The Major Histocompatibility Complex, MHC

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Medical School , Southeast University

The Nobel Prize in Physiology or Medicine 1980

"for their discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions"

Baruj Benacerraf

1/3 of the prize

USA

Harvard Medical School
Boston, MA, USA

b. 1920
(in Caracas, Venezuela)

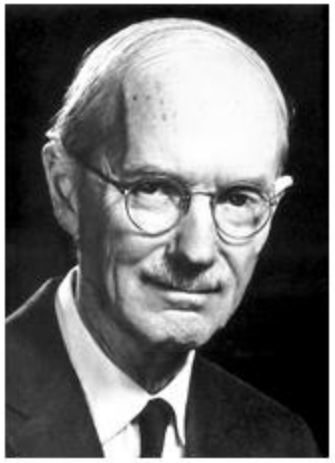
Jean Dausset

1/3 of the prize

France

Université de Paris,
Laboratoire Immuno-Hématologie
Paris, France

b. 1916
d. 2009



George D. Snell

1/3 of the prize

USA

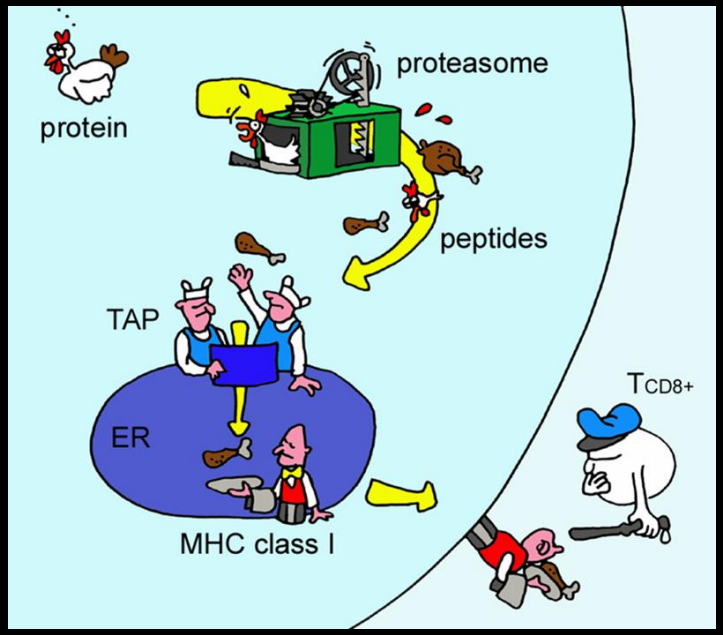
Jackson Laboratory
Bar Harbor, ME, USA

b. 1903
d. 1996

- George Snell (1903-1996) discovered the first components of the MHC through their role in rejecting transplants in mice, and created the word “histocompatibility”.

- Around a decade later, Jean Dausset (1916-2009) uncovered the first compatibility antigen in humans.

- Experiments by Baruj Benacerraf (1920-2011) in the 1970s provided the first indication that immune reactions are controlled by the MHC genes ('immune response genes').



- T cells do not recognize intact antigen (*the whole chicken*)
- Interact only with antigen fragments — peptide (*the drumstick*)
- Peptides are only recognized when they are associated with self-MHC molecules (*presented by a waiter*)

Terminology 1

- Histocompatible: transplanted tissue is successfully accepted as self
- Histocompatibility antigens: rejection of foreign tissue is the result of an immune response to cell-surface molecules
- Histocompatibility complex : a region of multiple loci that play major roles in determining whether transplanted tissue is with histocompatibility or inhistoincompatibility

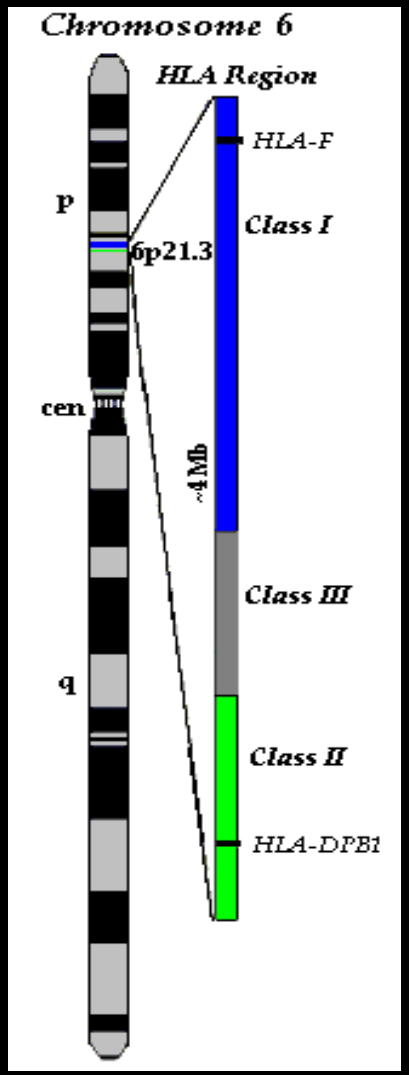
Terminology 2

- Major vs minor
  - Major Histocompatibility Complex, MHC : rapid graft rejection
  - Minor Histocompatibility complex, mHC : slow graft rejection
- HLA: human leukocyte antigen, MHC antigens in human
- H-2: MHC antigen in mice

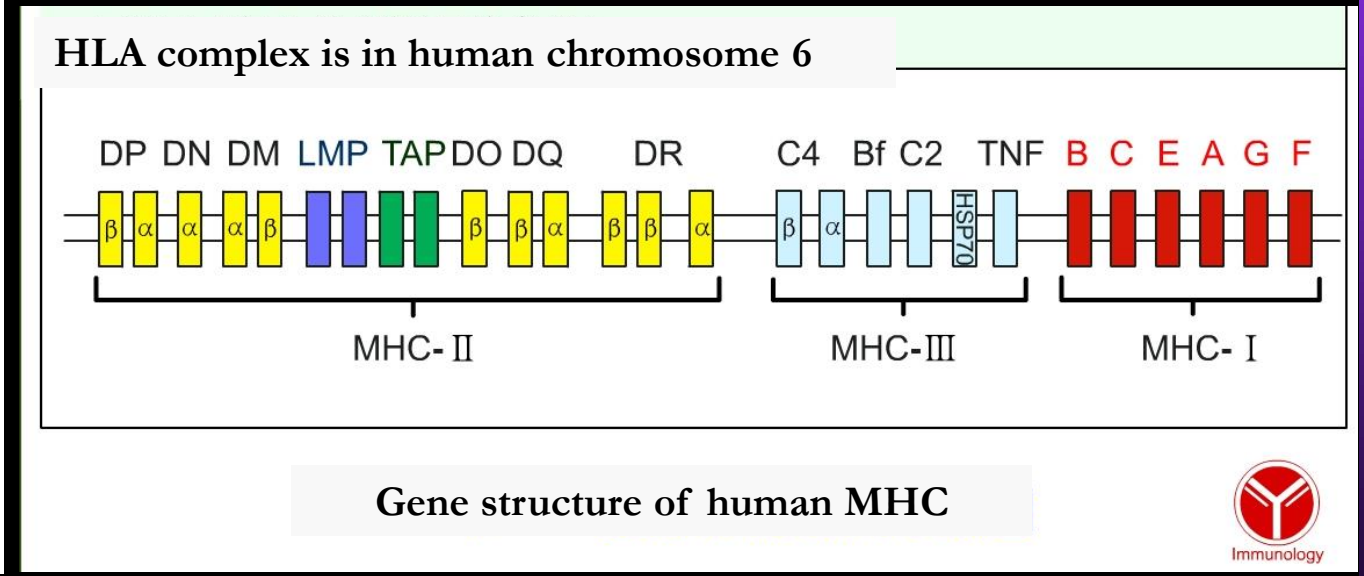
Terminology 3

- **HLA or MHC gene/complex — DNA**
- **HLA or MHC antigen/molecule — protein**

HLA complex

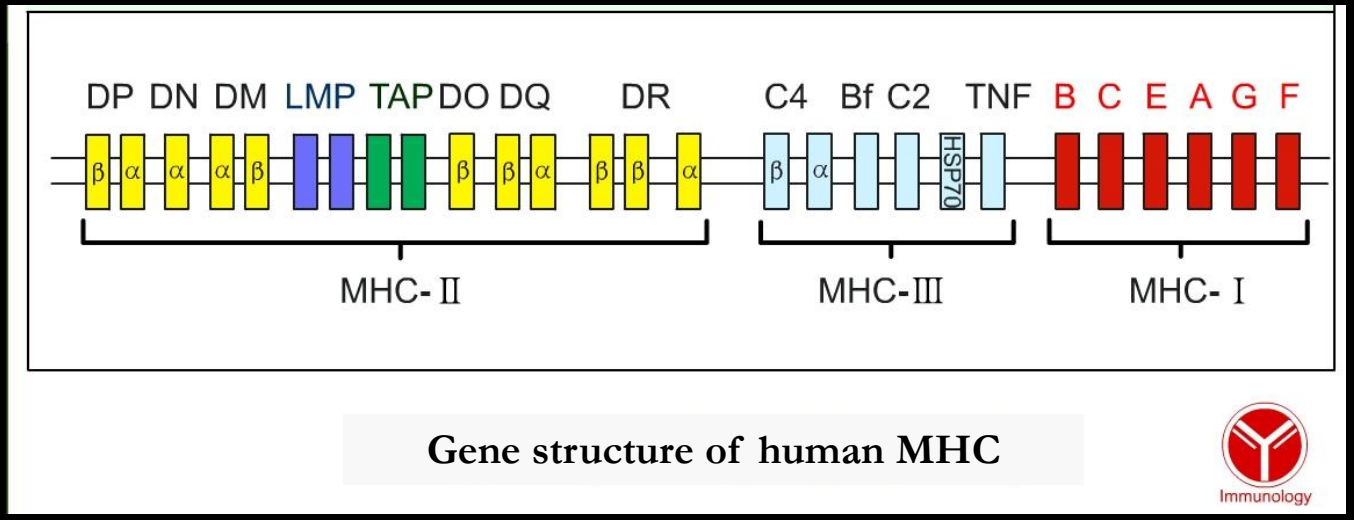


HLA complex spans 3.5 million bp on the short arm of chromosome 6



Classical v.s. nonclassical

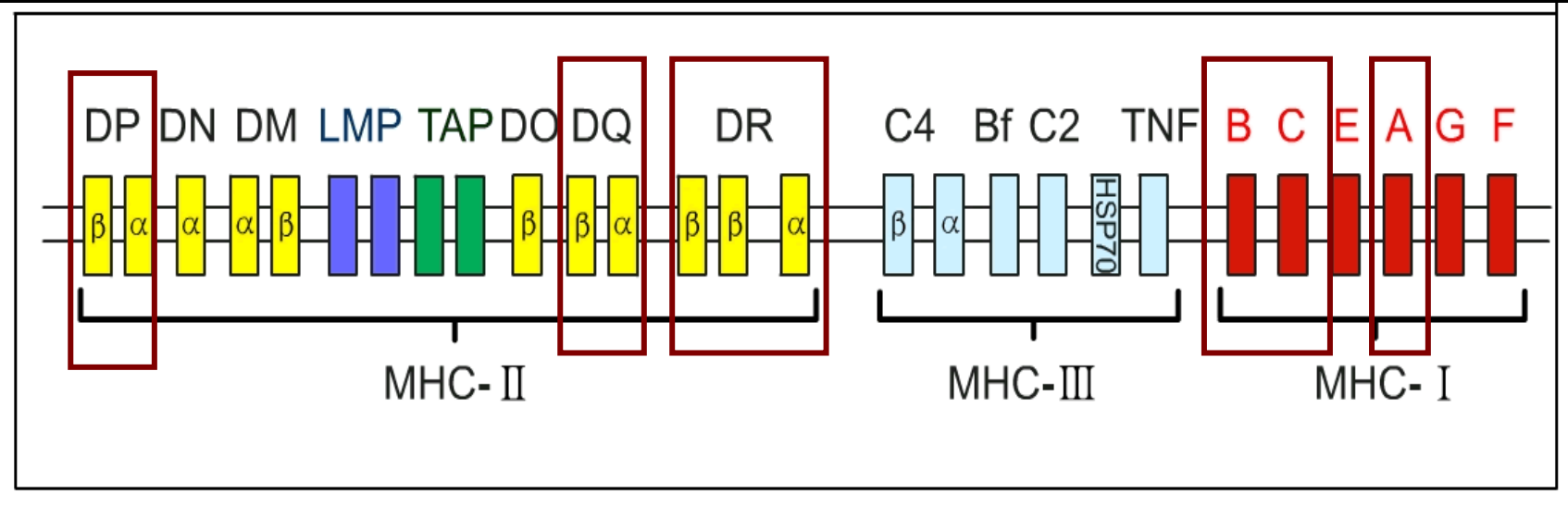
- Classical MHC:
  - present peptide directly to T cells
  - highly polymorphic
- Non-Classical MHC
  - not directly bind to the peptide
  - not highly polymorphic



Gene structure of human MHC

Classical HLA

- Class I
  - HLA-A, -B, and –C loci
  - encode the heavy chain (αchain) of HLA class I molecule
- Class II
  - HLA-DP, -DQ, and DR
  - Each has loci A and B, encode the αchain and β chain of HLA class II molecule, respectively

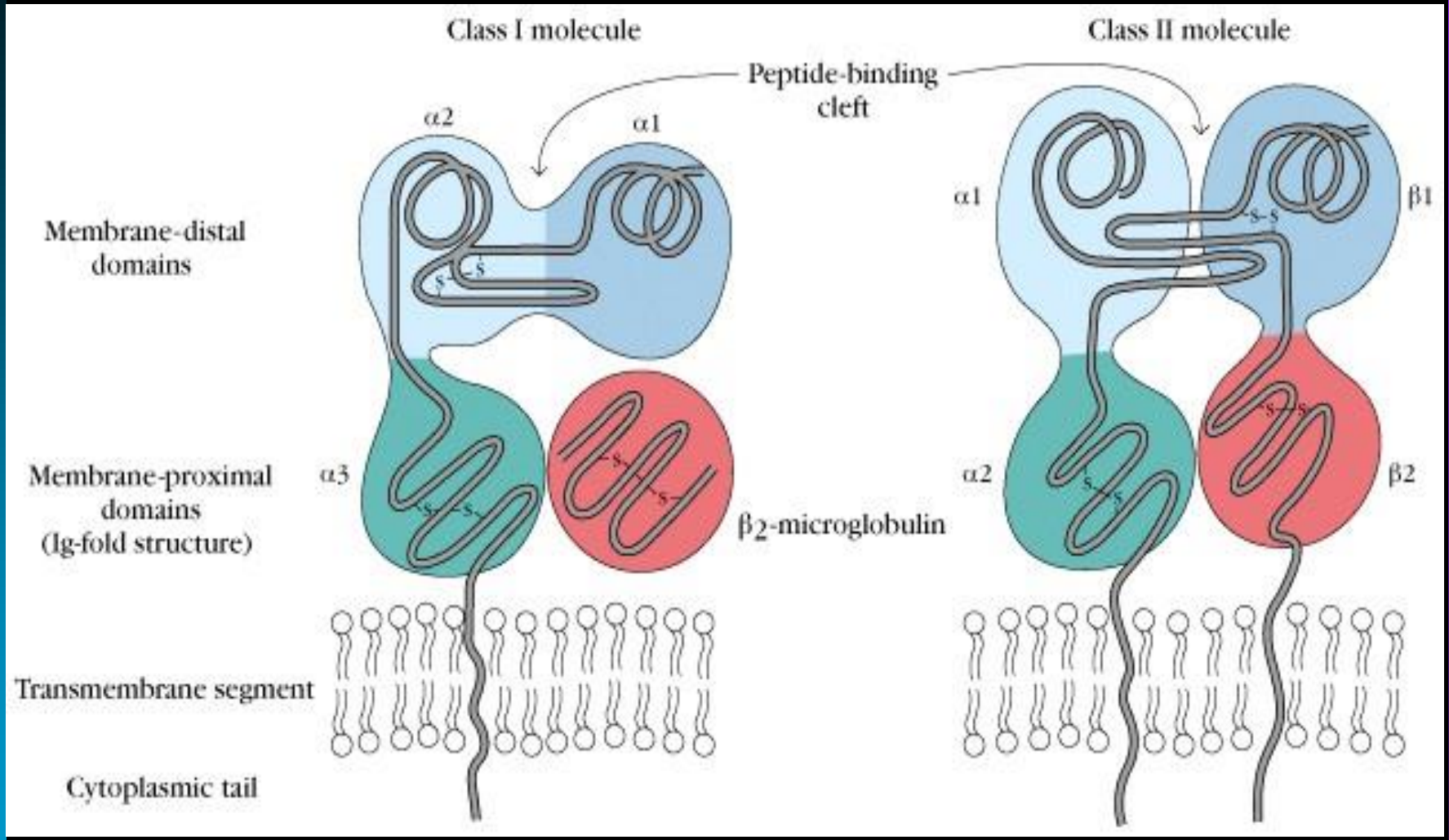


Non-Classical HLA genes

- Class III, Various secreted proteins with immune functions in inflammation: TNF, C2, C4…
- Other nonclassical genes and molecules: HLA-DM, CD1…

HLA molecules

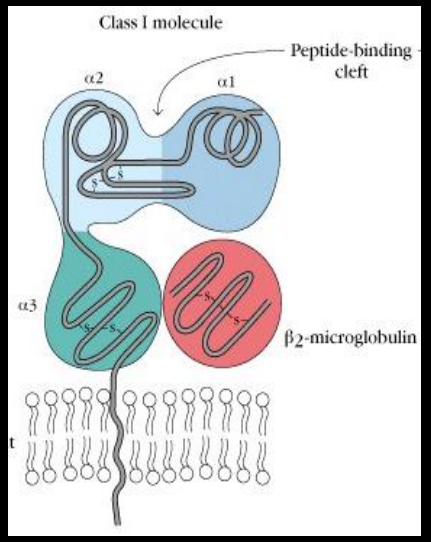
Structure of MHC Molecules. Domains



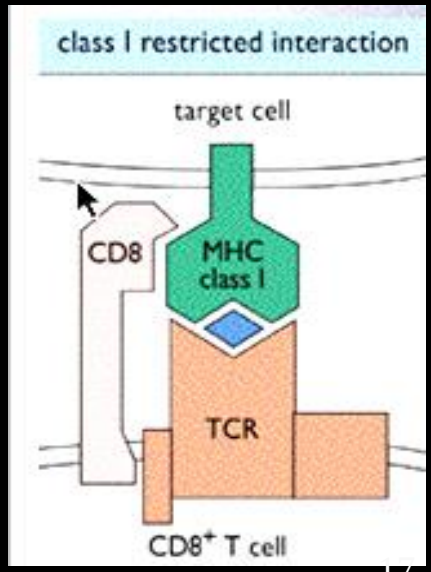
Class I and class II Molecules

- Both are membrane-bound glycoprotein containing external domains, a transmembrane segment, and a cytoplasmic segment
- Similar in three-dimensional structure
- both have peptide-binding cleft in membrane distal domains
- And two Ig-like domains membrane proximal domains

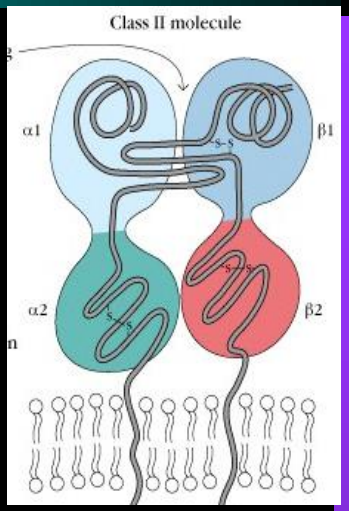
MHC class I Molecules



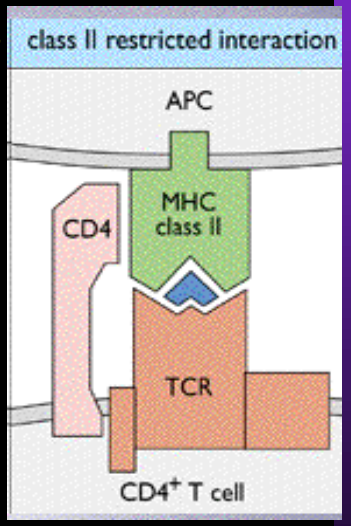
- α chain +β-2 microglobulin
  - α chain: polymorphic, transmembrane
    - α1 and α2 domains form peptide-binding cleft
    - α3 interacts with CD8 on T cells
  - β chain: no polymorphism, one folded domain, stabilize class I molecules (gene on chromosome 15)
- Expressed on almost all nucleated cells.
- Presentation of antigen to CD8+ T cells



MHC class II Molecules



- α chain plus β chain (each about 30 kd)
  - Both anchored in the cell membrane
  - Both are polymorphic
  - α1 and β 1 domains form peptide-binding cleft
- Expressed on professional ‘ antigen presenting cells, APC’ such as B cells, dendritic cells and macrophages.
- Ligand for CD4 and TCR (Presentation of antigen to CD4+ T)



Peptide- MHC Interactions

The Moose:
Wiley, Strominger et.al.

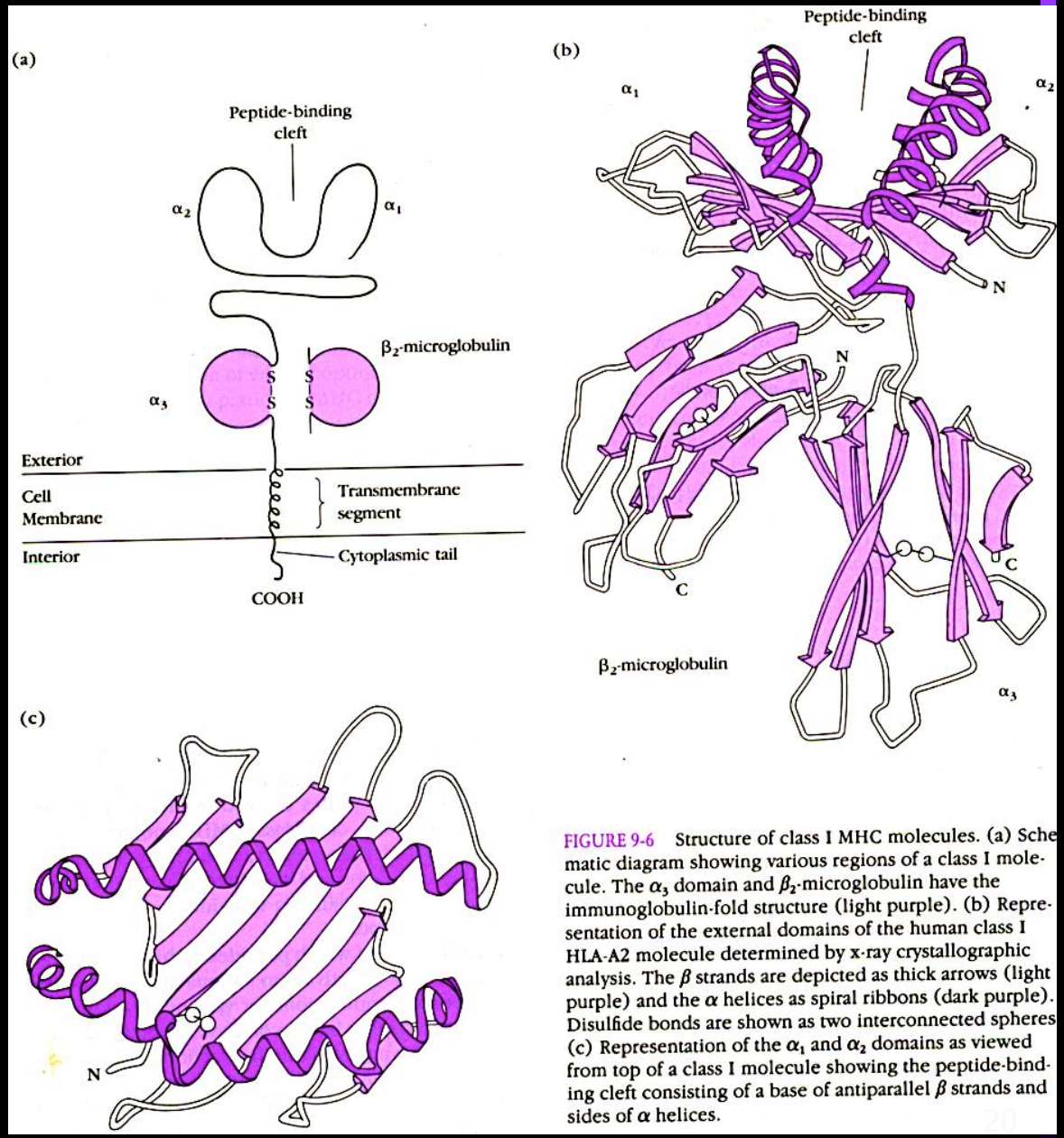
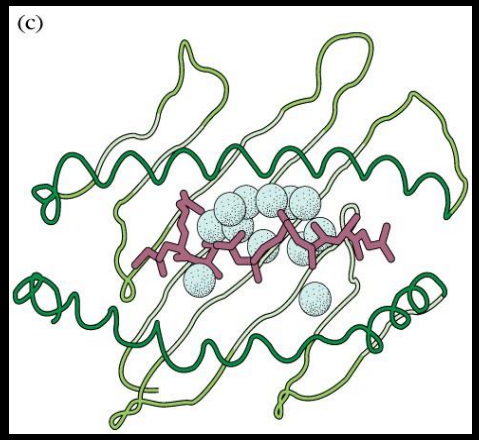


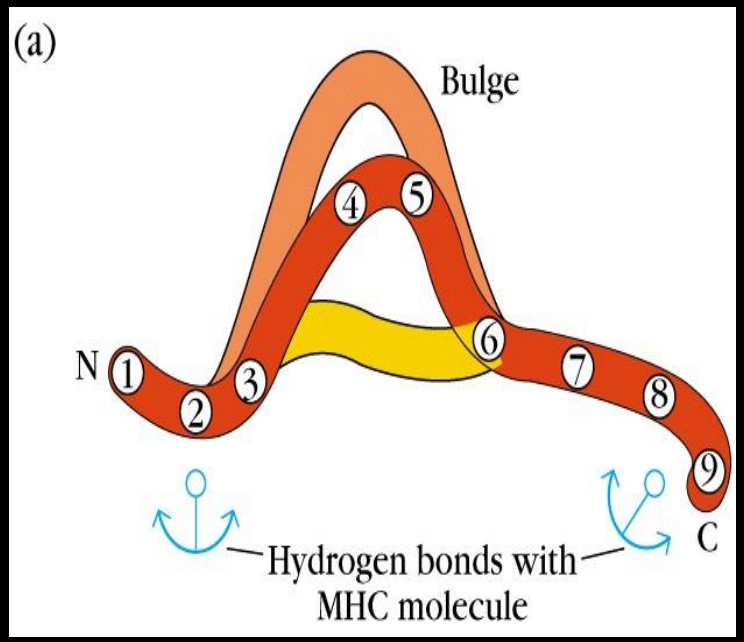
FIGURE 9-6 Structure of class I MHC molecules. (a) Schematic diagram showing various regions of a class I molecule. The α_3 domain and β_2-microglobulin have the immunoglobulin-fold structure (light purple). (b) Representation of the external domains of the human class I HLA-A2 molecule determined by x-ray crystallographic analysis. The β strands are depicted as thick arrows (light purple) and the α helices as spiral ribbons (dark purple). Disulfide bonds are shown as two interconnected spheres (c) Representation of the α_1 and α_2 domains as viewed from top of a class I molecule showing the peptide-binding cleft consisting of a base of antiparallel β strands and sides of α helices.

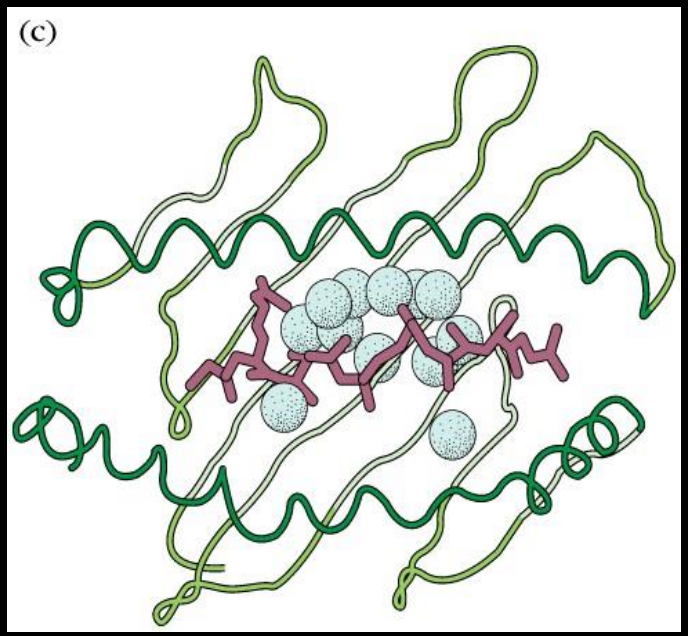
peptide-binding groove of MHC Class I

- **α1 and α2 domains form peptide-binding domains**
- **Antiparallel eight stranded β-pleated sheet form the floor**
- **Two long α helices, oriented adjacent and roughly parallel to each other form sides of the deep cleft**
- **Closed ends, accommodate about 8-11 aa in a flexible, extended conformation.**



The Bulge : Class I MHC
Ends are stuck. Middle bulges into accessibility.



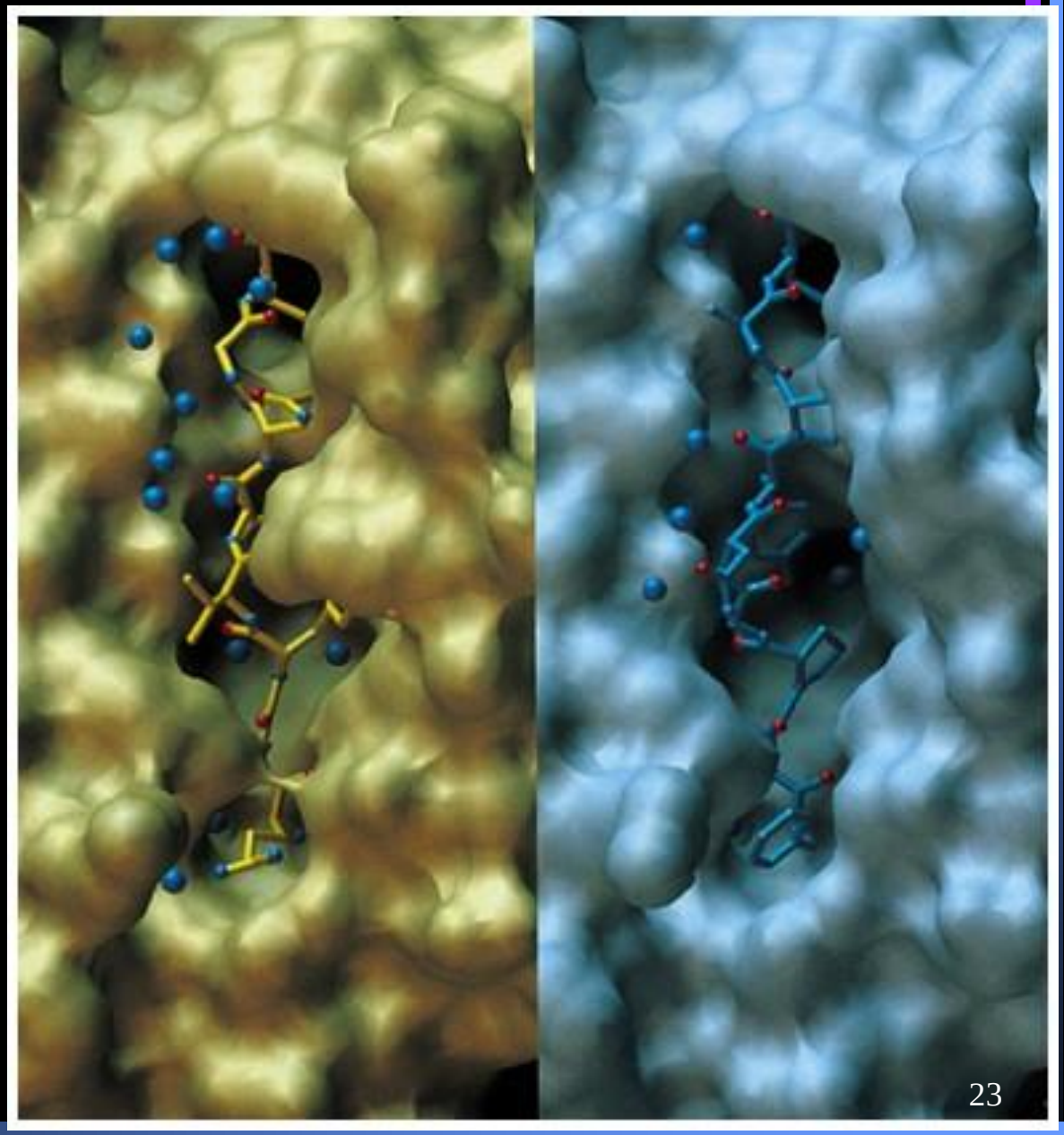


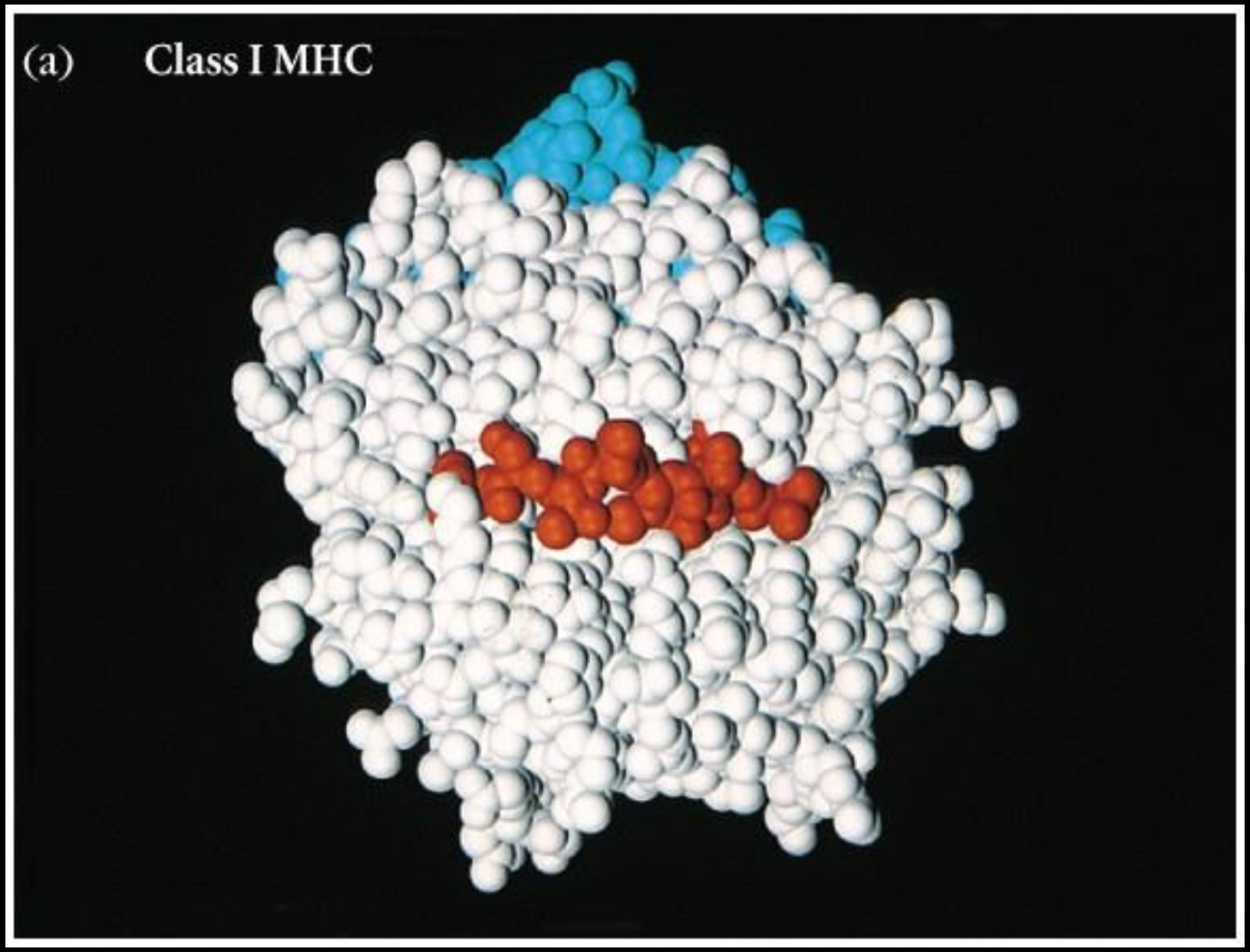
Peptide binding to Class I MHC

Solvent Accessibility

About 80% Buried.

Size does matter.
(9 mers best.)




(a) Class I MHC

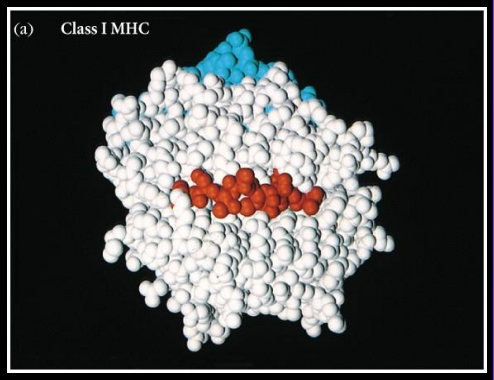
Class I and class II MHC are similar…but

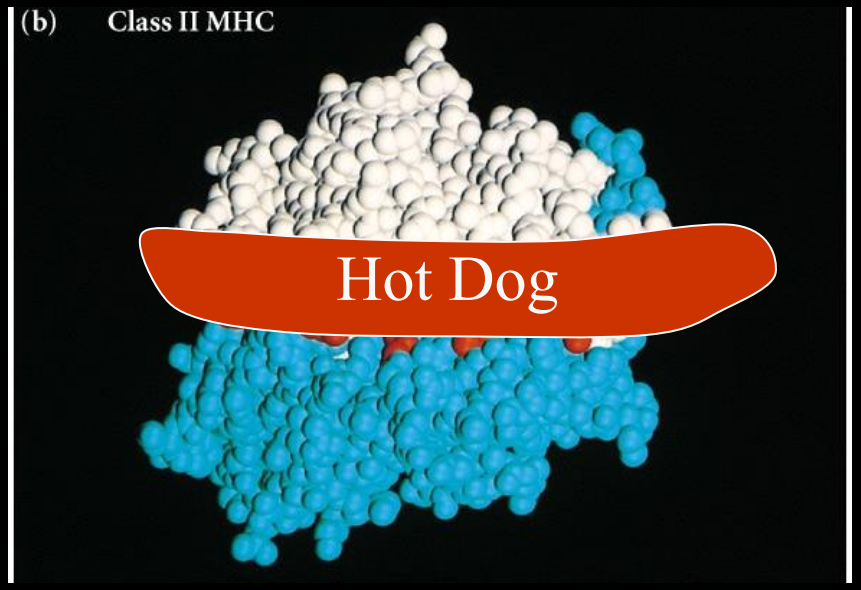
peptide-binding groove of MHC Class II

- **Two long α helices as sides and the β sheet as bottom**
- **The ends of class II peptide-binding cleft are more open, bind longer and irregular peptides (12-16 aa be optimal)**

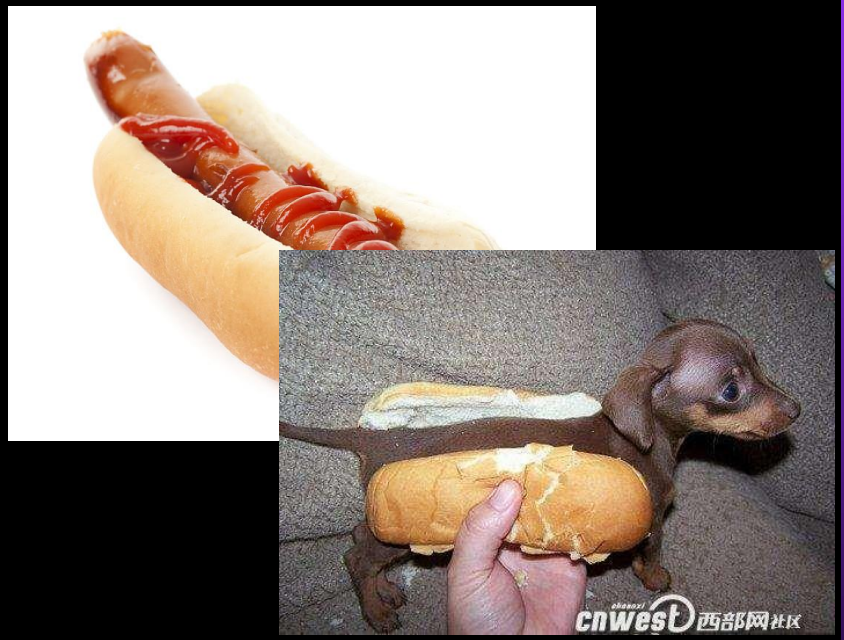
MHC Class II

- Longer peptides. Ends can hang out.
- Central core of about 13 amino acids.
- Allele-specific binding motifs.
- No bulge.



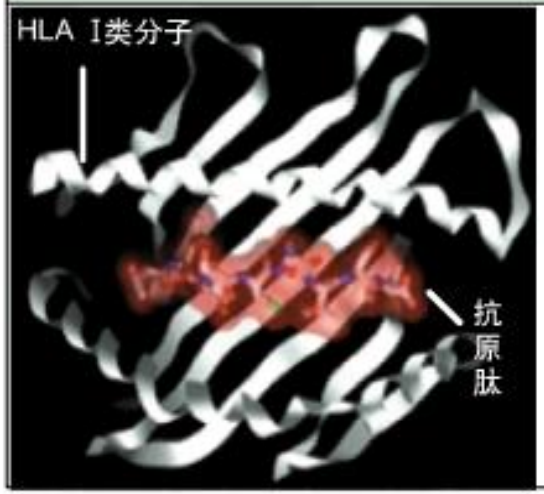


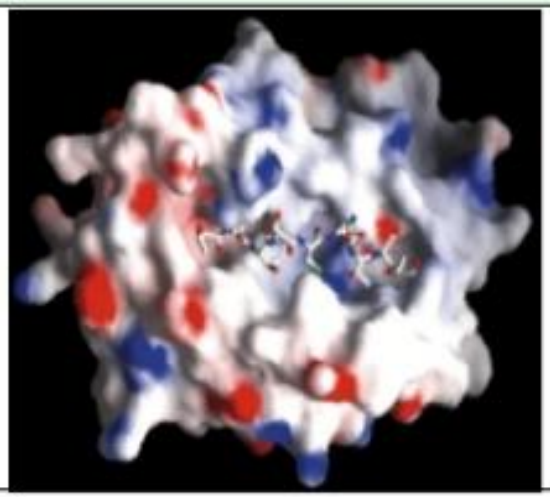
Hot Dog on a Bun



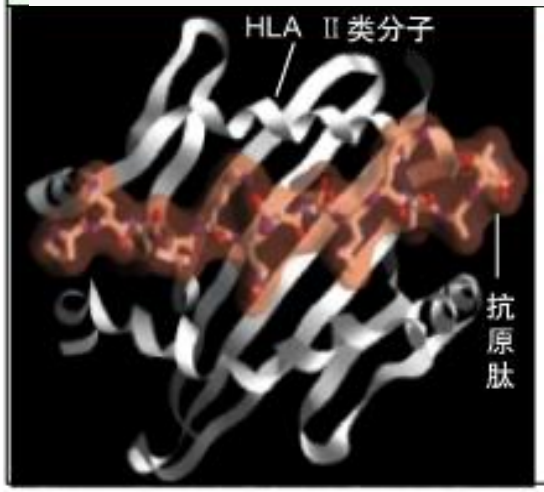
MHC Class II

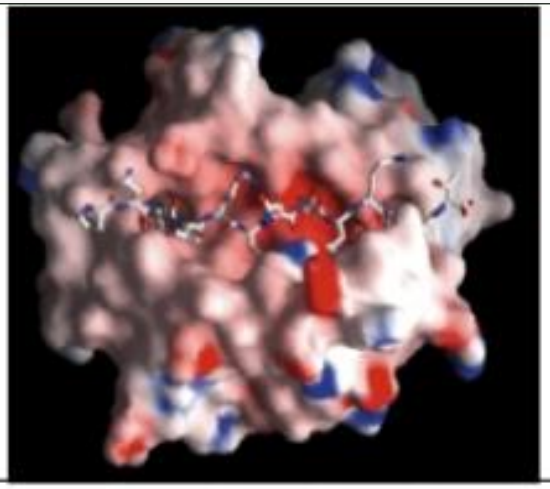
Pepetide-MHC class I complexes





Pepetide-MHC class II complexes





Peptide Binding by Class I and Class II MHC Molecules

TABLE 7-2 PEPTIDE BINDING BY CLASS I AND CLASS II MHC MOLECULES

	Class I molecules	Class II molecules
Peptide-binding domain	$\alpha 1/\alpha 2$	$\alpha 1/\beta 1$
Nature of peptide-binding cleft	Closed at both ends	Open at both ends
General size of bound peptides	8–10 amino acids	13–18 amino acids
Peptide motifs involved in binding to MHC molecule	Anchor residues at both ends of peptide; generally hydrophobic carboxyl-terminal anchor	Anchor residues distributed along the length of the peptide
Nature of bound peptide	Extended structure in which both ends interact with MHC cleft but middle arches up away from MHC molecule	Extended structure that is held at a constant elevation above the floor of MHC cleft

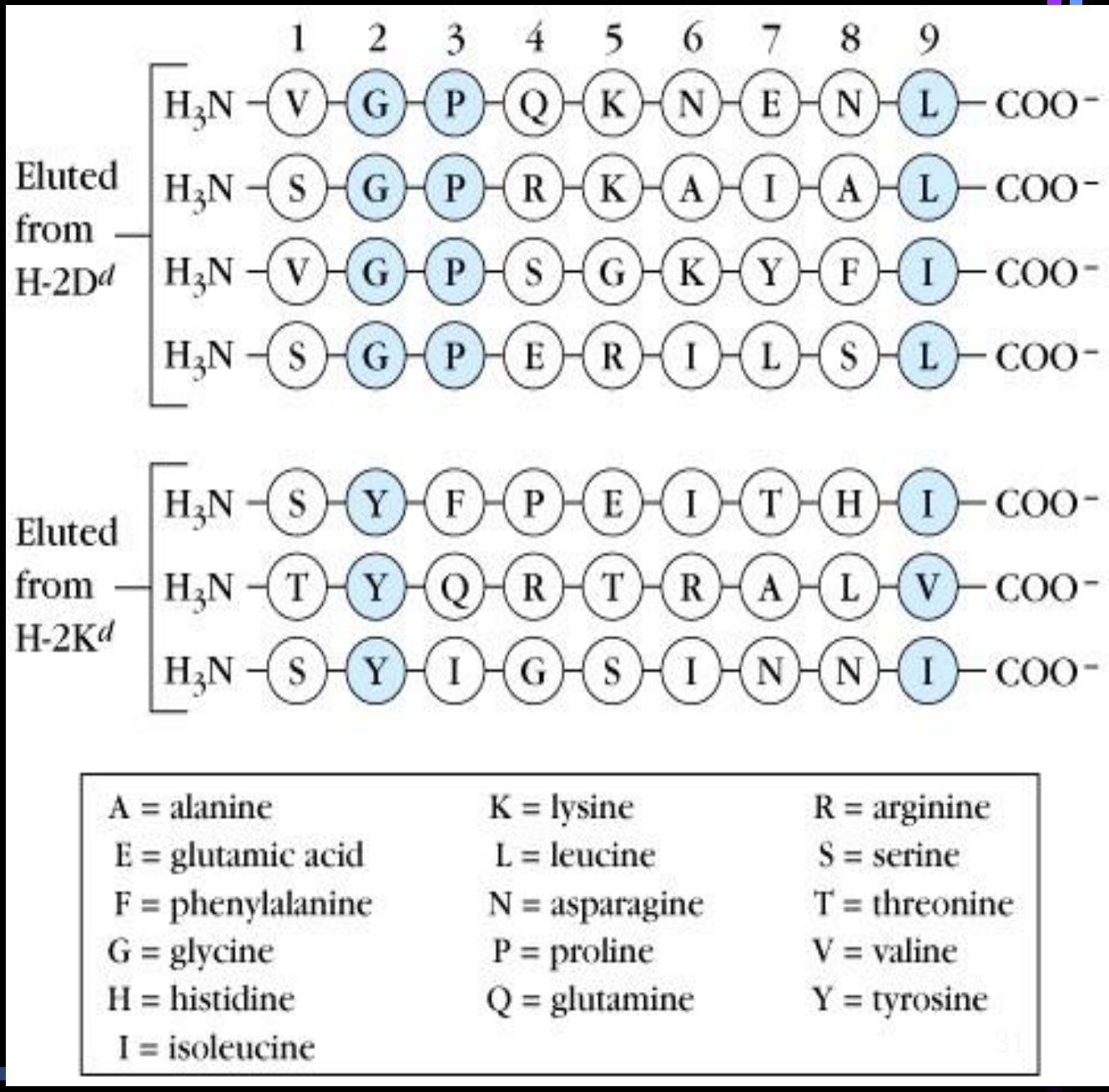
MHC-peptide interaction

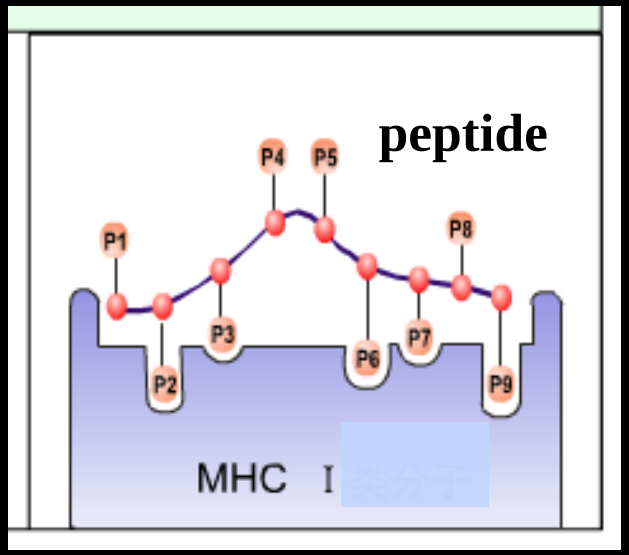
- **There are about a dozen of types of classical HLA molecules on the cell surface for one individual**
- **However, there are much, much, much more kinds of antigen peptides would be presented in one individual**

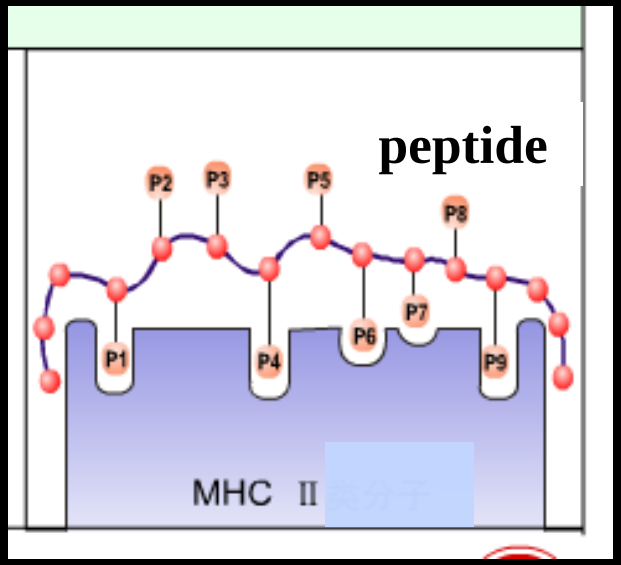
So, one type of HLA molecule can present large number of different peptides ?

Class I MHC
Elution of peptides

Anchor Residues.




peptide
P1
P2
P3
P4
P5
P6
P7
P8
P9
MHC Ⅰ类分子


peptide
P1
P2
P3
P4
P5
P6
P7
P8
P9
MHC Ⅱ类分子

- Some amino acid residues of peptides anchor the peptide into the pockets within the groove of the MHC molecule, called anchor residue.

So,

- a given MHC molecule binds a group peptides with same anchor residues
- The different MHC molecules bind different groups of peptides

Function of HLA molecules

- **Antigen presentation**
  - **process : endogenous antigen and exogenous antigen**
  - **presentation: TCR recognize MHC: peptide complex (double recognition)**
  - **MHC restriction of T cell: Any individual's T cells respond to a specific MHC allele expressed by that individual, that is to "self" MHC**

- **others**
  - **Genetically regulator of immune response, so to predispose individuals to particular susceptibility or disorders**
  - **Immune regulation**

All are features of cell-surface HLA-B molecules, EXCEPT:

A. They are associated with β2 microglobulin.
B. They bind exogenous peptides.
C. They are polymorphic.
D. They are expressed on B lymphocytes.
E. They can be bound by CD8 molecules.

Which one of the following is TRUE about class II MHC molecules?

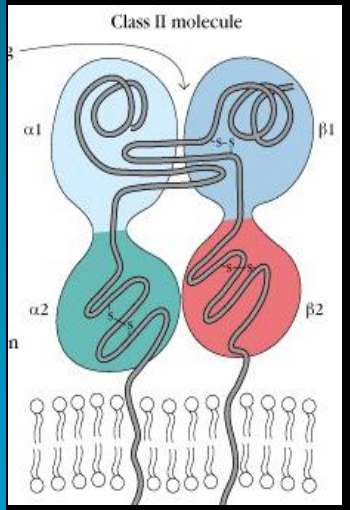
A. They consist of an alpha chain of three domains and a β2microglobulin.
B. They are found in all nucleated cells of our body.
C. They are involved in antigen presentation to CD8+ cytotoxic lymphocytes.
D. They consist of DR, DQ, and DP molecules.
E. They are located on the X chromosomes.

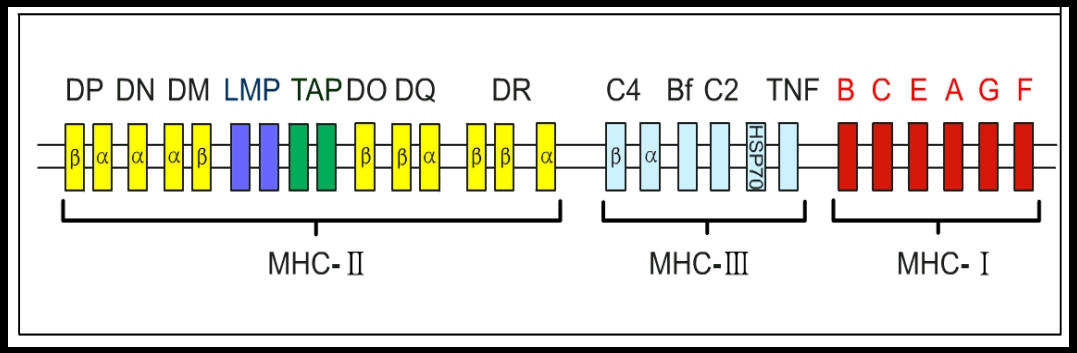
Features of MHC genes

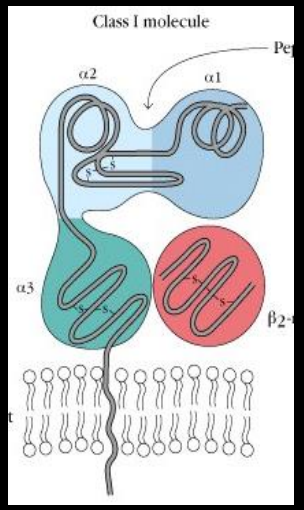
1. polygenicity
2. polymorphism
3. Haplotype inheritance
4. Linkage disequilibrium
5. Codominant expression

1.polygenicity

- **Multiple separate, functional genes encoding the similar MHC molecules**
- **HLA I: HLA-A, -B, and –C**
- **HLA II: HLA-DR, -DP, and -DQ**

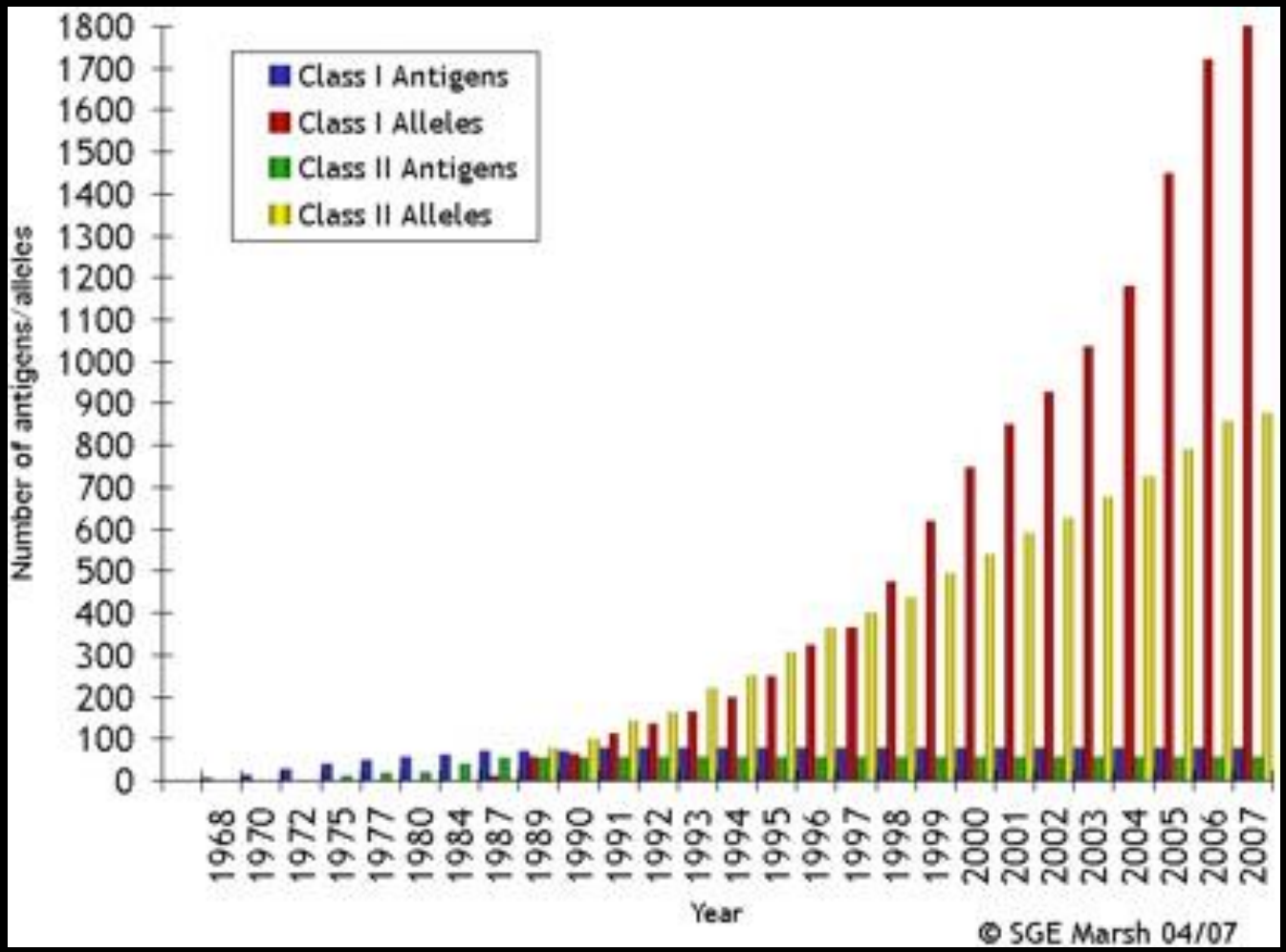






2. Polymorphisms

- There are many different alleles present among the different individuals in the population.
- Most Polymorphic genetic systems known in the higher vertebrates


Class I Antigens
Class I Alleles
Class II Antigens
Class II Alleles
Number of antigens/alleles
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
1968
1970
1972
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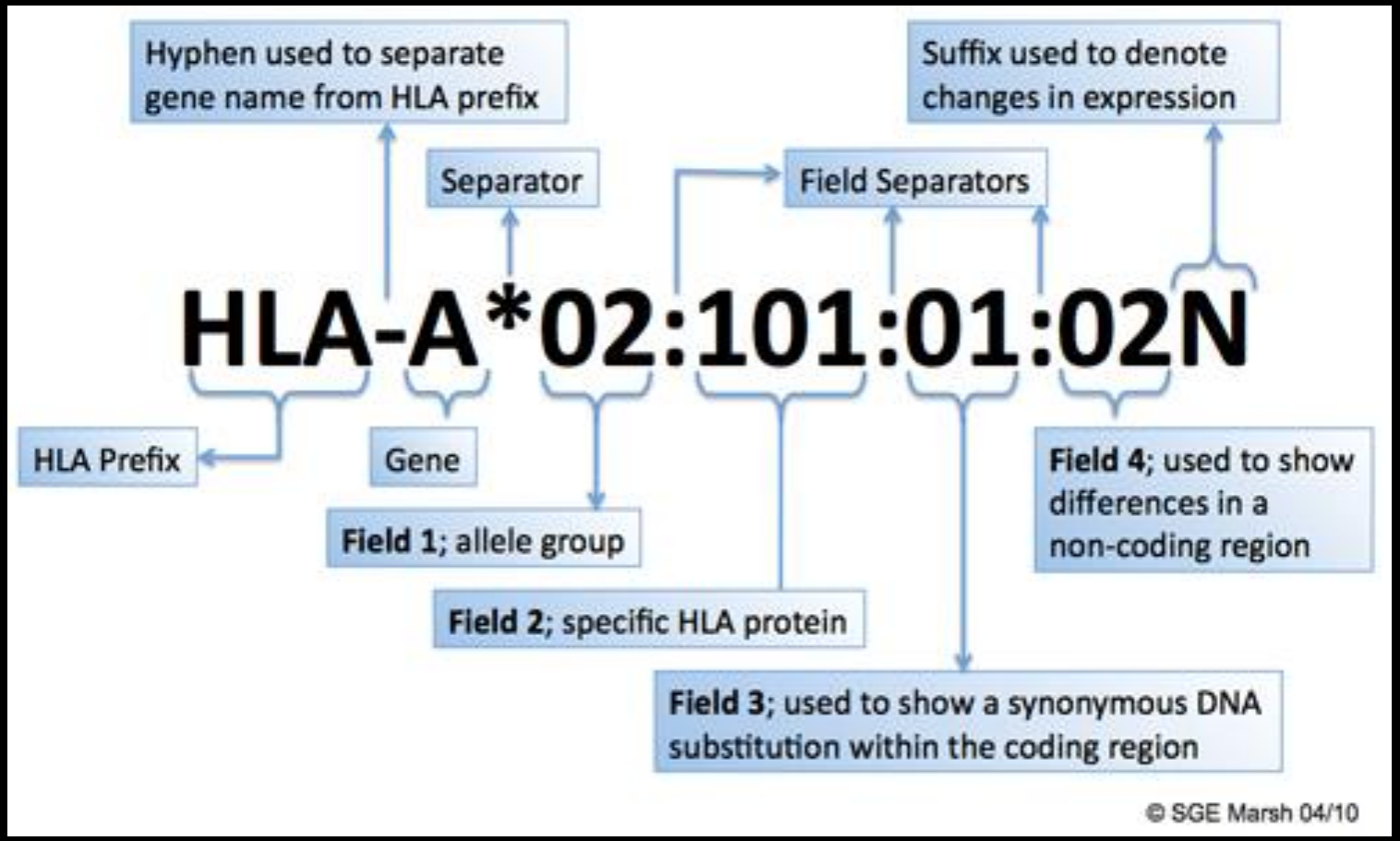
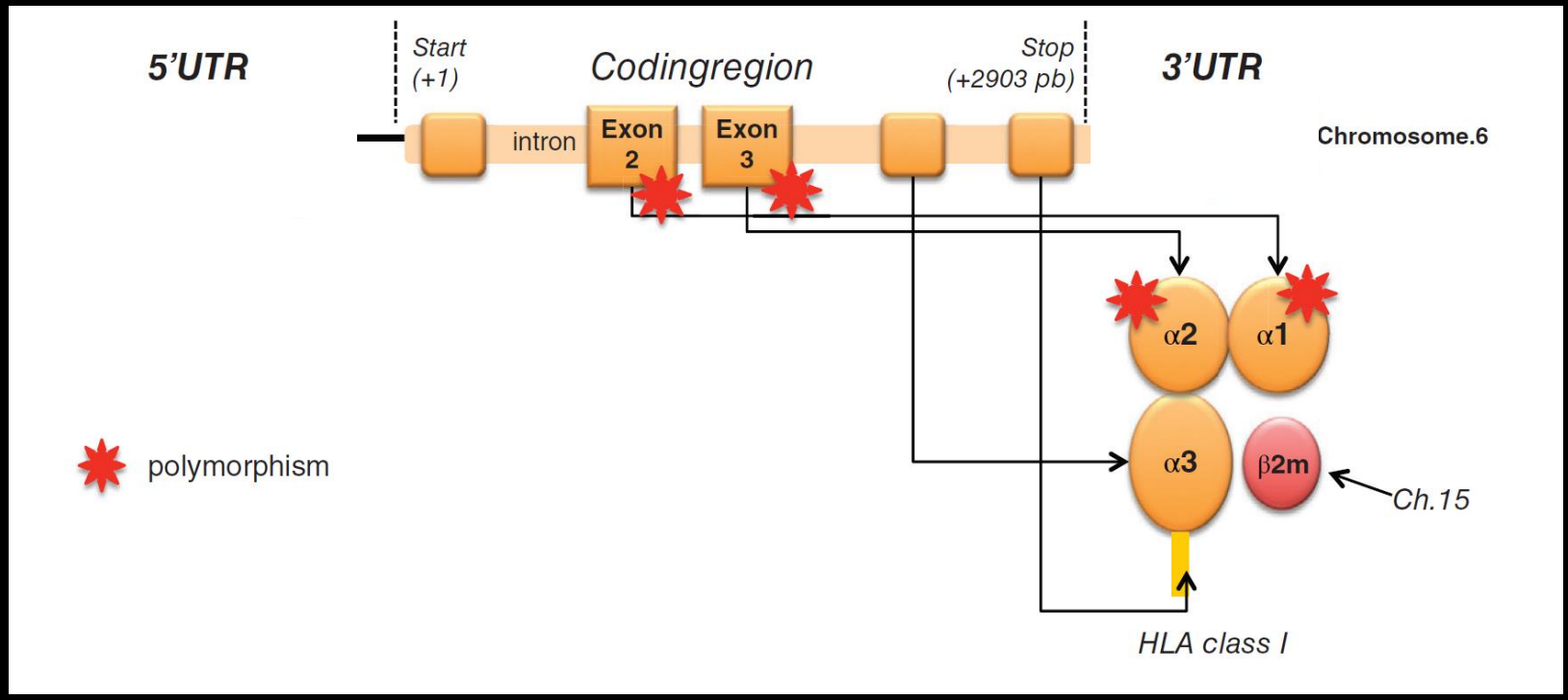
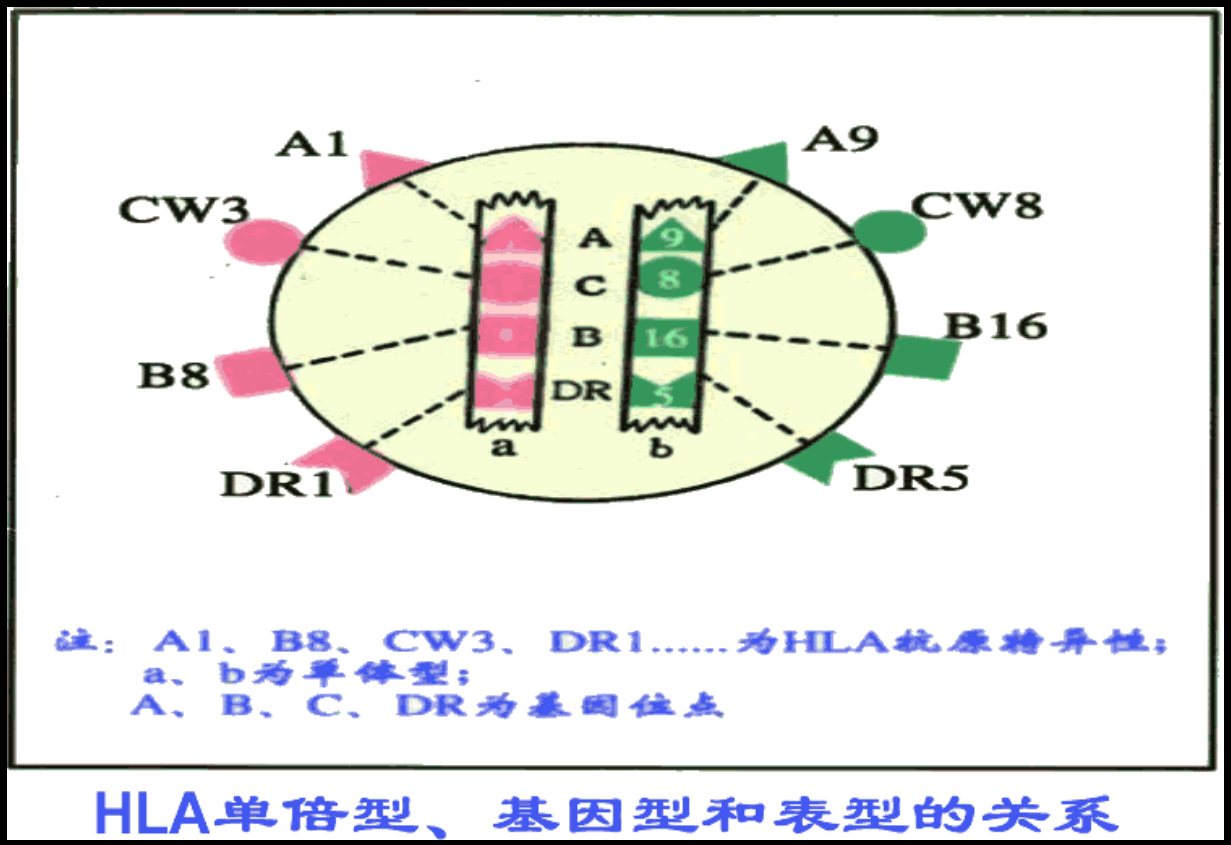

Hyphen used to separate gene name from HLA prefix
Suffix used to denote changes in expression
Separator
Field Separators
HLA-A*02:101:01:02N
HLA Prefix
Gene
Field 1; allele group
Field 4; used to show differences in a non-coding region
Field 2; specific HLA protein
Field 3; used to show a synonymous DNA substitution within the coding region
© SGE Marsh 04/10



HLA, 2016. 87(5): p. 338-49.

3. Haplotype inheritance



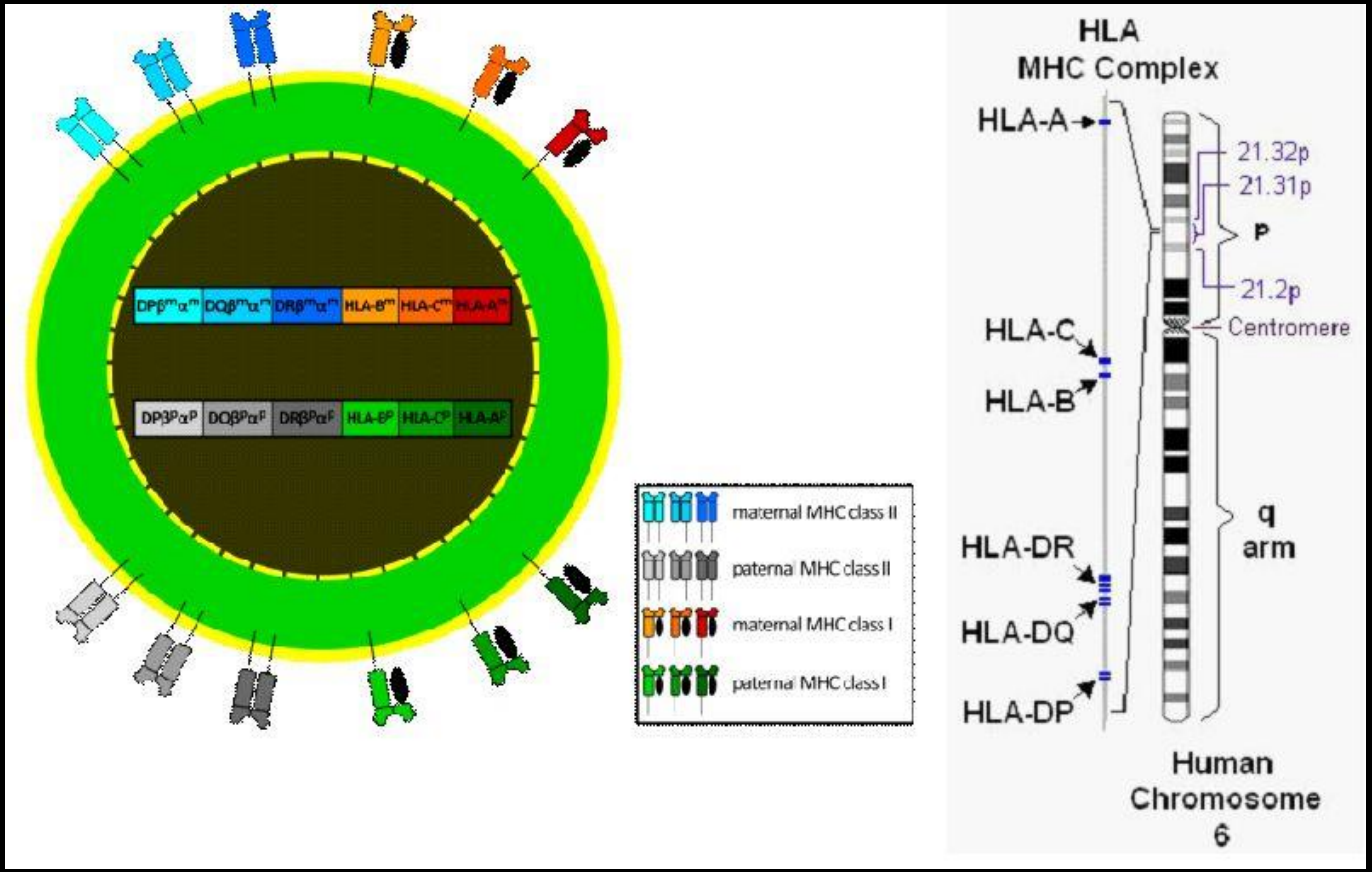
HLA单倍型、基因型和表型的关系

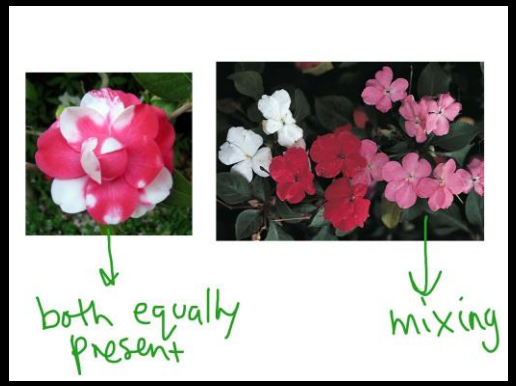
- haplotype：the specific set of alleles for all MHC loci on one single chromosome.
- Usually, intact haplotypes are passed on to the next generation
- Most people are heterozygous at HLA loci

4. Linkage disequilibrium

- **Certain MHC alleles at different loci are inherited together more or less frequently than would be predicted by random assortment**
- **HLA-A1, 16%, HLA-B8, 9%, the expected rate is 0.16*0.09=0.0144, 1.44% of individuals, however the observed rate is 8.8%**

5. Codominant expression





Codominance

Why does MHC need to be divers ?

- The MHC within a species exhibit an enormous diversity in human population (10^9).
- Almost all located in and around the peptide-binding groove
- Each has its own unique peptide-binding properties

Why does MHC need to be divers ?

MHC polymorphism benefits humanity at large because it increases the likelihood that at least some individuals will be able to present antigens from any pathogen that might be encountered, thus helping to ensure survival of the population as a whole.

Main features of MHC

- Providing the strongest barrier to transplantation
- Play a central role in generation and execution of immune response
  - Presentation of peptide antigens to T cells
- Susceptibility to infectious diseases and development of autoimmune diseases

HLA and Clinical medicine

1. HLA and transplantation rejection
2. HLA related-Disease
3. HLA abnormal expression and disease
4. HLA and human ID for crime medical detection and identification of progeny
5. Mating preference and olfactory sense ?
6. CNS development and repair ?

Summary of MHC

- What is MHC, HLA, MHC restriction
- Structure, distribution, and function of MHC I and II
- Peptide-MHC interaction
- Significance of MHC polymorphism

HLA	Classical genes	structure	Peptide-binding	distribution	function
I	A B C	α+β-2m	α1+α2	Almost all nucleated cells	present endogenous peptides to CD8+ T cells
II	DR DP DQ	α+β	α1+β1	APC, activated T cells	present exogenous peptides to CD4+ T cells