Basic Immunology

Lecture 3rd-4th

Molecular components of immunological recognition.

Definition of the antigen. Antibodies, T- and B-cell receptors: molecular structure, functions, subcalsses

Definition of the antigen

László Detre (Detsch) : **anti**body **gen**erator

- Old definition: foreign agent induces immune reaction
- Internationally accepted definition: substance recognized by T- or B-cell receptor and induces tolerating or active type immune response according to the MHC haplotype of the individual.
- Generally all materials are antigen recognized by the immune system and initiates targeting or tolerating type immune response.

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

Basic terms

immunogen (fine chemical structure can induce specific immune response)
epitope (antigen determinant) well circumscribed region of the antigen molecule targeted by Ig/BcR or TcR
paratop (ligand pair of the epitope)
hapten (small molecular weight antigen can not induce immune reaction itself, but specifically recognized by immunoglobulins)
carrier (indifferent, large molecular weight molecule, hold on the surface hapten molecules; carrier molecules did not participate in the anti-hapten immune reaction only hapten)

Antigen recognition

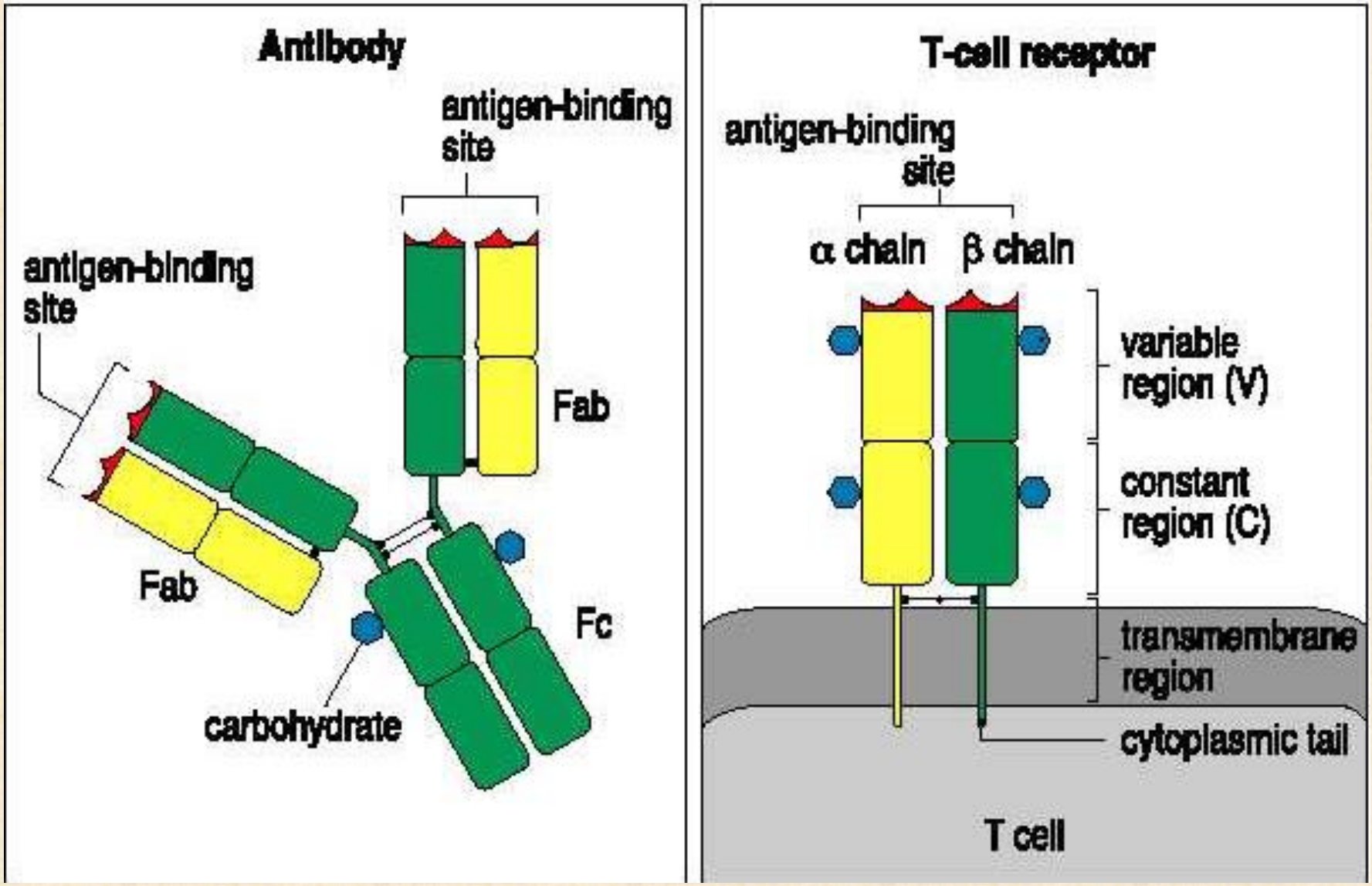
Innate immunity	Natural immunity	Acquired immunity
• Pattern recognition	• Pattern recognition	• Antigen recognition
• Mainly sugar recognition	• Mainly peptide patter recognition	• Mainly peptide pattern recognition
• PRR	• MHC	• MHC
• PAMP	• iTcR, γδTcR, BcR, IgM	• αβTcR, γδTcR, BcR, • IgM/G/A/E/D
• Low number of molecularly distinct receptors and high number of recognized patterns	• Limited number of molecularly distinct receptors and high number of recognized patterns	• High number of distinct antigen receptors and high number of specifically recognized antigens

Recognition molecules

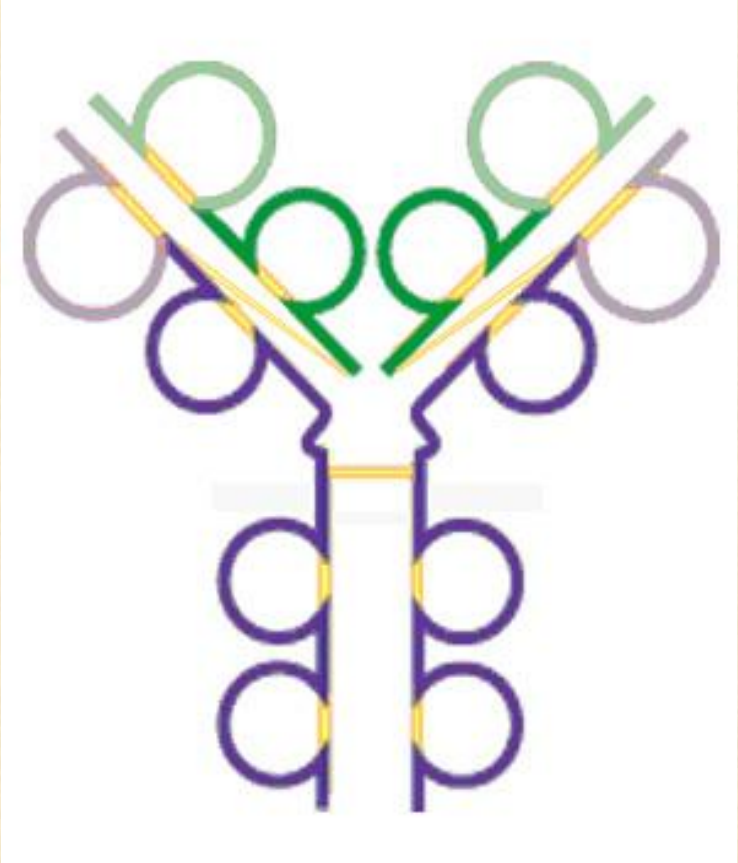
Immunoglobulins
B cell receptors (BcR)
T cell receptors (TcR)
MHC class I and class II

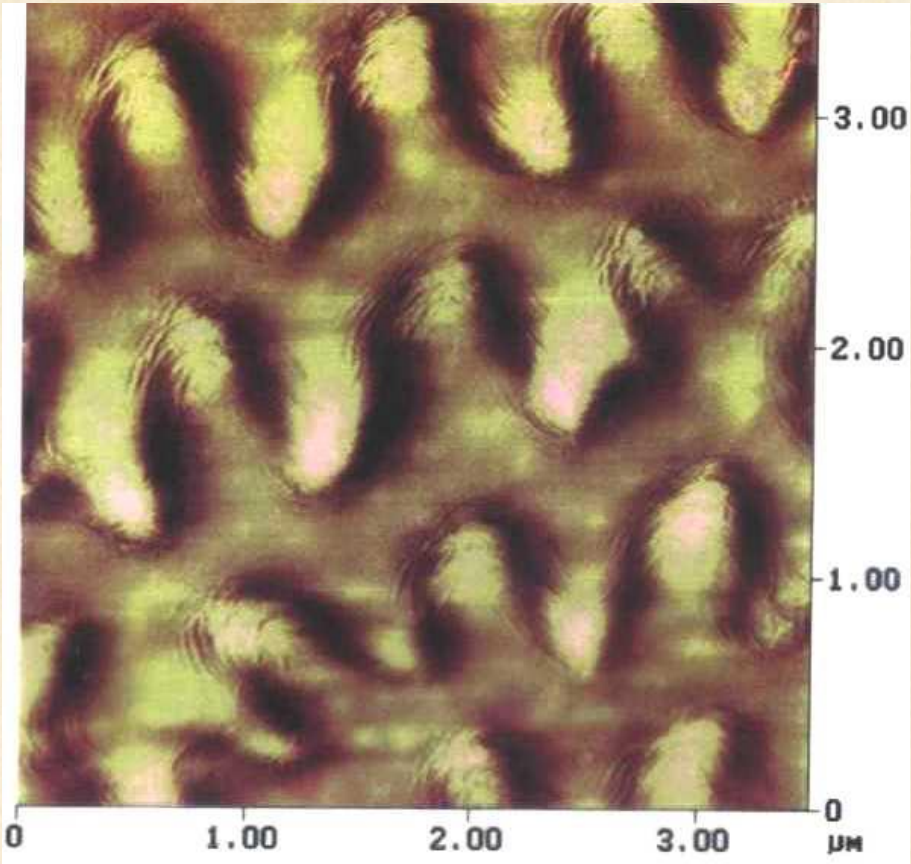
Specialized molecules manage antigen recognition. The common structural features of these molecules are the well-conserved (constant) basic elements (designed by **110 amino acids domain units**) containing variable, antigen specific parts (binding sites) for the recognition and ligand formation.

Antigen specific recognition molecules



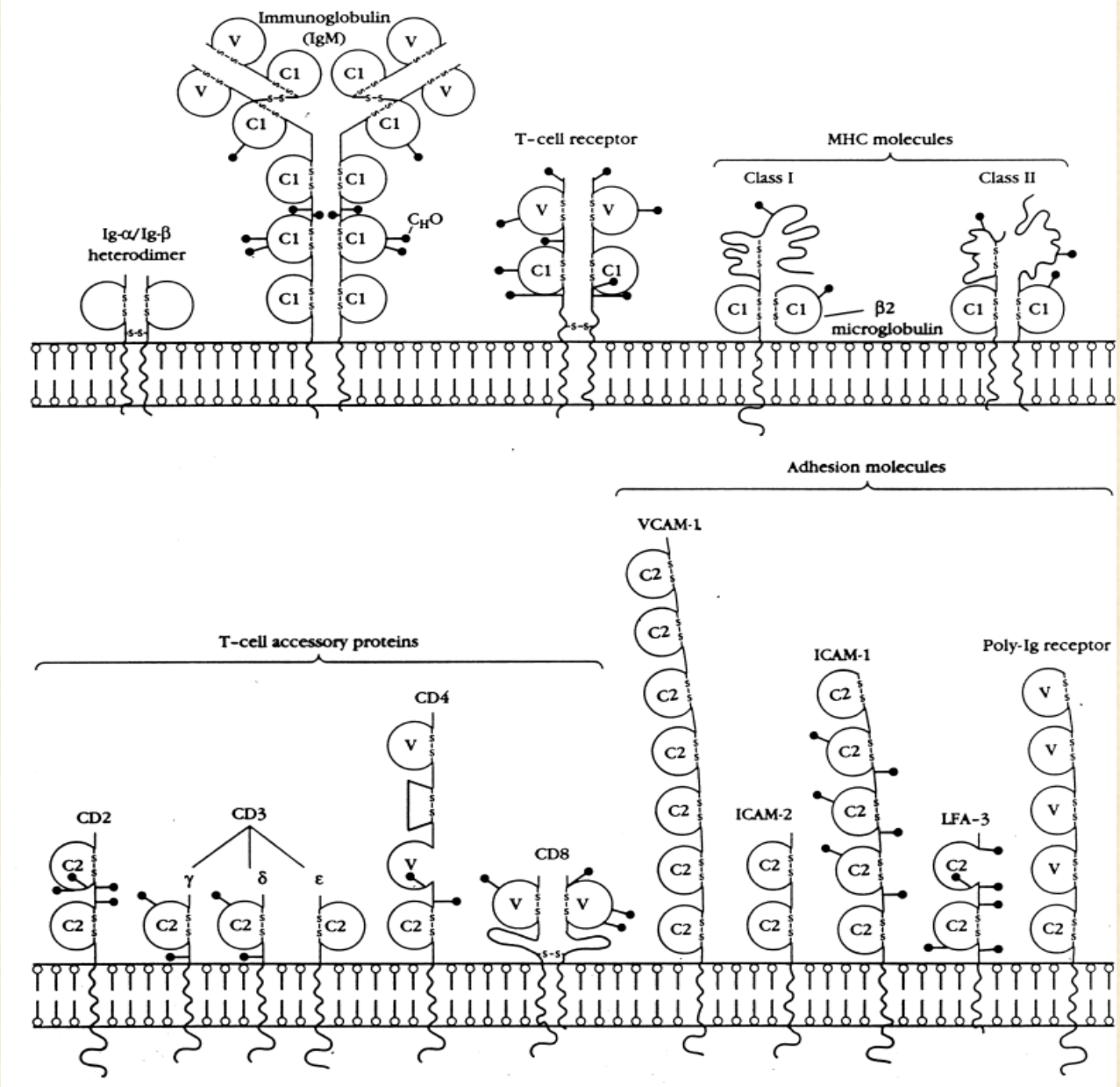
Domain structure





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

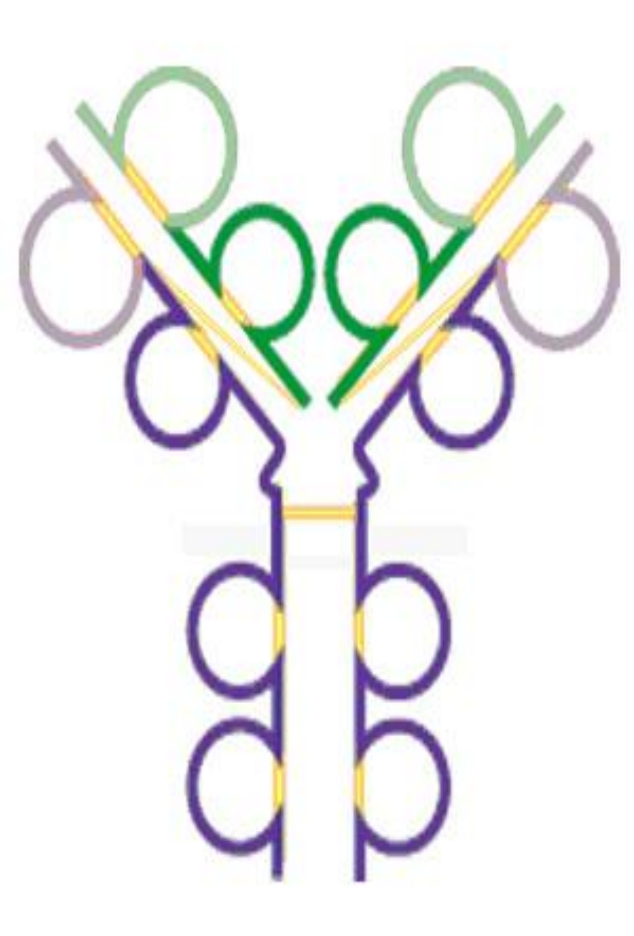
Immune recognition molecules



Antigen specific recognition molceules

Accessory molecules

Immunoglobulin molecule



CDR

Variable region

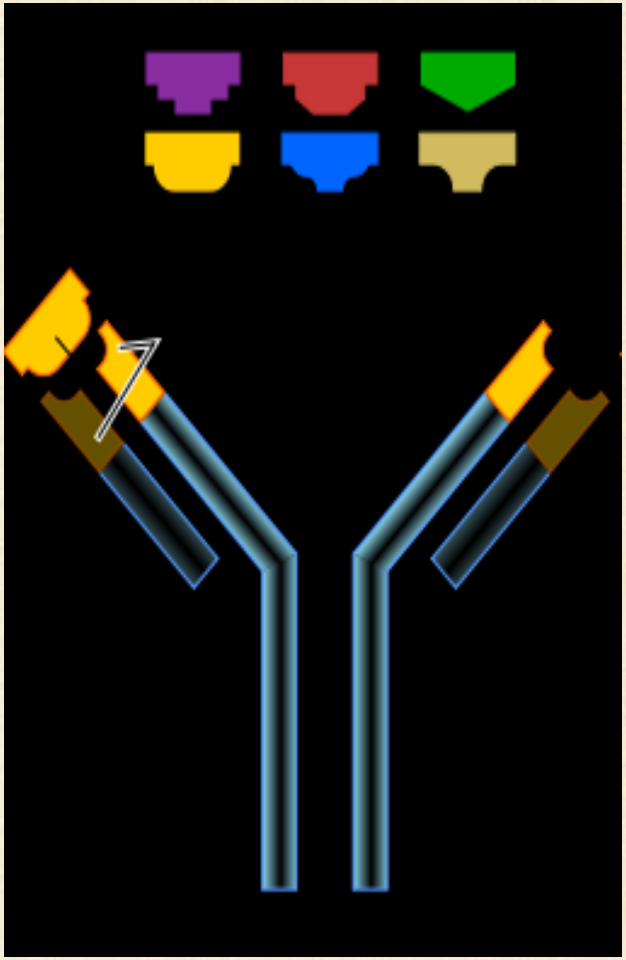
Idiotype

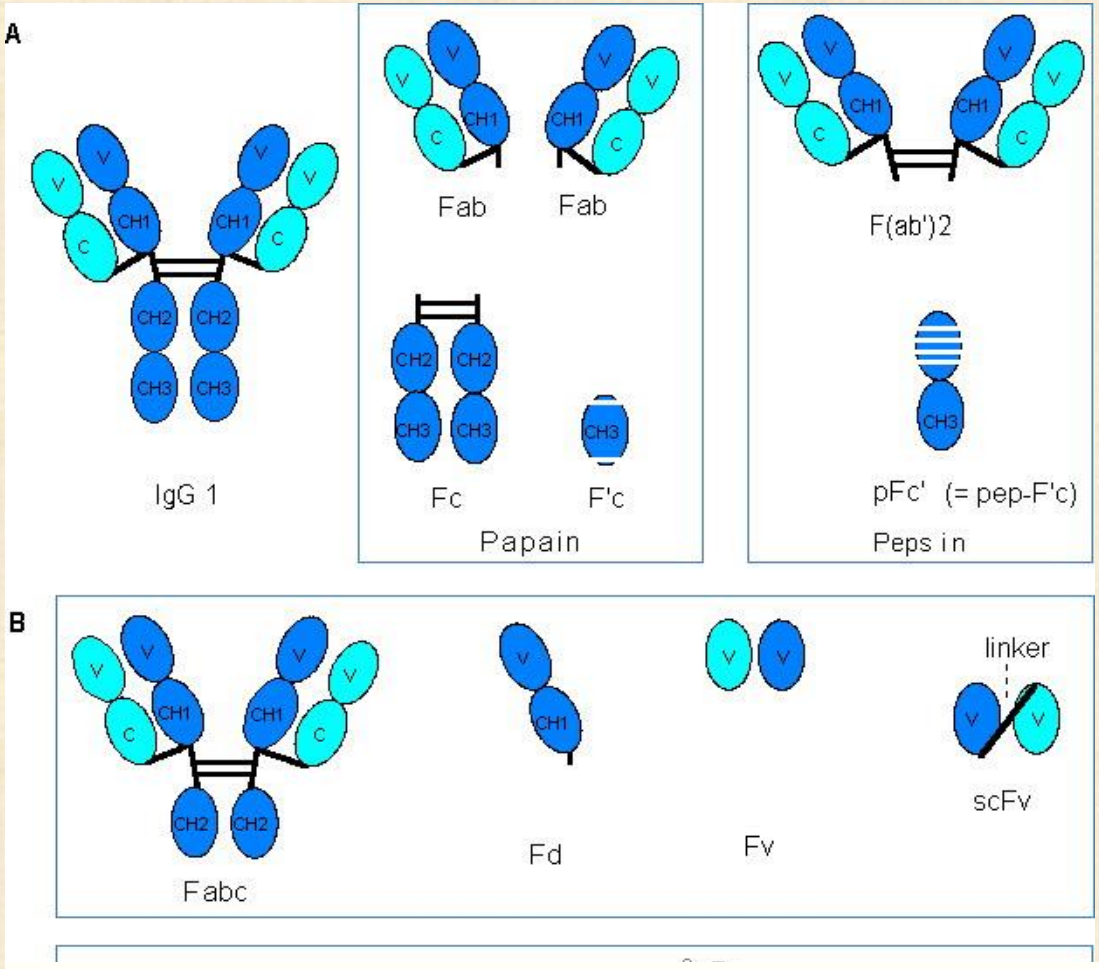
Fab fragment

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.

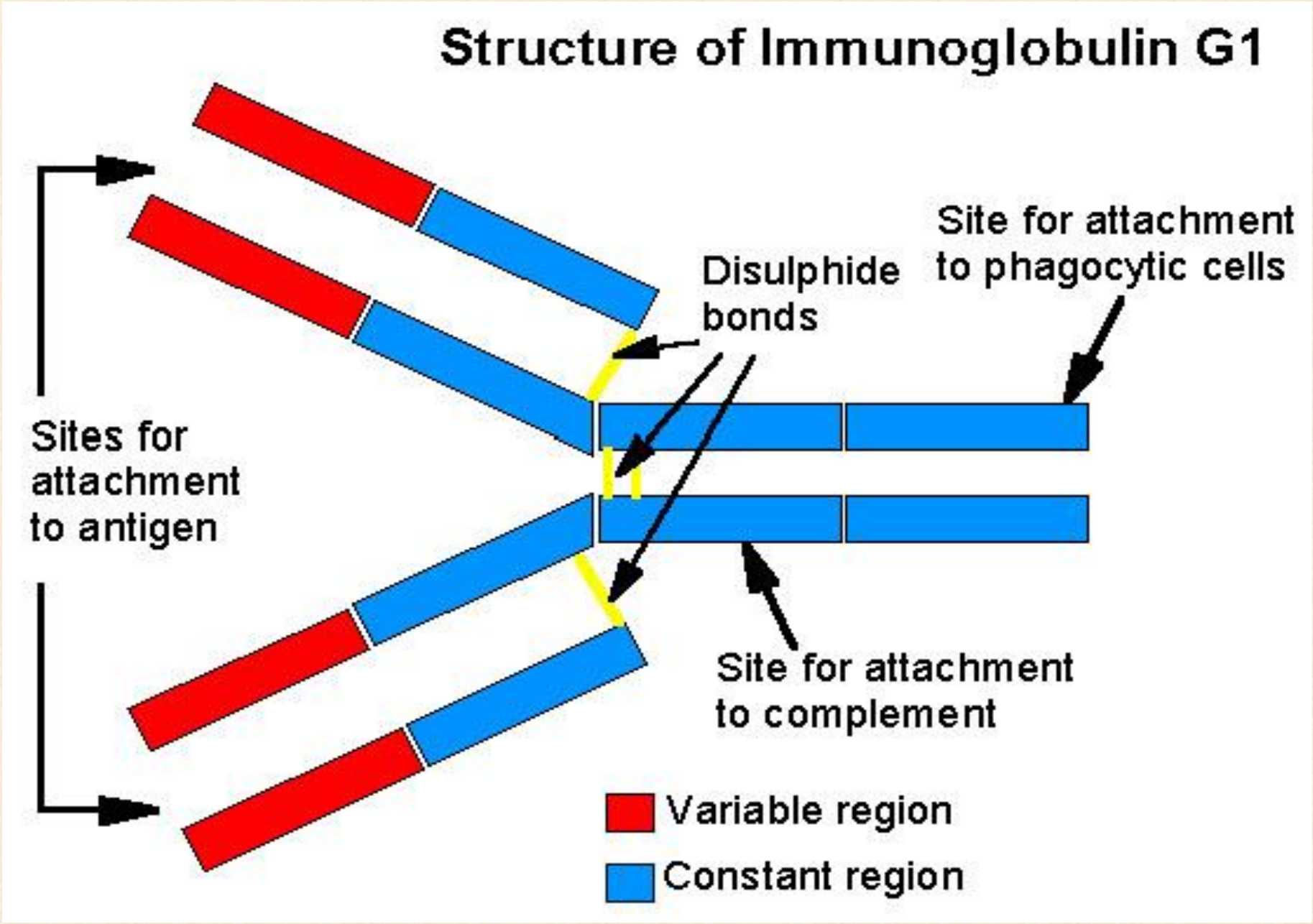
Immunoglobulin isotypes

- 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.

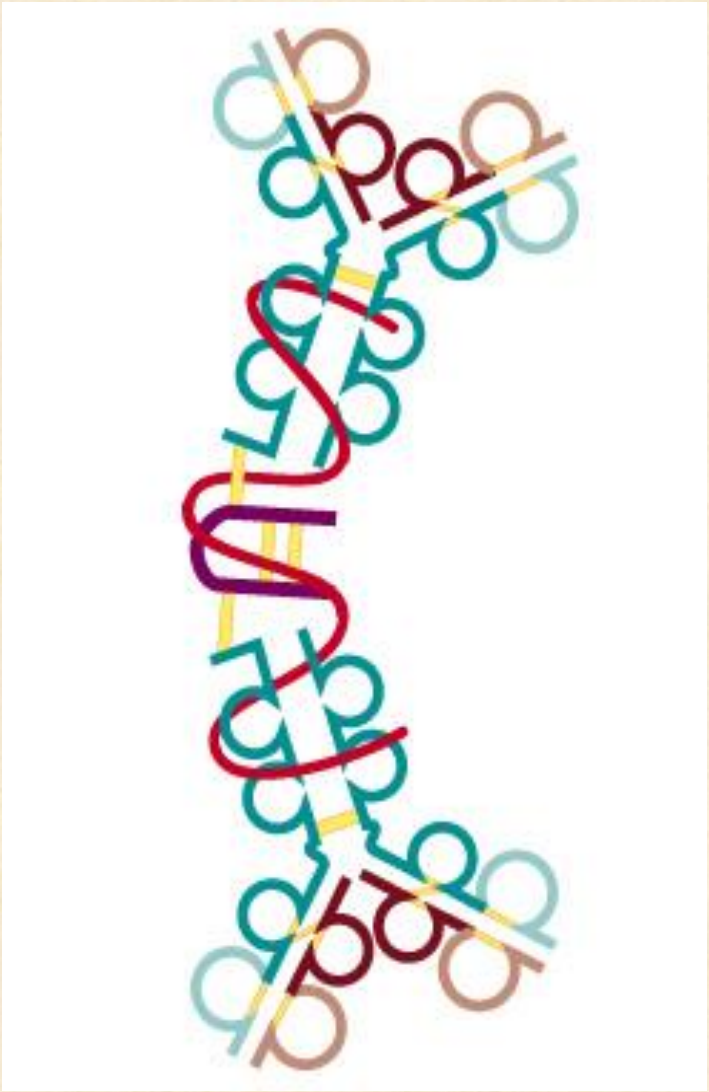
Heavy chain	Light chain	Immuno-globulin Class	Immuno-globulin Subclass
γ1	κ or λ	IgG	IgG1
γ2	κ or λ		IgG2
γ3	κ or λ		IgG3
γ4	κ or λ		IgG4
α1	κ or λ	IgA	IgA1
α2	κ or λ		IgA2
μ	κ or λ	IgM	
δ	κ or λ	IgD	
ε	κ or λ	IgE	

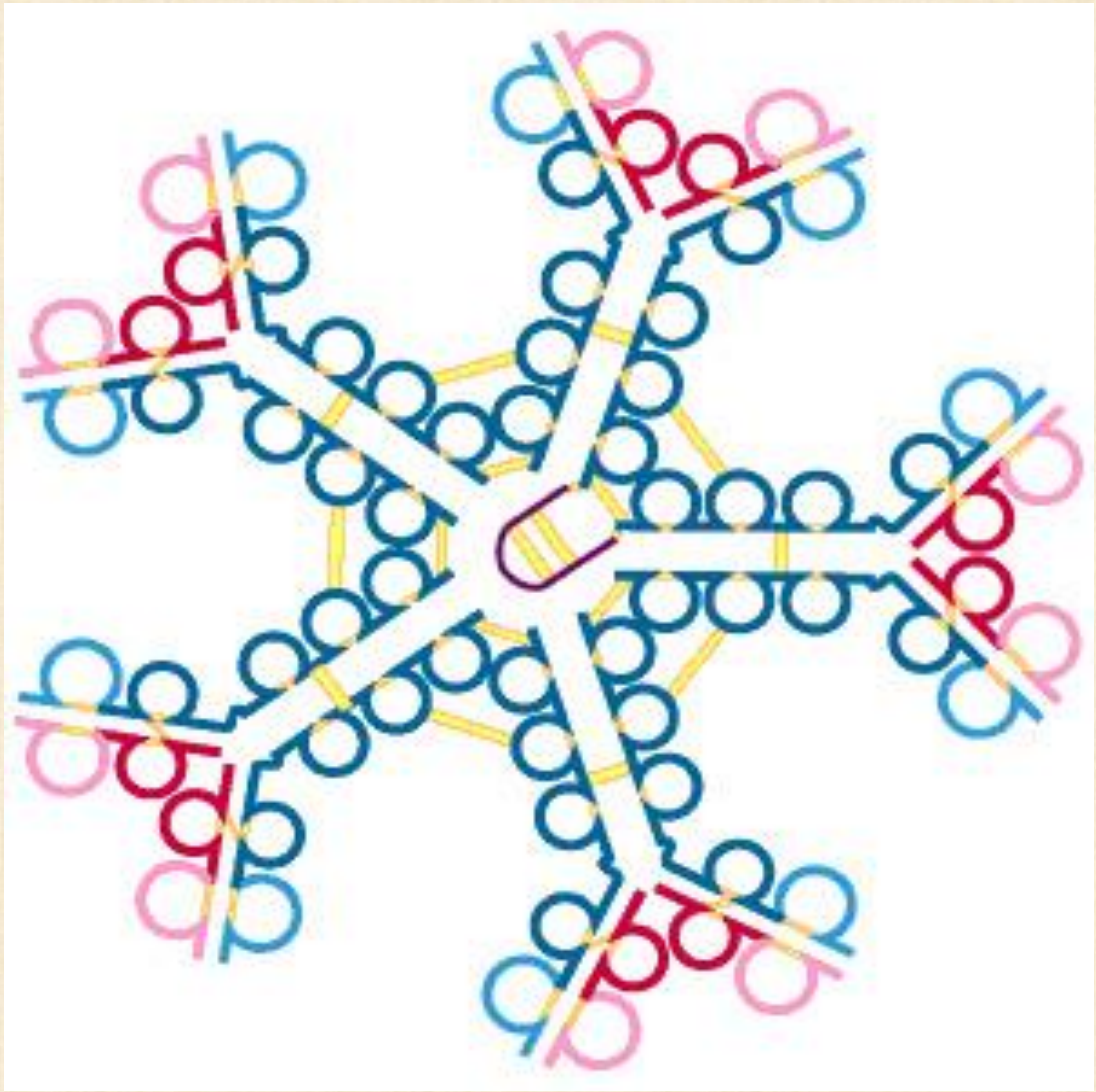
Pronunciation of Greek letters:

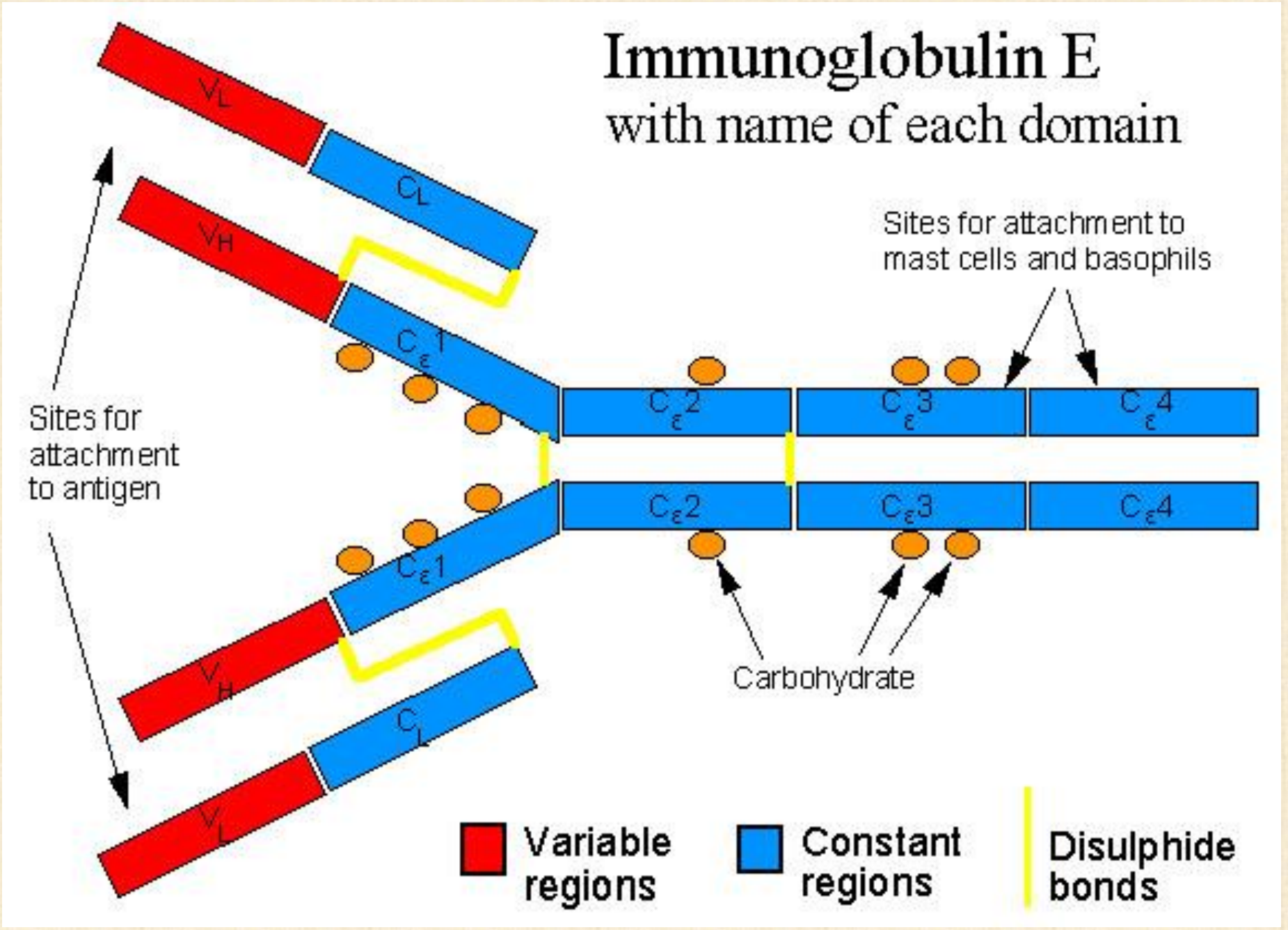
γ gamma α alpha μ mu δ delta
ε epsilon κ kappa λ lambda

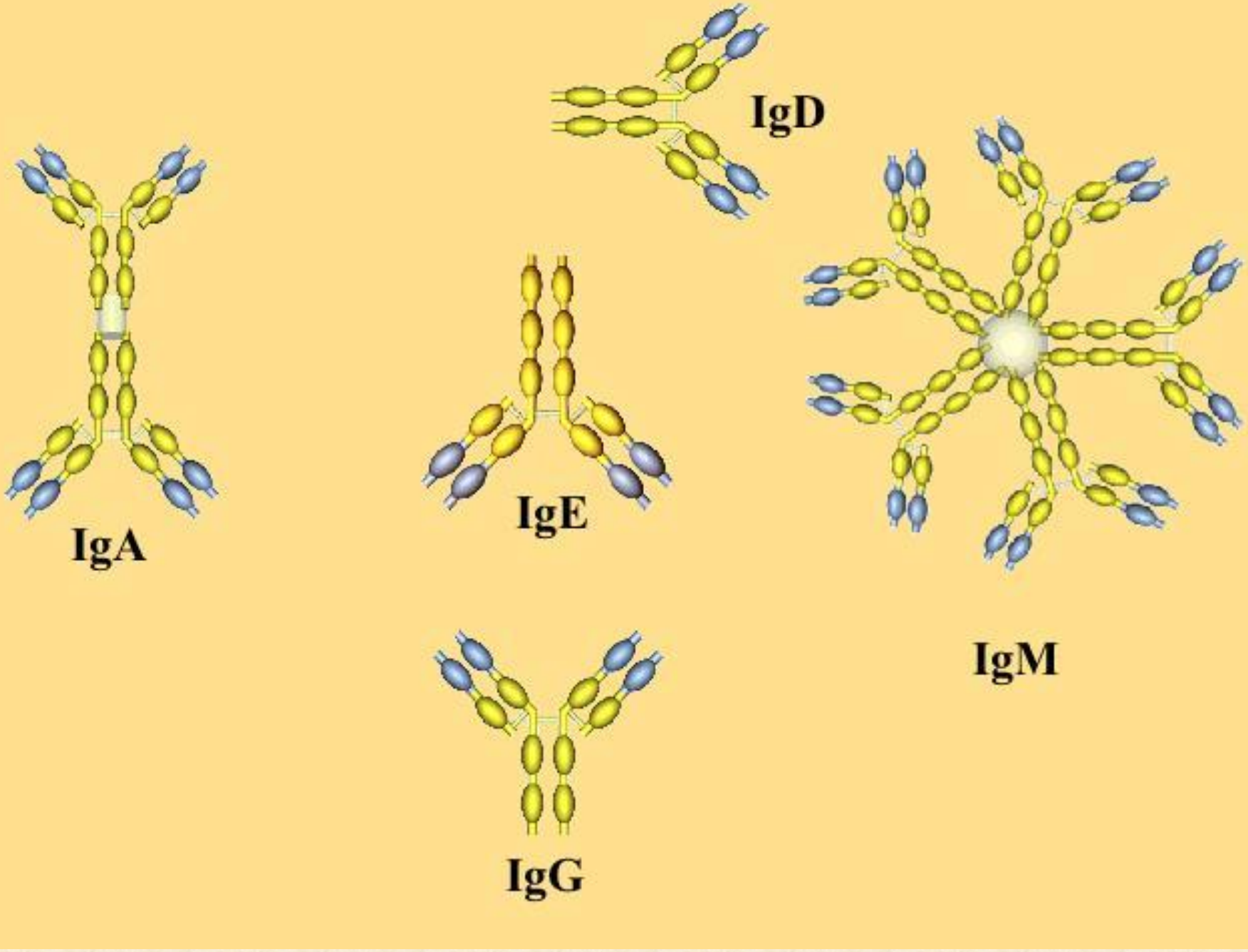

Structure of Immunoglobulin G1
Site for attachment to phagocytic cells
Disulphide bonds
Sites for attachment to antigen
Site for attachment to complement
Variable region
Constant region

IgA and IgM





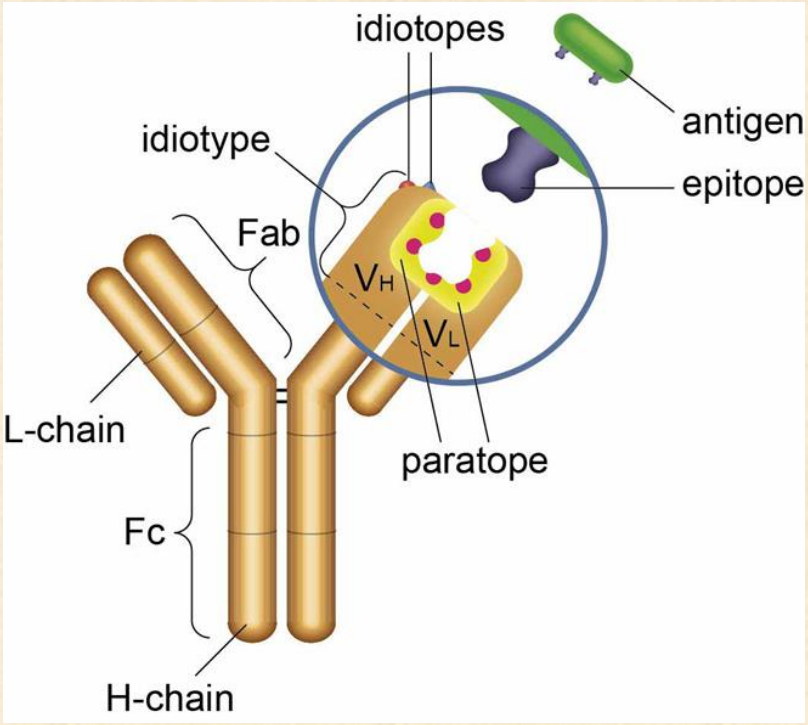

Immunoglobulin E
with name of each domain
V_L
C_L
V_H
$C_\varepsilon 1$
Sites for attachment to mast cells and basophils
Sites for attachment to antigen
$C_\varepsilon 2$
$C_\varepsilon 3$
$C_\varepsilon 4$
$C_\varepsilon 2$
$C_\varepsilon 3$
$C_\varepsilon 4$
$C_\varepsilon 1$
V_H
C_L
V_L
Carbohydrate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


IgD
IgA
IgE
IgM
IgG

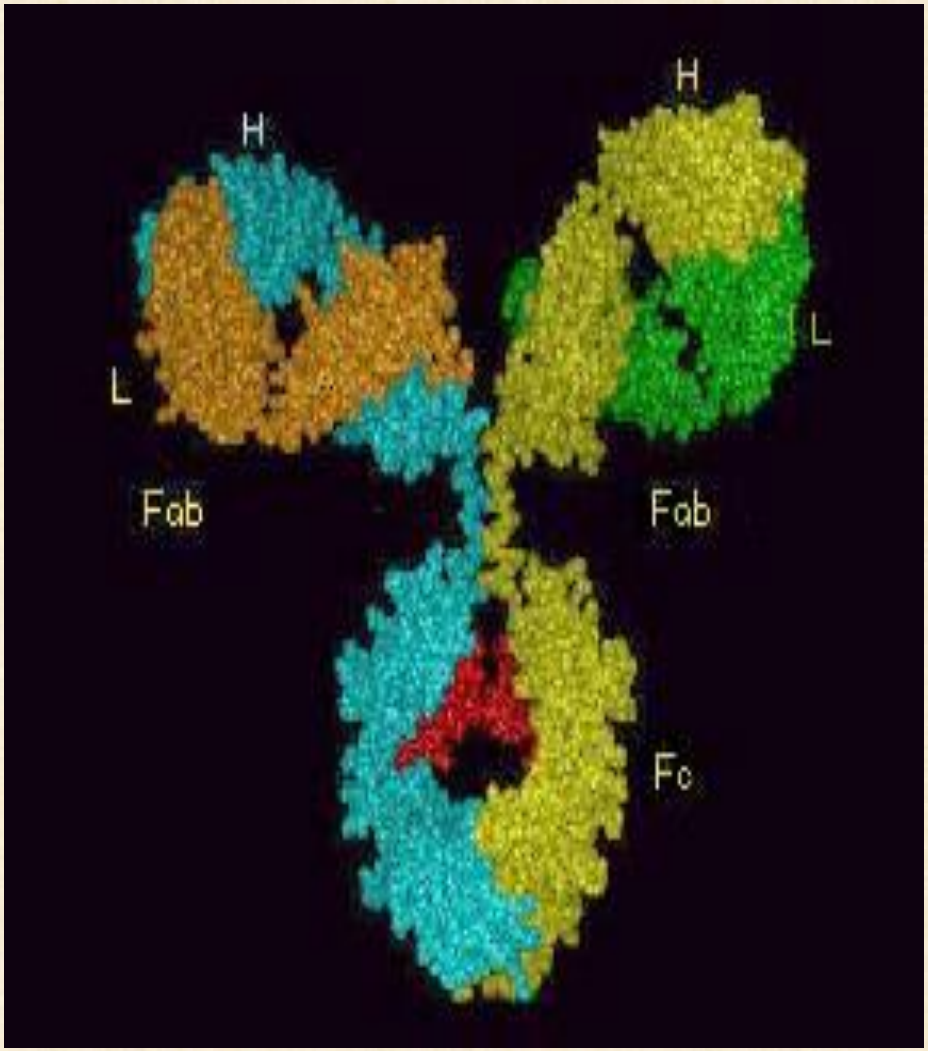
Immunoglobulin idiotype

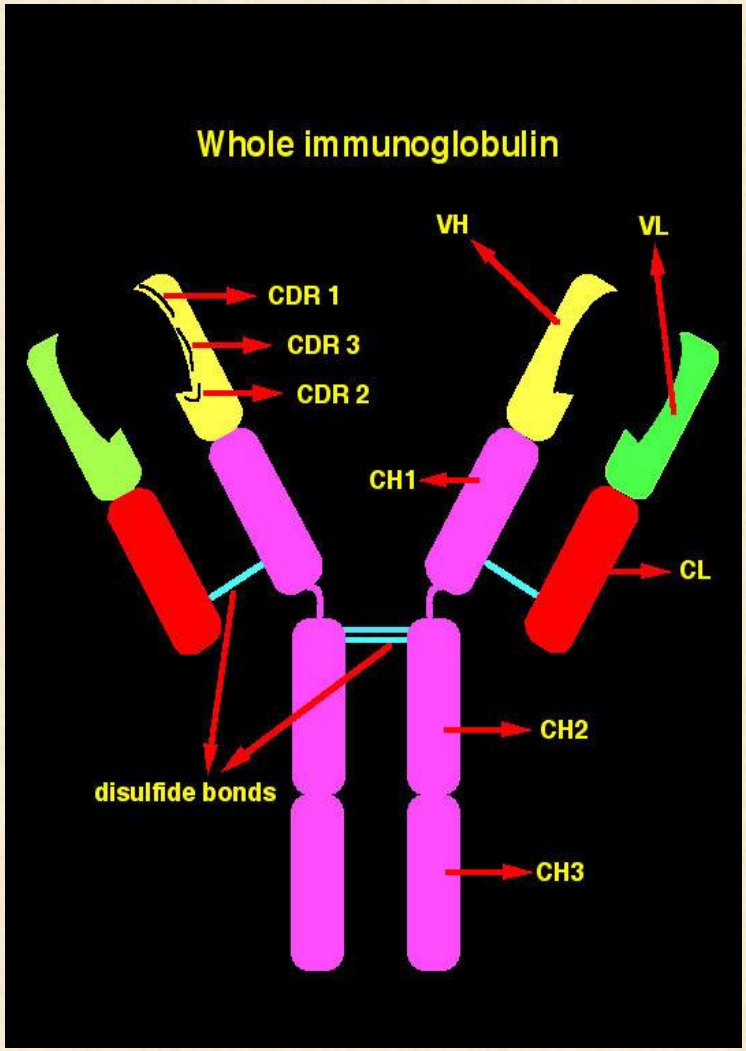
Individual determinants in **V regions**, specific for each antibody.

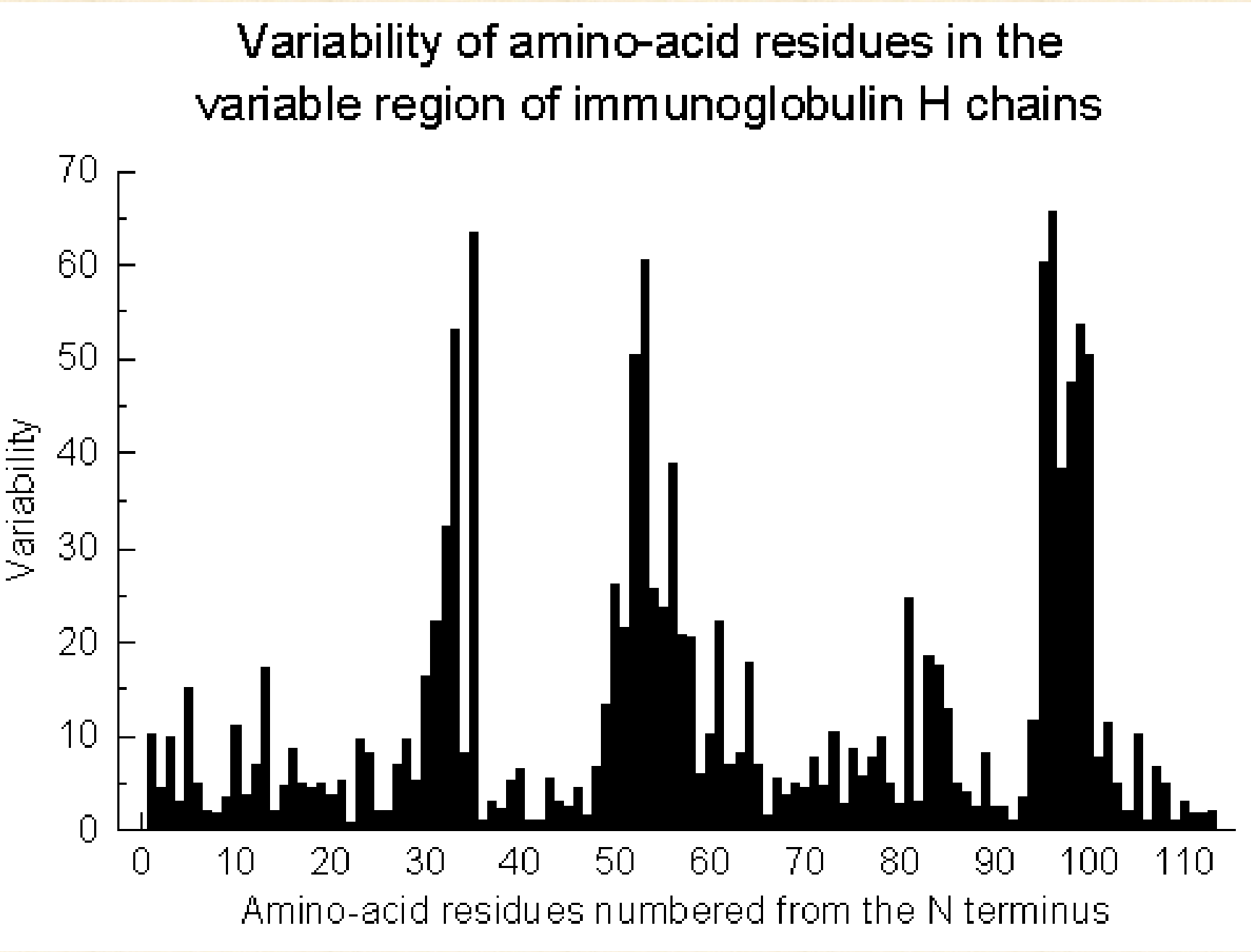
The N terminal Ig domain contains V region forming the antigen binding site: clustering the 3 hyper variable sequences close to each other on both chains - the variation of 3 x 3 results tremendous diversity.

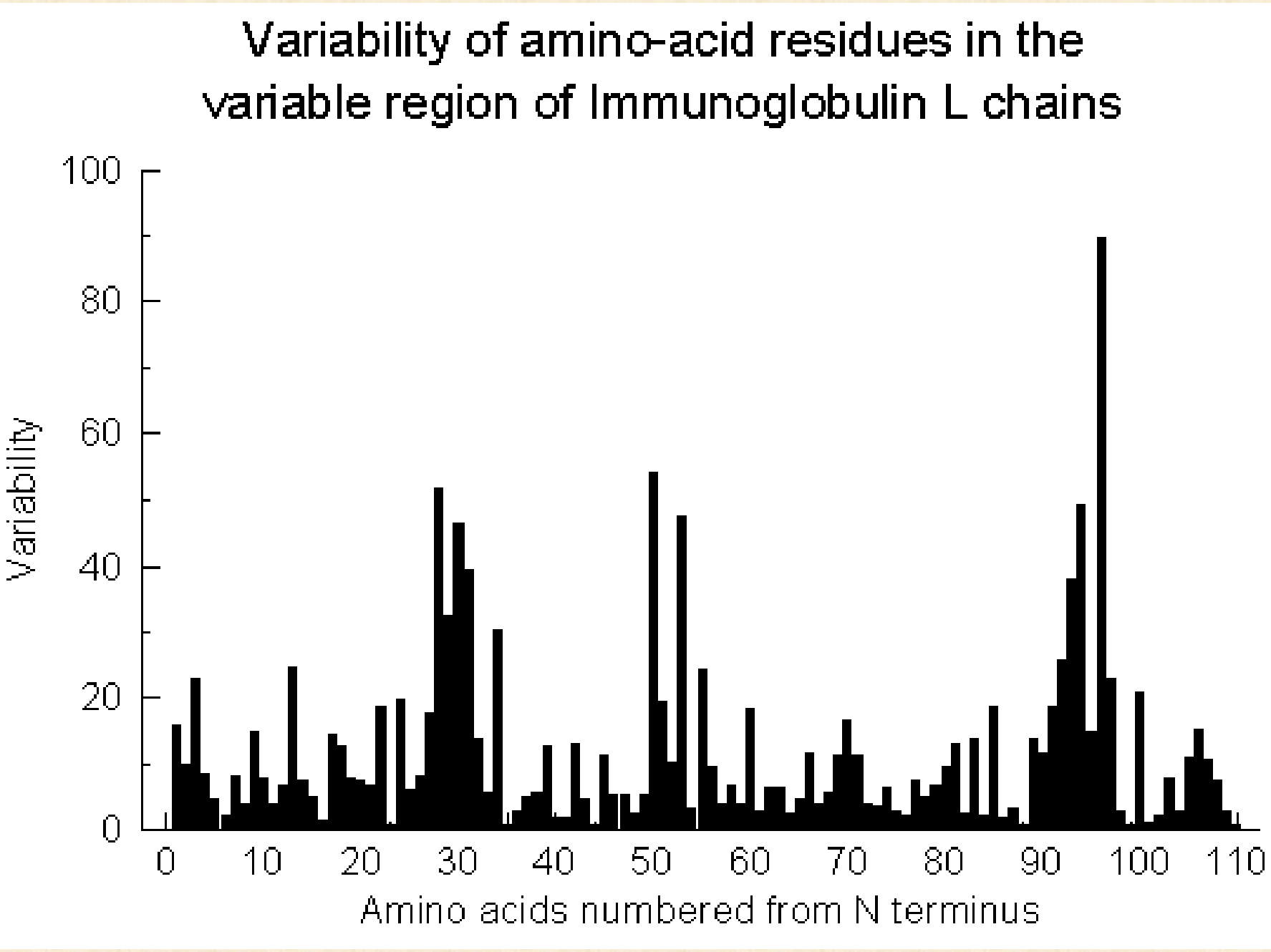


Structure of IgG



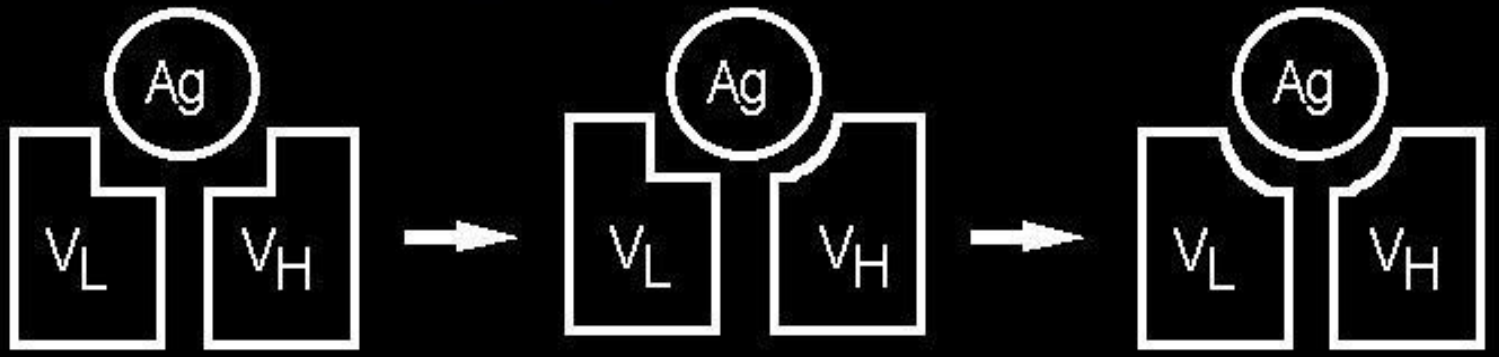


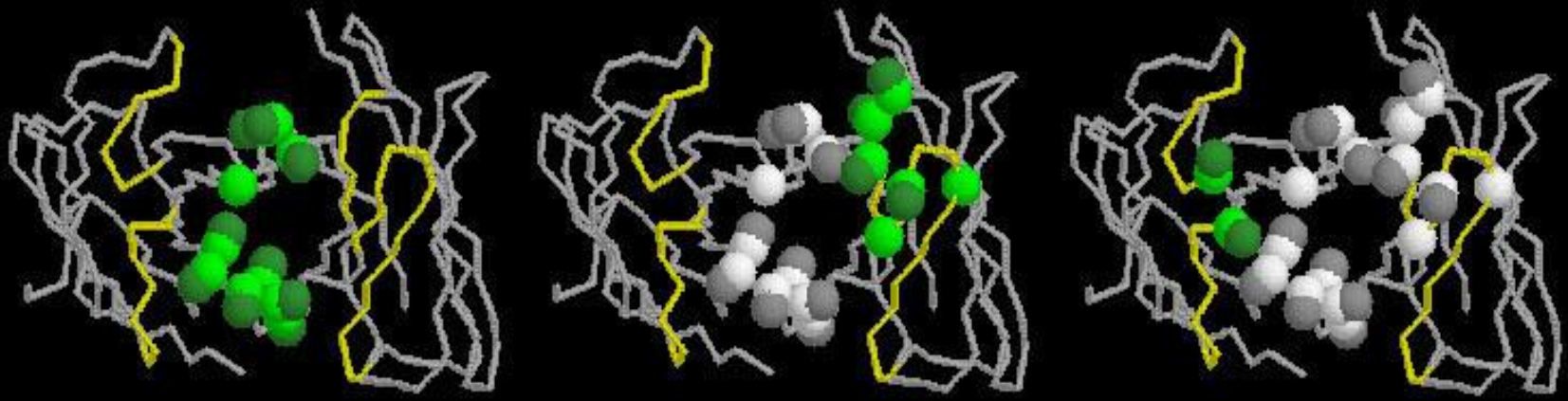

Variability of amino-acid residues in the variable region of immunoglobulin H chains
Variability
0
10
20
30
40
50
60
70
0
10
20
30
40
50
60
70
80
90
100
110
Amino-acid residues numbered from the N terminus


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

IgG – blood, lymph, make up 80% of Ig

- only Ig of maternal origin to pass the placenta wall give newborns (Mw 150 kD)
- neutralize toxins and viruses

IgM – Blood, lymph (cell surface) pentamer structure (Mw 900 kD)

- First antibodies formed in response to initial infection.

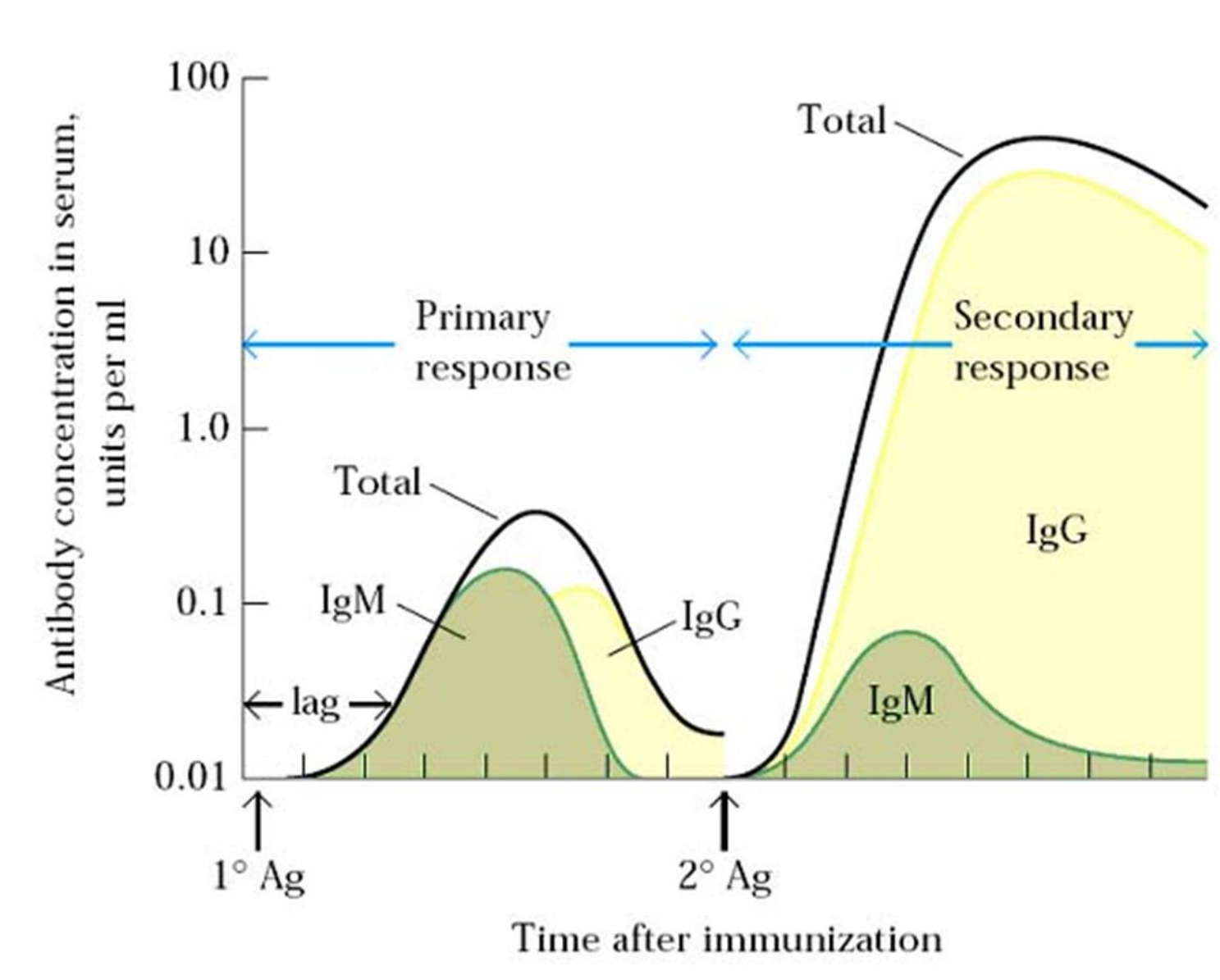
IgA – Mucosal surfaces, blood (active in dimeric or tetrameric form) (Mw 150-600 kD)

IgD – only membrane-bounded form in B-cell surfaces (Mw 150 kD)

- may function in initiation of antibody-antigen response

IgE – blood (bound to basophiles, mast cells) (Mw 190 kD) initiation of allergic reactions

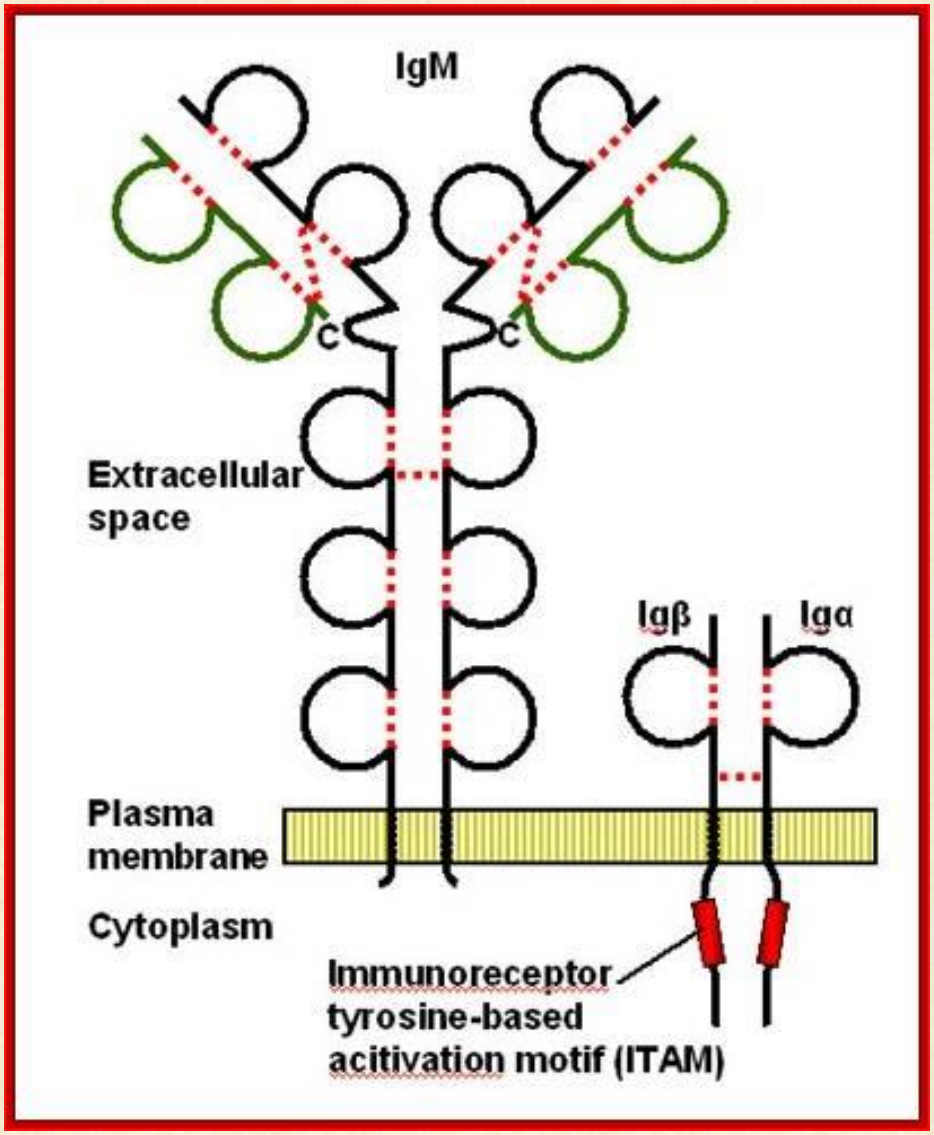
Kinetics of antibody production



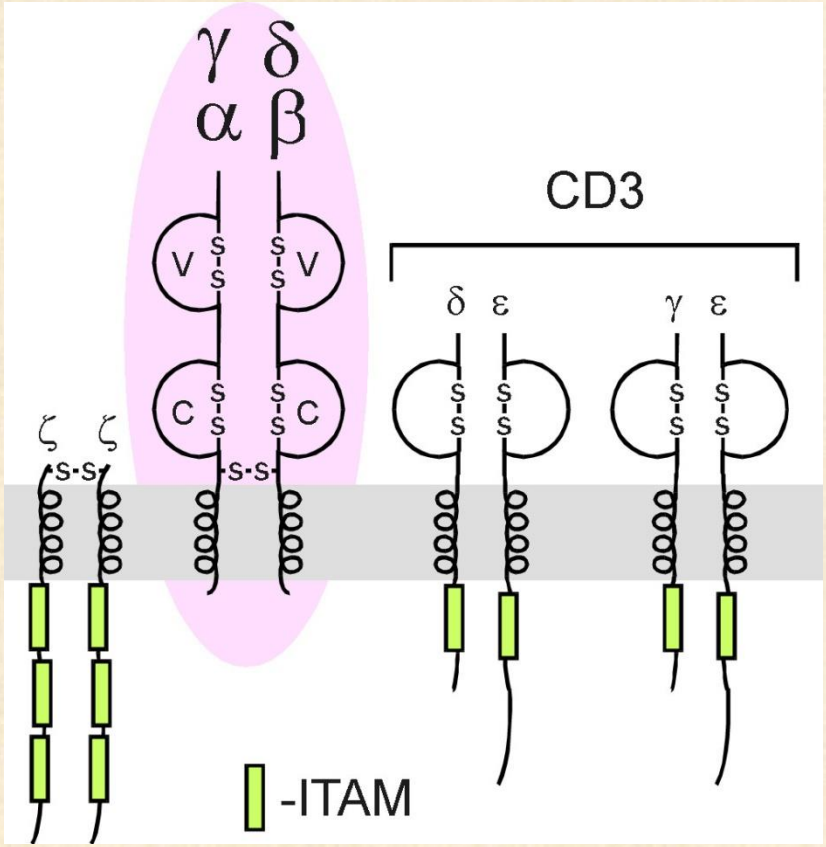
Antigen – antibody reactions

- Neutralization (e.g. toxins)
- Precipitation (soluble molecules)
- Agglutination (particles, cells)
- Opsonization (large particles)
- Complement fixation

B cell receptor complex



T cell receptor complex expressed in mature T cells



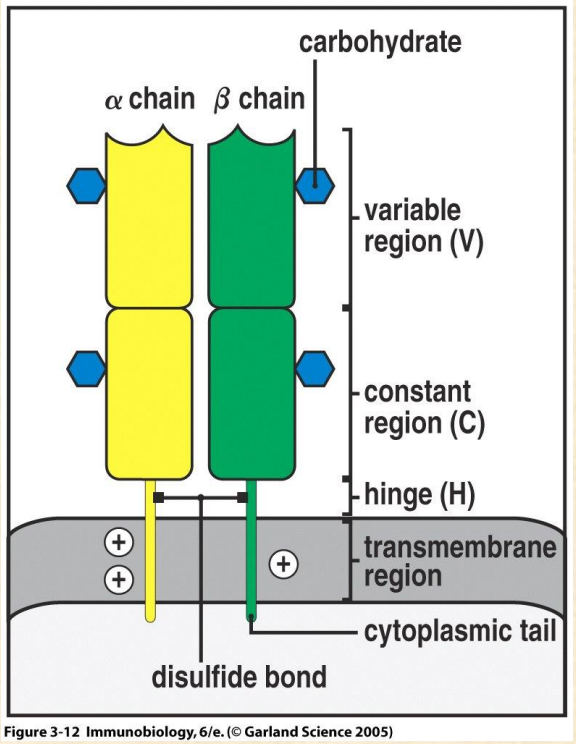


Figure 3-12 Immunobiology, 6/e. (© Garland Science 2005)

αβ TcR – SP(CD4+ or CD8+)
γδ TcR – DN (CD4-CD8-)

T Cell Receptor complex

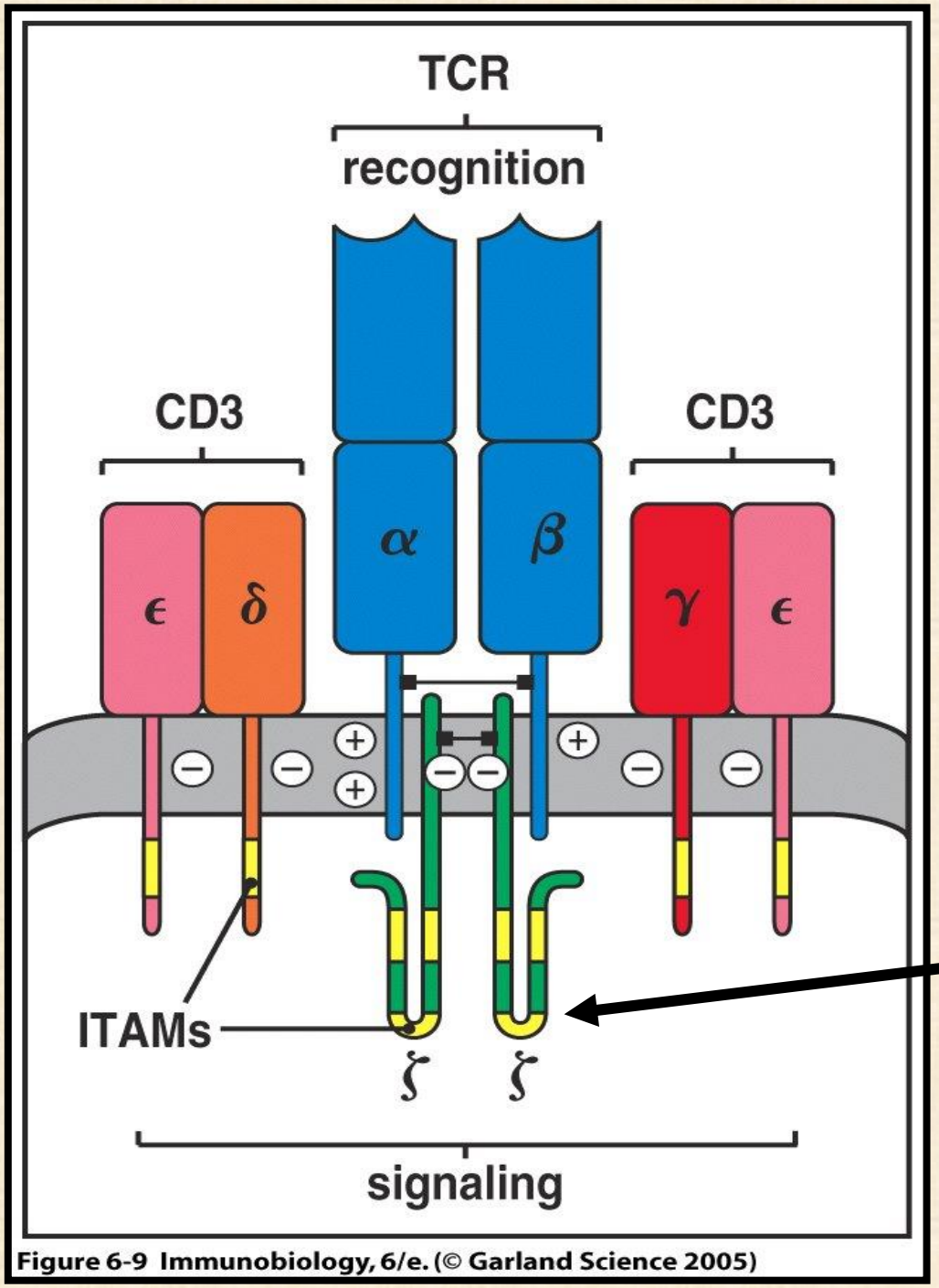


Figure 6-9 Immunobiology, 6/e. (© Garland Science 2005)

ITAMs
Immunoreceptor
Tyrosine-based
Activation
Motifs