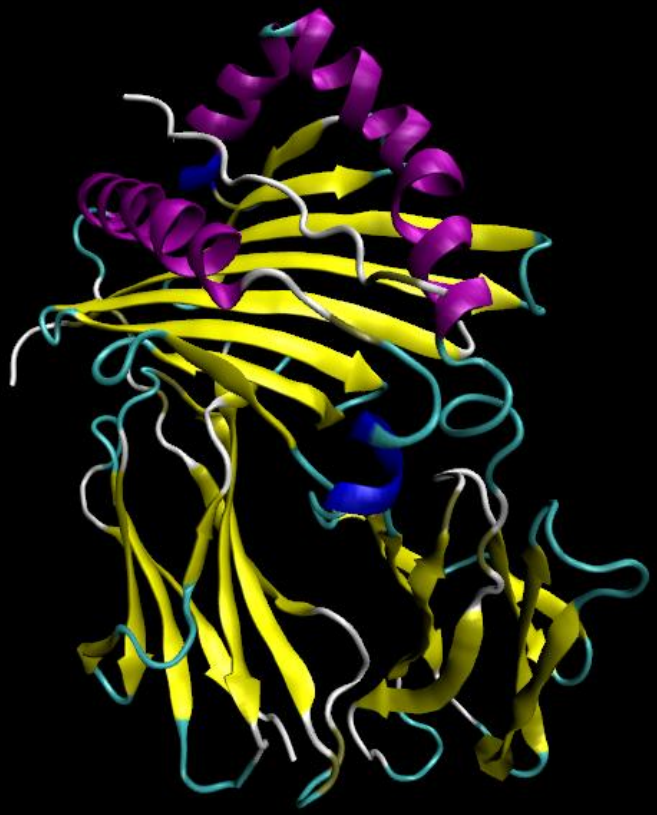
MHC Class II



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Structural Biology
Academic year 2012-2013
Universitat Pompeu Fabra

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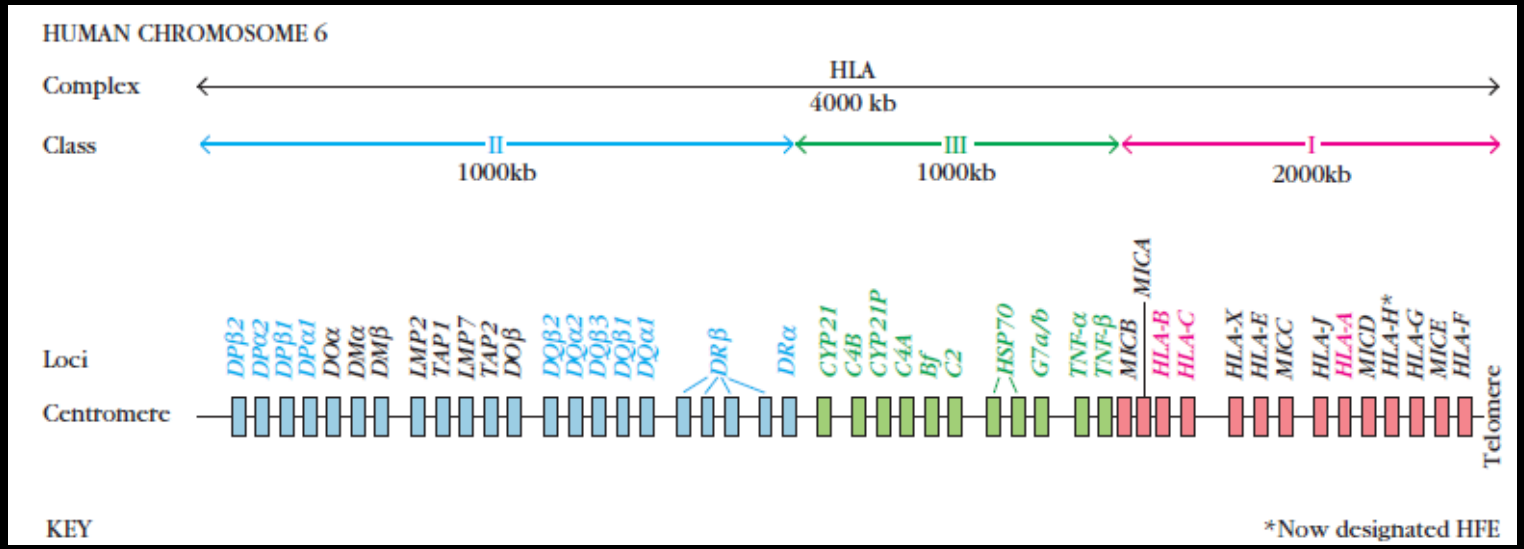
- Peptide binding to MHC class II
  - pockets
- Variable regions
  - Classical MHC class II superimposition
- Non classical MHC class II
  - Structure
  - Classical - Non classical MHC superimposition
- HLA-DR – HLA-DM interaction
- Conclusions

Introduction

Introduction

The major histocompatibility complex

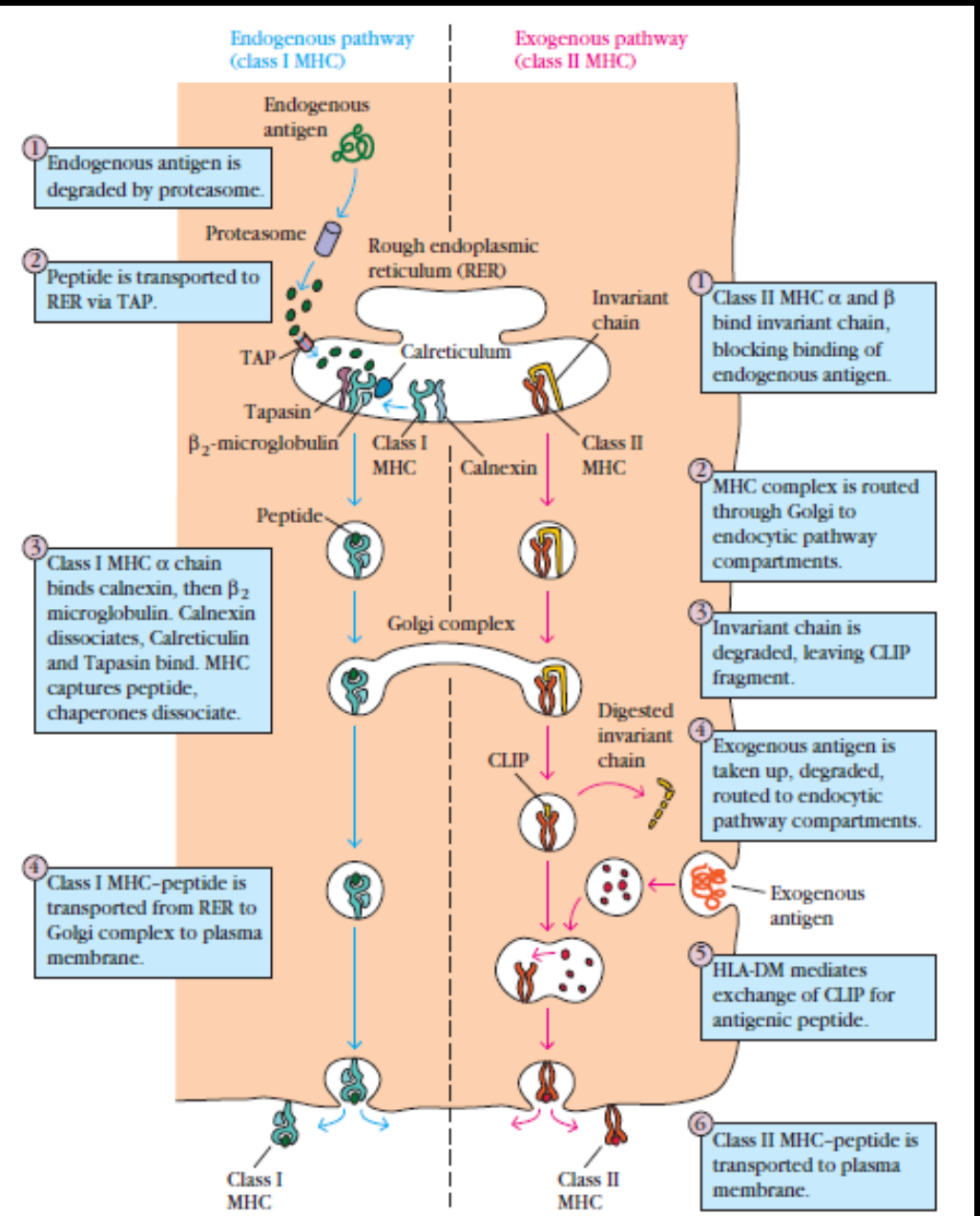


Human HLA complex

Complex	HLA							
MHC class	II			III		I		
Region	DP	DQ	DR	C4, C2, BF		B	C	A
Gene products	DP αβ	DQ αβ	DR αβ	C′ proteins	TNF-α TNF-β	HLA-B	HLA-C	HLA-A

Kindt TJ, Goldsby RA, Osborne BA. Inmunología de Kuby. México : McGraw-Hill, cop. 2007. Chapter 7: Major Histocompatibility Complex, 161-181.

Introduction



SELF MHC-RESTRICTION

Both CD4 and CD8 T cells can recognize antigen ONLY when it is presented by a self-MHC molecule

- Antigen processing
- Antigen presentation

	MHC class I	MHC class II
Cellular expression	All nucleated cells	Antigen-presenting cells
Recognized by	Tc cells (CD8)	Th cells (CD4)
	Endogenous antigens	Exogeneous antigens

Kindt TJ, Goldsby RA, Osborne BA. Inmunología de Kuby. México : McGraw-Hill, cop. 2007. Chapter 7: Major Histocompatibility Complex, 161-181.

Introduction

MHC class II

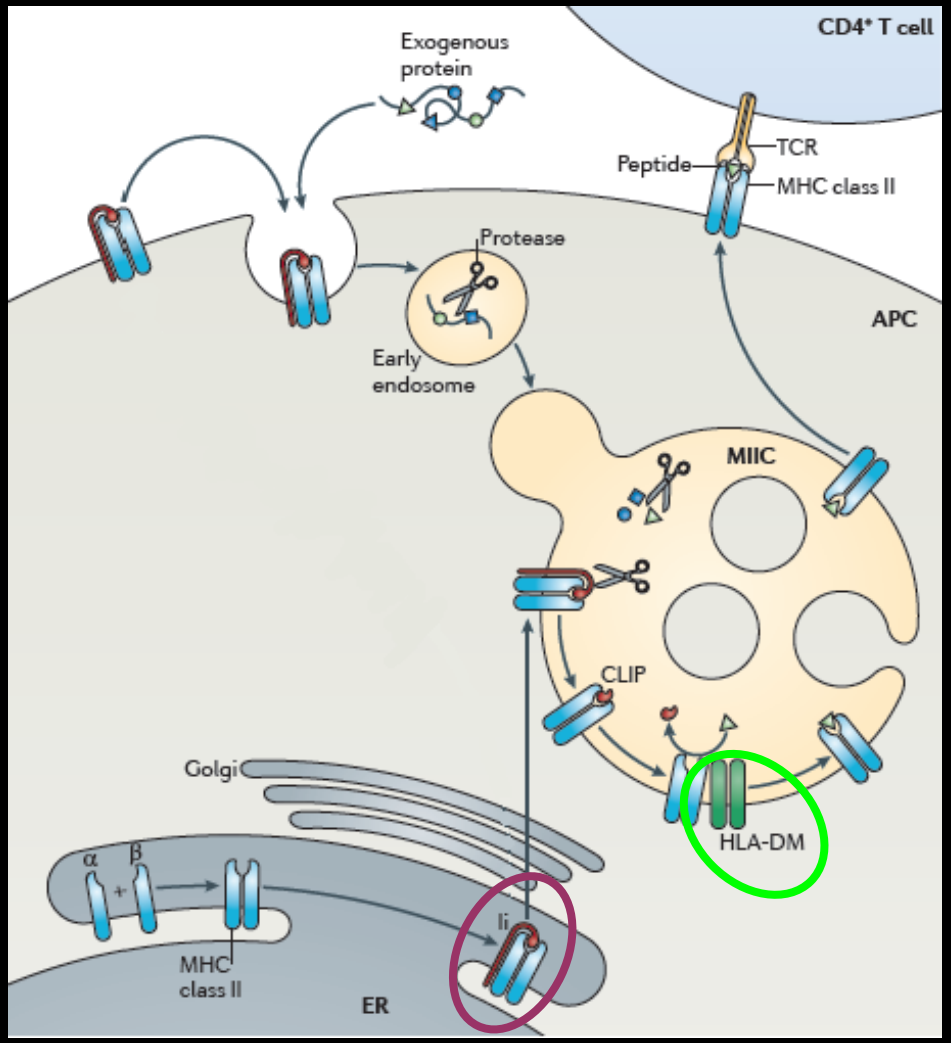
Invariant chain

CLIP

Non classical:

- **HLA-DM**

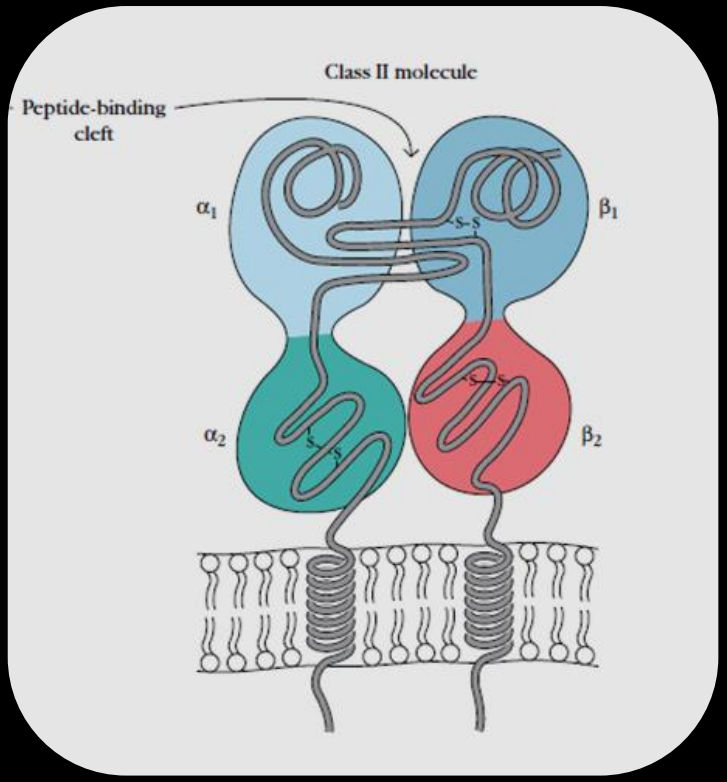
Exogenous pathway

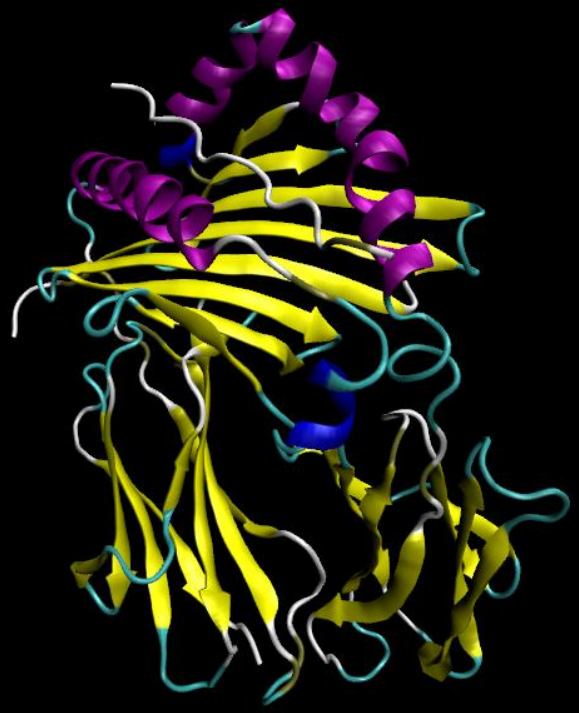


Neefjes J, Jongsma MLM. Towards a systems understanding of MHC class I and MHC class II antigen presentation. Nature, 2011; 11: 823-836.

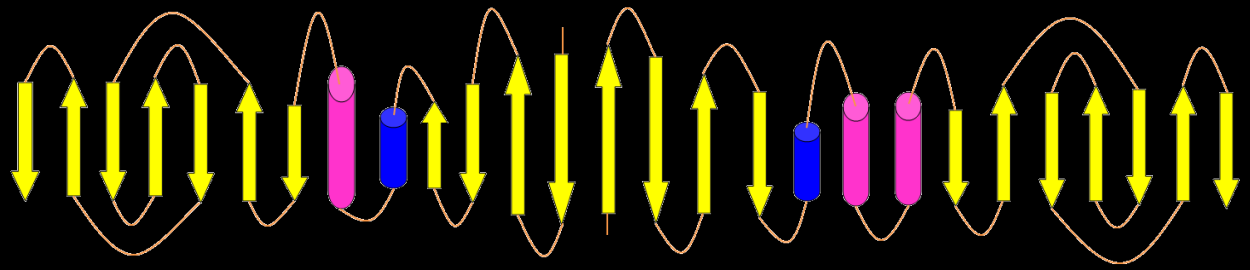
Introduction

Class II structure





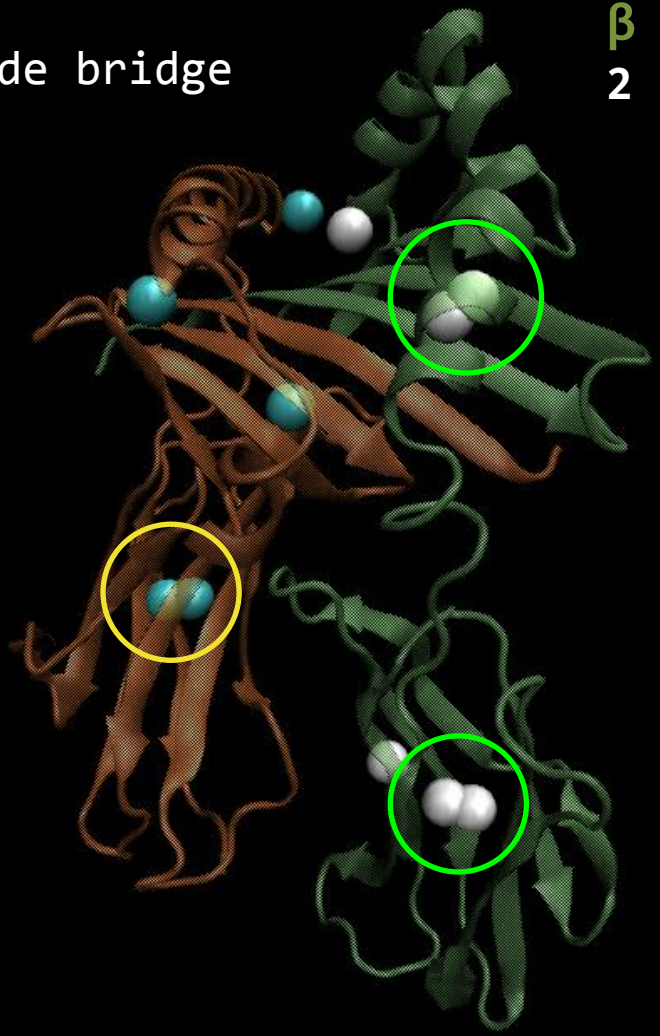
Kindt TJ, Goldsby RA, Osborne BA. Inmunología de Kuby. México : McGraw-Hill, cop. 2007. Chapter 7: Major Histocompatibility Complex, 161-181.

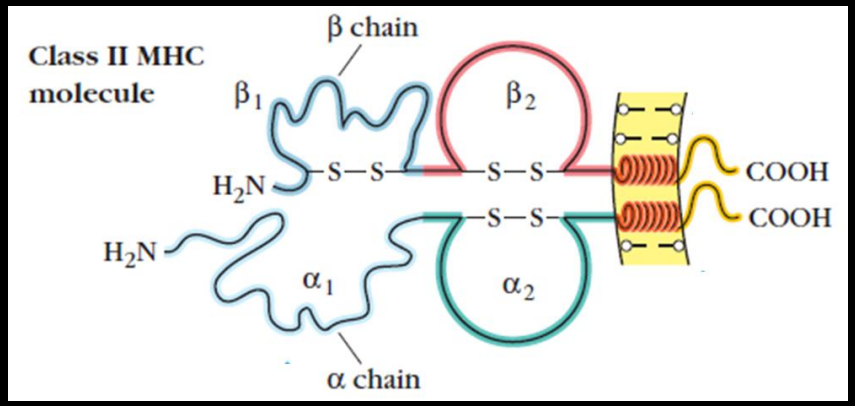


Disulfide bridges

α chain
1 disulfide bridge

β chain
2 disulfide bridges





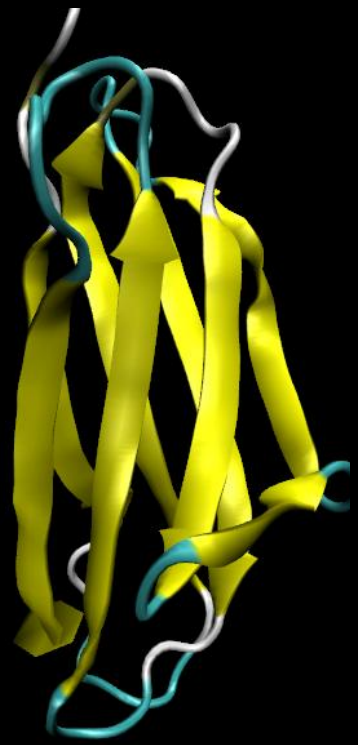
Kindt TJ, Goldsby RA, Osborne BA. Inmunología de Kuby. México : McGraw-Hill, cop. 2007. Chapter 7: Major Histocompatibility Complex, 161-181.

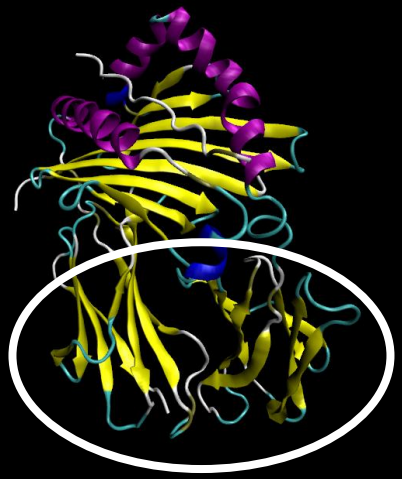
Introduction

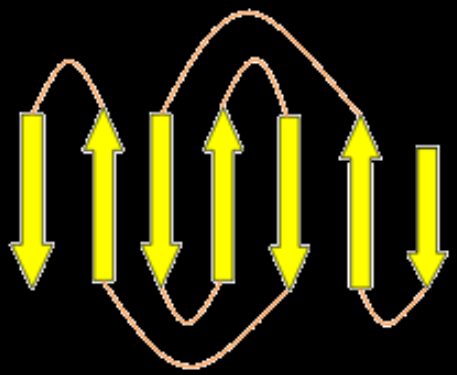
Class II structure

α2 and β2 domains

Immunoglobulin fold domain

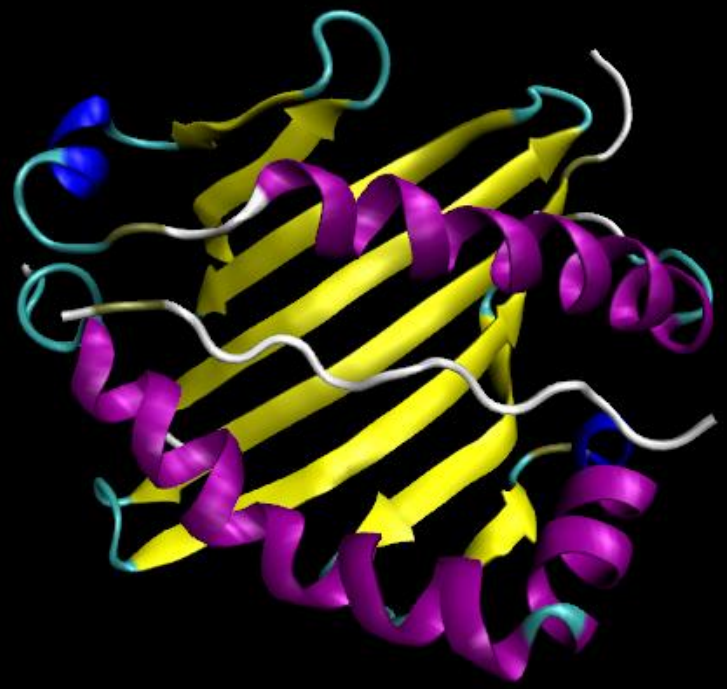




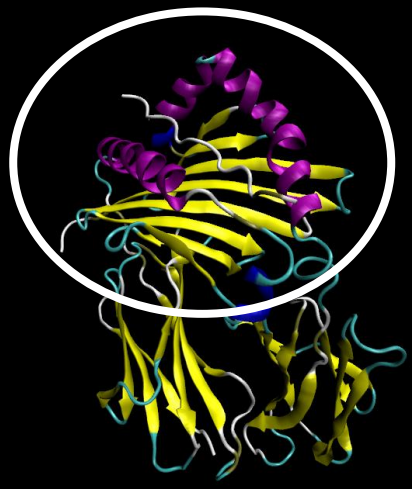


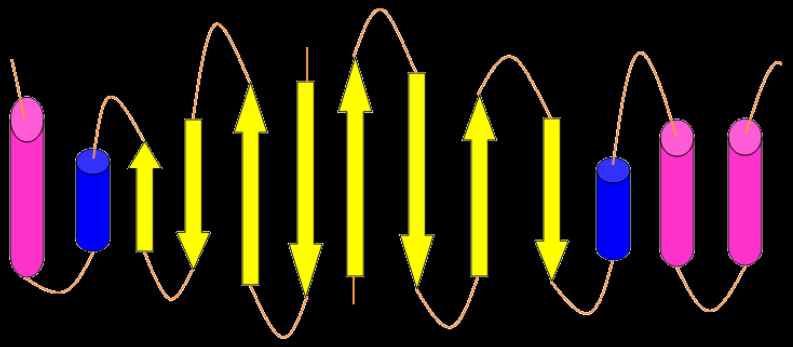
α1 and β1 domains

Binding groove



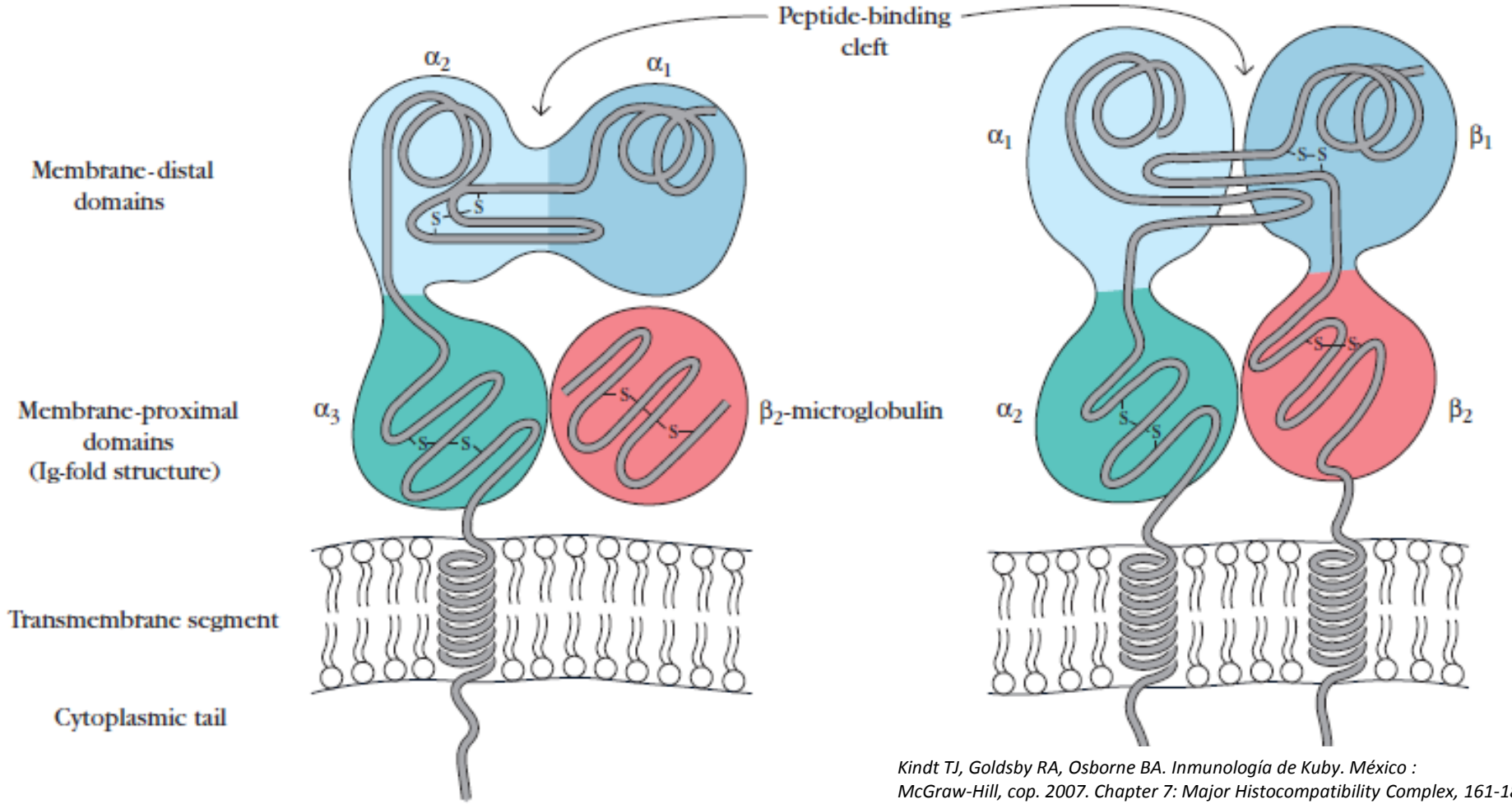
Antigenic peptide





MHC class I

MHC class II

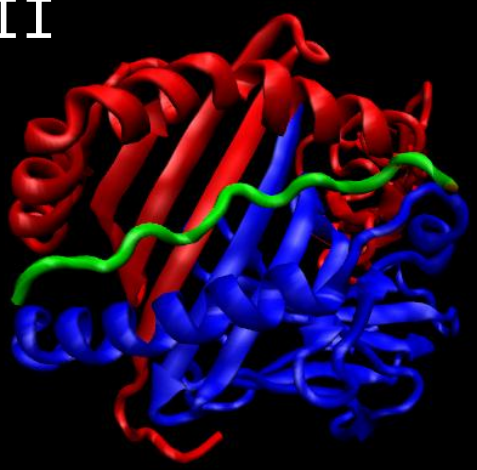


Kindt TJ, Goldsby RA, Osborne BA. Inmunología de Kuby. México : McGraw-Hill, cop. 2007. Chapter 7: Major Histocompatibility Complex, 161-181.

Binding groove

Class I

Class II



	Class I molecules	Class II molecules
Peptide-binding domain	α1/α2	α1/β1
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

Kindt TJ, Goldsby RA, Osborne BA. Inmunología de Kuby. México : McGraw-Hill, cop. 2007. Chapter 7: Major Histocompatibility Complex, 161-181.

Peptide binding site in MHC class II

Peptide binding site (MHC class II)

Superimposition of DR1-A2 and DR1-HA

Classical MHCII:

-DQ

-DPl

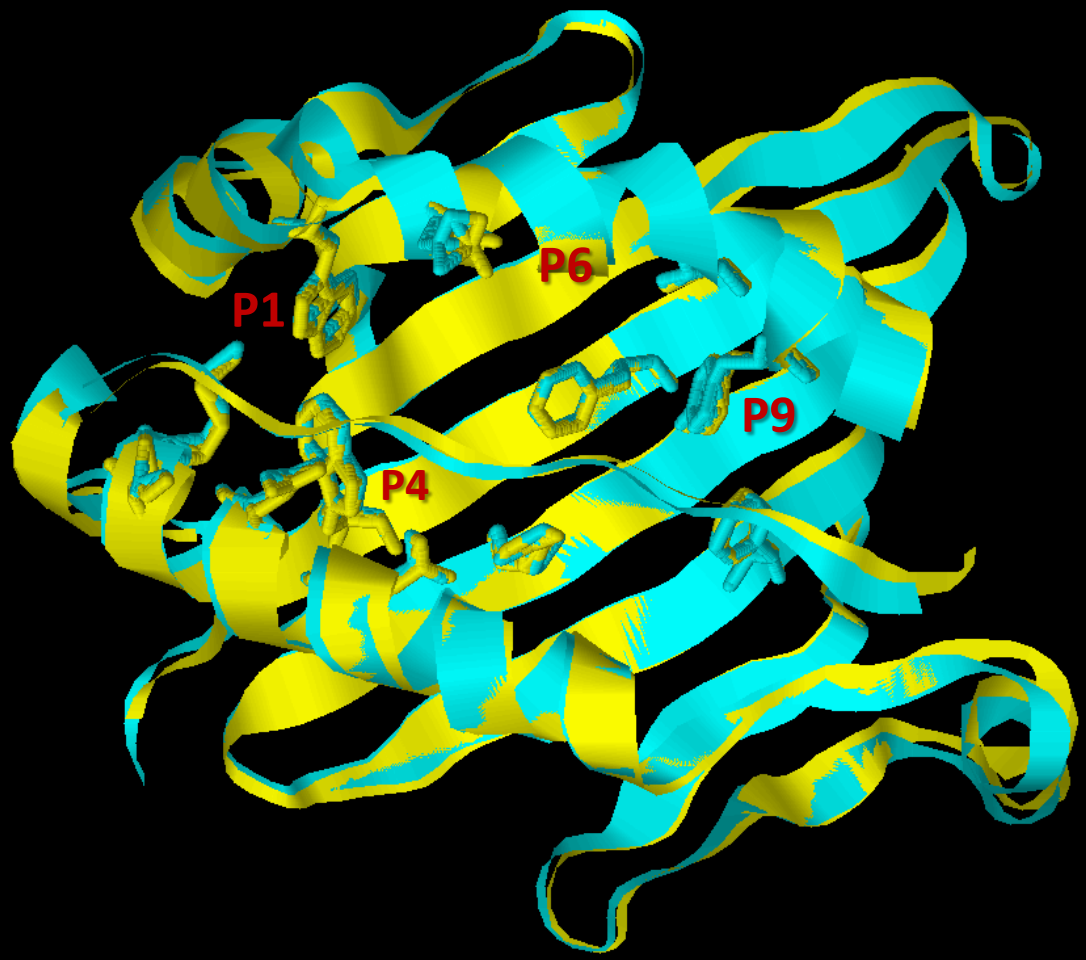
-DR → **A2** (endogenous peptide)

-DR → **HA** (hemaglutinin, influenza)

RMS 0.81

Sc 9.21

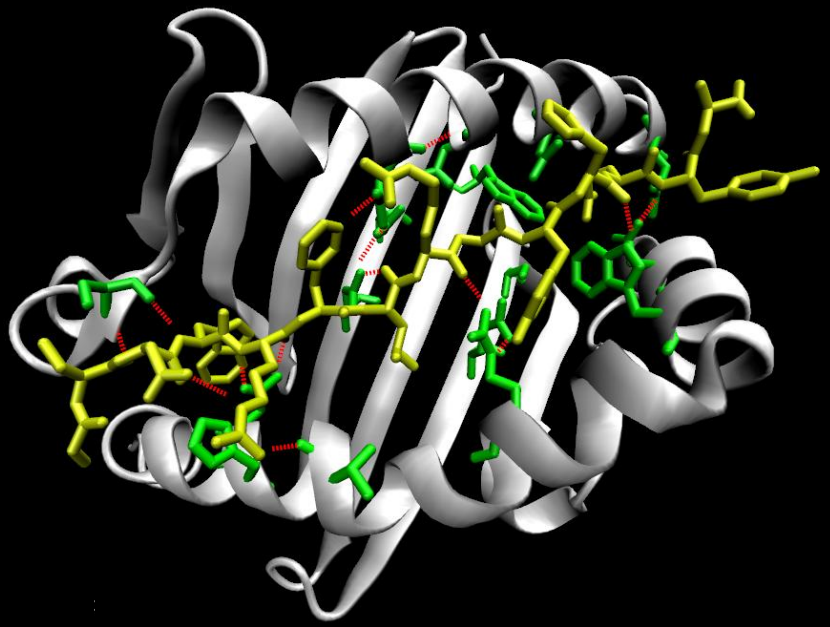
Peptide binding site (MHC class II)



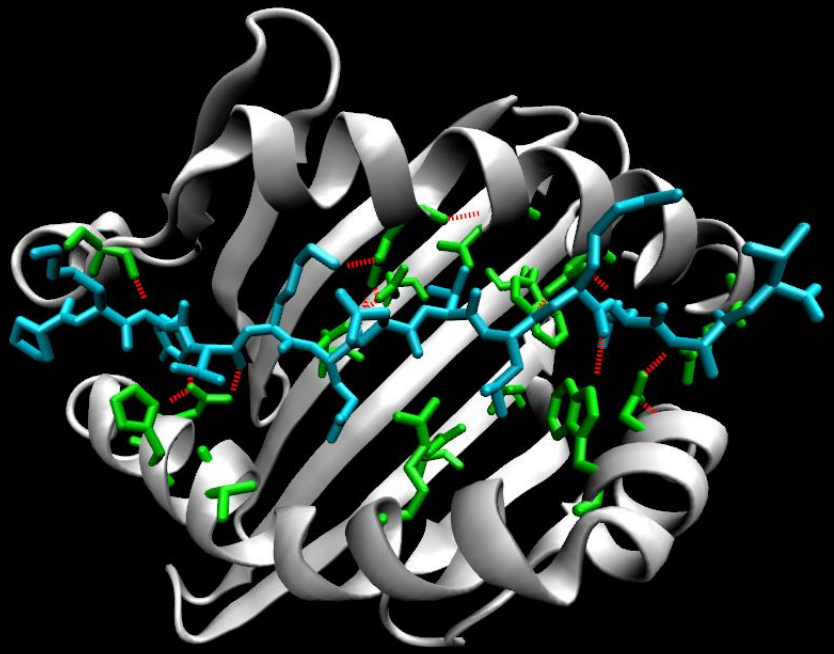
Peptide binding site
Residues from relevant pockets are shown

Peptide binding site (MHC class II)

Hydrogen bonds stabilize HLA-Peptide union



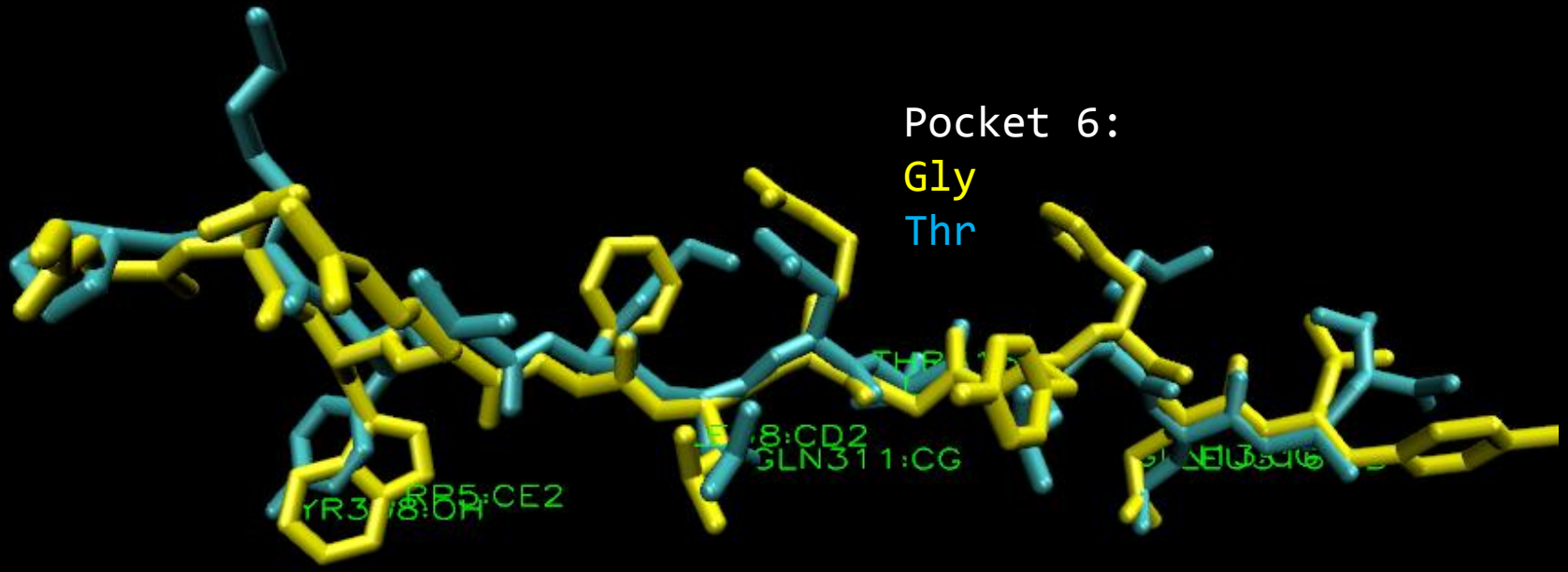
HLA-DR1 bound to A2



HLA-DR1 bound to HA

Peptide binding site (MHC class II)

Superimposition of peptide **A2** and **HA**



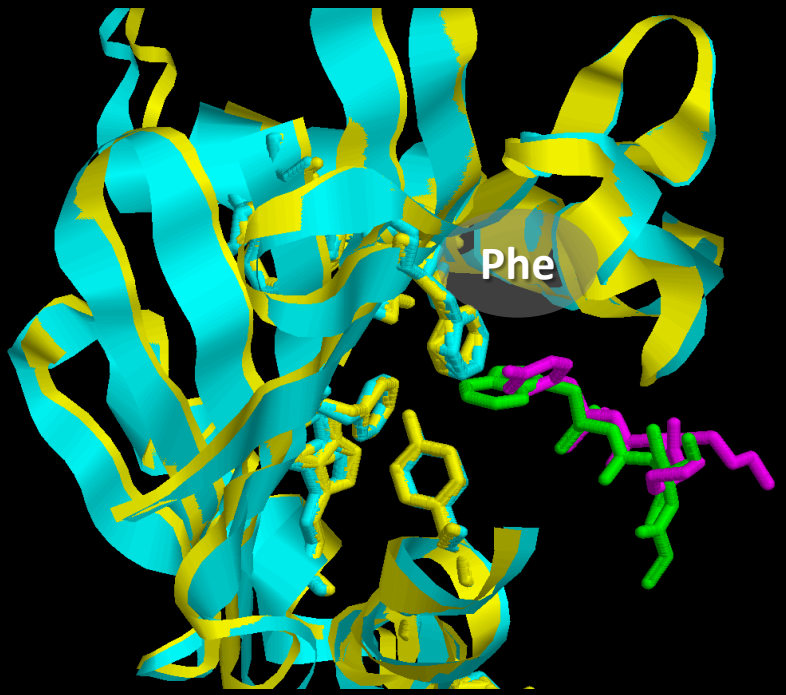
Pocket 1:
Trp
Tyr

Pocket 4:
Leu
Gln

Pocket 9:
Gln
Leu

Peptide binding site (MHC class II)

Pocket 1



Largest and most important

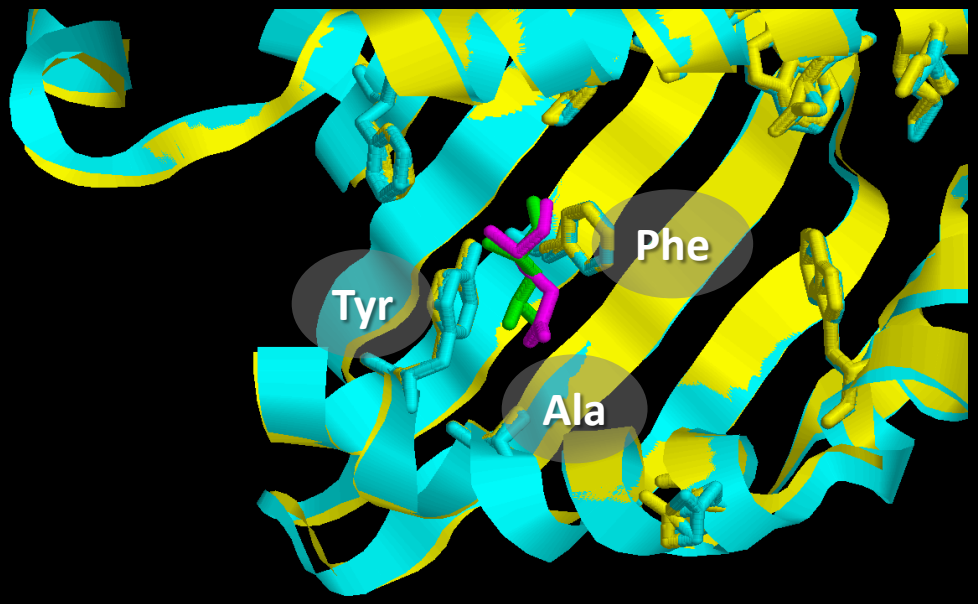
A2 places Trp
HA places Tyr

Electrostatical interaction with a **Pheα24** of MHCII

DR1-A2
DR1-HA

Peptide binding site (MHC class II)

Pocket 4



Preferences for hydrophobic residues

A2 places Leu
HA places Gln

Electrostatical interaction with MHC II:

Pheβ13

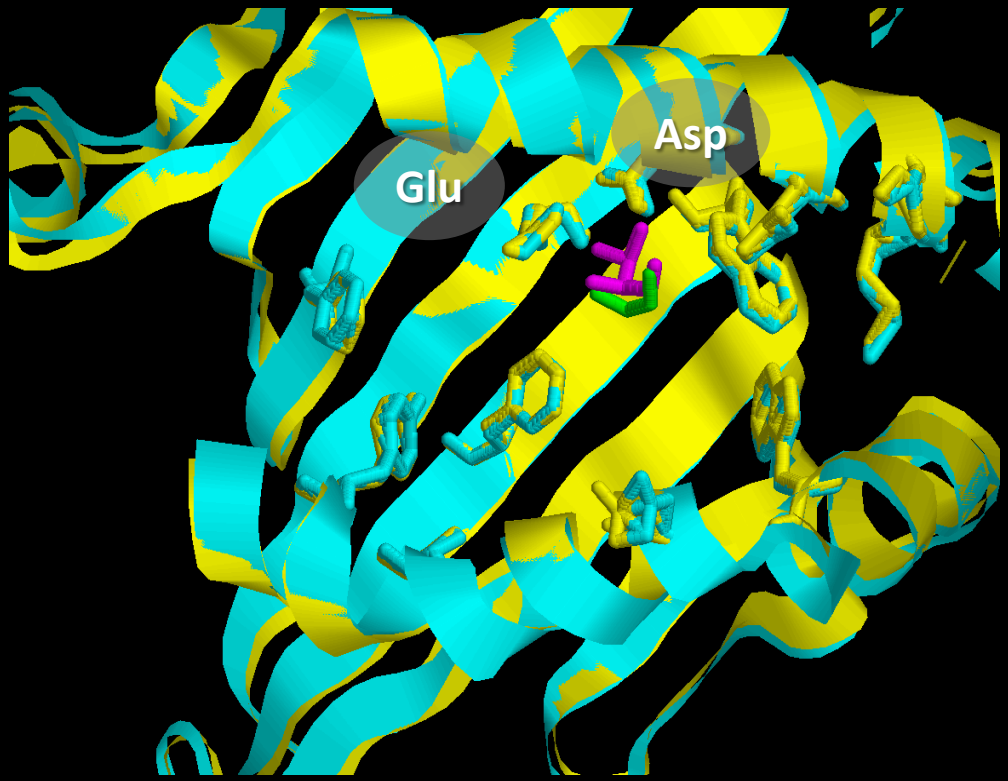
-Alaβ74

-Tyrβ78

DR1-A2
DR1-HA

Peptide binding site (MHC class II)

Pocket 6



DR1-A2
DR1-HA

Preference for small residues

A2 places Gly
HA places Thr (not favored)

H bonds through a water molecule with MHC II residues:

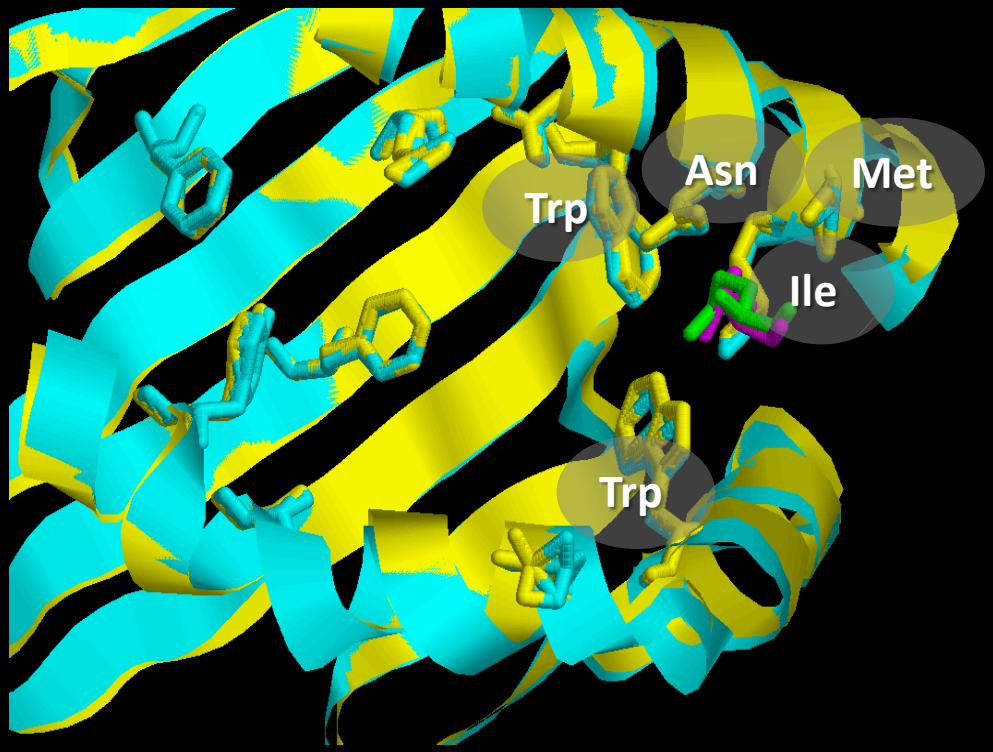
- Gluα11

-Aspα66

Peptide binding site (MHC class II)

Pockets

Pocket 9



DR1-A2
DR1-HA

Preferences for hydrophobic residues

A2 places Gln
HA places Leu

Electrostatic interactions with:

-Trpβ9

-Asnα69

-Metα73

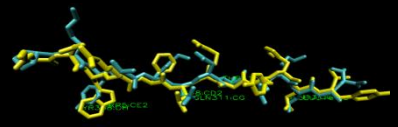
-Ileα72

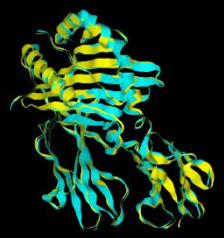
-Trpβ61

Peptide binding site (MHC class II)

Adjustment of the HLA-DR1 peptide binding site to different peptides

1. The **peptides** bind with similar conformation and placing sidechains at pockets 1, 4, 6 and 9.

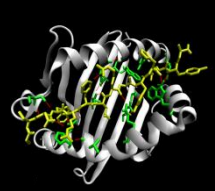




2. The conformation of the HLA-DR1 protein **mainchain** is unchanged between the A2 and HA

*The largest mainchain deviations occur at a kink in the **b-chain helical region** near P7.

3. The pattern of **hydrogen bonds** between HLA-DR1 and the peptide mainchain atoms is also similar between the two complexes.



4. The different peptide sequences are accommodated with essentially no change in the conformation of the **sidechains** of MHC residues contacting the peptide.

Variable regions

- Classical MHC class II -

Variable regions (classical MHC II)

RMS 0.48
Sc 9.59

Classical MHC class II superimposition

Superimposition of 21 MCH class II

Regions of structural heterogeneity

- β2 Ig-like domain
- kink in the β-subunit helical region
- α-subunit 3_{10} helical region

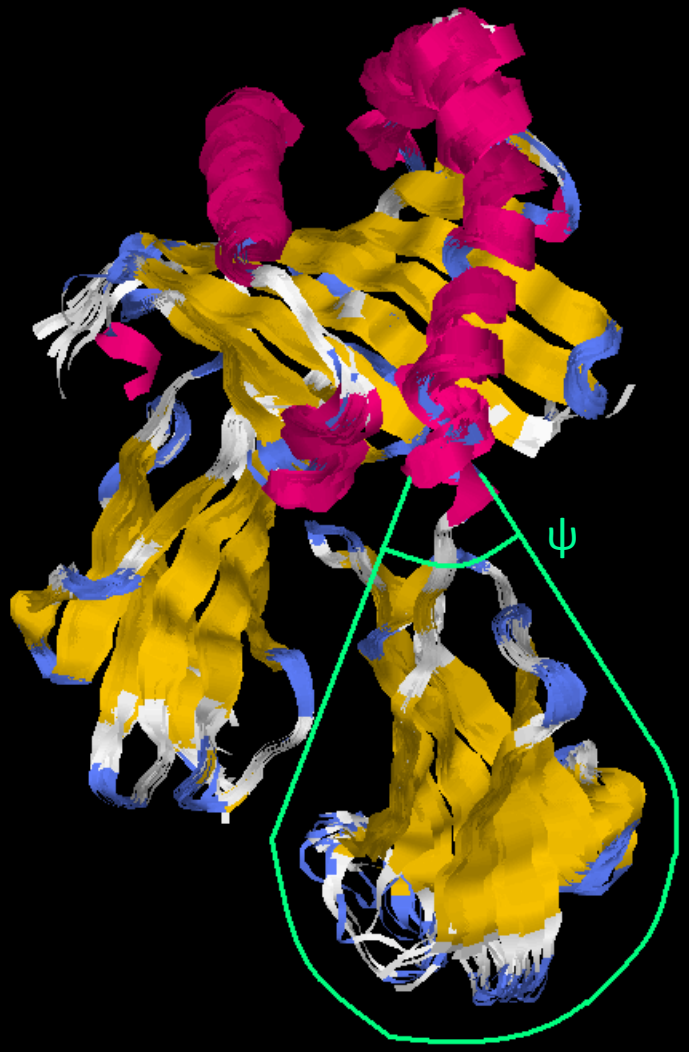
Variable regions (classical MHC II)

β2 Ig-like domain

The β2 Ig-like domain

Variable regions (classical MHC II)

β2 Ig-like domain



Variation of 10º

Variable regions (classical MHC II)

β2 Ig-like domain

Largest variation:

A–B loop between the first two strands of the Ig domain, residues 105–112

Variable regions (classical MHC II)

β2 Ig-like domain

Multiple alignment of β2 Ig-like domain

Variable regions (classical MHC II)

β-helix at the kinked region

The pronounced kink in the β-subunit helical region β62-71

The peptide induces conformational changes in this region

Variable regions (classical MHC II)

β-helix at the kinked region

1DLH
(HLA-DR1 -HA)
is our
reference
protein

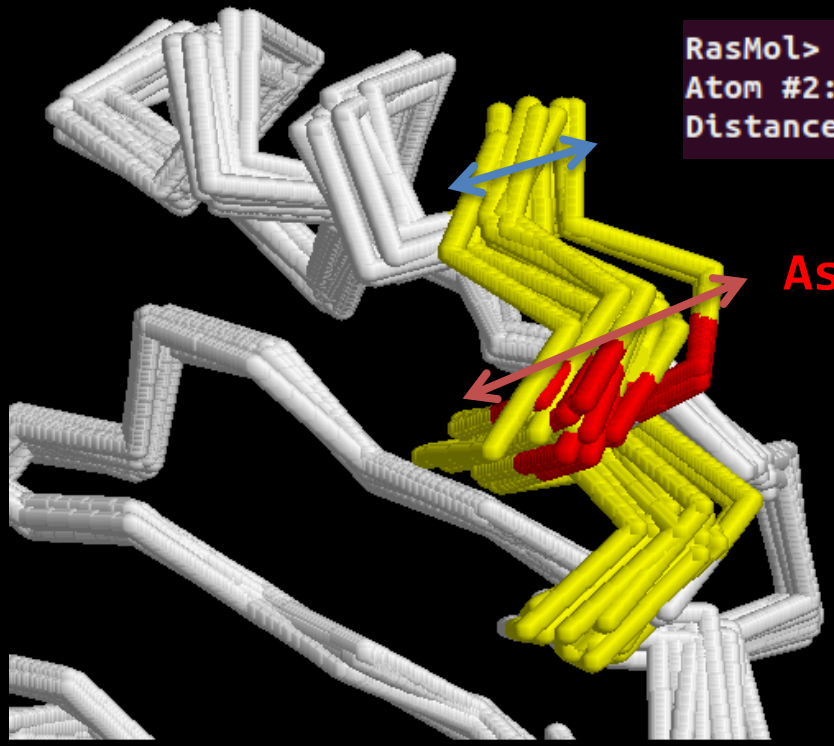
Variable regions (classical MHC II)

β-helix at the kinked region

1DLH
(HLA-DR1 -HA)
is our
reference
protein

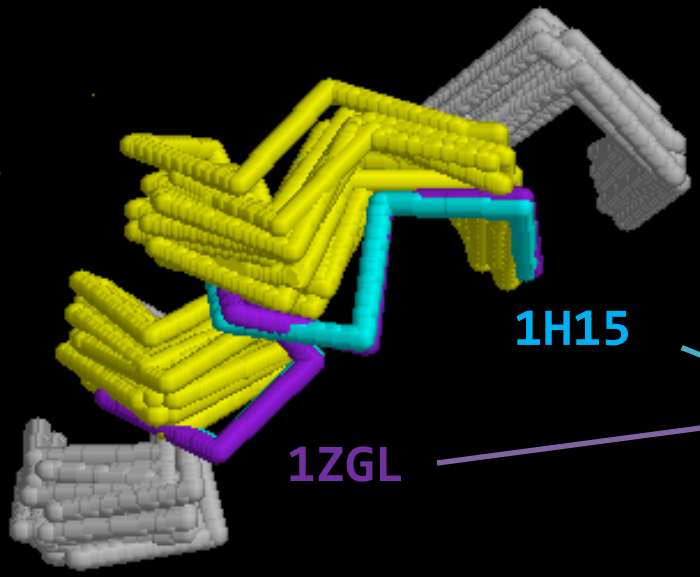
Variable regions (classical MHC II)

β-helix at the kinked region



Variable regions (classical MHC II)

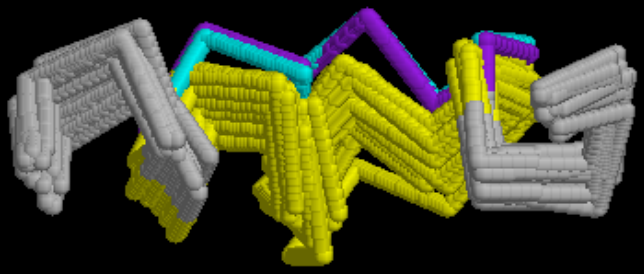
β-helix at the kinked region

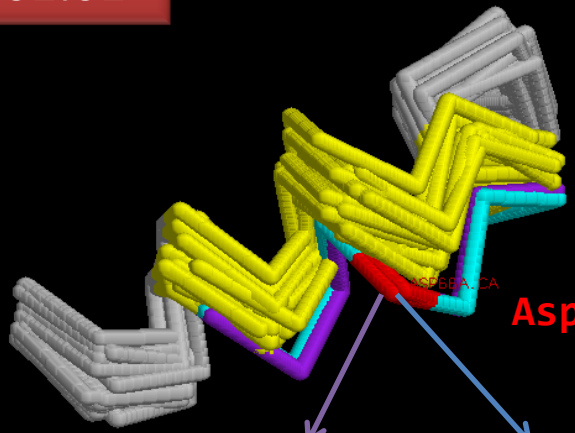


1H15

1ZGL

HLA-DR
B5*01:01





Asp β66

TCR

crystal

Variable regions (classical MHC II)

β-helix at the kinked region

Multiple alignment of the kink in the β-subunit helical region beta62-71

Variable regions (classical MHC II)

α-subunit 3_{10} helical region

3_{10} helix

→ 3 residues/turn

→NH-CO hydrogen bonds
(i and i+3 residues)

10-atoms rings

LESS STABLE

RARE

WHERE?

-α45-51 residues

-Connects:

• β sheet platform

• α helix that defines the binding groove

Variable regions (classical MHC II)

α-subunit 3_{10} helical region

The majority of class II structures:
Cα deviation: 2Å

Large deviations for the **HLA-DQ** proteins:

- **3PL6 (6.9Å)** (HLA-DQ1-MBP)
- **1UVQ (3.8Å)** (HLA-DQ1-Hypocretin)

* they share the same α-chain (A1*0102)

```
3PL6        EDIVADHVASCGVNLYQFYGPSGQYTHEFDGDEQFYVDLERKETAWRWPEFSKFGGFDPQ
1S9V        EDIVADHVASYGVNLYQSYGPSGQYTHEFDGDEQFYVDLGRKETVWCLPVLRQFR-FDPQ
1JK8        ---VADHVASYGVNLYQSYGPSGQYSHEFDGDEEFYVDLERKETVWQLPLFRRFRRFDPQ
2NNA        EDIVADHVASYGVNLYQSYGPSGQYSHEFDGDEEFYVDLERKETVWQLPLFRRFRRFDPQ
3QXD        --IKEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASCEAQ
1DLH        ----EEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
1JWU        --IKEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
1KLU        -----EHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
1SJH        ----EEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
2G9H        --IKEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
3L6F        --IKEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
1H15        --IKEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
1ZGL        --IKEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
1A6A        ------HVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
1D5M        --IKEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
1D5Z        --IKEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
2XN9        --IKEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
3C5J        --IKEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
1B5I        --IKEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
1UVQ        EDIVADHVASCGVNLYQFYGPSGQYTHEFDGDEQFYVDLERKETAWRWPEFSKFGGFDPQ
3LQZ        --IKADHVSTY-AAFVQTHRPTGEFMFEFDEDEMFYVDLDKKETVWHLEEFGQAFSFEAQ
                  **           .*..  .** ** * **. .*** *      .    . *
```

Variable regions (classical MHC II)

α-subunit 3_{10} helical region

Distance: **3PL6** (lys50) – **1DLH** (arg50)

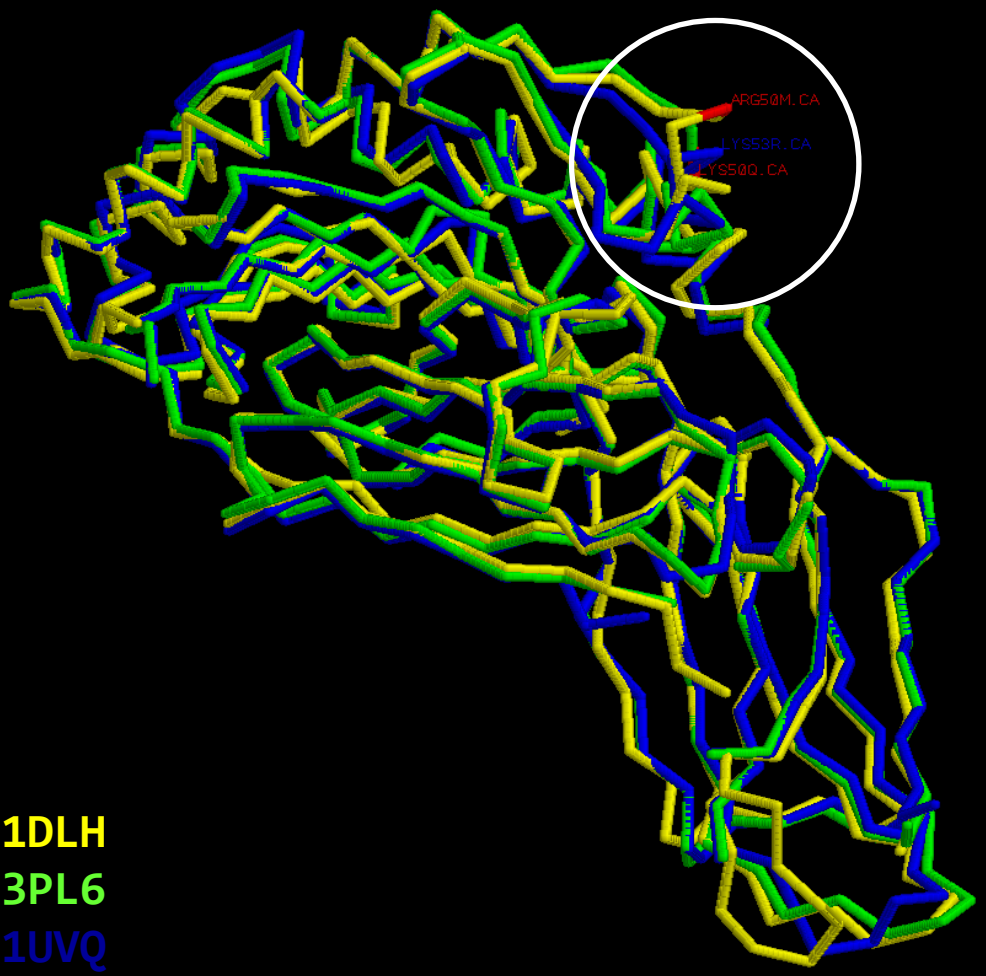

```
RasMol> set picking distance
RasMol>
Atom #1: ARG50M.CA (400)
RasMol>
Atom #2: LYS50Q.CA (414)
Distance ARG50M.CA-LYS50Q.CA: 6.966
```

1DLH
3PL6

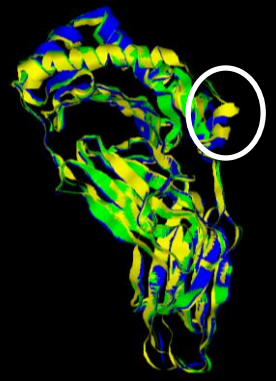
Variable regions (classical MHC II)

α-subunit 3_{10} helical region

Distance: 1UVQ (lys53) – 1DLH (arg50)




```
RasMol> set picking distance
RasMol>
Atom #1: ARG50M.CA (400)
RasMol>
Atom #2: LYS53R.CA (428)
Distance ARG50M.CA-LYS53R.CA: 3.896
```



1DLH
3PL6
1UVQ

Variable regions (classical MHC II)

α-subunit 3_{10} helical region

HLA-DQA*01:02 alleles also show variation between each other

Sc 9.32 RMS 0.87

A1*0102 alleles:

2 glycines

→ Structural lability

→ Multiple conformations can be adopted

```
3PL6        EDIVADHVASCGVNLYQFYGPSGQYTHEFDGDEQFYVDLERKETAWRWPEFSKFGGFDPQ
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1JWU        --IKEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
1KLU        -----EHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
1SJH        ----EEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
2G9H        --IKEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
3L6F        --IKEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
1H15        --IKEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
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1D5M        --IKEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQ
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3LQZ        --IKADHVSTY-AAFVQTHRPTGEFMFEFDEDEMFYVDLDKKETVWHLEEFGQAFSFEAQ
                    **            .*..  .** ** * **. .*** *      .    . *
```

Variable regions (classical MHC II)

α-subunit 3_{10} helical region

HLA-DQ 1SV9

Deletion at the α52 residue → DM resistant allele

Insertion of a residue restores the DM susceptibility

Deviations are not due to **insertions** or **deletions**

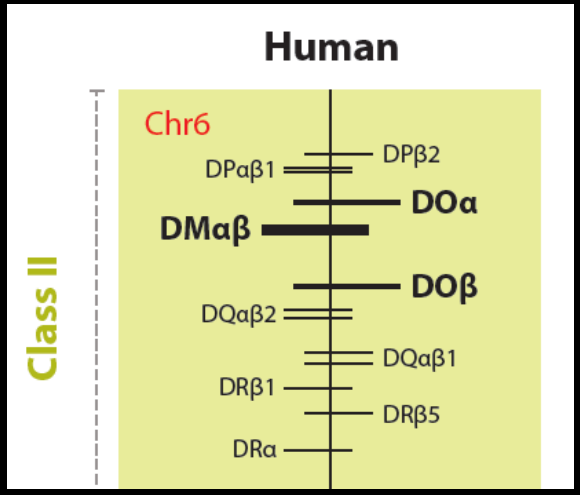
Non classical MHC II

Non classical MHC class II

The MHCII locus includes:

- genes encoding **classical** MHCII proteins that bind peptide antigens and present them to T cells

- genes for **non-classical** MHCII proteins that have accessory roles in the antigen-loading process.



Adams EJ, Luoma AM. The adaptable major histocompatibility complex (MHC) fold: structure and funtion of non classical and MHC class I-like molecules. Annu. Rev. Immunol. 2013. 31:529–61

HLA - DM

- chaperones peptide-free MHCII, protecting it against inactivation
- catalyzes peptide exchange on loaded MHCII

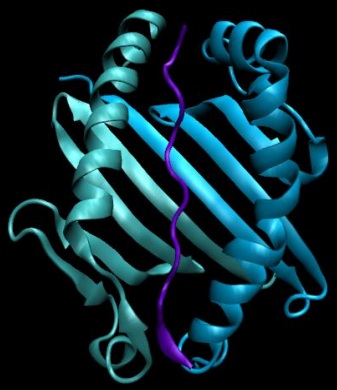
HLA - DO

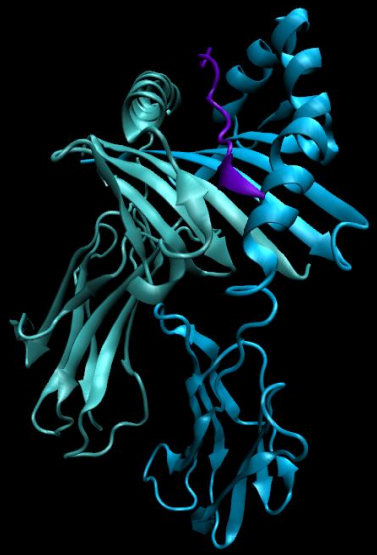
- binds HLA-DM and influences the repertoire of peptides presented by MHCII proteins

Non classical MHC class II

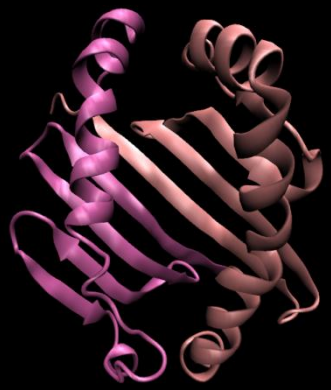
Structure

HLA-DR

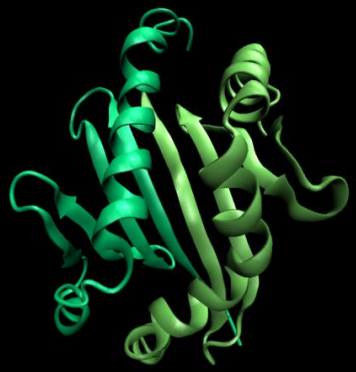




HLA-DO



HLA-DM



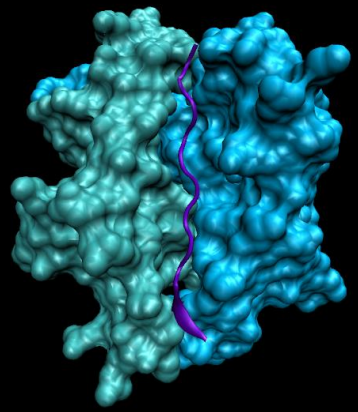
Non classical MHC class II

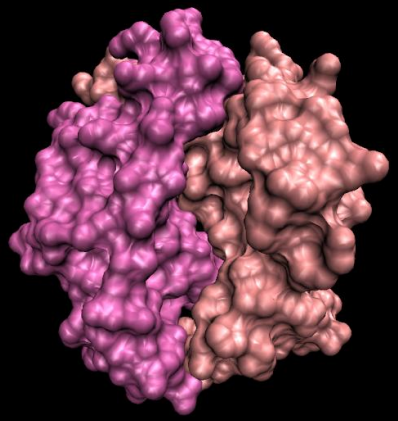
Structure

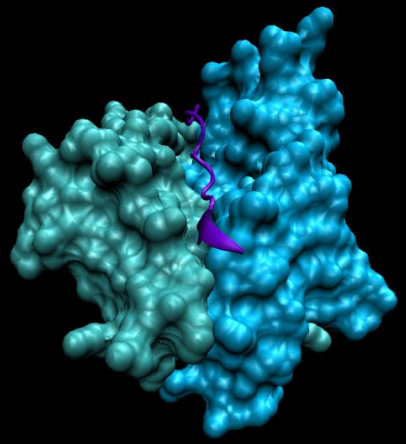
HLA-DR

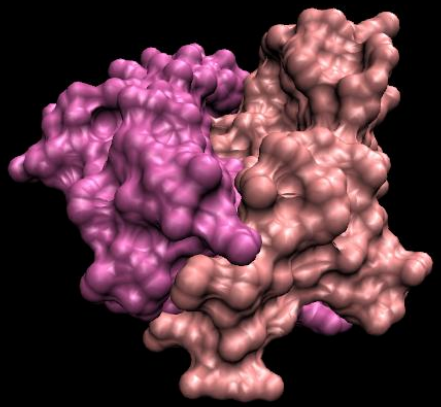
HLA-DO

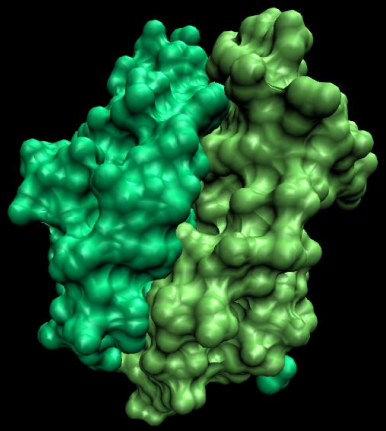
HLA-DM











Non classical MHC class II

Superimposition classical - non classical

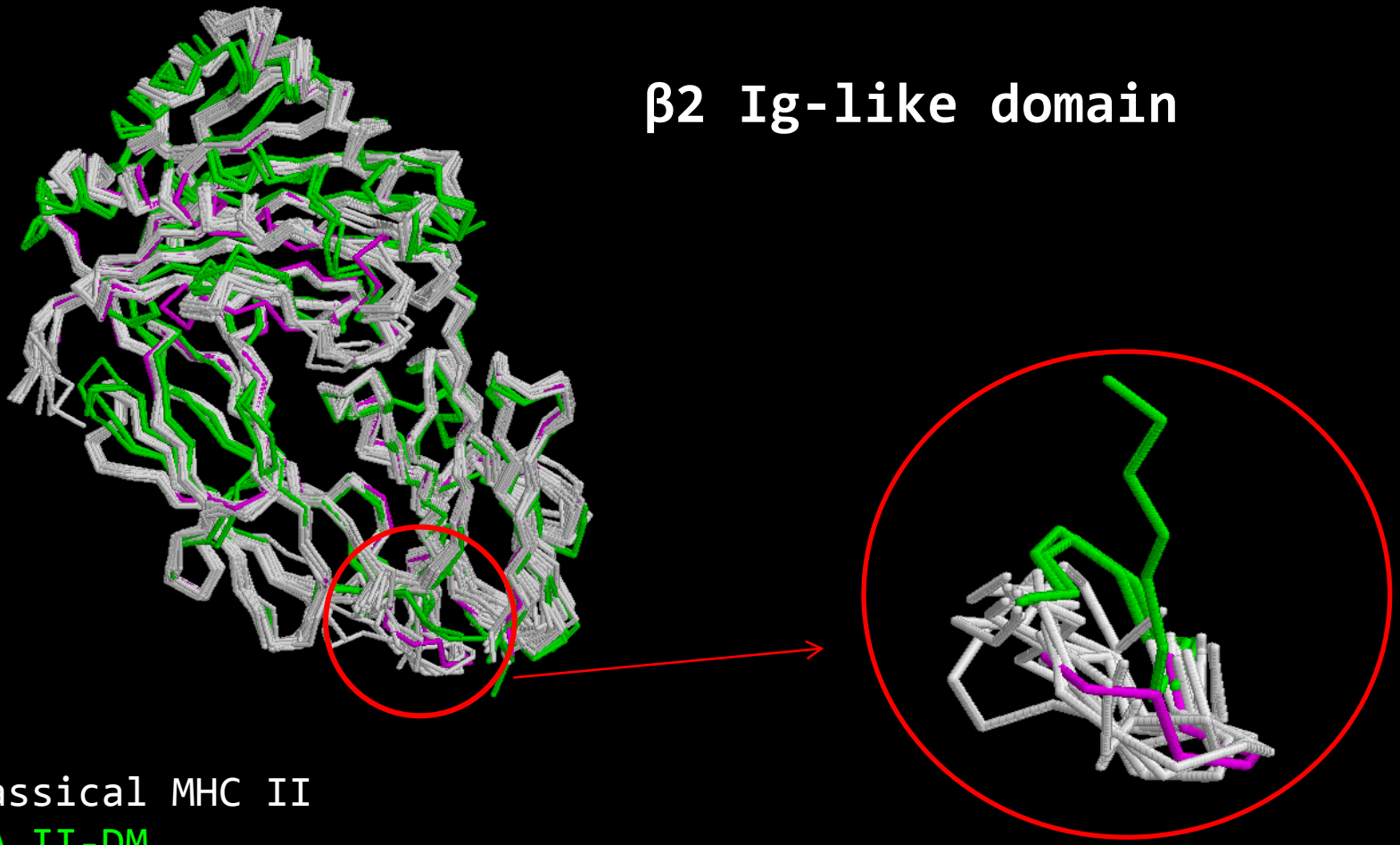
- Structure resemblance for DR, DM and DO
- Variable regions:
  - β2 Ig-like domain
  - α-subunit 310 helical region
  - β1 helix at kinked region
- DO structure is more similar to DR1

Classical MHC II
HLA II-DM
HLA II-DO

RMS 1.75
Sc 8.29

Non classical MHC class II

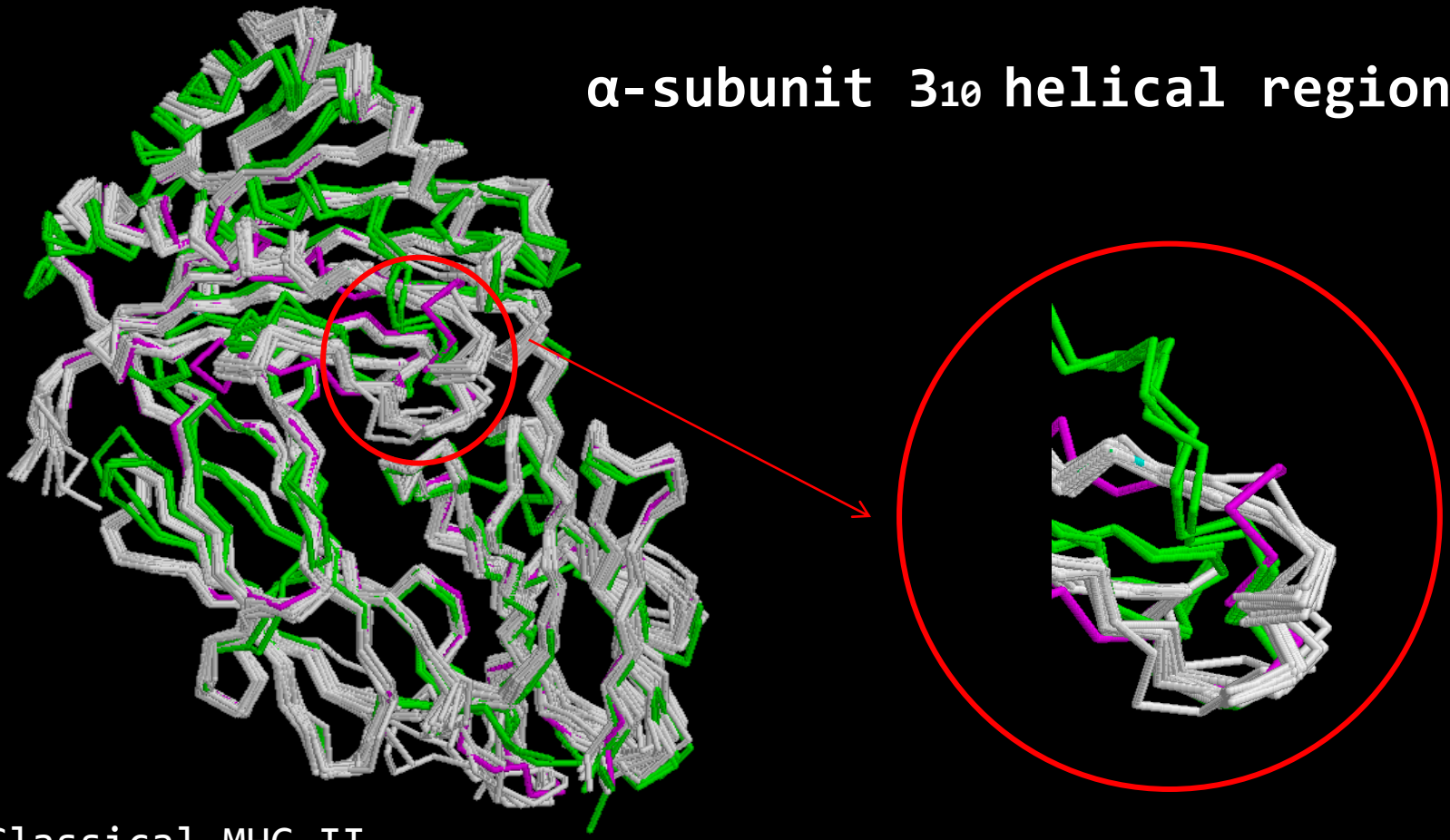
Superimposition classical - non classical



Classical MHC II
HLA II-DM
HLA II-DO

Non classical MHC class II

Superimposition classical - non classical

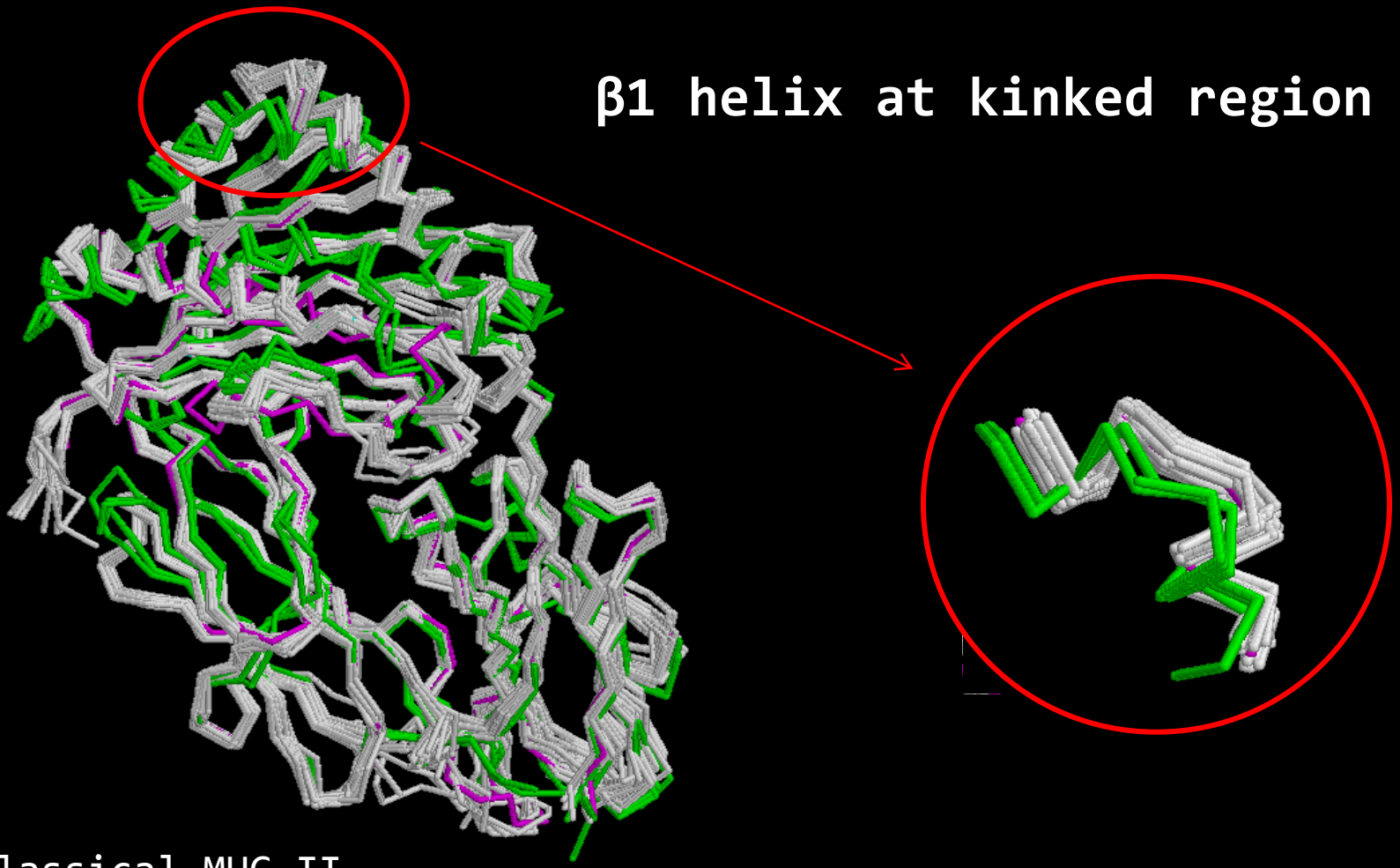


Classical MHC II
HLA II-DM
HLA II-DO

Non classical MHC class II

Superimposition classical - non classical

β1 helix at kinked region



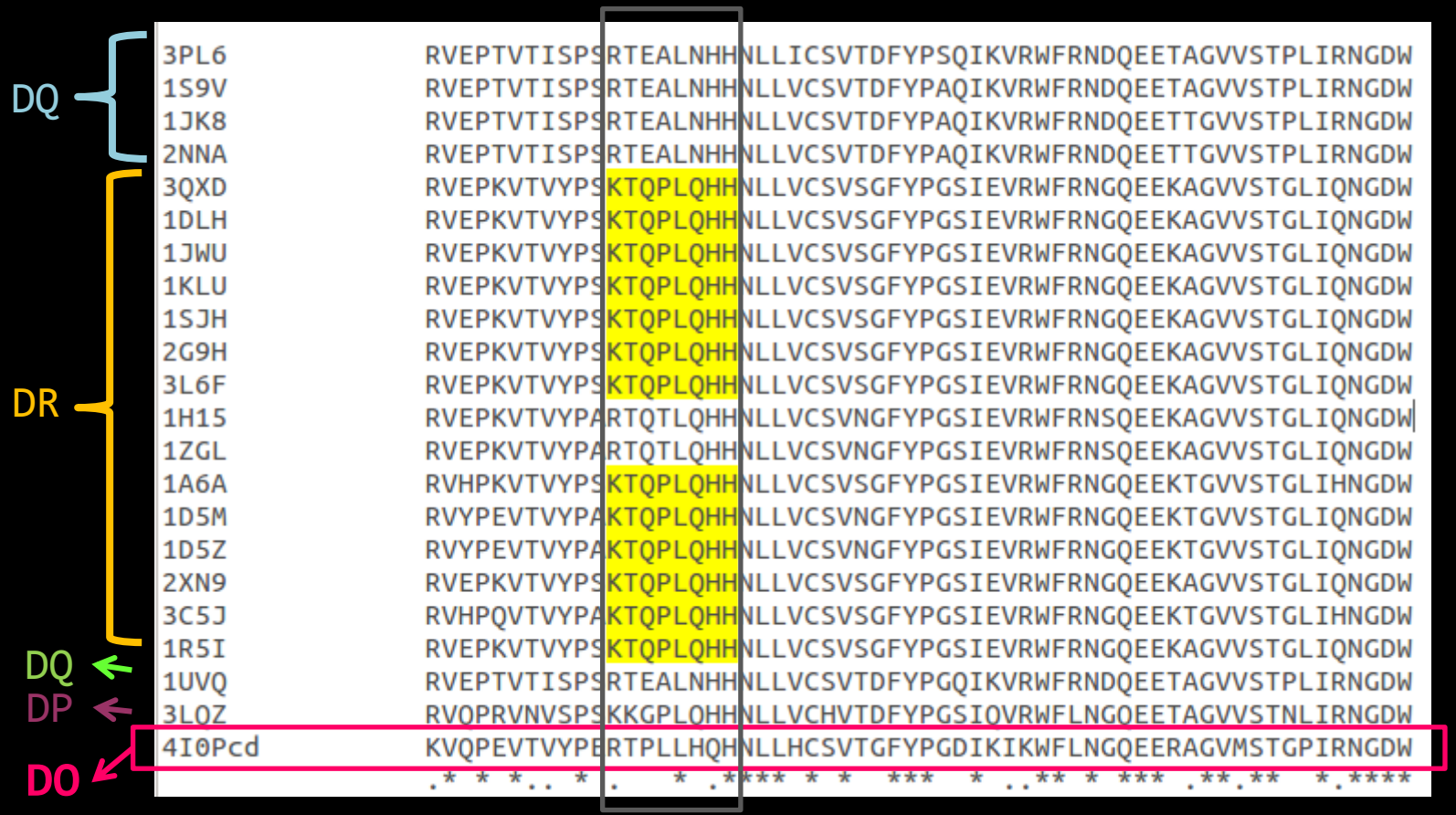
Classical MHC II
HLA II-DM
HLA II-DO

Non classical MHC class II

Multiple alignment

Classical MHCA Class II – HLA-DO

β2 Ig-like domain

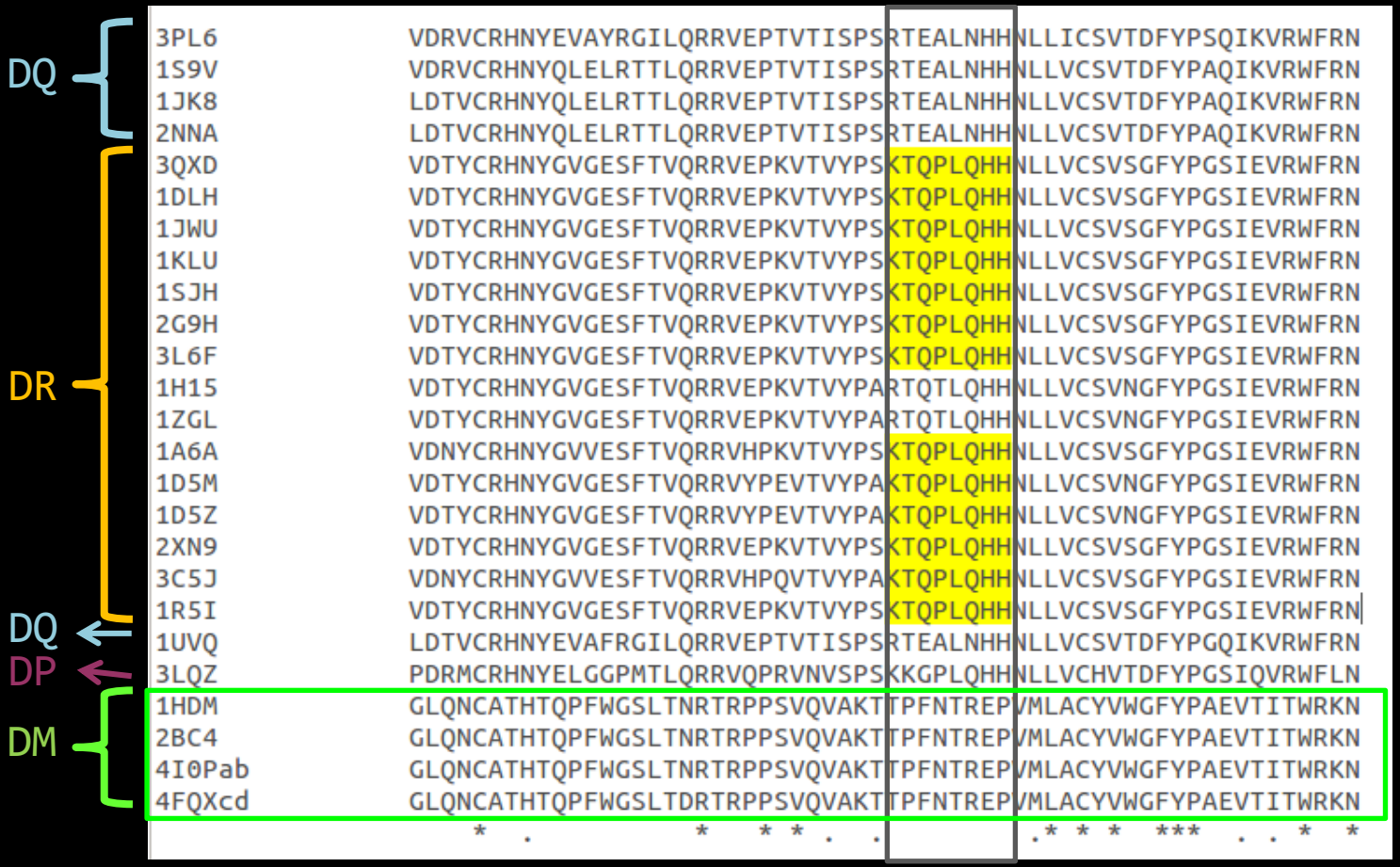


Non classical MHC class II

Multiple alignment

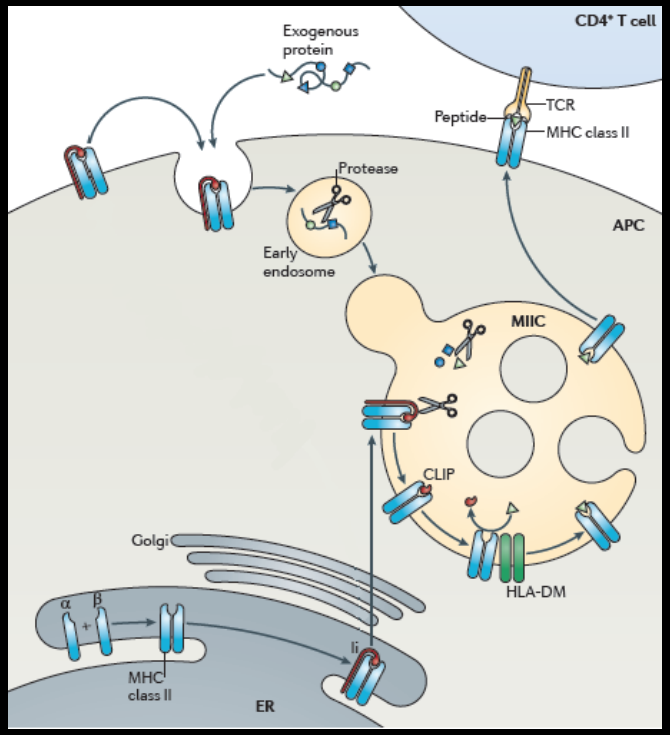
Classical MHCA Class II – HLA-DM

β2 Ig-like domain



HLA DR1 – HLA DM interaction

Interaction HLA-DR1 – HLA-DM



HLA-DM Functions

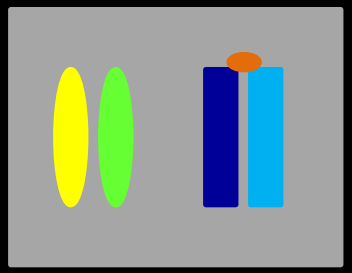
- Catalyze CLIP and low affinity peptides dissociation from DR molecules
- Stabilize empty DR proteins
- Enable rapid binding of high affinity peptides generated by proteolysis to DR

Neefjes J, Jongsma MLM. Towards a systems understanding of MHC class I and MHC class II antigen presentation. Nature, 2011; 11: 823-836.

Interaction HLA-DR1 – HLA-DM

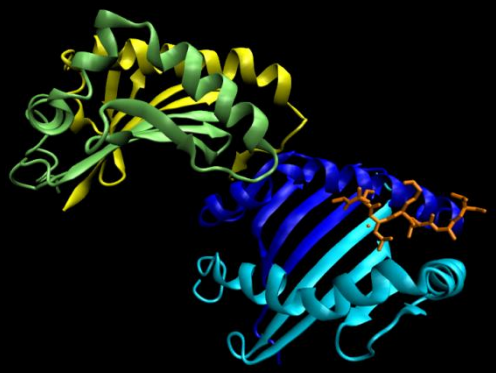
Overview of the complex

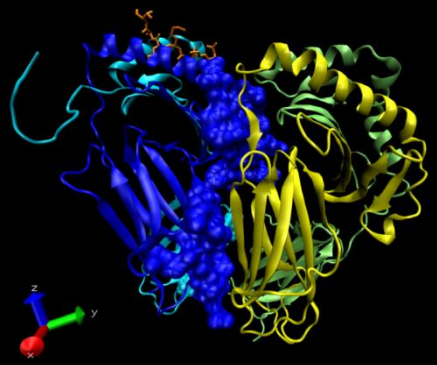
DM - DR1

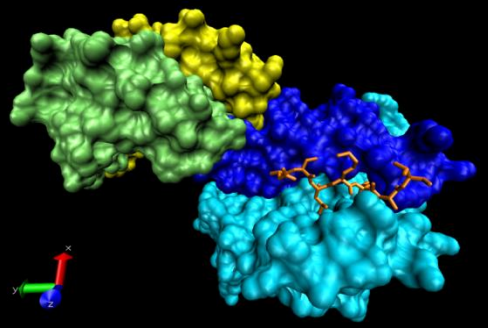


- The interface is dominated by the α chains of DM and DR1

- DM does NOT obstruct the open end of the groove







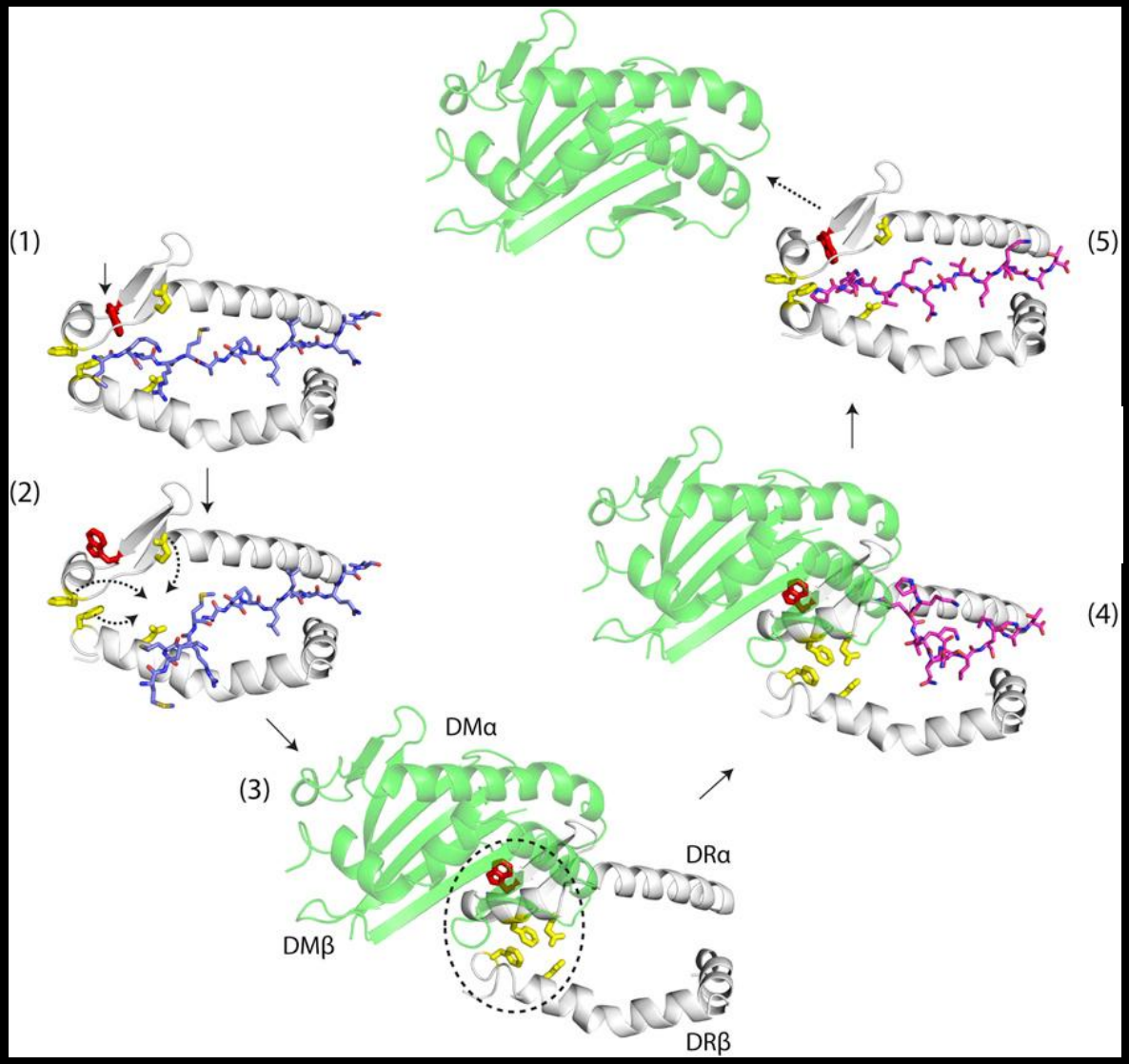
Interaction HLA-DR1 – HLA-DM

First glance

CLIP

Trp43

DM



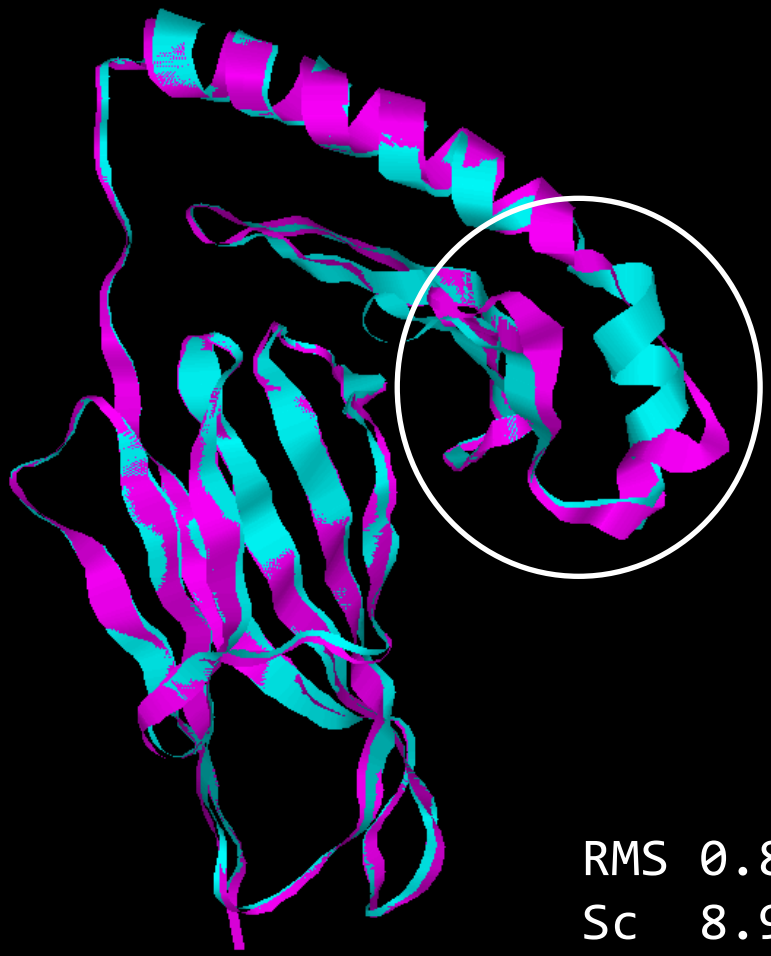
Antigen peptide

Pos W, Sethi DK, et al. Crystal strucutre of the HLA-DM—HLA-DR1 complex defines mechanisms for rapid peptide selection. Cell, 2012; 151:1557-1568.

Interaction HLA-DR1 – HLA-DM

Step by step

1 α43W



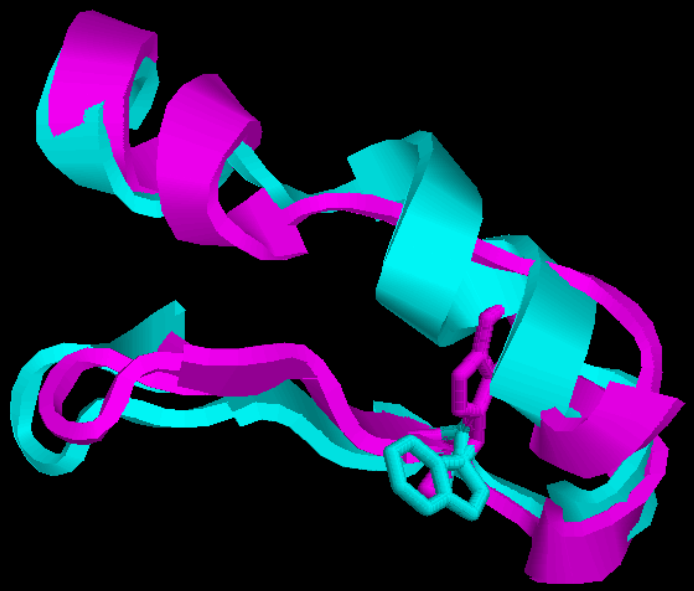
RMS 0.84
Sc 8.92

αDR1
αDR1 in complex with DM

Interaction HLA-DR1 – HLA-DM

Step by step

1 α43W



αDR1
αDR1 in complex with DM

DR1:

- lateral wall of the pocket 1
- interacts with P1 tyrosine antigen HA
-stabilizes residues in the vicinity of the P1 pocket through many interactions

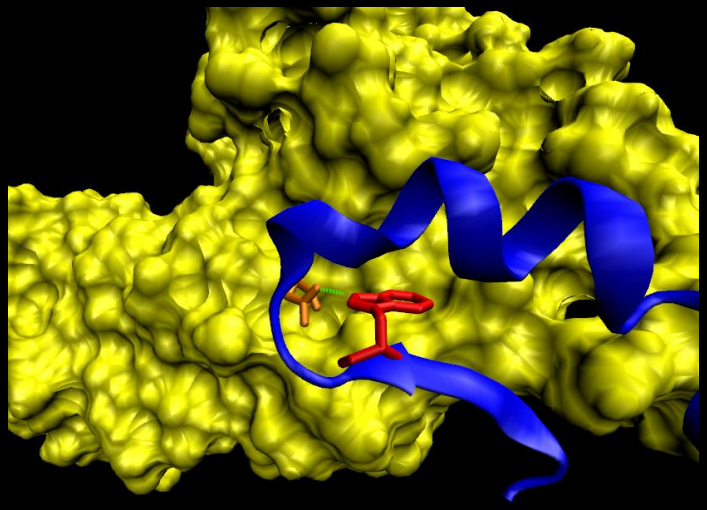
DM-DR1 complex:

- rotates out of the groove

Interaction HLA-DR1 – HLA-DM

Step by step

1 α43W



α DR1 in complex with DM

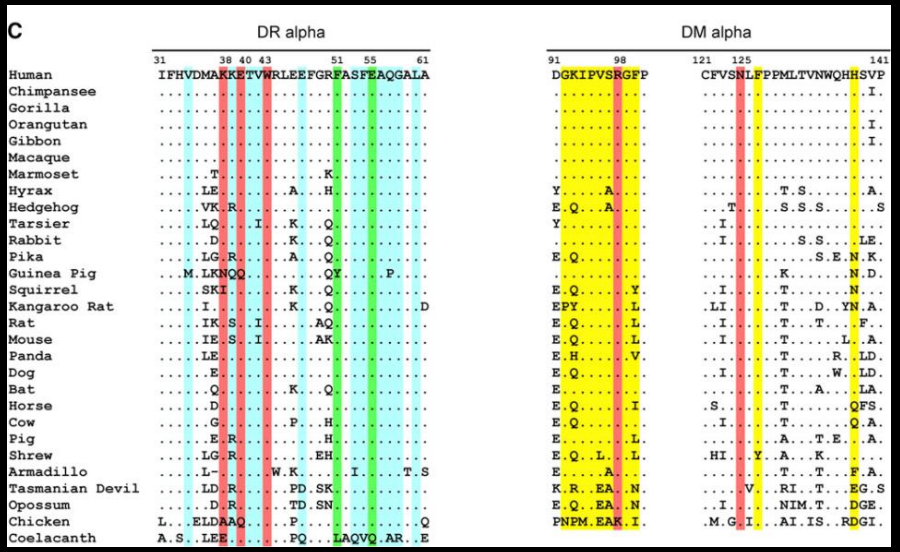
DM

DM-DR1 complex:

- **α43W** is rotated out of the groove

-indole ring nitrogen of DR α43W forms a hydrogen bond with DM **α 125N**

Both residues are fully conserved



Pos W, Sethi DK, et al. Crystal strucutre of the HLA-DM—HLA-DR1 complex defines mechanisms for rapid peptide selection. Cell, 2012; 151:1557-1568

Interaction HLA-DR1 – HLA-DM

Step by step

2 DR α-chain

DR1:

- 52-55: short strand parallel to the bound peptide
- 46-50: 3_{10} helix

DM-DR1 complex

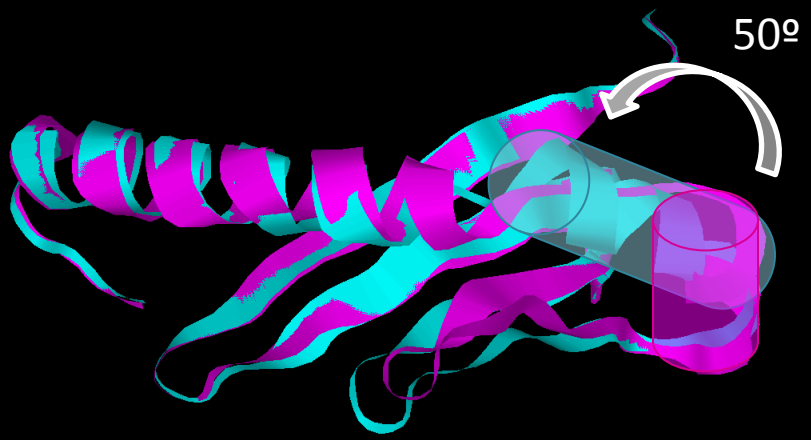
-The strand and the 3_{10} helix are transformed into a helix

The change is facilitated by loss of stabilizing interactions of αW43 with neighboring structures

Interaction HLA-DR1 – HLA-DM

Step by step

2 DR α-chain



DR1:

- 52-55: short strand parallel to the bound peptide
-46-50: 3_{10} helix

DM-DR1 complex

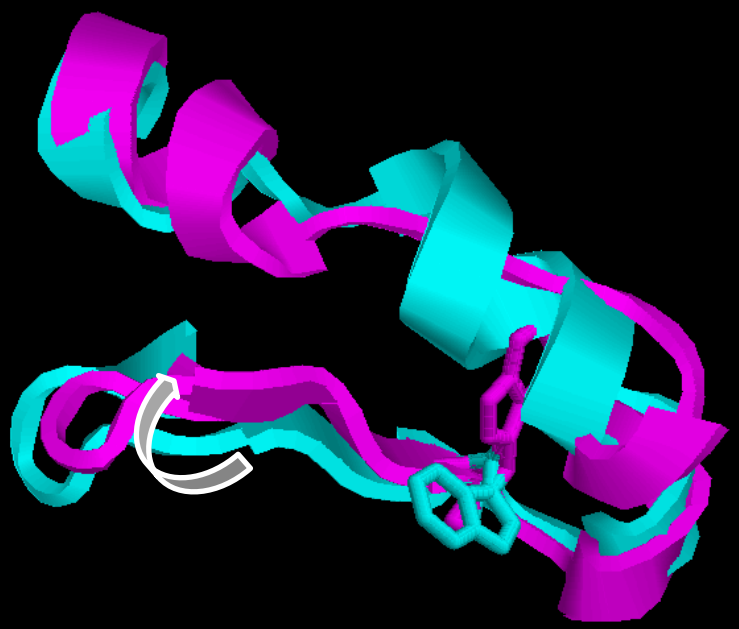
-The strand and the 3_{10} helix are transformed into a helix

The change is facilitated by loss of stabilizing interactions of αW43 with neighboring structures

Interaction HLA-DR1 – HLA-DM

Step by step

3 Floor of peptide-binding groove



DR1:
-strands S3 and S4 are in a strained conformation

DM-DR1 complex:
-both strands move away from the α-helix and towards the main β-sheet platform

αDR1
α DR1 in complex with DM

Interaction HLA-DR1 – HLA-DM

Step by step

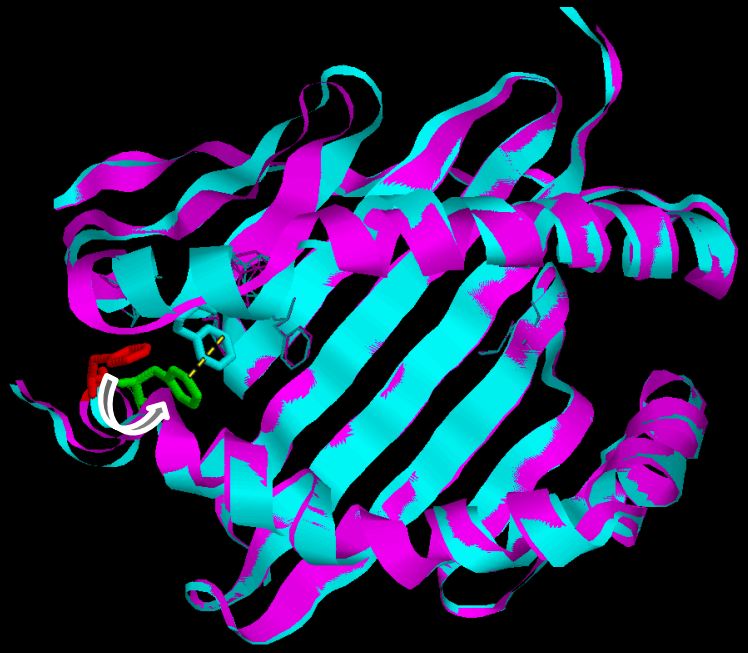
4 Stabilization of the P1 pocket

αF51:

DR1: points out of the groove
DM-DR1 complex: moves into the P1

βF89:

DM-DR1 complex: moves near the P1
close interaction with DRαF51

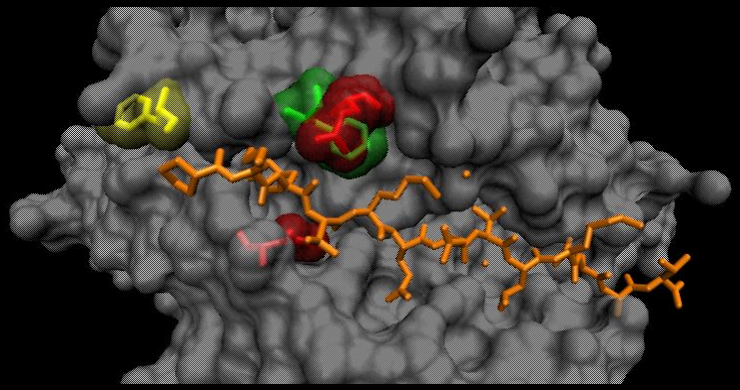


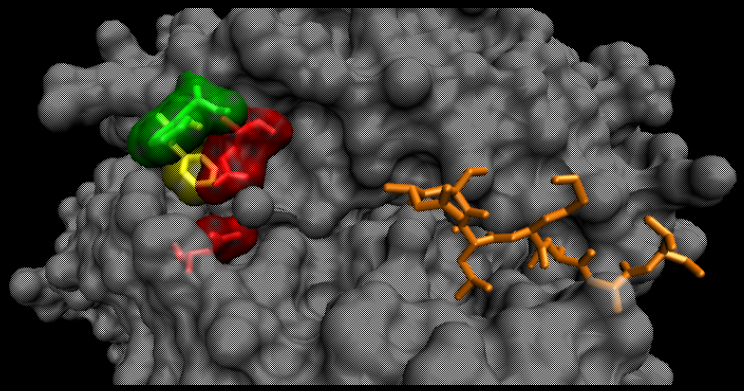
Interaction HLA-DR1 – HLA-DM

Step by step

4 Stabilization of the P1 pocket

αE55





DR1:
-βN82 interacts with the peptide

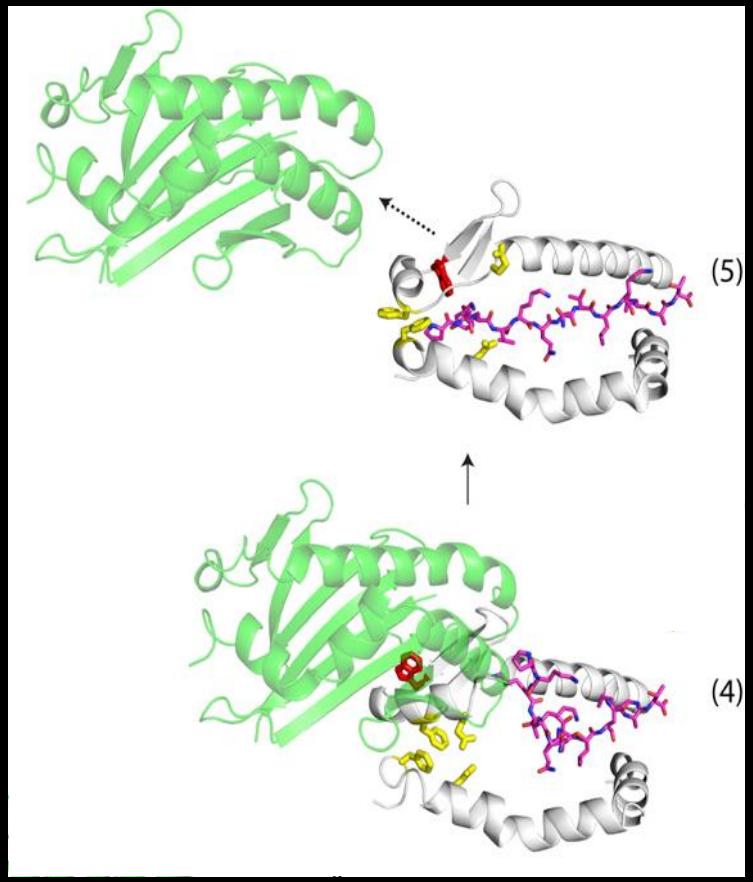
DM-DR1 complex:
-αE55 moves into the groove where it forms a hydrogen bond with DR βN82, so it can not interact with the peptide.

DR αF51, βF89, and αE55 stabilize the empty groove and catalyze peptide dissociation

Interaction HLA-DR1 – HLA-DM

Step by step

5 Selection of the highest affinity peptide ligands



Only peptides that successfully compete with DR residues for access to the **P2** site and the **P1** pocket are stably bound.

Full occupancy of the groove reverses the conformational changes associated with **DM** binding and results in **DM** dissociation.

Pos W, Sethi DK, et al. Crystal strucutre of the HLA-DM—HLA-DR1 complex defines mechanisms for rapid peptide selection. Cell, 2012; 151:1557-1568.

Conclusions

Take home message

❖ Peptide selection by class II MHC proteins can be characterized by 'motifs' consisting of sidechain preferences at particular positions within the peptide.

❖ Completely different peptide sequences can adopt essentially the same bound conformation, with little or no adjustment of the MHC protein residues.

❖ Analysis of available structural information on MHC class II proteins reveals three areas of conformational lability:

- β2 Ig-like domain
- α-subunit 3_{10} helical region
- kink in the β-subunit helical region

❖ HLA-DM has a well-understood function in catalyzing peptide exchange on MHC II proteins

❖ HLA-DO is also involved in antigen presentation although its role is less well-defined

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Pos W, Sethi DK, et al. Crystal strucutre of the HLA-DM—HLA-DR1 complex defines mechanisms for rapid peptide selection. Cell, 2012; 151:1557-1568.

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Neefjes J, Jongsma MLM. Towards a systems understanding of MHC class I and MHC class II antigen presentation. Nature, 2011; 11: 823-836.

Multiple choice questions

1. MHC Class III genes encode molecules that are critical to immune function. These are:
a) Complement components and inflammatory cytokines such as TNF-α
b) HLA-DR which presents peptides to T cells
c) HLA-DM which mediates the exchange between CLIP and the antigenic peptide
d) HLA-A which presents peptides to T cells
e) HLA-DM which presents peptides to T cells

2. Which of the following statements related to the binding groove is true?
1. MHC class I groove is blocked at both ends so it is only able to bind peptides of 8 to 10 residues
2. Peptide binding cleft in class II molecules is open at both ends allowing longer peptides to extend beyond the ends
3. In class I molecules, the binding is carried by anchored residues found at the ends of the peptides
4. Peptides that bind to class II molecules present internal conserved motifs that form hydrogen bonds distributed throughout the binding site
a) 1, 2, 3
b) 1, 3
c) 2, 4
d) 4
e) 1, 2, 3, 4

Multiple choice questions

3. Which of the following sentences are true?

1. The immunoglobulin fold consists of a sandwich of between 7 and 9 antiparallel β-strands arranged in two β-sheets with a Greek key topology
2. Class II MHC molecules present intrachain disulfide bridges
3. MHC class III molecules are classified in the immunoglobulin superfamily
4. Class I MHC molecules are encoded by the DP, DQ and DR regions in humans

a) 1, 2, 3
b) 1, 3
c) 2, 4
d) 4
e) 1, 2, 3, 4

4. Choose the correct option:

a) The peptides bound to DR keep a similar conformation, despite having a different aminoacidic sequence.
b) The conformation of DR protein is unchanged with the binding of different peptides
c) The previous sentences are correct
d)The pattern of hydrogen bonds between the DR and the different peptides is very similar.
e) All sentences are correct

Multiple choice questions

5. Choose the correct option about the non-classical MHC II proteins:
a) DM and DO are two non classical MHCII with an accessory role in the antigen-loading process
b) DO is structurally more similar to DM (the other non classical protein) than to the classical MHCII proteins
c)The previous sentences are correct
d)The structural similarities can not be seen at a sequence level.
e)All the previous sentences are correct

6. What's the region of the largest conformational heterogeneity?
a) The α-subunit 3_{10} helical region
b) The β-2 Ig-like domain
c) The two previous are correct
d) Pronounced kink in the β-subunit helical region
e) All are incorrect

7. Which sentence is true about the group of outliers in the pronounced kink of the β-subunit helical region?
a) This group is consists of the HLADR molecules that present the allele B1
b) This group is form by only two proteins
c) The two previous are false
d) In its crystal lattice there are intermolecular contacts at Gly 66
e) All are false

Multiple choice questions

8. When HLA-DR1 interacts with HLA-DM there are conformational changes in:
a) αW43
b) α-chain of DR1
c) The two previous are correct
d) Floor of the peptide-binding groove
e) All answers are correct

9. HLA-DM protein's functions are:
a) Catalyze CLIP and low affinity antigenic peptides dissociation from DR molecules
b) Stabilize the empty DR proteins
c) The two previous are correct
d) Enable rapid binding of high affinity peptides to DR
e) All answers are correct

10. Which of the following statements is true about the sequence alignment of MCH II?
a) The sequences within the same family are very conserved
b) In the variable regions there are many differences between different families
c) The two previous answers are correct
d) We cannot find any relationship between the sequence and the family
e) All are correct