Corso di Immunologia - III anno
Prof. Paolini

Lezione 16/10/2026

"Antigeni e recettori per l'antigene"
"Il sistema MHC"

Il materiale presente in questo documento viene distribuito esclusivamente ad uso interno e per scopi didattici.

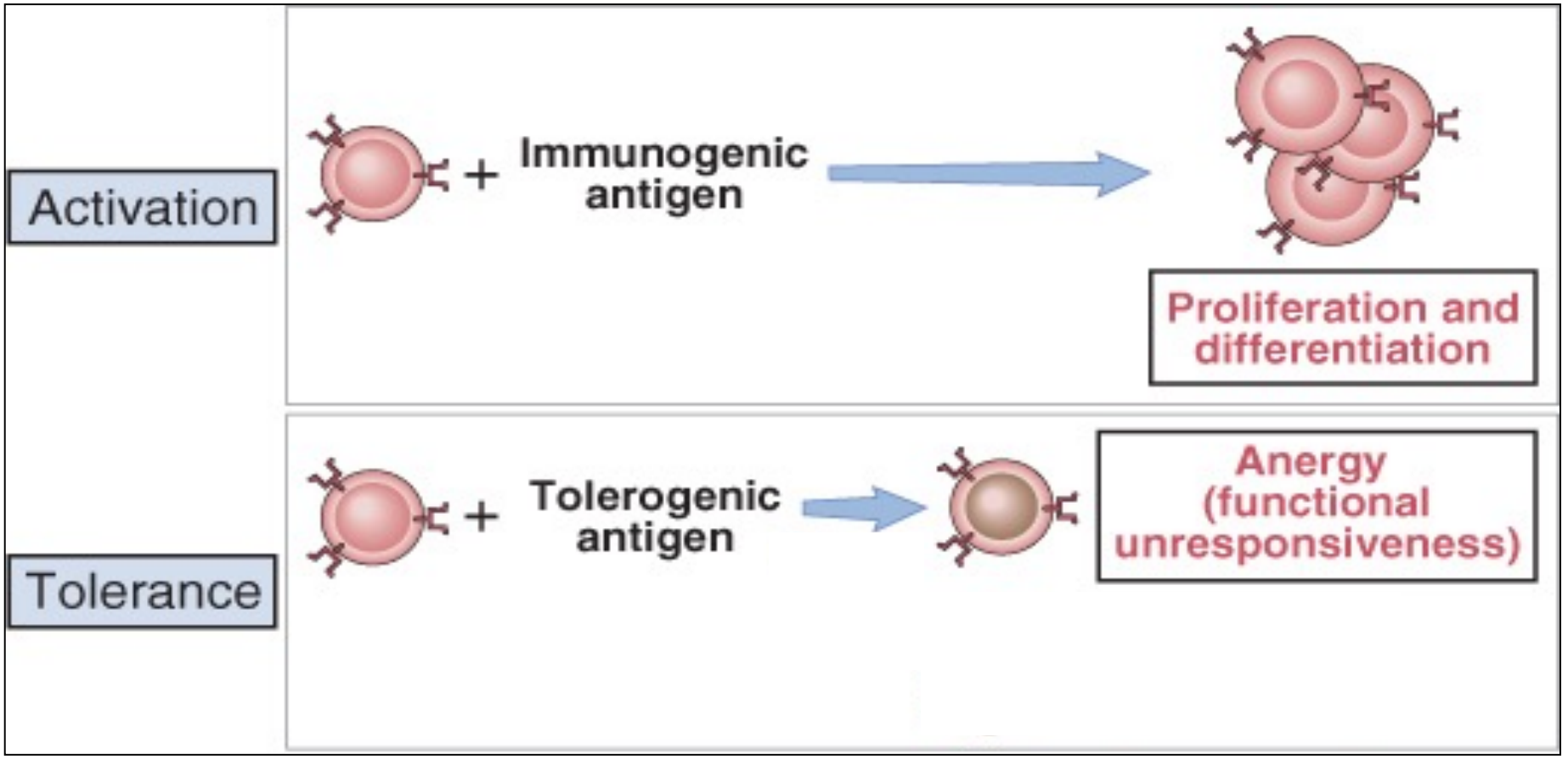
Innate vs Adaptive Molecular Recognition

Most important difference: Receptors used to recognize pathogens

- Innate immunity: Receptors recognize conserved structures present in many pathogens

- Adaptive immunity: Receptors recognize a specific structure unique to that pathogen

Antigen recognition does not necessarily leads to B and T cell activation!



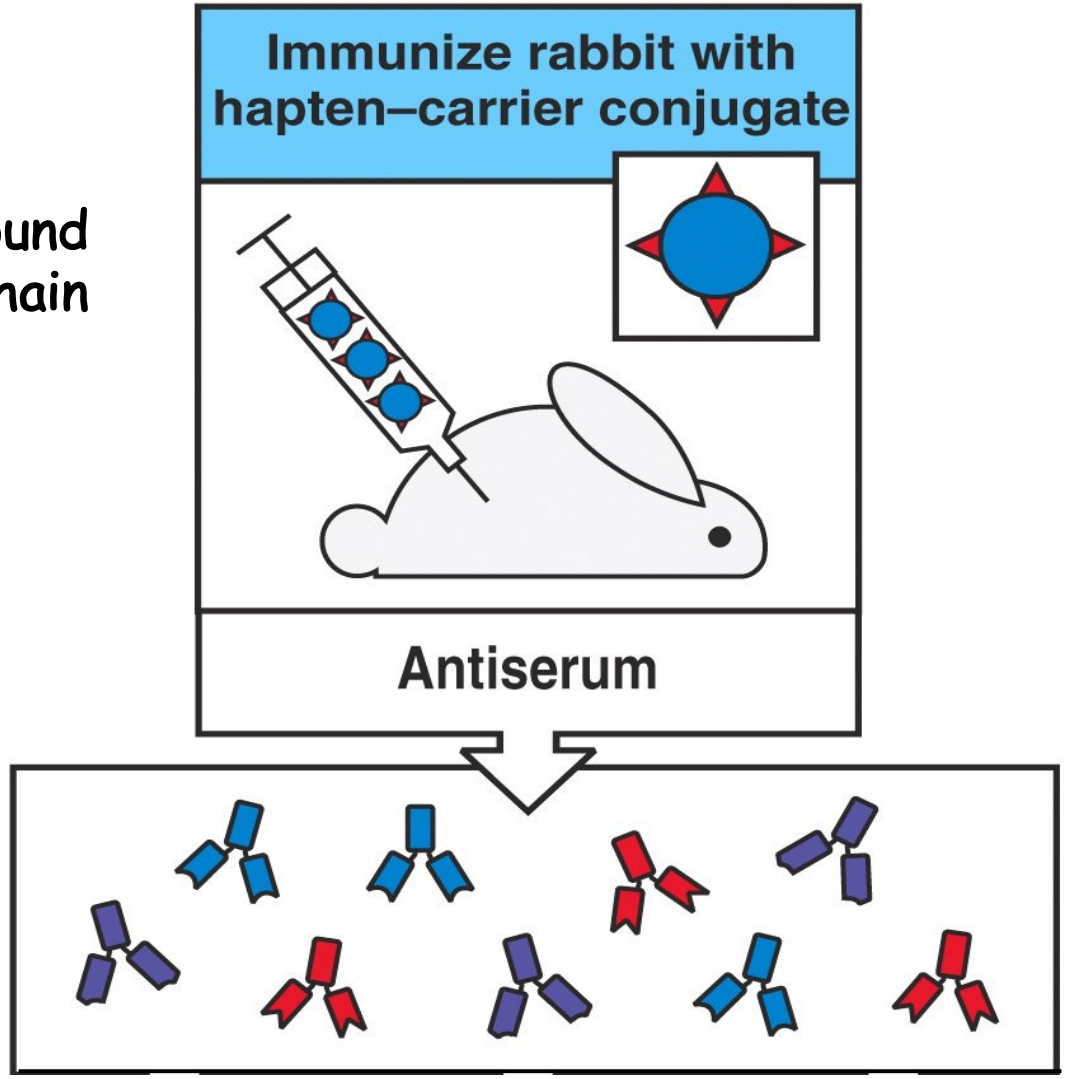
IMMUNOGENICITY is linked to some properties of the antigen::

-Foreignness. To trigger an immune response, a molecule must be recognized as non-self.

-Molecular weight. The best immunogens typically weigh more than 10,000 Daltons.

An example of a non-immunogenic antigen is the hapten, which can induce an immune response only when bound to a carrier protein.

Hapten = chemical compound the size of a tyrosine side chain (< 4000 Daltons).



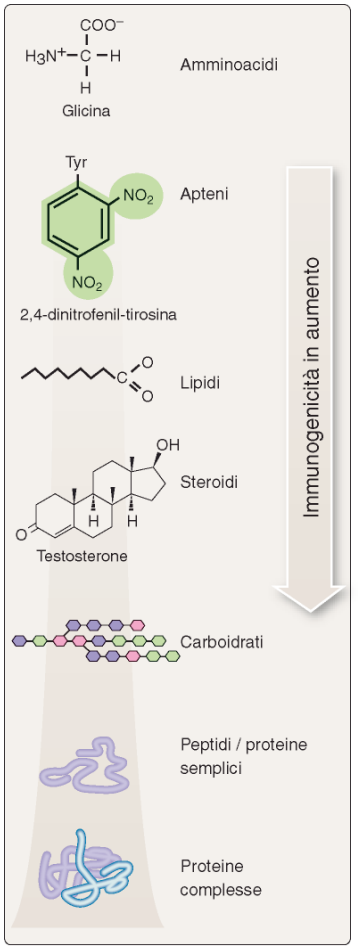
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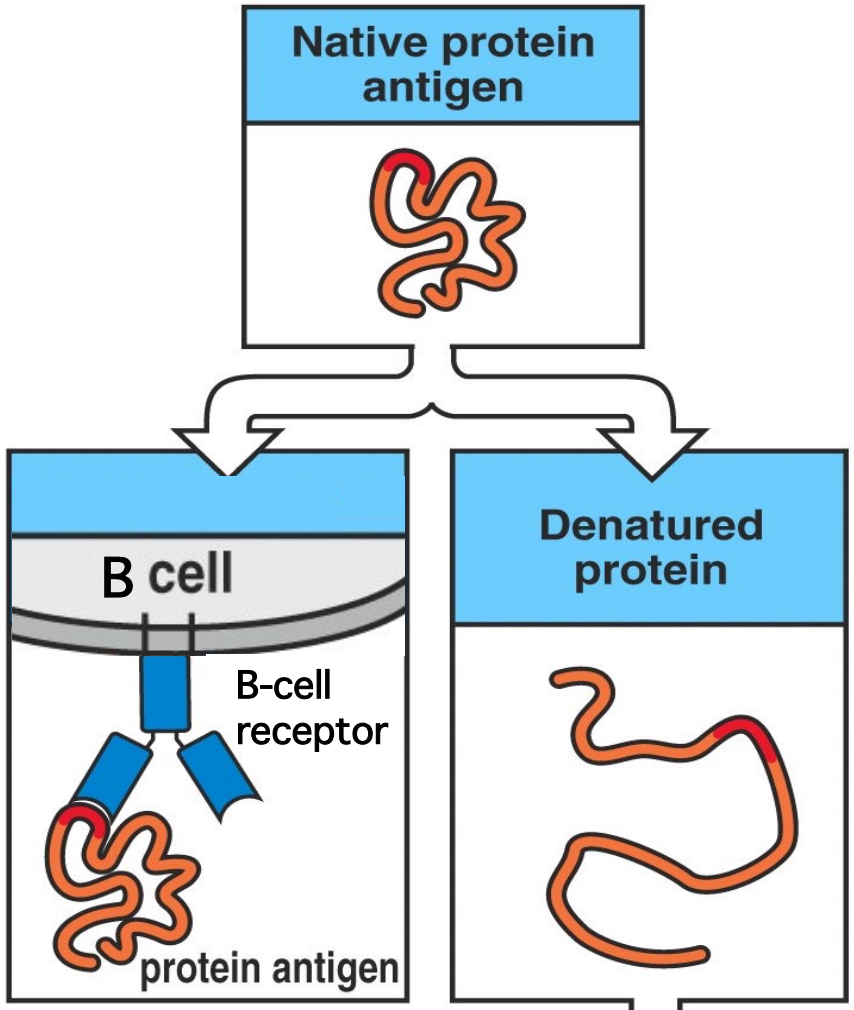
-Molecular weight. The best immunogens typically weigh more than 10,000 Daltons.

-The chemical nature. Proteins, followed closely by carbohydrates, are among the most powerful immunogens.

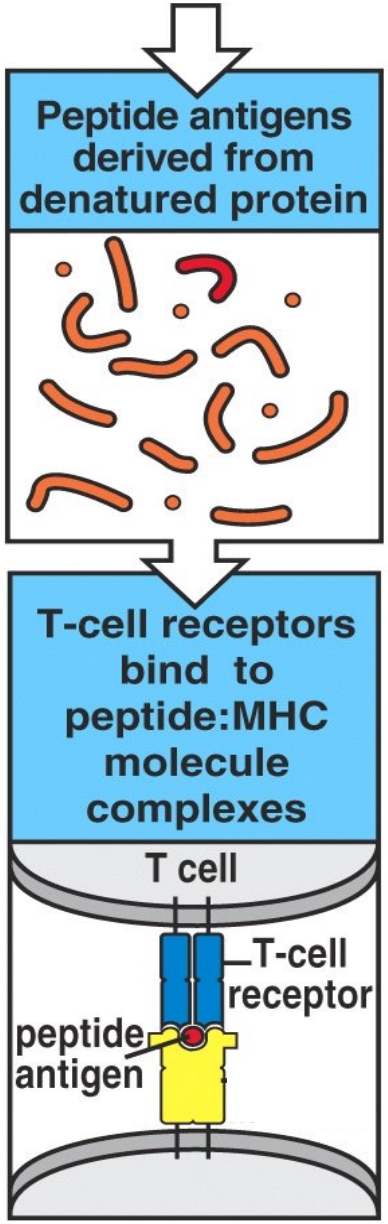
-Susceptibility to processing and presentation.



DISTINCT FEATURES OF B AND T CELL ANTIGEN RECOGNITION



B lymphocyte is able to recognize antigen in its native conformation



TCR recognizes a short peptide.....

that is complexed with MHC

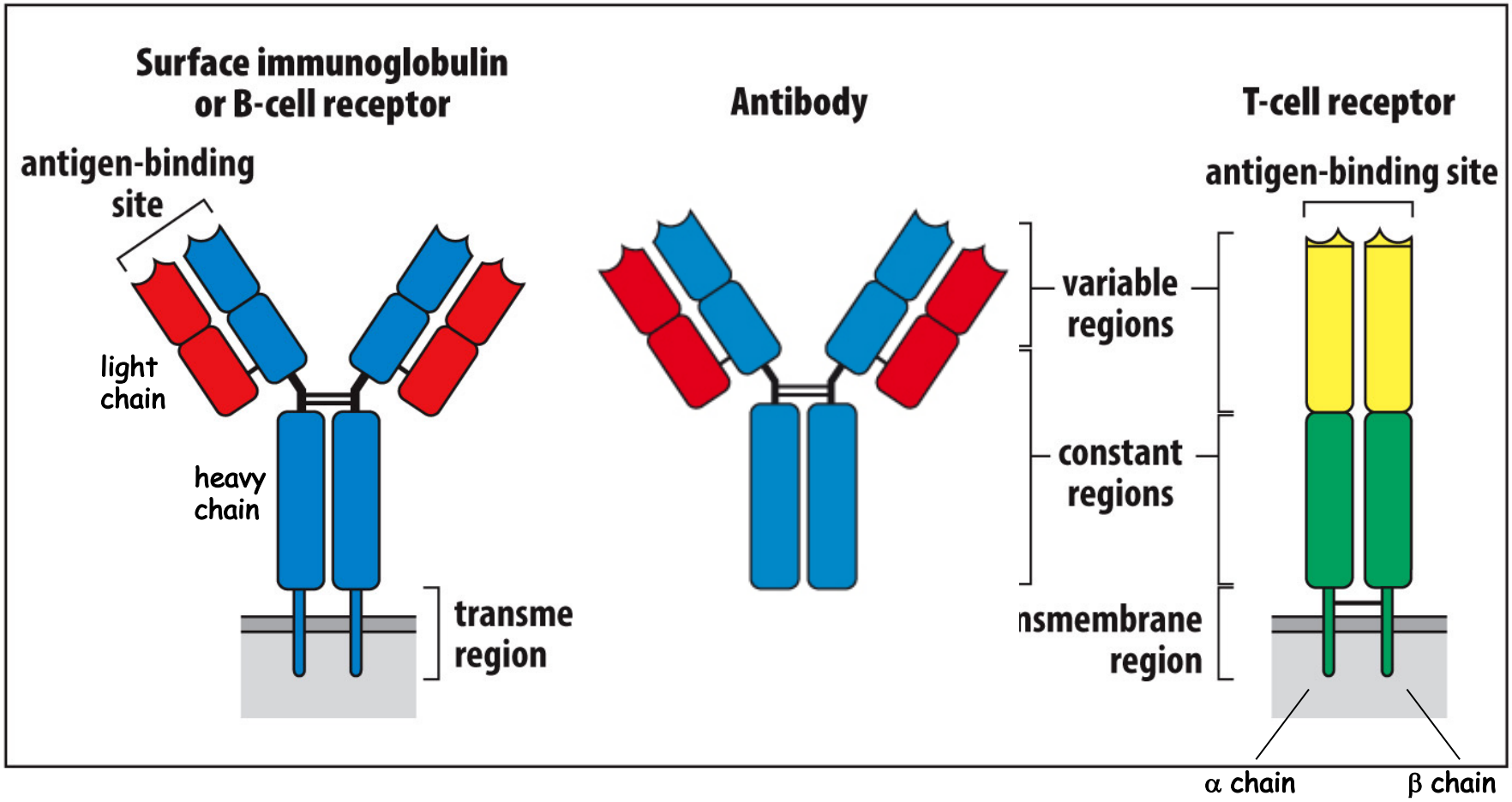
Other factors that influence the induction of an immune response:

-Dose of immunogen.

-Route of somministration.

-Use of adjuvants. Adjuvants are substances that, when administered with an antigen, enhance the immune response evoked against that antigen.

Antigen recognition molecules



B cells

T cells

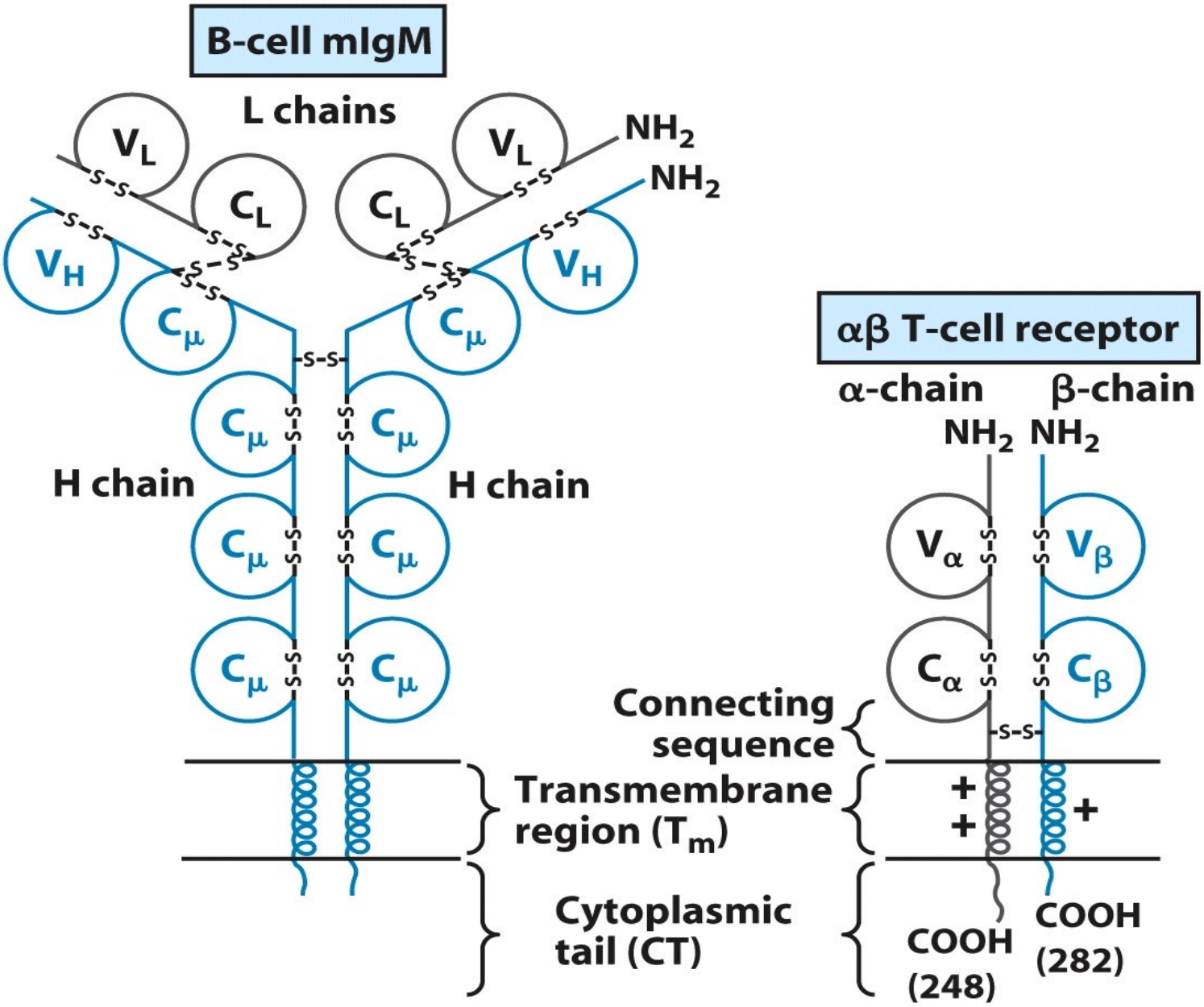


Figure 9-3
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The immunoglobulin domains

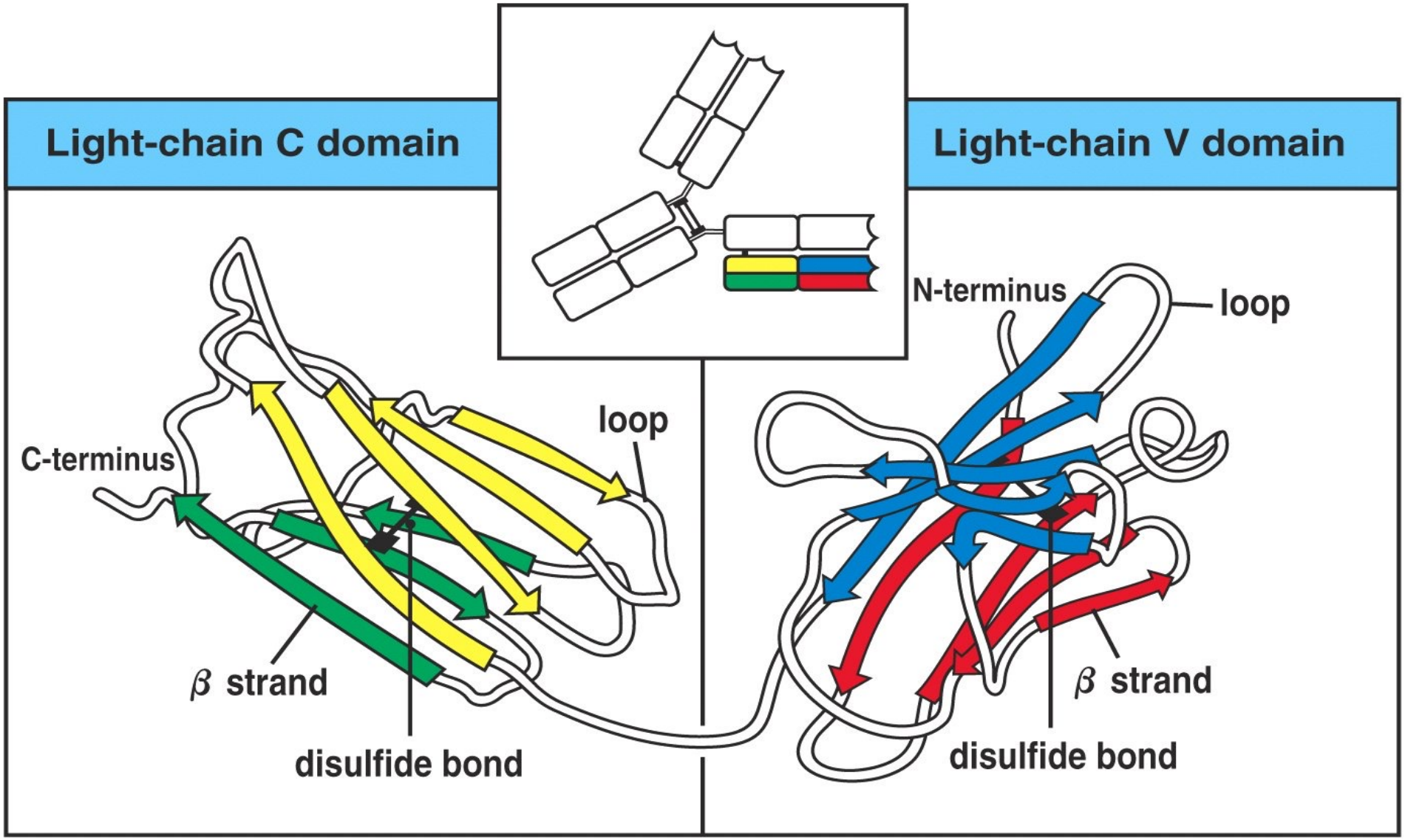
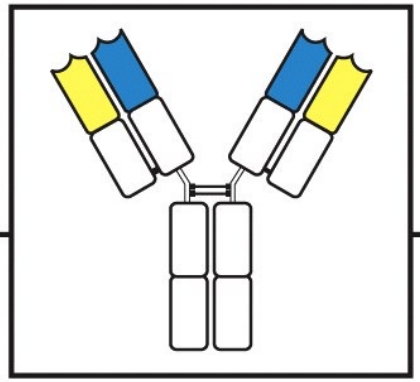
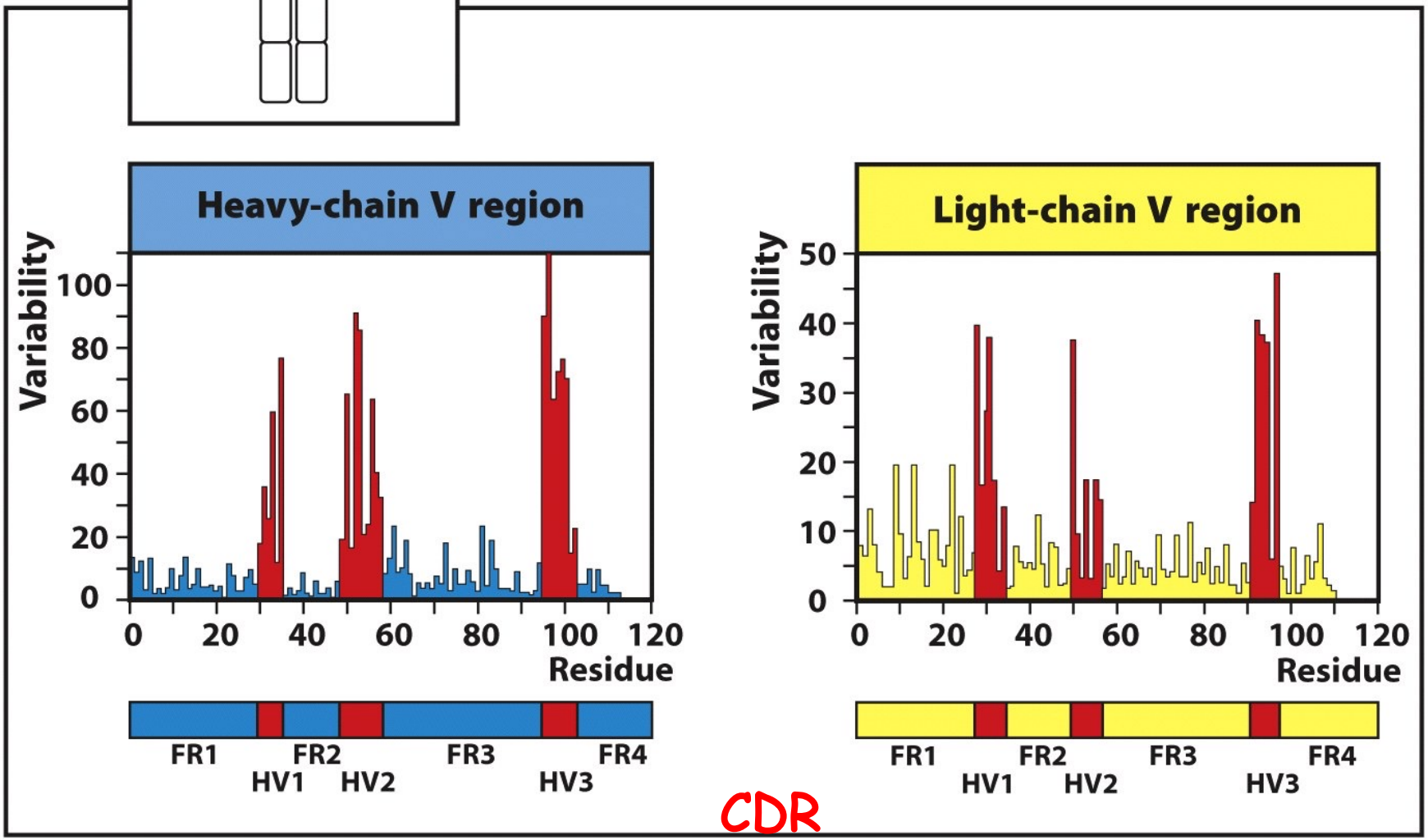


Figure 2-6 The Immune System, 2/e (© Garland Science 2005)

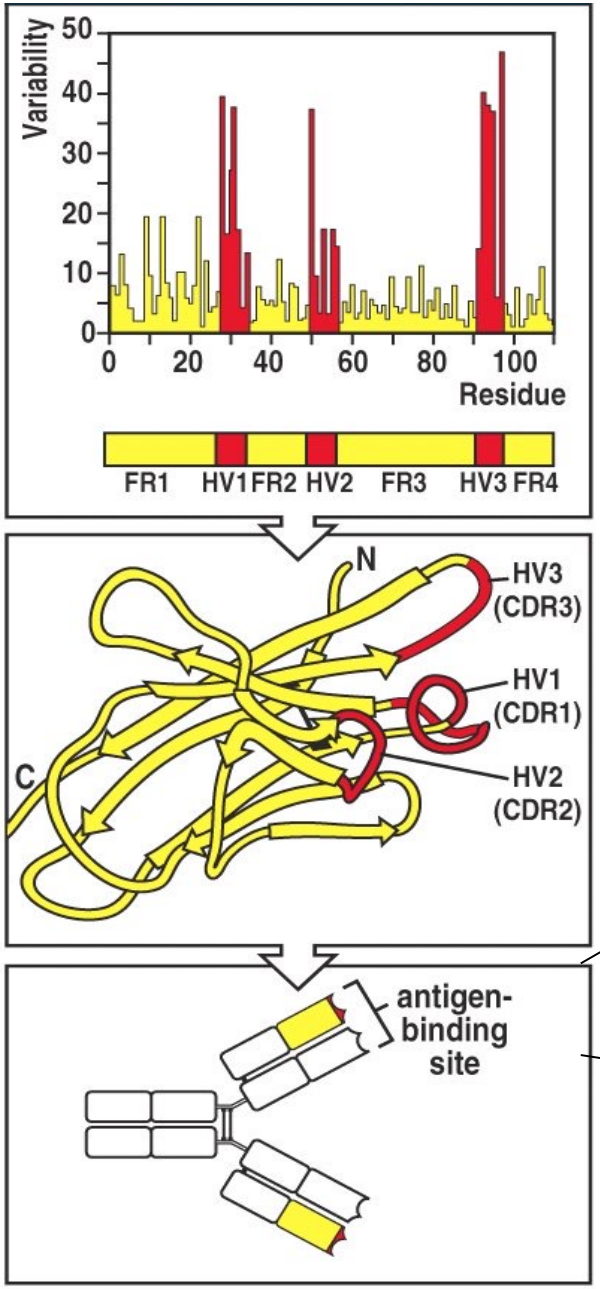
Each V domain contains
three hypervariable regions called CDRs



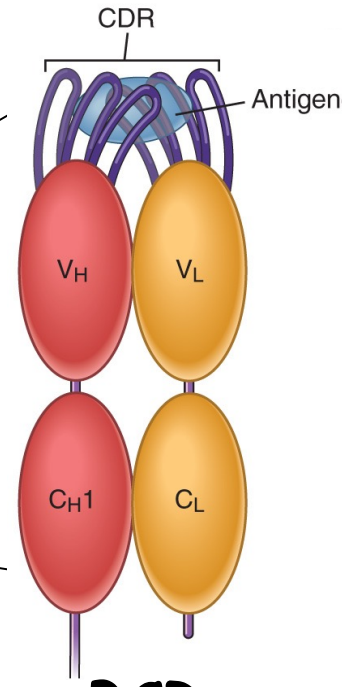


CDR

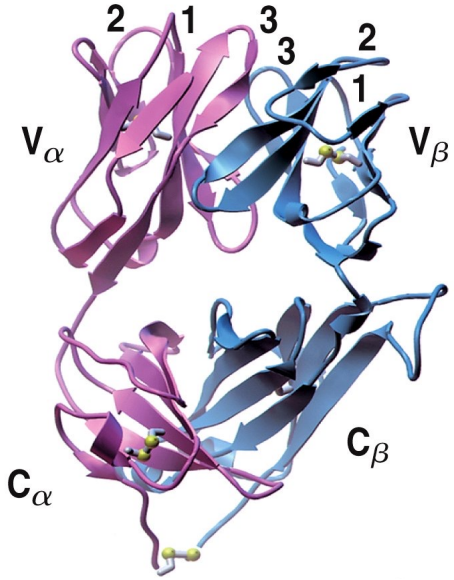
Regioni Determinanti la Complementarietà



Within each V domain the three CDR regions are arranged to form the combinatorial site for the antigen

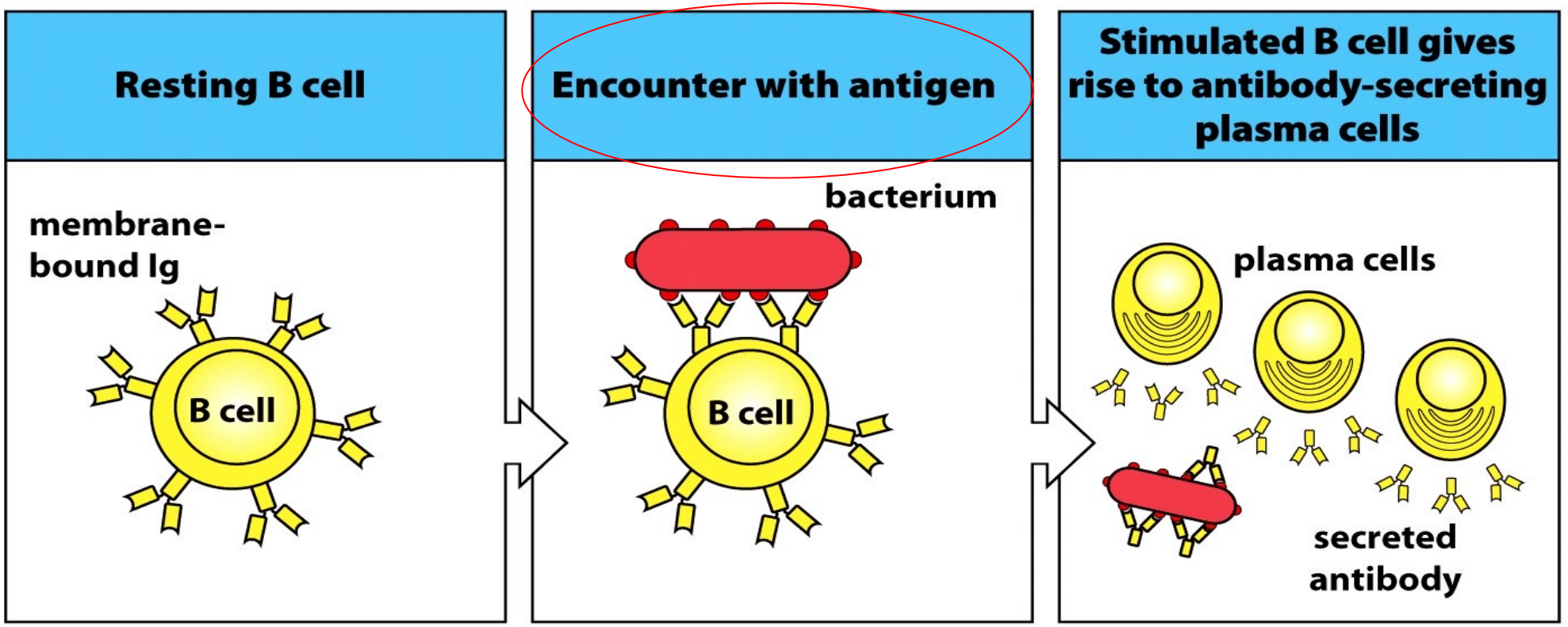


BCR



TCR

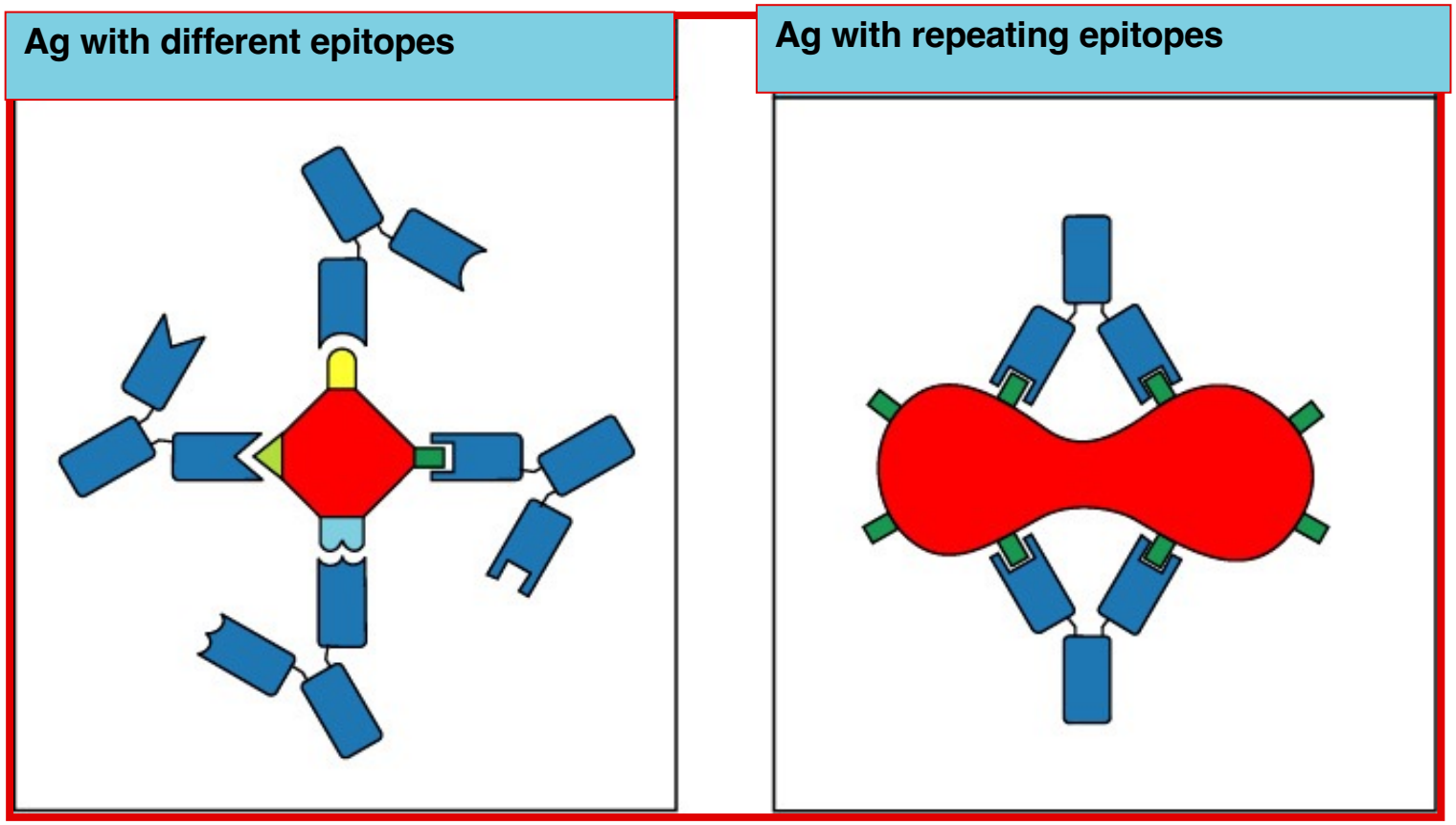
The effector cells of the B lymphocytes are plasma cells



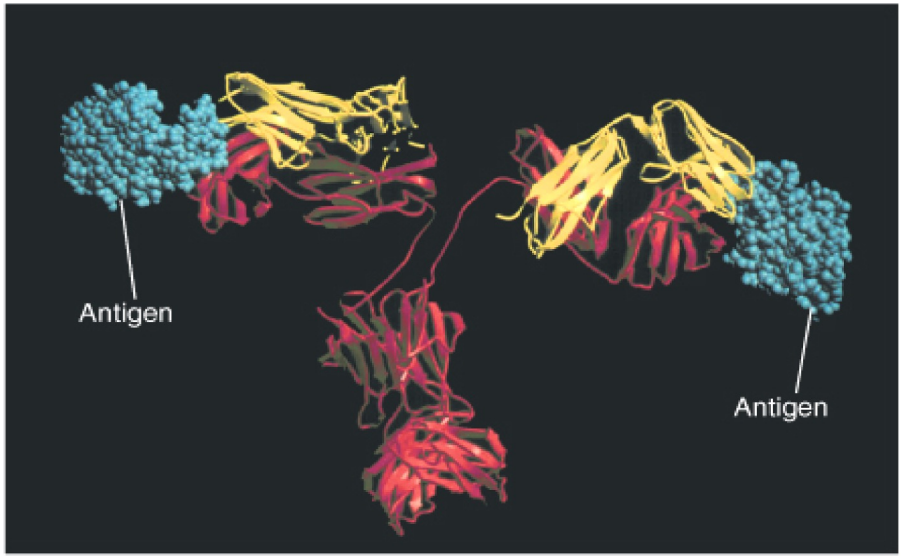
.. able to release membrane bound BCR in secreted antibody

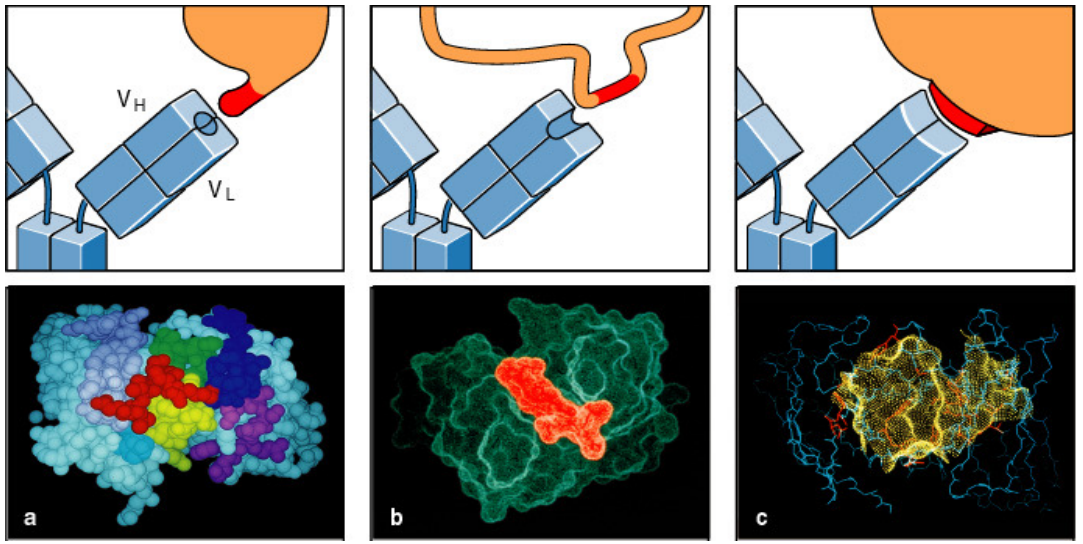
Antibodies recognize different types of antigenic determinants called epitopes

Most antigens are multivalent



Epitops can be of different shapes and sizes…

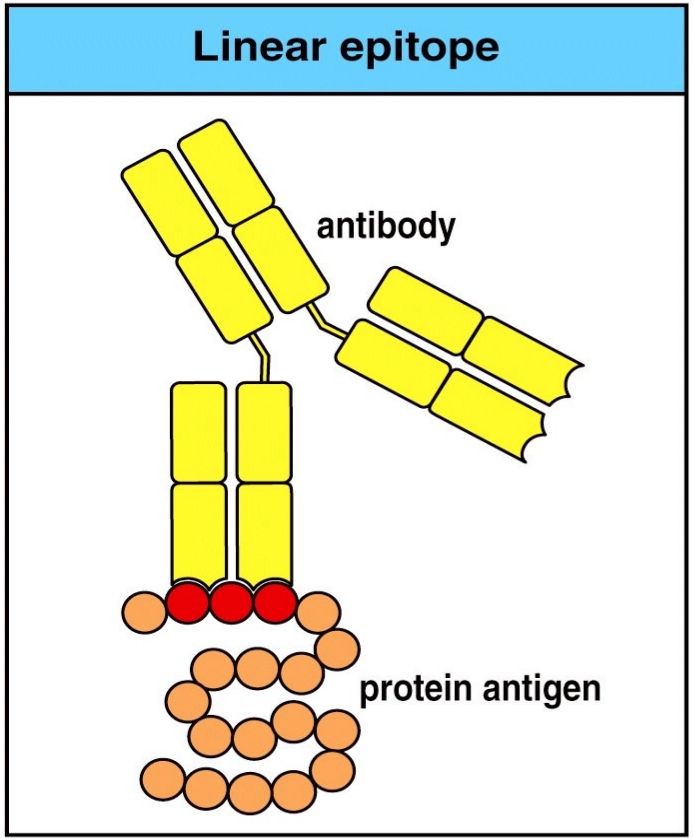


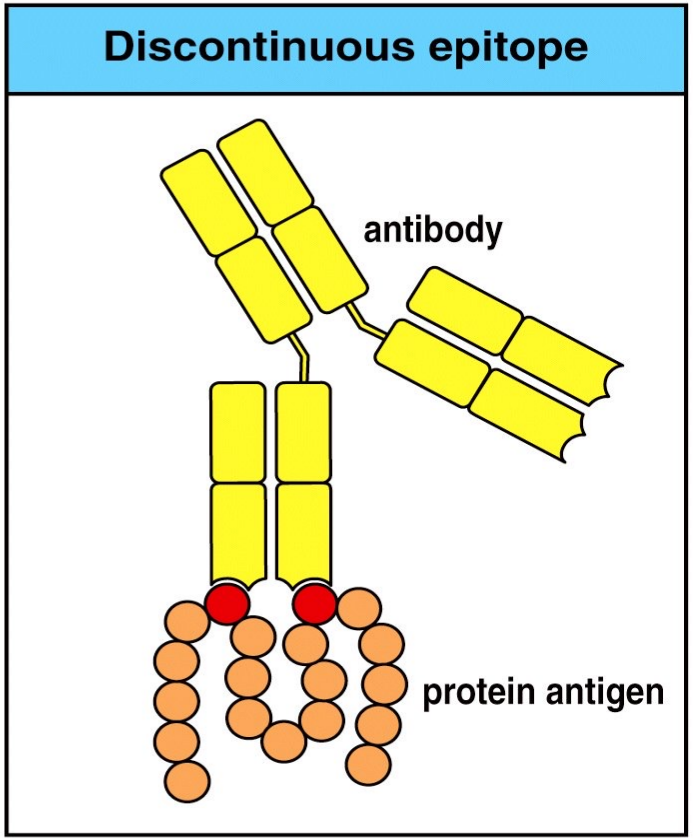


… and noncovalent and reversible forces are responsible for receptor binding

Noncovalent forces	Origin	
Electrostatic forces	Attraction between opposite charges	$-\overset{\oplus}{N}H_3 \quad \overset{\ominus}{O}OC-$
Hydrogen bonds	Hydrogen shared between electronegative atoms (N,O)	$N-H\cdots O=C$ (δ^- δ^+ δ^-)
Van der Waals forces	Fluctuations in electron clouds around molecules polarize neighboring atoms oppositely	δ^+ δ^- ⇄ δ^- δ^+
Hydrophobic forces	Hydrophobic groups interact unfavorably with water and tend to pack together to exclude water molecules. The attraction also involves van der Waals forces	

Linear and discontinuos epitopes

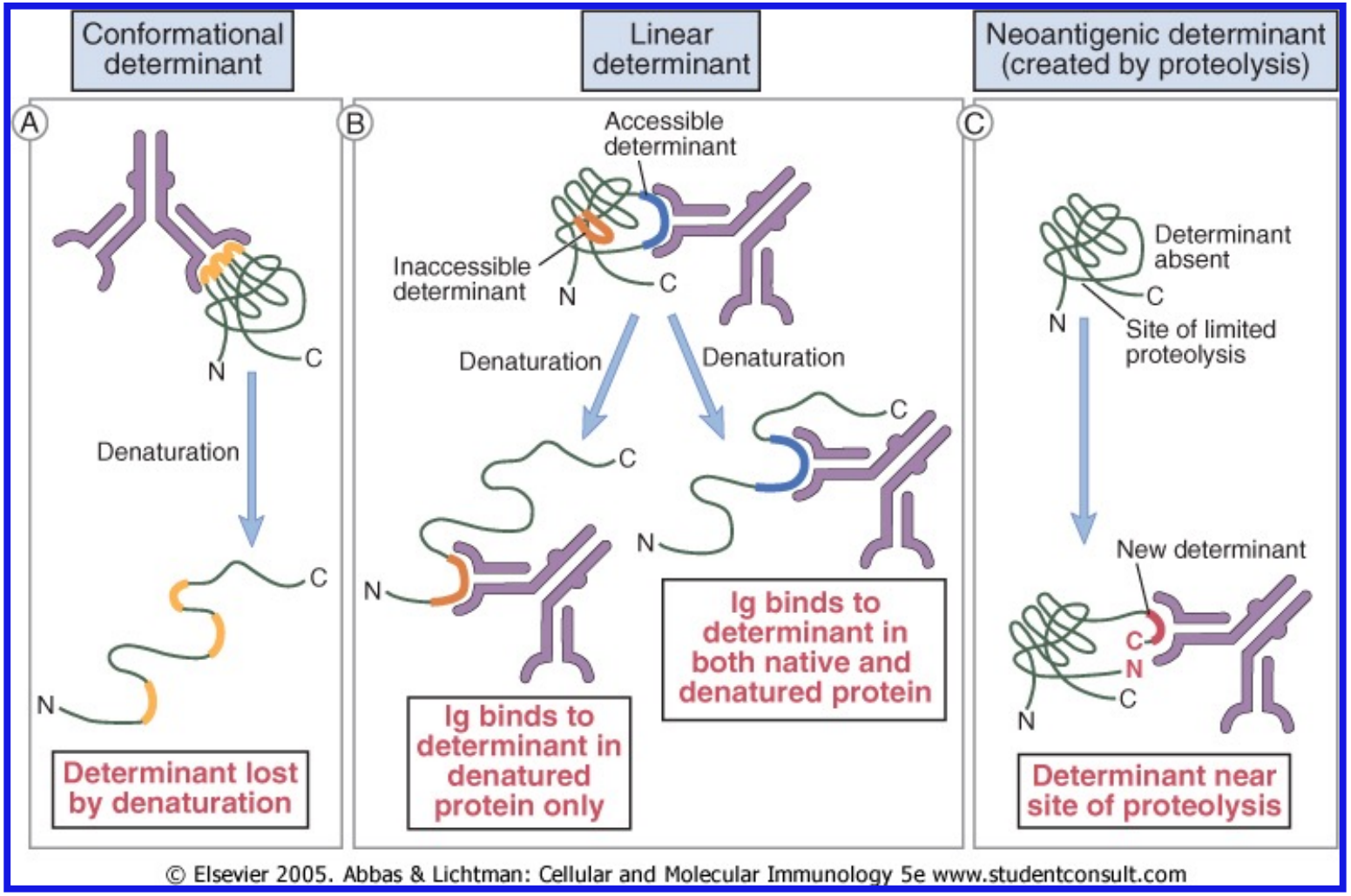




A linear epitope is made up of contiguous amino acids, that is, arranged one after the other in the primary structure.

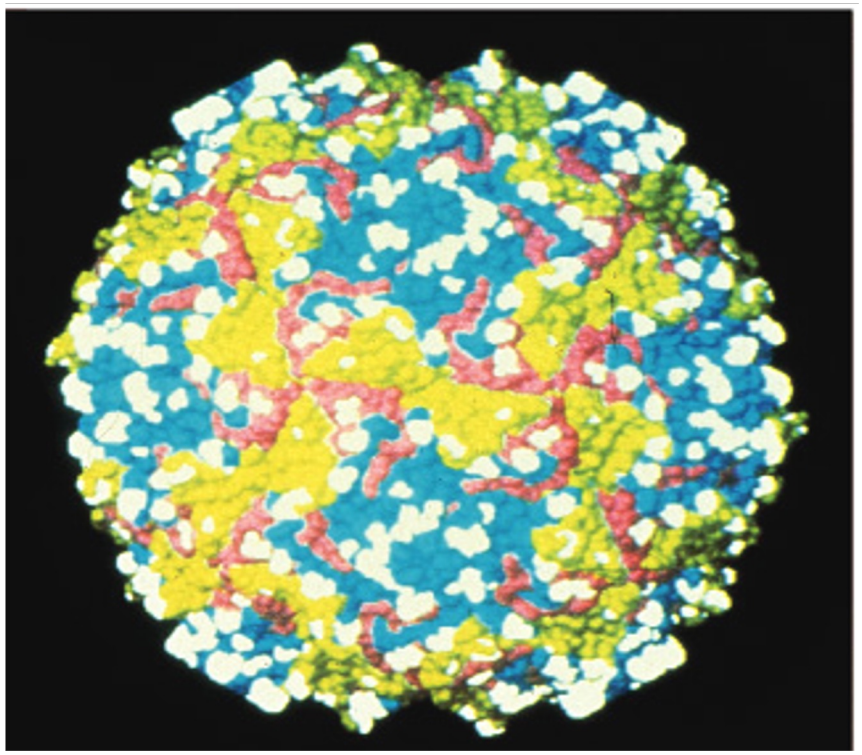
A discontinuous epitope is formed by amino acid residues that become contiguous in the tertiary structure.

Antibodies recognize different types of epitopes (antigenic determinants)



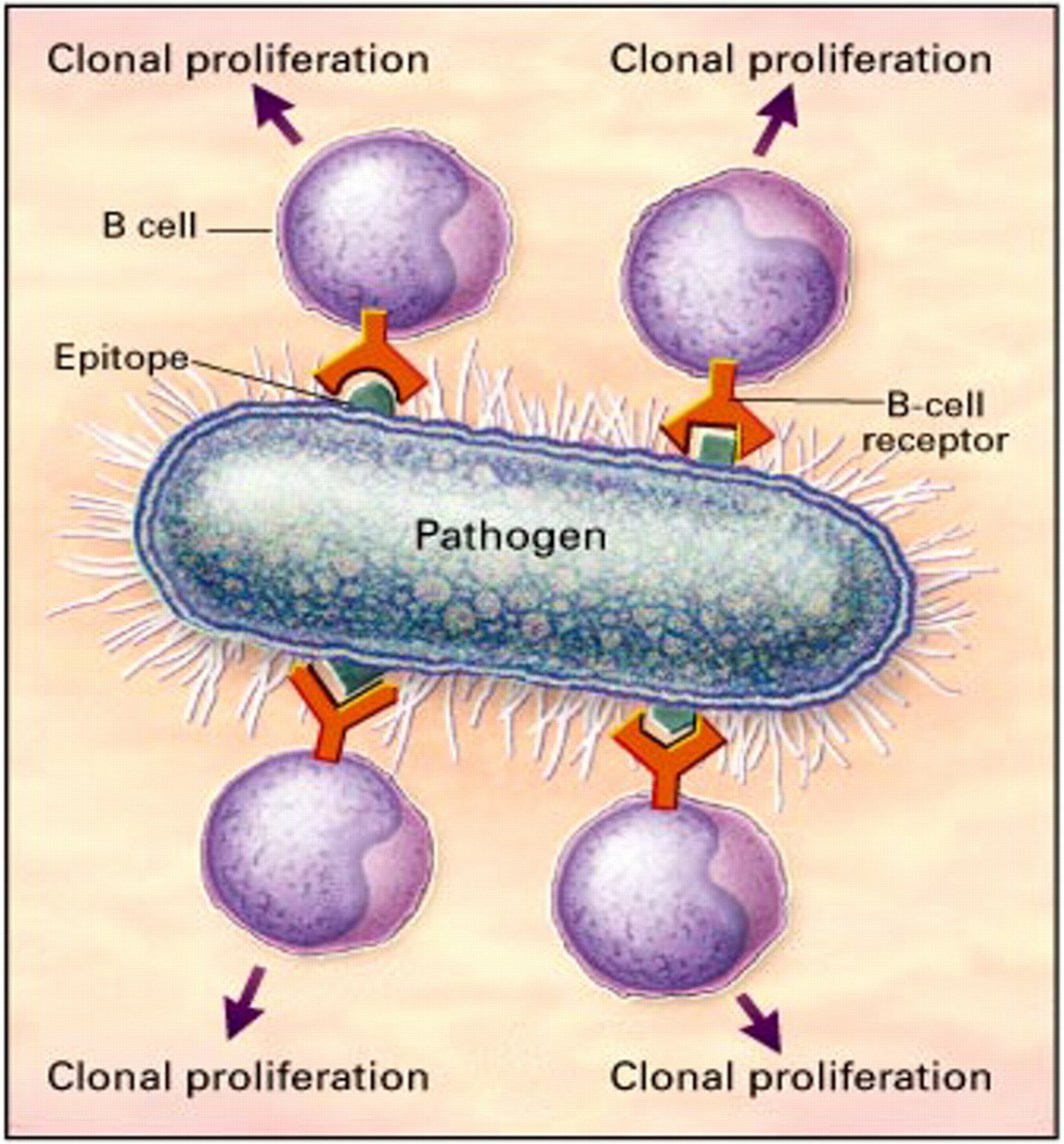
B cells recognize accessible and hydrophobic epitopes

Poliovirus

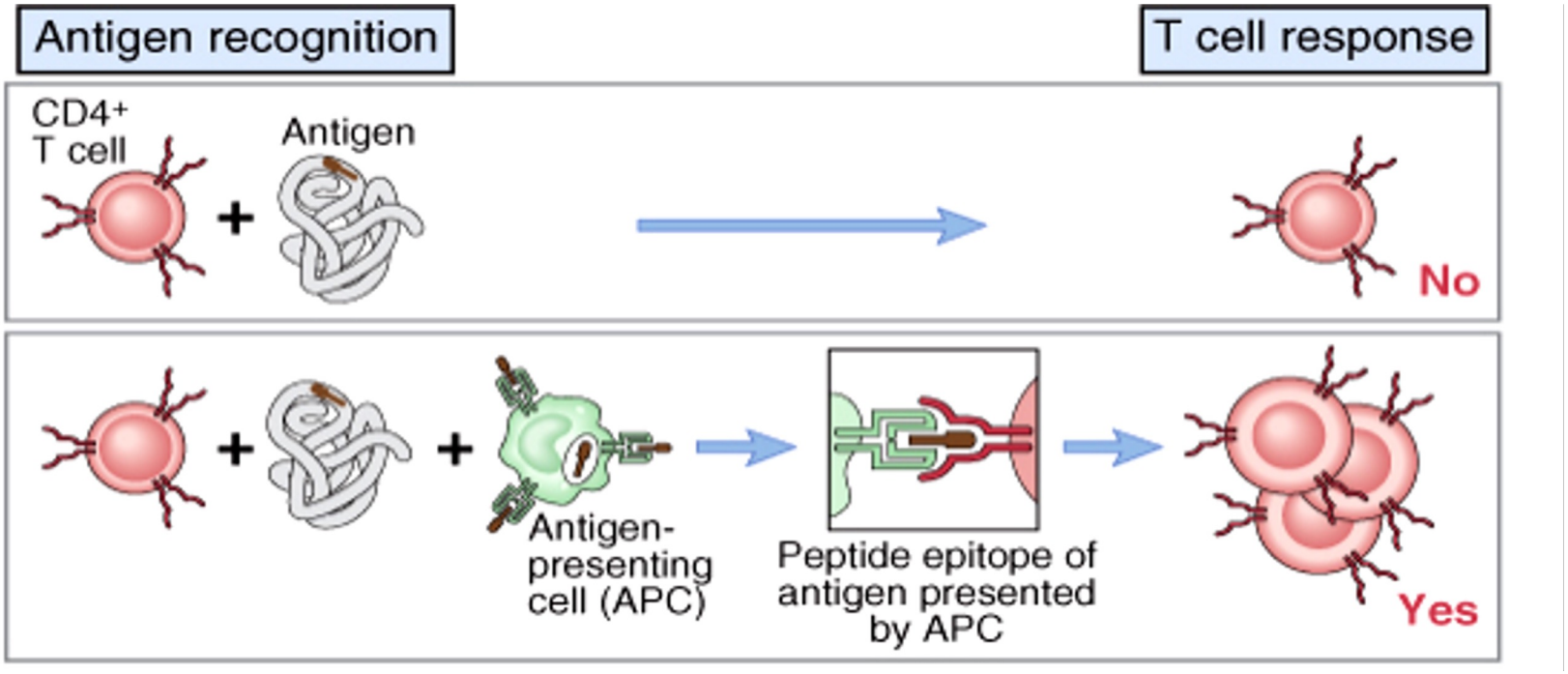


The viral envelope is composed of several structural proteins (yellow, blue, and pink).
The antigenic epitopes are highlighted in white.

Recognition of Epitopes by B Cells

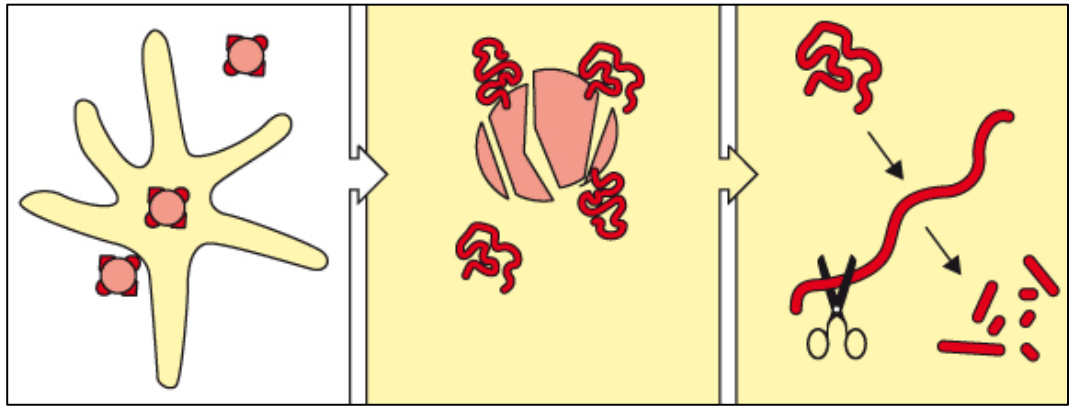


T lymphocyte is NOT able to recognize antigen in its native conformation……



…..but needs the function of accessory cells!

Le APC degradano l'antigene proteico in piccoli peptidi …



… rendendo accessibili ai linfociti T epitopi lineari interni

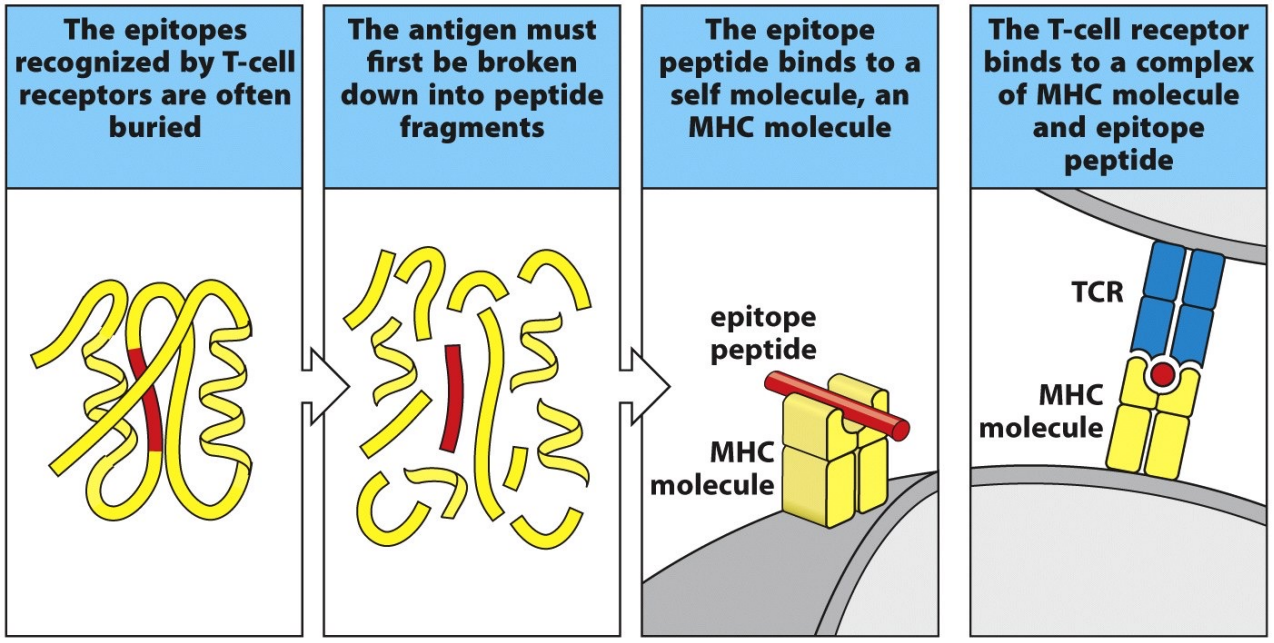
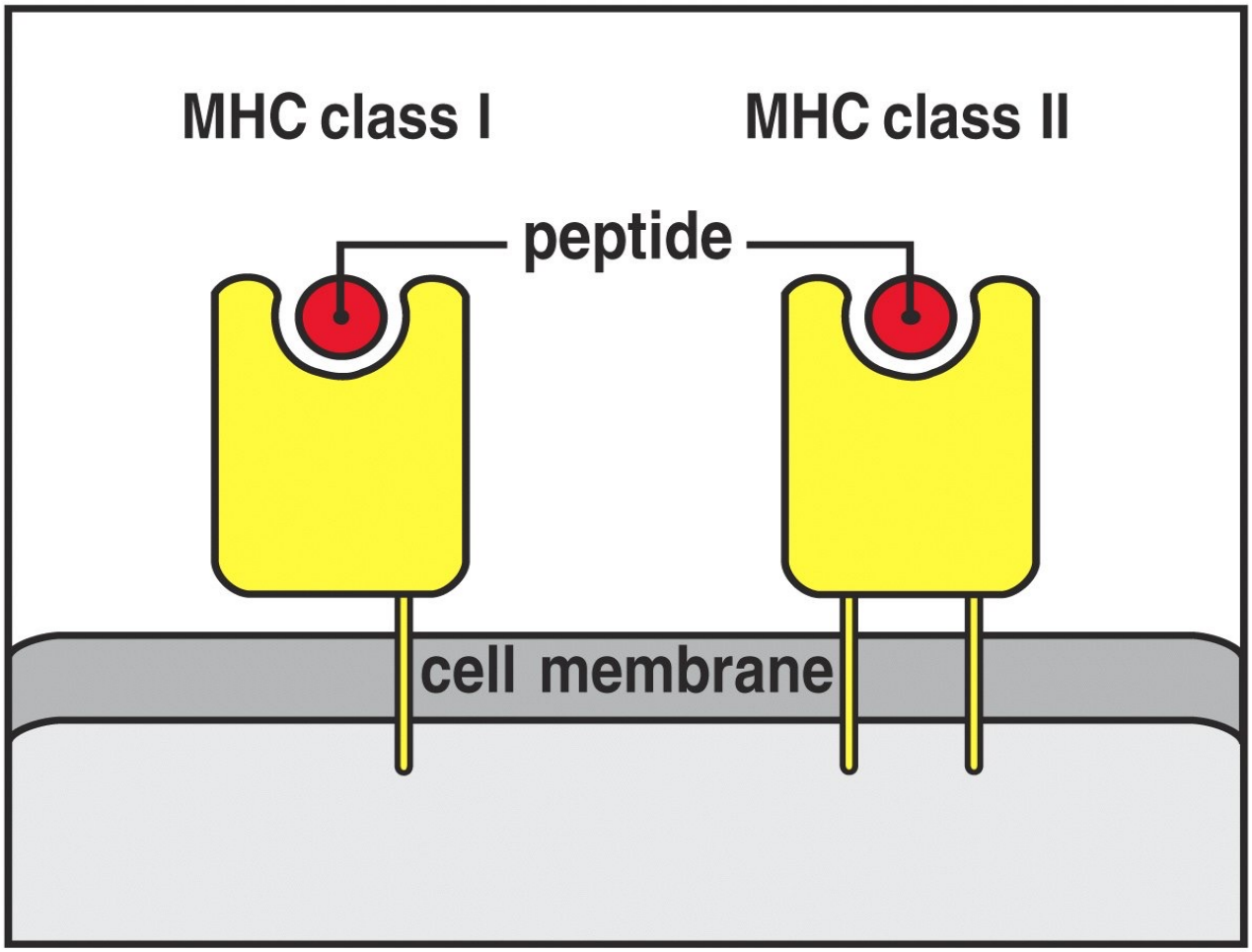
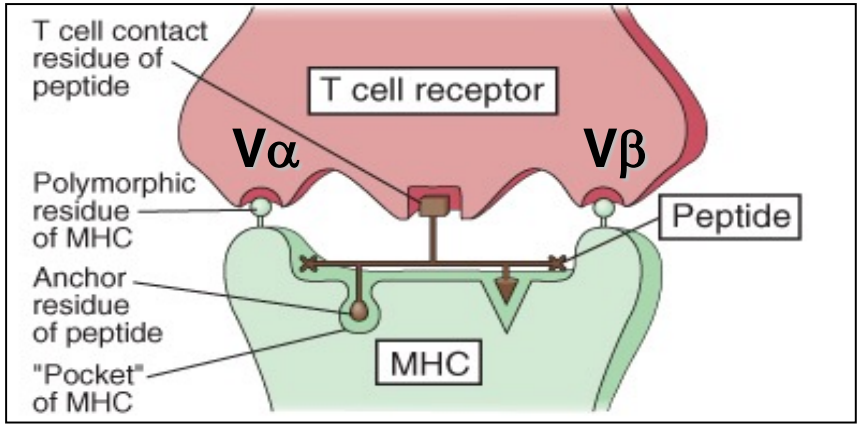


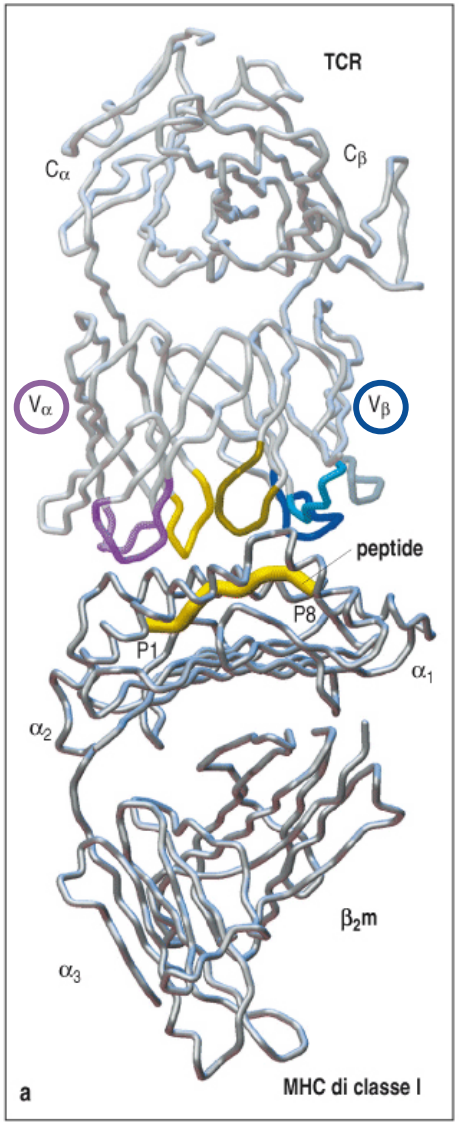
Figure 1.16 Janeway's Immunobiology, 8ed. (© Garland Science 2012)



MHC molecules bind peptides and display them on APC for recognition by T cells

T cell antigen recognition depends on a TRIMOLECULAR interaction



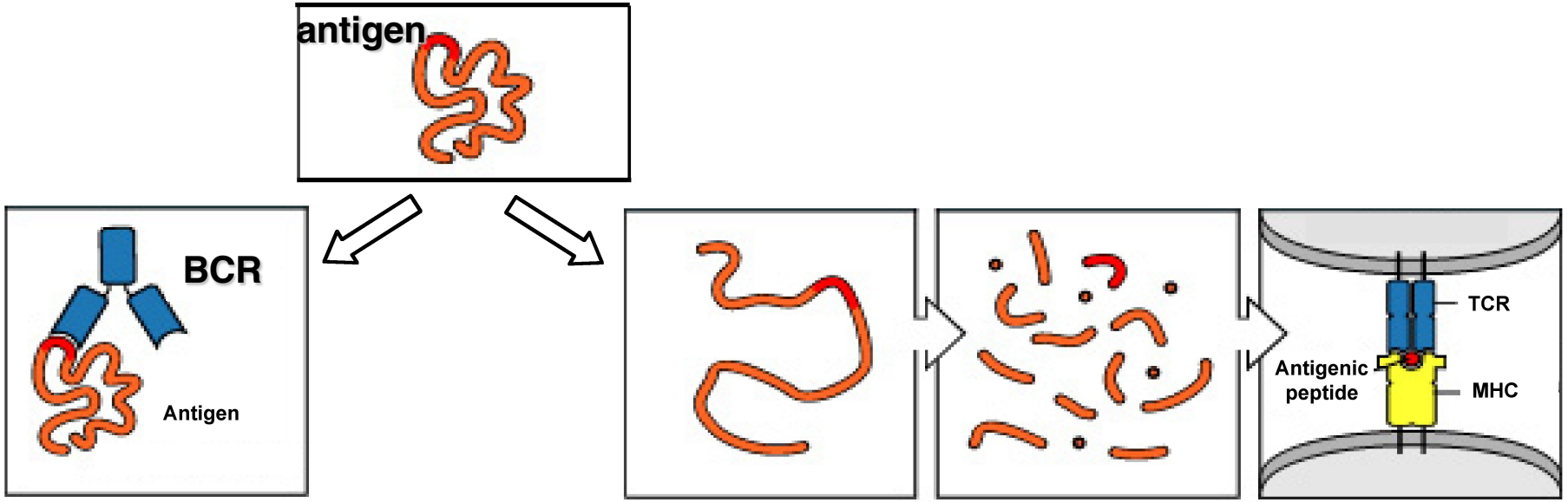


There are three CDR regions of the TCR chains in each V domain: CDR1, CDR2, and CDR3.

The CDR1 and CDR2 regions form the edges of the binding site and contact the MHC molecule, while the CDR3 regions of both chains form the central part of the binding site and interact with the ends of the peptide (P1 and P8).

CDR1 and CDR2 of the alpha chain are colored lilac/purple; CDR1 and CDR2 of the beta chain are colored blue/light blue; CDR3 is light yellow in Valpha and dark yellow in Vbeta.

T cells and B cells "see" antigen differently!



B

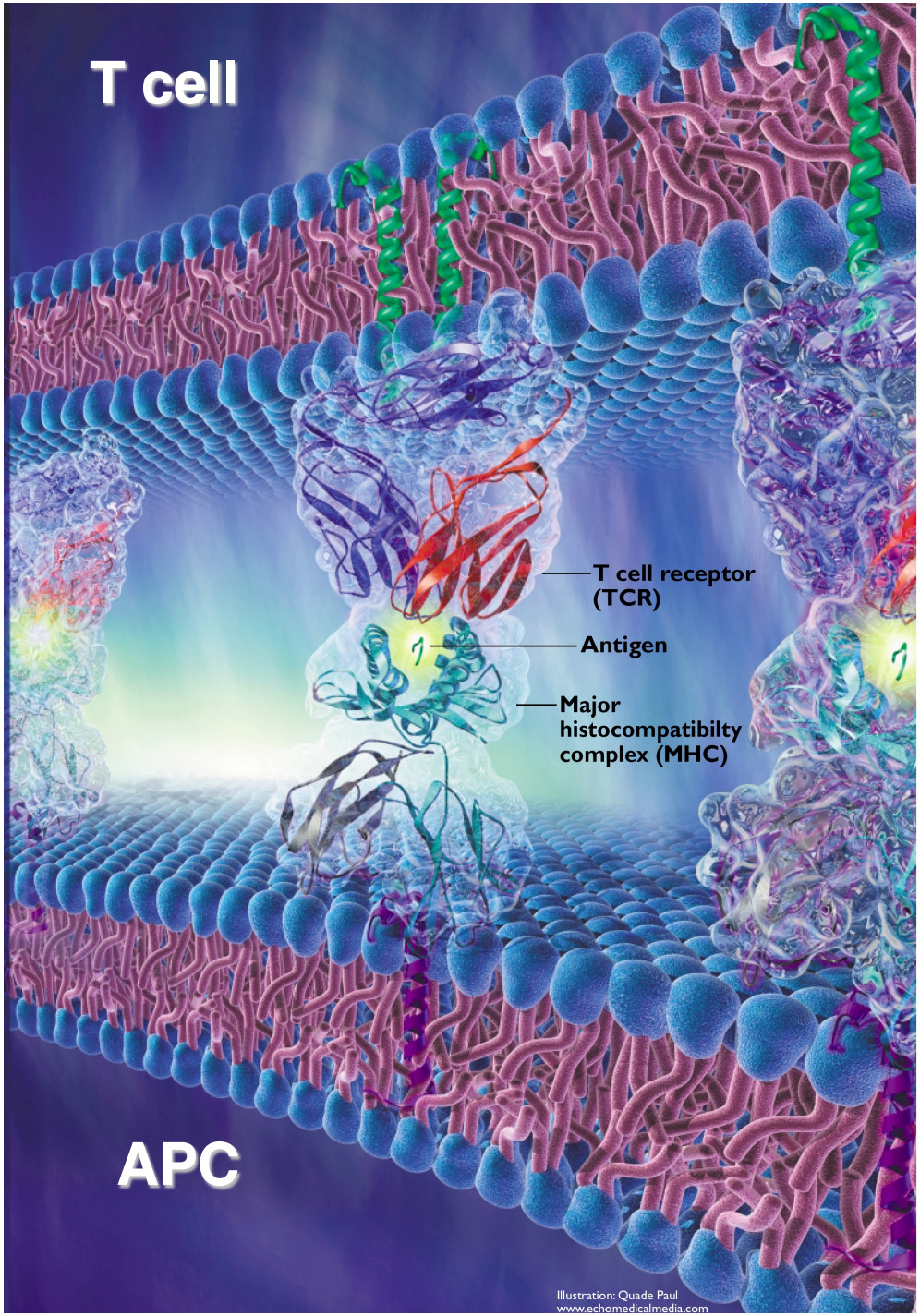
- Native, soluble
- Hydrophilic, accessible
- Linear or conformational

- Proteins, lipids, polysaccharides
- Affinity=10^{-7}-10^{-11} M, augments during response

T

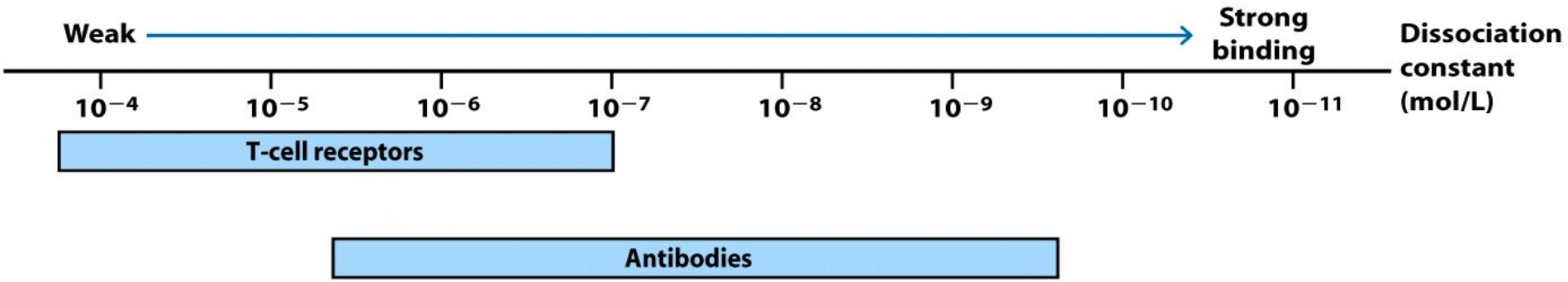
- Denatured, linear,
- Associated with MHC molecules,
- Requires processing
- CD4 and CD8 participate
- Mostly proteins

- Affinity=10^{-5}-10^{-7} M

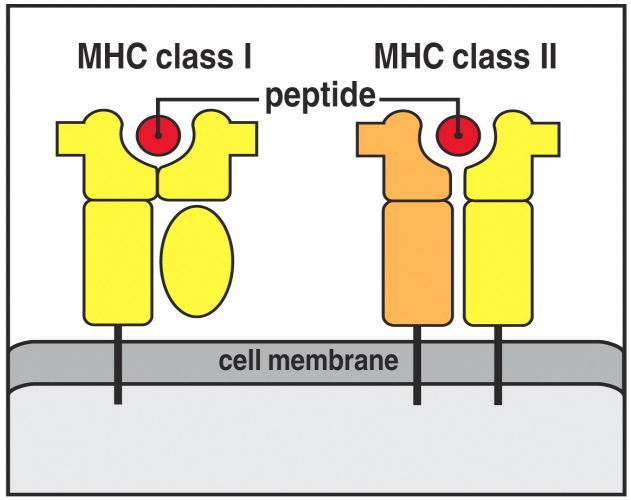


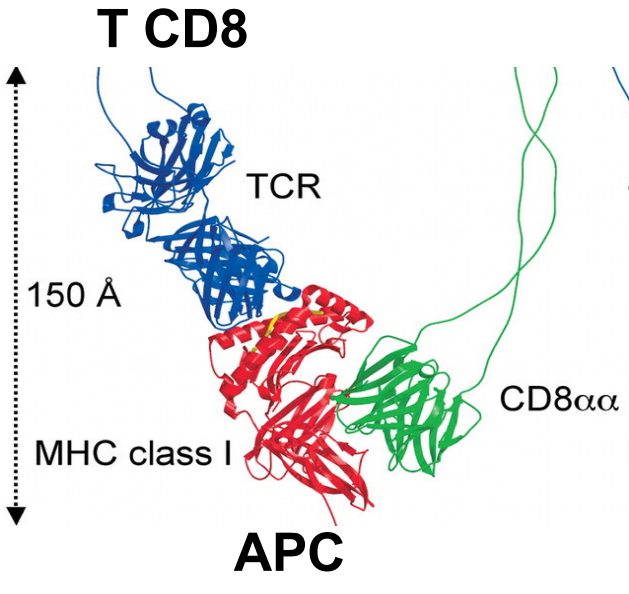
T cell recognition occurs at the surface of antigen presenting cell (APC)

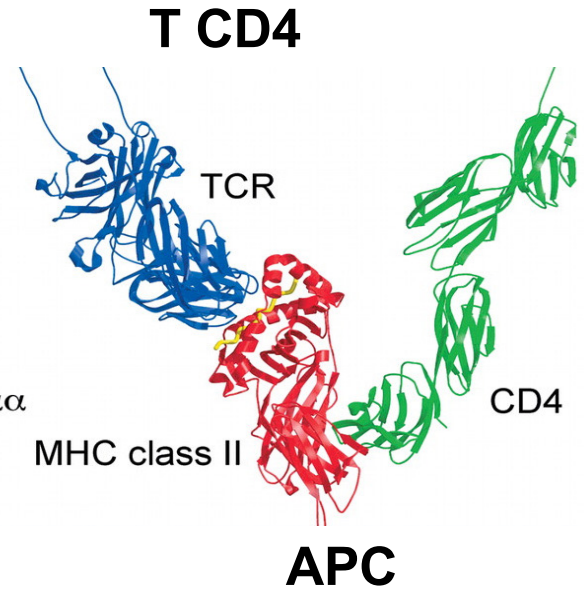
The binding between TCR and the MHC/peptide complex is a low-affinity bond..



… But the intervention of the co-receptors increases its strength: CD8 binds MHC class I while CD4 binds MHC class II







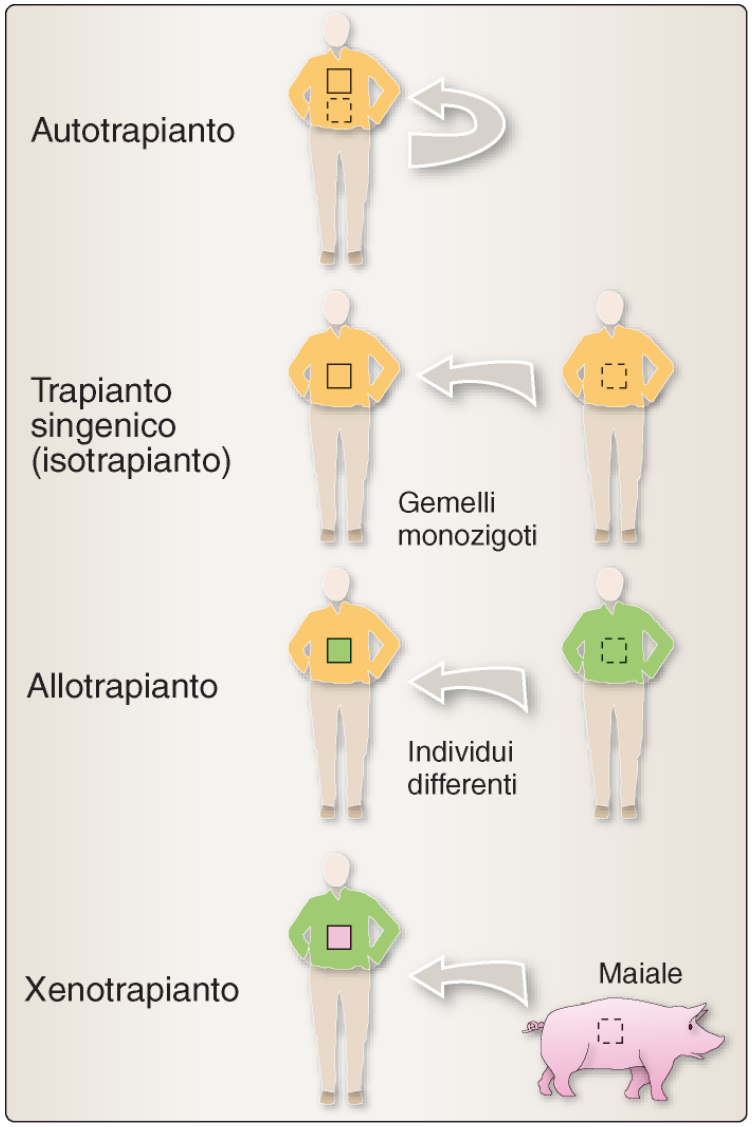
MHC

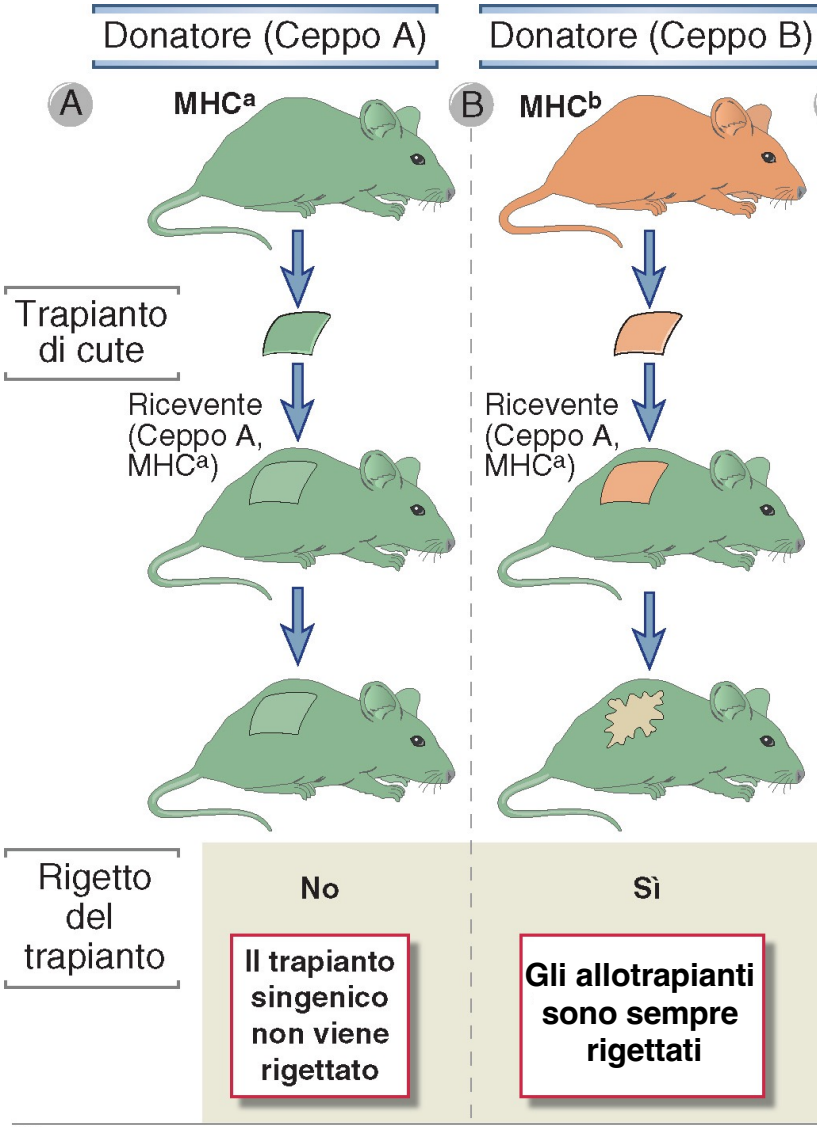
MAJOR HISTOCOMPATIBILITY COMPLEX

- It consists of glycoproteins expressed on the cell surface
- that confer an immunological identity.

- It's so called because it has historically been associated
- with transplant rejections.

Transplant rejection between genetically unrelated individuals is caused by major histocompatibility antigens





MHC

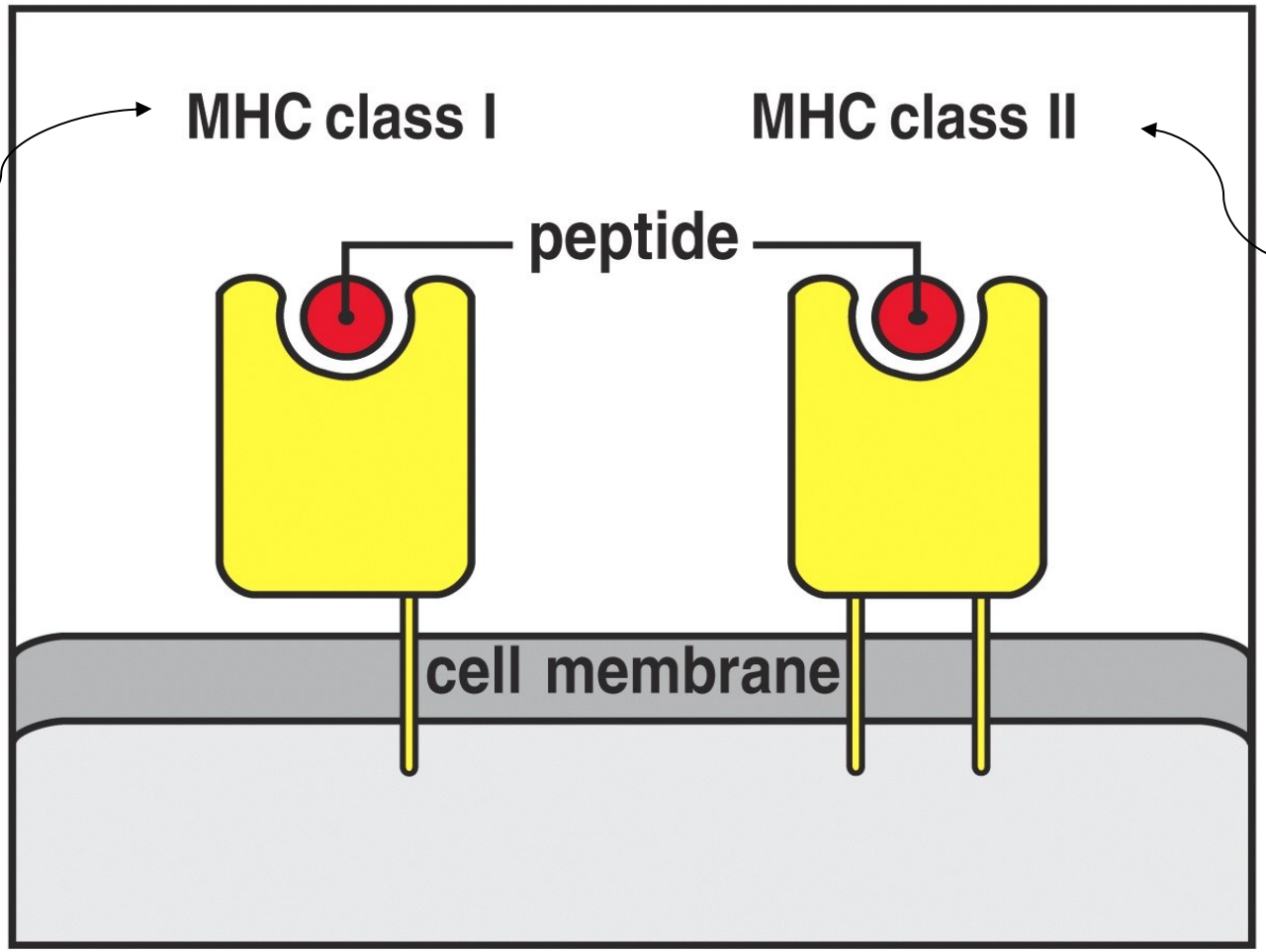
MAJOR HISTOCOMPATIBILITY COMPLEX

- It consists of glycoproteins expressed on the cell surface
- that confer an immunological identity.

- It's so called because it has historically been associated
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In the 1960s and 1970s, it was discovered that MHC genes play a critical role in immune responsiveness : MHC molecules bind peptides and display them on APC for recognition by T cells.

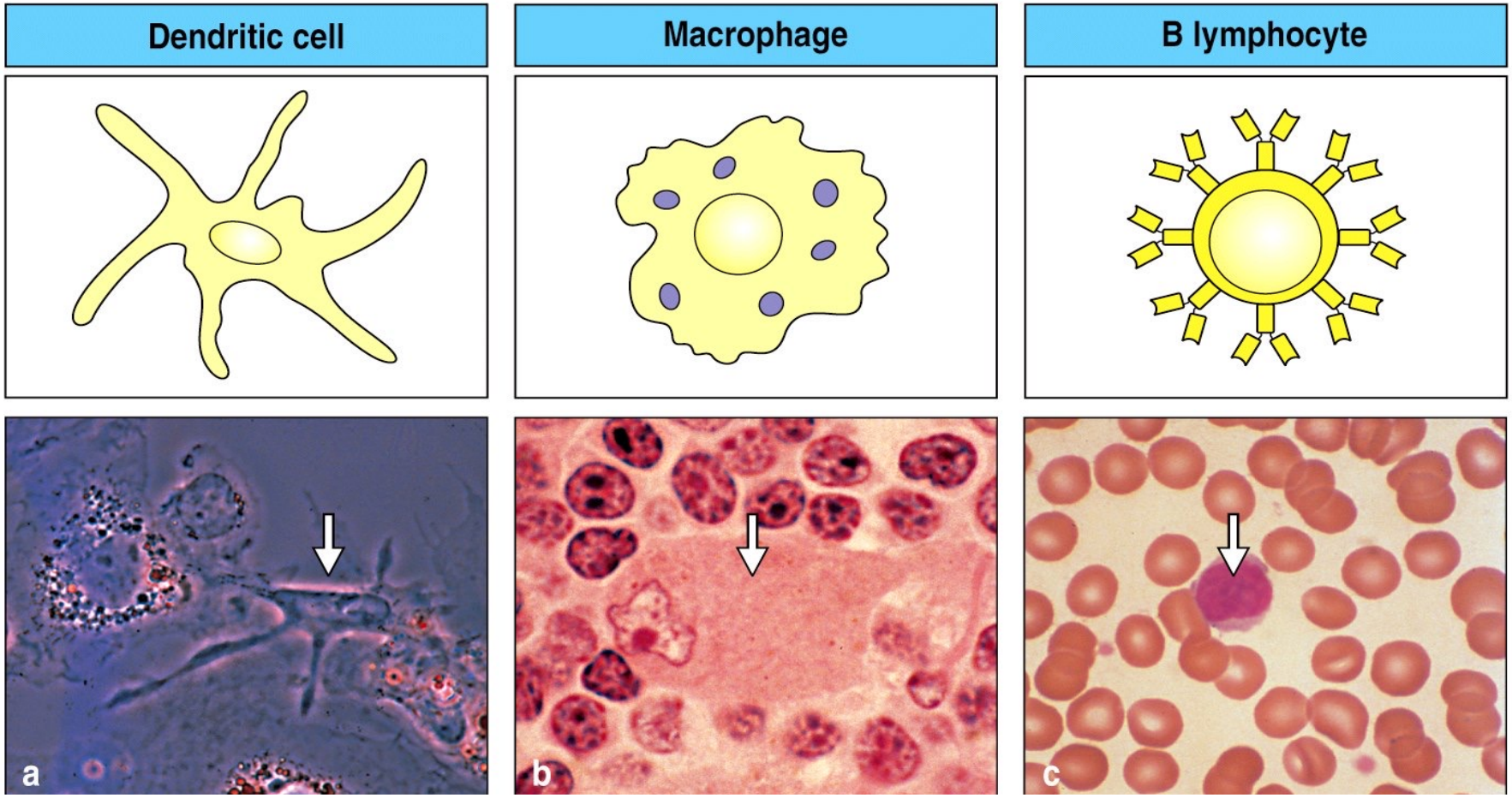
In all mammals, the MHC locus encode two different classes of MHC molecules, called MHC class I and class II



Expressed on all nucleated cells

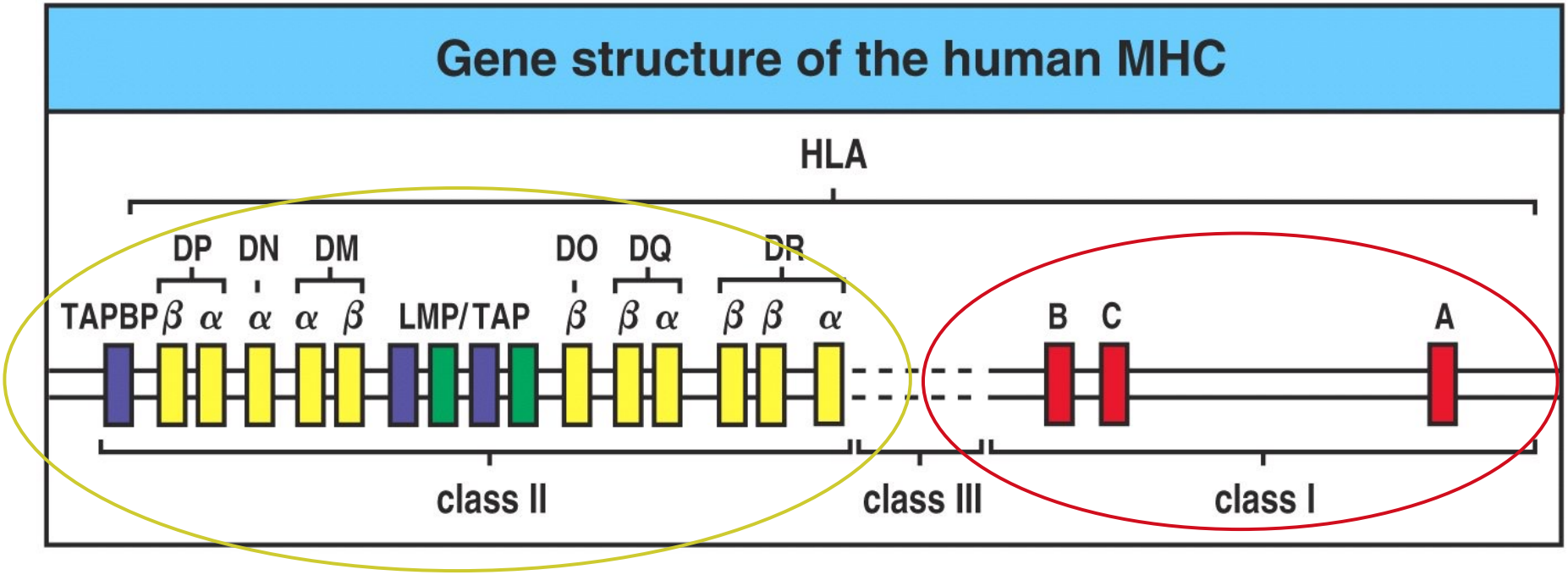
Expressed only on antigen-presenting cells
APC

The "specialized" Antigen Presenting Cells



Dendritic cells, macrophages and B cells are APC specialized in antigen presentation to T cells

The major histocompatibility complex (MHC)

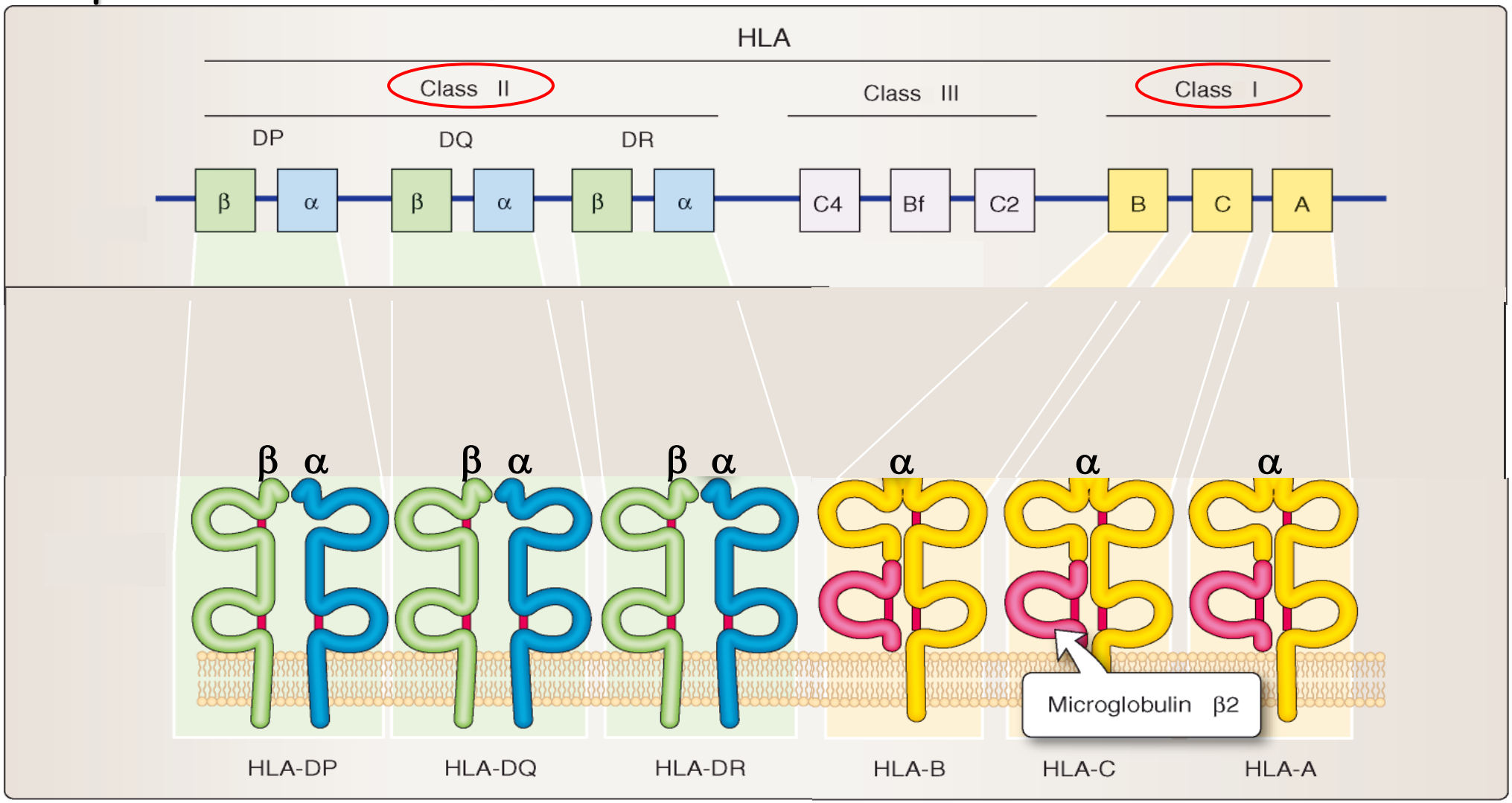


The human MHC complex (HLA) maps on chr. 6p
Human Leukocyte Antigens

MHC proteins are cell membrane receptors

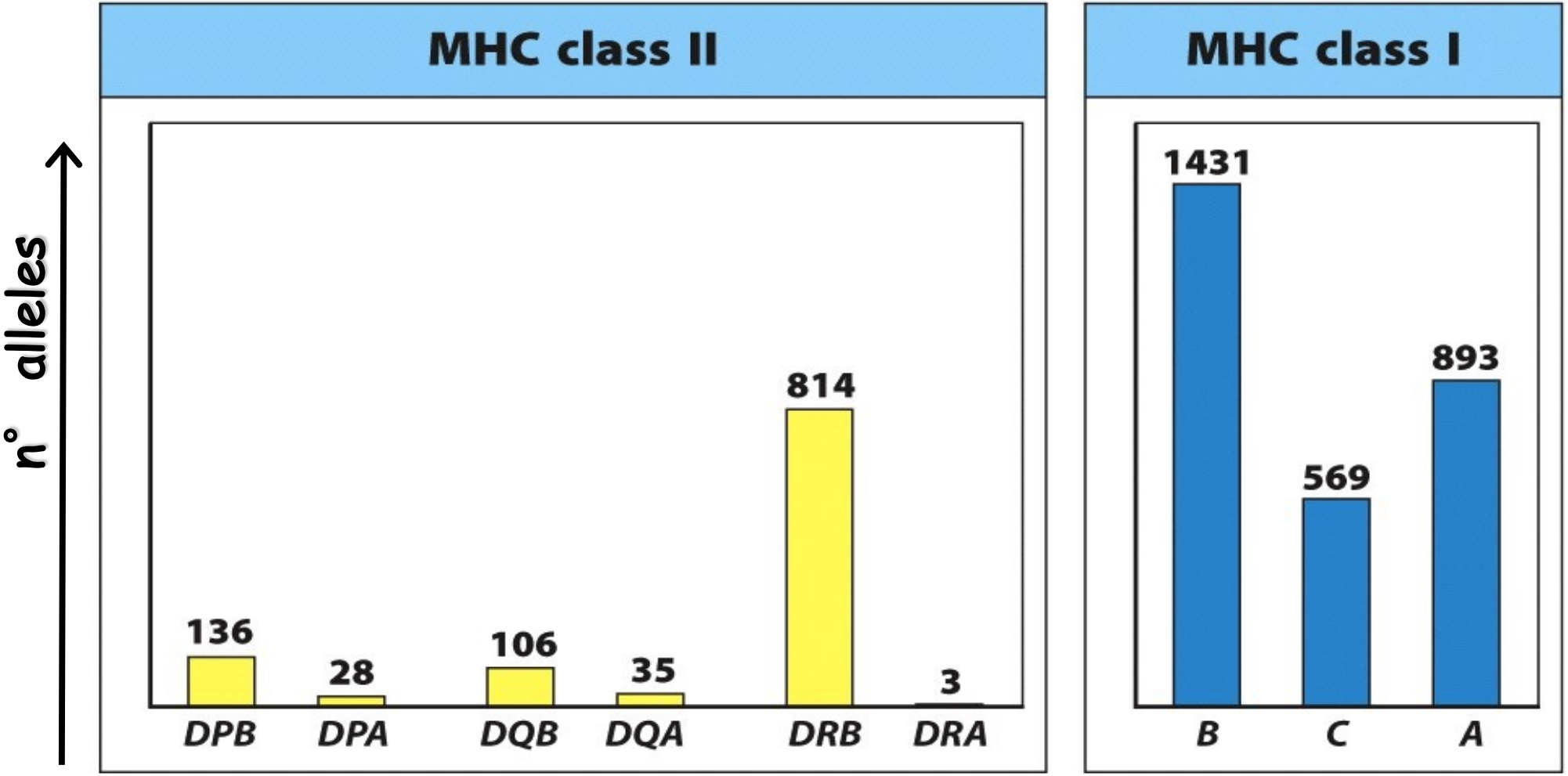
The major histocompatibility complex (MHC)

The human MHC complex is also called HLA= Human Leukocyte Antigens and maps to the short arm of chromosome 6.



MHC is a POLYGENIC locus

MHC genes are highly POLYMORPHIC



MHC alleles are expressed in a CODOMINANT fashion

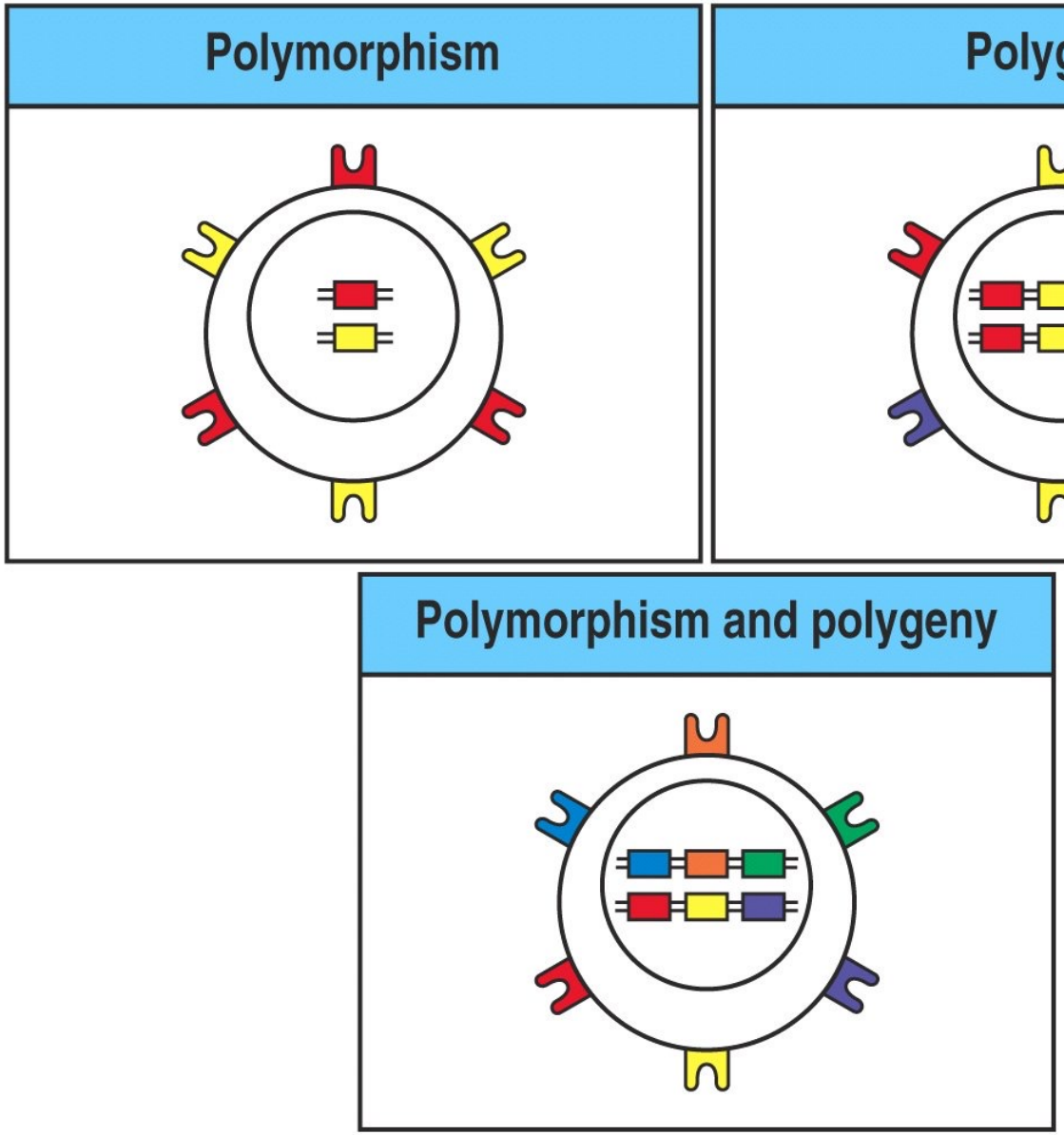


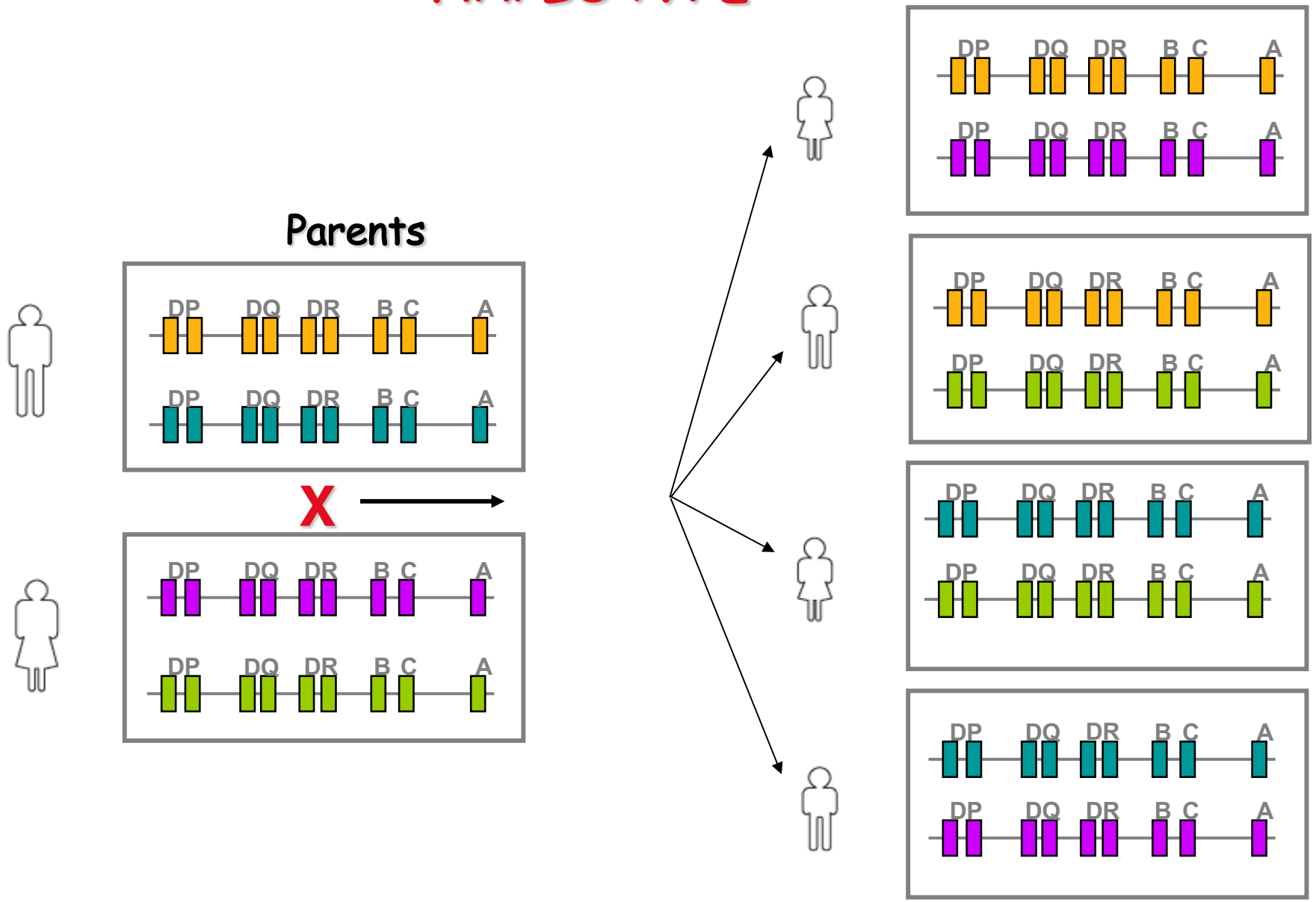
Figure 5-15 Immunobiology, 6/e. (© Garland Science 2005)

Our cells express up to 6 different MHC class I molecules

3 genes x 2 alleles=6

(even more for class II!)

❖MHC genes are tightly LINKED and usually inherited in a group called HAPLOTYPE



MHC molecule structure

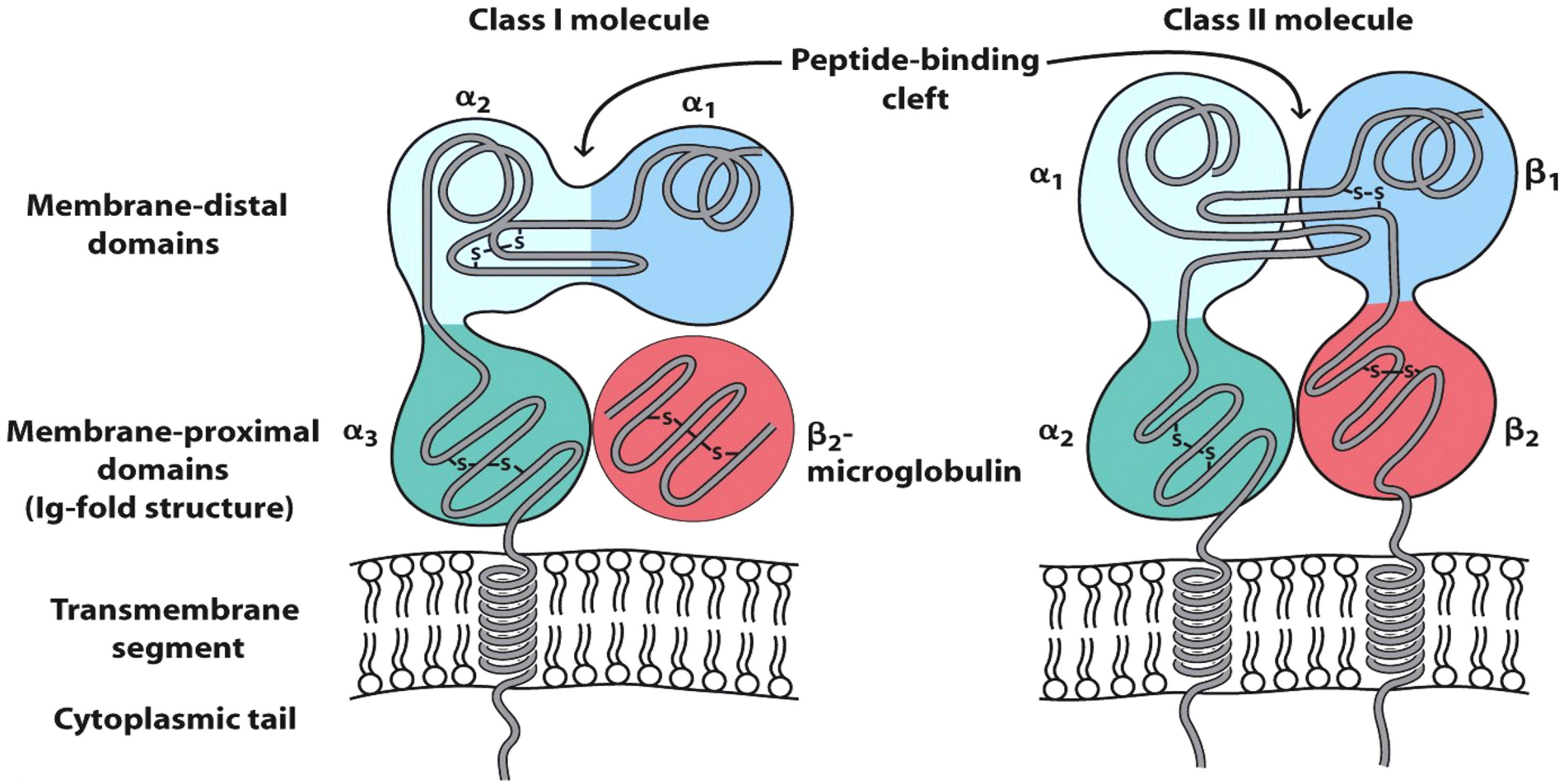
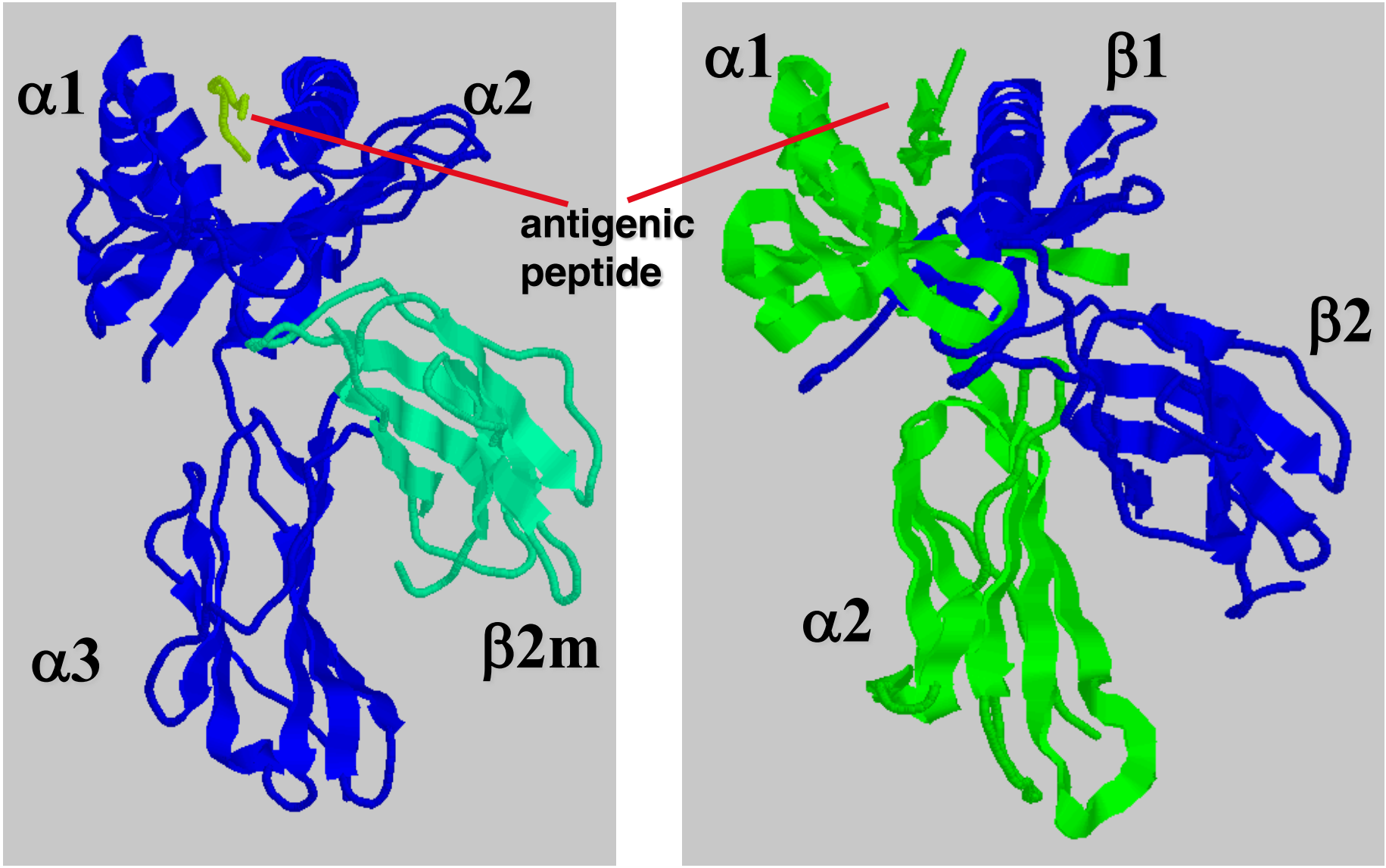


Figure 8-3
Kuby IMMUNOLOGY, Sixth Edition
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- Two polypeptide chains, α and β,
- noncovalently associated with secondary structures
- consisting of β-ribbons and α-helices

MHC molecule structure



HLA-A, B, C

HLA-DP, DQ, DR

The peptide-binding regions of MHC class I and II are structurally and conformationally homologous

MHC class I

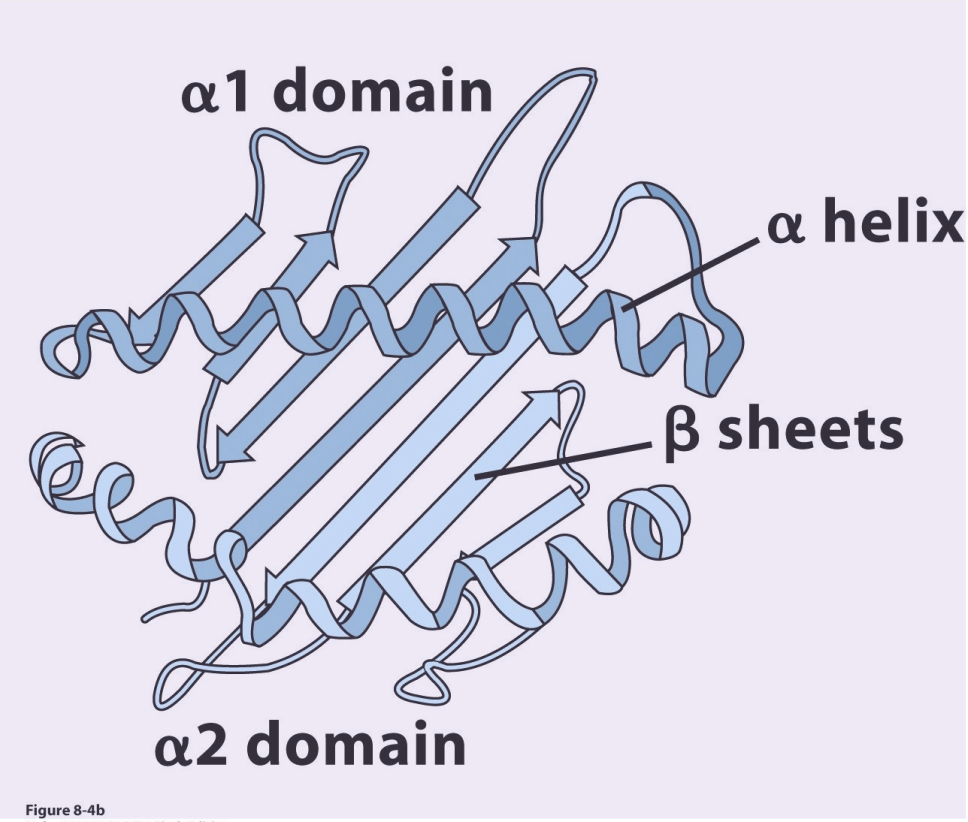
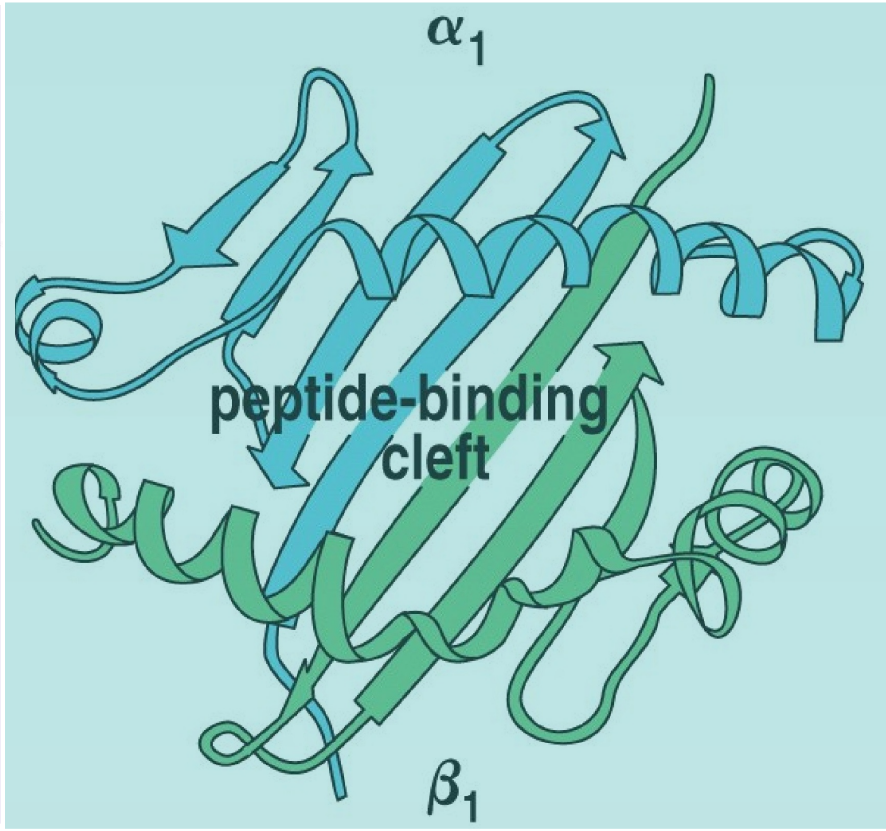
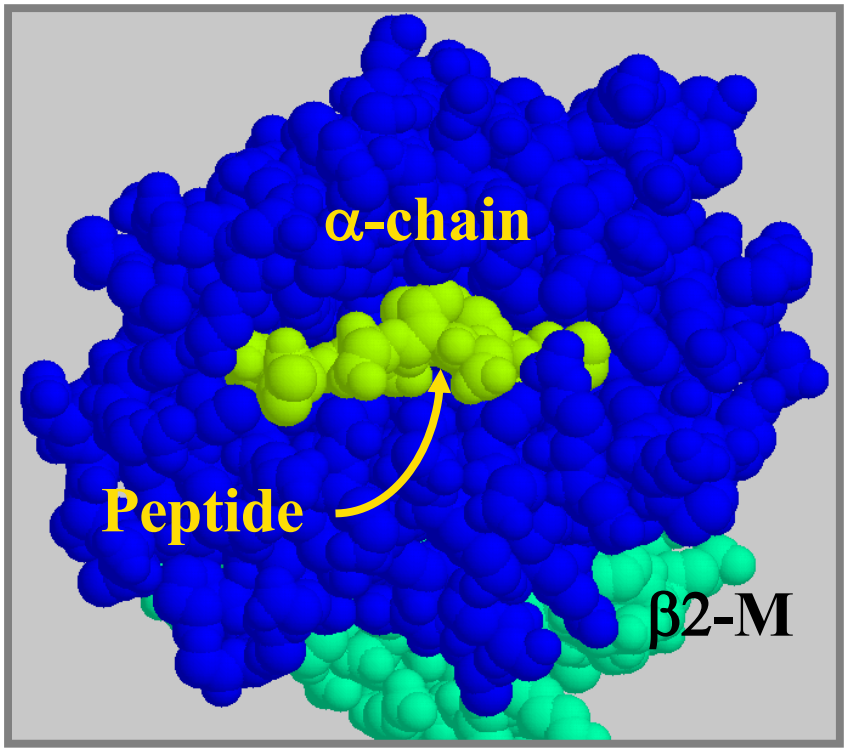


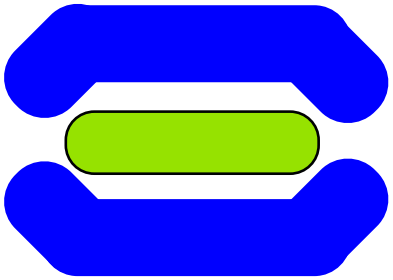
Figure 8-4b
Kuby IMMUNOLOGY, Sixth Edition
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MHC class II

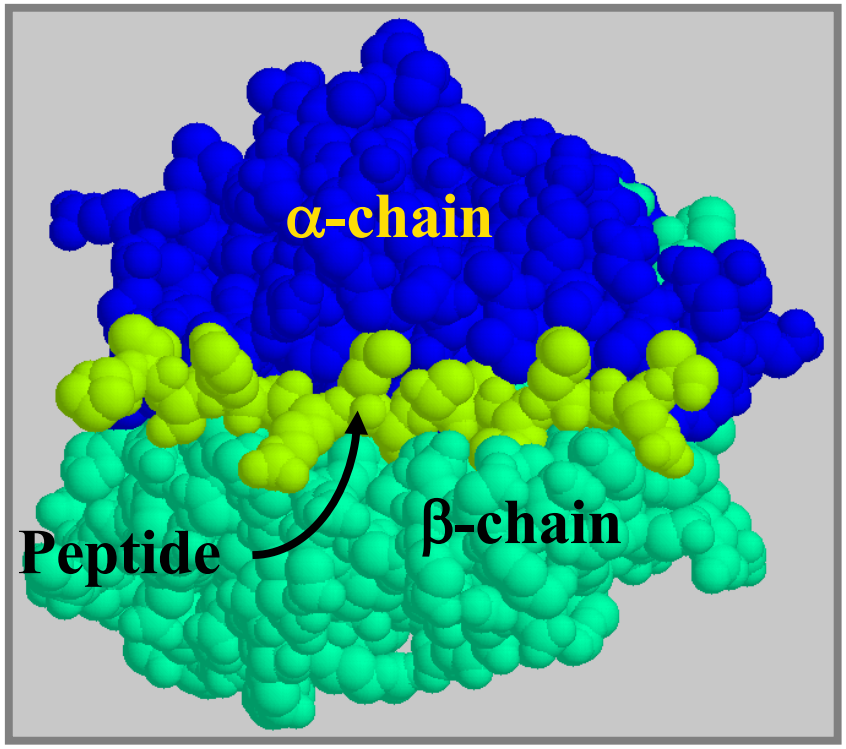


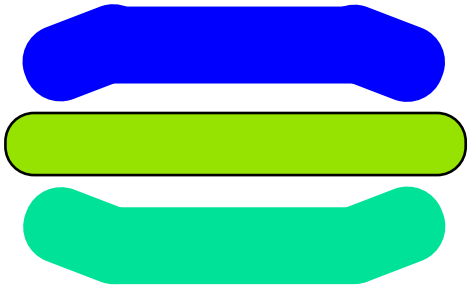
Cleft geometry





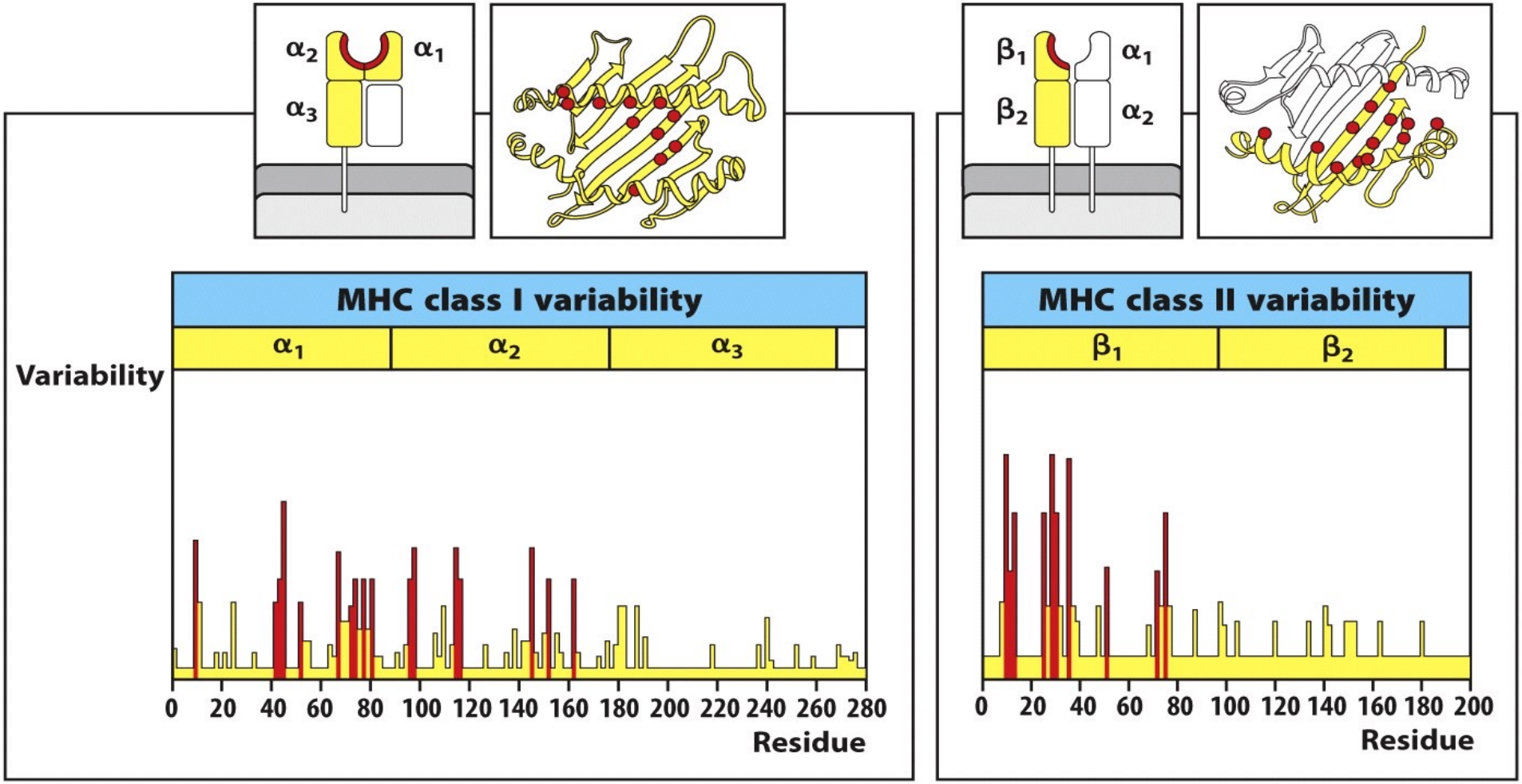
MHC class I accomodates peptides of 8-10 amino acids





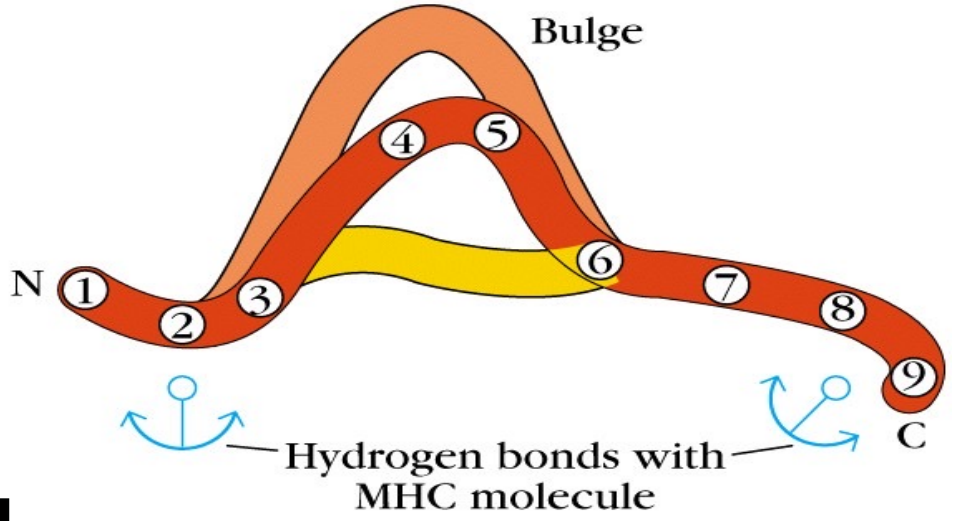
MHC class II accomodates peptides of >13 amino acids

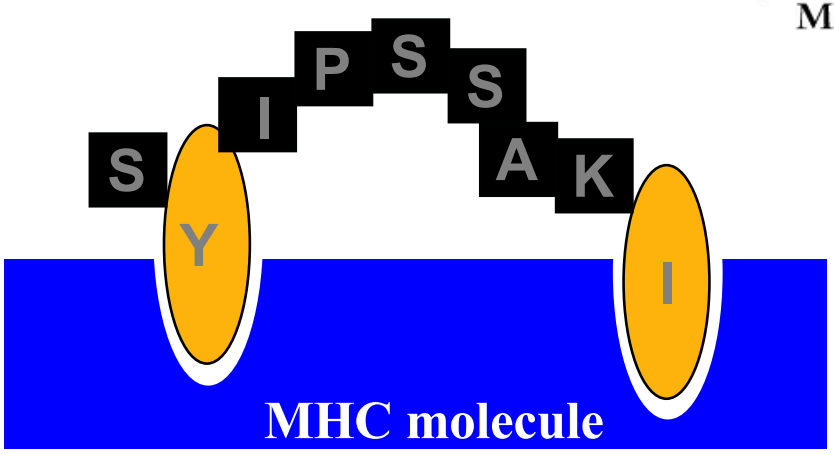
MHC polymorphism in the MHC is concentrated in the peptide binding pocket….

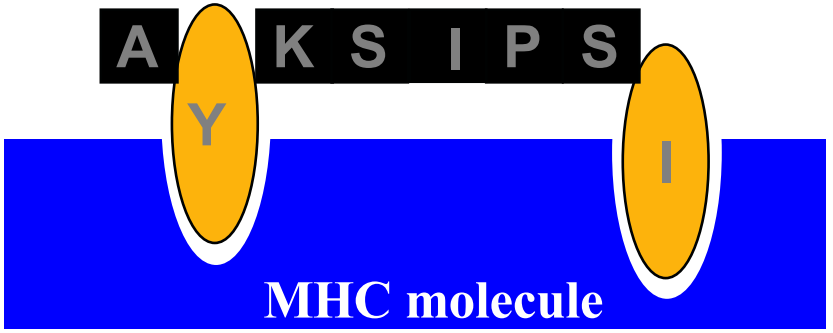


…influencing peptide antigen binding!

Each MHC molecule can bind many peptides of different length and sequence!

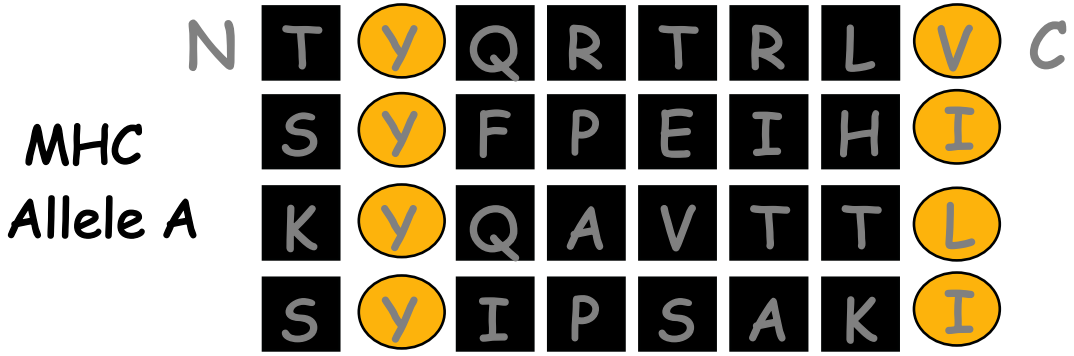






Number of amino acids between anchors can vary

The same MHC I can bind different peptides as long as they have the same anchor residues



HLA molecule (allele)	HLA-binding residues required in peptides at position #		
	#2	#5	#8/9
HLA-A2	Leucine/isoleucine	Variable	Variable; usually valine/ leucine/isoleucine
HLA-B27	Arginine	Variable	Arginine/lysine
HLA-B8	Lysine/arginine	Lysine/arginine	Valine/leucine/isoleucine
HLA-B35	Proline	Variable	Tyrosine/phenylalanine/ tryptophan

MHC class I molecules bind residues located at both ends of the peptide

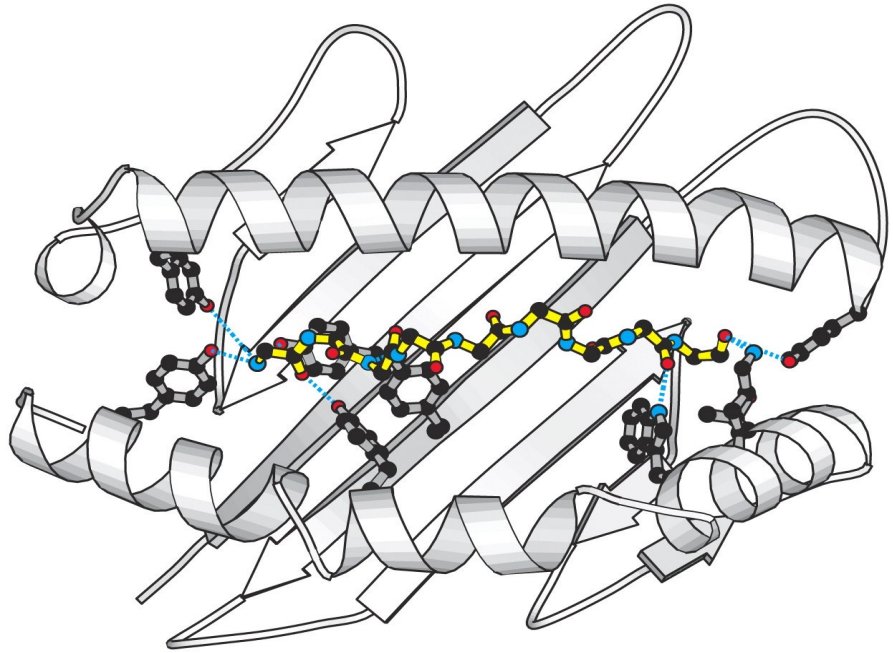


Figure 3-23 Immunobiology, 6/e. (© Garland Science 2005)

MHC class II molecules interact with residues distributed throughout the peptide

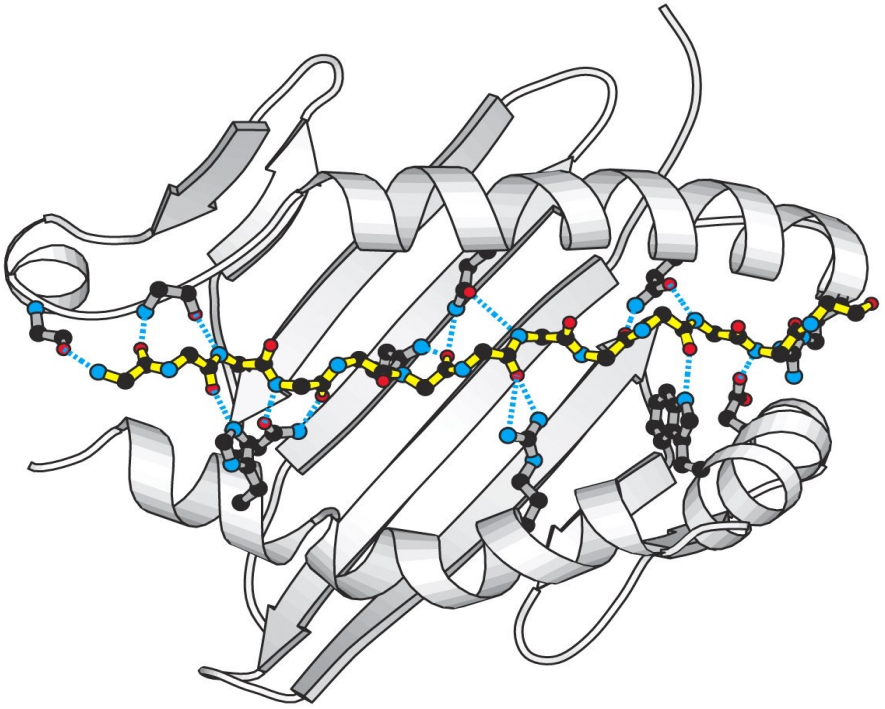
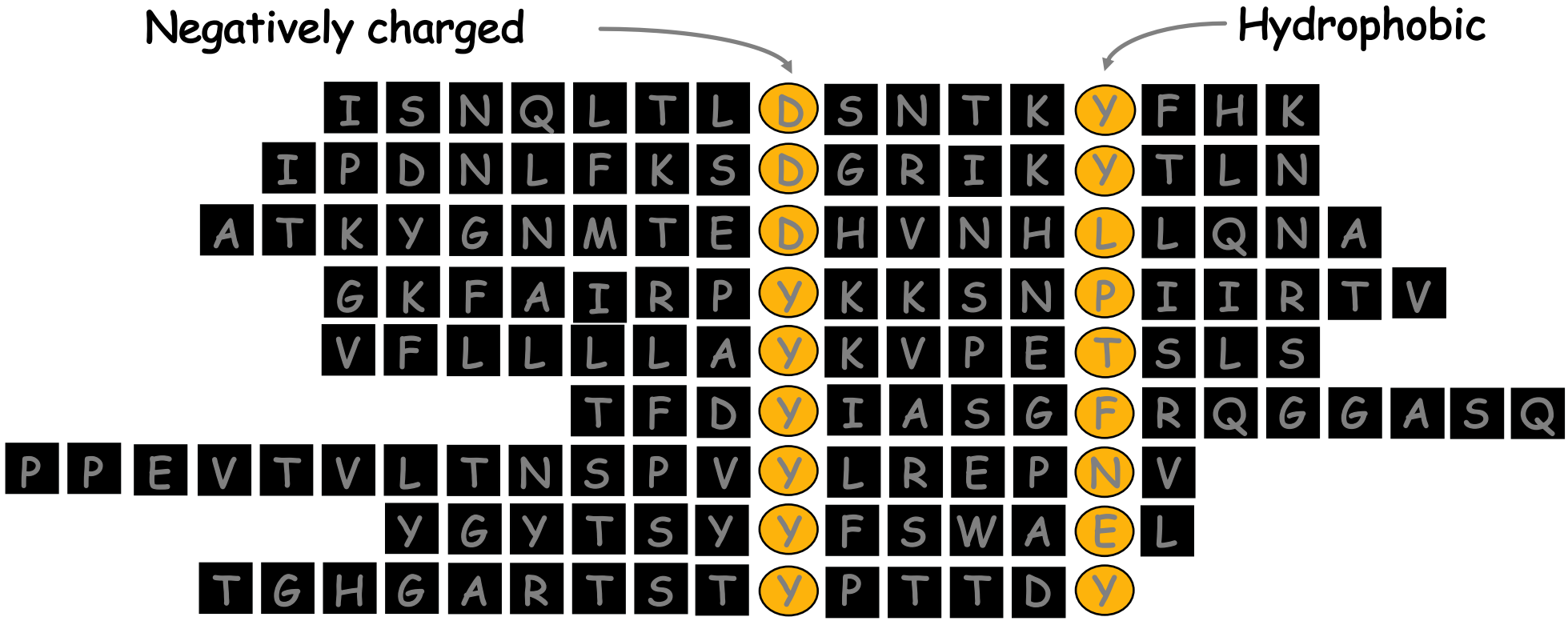


Figure 3-25 Immunobiology, 6/e. (© Garland Science 2005)

Peptide antigen binding to MHC class II molecules



- Anchor residues *are not* localised at the N and C termini
- Ends of the peptide are in extended conformation and may be trimmed
- Motifs are less clear than in class I-binding peptides
- Pockets are more permissive

Characteristics of MHC/peptide interactions

-Each MHC-I or -II molecule has a single peptide-binding pocket, which can accommodate, at different times, many different peptides (promiscuous binding), but with some structural features in common;

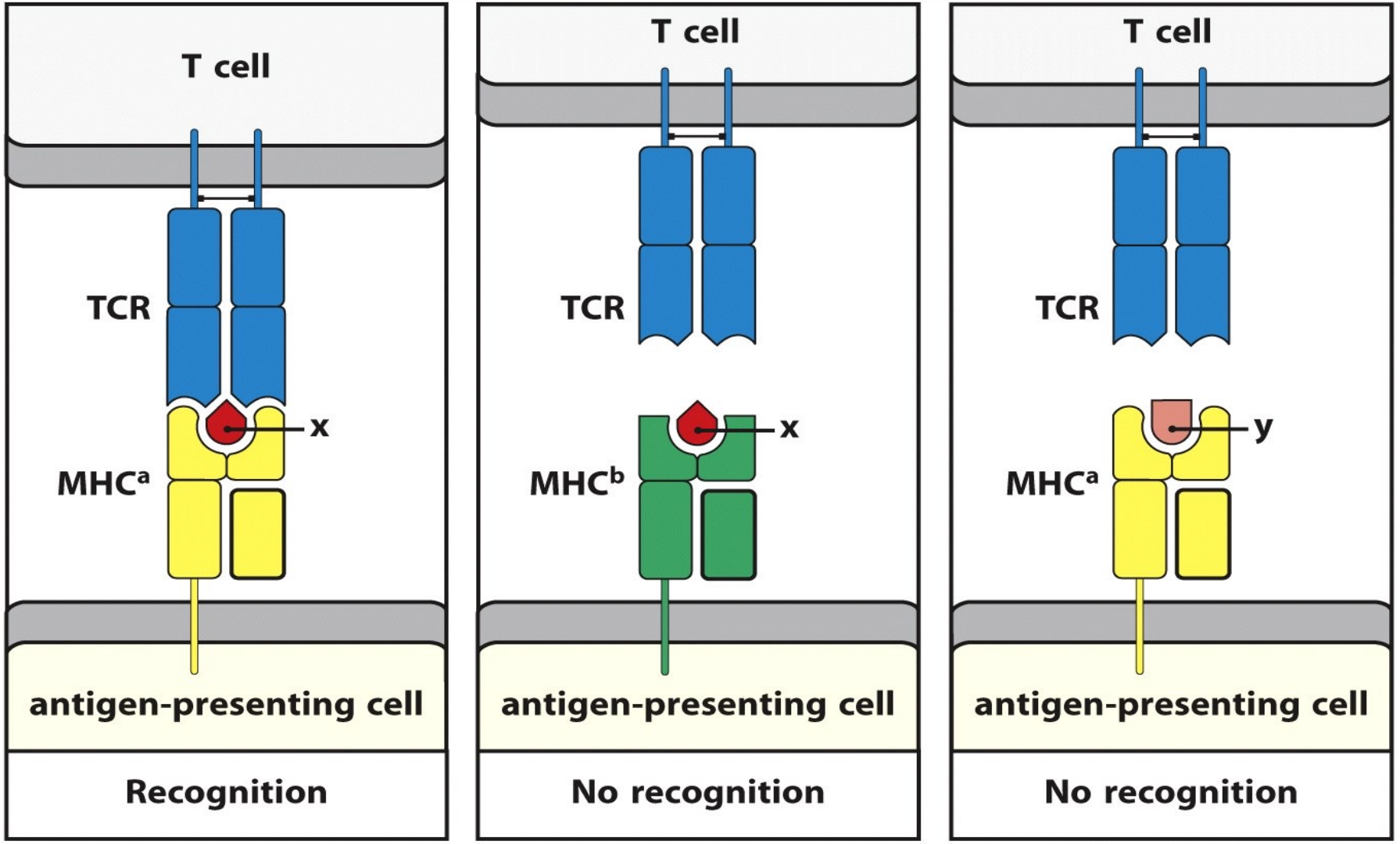
- the binding of peptides to MHC molecules is a non-covalent interaction between the anchor residues of the peptide and complementary residues in the pocket of the MHC molecule, with low rates of association and dissociation i.e. low affinity;

-MHC molecules do not distinguish between foreign peptides (e.g., derived from microbial antigens) and self-peptides (derived from one's own proteins);

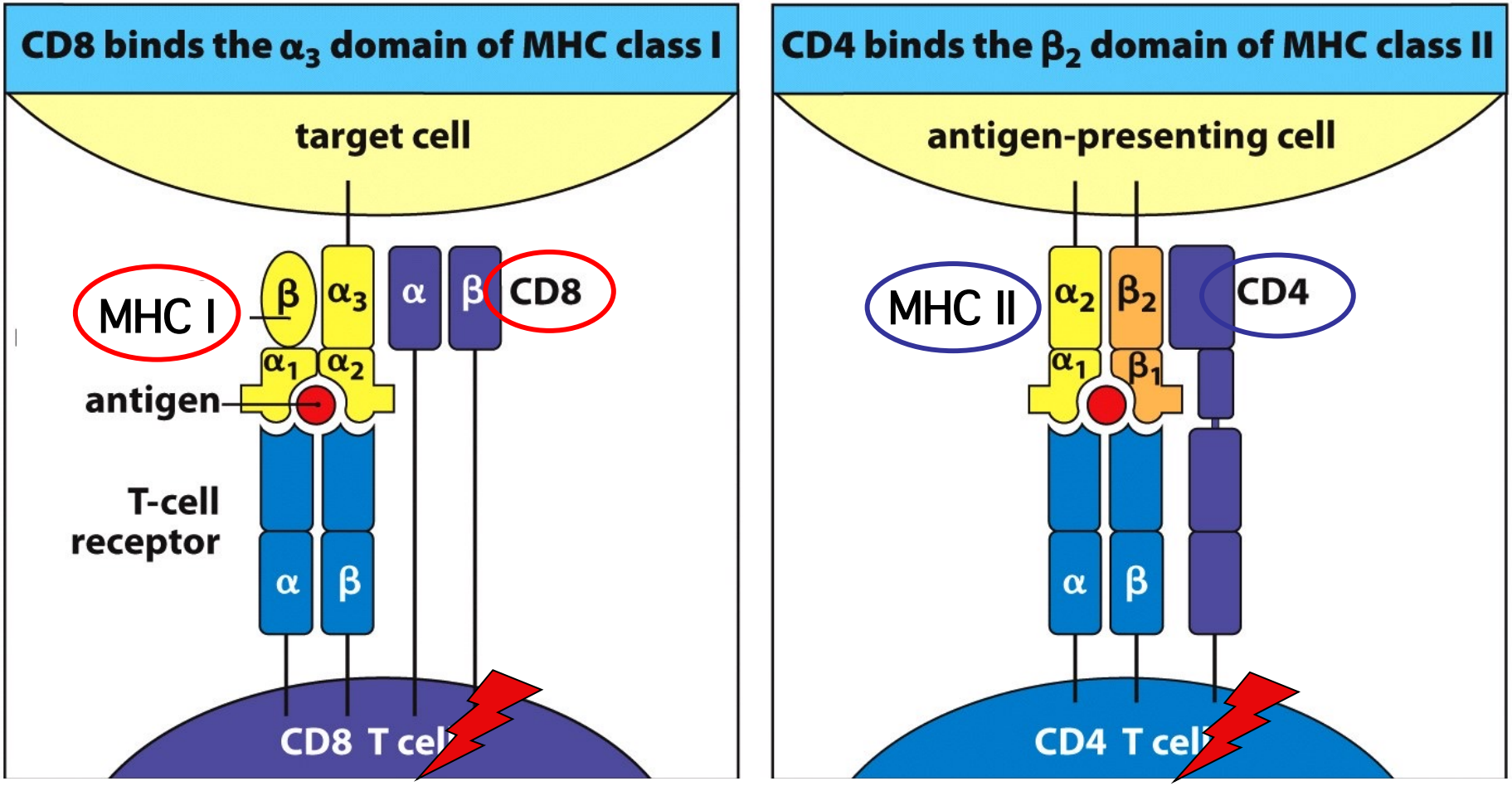
-A few identical MHC/peptide complexes (about 100) are sufficient to activate the T cell specific for that complex;

-The fine specificity of antigen recognition is mainly due to the selectivity of the TCR.

The TCR specifically recognizes both the non-self peptide and the self MHC molecule



CD4 and CD8 coreceptors of T cells



Bind to a <u>non-polymorphic</u> region of MHC class I and II molecules
- stabilize TCR/MHC interaction
- participate to T cell activation

Where are MHC molecules expressed?

Tissue	MHC class I	MHC class II
Lymphoid tissues		
T cells	+++	+*
B cells	+++	+++
Macrophages	+++	++
Dendritic cells	+++	+++
Epithelial cells of the thymus	+	+++
Other nucleated cells		
Neutrophils	+++	–
Hepatocytes	+	–
Kidney	+	–
Brain	+	–†
Nonnucleated cells		
Red blood cells	–	–

Figure 4.27 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

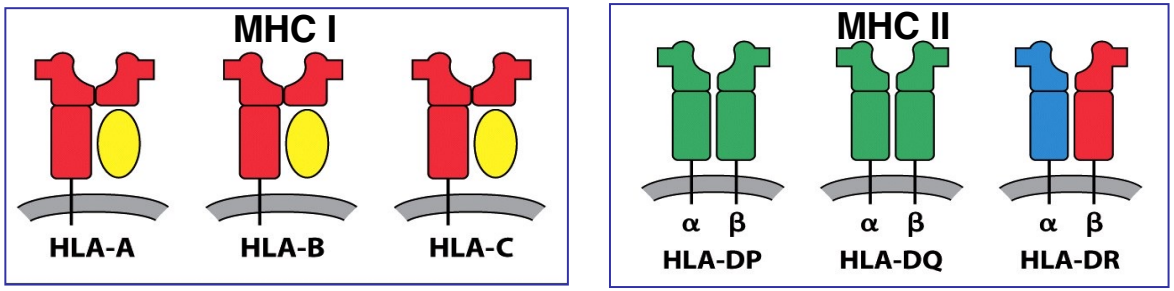
MHC expression can be modulated:

IFN α/β upregulate class I levels
IFN γ upregulates class II and induces de novo expression

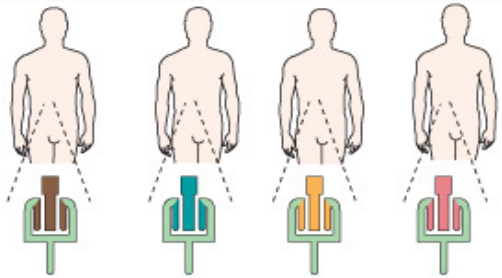
Some pathogens induce MHC class I downregulation!

MHC genes are:

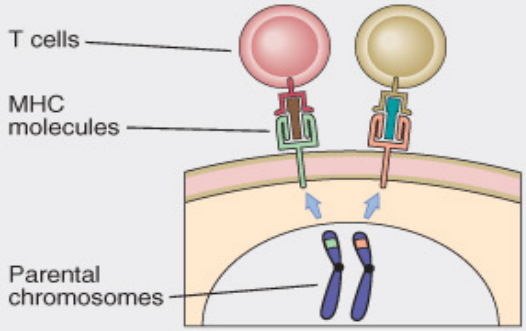
- **Poligenic**: several different genes for MHC class I and II molecules.



- **Polymorphyc**: many alleles exist for each gene in the population

Polymorphic genes: Many different alleles are present in the population	Ensures that different individuals are able to present and respond to different microbial peptides	

- **Codominantly express**: both maternal and paternal copies of each gene are expressed

Co-dominant expression: Both parental alleles of each MHC gene are expressed	Increases number of different MHC molecules that can present peptides to T cells	

To counteract the flexibility of pathogens:

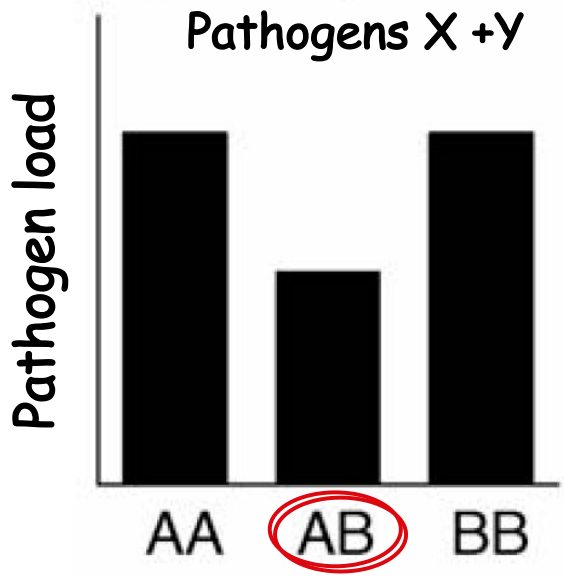
- We have many alleles for each type of MHC molecule
- These variants may not necessarily protect all individuals from every pathogen, but will protect the population from extinction

Genetic problem:

How to keep polymorphysm?

Mechanism to mantain elevated polimorfism rate:

•Natural selection: patogen positively select for MHC heterozigosity;



•Sexual selection: through sexual choices that favor dissimilar MHC crosses

The MHC system influences social behavior

In rodents, the male releases different olfactory molecules in the urine that provide information about his MHC, influencing the sexual choice of the female..



In most cases the choice is for males with MHC genes different from their own.

The study of "sweaty" T-shirts

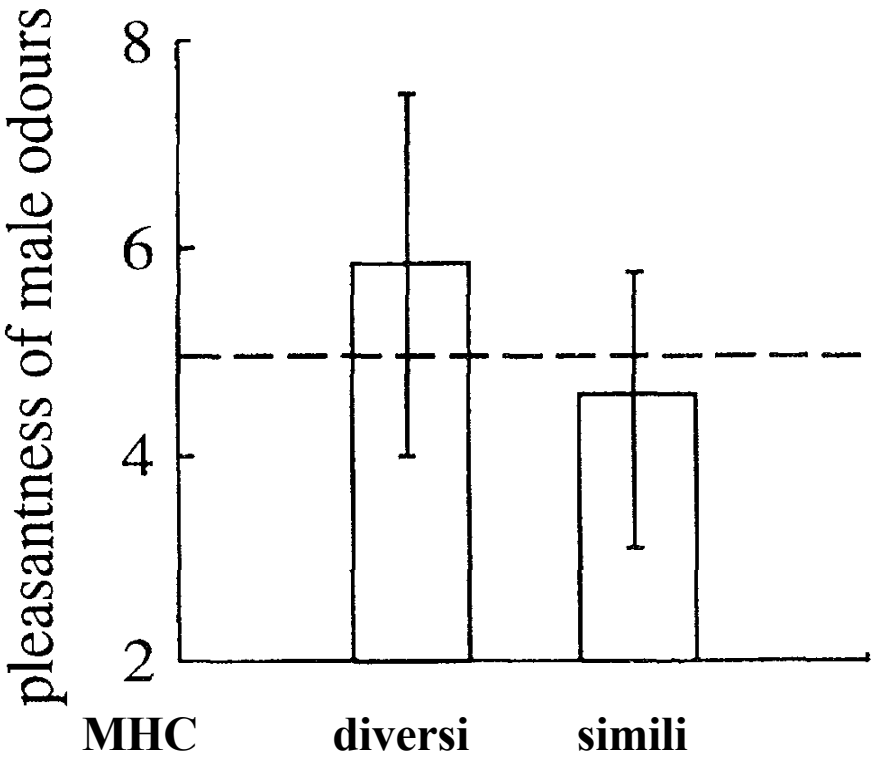
Wedekind, C., T. Seebeck, F. Bettens, and A. Paepke. 1995. MHC-dependent mate preferences in humans. Proceedings of the Royal Society of London B, Biological Sciences 260:245–249.



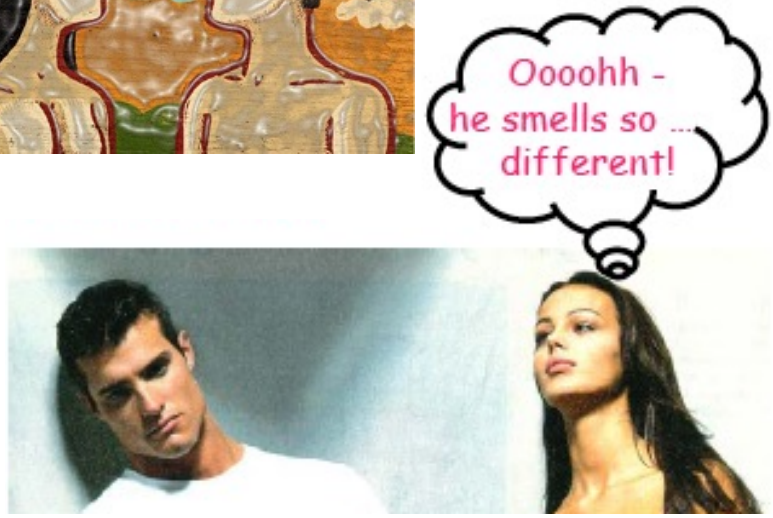
- Forty-nine female and 44 male undergraduate students were typed for MHC loci (HLA-A, -B, and -DR).
- Each male wore the same T-shirt for three consecutive nights.
- Each female was asked to choose the one with the most pleasant odor from six different T-shirts (three MHC-similar, three MHC-dissimilar).

The study of "sweaty" T-shirts

The smell you like the most belongs to the person with different MHC genes than yours!







What is the functional significance of this choice?

- Avoid inbreeding
- Generate offspring heterozygous for MHC loci

From an evolutionary point of view, this means privileging the choice of a partner who can guarantee children with reduced levels of infections or genetic diseases