

# AD pathology of TAU protein ir, 14-3-3 pathway

TAU蛋白与14-3-3蛋白相互作用在阿兹海默疾病的作用

**G17**

Yunxing Liu

Jiamiao Fu

Zongliang Wang

Tianyu Wang

Addresser : Tianyu Wang

# Background

- Tau protein: **Microtubule-associated protein tau** 微管结合蛋白-tau

Protein | **Microtubule-associated protein tau**



Gene | **MAPT**

Organism | *Homo sapiens (Human)*

Status |  Reviewed - Annotation score: ●●●●●● - Experimental evidence at protein level<sup>i</sup>

## Function<sup>i</sup>

---

Promotes microtubule assembly and stability, and might be involved in the establishment and maintenance of neuronal polarity. The C-terminus binds axonal microtubules while the N-terminus binds neural plasma membrane components, suggesting that tau functions as a linker protein between both. Axonal polarity is predetermined by TAU/MAPT localization (in the neuronal cell) in the domain of the cell body defined by the centrosome. The short isoforms allow plasticity of the cytoskeleton whereas the longer isoforms may preferentially play a role in its stabilization.  1 Publication 

# Background

- 6 isoforms in human and distinguish by their number of binding domains , cased by alternative splicing in exons 2,3 and 10 of tau gene located in chromosome 17.

## Family & Domains<sup>i</sup>

---

### Domains and Repeats

Feature key	Position(s)	Description	Actions	Graphical view	Length
Repeat <sup>i</sup>	561 - 591	Tau/MAP 1	 Add  BLAST		31
Repeat <sup>i</sup>	592 - 622	Tau/MAP 2	 Add  BLAST		31
Repeat <sup>i</sup>	623 - 653	Tau/MAP 3	 Add  BLAST		31
Repeat <sup>i</sup>	654 - 685	Tau/MAP 4	 Add  BLAST		32

# Background

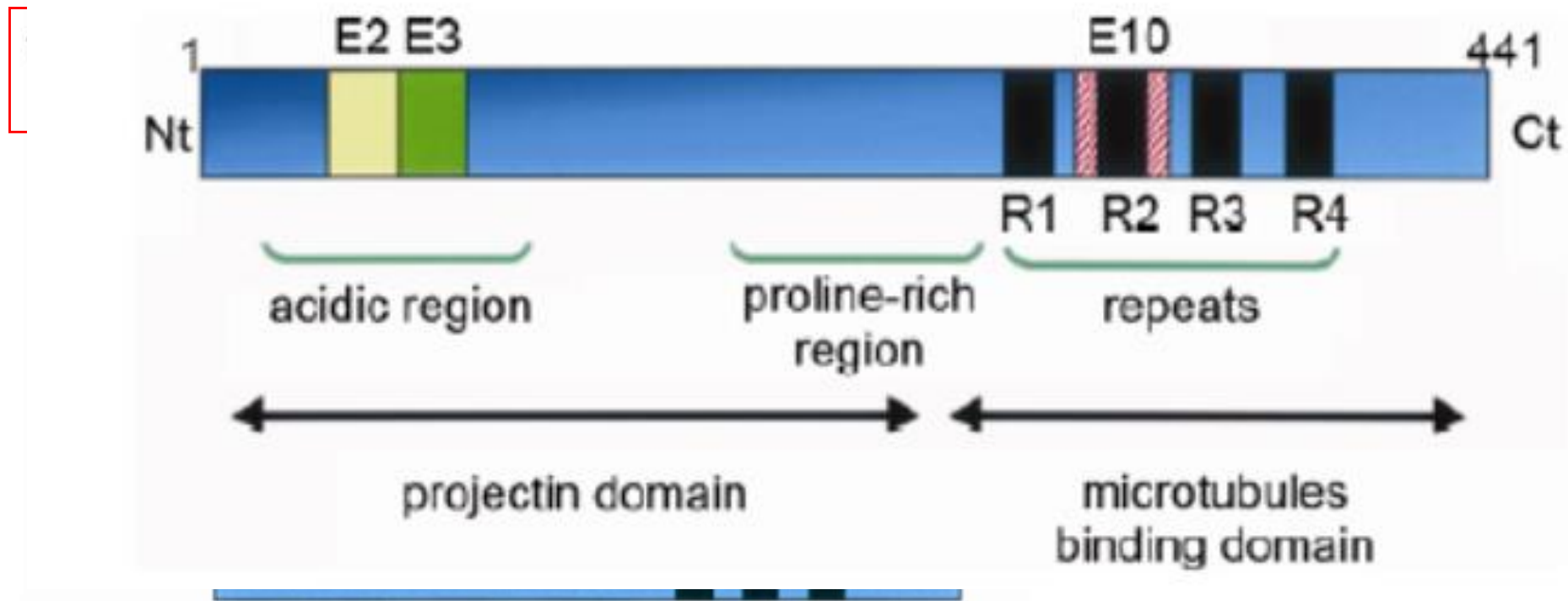
M7: Alignment Explorer

Data Edit Search Alignment Web Sequencer Display Help

Protein Sequences

Species/Abbrev	Group Name					*			*	*	*	*		*		*	*	*	*													
1. sp P10636 562-591		T	A	P	V	P	M	P	D	L	K	N	-	V	K	S	K	I	G	S	T	E	N	L	K	H	Q	P	G	G	G	K
2. sp P10636 245-274		T	A	P	V	P	M	P	D	L	K	N	-	V	K	S	K	I	G	S	T	E	N	L	K	H	Q	P	G	G	G	K
3. sp P10636 598-622		-	-	K	L	-	-	-	D	L	S	N	-	V	Q	S	K	C	G	S	K	D	N	I	K	H	V	P	G	G	G	S
4. sp P10636 281-305		-	-	K	L	-	-	-	D	L	S	N	-	V	Q	S	K	C	G	S	K	D	N	I	K	H	V	P	G	G	G	S
5. sp P10636 629-654		-	-	P	V	-	-	-	D	L	S	K	-	V	T	S	K	C	G	S	L	G	N	I	H	H	K	P	G	G	G	Q
6. sp P10636 312-337		-	-	P	V	-	-	-	D	L	S	K	-	V	T	S	K	C	G	S	L	G	N	I	H	H	K	P	G	G	G	Q
7. sp P10636 655-685		E	V	K	S	E	K	L	D	F	K	D	R	V	Q	S	K	I	G	S	L	D	N	I	T	H	V	P	G	G	G	N
8. sp P10636 338-368		E	V	K	S	E	K	L	D	F	K	D	R	V	Q	S	K	I	G	S	L	D	N	I	T	H	V	P	G	G	G	N

# Background



# Background

## Structure<sup>1</sup>

### Secondary structure

1

758

Legend: ■ Helix ■ Turn ■ Beta strand ■ PDB Structure known for this area

[Show more details](#)

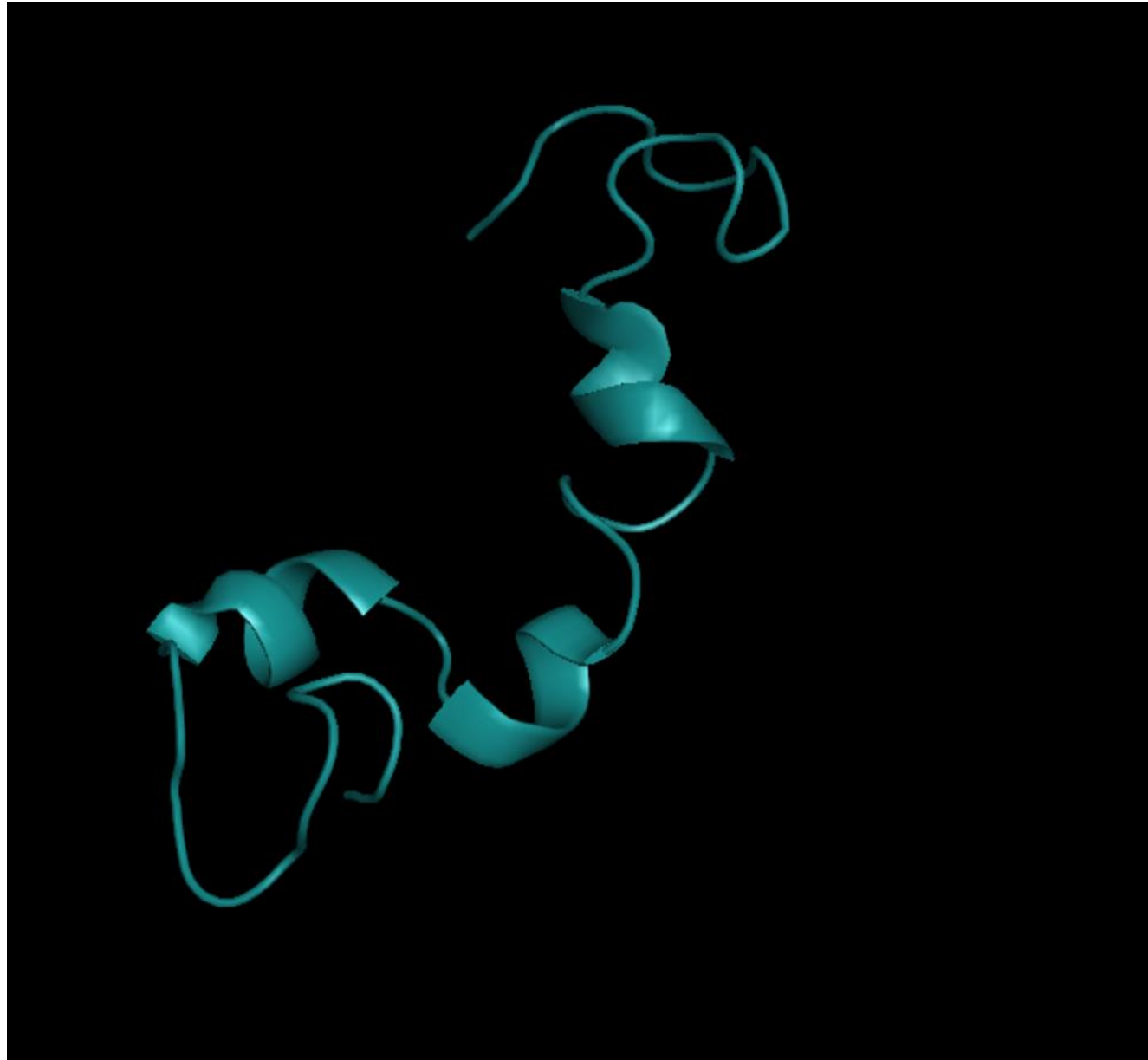
### 3D structure databases

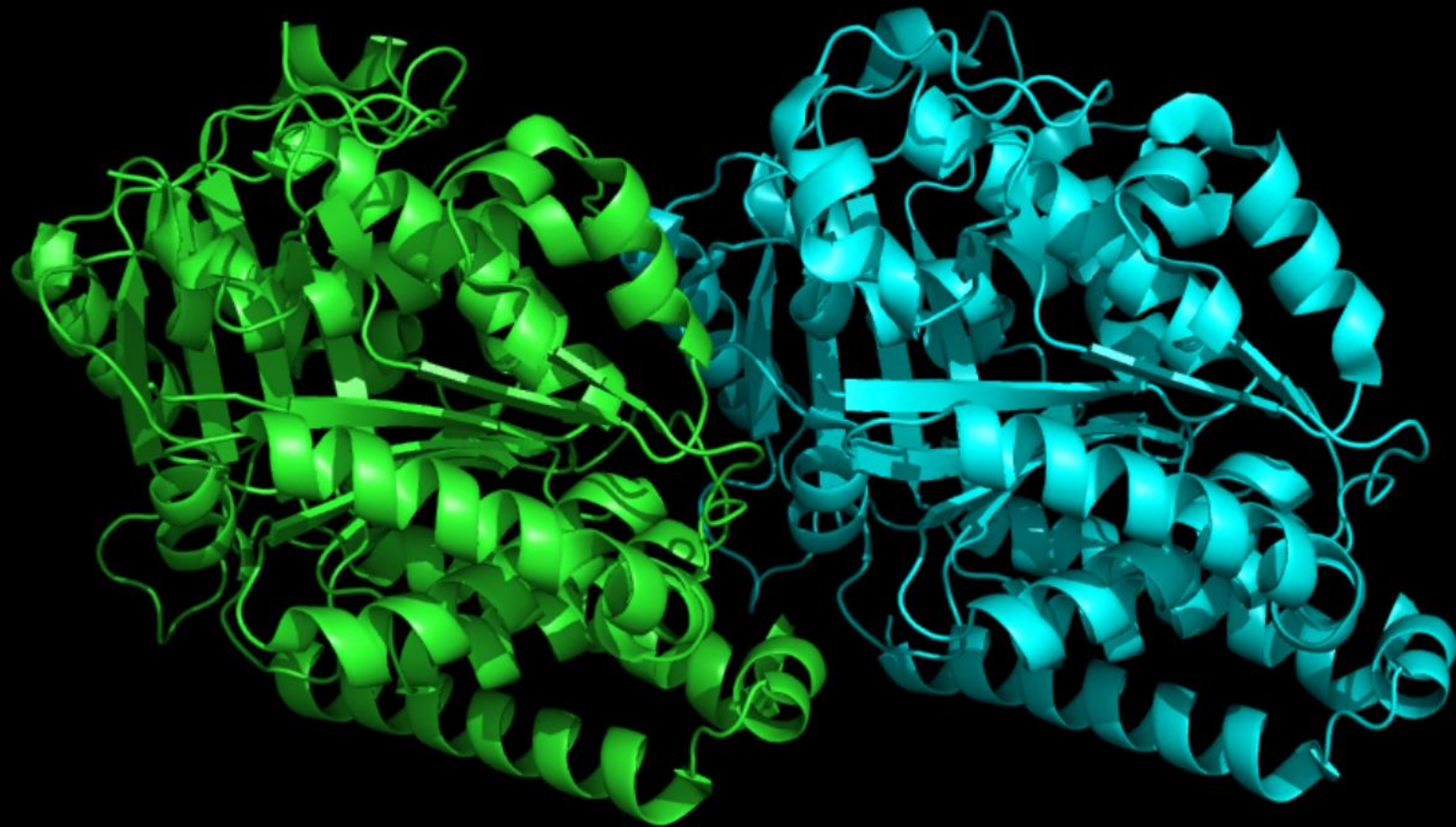
Select the link destinations:	PDB entry	Method	Resolution (Å)	Chain	Positions	PDBsum
<input type="radio"/> PDB <sup>i</sup>	1I8H	NMR	-	A	542-554	[>]
<input checked="" type="radio"/> RCSB PDB <sup>i</sup>	2MZ7	NMR	-	A	584-629	[>]
<input type="radio"/> PDBj <sup>i</sup>	2ON9	X-ray	1.51	A/B	623-628	[>]
	3OVL	X-ray	1.81	A	623-628	[>]
	4E0M	X-ray	1.75	A/B/C/D	622-634	[>]
	4E0N	X-ray	1.65	A/B/C/D	622-634	[>]
	4E0O	X-ray	1.82	A/B/C/D	622-634	[>]
	4FL5	X-ray	1.90	P/Q	527-536	[>]
	4GLR	X-ray	1.90	A/B	541-557	[>]
	4NP8	X-ray	1.51	A	623-628	[>]
	4TQE	X-ray	1.60	A	532-547	[>]
	4Y32	X-ray	1.70	C/D	528-534	[>]
	4Y3B	X-ray	1.80	C/D	528-534	[>]
	4Y5I	X-ray	1.40	F/G	528-534	[>]
	5DMG	X-ray	2.50	P/X/Z	733-747	[>]
	5E2V	X-ray	1.64	P	511-528	[>]
	5E2W	X-ray	1.50	P	511-528	[>]
	5HF3	X-ray	1.80	B	528-534	[>]
DisProt <sup>i</sup>	DP00126.					
ProteinModelPortal <sup>i</sup>	P10636.					
SMR <sup>i</sup>	P10636.					
ModBase <sup>i</sup>	Search...					
MobiDB <sup>i</sup>	Search...					

**Tau structure  
in PDB**

**267-312**

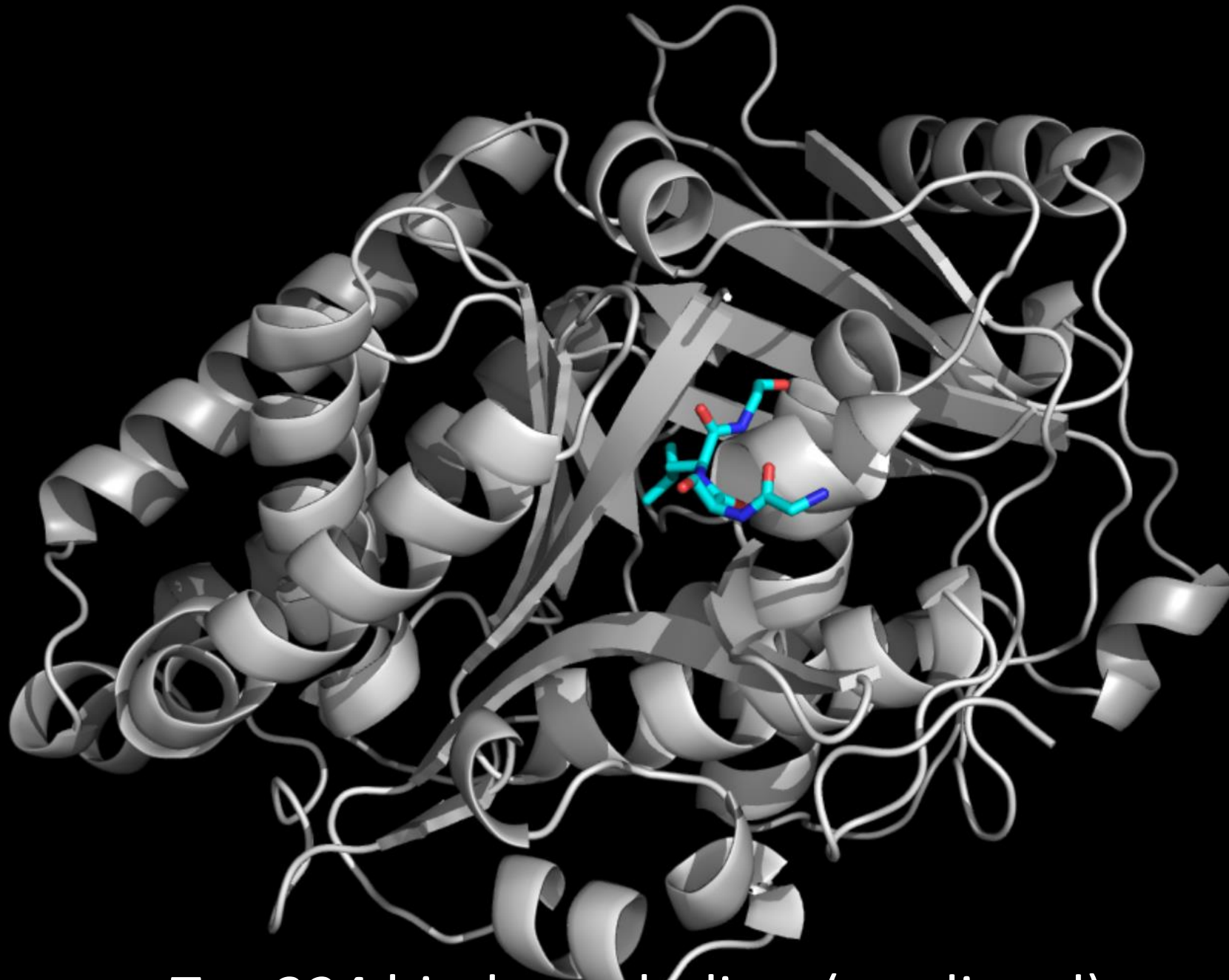
**Contain two  
repeat region**



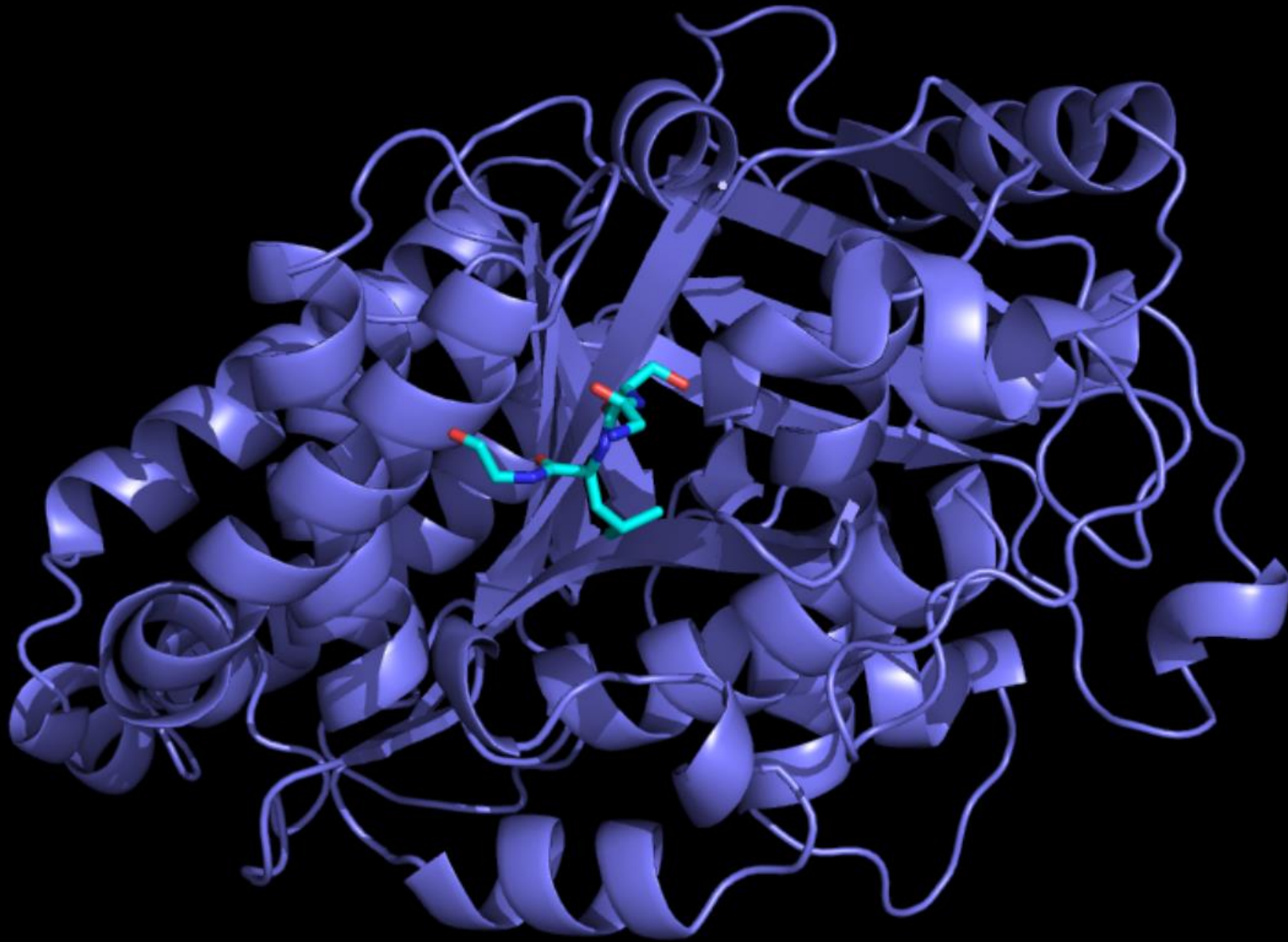


**Tubulin $\alpha$ & $\beta$**

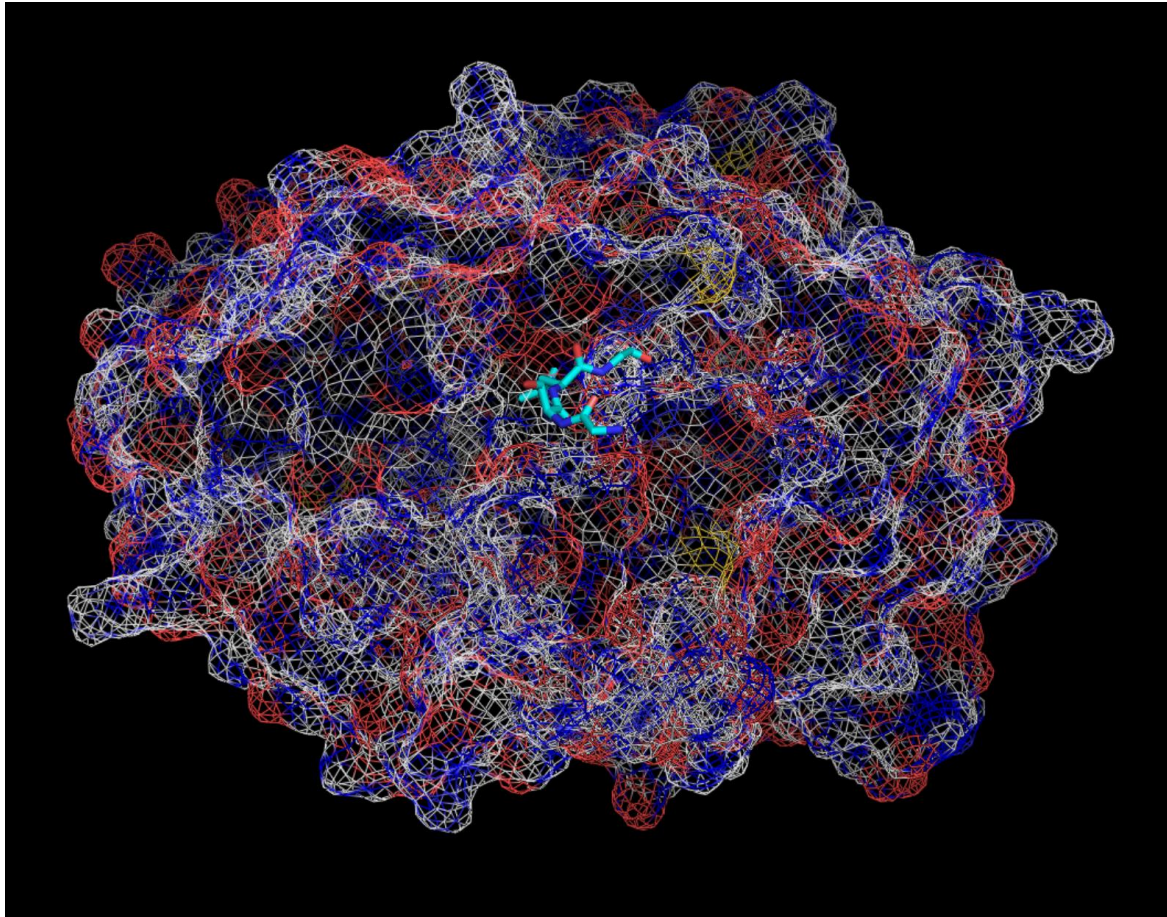




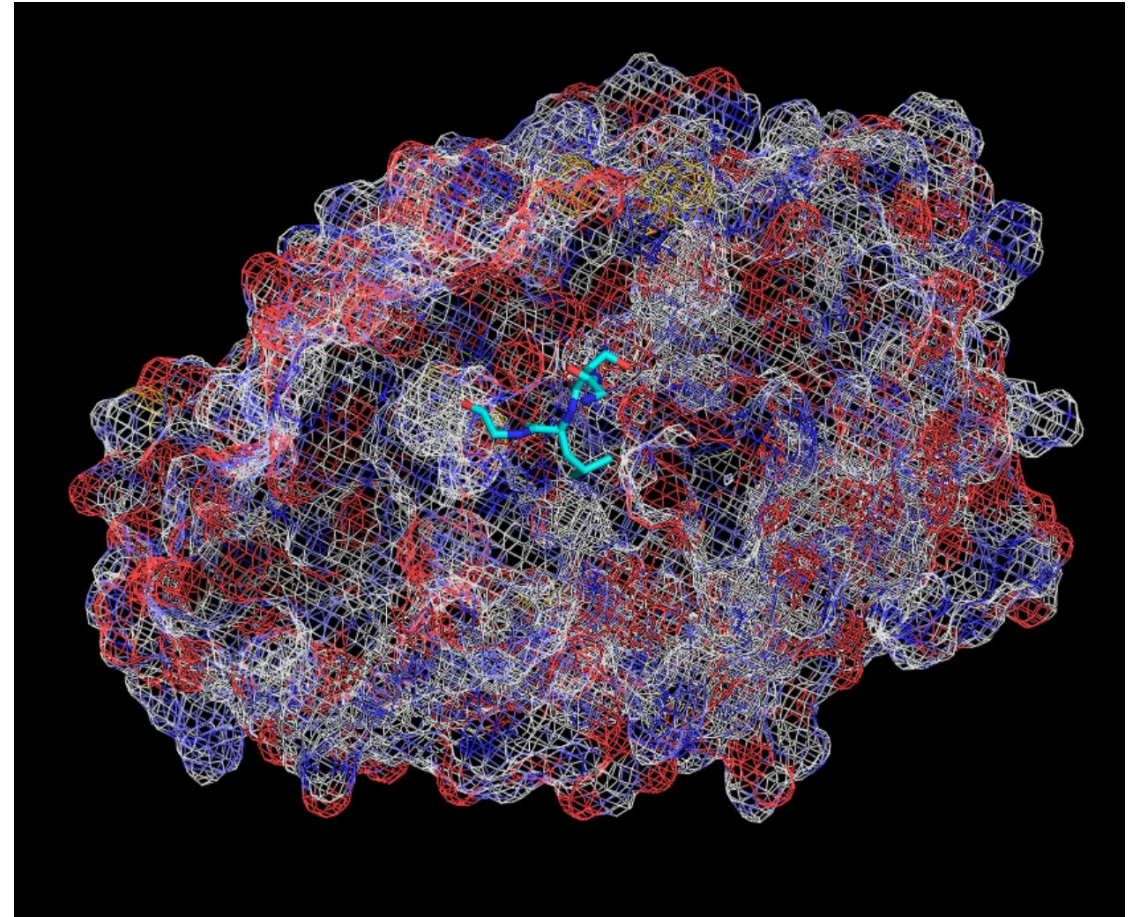
Tau 324 bind to tubulin- $\alpha$ (predicted)



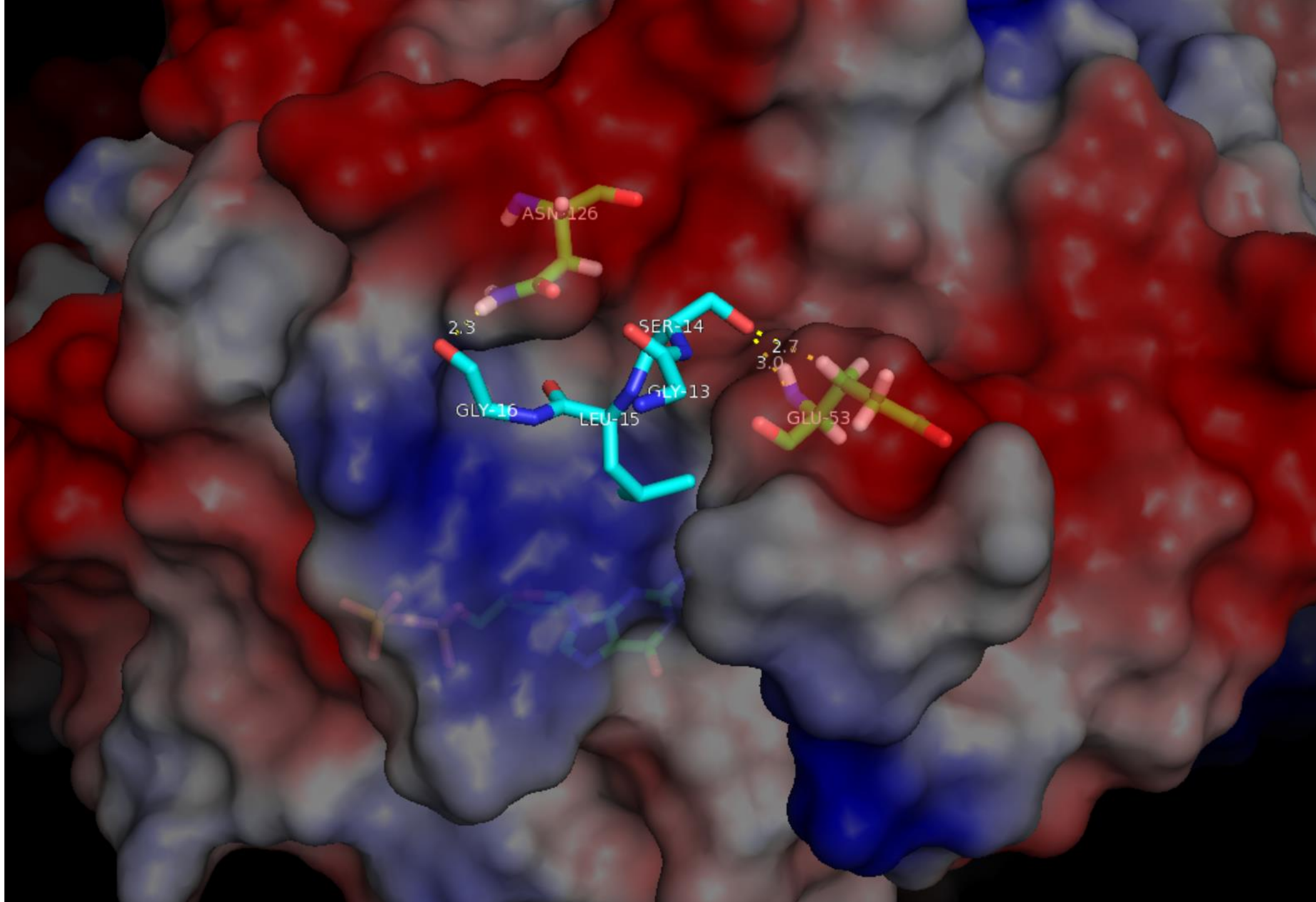
Tau 324 bind to tubulin- $\beta$ (predicted)

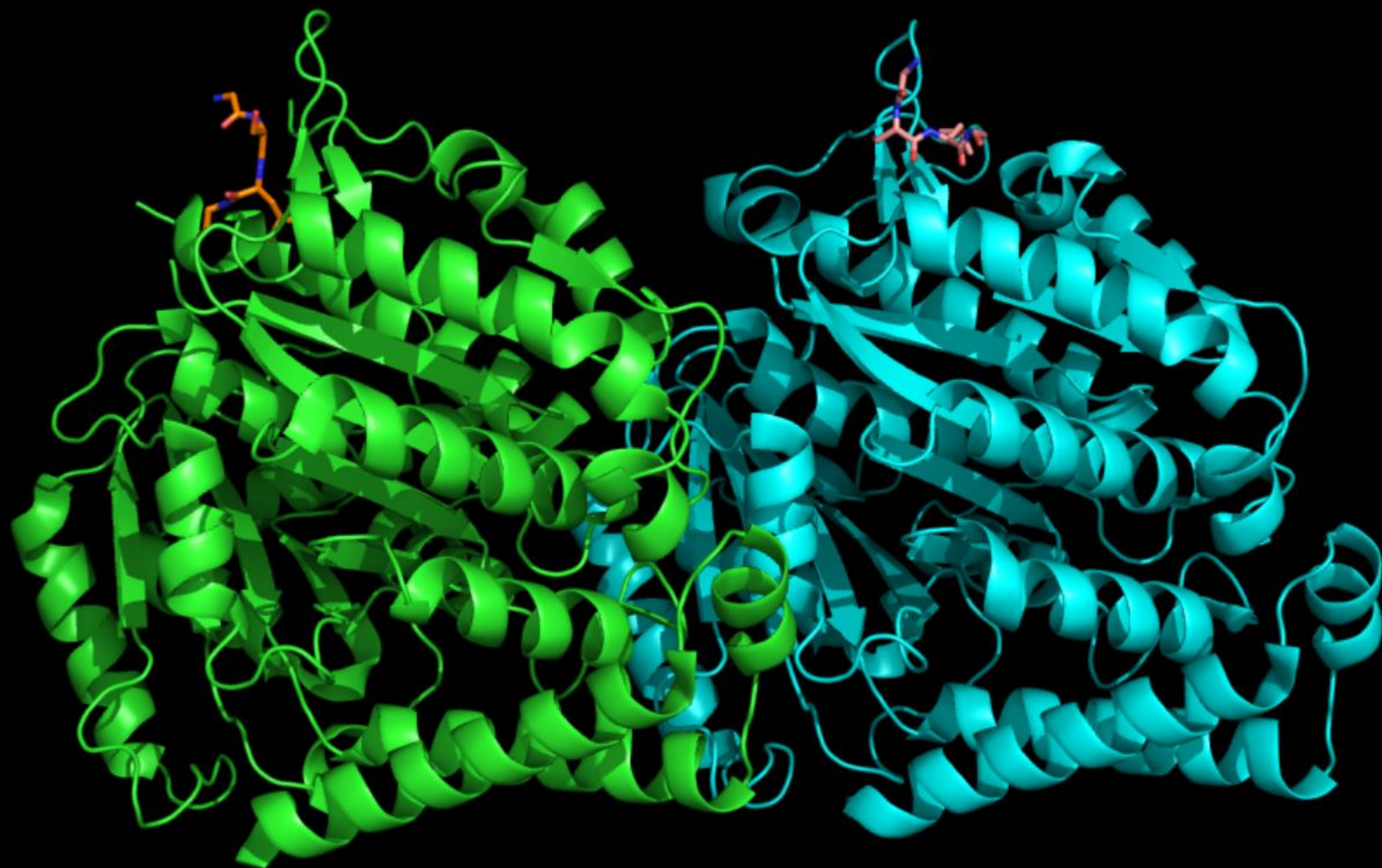


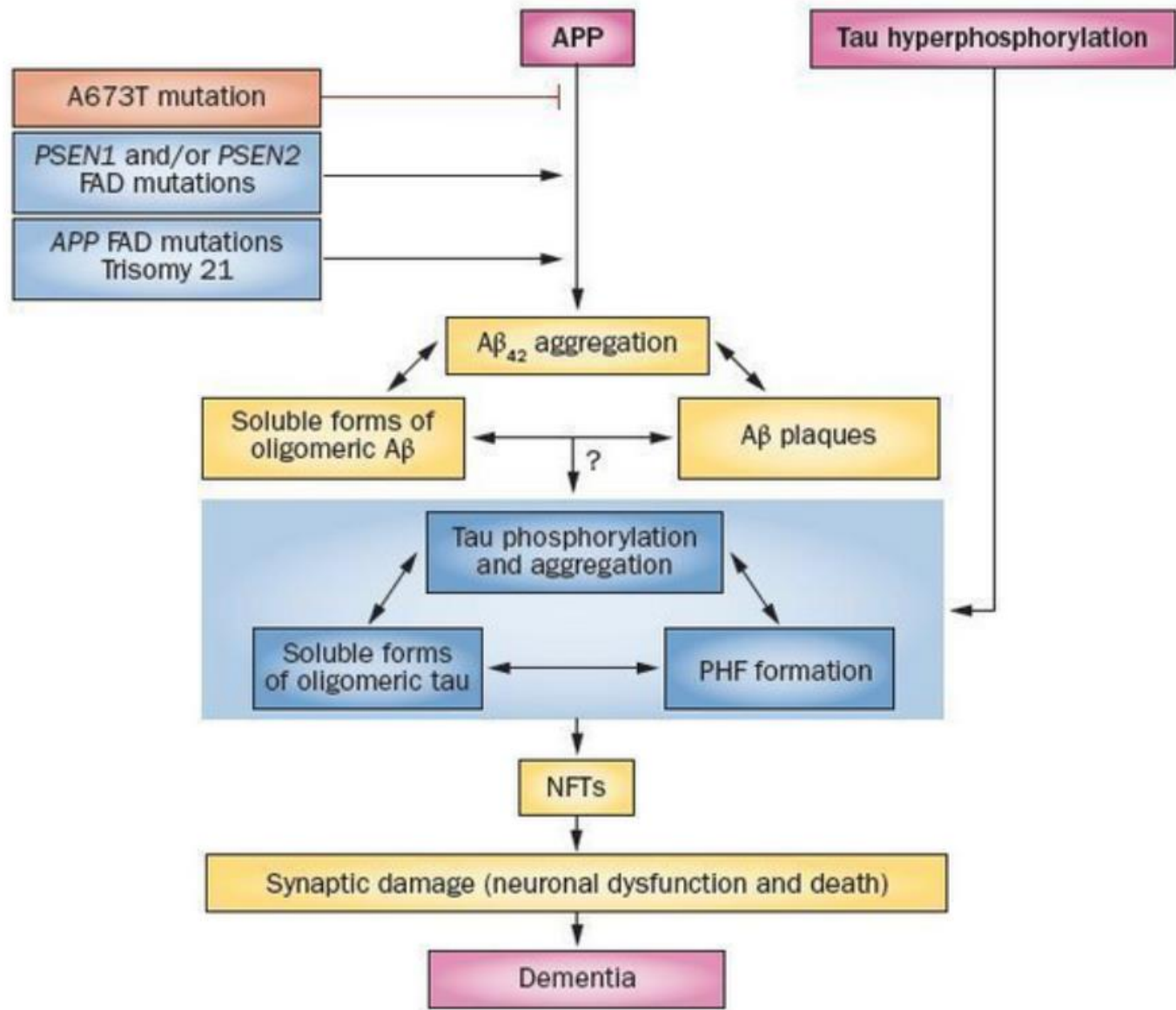
**$\alpha$ - tubulin**



**$\beta$ - tubulin**







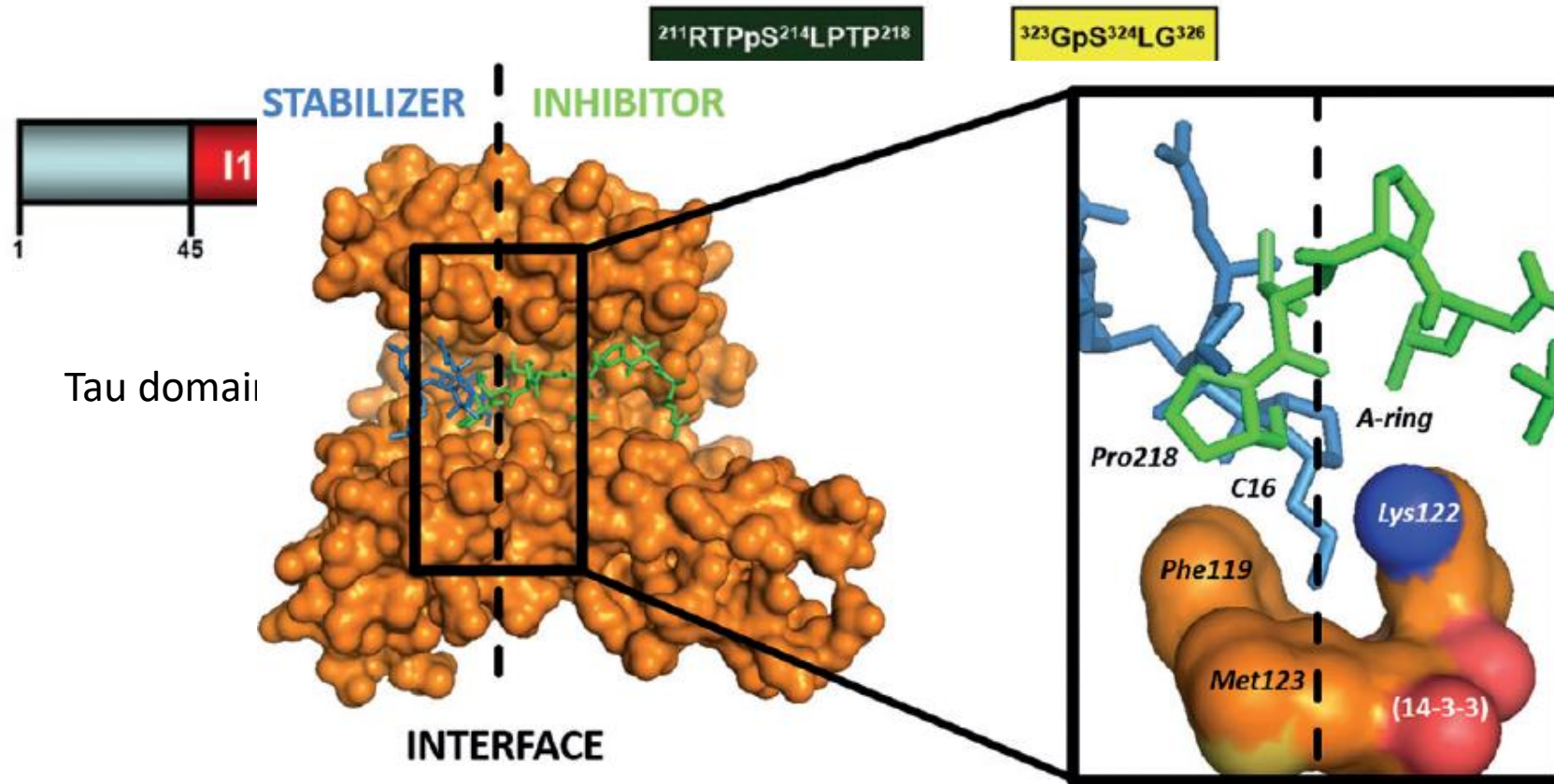
# 14-3-3 pathway

- **14-3-3 proteins** are a family of conserved regulatory molecules that are expressed in all eukaryotic cells. 14-3-3 proteins have the ability to bind a multitude of functionally diverse signaling proteins, including kinases, phosphatases, and transmembrane receptors.

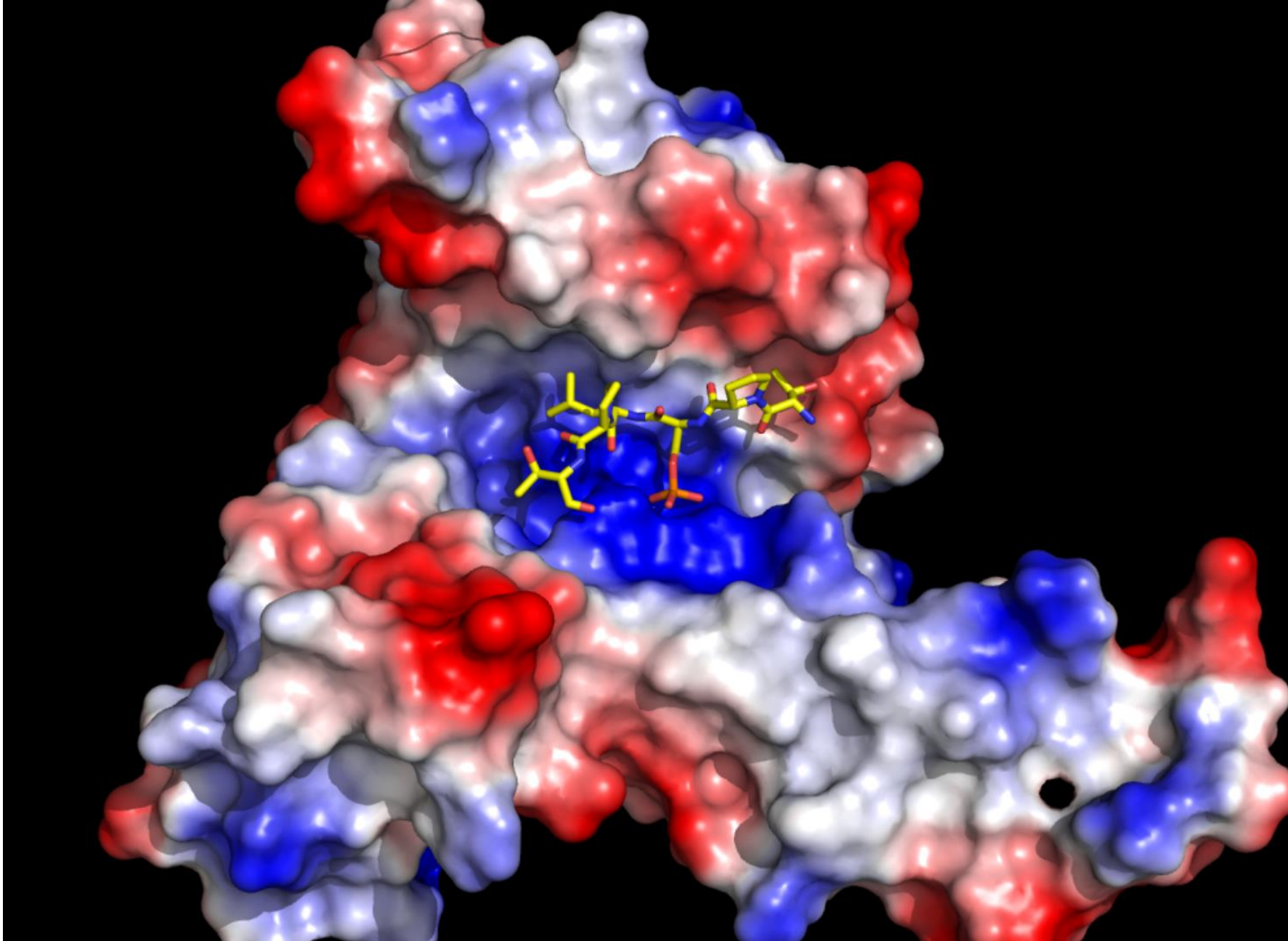
## 14-3-3 regulating cell-signaling

- **Raf-1**
- **Bad** - see Bcl-2 **Bax**
- **Cdc25**
- **Akt**
- **SOS1** - see RSK

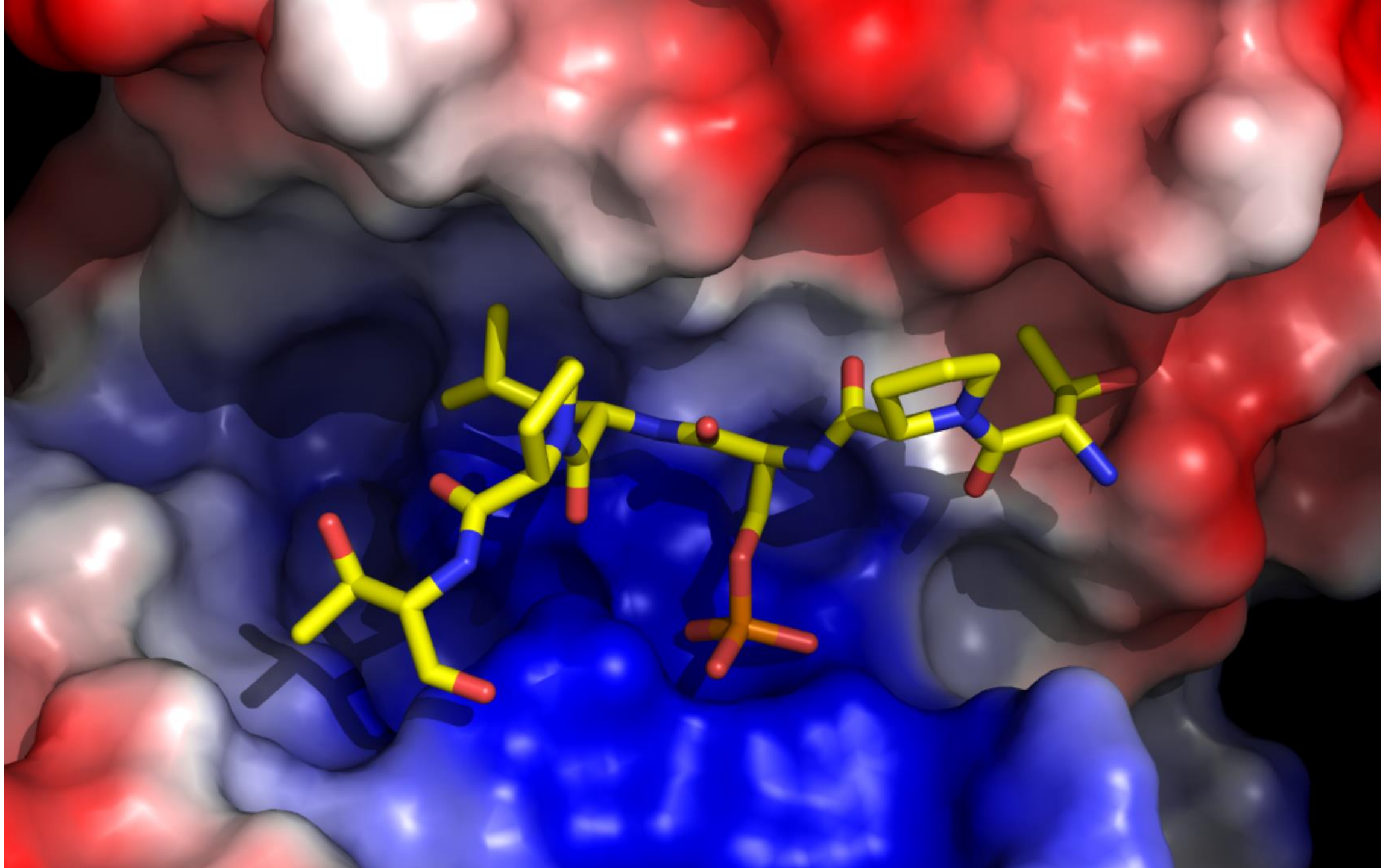
- Binding to phosphate tau protein

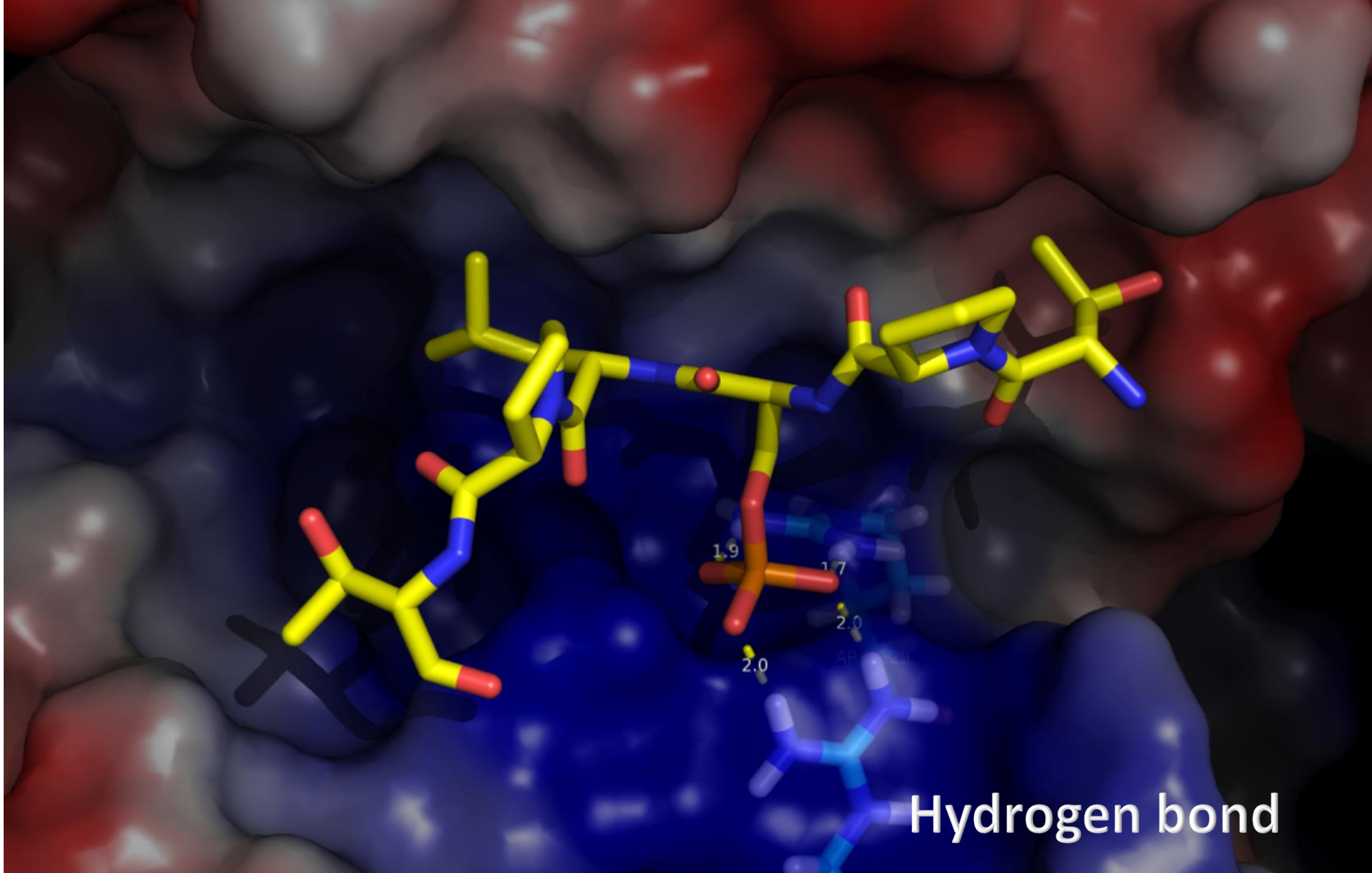


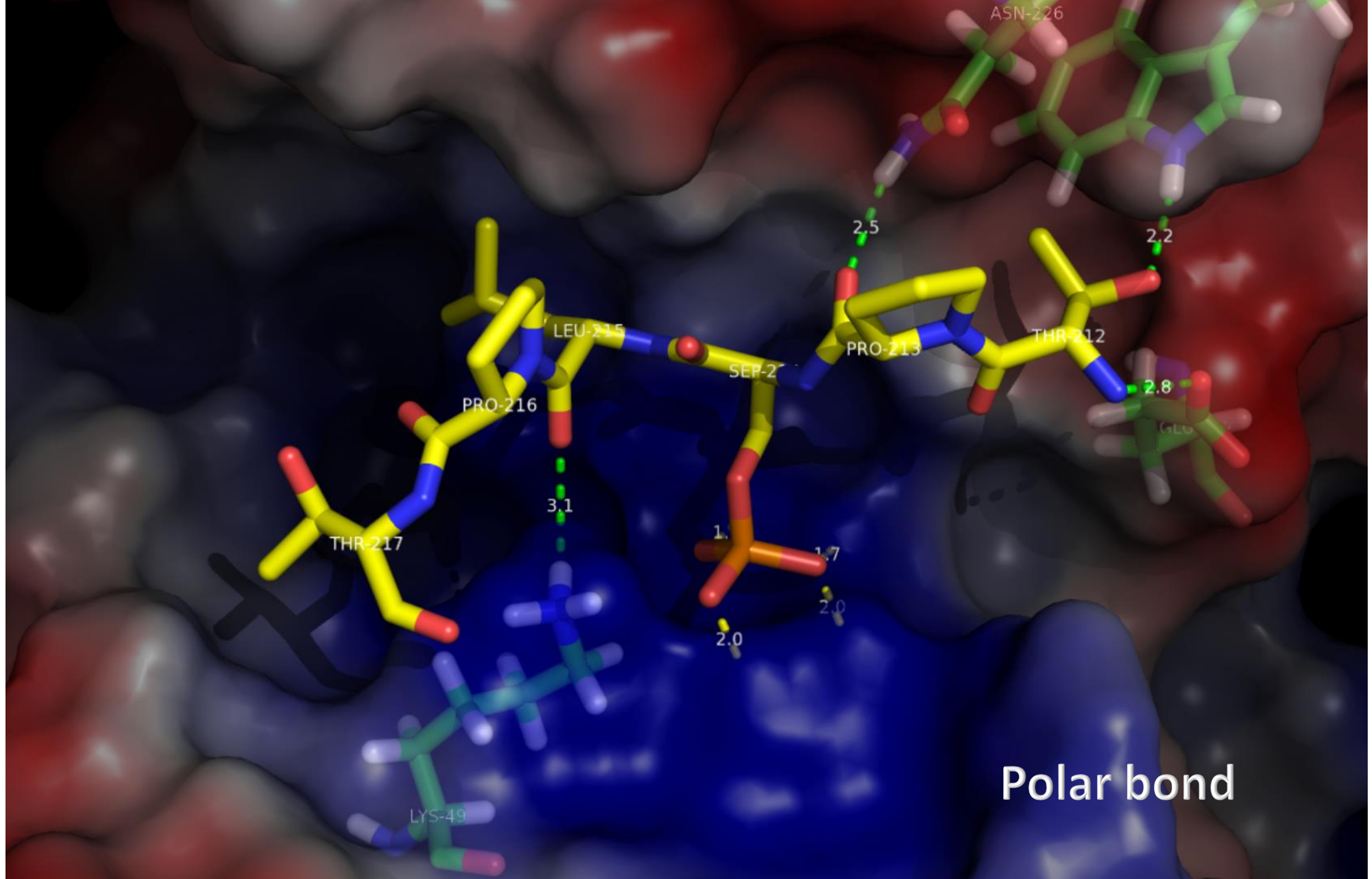


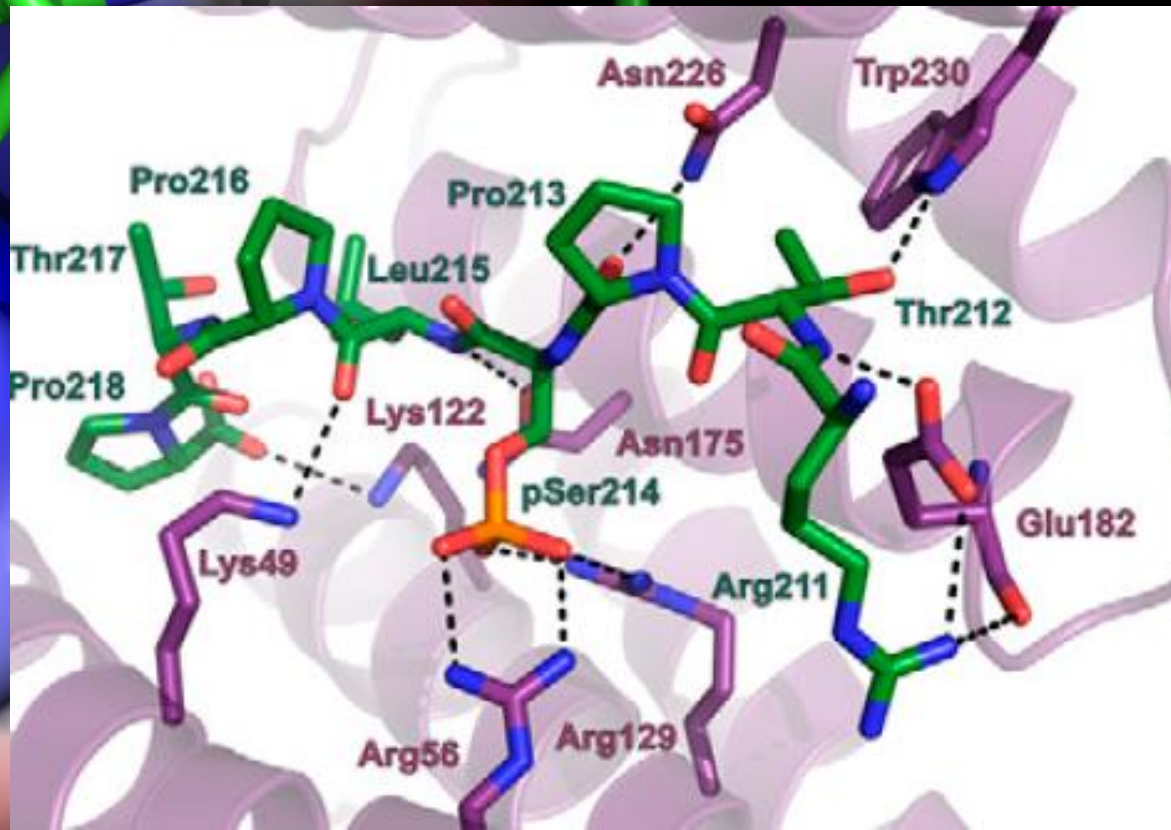
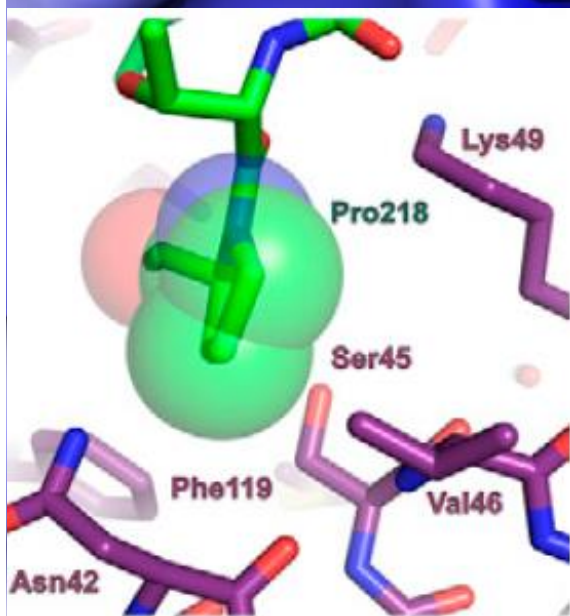
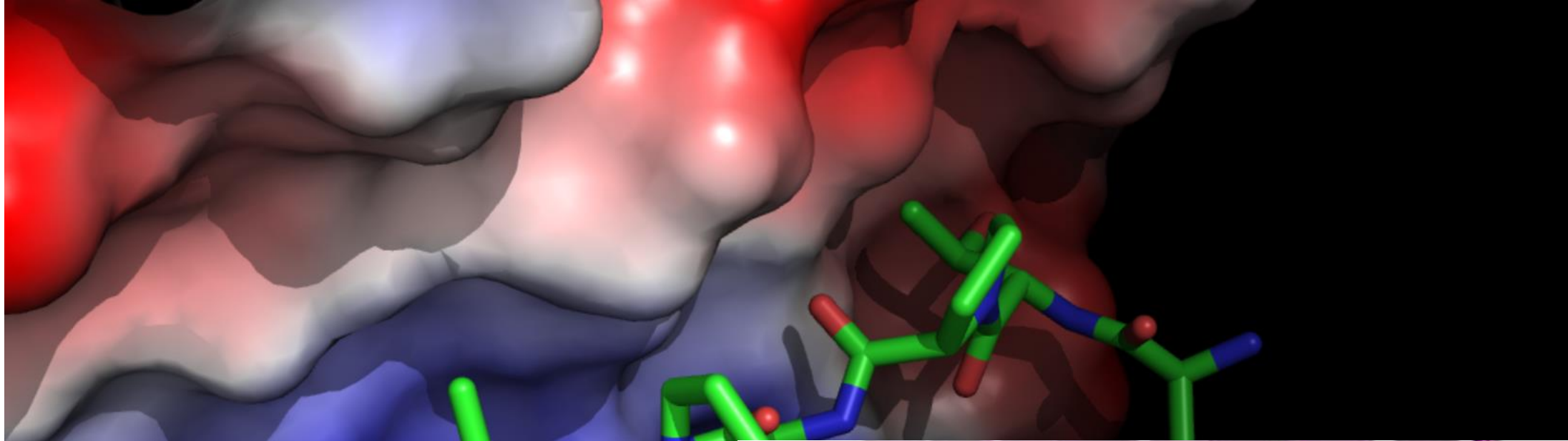


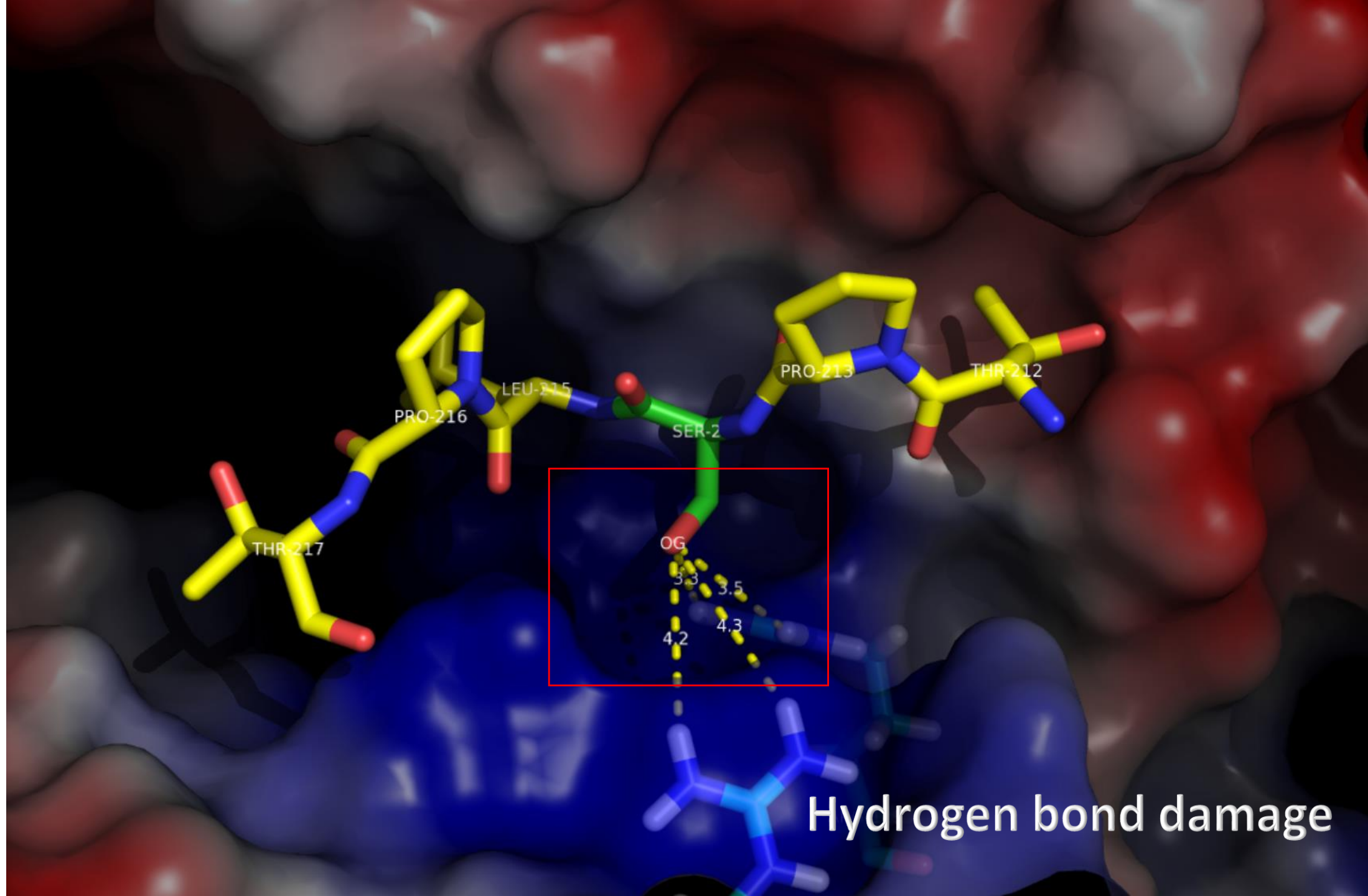
Tau site 214 phosphorylation bind to 14-3-3











tau 311-341 Created: today at 12:26

Summary Templates **2** Models **1**



Model Results

Order by: GMQE

Model 01

Oligo-State ? Ligands  
MONOMER None

Global Quality

QMEAN	-4.46	
CP	-2.16	
All Atom	-1.85	
Solvation	-1.08	
Torsion	-4.33	

GMQE ? QMEAN ?  
0.75 -4.46

Local Quality

Comparison

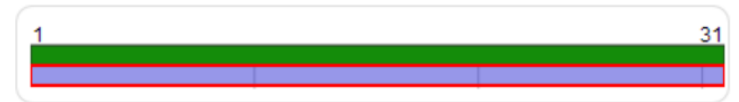
Template	Seq Identity	Coverage	Description
2mz7.1.A	58.06%	<div style="width: 80%; background-color: #0056b3;"></div>	Microtubule-associated protein tau

Model-Template Alignment

Model_01	K P V D L S K V T S K C G S L G N I H H K P G G G Q V E V K S	31
2mz7.1.A	K K L D L S N V Q S K C G S K D N I K H V P G G S V Q I V Y	44



View



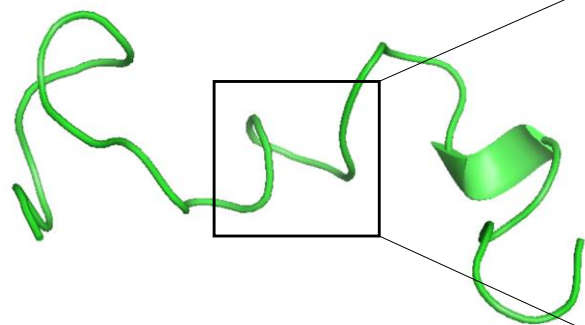
M7: Alignment Explorer

Data Edit Search Alignment Web Sequencer Display Help

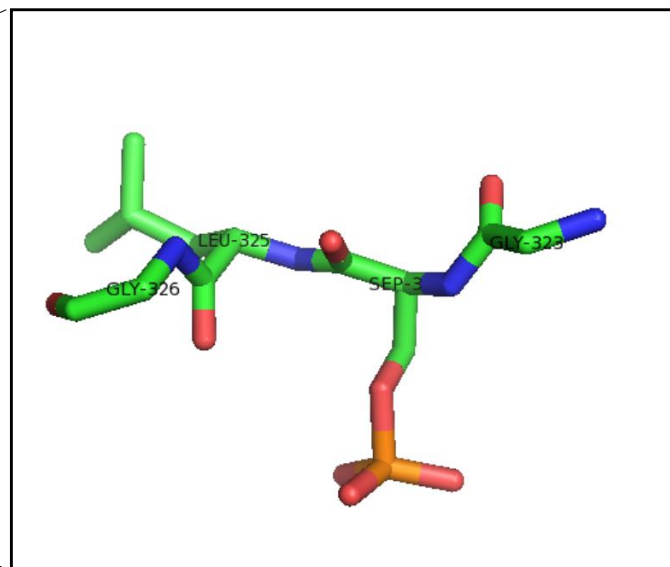
---

Protein Sequences

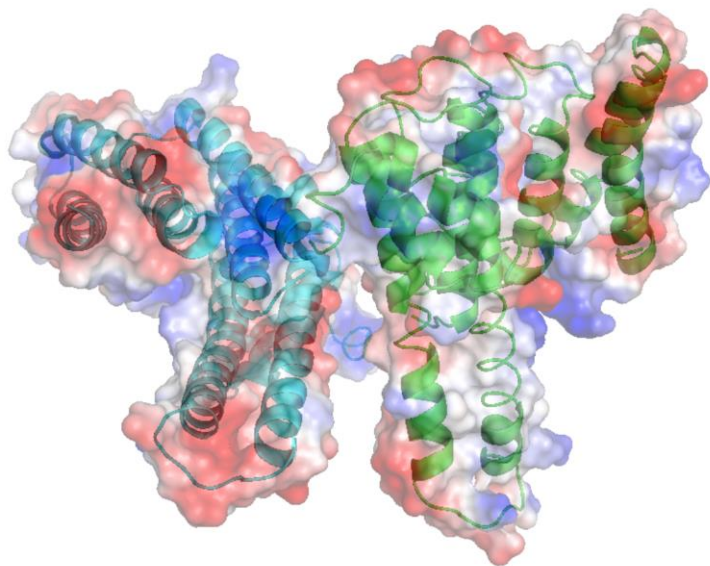
Species/Abbrv	Group Name	*	* * *	*	* * * * *	*	* * *	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*							
1. sp 2mz7.1.A		K	K	L	D	L	S	N	V	Q	S	K	C	G	S	K	D	N	I	K	H	V	P	G	G	S	V	Q	I	V	Y
2. sp Model_01		K	P	V	D	L	S	K	V	T	S	K	C	G	S	L	G	N	I	H	H	K	P	G	G	Q	V	E	V	K	S



Tau 311-341 model



Tau 323-326 phosphate model



14-3-3 dimer

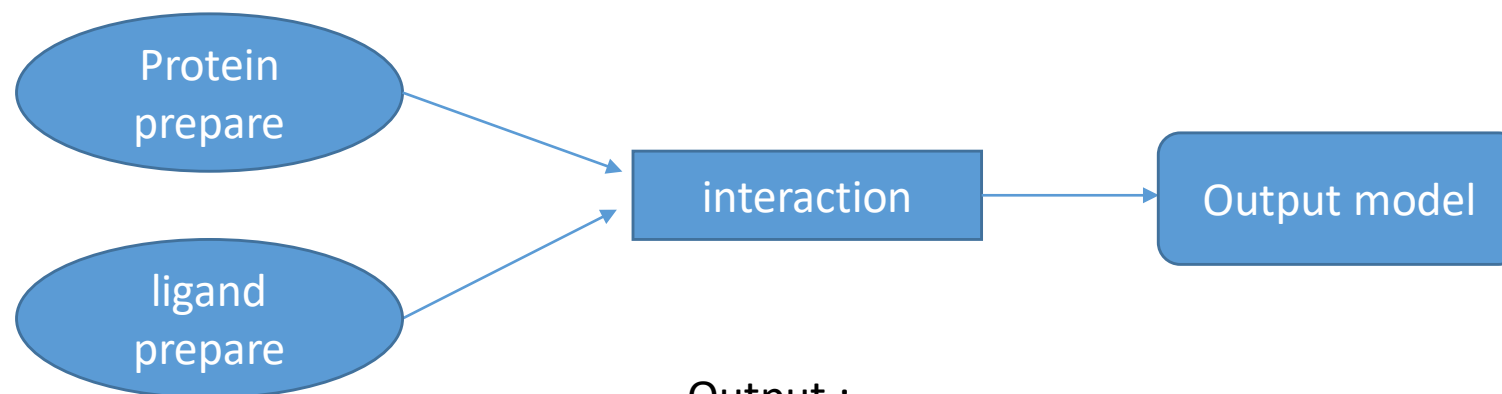


# Autodock vina

- AutoDock is a suite of automated docking tools. It is designed to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structure.
- Using with autodocktools to find protein-protein interaction or other small molecule(ligand) bind to protein(receptor).
- Progress:

- Application

- 1.X-ray crystallography;
- 2.structure-based drug design;
- 3.lead optimization;
- 4.virtual screening (HTS);
- 5.combinatorial library design;
- 6.protein-protein docking;
- 7.chemical mechanism studies.



**Output :**

Affinity(结合能),RMSD(标准差), 一般认为结合能越小越好。

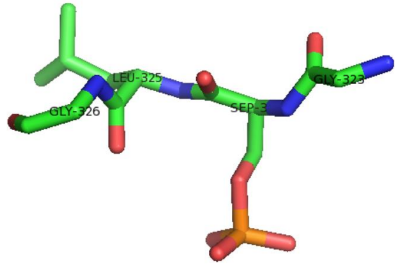
# Principle

- Finding the minimal energy between the protein and ligand binding complex, which may cost large time.
- Autodock vina adopt rapid grid-based energy evaluation and efficient search of torisional freedom
- 1. electrostatic interaction(van der waals)

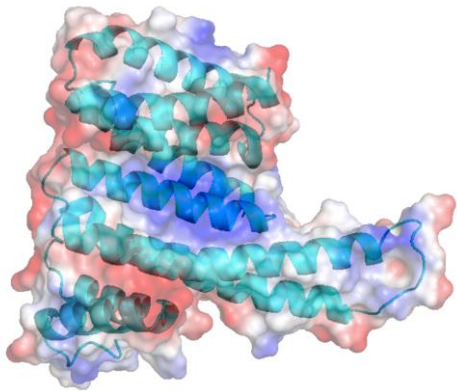
静电相互作用的计算采用了一个静电势格点，在格点上储存受体分子的静电势。当配体和受体分子对接时，某个原子和受体之间的静电相互作用能通过周围格点上静电势以及原子上的部分电荷就可以计算得到。

- 2. hydrogen bond

计算氢键相互作用时，格点的处理和范德华相互作用有点类似，每个格点上需要保存配体分子中所有氢键给体与氢键受体之间的相互作用能量，而且这些能量都是在氢键在最佳情况下的氢键能量值。



Protein-protein interaction



```
C:\test\test1>.\vina.exe --config conf3.6.txt
#####
# If you used AutoDock Vina in your work, please cite:      #
#                                                           #
# O. Trott, A. J. Olson,                                    #
# AutoDock Vina: improving the speed and accuracy of docking #
# with a new scoring function, efficient optimization and    #
# multithreading, Journal of Computational Chemistry 31 (2010) #
# 455-461                                                    #
#                                                           #
# DOI 10.1002/jcc.21334                                     #
#                                                           #
# Please see http://vina.scripps.edu for more information.  #
#####

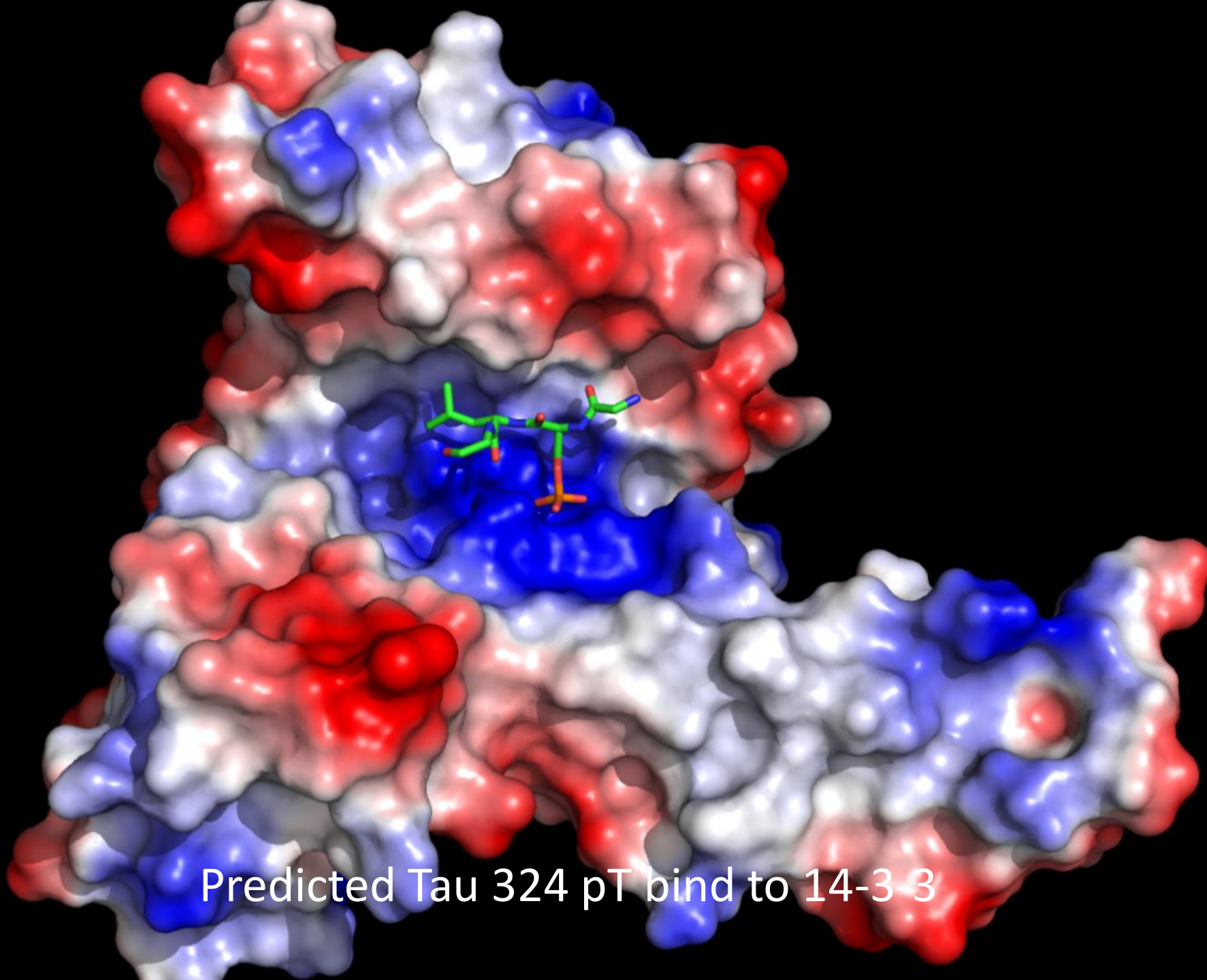
Output will be tau324p_out.pdbqt
Detected 4 CPUs
Reading input ... done.
Setting up the scoring function ... done.
Analyzing the binding site ... done.
Using random seed: 2140383980
Performing search ...
0% 10 20 30 40 50 60 70 80 90 100%
|---|---|---|---|---|---|---|---|---|
*****
done.
Refining results ... done.

mode | affinity | dist from best mode
    | (kcal/mol) | rmsd l.b. | rmsd u.b.
-----+-----+-----+-----
1      -5.5      0.000      0.000
2      -5.5      2.726      3.741
3      -5.4      2.026      2.789
4      -5.3      1.734      2.449
5      -5.3      2.199      2.680
6      -5.3      2.528      4.051
7      -5.2      3.012      4.373
8      -5.2      1.883      4.084
9      -5.0      2.451      4.568

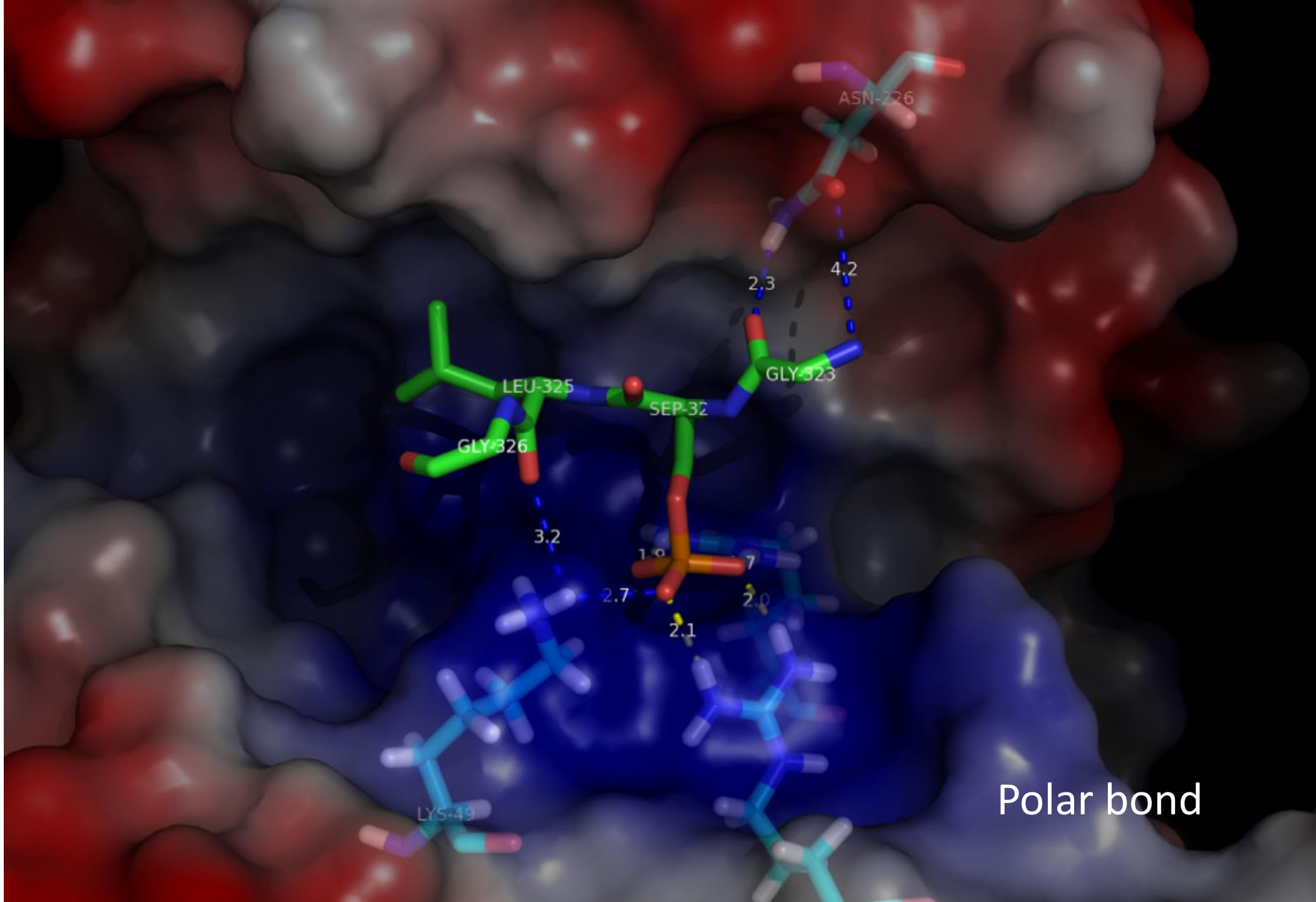
Writing output ... done.

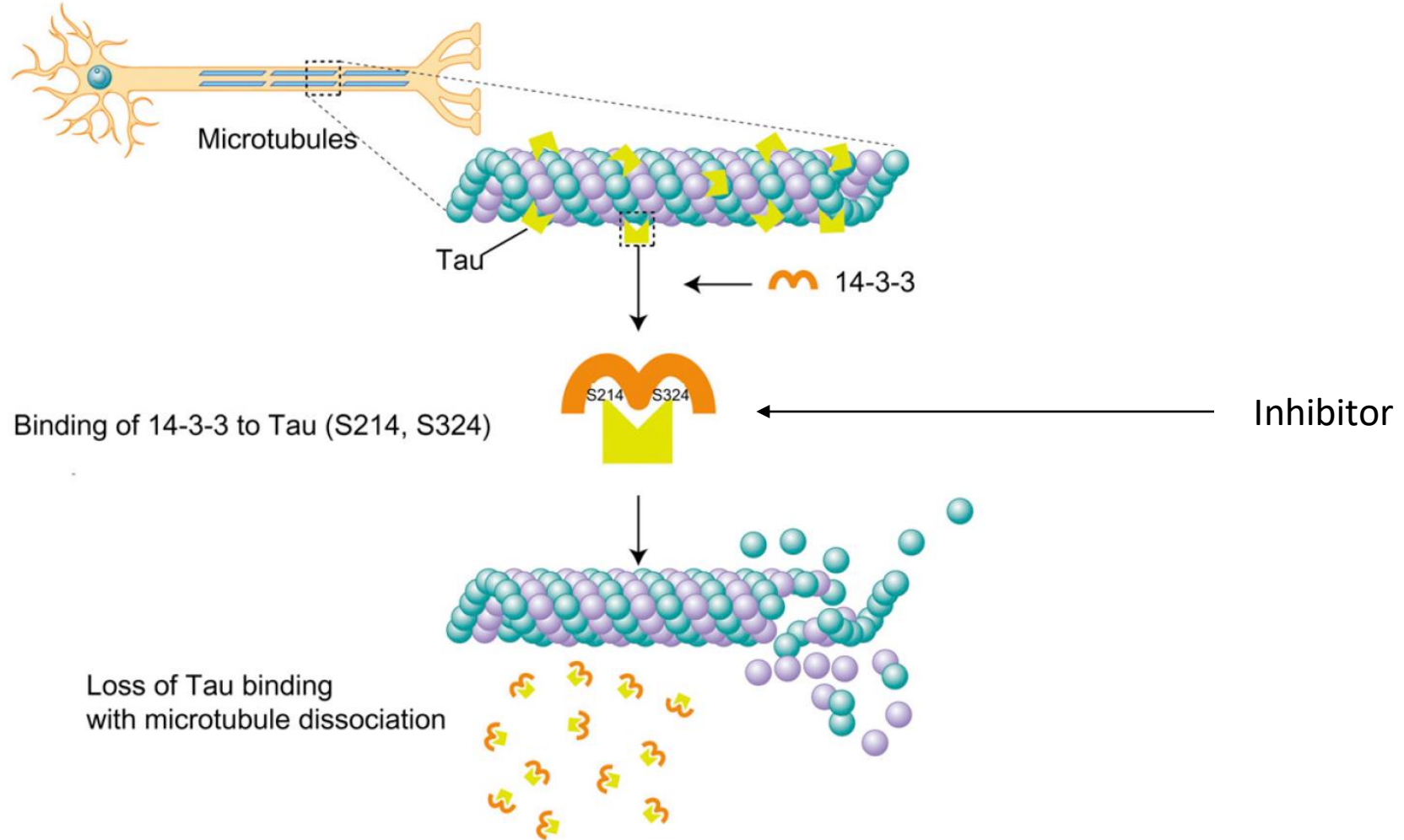
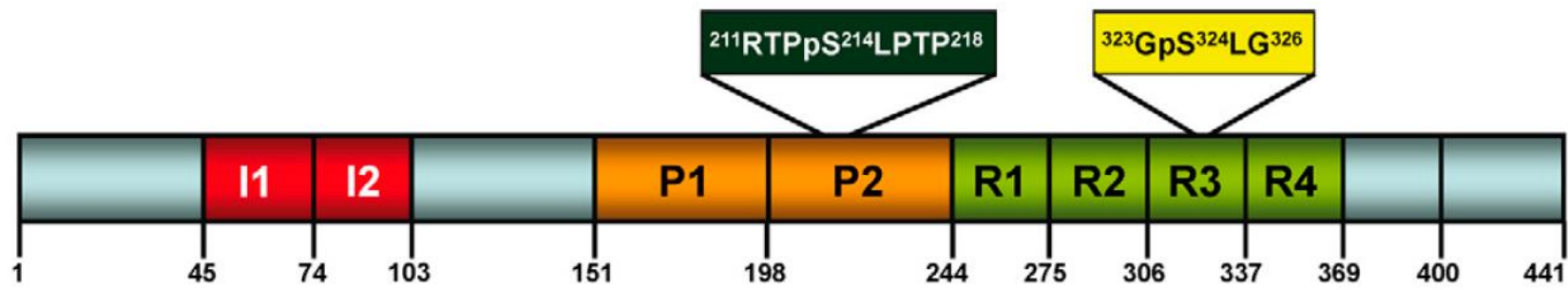
C:\test\test1>
```

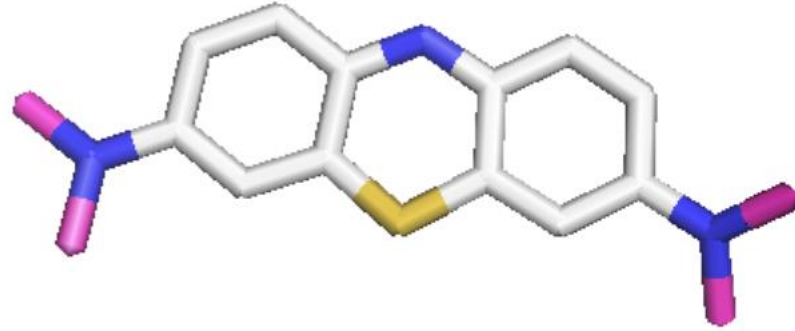
Autodock vina



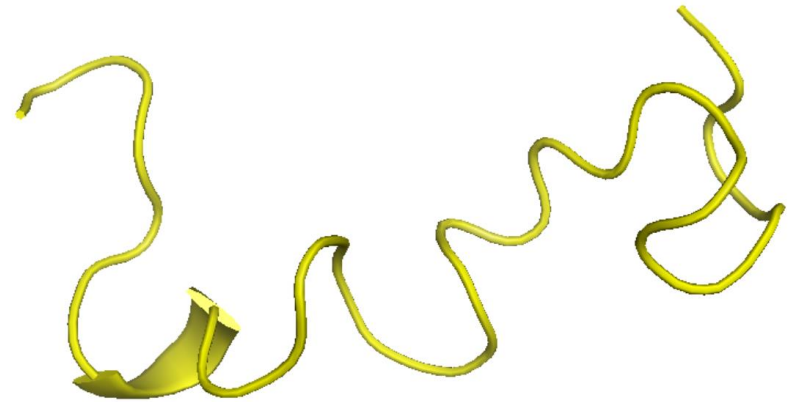
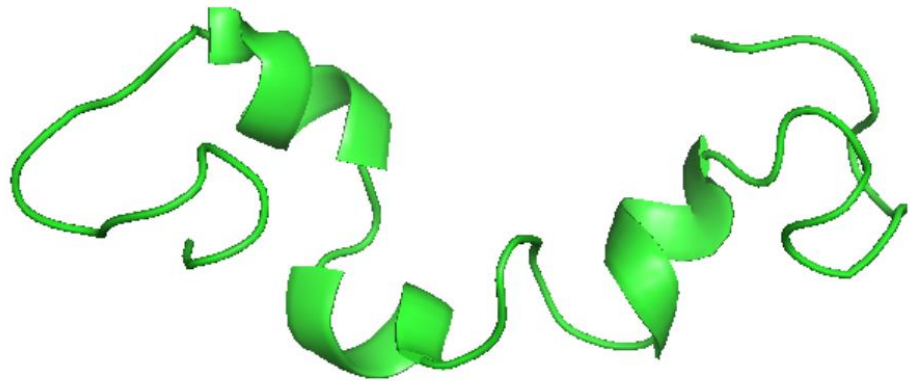
Predicted Tau 324 pT bind to 14-3-3

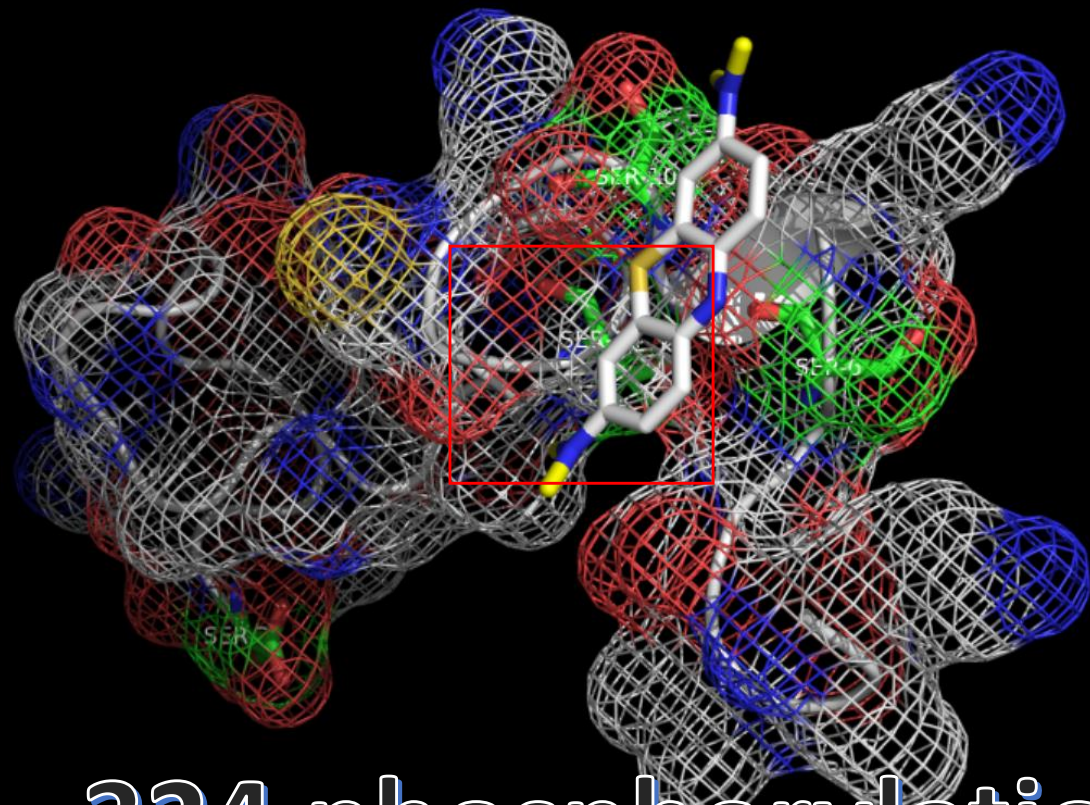
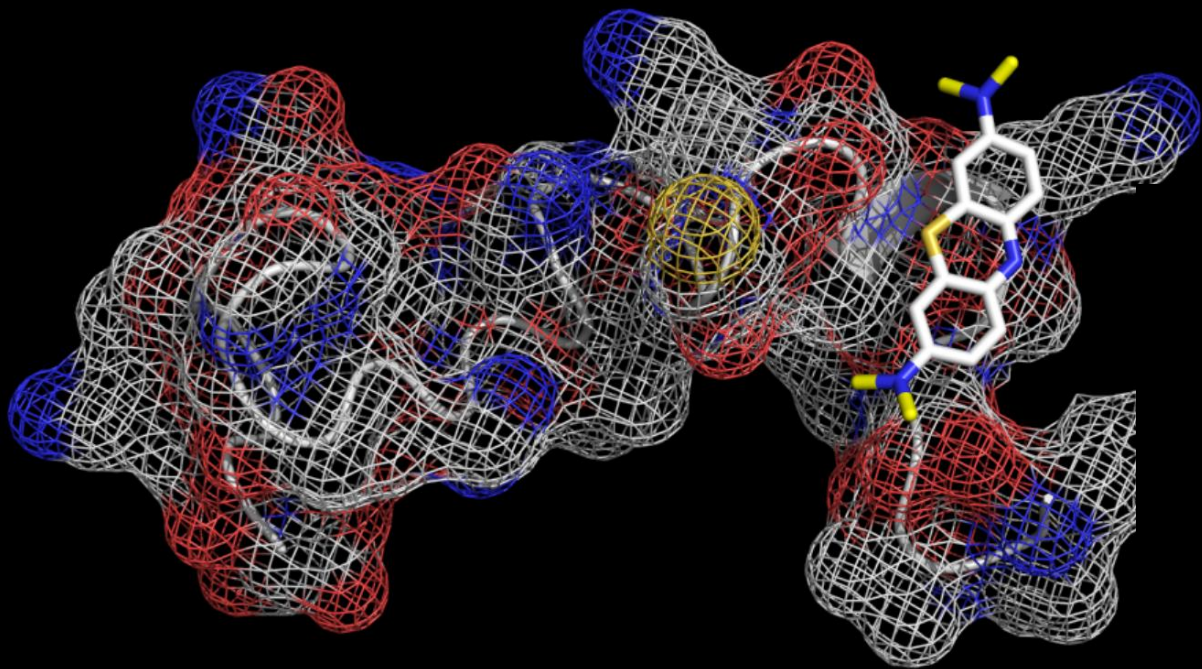






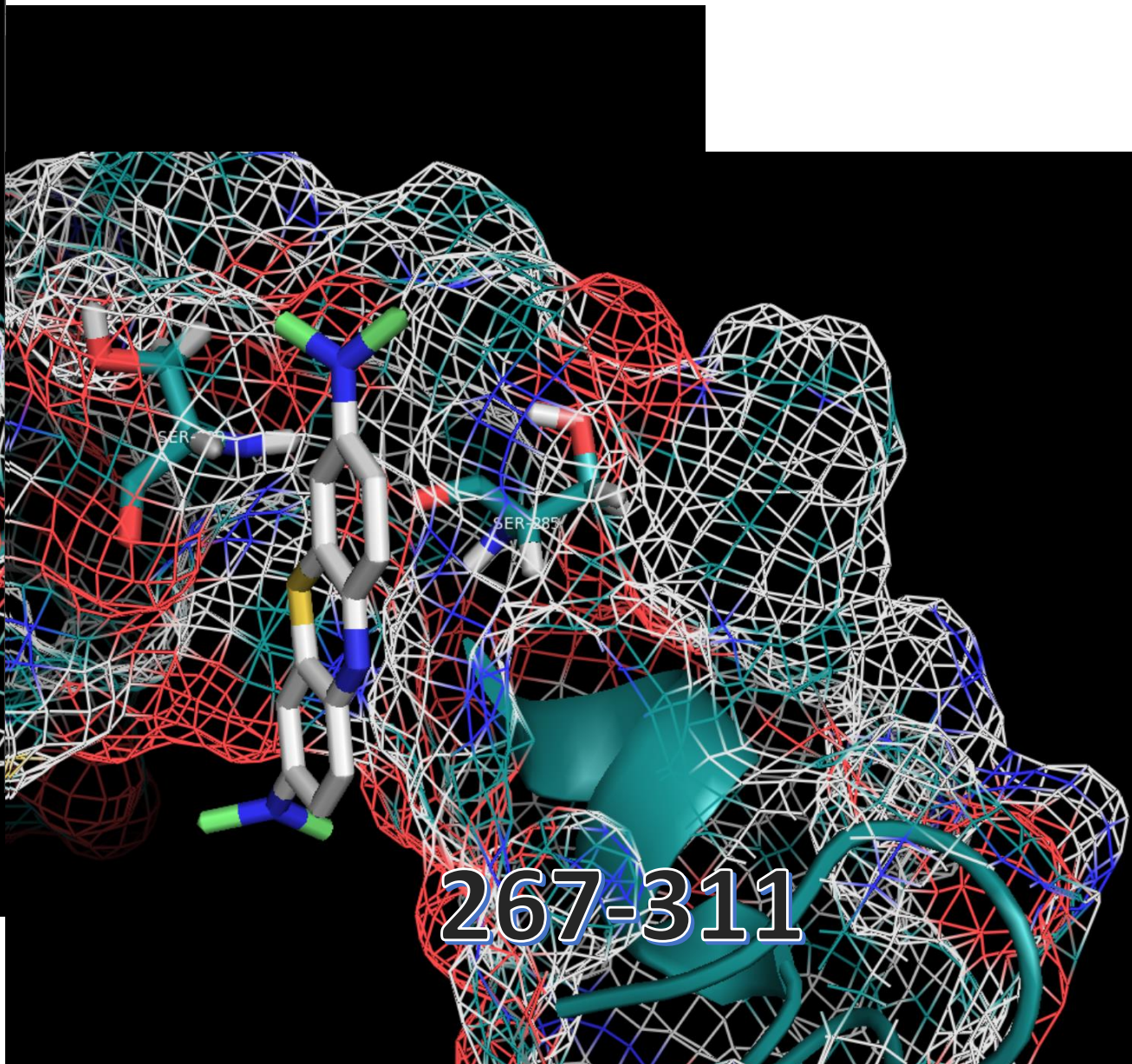
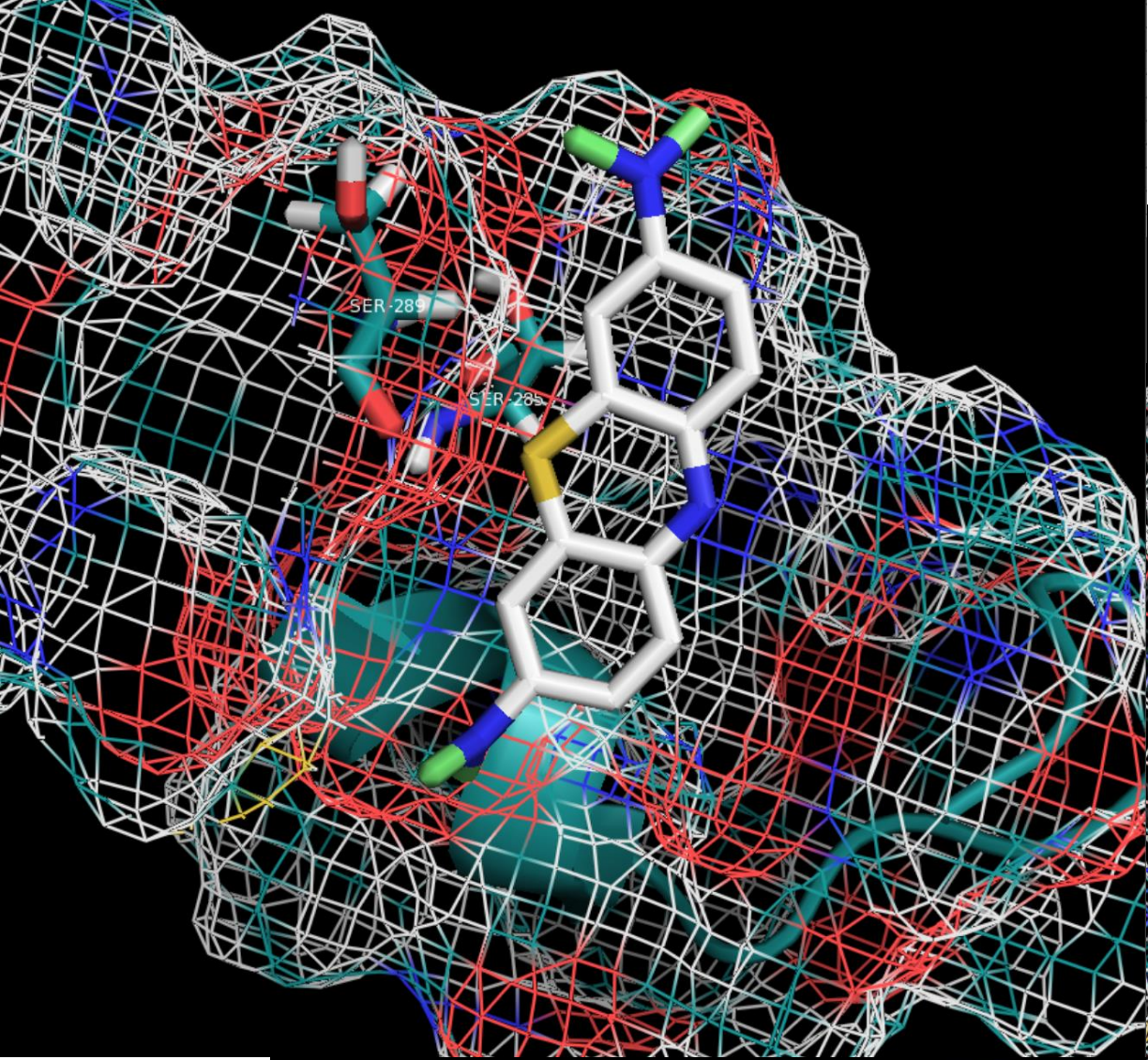
**LMTM**



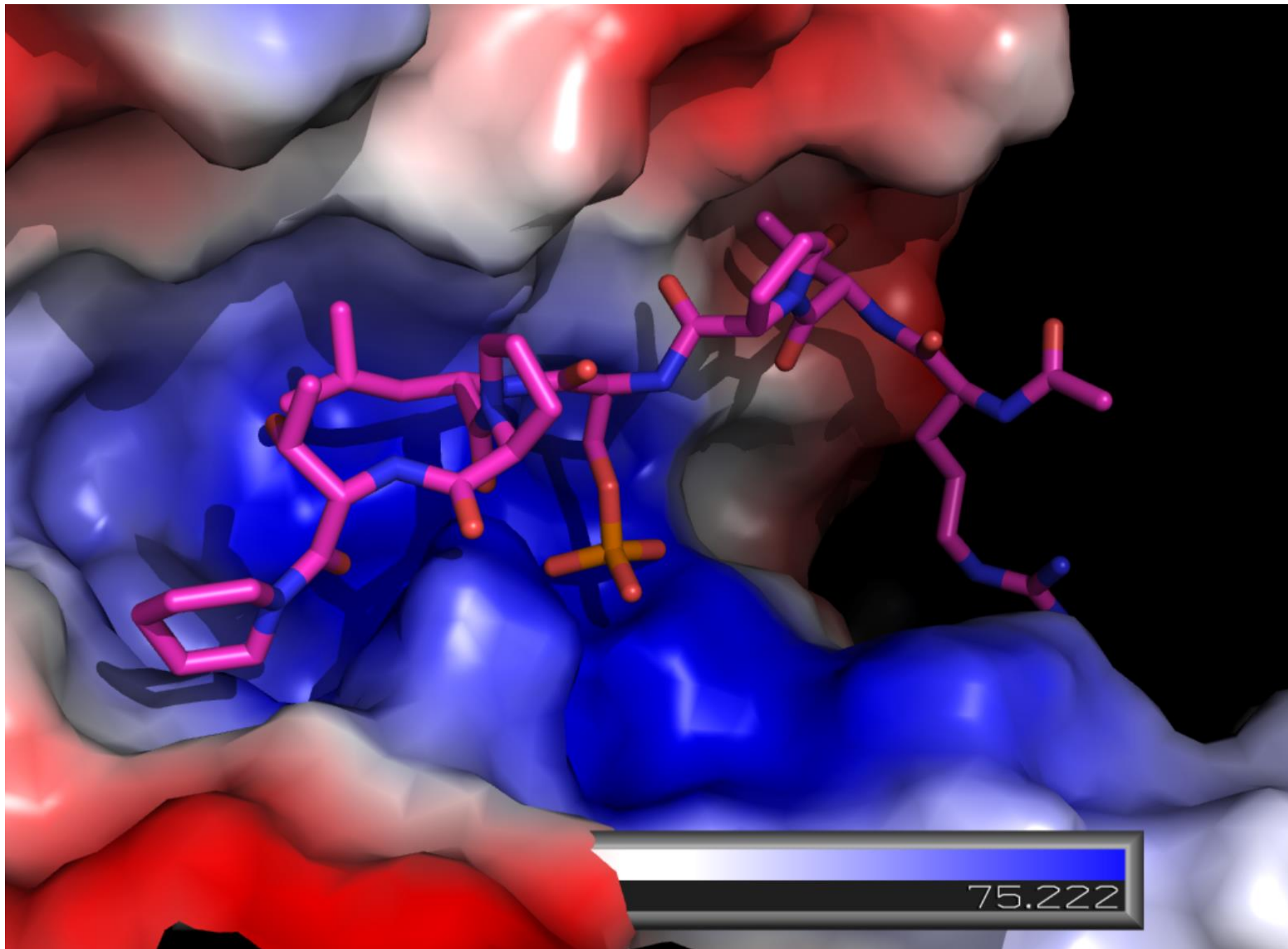


324 phosphorylation

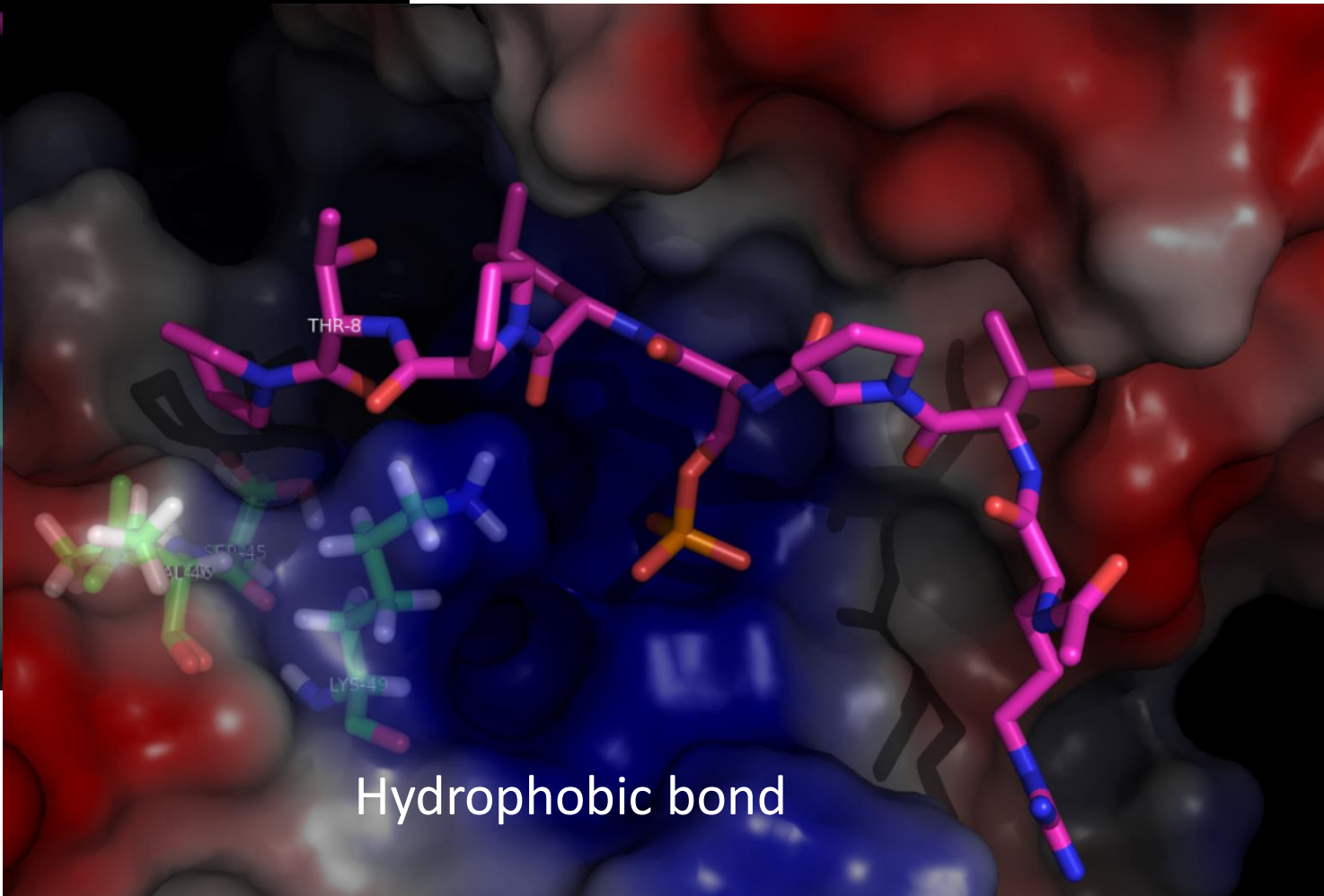
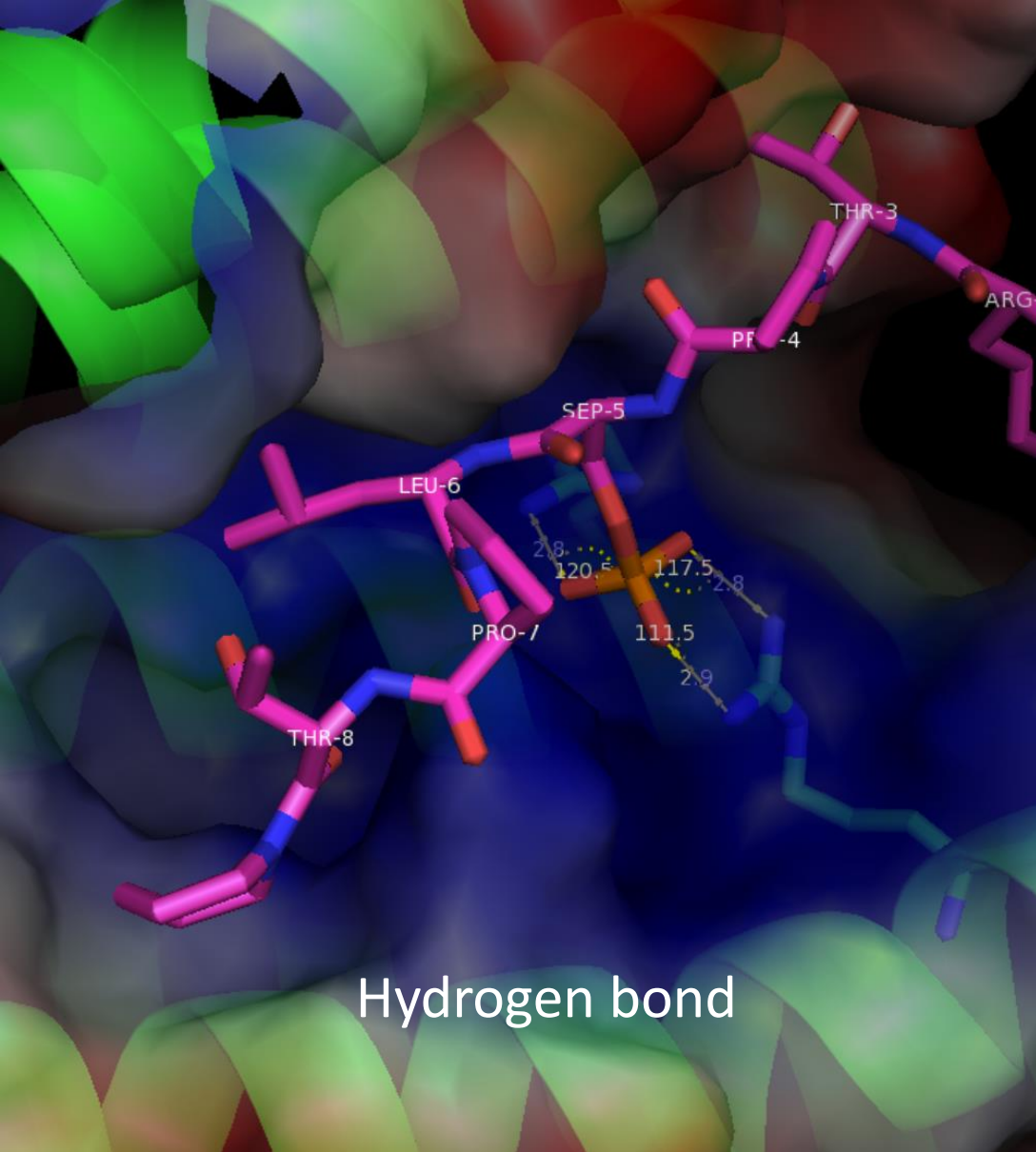


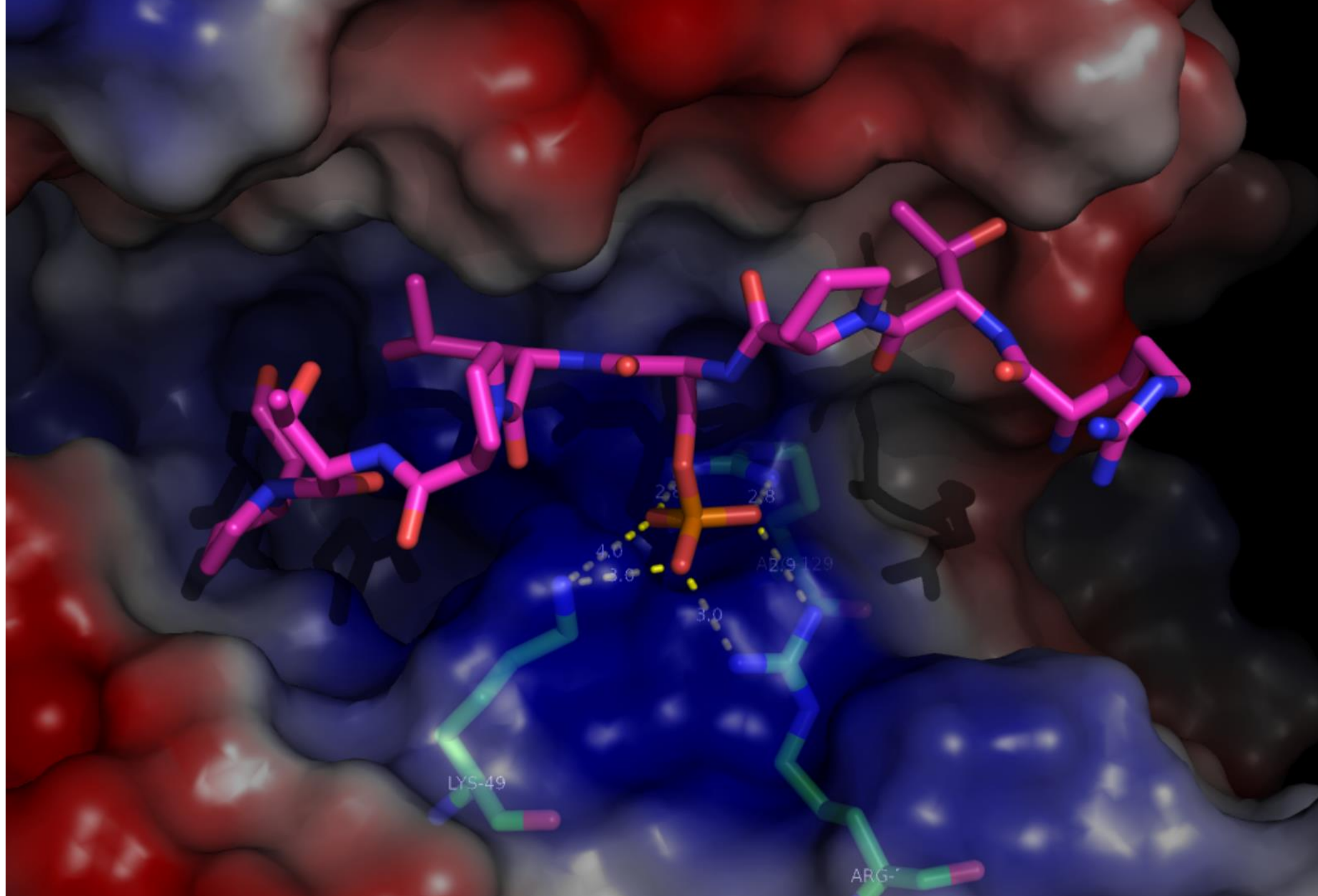


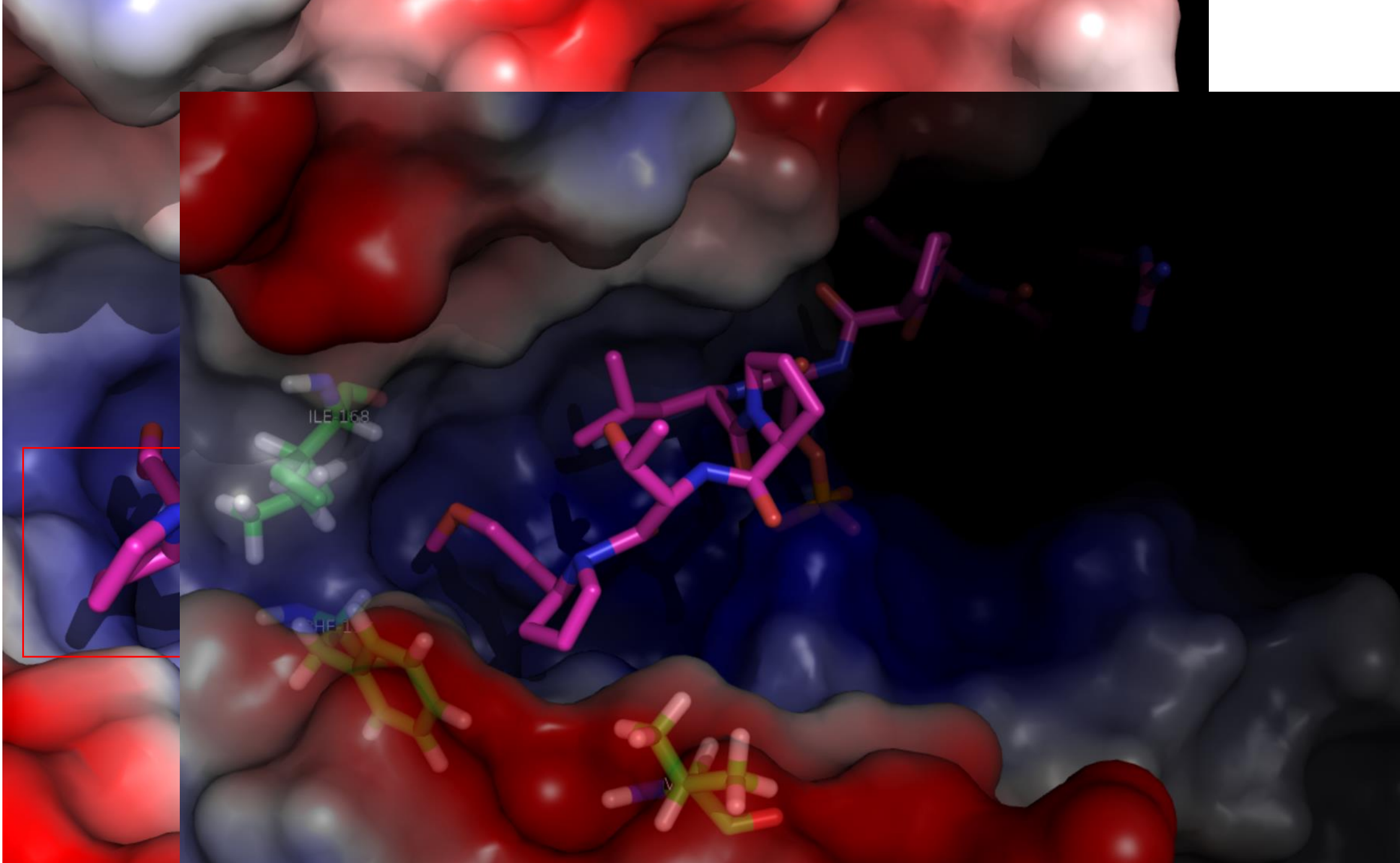
267-311



Chimeric  
inhibitor

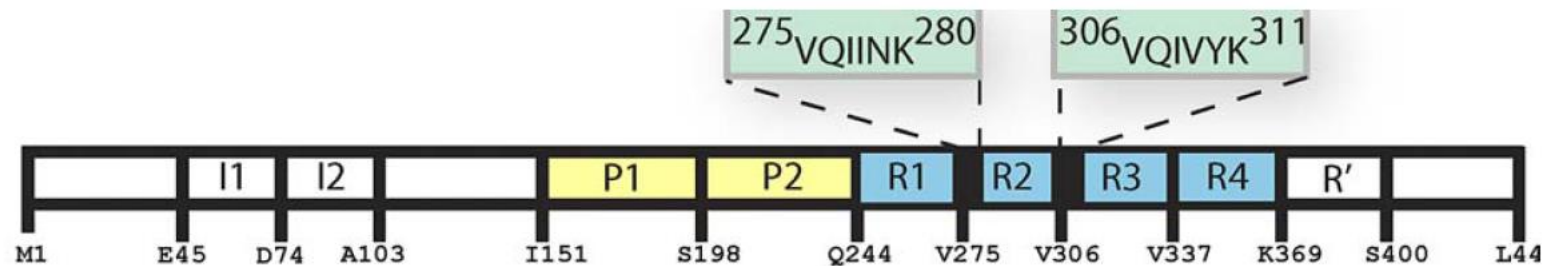


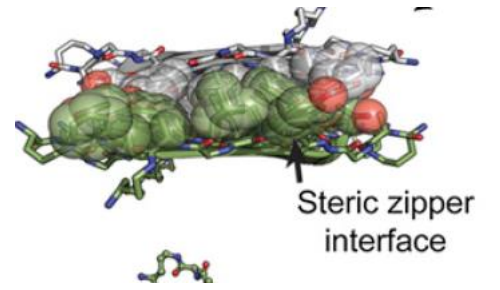
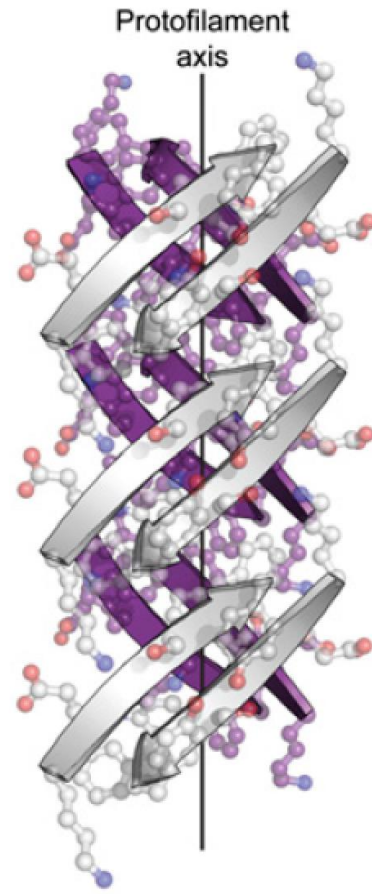
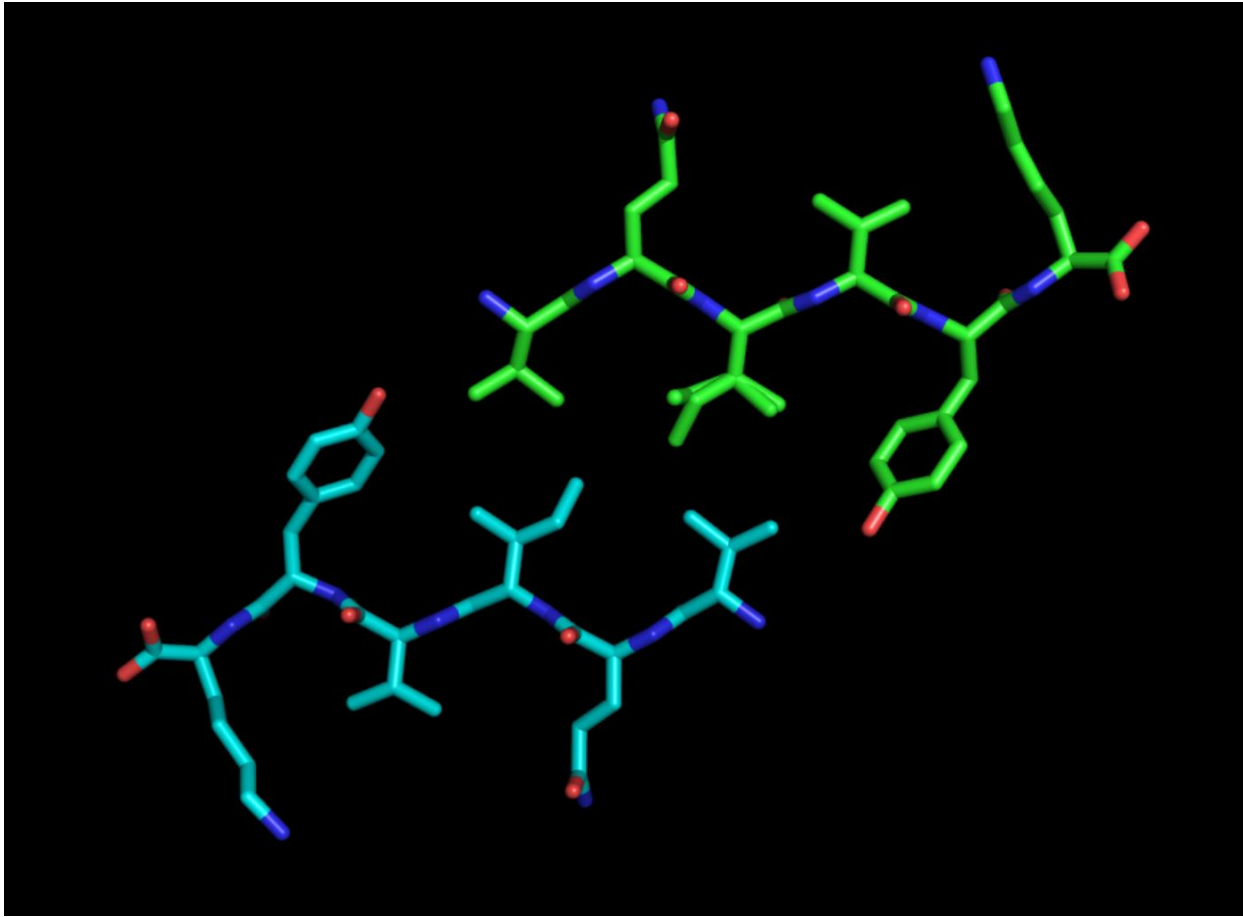




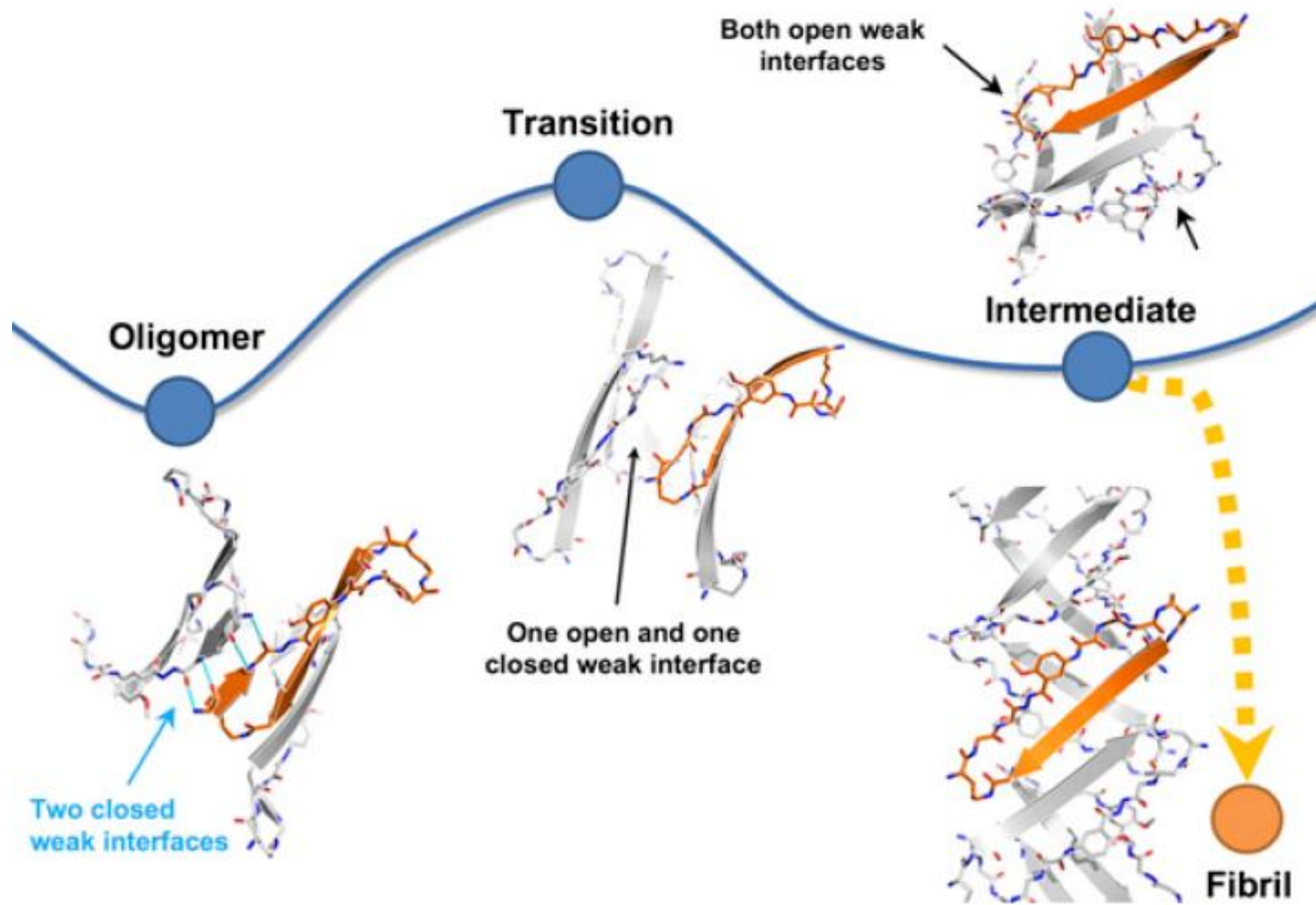
ILE 168

HE 1





$\beta$ - sheet





# Acknowledgement

- Pro. Luo
- My group members
- All of my classmates

