Basic Immunology

Lecture 1st and 2nd

Introduction

Requirements of the Department.

Historical overview. Composition of the immune system.

Molecular components of the immune systemes

Immunological recognition in innate, adaptive, and natural immunity. Definition of the antigen. Molecular structures of immunoglobulins, T-cell and B-cell receptors.

Requirements and information

- **Lectures:** 14 hours (participation is obligatory, importance of the preparation of own lecture notes), no more abscences as 3!
- **Practices:** 14 hours laboratory practices & seminars.

No more absences as 3!

- **Bonus points:** Minimum requirement is 10 points for acceptance of semester. All points are plus 1 to the exam scores after the 10 basic points.
- Collection of extra points is available during seminars and lectures.

- **Examination:** written from the lectures and laboratory practices/seminars
- **Exam scores:** (minimum level: 66%) satisfactory 66-71%, average 72- 77%, good 78-83%, excellent 84%

www.immbio.hu

What is the *immunity*?

What is the immune system?

- **The immune system is a complex 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.**

Basic terms

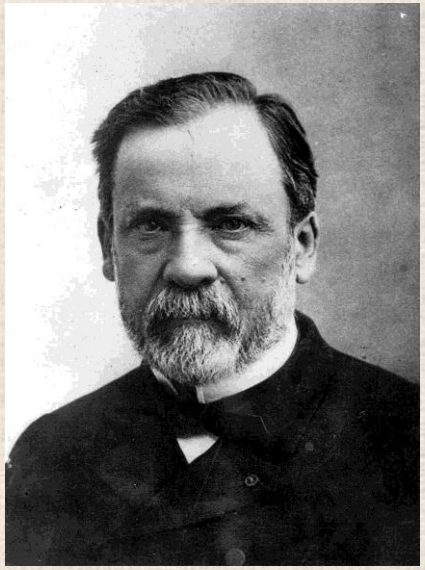
- **Immunis,- e** (*Julius Caesar*) = exempt, free of burden (E.g. tax, law, or diseases)
- **IMMUNE:** individuals who do not capitulate to a disease when infected;
- **IMMUNITY:** status of **specific** resistance to a disease;
- **IMMUNOLOGY:** branch of theoretical biology focuses on mechanisms responsible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

History

- Athen (B.C. 5th century Thukidites - plaque survivors), 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)

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.

Immune system

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

Structural and functional network

Composition of the immune system

Innate

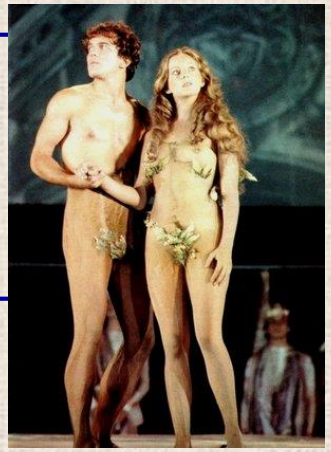
- None antigen specific
- No immunological memory
- Rapid reactivity
- Linear amplification of the reaction

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**

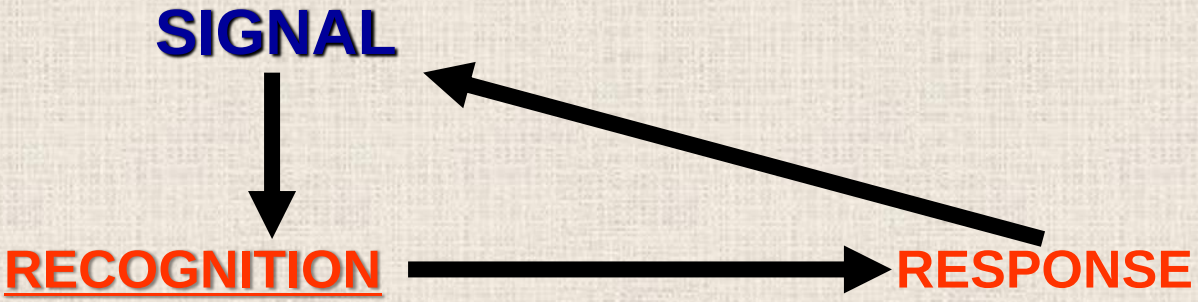
Adaptive immune system

- Antigen receptor (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

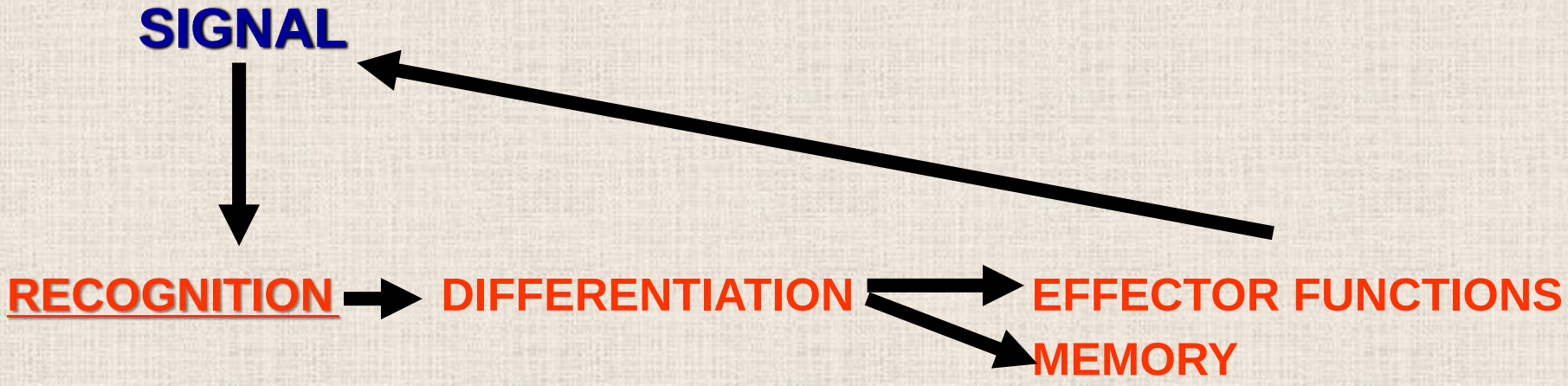
Natural immune system

- **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 molcelar components: natural (auto)antibodies**

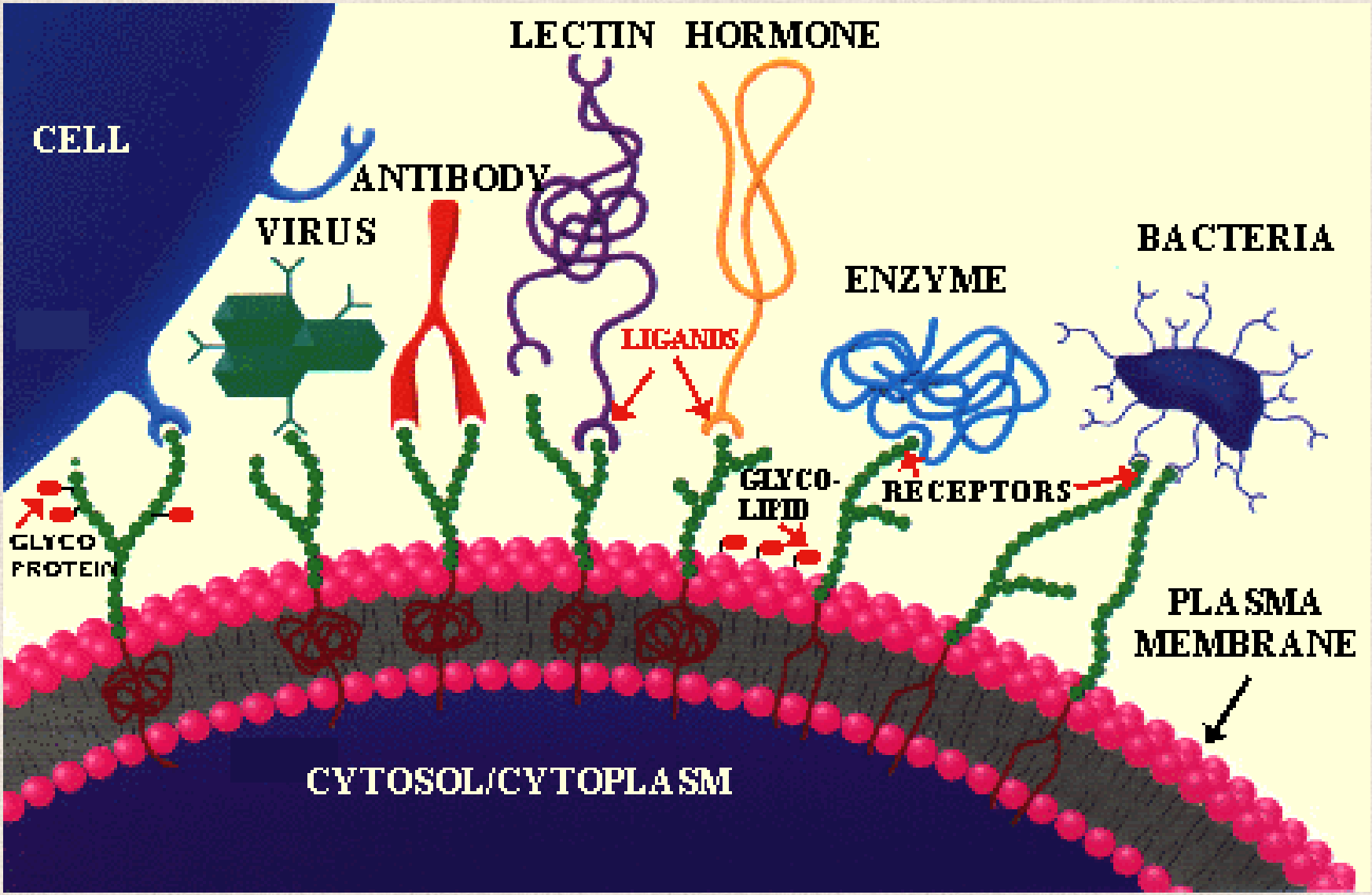
Theoretical scheme of the innate and natural immunity



Theoretical scheme of the adaptive immunity



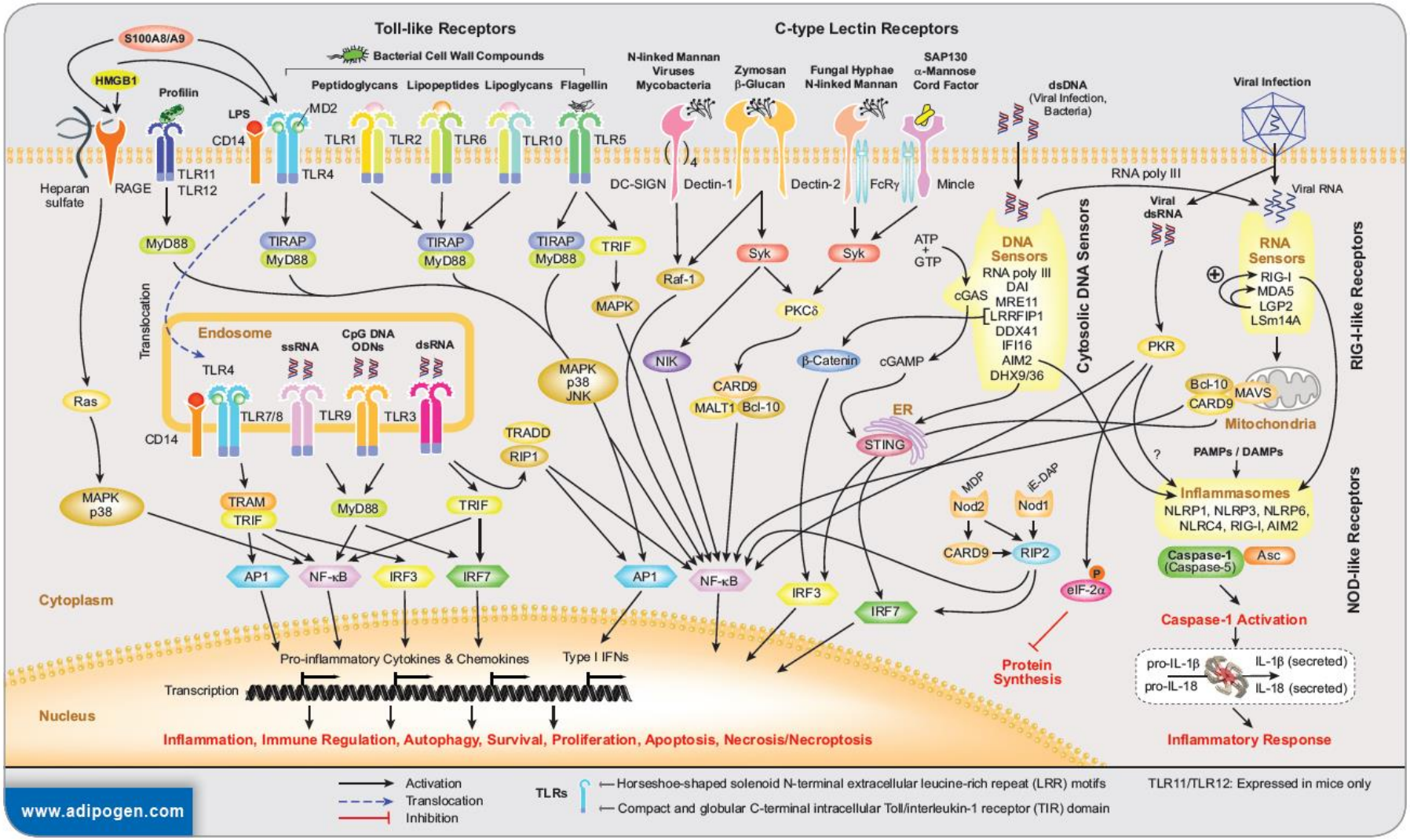
Molecular recognition



Pattern Recognition Receptors (PRRs) Signaling Pathways

Adipogen International
Schützenstrasse 12 · CH-4410 Liestal · Switzerland
TEL: +41-61-926-60-40 · FAX: +41-61-926-60-49
E-Mail: info@adipogen.com · www.adipogen.com

AdipoGen®
Connecting Immunology to Metabolism™



www.adipogen.com

NOV 2013

Macrophages express receptors for many microbial constituents

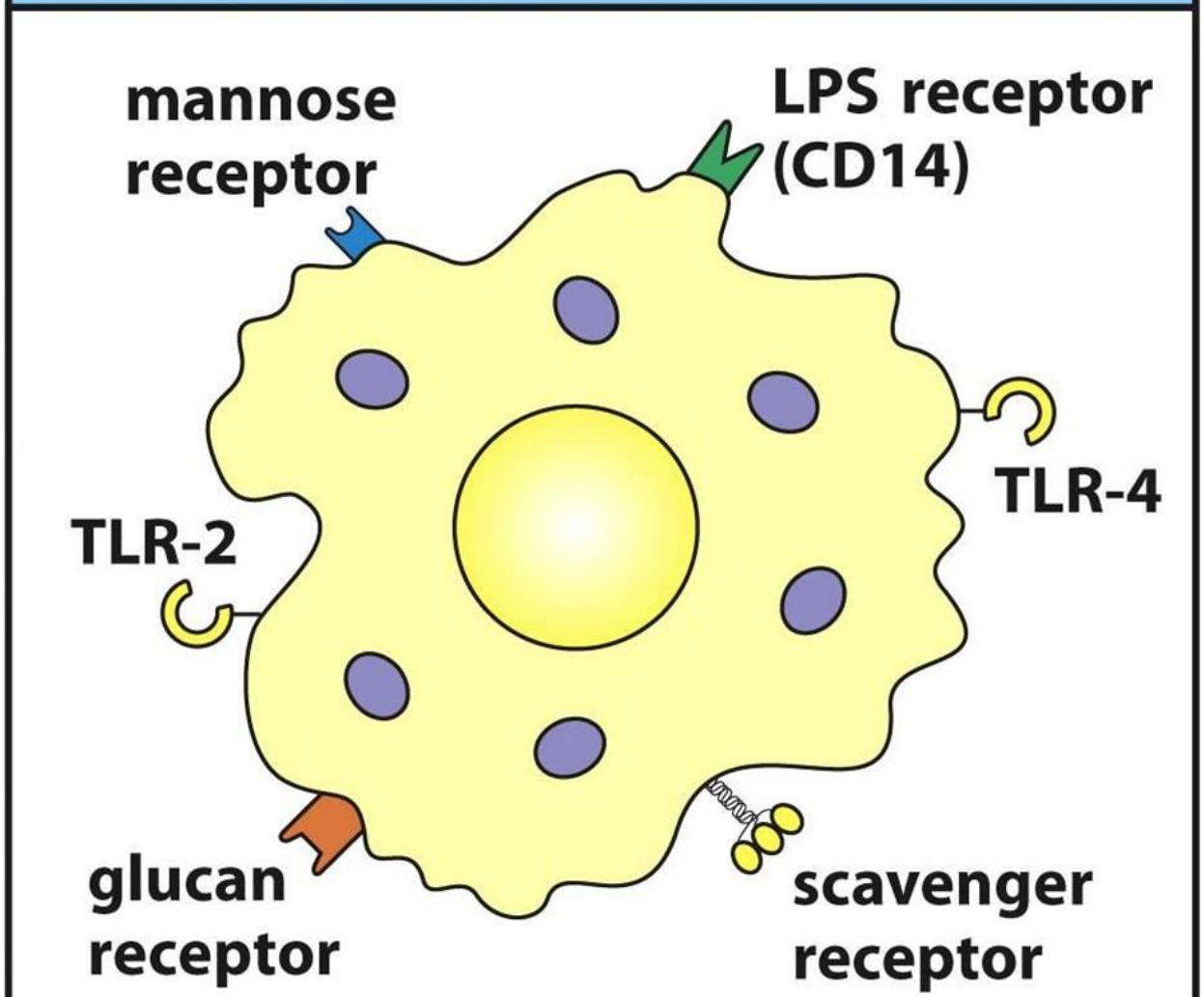
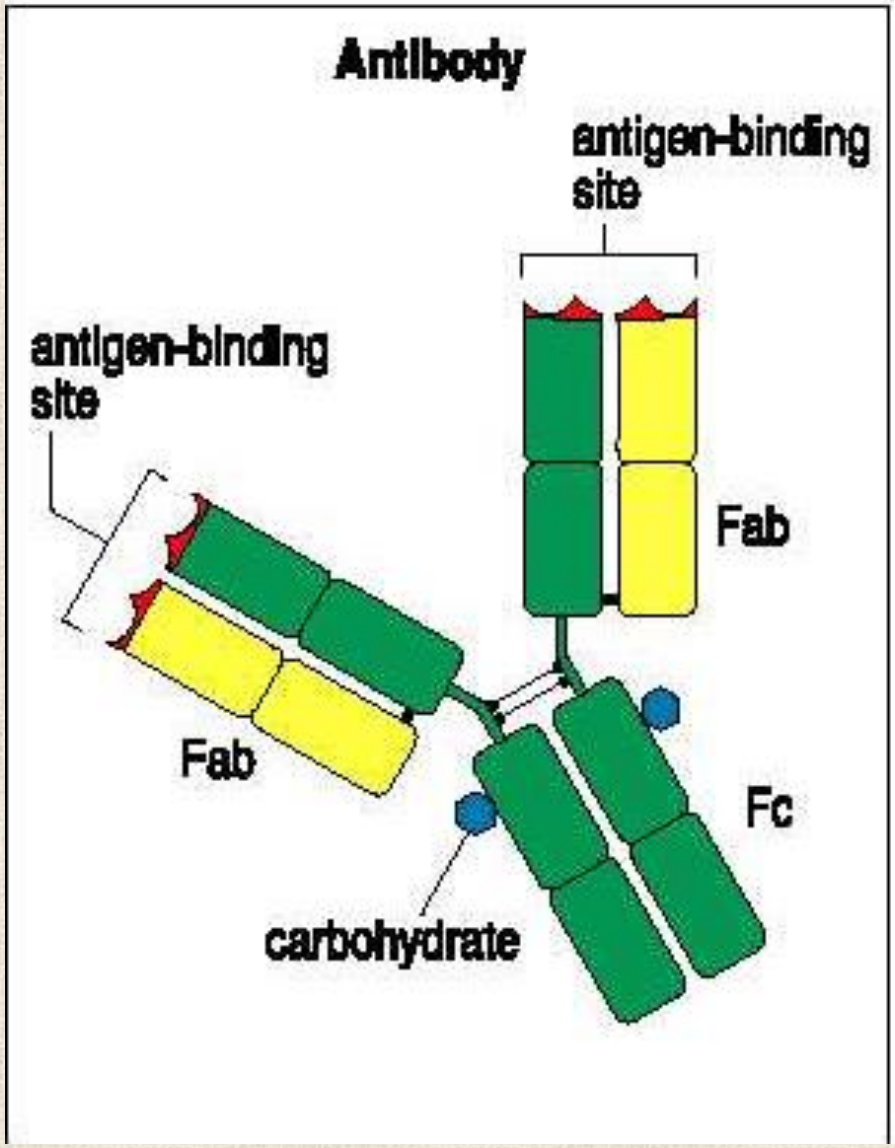
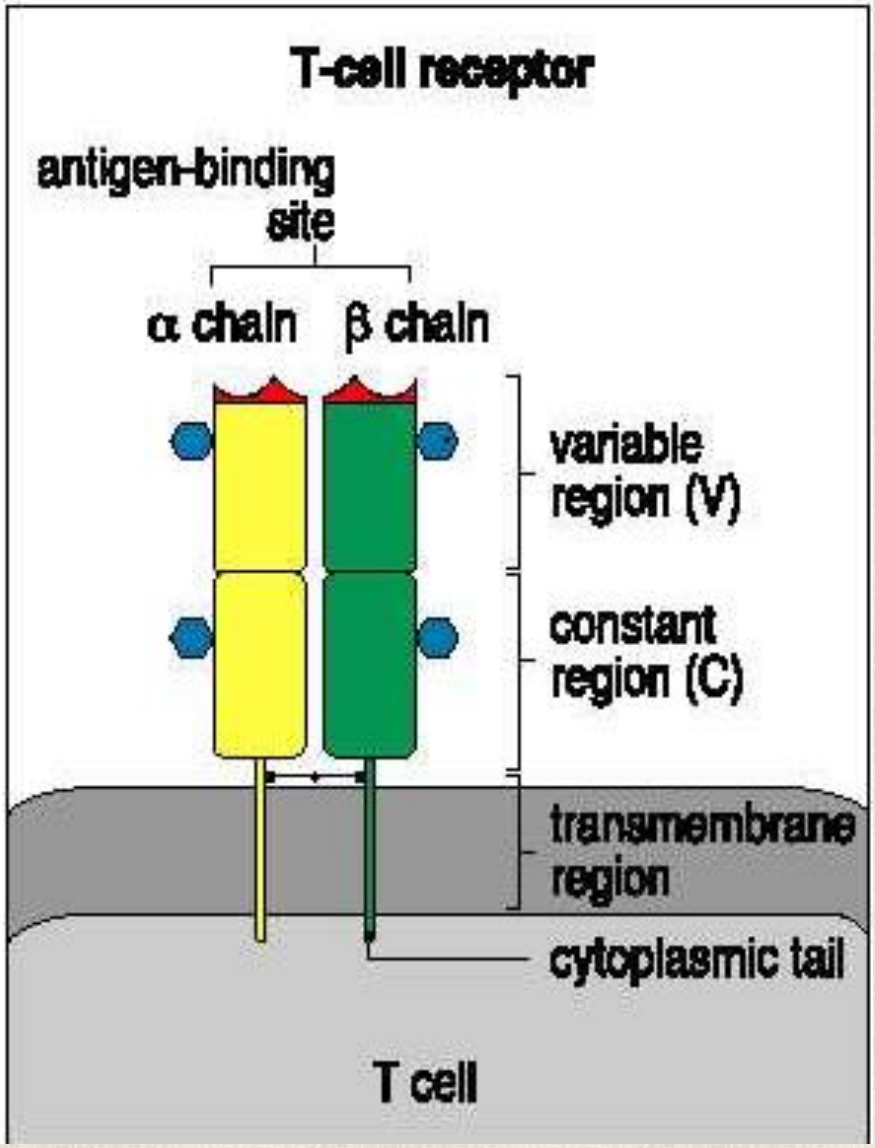


Figure 1.10 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Antigen specific recognition molecules





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 T cell 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

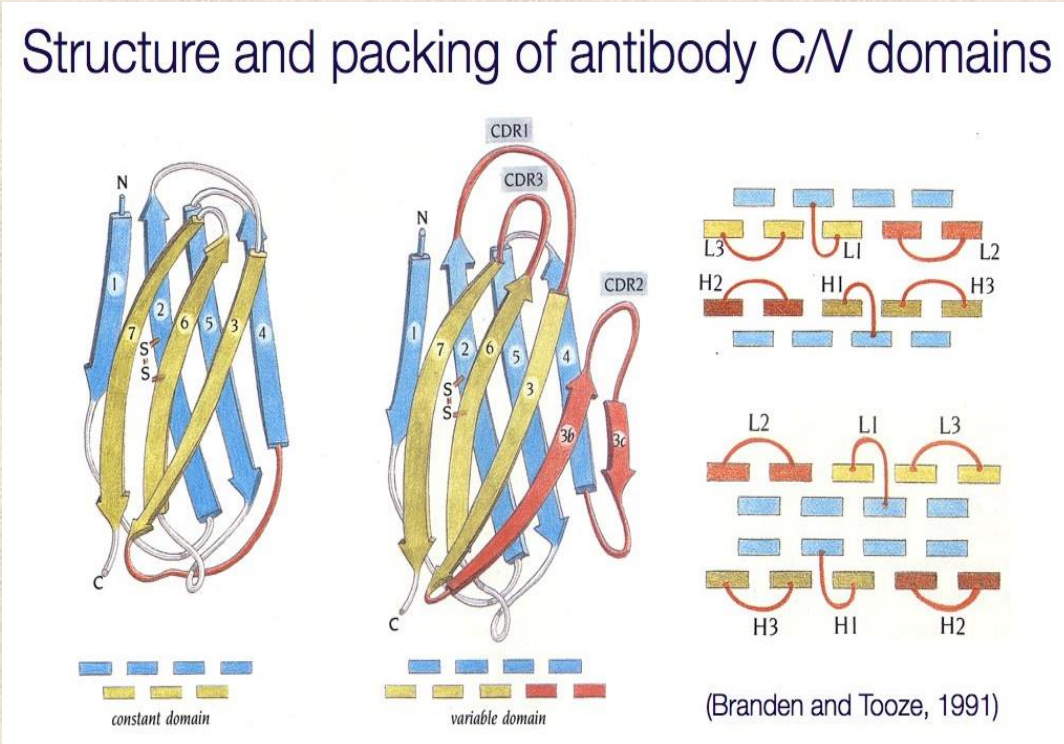
- **immunodominant regions**
- **chemical structure** (inorganic molecules are not antigens at general, but e.g. heavy metals in protein complex are able to induce specific metal allergies). The best antigens are proteins>polypeptides>polysaccharides>lipides>nucleic acids
- **physico-chemical nature** (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

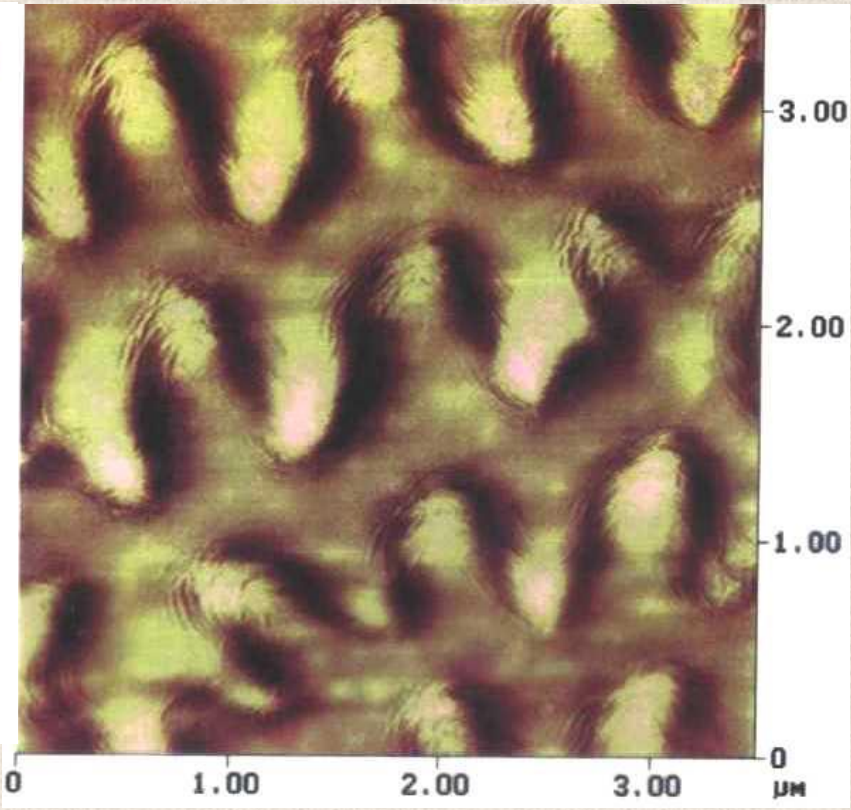
Recognition molecules in the adaptive immune system

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

Specialized molecules manage antigen recognition. The common structural features of these molecules are the well-conserved (constant) basic elements (designed by **110 amino acids domain units**) containing variable, antigen specific parts (binding sites) for the recognition and ligand formation.

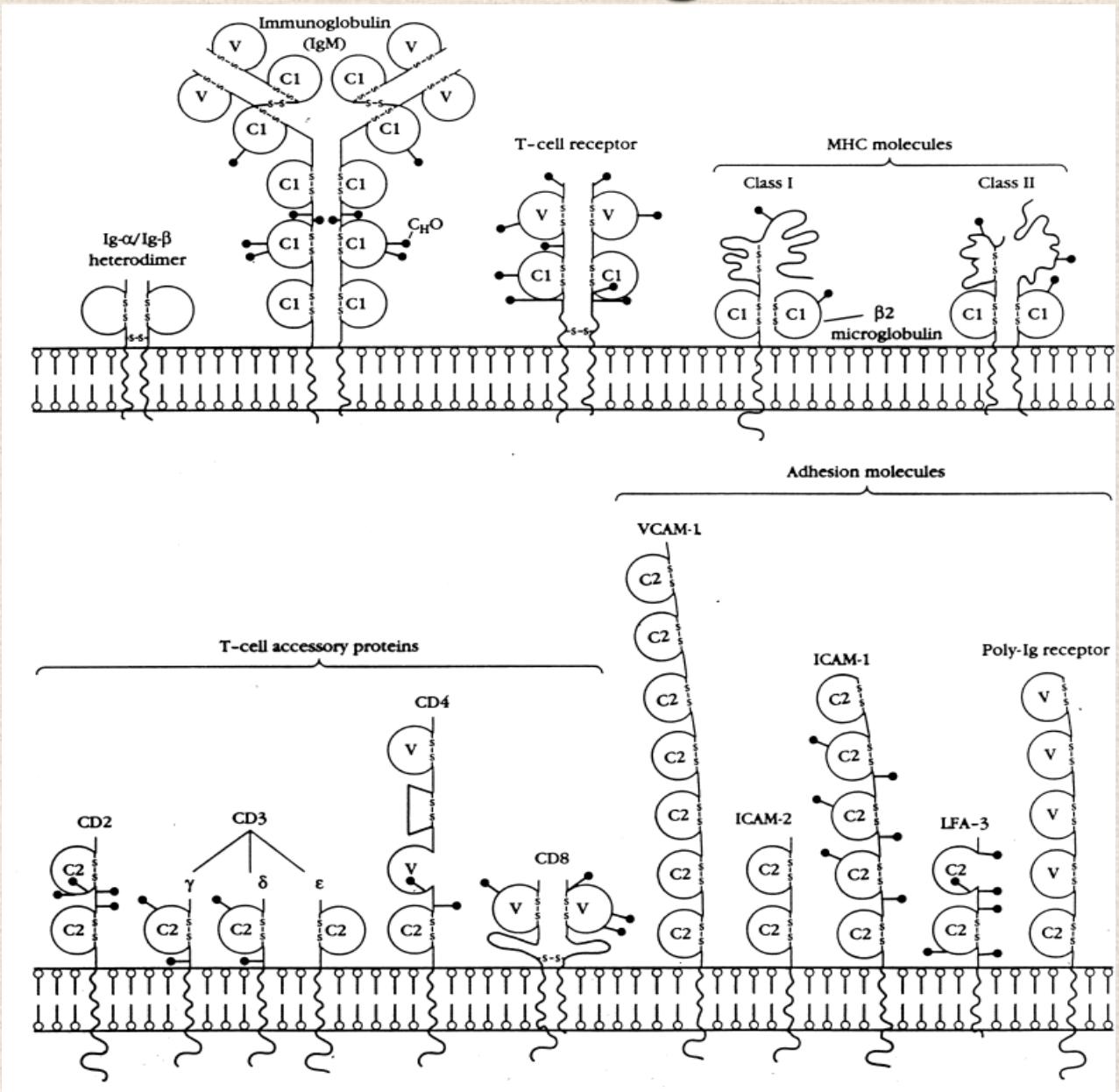
Domain structure





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

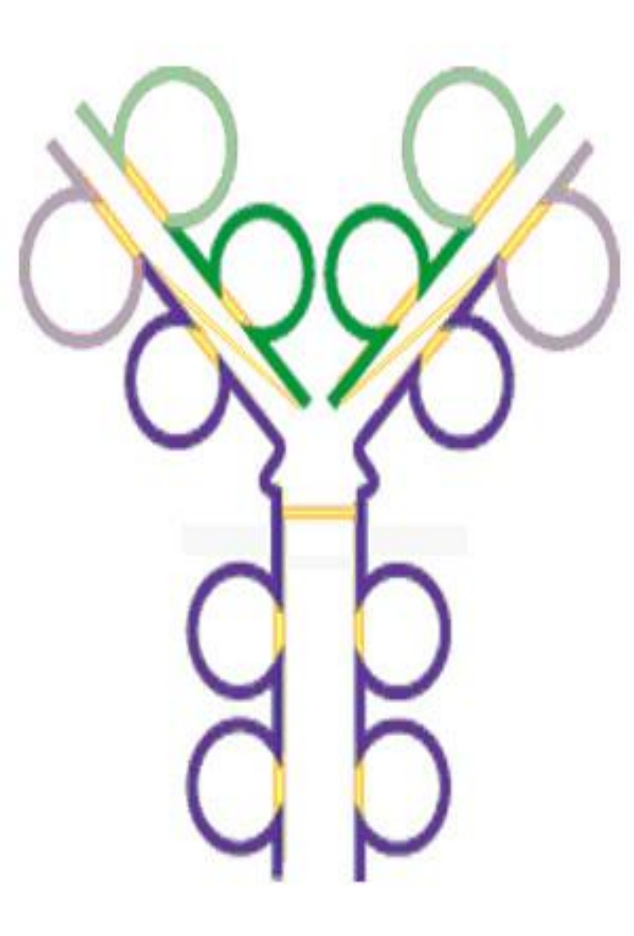
Immune recognition molecules



Antigen specific recognition molceules

Accessory molecules of cell-cell communication

Immunoglobulin molecule



CDR

Variable region

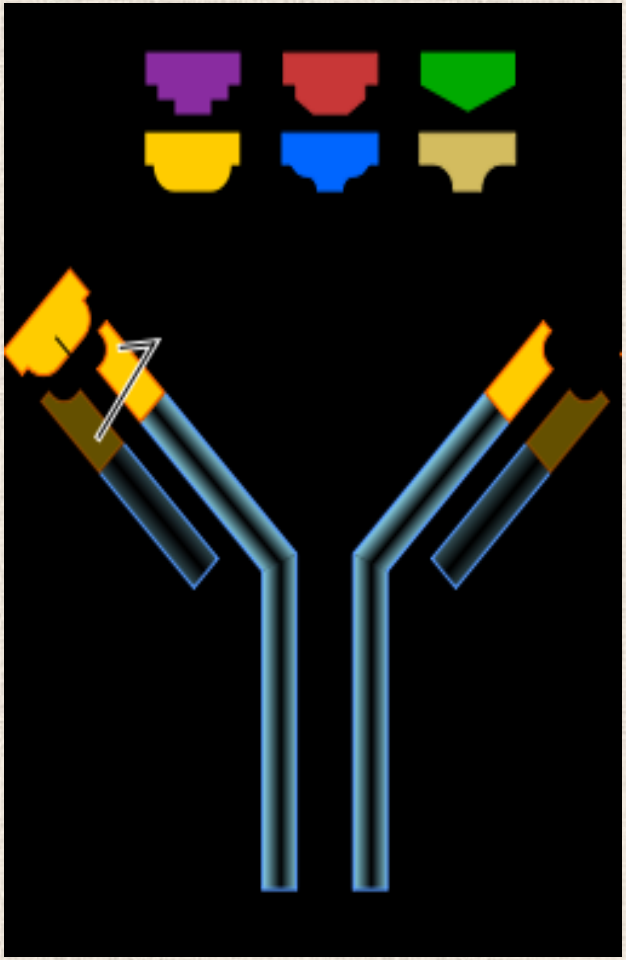
Idiotype

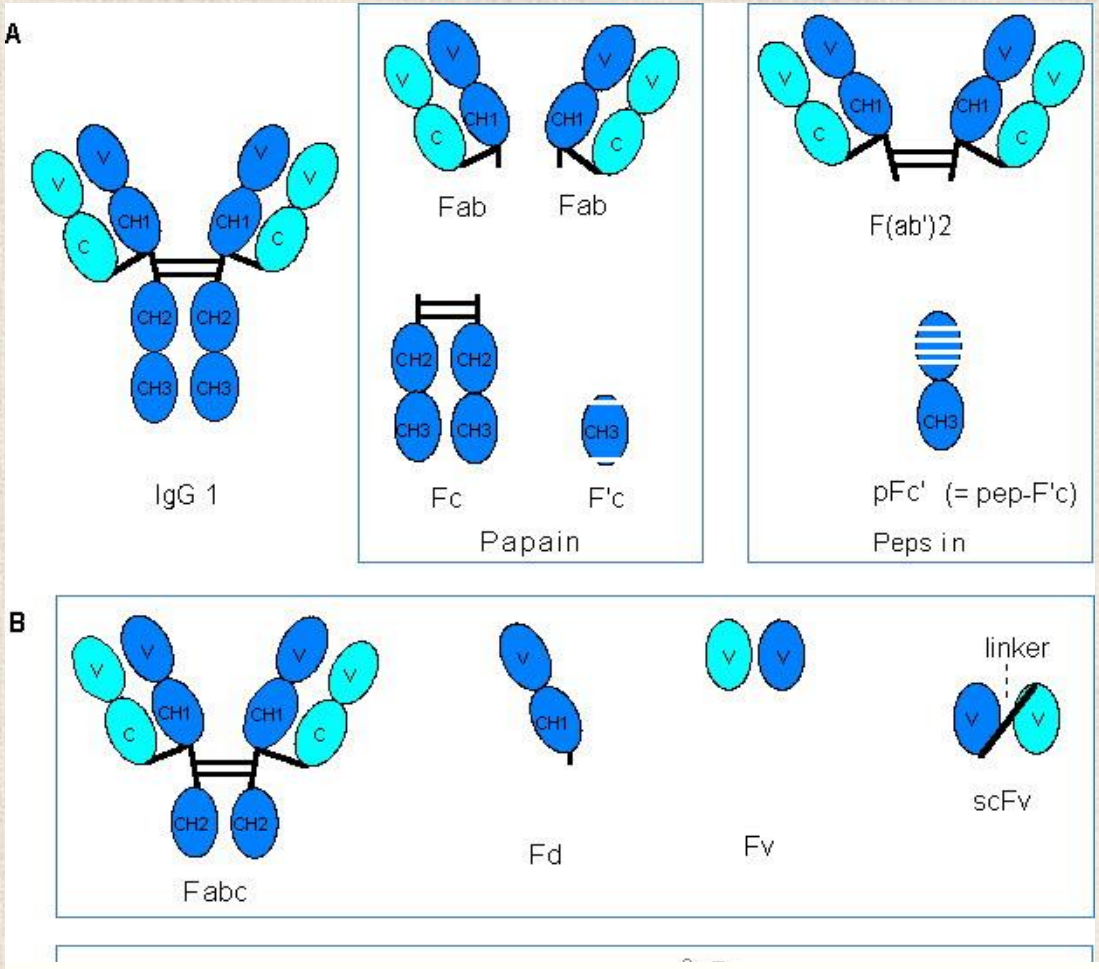
Fab fragment

Constant region

Isotype

Fc fragment





Ig domains: intra-chain disulphide bonds form loops in the peptide chain, the loops are globular, constructed from beta-plated sheets and beta-turn loops.

Immunoglobulins

Monofunctional character (specific antigen recognition and binding) ***before*** the antigen administration. **Fab** dependent function.

Polyfunctional character ***after*** the antigen administration (signal transduction, complement fixation, opsonization, immunocomplex formation, FcR binding, etc). **Fc** dependent functions.

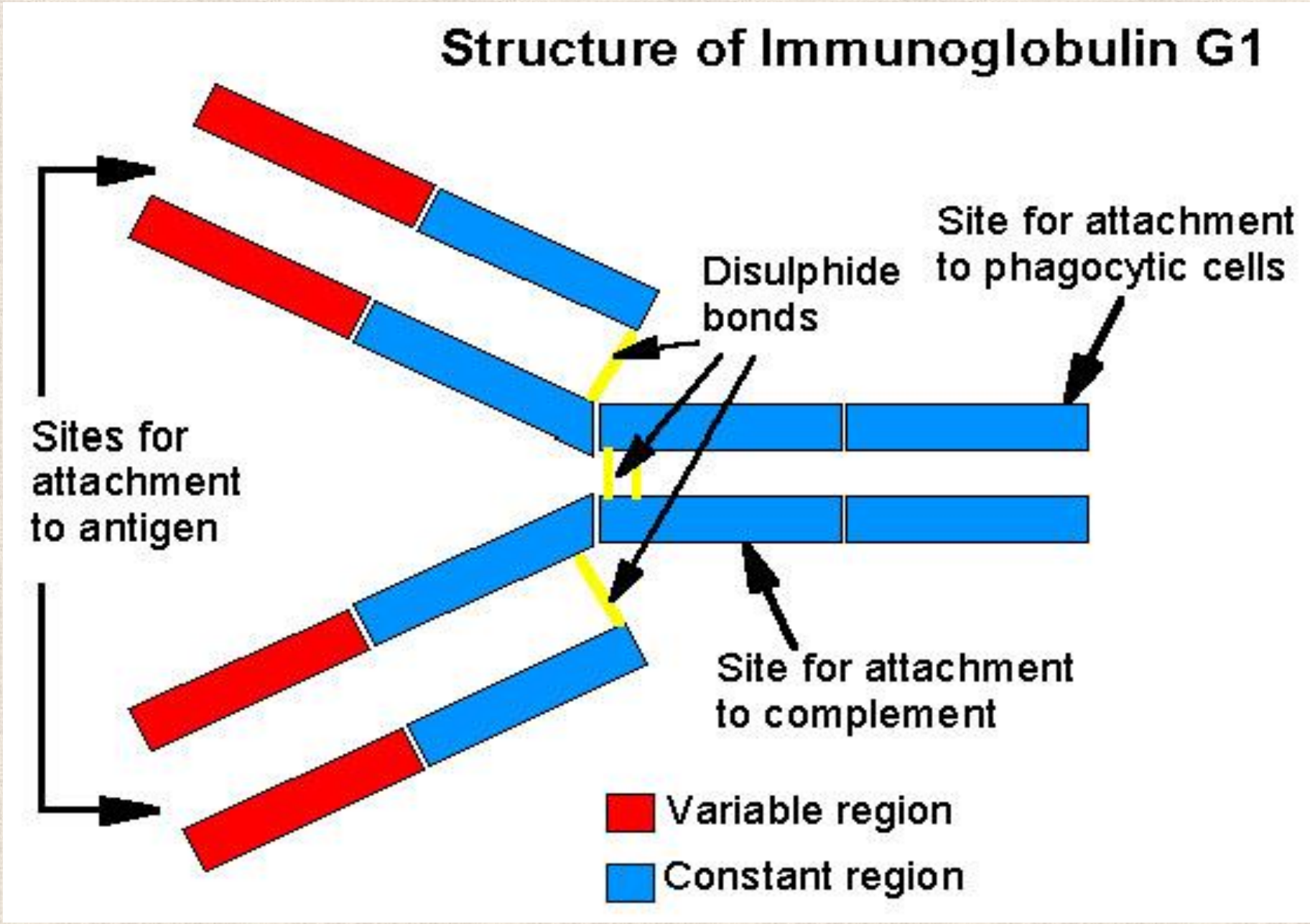
Immunoglobulin isotypes

- Based upon the constant structures of heavy **(H)** and light **(L)** chains
- **CH isotypes:** called Ig classes and subclasses as **IgG, IgM, IgA, IgD** and **IgE**. All classes are represented in a normal serum (except the membrane bound IgD) as isotype variants.
- **CL** chain exists in two **isotypic forms:** kappa **(κ)** and lambda **(λ),** which can associate with all heavy chain isotypes.

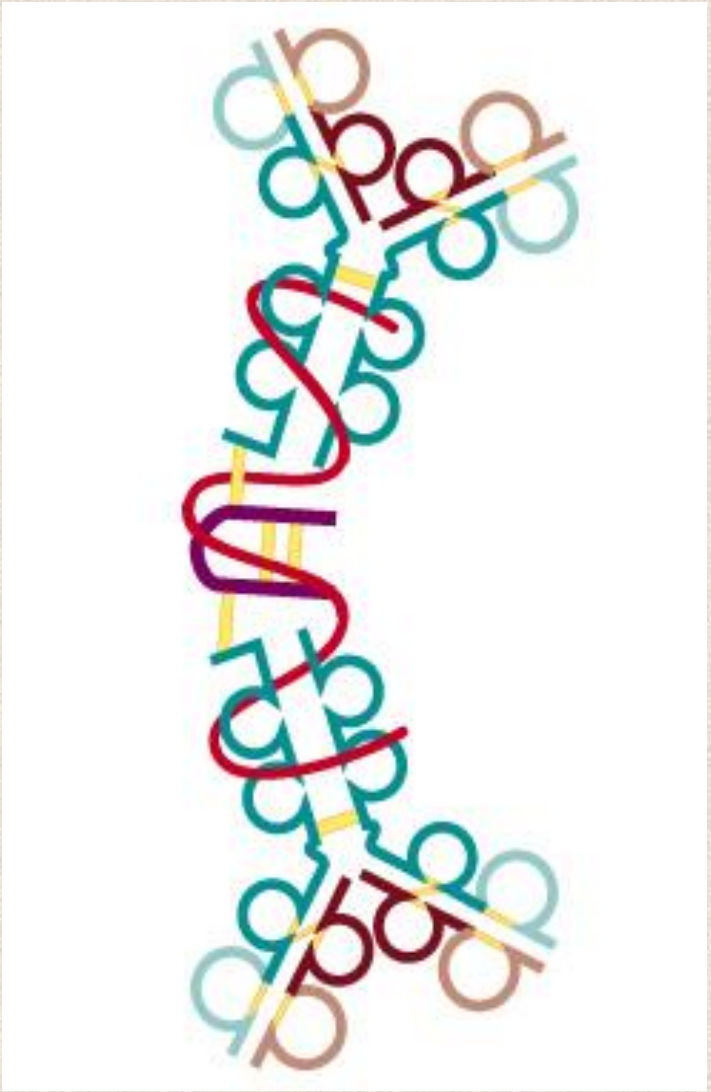
Heavy chain	Light chain	Immuno-globulin Class	Immuno-globulin Subclass
γ1	κ or λ	IgG	IgG1
γ2	κ or λ		IgG2
γ3	κ or λ		IgG3
γ4	κ or λ		IgG4
α1	κ or λ	IgA	IgA1
α2	κ or λ		IgA2
μ	κ or λ	IgM	
δ	κ or λ	IgD	
ε	κ or λ	IgE	

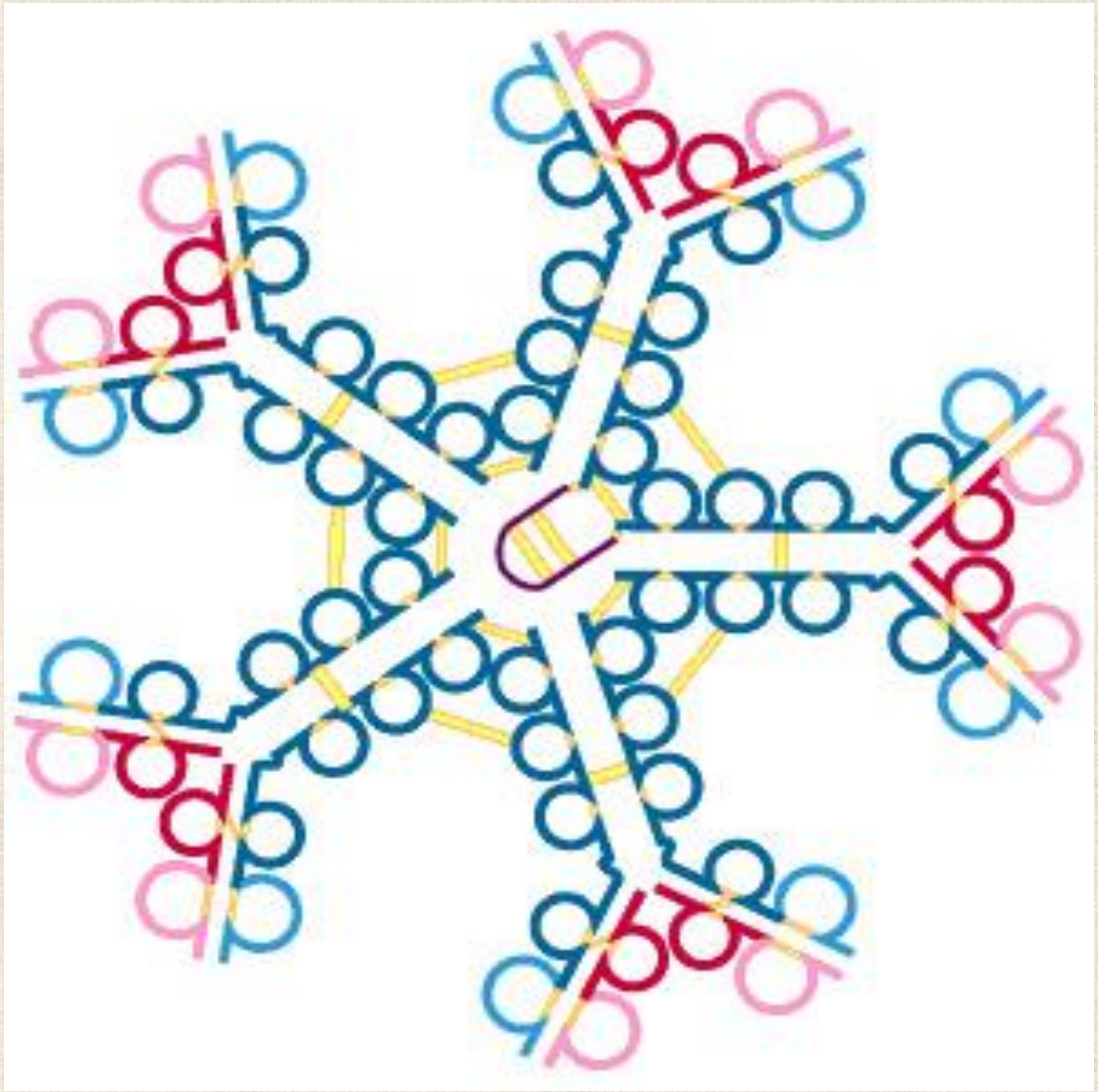
Pronunciation of Greek letters:

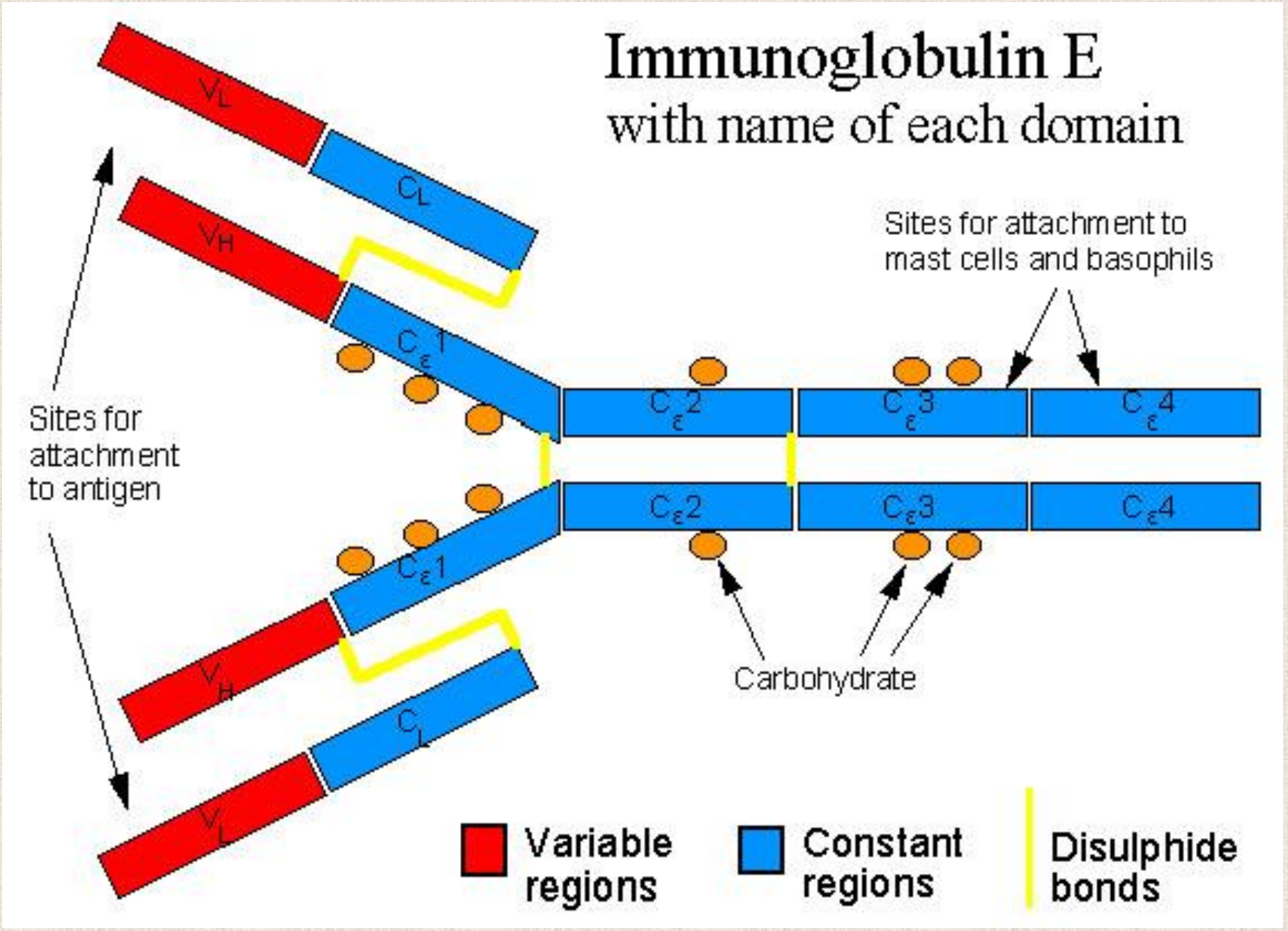
γ gamma α alpha μ mu δ delta
ε epsilon κ kappa λ lambda

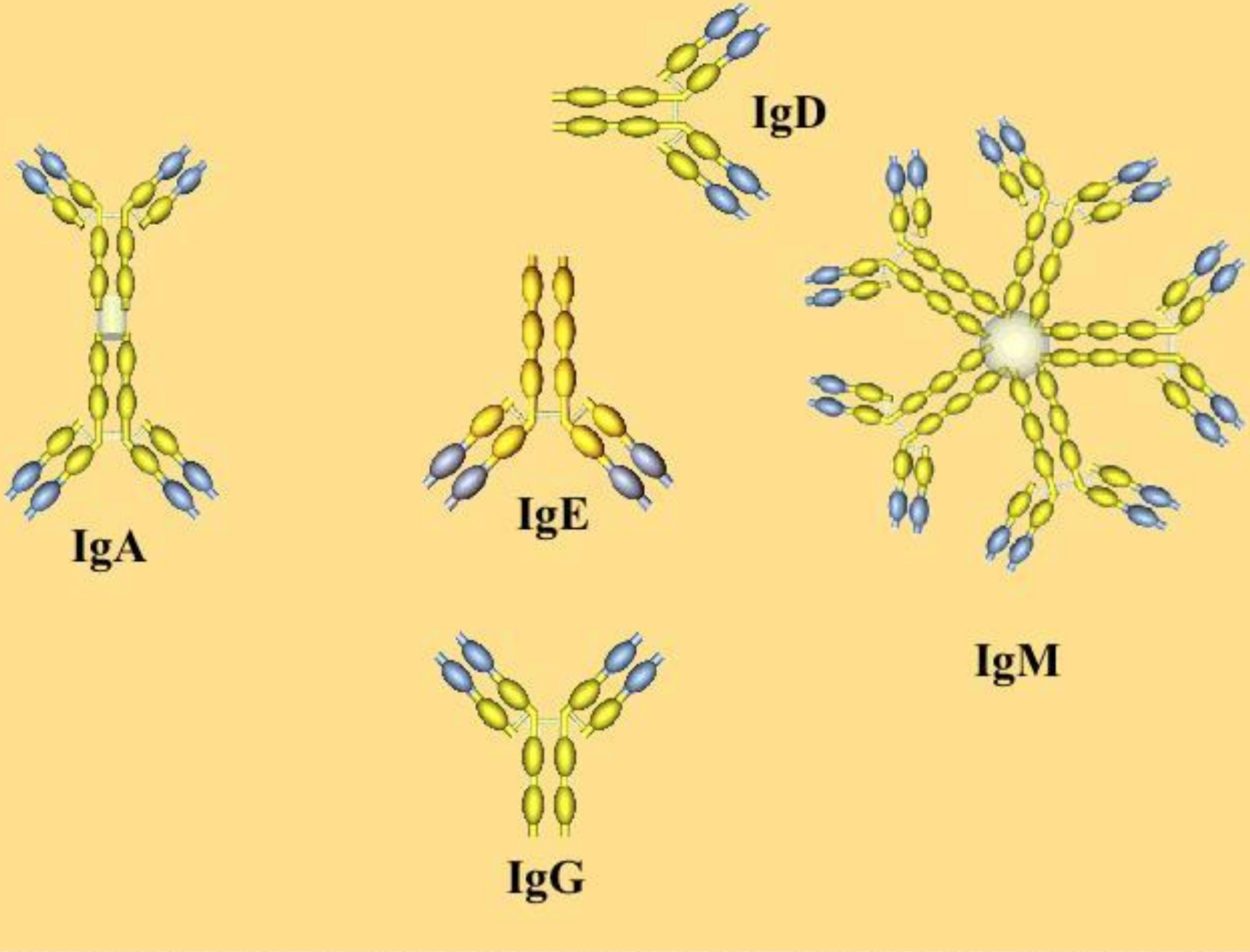

Structure of Immunoglobulin G1
Site for attachment to phagocytic cells
Disulphide bonds
Sites for attachment to antigen
Site for attachment to complement
Variable region
Constant region

IgA and IgM

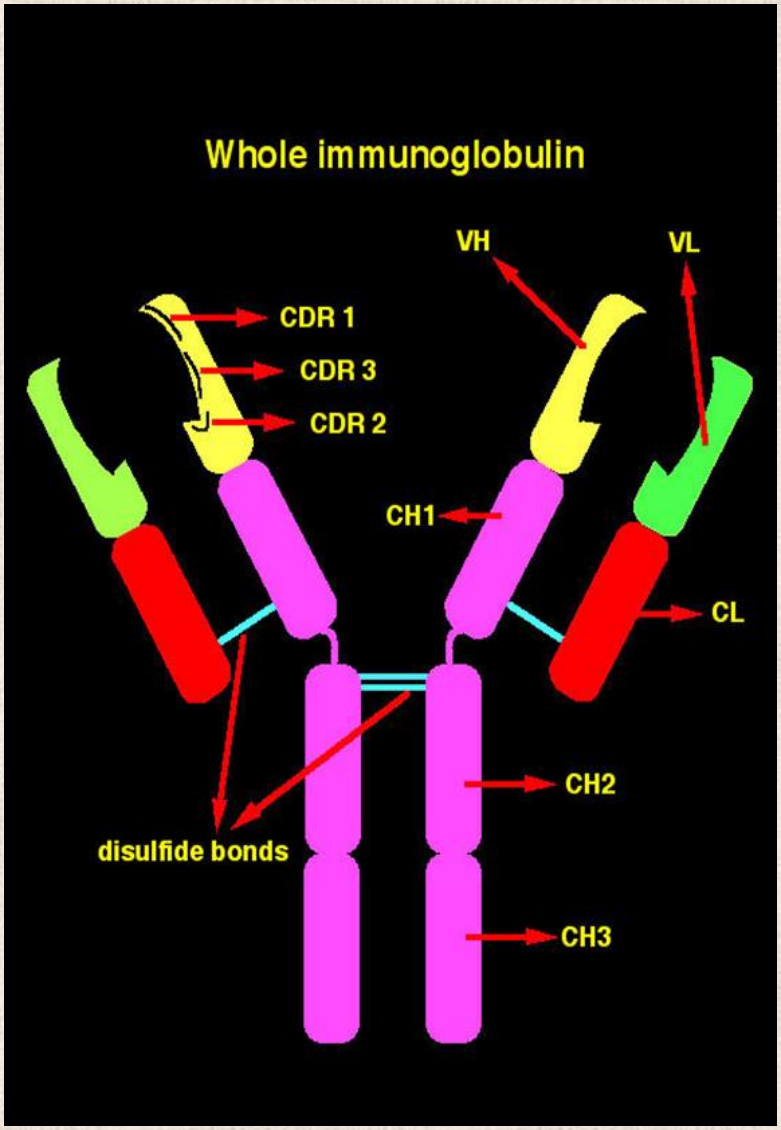





Immunoglobulin E
with name of each domain
V_L
C_L
V_H
$C_\varepsilon 1$
Sites for attachment to mast cells and basophils
$C_\varepsilon 2$
$C_\varepsilon 3$
$C_\varepsilon 4$
Sites for attachment to antigen
$C_\varepsilon 2$
$C_\varepsilon 3$
$C_\varepsilon 4$
$C_\varepsilon 1$
V_H
C_L
V_L
Carbohydrate
Variable regions
Constant regions
Disulphide bonds

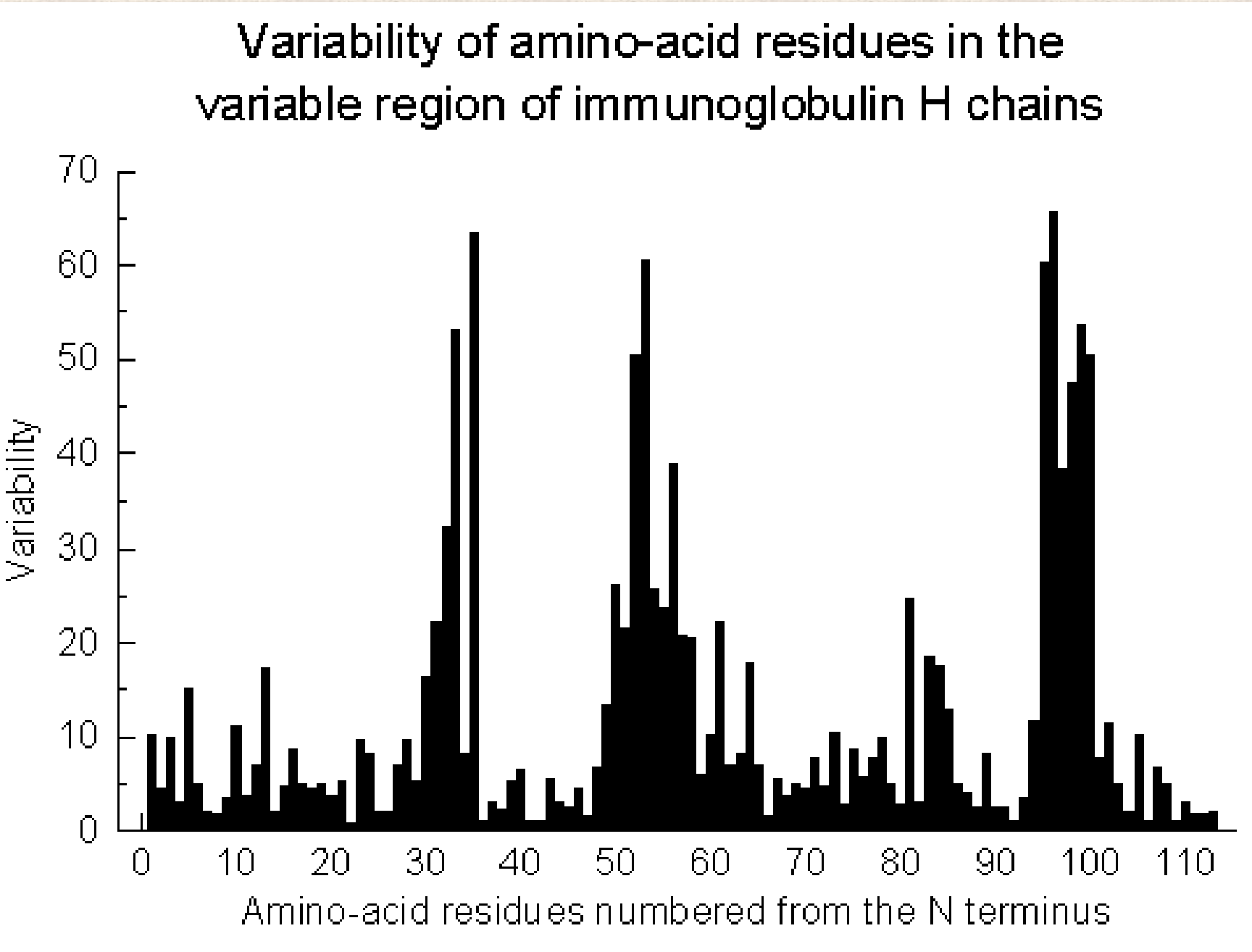

IgD
IgA
IgE
IgM
IgG

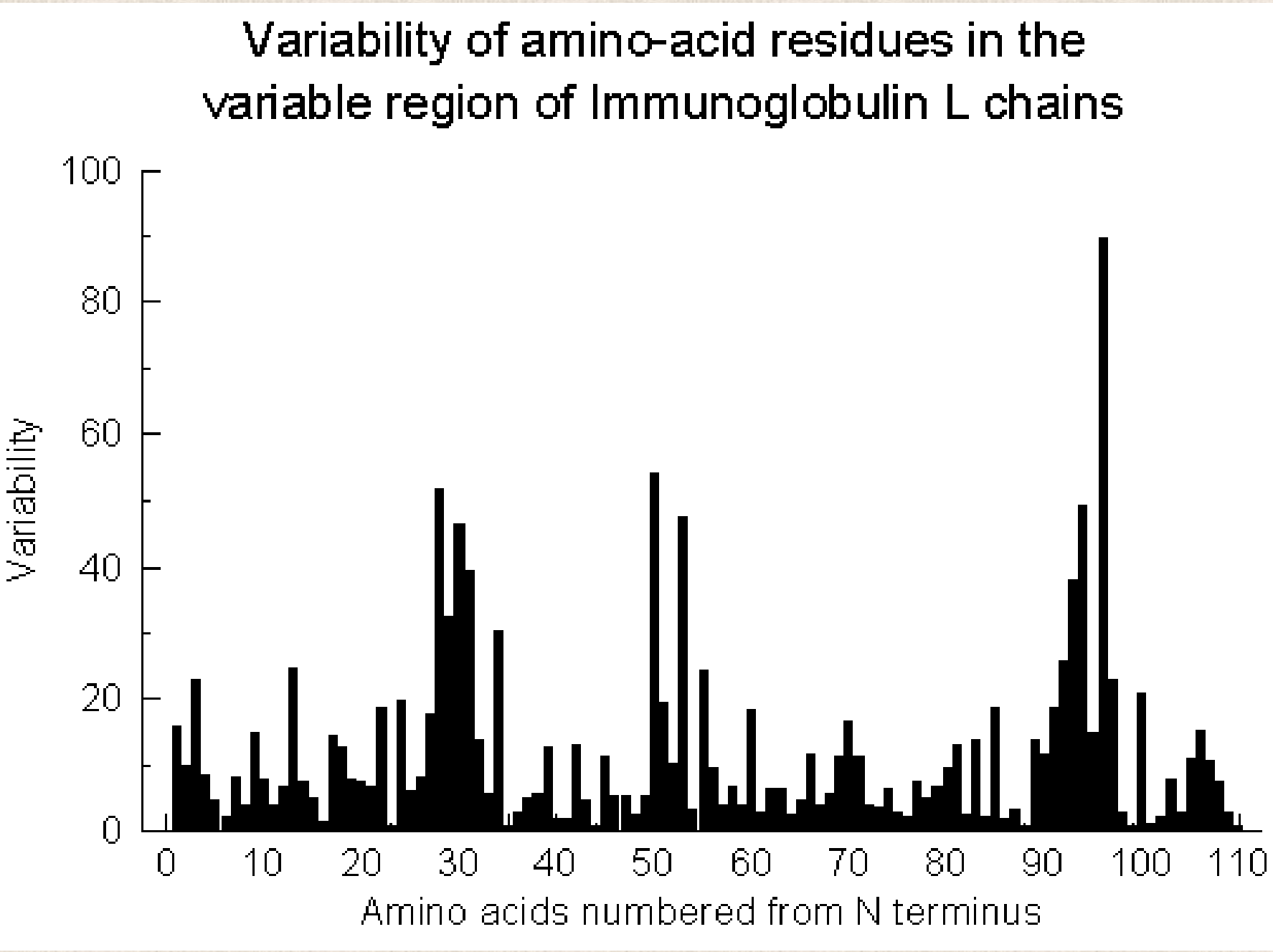
Immunoglobulin idiotype



Individual determinants in **V regions**, specific for each antibody.

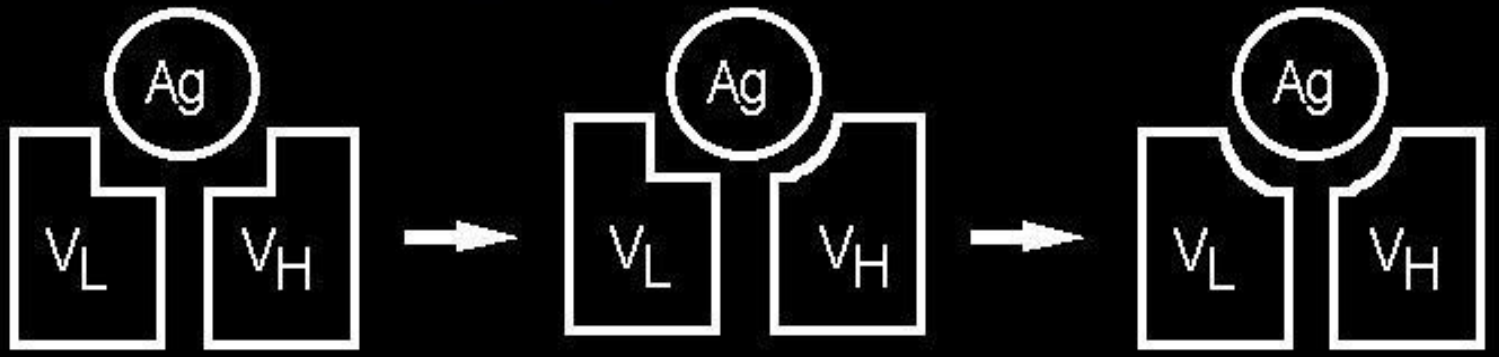
The N terminal Ig domain contains V region forming the antigen binding site: clustering the 3 hyper variable sequences close to each other on both chains - the variation of 3 x 3 results tremendous diversity.

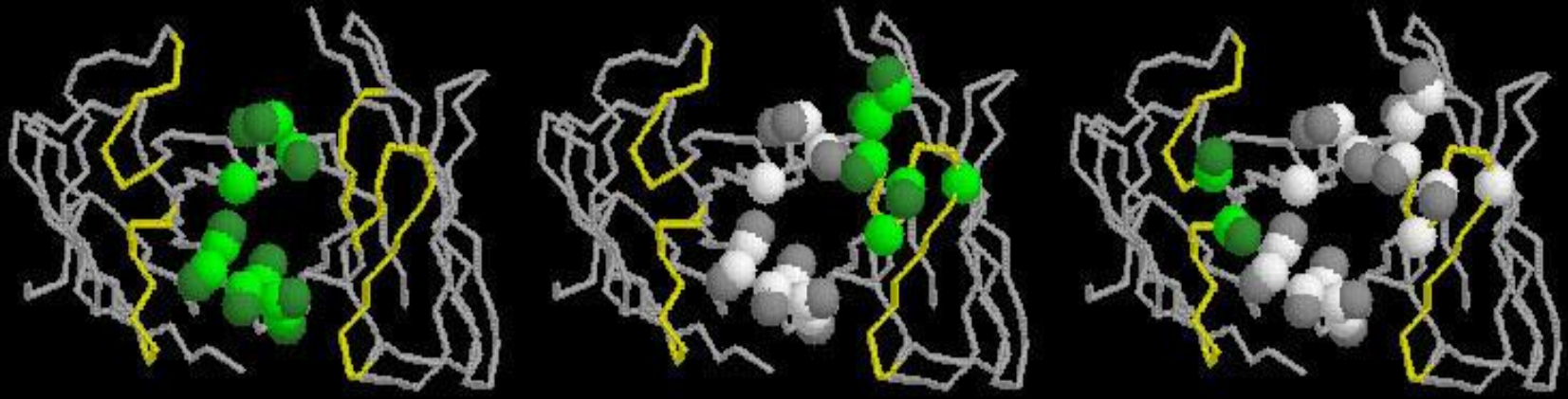

Variability of amino-acid residues in the variable region of immunoglobulin H chains
Variability
0
10
20
30
40
50
60
70
0
10
20
30
40
50
60
70
80
90
100
110
Amino-acid residues numbered from the N terminus


Variability of amino-acid residues in the variable region of Immunoglobulin L chains
Variability
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
90
100
110
Amino acids numbered from N terminus

Antibody affinity maturation

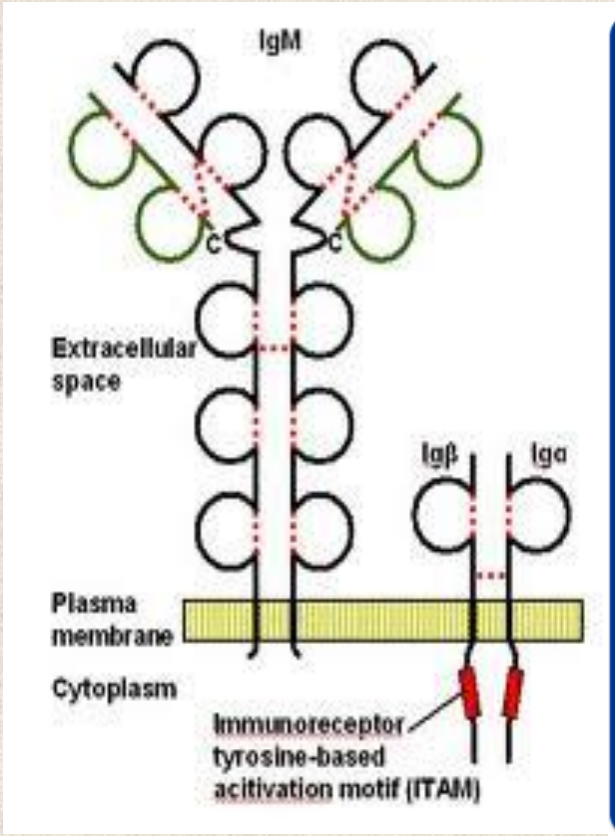
Pini et al. (1998) J. Biol. Chem. *273, 21769-21776*

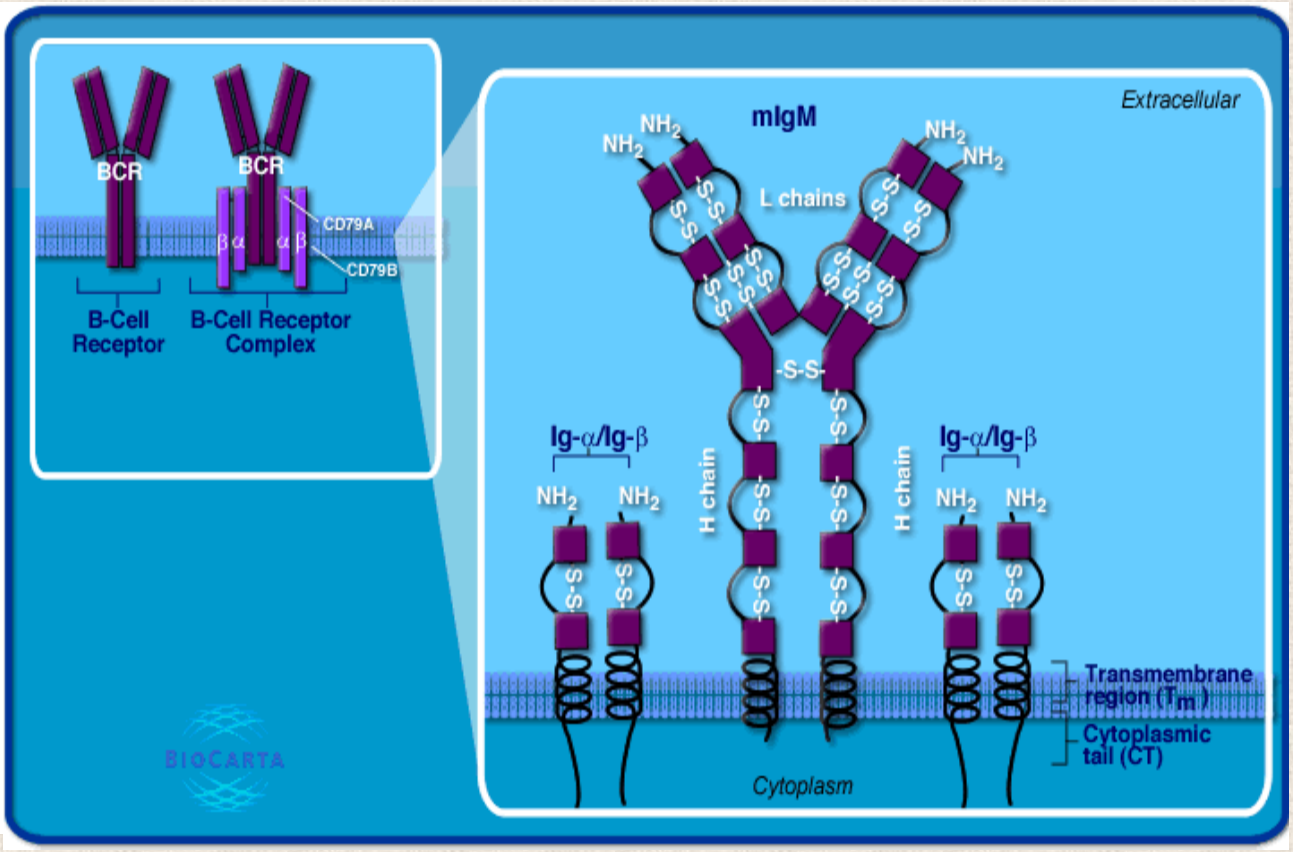




1st library 2nd library 3rd library

B cell Receptor (BcR) Complex





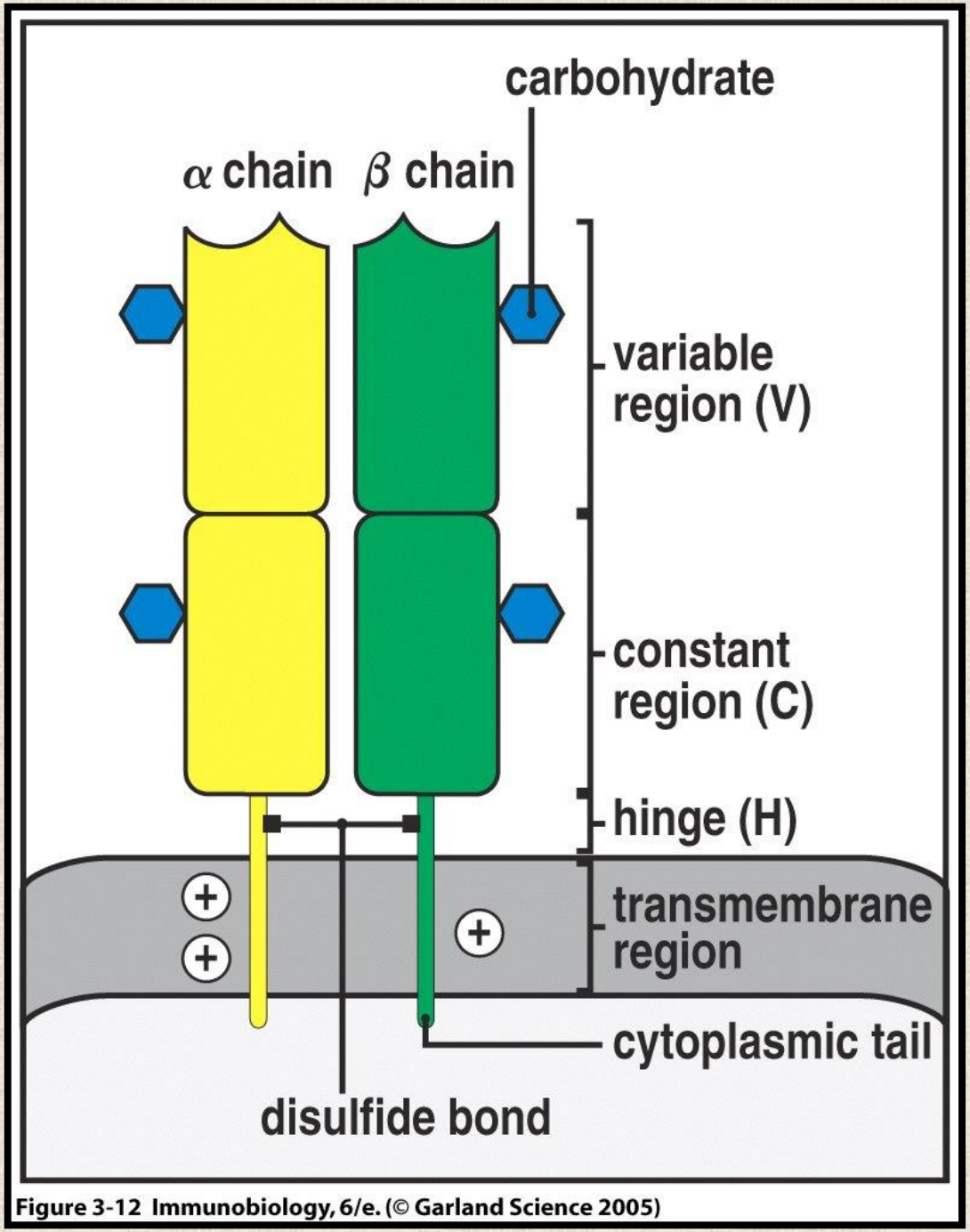


Figure 3-12 Immunobiology, 6/e. (© Garland Science 2005)

T Cell receptor

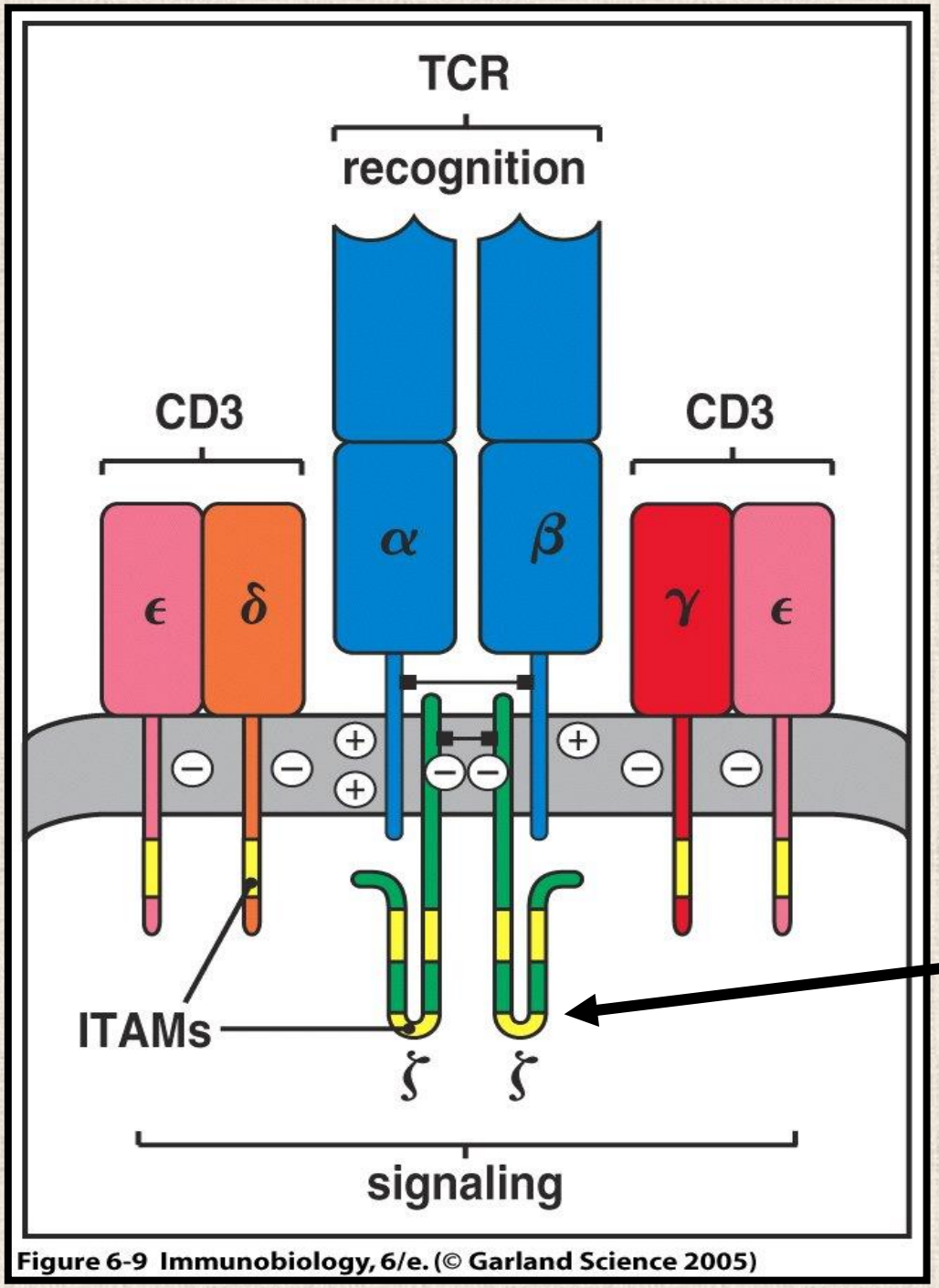


Figure 6-9 Immunobiology, 6/e. (© Garland Science 2005)

T Cell Receptor complex

ITAMs
Immunoreceptor
Tyrosine-based
Activation
Motifs