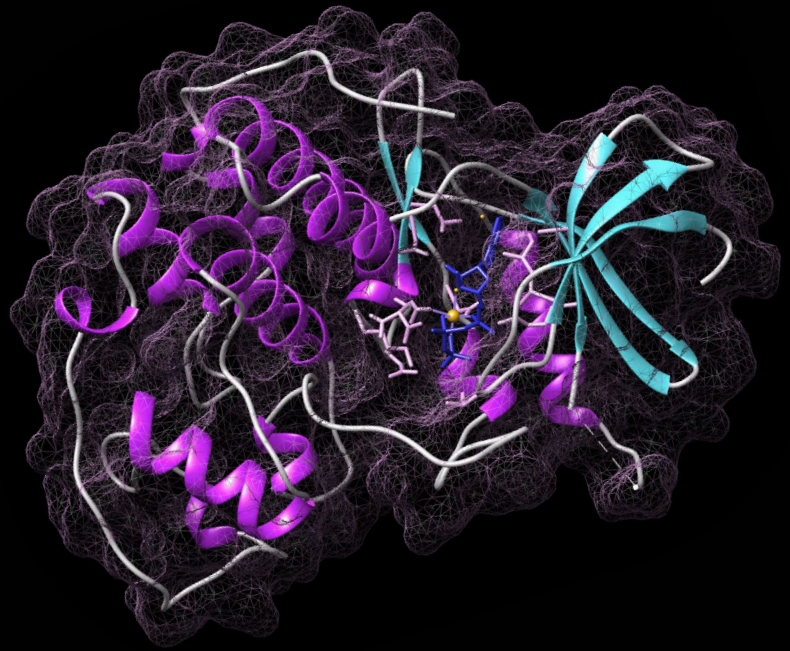
CDK PROTEINS

A study on CDK2



Universitat Pompeu Fabra Barcelona

Marusi Fernández Torres, Mireia López Burgos, Oriol López Roselló & Victoria Sanmartín Cerrato

Structural Biology 2023/2024

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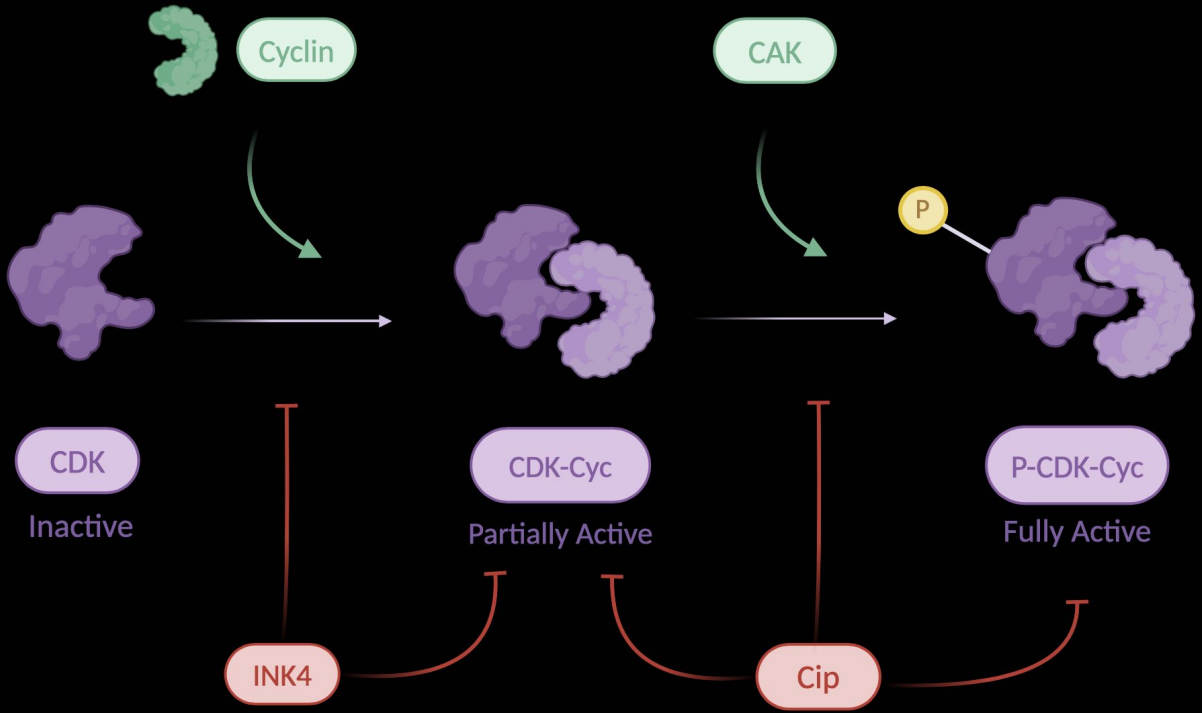
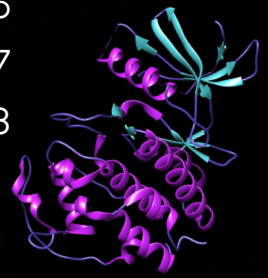
What are Cyclin-Dependent Kinases?



CDK classification

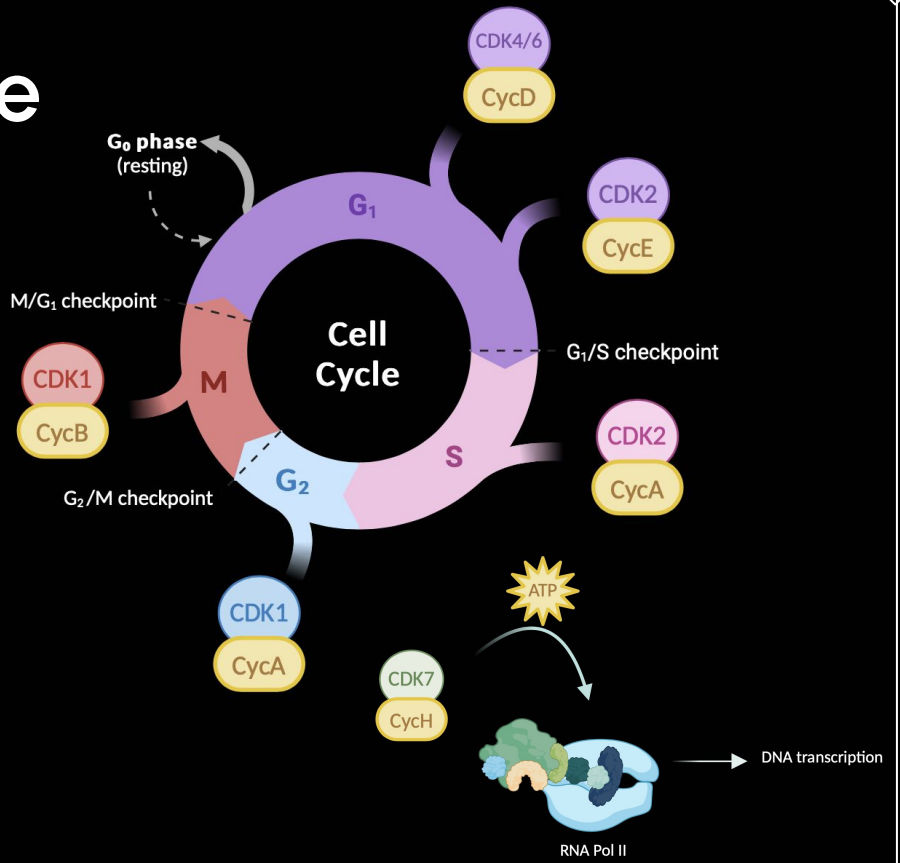
40% of similarities
Size of 30-40 kDa

Cell Cycle	Atypical	Transcriptional
• CDK1 • CDK2 • CDK3 • CDK4 • CDK6	• CDK5 • CDK14 • CDK15 • CDK16 • CDK17 • CDK18	• CDK7 • CDK8 • CDK9 • CDK10 • CDK11 • CDK12 • CDK13 • CDK19 • CDK20



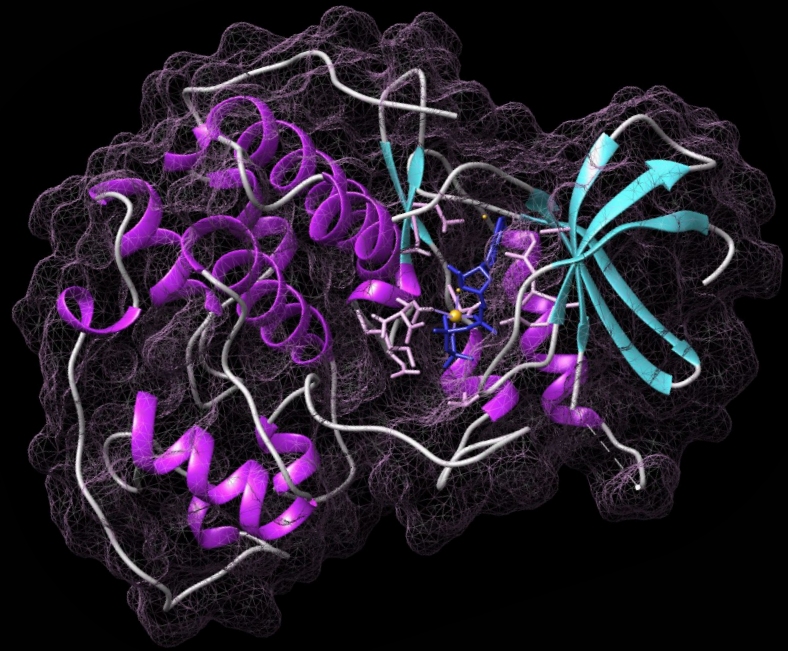
CDKs in the cell cycle

- Cell cycle progression
- DNA replication
- Transcriptional regulation
- Mitosis initiation
- Apoptosis



CDK2 model of study: 1HCK

Method	X-Ray Diffraction
Resolution	1.90 Å
Weight	34.51 kDa
Residues	298
Chains	1: A
Species	*Homo Sapiens*



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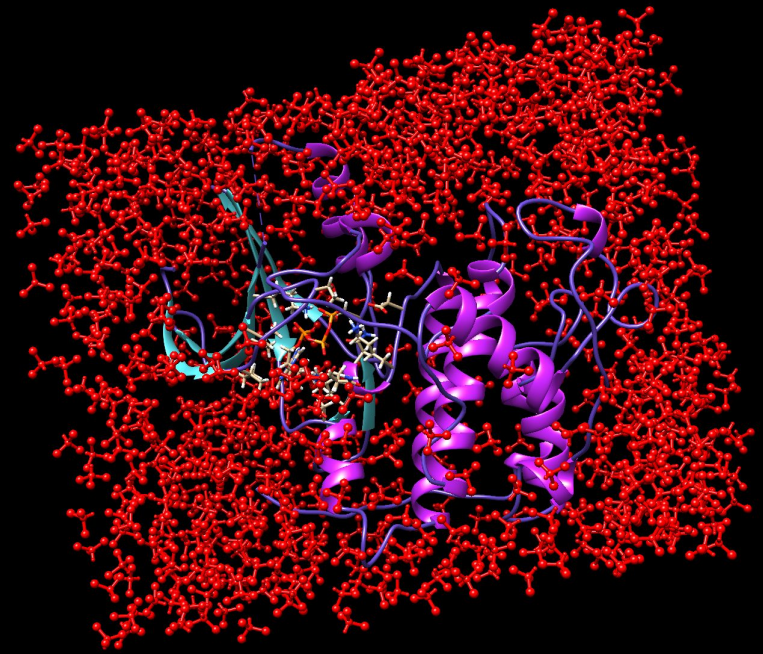


CDK2 model of study: 1HCK

Gene Ontology

Molecular function

ATP binding

Cyclin binding

Cyclin-dependent protein kinase activity

Biological process

Cell division

Cellular senescence

Coordinates cyclin B/cdk1 activation

Cell cycle regulation

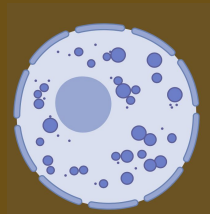
Cellular component

Cajal body

Centrosome

Chromosome

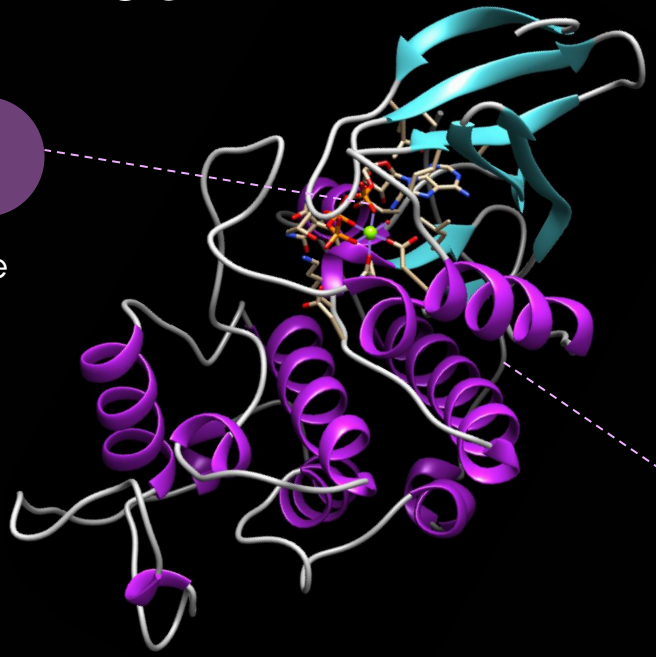
Telomeric region



CDK2 properties

Hydrophobic

ATP Binding Site



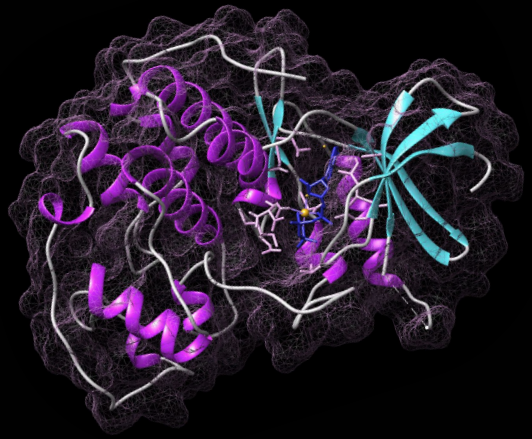
Flexible

- TLoop
- Hinge Region

02

CDK2 STRUCTURAL BIOLOGY

Description of the molecule and inner interactions



SCOP cyclin-dependent kinase 2

Class 1000003
Alpha and beta proteins
(a+b)

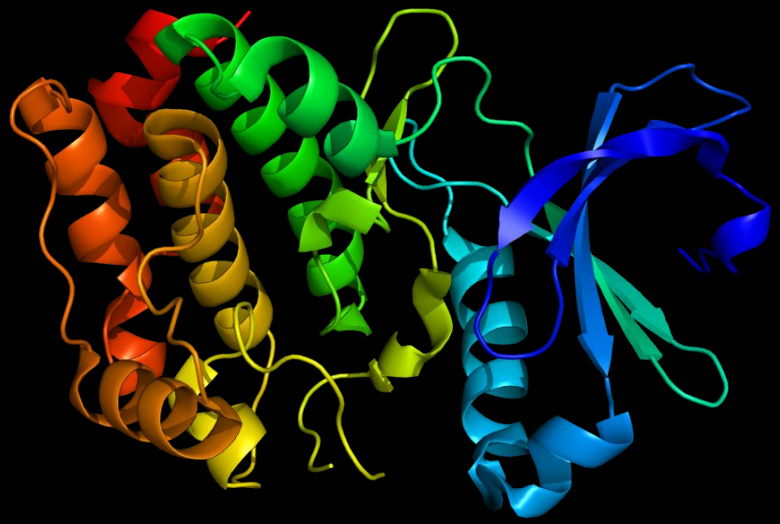
Fold 2000046
Protein kinase like (PK-like)

Superfamily 3000066
Protein kinase like (PK-like)

Family 4003661
Protein kinases catalytic
domain-like

Domain 8027931

ATP-binding site
Catalytic loop
Activation loop



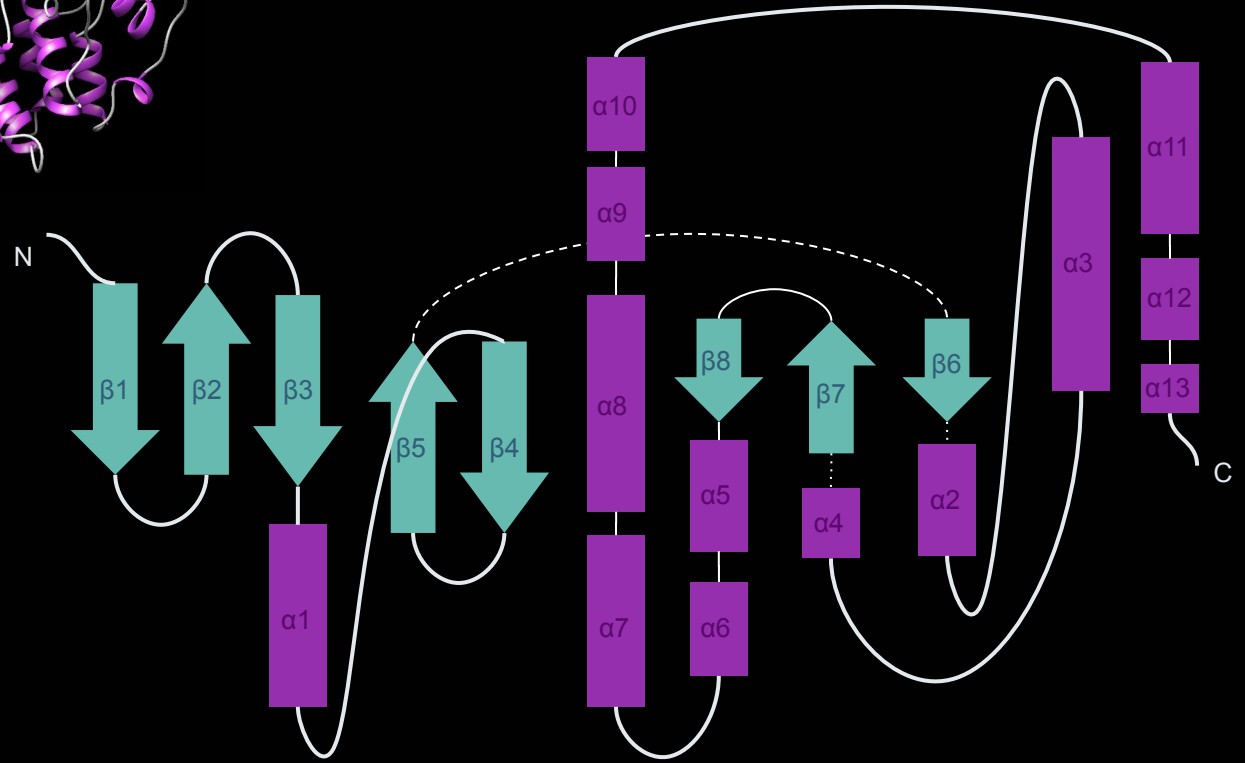
CDK2 subdomains

N-terminal lobe
(residues 1-80)

Hinge region
(residues 81-83)

C terminal lobe
(residues 84-298)

Topology Diagram



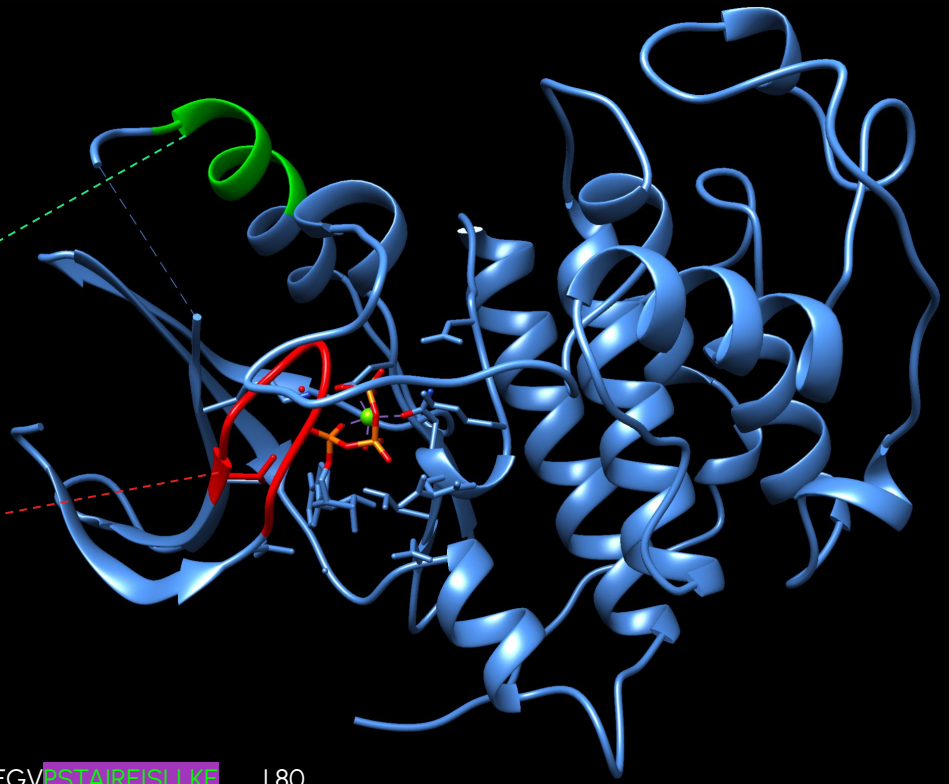
Sequence and structure

```
1   | MENFQKVEKIGEGTYGVVYKARNKLTGEVVALKKIRLDTETEGVPSTAIR | 50
        β1              β2              β3              α1

51  | EISLLKELNHPNIVKLLDVIHTENKLYLVFEFLHQDLKKFMDASALTGIP | 100
                    β4      β5      β6  α2

101 | LPLIKSYLFQLLQGLAFCHSHRVLHRDLKPQNLLINTEGAIKLADFGLAR | 150
          α3                    α4  β7      β8      α5

151 | AFGVPVRTYTHEVVTLWYRAPEILLGCKYYSTAVDIWSLGCIFAEMVTRR | 200
                          α6              α7

201 | ALFPGDSEIDQLFRIFRTLGTPDEVVWPGVTSMPDYKPSFPKWARQDFSK | 250
              α8              α9              α10

251 | VVPPLDEDGRSLLSQMLHYDPNKRISAKAALAHPFFQDVTKPVPHLRL | 298
          α11             α12     α13
```

N-terminal lobe

PSTAIRE
(residues 45-51)

G-loop
(residues 11-16)

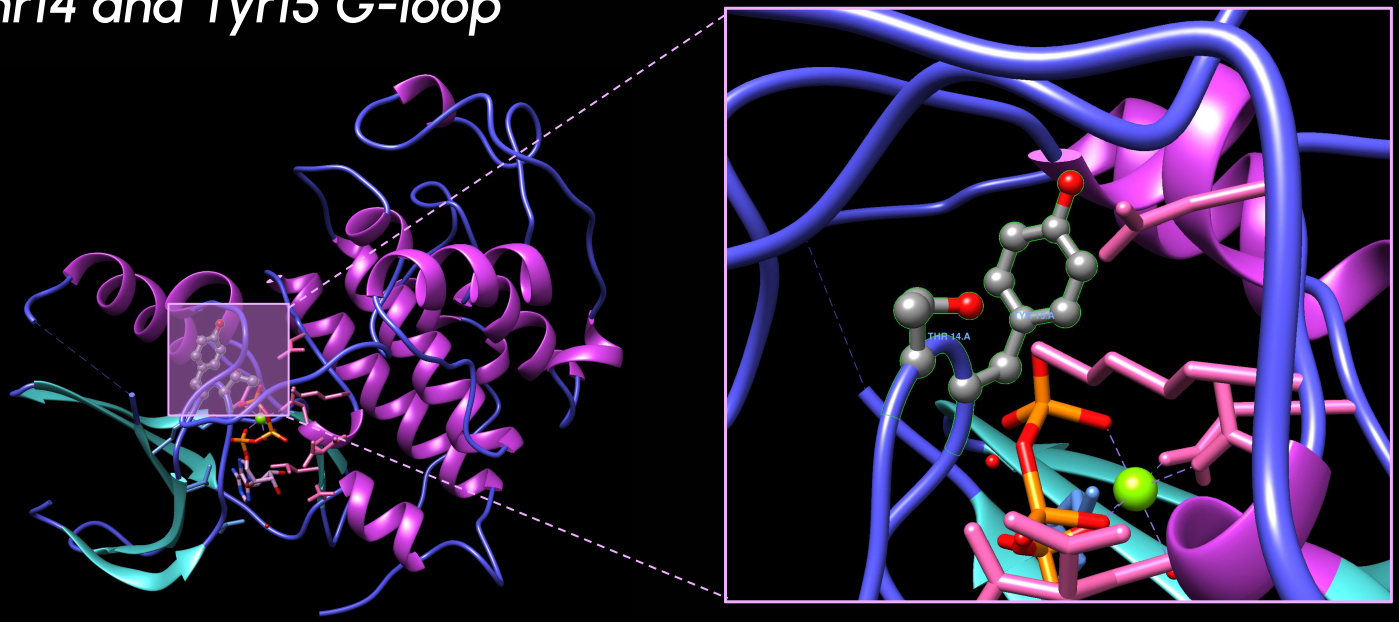


1 | MENFQKVEKIGEGTYGVVYKARNKLTGEVVALKKIRLDTETEGVPSTAIREISLLKE | 80

β1 β2 β3 α1

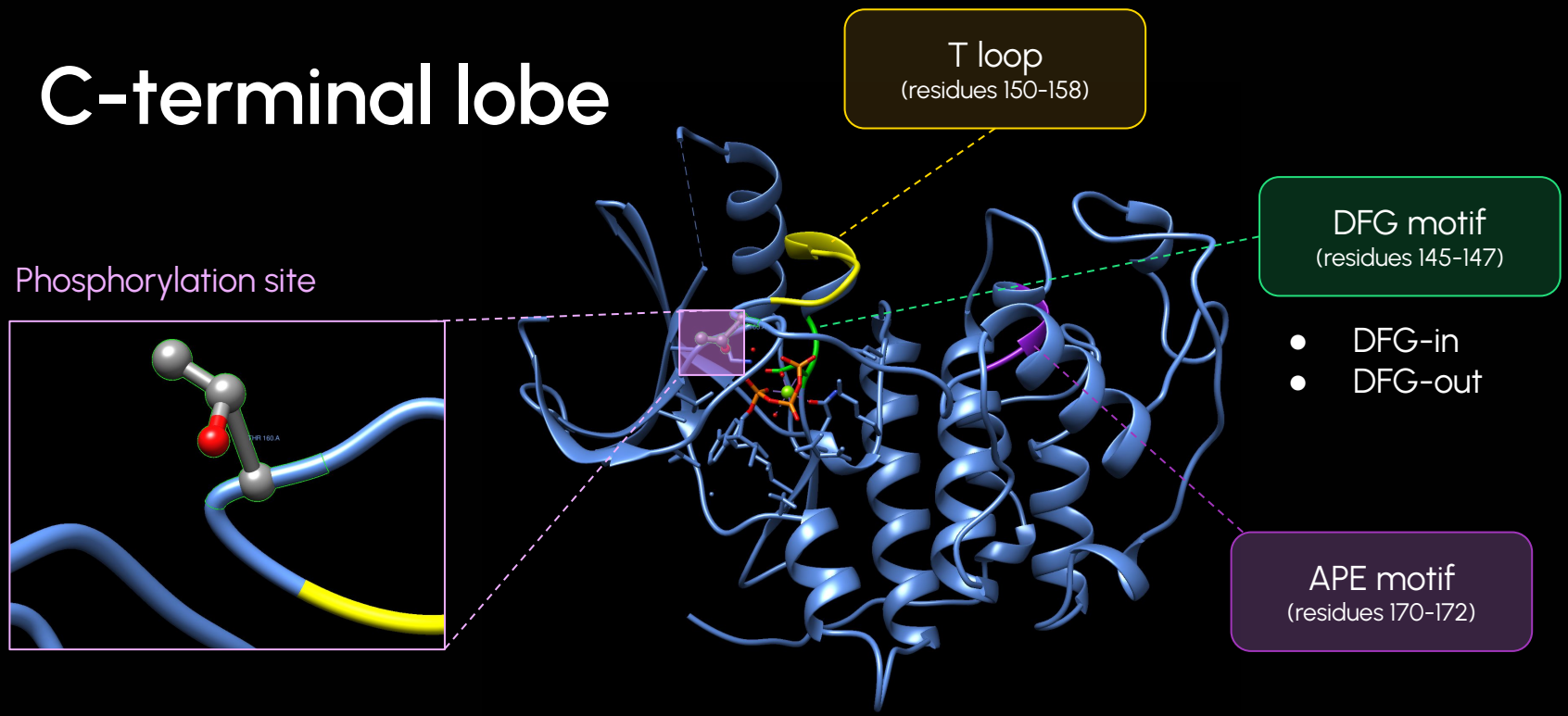
N-terminal lobe

Thr14 and Tyr15 G-loop



1 | MENFQKVEKIGEGTYGVVYKARNKLTGEVVALKKIRLDTETEGVPSTAIREISLLKE | 80

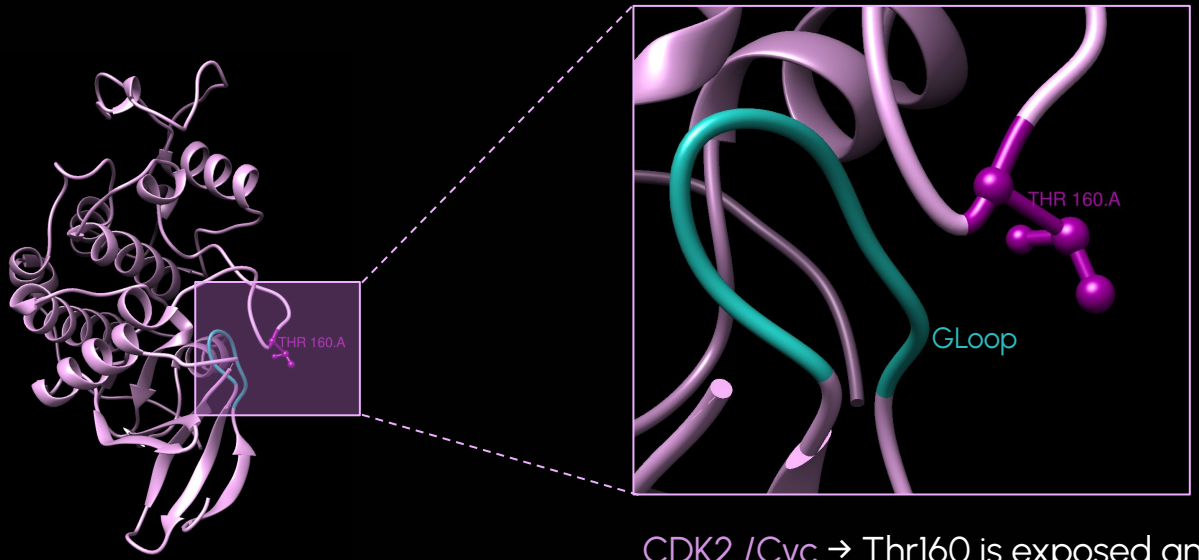
C-terminal lobe



C-terminal lobe

Thr160

Monomeric CDK2 → Thr160 faces the G-loop, away from the solvent

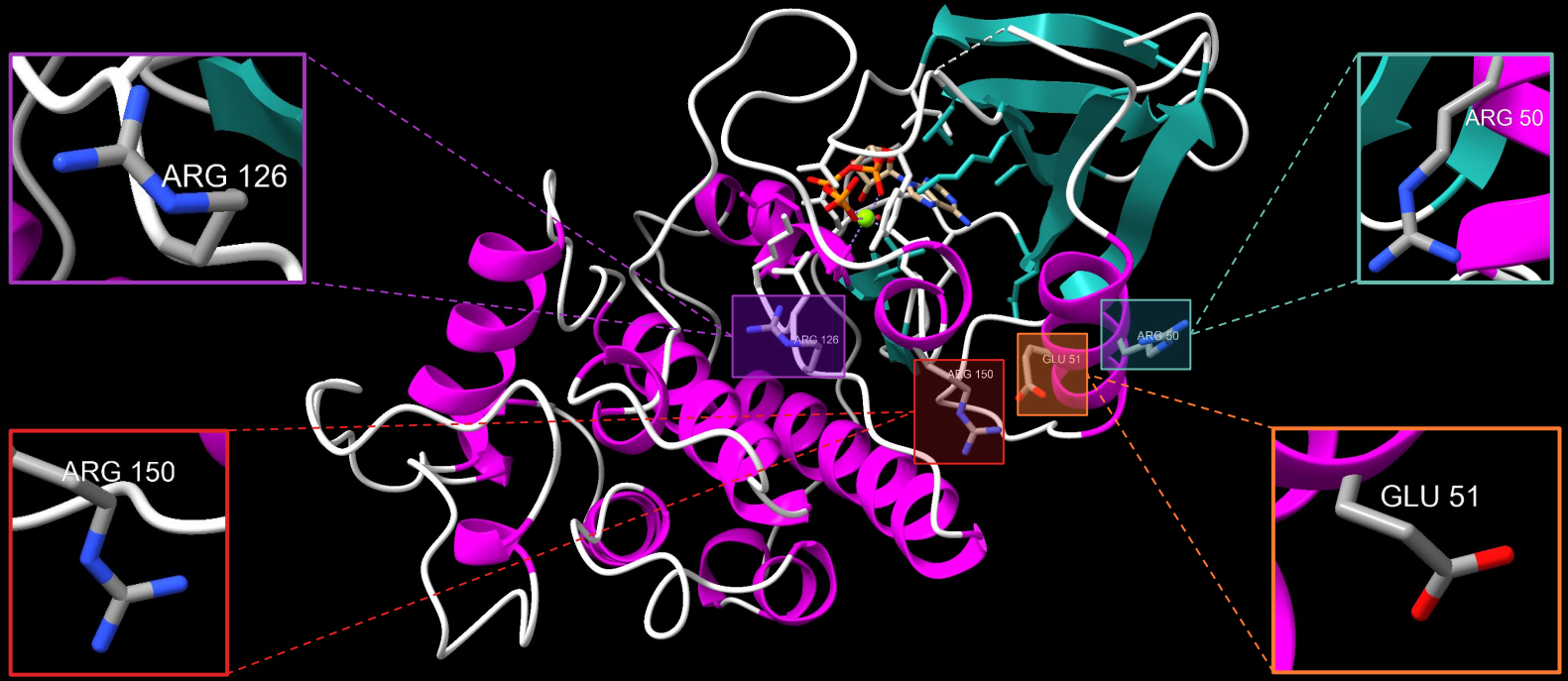


CDK2 /Cyc → Thr160 is exposed and phosphorylated

ATP-binding site

Residues 10-146

Catalytic cleft

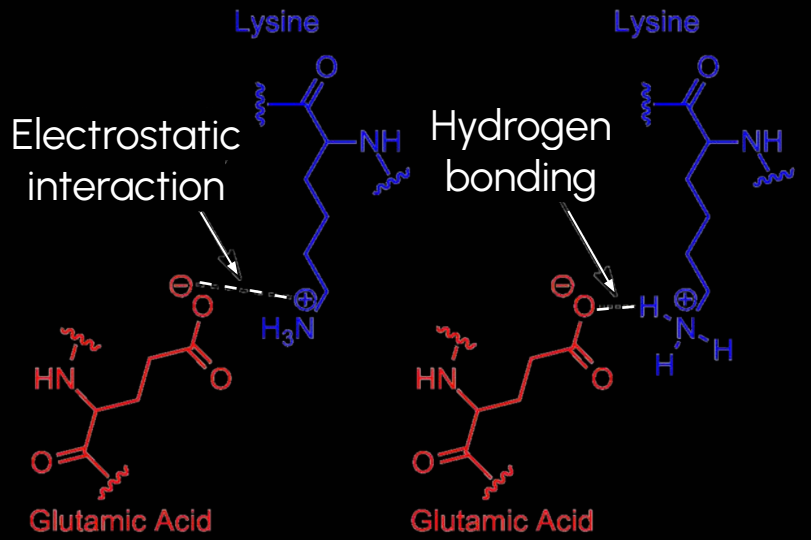


Salt bridges

Non-covalent interactions

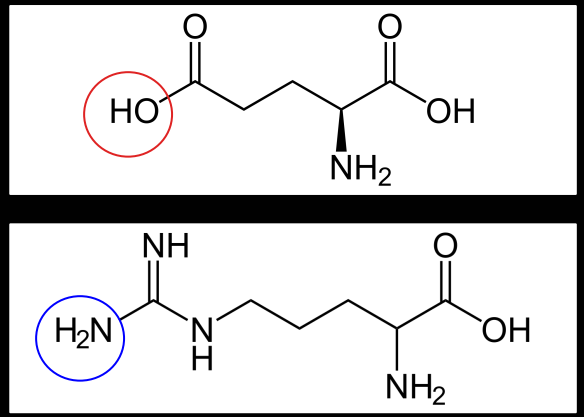
Electrostatic interaction

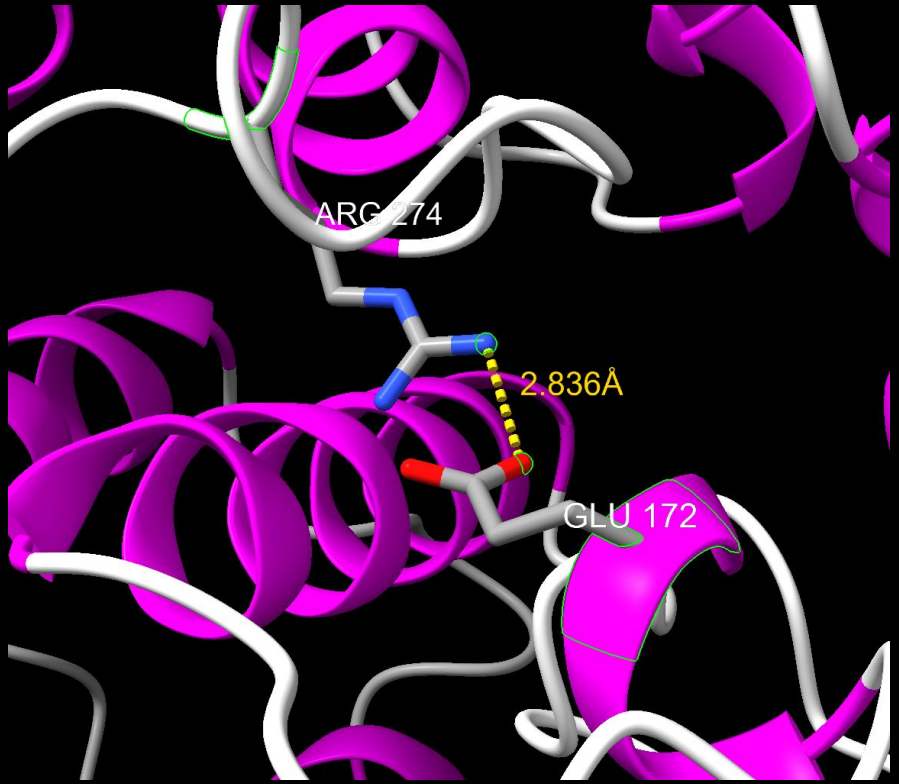
Hydrogen binding



Salt bridges

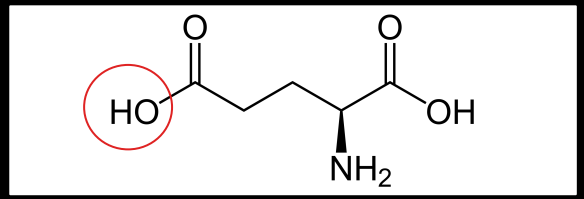
Glu172 - Arg274

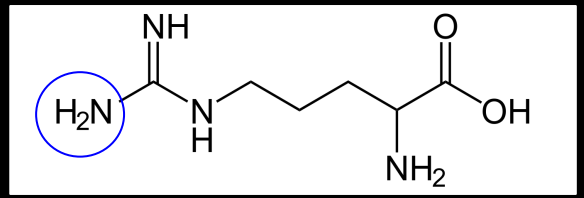


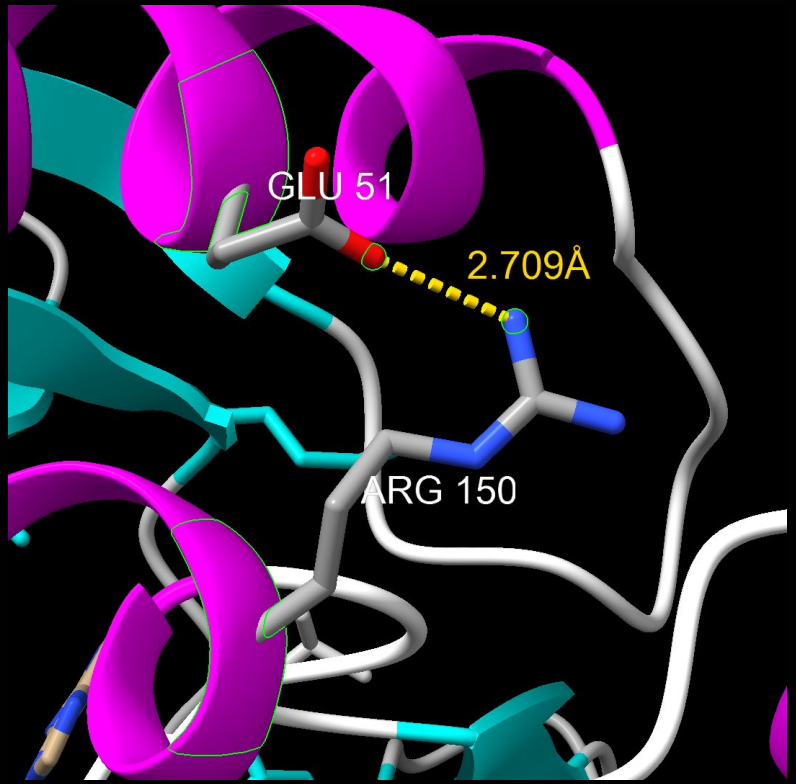


Salt bridges

Glu51-Arg150

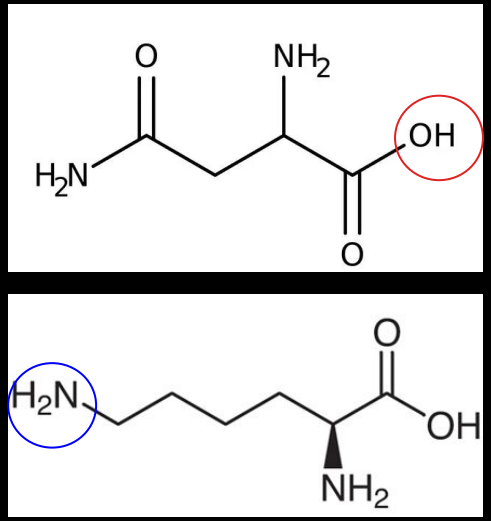


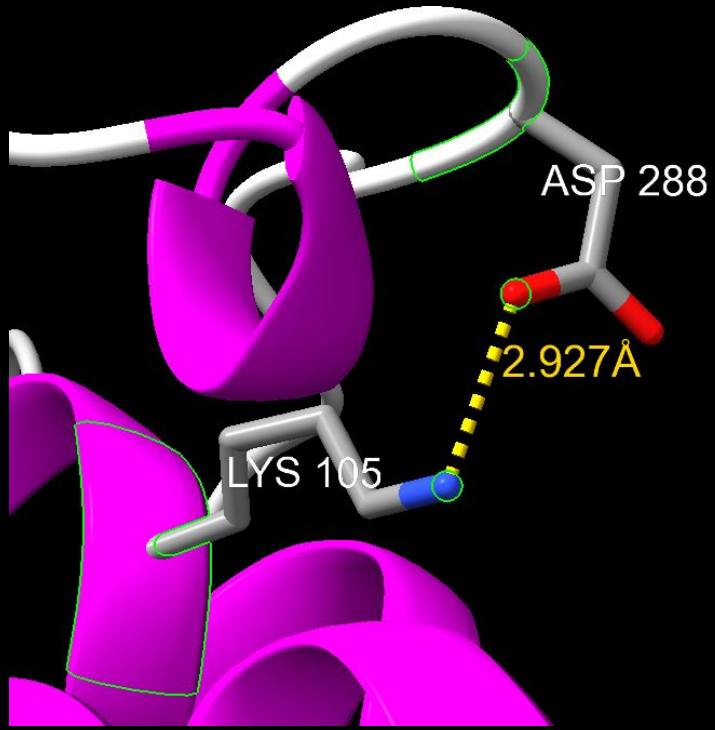




Salt bridges

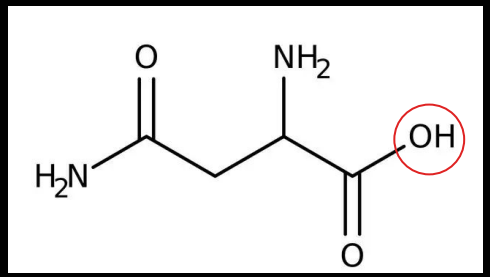
Asp288-Lys105

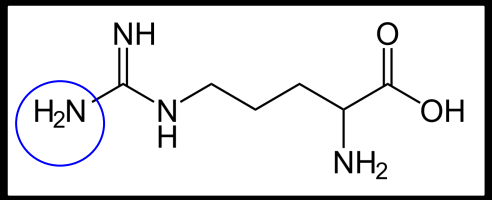


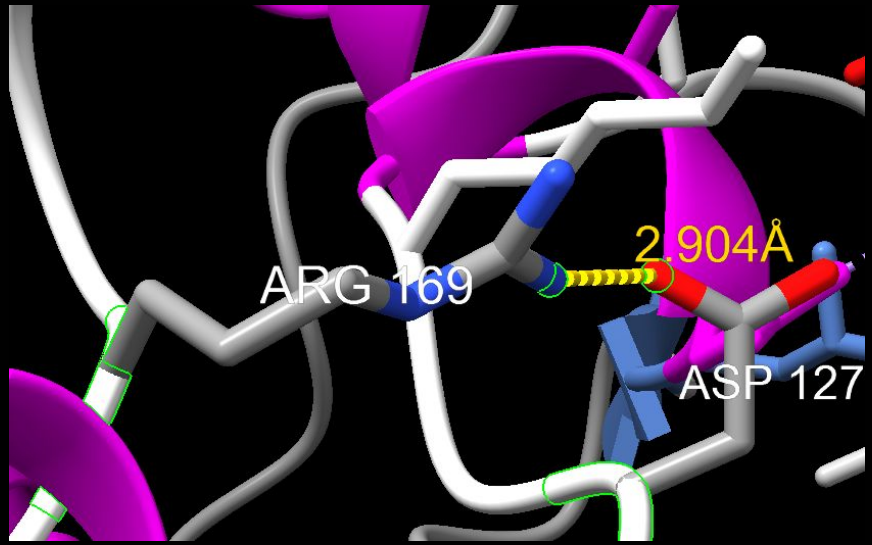


Salt bridges

Asp127-Arg169



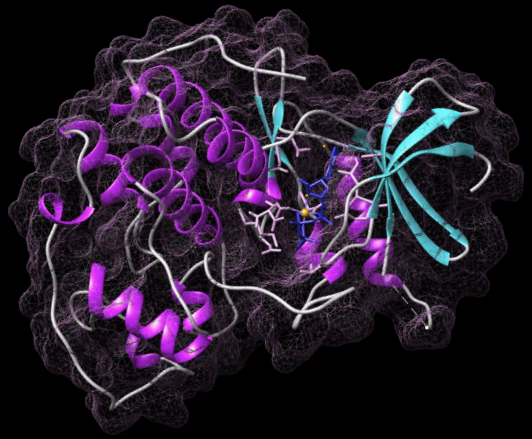




03

INTERACTIONS WITH LIGANDS

With cyclins and inhibitors

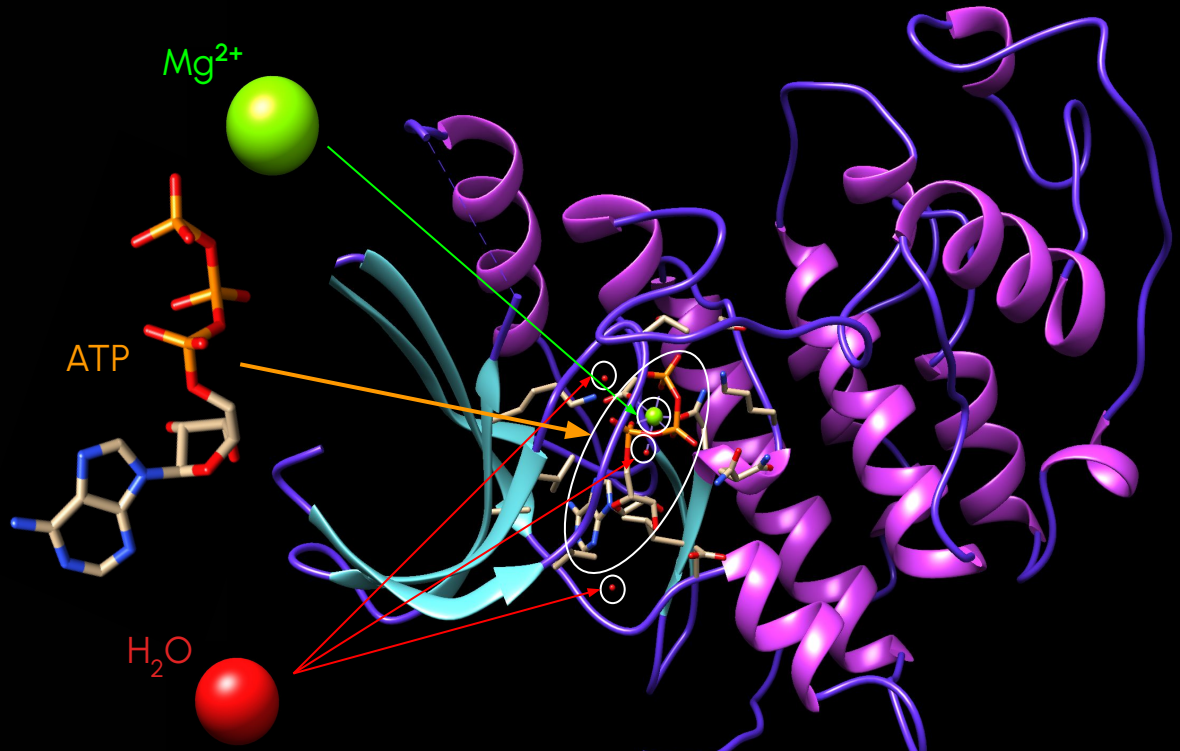


Interactions

Mg^{2+} (inorganic cofactor):
- Coordinates the phosphates groups of ATP (Metal Complex Interactions)
- Facilitates the phosphate transfer

ATP:
- Primary substrate for kinase activity
- Binds for phosphoryl transfer

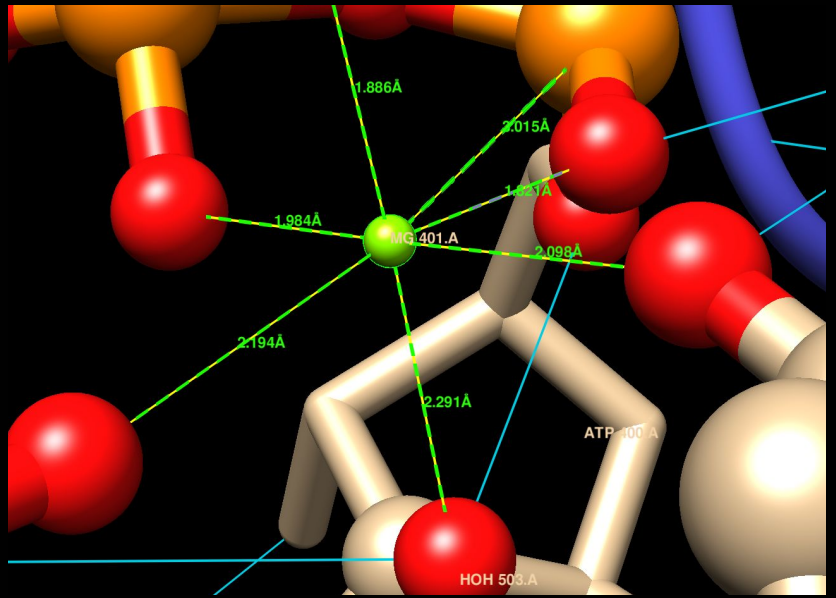
H2O:
- Forms H bonds
- Stabilize ATP binding



01 Interaction with Mg^{2+}

	Binds to:		Distance	
Mg^{2+} 401	1. ASN 132	OD1	2.194 A	→ Van der Waals
	2. ATP 400	OB2	1.984 A	
	3. ATP 400	OG1	1.886 A	
	4. ATP 400	PA	3.015 A	→ Van der Waals
	5. ATP 400	OA1	1.821 A	
	6. ASP 145	OD2	2.098 A	→ Ionic Bond
	7. H2O 503	O	2.291 A	→ Van der Waals

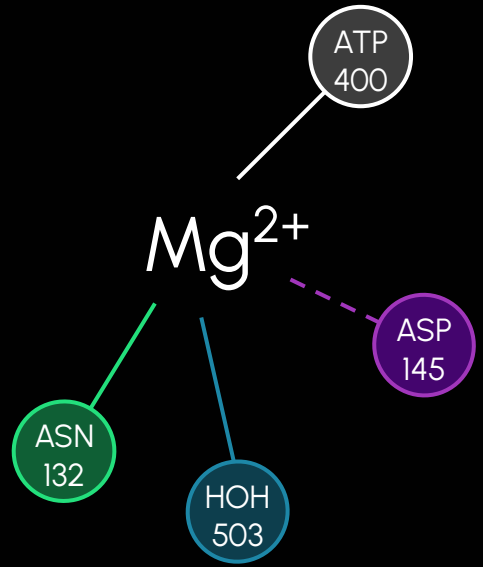
Metal Complex Interactions

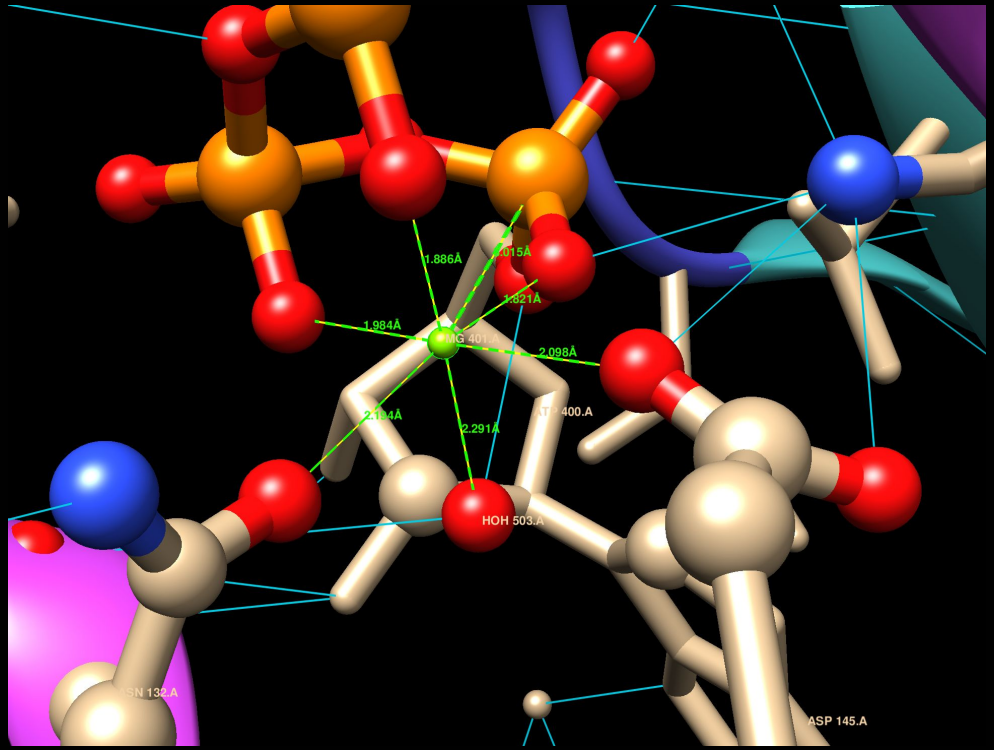


Mg^{2+} binding site

MENFQKVEKIGEGTYGVVYKARNKLTGEVVALKKIRLDTETEGVPSTAIREISLLKELNHPNIVKLLDVIHTENKLYLVFEFLHQDLKKFMDASALTGI
PLPLIKSYLFQLLQGLAFCHSHRVLHRDLKPQNLLINTEGAIKLADFGLARAFGVPVRTYTHEVVTLWYRAPEILLGCKYYSTAVDIWSLGCIFAEMV
TRRALFPGDSEIDQLFRIFRTLGTPDEVVWPGVTSMPDYKPSFPKWARQDFSKVVPPLDEDGRSLLSQMLHYDPNKRISAKAALAHPFFQDVTKP
VPHLRL

01 Interaction with Mg^{2+}





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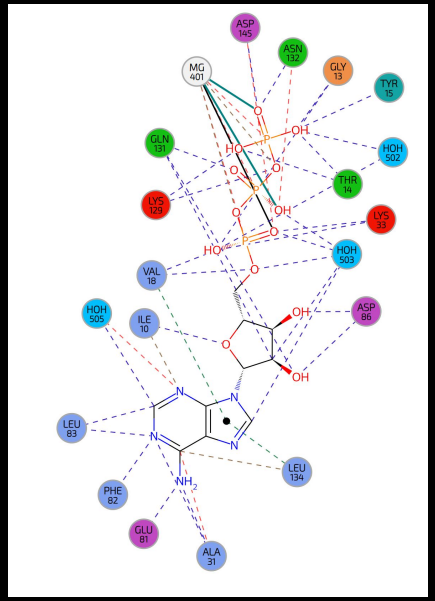
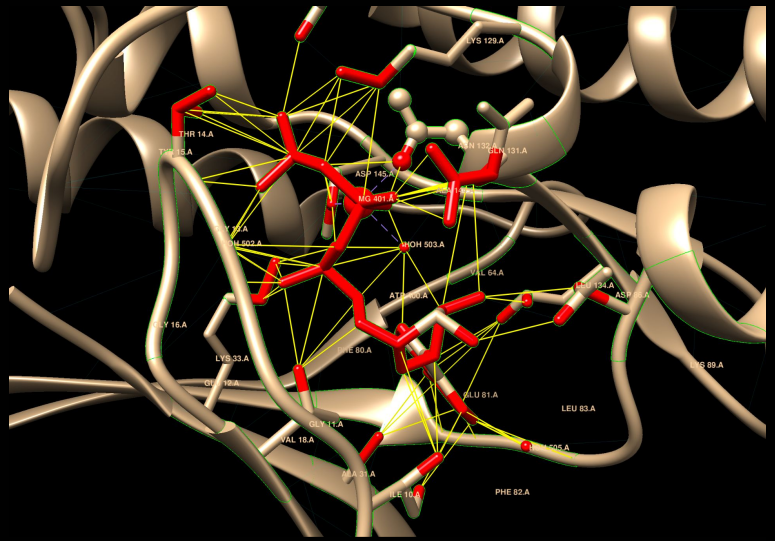
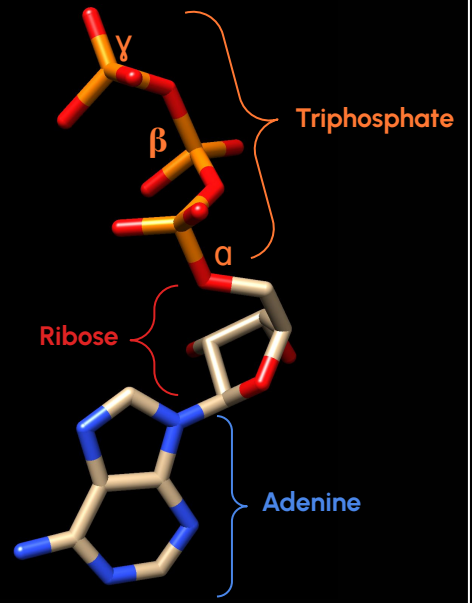
02 Interaction with ATP







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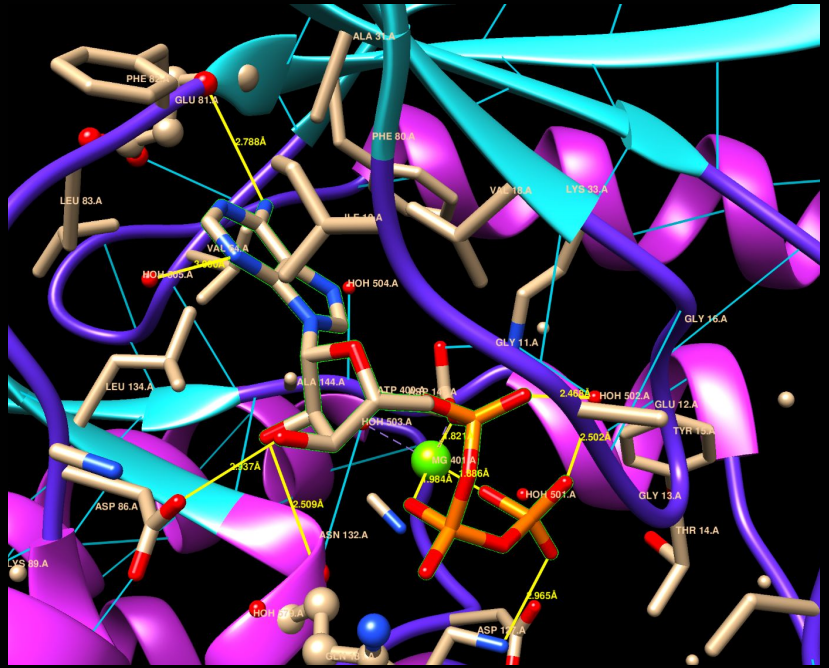
02 Interaction with ATP

		Binds to:		Distance	
ATP 400	1. N3	H2O 505	O	3.000 A	Van der Waals
	2. N6	GLU 81	O	2.788 A	
	3. O2A	H2O 502	O	2.468 A	
	4. O2G	H2O 502	O	2.502 A	
	5. O3G	LYS 129	NZ	2.965 A	Ionic Bond

Hbonds



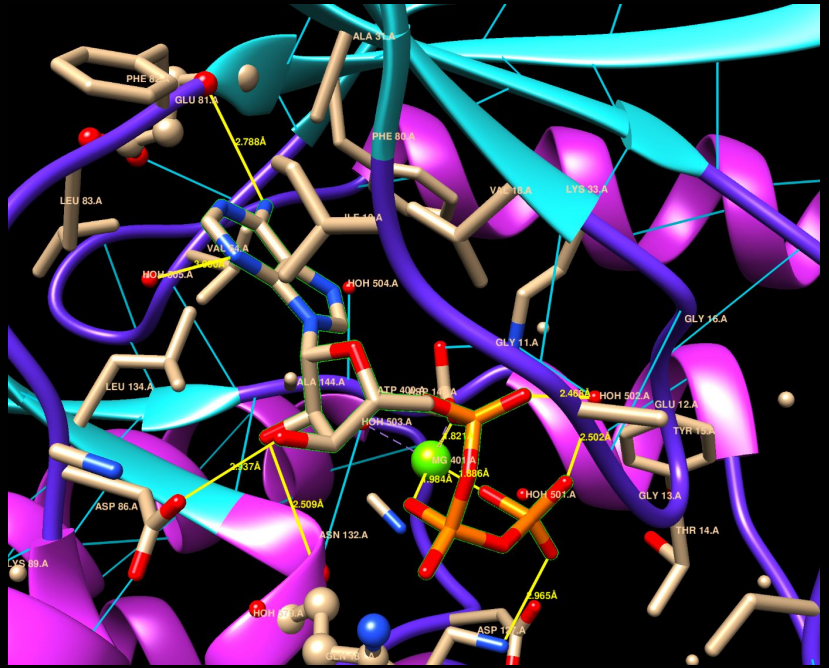
ATP Binding site

MENFQKVEKIGEGTYGVVYKARNKLTGEVVALKKIRLDTETEGVPSTAIREISLLKELNHPNIVKLLDVIHTENKLYLVFEFLHQDLKKFMDASALTGI
PLPLIKSYLFQLLQGLAFCHSHRVLHRDLKPQNLLINTEGAIKLADFGLARAFGVPVRTYTHEVVTLWYRAPEILLGCKYYSTAVDIWSLGCIFAEMV
TRRALFPGDSEIDQLFRIFRTLGTPDEVVWPGVTSMPDYKPSFPKWARQDFSKVVPPLDEDGRSLLSQMLHYDPNKRISAKAALAHPFFQDVTKP
VPHLRL

02 Interaction with ATP

		Binds to:		Distance	
ATP 400	6. O1A	MG 401	MG	1.821 A	Metal Complex
	7. O1G	MG 401	MG	1.886 A	
	8. O2B	MG 401	MG	1.984 A	
	9. O2’	GLN 131	O	2.509 A	Van der Waals
	10. O3’	ASP 86	OD2	2.937 A	

Hbonds

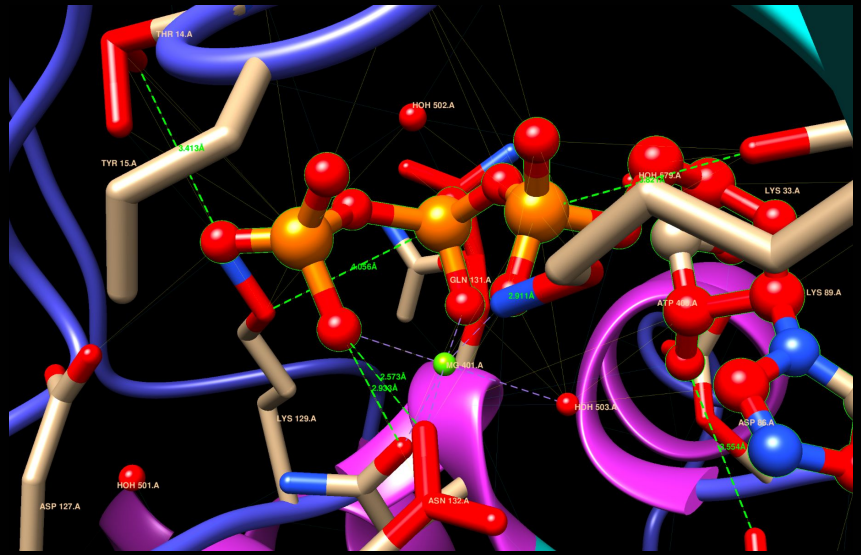


ATP Binding site

MENFQKVEKIGEGTYGVVYKARNKLTGEVVALKKIRLDTETEGVPSTAIREISLLKELNHPNIVKLLDVIHTENKLYLVFEFLHQDLKKFMDASALTGI
PLPLIKSYLFQLLQGLAFCHSHRVLHRDLKPQNLLINTEGAIKLADFGLARAFGVPVRTYTHEVVTLWYRAPEILLGCKYYSTAVDIWSLGCIFAEMV
TRRALFPGDSEIDQLFRIFRTLGTPDEVVWPGVTSMPDYKPSFPKWARQDFSKVVPPLDEDGRSLLSQMLHYDPNKRISAKAALAHPFFQDVTKP
VPHLRL

02 Interaction with ATP

		Binds to:		Distance	
ATP 400	11. O3G	THR 14	CG2	3.413 A	Polar Bond
	12. PB	LYS 129	CE	4.056 A	
	13. O1G	ASN 132	OD1	2.933 A	Van der Waals
	14. O1G	ASP 145	OD2	2.573 A	
	15. PA	VAL 18	CG2	3.821 A	Polar Bond

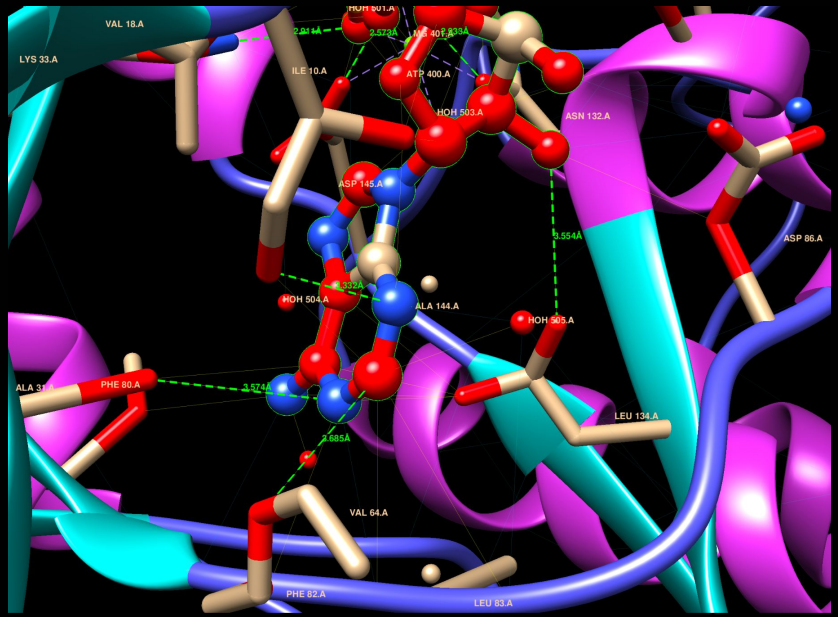


ATP Binding site

MENFQKVEKIGEGTYGVVYKARNKLTGEVVALKKIRLDTETEGVPSTAIREISLLKELNHPNIVKLLDVIHTENKLYLVFEFLHQDLKKFMDASALTGI
PLPLIKSYLFQLLQGLAFCHSHRVLHRDLKPQNLLINTEGAIKLADFGLARAFGVPVRTYTHEVVTLWYRAPEILLGCKYYSTAVDIWSLGCIFAEMV
TRRALFPGDSEIDQLFRIFRTLGTPDEVVWPGVTSMPDYKPSFPKWARQDFSKVVPPLDEDGRSLLSQMLHYDPNKRISAKAALAHPFFQDVTKP
VPHLRL

02 Interaction with ATP

		Binds to:		Distance	
ATP 400	16. O1A	LYS 33	NZ	2.911 A	Van der Waals
	17. O2'	LEU 134	CD2	3.554 A	
	18. N3	ILE 10	CD1	3.332 A	
	19. N1	ALA 31	CB	3.574 A	H Bond
	20. C2	PHE 82	CD2	3.685 A	



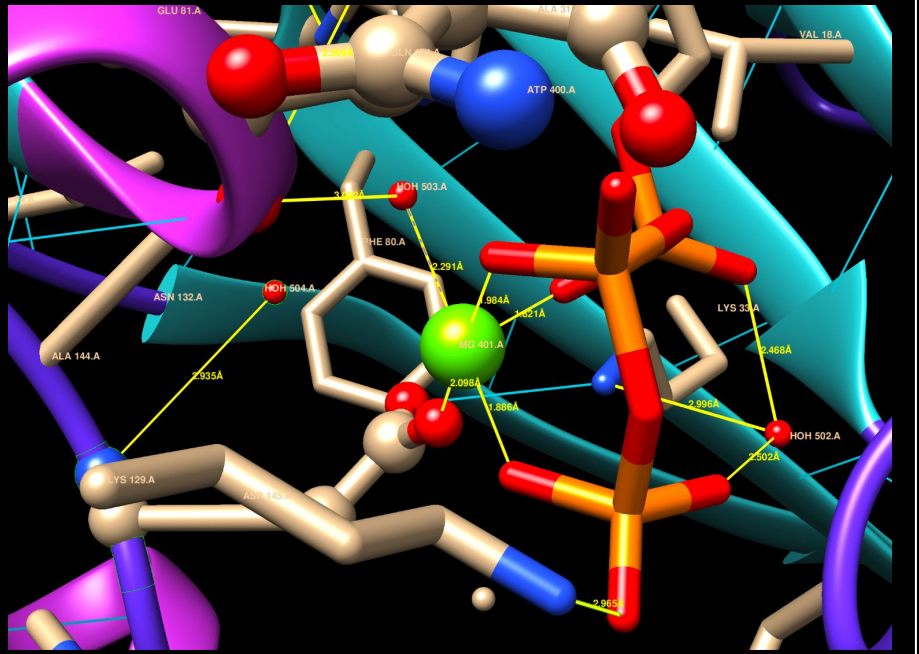
ATP Binding site

MENFQKVEKIGEGTYGVVYKARNKLTGEVVALKKIRLDTETEGVPSTAIREISLLKELNHPNIVKLLDVIHTENKLYLVFEFLHQDLKKFMDASALTGI
PLPLIKSYLFQLLQGLAFCHSHRVLHRDLKPQNLLINTEGAIKLADFGLARAFGVPVRTYTHEVVTLWYRAPEILLGCKYYSTAVDIWSLGCIFAEMV
TRRALFPGDSEIDQLFRIFRTLGTPDEVVWPGVTSMPDYKPSFPKWARQDFSKVVPPLDEDGRSLLSQMLHYDPNKRISAKAALAHPFFQDVTKP
VPHLRL

03 Interaction with H_2O

		Binds to:		Distance
H2O 504	O	ASP 145	N	2.935 A
H2O 503	O	MG 401	MG	2.291 A
H2O 502	O	ATP 400	O2A	2.468 A
H2O 502	O	ATP 400	O2G	2.502 A

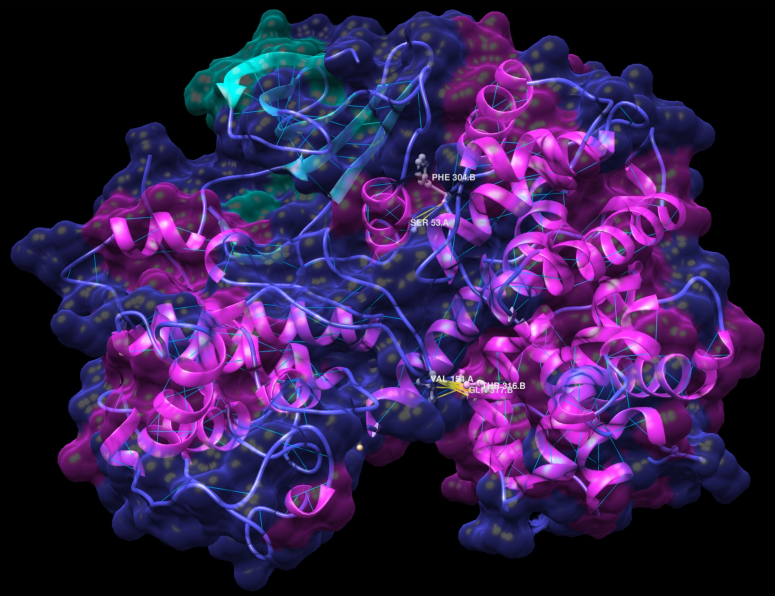
Hbonds

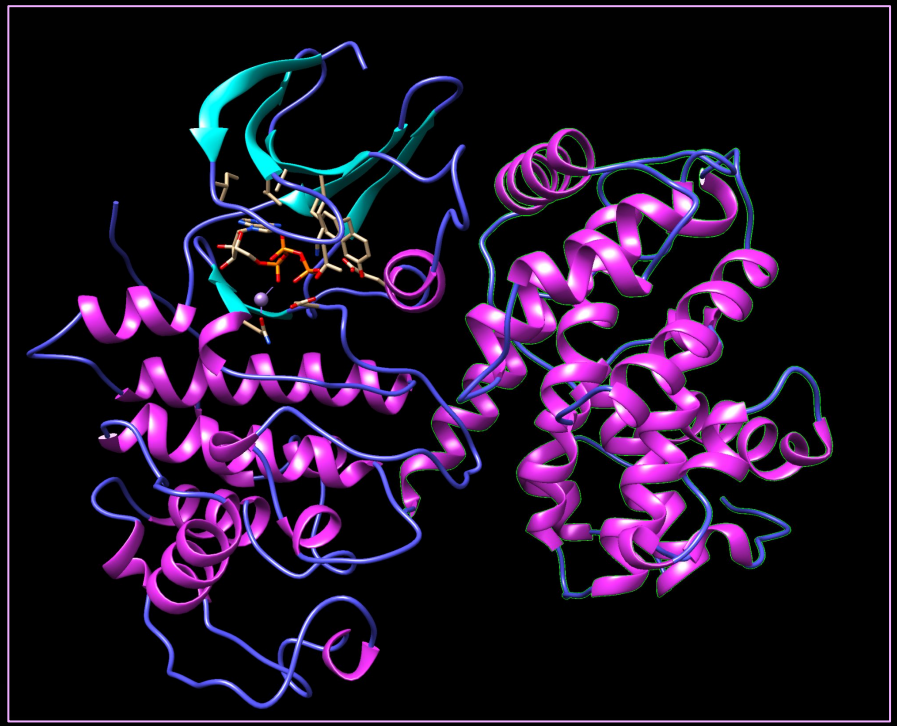


Active site, proton acceptor

MENFQKVEKIGEGTYGVVYKARNKLTGEVVALKKIRLDTETEGVPSTAIREISLLKELNHPNIVKLLDVIHTENKLYLVFEFLHQDLKKFMDASALTGI
PLPLIKSYLFQLLQGLAFCHSHRVLHRDLKPQNLLINTEGAIKLADFGLARAFGVPVRTYTHEVVTLWYRAPEILLGCKYYSTAVDIWSLGCIFAEMV
TRRALFPGDSEIDQLFRIFRTLGTPDEVVWPGVTSMPDYKPSFPKWARQDFSKVVPPLDEDGRSLLSQMLHYDPNKRISAKAALAHPFFQDVTKP
VPHLRL

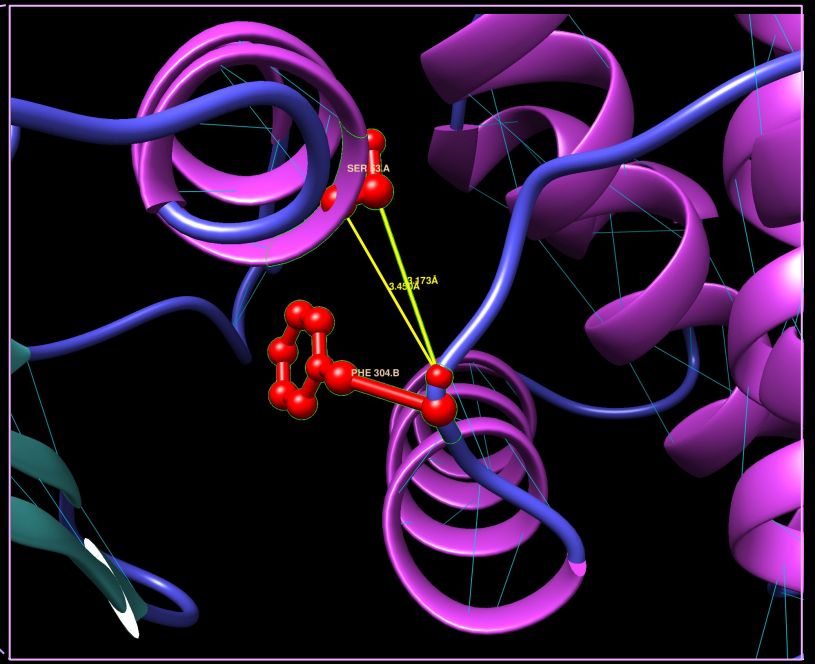
CDK2/Cyclin A Complex





CDK2/Cyclin A Complex

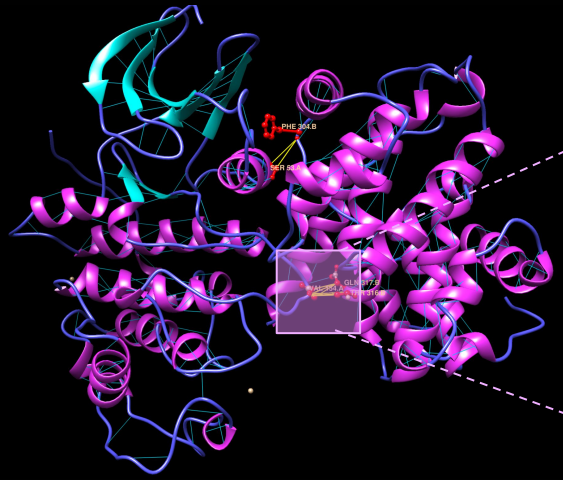
Hydrophobic interactions

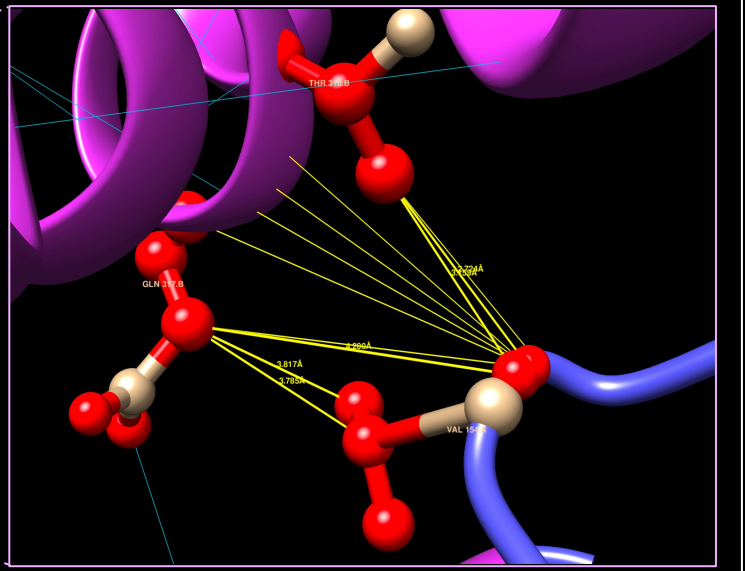


CDK2	Cyclin A	Distance
SER 53.A (CB)	PHE 304.B (CA)	3.173 A
SER 53.A (CA)	PHE 304.B (CA)	3.450 A

CDK2/Cyclin A Complex

Hydrophobic interactions





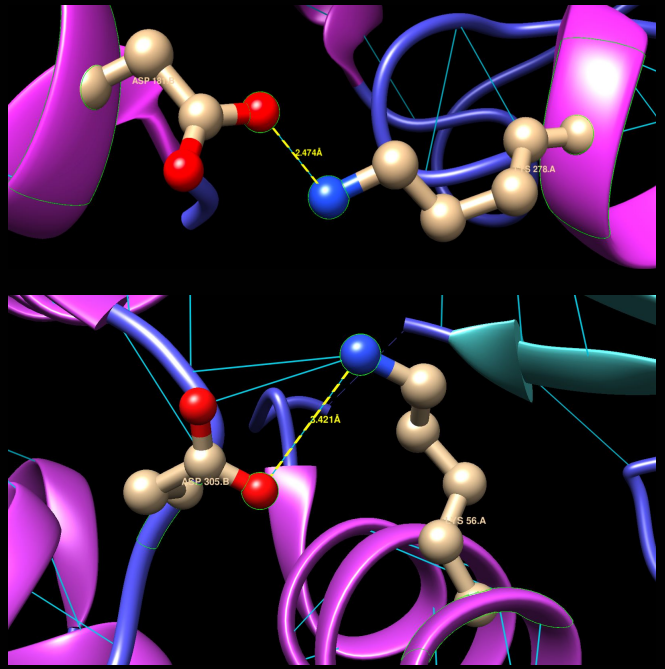
CDK2	Cyclin A	Distance
VAL 154.A (CB)	GLN 317.B (CG)	3.785 A
VAL 154.A (CG1)	GLN 317.B (CG)	3.817 A
VAL 154.A (C)	GLN 317.B (CG)	4.200 A

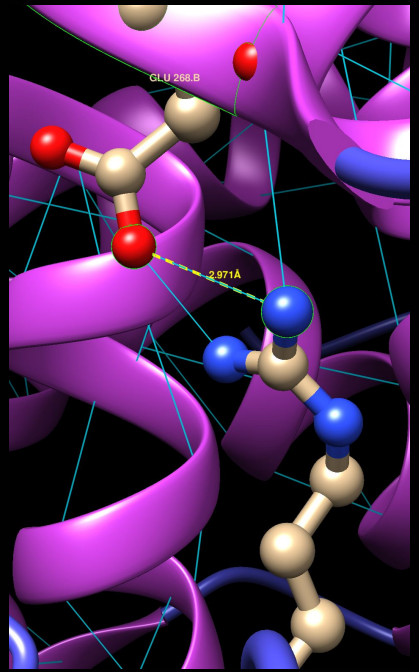
CDK2	Cyclin A	Distance
VAL 154.A (C)	THR 316.B (CG2)	3.159 A
VAL 154.A (O)	THR 316.B (CG2)	2.724 A

CDK2/Cyclin A Complex

Salt bridges

Cyclin A	Distance	CDK2
B:ASP 181[OD1]	3.89	A:LYS 278[NZ]
B:ASP 181[OD2]	2.47	A:LYS 278[NZ]
B:GLU 268[OE2]	3.30	A:ARG 150[NH1]
B:GLU 268[OE2]	2.97	A:ARG 157[NH2]
B:GLU 268[OE2]	2.59	A:ARG 157[NH1]
B:ASP 305[OD1]	3.42	A:LYS 56[NZ]
B:ASP 305[OD2]	3.49	A:LYS 56[NZ]





CDK2/Cyclin A Complex

Hydrogen bonds

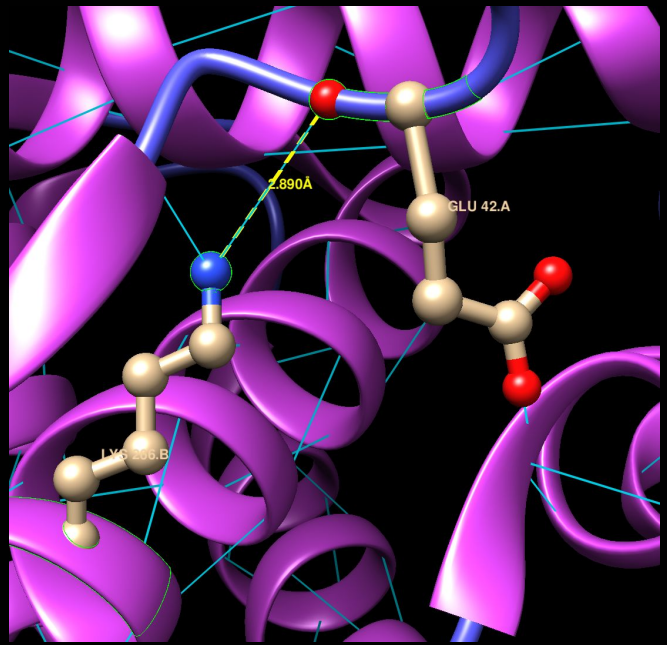
Cyclin A	Distance	CDK2
B:TYR 185[OH]	2.46	A:GLU 57[OE1]
B:LYS 266[NZ]	2.89	A:GLU 42[O]
B:LYS 266[NZ]	2.83	A:VAL 44[O]
B:VAL 275[N]	3.03	A:GLU 42[OE1]
B:LYS 288[NZ]	2.75	A:THR 41[O]
B:HIS 296[NE2]	2.95	A:THR 72[O]
B:THR 316[OG1]	2.67	A:VAL 154[O]
B:ASP 177[OD1]	2.88	A:SER 276[OG]
B:TYR 178[OH]	3.35	A:ALA 277[N]
B:TYR 178[OH]	3.08	A:LYS 278[N]
B:ASP 181[OD2]	3.42	A:SER 120[OG]
B:GLN 317[N]	3.41	A:VAL 154[O]
B:ASP 181[OD2]	2.47	A:LYS 278[NZ]

Cyclin A	Distance	CDK2
B:LYS 266[O]	3.89	A:ARG 50[NE]
B:PHE 267[O]	2.98	A:ARG 50[NE]
B:PHE 267[O]	3.32	A:ARG 50[NH2]
B:GLU 268[O]	3.11	A:ARG 150[NH1]
B:GLU 268[O]	3.14	A:ARG 150[NH2]
B:GLU 268[O]	3.15	A:ARG 157[NH2]
B:GLU 268[OE2]	3.30	A:ARG 150[NH1]
B:GLU 268[OE2]	2.59	A:ARG 157[NH1]
B:GLU 269[O]	3.53	A:ARG 50[NH2]
B:GLU 295[OE1]	3.00	A:VAL 44[N]
B:THR 303[O]	2.96	A:LYS 56[NZ]
B:ASP 305[OD1]	3.42	A:LYS 56[NZ]
B:ASP 305[OD2]	3.49	A:LYS 56[NZ]
B:ALA 307[O]	2.74	A:ARG 122[NH2]

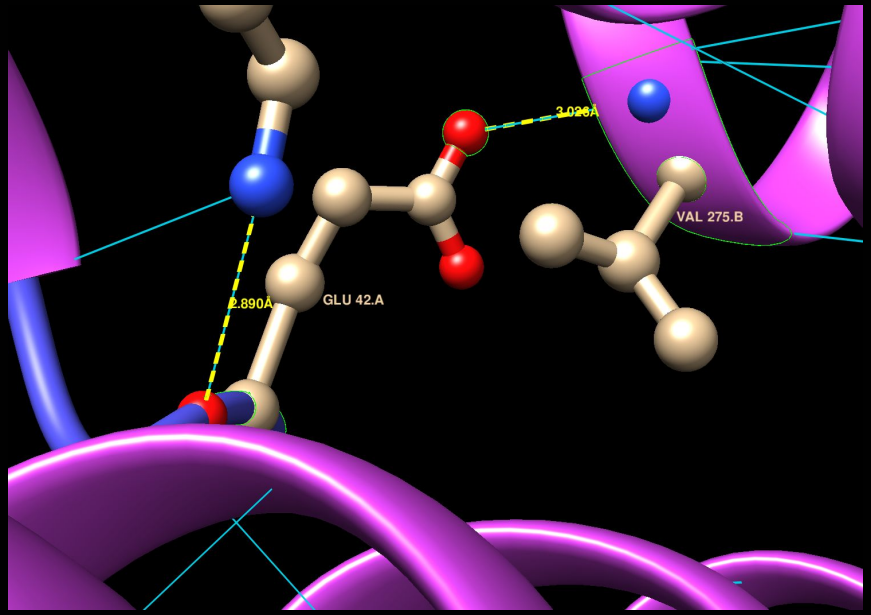
CDK2/Cyclin A Complex

Hydrogen bonds

B:LYS 266[NZ]	2.89	A:GLU 42[O]



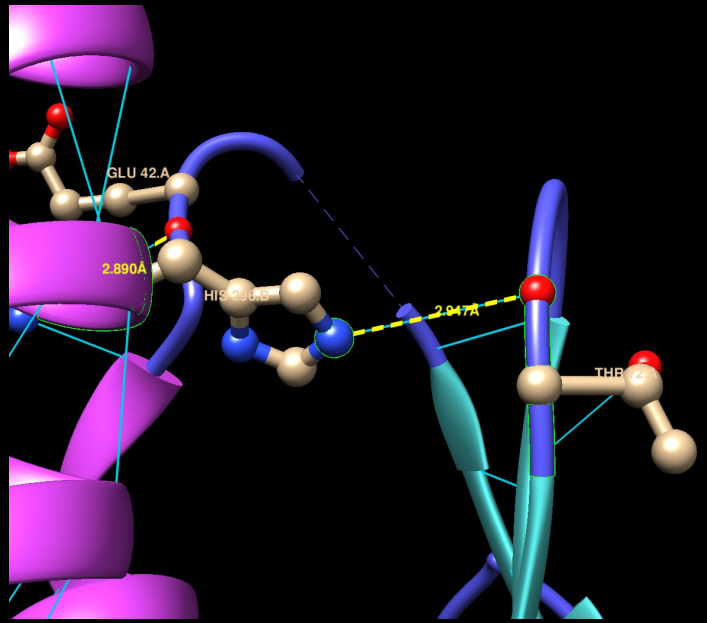
B:VAL 275[N]	3.03	A:GLU 42[OE1]



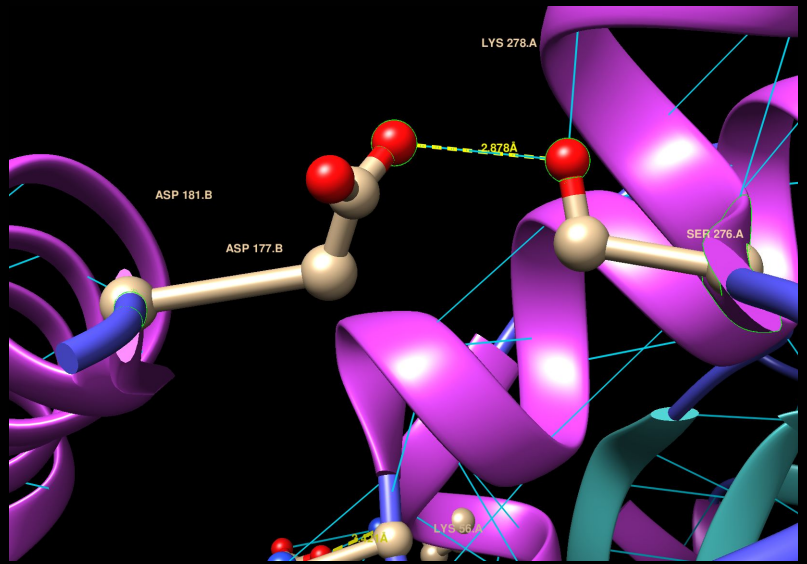
CDK2/Cyclin A Complex

Hydrogen bonds

B:HIS 296[NE2]	2.95	A:THR 72[O]



B:ASP 177[OD1]	2.88	A:SER 276[OG]



CDK2/Cyclin A Complex

Hydrogen bonds - all represented

CDK2 activation

Free state - Partially activated superimposition

1HCK.pdb → free state cdk2

1FIN.pdb → partially activated cdk2

Main differences:

- α helix & β-sheet reorientation
- PSTAIRE against the β-sheet
- Reorientation of Ile49 and Glu51 (Lys33)
- α12 helix → β-strand 9 —β-strand 6

↘ Cyclin

CDK2 activation

Partially activated - Fully activated state superimposition

1FIN.pdb → partially activated cdk2

4EOM.pdb → fully activated cdk2

Main differences:

- Glu162 → P-Thr160 (active site cleft)
- Arg50, 126 & 150 CDK interactions (T loop, N and C lobes)
- P-Thr160 → No Glu12-Thr14 interactions in the activation site

CDK2/Cyclin A

Organizing center

PSTAIRE
(residues 45-51)

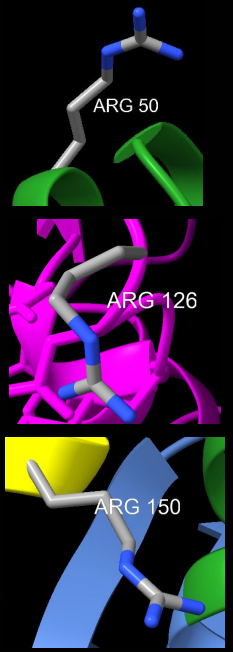
Arg50

C terminal lobe
(residues 86-298)

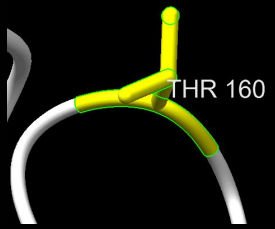
Arg126

T loop
(residues 150-158)

Arg150



Thr160



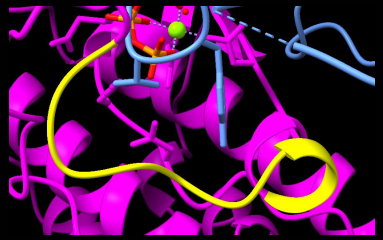
Is phosphorylated

Complete activation of CDK2

CDK2/Cyclin A

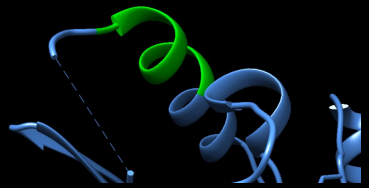
Changes

T loop
(residues 150-158)



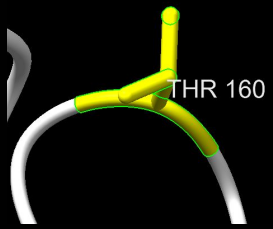
It's exposed to the solvent

PSTAIRE
(residues 45-51)



Rotates 90°

Thr160

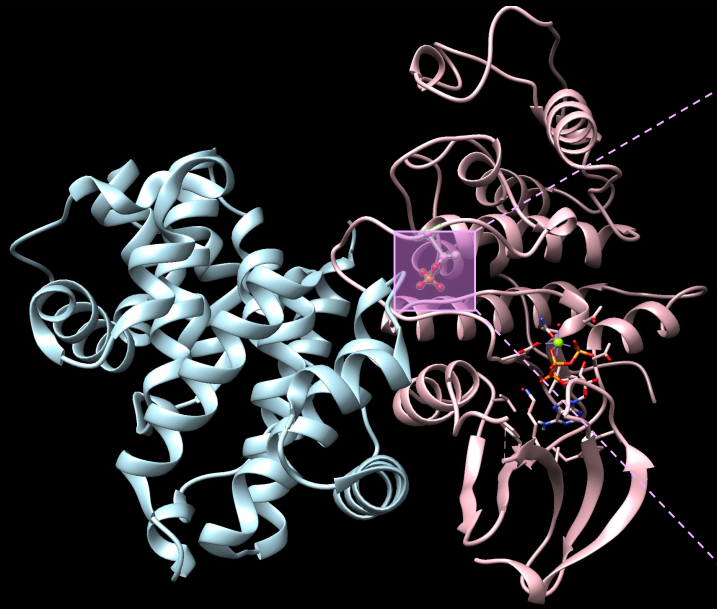


Is phosphorylated

Complete activation of CDK2

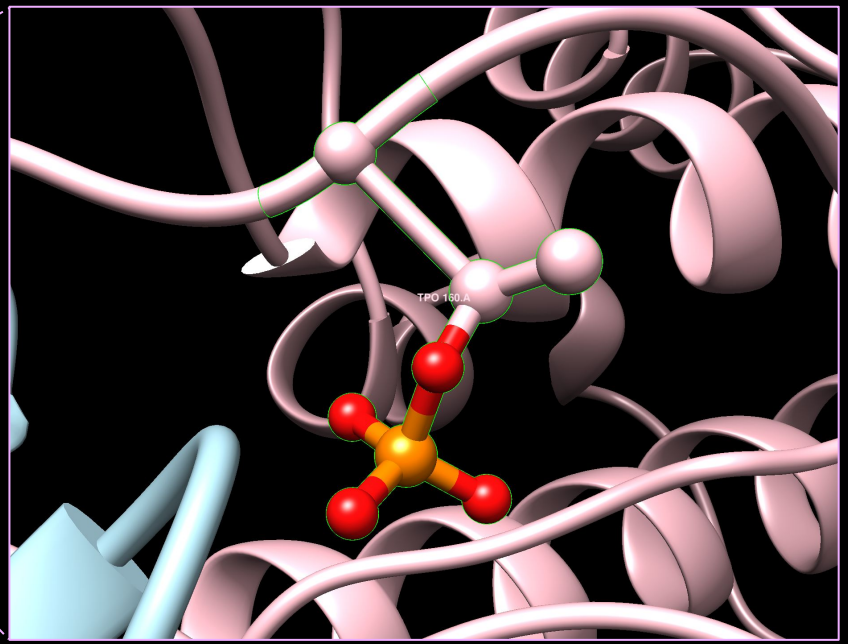
CDK2 activation

Fully activated state + cyclin A



Fully activated cdk2

Cyclin A



Phosphorylated Thr 160

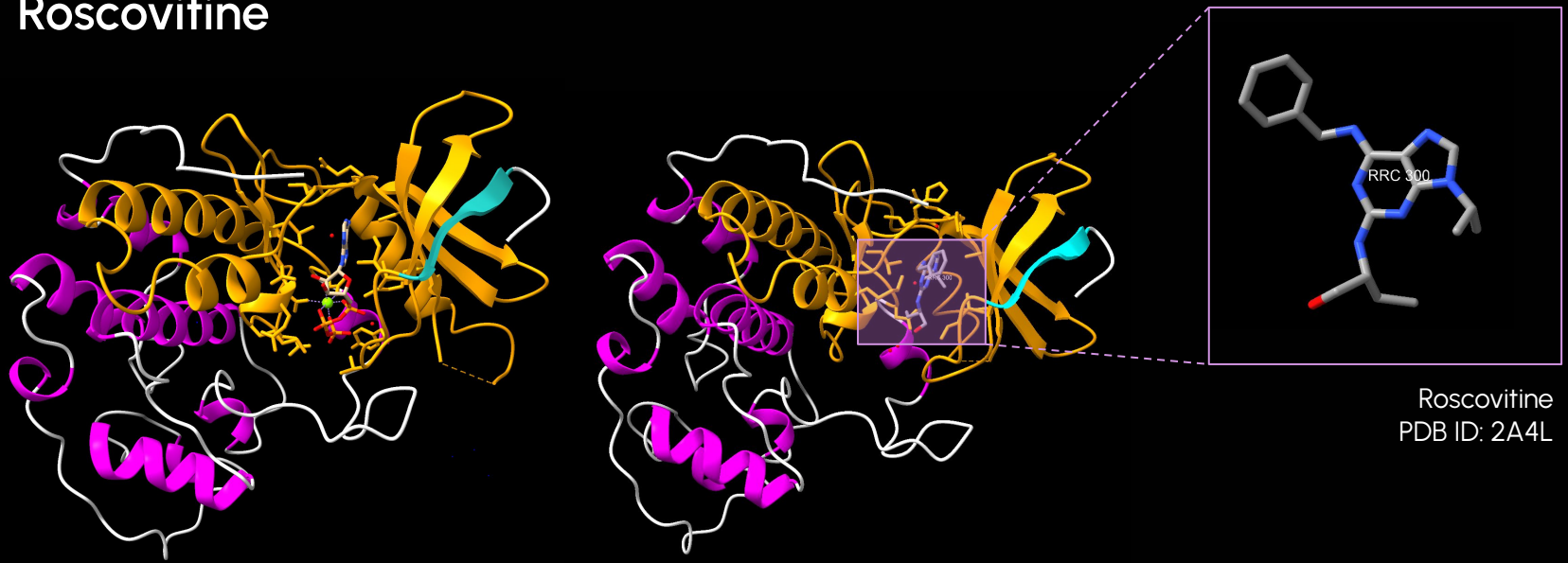
CDK2 interactions with inhibitors

ATP-competitive

Non ATP-competitive

CDK2 interactions with inhibitors

ATP-competitive:
Roscovitine



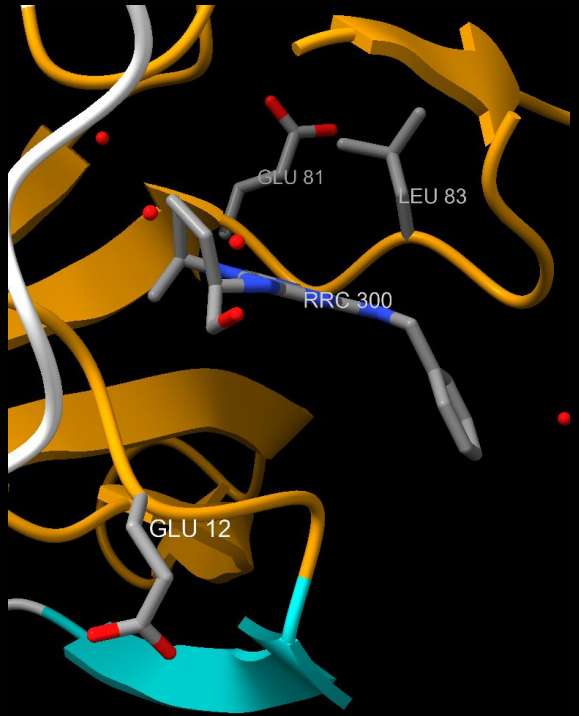
Roscovitine
PDB ID: 2A4L

CDK2 interactions with inhibitors

ATP-competitive: Roscovitine

Hydrogen bonds

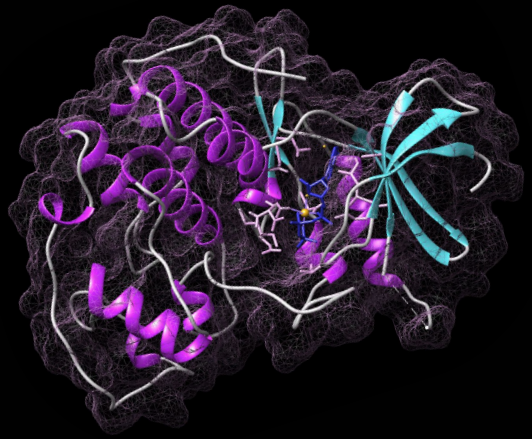
- Leu83 - N7
- Leu83 - NH position 6
- Glu12 - Hydroxybutylamine C2



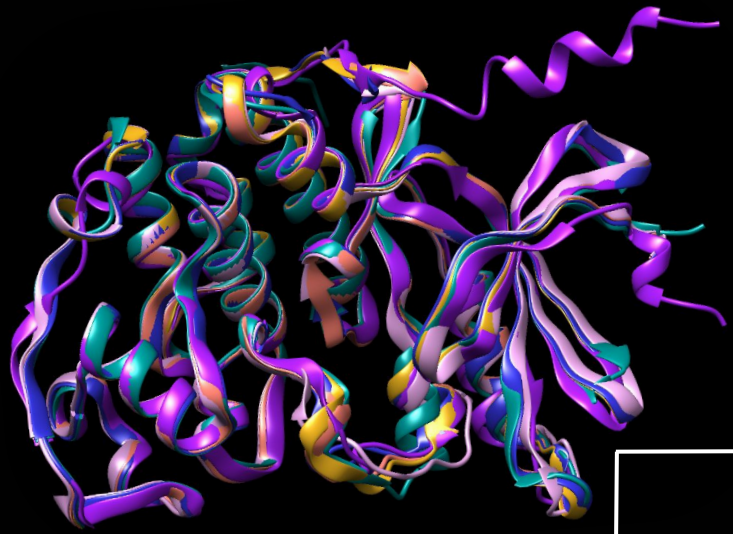
03

CONSERVATION

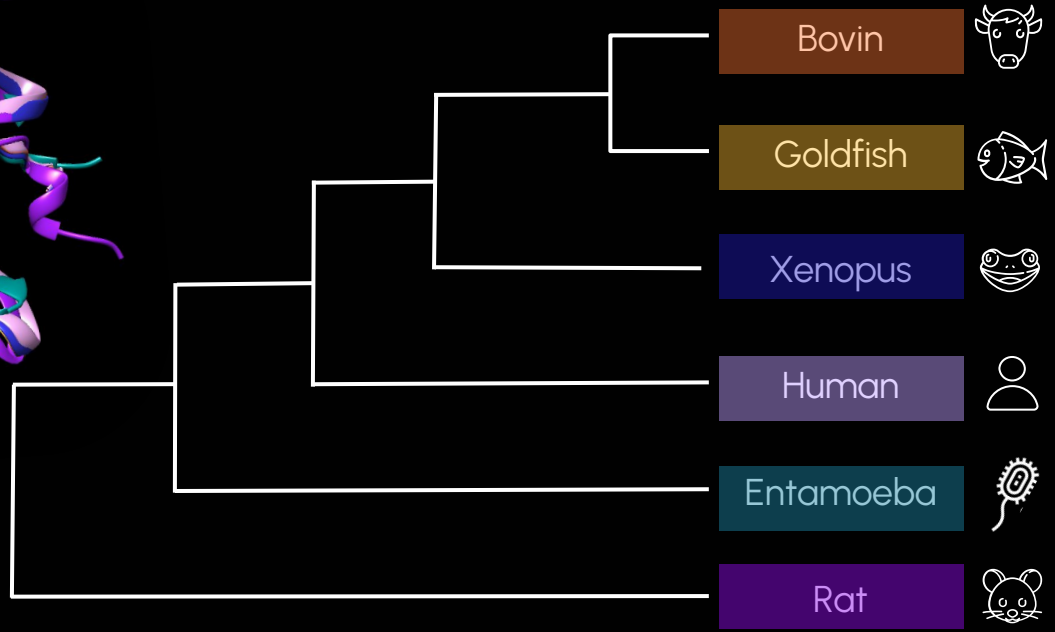
With cyclins and inhibitors



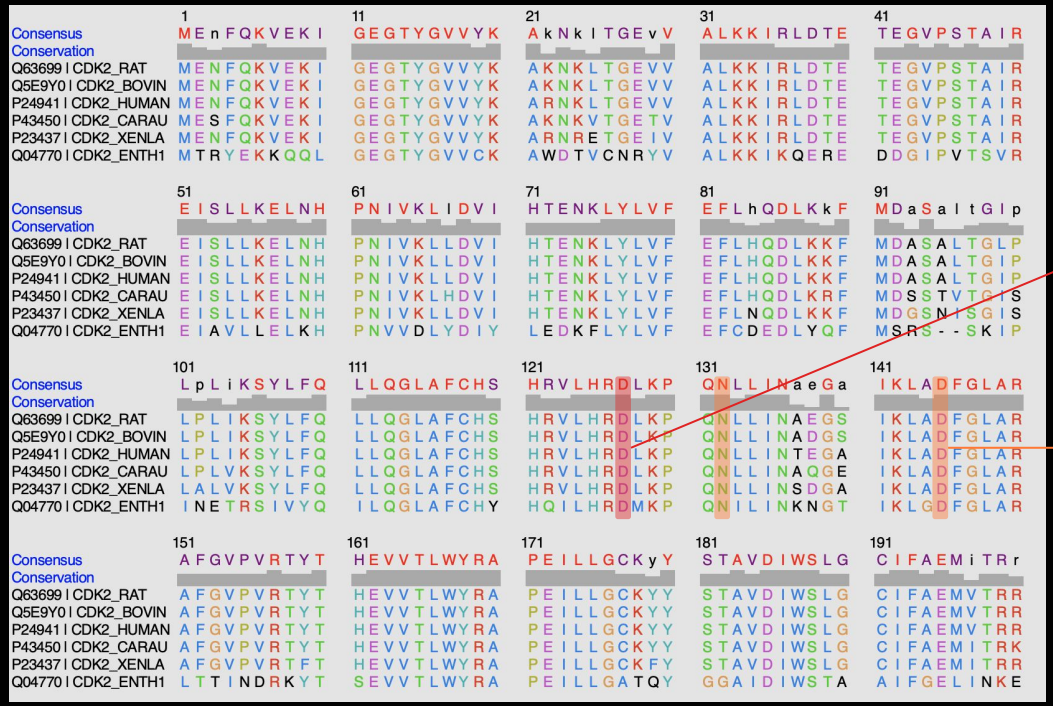
CDK2 between species



Score	9.03
RMSD	1.18



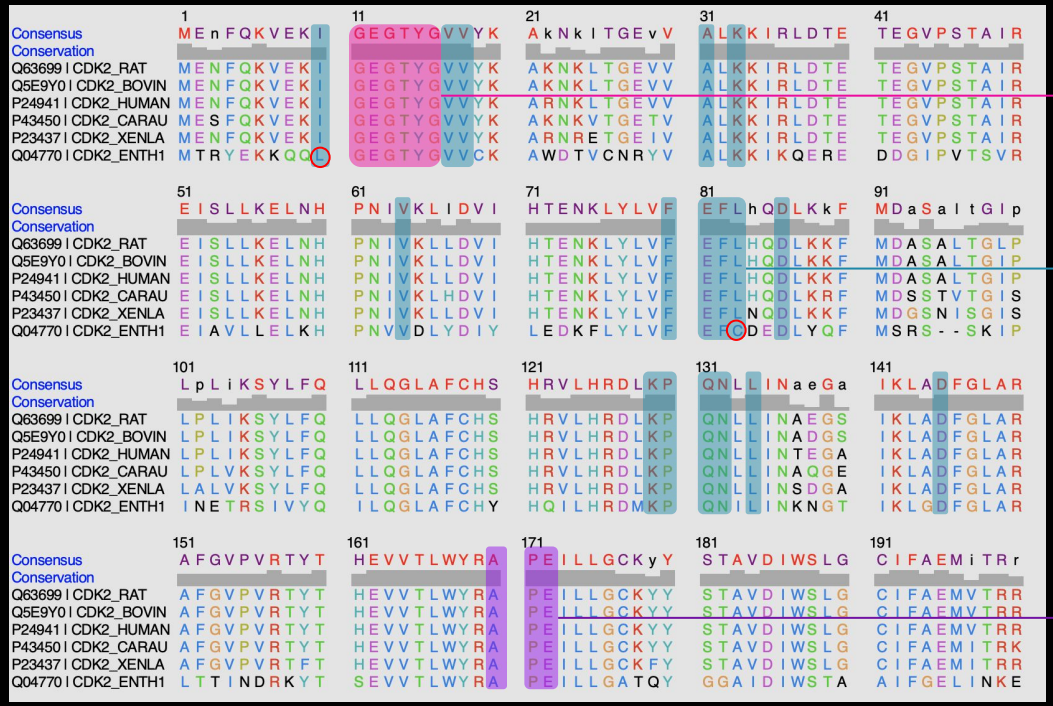
CDK2 between species



Proton acceptor conserved in all species

Coordination of the Mg^{2+} ion conserved in all species

CDK2 between species



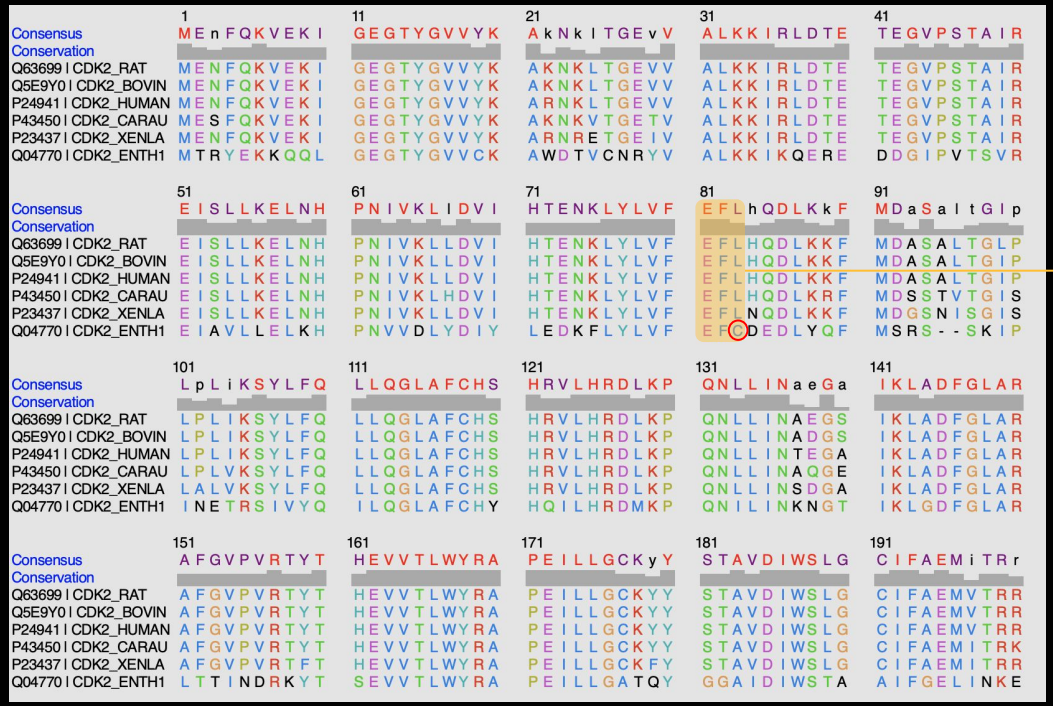
ATP-binding site

G loop conserved in all species

Residues that bind to ATP mostly conserved in all species

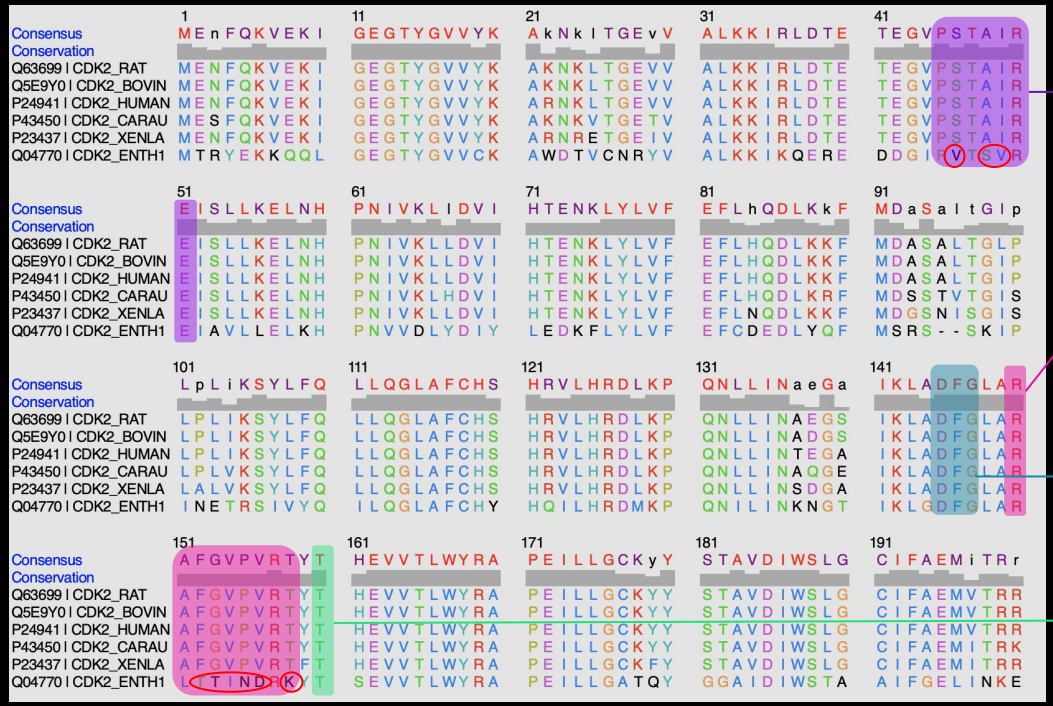
APE motif conserved in all species

CDK2 between species



Hinge region mostly conserved in all species

CDK2 between species



Activation of CDK2

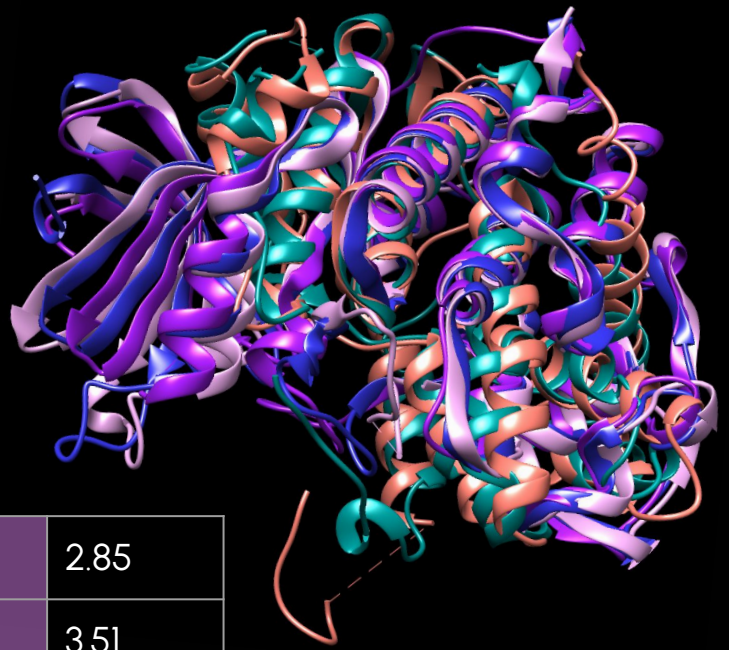
PSTAIRE Domain mostly conserved in all species

T loop mostly conserved

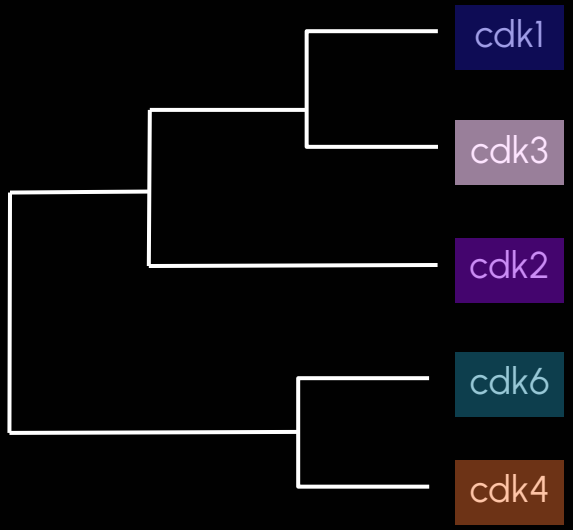
DFG motif conserved in all species

Thr 160 conserved in all species

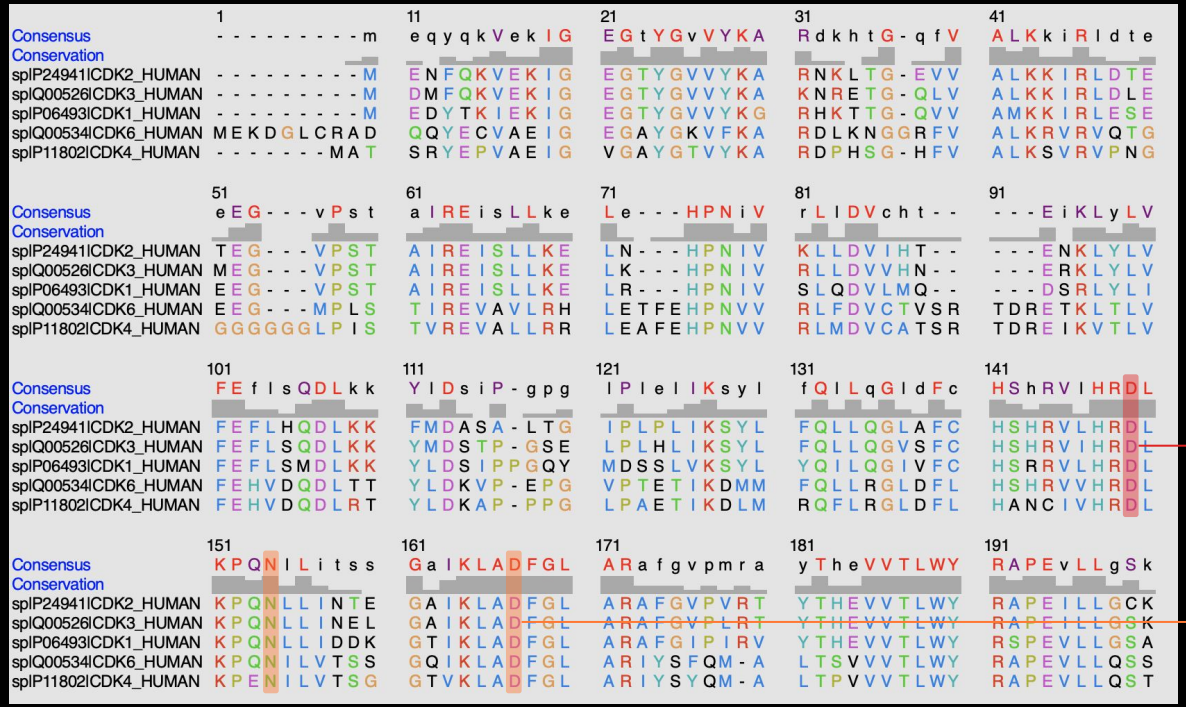
Cell Cycle CDK's



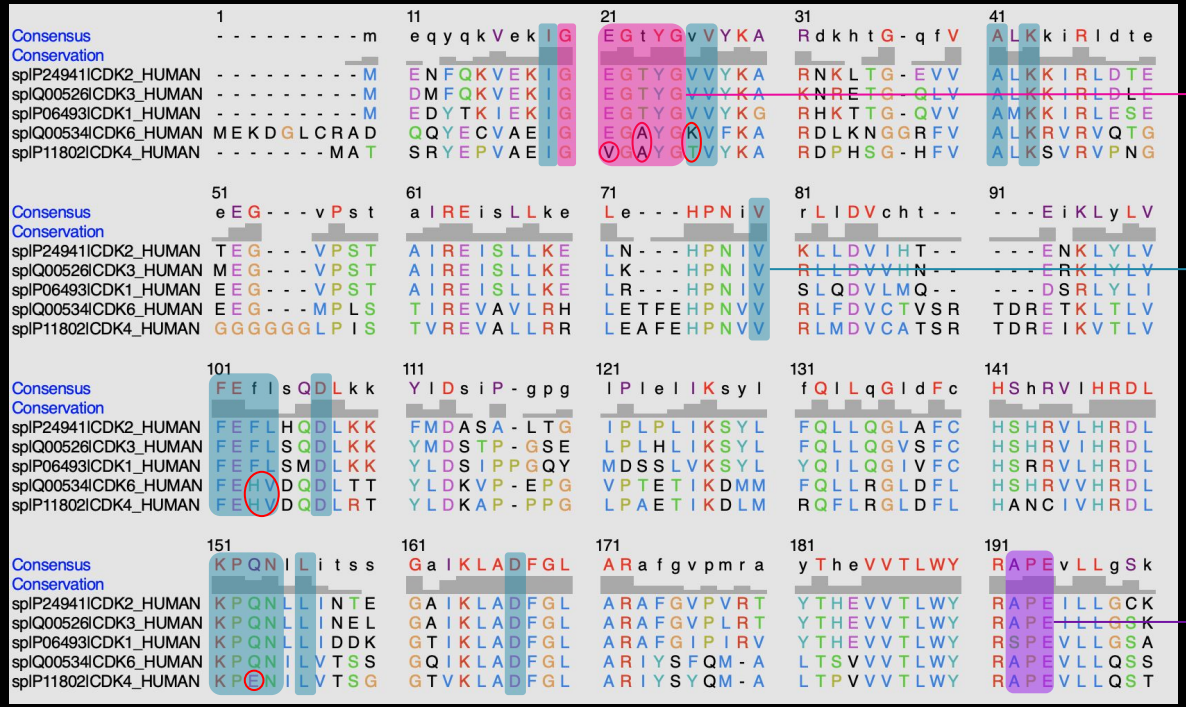
Score	2.85
RMSD	3.51



Cell Cycle CDK's



Cell Cycle CDK's



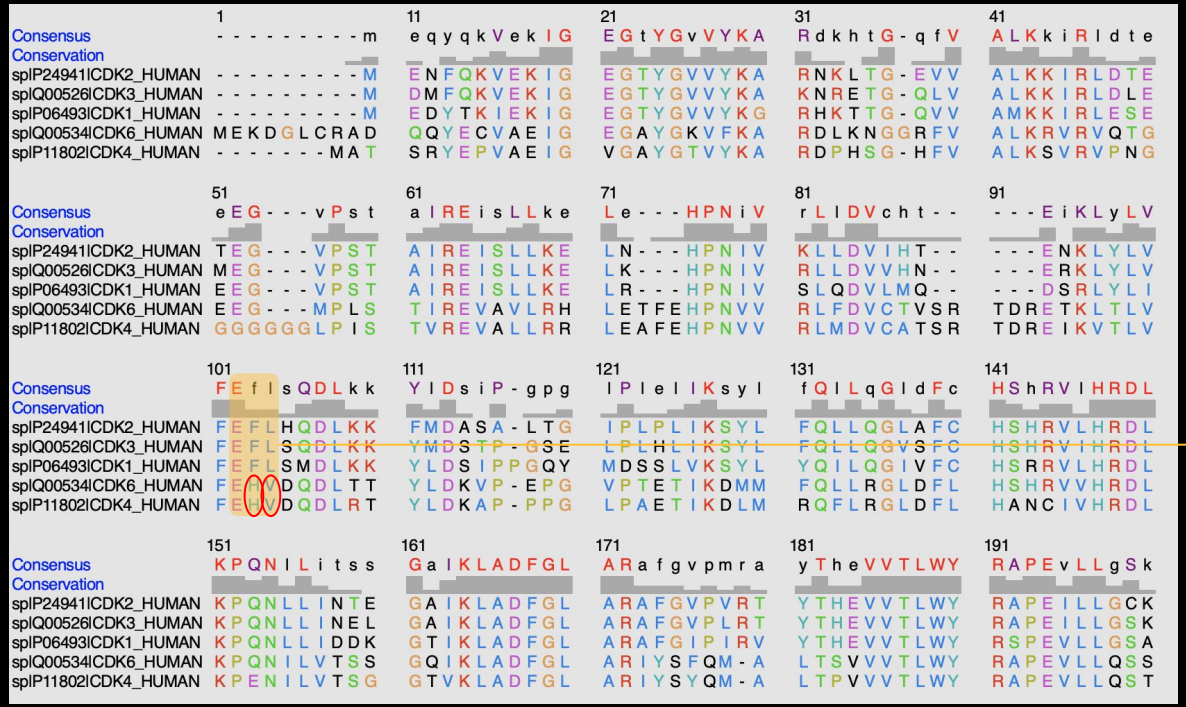
ATP-binding site

G-G-G motif (GLoop) conserved

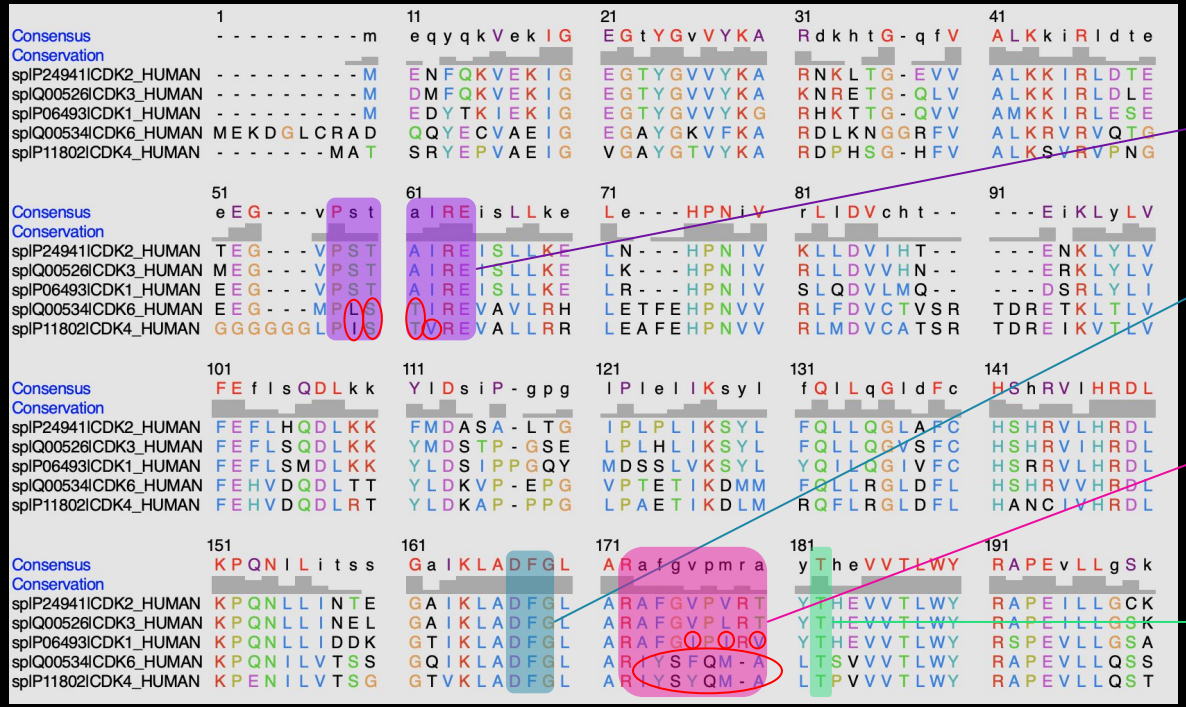
Residues that bind to ATP partially conserved

APE motif conserved

Cell Cycle CDK's



Cell Cycle CDK's



Activation of CDK

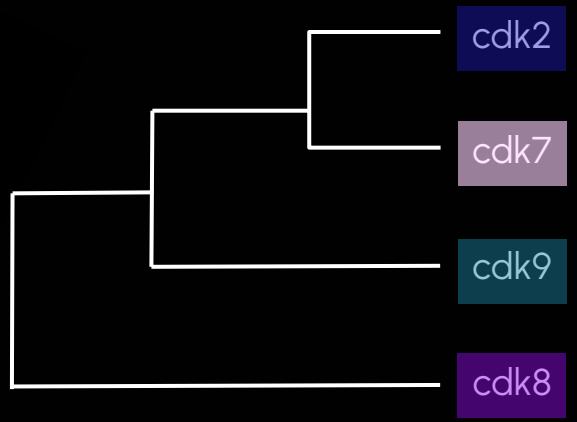
PSTAIRE domain partially conserved

DFG motif conserved

T loop partially conserved in CDK2, CDK3 and CDK1

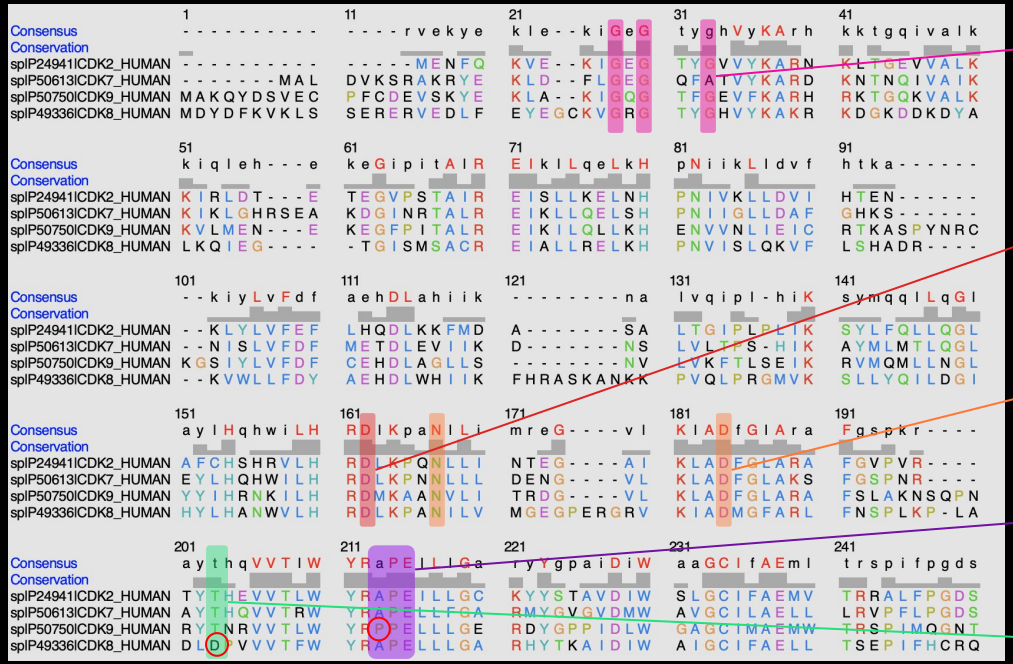
Thr 160 conserved

Transcriptional CDK’s



Score	1.43
RMSD	4.22

Transcriptional CDK's



G-G-G motif (GLoop)

Proton acceptor

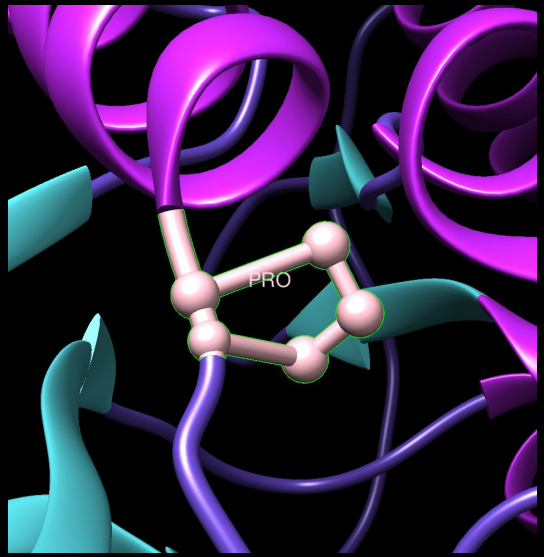
Coordination of the Mg2+ ion

APE motif

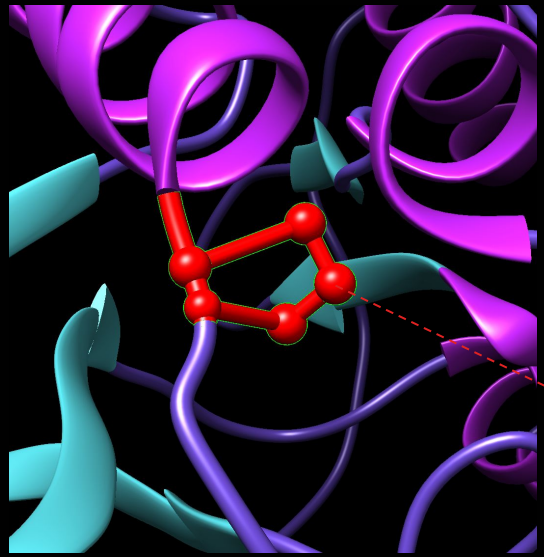
Thr 160

CDK2 mutant variant: P45 → L45

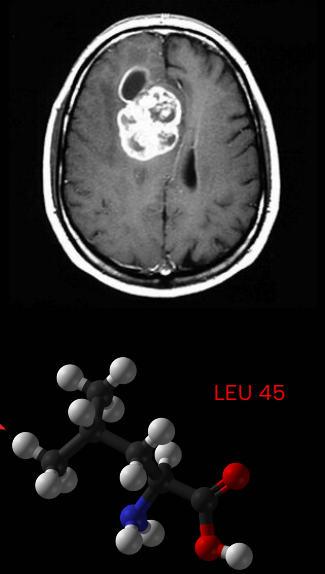
In a Glioblastoma multiforme sample somatic mutation



TEGVPSTAIRE

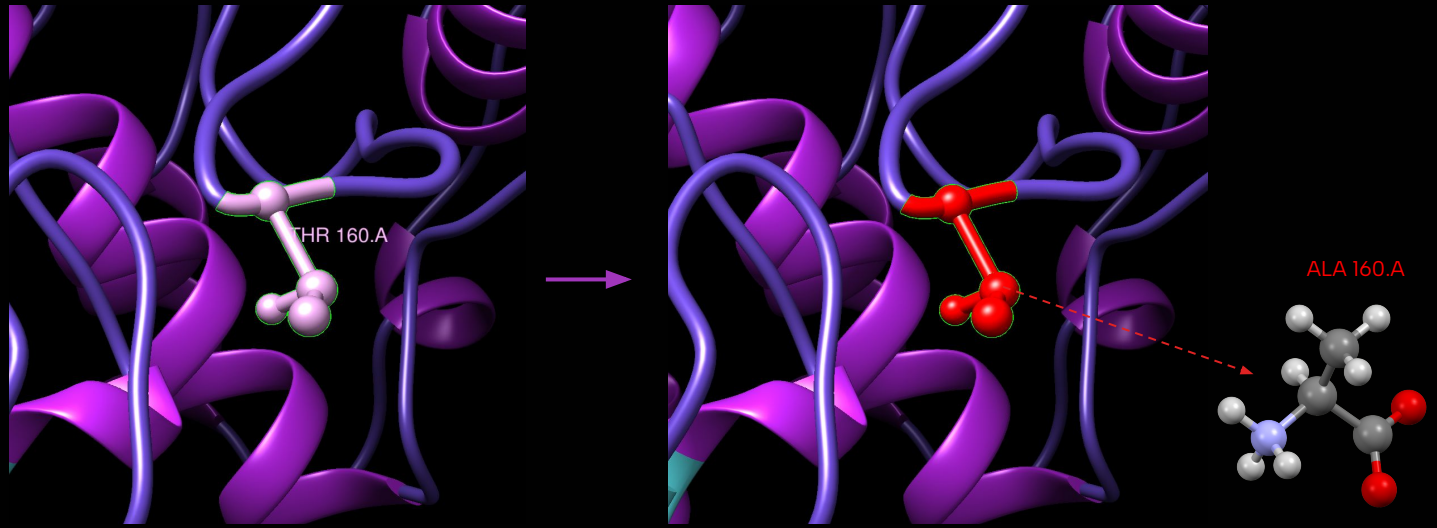


TEGVLSTAIRE



CDK2 mutant variant: T160 → A160

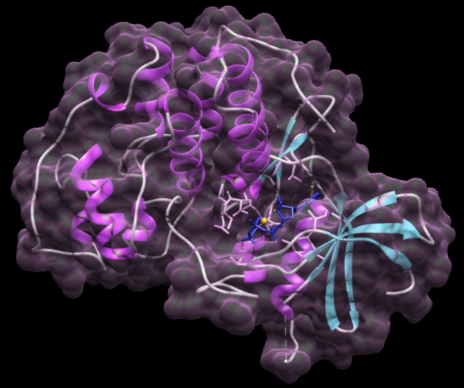
Abolishes activity



FINAL REMARKS

01 Biological importance of CDK2

02 Structure-function relationship



03 Important residues include the Thr160, the TLoop, Gloop, PSTAIRE domain, DFG and APE motif.

04 Further studies on cyclin-CDK interaction needed

PEM QUESTIONS

1. **Which Cyclin-Dependent Kinase (CDK) is essential for the transition from G1 phase to S phase?**

a) CDK1 coupled with cyclin A
b) CDK2 coupled with cyclin E
c) CDK1 coupled with cyclin A
d) CDK4 in association with cyclin D
e) CDK2 bound to cyclin A

2. **Regarding CDKs...**

a) CIP is a specific inhibitor of CDK4
b) Cyclins are generally sufficient to activate CDKs
c) CDKs require both cyclins and phosphorylation at specific residues to become fully active
d) Tyrosine at position 160 is the one phosphorylated by CAK, leading to a full activation state of a CDK
e) CIP is a non-competitive inhibitor of ATP that binds to the catalytic site

3. **Which of the following residues of the CDK2 is conserved between species?**

a) GLoop
a) TLoop
b) a and b
c) Thr160
d) all of the above

PEM QUESTIONS

4. Which of the following residues participate in the coordination of the Mg2+ ion?

a) N154
b) D157
c) a and b
d) D149
e) all of the above

5. What types of interactions can we find in cdk2?

1. Hydrogen bond
2. Disulfide bond
3. Van der Waals
4. Metallic Complex Interactions

a) 1, 2, 3
b) 1 and 3
c) 1, 3 and 4
d) 4
e) All options

PEM QUESTIONS

6. Regarding the role of the Mg ion in the ATP binding of cdk2, mark the false one.

a) Stabilizes the ATP binding
b) It is an inorganic cofactor required for the catalytic activity
c) Coordinates the phosphates groups of ATP by forming metal complex interactions
d) It can be substituted by any electronegative ion
e) Facilitates the phosphate transfer from ATP to specific protein

7. Which change occurs in the inactive - active cdk2 transition?

a) Reorientation of β-sheet and the α-helix
b) Glu162 (glutamic acid) is replaced by P-Thr160
c) Inhibition of interactions of T-loop and C and N lobes
d) Degradation of ATP
e) Kcat decreases and KM increases (activated state)

PEM QUESTIONS

8. The ATP binding site is formed by...

a) The beta sheets of both lobes
b) The C-helix and the helixes of the C-terminal lobe
c) The beta strands 1 and 3
d) 4 beta strands
e) 2 beta strands and 2 alpha helices

9. What happens when CDK2 interacts with Cyclin A?

a) The TLoop is exposed to the solvent
b) The PSTAIRE rotates 90°
c) Thr 160 is phosphorylation
d) All of the above
e) None of the above

10. Which structure does the CDK2 have?

a) It's an all beta protein
b) It has two subdomains; the N-terminal lobe and the C-terminal lobe
c) The G-loop has a Thr160 important for CDK2 activation
d) The PSTAIRE motif corresponds to the C-helix (helix alpha 1)
e) B and D are correct

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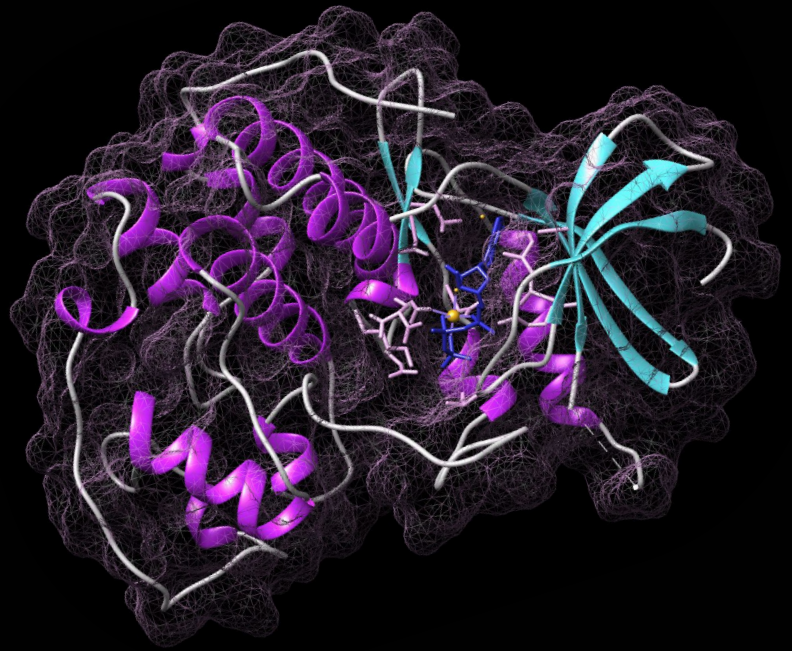
CDK PROTEINS

A study on CDK2



Thanks!

upf. Universitat Pompeu Fabra Barcelona

Marusi Fernández Torres, Mireia López Burgos, Oriol López Roselló & Victoria Sanmartín Cerrato

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