Basic Immunology

Lecture 1st and 2nd

Introduction

Historical overview.

Components and structure of the immune network

Composition of the immune system.

Immunological recognition in innate, adaptive, and natural immunity. Definition of the antigen. Basic molecular structures of immunoglogical recognition molecules.

What is the *immunity*?

What is the immune system?

- **The immune system is a complex structural and functional NETWORK composed by molecular and cellular elements.**
- **The main function of the immune system is managing of the individual integrity with defence against outside parasites and against modifications of self structures (by viral infections, tumorous transformations or other mutations).**
- **The immune network is formed by balance of attacking and tolerating type immune responses.**
- **The immune system links to the other (endocrine, neural, metabolic) regulatory systems of the body in multiple levels influencing each other.**

Mi az immunrendszer?

Az immunrendszer molekuláris és sejtes elemekből álló összetett struktúrális és funkcionális **HÁLÓZAT**.

Az immunrendszer fő funkciója az **egyéni integritás fenntartása** a külső paraziták és a saját struktúrák (vírusok, tumoros átalakulások vagy egyéb mutációk által okozott) módosulása elleni védekezéssel.

Az immunhálózatot a **támadó és toleráló** típusú immunválaszok egyensúlya alkotja.

Az immunrendszer több szinten kapcsolódik a szervezet egyéb (endokrin, idegi, metabolikus) szabályozó rendszereihez, amelyek egymás működését is befolyásolják.

Basic terms

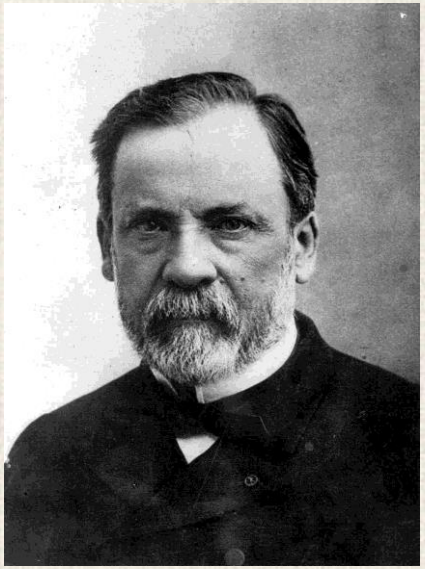
- **Immunis,- e** (*Julius Caesar*) = exempt, free of burden (E.g. tax, law, or diseases)
- **IMMUNE:** individuals who do not capitulate to a disease when infected;
- **IMMUNITY:** status of **specific** resistance to a disease;
- **IMMUNOLOGY:** branch of theoretical biology focuses on mechanisms responsible for **both self and non-self recognition, elimination of the invaders and protection of the basic self structural elements.**

History

- Ancient Athens B.C. 431-404: description of plague epidemic by Thucydides and Hippocrates. (Pericles, the leader of Athens, died from the plague), ancient Chinese papers about the pox immunity
- Infections, epidemies, vaccination

Edward Jenner

(1749 - 1823)



Louis Pasteur

(1822 - 1895)

Edward Jenner (1749 - 1823)

- He was a doctor in Berkeley, Gloucestershire. In 1796 he carried out his now famous experiment on eight-year-old orphan boy James Phipps. Jenner inserted pus taken from a cowpox pustule on the hand of milkmaid Sarah Nelmes and inserted it into an incision on the boy's arm. He was testing his theory, drawn from the folklore of the countryside, that milkmaids who suffered the mild disease of cowpox never contracted smallpox.
- Jenner subsequently proved that having been inoculated with cowpox Phipps was now immune to smallpox. He submitted a paper to the Royal Society in 1797 describing his experiment but was told that his ideas were too revolutionary and that he needed more proof. Undaunted, Jenner experimented on several other children, including his own 11-month-old son. In 1798 the results were finally published and Jenner coined the word vaccine from the Latin *vacca* for cow, and called the process *vaccination*.

Smallpox vaccination (1796 – 1979)

Karikó and Weissman win Nobel Prize in medicine for work that enabled mRNA vaccines against COVID-19

THE NOBEL PRIZE LAUREATES IN IMMUNOLOGY

1901 **E.A. Von Behring** *(Germany)* for the work on serum therapy especially its application against diphtheria.

1905 **R. Koch** *(Germany)* for the investigations concerning tuberculosis.

1908 **E. Metchnikoff** *(Russia)* and **P. Ehrlich** *(Germany)* for their work on immunity (respectively, phagocytosis/cellular theory and humoral theory).

1913 **C.R. Richet** *(France)* for the work on anaphylaxis.

1919 **J. Bordet** *(Belgium)* for the discoveries relating to immunity (complement).

1930 **K. Landsteiner** *(Austria/USA)* for the discovery of human blood groups.

1951 **M. Theiler** *(South Africa)* for the discoveries and developments concerning yellow fever.

1957 **D. Bovet** *(Italy/Switzerland)* for the discoveries related to histamine and compounds, which inhibit action of histamine and other substances on the vascular system and the skeleton muscles.

1960 **Sir F.McFarlane Burnet** *(Australia)* and **Sir P.B. Medawar** *(Great Britain)* for the discovery of acquired immunological tolerance.

1972 **G.M. Edelman** *(USA)* and **R.R. Porter** *(Great Britain)* for their discovery concerning the chemical structure of antibodies.

1977 **R. Yalow** *(USA)* for the development of radioimmunoassays of peptide hormones.

1980 **B. Benacerraf** *(USA)*, **J. Dausset** *(France)* and **G.D. Snell** *(USA)* for their discoveries concerning genetically determined structures on the cell surface (major histocompatibility complex) that regulate immunological reactions.

1982 **S. K. Bergstrom** *(Sweden)*, **B. I. Samuelsson** *(Sweden)* and **J. R. Vane** *(UK)* for their discoveries concerning prostaglandins and related biologically active substances.

1984 **N.K. Jerne** *(Denmark/Switzerland)* for theories concerning the specificity in development (lymphocyte clonality) and control of the immune system; **G.J.F. Köhler** *(Germany/Switzerland)* and **C. Milstein** *(Argentina/Great Britain)* for the discovery of the principle for production of monoclonal antibodies.

1987 **S. Tonegawa** *(Japan/USA)* for the discovery of the genetic principle for generation of antibody diversity.

1990 **J.E. Murray** and **E.D. Thomas** *(USA)* for their discovery concerning organ and cell transplantation in the treatment of human diseases.

1996 **P.C. Doherty** *(Australia/USA)* and **R.M. Zinkernagel** *(Switzerland)* for their discoveries concerning the specificity of the cell mediated immune defense ("dual recognition").

1997 **S.B. Prusiner** *(USA)* for the discovery of prions as a new biological principle of infection.

1999 **G. Blobel** *(USA)* for discoveries concerning signal transduction.

2011 **B.A. Beutler** (USA), **J.A. Hoffmann** (France/Luxemburg) and **R.M.Steiman** (Canada) for their discoveries concerning the activation of innate immunity.

2018 **J. P. Allison** (USA) and **T. Honjo** (Japan) for their discovery of cancer therapy by inhibition of negative. immune regulation

2023 K. Karikó (Hungary) and D. Weissman (USA) for mRNA vaccine technology

Immune system

- Individuals and species
- Organs
- Cells
- Molecules
- Functions

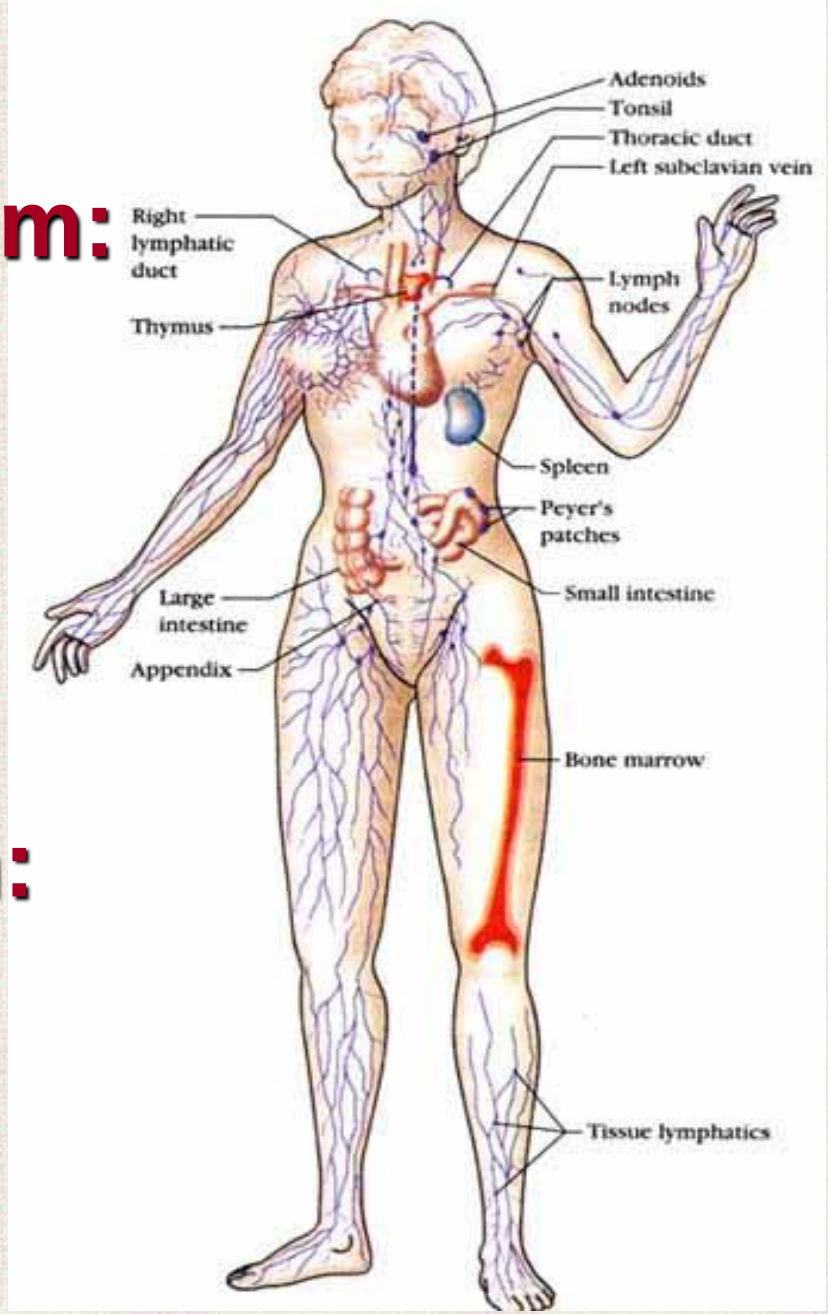
Structural and functional NETWORK

Central immune system:

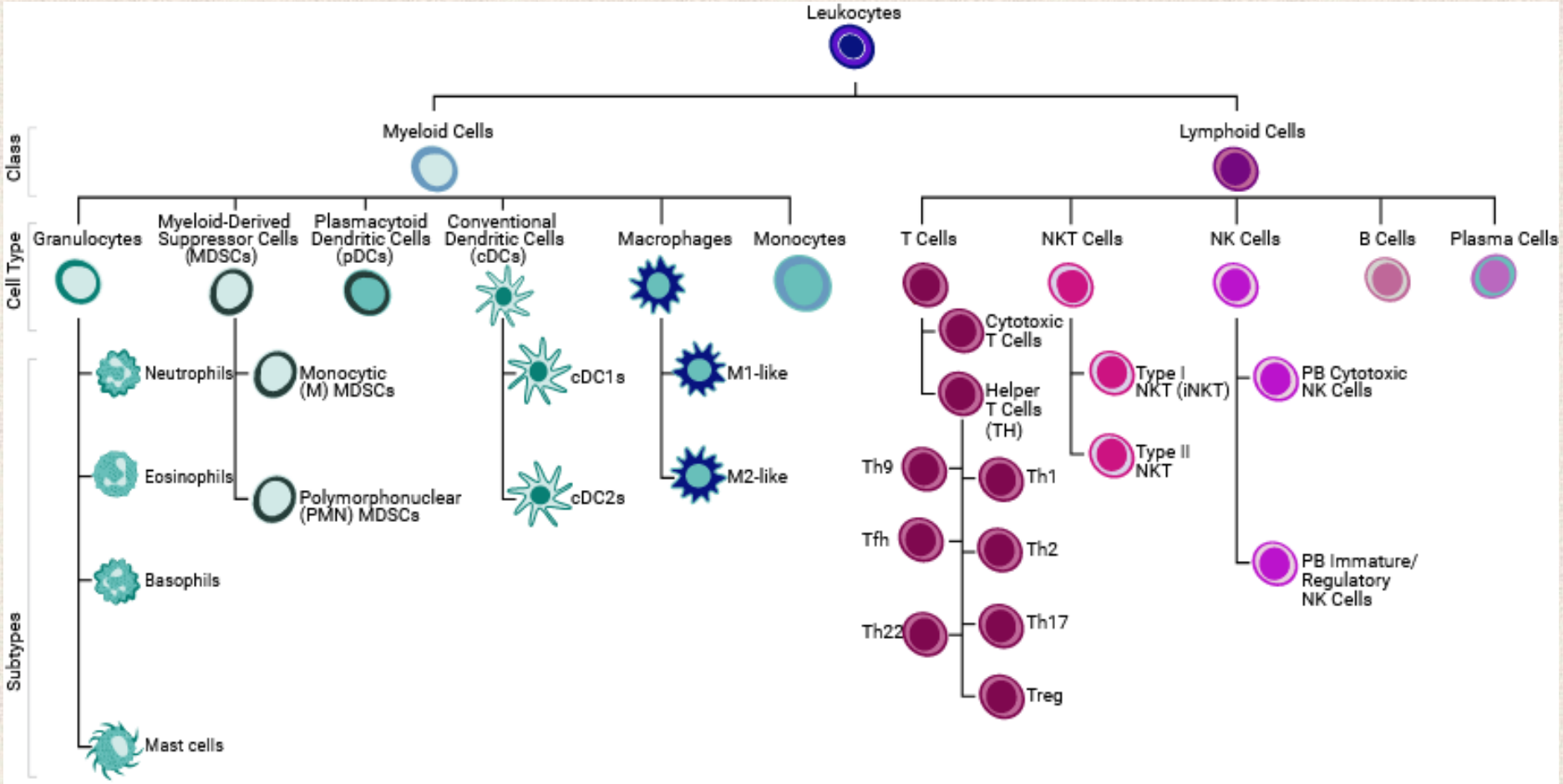
- bone marrow
- thymus
- spleen
- lymph nodes

Local immune system:

- SALT
- MALT



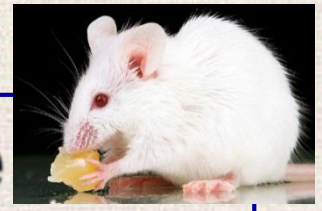
Main cellular components of the immune system



Composition of the immune system

Innate

- None antigen specific
- No immunological memory
- Rapid reactivity
- Linear amplification of the reaction

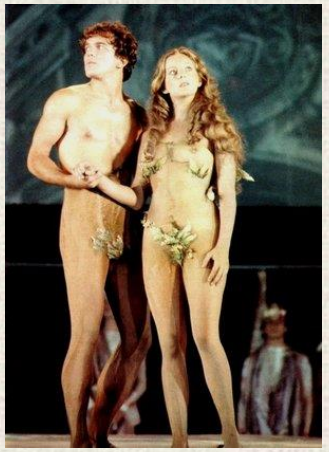


Adaptive

- Antigen specific
- Immunological memory
- Activated after a latency
- Exponential amplification of the reaction

Natural

Innate-like immunity with adaptive features



Innate immune system

- **Pattern recognition receptors (PRR)**
- **Pathogen associated molecular patterns (PAMP)**
- **First line of defence**
- **Low number of molecularly distinct receptors and high number of recognized patterns**
- **Main molecular components: Antibacterial peptides, Complement factors and their receptors, Heat shock proteins, Fc receptors, Inflammatory cytokines, Growth factors, Histamine**
- **Main cellular components: Macrophages, Monocytes, NK cells, Granulocytes, Mast cells**

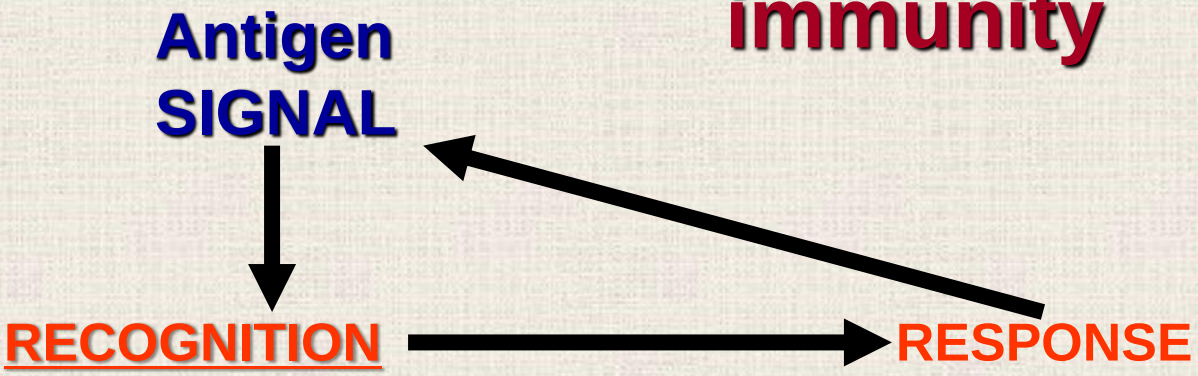
Adaptive immune system

- **Antigen receptors (BCR,TCR)**
- **Epitope specific in a given antigen**
- **Adaptive immune response**
- **High number of distinct antigen receptors and high number of recognized antigens**
- **Main molcelar components: Antibodies, MHC, T and B cell receptors, Lymphatic citokines**
- **Main cellular components: T cells (both αβ and γδ), B cells, Antigen presenting cells**

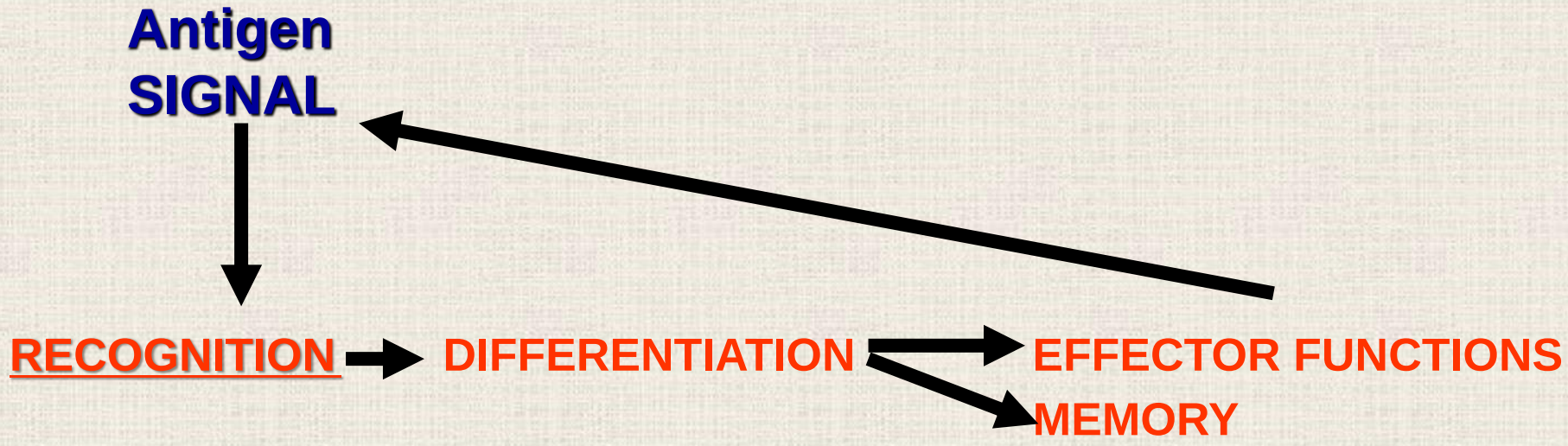
Natural immune system

- **Antigen recognition receptors (BCR,TCR) with limited specificity**
- **Patern recognition profile**
- **Innate-like immune response**
- **Limited number of distinct antigen receptors and high number of recognized antigens**
- **Main cellular components: iNKT cells, iγδT cells, MAIT cells, IEL cells, CD5+ B cells**
- **Main molecular components: natural (auto)antibodies**

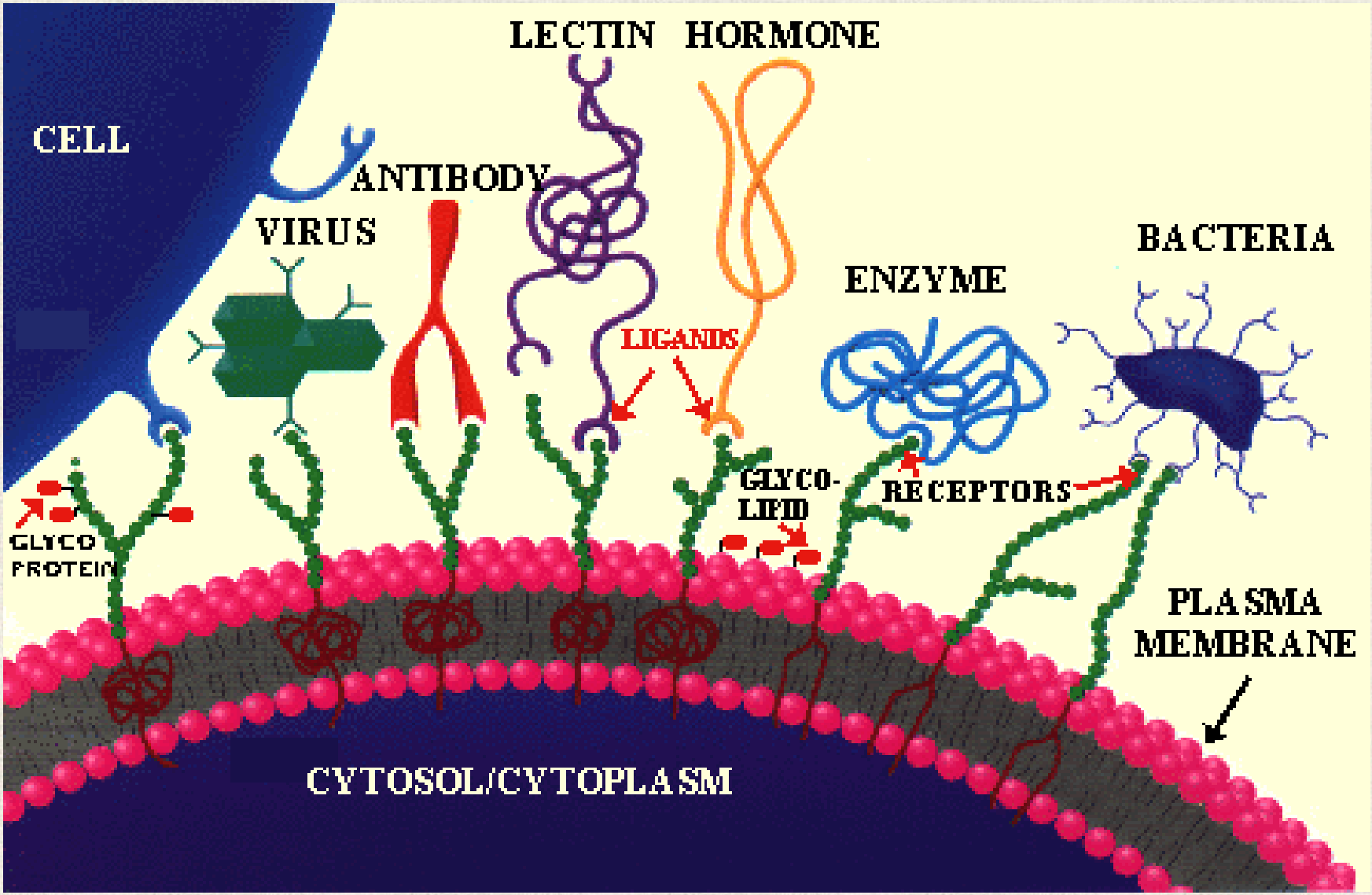
Theoretical scheme of the innate and natural immunity



Theoretical scheme of the adaptive immunity



Molecular recognition



Pattern Recognition Receptors (PRRs) Signaling Pathways

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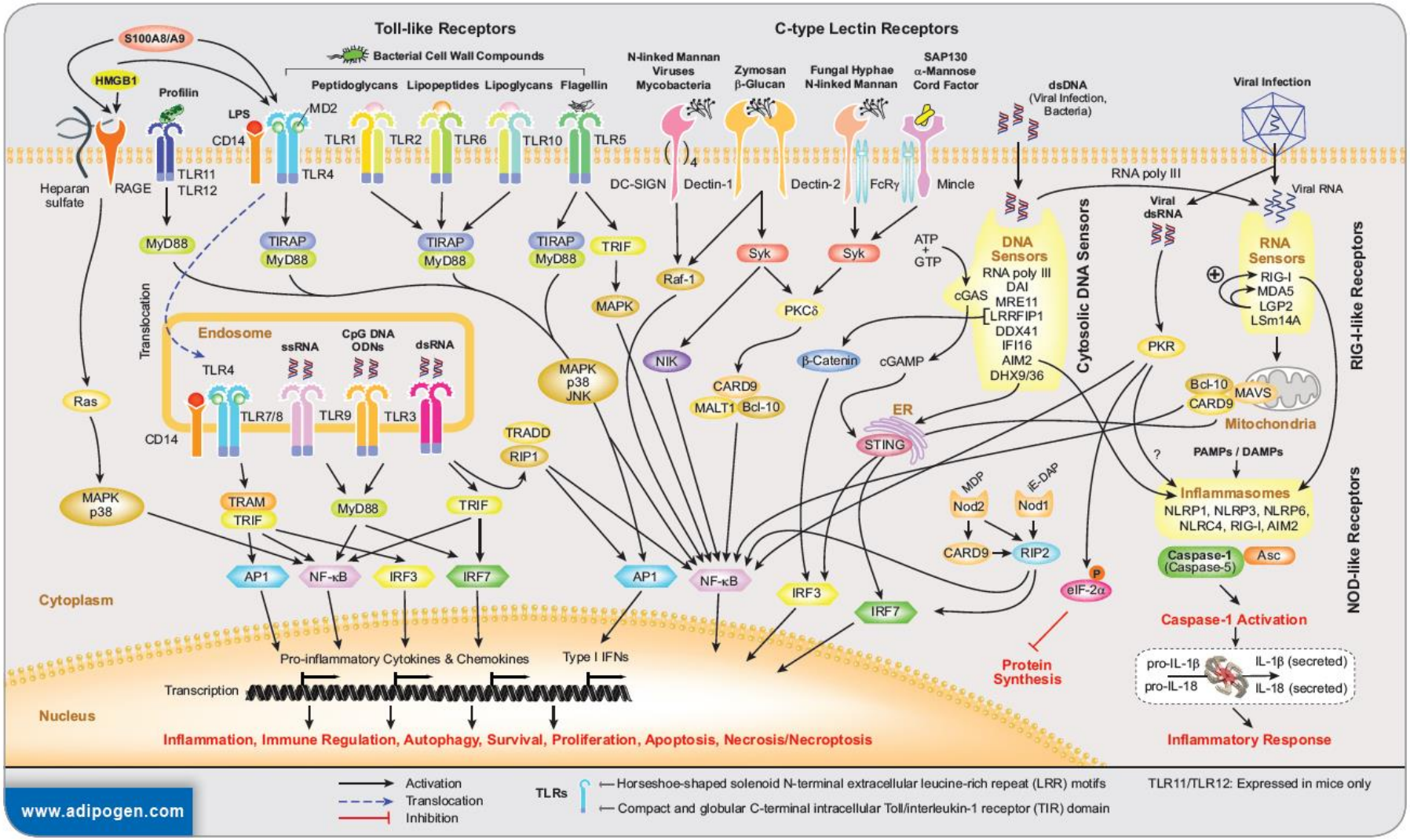

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Macrophages express receptors for many microbial constituents

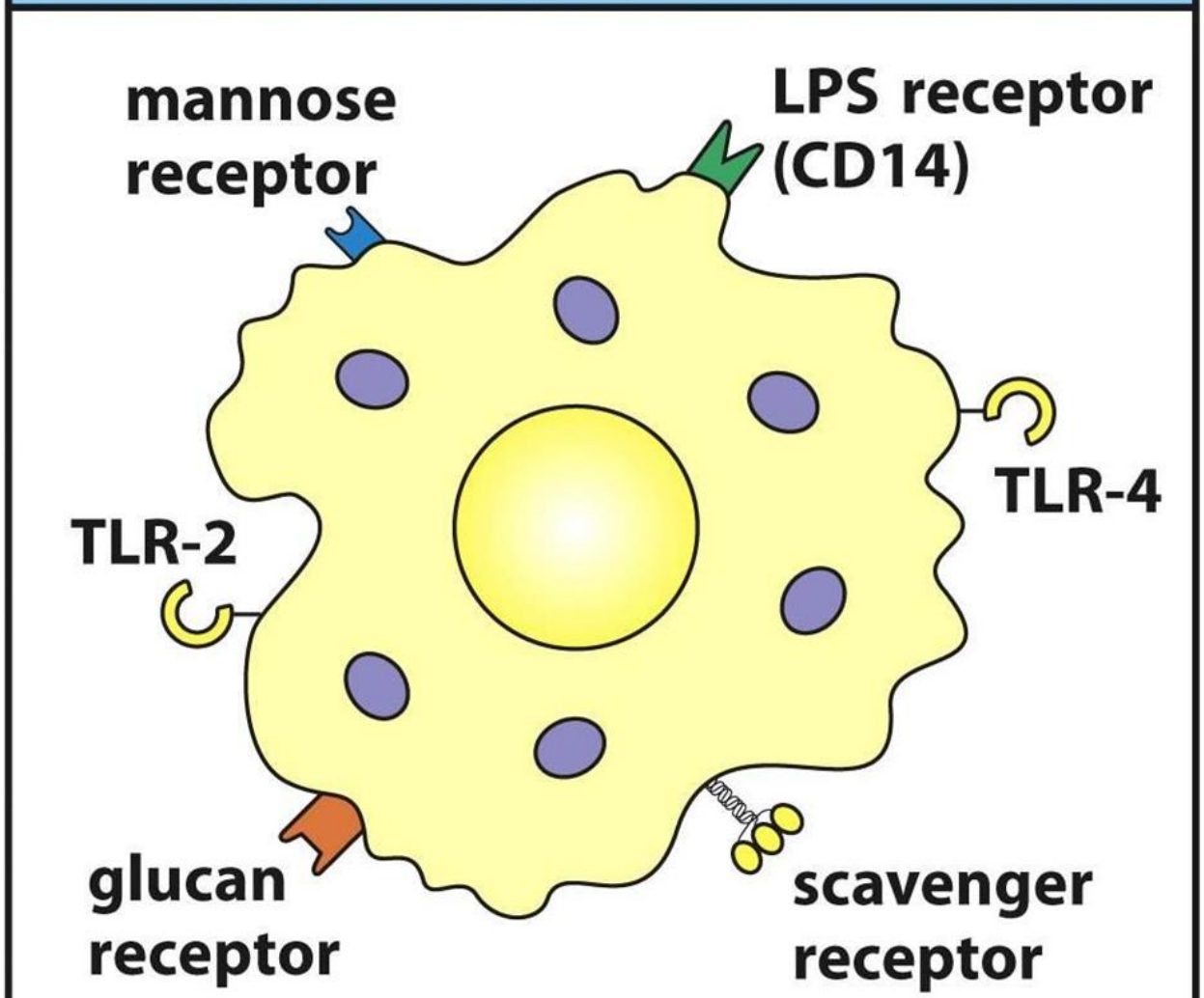
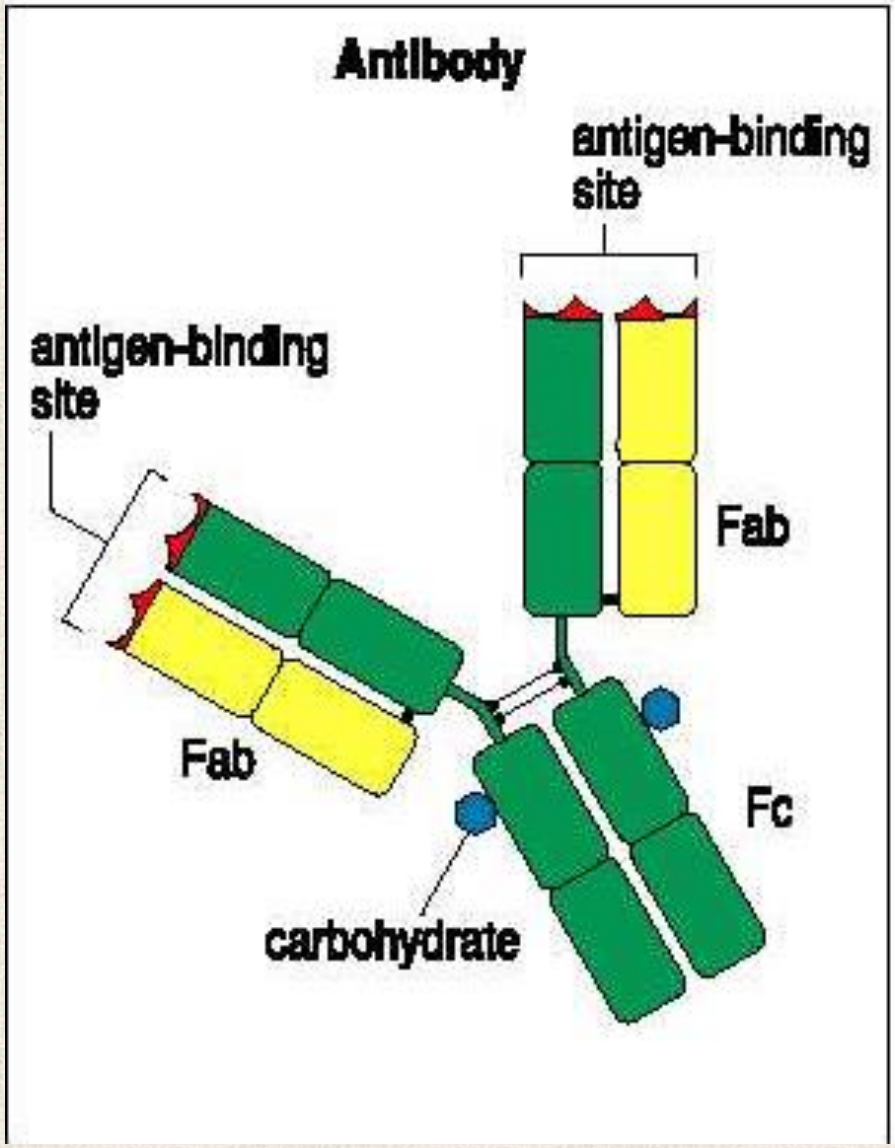
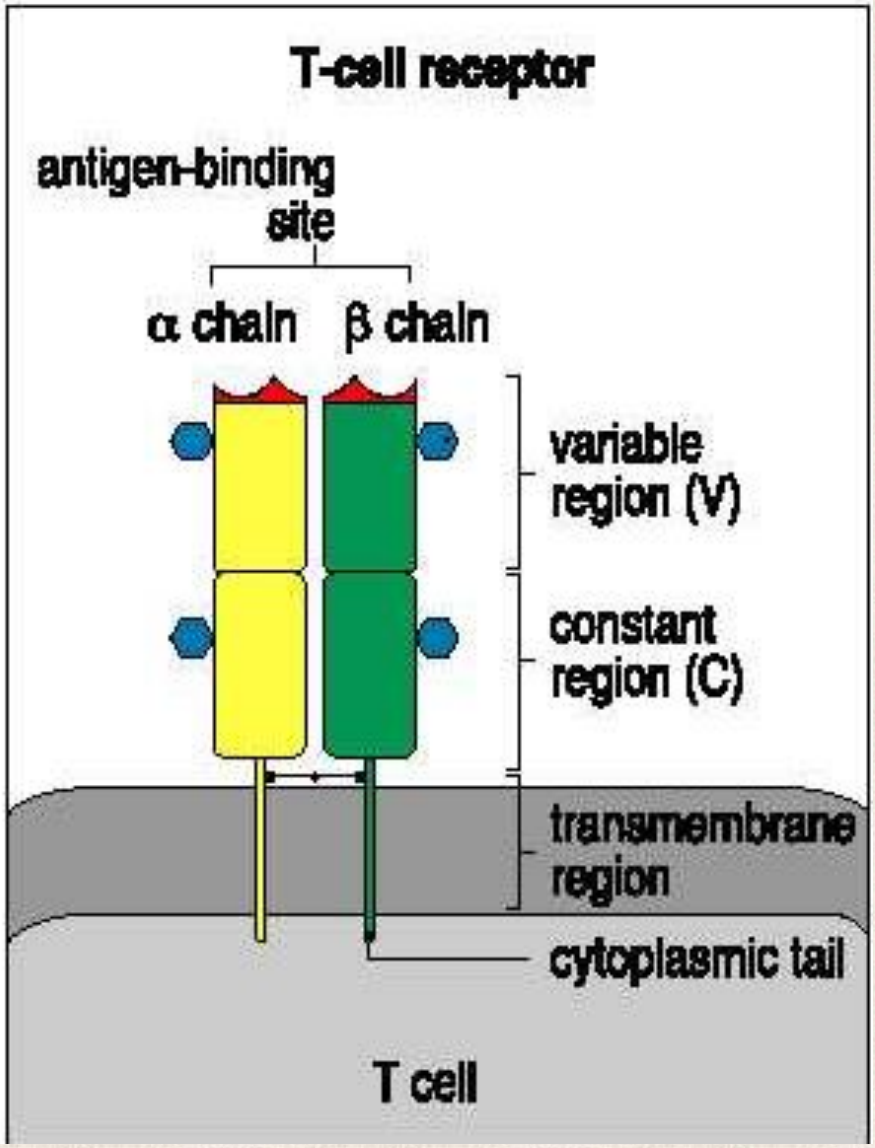


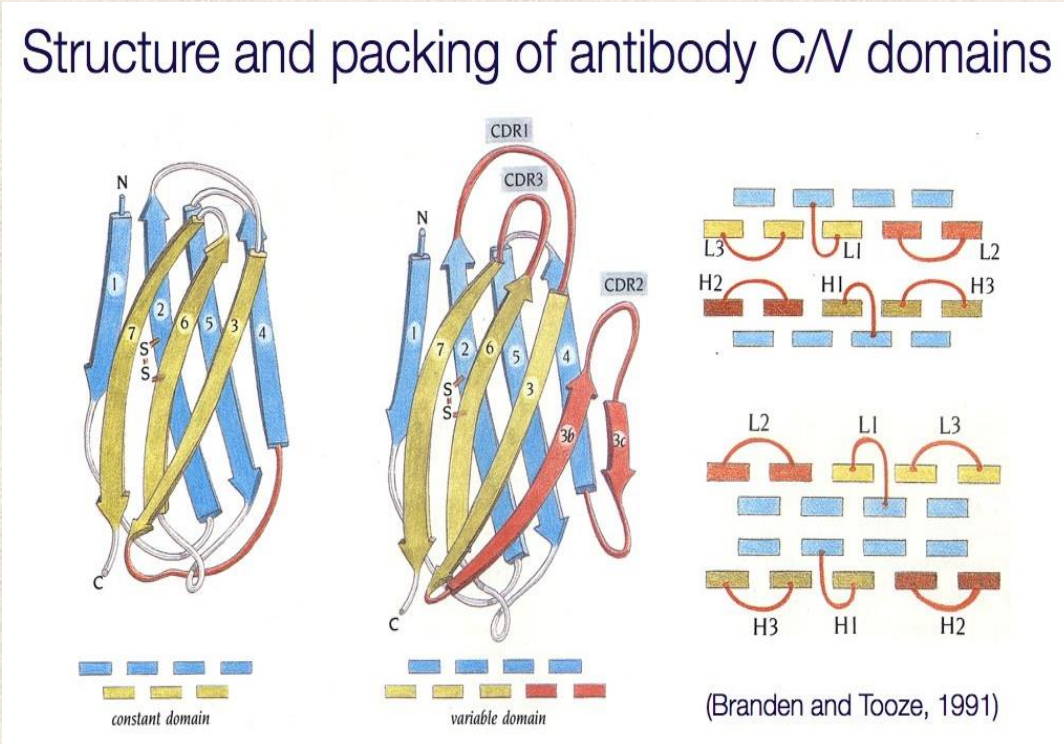
Figure 1.10 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

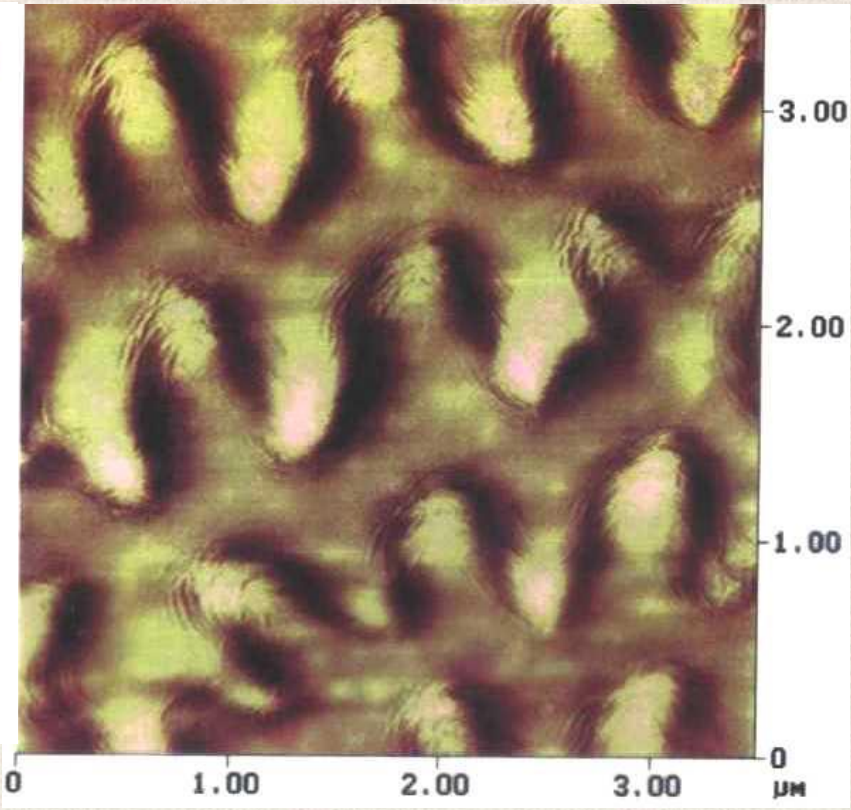
Antigen specific recognition molecules





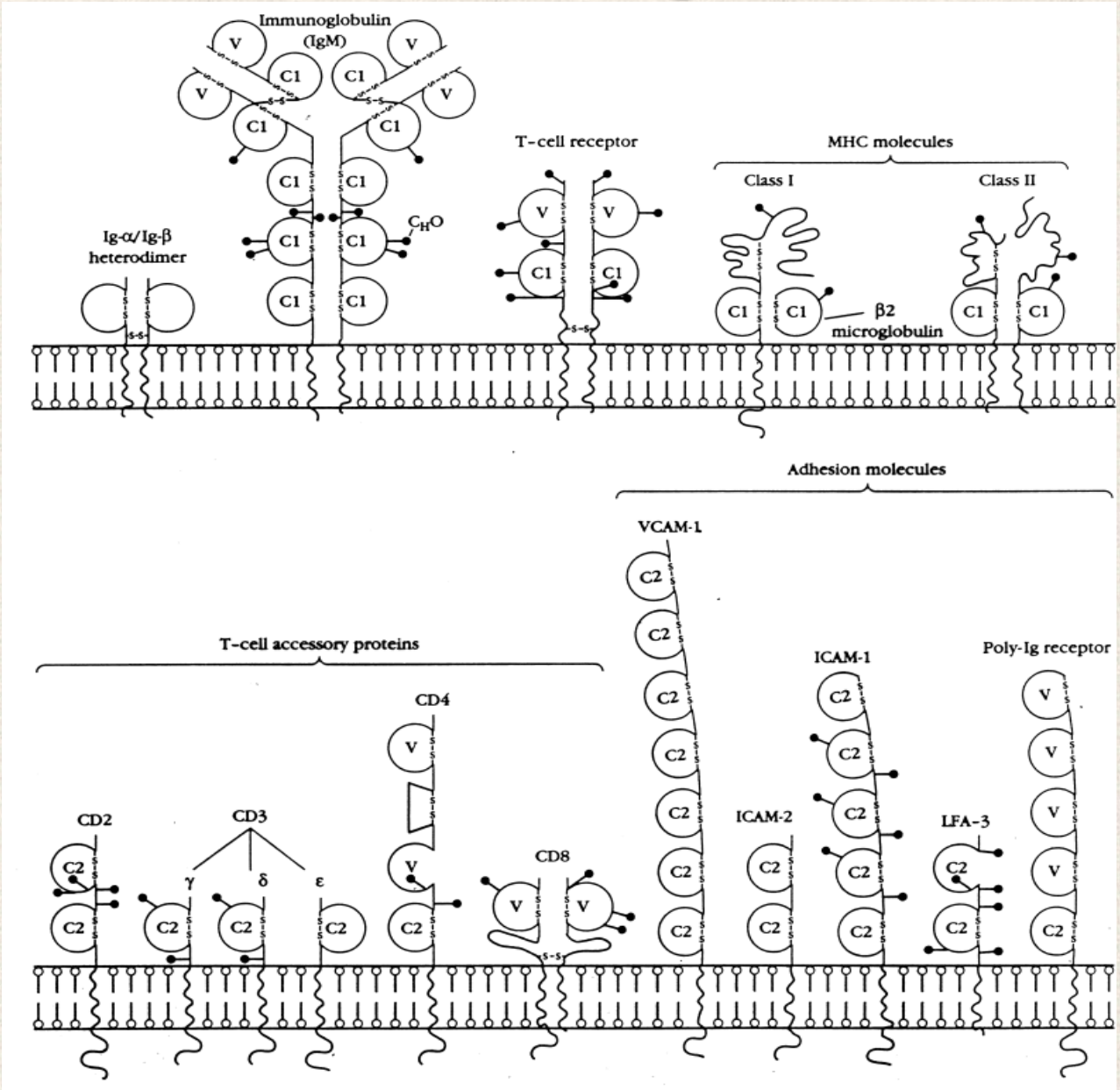
Domain structure





Well conserved amino acid sequence designed by 110 amino acids closed to a “ring shape” with disulphide bound.

Immune recognition molecules



Antigen specific recognition molceules

Accessory molecules for cell-cell communication

Definition of the antigen

Detre (Deutsch) László (1874-1939):

ANTIBODY **GEN**ERATOR: foreign substance induces antibody production (1899)

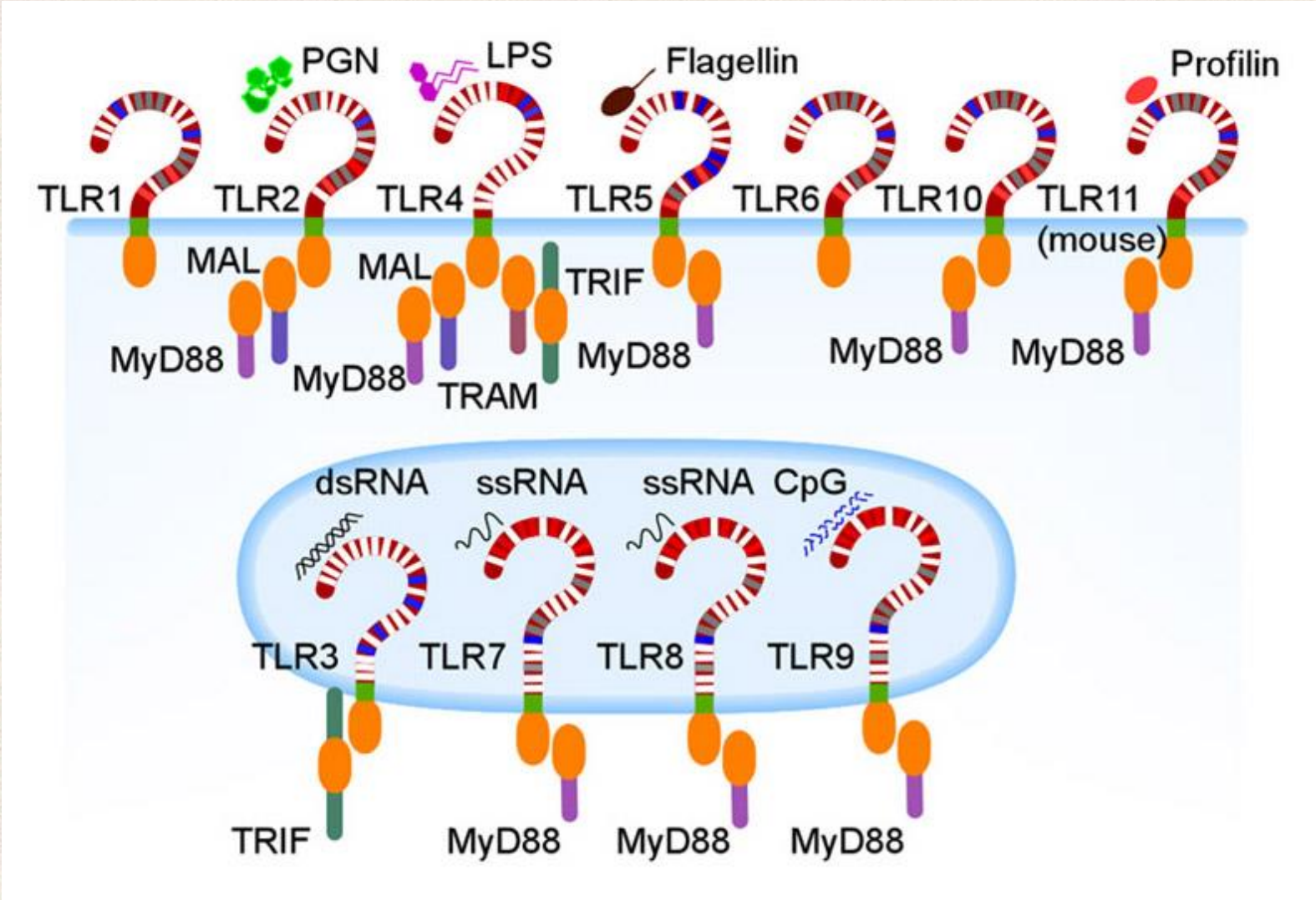
Modern definition: substance, which is recognized by immune recognition molecules including T and/or B cell receptors, and it is able to induce ***active immune response or tolerance*** according to the host immunogenetic background (MHC haplotype).

Factors determining the immunogenity

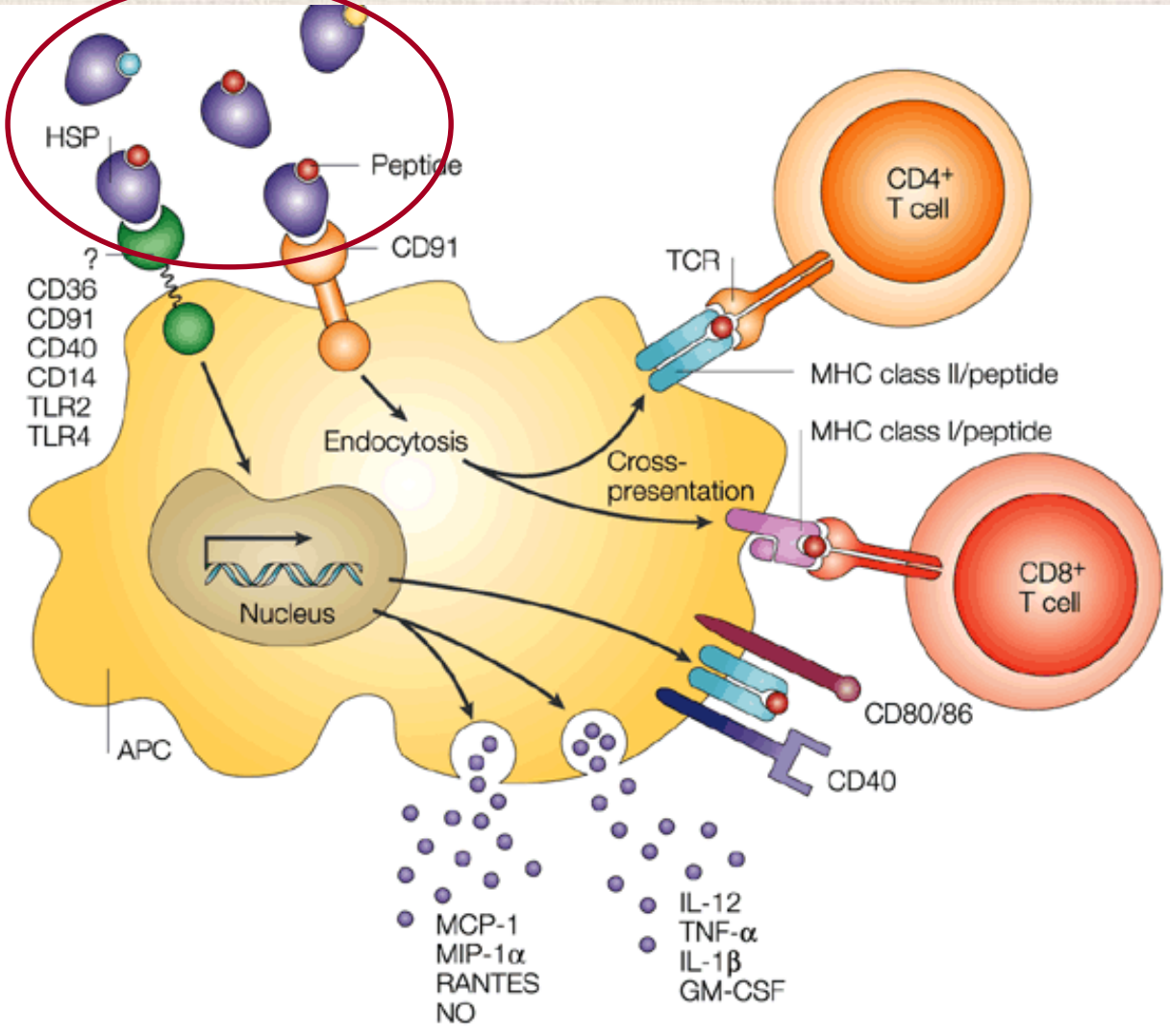
- **immunodominant regions**
- **chemical structure** (inorganic molecules are not antigens at general, but e.g. heavy metals in protein complex are able to induce specific metal allergies). The best antigens are proteins>polypeptides>polysaccharides>lipides>nucleic acids
- **physico-chemical nature** (D and L configuration; ortho-, para,- meta position; hydrophilic and hydrophobic amino acid sequence)
- **molecular weight** (not an absolute category)
- **conformation sensitivity** (folding and refolding)
- **Origin** auto-, allo-, xenoantigen
- **mode and anatomic region of the administration** (e.g. peripheral immune reaction and oral tolerance for the same antigen depending from the place of the antigen presentation)
- **dose dependence** (large and low dose)
- **Valency**: monovalent, bivalent, and multivalent antigens

Immunological recognition molecules

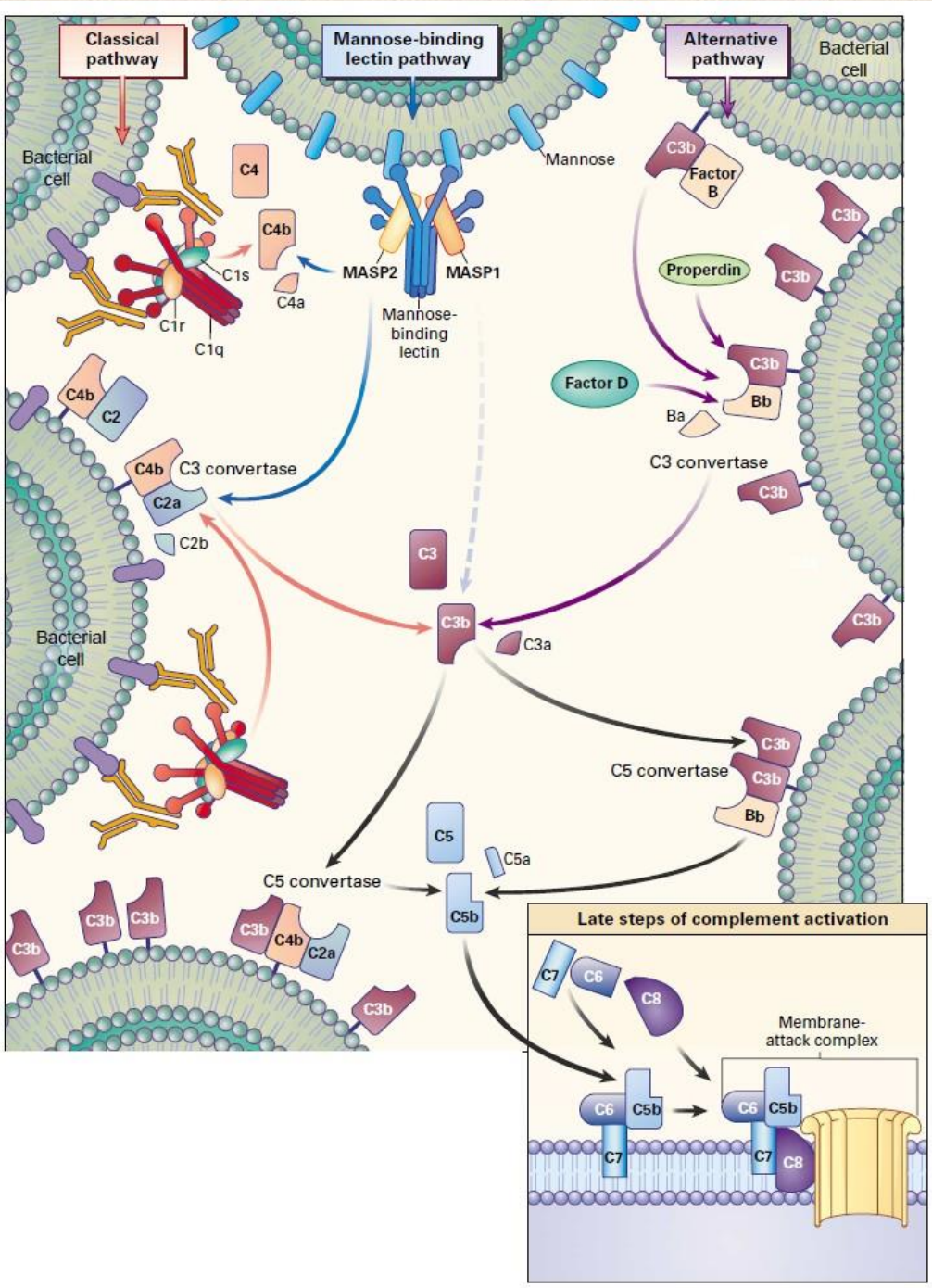
Innate	Natural	Adaptive
TLRs Heat shock proteins Complement	Invariant TcRs (both γδ and αβ) Natural (auto) antibodies	Immunoglobulins BcR TcR MHC I and MHC II



Toll Like Receptors (TLR) recognize molecular patterns associated with a broad range of lipid-based cell wall components on pathogens including bacteria, fungi, protozoa and viruses.



Heat shock proteins (Hsp60, 70, 90, gp96) play important role in antigen presentation, activation of macrophages, lymphocytes and dendritic cells. As part of their molecular chaperone functions play role in antigen presentation by MHC molecules.



Complement system

The complement system is a part of the immune system that enhances (complements) the ability of antibodies and phagocytic cells to clear pathogens from an organism. It is part of the innate immune system, which is not adaptable and does not change over the course of an individual's lifetime. However, it can be recruited and brought into action by the adaptive immune system.

Recognition molecules in the adaptive immune system

Immunoglobulins
B cell receptors (BcR)
T cell receptors (TcR)
MHC class I and class II

Special molecules manage antigen recognition. Domain structure is a common structural feature of these molecules. Well conserved (constant) basic elements and variable elements containing antigen-specific parts (binding sites) build up these molecules. The variable elements are involved in antigen recognition and ligand formation. The constant parts direct the immune reaction.

Antigen recognition in adaptive immunity

Native antigens are recognized by immunoglobulins or B cell receptors.

T cells can recognize exclusively in denatured (presented) forms of the antigens.

Antigén felismerés az adaptív immunválaszban

A natív antigéneket immunglobulinok vagy B-sejt receptorok ismerik fel.

A T-sejtek kizárólag az antigének denaturált (prezentált) formáit képesek felismerni.