MHC

STRUCTURE ANALYSIS OF THE MAJOR HISTOCOMPATIBILITY COMPLEX

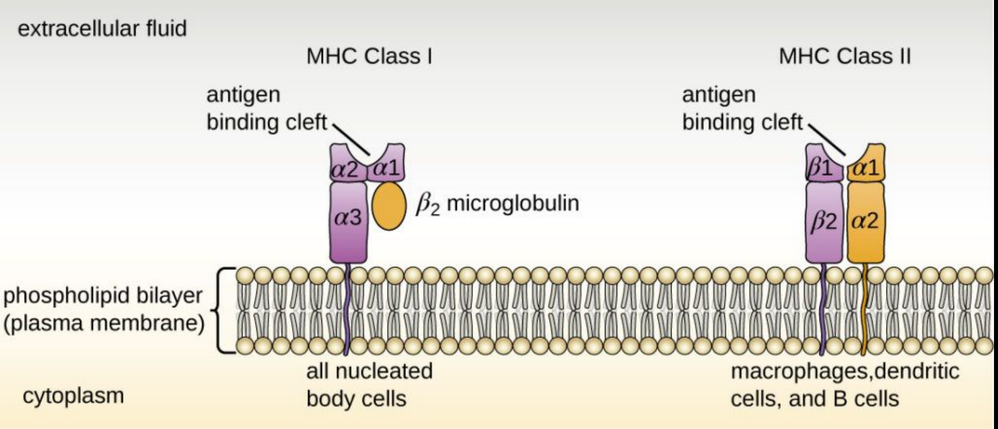
Laura Cañadas, Clàudia Garcia, Laia Joval and Ariadna Pinar

INDEX

1. INTRODUCTION

The major histocompatibility complex

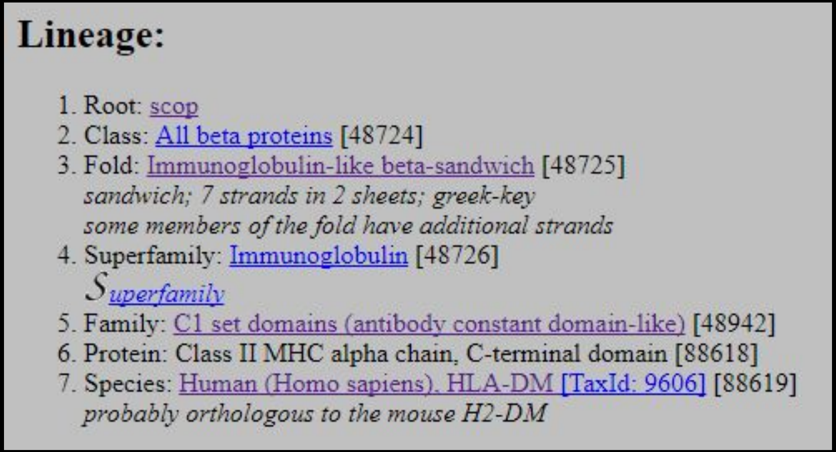
- Family of genes found in all vertebrates.
- Function: to present peptidic fragments to T lymphocytes
- Two different classes: HLA-I and HLA-II



Courses.lumenlearning.com. (2018). *Major Histocompatibility Complexes and Antigen-Presenting Cells* | *Microbiology*. [online]

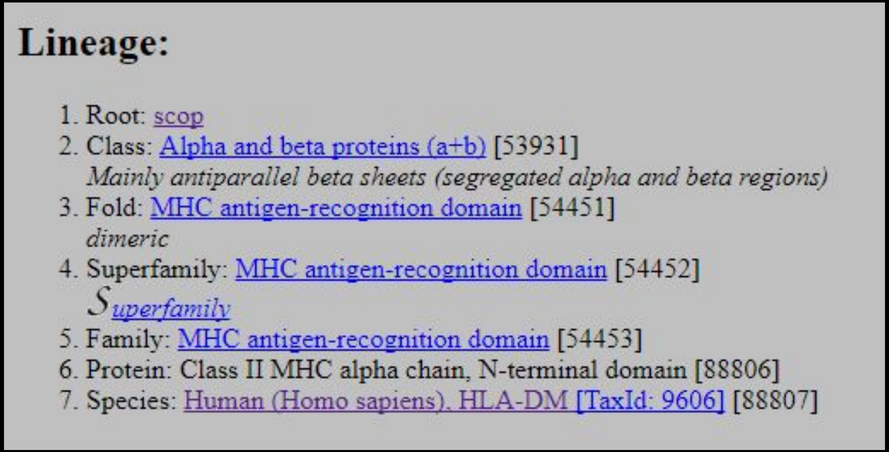
The major histocompatibility complex

SCOP CLASSIFICATION



Lineage:

1. Root: scop
2. Class: All beta proteins [48724]
3. Fold: Immunoglobulin-like beta-sandwich [48725]
   sandwich; 7 strands in 2 sheets; greek-key
   some members of the fold have additional strands
4. Superfamily: Immunoglobulin [48726]
   Superfamily
5. Family: C1 set domains (antibody constant domain-like) [48942]
6. Protein: Class II MHC alpha chain, C-terminal domain [88618]
7. Species: Human (Homo sapiens), HLA-DM [TaxId: 9606] [88619]
   probably orthologous to the mouse H2-DM



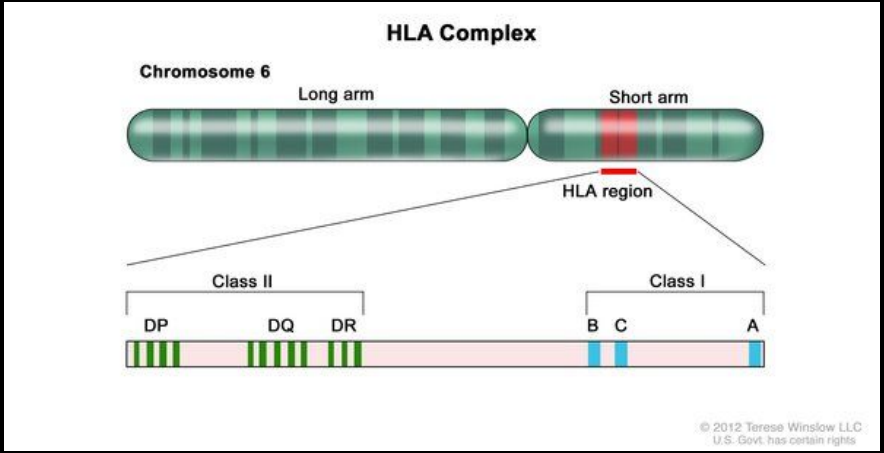
Lineage:

1. Root: scop
2. Class: Alpha and beta proteins (a+b) [53931]
   Mainly antiparallel beta sheets (segregated alpha and beta regions)
3. Fold: MHC antigen-recognition domain [54451]
   dimeric
4. Superfamily: MHC antigen-recognition domain [54452]
   Superfamily
5. Family: MHC antigen-recognition domain [54453]
6. Protein: Class II MHC alpha chain, N-terminal domain [88806]
7. Species: Human (Homo sapiens), HLA-DM [TaxId: 9606] [88807]

Scop.mrc-lmb.cam.ac.uk. (2018). *SCOP: Structural Classification of Proteins*. [online] Available at: http://scop.mrc-lmb.cam.ac.uk/scop/ [Accessed 24 Feb. 2018].

The major histocompatibility complex

- Human leucocytic antigen (HLA)
- Polygenic and polymorphic
- HLA-I
  - A
  - B
  - C
- HLA-II
  - DP (a, b)
  - DQ (a, b)
  - DR (a, b)



Reference, G. (2018). *Narcolepsy*. [online] Genetics Home Reference. Available at: https://ghr.nlm.nih.gov/condition/narcolepsy [Accessed 24 Feb. 2018].

The major histocompatibility complex

HLA I

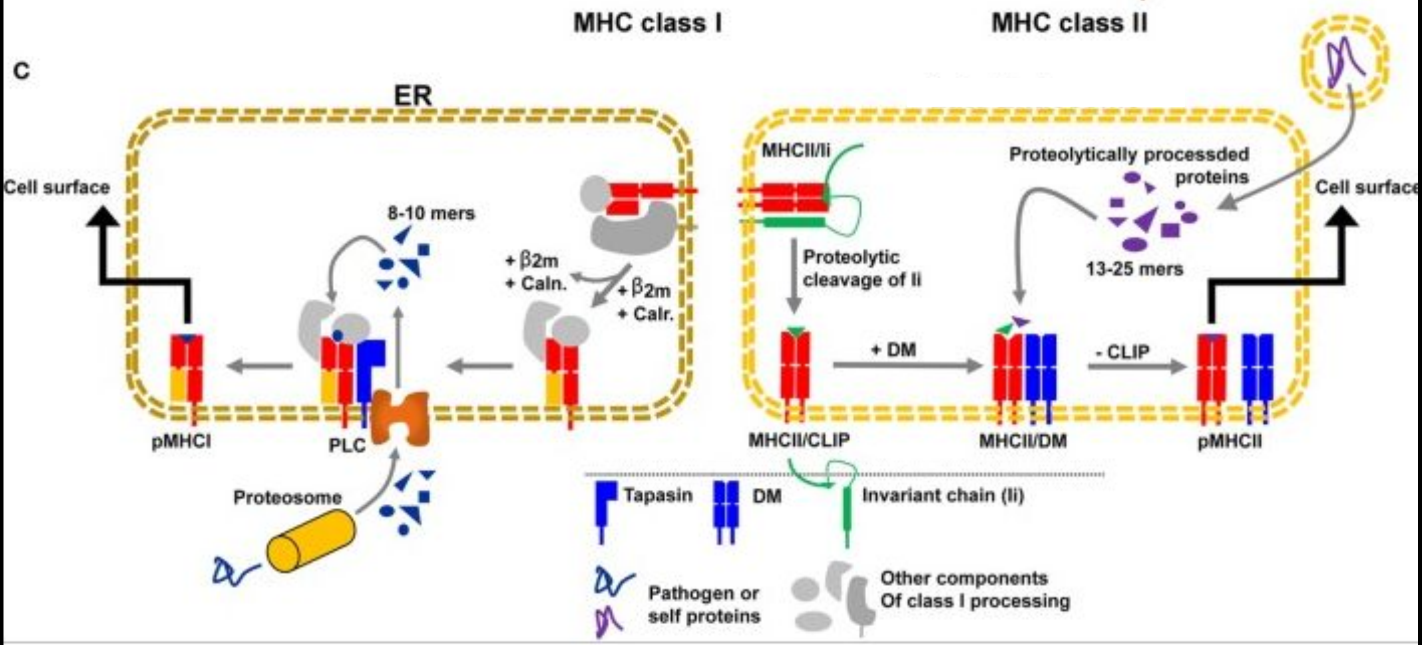
- Expressed in all nucleated cells
- Interacts with cytotoxic T cells (CD8+)
- Presents inner antigens

HLA II

- Expressed by exclusively by APCs (dendritic cells, macrophages, B cells)
- Interacts with helper T cells (CD4+)
- Presents exogenous antigens

The major histocompatibility complex

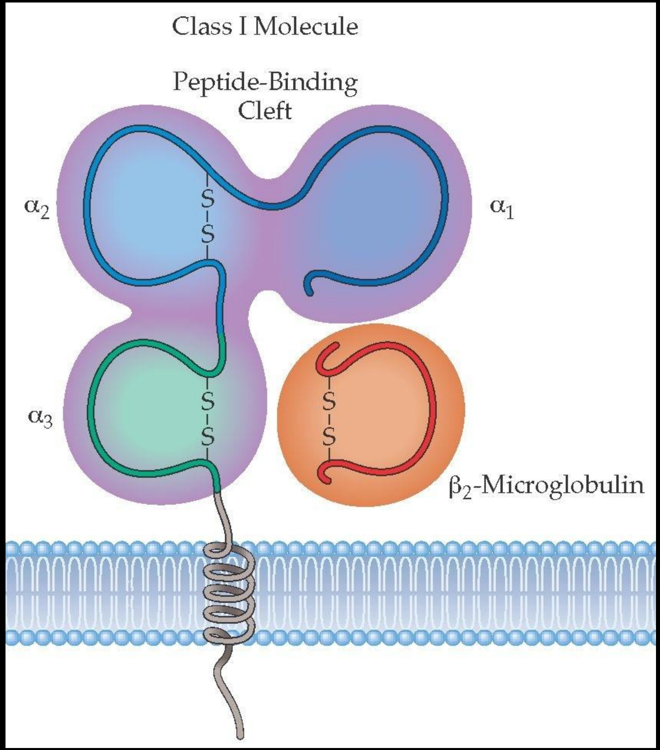
Antigen processing + antigen presentation:



Wieczorek, M., Abualrous, E., Sticht, J., Álvaro-Benito, M., Stolzenberg, S., Noé, F. and Freund, C. (2017). Major Histocompatibility Complex (MHC) Class I and MHC Class II Proteins: Conformational Plasticity in Antigen Presentation. *Frontiers in Immunology*, 8.

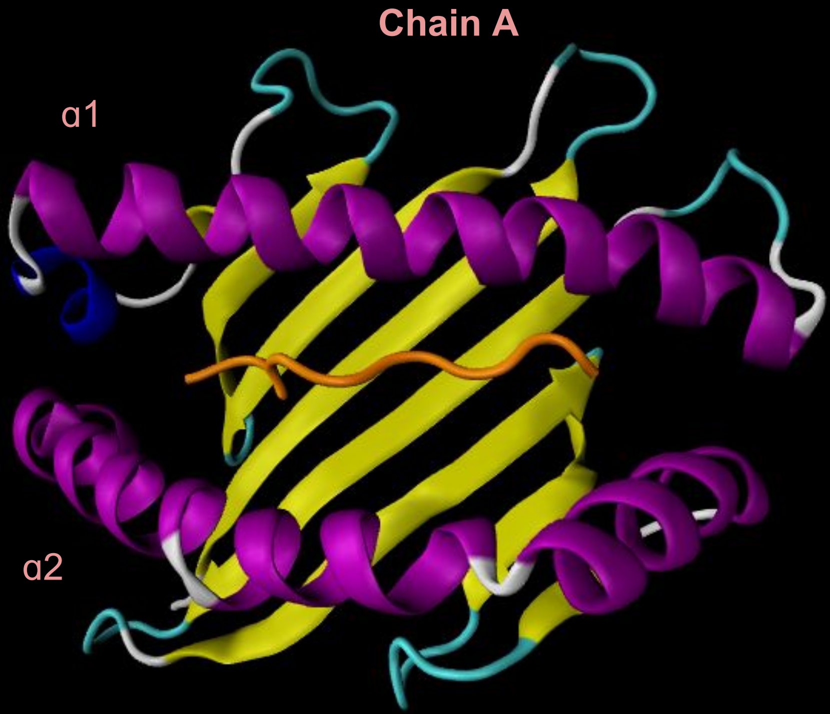
2. HLA I STRUCTURE

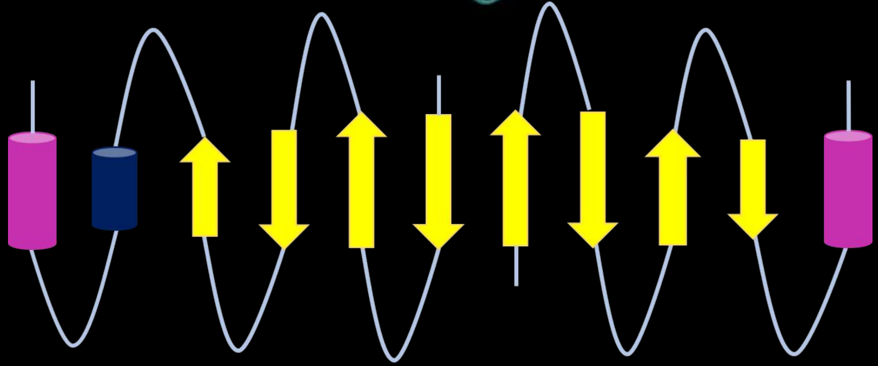
HLA I - Structure



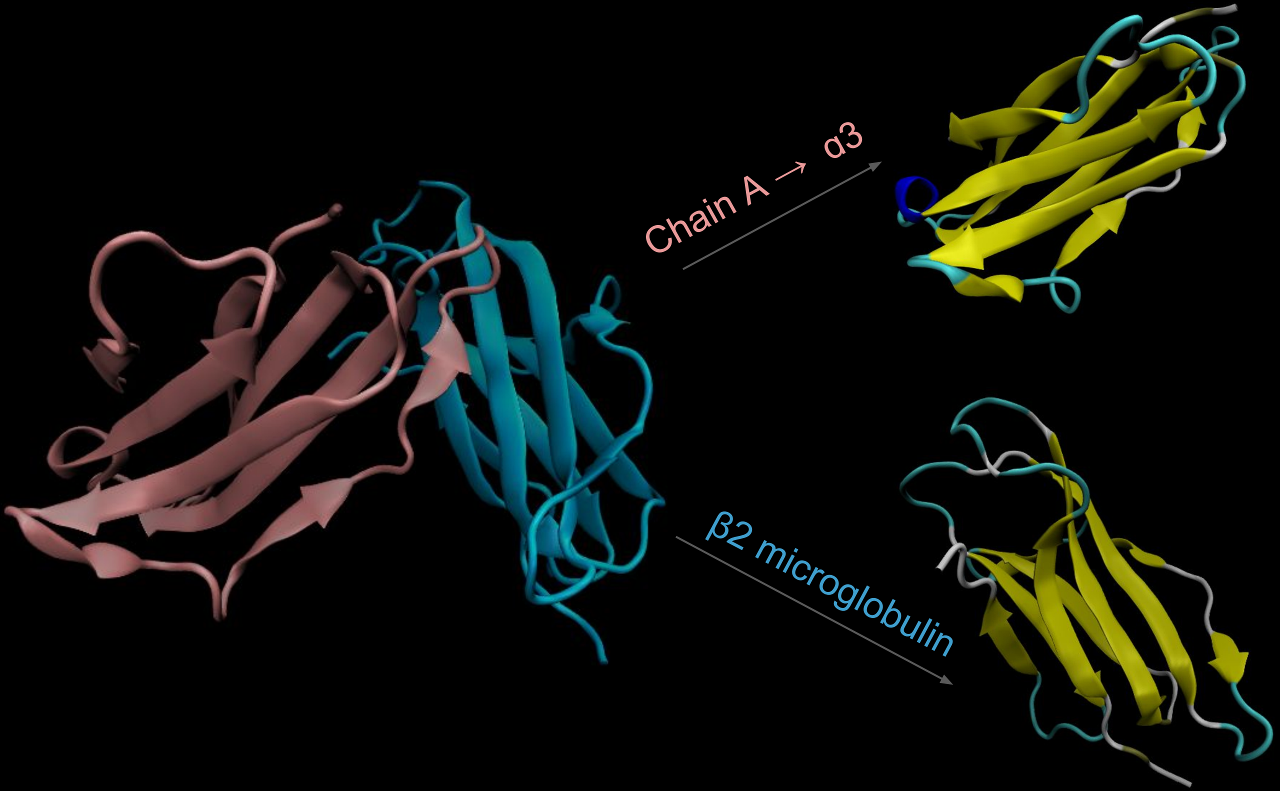
Acharya, T. (2018). *Difference between MHC Class I and MHC Class II Proteins - microbeonline*. [online] microbeonline. Available at: https://microbeonline.com/difference-mhc-class-mhc-class-ii-proteins/ [Accessed 25 Feb. 2018].

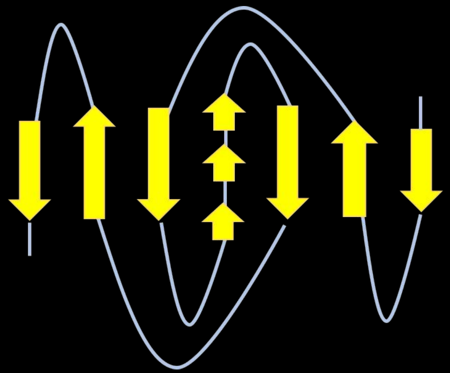
HLA I - Binding Groove



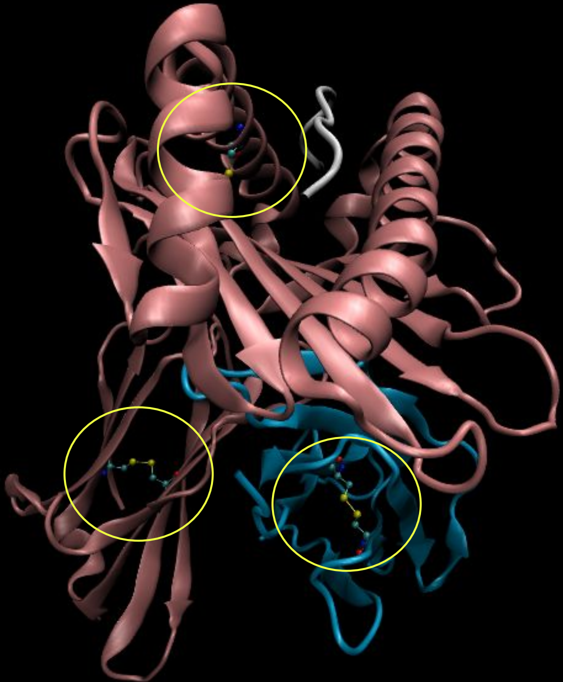


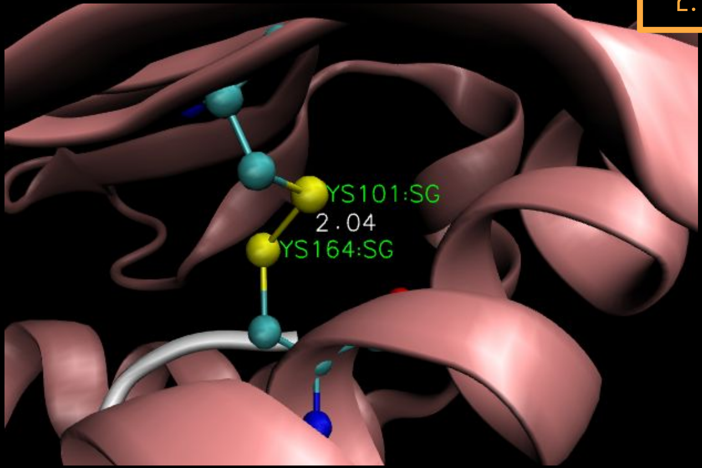
HLA I - Ig-like domains

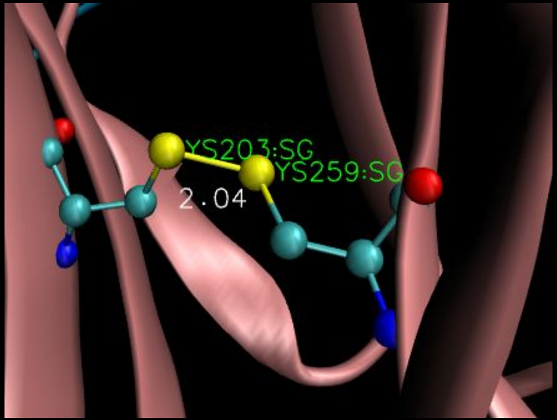


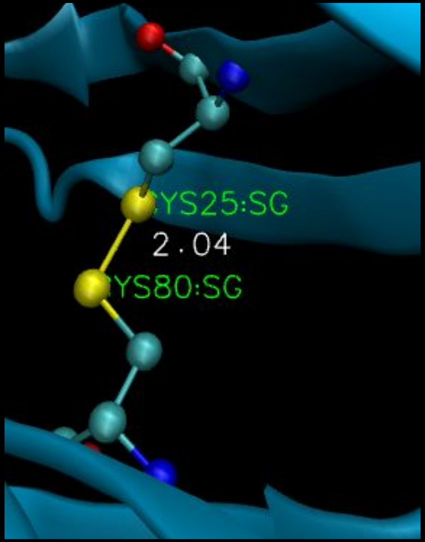


HLA I - Disulfide bridges



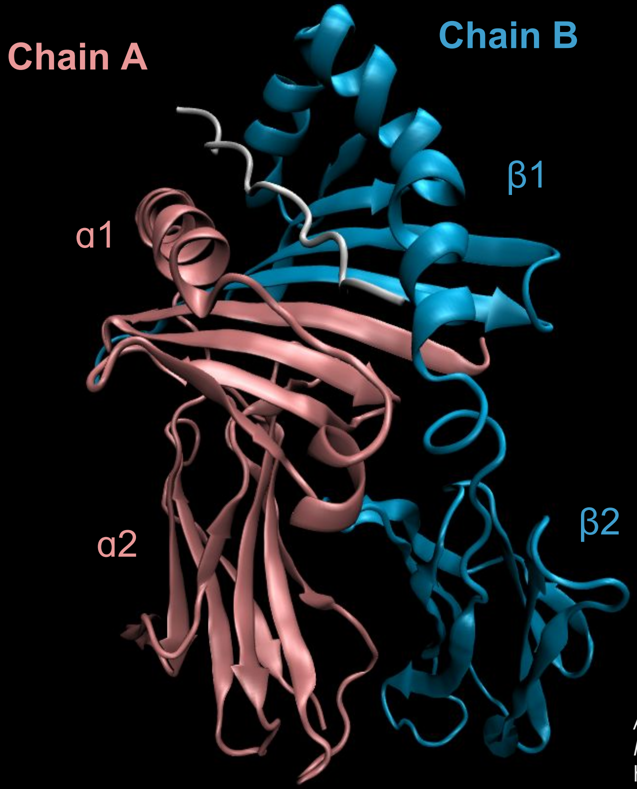


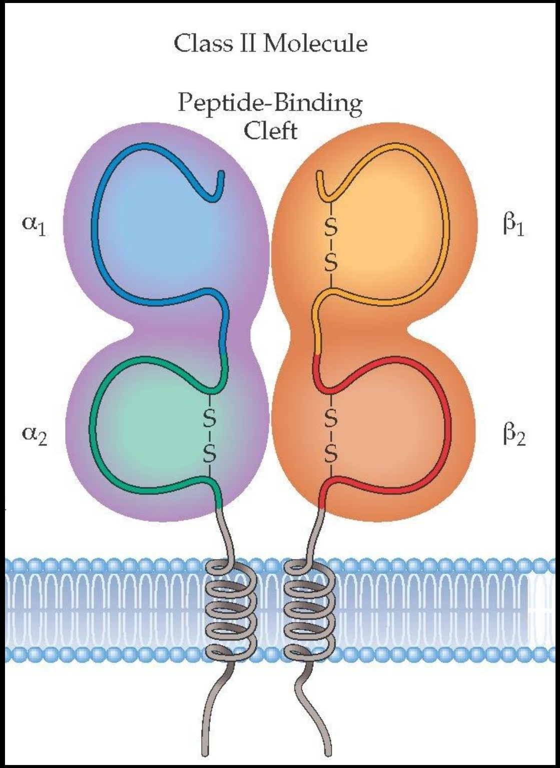




3. HLA II STRUCTURE

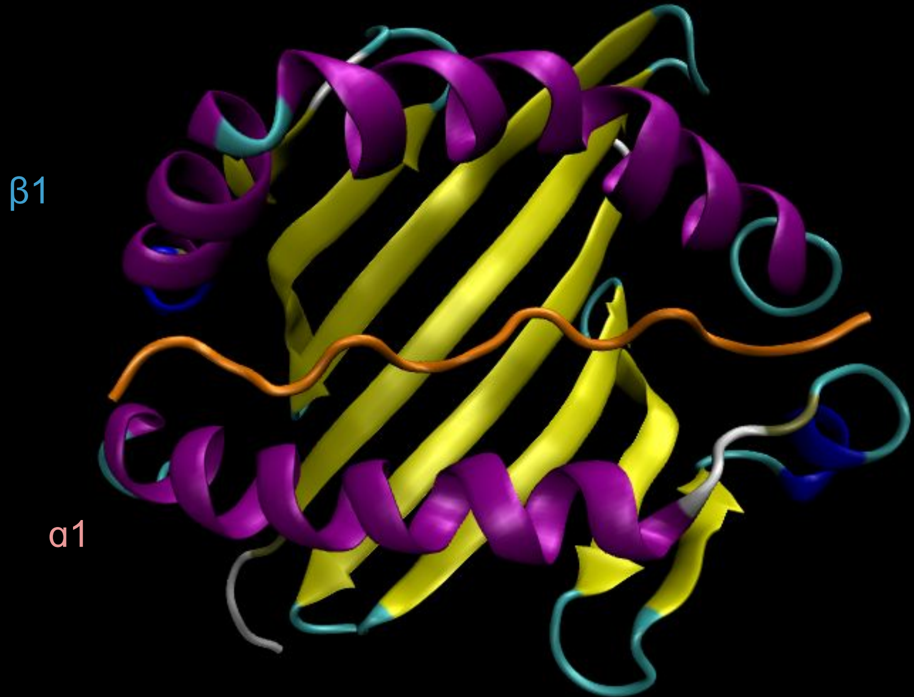
HLA II - Structure

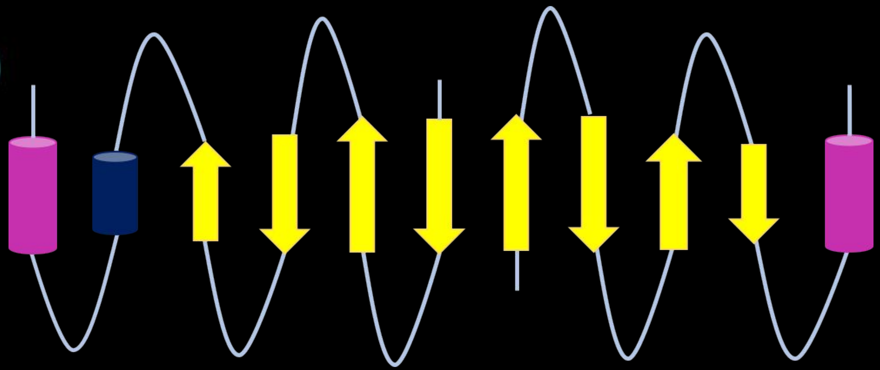




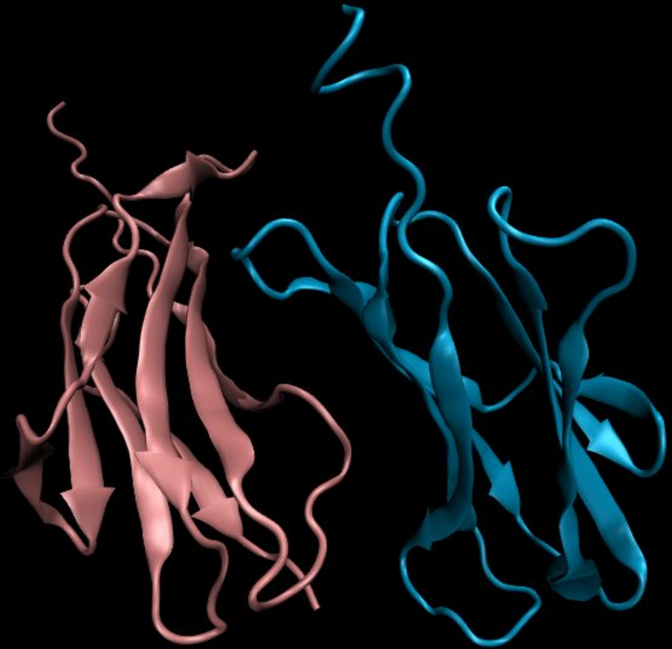
Acharya, T. (2018). *Difference between MHC Class I and MHC Class II Proteins - microbeonline*. [online] microbeonline. Available at: https://microbeonline.com/difference-mhc-class-mhc-class-ii-proteins/ [Accessed 25 Feb. 2018].

HLA II - Binding Groove

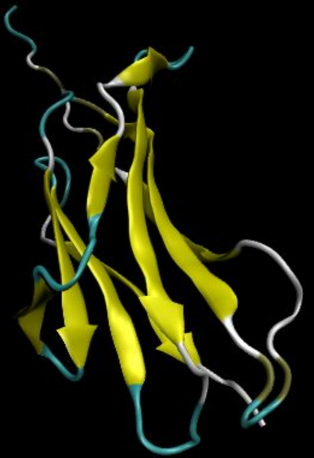




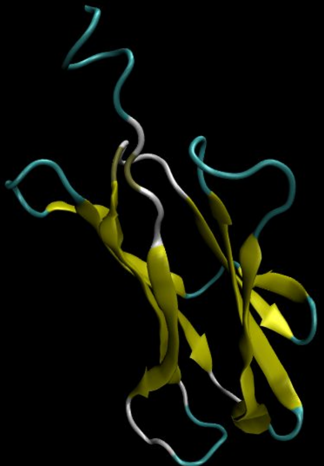
HLA II - Ig-like domains

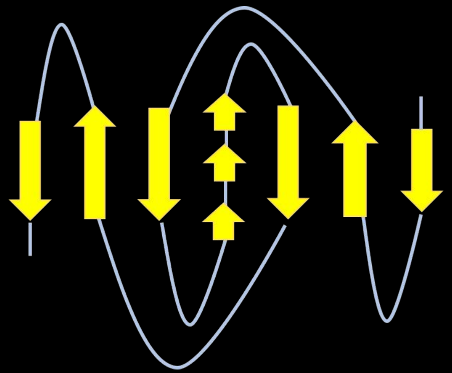


Chain A → α2

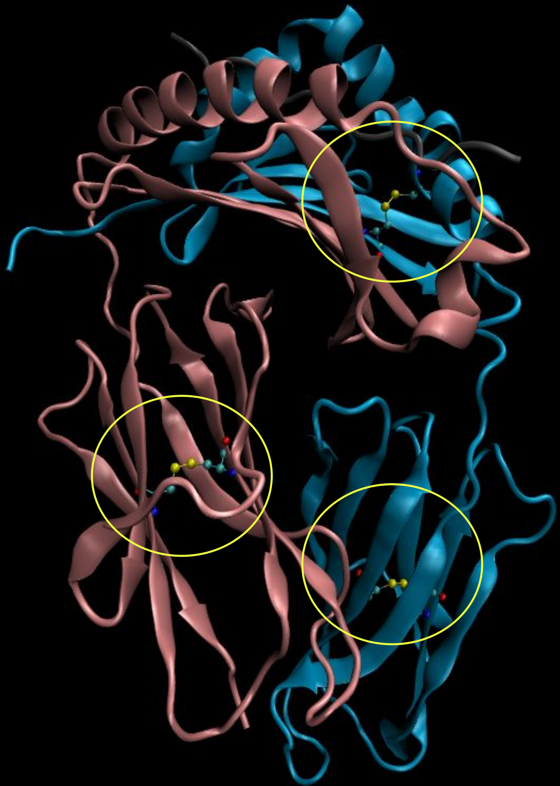


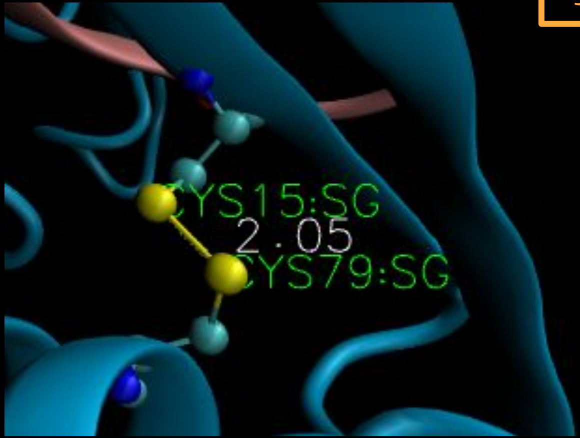
Chain B → β2

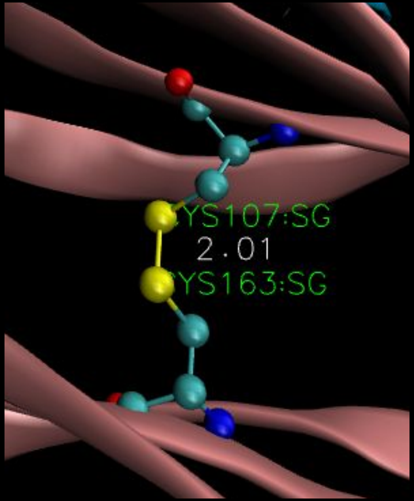


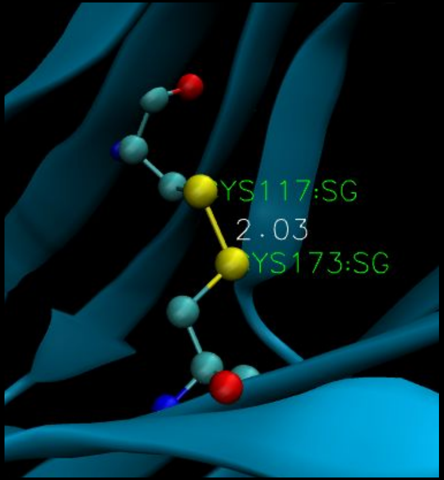


HLA II - Disulfide bridges



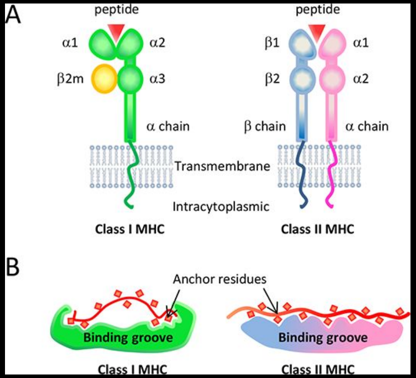




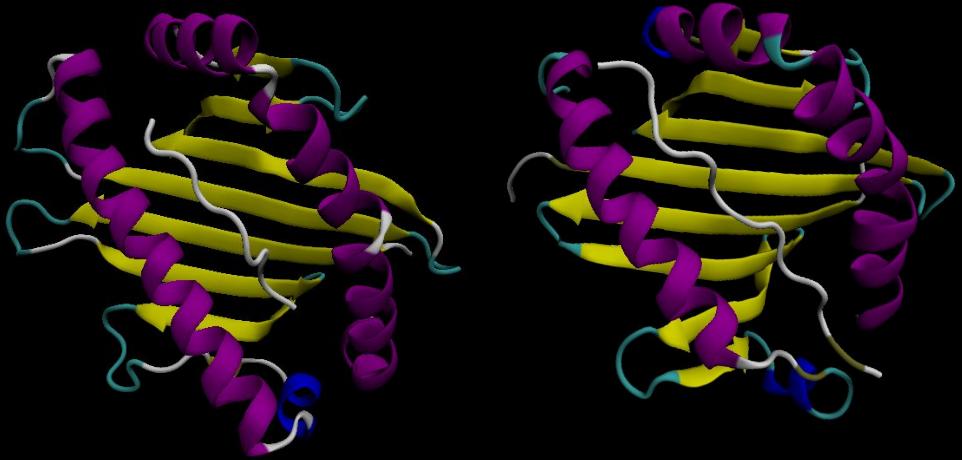


4. BINDING GROOVE

Binding groove: HLA I vs HLA II

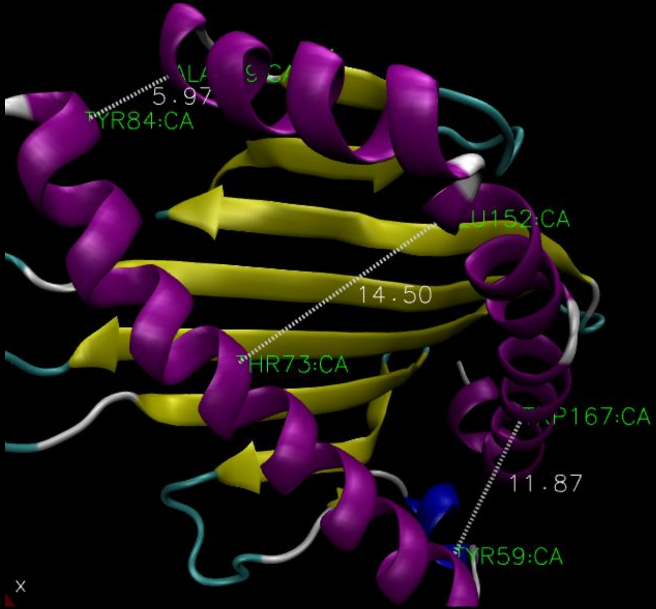


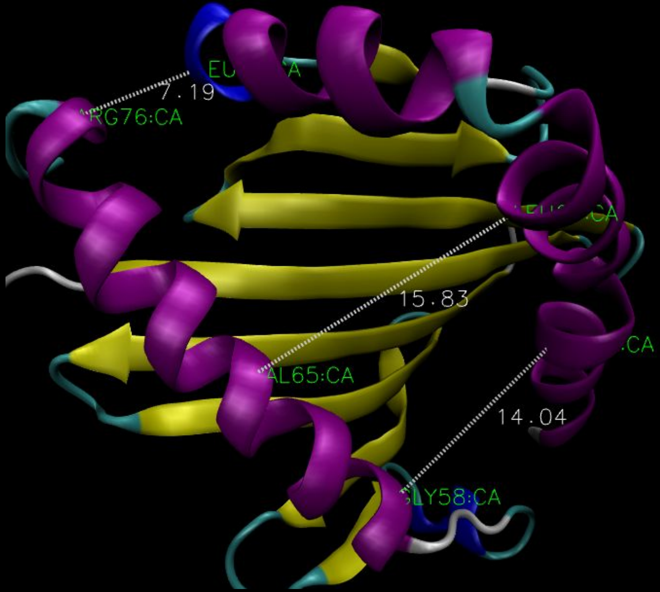
Gutiérrez, S., Esteban, E., Lützelschwab, C. and Juliarena, M. (2017). Major Histocompatibility Complex-Associated Resistance to Infectious Diseases: The Case of Bovine Leukemia Virus Infection. *Trends and Advances in Veterinary Genetics*.



	HLA I	**HLA II**
Peptide-binding domain	alfa-1 and alfa-2	alfa-1 and beta-1
Size of peptides (aa)	8-14	13-25
Nature of bound peptide	endogen	exogen
Bounding	both ends tightly bound at either end of the cleft	the ends are not tightly bound the peptide extends beyond the cleft

Binding groove: HLA I vs HLA II



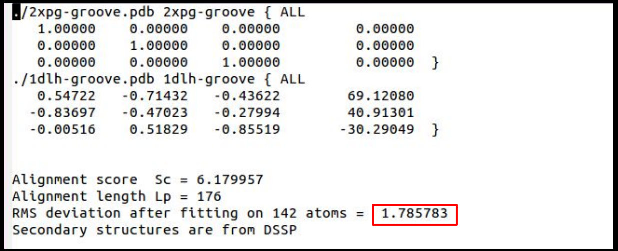


HLA I: TYR84 - ALA-139
THR73 - GLU152
TYR59 - GLU152

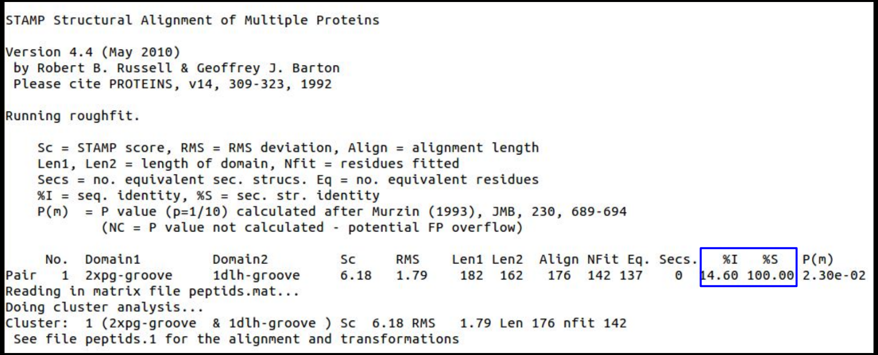
HLA II: ARG76 - LEU53
VAL65 - LEU67
GLY58 - TYR78

Binding groove: Superimposition

Blue: HLA-I   Gold: HLA-II



```
./2xpg-groove.pdb 2xpg-groove { ALL
   1.00000    0.00000    0.00000         0.00000
   0.00000    1.00000    0.00000         0.00000
   0.00000    0.00000    1.00000         0.00000  }
./1dlh-groove.pdb 1dlh-groove { ALL
   0.54722   -0.71432   -0.43622        69.12080
  -0.83697   -0.47023   -0.27994        40.91301
  -0.00516    0.51829   -0.85519       -30.29049  }


Alignment score  Sc = 6.179957
Alignment length Lp = 176
RMS deviation after fitting on 142 atoms =  1.785783
Secondary structures are from DSSP
```



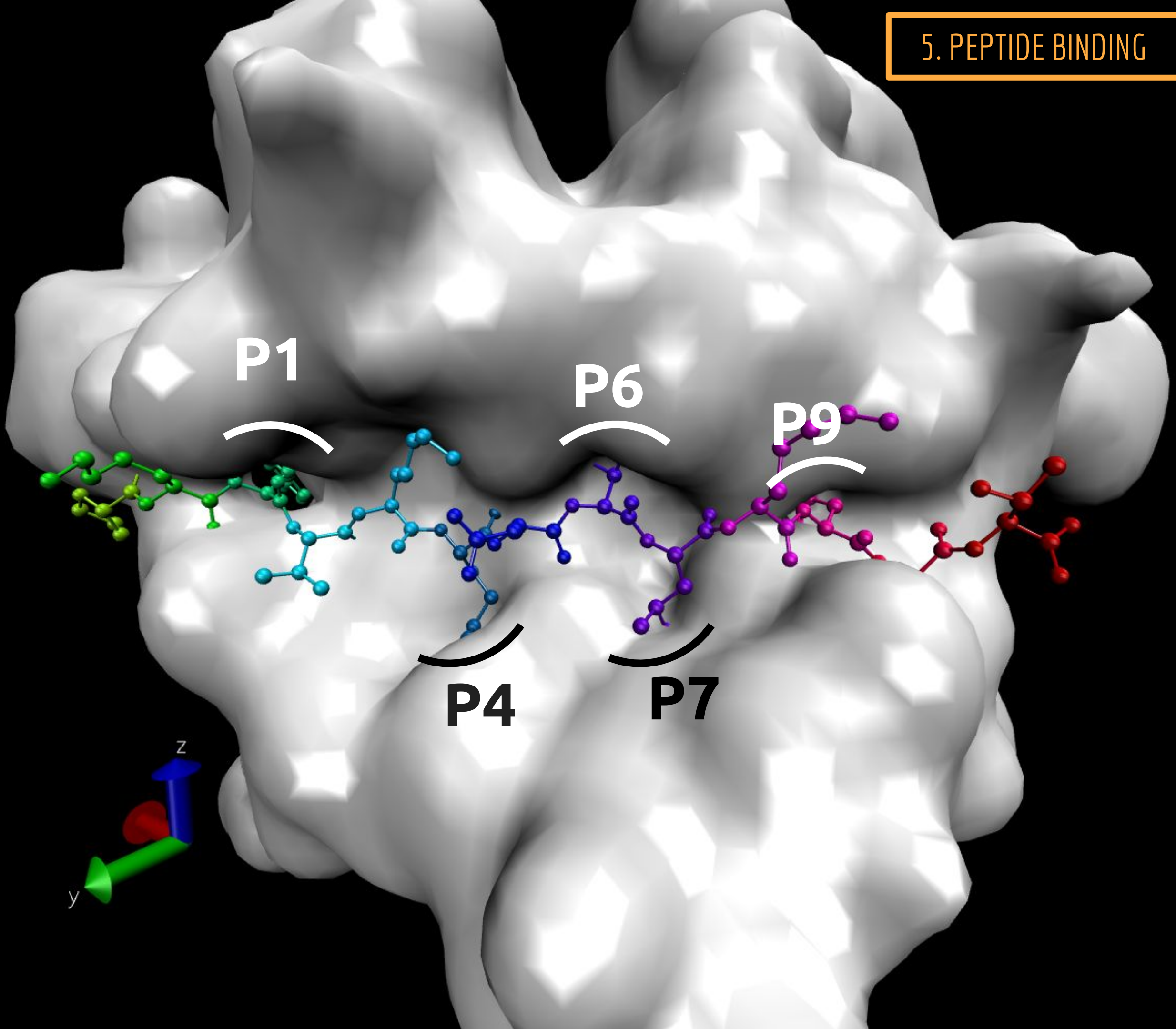
```
STAMP Structural Alignment of Multiple Proteins

Version 4.4 (May 2010)
 by Robert B. Russell & Geoffrey J. Barton
 Please cite PROTEINS, v14, 309-323, 1992

Running roughfit.

    Sc = STAMP score, RMS = RMS deviation, Align = alignment length
    Len1, Len2 = length of domain, Nfit = residues fitted
    Secs = no. equivalent sec. strucs. Eq = no. equivalent residues
    %I = seq. identity, %S = sec. str. identity
    P(m)   = P value (p=1/10) calculated after Murzin (1993), JMB, 230, 689-694
            (NC = P value not calculated - potential FP overflow)

     No.  Domain1          Domain2          Sc     RMS    Len1 Len2  Align NFit Eq. Secs.   %I    %S  P(m)
Pair   1  2xpg-groove      1dlh-groove      6.18    1.79    182  162   176  142 137    0 14.60 100.00 2.30e-02
Reading in matrix file peptids.mat...
Doing cluster analysis...
Cluster:  1 (2xpg-groove  & 1dlh-groove ) Sc  6.18 RMS    1.79 Len 176 nfit 142
 See file peptids.1 for the alignment and transformations
```

5. PEPTIDE BINDING: HLA II

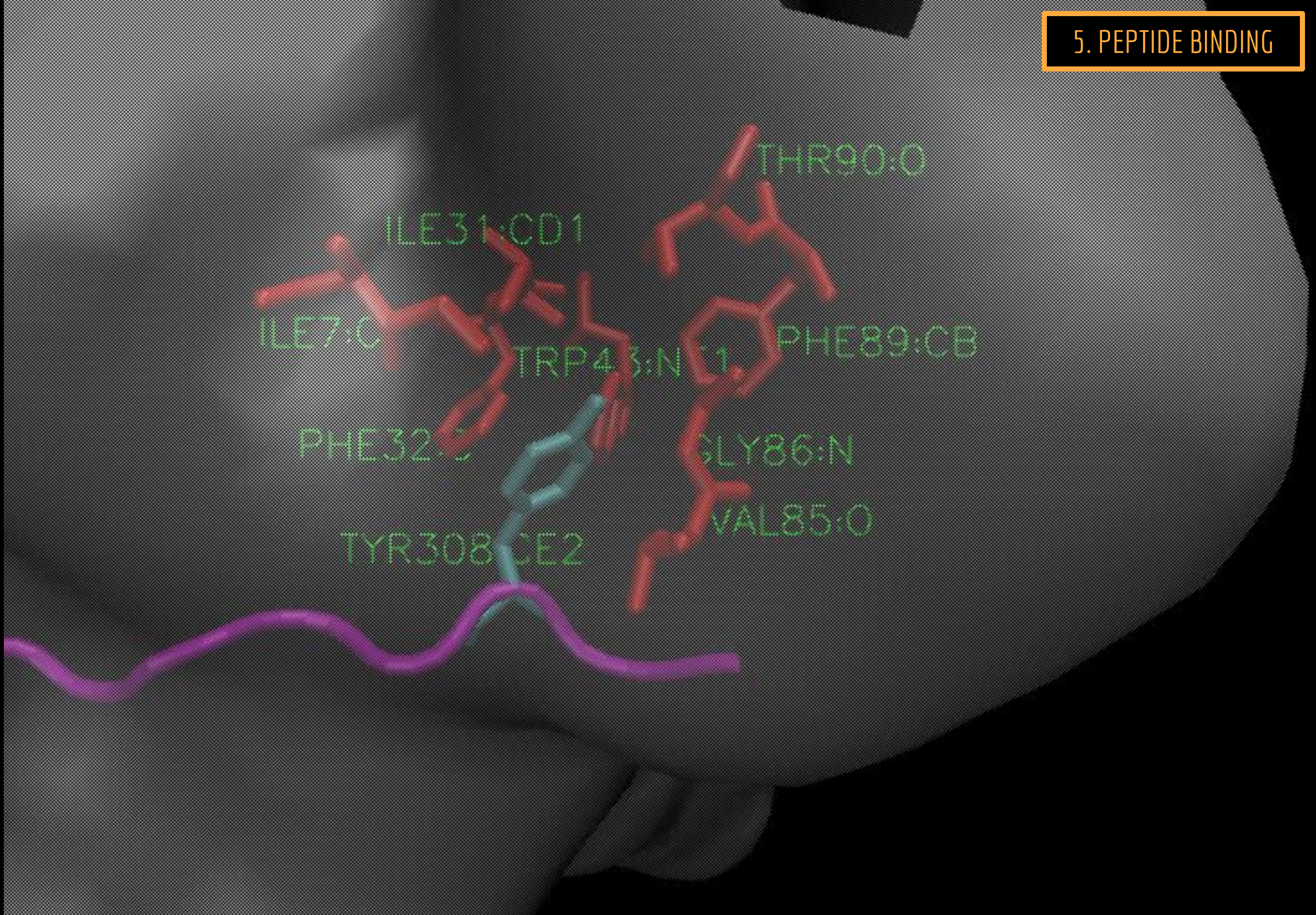
Hydrophobic pockets

HLA-DR1(DRA, DRB1*0101)
Pdb id: 1dlh

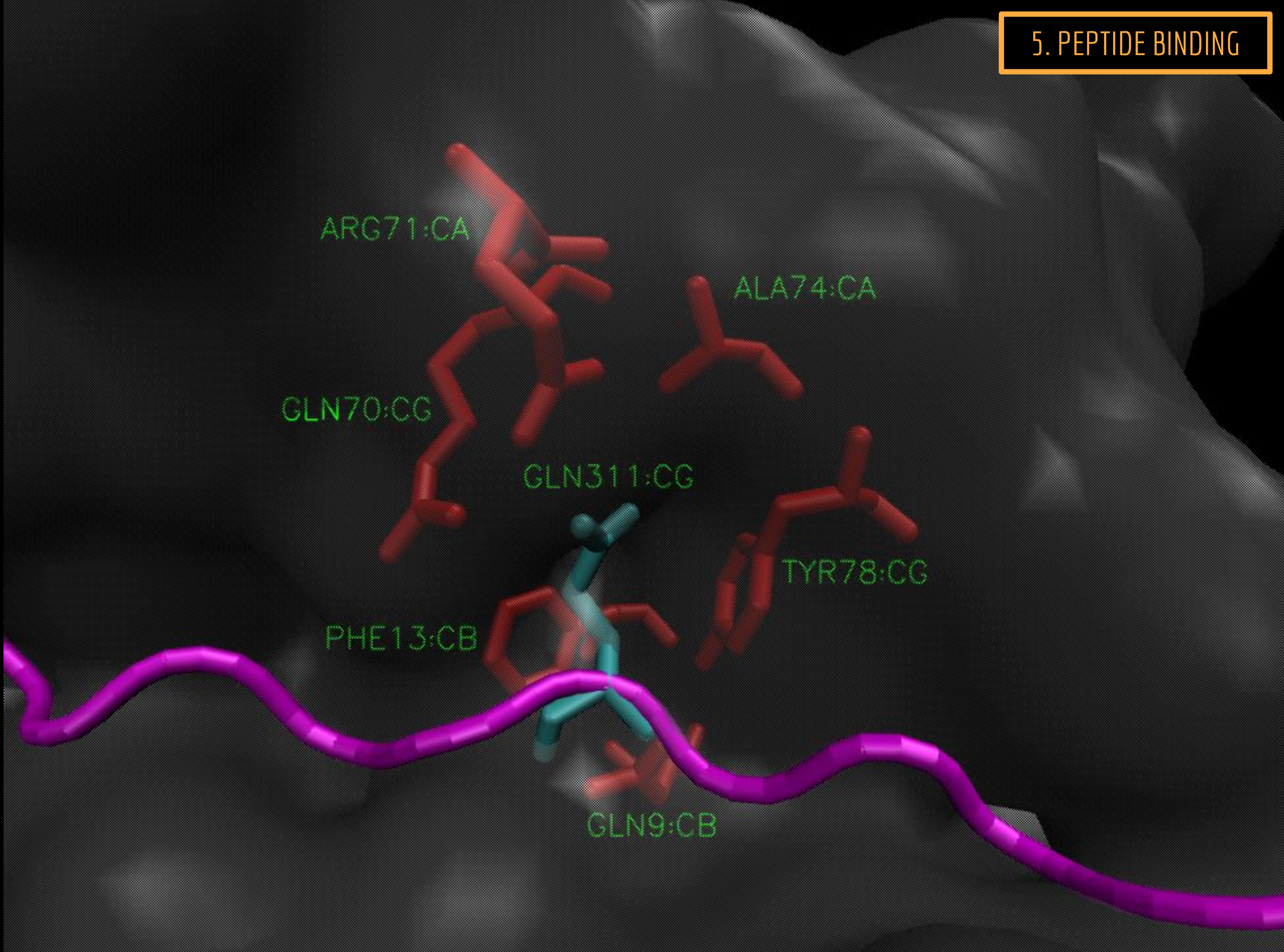
Influenza Virus
Haemagglutinin Peptide
(residues 306-318:
PKYVKQNTLKLAT)



POCKET 1

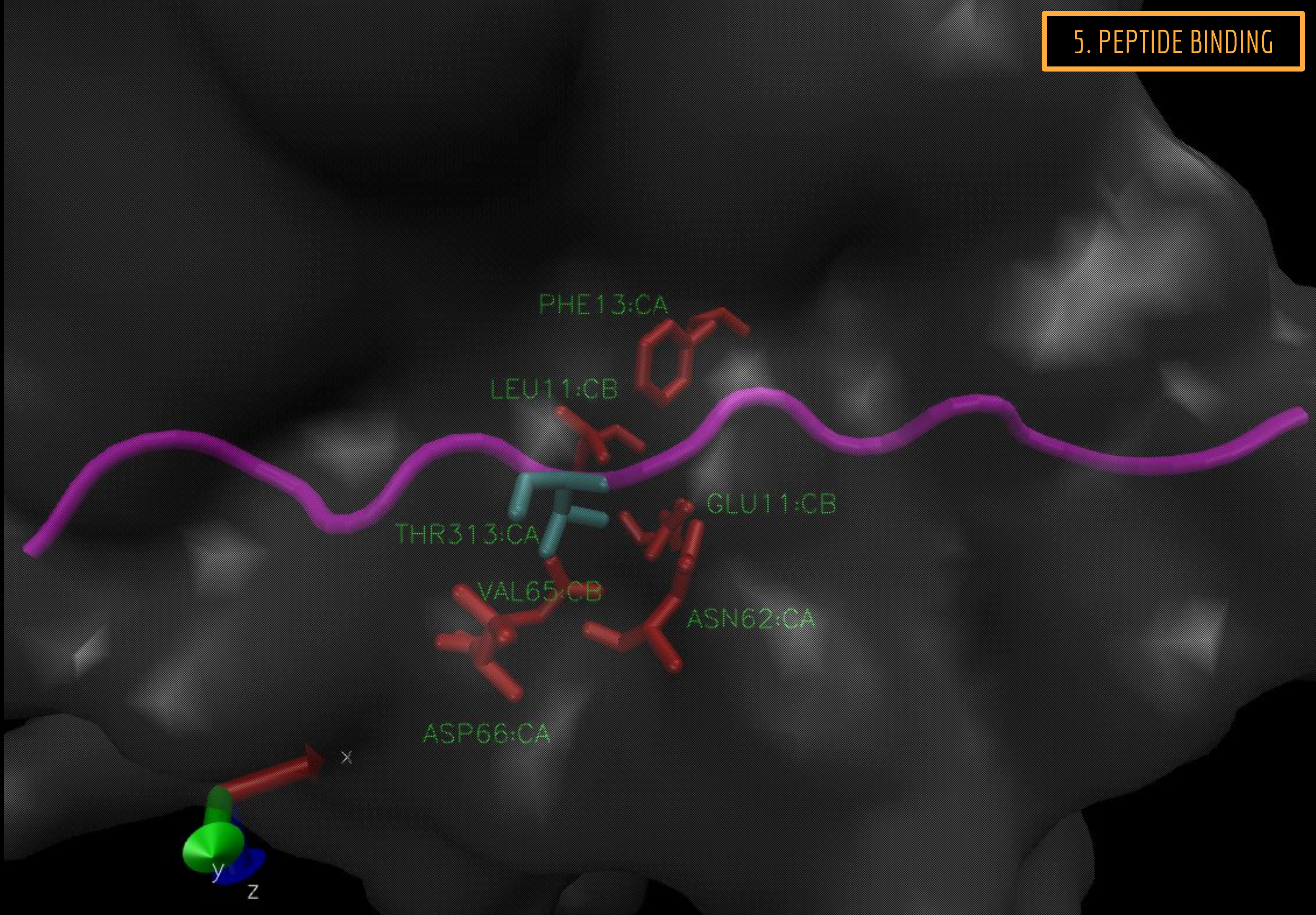

THR90:O
ILE31:CD1
ILE7:C
TRP43:NE1
PHE89:CB
PHE32:
GLY86:N
VAL85:O
TYR308:CE2

POCKET 4

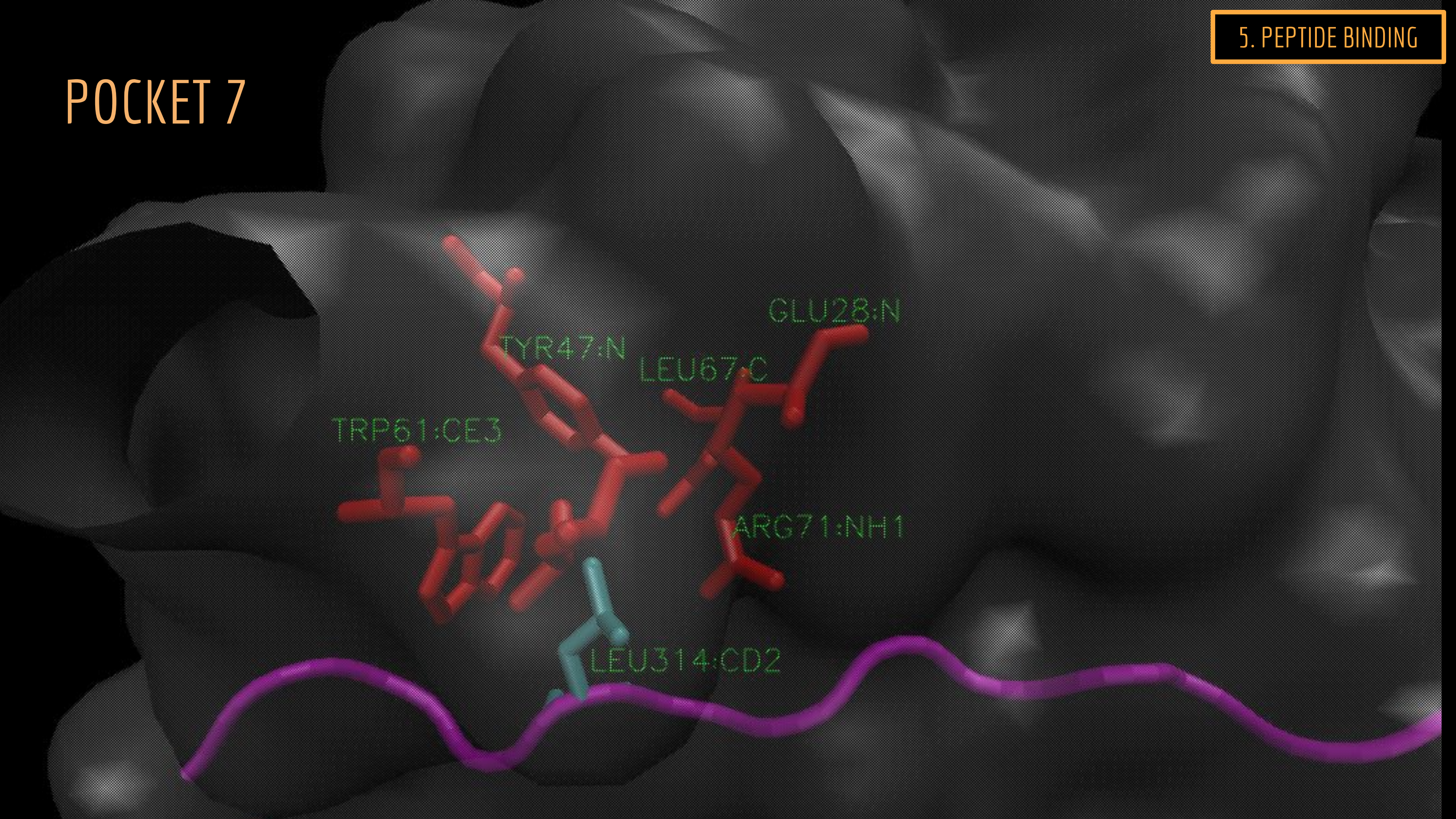


5. PEPTIDE BINDING

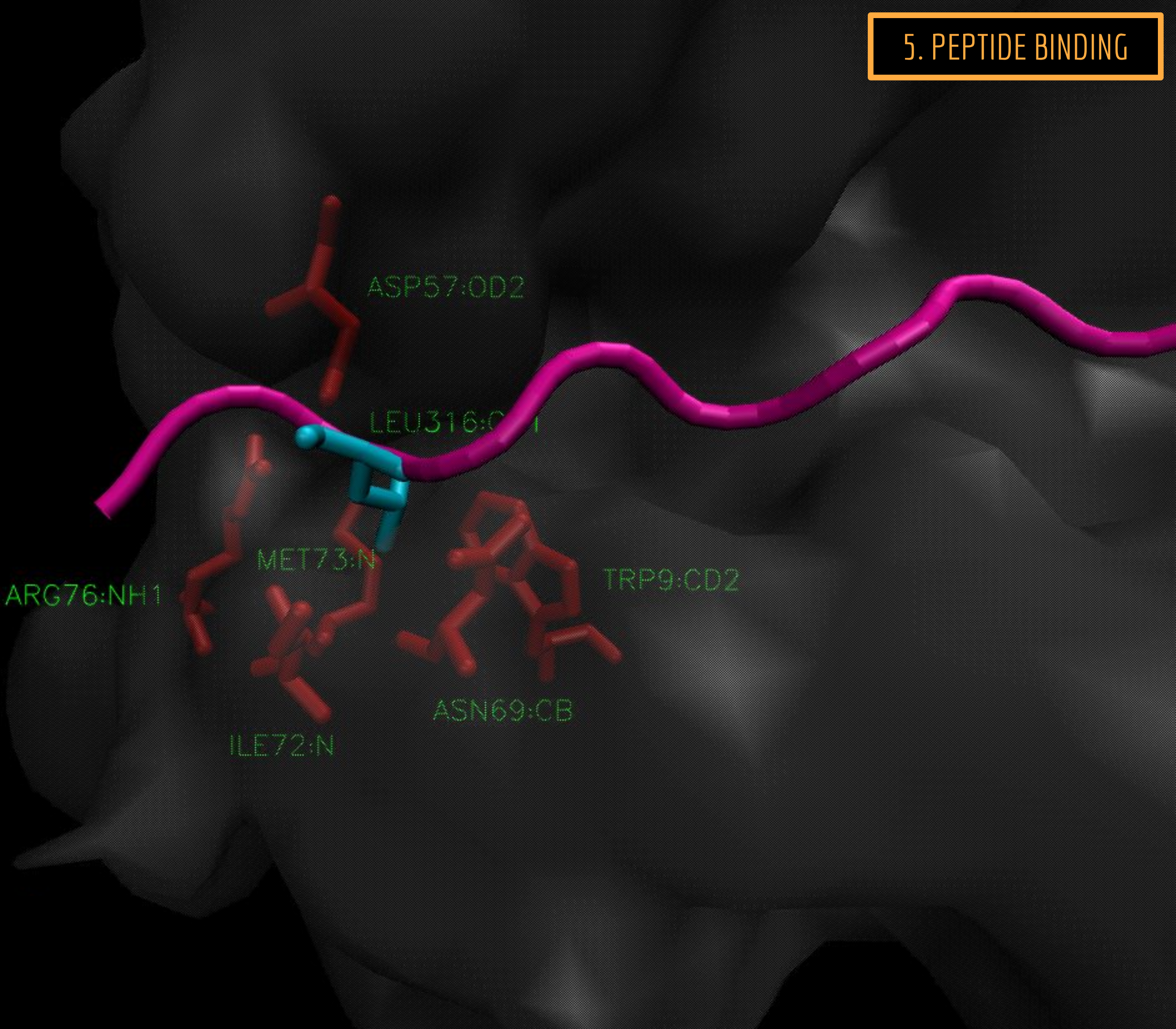
POCKET 6



POCKET 7



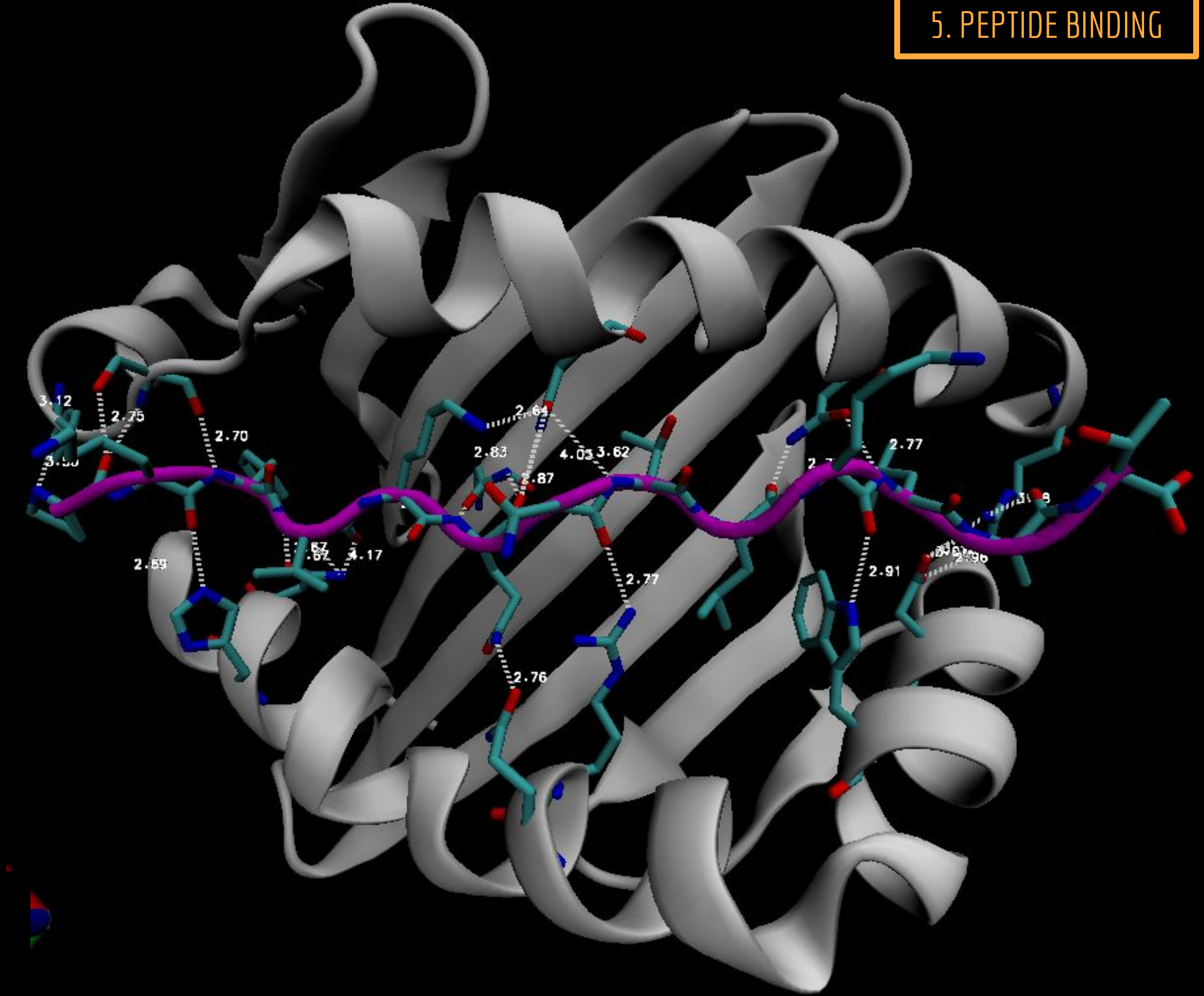
POCKET 9


ASP57:OD2
LEU316:C 1
MET73:N
ARG76:NH1
TRP9:CD2
ASN69:CB
ILE72:N

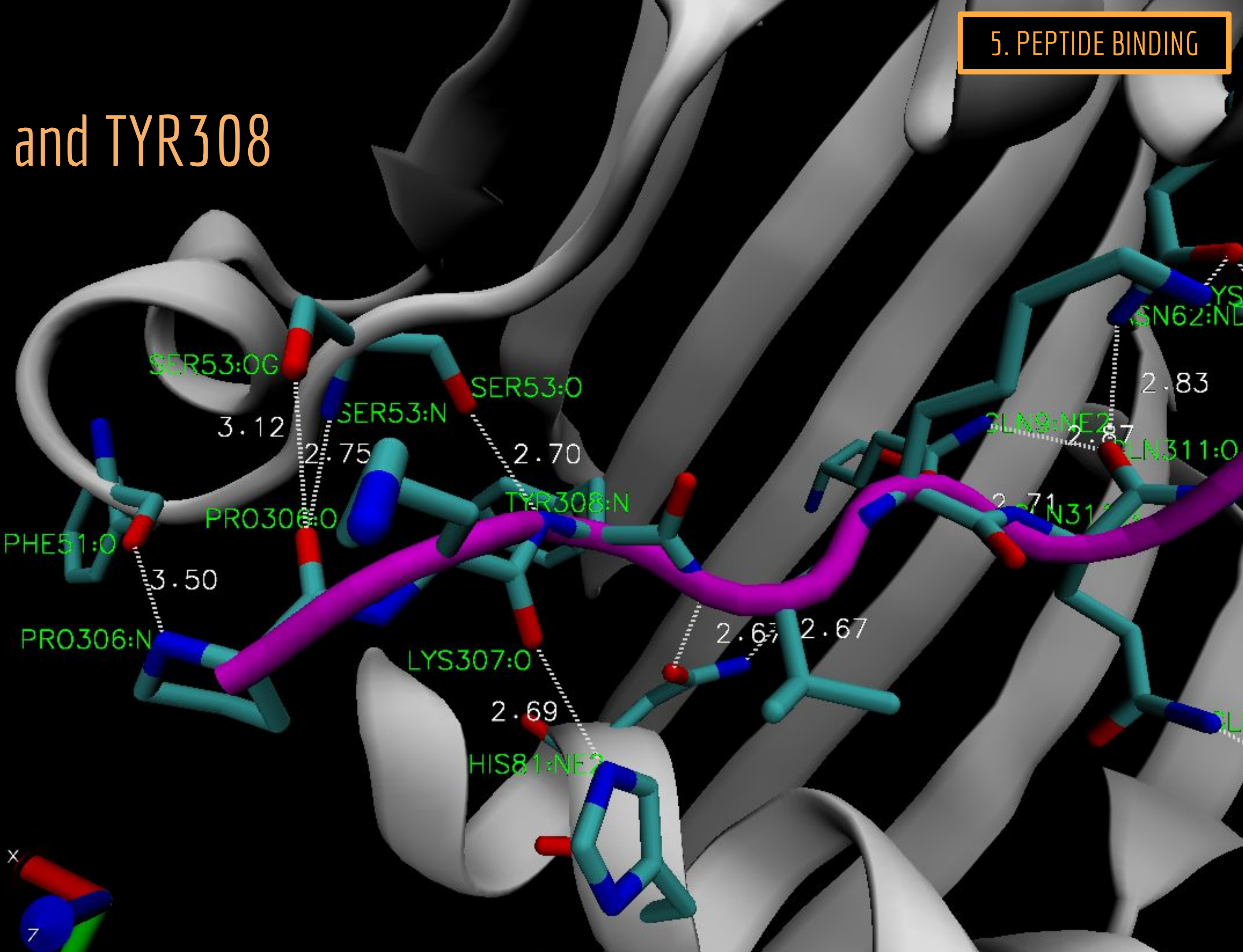
Hydrogen bonds

HLA-DR1(DRA, DRB1*0101)
Pdb id: 1dlh

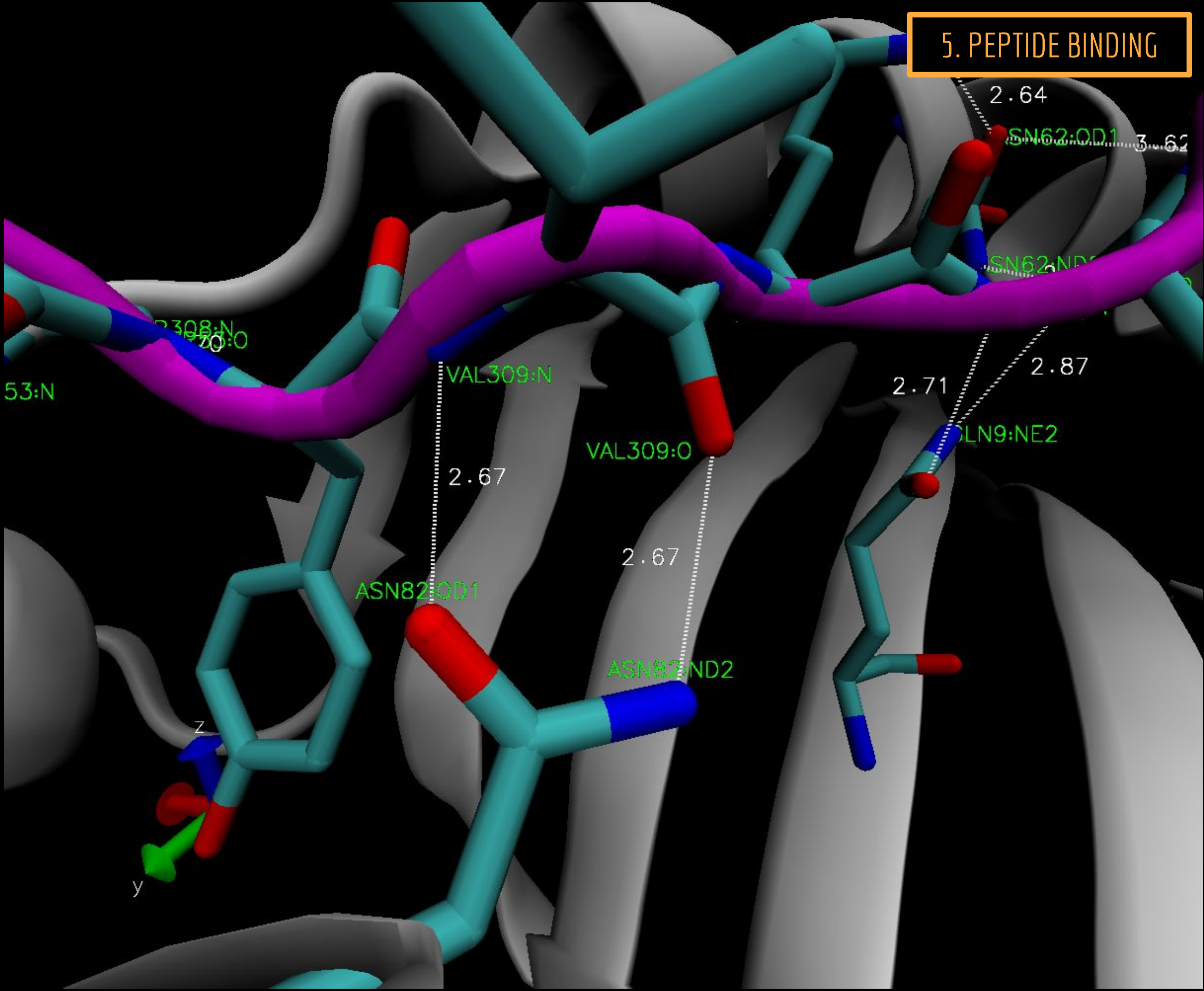
Influenza Virus
Haemagglutinin Peptide
(residues 306-318:
PKYVKQNTLKLAT)



PRO306, LYS307 and TYR308

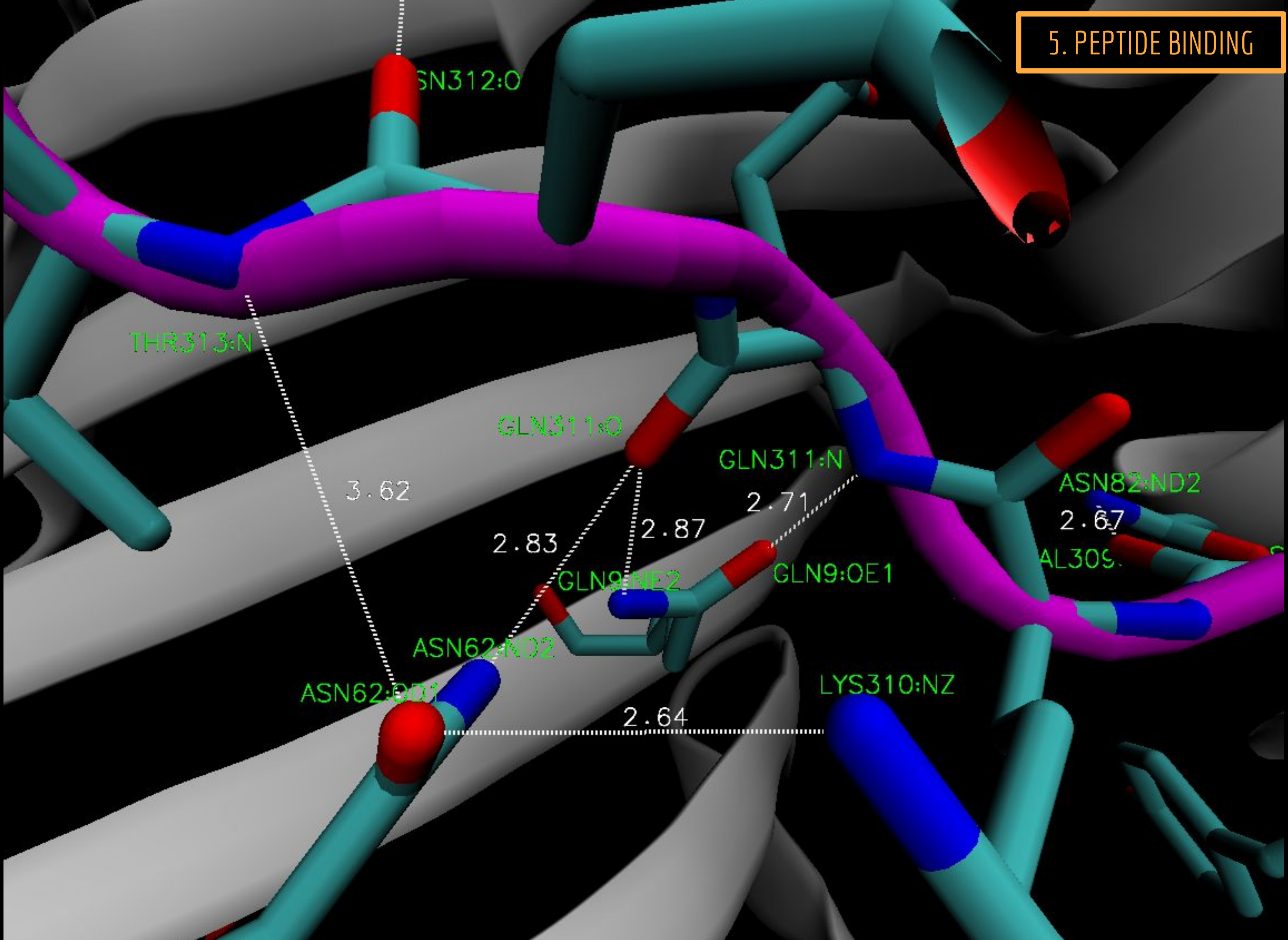


VAL309

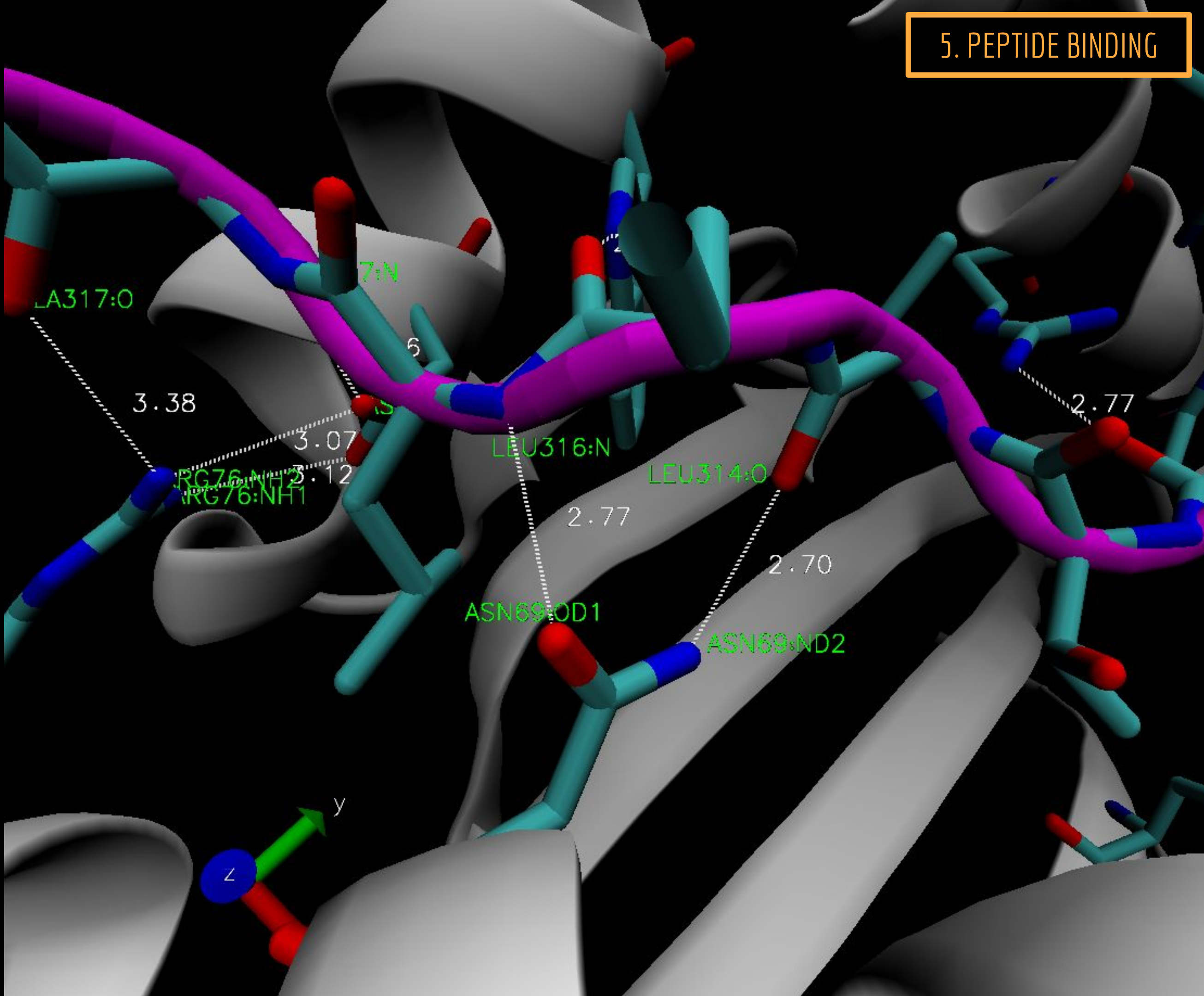

2.64
SN62:OD1
3.62
SN62:ND
308:N
70:O
53:N
VAL309:N
VAL309:O
2.71
2.87
LN9:NE2
2.67
2.67
ASN82:OD1
ASN82:ND2
z
y

5. PEPTIDE BINDING

GLN311, ASN312 and THR313

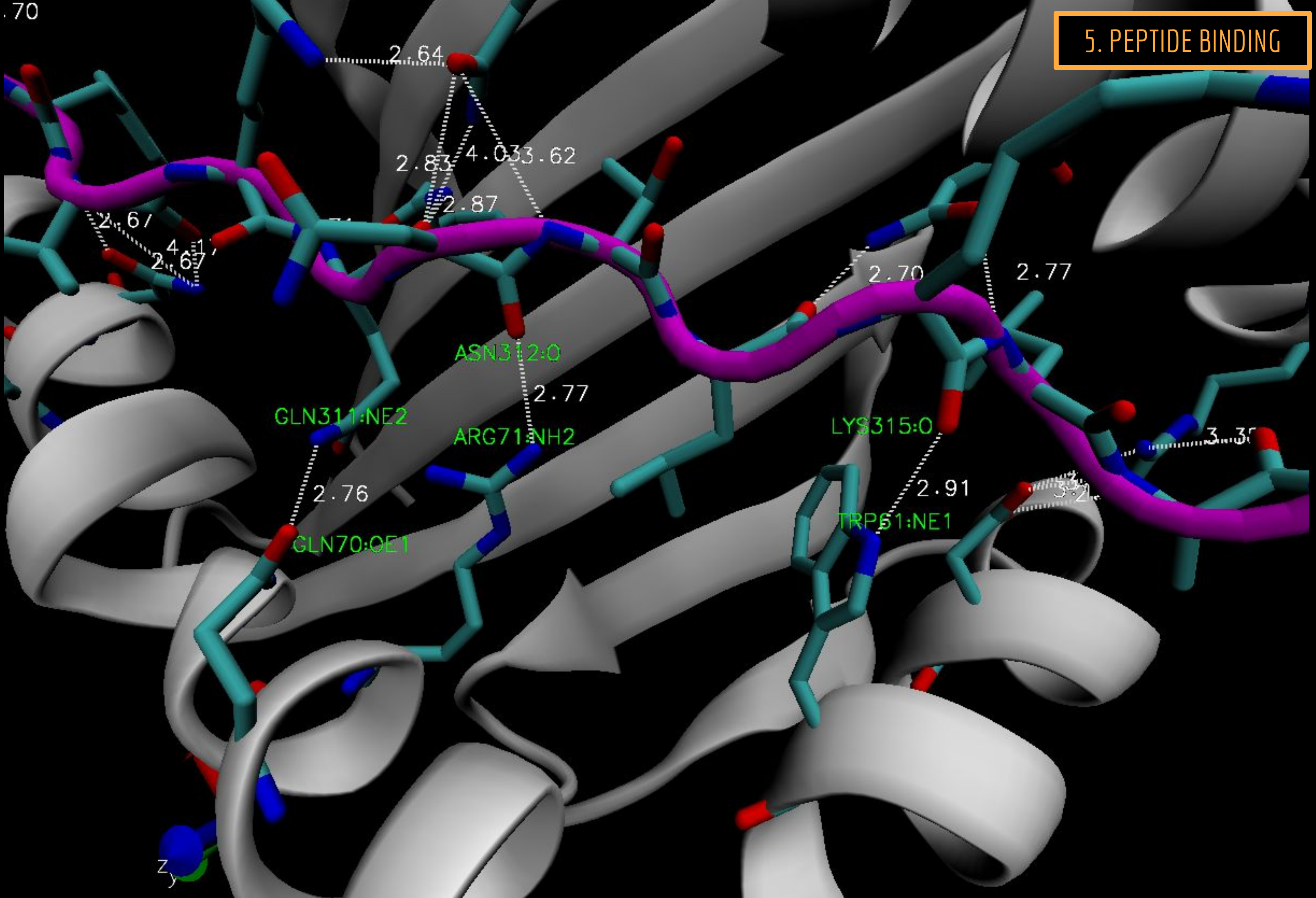


LEU314 and LEU316

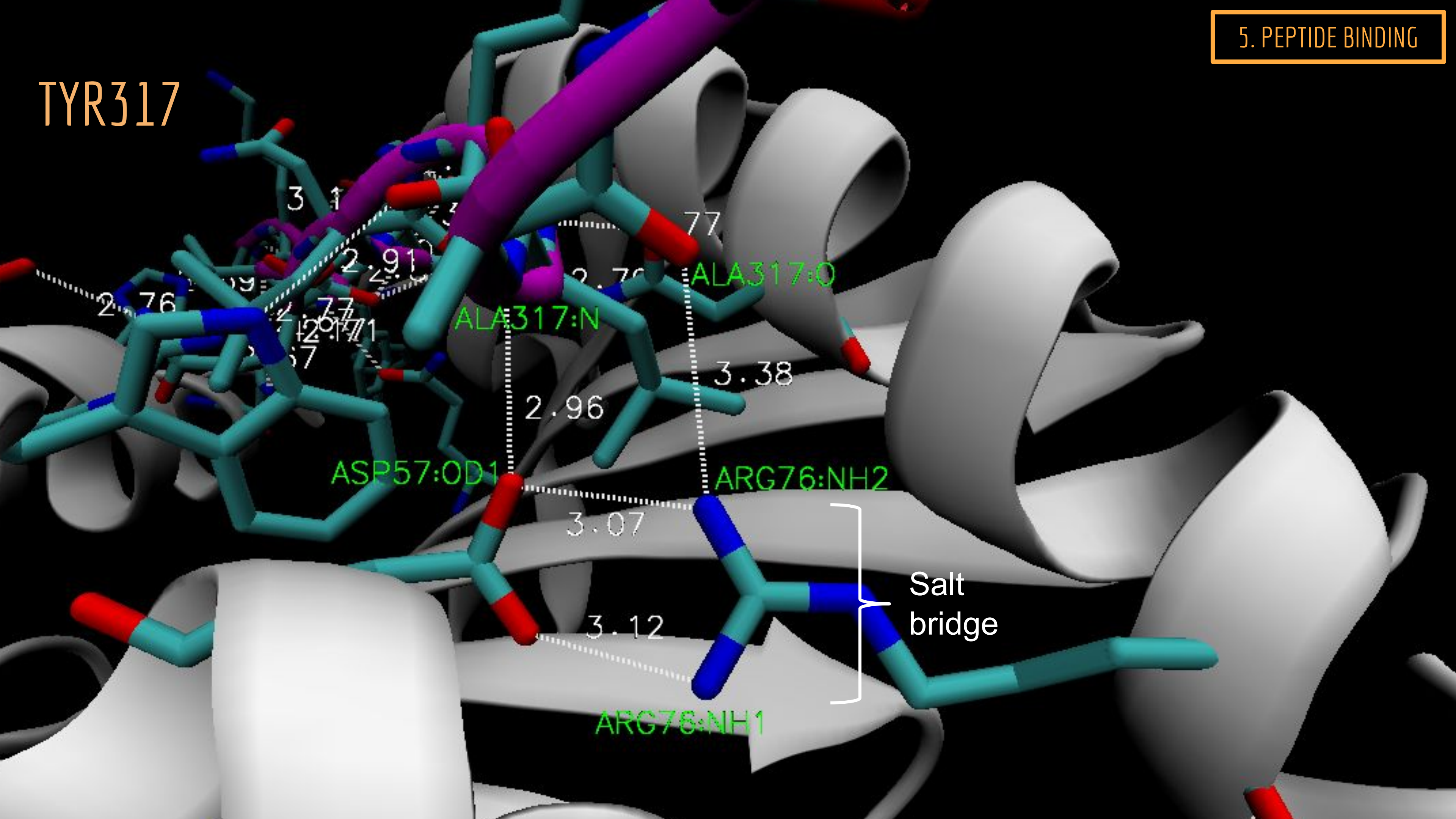


5. PEPTIDE BINDING

GLN311, ASN312 and LYS315



TYR317

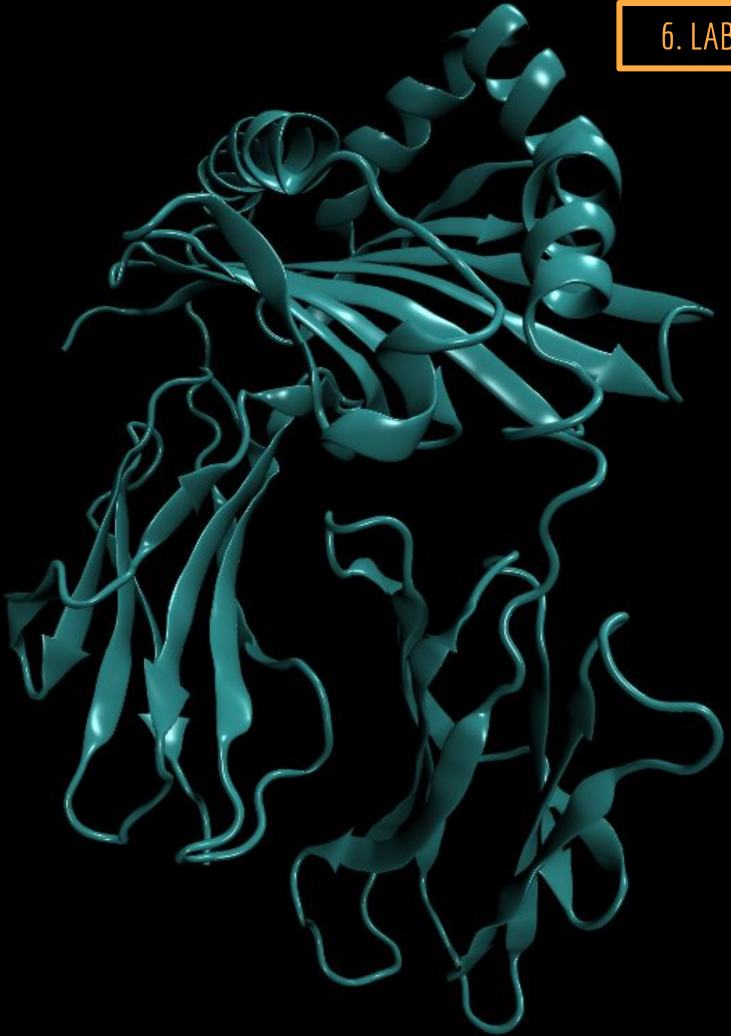


Salt bridge

6. LABILE REGIONS

HLA-II Structures Comparison

- Structural superimposicions:
  - 3 superimpositions
    - All classical HLA-II
    - Only DR
    - Only DQ
- Sequence alignment



HLA-II Superimposition

5 HLA-DR

5 HLA-DQ

1 HLA-DP

Sc 9.41

RMSD 0.95

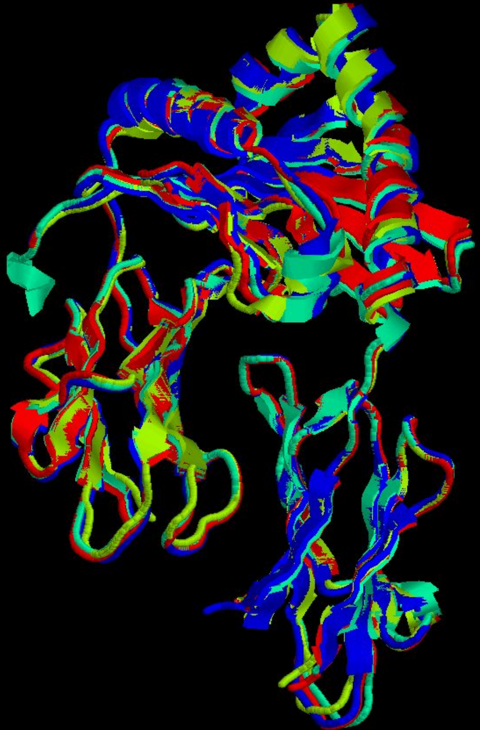
HLA-II Superimposition

HLA-DR

Sc 9.73

RMSD 0.56

HLA-DQ



Sc 9.70

RMSD 0.88

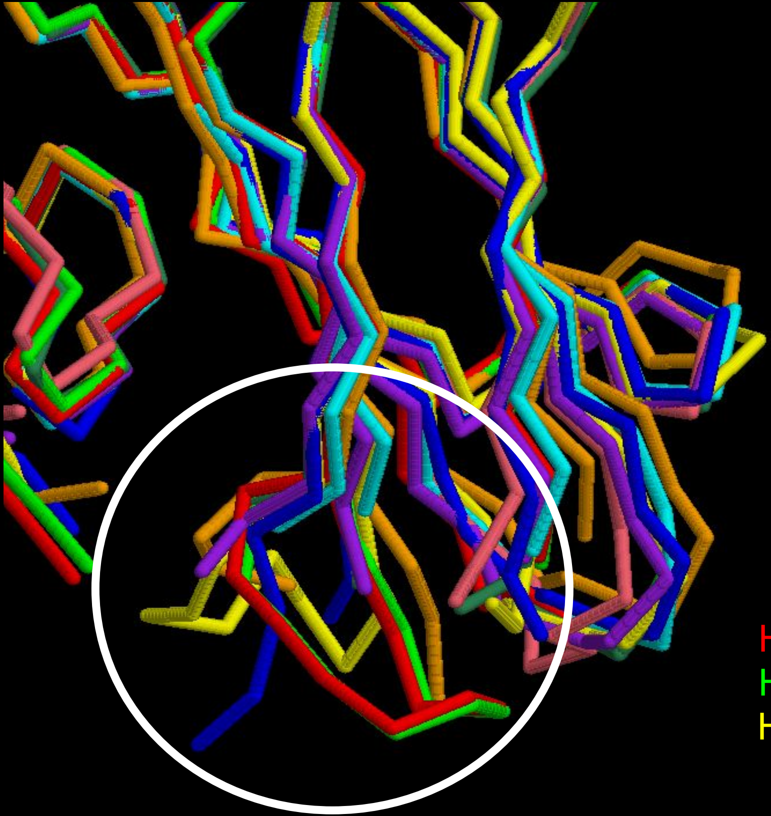
Variable regions

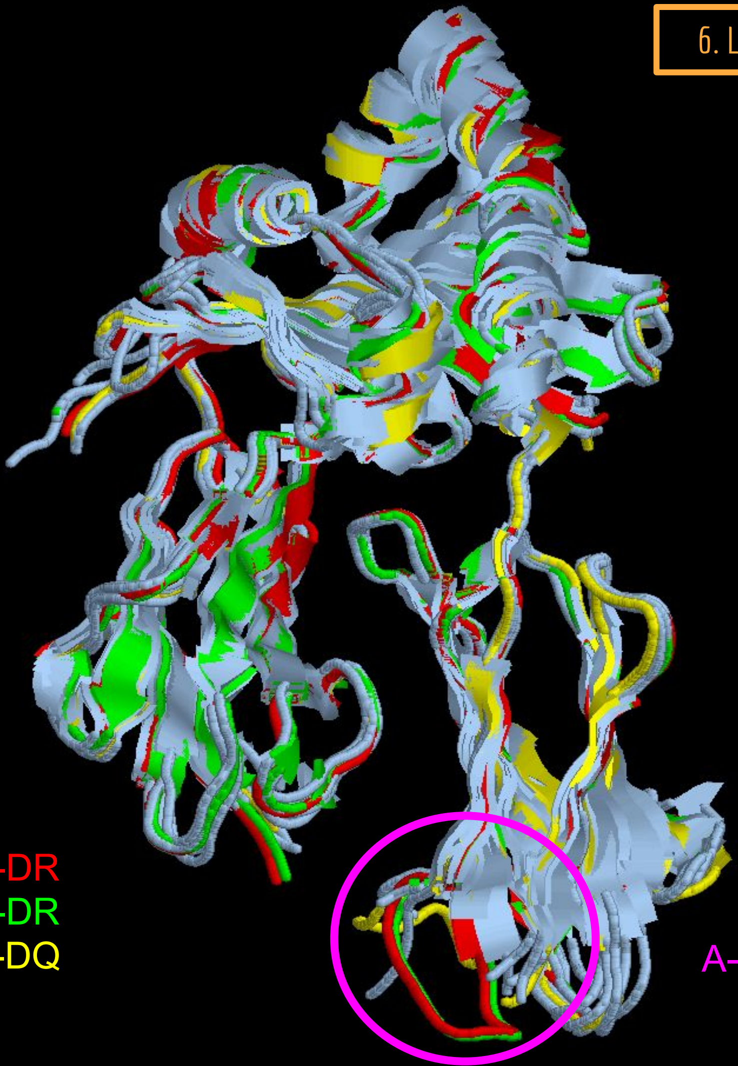
Helical kink on the β1 domain

3_{10} Helix on the α chain

β2 Ig-like domain

β2 Ig-like Domain



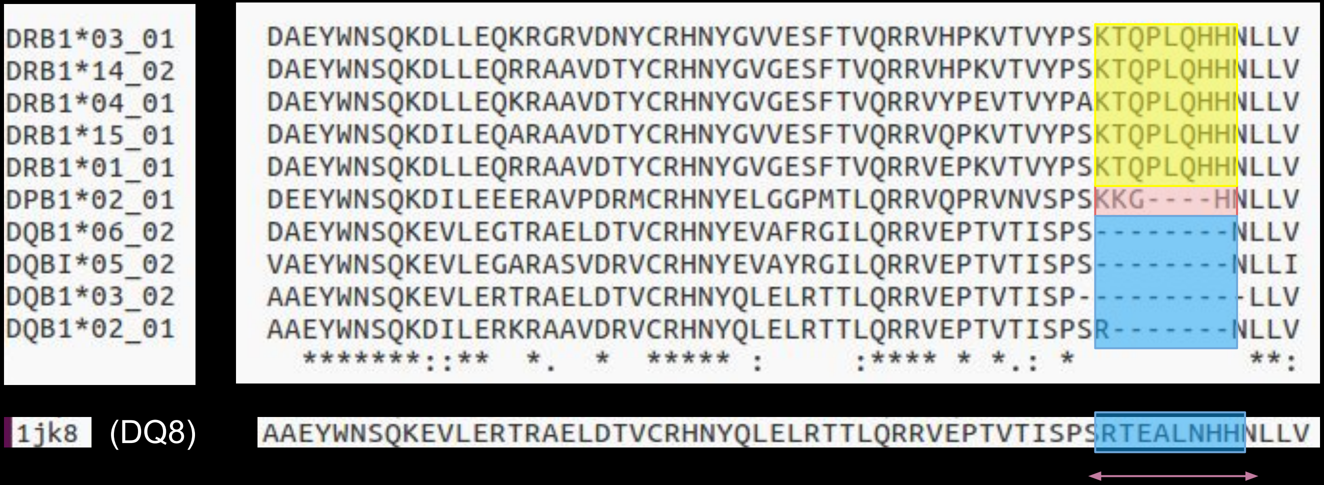


HLA-DR
HLA-DR
HLA-DQ

6. LABILE REGIONS

β2 Ig-like Domain

Sequence Alignment (A-B loop)

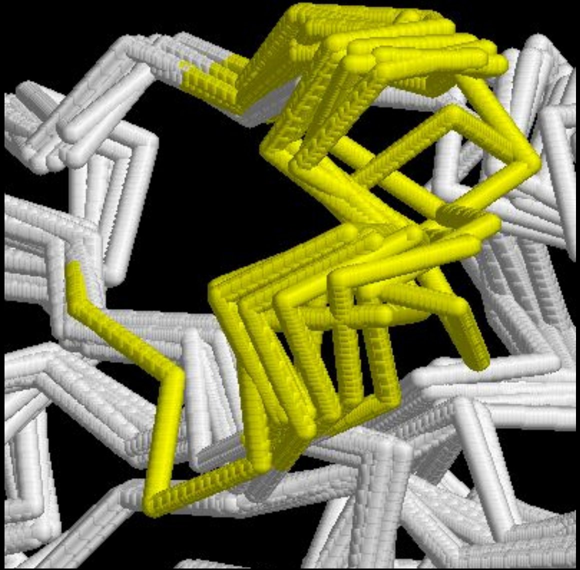


```
DRB1*03_01  DAEYWNSQKDLLEQKRGRVDNYCRHNYGVVESFTVQRRVHPKVTVYPSKTQPLQHHNLLV
DRB1*14_02  DAEYWNSQKDLLEQRRAAVDTYCRHNYGVGESFTVQRRVHPKVTVYPSKTQPLQHHNLLV
DRB1*04_01  DAEYWNSQKDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKTQPLQHHNLLV
DRB1*15_01  DAEYWNSQKDILEQARAAVDTYCRHNYGVVESFTVQRRVQPKVTVYPSKTQPLQHHNLLV
DRB1*01_01  DAEYWNSQKDLLEQRRAAVDTYCRHNYGVGESFTVQRRVEPKVTVYPSKTQPLQHHNLLV
DPB1*02_01  DEEYWNSQKDILEEERAVPDRMCRHNYELGGPMTLQRRVQPRVNVSPSKKG----HNLLV
DQB1*06_02  DAEYWNSQKEVLEGTRAELDTVCRHNYEVAFRGILQRRVEPTVTISPS--------NLLV
DQBI*05_02  VAEYWNSQKEVLEGARASVDRVCRHNYEVAYRGILQRRVEPTVTISPS--------NLLI
DQB1*03_02  AAEYWNSQKEVLERTRAELDTVCRHNYQLELRTTLQRRVEPTVTISP----------LLV
DQB1*02_01  AAEYWNSQKDILERKRAAVDRVCRHNYQLELRTTLQRRVEPTVTISPSR-------NLLV
              *******::**  *.  *  ***** :     :**** * *.: *          **:

1jk8 (DQ8)   AAEYWNSQKEVLERTRAELDTVCRHNYQLELRTTLQRRVEPTVTISPSRTEALNHHNLLV
```

A-B loop

3_{10} Helix

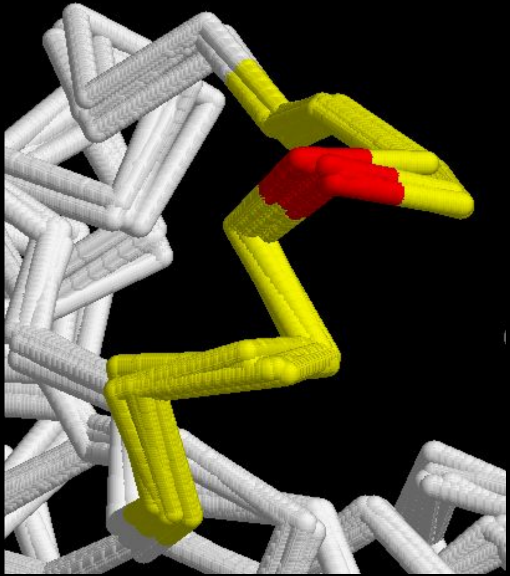
- From α45 to α51
- 3 residues/turn
- Hydrogen bonds between i and i+3 residues



3_{10} Helix

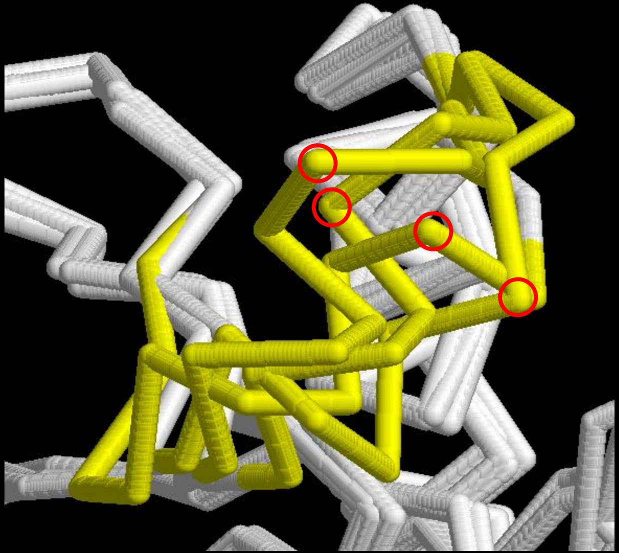
HLA-II DQ proteins show a higher desviation at the 3_{10} helix

HLA-DR



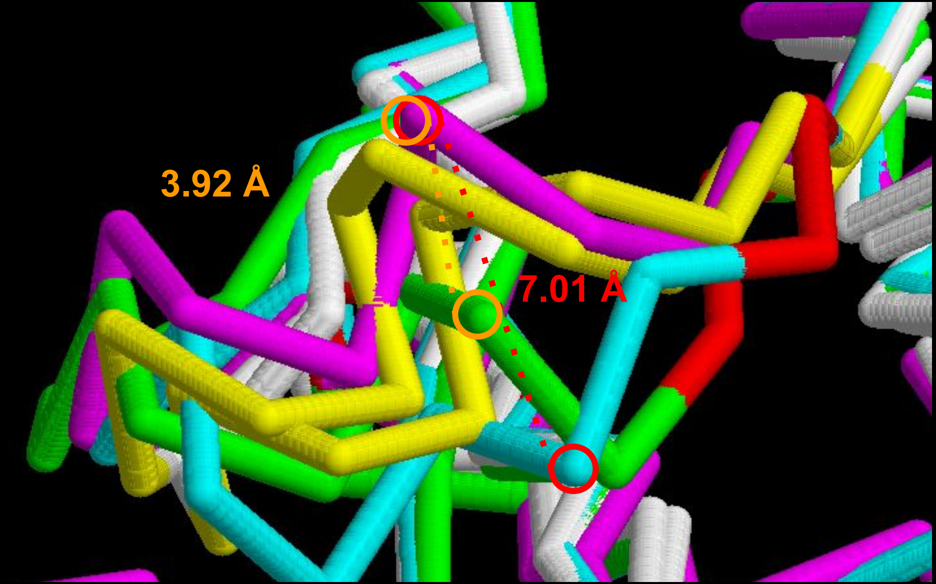
residue α50

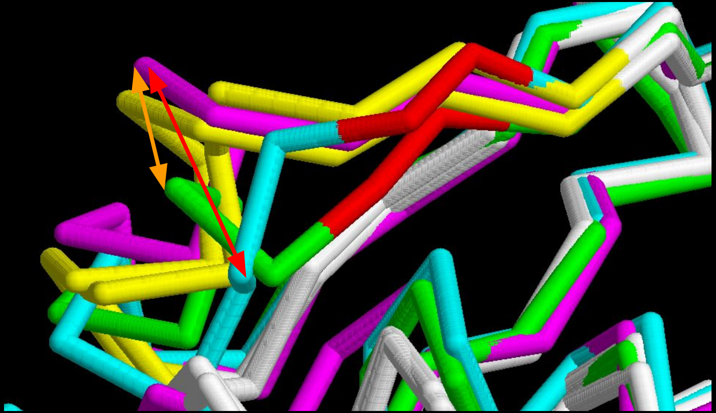
HLA-DQ



3_{10} Helix

Glycines on positions α52 and α53 increase structural lability of the 3_{10} helix





Glycines
1DLH
3PL6
1UVQ

3_{10} Helix

Sequence alignment

```
DRB1*03_01   -----HVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQG
DRB1*14_02   ---EEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQG
DRB1*04_01   --KEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQG
DRB1*15_01   --KEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQG
DRB1*01_01   ---EEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQG
DPB1*02_01   -IKADHVSTY-AAFVQTHRPTGEFMFEFDEDEMFYVDLDKKETVWHLEEFGQAFSFEAQG
DQB1*06_02   DIVADHVASCGVNLYQFYGPSGQYTHEFDGDEQFYVDLERKETAWRWPEFSKFGGFDPQG
DQBI*05_02   DIVADHVASCGVNLYQFYGPSGQYTHEFDGDEQFYVDLERKETAWRWPEFSKFGGFDPQG
DQB1*03_02   DIVADHVASYGVNLYQSYGPSGQYSHEFDGDEEFYVDLERKETVWQLPLFRRFRRFDPQF
DQB1*02_01   --VADHVASYGVNLYQSYGPSGQYTHEFDGDEQFYVDLGRKETVWCLPVLRQFR-FDPQF
                  **    . :      :*:: .:** ** *:**: :***.*    : :   *:.*
```

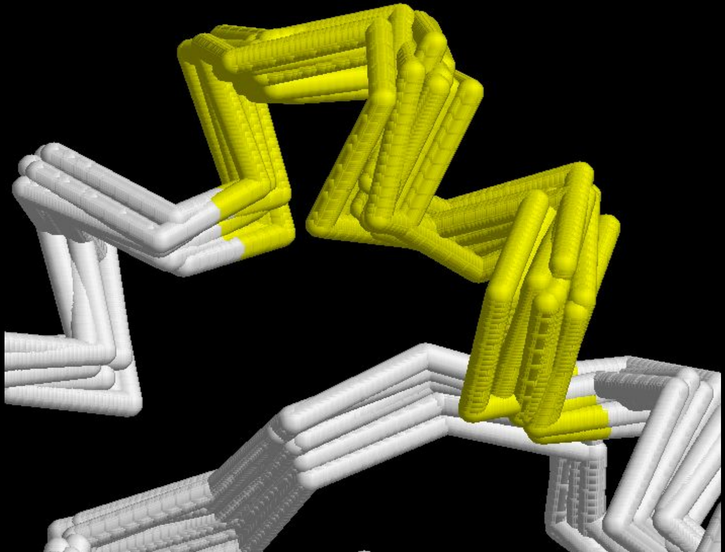
1UVQ

3PL6

Glycines on positions α52 and α53 increase affinity with HLA-DM proteins

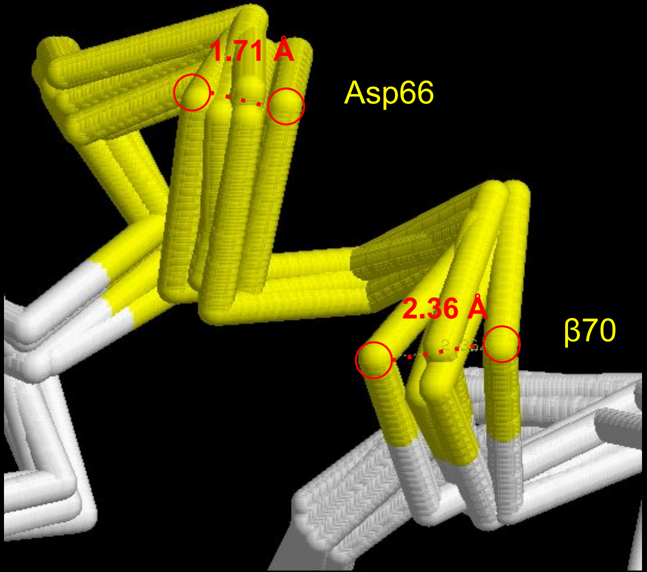
β1-Helical Kink

- From β62 to β70
- Involved in peptide-induced conformational changes
- Interacts with TCR

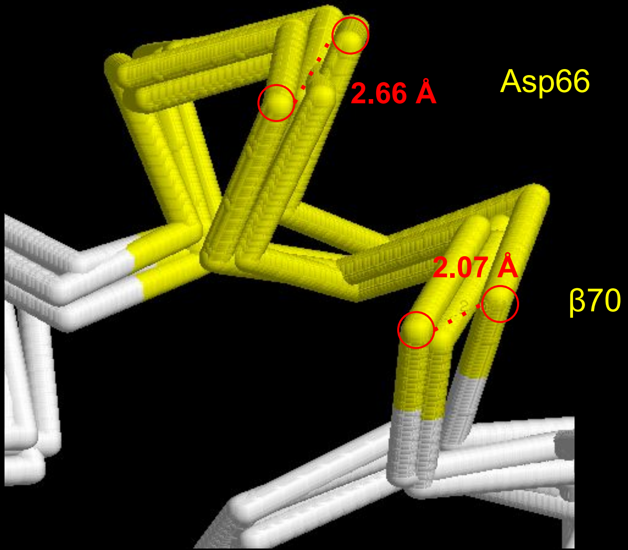


β1-Helical Kink

HLA-DR



HLA-DQ



β1-Helical Kink

Sequence alignment

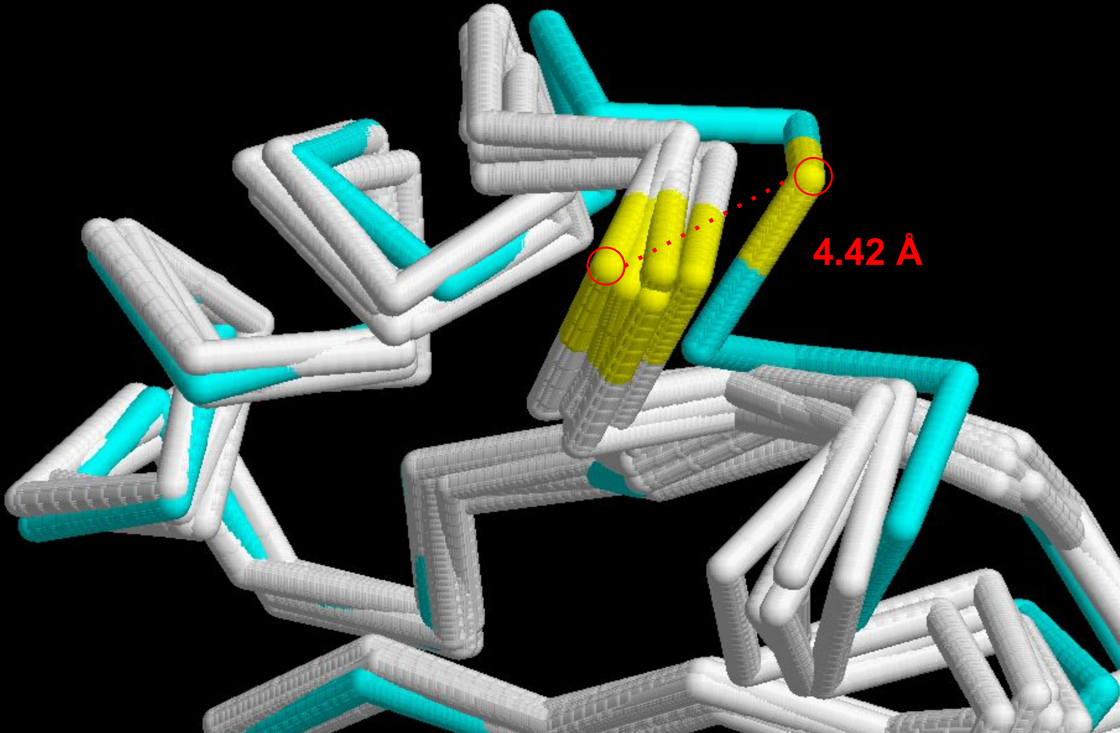
```
DRB1*03_01    DAEYWNSQKDLLEQKRGRVDNYCRHNYGVVESFTVQRRVHPKVTVYPSKTQPLQHHNLLV
DRB1*14_02    DAEYWNSQKDLLEQRRAAVDTYCRHNYGVGESFTVQRRVHPKVTVYPSKTQPLQHHNLLV
DRB1*04_01    DAEYWNSQKDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKTQPLQHHNLLV
DRB1*15_01    DAEYWNSQKDILEQARAAVDTYCRHNYGVVESFTVQRRVQPKVTVYPSKTQPLQHHNLLV
DRB1*01_01    DAEYWNSQKDLLEQRRAAVDTYCRHNYGVGESFTVQRRVEPKVTVYPSKTQPLQHHNLLV
DPB1*02_01    DEEYWNSQKDILEEERAVPDRMCRHNYELGGPMTLQRRVQPRVNVSPSKKG----HNLLV
DQB1*06_02    DAEYWNSQKEVLEGTRAELDTVCRHNYEVAFRGILQRRVEPTVTISPS--------NLLV
DQBI*05_02    VAEYWNSQKEVLEGARASVDRVCRHNYEVAYRGILQRRVEPTVTISPS--------NLLI
DQB1*03_02    AAEYWNSQKEVLERTRAELDTVCRHNYQLELRTTLQRRVEPTVTISP----------LLV
DQB1*02_01    AAEYWNSQKDILERKRAAVDRVCRHNYQLELRTTLQRRVEPTVTISPSR-------NLLV
                *******::**  *.  *  ***** :     :**** * *.: *          **:
```

β1-Helical Kink

- The β1-helical kink changes it’s conformation in response to interactions with TCR

- There’s a higher desviation at Asp66

1ZGL: Bound to TCR



7. CLASSICAL HLA II

VS.

NON-CLASSICAL HLA II

Classical and Non-classical HLA II

Classical HLA II

- **DR**
- **DP**
- **DQ**

- Highly polymorphic
- Peptide-binding

Non-Classical HLA II

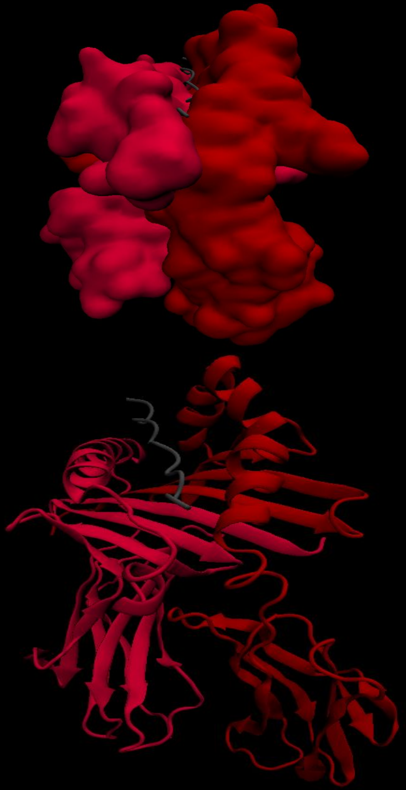
- **DM** → regulation of peptide exhange in HLA II molecules
- **DO** → inhibit DM-mediated catalysis of peptide exchange

- Non- polymorphic
- Non-peptide binding

Structural comparison

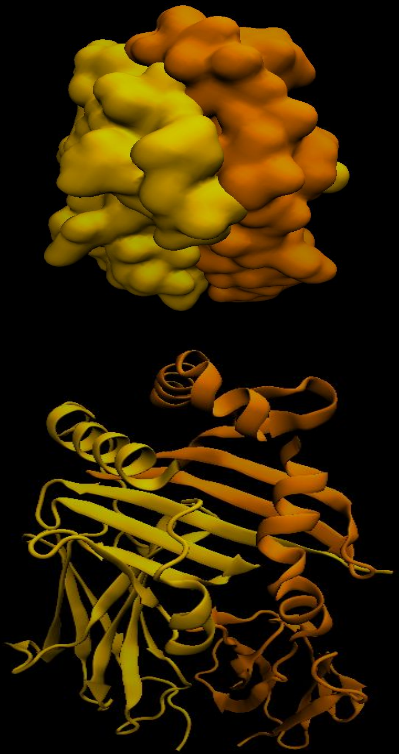
Classical

HLA- DR1

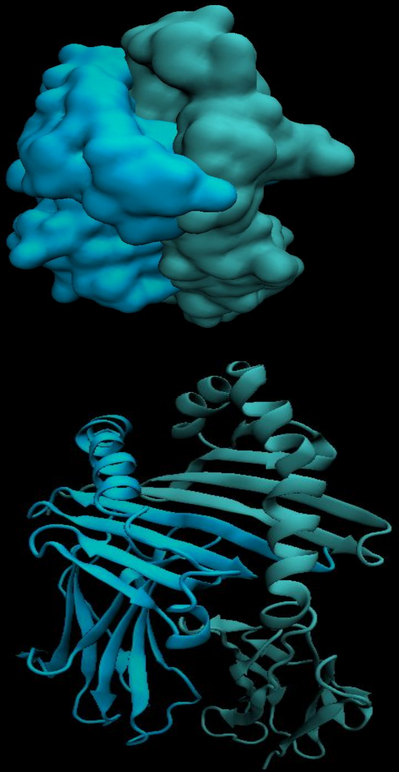


Non-classical

HLA- DM



HLA- DO

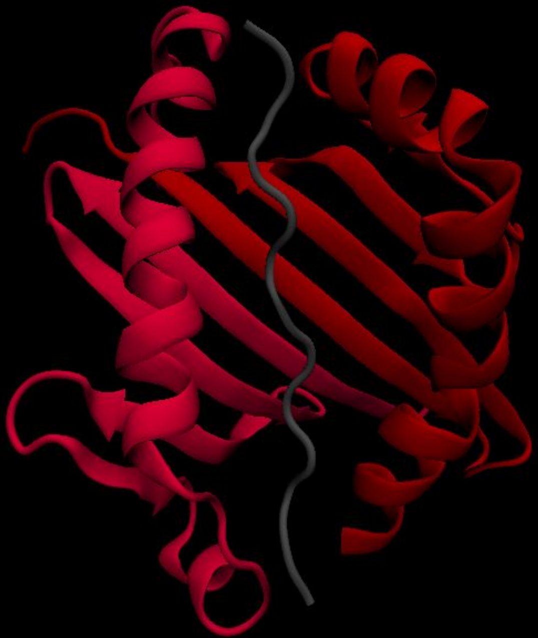


Binding groove comparison

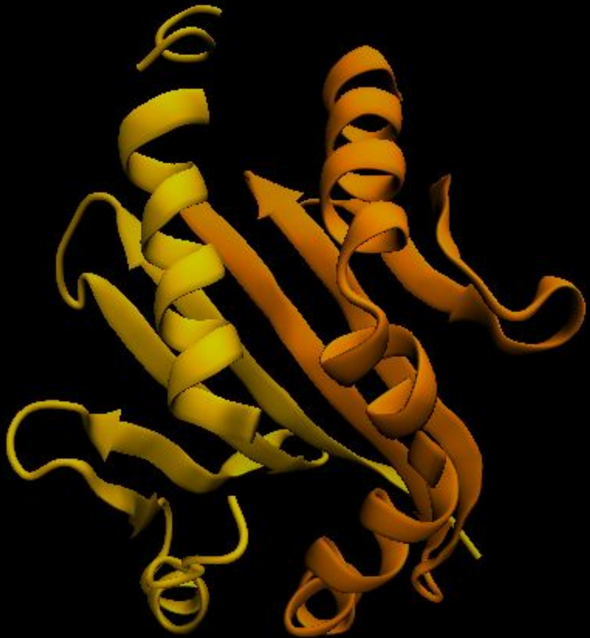
Non-classical

Classical

HLA- DR1



HLA- DM



HLA- DO

Superimposition

Sc 8.41 RMSD 1.73 → Generally sharing same structure

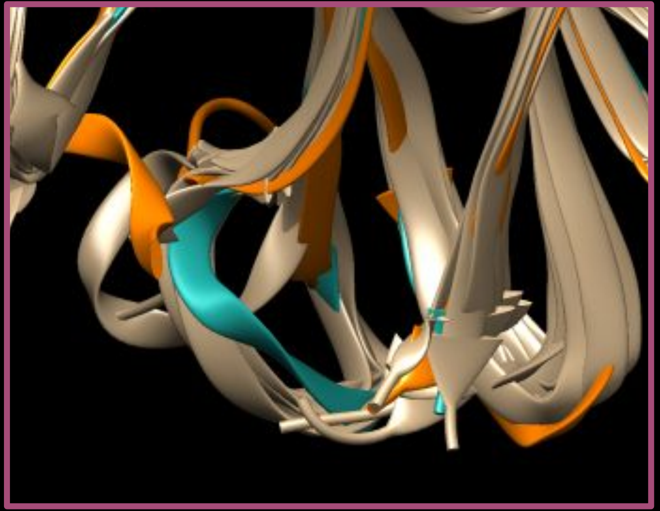
10 Classical HLA II : 4 HLA-DQ +

5 HLA-DR + 1 HLA-DP

2 Non-classical HLA II : 1 HLA -DM +

1 HLA - DO

β2 Ig-like Domain



10 Classical HLA II : 4 HLA-DQ +

5 HLA-DR + 1 HLA-DP

2 Non-classical HLA II : 1 HLA -DM

+ 1 HLA - DO

β2 Ig-like Domain

CLASICAL

DQ

DR

DP

NON-CLASICAL

DO

DM

```
1uvq            DAEYWNSQKEVLEGTRAELDTVCRHNYEVAFRGILQRRVEPTVTISPS--------NLLV
3pl6            VAEYWNSQKEVLEGARASVDRVCRHNYEVAYRGILQRRVEPTVTISPS--------NLLI
2nna            AAEYWNSQKEVLERTRAELDTVCRHNYQLELRTTLQRRVEPTVTISP----------LLV
1s9v            AAEYWNSQKDILERKRAAVDRVCRHNYQLELRTTLQRRVEPTVTISPSR-------NLLV
1a6a            DAEYWNSQKDLLEQKRGRVDNYCRHNYGVVESFTVQRRVHPKVTVYPSKTQPLQHHNLLV
6atf            DAEYWNSQKDLLEQRRAAVDTYCRHNYGVGESFTVQRRVHPKVTVYPSKTQPLQHHNLLV
5jlz            DAEYWNSQKDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKTQPLQHHNLLV
1bx2            DAEYWNSQKDILEQARAAVDTYCRHNYGVVESFTVQRRVQPKVTVYPSKTQPLQHHNLLV
1dlh            DAEYWNSQKDLLEQRRAAVDTYCRHNYGVGESFTVQRRVEPKVTVYPSKTQPLQHHNLLV
3lqz            DEEYWNSQKDILEEERAVPDRMCRHNYELGGPMTLQRRVQPRVNVSPSKKG----HNLLV
4i0p            DAEQWNSRLDLLERSRQAVDGVCRHNYRLGAPFTVGRKVQPEVTVYPERTPLLHQHNLLH
1hdm            LSQHLNQKDTLMQRLNGLQN--CATHTQPFWGSLTNRTRPPSVQVAKTTPFNTREPVMLA
                  :  *.:  :::  .   :  *  :          *   * * :            :*
```

β2 Ig-like Domain sequence is not conserved in DM either in DO

β2 Ig-like Domain sequence has highly heterogeneity between different subtypes of HLA

β1-Helical Kink

10 Classical HLA II : 4 HLA-DQ +
5 HLA-DR + 1 HLA-DP
2 Non-classical HLA II : 1 HLA -DM
+ 1 HLA - DO

β1-Helical Kink

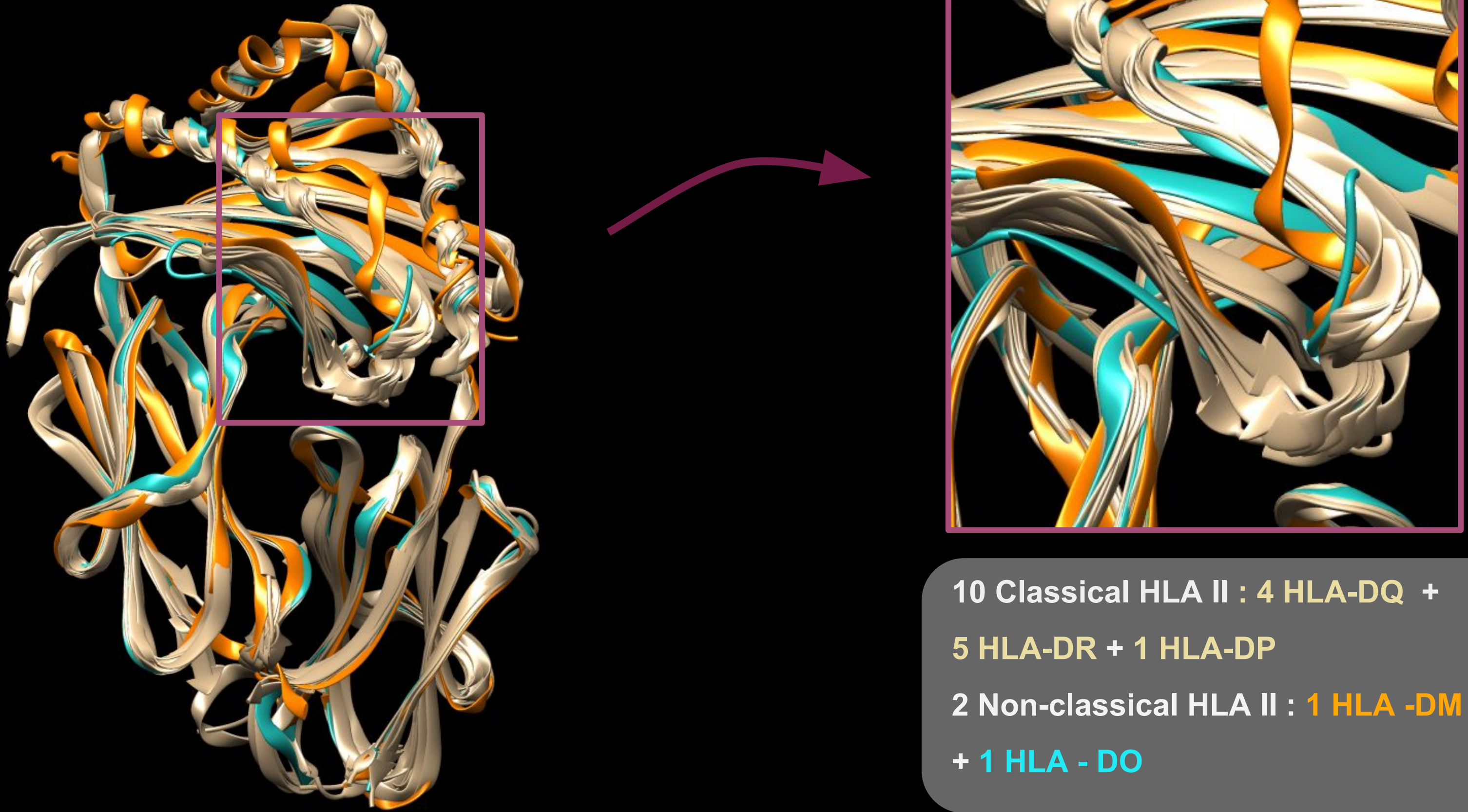
```
1uvq            DAEYWNSQKEVLEGTRAELDTVCRHNYEVAFRGILQRRVEPTVTISPS--------NLLV
3pl6            VAEYWNSQKEVLEGARASVDRVCRHNYEVAYRGILQRRVEPTVTISPS--------NLLI
2nna            AAEYWNSQKEVLERTRAELDTVCRHNYQLELRTTLQRRVEPTVTISP----------LLV
1s9v            AAEYWNSQKDILERKRAAVDRVCRHNYQLELRTTLQRRVEPTVTISPSR-------NLLV
1a6a            DAEYWNSQKDLLEQKRGRVDNYCRHNYGVVESFTVQRRVHPKVTVYPSKTQPLQHHNLLV
6atf            DAEYWNSQKDLLEQRRAAVDTYCRHNYGVGESFTVQRRVHPKVTVYPSKTQPLQHHNLLV
5jlz            DAEYWNSQKDLLEQKRAAVDTYCRHNYGVGESFTVQRRVYPEVTVYPAKTQPLQHHNLLV
1bx2            DAEYWNSQKDILEQARAAVDTYCRHNYGVVESFTVQRRVQPKVTVYPSKTQPLQHHNLLV
1dlh            DAEYWNSQKDLLEQRRAAVDTYCRHNYGVGESFTVQRRVEPKVTVYPSKTQPLQHHNLLV
3lqz            DEEYWNSQKDILEEERAVPDRMCRHNYELGGPMTLQRRVQPRVNVSPSKKG----HNLLV
4i0p            DAEQWNSRLDLLERSRQAVDGVCRHNYRLGAPFTVGRKVQPEVTVYPERTPLLHQHNLLH
1hdm            LSQHLNQKDTLMQRLNGLQN--CATHTQPFWGSLTNRTRPPSVQVAKTTPFNTREPVMLA
                  :  *.:  :::  .   :  *  :          *   * * :            :* 
```

β1-Helical Kink sequence is mainly conserved in Classical HLA II

β1-Helical Kink sequence is mainly different in DM and DO

However, sequence differs more in DM than in DO in comparisson to Classical HLA II

3_{10} Helix



10 Classical HLA II : 4 HLA-DQ +
5 HLA-DR + 1 HLA-DP
2 Non-classical HLA II : 1 HLA -DM
+ 1 HLA - DO

3_{10} Helix

```
1uvq            DIVADHVASCGVNLYQFYGPSGQYTHEFDGDEQFYVDLERKETAWRWPEFSKFGGFDPQG
3pl6            DIVADHVASCGVNLYQFYGPSGQYTHEFDGDEQFYVDLERKETAWRWPEFSKFGGFDPQG
2nna            DIVADHVASYGVNLYQSYGPSGQYSHEFDGDEEFYVDLERKETVWQLPLFRRFRRFDPQF
1s9v            --VADHVASYGVNLYQSYGPSGQYTHEFDGDEQFYVDLGRKETVWCLPVLRQFR-FDPQF
1a6a            -----HVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQG
6atf            ---EEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQG
5jlz            --KEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQG
1bx2            --KEEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQG
1dlb            ---EEHVIIQ-AEFYLNPDQSGEFMFDFDGDEIFHVDMAKKETVWRLEEFGRFASFEAQG
3lqz            -IKADHVSTY-AAFVQTHRPTGEFMFEFDEDEMFYVDLDKKETVWHLEEFGQAFSFEAQG
4i0p            --KADHMGSYGPAFYQSYGASGQFTHEFDEEQLFSVDLKKSEAVWRLPEFGDFARFDPQG
1hdm            --LQNHTFLH-TVYCQDGSPSVGLSEAYDEDQLFFFDFSQNTRVPRLPEFADWAQEQGDA
                     *              :      :* :: * .*: :.  .     :      : :
```

3_{10} Helix sequence is not conserved in classical HLA II molecules
3_{10} Helix sequence is either conserved in non-classical HLA molecules
However, sequence differs more in DM than in DO in comparisson to classical HLA II

General Conclusions

- The HLA-II binding groove is wider than in HLA-I.
- HLA-II present a typical pattern of hydrophobic pockets and a conserved hydrogen bond network.
- The beta 2 Ig-like domain is one of the most labile regions in HLA-II.
- Glycines at the α52 and α53 positions may confer structural lability in the 3-10 helix region, allowing multiple conformers to be adopted, and may increase affinity with the HLA-DM.
- The first helical kink at the alpha helix from beta 1 domain is involved in conformational changes related to antigenic peptide binding and TCR interactions.
- HLA-DM structure differs more in structure and sequence than HLA-DO in comparison to classical HLA II.
- HLA-DM has a closed-up binding groove.
- Classical HLA-II and non-classical HLA-II seem to be paralogs.

Bibliography

1. Bank, R. (2018). RCSB PDB: Homepage. [online] Rcsb.org. Available at: https://www.rcsb.org/ [Accessed 24 Feb. 2018].
2. Guce, A., Mortimer, S., Yoon, T., Painter, C., Jiang, W., Mellins, E. and Stern, L. (2012). HLA-DO acts as a substrate mimic to inhibit HLA-DM by a competitive mechanism. Nature Structural & Molecular Biology, 20(1), pp.90-98.
3. Hla.alleles.org. (2017). HLA Nomenclature. [online] hla.alleles.org. Available at: http://hla.alleles.org/nomenclature/naming.html [Accessed 24 Feb. 2018].
4. Hou, T., Macmillan, H., Chen, Z., Keech, C., Jin, X., Sidney, J., Strohman, M., Yoon, T. and Mellins, E. (2011). An Insertion Mutant in DQA1*0501 Restores Susceptibility to HLA-DM: Implications for Disease Associations. *The Journal of Immunology*, 187(5), pp.2442-2452.
5. Hulpke, S. and Tampé, R. (2013). The MHC I loading complex: a multitasking machinery in adaptive immunity. *Trends in Biochemical Sciences*, 38(8), pp.412-420.
6. Janeway, ,C. (1999). *Immunobiology*. London: Harcourt Brace & Company.
7. Kropshofer, H., Hammerling, G. and Vogt, A. (1999). The impact of the non-classical MHC proteins HLA-DM and HLA-DO on loading of MHC class II molecules. Immunological Reviews, 172(1), pp.267-278.
8. Li, Y., Huang, Y., Lue, J., Quandt, J., Martin, R. and Mariuzza, R. (2005). Structure of a human autoimmune TCR bound to a myelin basic protein self-peptide and a multiple sclerosis-associated MHC class II molecule. *The EMBO Journal,* 24(17), pp.2968-2979.
9. McMahon, R., Friis, L., Siebold, C., Friese, M., Fugger, L. and Jones, E. (2011). Structure of HLA-A*0301 in complex with a peptide of proteolipid protein: insights into the role of HLA-A alleles in susceptibility to multiple sclerosis. Acta Crystallographica Section D Biological Crystallography, 67(5), pp.447-454.

Bibliography

10. Mellins, E. and Stern, L. (2014). HLA-DM and HLA-DO, key regulators of MHC-II processing and presentation. Current Opinion in Immunology, 26, pp.115-122.
11. Mosyak, L., Zaller, D. and Wiley, D. (1998). The Structure of HLA-DM, the Peptide Exchange Catalyst that Loads Antigen onto Class II MHC Molecules during Antigen Presentation. Immunity, 9(3), pp.377-383
12. Painter, C. and Stern, L. (2012). Conformational variation in structures of classical and non-classical MHCII proteins and functional implications. *Immunological Reviews*, 250(1), pp.144-157.
13. Schulze, M. and Wucherpfennig, K. (2012). The mechanism of HLA-DM induced peptide exchange in the MHC class II antigen presentation pathway. Current Opinion in Immunology, 24(1), pp.105-111.
14. Scop.mrc-lmb.cam.ac.uk. (2018). *SCOP: Protein: Class II MHC alpha chain, C-terminal domain from Human (Homo sapiens), HLA-DM [TaxId: 9606]*. [online] Available at: http://scop.mrc-lmb.cam.ac.uk/scop/data/scop.b.c.b.b.c.fi.html [Accessed 25 Feb. 2018].
15. Stern, L., Brown, J., Jardetzky, T., Gorga, J., Urban, R., Strominger, J. and Wiley, D. (1994). Crystal structure of the human class II MHC protein HLA-DR1 complexed with an influenza virus peptide. Nature, 368(6468), pp.215-221.
16. Ting, J. and Trowsdale, J. (2002). Genetic Control of MHC Class II Expression. Cell, 109(2), pp.S21-S33.
17. Wieczorek, M., Abualrous E., Sticht, J., Álvaro-Benito, M., Stolzenberg, S., Noé, F. and Freund, C. (2017). Major Histocompatibility Complex (MHC) Class I and MHC Class II Proteins: Conformational Plasticity in Antigen Presentation. Frontiers in Immunology, 8.

PEM Questions

1. The MHC complex is a family of genes that is found in all vertebrates. In humans, this complex is called:
   a) Human labile complex (HLC)
   b) Human leukocytic antigen (HLA)
   c) Human leukocytic complex (HLC)
   d) Human labile antigen (HLA)
   e) Human long region (HLR)

2. The main difference between HLA-I and HLA-I molecules is:
   a) HLA-I is expressed in macrophages and HLA-II in nucleated cells.
   b) HLA-I presents peptides to CD4+ T cells and HLA-II to CD8+ T cells.
   c) HLA-I is expressed in all nucleated cells and HLA-II in antigen presenting cells.
   d) HLA-I and HLA-II are expressed in the same cells.
   e) HLA-I and HLA-II are expressed in all cell types.

3. Which of the following regions show structural variability in classical MHC II proteins?
   a) The β2 Ig-like domain
   b) The 3-10 helix
   c) a and b
   d) the β1 helical kink
   e) All of the above

4. Which classical HLA II proteins show more variability in the 3-10 helix?
   a) HLA-DR
   b) HLA-DQ
   c) a and b
   d) HLA-DP
   e) All of the above

PEM Questions

5. Which secondary structure forms the groove of a HLA II protein?
   a) 8-antiparallel beta strand bordered by two alpha helices
   b) 4-antiparallel beta strand bordered by four alpha helices
   c) beta barrel
   d) 8 alpha helices
   e) 8 antiparallel beta strand

6. Which of the following statement is true about classical and non-classical HLA II molecules?
   a) DR, DO and DM are the three types of non-classical HLA II molecules
   b) DO and DM are types of classical HLA II molecules
   c) Between DO and DM the most similar to DR is DO
   d) Between DO and DM the more similar to DR is DM
   e) DO and DM share the same sequence.

7. Which pockets are tipycally presented in HLA-II proteins?
   a) Pocket 1, pocket 2, pocket 3, pocket 4 and pocket 5
   b) Pocket 1, pocket 4, pocket 6, pocket 7 and pocket 9
   c) Only pocket 1
   d) They are different for each serotype
   e) As many pockets as residues the peptide bound has

8. Which type of interactions are stablished between the peptide and the HLA-II protein?
   a) Salt bridges
   b) Hydrogen bonds
   c) Hydrophobic interactions
   d) Salt bridges and Hydrogen bonds
   e) Hydrophobic interactions and Hydrogen bonds

9. Classical and non-classical HLA proteins:
   a) Have different functions
   b) Have similar structure
   c) Have different functions and similar structures
   d) Have the same function
   e) Have the same functions and different structures

10. In HLA II, which of the following domains interacts with TCR?
    a) The β2 Ig-like domain
    b) The 3-10 helix
    c) The β1 helical kink
    d) All of the above
    e) None of the above

MHC

STRUCTURE ANALYSIS OF THE MAJOR HISTOCOMPATIBILITY COMPLEX

Laura Cañadas, Clàudia Garcia, Laia Joval i Ariadna Pinar