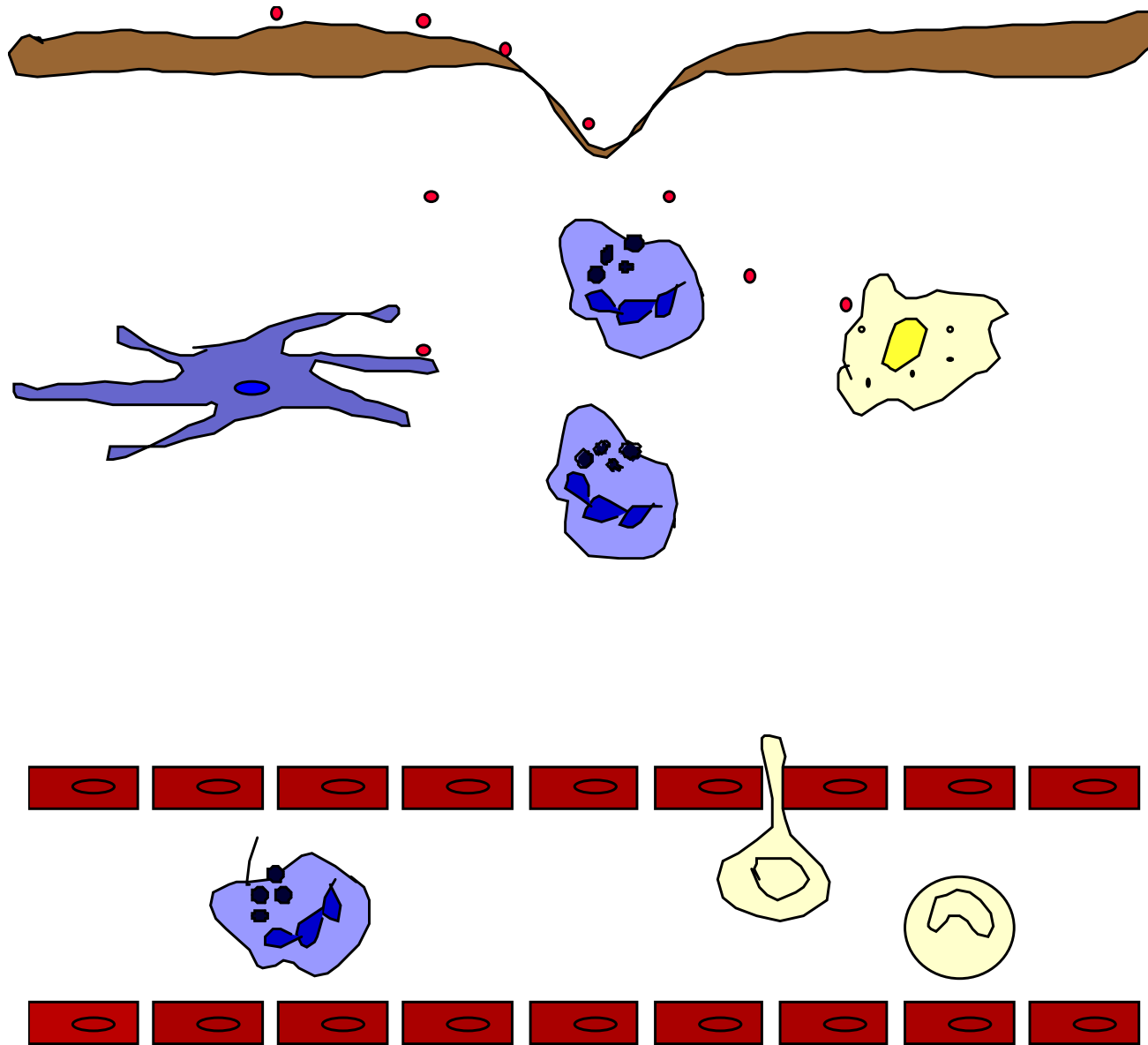


Neutrophil extravasation

CXCL8



Monocytes extravasation and become macrophages



Microbiological stimuli

pathogen-associated molecular patterns (PAMPs)



Host-derived non-microbial stimuli

Wound healing, atherosclerosis,
Alzheimer etc.



Sterile stimuli, which induce innate immunity

- Damage-associated molecular patterns (DAMPs); host-derived non-microbial stimuli are released following tissue injury or cell death and have similar functions as PAMPs in terms of their ability to activate pro-inflammatory pathways



DAMPs

- β -amyloid Alzheimer's disease
- Cholesterol crystals Atherosclerosis
- Uric acid and MSU crystals Gout
- HSPs
- S100 proteins
- HMGB1
- Hyaluronan
- Silica
- Asbestos



Wound healing

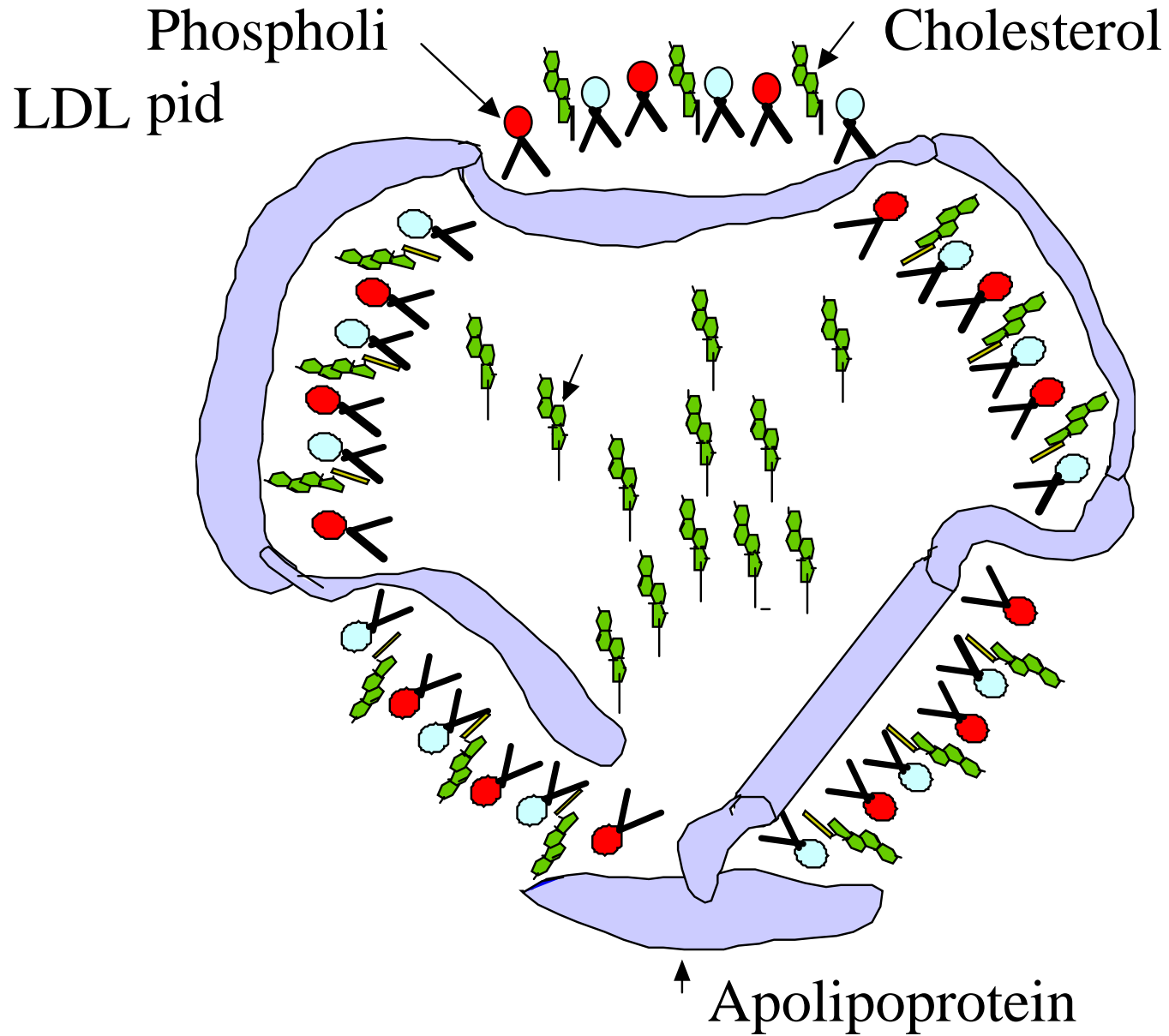
- In response to injury that disrupts the parenchyma and causes blood vessel damage, the coagulation system (platelets etc) is activated, which begins the initial stages of wound healing.
- Activated platelets produce transforming growth factor- β (TGF β) and platelet-derived growth factor (PDGF), which activate fibroblasts and act as chemoattractants for leukocytes.
- Infiltration of neutrophils.
- Monocytes infiltration and become macrophages.

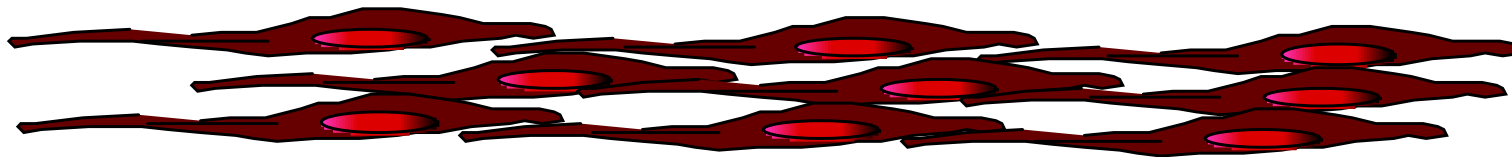
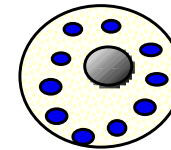
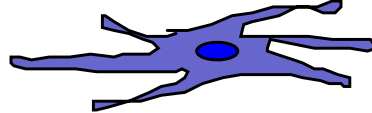
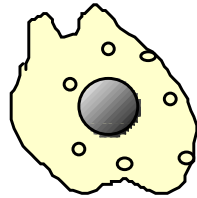
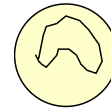


Atherosclerosis

LDL



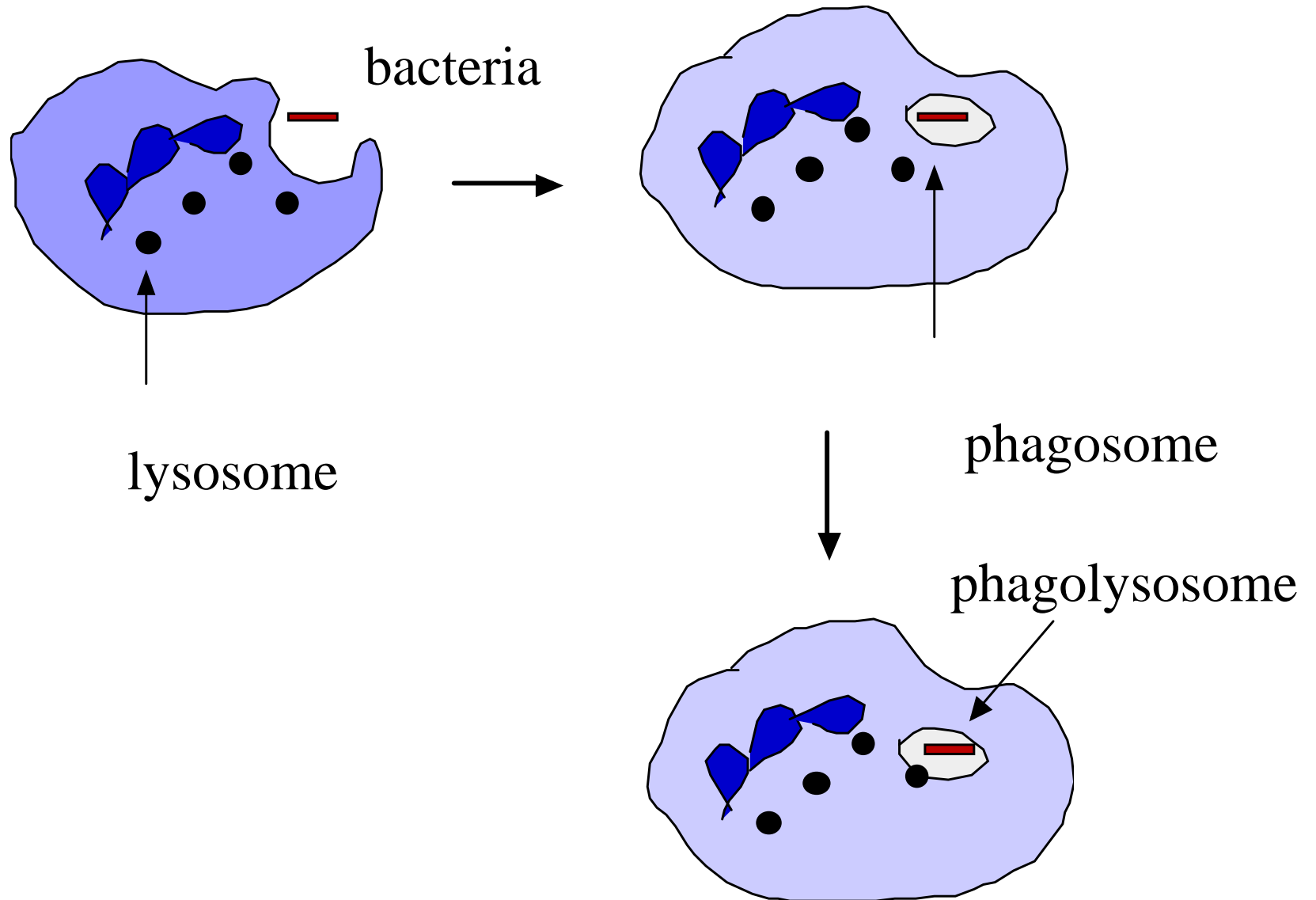




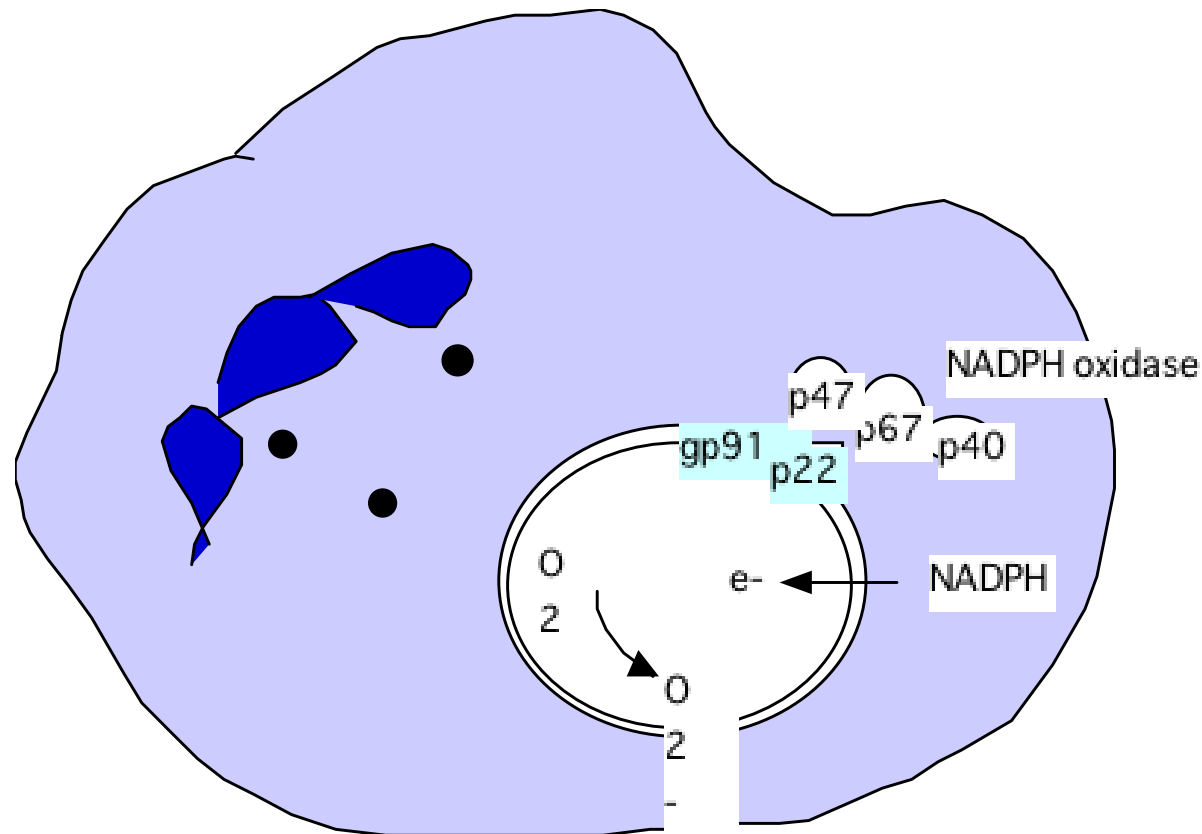
Phagocytosis



Phagocytosis



Production of ROS, NO



Reactive oxygen intermediates are generated by an enzyme complex that has NADPH oxidase activity

Microorganisms and autophagy

Eukaryotic cells possess the lysosomal degradation pathway known as autophagy to dispose of intracellular organelles and protein aggregates

This pathway is also used to degrade microorganisms (such as viruses, bacteria and protozoa) that invade intracellularly.



How to recognize microorganisms

Cell-associated pattern-recognition
molecules (PRMs)



TLR, NOD, RIG, SR

- Cell-associated pattern-recognition molecules (PRMs) are strategically located in different cellular compartments (plasma membrane, endosomes, cytoplasm) and belong to different molecular classes.
- Toll-like receptors (TLRs)
- NOD-like receptors (NLRs)
- RIG-I-like receptors (RLRs)
- C-type lectin receptors (CLRs)
- absence in melanoma 2 (AIM2)-like receptors

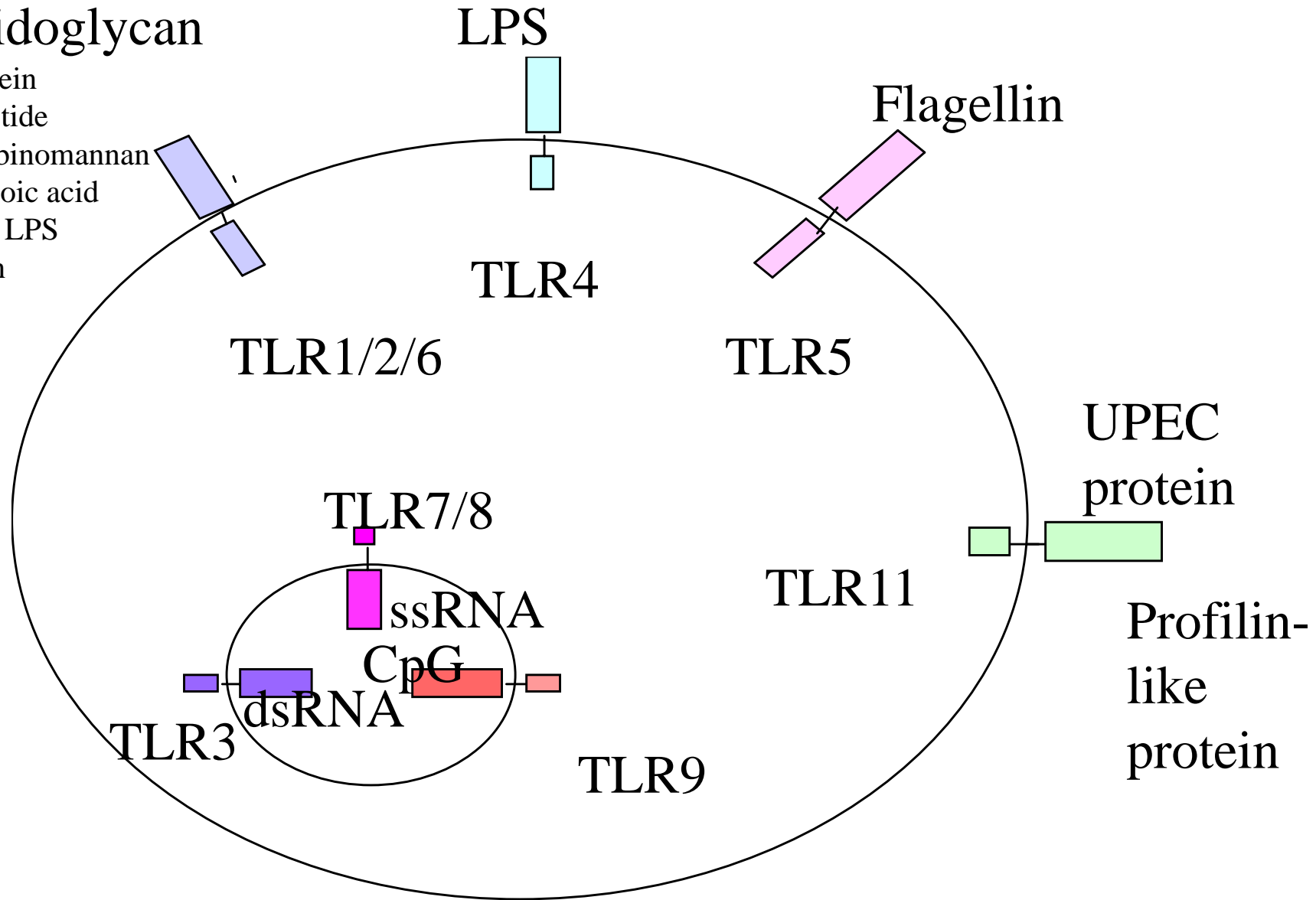


Peptidoglycan

- Lipoprotein
- Lipopeptide
- Lipoarabinomannan
- Lipotechoic acid
- Atypical LPS
- Zymosan

LPS

Flagellin

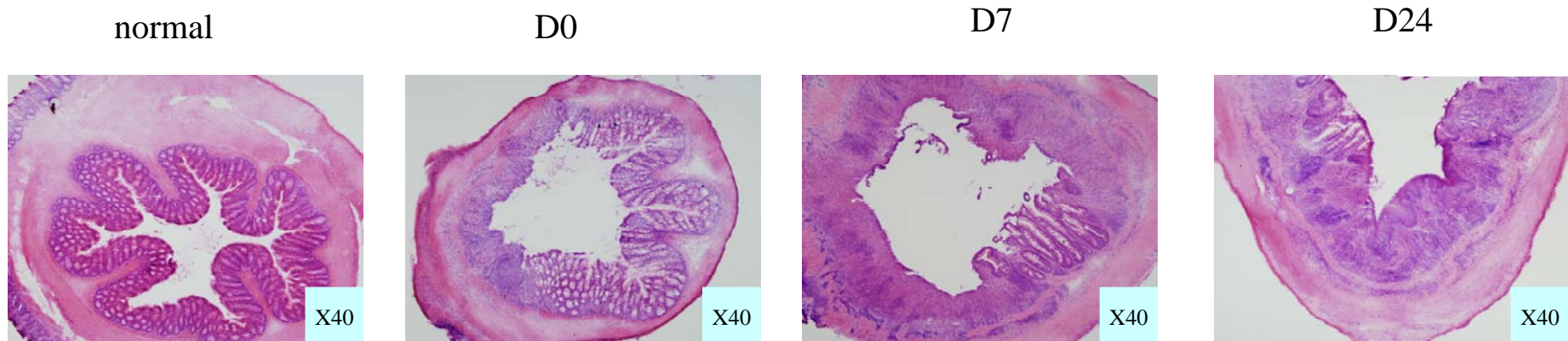


[Recognition and Signaling by Toll-Like Receptors](#). Phillip West, Anna Alicia Koblansky, and Sankar Ghosh.
Annual Review of Cell and Developmental Biology Vol. 22 (2006): 409-437



Example of tissue injury and bacterial infection

Following tissue damage with the intestinal epithelial cell (IEC) cytotoxic agent dextran sulphate sodium (DSS), commensal bacteria translocate.



2% DSS administered to C57BL/6 mice for 5 days (D0).

From innate immunity to acquired immunity

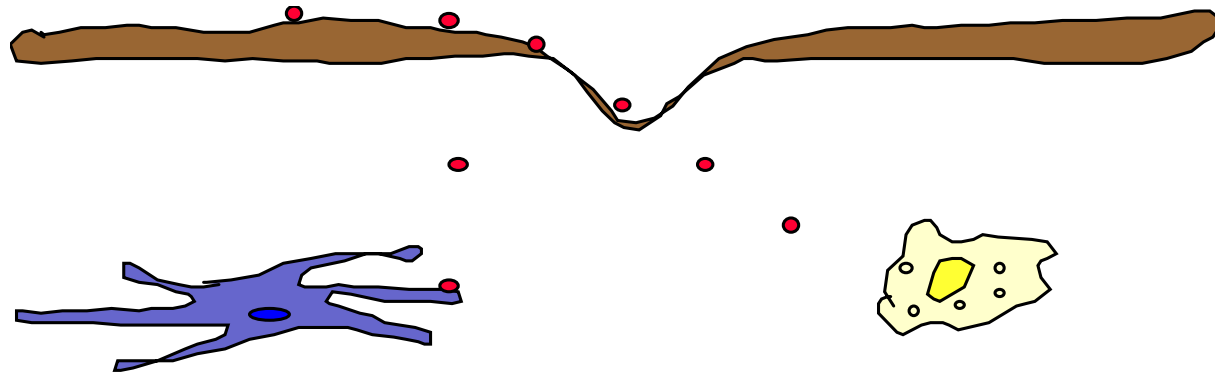
Antigen presentation



Antigen presentation

- Antigen captured by dendritic cells (DC), macrophages, B cells are processed and loaded on MHC class II molecule as a peptide and presented on cell surface.
- DC, which captured antigens, enter the lymph node and present antigens to T cells.



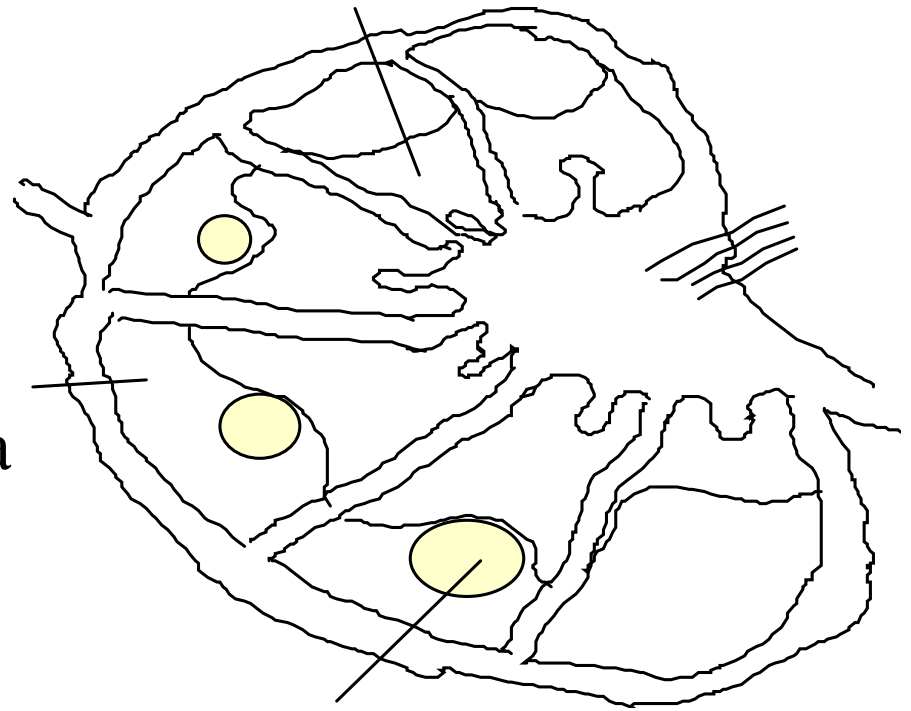


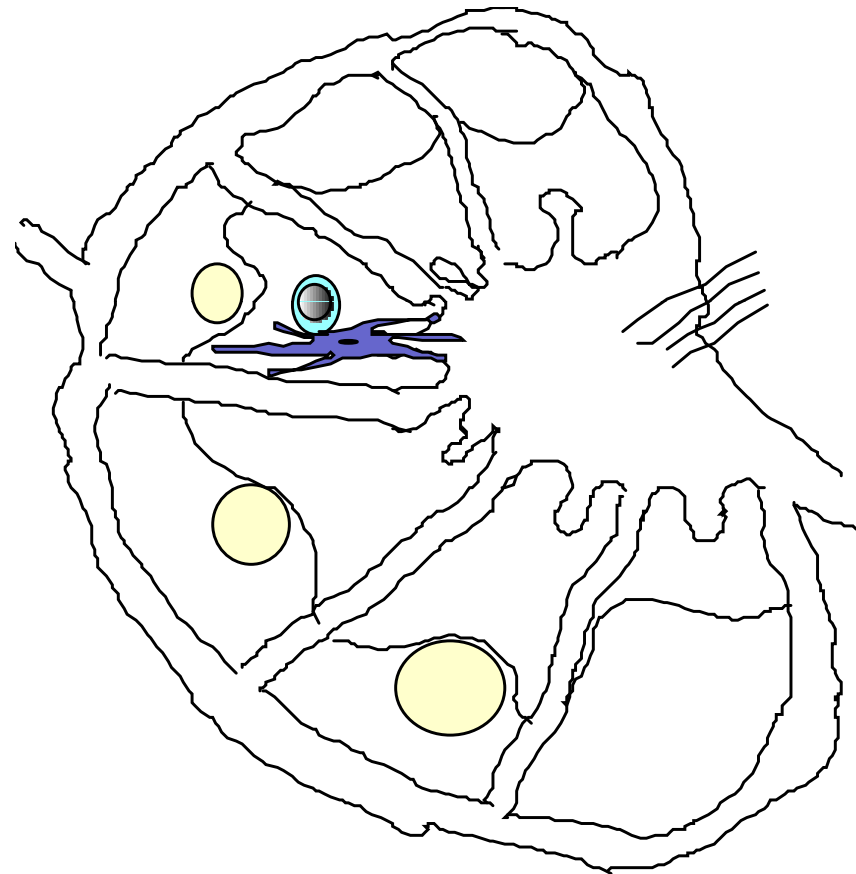
Afferent lymphatics

T cell area

B cell area

Follicle





Acquired immunity

T cells and B cells

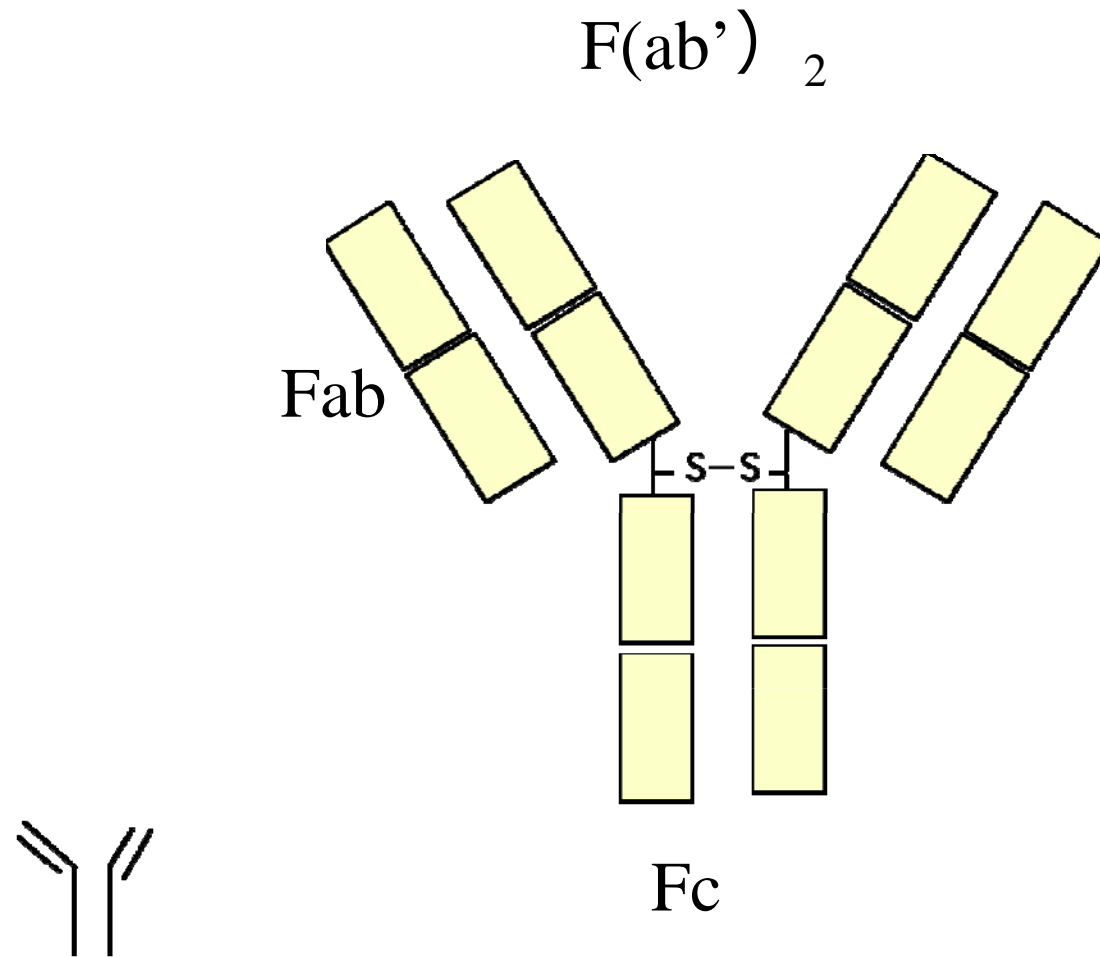


Structure of Immunoglobulins

- Five major classes of immunoglobulin (Ig) are IgM, IgD, IgG, IgA and IgE.
- IgG molecule is a prototype of other Ig molecules
- IgG is Y-shaped having heavy (H) chain and light (L) chain

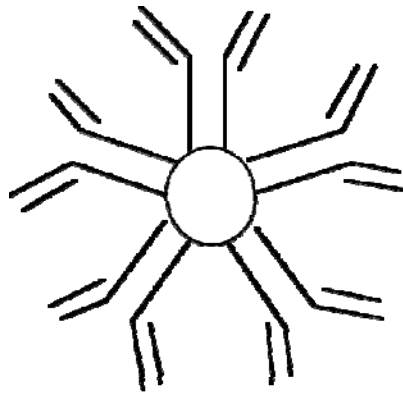


IgG molecule



Isotype

IgM



IgG



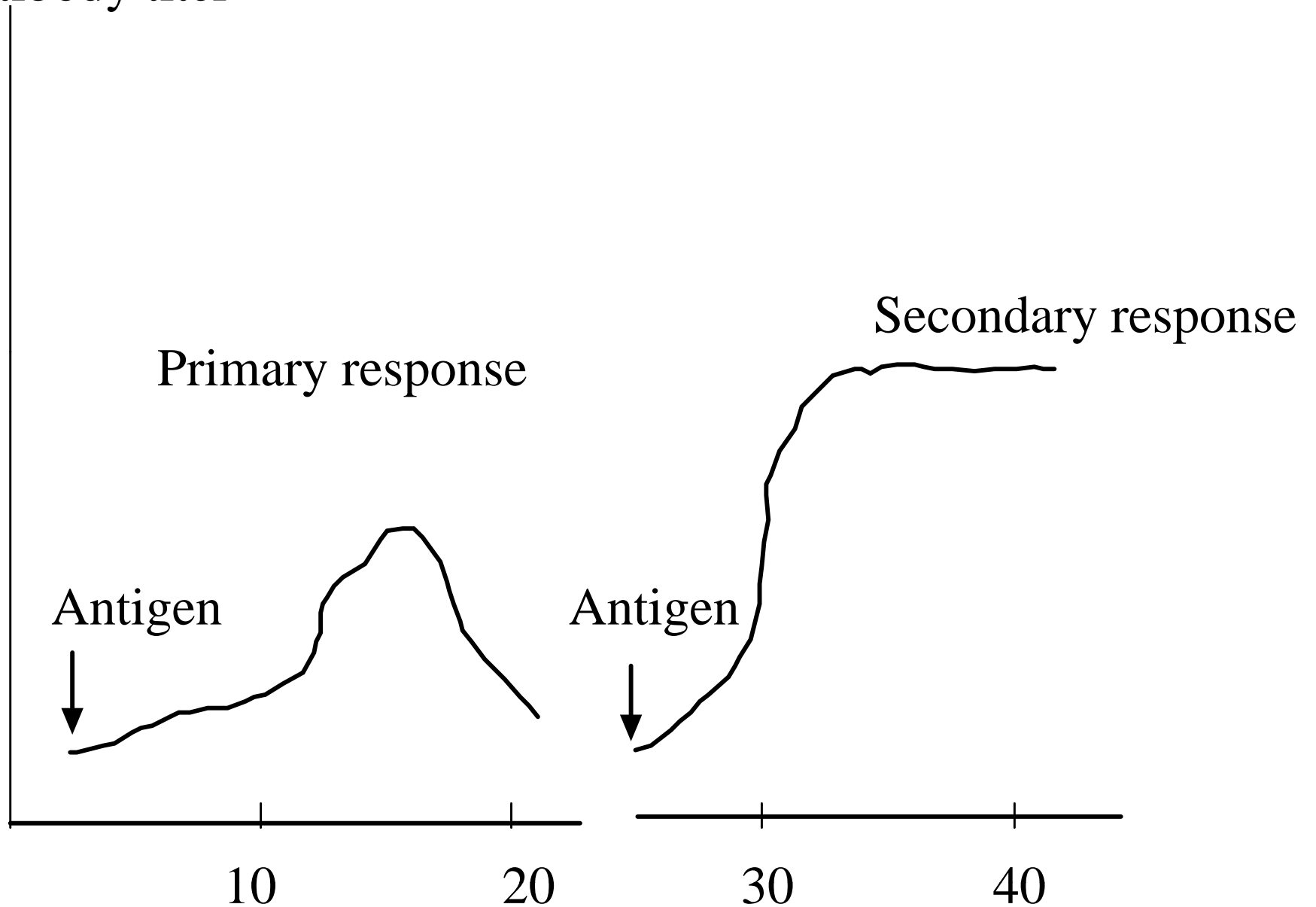
IgA



IgE



Antibody titer



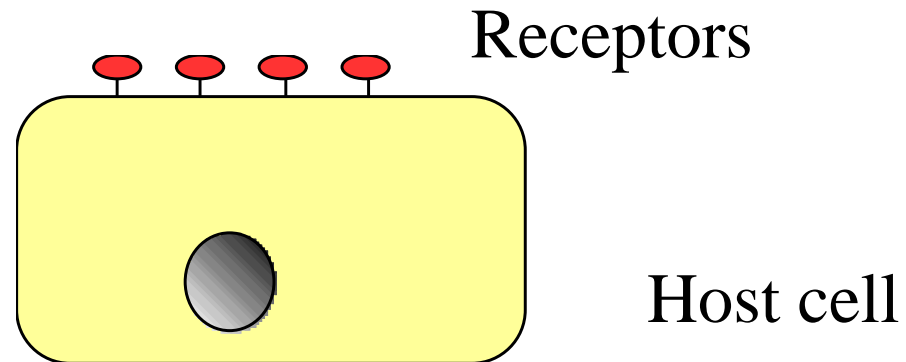
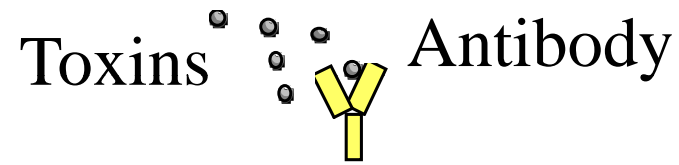
Tree functions of antibody

1. Neutralization
2. Opsonization
3. Complement activation

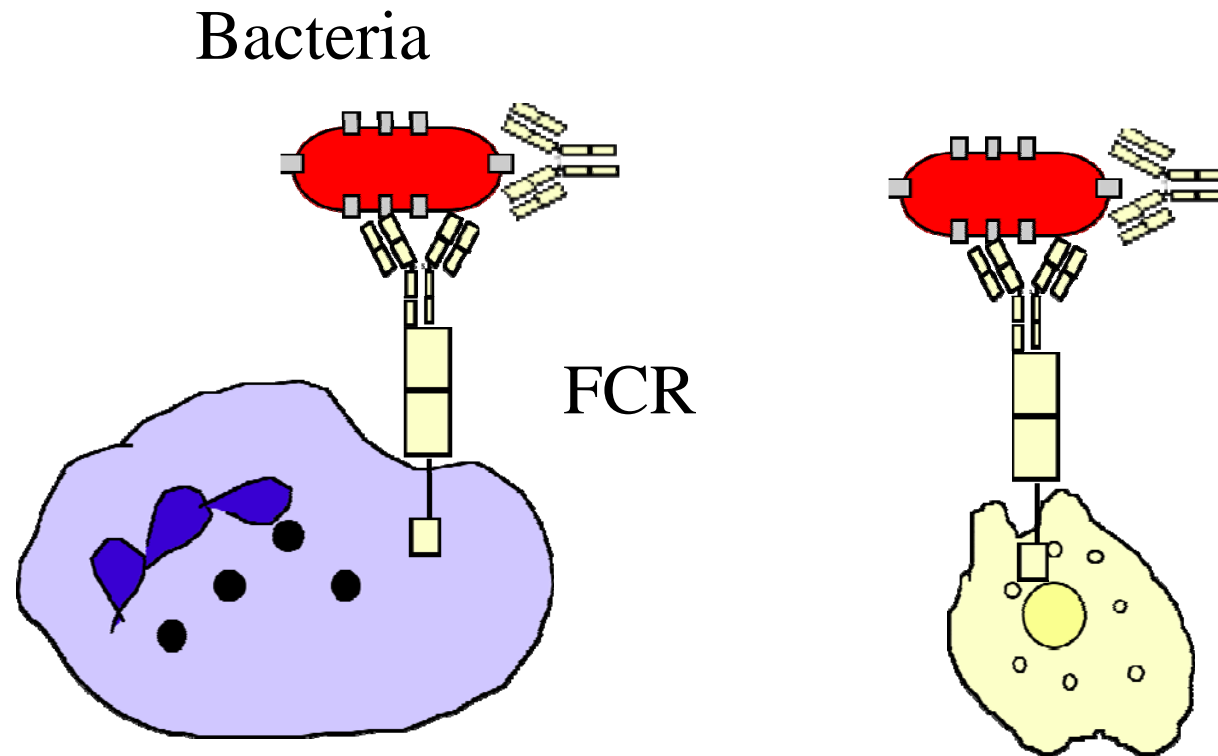


Neutralization

Bacteria

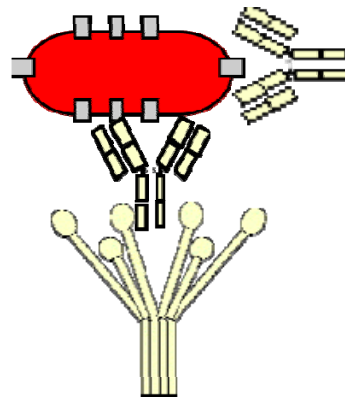


Opsonization



Complement activation

Bacterial
Antigens



Antibody

C1q

Bacterial lysis

Antibodies to wounded tissue enhance cutaneous wound healing

opsonized damaged tissues were effectively phagocytosed and removed by macrophages

Nishio N, Ito S, Suzuki H, Isobe K. [Antibodies to wounded tissue enhance cutaneous wound healing](#). *Immunology*. 2009 Nov;128(3):369-80.



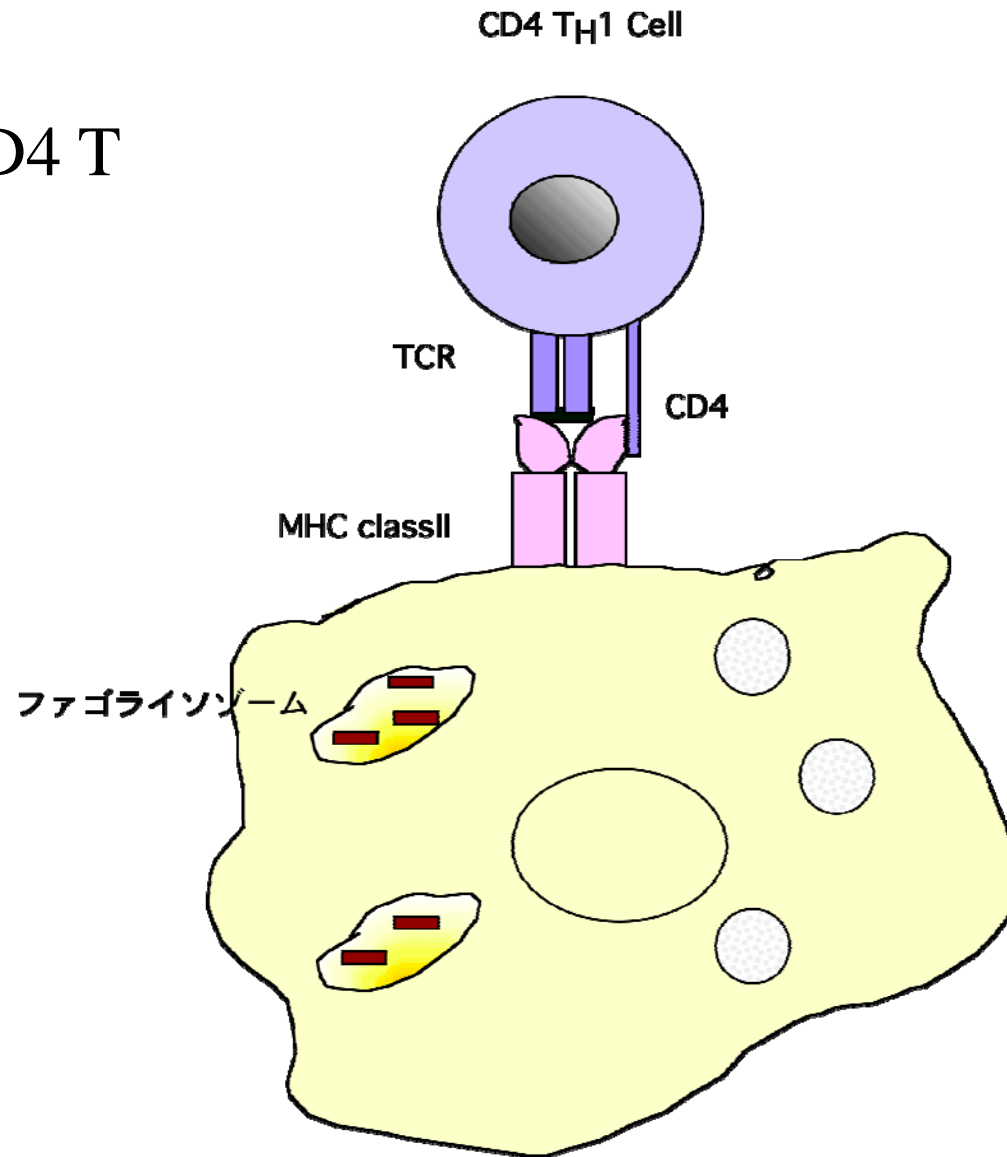
Functions of T cells

Three effector functions

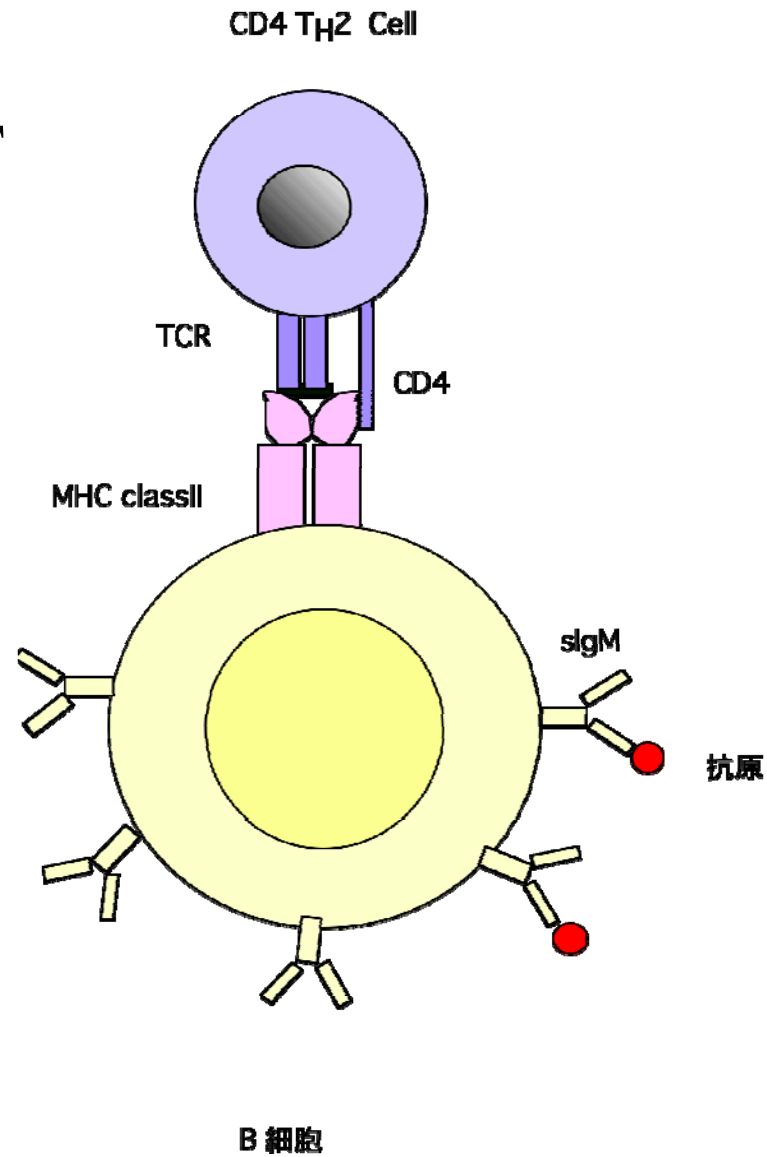
Th1, Th2, CTL



T_H1 CD4 T



T_H2 CD4 T



CTL CD8 T

