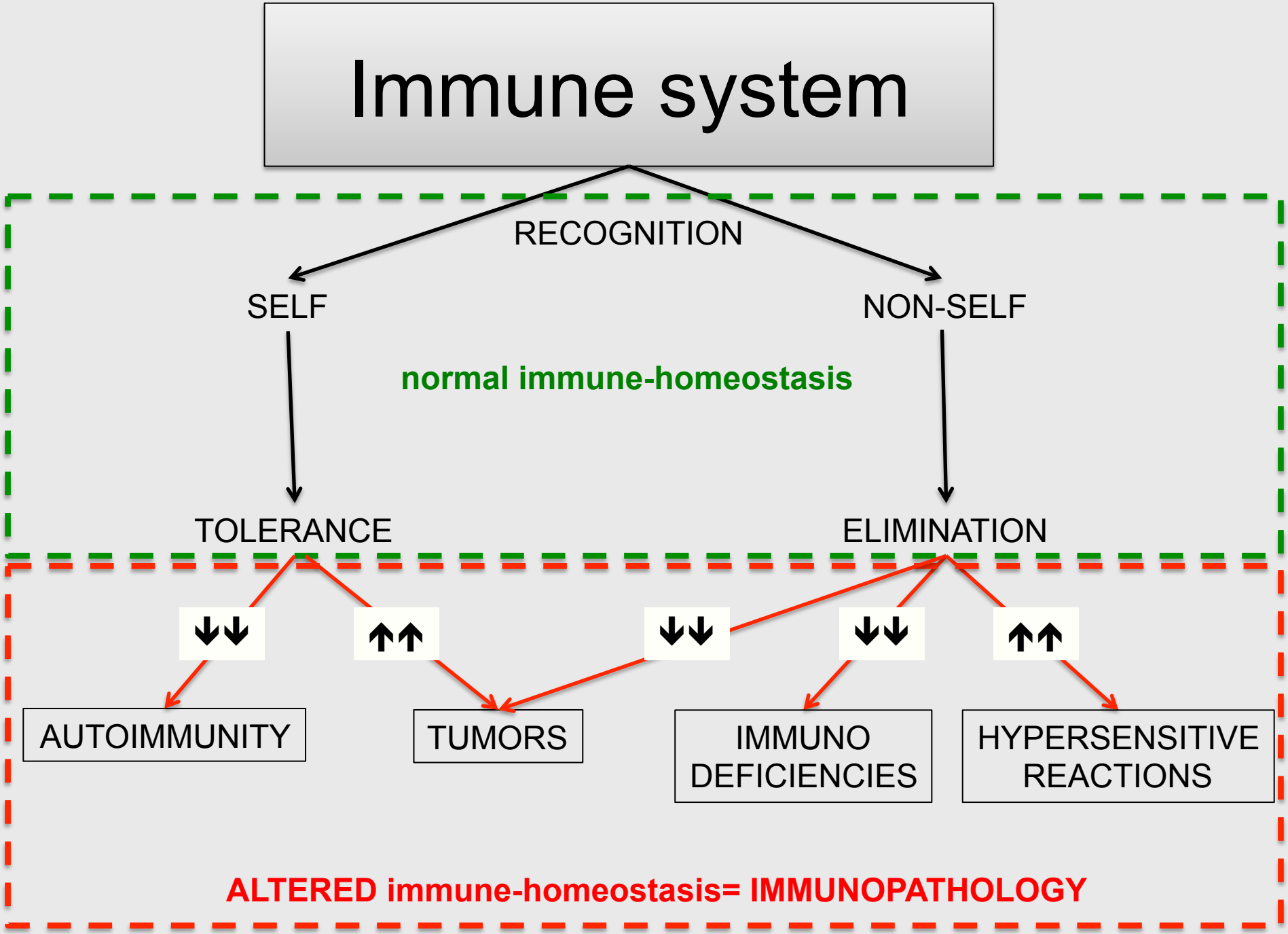
Basic Immunology
(Dentistry)

Lecture 3.-4.

Molecular components of the immune system.

1. ***Antigen recognition molecules: Immunoglobulins, T cell receptor***
2. ***MHC and antigen presentation***

Ferenc Boldizsar MD, PhD


Immune system
RECOGNITION
SELF
NON-SELF
normal immune-homeostasis
TOLERANCE
ELIMINATION
AUTOIMMUNITY
TUMORS
IMMUNO DEFICIENCIES
HYPERSENSITIVE REACTIONS
ALTERED immune-homeostasis= IMMUNOPATHOLOGY

Composition of the immune system

Innate

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

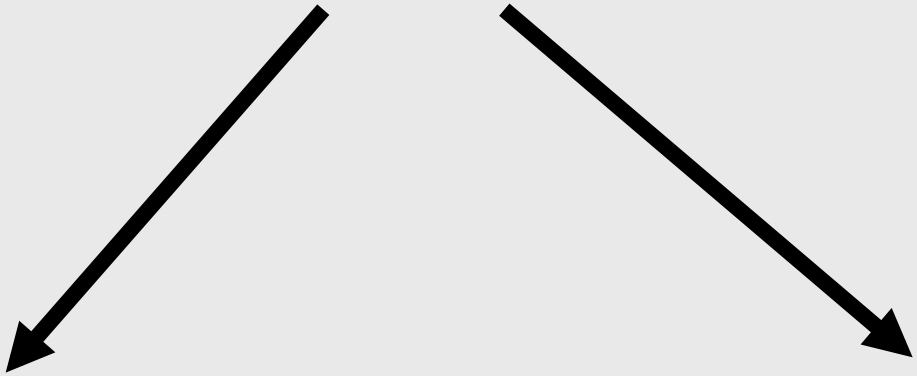
Adaptive

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

Natural

Innate-like immunity with adaptive features

Immunological Recognition (Receptors)



Innate immunity

general microbial
Molecular PATTERNs

(„pattern recognition receptors”)

Adaptive immunity

Antigenspecific (EPITOP)

Recognition molecules

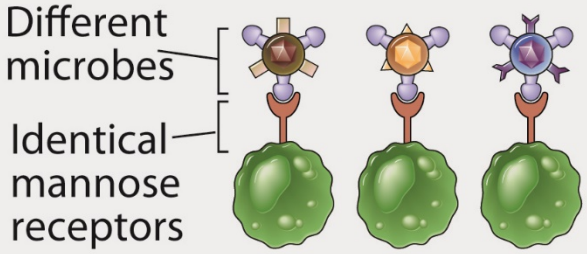
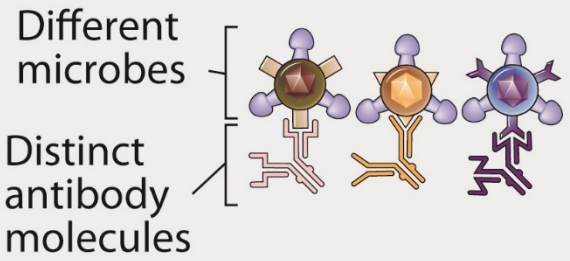
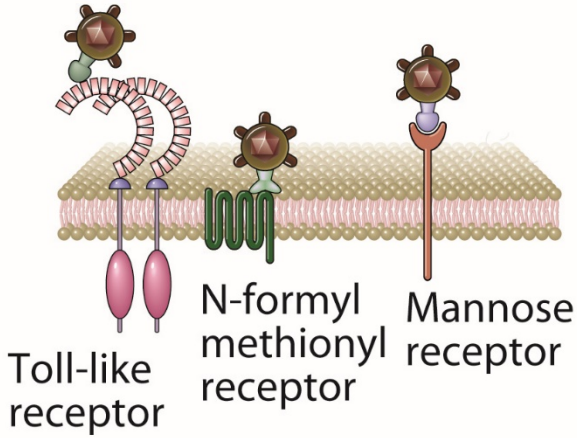
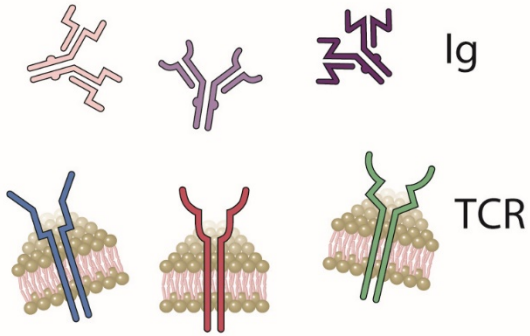
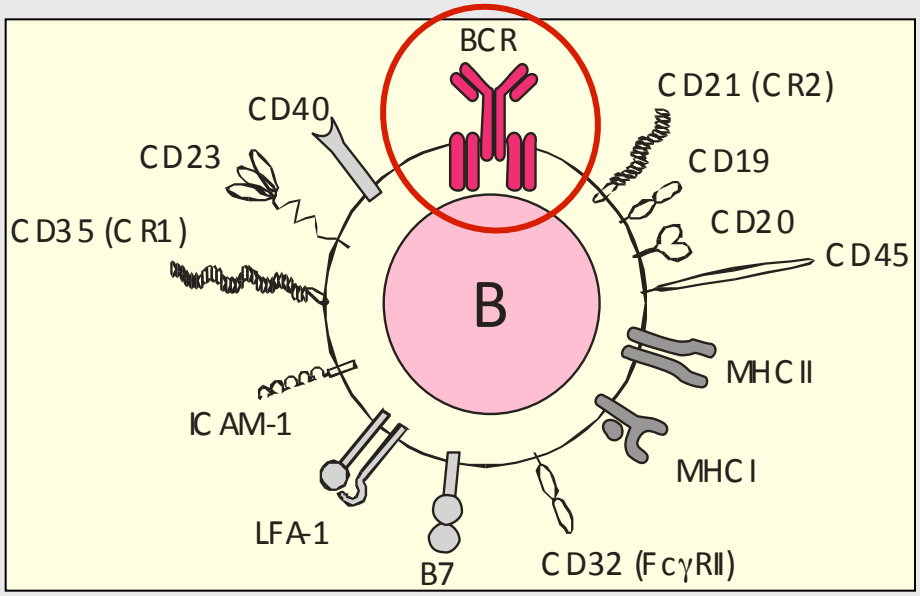
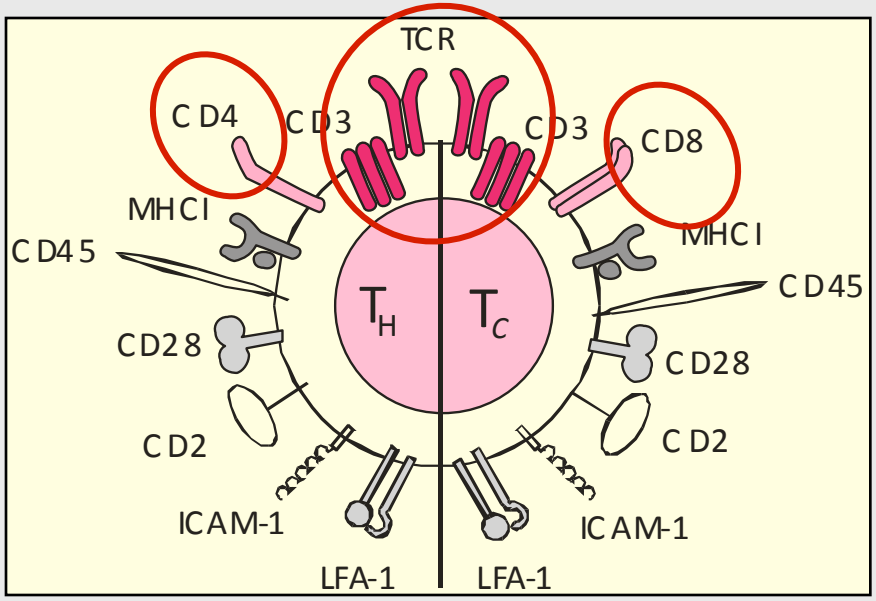
	Innate immunity	Adaptive immunity
Specificity	**For pathogen-associated molecular patterns (PAMPS)** 	**For structural details of any molecules (antigens)** 
Receptors	**Encoded in germline (pattern recognition receptors)** 	**Encoded by lymphocyte genes produced by somatic recombination** 
Distribution of receptors	**Non-clonal**	**Clonal**

Table 4-1

Antigen-Receptors of Lymphocytes





BcR= B-Zellrezeptor

TcR= T-Zellrezeptor

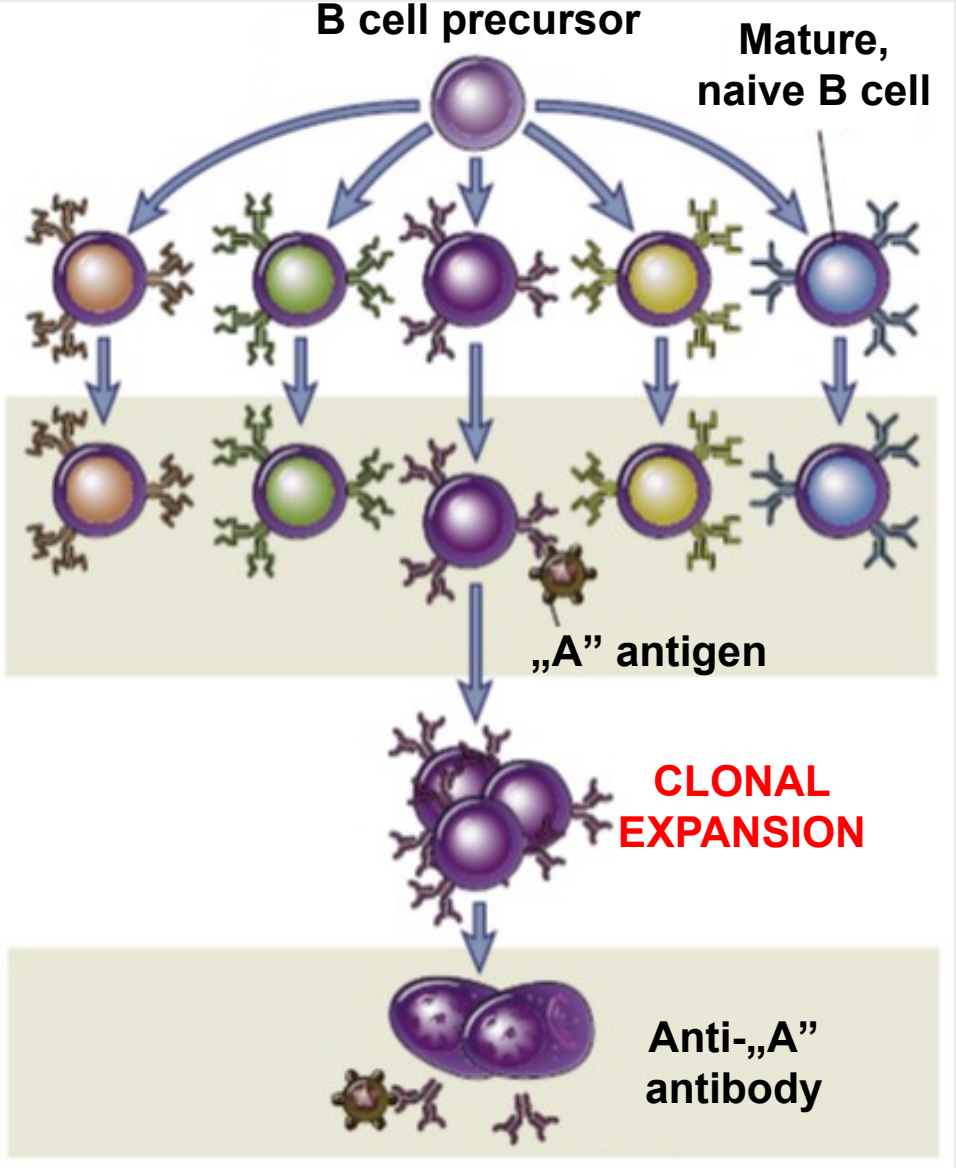
BcR and TcR are **Antigen-Receptors,** which are different on each individual lymphocyte. Every single Antigenreceptor recognizes and binds only ONE specific Antigen (EPITOP)

The Clonal Selection Hypothesis

1. Each newly produced lymphocyte expresses a **unique antigen-binding receptor**.

2. **Only those lymphocytes will become activated which recognize an antigen**. These selected cells will proliferate and produce **clones** of themselves with each sister cell having the same antigen-recognition receptor.

3. These clones will differentiate into **effector cells** which will participate in the immune response. (e.g. effector plasma cells produce antibodies)

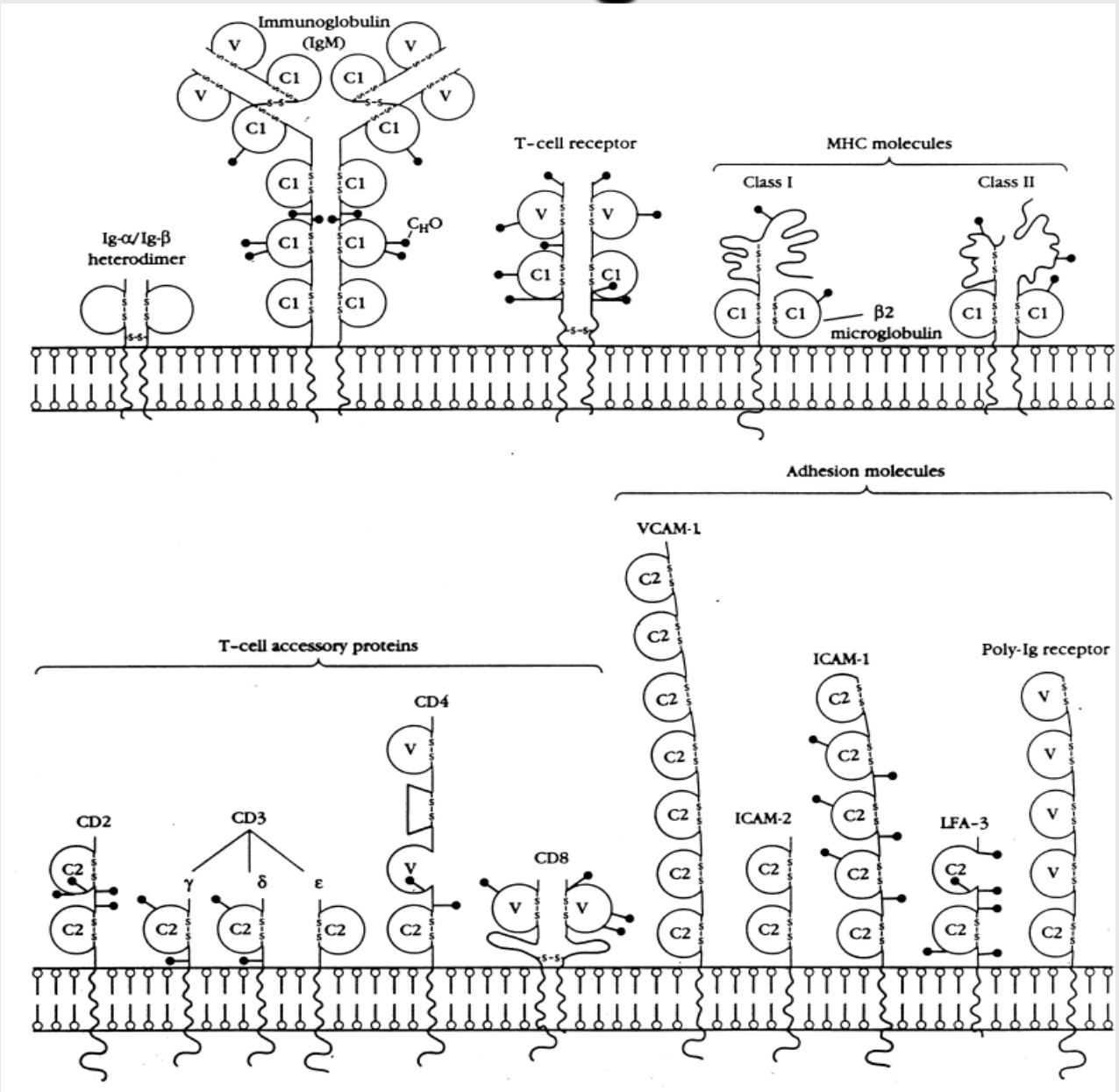


Recognition molecules in the adaptive immune system

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.

Immune recognition molecules



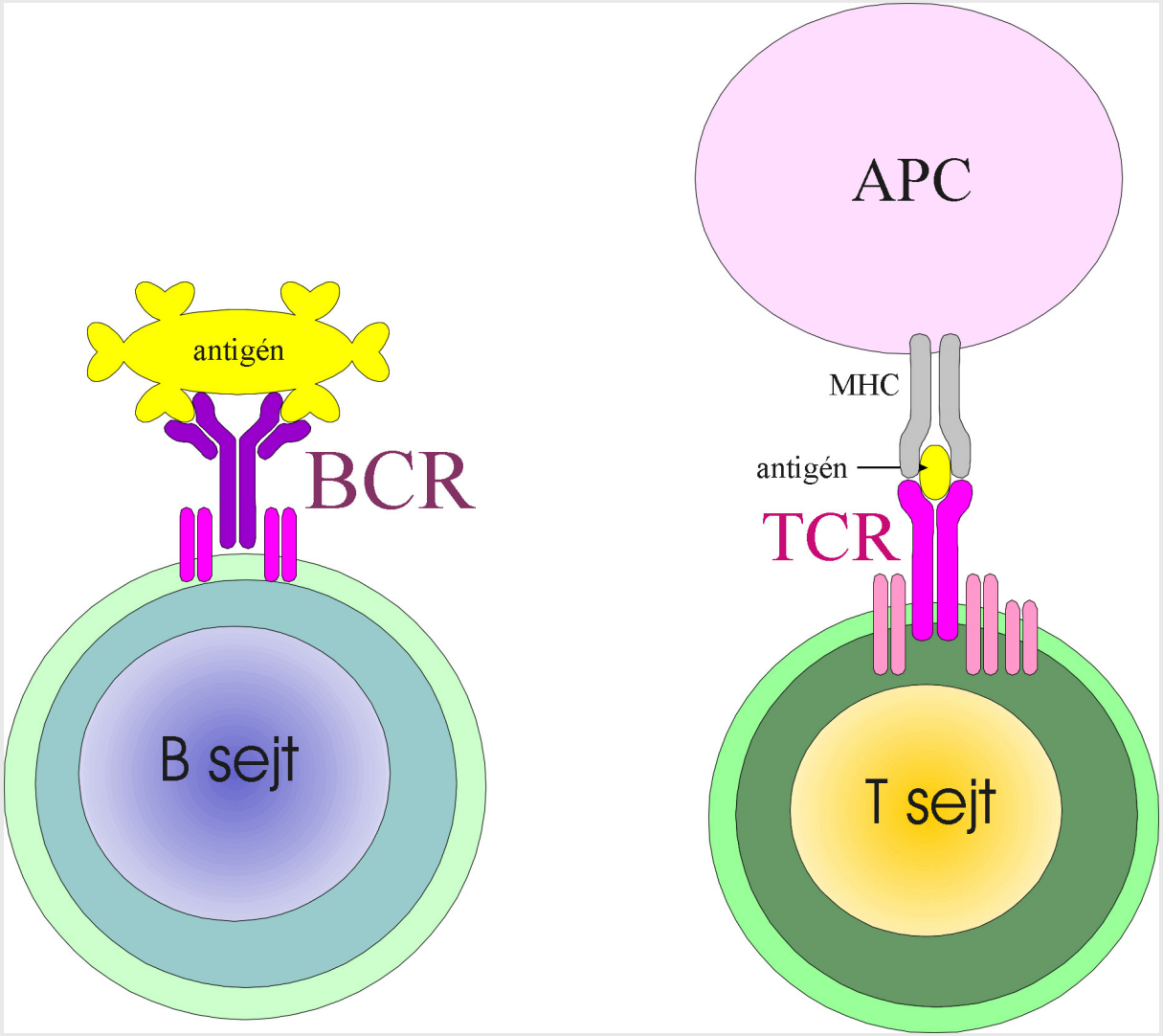
Antigen specific recognition molceules

Accessory molecules

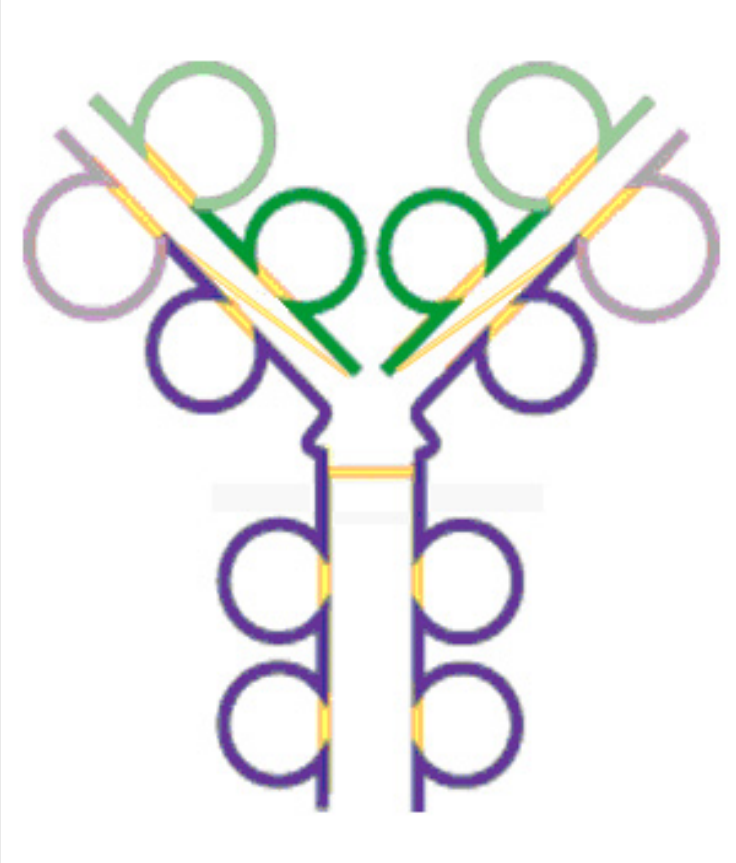
Antigen recognition

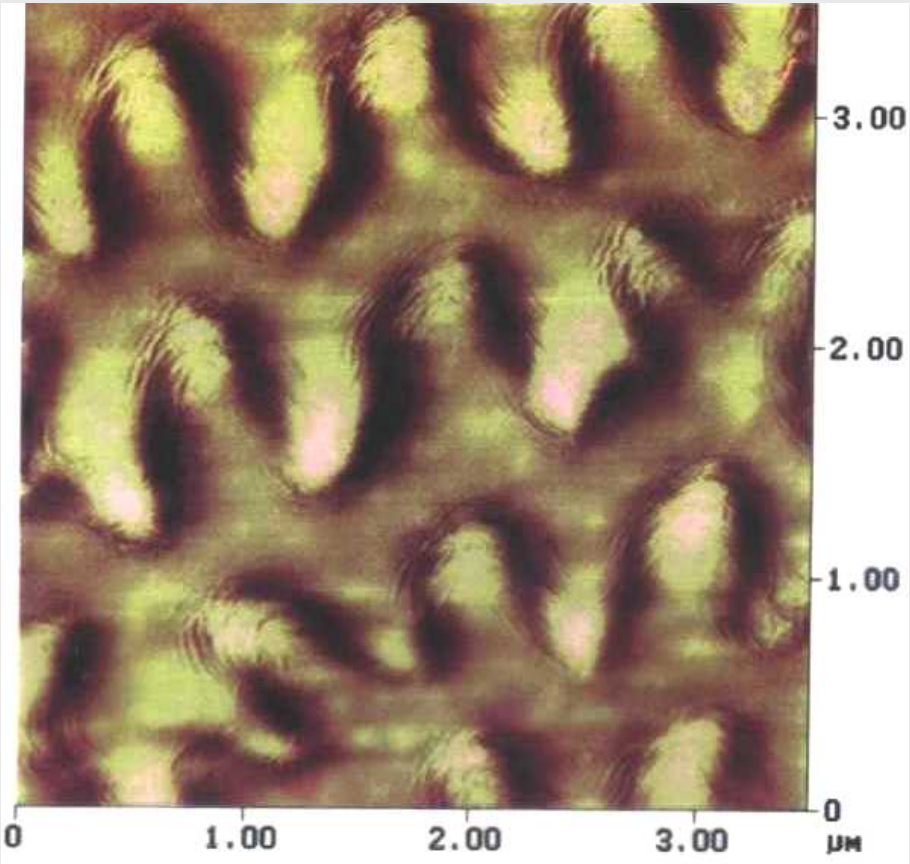
	B cells	**T cells**
Receptor	BcR (Ig)	TcR
Antigen	native	denatured (presented)
APC	not needed	needed

B cells and T cell antigen recognition



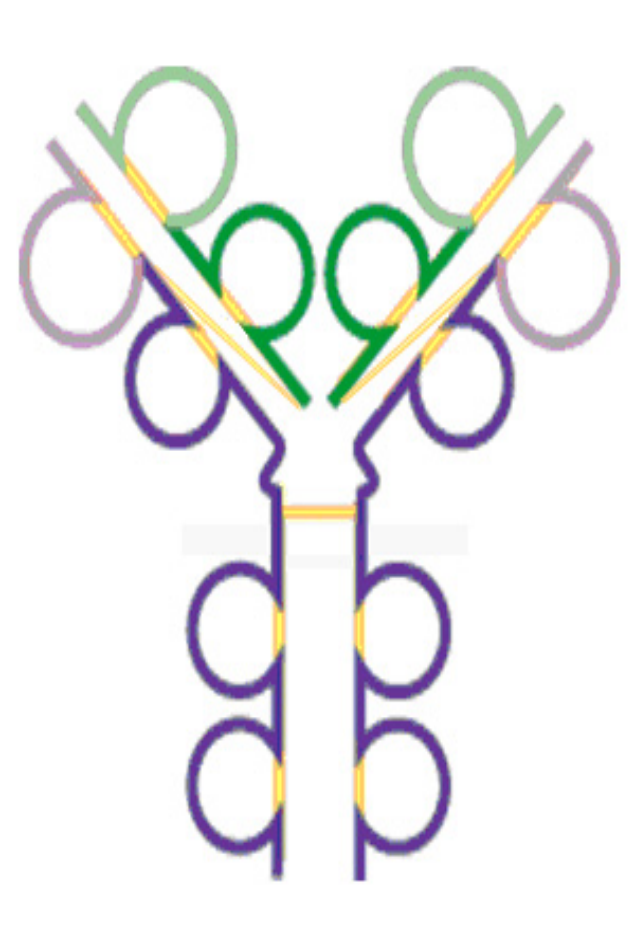
Domain structure





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

Immunoglobulin molecule



CDR

Variable region

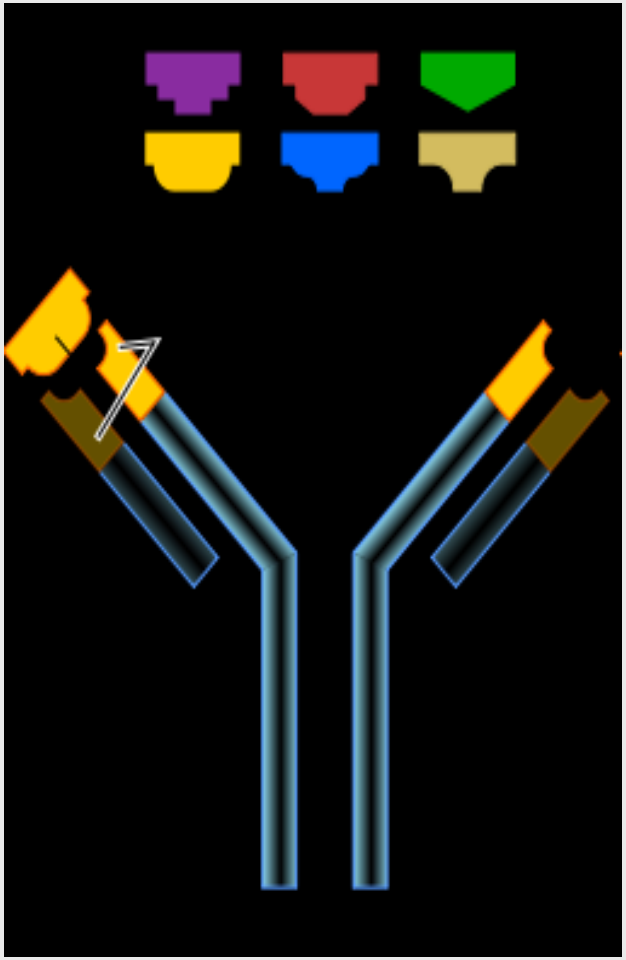
Idiotype

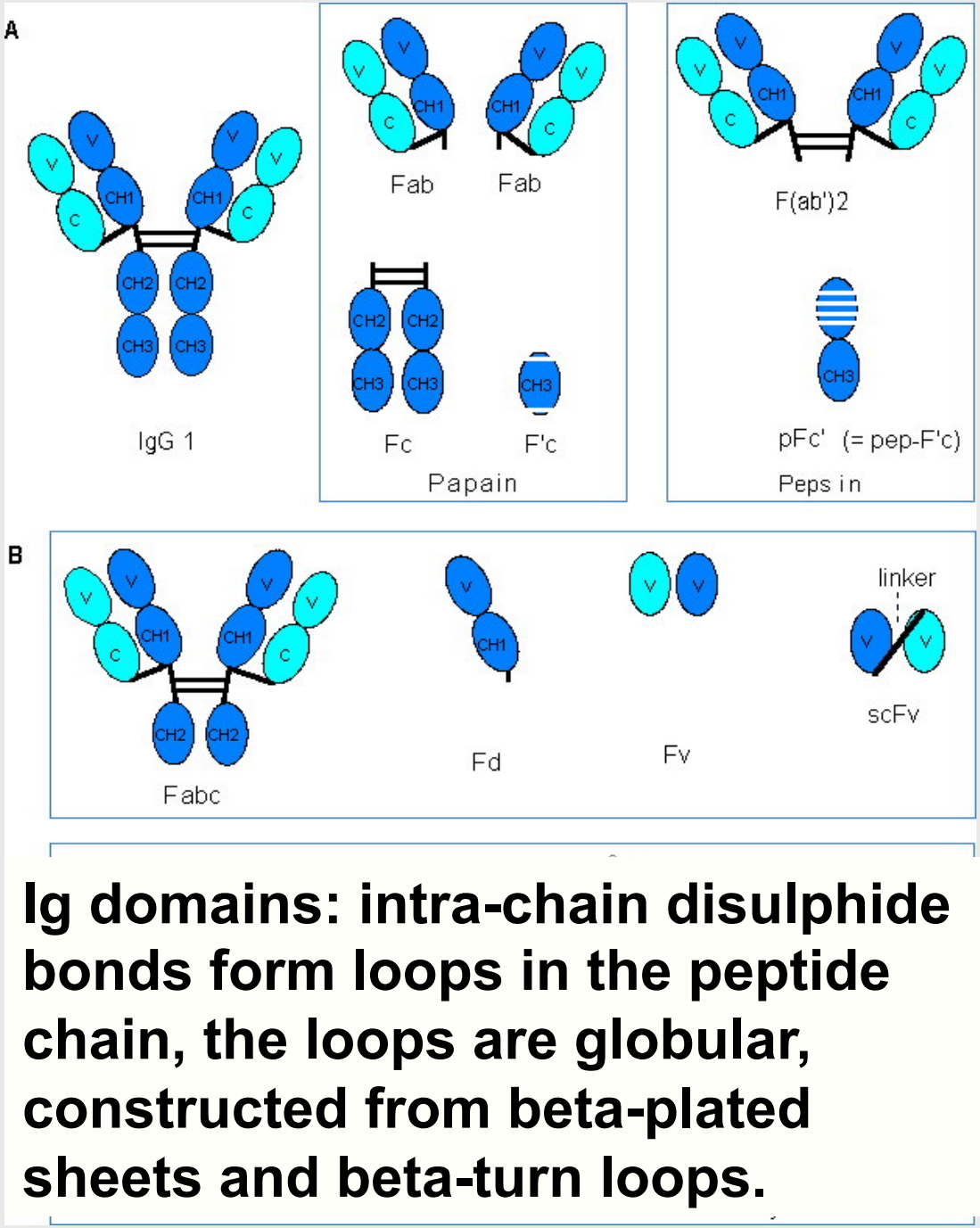
Fab fragment

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.

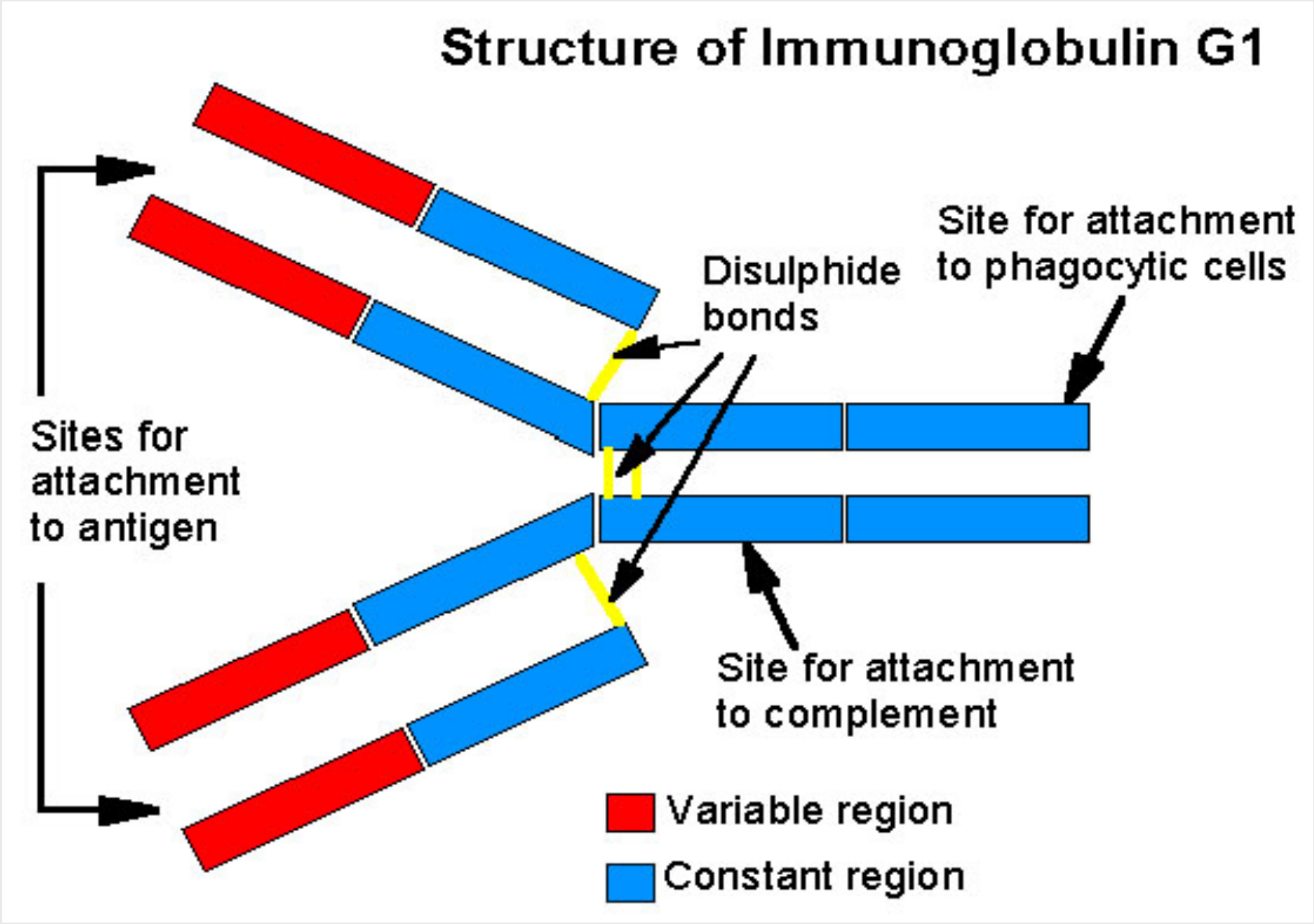
Immunoglobulin isotypes

- 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.

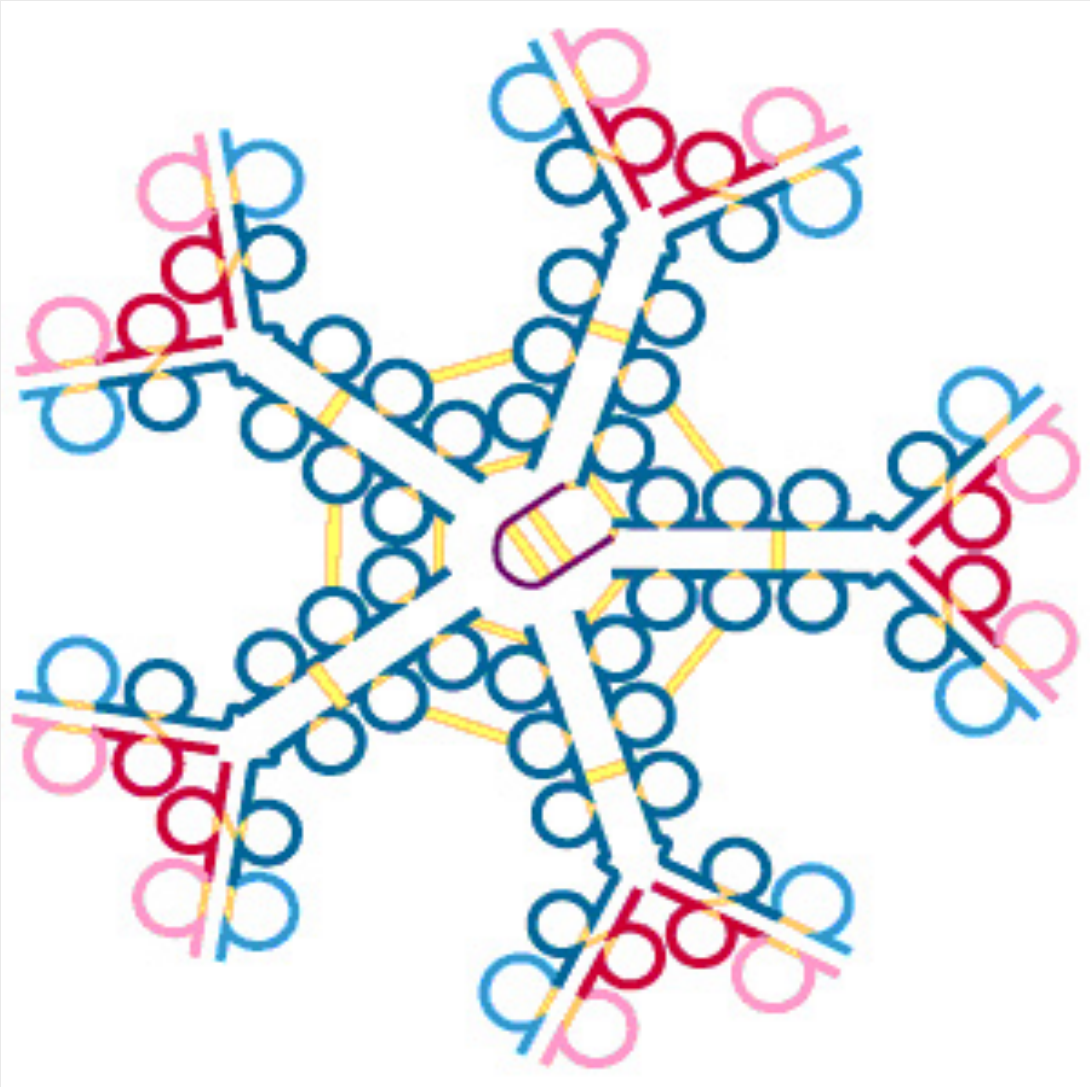
Heavy chain	Light chain	Immuno-globulin Class	Immuno-globulin Subclass
γ1	κ or λ	IgG	IgG1
γ2	κ or λ		IgG2
γ3	κ or λ		IgG3
γ4	κ or λ		IgG4
α1	κ or λ	IgA	IgA1
α2	κ or λ		IgA2
μ	κ or λ	IgM	
δ	κ or λ	IgD	
ε	κ or λ	IgE	

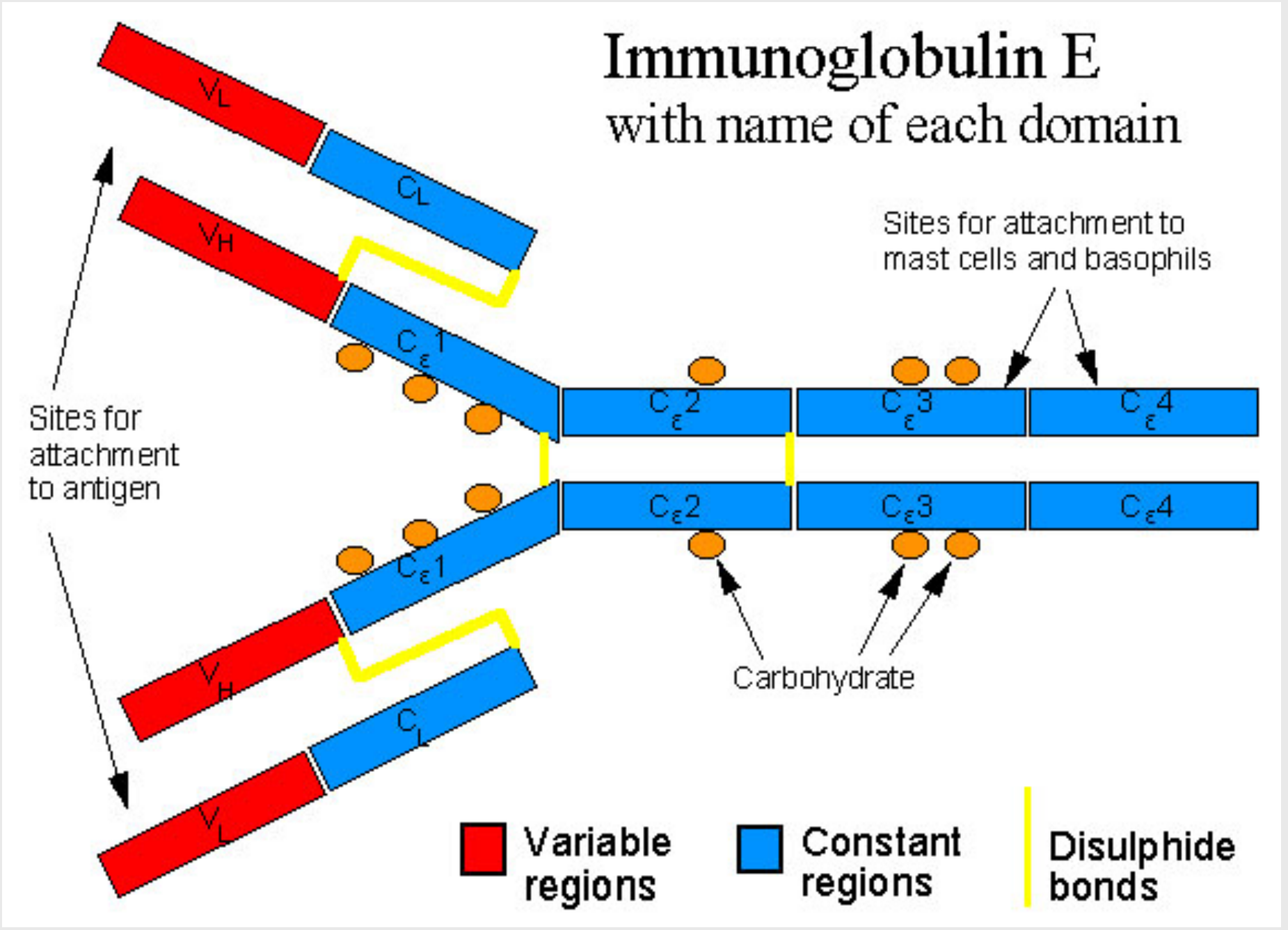
Pronunciation of Greek letters:

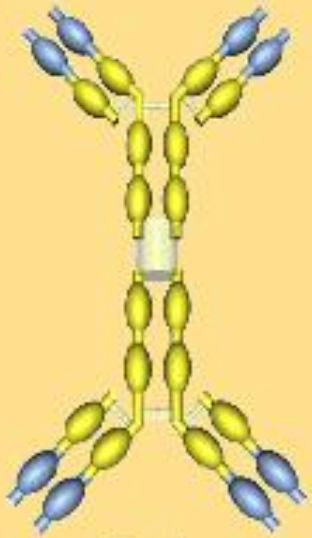
γ gamma α alpha μ mu δ delta
ε epsilon κ kappa λ lambda


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

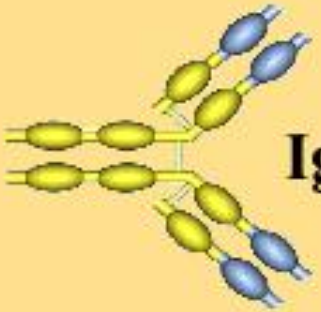
IgA and IgM



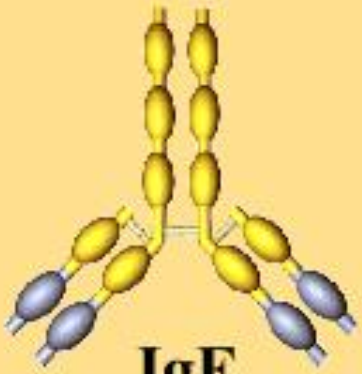

Immunoglobulin E
with name of each domain
V_L
C_L
V_H
$C_\varepsilon 1$
Sites for attachment to mast cells and basophils
Sites for attachment to antigen
$C_\varepsilon 2$
$C_\varepsilon 3$
$C_\varepsilon 4$
$C_\varepsilon 2$
$C_\varepsilon 3$
$C_\varepsilon 4$
$C_\varepsilon 1$
V_H
C_L
V_L
Carbohydrate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



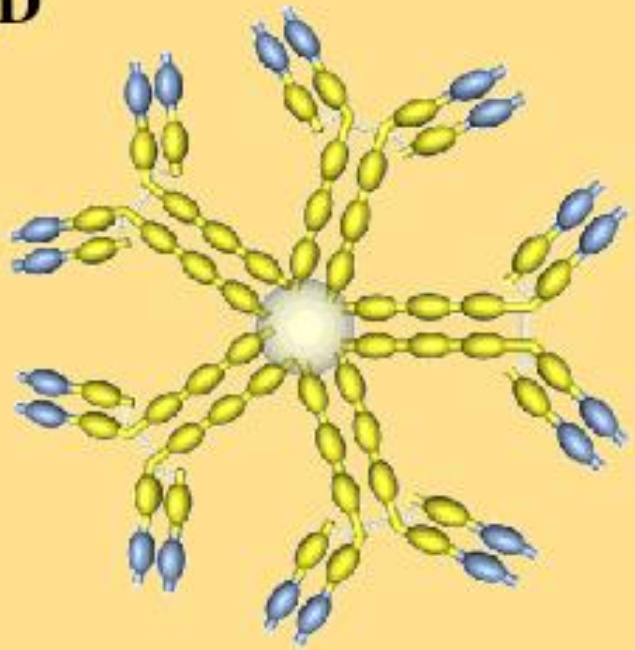
IgA



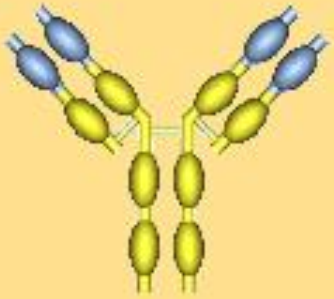
IgD



IgE

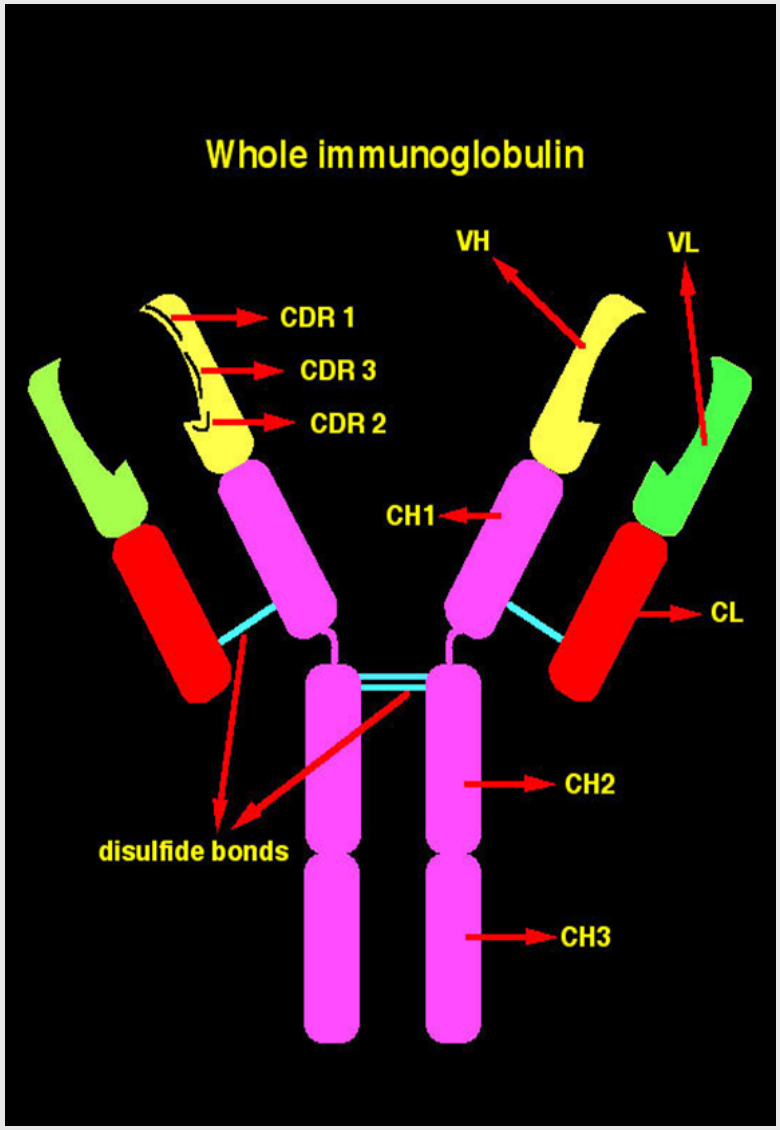


IgM



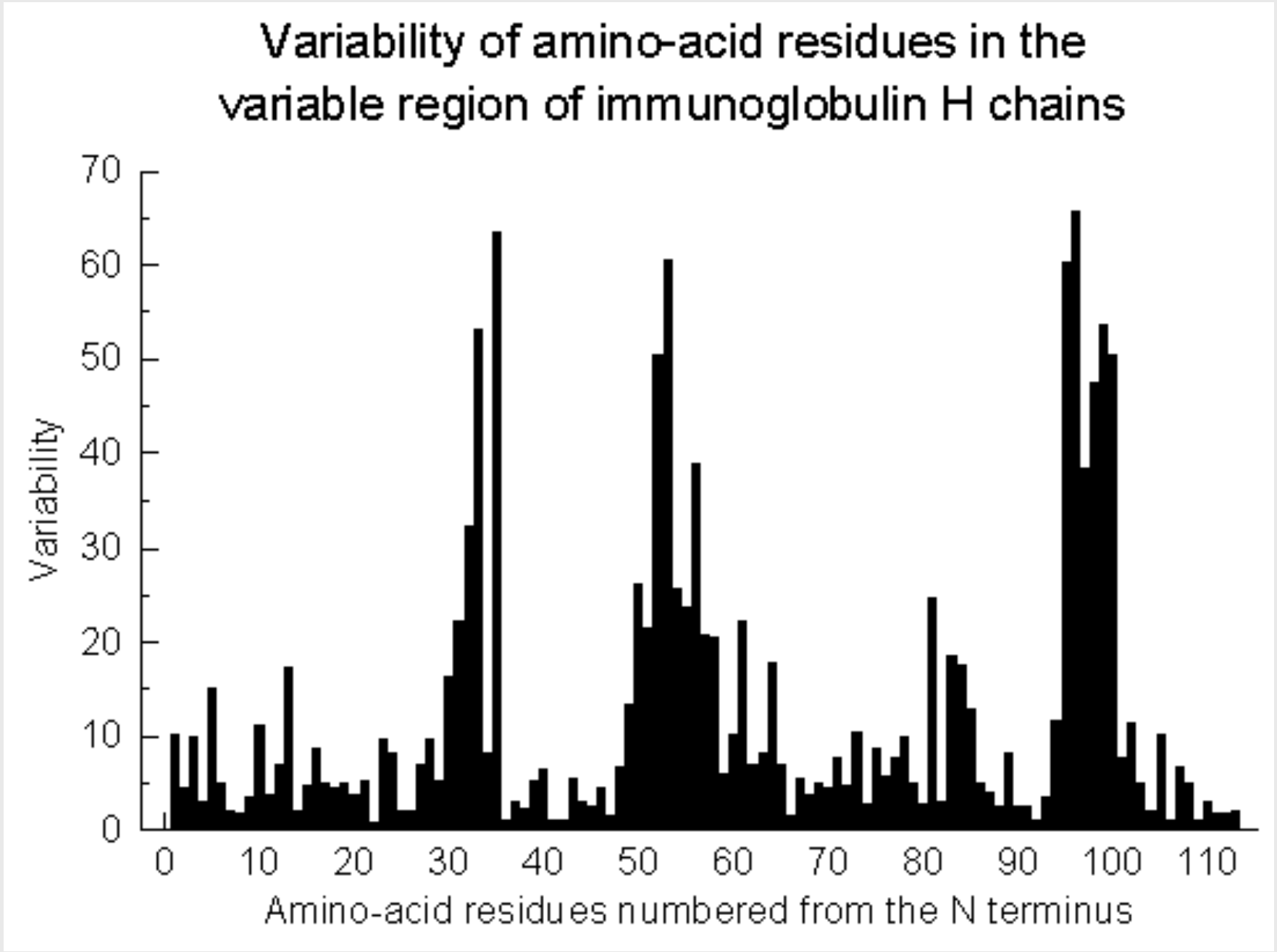
IgG

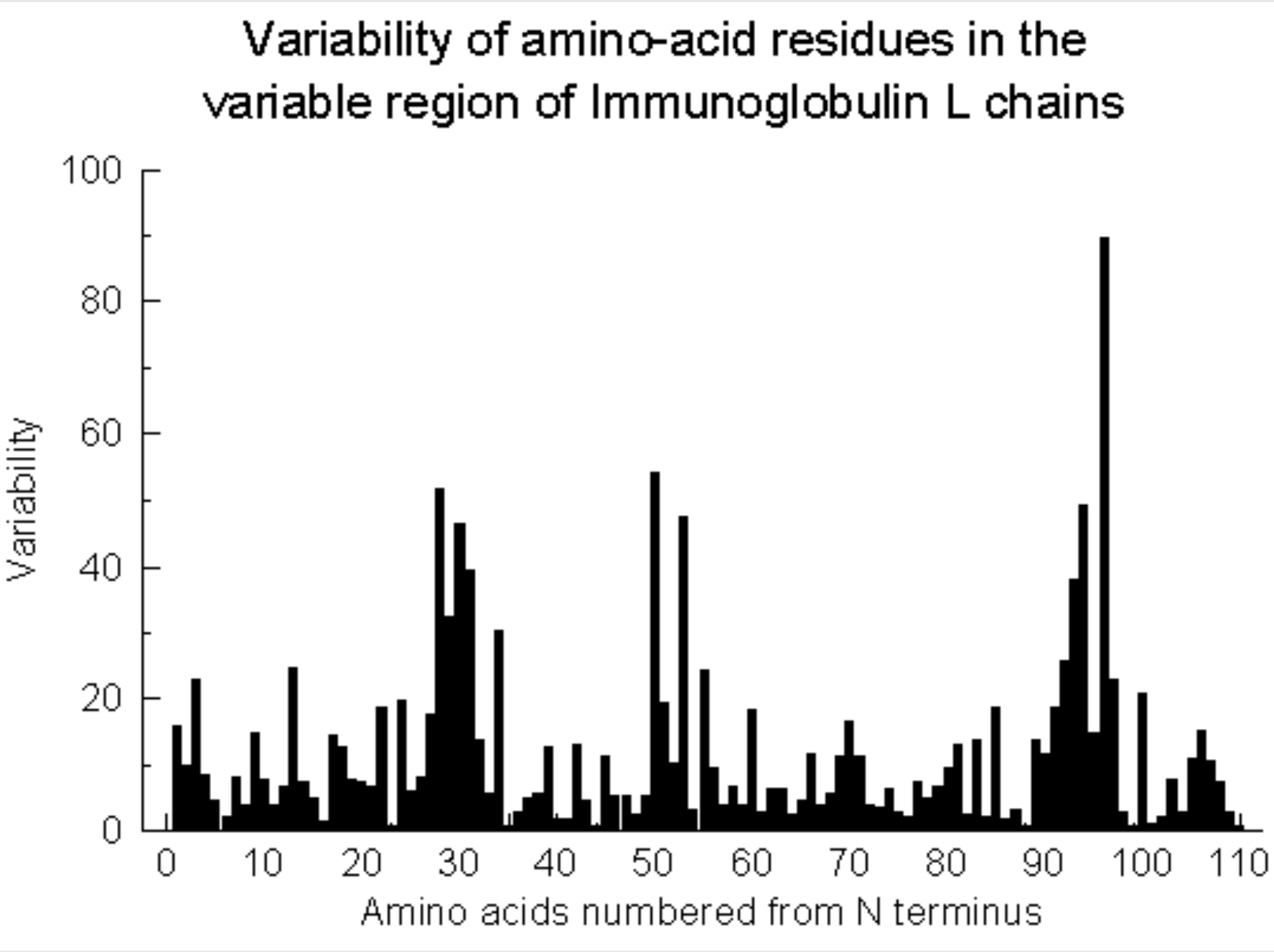
Immunoglobulin idiotype



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

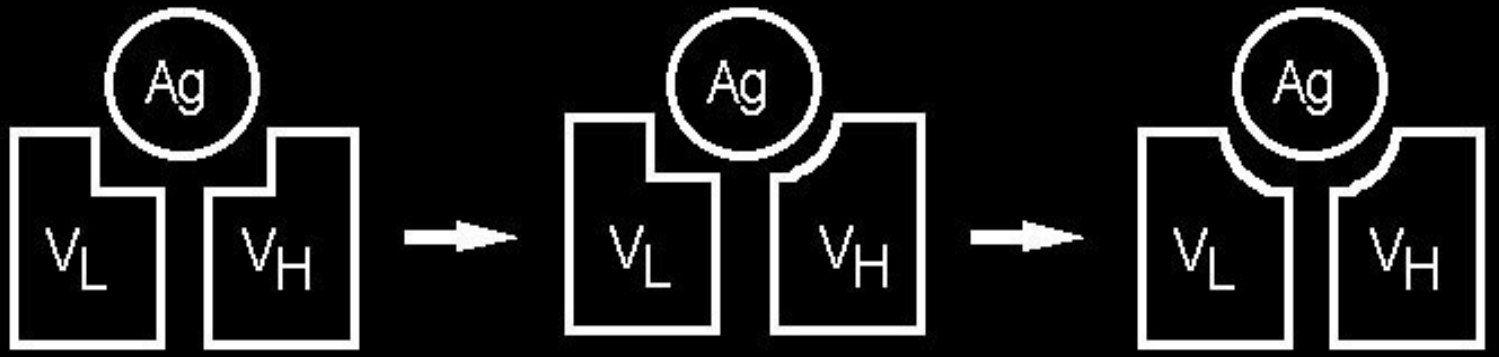
The N terminal Ig domain contains V region forming the antigen binding site: clustering the 3 hyper variable sequences close to each other on both chains - the variation of 3 x 3 results tremendous diversity.

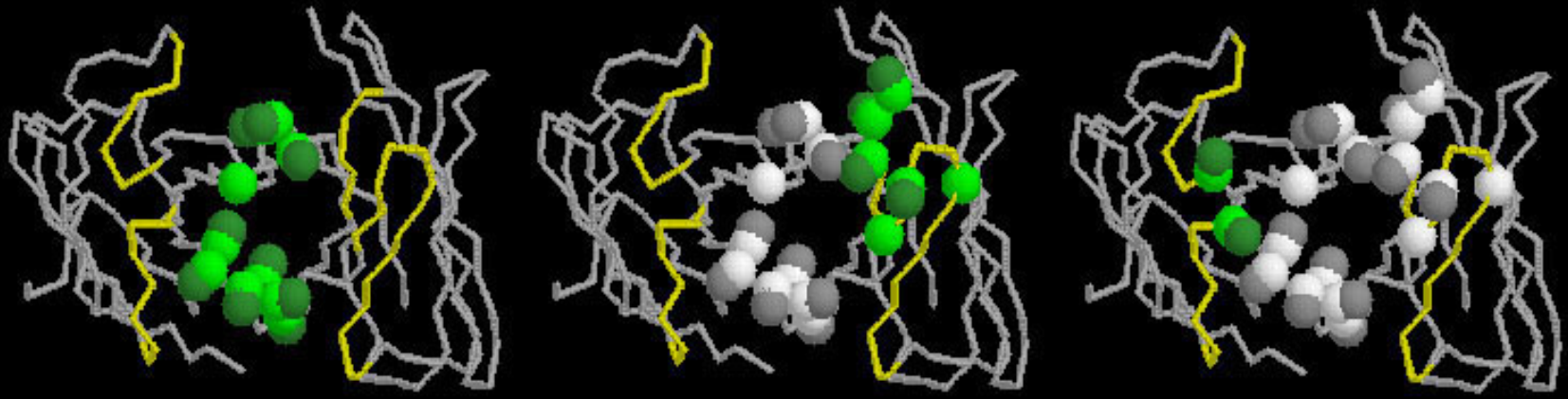

Variability of amino-acid residues in the variable region of immunoglobulin H chains
Variability
0
10
20
30
40
50
60
70
0
10
20
30
40
50
60
70
80
90
100
110
Amino-acid residues numbered from the N terminus


Variability of amino-acid residues in the variable region of Immunoglobulin L chains
Variability
0
20
40
60
80
100
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

Antigen Recognition by T Cells

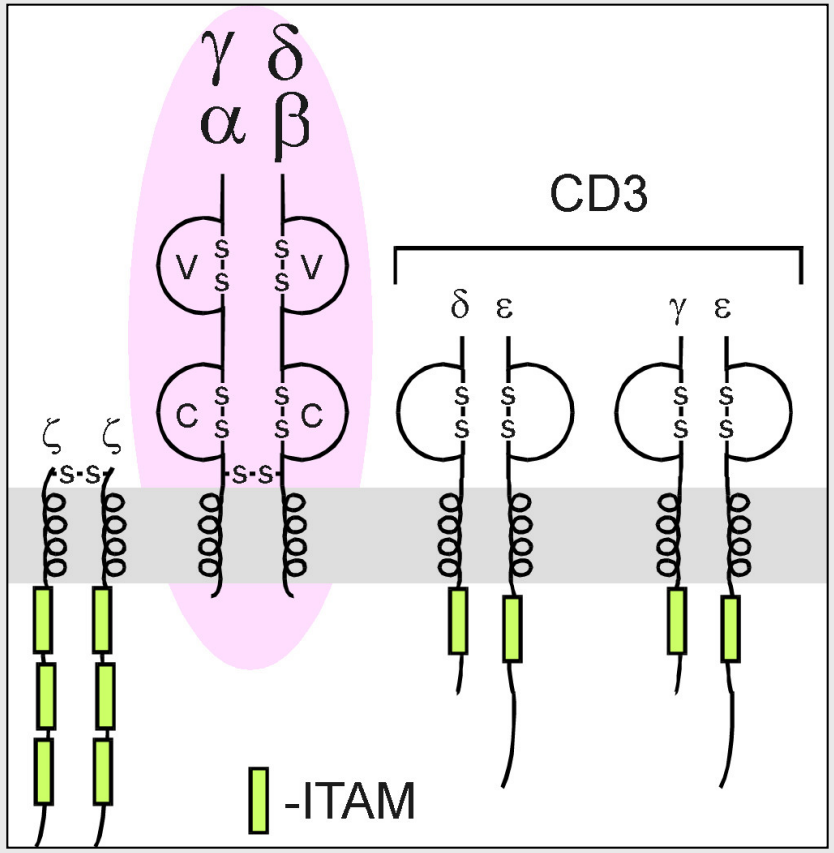
"MHC-restriction"

T cells recognize antigens only displayed on surfaces of the body's own cells as MHC-peptide complexes.

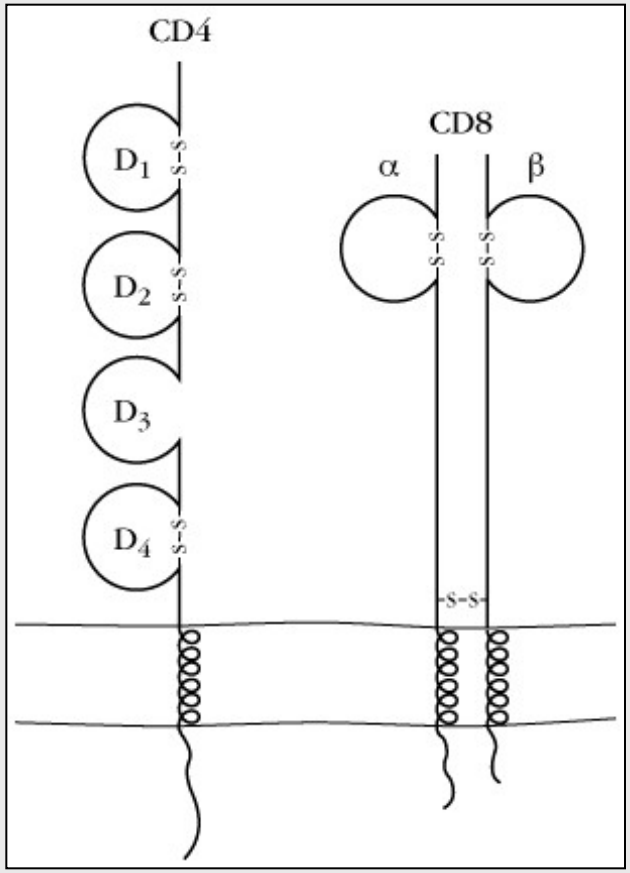
CD8+ (cytotoxic) T-cells	**MHC I-peptide complex**
CD4+ (helper) T-cells	**MHC II-peptide complex**

R. M. Zinkernagel & P. C. Doherty – Nobel Prize for Physiology or Medicine (1996.)

T cell receptor complex on mature T cells



+



αβ TcR – CD4+ vagy CD8+)
γδ TcR – CD4-CD8-

Definition

- **MHC=Major Histocompatibility Complex; HLA=Human Leukocyte Antigen**

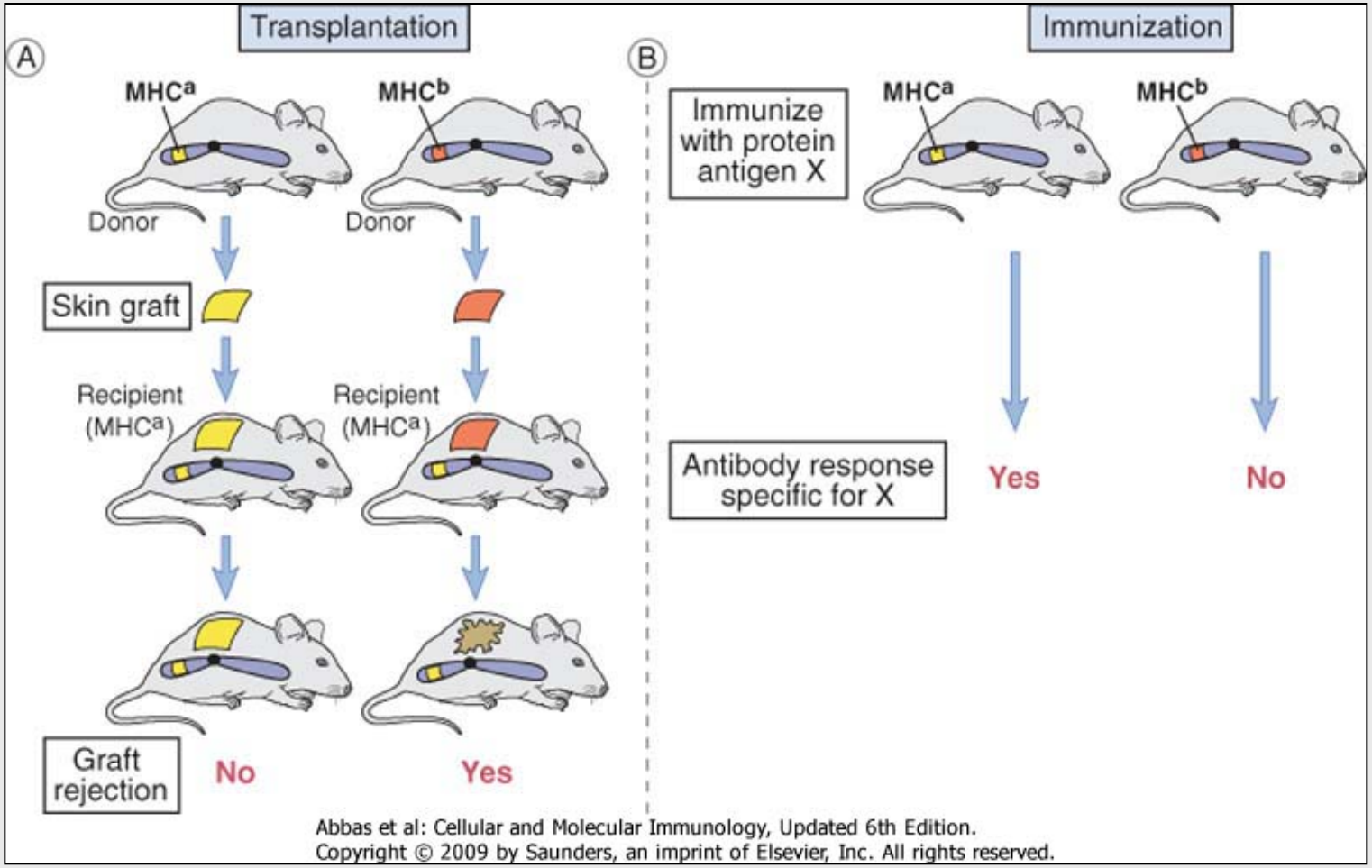
- Discovery: transplantation experiments between inbred mouse strains expressing different MHC genes.

- **Inbred mouse strains**: mating of siblings for 20 generations ➔ all mice are homozygous at every genetic locus (genetically identical = ***"syngeneic"***)

- In case of polymorphic genes (eg. MHC) each inbred strain expresses a single allele from the original population

- Different inbred strains are ***"allogeneic"*** to each other = carry different alleles

Discovery of the mouse MHC



Histocompatibility-2 (H-2) locus

K, D (MHC Class I) genes responsible for graft rejection

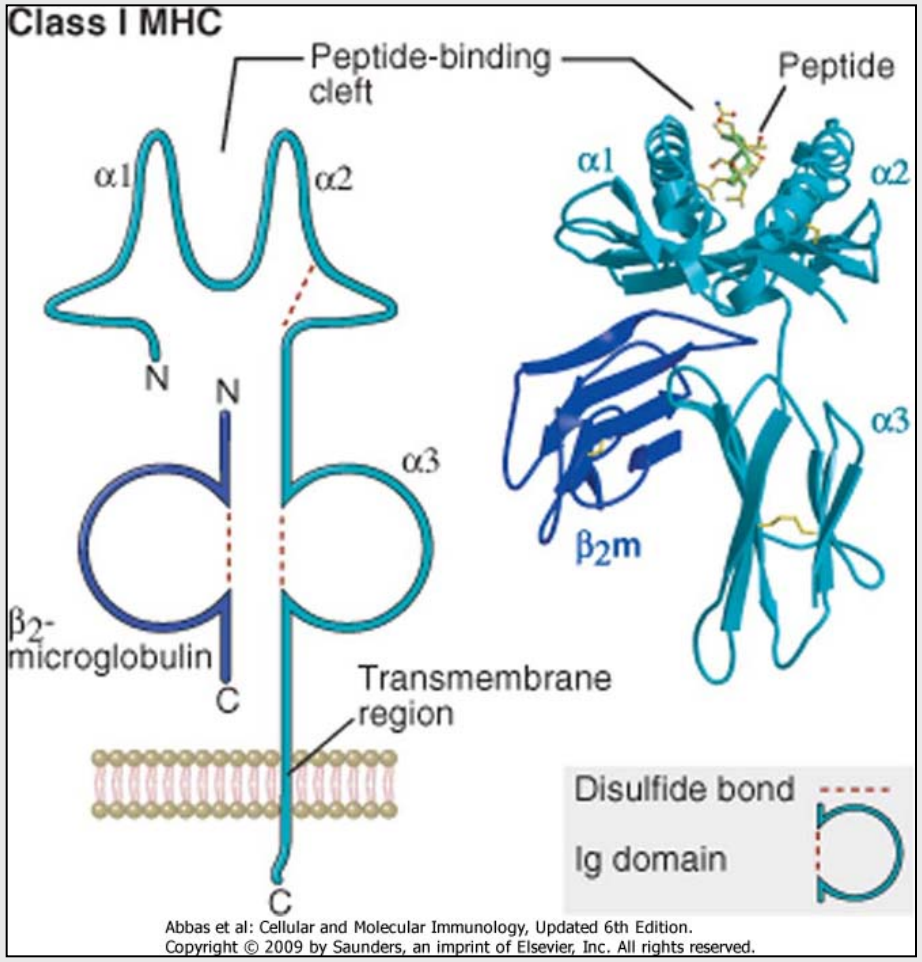
Immune response (Ir) genes

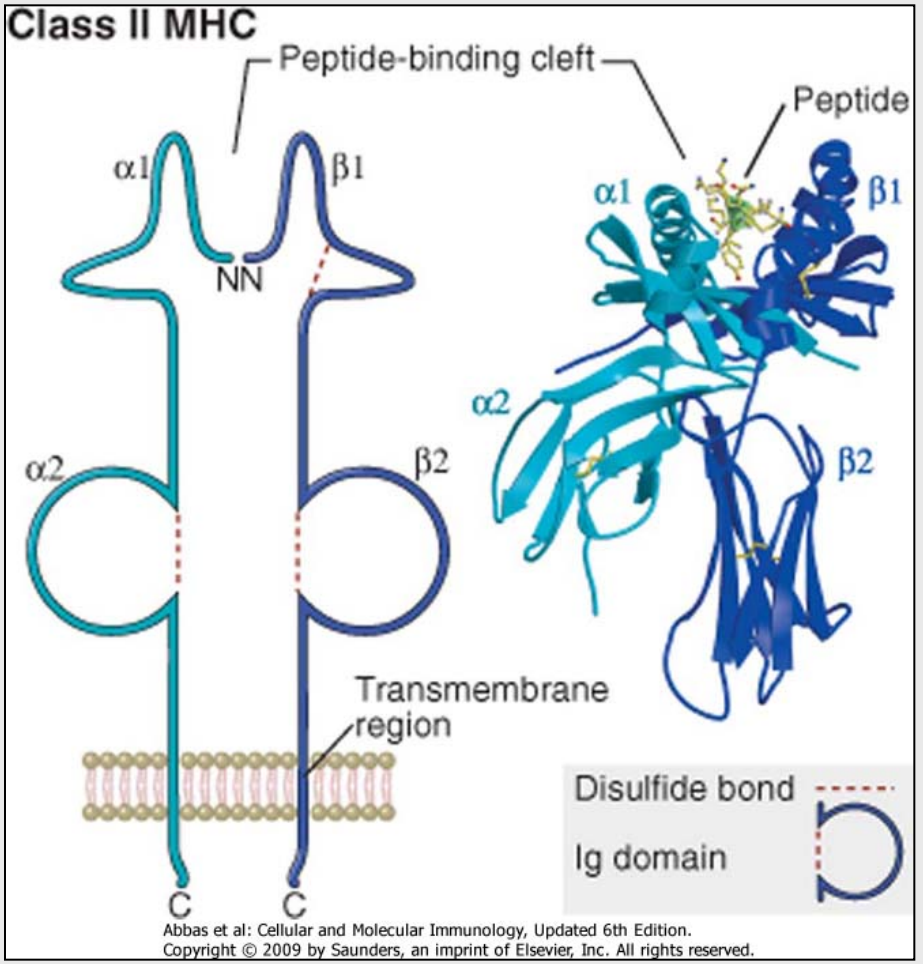
A, E (MHC Class I) genes determine reactivity to different protein antigens

Features of MHC-I and MHC-II molecules

Feature	Class I MHC	Class II MHC
Polypeptide chains	α (44-47 kD) β_2-Microglobulin (12 kD)	α (32-34 kD) β (29-32 kD)
Locations of polymorphic residues	α1 and α2 domains	α1 and β1 domains
Binding site for T cell coreceptor	α3 region binds CD8	β2 region binds CD4
Size of peptide-binding cleft	8-11 AA peptides	10-25 AA peptides
Nomenclature		
Human	HLA-A, -B, -C	HLA-DR, -DQ, -DP
Mouse	H-2K, H-2D, H-2L	I-A, I-E

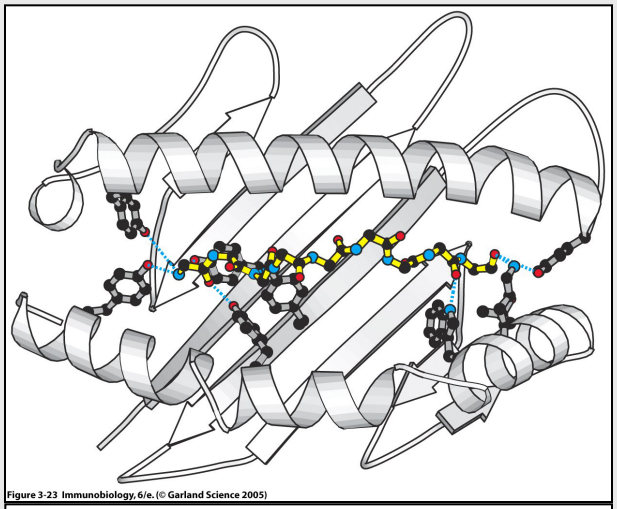
The structure of MHC-I and MHC-II



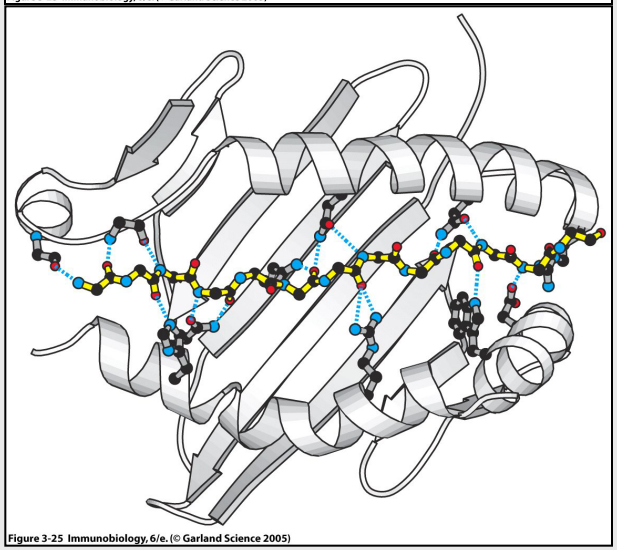


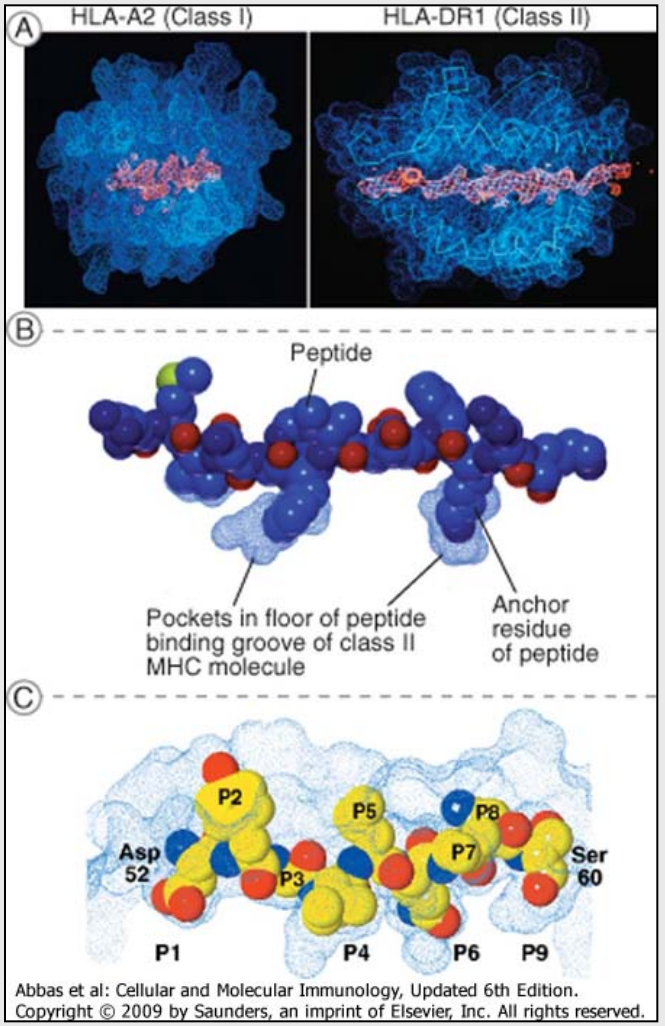
Peptide binding of MHC-I and MHC-II

MHC-I



MHC-II





Non-covalent interaction between **“anchor”-residues** of the peptides and the small pockets in the β-sheet “floor” of the peptide-binding cleft.

Peptide binding of MHC-I and MHC-II

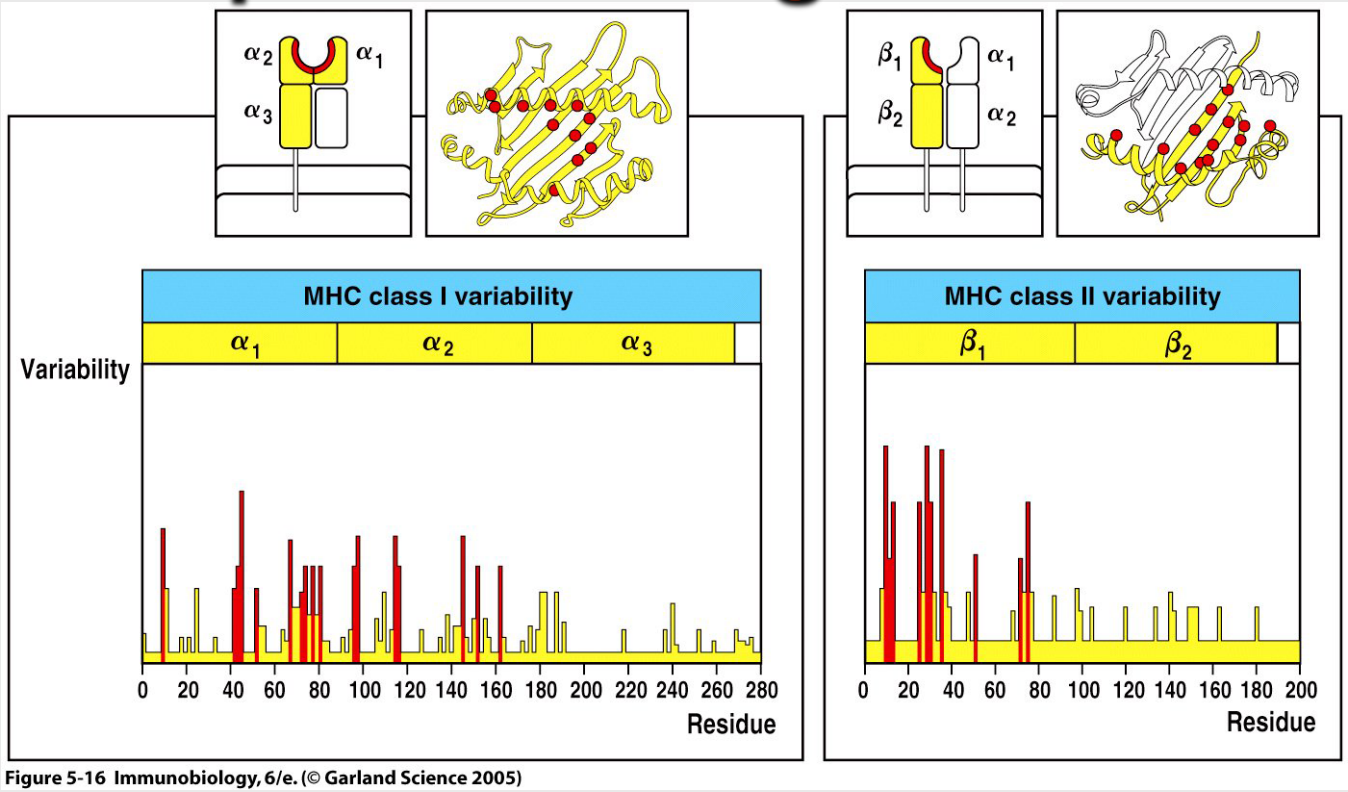
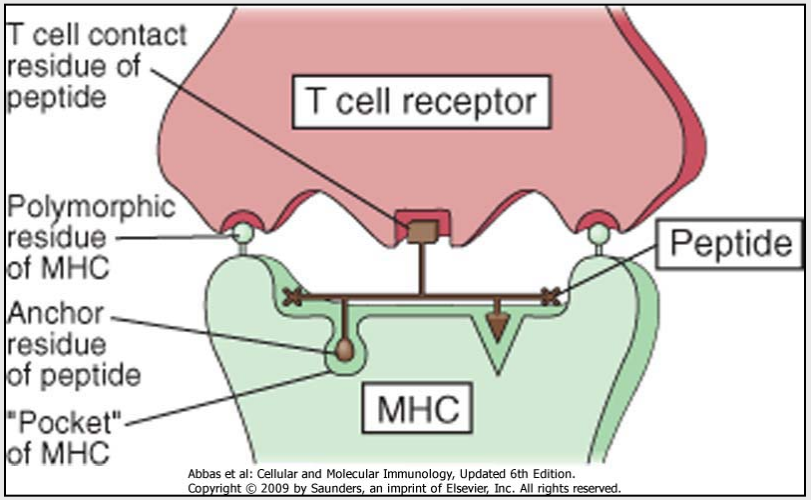


Figure 5-16 Immunobiology, 6/e. (© Garland Science 2005)

1 MHC molecule can bind 3-500 different peptides which contain the appropriate **"anchor"-residues** at key positions.

Polymorphic AA residues of the MHC molecules are located around the peptide-binding cleft – responsible for **peptide-specificity** and **TcR-binding**.



MHC-II peptide binding

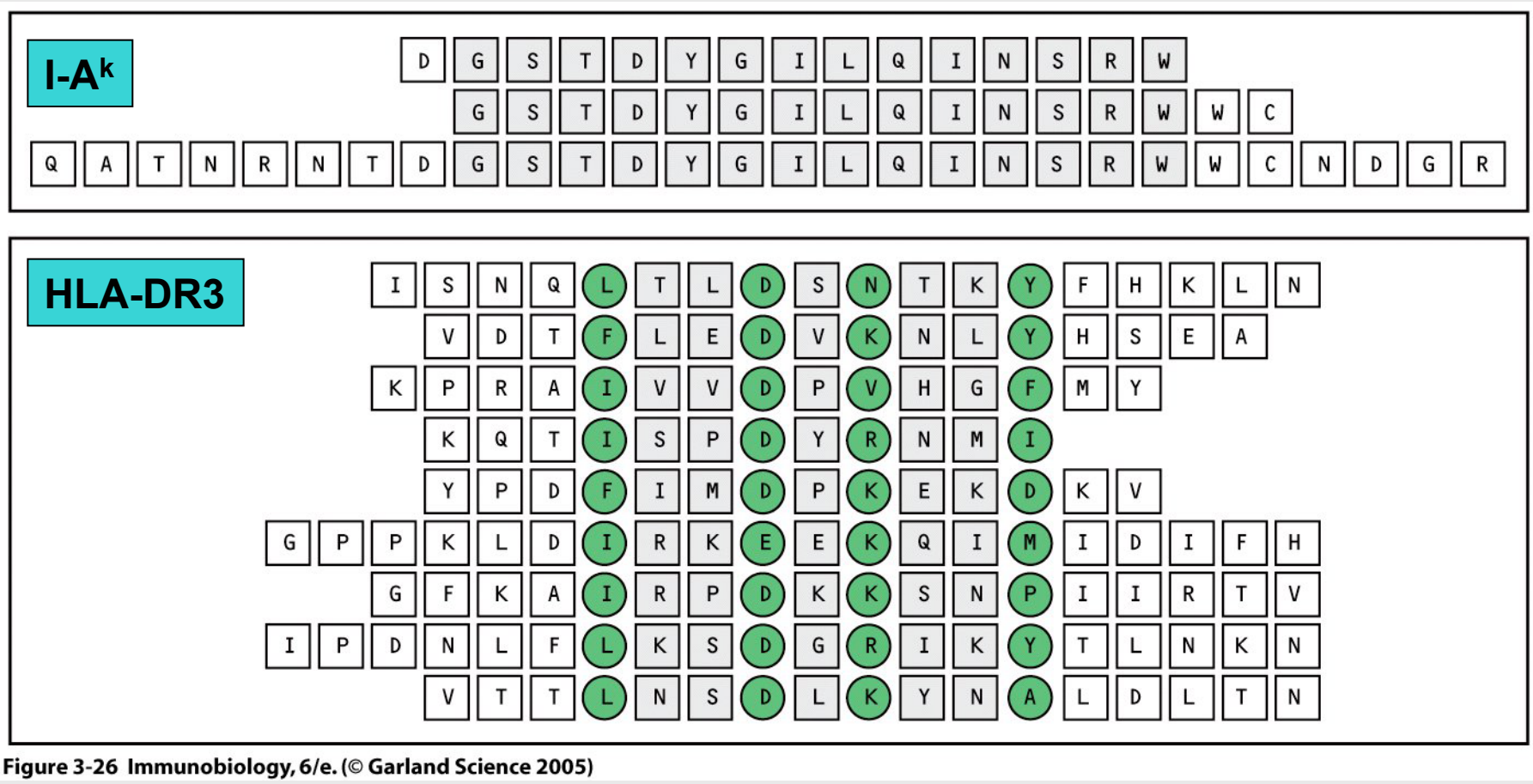
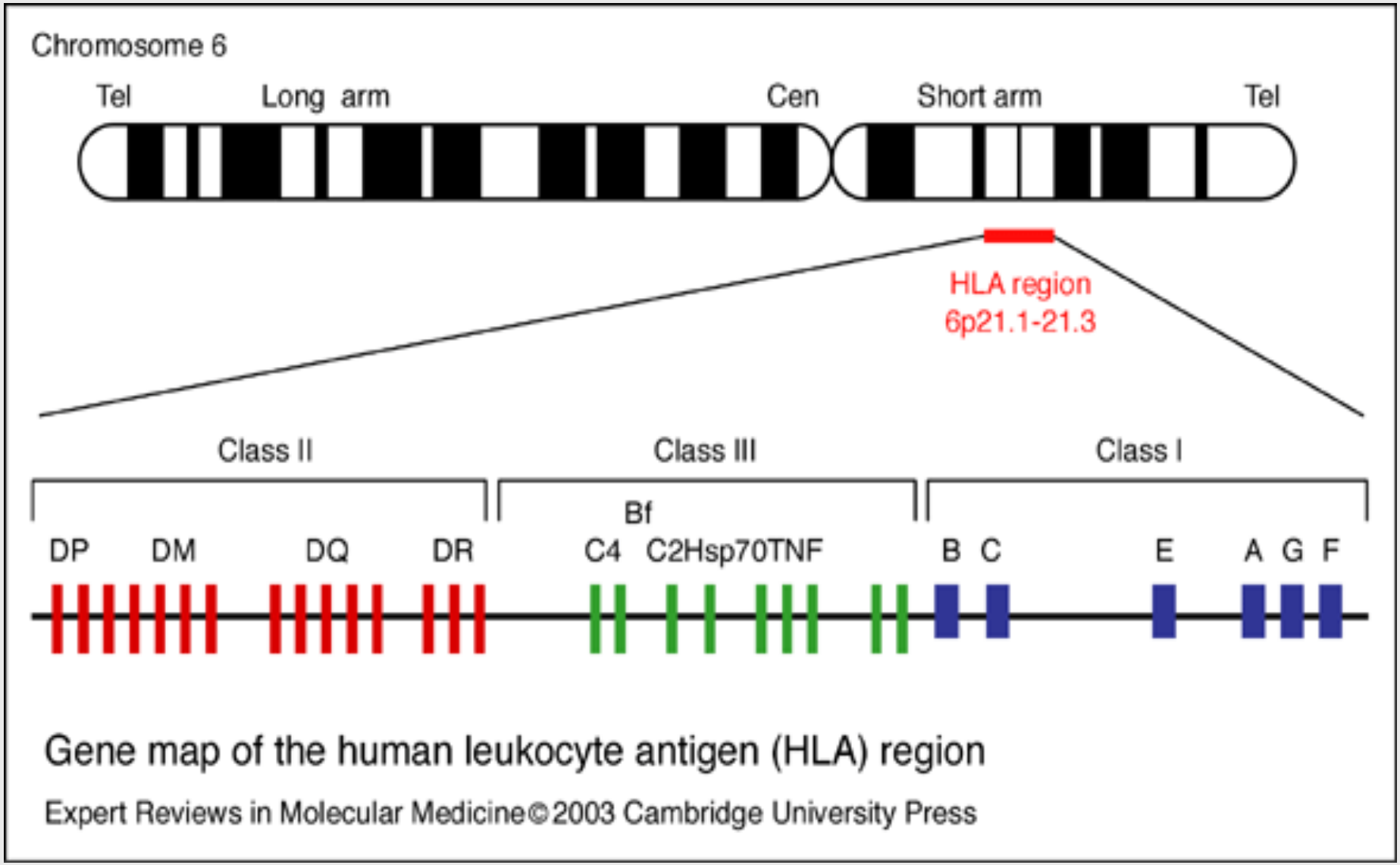


Figure 3-26 Immunobiology, 6/e. (© Garland Science 2005)

HLA map



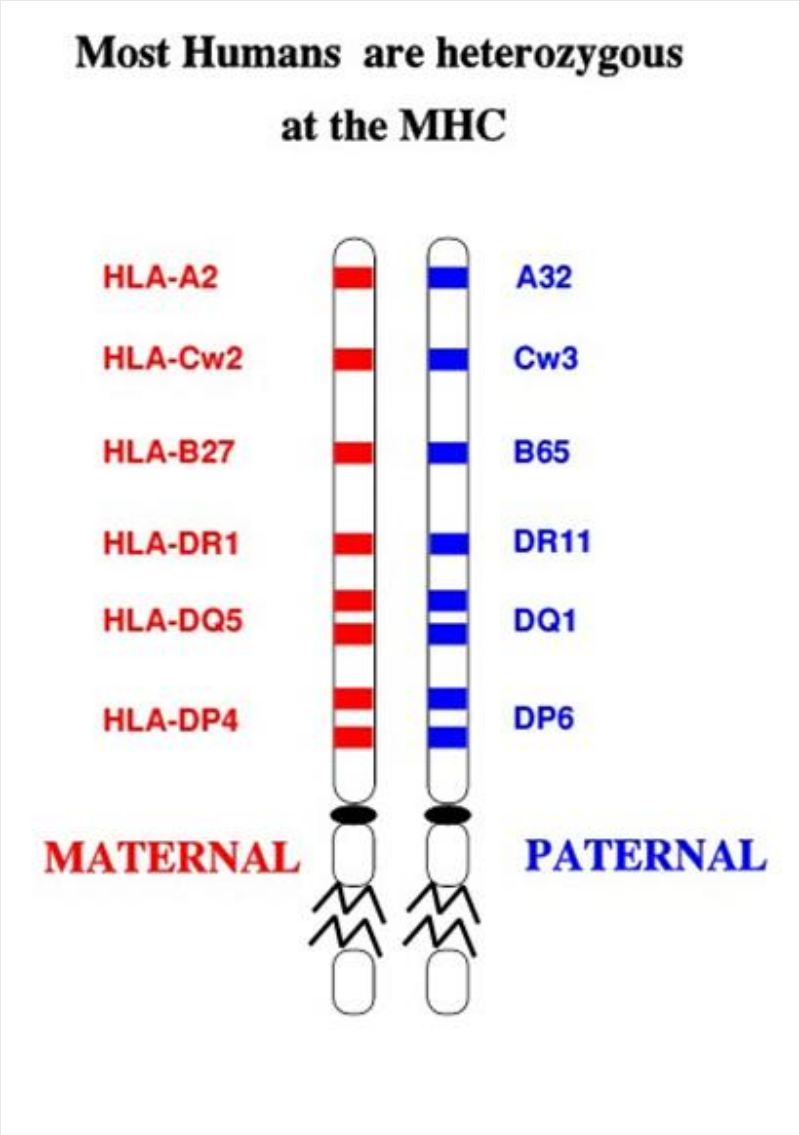
Gene map of the human leukocyte antigen (HLA) region

Genetics of MHC (HLA)

1. **polygenic:** ***several*** different class I and class II ***genes*** encoding proteins with different specificities. In human there are 3 classical class I molecules (**HLA-A, B, C**) and 3 classical class II molecules (**HLA-DR, DP, DQ**).
2. highly **polymorphic:** ***multiple alleles of each gene*** (most individuals are likely to be heterozygous at each locus). The HLA-A has more than 20, B has more 50, and C more than 10 alleles. HLA-DR has 20, HLA-DQ has 9, and HLA-DP has 6 alleles.

   Nomenclature: eg. HLA-B*2705= first 2 places – main alleles, last 2 places - suballeles. (w=workshop - not final)
3. **co-dominant:** Alleles are expressed from both MHC haplotypes in any one individual, and the products of all alleles are found on all expressing cells.

Genetics of MHC (HLA)



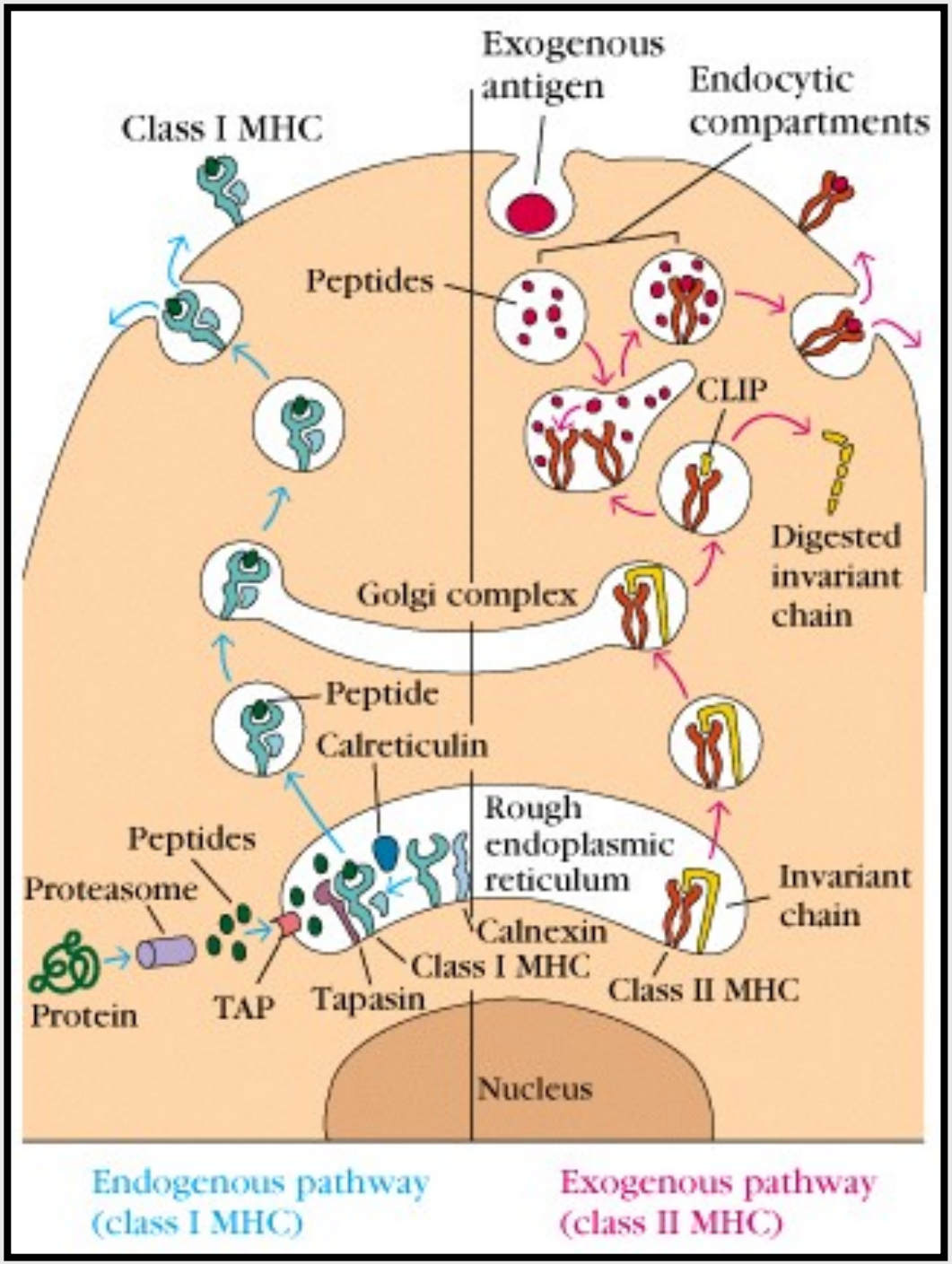
Expression pattern of MHC I and MHC II

MHC I All nucleated cells + platelets

MHC II Professional antigen presenting cells

- Dendritic cells
- B cells
- Macrophages
- (Thymic epithelial cells)

Facultative antigen presenting cells
eg. inflammatory epithel


Exogenous antigen
Endocytic compartments
Class I MHC
Peptides
CLIP
Digested invariant chain
Golgi complex
Peptide
Calreticulin
Rough endoplasmic reticulum
Peptides
Proteasome
Invariant chain
Calnexin
Class I MHC
Class II MHC
Protein
TAP
Tapasin
Nucleus
Endogenous pathway (class I MHC)
Exogenous pathway (class II MHC)

Antigen Presentation on MHC I

- Cytosolic, mainly normal or viral/modified proteins
- Proteasomal degradation

Peptide transfer to the ER (TAP1&2)

MHC I chains produced into ER by ribosomes

Chaperons: calnexin, calreticulin, Erp57

Tapasin and TAP1&2

MHCI & peptide binding within the ER

Antigen Presentation on MHC II

-Endocytosed proteins: bacteria, bacterial product, internalised receptor bound peptide, parts of another cell

-Endosomal degradation

-MHCII chains produced into the ER by ribosomes

-invariant chain

-HLA-DM: MHC II specific chaperon

-CLIP=class II associated invariant chain peptide

-MHC II & peptide binding in endosomes outside the ER

Superantigens

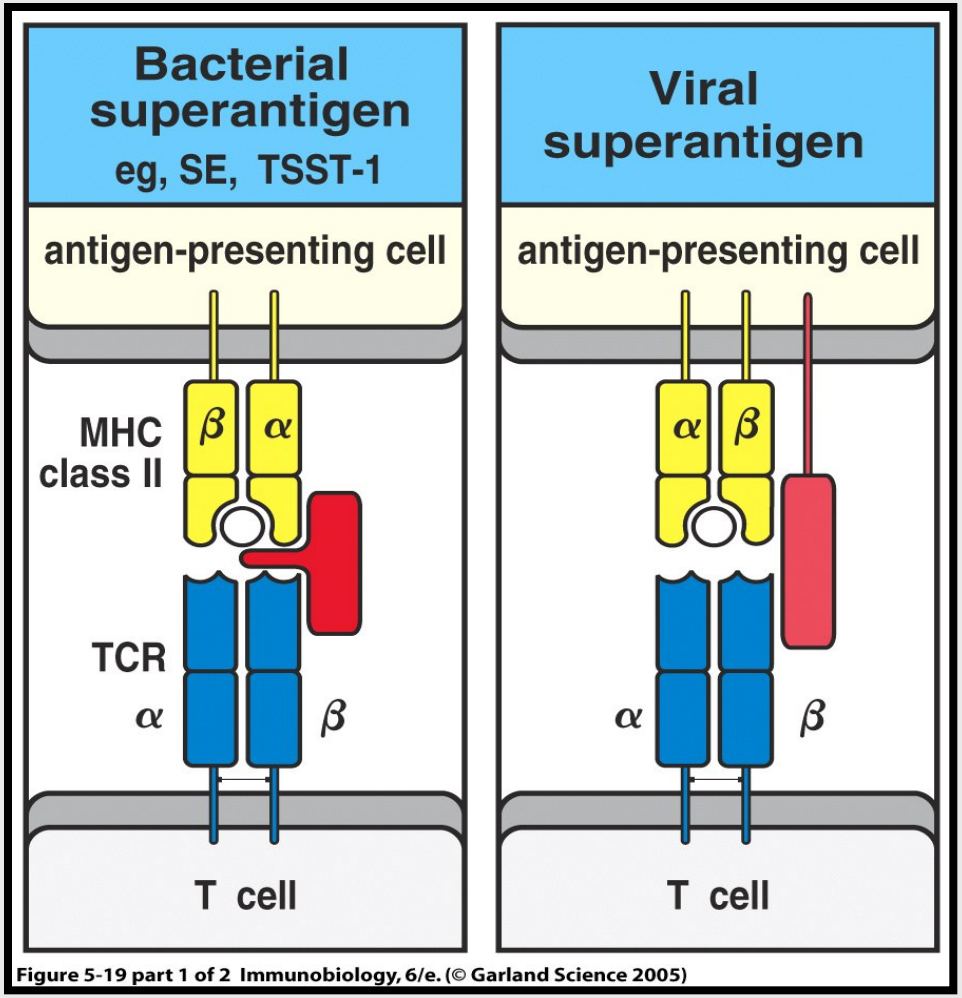


Figure 5-19 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Compared to a normal antigen-induced T-cell response where 0.001-0.0001% of the body's T-cells are activated, SAgs (endotoxins) are capable of activating up to 20% of the body's T-cells. This causes a massive immune response (toxic shock syndrome) that is not specific to any particular epitope on the SAg.

T cells produce cytokines - systemic toxicity, suppression of adaptive immune response („Cytokine tsunami")

Medical aspects of MHC

- Tissue/organ transplantation – donor and recipient must have matching HLA haplotype

- HLA-association of diseases (“disease susceptibility”) – certain diseases appear more frequently in individuals with a specific HLA type

HLA-association of diseases

Some HLA associated autoimmune diseases

Disease	HLA	Pts[a]	Ctrls[a]	RR[b]
Ankylosing spondylitis	B27	> 95	9	> 150
Subacute thyroiditis	B35	70	14	14
Psoriasis vulgaris	Cw6	87	33	7
Graves disease	DR3	65	27	4
Myasthenia gravis	DR3	50	27	2
Addisons disease	DR3	69	27	5
Rheumatoid arthritis	DR4(some)	81	33	9
Juvenile idiopathic arthiritis	DR8	38	7	8
Celiac disease	DQ2 (+DQ8)	92	28	30
Narcolepsy	DQ6(02)	> 95	33	> 40
Multiple sclerosis	DQ6(02)	86	33	12
Type 1 diabetes	DQ8(+)	81	23	14
Type 1 diabetes	DQ6(02)	< 0.01	33	0.02

[a] The figures show antigen frequencies in a Norwegian population.

[b] RR: relative risk; i.e. how many times more frequent the disease is in those having the corresponding HLA molecule compared to those lacking it.

In: E. Thorsby, B.A. Lie: HLA associated genetic predisposition to autoimmune diseases: Genes involved and possible mechanisms. *Transplant Immunology* 14 (2005) 175 – 182.

Table 2. Association between human leukocyte antigen (HLA) and some infectious diseases

Disease	HLA Association
Bacterial	
Ankylosing spondylitis	B27
Reiter disease	B27
Acute anterior uveitis	B7
Mycobacterial	
Tuberculosis and leprosy	DR2
(multibacillary forms)	(DRB1*1501, 1502)
lepromatous leprosy	DR2 and DQ1
paucibacillary tuberculoid	DR3
Viral	
Dengue fever virus	DR15
Human immunodeficiency	DR13
virus 1	(DRB1*1301, 1302, 1303)
	DR2
	(DRB1*1501)
	DRB1*03011
Hepatitis B virus	DR13
Hepatitis C virus	A2
	DR5
Epstein-Barr virus	B35.01
	A11
	B7
Parasitic	
Malaria	B53
Scabies	A11
Diffuse cutaneous	A11, B5, B7
leishmaniasis	
Localized cutaneous	A28, Bw22, DQw8
leishmaniasis	Bw22, DR11, Qw7
	Bw22, Dqw3
Schistosomiasis	B5, DR3
Visceral leishmaniasis	A26

In: N. Singh, S. Agrawal, A.K. Rastogi Infectious Diseases and Immunity: Special Reference to Major Histocompatibility Complex. *Emerging Infectious Diseases* 3 (1997) 41-49.

Thank you for your attention!