HLA | HUMAN LEUKOCYTE ANTIGEN

An structural analysis

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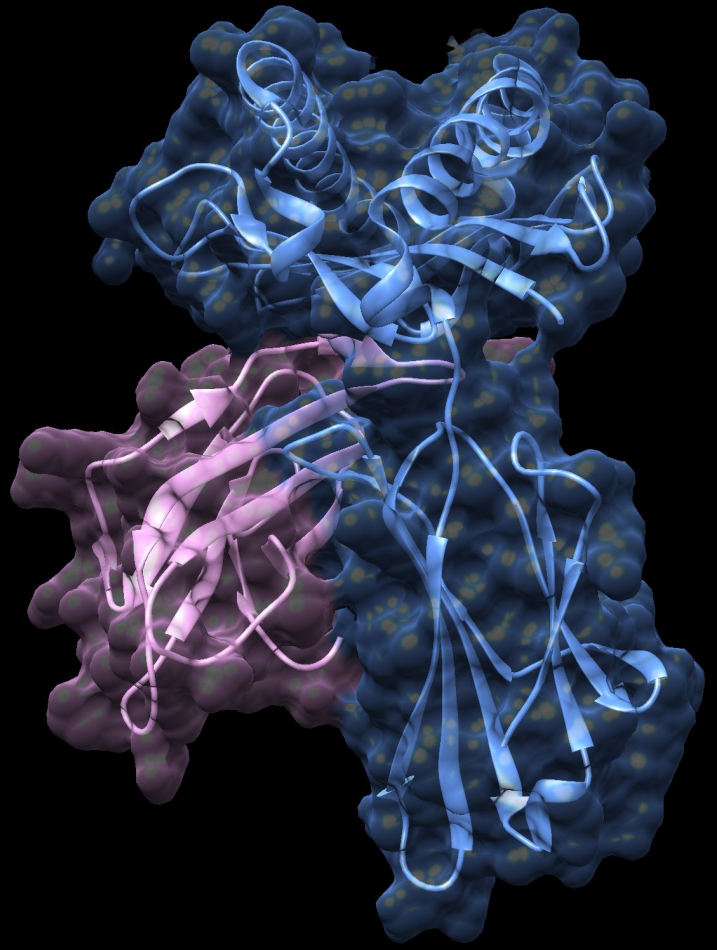
Structural Biology | Human Biology | 23-24



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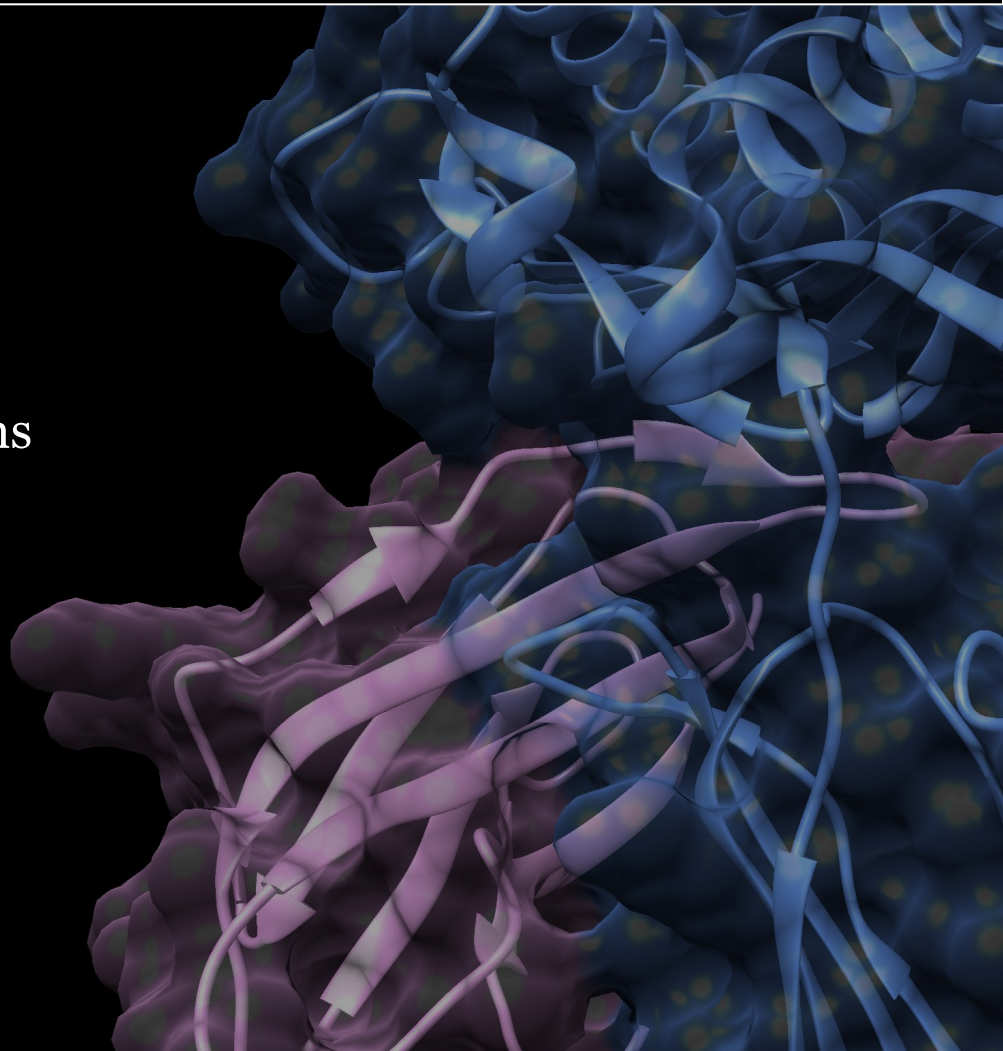
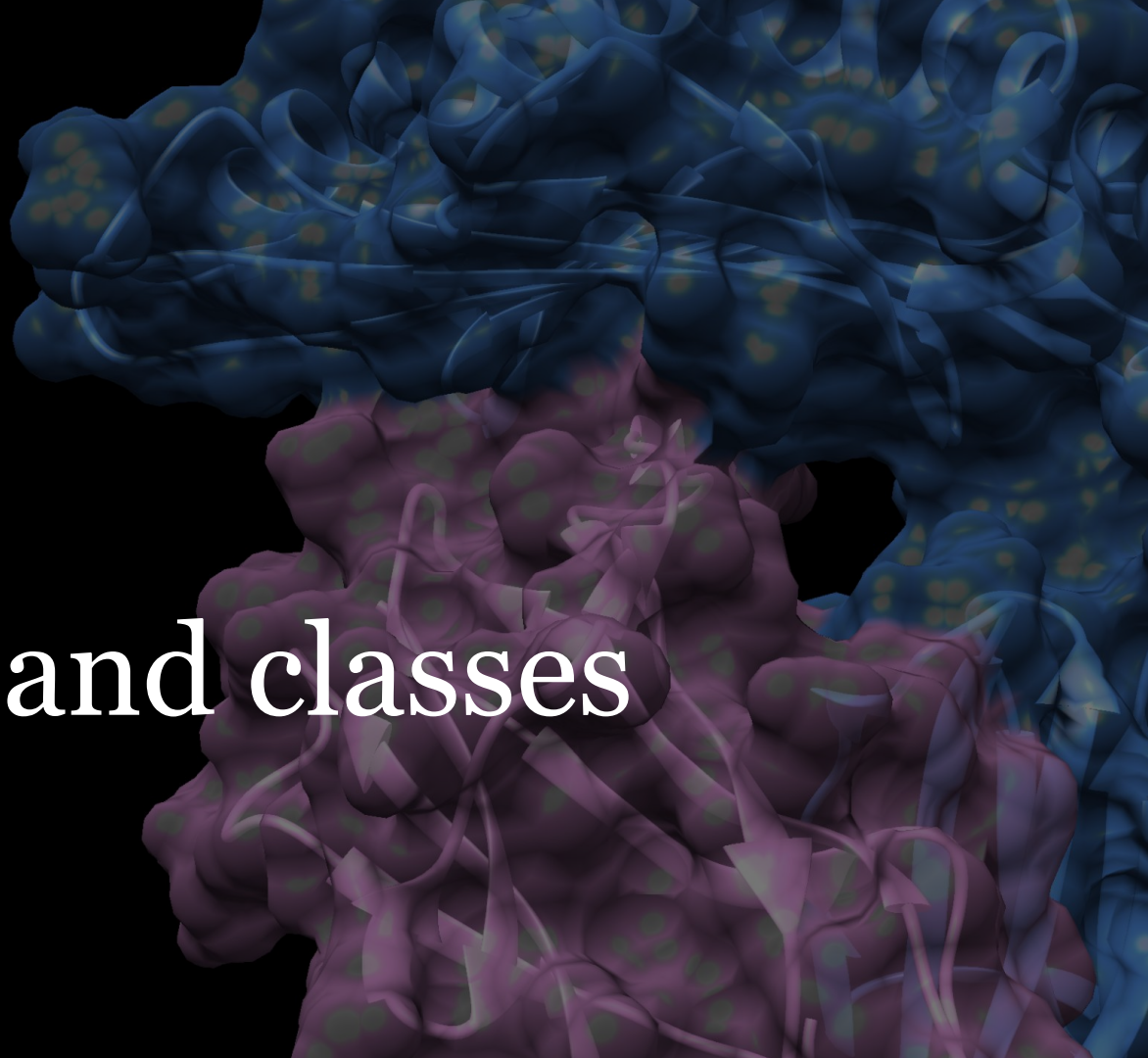


01

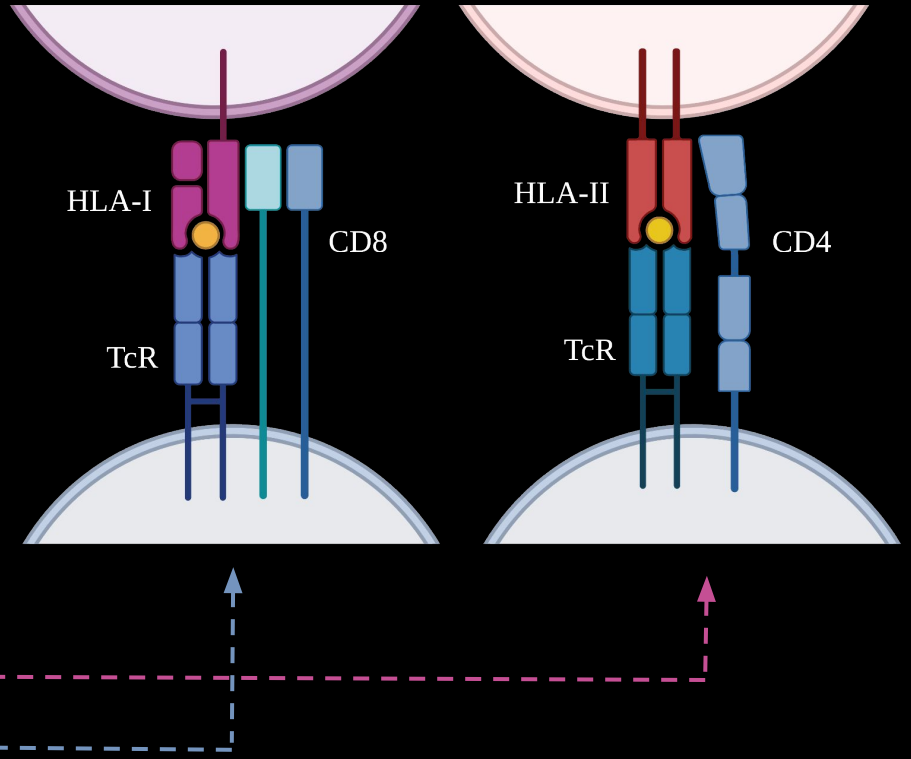
HLA: function and classes



HLA molecules | HLA-I and HLA-II

There are two classes of HLA molecules:

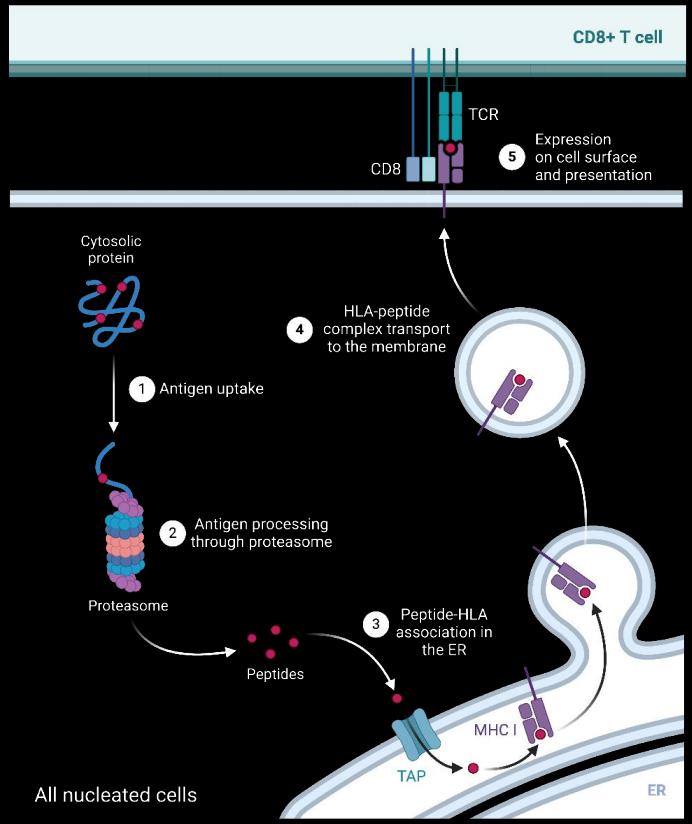
	HLA-I	HLA-II
Localization	All nucleated cells	Antigen presenting cells
T cell	CD8+	CD4+
Peptides' localization	Intracellular	Extracellular
Peptides' length	8-10 amino acids	15-25 amino acids



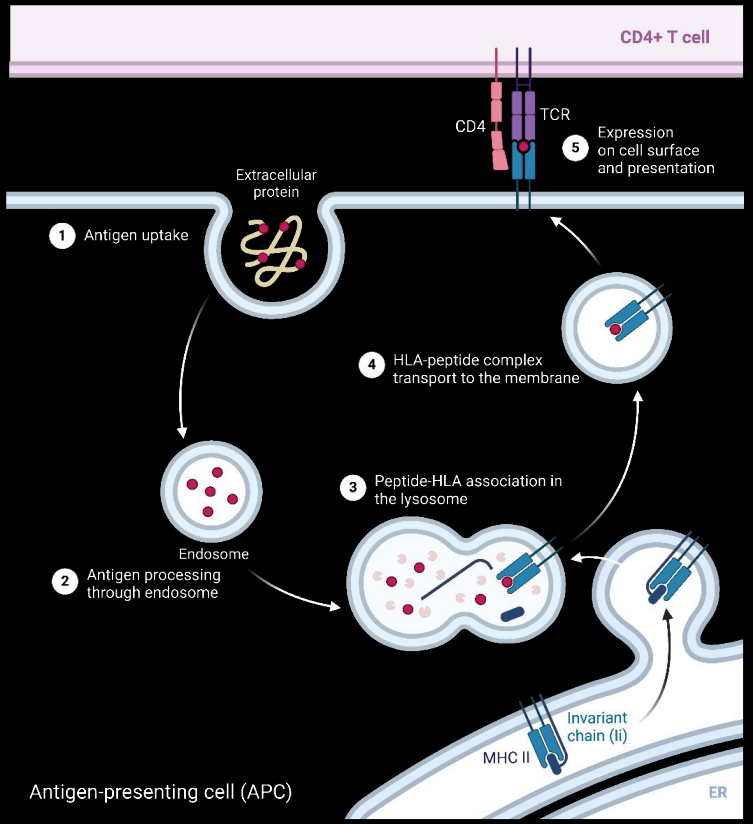
Images created with Biorender

Function of HLA molecules | Antigen presentation

HLA-I pathway

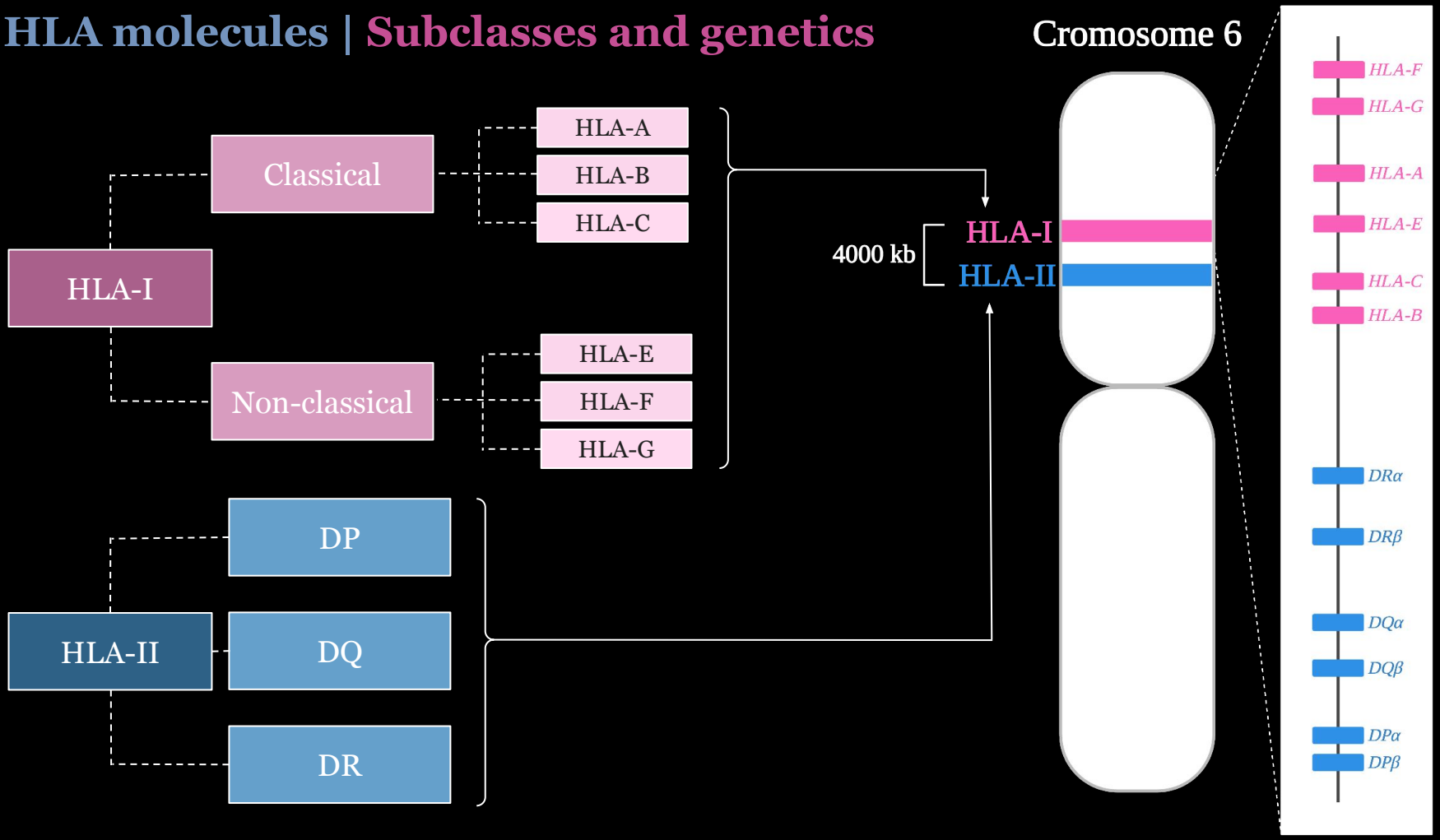


HLA-II pathway



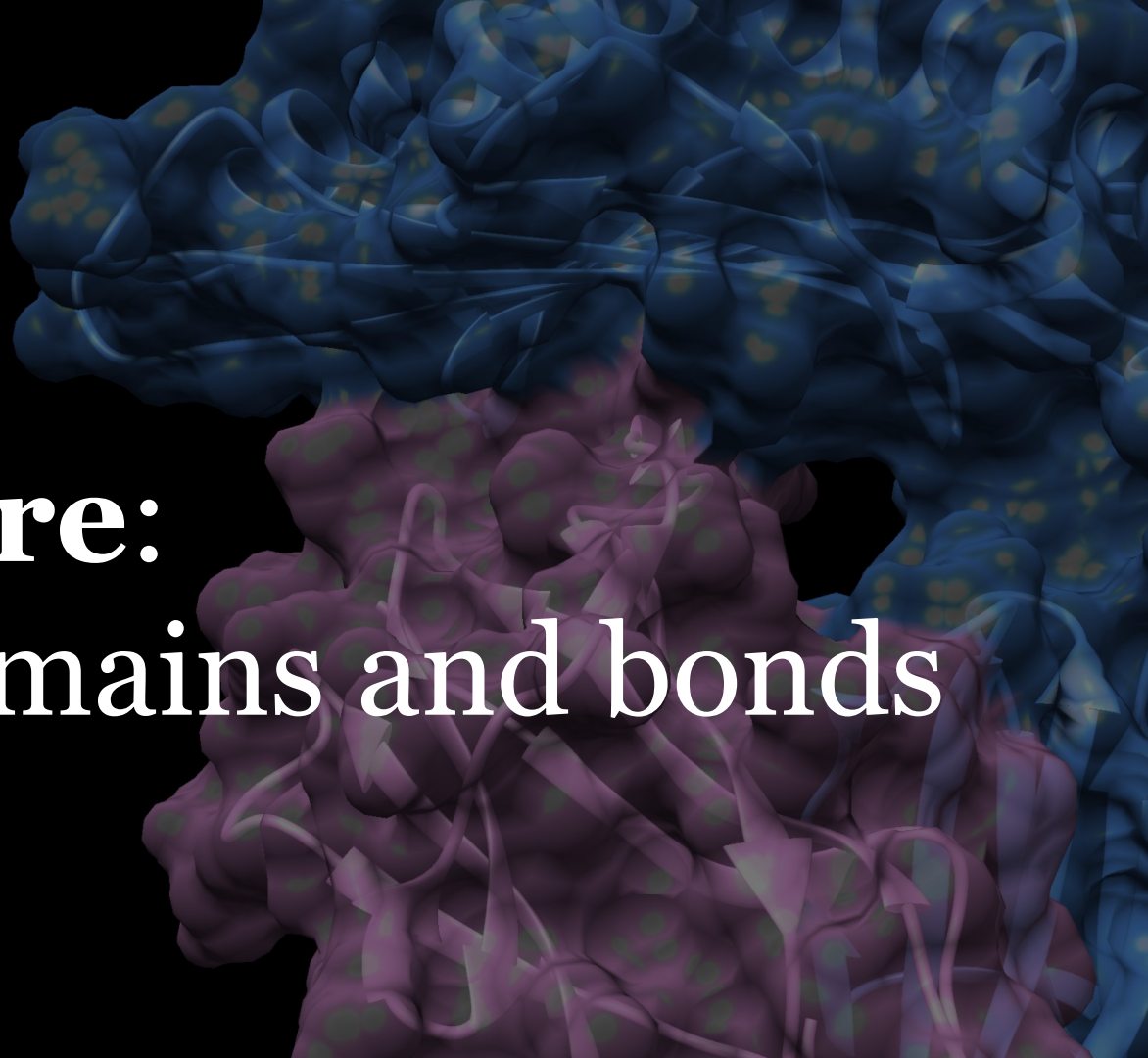
Images created with Biorender based on Iwasaki, A. (2020). MHC Class I and II Pathways.

HLA molecules | Subclasses and genetics



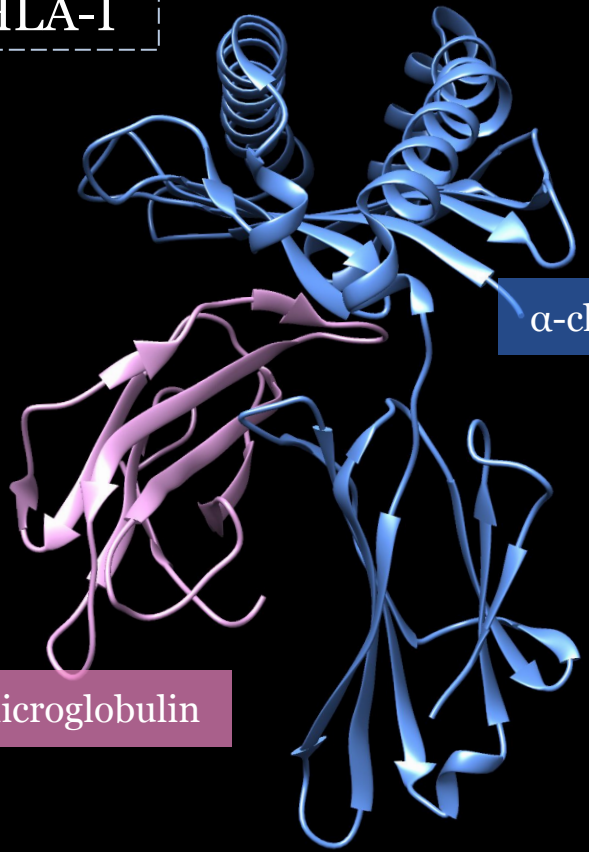
02

Structure: folds, domains and bonds

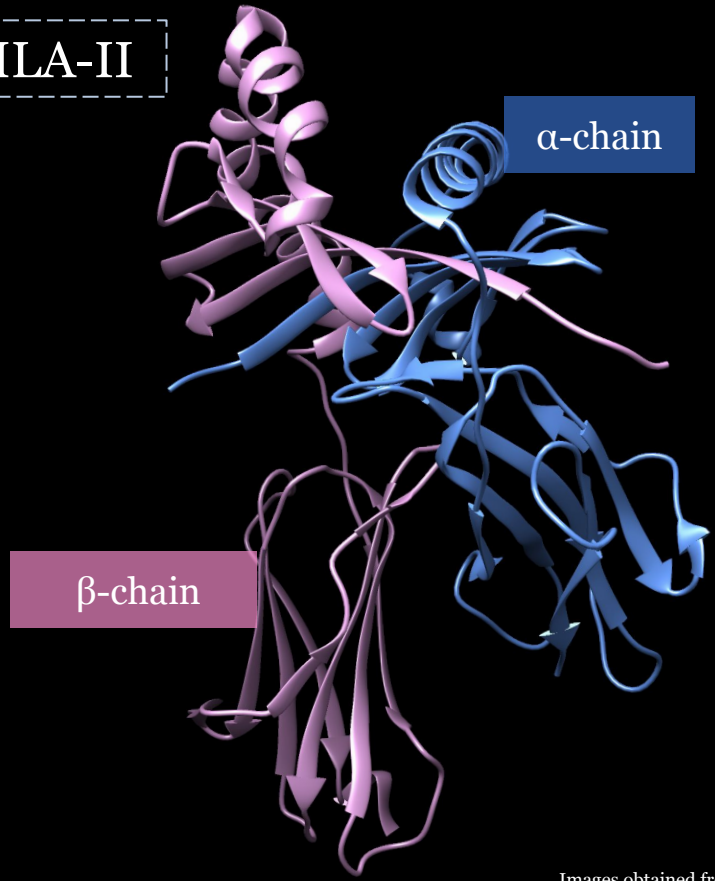


HLA structure | Chains

HLA-I

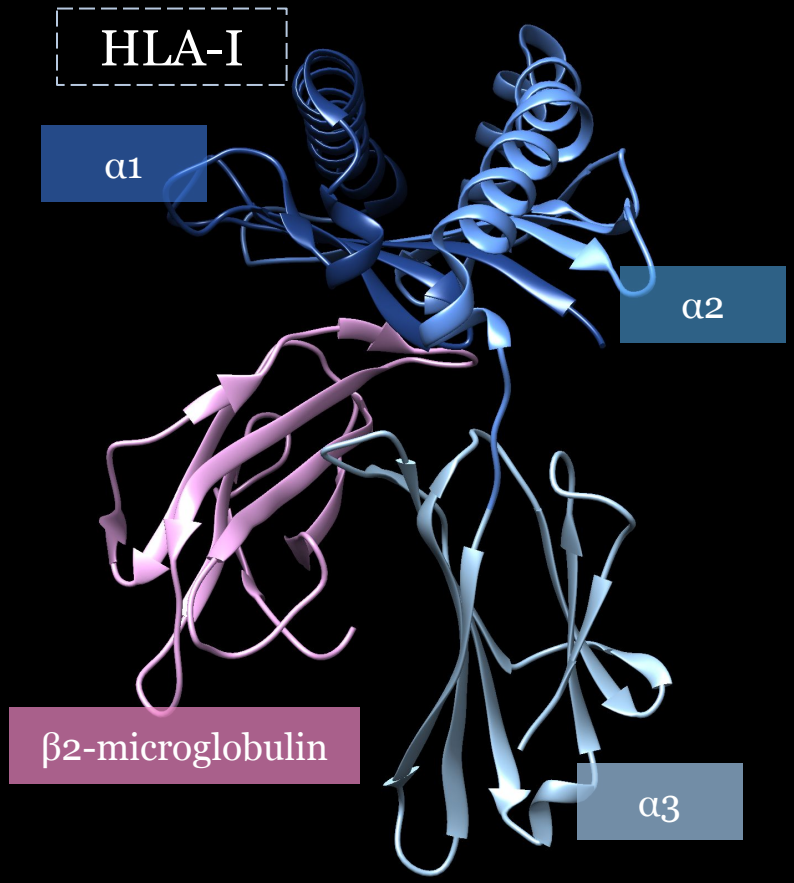


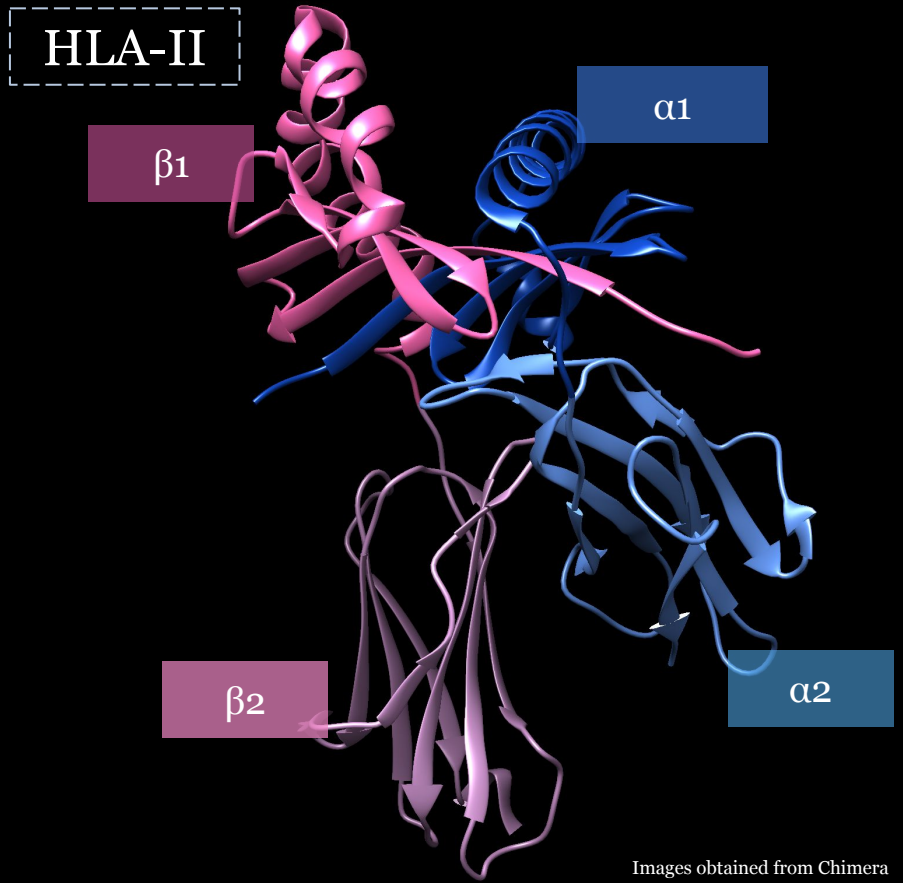
HLA-II



Images obtained from Chimera

HLA structure | Domains





Images obtained from Chimera

HLA structure | SCOP classification

HLA-I
α3 domain and
β2-microglobulin

HLA-II
α2 and β2 domains

β-sheet

Helix

Images obtained from Chimera

Class
All beta proteins

↓

Fold
Immunoglobulin-like
beta-sandwich

↓

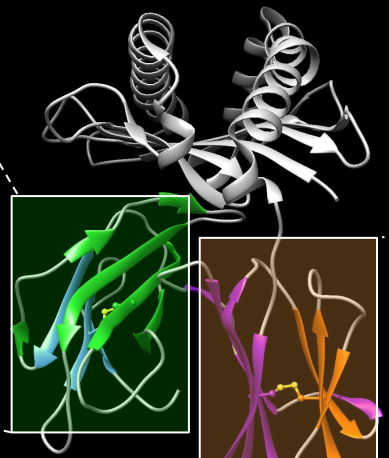
Domain
Immunoglobulin (Ig)
domain-like

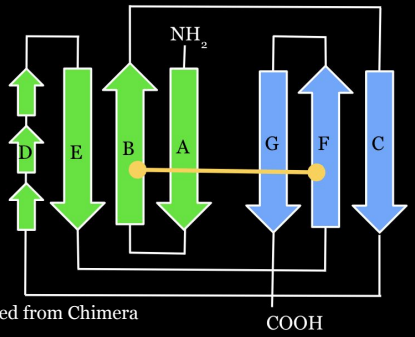
↓

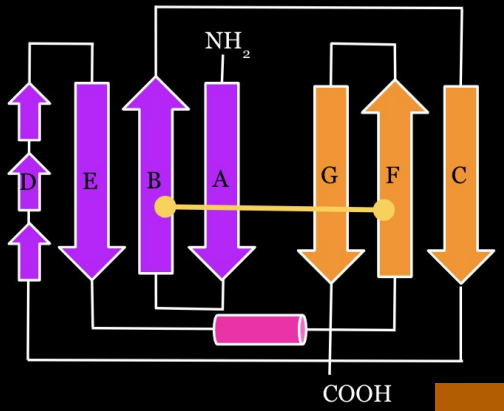
Family
C1 set domains-like

HLA-I structure | Ig-like beta-sandwich

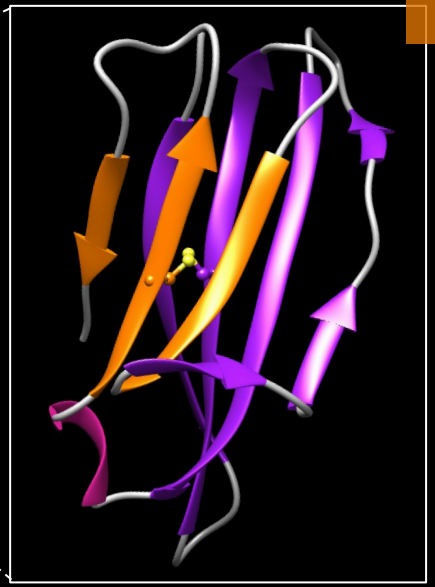
β2-microglobulin







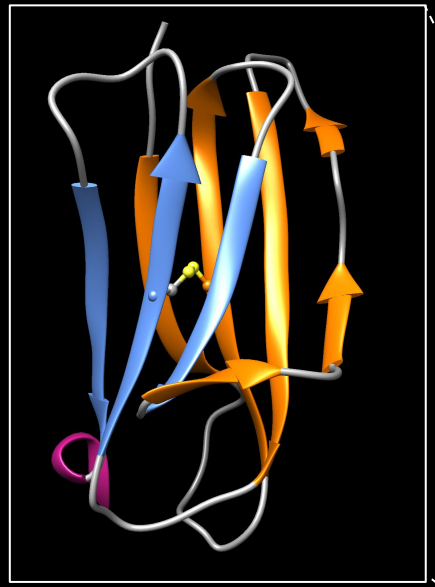
α3

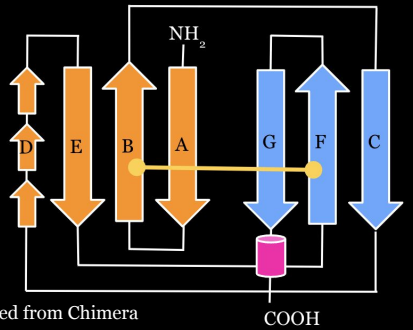


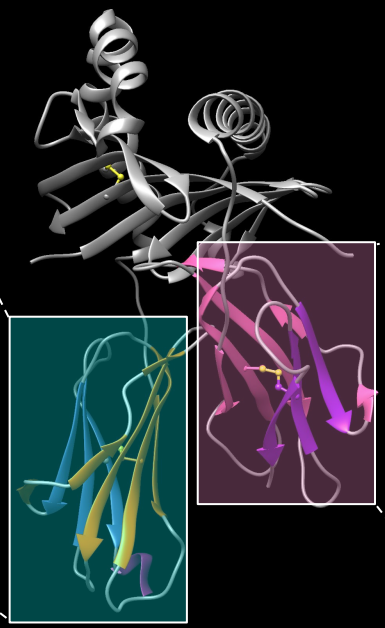
Images obtained from Chimera

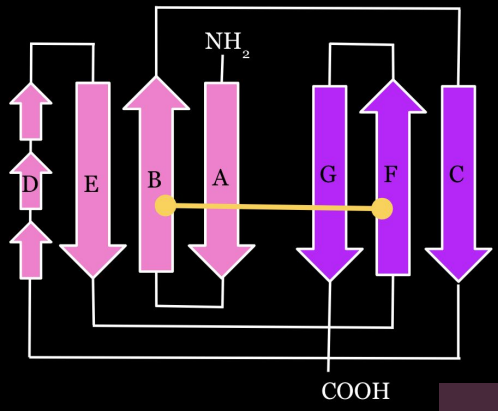
HLA-II structure | Ig-like beta-sandwich

β2

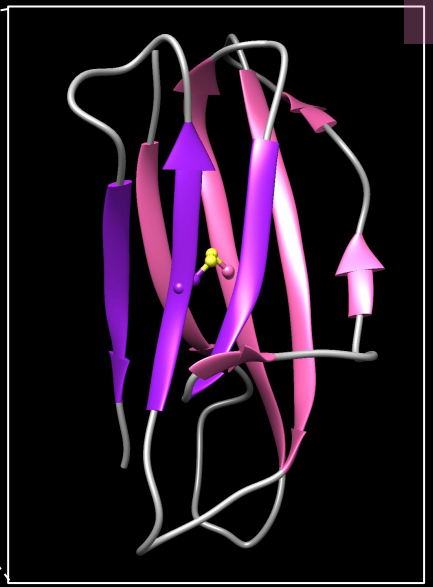








α2



Images obtained from Chimera

HLA structure | SCOP classification

HLA-I
α1 and α2 domains

HLA-II
α1 and β1 domains

β-sheet

Helix

Class
Alpha and beta (α+β)

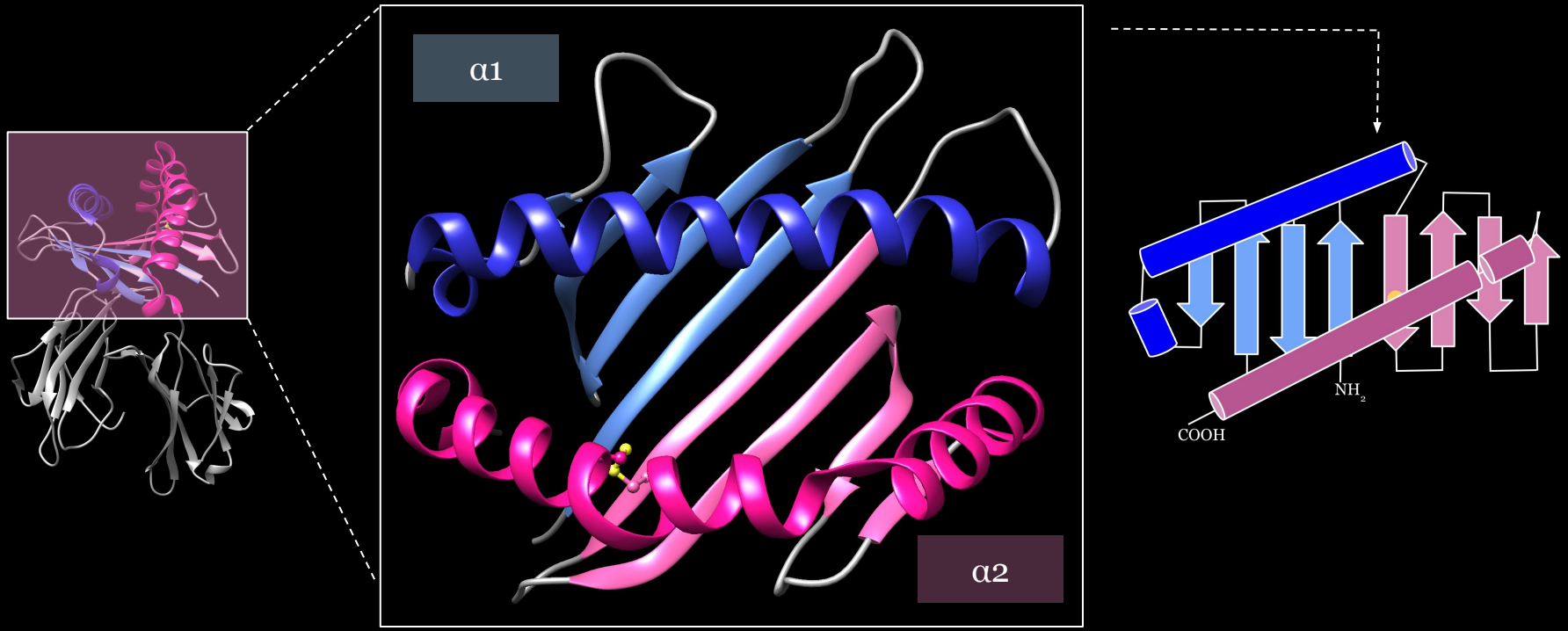
Fold
MHC antigen-recognition domain

Domain
MHC antigen-recognition domain

Family
MHC antigen-recognition domain

Images obtained from Chimera

HLA-I structure | MHC antigen-recognition domain



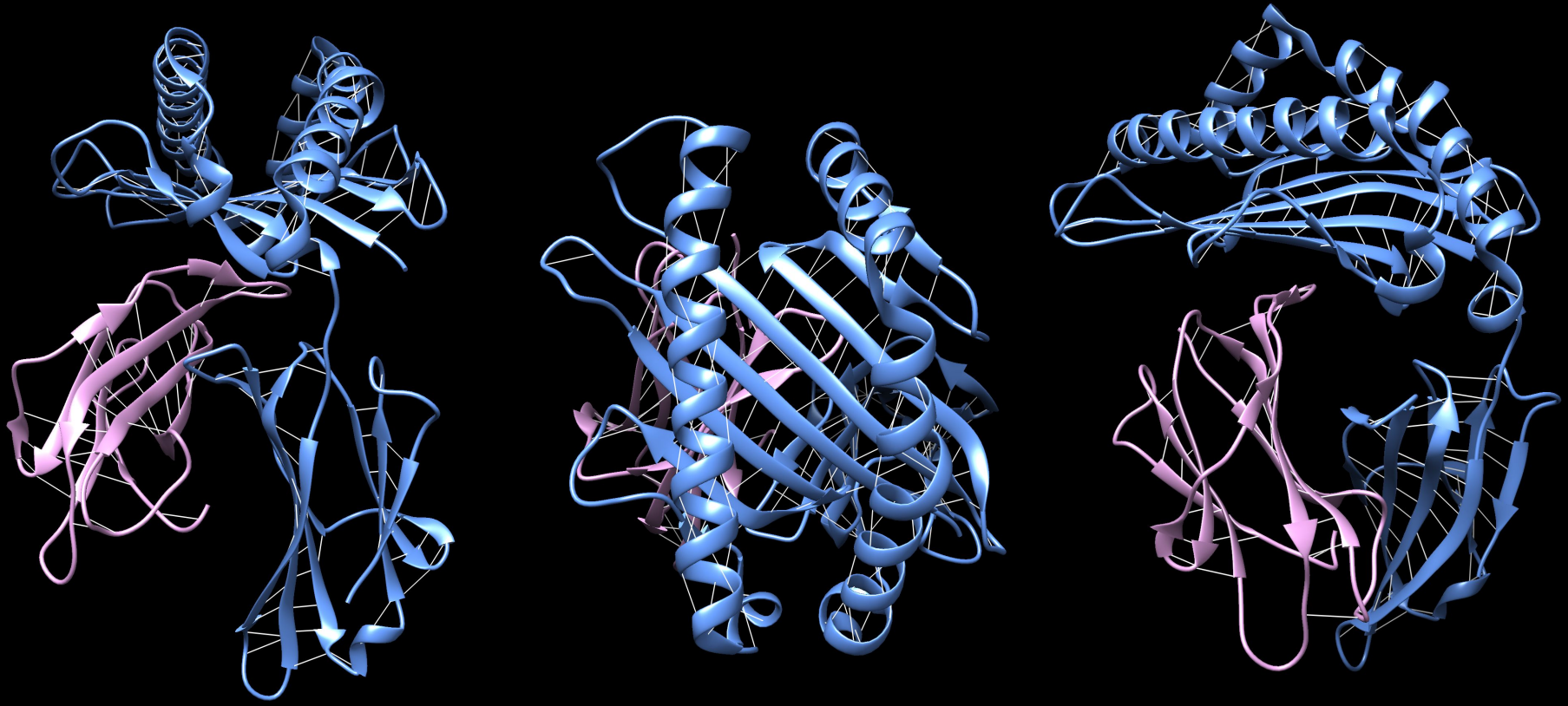
Images obtained from Chimera

HLA-II structure | MHC antigen-recognition domain

Images obtained from Chimera

Structure stabilization| Intrachain hydrogen bonds

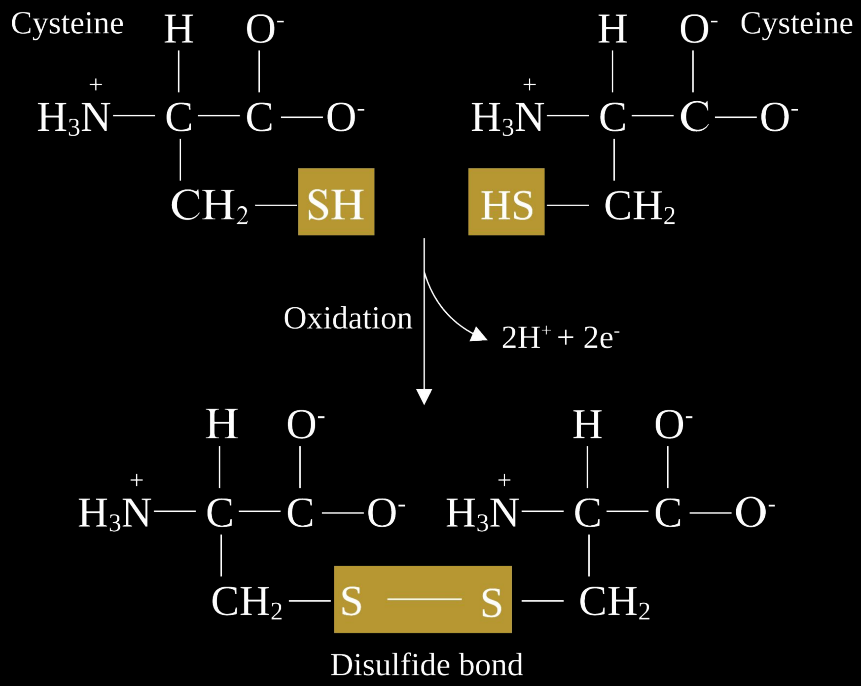
Intrachain hydrogen bonds are important to **stabilize** protein structures.

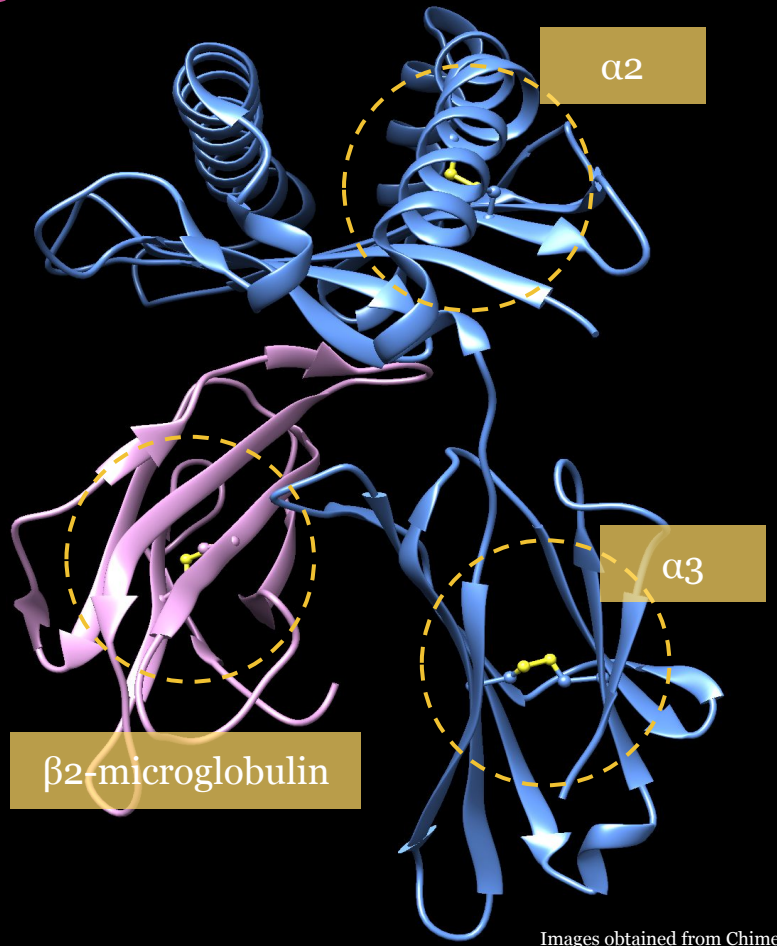


Images obtained from Chimera

Structure stabilization| Disulfide bonds

Disulfide bonds are **covalent** bonds that form after the oxidation of two sulfhydryl groups. They are highly **strong** and so, they can **stabilize** tertiary and quaternary structures of proteins.



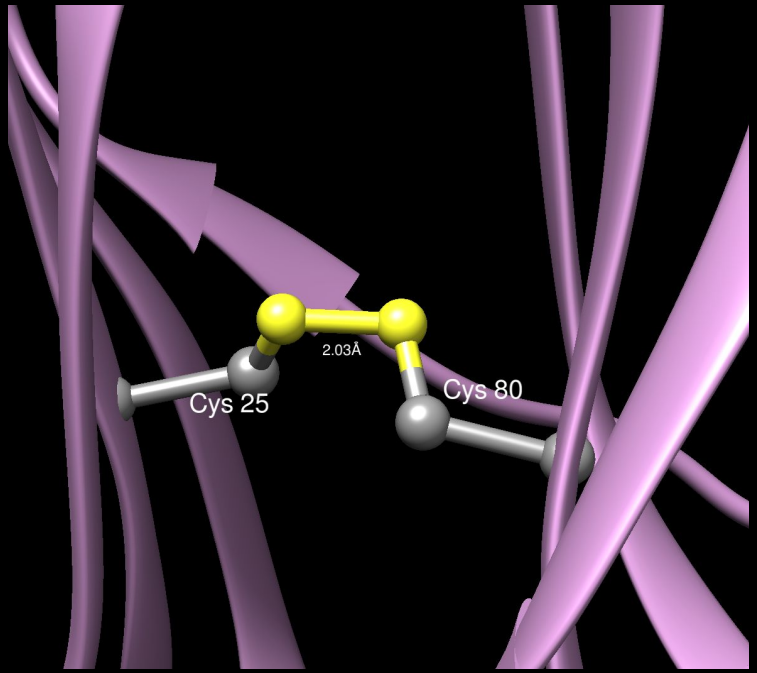


Images obtained from Chimera

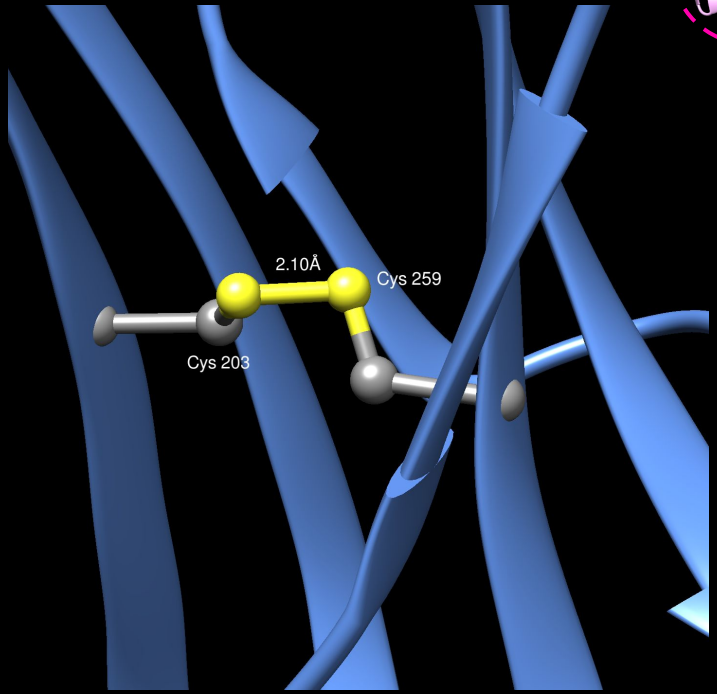
Structure stabilization| Disulfide bonds

The disulfide bonds link the two sheets of the β-sandwich structure in β2-microglobulin and the α3 domain.

β2-microglobulin



α3

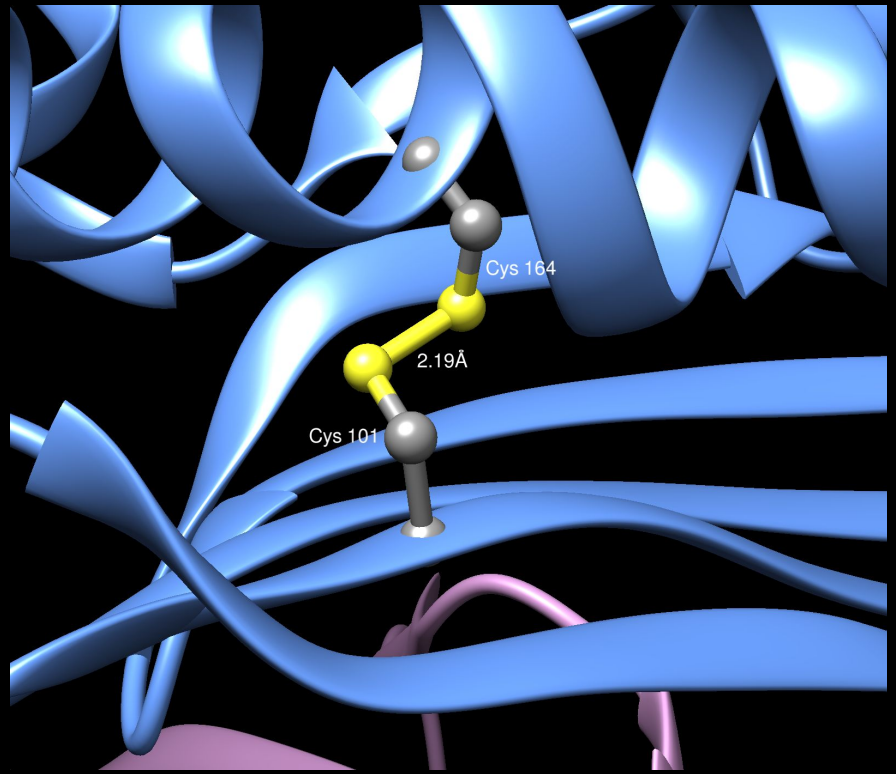


Images obtained from Chimera

Structure stabilization| Disulfide bonds

The disulfide bond links the α-helix with the β-sheet in the α2 domain.

α2



α-helix

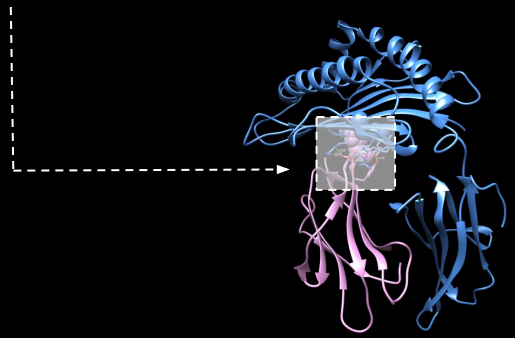
β-sheet

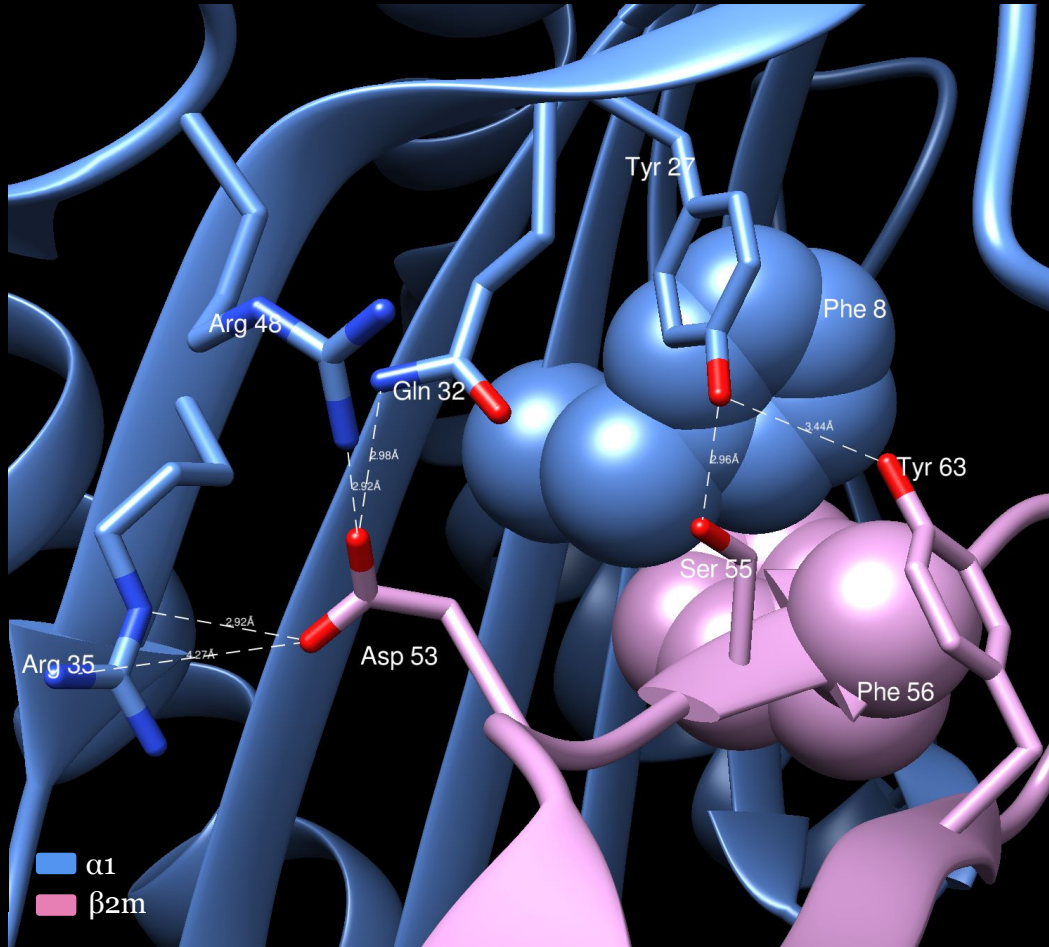
Images obtained from Chimera

Structure stabilization | β2-microglobulin and α1 interactions

The main interactions between β2-microglobulin (β2m) and the α1 domain are the following ones:

β2m	α1	Type of bond	Distance (Å)
Asp 53	Gln 32	H-Bond	2.98
	Arg 35	Ionic bond	4.27
	Arg 48	Ionic bond	2.92
Ser 55	Tyr 27	H-Bond	2.96
Phe 56	Phe 8	Hydrophobic	
Tyr 63	Tyr 27	H-Bond	3.44



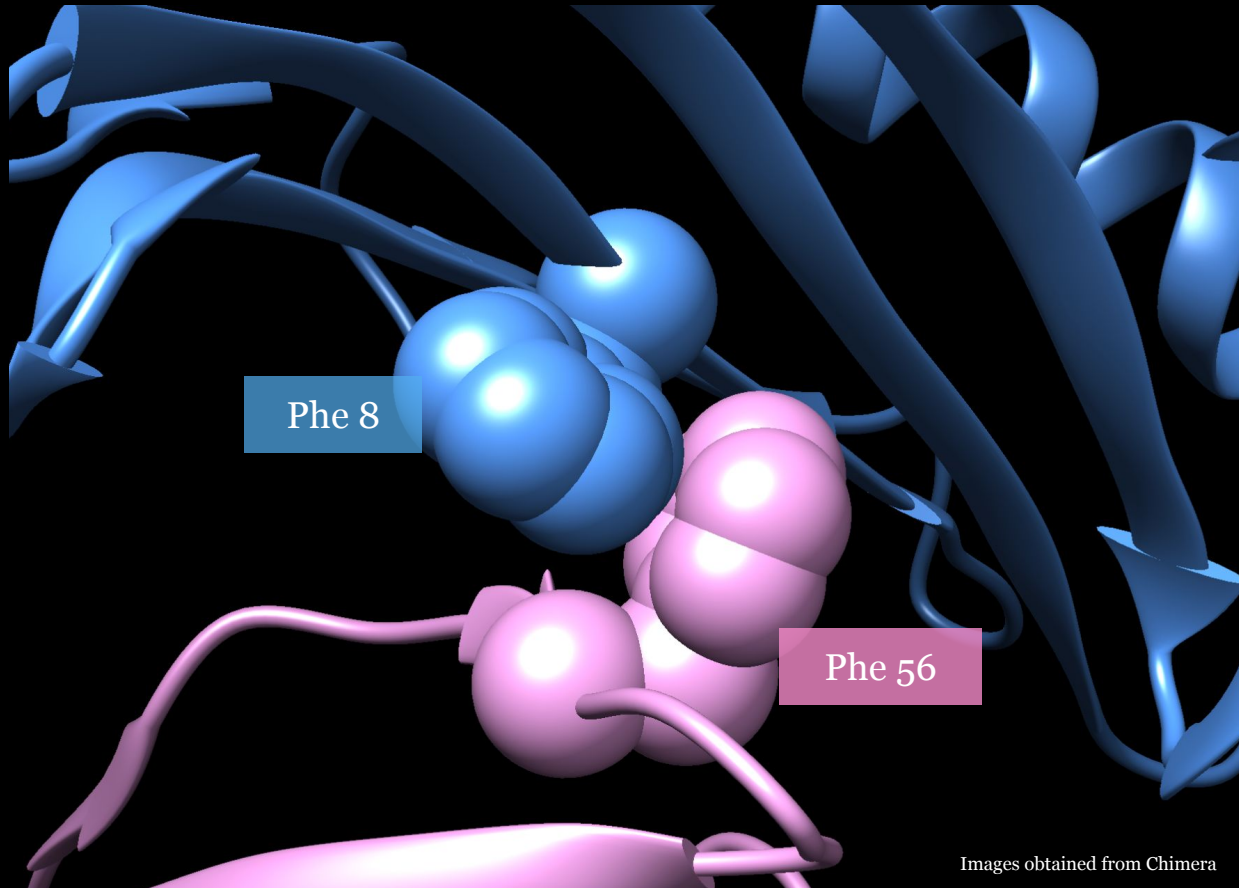


Images obtained from Chimera

Structure stabilization | β2-microglobulin and α1 interactions

Hydrophobic interaction

The **hydrophobic interaction** is described as the tendency of **nonpolar** groups or residues to aggregate in water solution.



Images obtained from Chimera

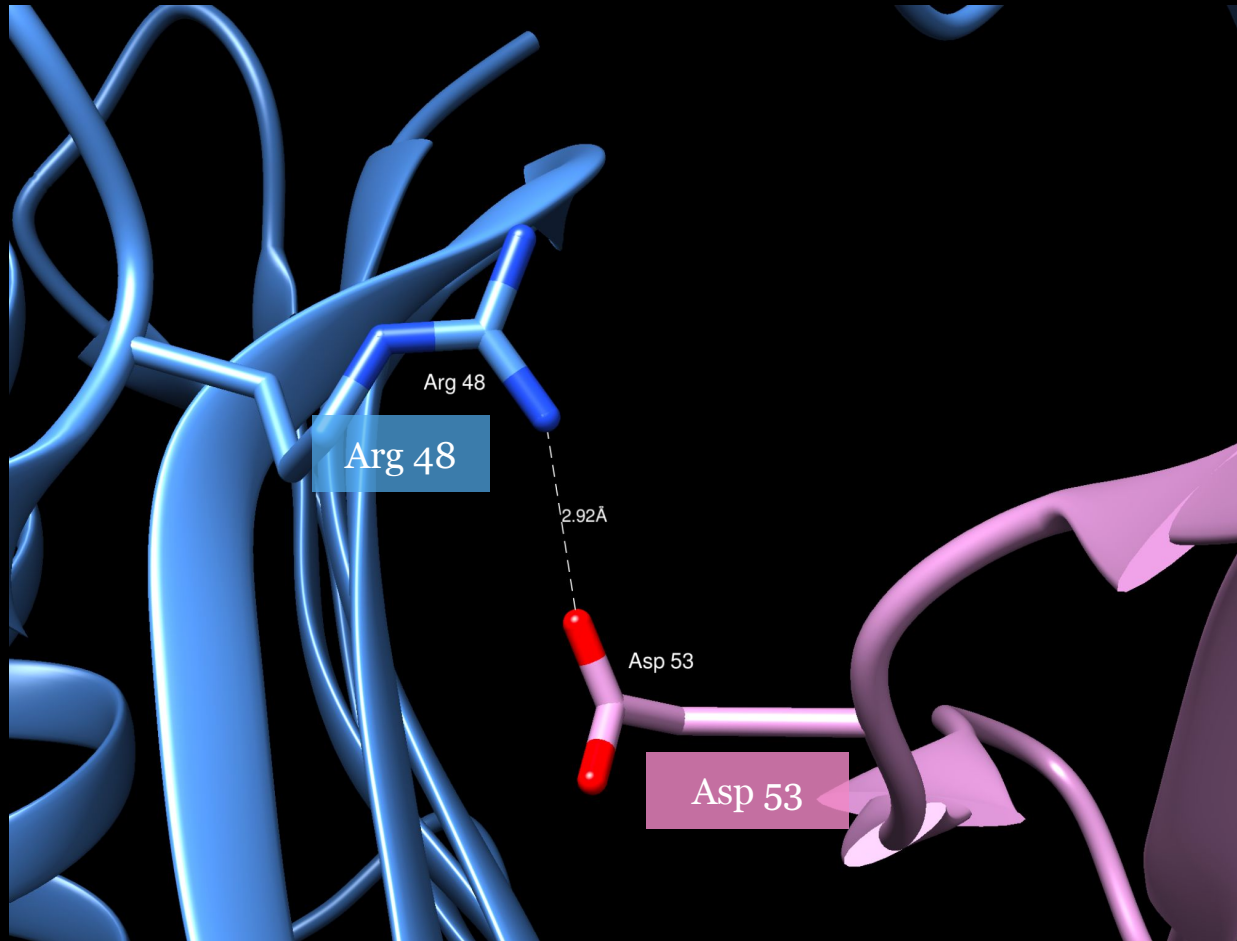
Structure stabilization | β2-microglobulin and α1 interactions

Ionic bond

An **ionic bond** is an **electrostatic interaction** between two oppositely charged groups.

α1
β2m

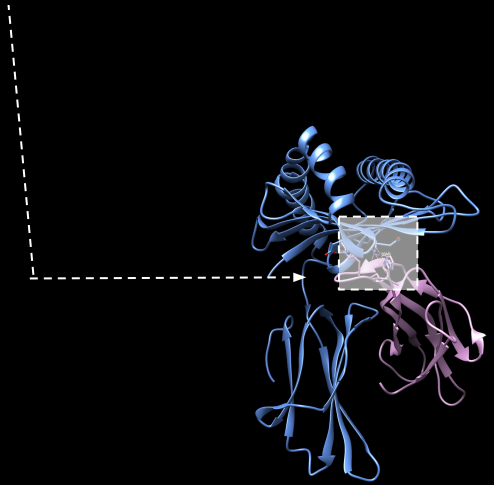
Images obtained from Chimera

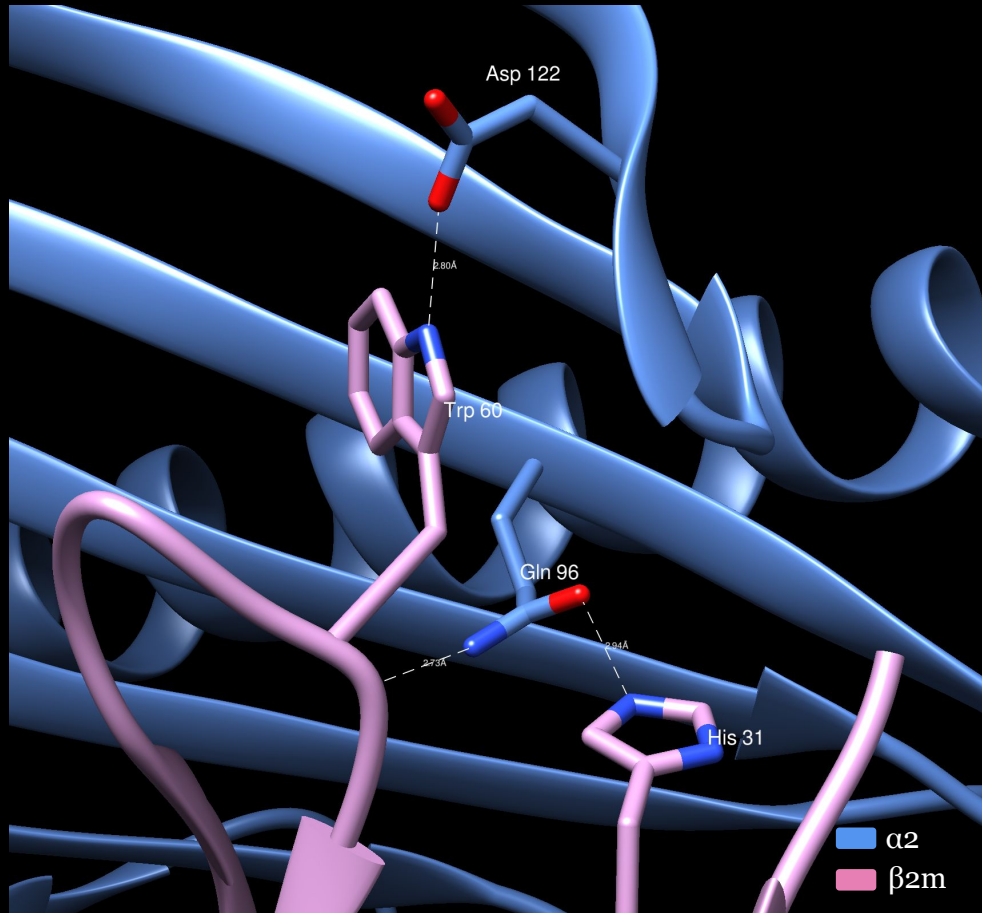


Structure stabilization | β2-microglobulin and α2 interactions

The main interactions between β2-microglobulin (β2m) and the α2 domain are the following ones:

β2m	α2	Type of bond	Distance (Å)
His 31	Gln 96	H-Bond	2.94
Trp 60		H-Bond	2.73
	Asp 122	H-Bond	2.80



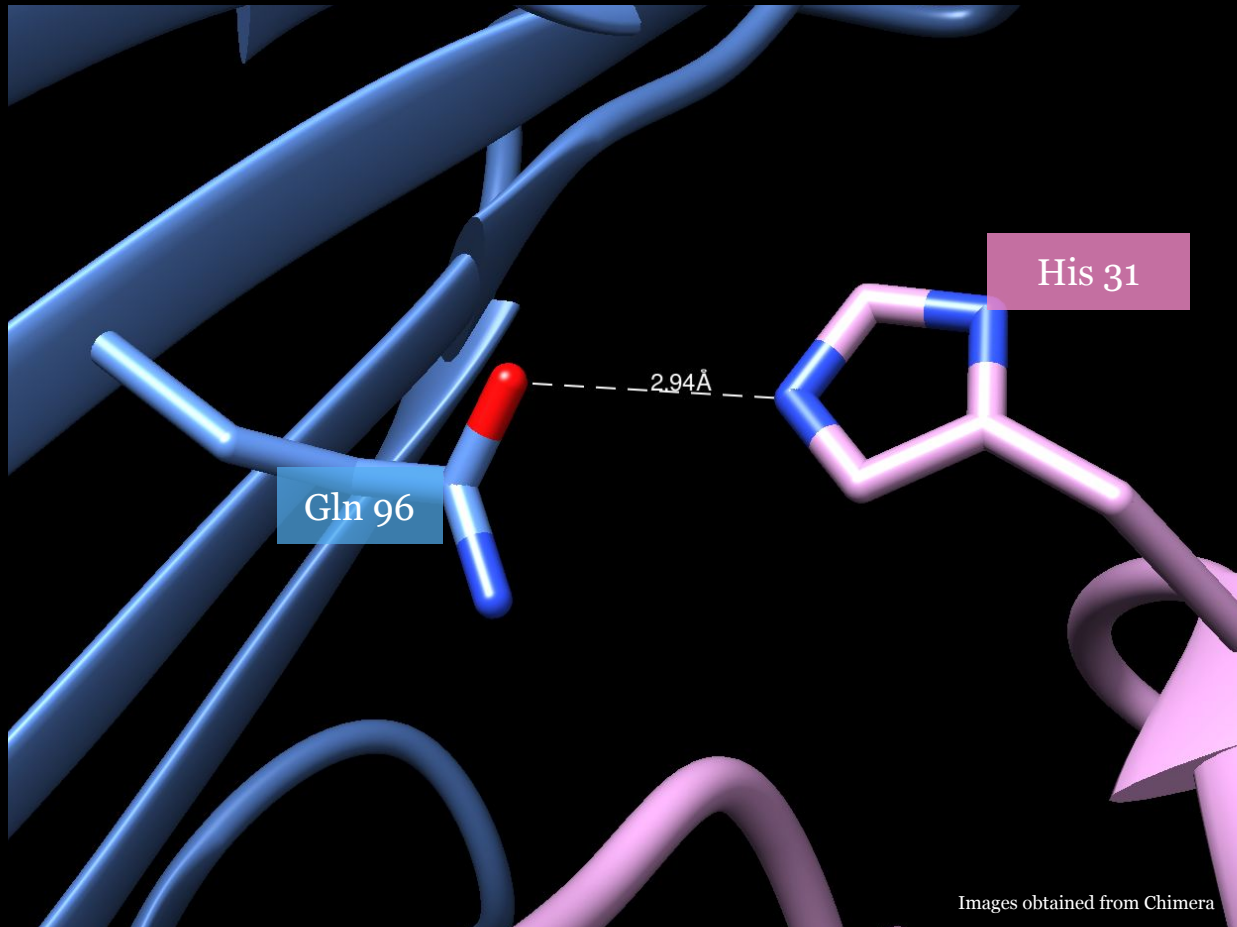


Images obtained from Chimera

Structure stabilization | β2-microglobulin and α2 interactions

Hydrogen bond

Hydrogen bonds are **dipole-dipole attractions** between an electronegative atom bonded to a hydrogen (bonded to a second electronegative atom).

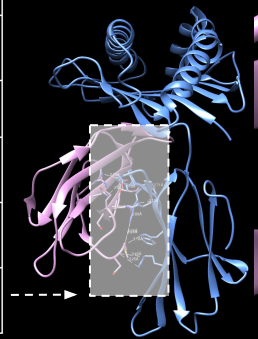


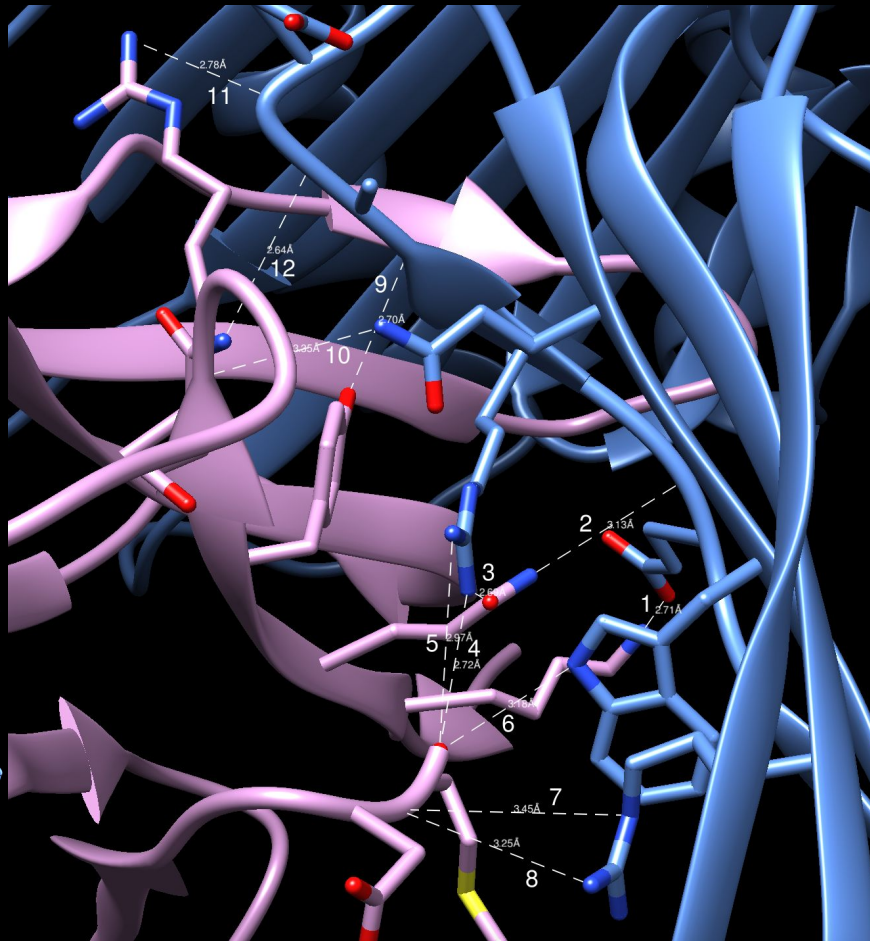
Images obtained from Chimera

Structure stabilization | β2-microglobulin and α3 interactions

The main interactions between β2-microglobulin (β2m) and the α3 domain are the following ones:

β2m	α2	Type of bond	Distance (Å)
Lys 6	Glu 232	Salt bridge	2.71
Gln 8		H-Bond	3.13
	Arg 234	H-Bond	2.69
Tyr 10	Pro 235	H-Bond	2.70
Ser 11	Gln 242	H-Bond	3.35
Arg 12	Gly 237	H-Bond	2.78
Asn 24	Ala 236	H-Bond	2.54
Asp 98	Arg 202	2 H-Bond	3.25/3.45
Met 99	Arg 234	2 H-Bond	2.72/2.97
	Trp 244	H-Bond	3.18



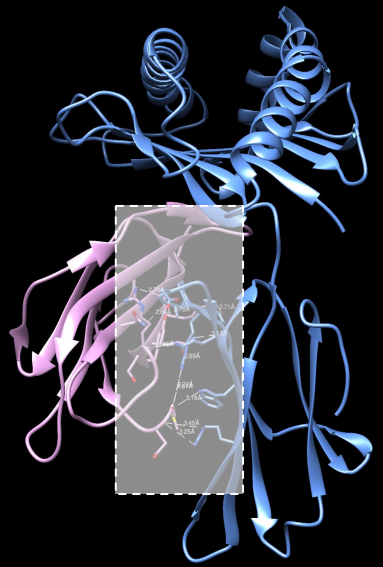


Images obtained from Chimera

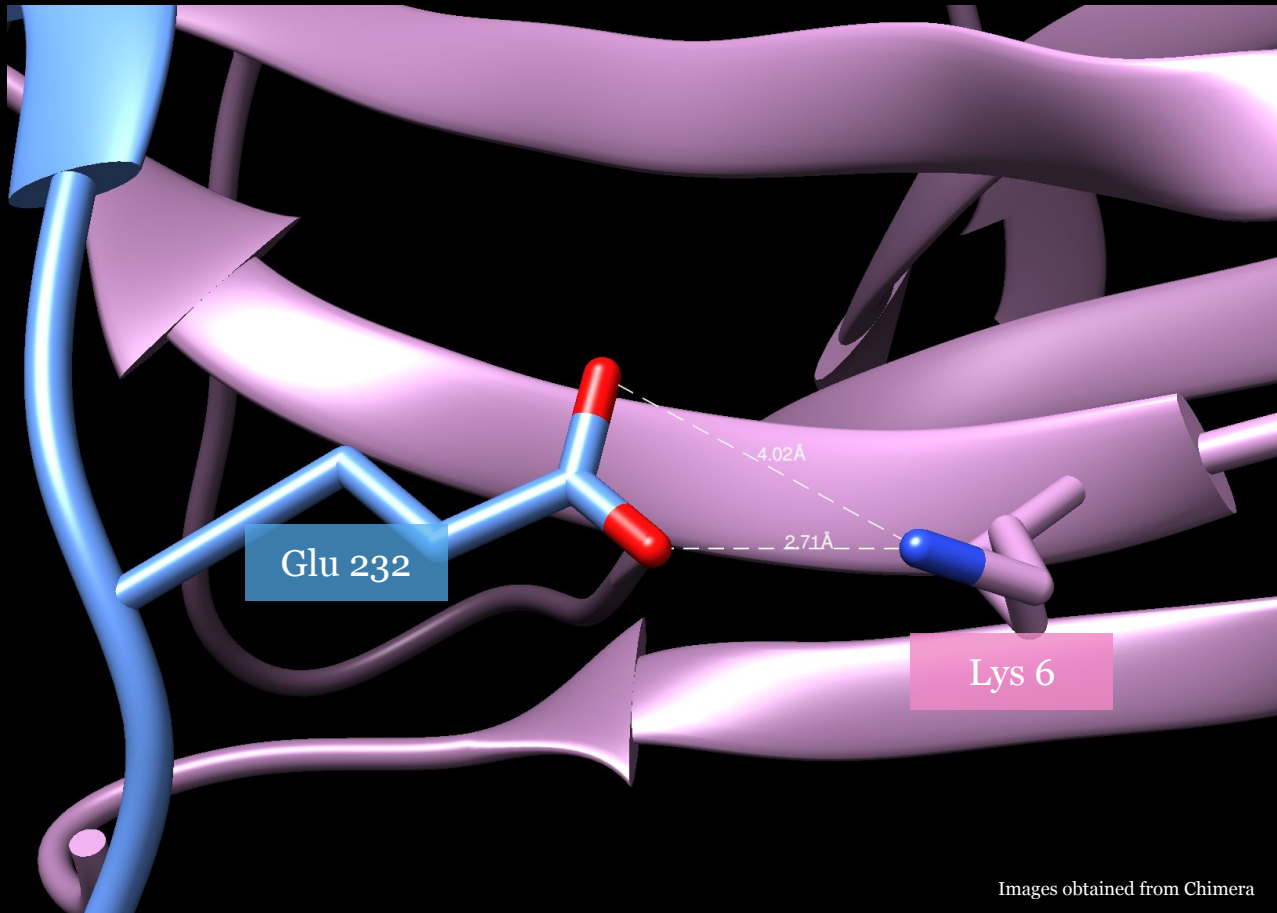
Structure stabilization | β2-microglobulin and α3 interactions

Salt bridge

A **salt bridge** combines electrostatic interactions and hydrogen bonds.

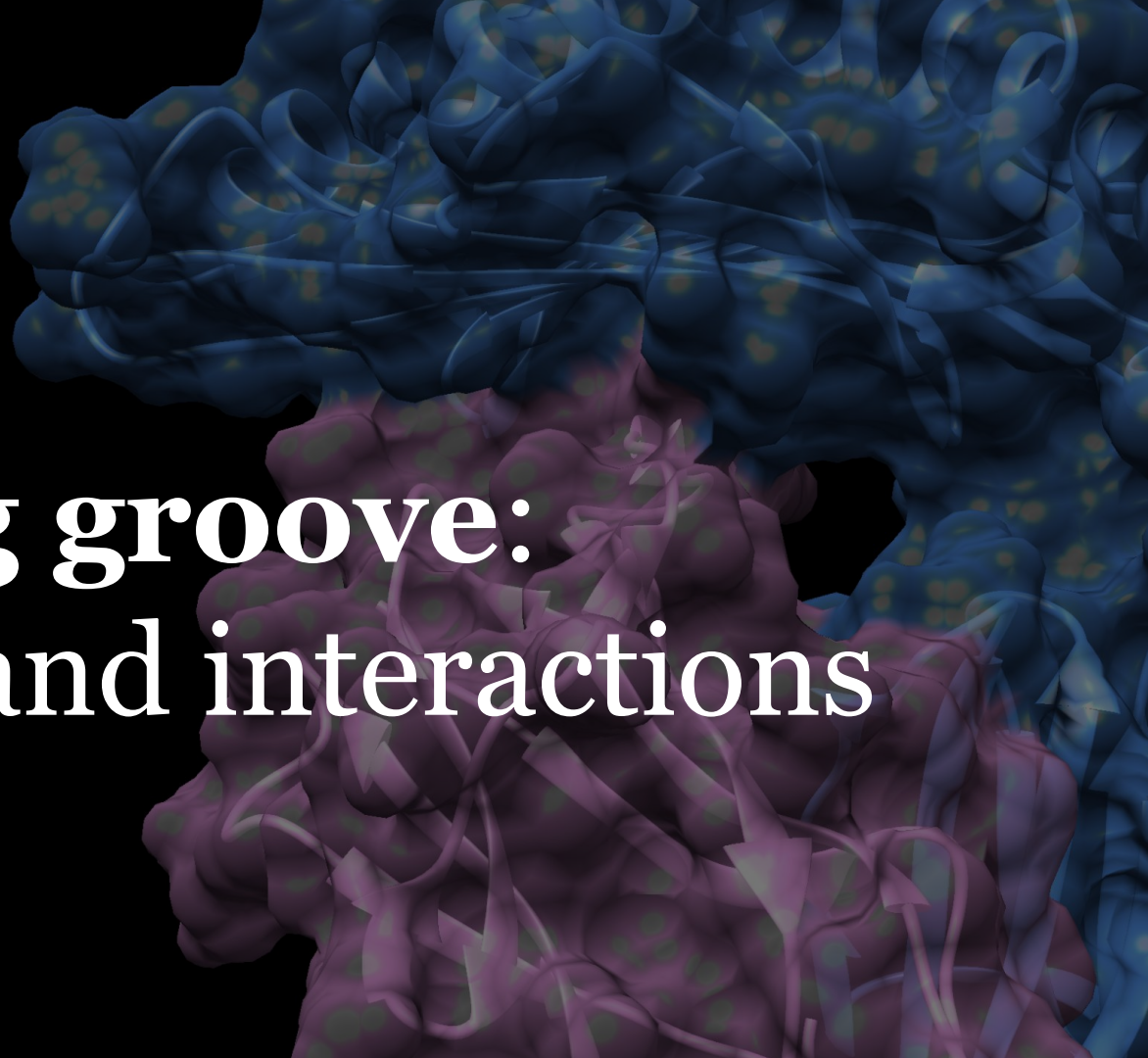


α3
β2m



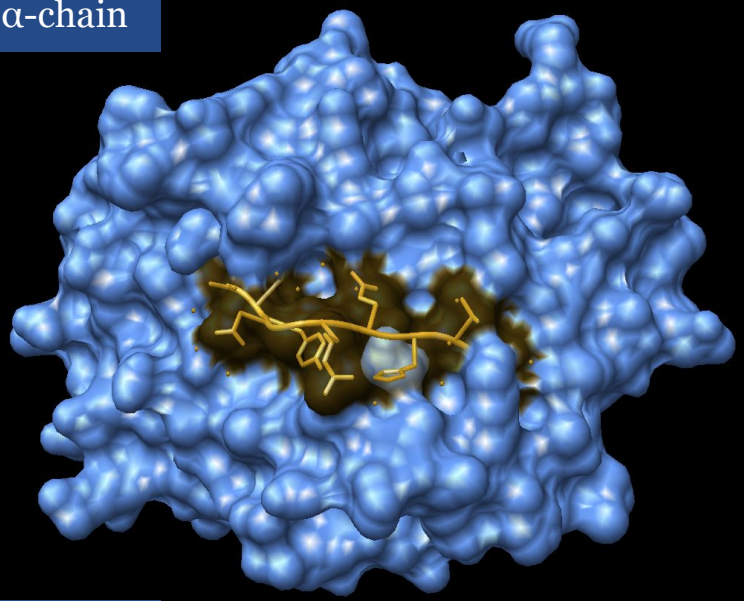
Images obtained from Chimera

03
Binding groove: pockets and interactions



HLA I and HLA II | Binding groove

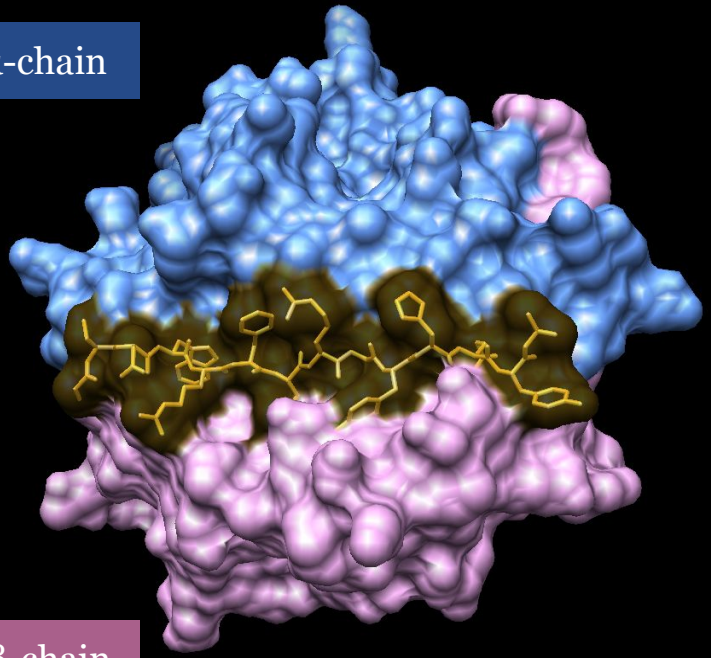
α-chain



α-chain

HLA-I
6 pockets (A-F)
Closed binding cleft

α-chain

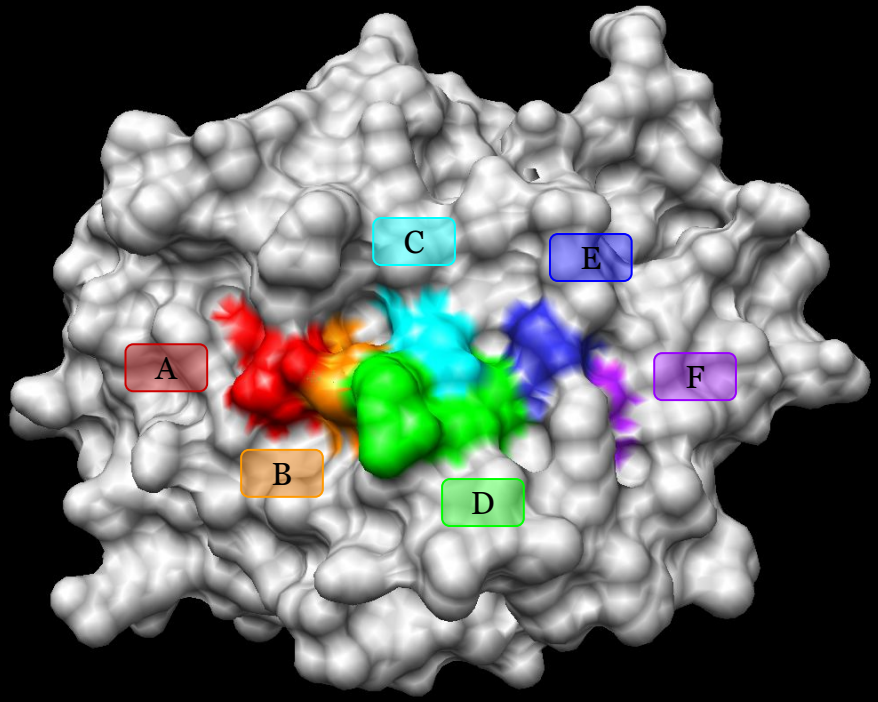


β-chain

HLA-II
9 pockets (A-I)
Open binding cleft

Images obtained from Chimera

HLA I | Binding groove

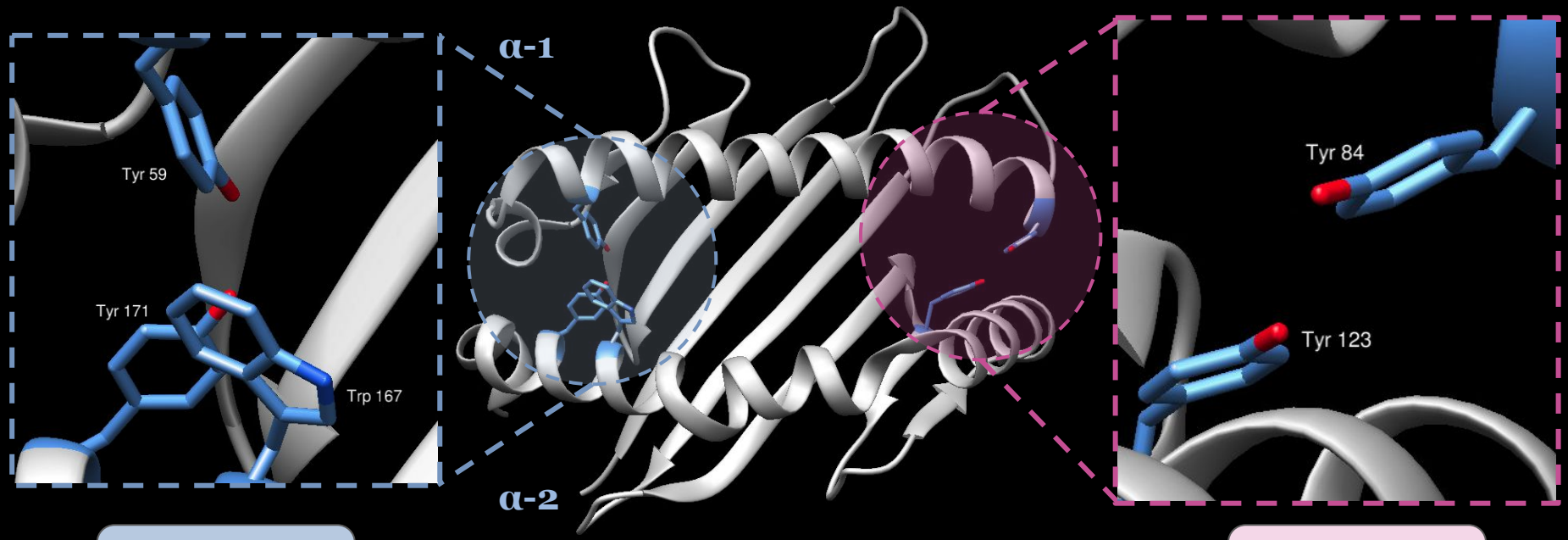


Pocket	Role of the pocket
A	Wall of the N-terminal part of the binding cleft
B	Bind primary anchor residue P2
C	Bind secondary anchor residue at P3 and P5/P6 when presents, face pocket D
D	Bind secondary anchor residue at P3 and P5/P6 when presents, face pocket C
E	Overlap with C/D pockets and secondary anchor residue at P5/P6 when presents and the C-terminal part of the peptide
F	Bind primary anchor residue PΩ, wall of the C-terminal part of the binding cleft

Adapted from Nguyen et al.

Images obtained from Chimera

HLA I | N and C termini

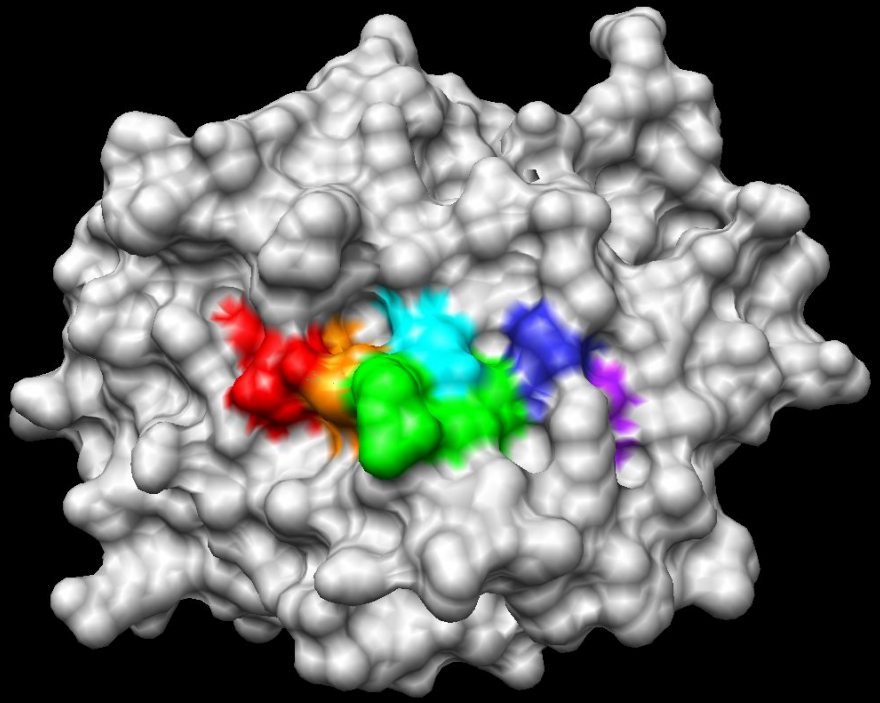


N-terminal Pocket A

C-terminal Pocket F

Images obtained from Chimera

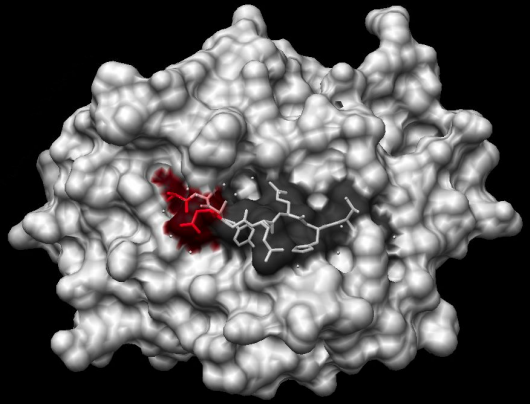
HLA I | Binding groove

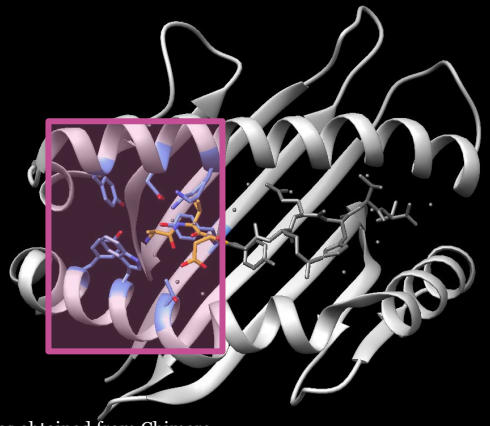


MAGE-A4 | **AVYDGREHTV**	
Pocket	Peptide residue
A	Ala 1, Asp 4
B	Val 2
C	Glu 7
D	Tyr 3, Gly 5, Arg 6, His 8
E	Thr 9
F	Val 10

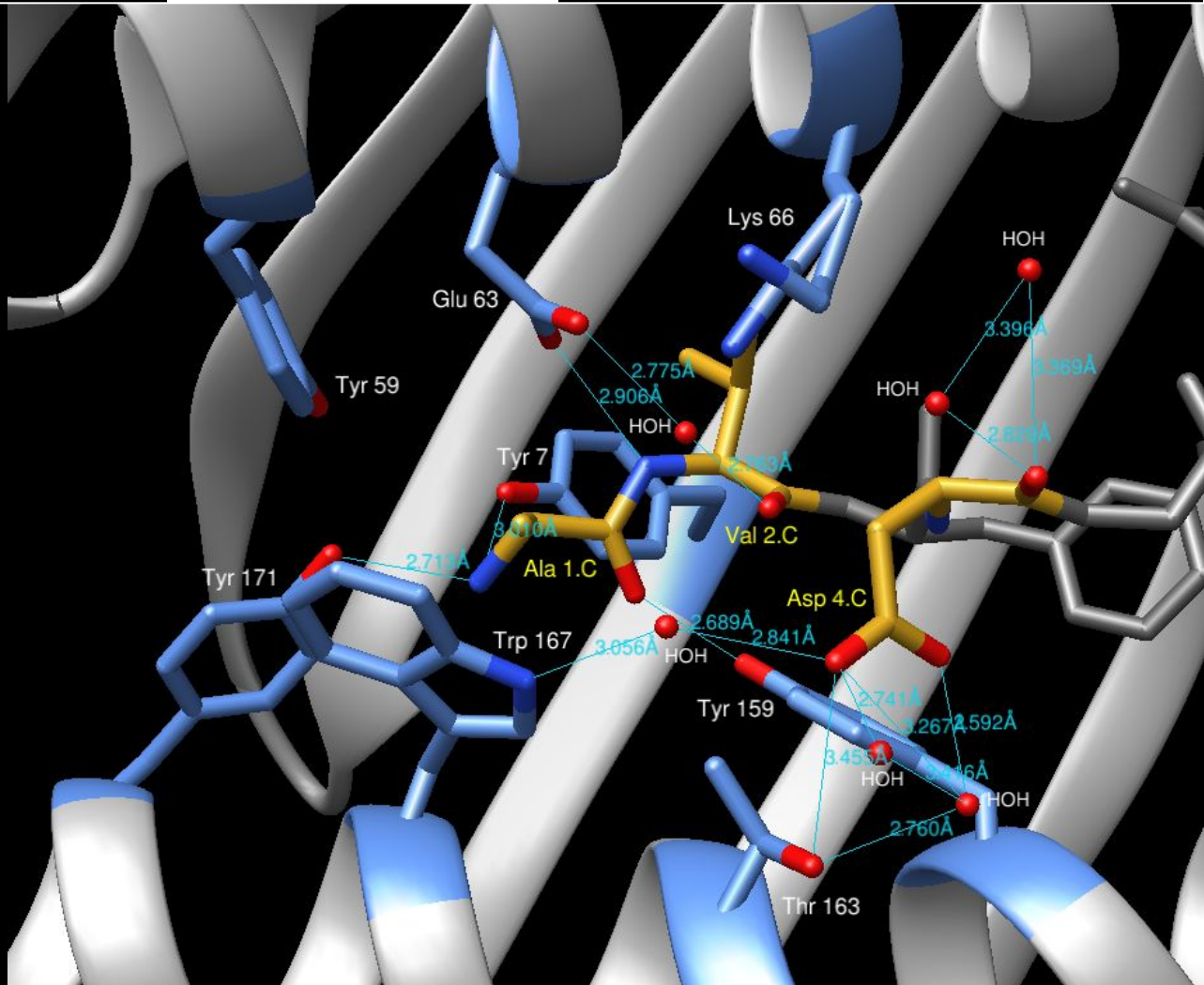
Images obtained from Chimera

Pocket A





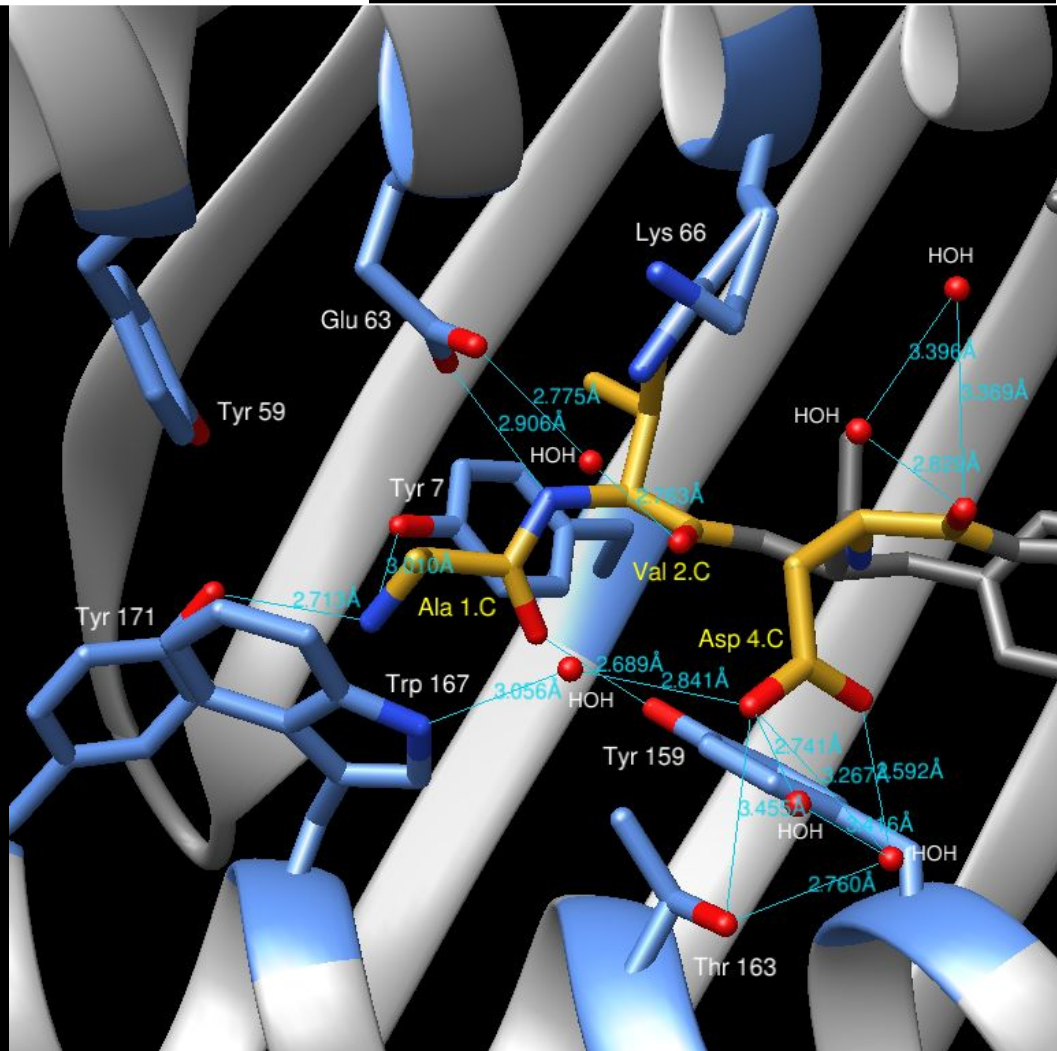
Images obtained from Chimera



Pocket A
Hydrogen bonds

Peptide	Atom	HLA-I	Atom	Length (Å)
Ala 1	N	Tyr 7	OH	3.01
	O2	Trp 159	OH	2.68
	N	Tyr 171	OH	2.71
	N	Met 5	SD	3.05

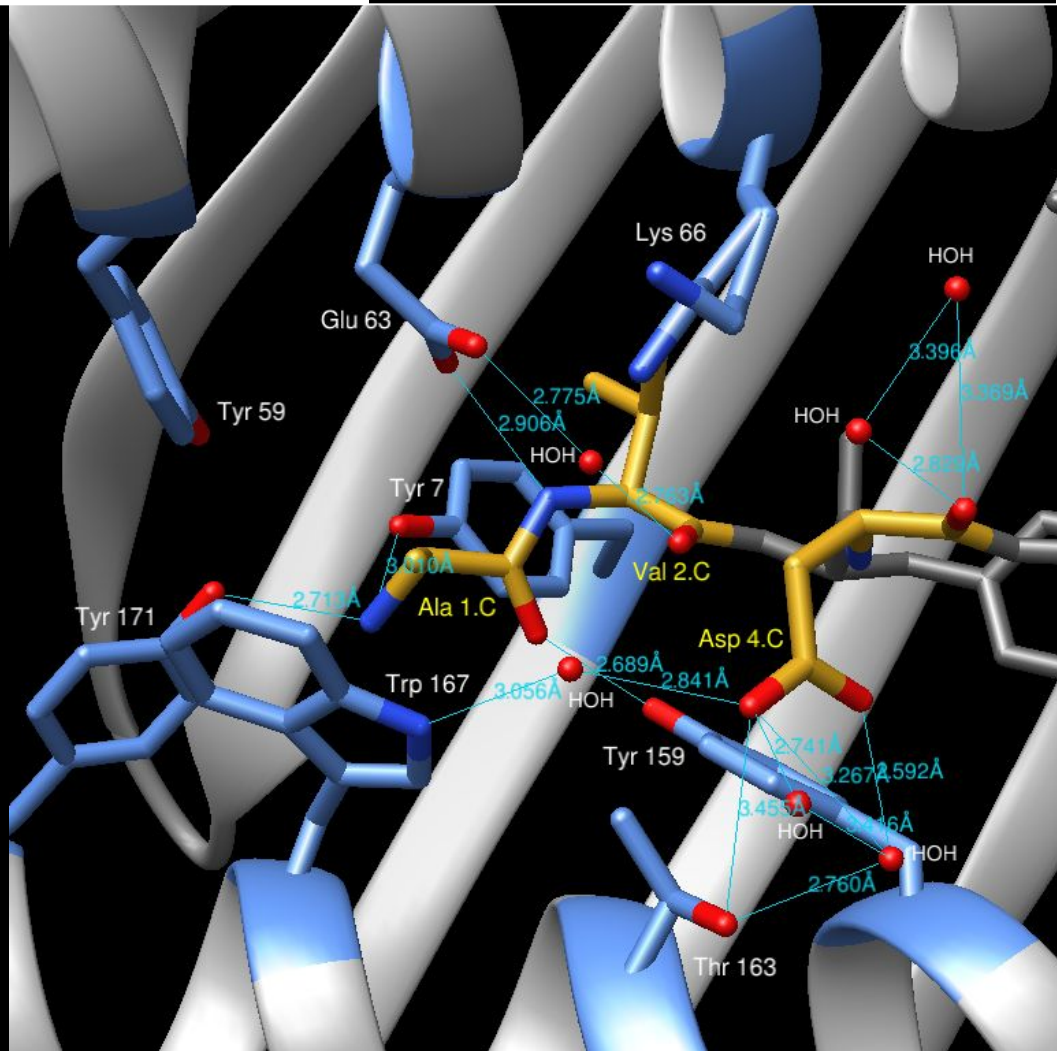
Peptide-molecule bond



Images obtained from Chimera

Pocket A
Hydrogen bonds

Peptide	Atom	HLA-I	Atom	Length (Å)
Val 2	N	Glu 63	OE2	2.90
	O2	HOH 106	HOH	2.76
Asp 4	OD1	HOH 102	O	2.59
	OD2	HOH 102	O	3.26
	OD2	HOH 103	O	2.74
	O2	HOH 107	O	2.82
	OD2	HOH 108	O	2.84
	O2	HOH 114	O	3.36
	OD2	Thr 163	OG1	3.46

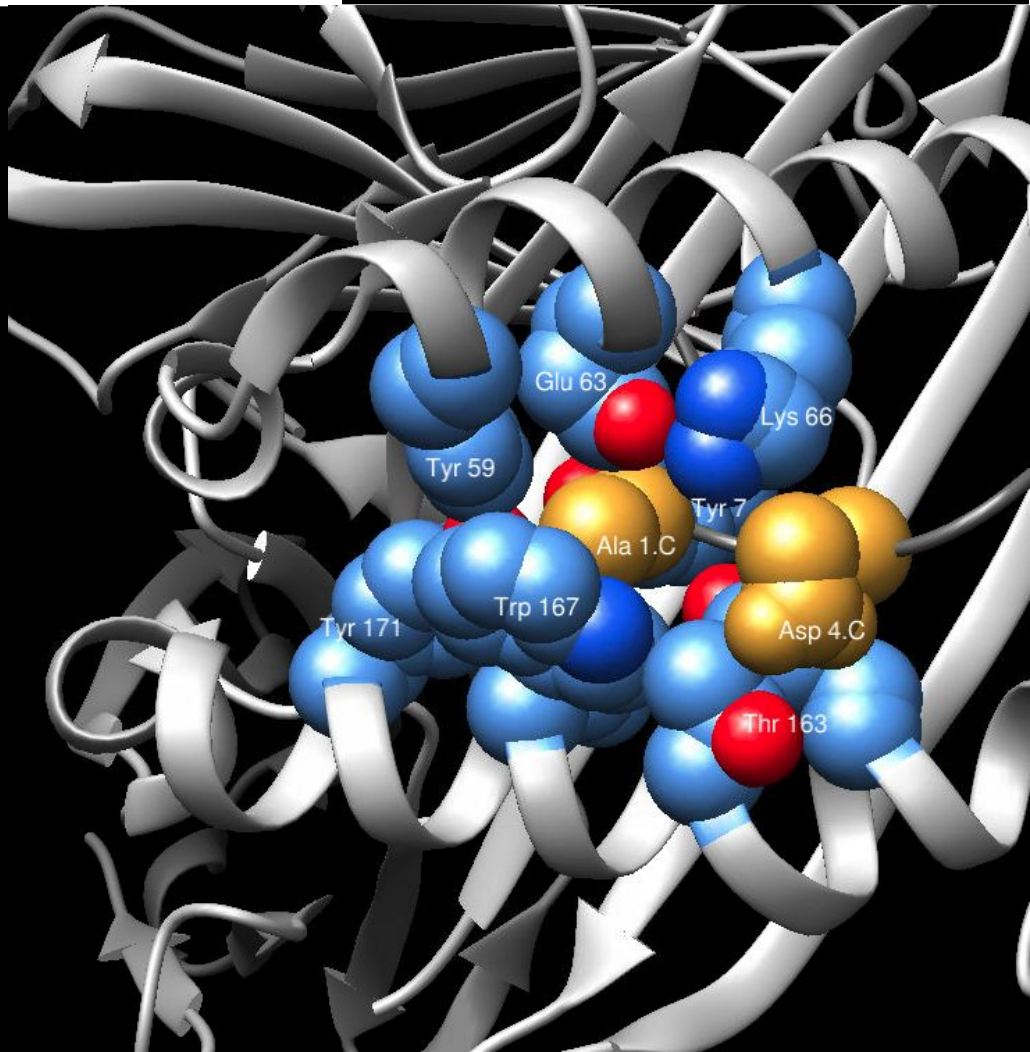


Images obtained from Chimera

Pocket A
Van der Waals interactions

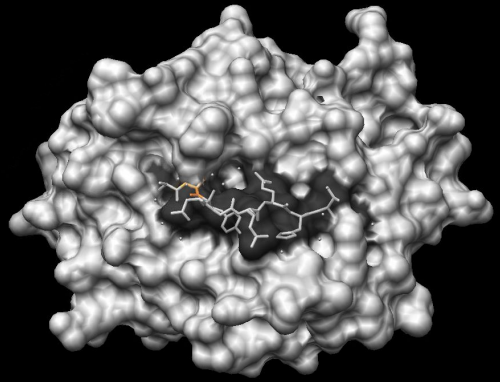
Peptide	HLA-I
Ala 1	Tyr 7
	Glu 63
	Tyr 59
	Lys 66
	Thr 163
	Trp 167
	Trp 171

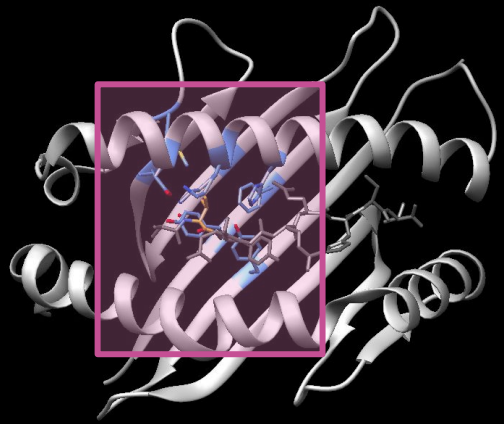
Non polar residue



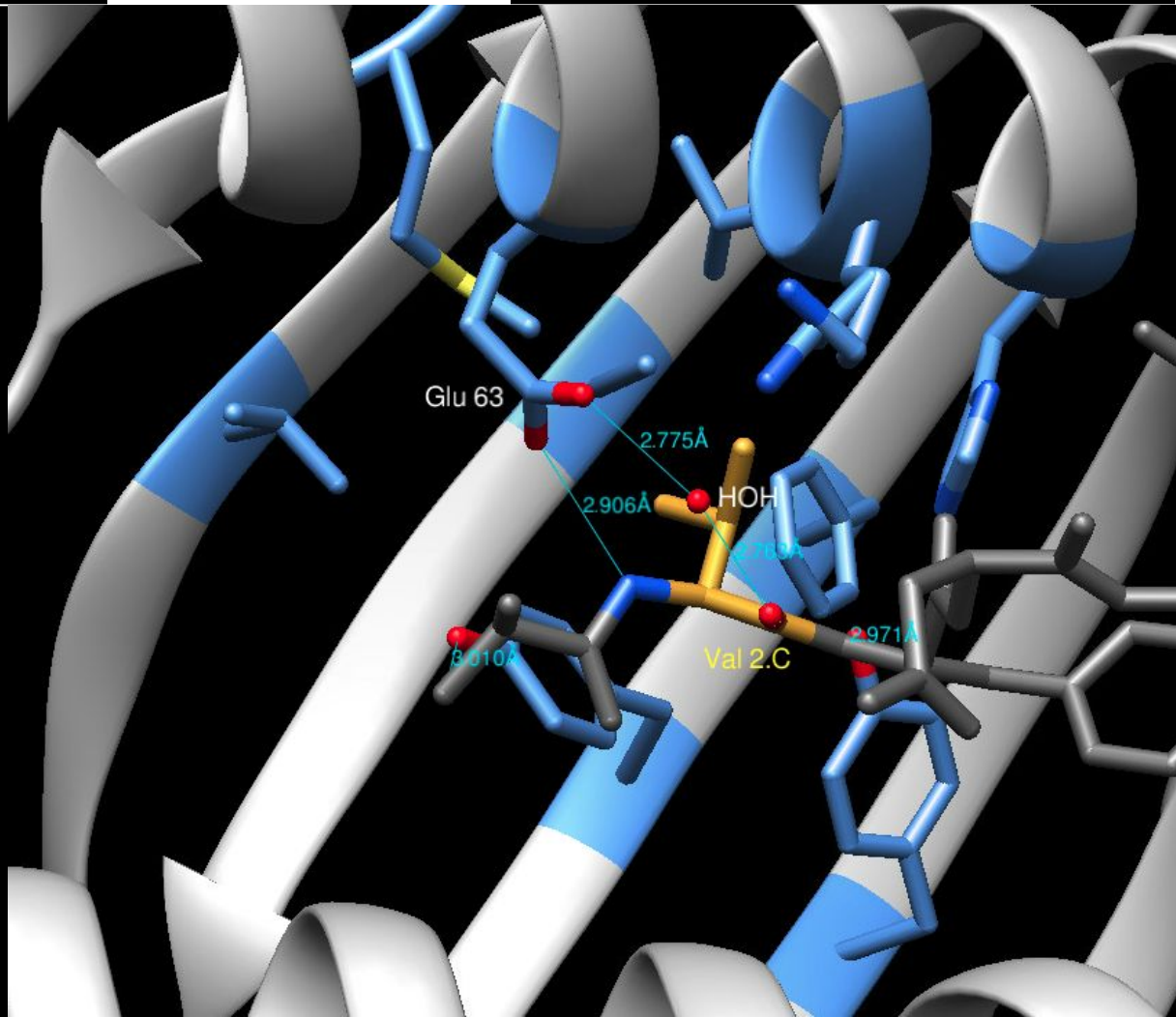
Images obtained from Chimera

Pocket B





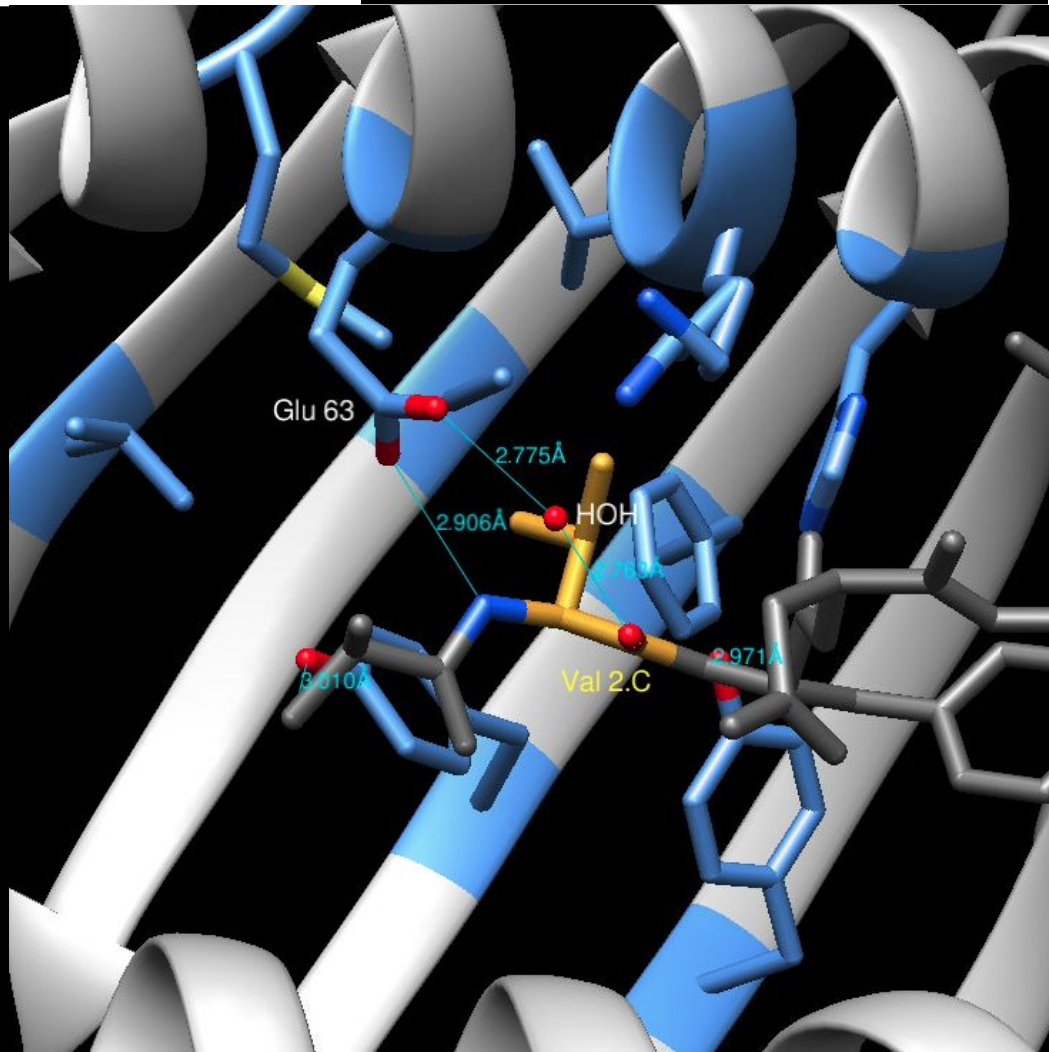
Images obtained from Chimera



Pocket B
Hydrogen bonds

Peptide	Atom	HLA-I	Atom	Length (Å)
Val 2	N	Glu 63	OE2	2.90
	O2	Glu 63	O2	2.77
	O2	HOH 106	HOH	2.76

Peptide-molecule bond

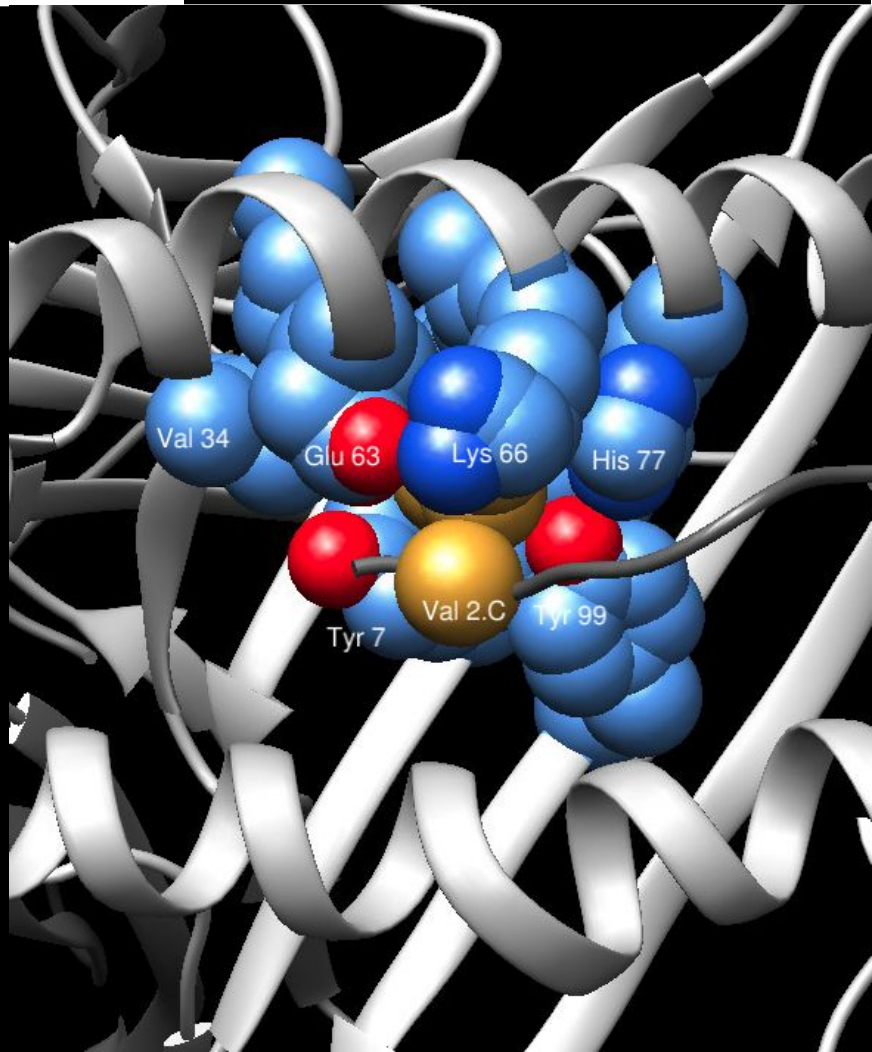


Images obtained from Chimera

Pocket B
Van der Waals interactions

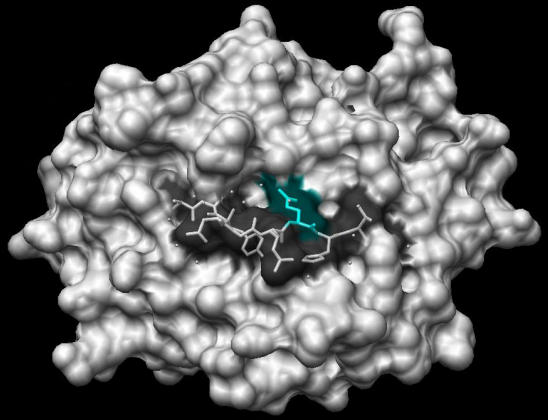
Peptide	HLA-I
Val 2	Tyr 7
	Glu 63
	Lys 66
	His 77
	Tyr 99

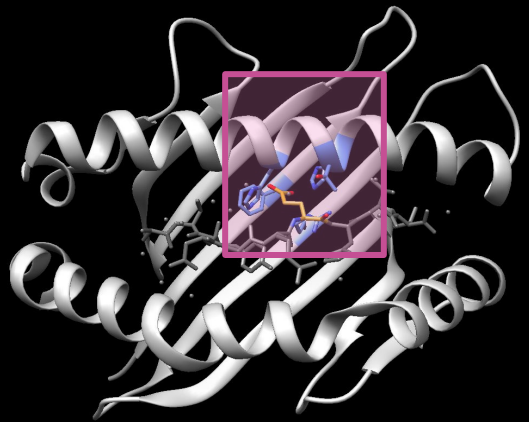
Non polar residue



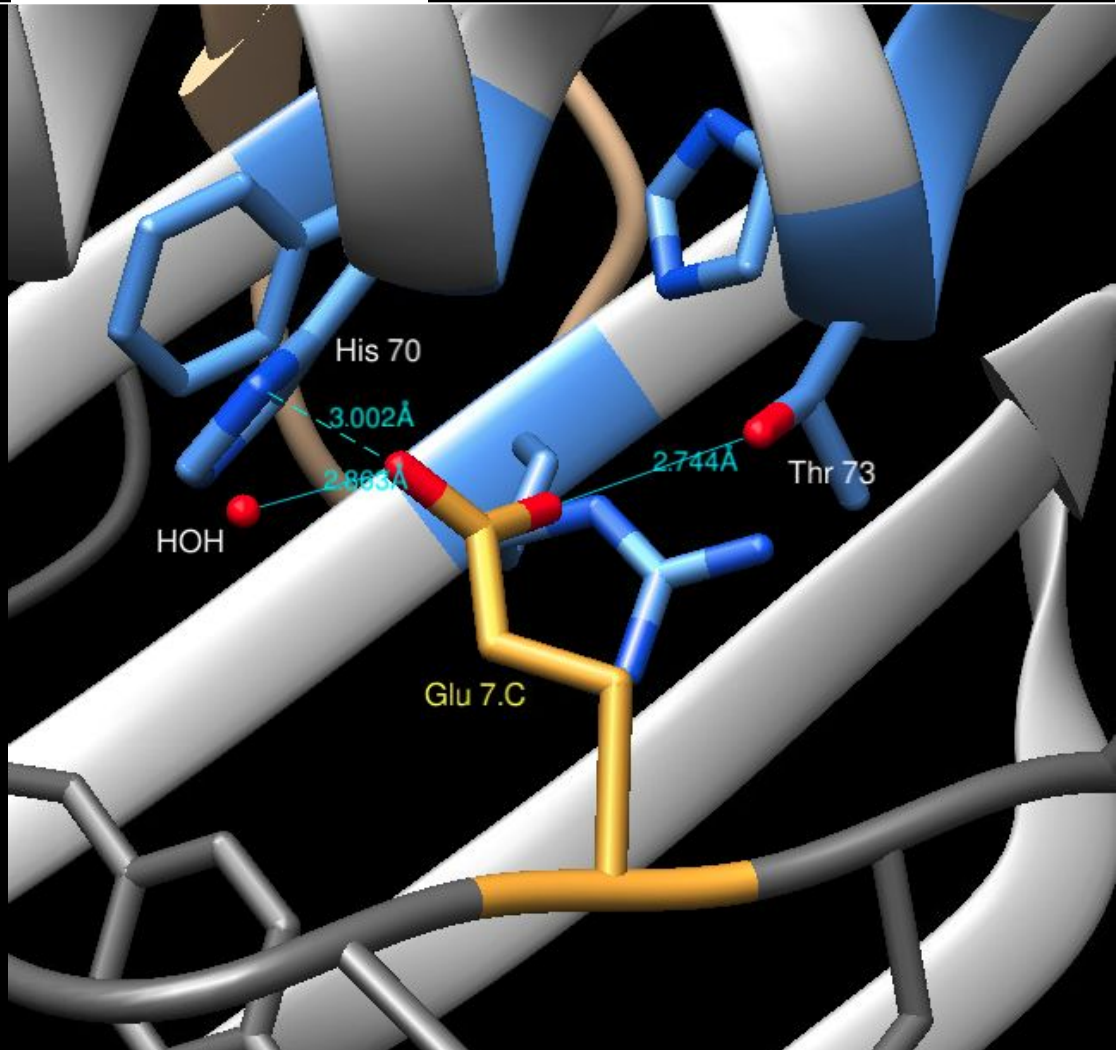
Images obtained from Chimera

Pocket C





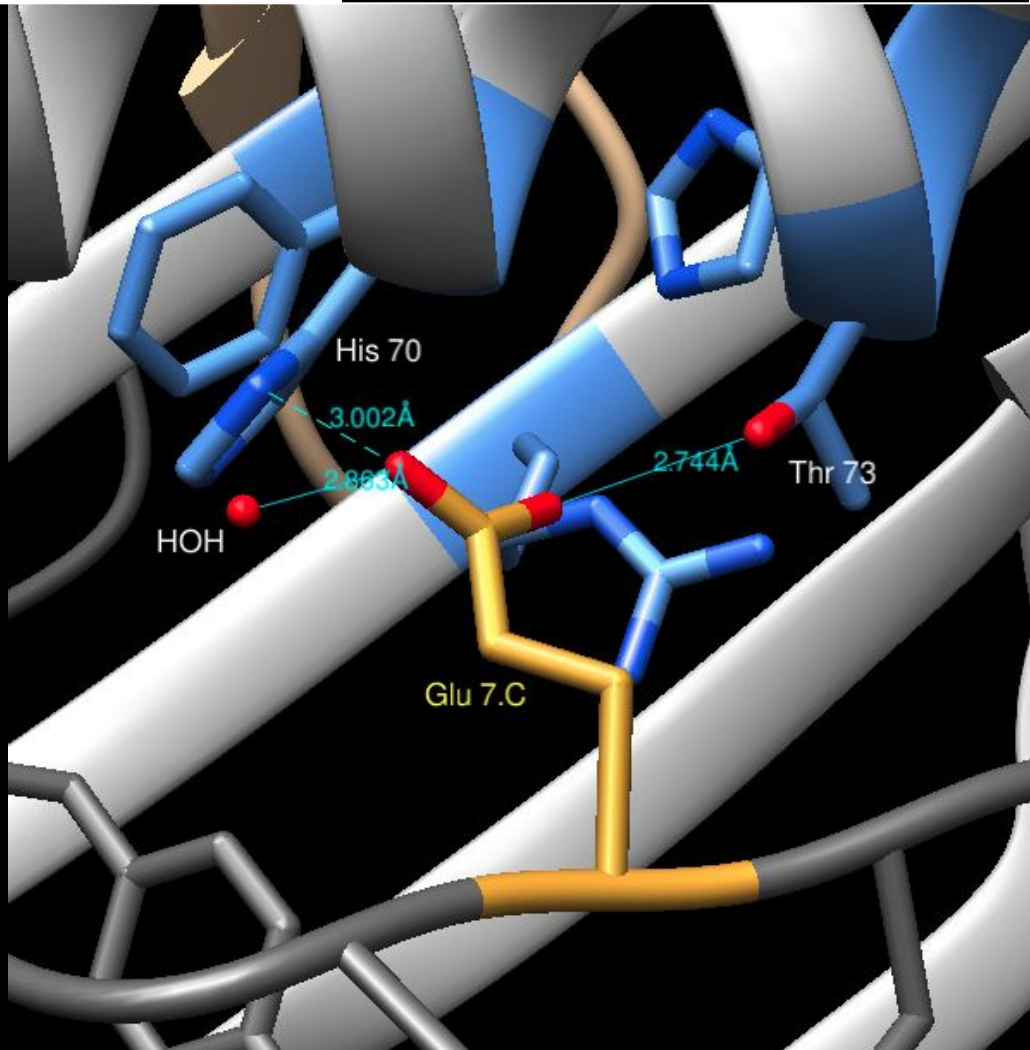
Images obtained from Chimera



Pocket C
Hydrogen bonds

Peptide	Atom	HLA-I	Atom	Length (Å)
Glu 7	OE1	Thr 73	O	2.74
	OE2	His 70	N	3.00
	OE2	HOH 109	O	2.86

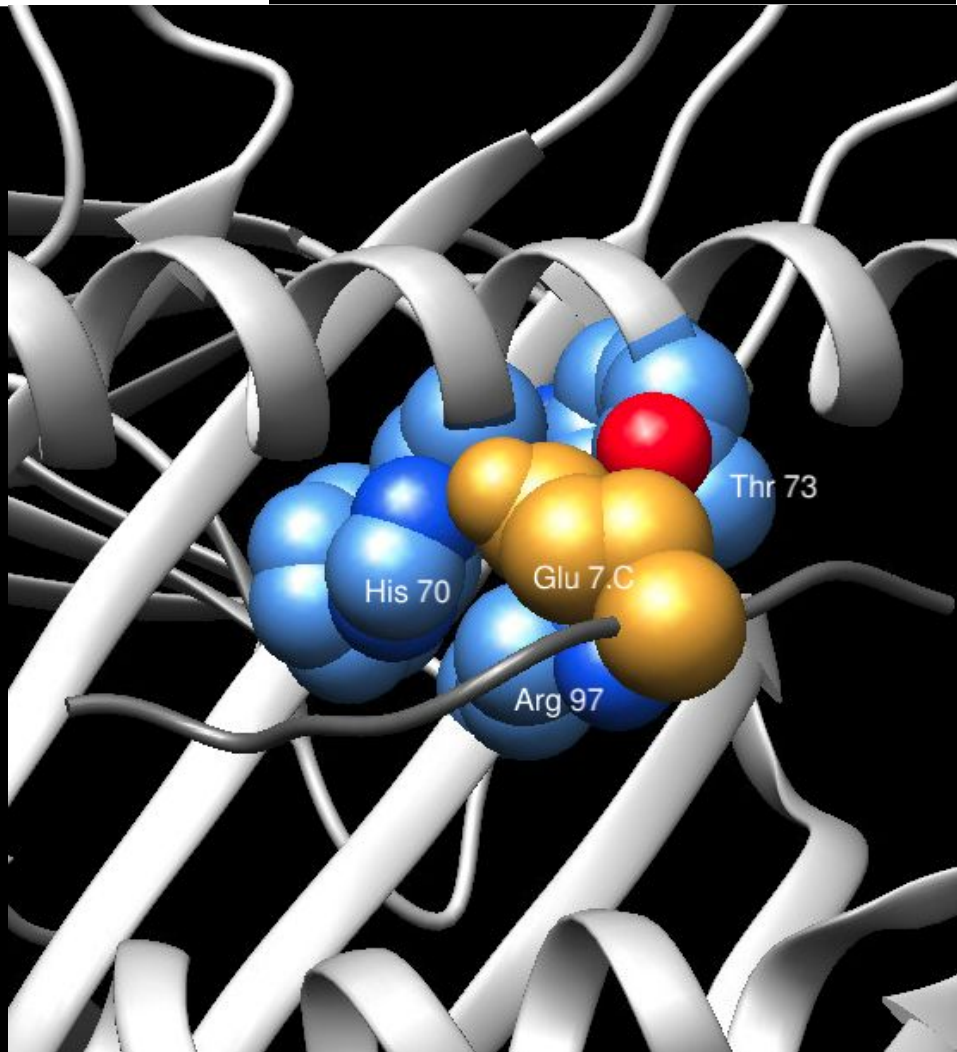
Peptide-molecule bond



Images obtained from Chimera

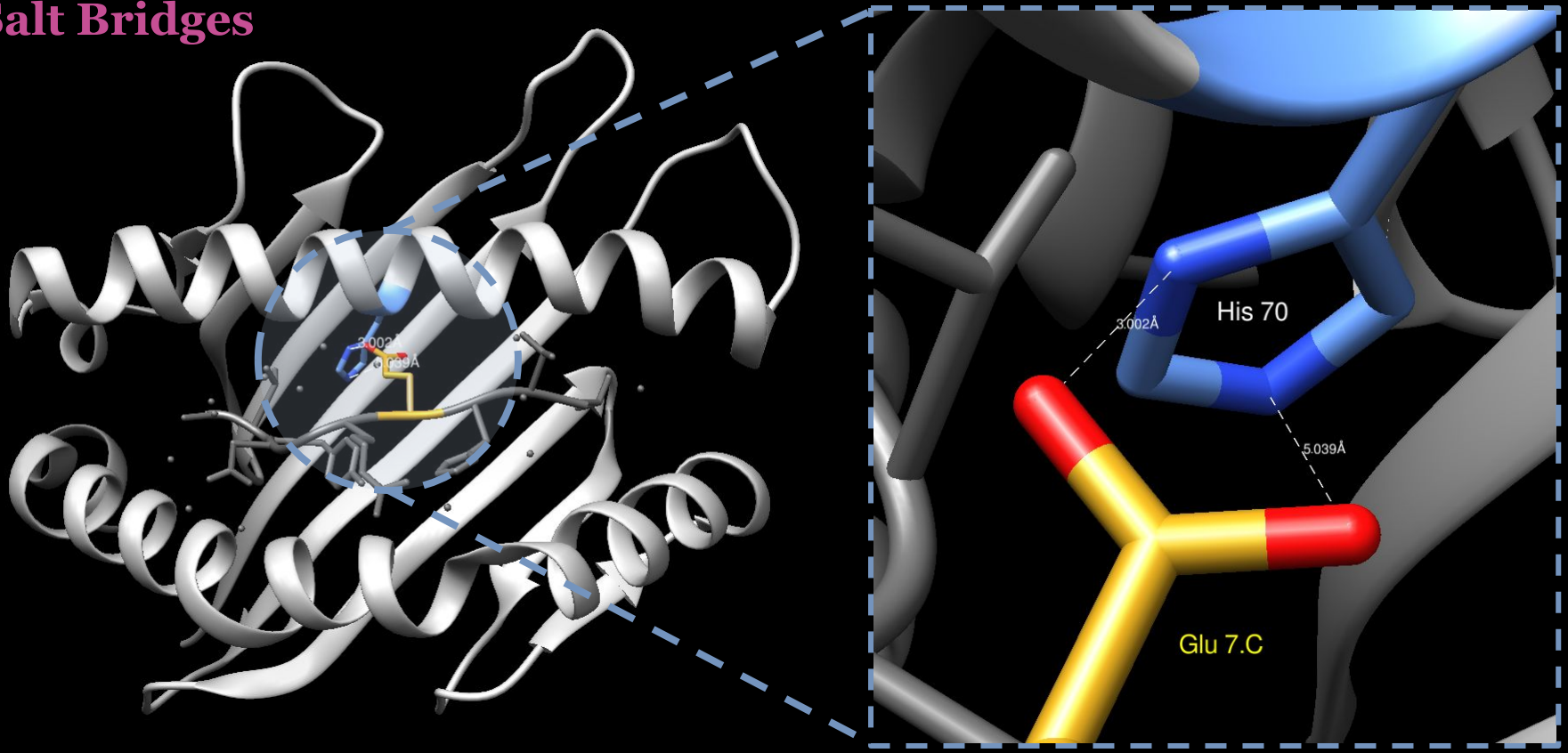
Pocket C
Van der Waals interactions

Peptide	HLA-I
Glu 7	His 70
	Thr 73
	Arg 97



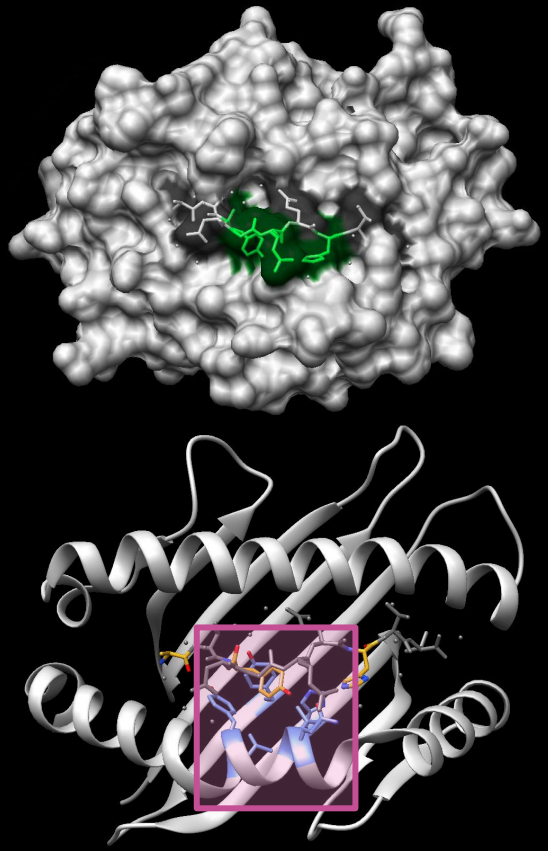
Images obtained from Chimera

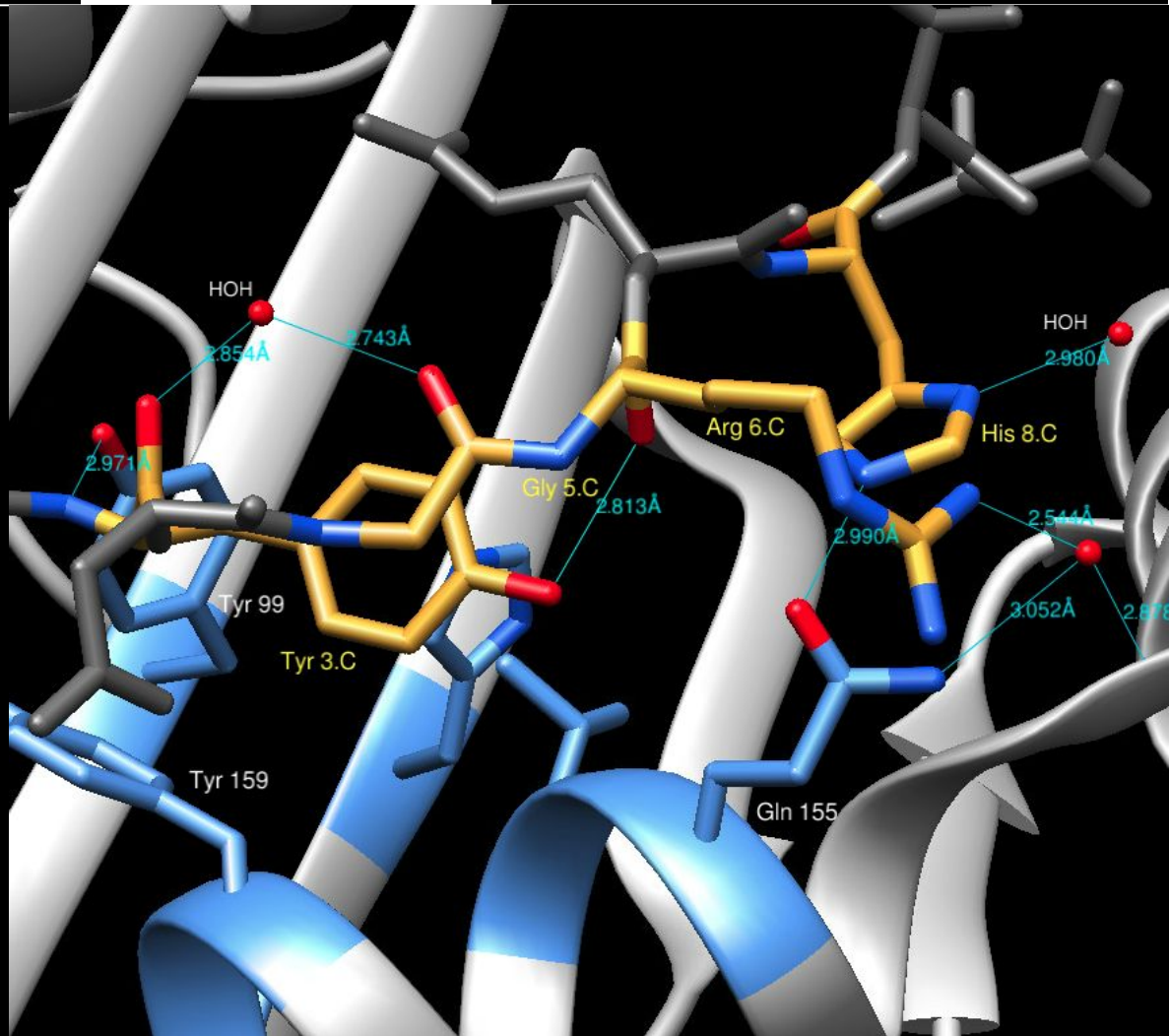
Pocket C
Salt Bridges



Images obtained from Chimera

Pocket D



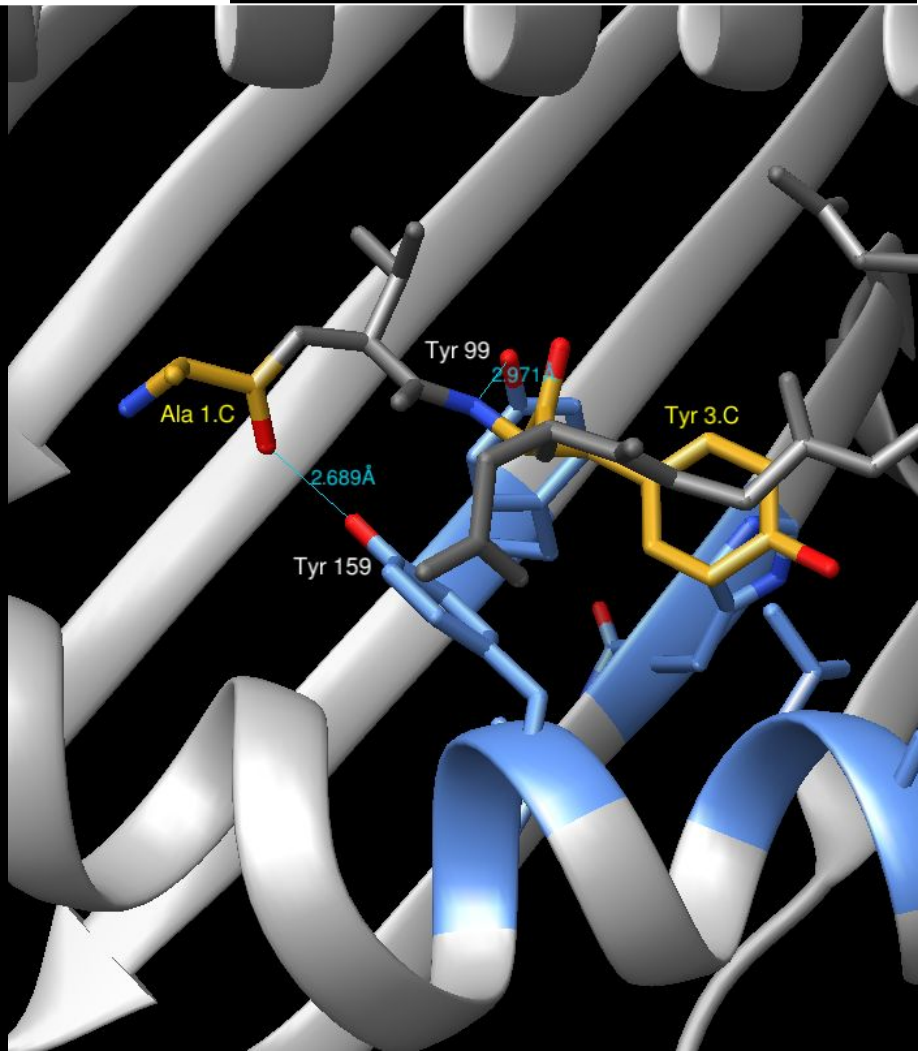


Images obtained from Chimera

Pocket D
Hydrogen bonds

Peptide	Atom	HLA-I	Atom	Length (Å)
Ala 1	O2	Trp 159	OH	2.68

Peptide-molecule bond



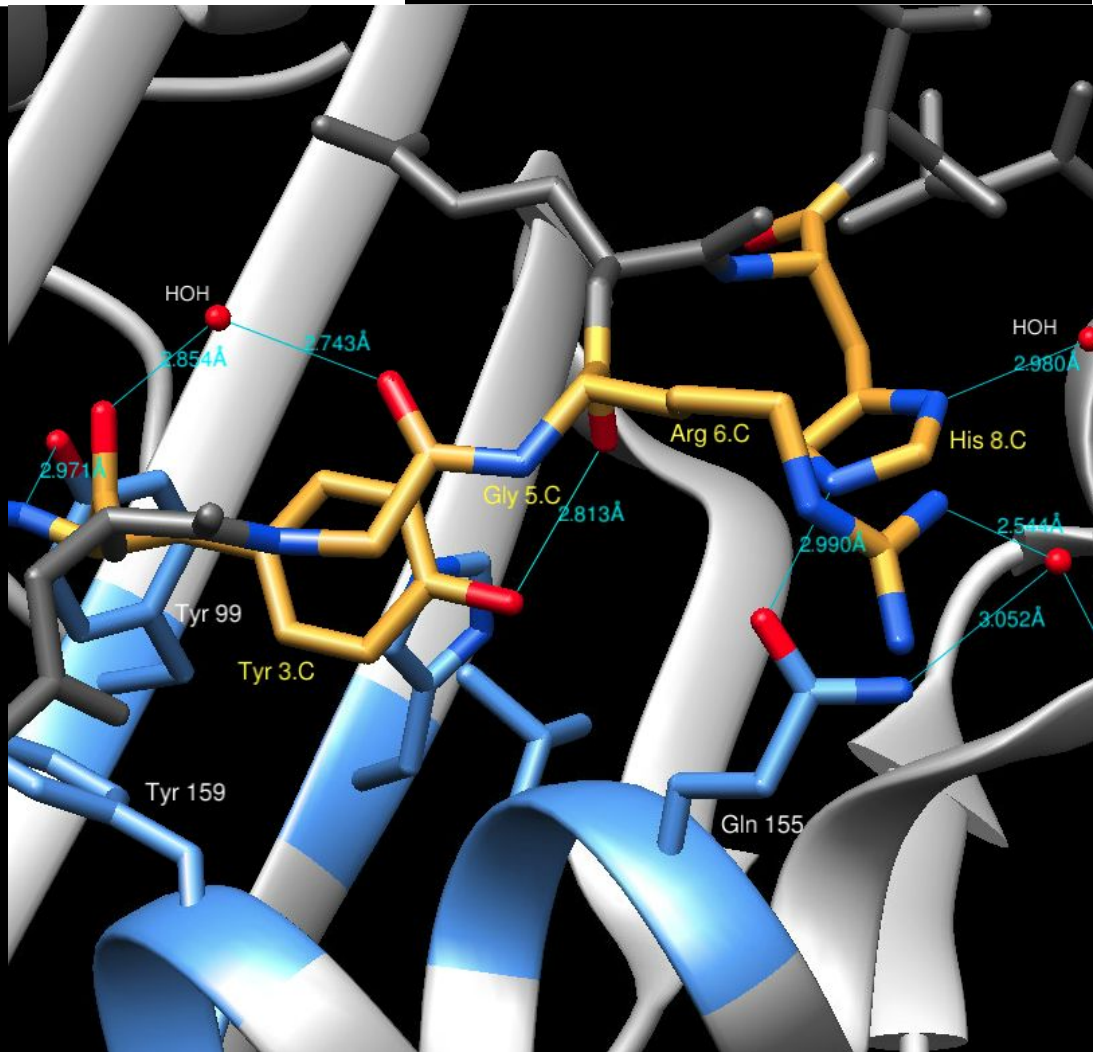
Images obtained from Chimera

Pocket D
Hydrogen bonds

Peptide	Atom	HLA-I	Atom	Length (Å)
Tyr 3	N	Tyr 99	OH	2.97
	O	HOH 104	O	2.85
	O	Gly 5 (P)	O2	2.74
	OH	Arg 6 (P)	O	2.81
His 8	ND1	HOH 112	O	2.95
	NE2	Gln 155	OE1	2.99

Peptide-molecule bond

Peptide-peptide bond

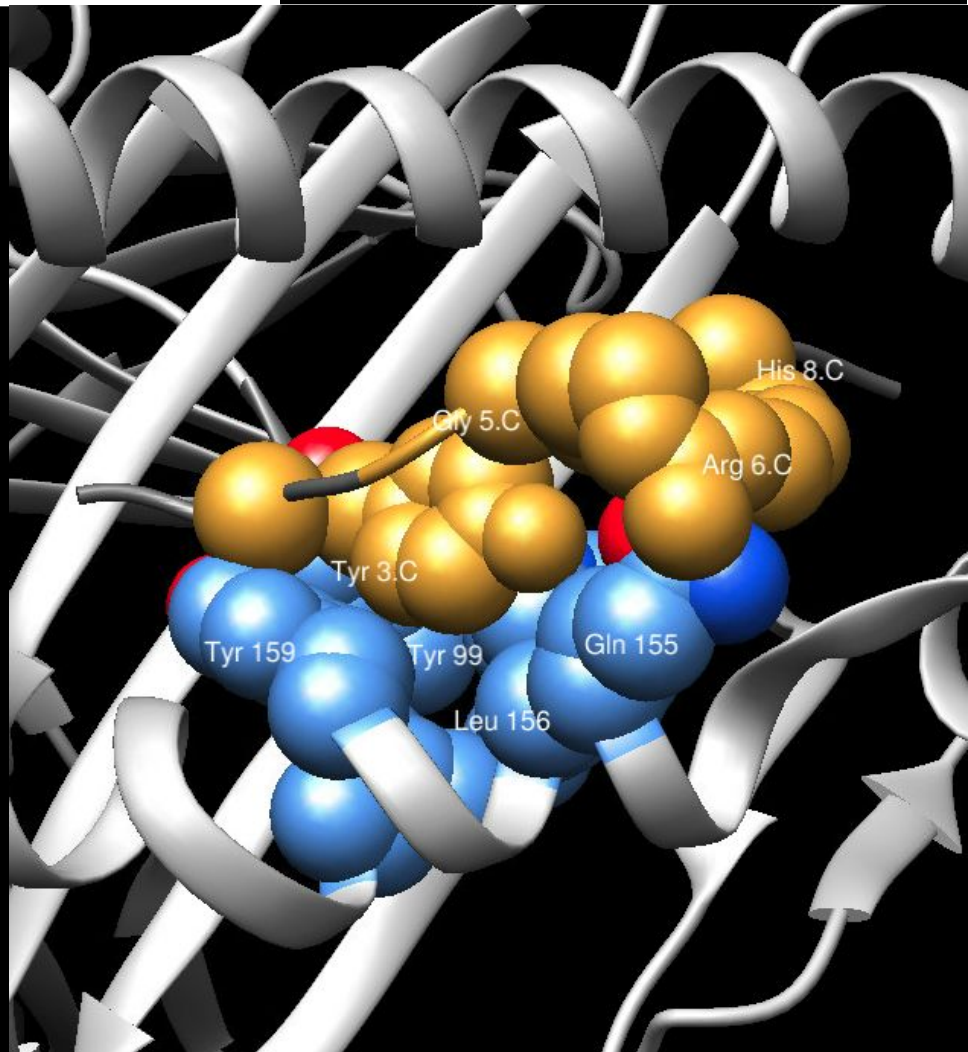


Images obtained from Chimera

Pocket D
Van der Waals interactions

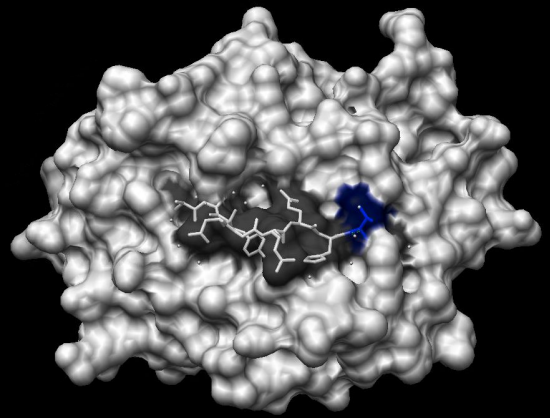
Peptide	HLA-I
Tyr 3	Tyr 99
	Leu 156
	Tyr 159
	Gly 5 (P)
	Arg 6 (P)

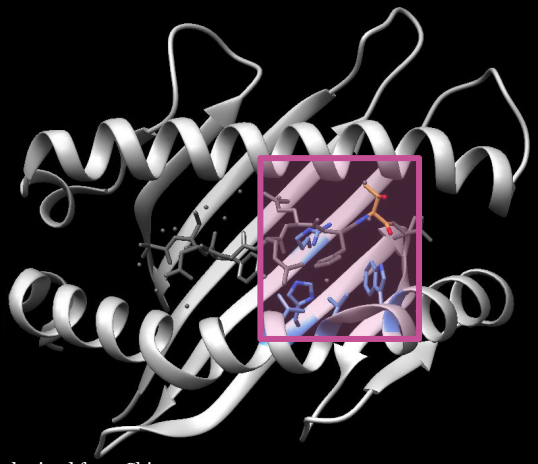
His 8	Gln 155



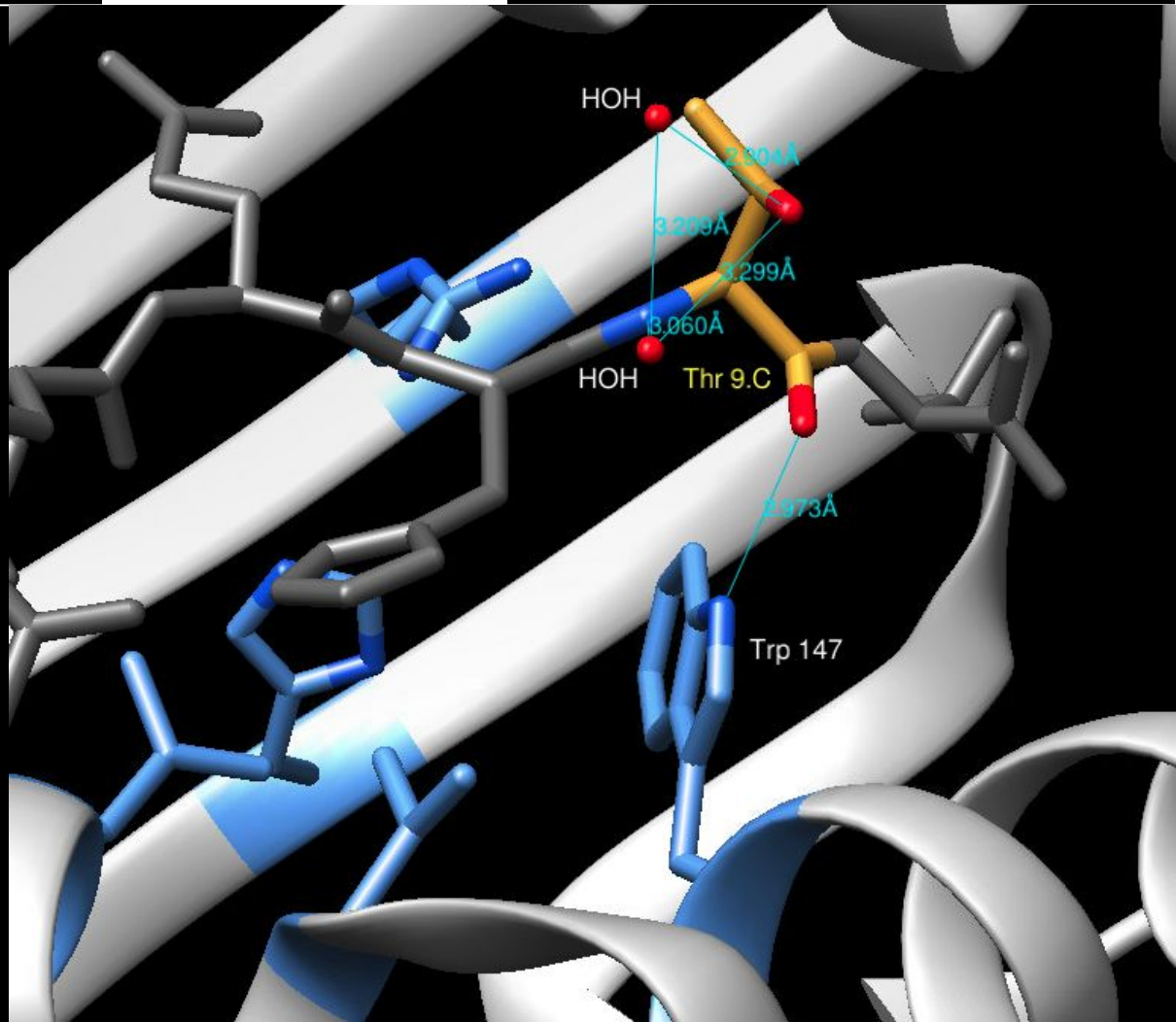
Images obtained from Chimera

Pocket E





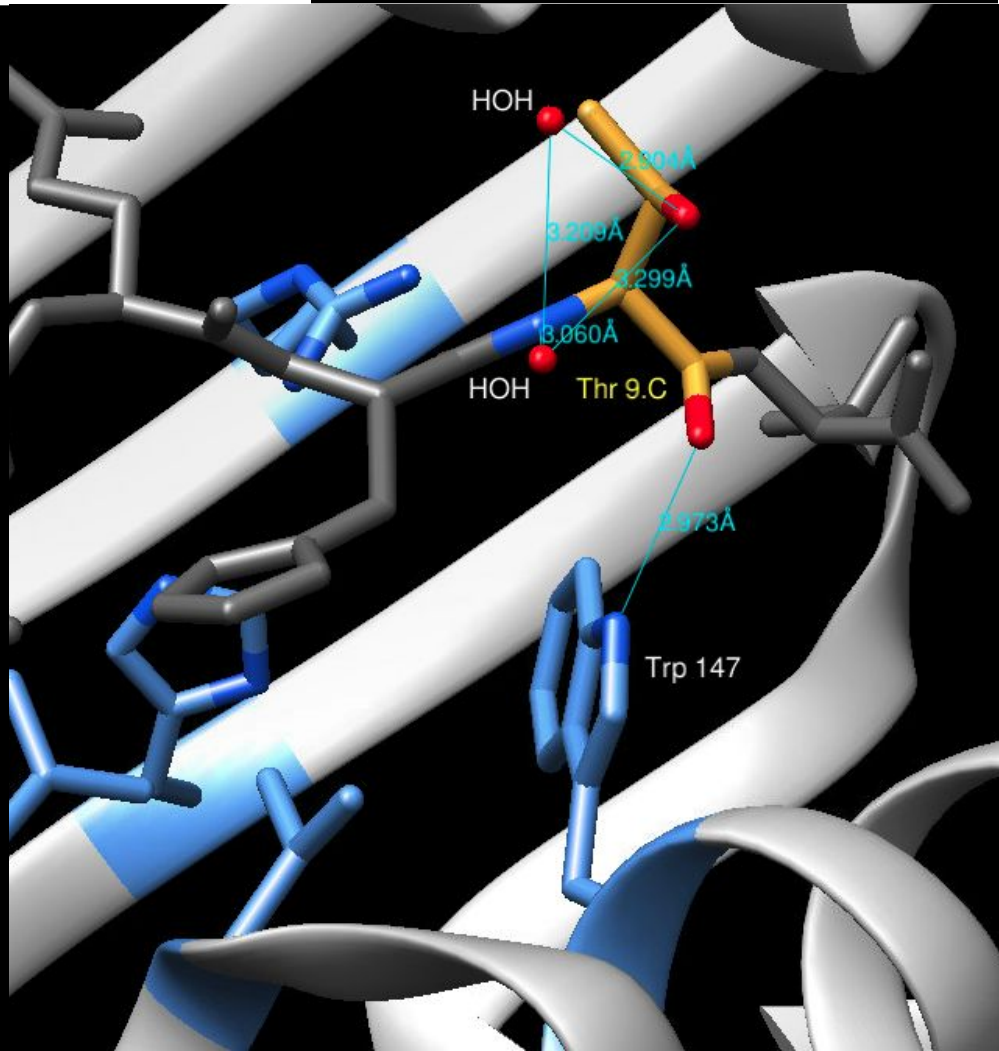
Images obtained from Chimera



Pocket E
Hydrogen bonds

Peptide	Atom	HLA-I	Atom	Length (Å)
Thr 9	OG1	HOH 110	O	2.90
	OG1	HOH 113	O	3.29
	O	Trp 147	NE1	2.97

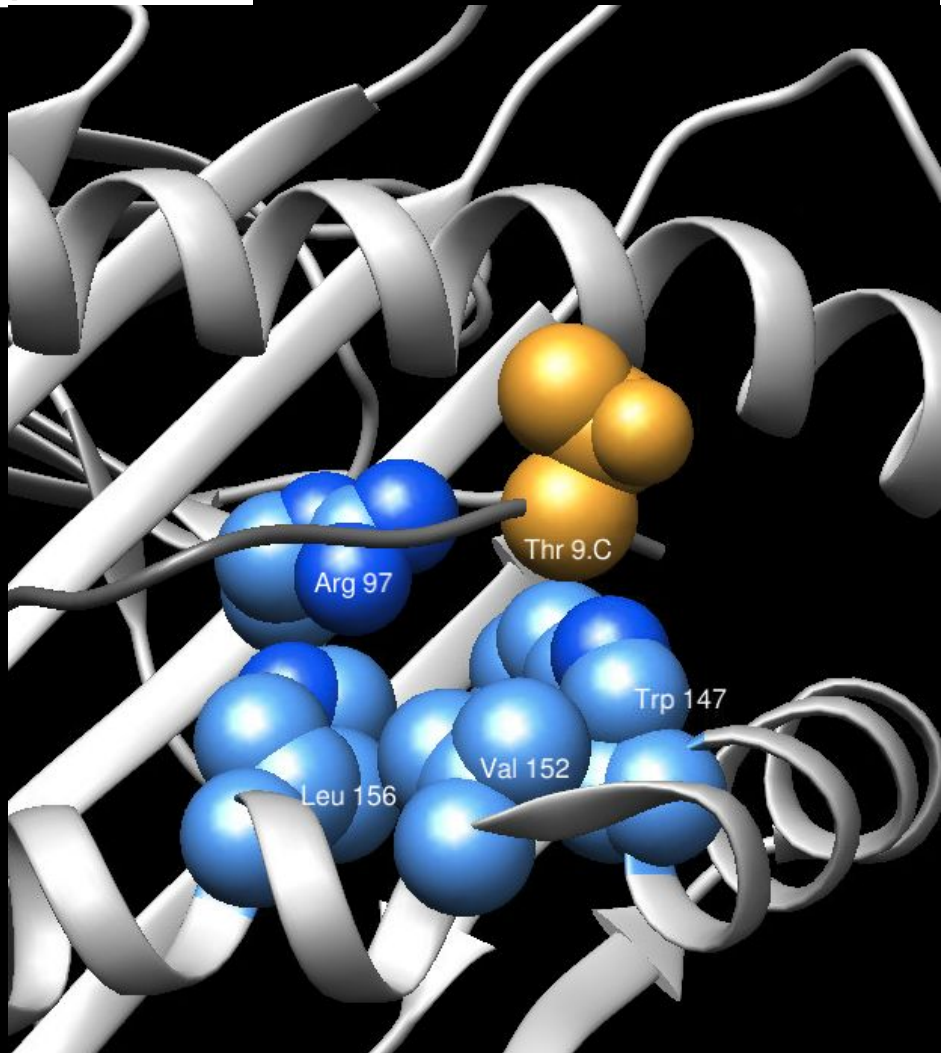
Peptide-molecule bond



Images obtained from Chimera

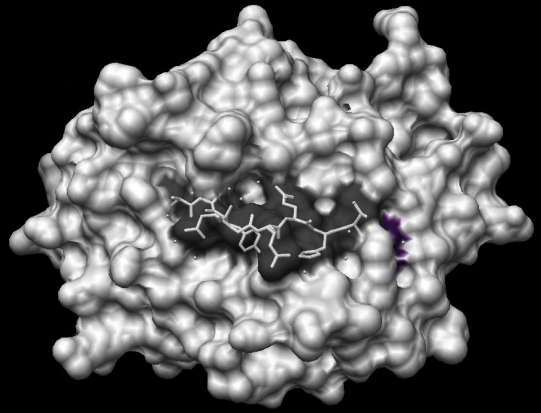
Pocket E
Van der Waals interactions

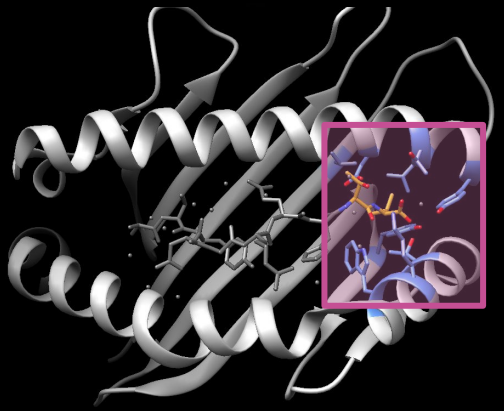
Peptide	HLA-I
Thr 9	Arg 97
	Trp 147
	Val 152
	Leu 156



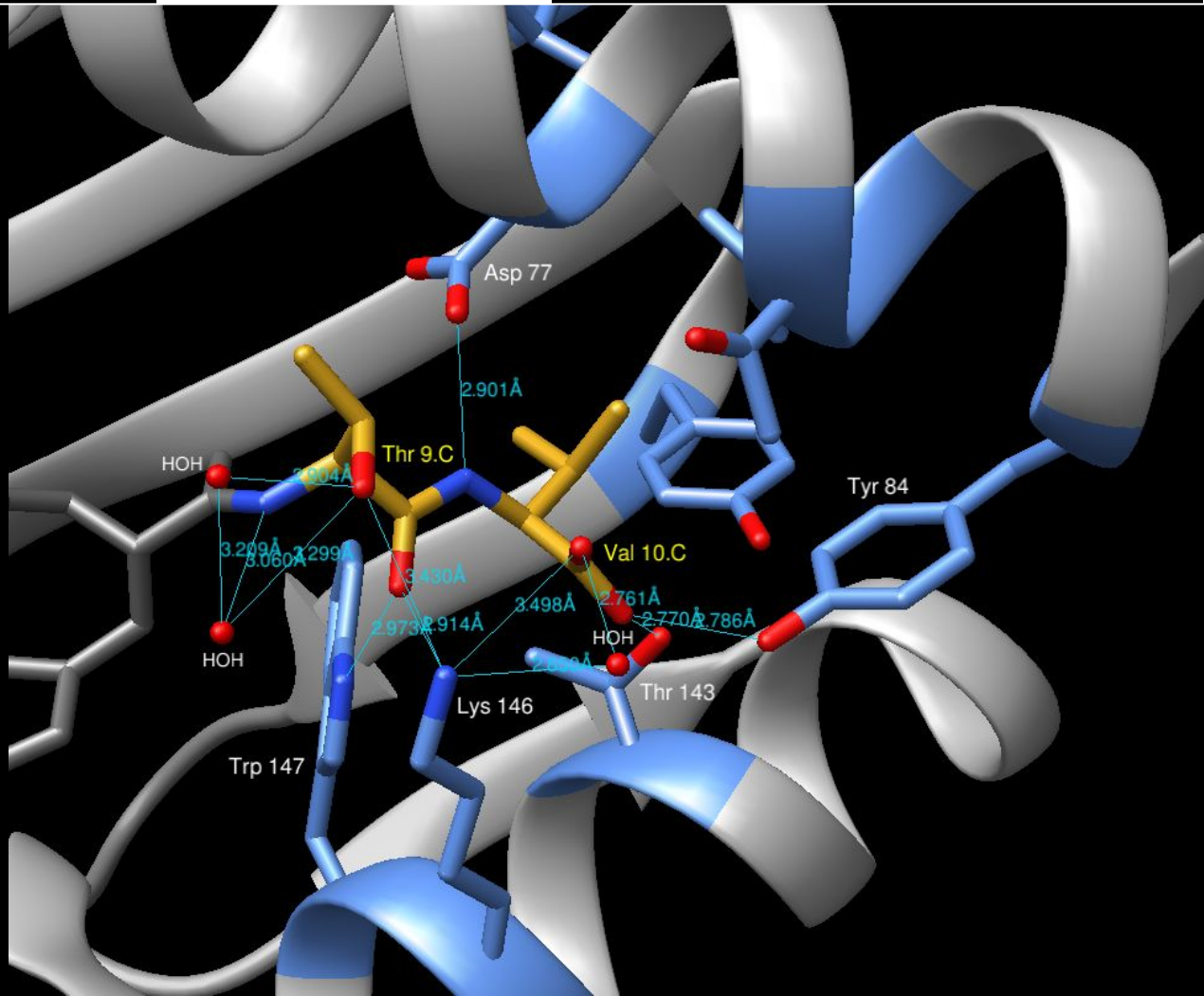
Images obtained from Chimera

Pocket F





Images obtained from Chimera

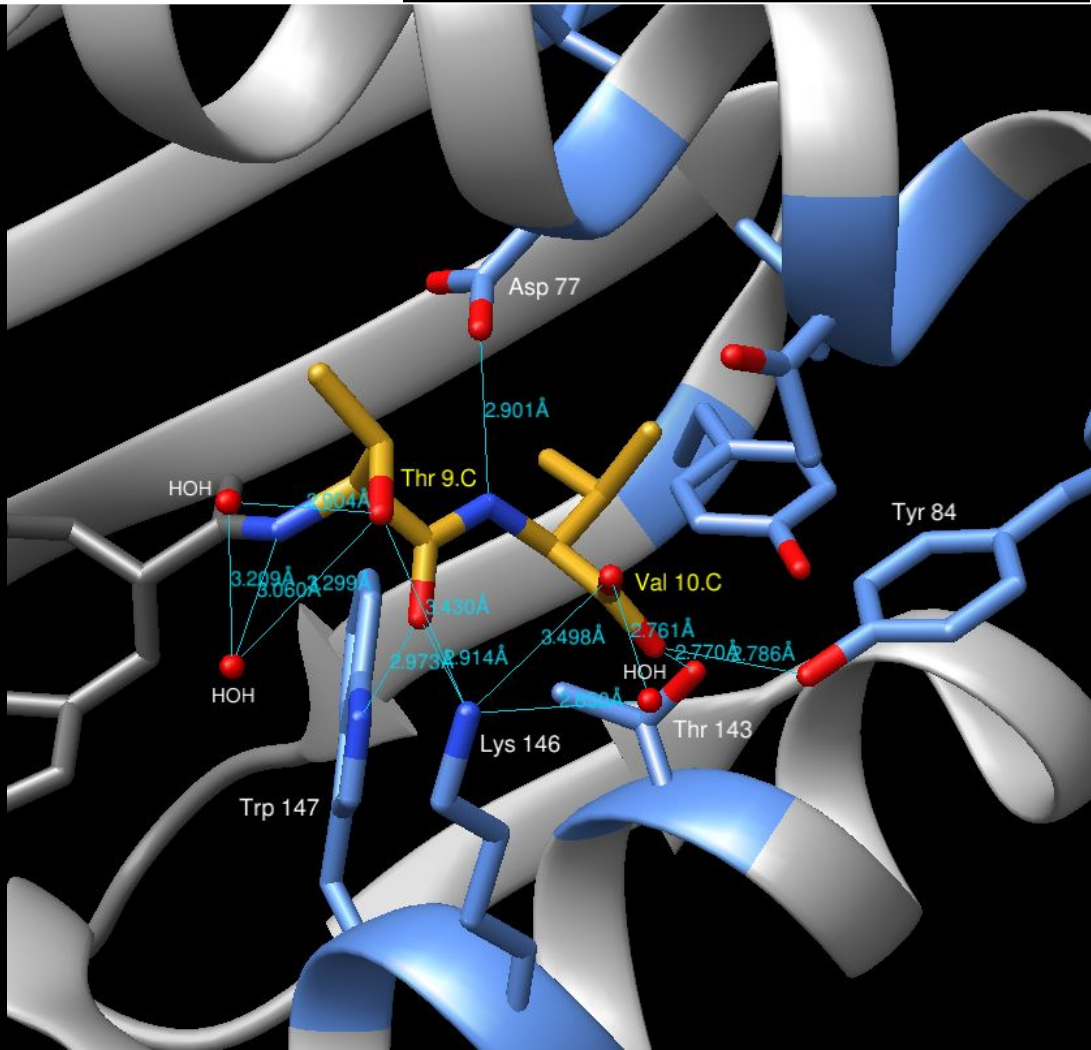


Pocket F
Hydrogen bonds

Peptide	Atom	HLA-I	Atom	Length (Å)
Thr 9	O	Trp 147	NE1	2.97
	OG1	Lys 146	Nz	2.91
	O	Lys 146	Nz	3.43
Val 10	OXT	Asp 77	O2	2.90
	OXT	HOH 105	O	2.76
	OXT	Lys 146	Nz	3.49
	OXT	Lys 146	Nz	2.85

Peptide-molecule bond

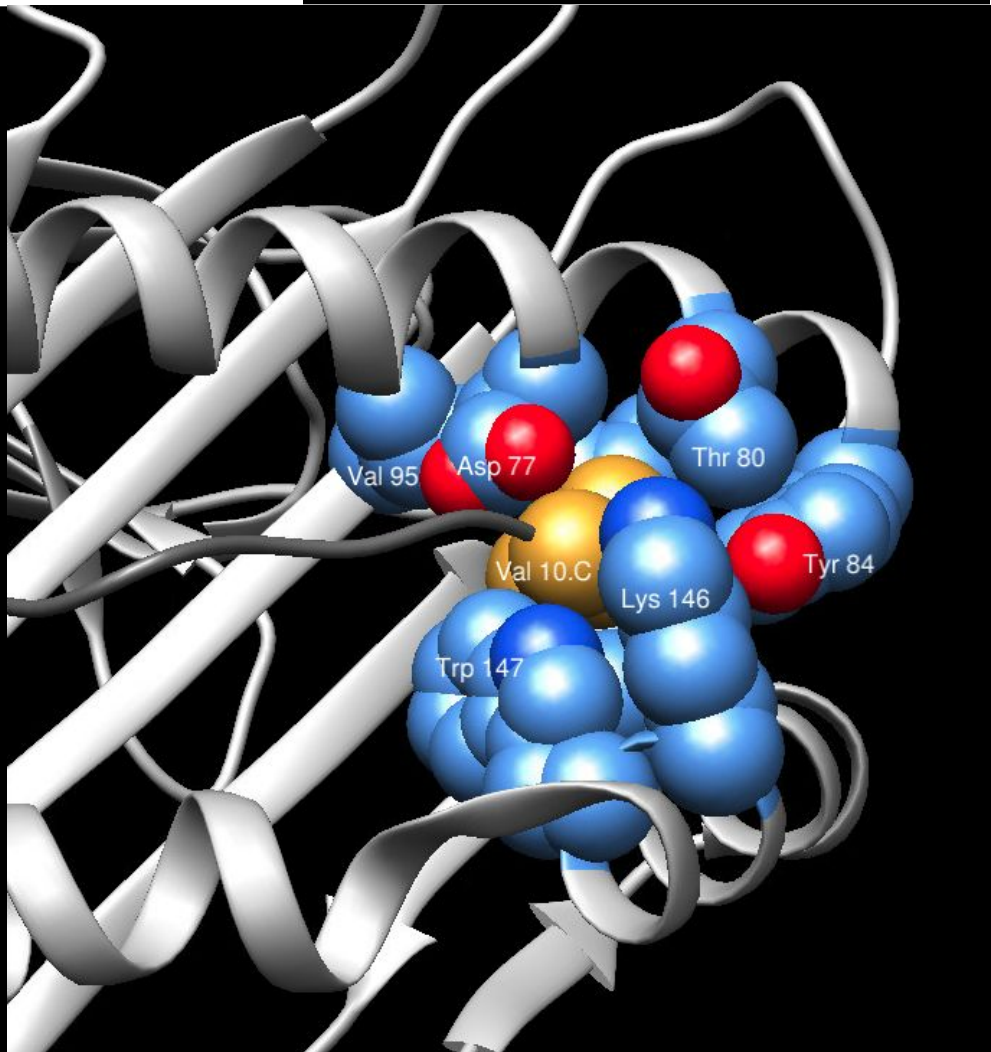
Images obtained from Chimera



Pocket F
Van der Waals interactions

Peptide	HLA-I
Val 10	Asp 77
	Thr 80
	Val 81
	Tyr 84
	Val 95
	Tyr 123
	Lys 146
	Trp 147

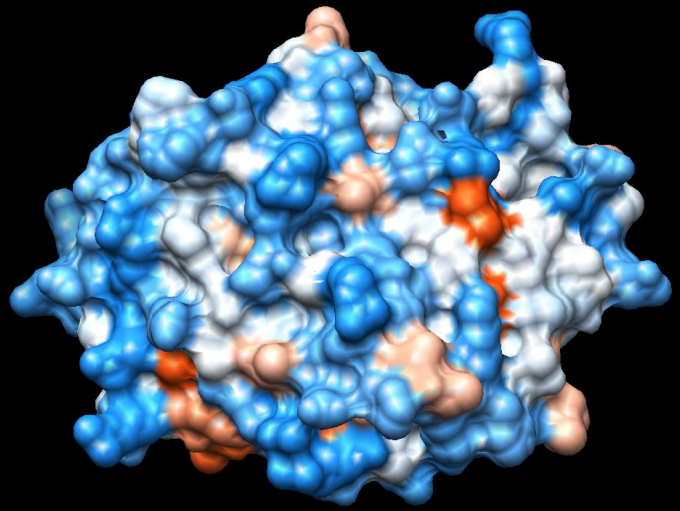
Non polar residue

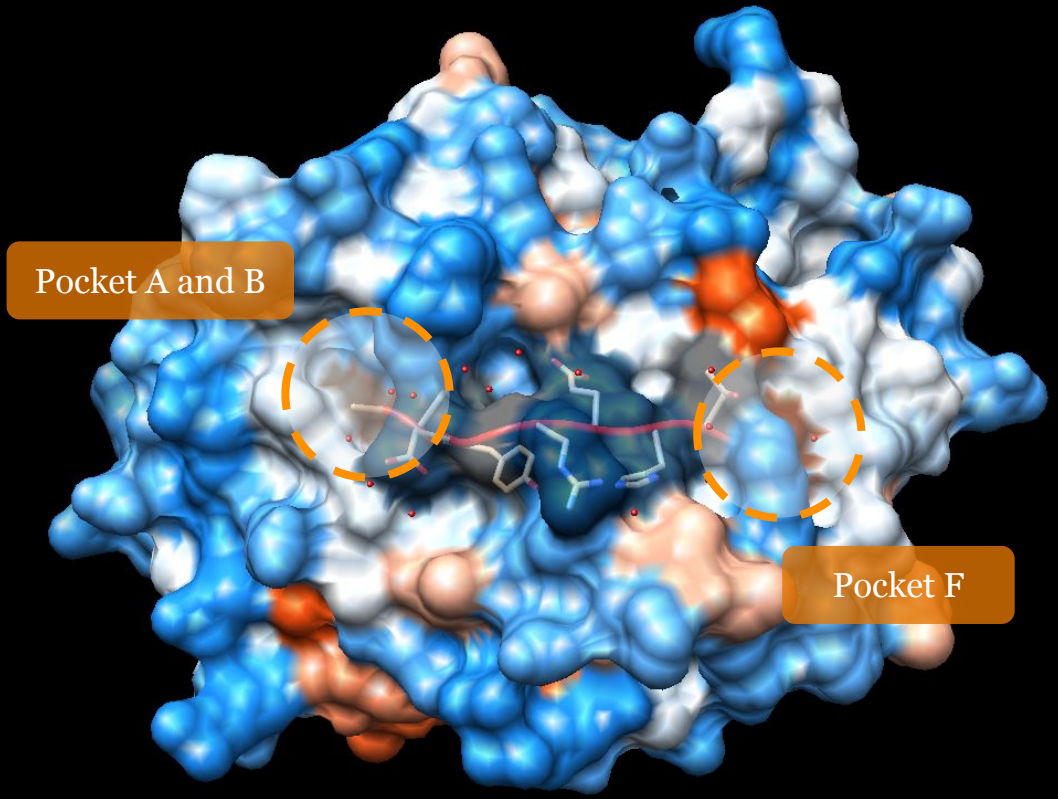


Images obtained from Chimera

Hydrophobicity pockets

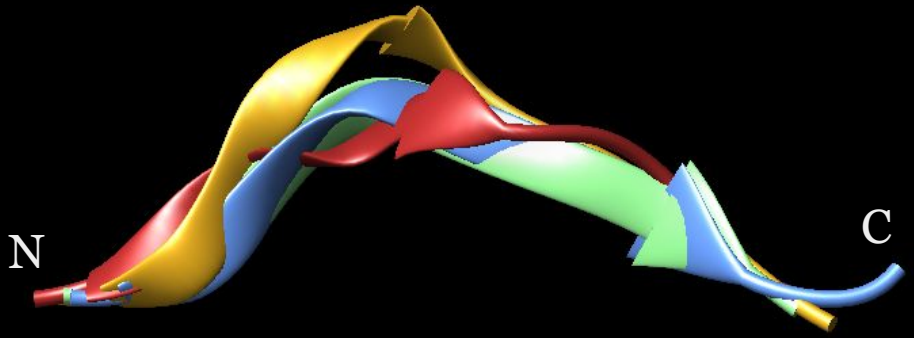
Hydrophobic pockets
Pocket A Pocket B Pocket F





Images obtained from Chimera

Peptides diversity | Alignment



- Chain A. HBV
- Chain B. MAGE-A4
- Chain C. MAGE-A3
- Chain D. Calreticulin

Alignment with Chimera

Pocket A

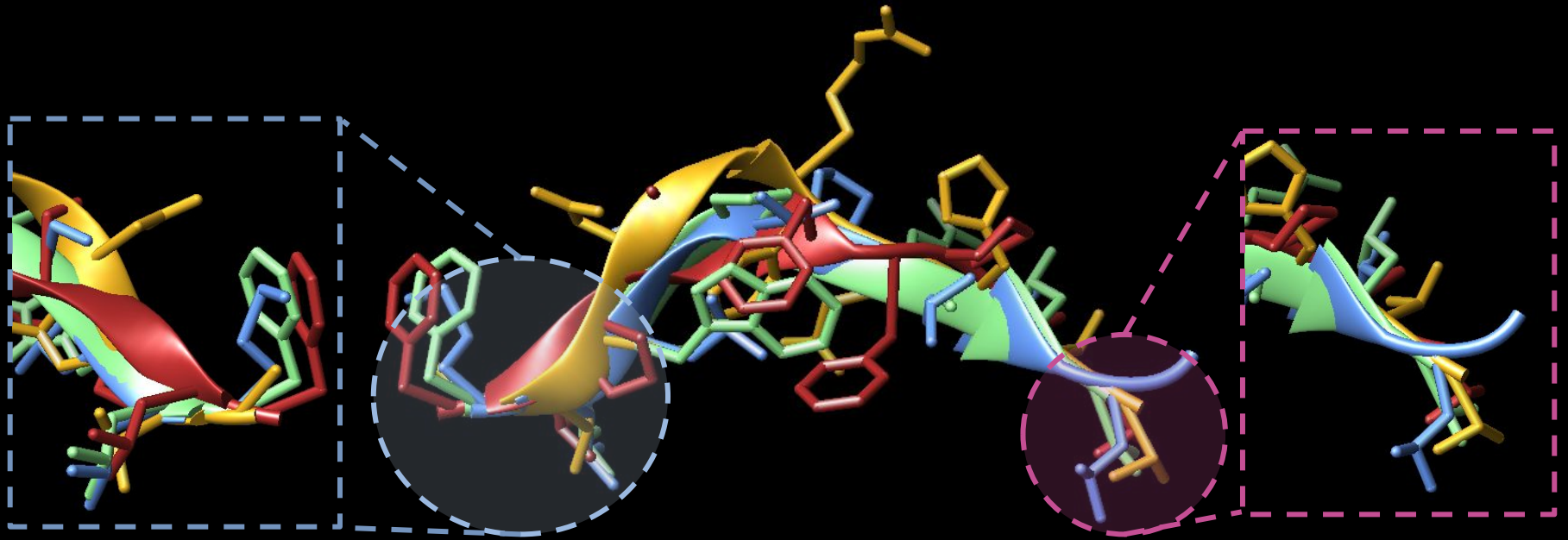
Pocket B

Pocket F

Hydrophobic amino acids

Sequence alignment made by ClustaIw and images visualized by Chimera

Peptides diversity | STAMP



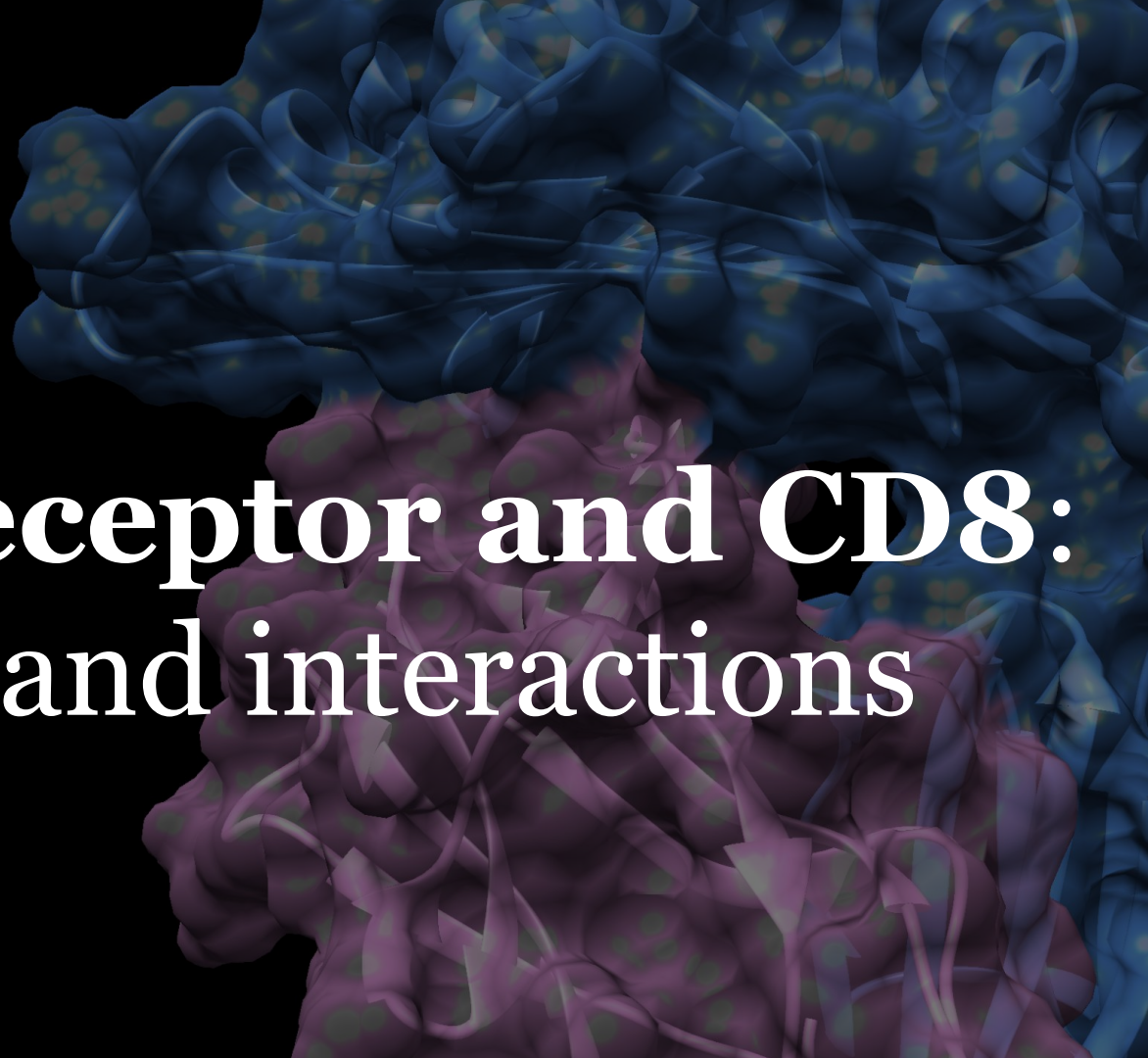
Residue P1 and P2

Residue PΩ

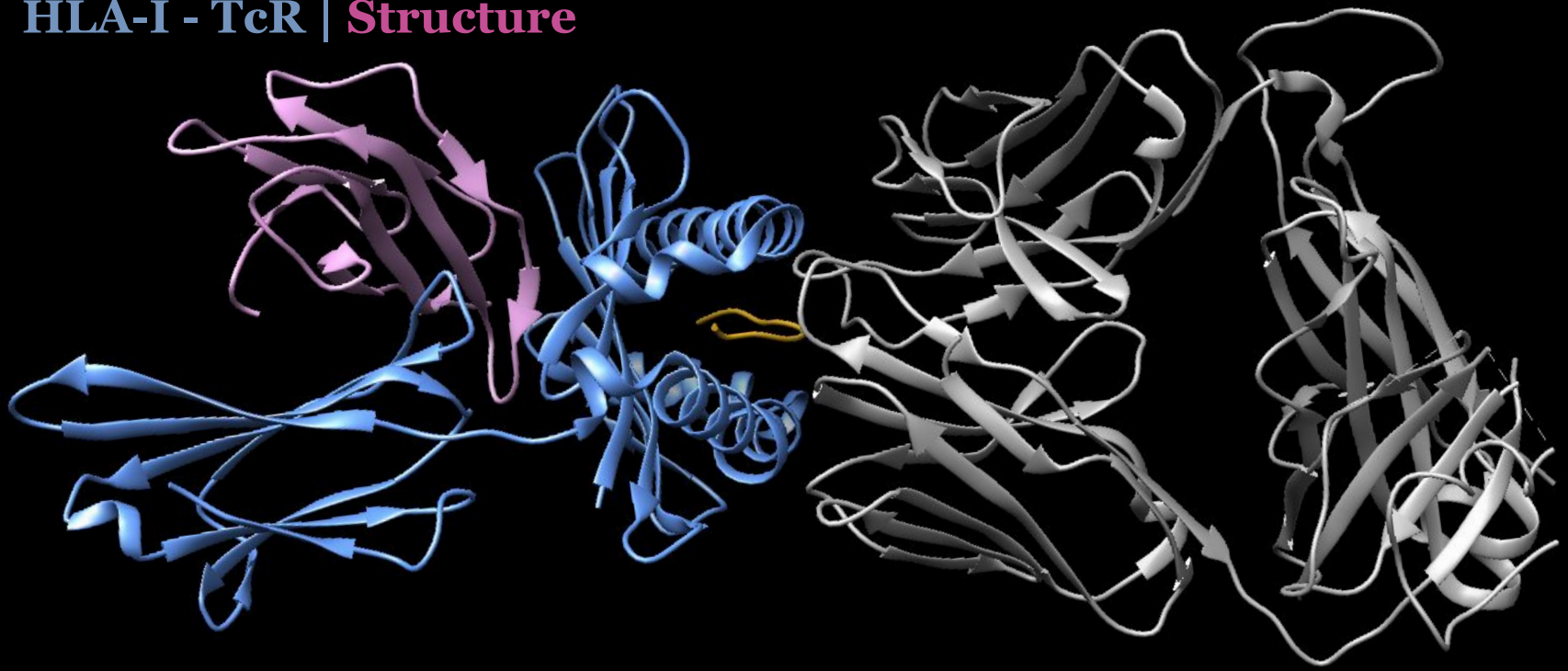
Images obtained from Chimera

04

T cell receptor and CD8: residues and interactions



HLA-I - TcR | Structure



HLA-I

Peptide

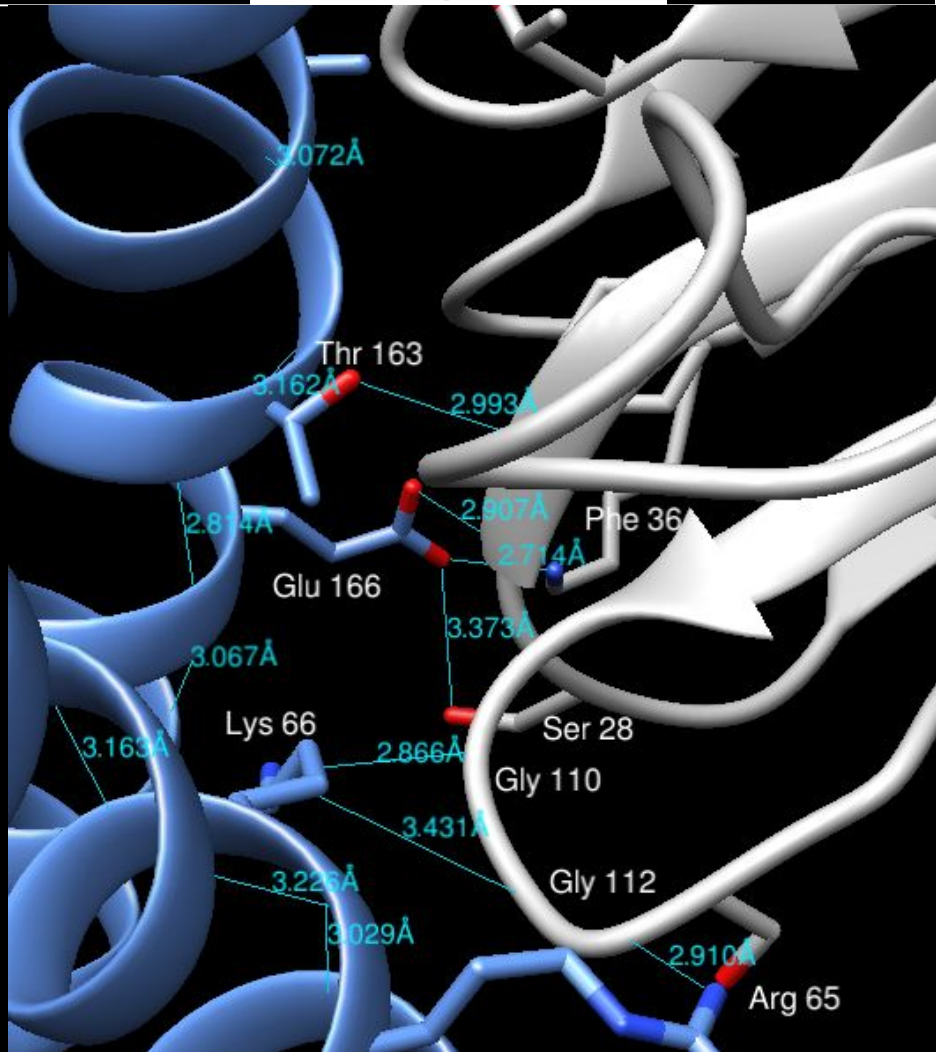
β2-microglobulin

TCR

Images obtained from Chimera

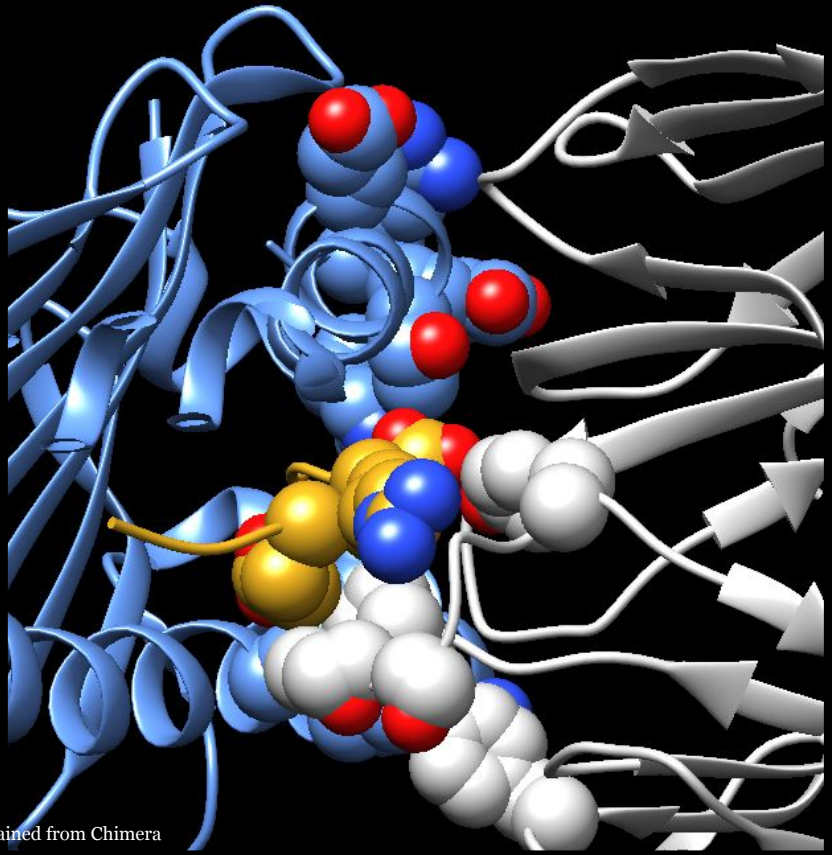
HLA-I - TcR | Hydrogen bonds

TCR	HLA-I	Length (Å)
Ser 28	Glu 166	3.37
Phe 36	Thr 163	2.71
Phe 36	Glu 166	2.90
Ser 109	Lys 66	2.86
Gly 110	Lys 66	3.43
Gly 112	Arg 65	2.91
Ser 113	Arg 65	2.90
Tyr 51	Asp 227	3.01
Ser 34	Gln 226	3.85
Leu 94	Ile 101	3.05
Ile 101	Gln 226	3.01



Images obtained from Chimera

HLA-I - TcR - Peptide
Van der Waals interactions



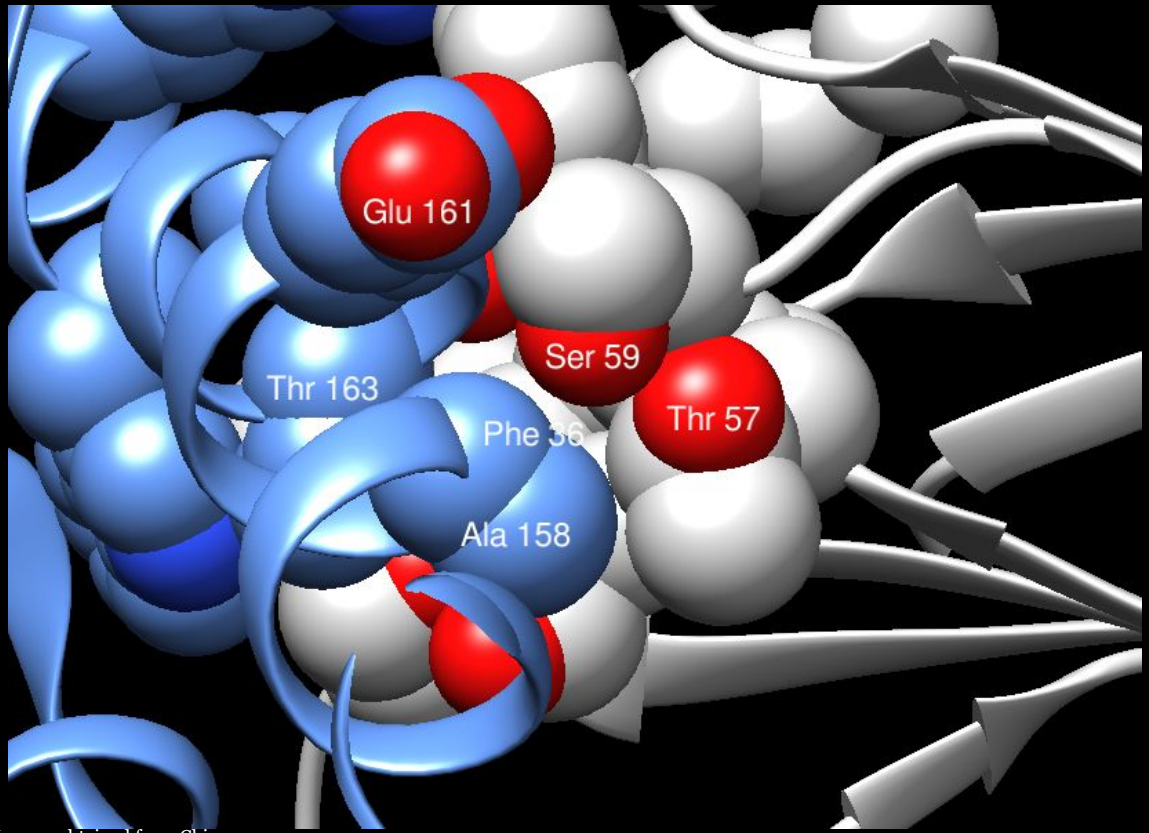
Images obtained from Chimera

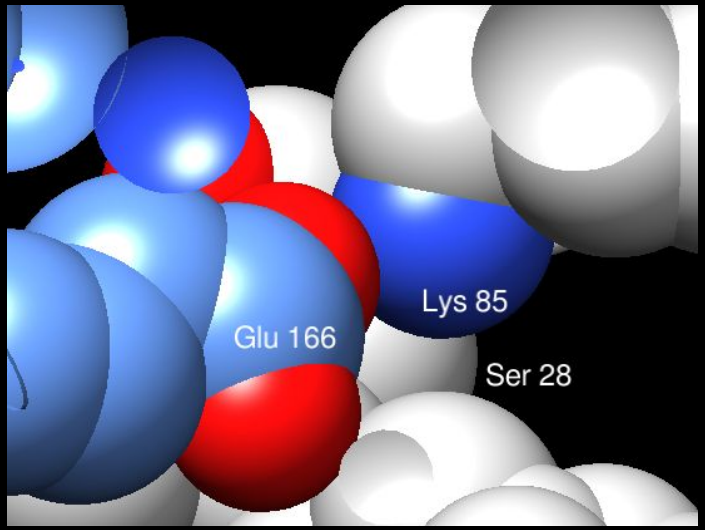
TCR	HLA-I
Ser 28	Glu 166
Pro 29	Glu 166
Pro 29	Trp 167
Phe 36	Thr 163
Phe 36	Glu 166
Ser 37	Thr 163
Thr 57	Ala 158
Phe 58	Glu 161
Phe 58	Gly 162
Ser 59	Ala 158
Ser 59	Glu 161
Asp 83	Arg 169

TCR	HLA-I
Lys 85	Glu 166
Ser 109	Thr 163
Ser 109	Trp 167
Gly 110	Gly 62
Gly 110	Lys 66
TCR	**Peptide**
Ser 37	Asp 4
Ser 109	Asp 4
Tyr 114	Asp 4
Met 110	Gly 5
Met 110	Glu 7
Asp 112	Arg 6

HLA-I - TcR
Van der Waals interactions

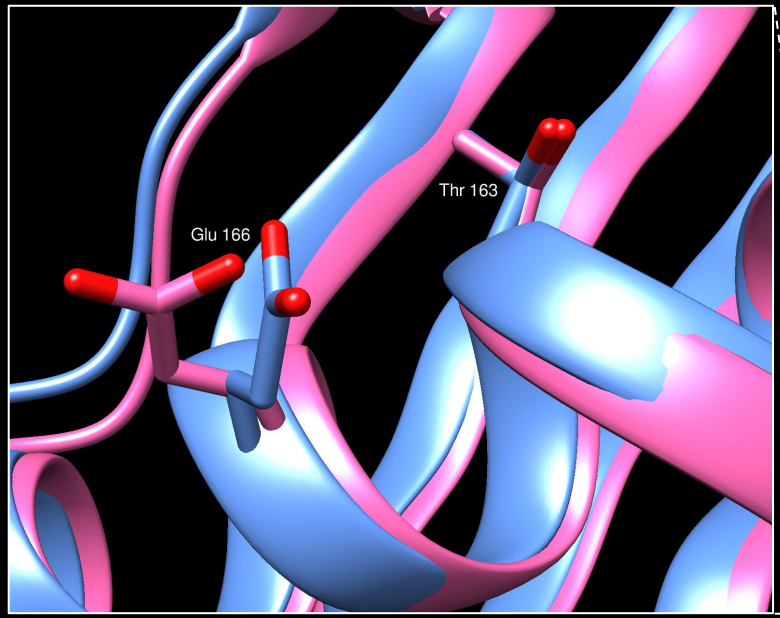
TCR	HLA-I
Ser 59	Glu 161
Phe 36	Thr 163
Thr 57	Ala 158
Lys 85	Glu 166
Ser 28	Glu 166

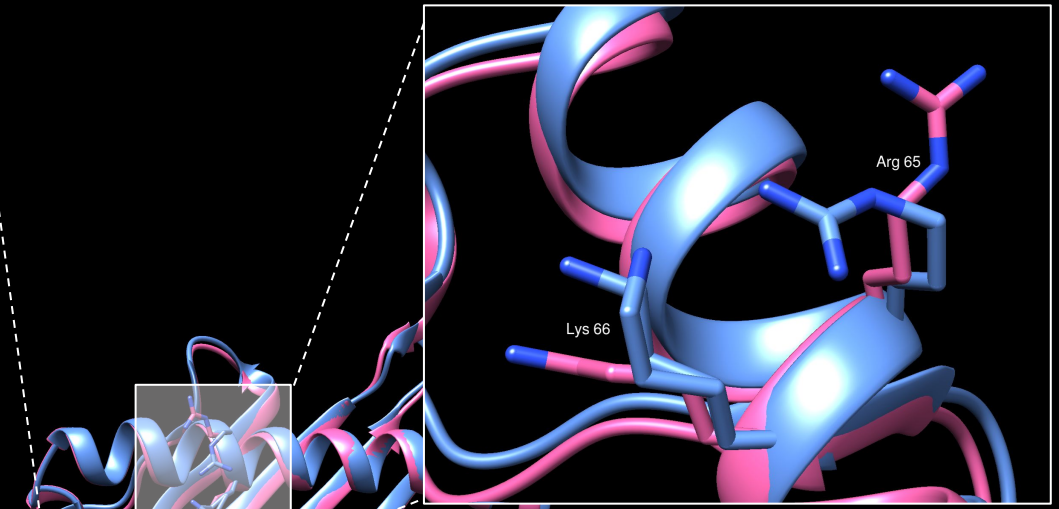




Images obtained from Chimera

HLA-I and TcR | STAMP





HLA-I not binded to TcR

HLA-I binded to TcR

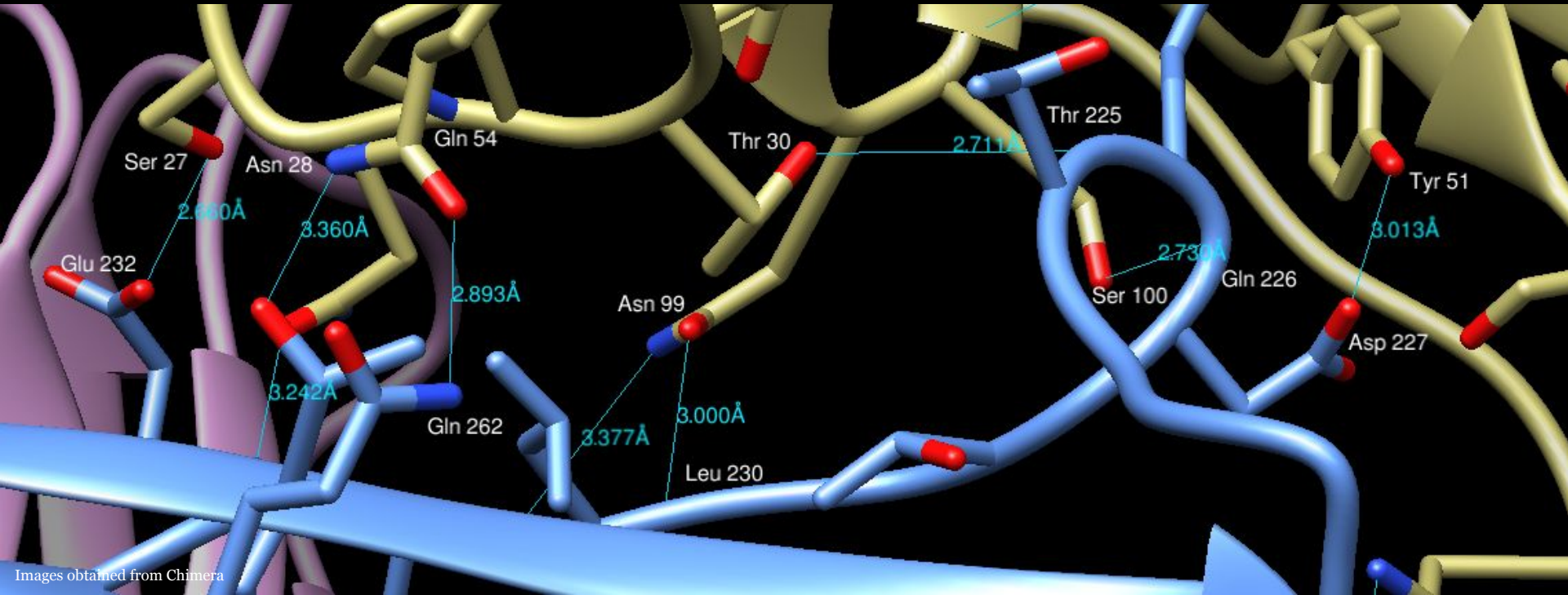
RMSD: 0.74
Score: 9.42
Len: 273
nfit: 272

Images obtained from Chimera

CD8 - HLA-I
Hydrogen bonds

CD8	HLA-I	Length (Å)
Gln 54	Gln 262	2.89
Ser 27	Glu 232	2.68
Asn 99	Leu 230	3.00

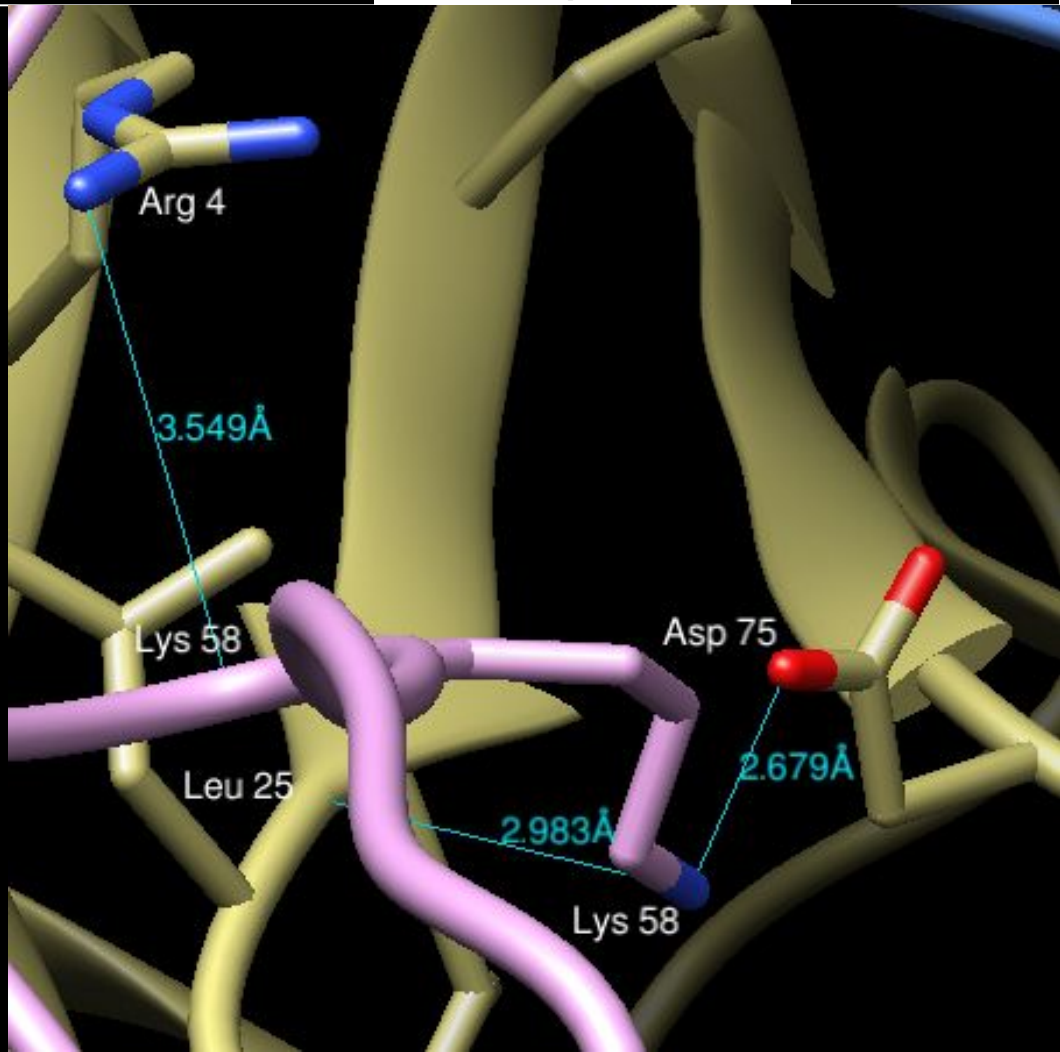
CD8	HLA-I	Length (Å)
Thr 30	Thr 225	2.71
Ser 100	Gln 226	2.73
Tyr 51	Asp 227	3.01



Images obtained from Chimera

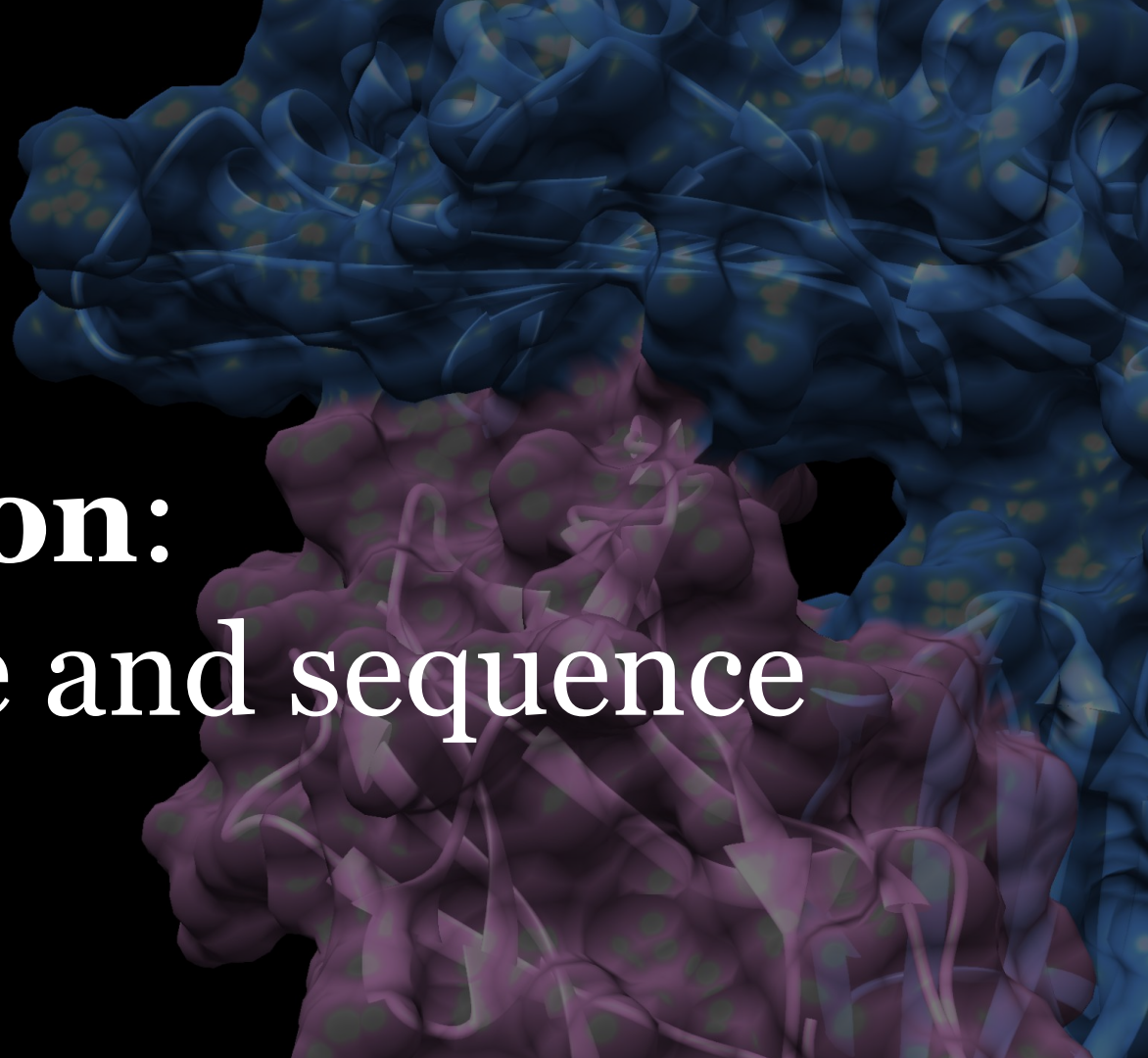
CD8 - β2-microglobulin
Hydrogen bonds

CD8	β2-microglobulin	Length (Å)
Arg 4	Lys 58	3.54
Leu 25	Lys 58	2.98
Asp 75	Lys 58	2.67



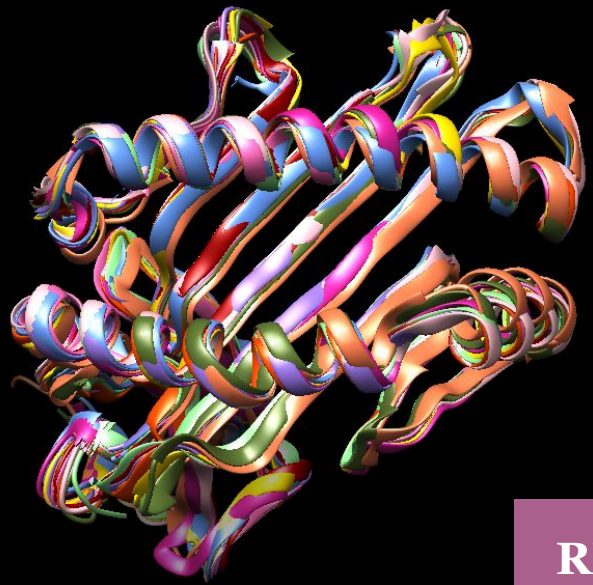
Images obtained from Chimera

05
Evolution: structure and sequence



HLA-I paralogues | STAMP

α-chain



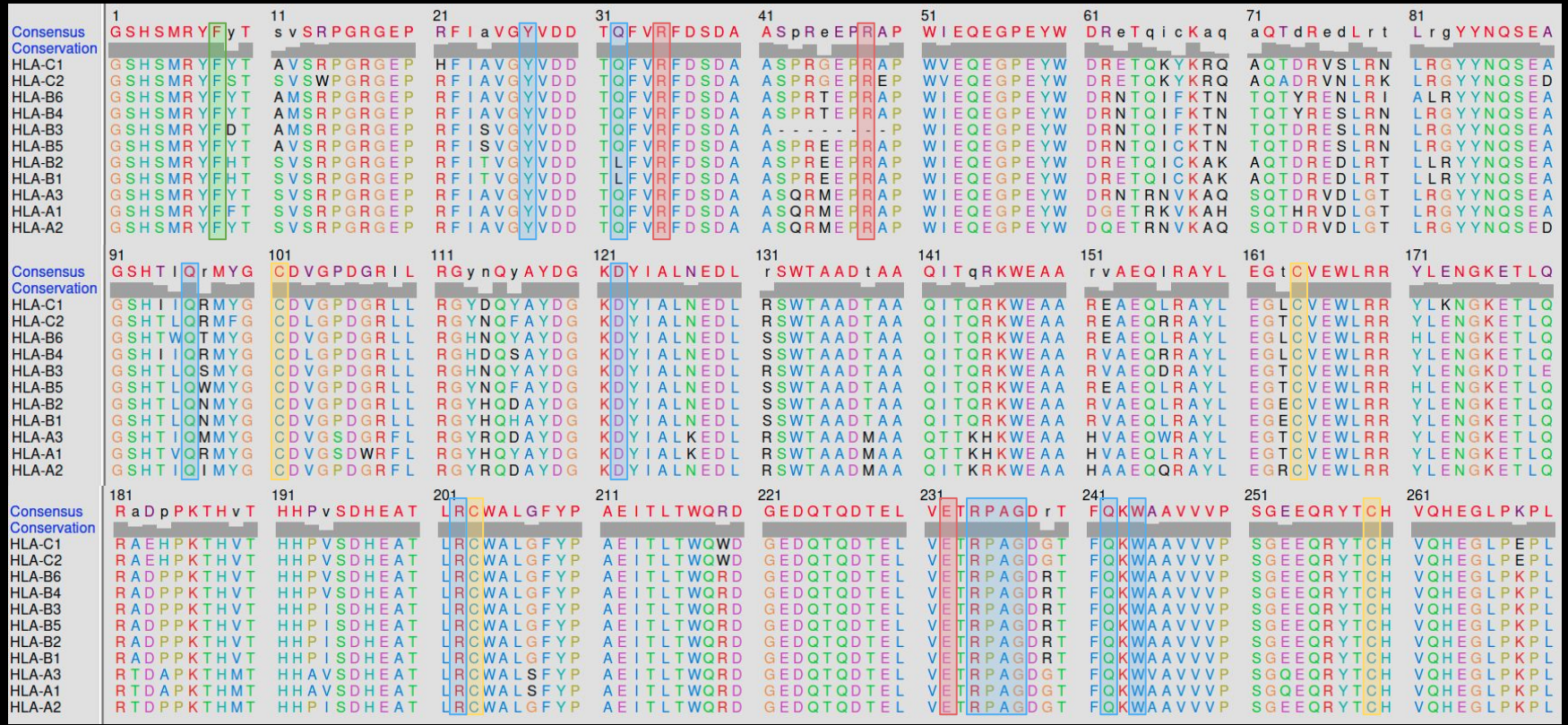
RMSD: 1.44
Score: 9.48
Len: 278
nfit: 261

Images obtained from Chimera

HLA-Ia paralogues| Inner interactions in HLA-Ia

α-chain

H-Bond-involved
Salt bridge-involved
Disulfur bond-involved
Hydrophobic bond-involved



Sequence alignment made by ClustaIw and images visualized by Chimera

HLA-Ia paralogues| Inner interactions in HLA-I

β2-microglobulin

H-Bond-involved
Salt bridge-involved
Disulfur bond-involved
Hydrophobic bond-involved

RMSD: 0.40
Score: 9.72
Len: 100
nfit: 98

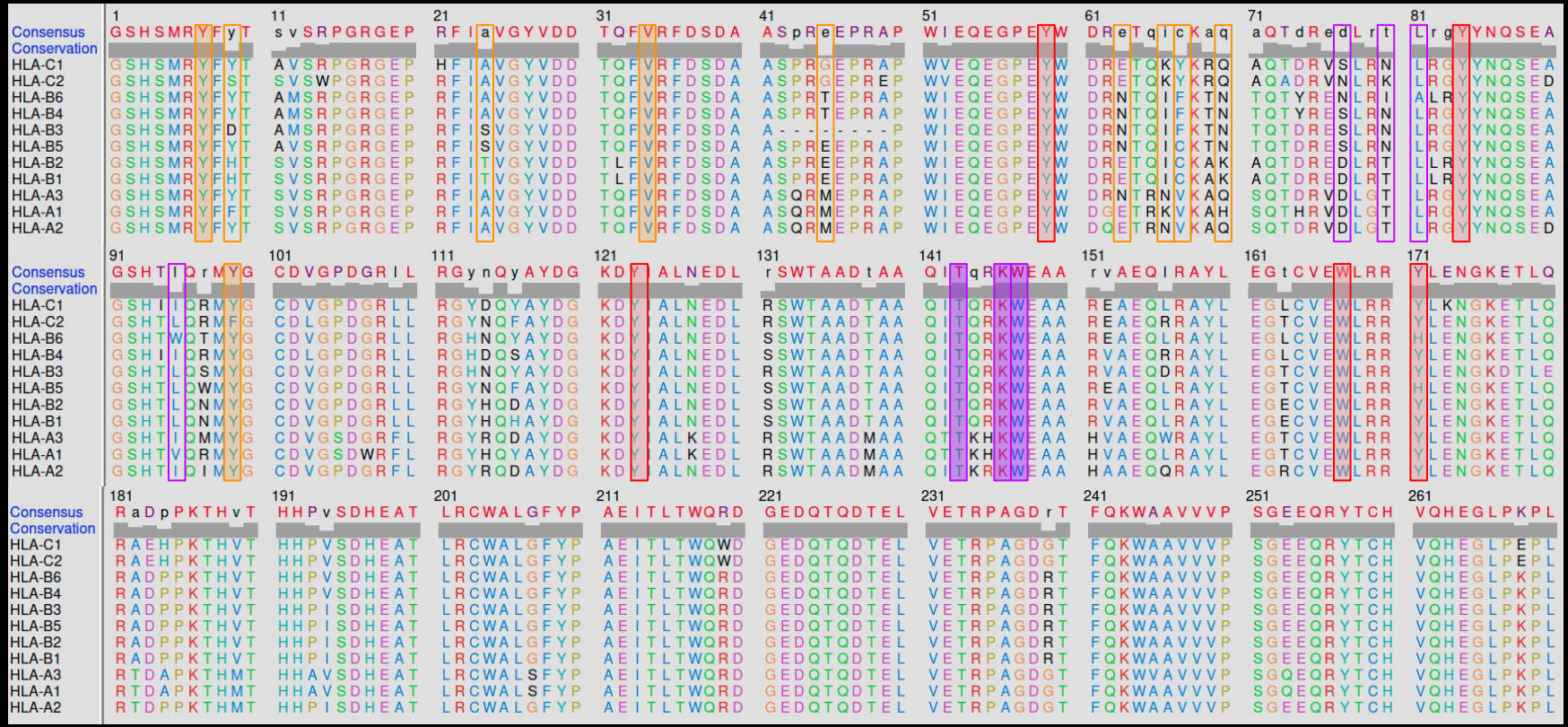
Sequence alignment made by ClustaIw and images visualized by Chimera

HLA-Ia paralogues |Binding groove

α-chain

Cleft wall
Pocket B
Pocket F

Conserved	Variable
Conserved	Variable



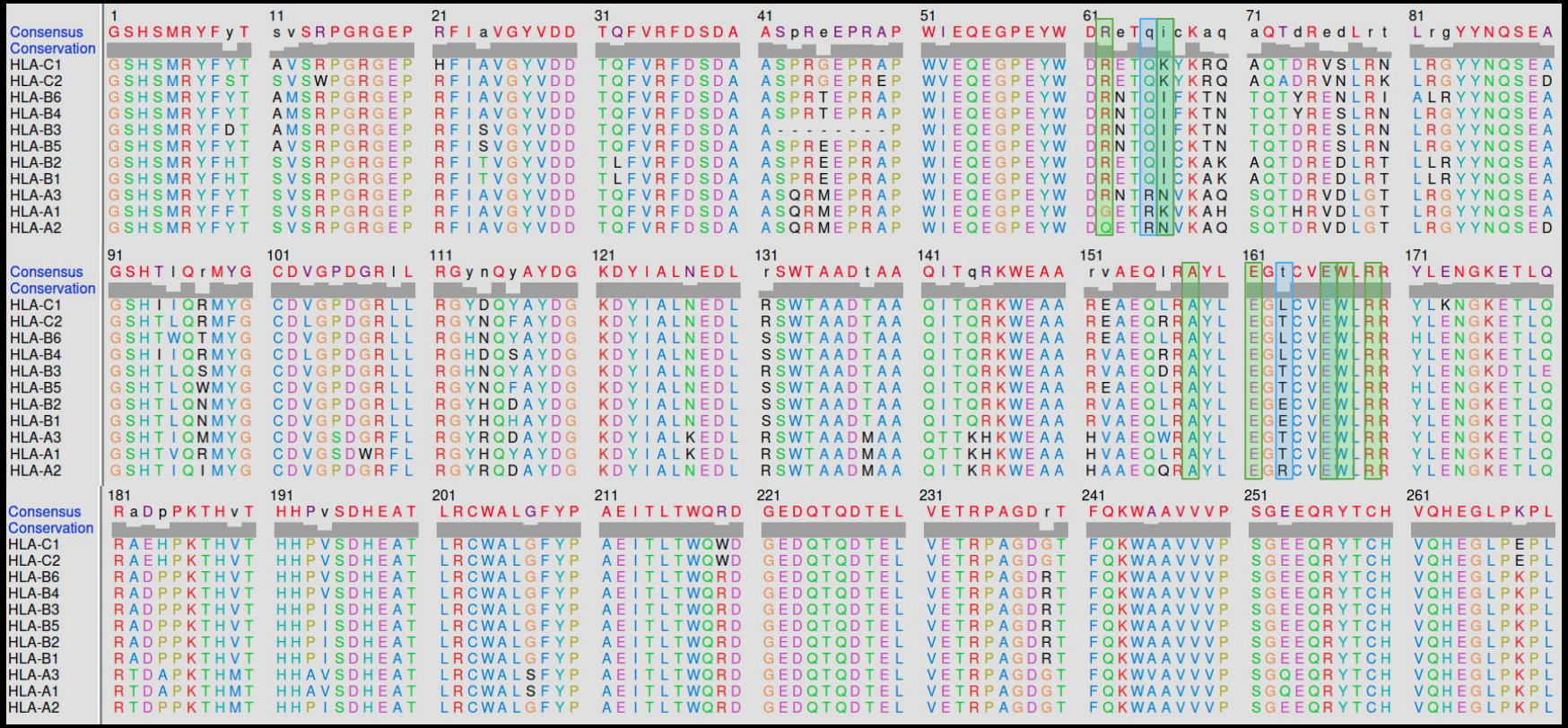
Sequence alignment made by ClustaIw and images visualized by Chimera

HLA-Ia paralogues| HLA-I - TcR interactions

α-chain

H-Bond-involved

Van der Waals interactions



Sequence alignment made by ClustaIw and images visualized by Chimera

HLA-Ia paralogues| HLA-I - CD8 interactions

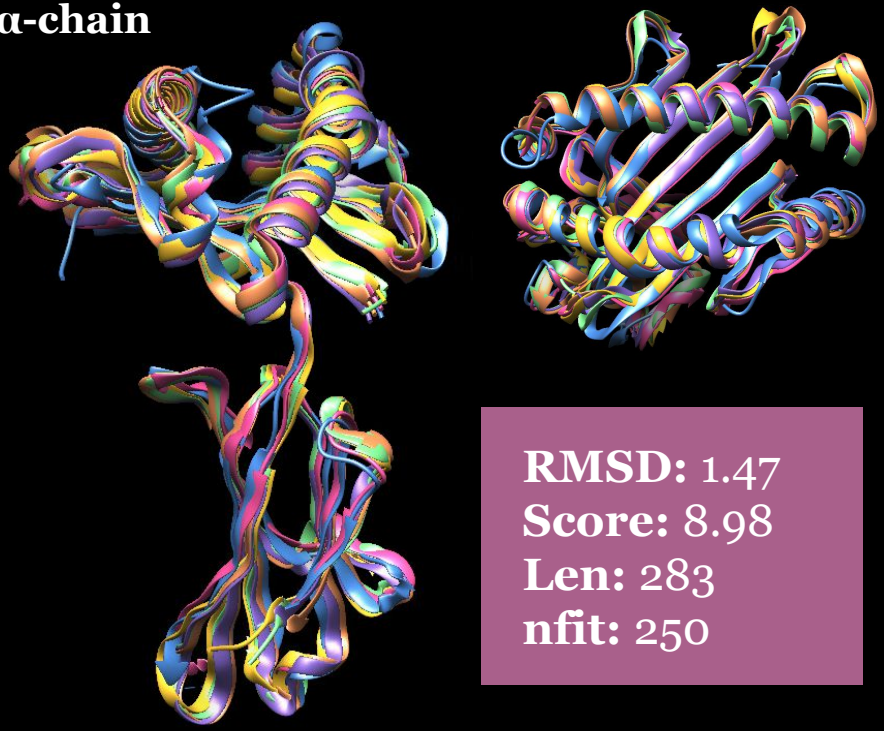
H-Bond-involved

α-chain

Sequence alignment made by ClustaIw and images visualized by Chimera

HLA-A orthologs | STAMP and dendrogram

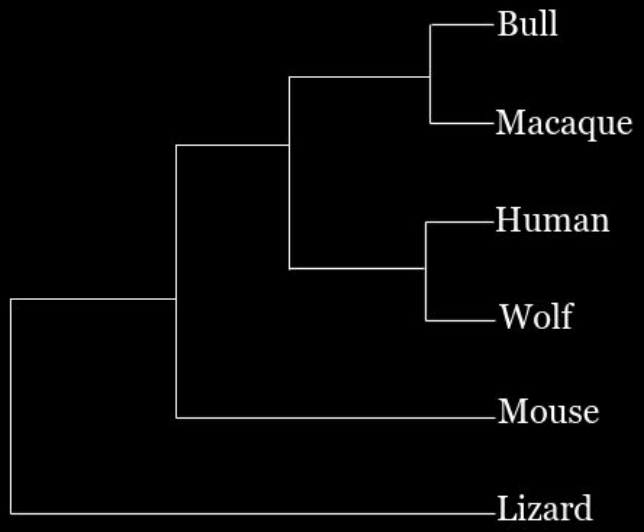
α-chain



RMSD: 1.47
Score: 8.98
Len: 283
nfit: 250

Bull
Macaque
Human
Wolf
Mouse
Lizard

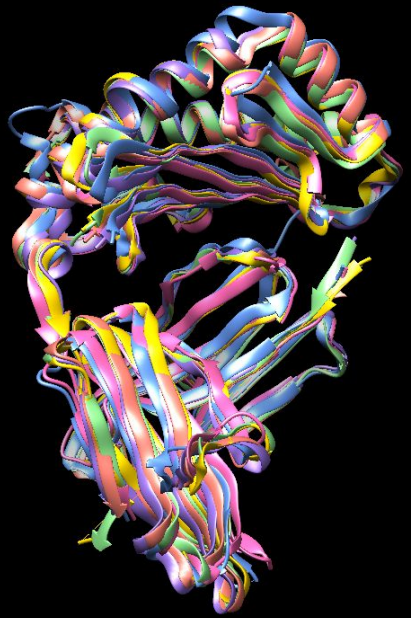
Structural dendrogram



Images obtained from Chimera

HLA-A orthologs | STAMP and dendrogram

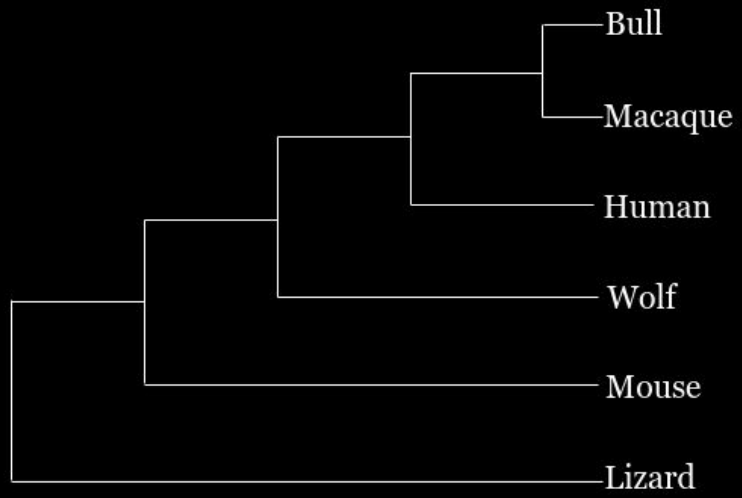
α-chain
β2-microglobulin



RMSD: 1.44
Score: 9.19
Len: 384
nfit: 342

Bull
Macaque
Human
Wolf
Mouse
Lizard

Structural dendrogram



Images obtained from Chimera

HLA-A orthologs |Inner interactions in HLA-I

α-chain

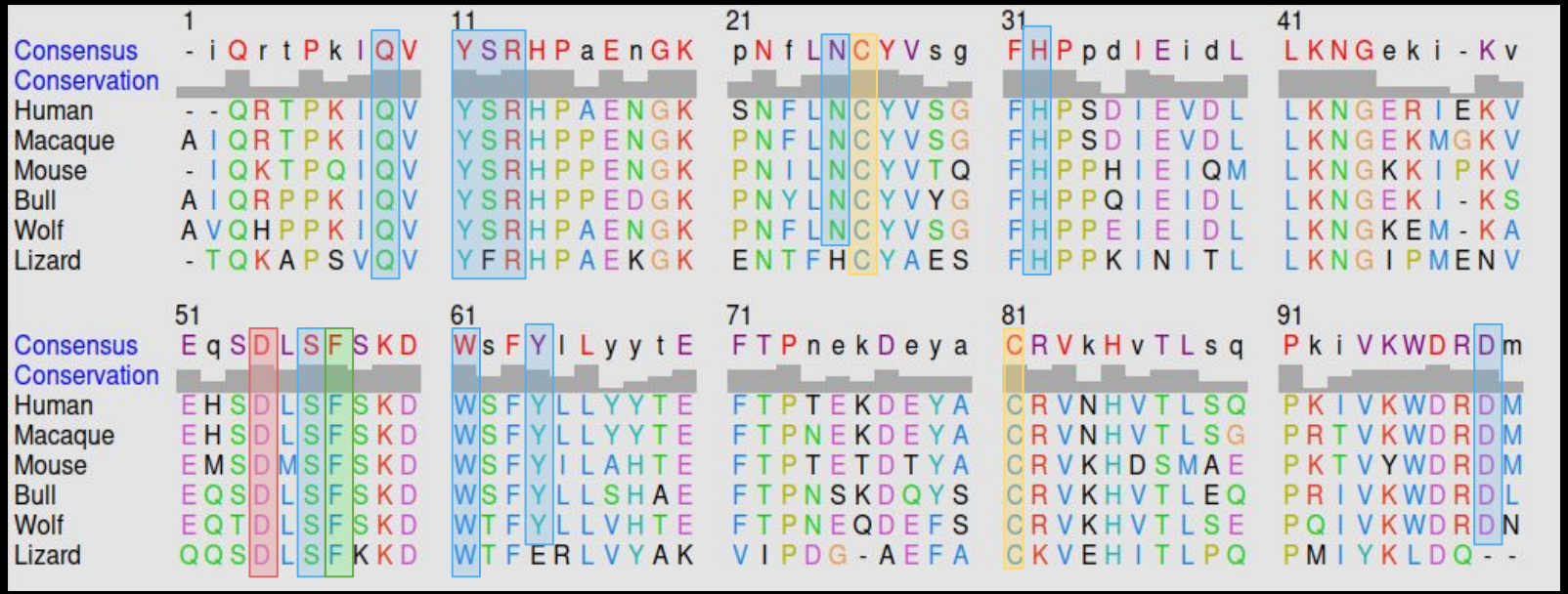
- H-Bond-involved
- Salt bridge-involved
- Disulfur bond-involved
- Hydrophobic bond-involved

Sequence alignment made by ClustaIw and images visualized by Chimera

HLA-A orthologs |Inner interactions in HLA-I

β2-microglobulin

H-Bond-involved
Salt bridge-involved
Disulfur bond-involved
Hydrophobic bond-involved



Sequence alignment made by ClustaIw and images visualized by Chimera

HLA-A orthologs | Binding groove

α-chain

Cleft wall
Pocket B
Pocket F

Conserved	Variable
Conserved	Variable

Sequence alignment made by ClustaIw and images visualized by Chimera

HLA-A orthologs |HLA-I - TcR interactions

α-chain

H-Bond-involved

Van der Waals interactions

Sequence alignment made by ClustaIw and images visualized by Chimera

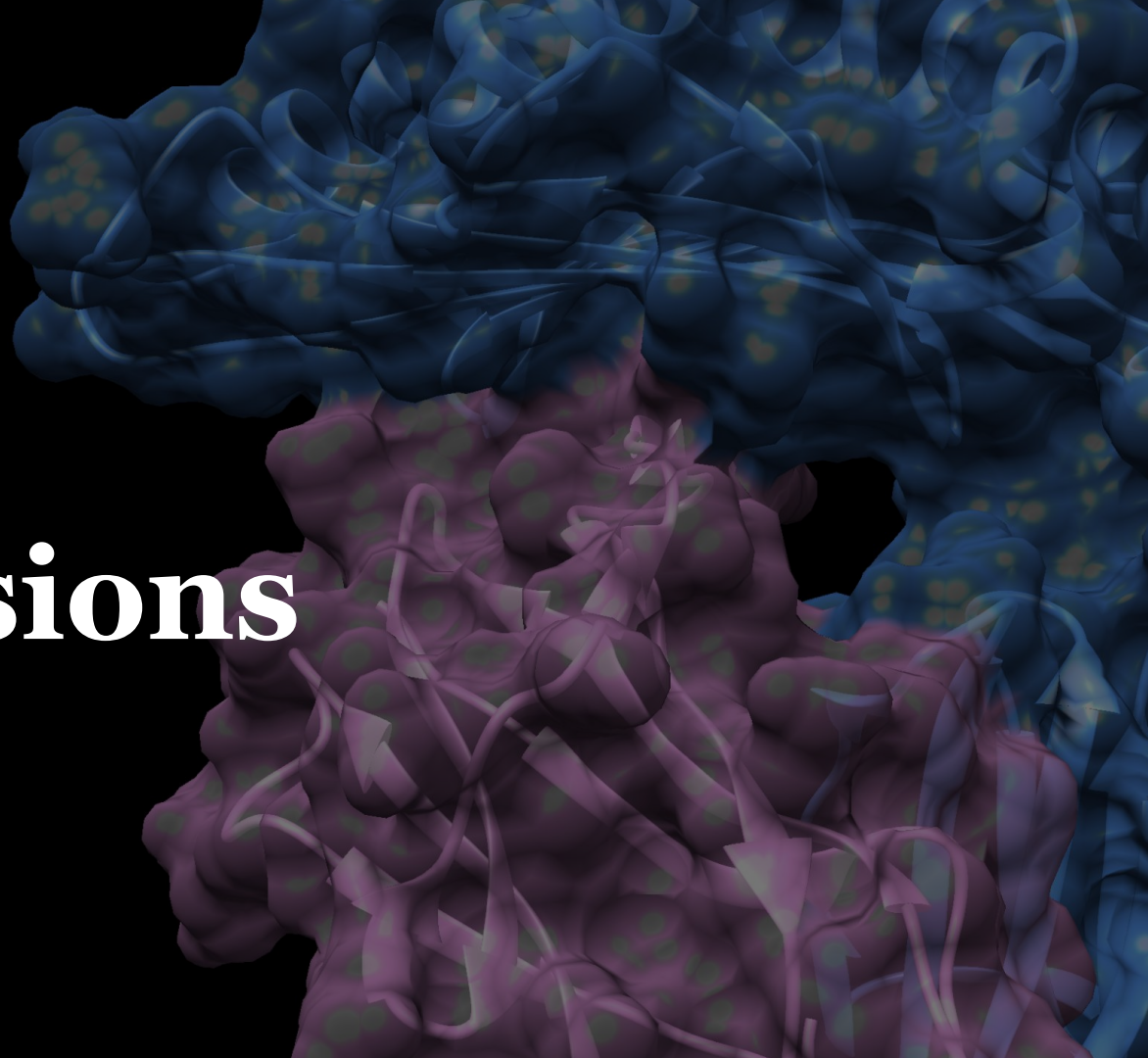
HLA-A orthologs |HLA-I - CD8 interactions

H-Bond-involved

α-chain

Sequence alignment made by ClustaIw and images visualized by Chimera

Conclusions



Conclusions

01

HLA structure

Conservation in residues involved in HLA inner interactions, especially cysteines, is important to preserve their structure and function along evolution.

02

Binding groove

The three pockets with the most important roles (A, B, F) present hydrophobicity, as well as conserved and variable residues, both between the paralogues and the orthologues.

03

TcR

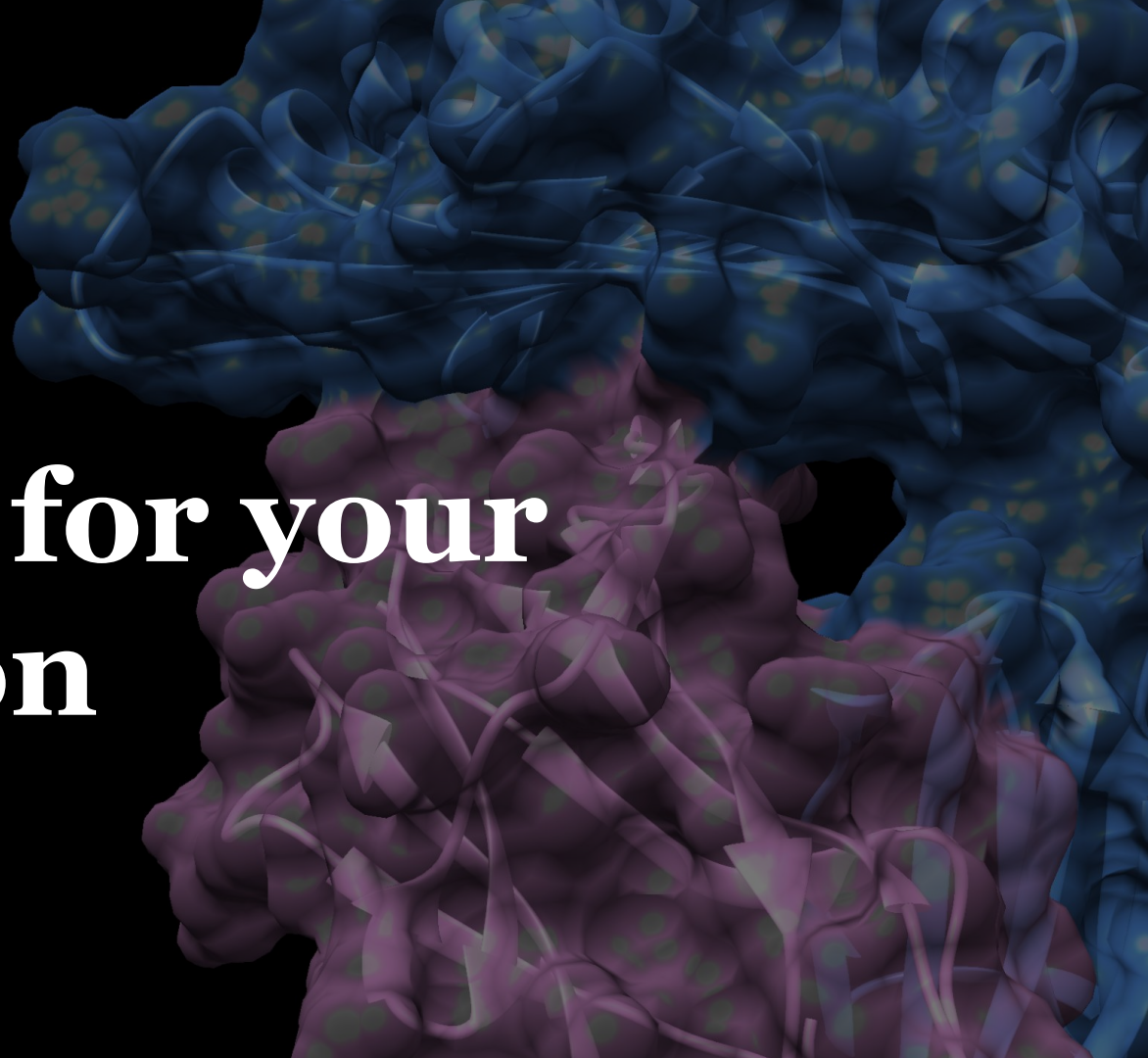
TcR recognition of peptide-HLA complexes is essential for disease control and survival.

04

Evolution

The high conservation of HLA-I sequence confirms its essential role.

Thanks for your attention



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Multiple choice questions

1. Which is the optimal length for a peptide bound in HLA-I?
   a. 5-6 amino acids
   b. 8-10 amino acids
   c. 18-25 amino acids
   d. +12 amino acids
   e. 25-30 amino acids

2. Which are the pockets that form the main interactions between the peptide and the molecule?
   a. Pocket A and B
   b. Pocket B and D
   c. Pocket A and F
   d. Pocket A and D
   e. Pocket B and F

3. Regarding the binding pockets, choose the correct answer:
   a. HLA-I has an open binding cleft with 9 pockets but HLA-II has a closed binding cleft with 6 pockets.
   b. The HLA-I binding groove contains both conserved and variable residues.
   c. Pockets A and F are the wall of the cleft that close the groove.
   d. a and c are correct.
   e. b and c are correct.

Multiple choice questions

4. Regarding disulfide bonds in HLA-I molecules, choose the correct statement:
   a. They stabilize the Ig-like beta-sandwich structure.
   b. They are found in all the domains of HLA molecules.
   c. They connect the two β-sheets to generate the Ig-like beta-sandwich structure.
   d. a and c are correct.
   e. All of the above are correct.

5. Regarding the inner interactions of HLA molecules, choose the correct statement:
   a. The great amount of hydrogen bonds help stabilize the structure of HLA molecules.
   b. β2-microglobulin interacts with the 3 different domains of the α-chain.
   c. Disulfide bonds are formed between the 2 different chains of HLA molecules.
   d. a and b are correct.
   e. All of the above are correct.

6. Choose the incorrect statement regarding to HLA molecules' structure:
   a. Both HLA class I and II are composed of two different chains.
   b. Class I's α1 and α2 domains and Class II's α1 and β1 domains form the antigen binding groove.
   c. SCOP classifies all the HLA domains as alpha+beta proteins.
   d. b and c are incorrect.
   e. All of the above are incorrect.

Multiple choice questions

7. Which affirmation is false?
   a. CD8 is a coreceptor for TCR.
   b. CD8 is specific for HLA-II.
   c. HLA interacts with TCR CDR1 and CDR2.
   d. Peptides interact with TCR CDR3.
   e. Between TCR and the peptide there are different Van der Waals interactions where Asp 4 is involved.

8. Which affirmation is false?
   a. In paralogs the conservation of hydrogen bonds between HLA-I and CD8 is 100%
   b. Hydrophobic interactions between HLA-I and TCR are almost fully conserved.
   c. Residues that form a salt bridge between HLA-I and TCR are conserved in all species.
   d. Wolf is the specie in which hydrogen bonds formed between HLA-I and CD8 are less conserved.
   e. All types of interactions between HLA-I and TCR in paralogs are really conserved.

9. Choose the incorrect statement about the alpha chain of HLA-A in orthologs
   a. Lizard is the specie which HLA-A structure is more different.
   b. Bull and macaques are clustered together.
   c. Humans and wolves are clustered together.
   d. Humans and macaques are clustered together.
   e. As the score is high, we can consider the dendrogram as correct.

Multiple choice questions

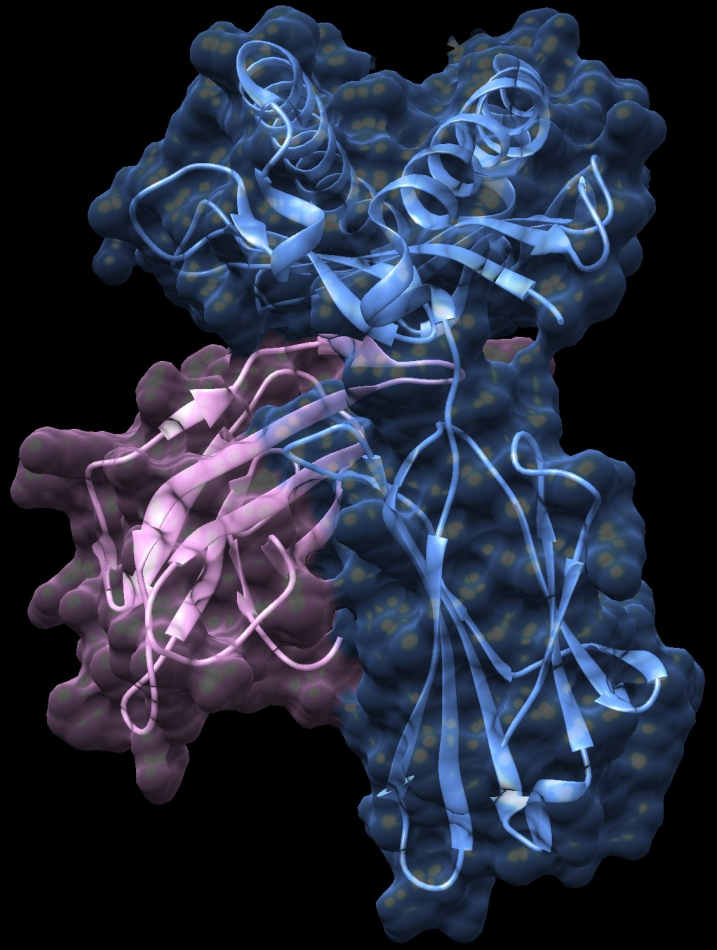
10. Choose the correct answer about HLA-I:
    a. The structure of HLA-I is formed with 3 α-domains and a β2-microglobulin.
    b. HLA-I has a closed binding cleft with 6 pockets (A-F).
    c. a and b are correct.
    d. HLA-I does not have hydrophobic pockets.
    e. All of the above are correct.

HLA | HUMAN LEUKOCYTE ANTIGEN

An structural analysis

Marina Carreras, Mireia Roig, Mònica Sancho

Structural Biology | Human Biology | 23-24



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