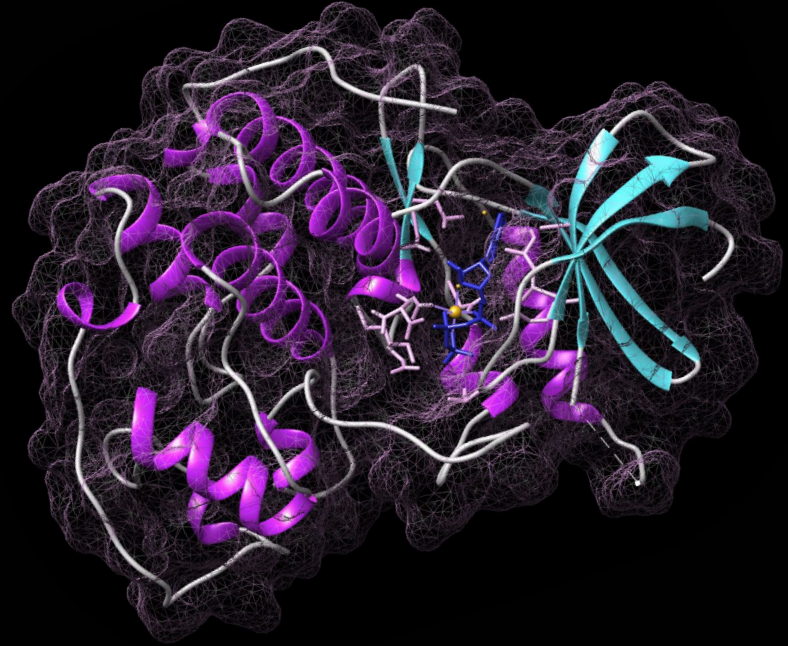


CDK PROTEINS

A study on CDK2



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López Roselló & Victoria Sanmartín Cerrato
Structural Biology 2023/2024

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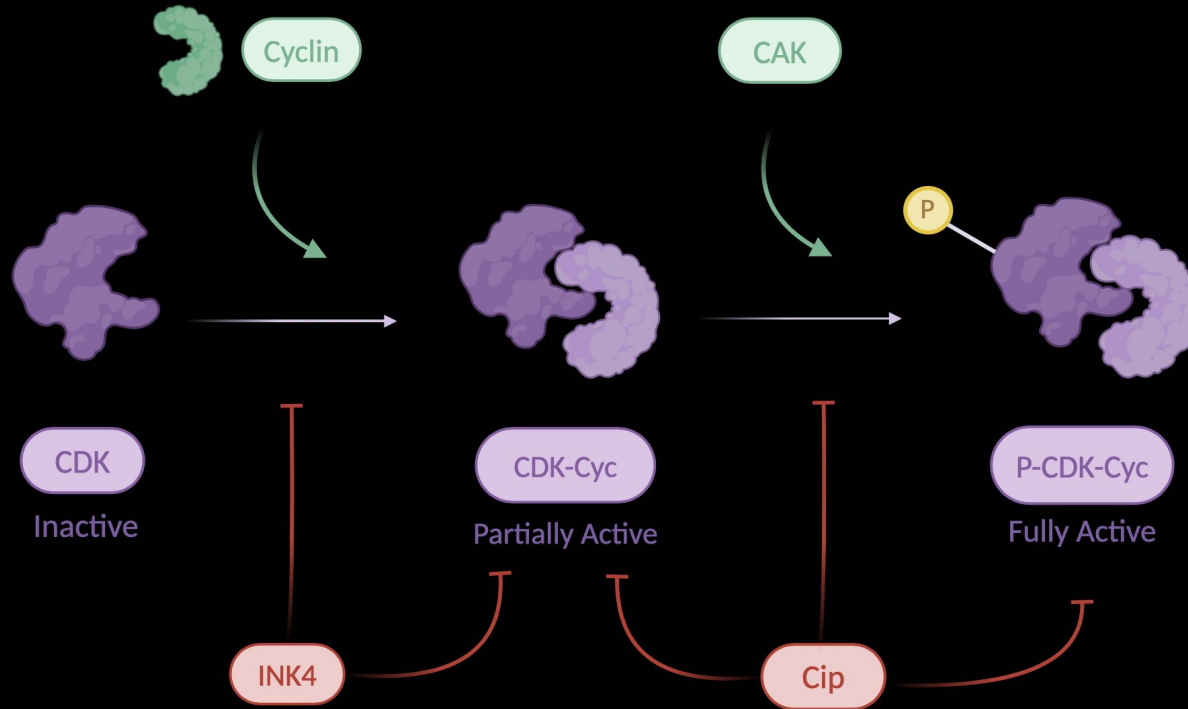
Cyclins and inhibitors

04

CONSERVATION

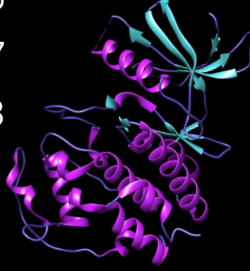
Superimpositions and
alignments

What are Cyclin-Dependent Kinases?



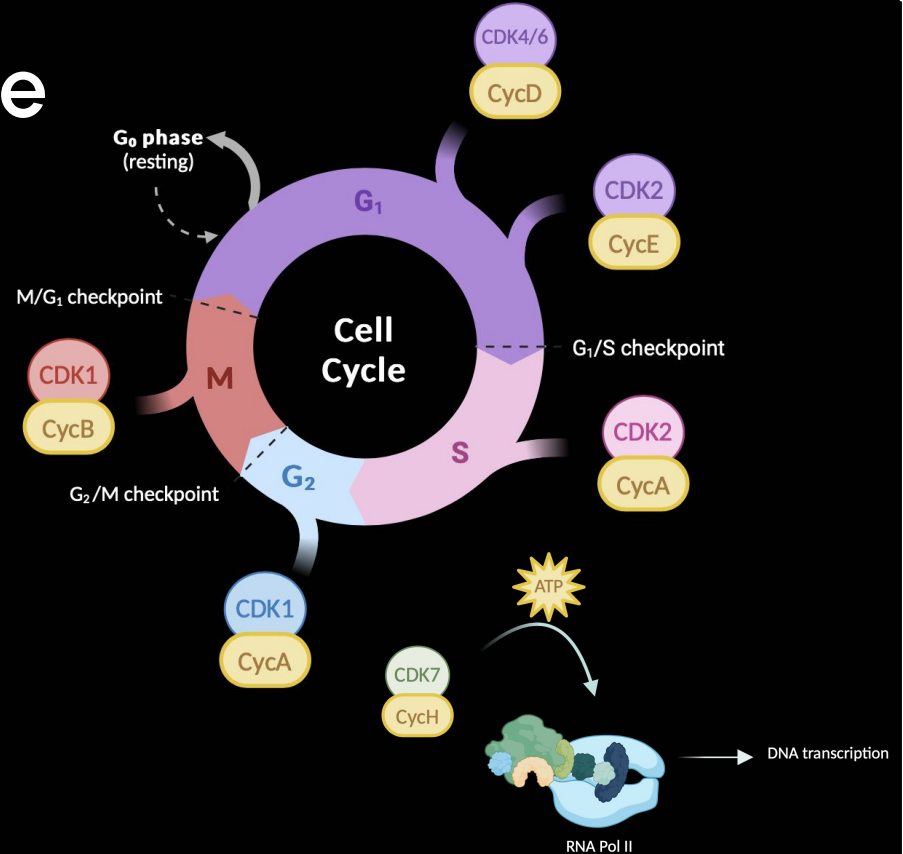
CDK classification

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



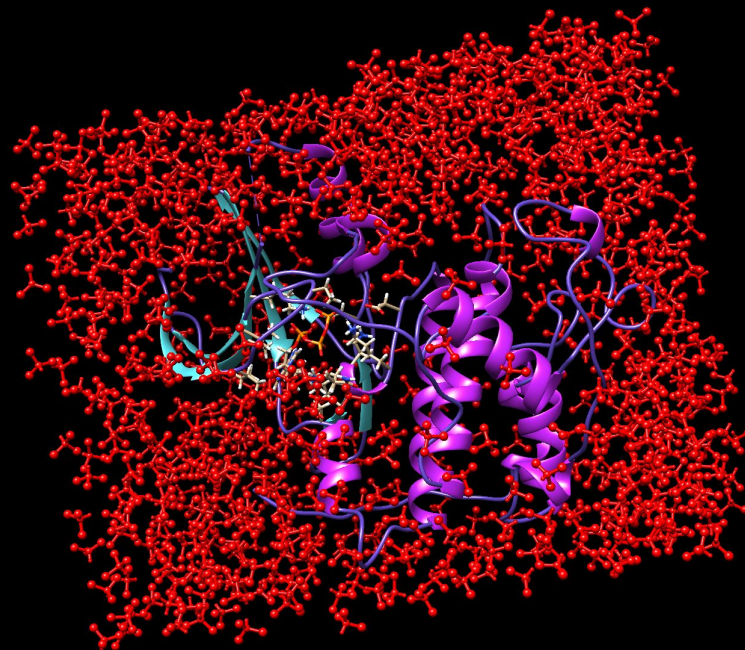
CDK2 model of study: 1HCK

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



CDK2 model of study: 1HCK

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



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

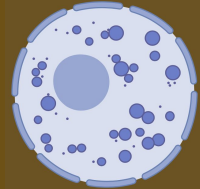
Cellular component

Cajal body

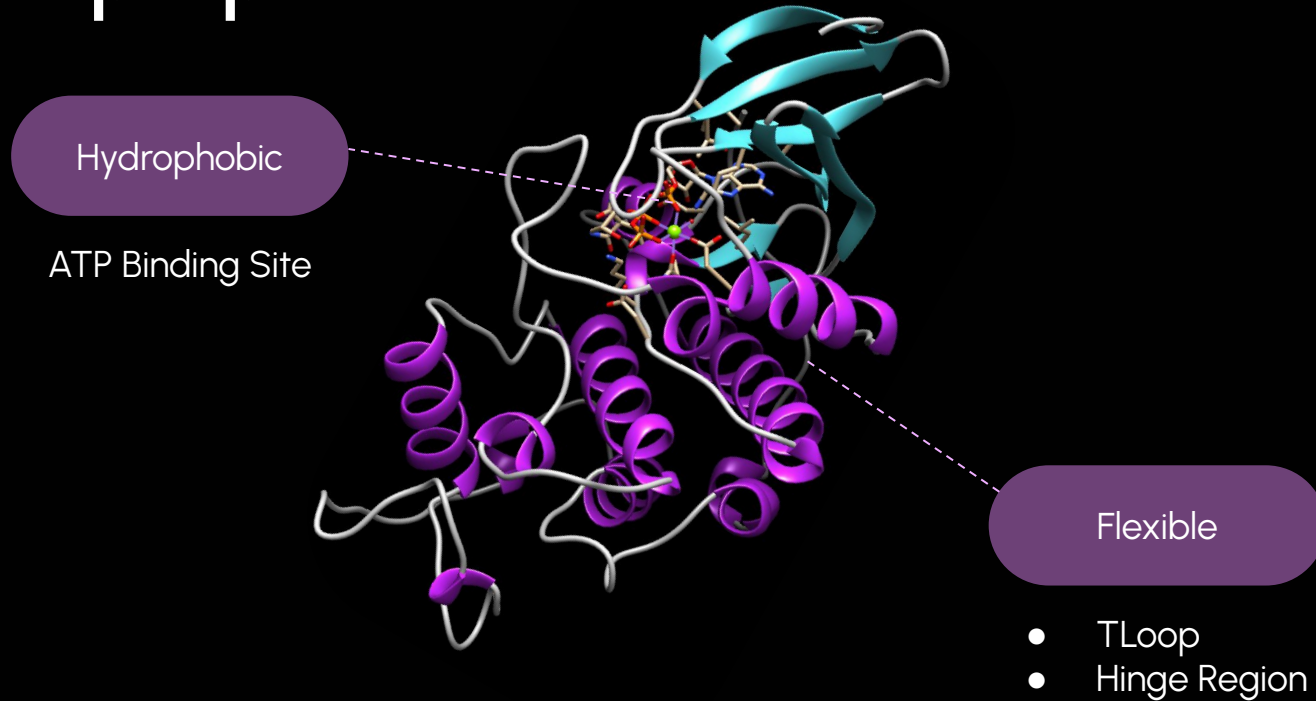
Centrosome

Chromosome

Telomeric region



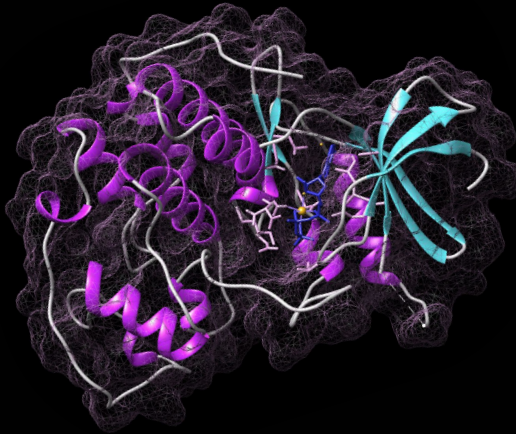
CDK2 properties



02

CDK2 STRUCTURAL BIOLOGY

Description of the molecule and inner interactions



SCOP cyclin-dependent kinase 2

Class 1000003
Alpha and beta proteins
($\alpha+\beta$)

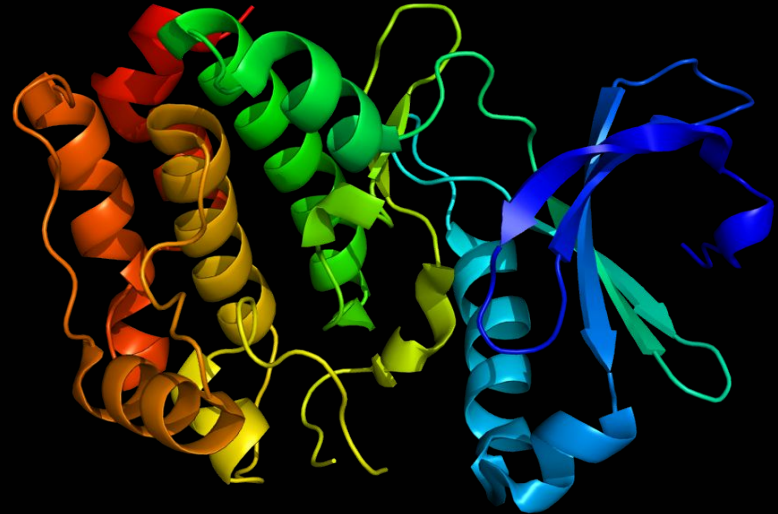
Fold 2000046
Protein kinase like (PK-like)

Superfamily 3000066
Protein kinase like (PK-like)

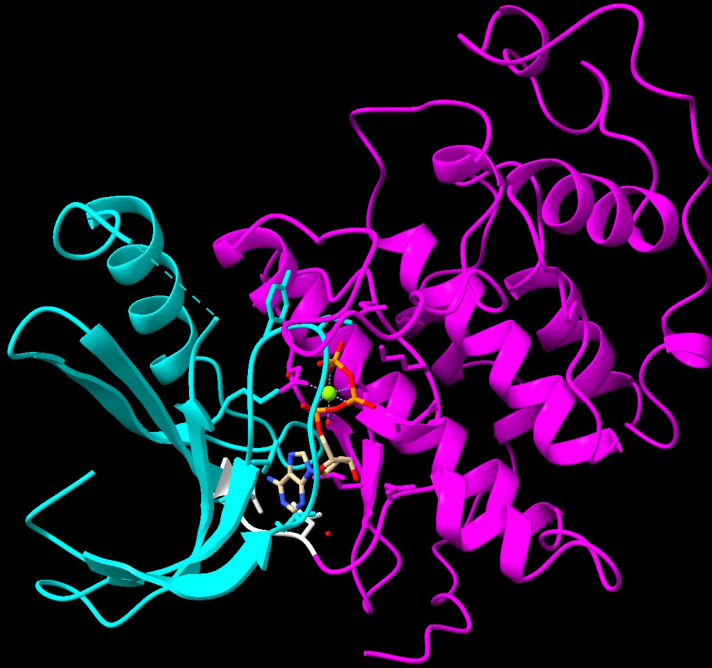
Family 4003661
Protein kinases catalytic
domain-like

Domain 8027931

ATP-binding site
Catalytic loop
Activation loop



CDK2 subdomains

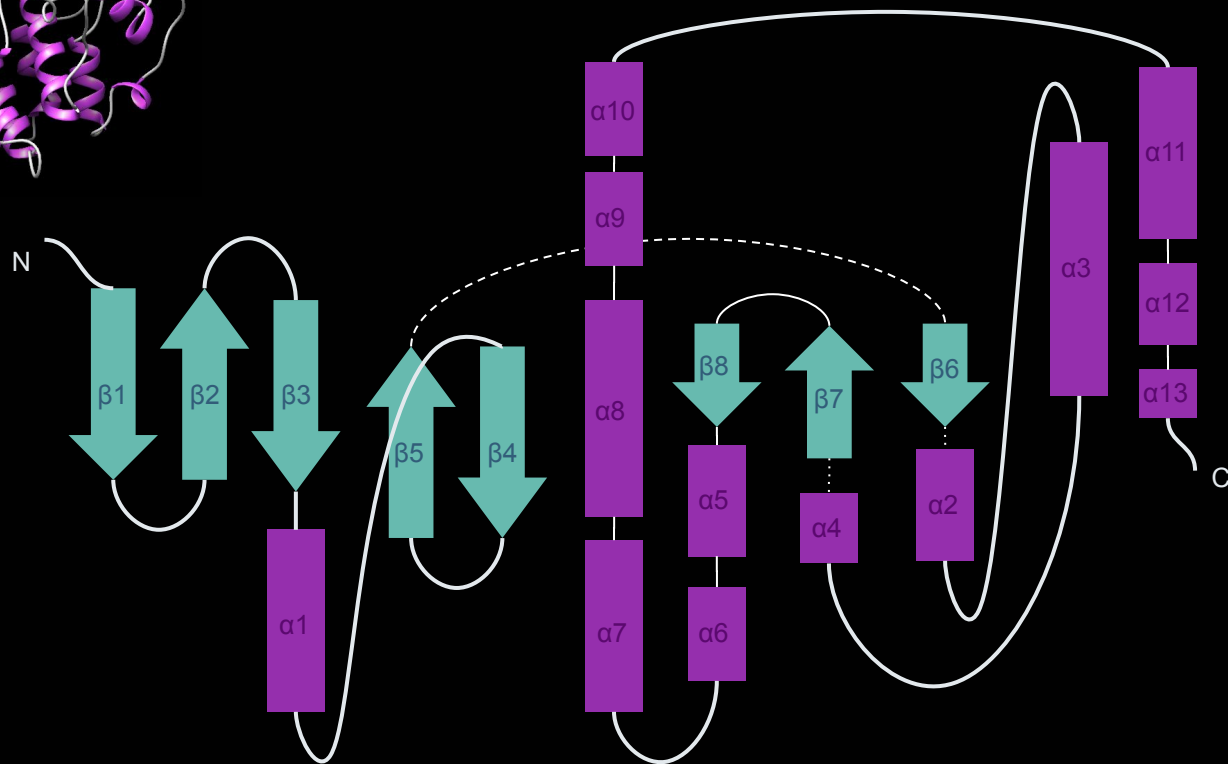


N-terminal lobe
(residues 1-80)

Hinge region
(residues 81-83)

C terminal lobe
(residues 84-298)

Topology Diagram



$\beta 1$ β_2

β3

 α_1 β_4

β5

β6

 α_2 $\alpha 3$ α_4

$\beta 7$

β8

α5

α6

 α_7

α8

 $\alpha 9$ $\alpha 10$ α_{11}

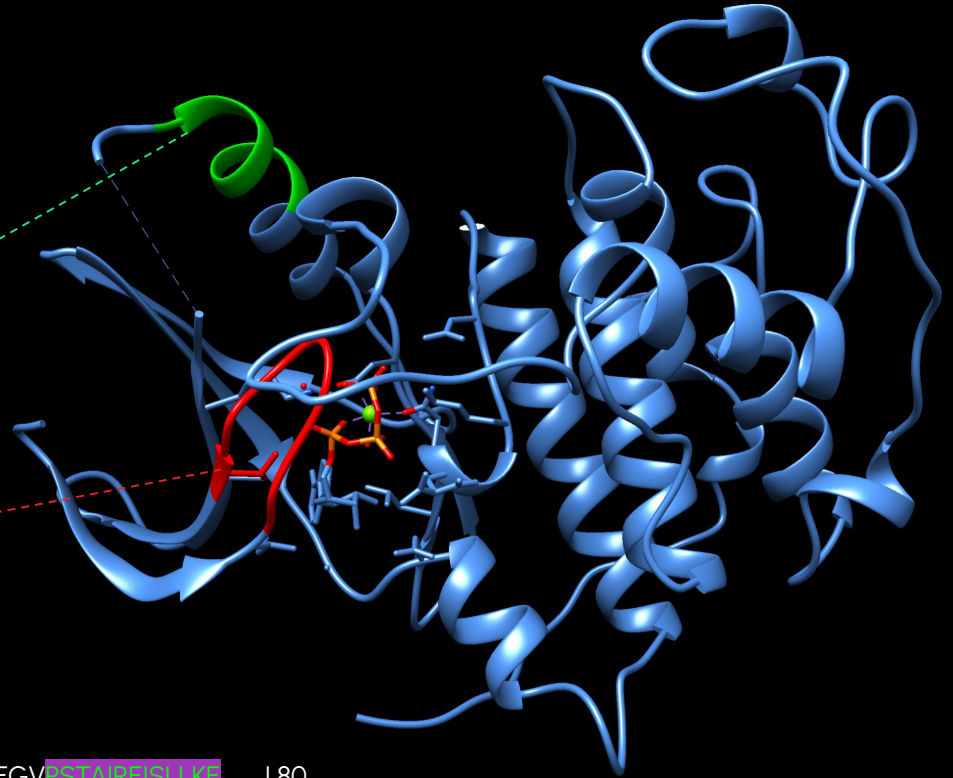
α_{12}

$\alpha 13$

N-terminal lobe

PSTAIRE
(residues 45-51)

G-loop
(residues 11-16)

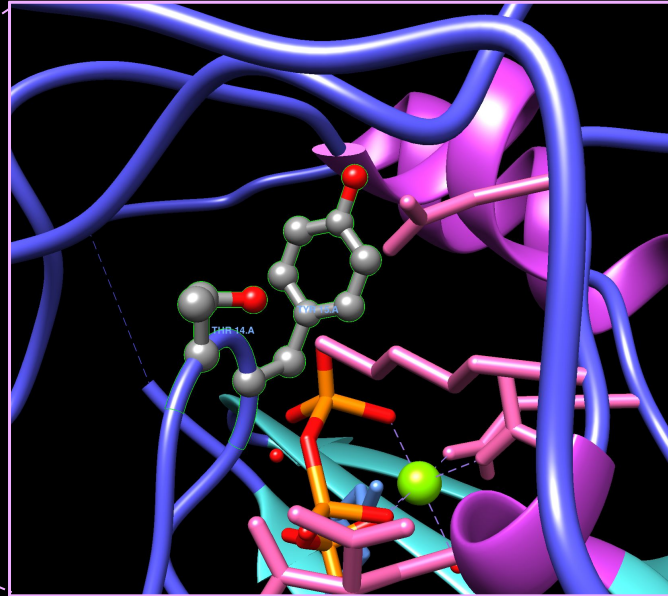
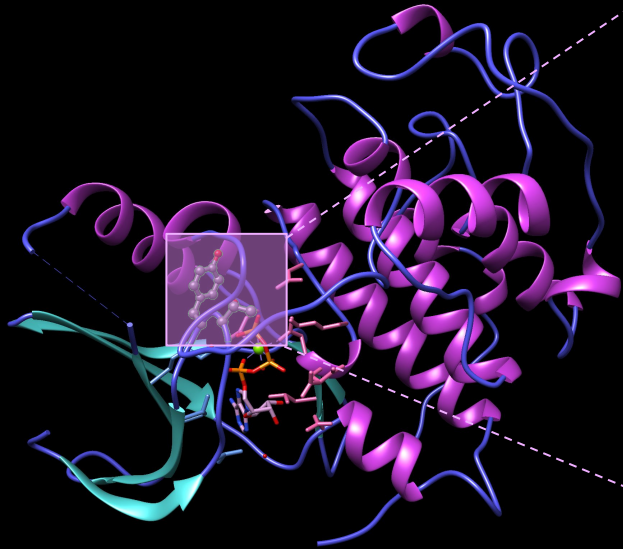


1 | MENFQKVEKIGEGTYGVVYKARNKLTGEVVALKKIRLDTETEGVPSTAREISLKE | 80

β1 β2 β3 α1

N-terminal lobe

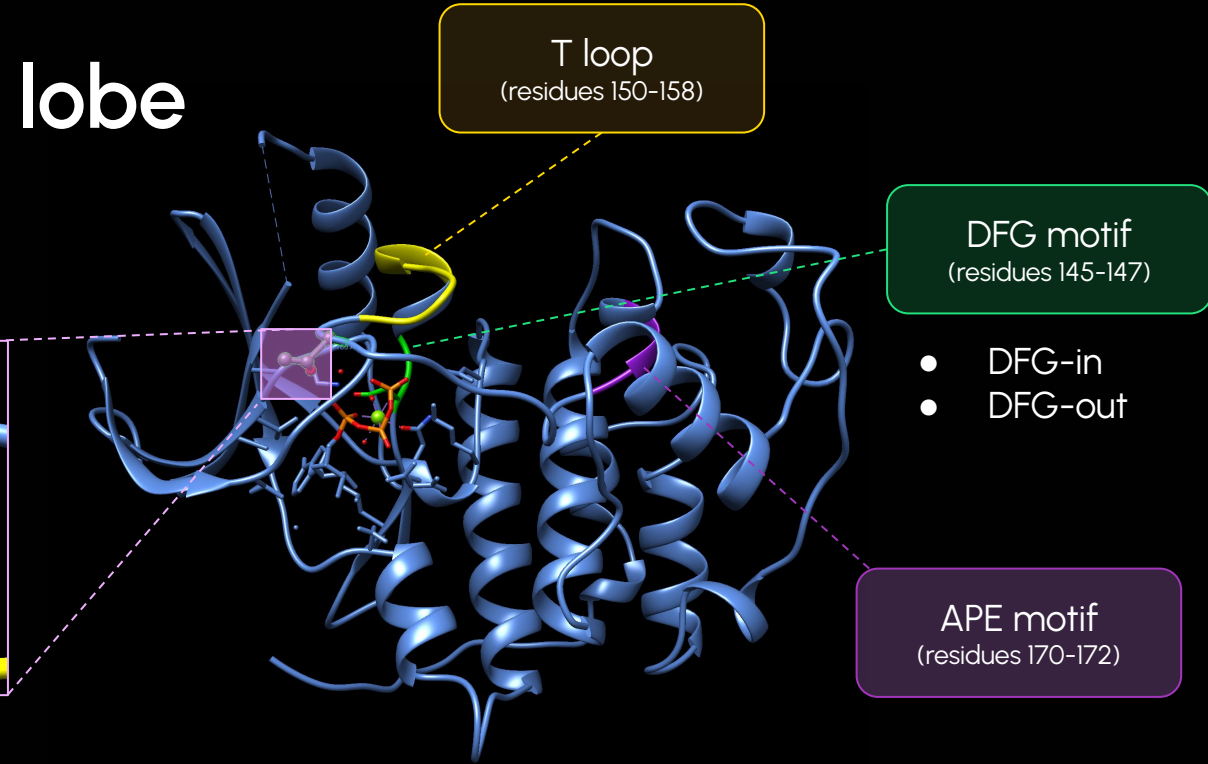
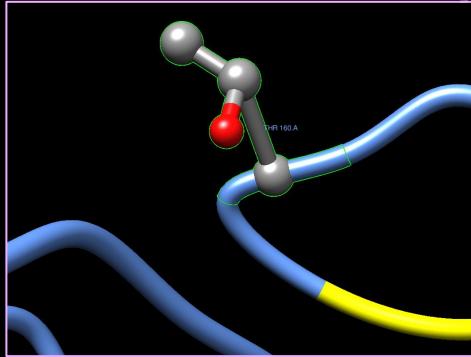
Thr14 and Tyr15 G-loop



1 | MENFQKVEKIGEGTYGVVYKARNKLTGEVVALKKIRLDTETEGVPSTAIETSLIKE | 80

C-terminal lobe

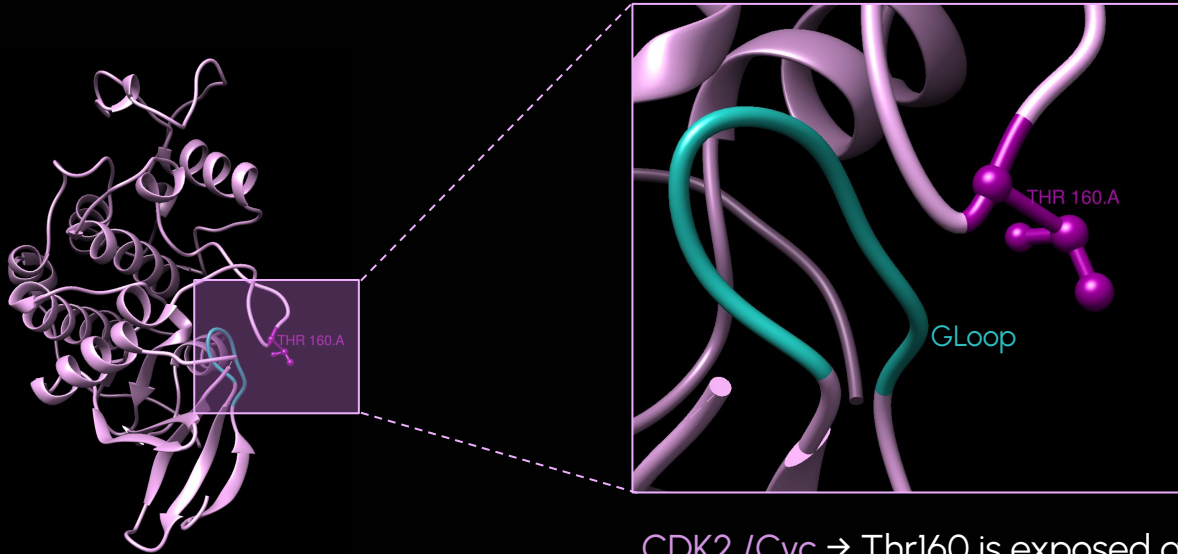
Phosphorylation site



C-terminal lobe

Thr160

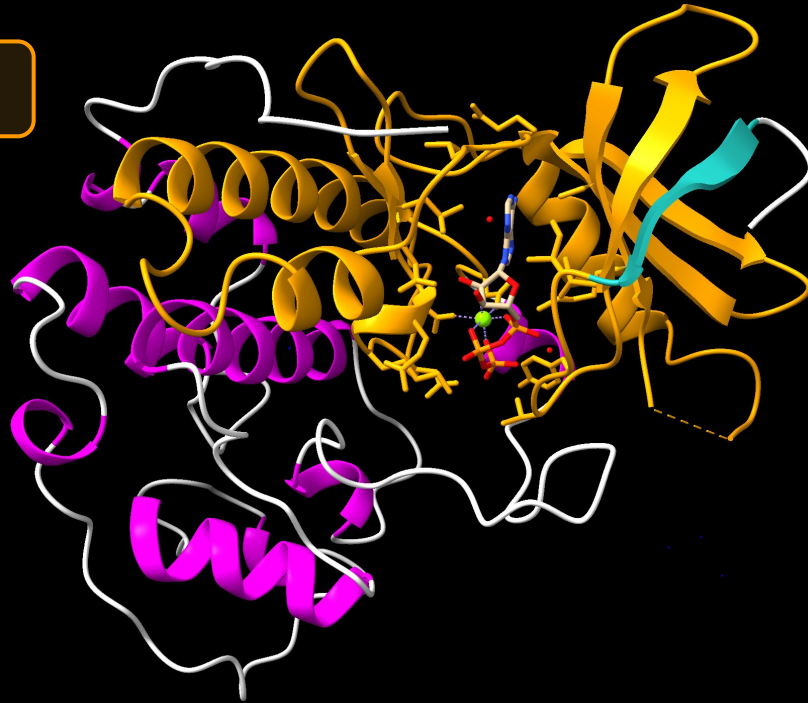
Monomeric CDK2 → Thr160 faces the G-loop, away from the solvent



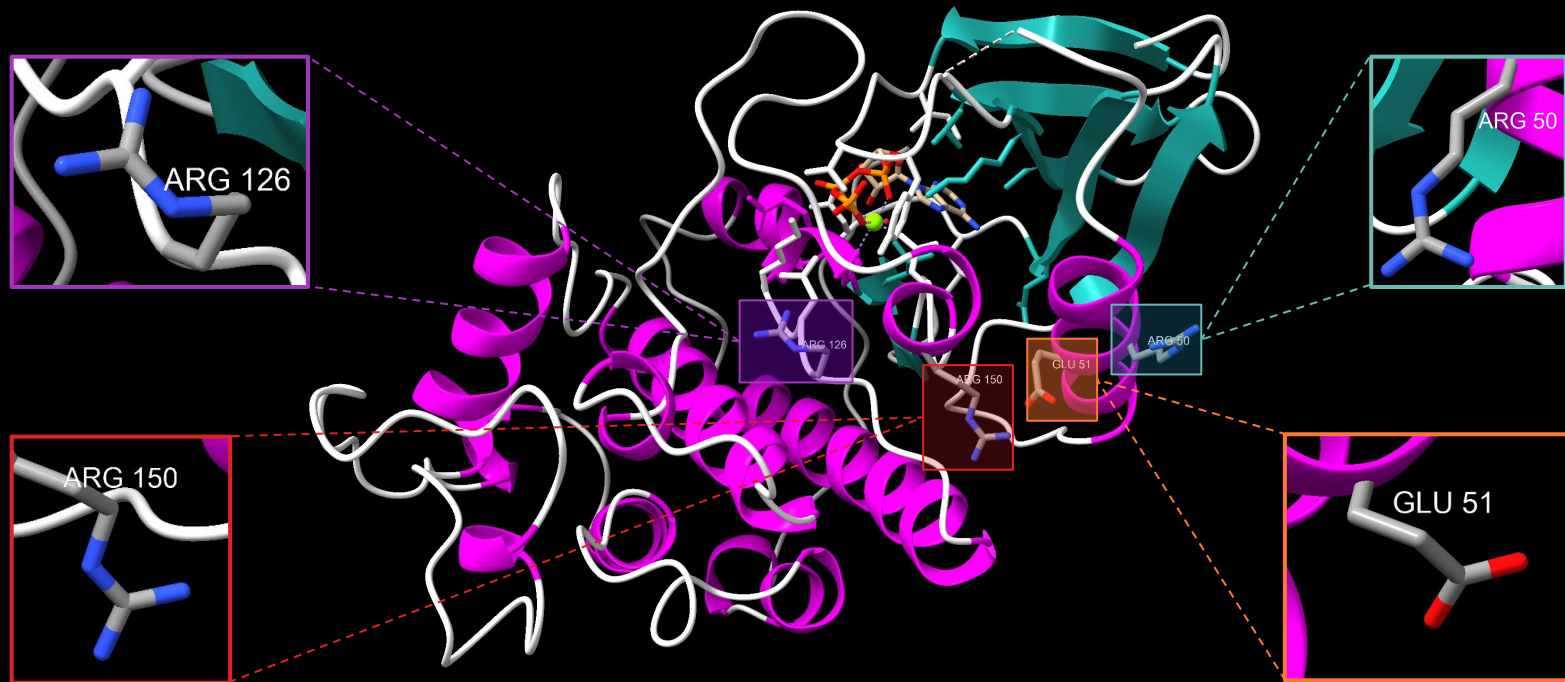
CDK2 /Cyc → Thr160 is exposed and phosphorylated

ATP-binding site

Residues 10-146



Catalytic cleft

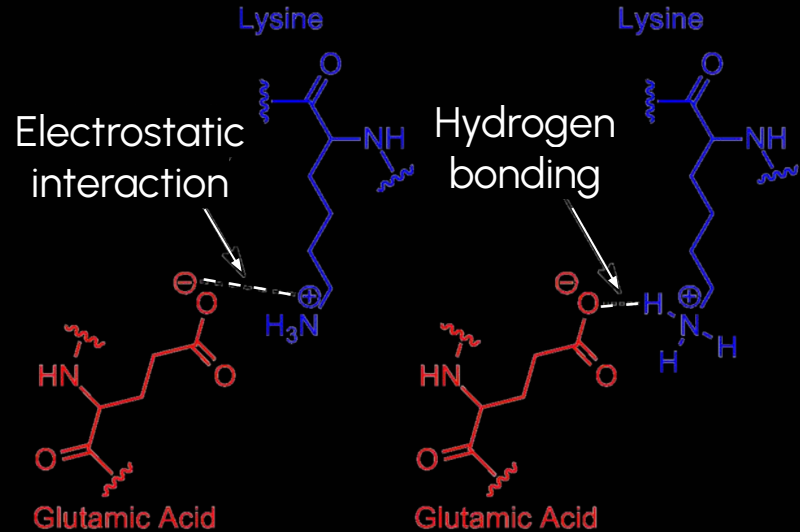


Salt bridges

Non-covalent interactions

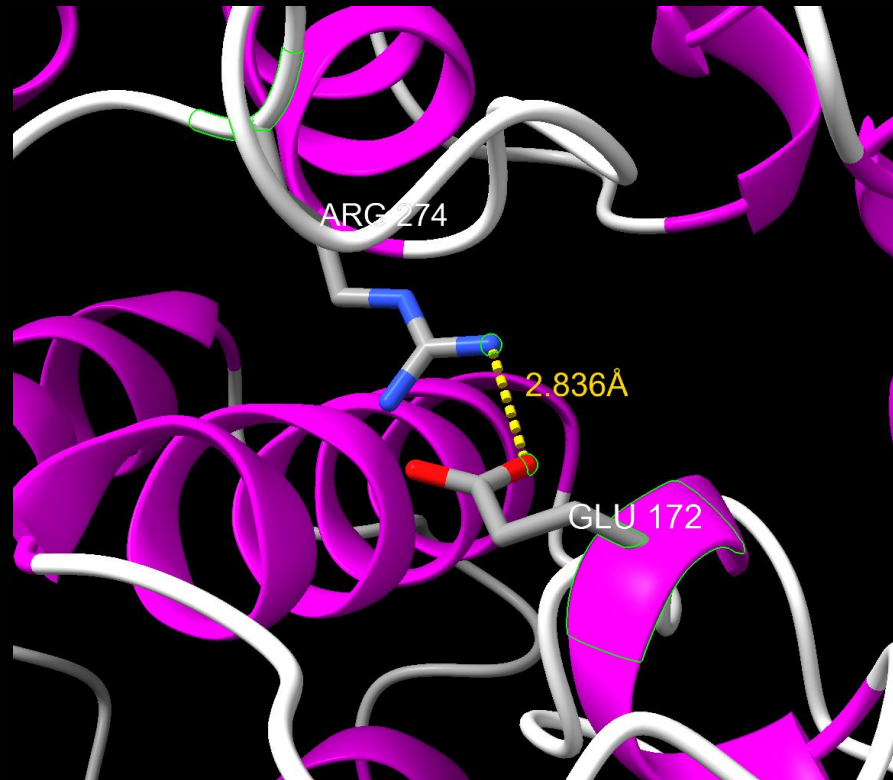
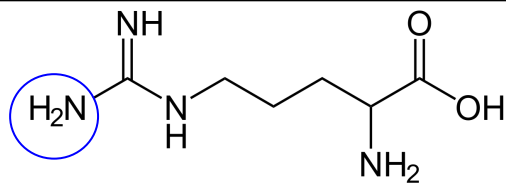
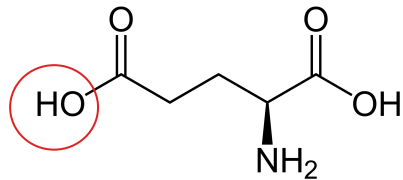
Electrostatic interaction

Hydrogen binding



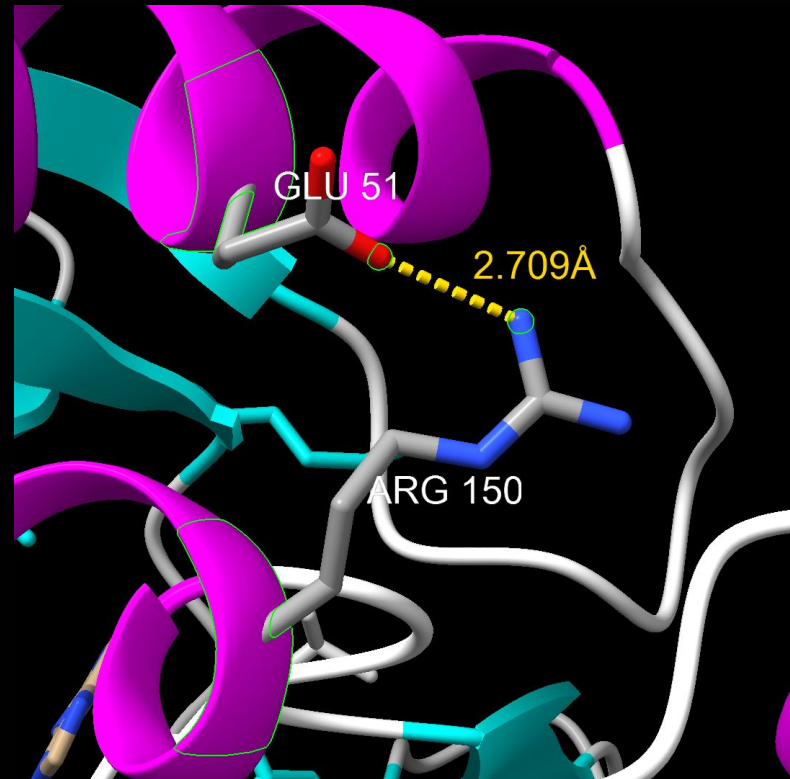
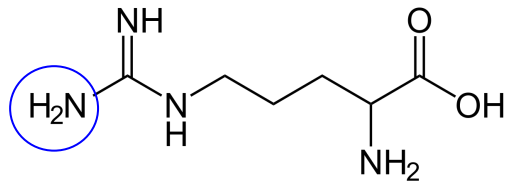
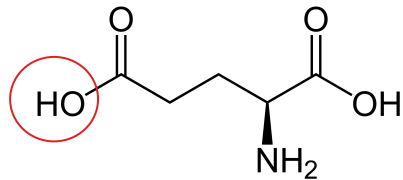
Salt bridges

Glu172 - Arg274



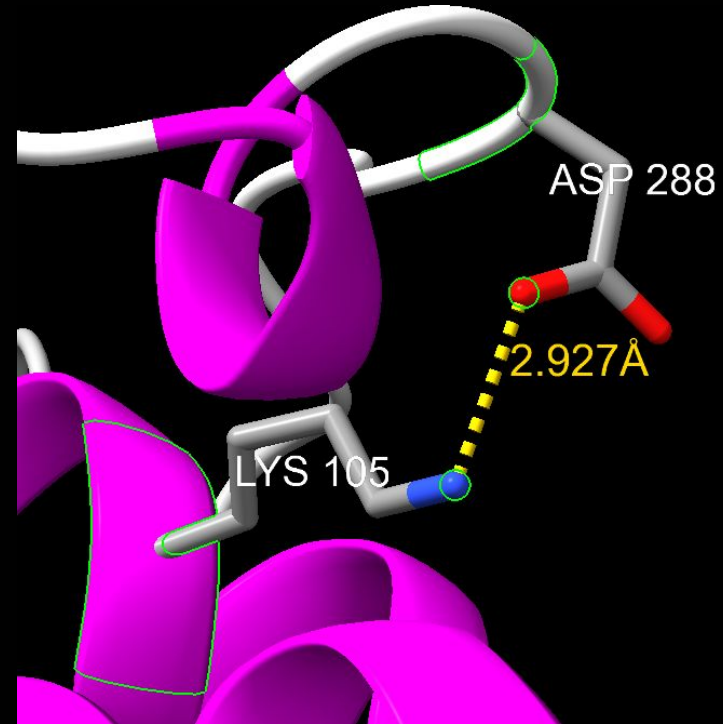
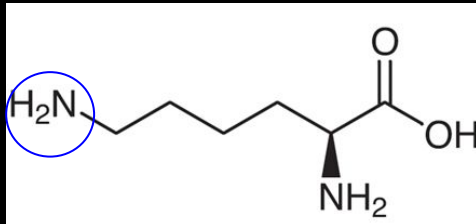
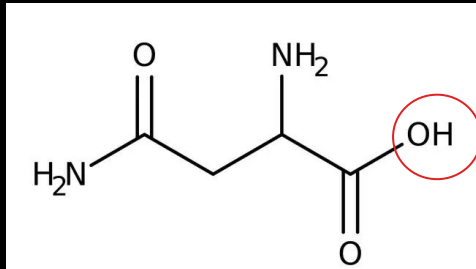
Salt bridges

Glu51-Arg150



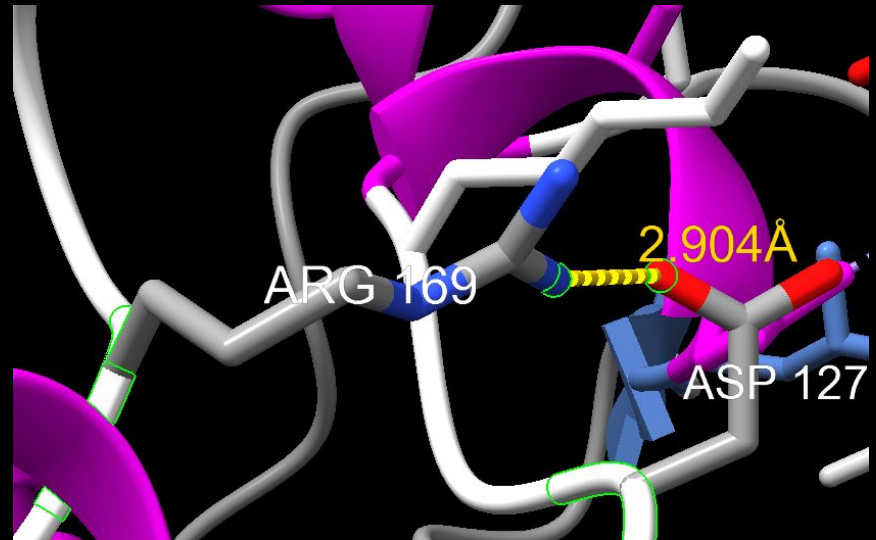
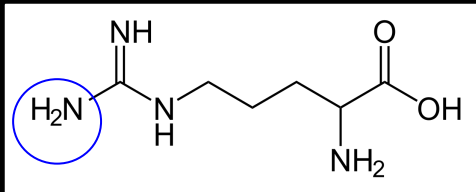
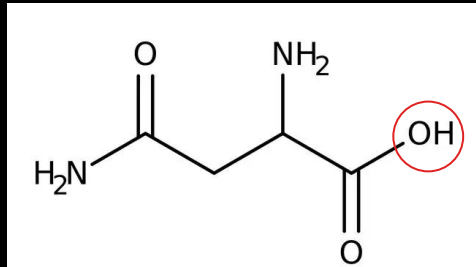
Salt bridges

Asp288-Lys105



Salt bridges

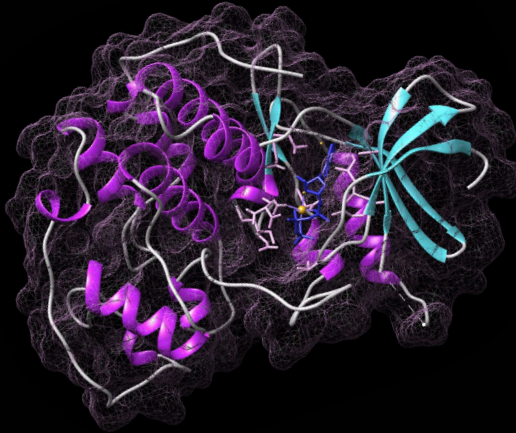
Asp127-Arg169



03

INTERACTIONS WITH LIGANDS

With cyclins and inhibitors



Interactions

Mg^{2+} (inorganic cofactor):

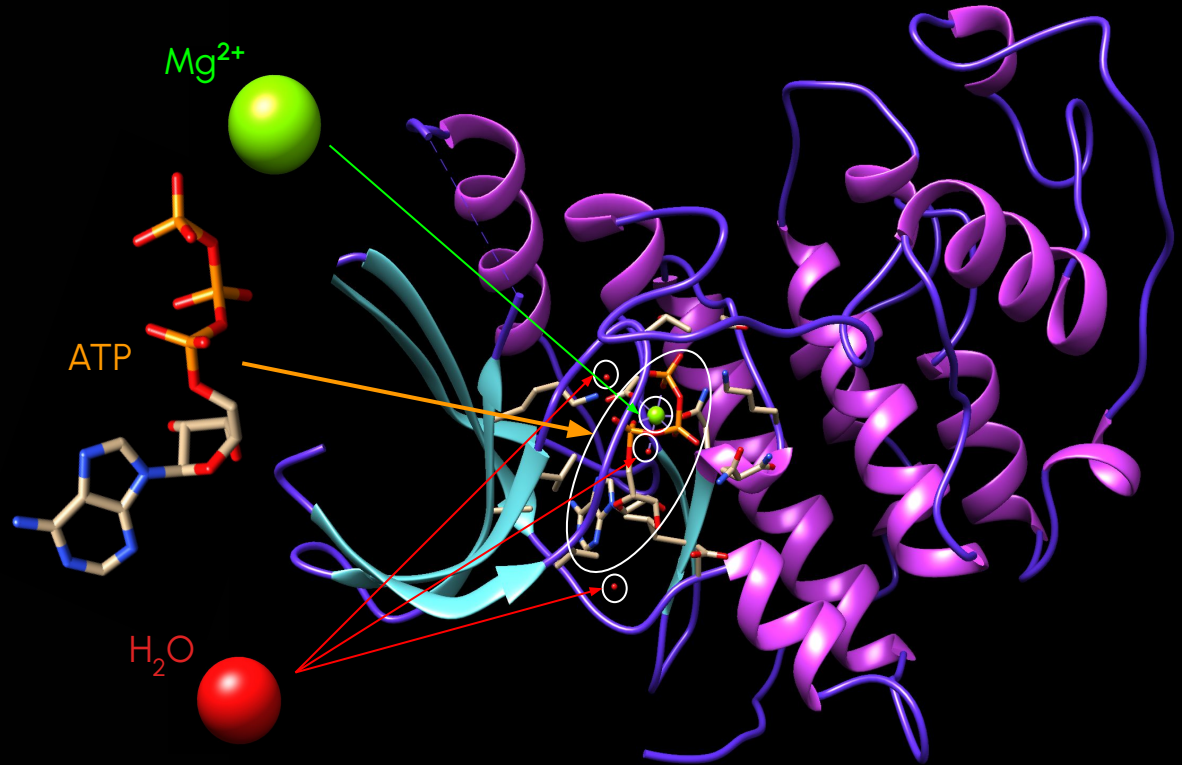
- Coordinates the phosphates groups of ATP (Metal Complex Interactions)
- Facilitates the phosphate transfer

ATP:

- Primary substrate for kinase activity
- Binds for phosphoryl transfer

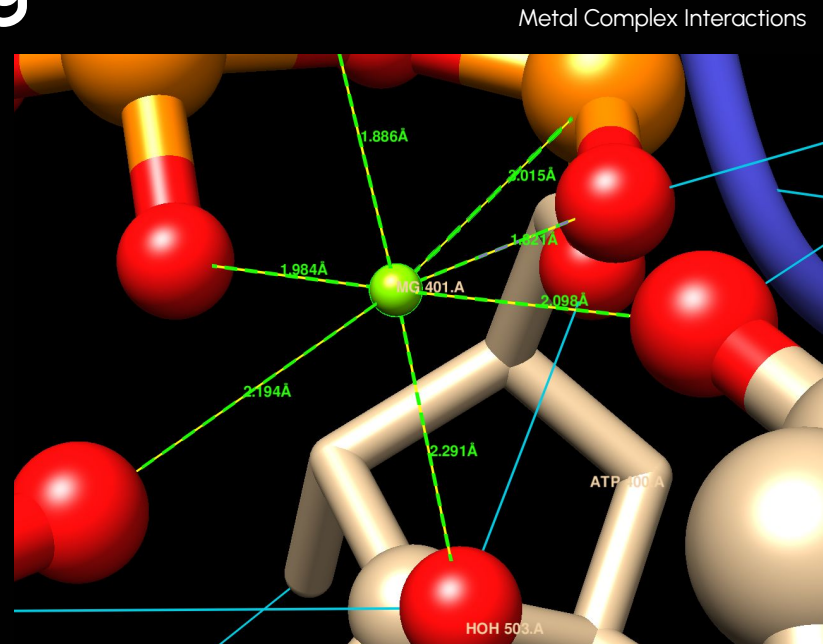
H_2O :

- Forms H bonds
- Stabilize ATP binding



01 Interaction with Mg^{2+}

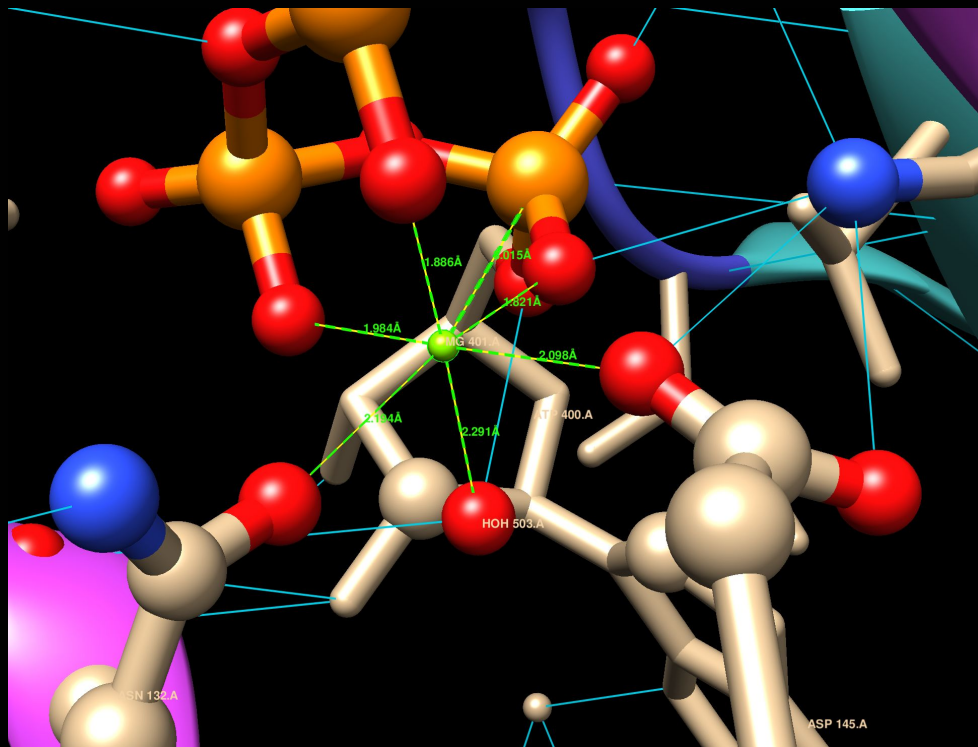
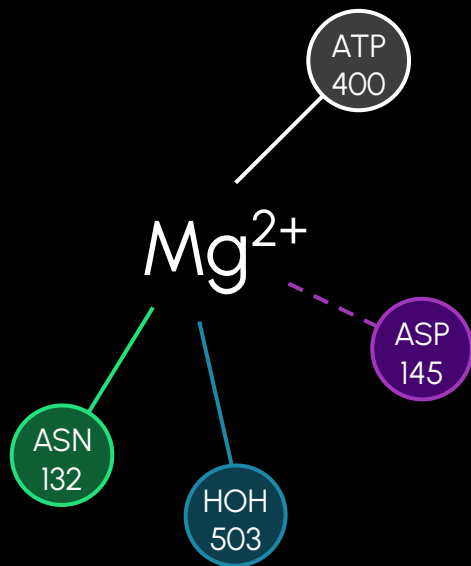
Binds to:			Distance	
Mg^{2+} 401	1. ASN 132	OD1	2.194 Å	→ Van der Waals
	2. ATP 400	OB2	1.984 Å	
	3. ATP 400	OG1	1.886 Å	
	4. ATP 400	PA	3.015 Å	→ Van der Waals
	5. ATP 400	OA1	1.821 Å	
	6. ASP 145	OD2	2.098 Å	→ Ionic Bond
	7. H2O 503	O	2.291 Å	→ Van der Waals



Mg^{2+} binding site

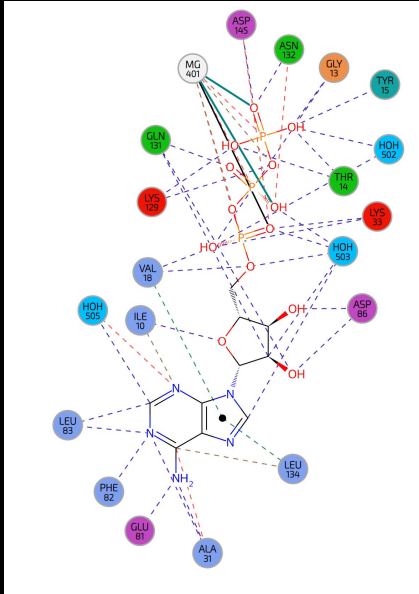
MENFQKVEKIGEGTYGVVYKARNKLTGEVVALKKIRLDTETEGVPSTAIREISLLKELNHPNIVKLLDVIHTENKLYLVFEFLHQDLKKFMDASALTGI
 PLPLIKSYLFQLLQGLAFCHSHRVLHRDLKPQNLLINTEGAIKLADFGLARAFGVPVRTYTHEVVT LWYRAPEILLGCKYYSTAVDIWLSLGCIFAEMV
 TRRALFPGDSEIDQLFRIFRTLGTGPDEVVWPGVTSMPDYKPSFPKWARQDFSKVVPPLDEDGRSLLSQMLHYDPNKRISAKAALAHPPFQDVTKP
 VPHLRRL

01 Interaction with Mg^{2+}

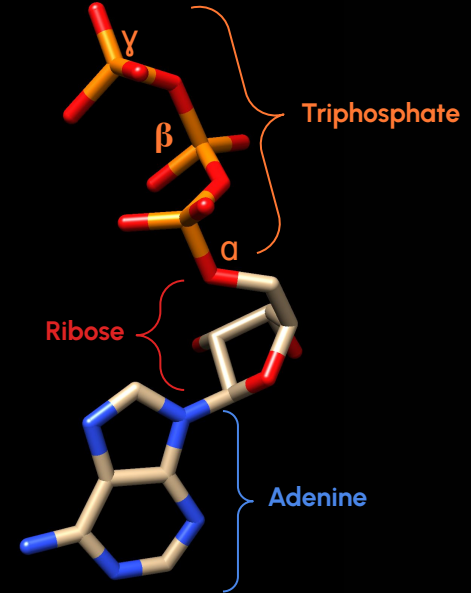
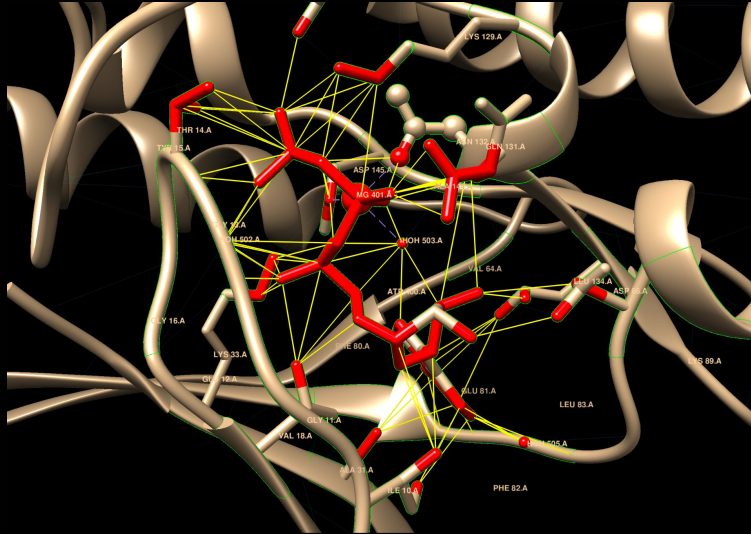


Europe, PDB. in (no date) *MG in pdbechem*, EBI. Available at: <https://www.ebi.ac.uk/pdbe/entry/pdb/lhck/bound/MG#401A> (Accessed: 10 February 2024).

02 Interaction with ATP



Europe, P.D.B. in (no date a) Contain
substructure, EBI. Available at:
[https://www.ebi.ac.uk/pdbe/entry/pdb/1hck/b
ound/ATP#400A](https://www.ebi.ac.uk/pdbe/entry/pdb/1hck/bound/ATP#400A) (Accessed: 10 February
2024).



02

Van der Waals

→ Ionic Bond

ATP Binding site

MENFQKVEK**IGEGTYGVV**YKARNKLTGEVVAL**KK**IRLDTETEGVPSTAIREISLLKELNHPNIVKLLDVIHTENKLYLVF**EFL**HQ**D**LKKFMDASALTGI
 PLPLIKSYLFQLLQGLAFCHSHRVLHRDL**KPQN**LLINTEGAIKLAD**F**GLARAFGVPVRTYTHEVVTLWYRAPEILLGCKYYSTAVDIWSLGCIFAEMV
 TRRALFPGDSEIDQLFRIFRTLGTDPDEVWPGVTSMPDYKPSFPKWARQDFSKVVPPLDEDGRSLLSQMLHYDPNKRISAKAALAHPPFFQDVTKP
 VPHLR**L**

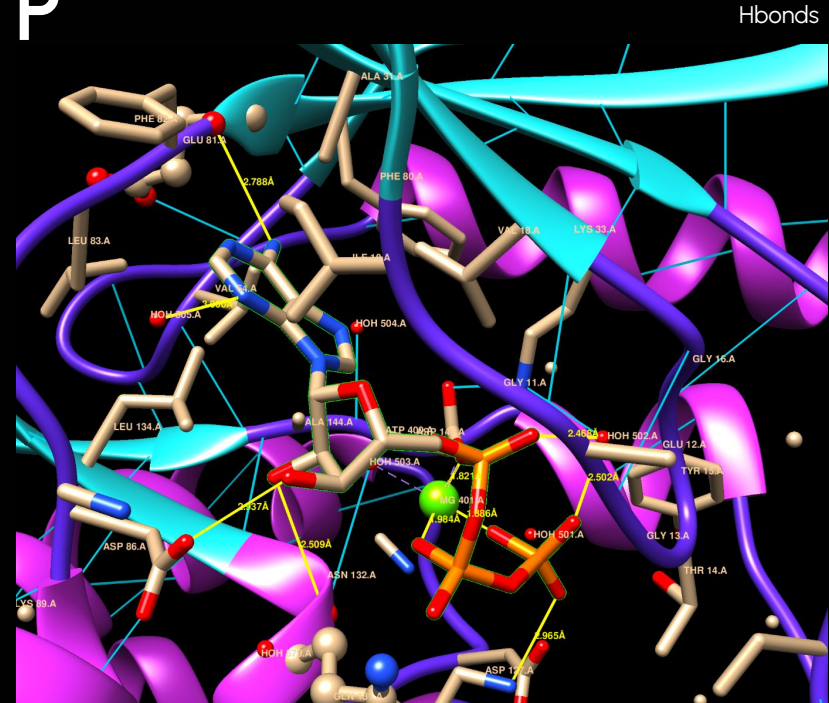


02 Interaction with ATP

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

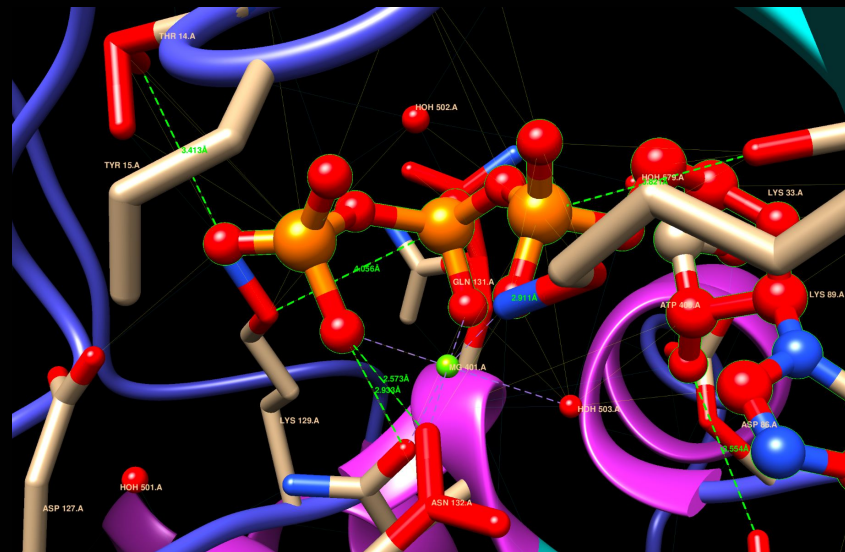
ATP Binding site

MENFQKVEKIGEGTYGVVYKARNKLTGEVVALKKIRLDTETEGVPSTAIREISLLKELNHPNIVKLLDVIHTENKLYLVFEFLHQDLKKFMDASALTGI
 PLPLIKSYLFQLLQGLAFCHSHRVLHRDLKPQNLLINTEGAIKLADFGLARAFGVPVRTYTHEVTLWYRAPEILLGCKYYSTAVDIWLSLGCIFAEMV
 TRRALFPGDSEIDQLFRIFRTLGTGPDEVVWPGVTSMPDYKPSFPKWARQDFSKVVPLDEDGRSLLSQMLHYDPNKRISAKAALAHPPFQDVTKP
 VPHLRRL



02 Interaction with ATP

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

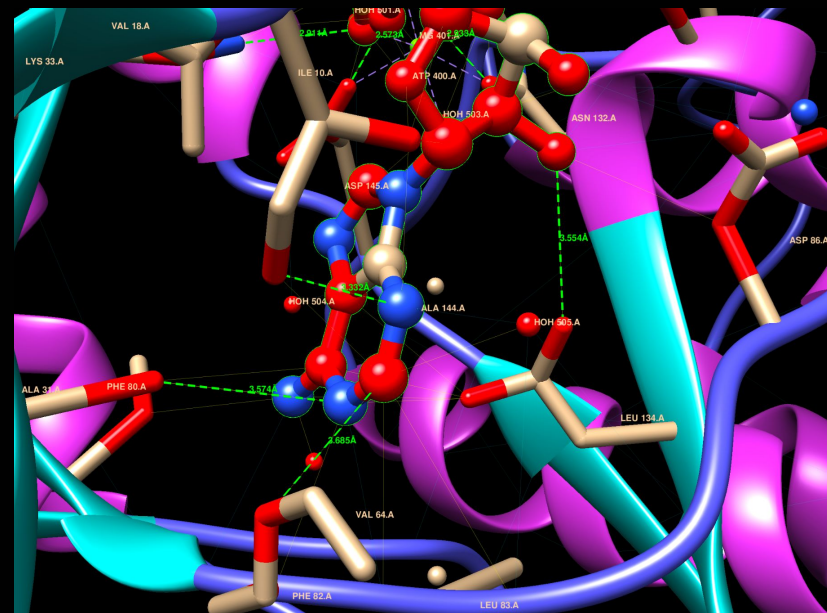


ATP Binding site

MENFQKVEKIGEGTYGVVYKARNKLTGEVVALKKIRLDTETEGVPSTAIREISLLKELNHPNIVKLLDVIHTENKLYLVFEFLHQDLKKFMDASALTGI
 PLPLIKSYLFQLLQGLAFCHSHRVLHRDLKPQNLLINTEGAIKLADFGLARAFGVPVRTYTHEVVTWYRAPEILLGCKYYSTAVDIWVSLGCIFAEMV
 TRRALFPGDSEIDQLFRIFRTLGTGPDEVVWPGVTSMPDYKPSFPKWARQDFSKVVPPLDEDGRSLLSQMLHYDPNKRISAKAALAHPPFQDVTKP
 VPHLRL

02 Interaction with ATP

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



ATP Binding site

MENFQKVEKIGEGTYGVVYKARNKLTGEVVALKKIRLDTETEGVPSTAIREISLLKELNHPNIVKLLDVIHTENKLYLVFEFLHQDLKKFMDASALTGI
 PLPLIKSYLFQLLQGLAFCHSHRVLHRDLKPQNLLINTEGAIKLADFGLARAFGVPVRTYTHEVTLWYRAPEILLGCKYYSTAVDIWVSLGCIFAEMV
 TRRALFPGDSEIDQLFRIFRTLGTGPDEVVWPGVTSMPDYKPSFPKWARQDFSKVVPLDEDGRSLLSQMLHYDPNKRISAKAALAHPPFQDVTKP
 VPHRLRL

03

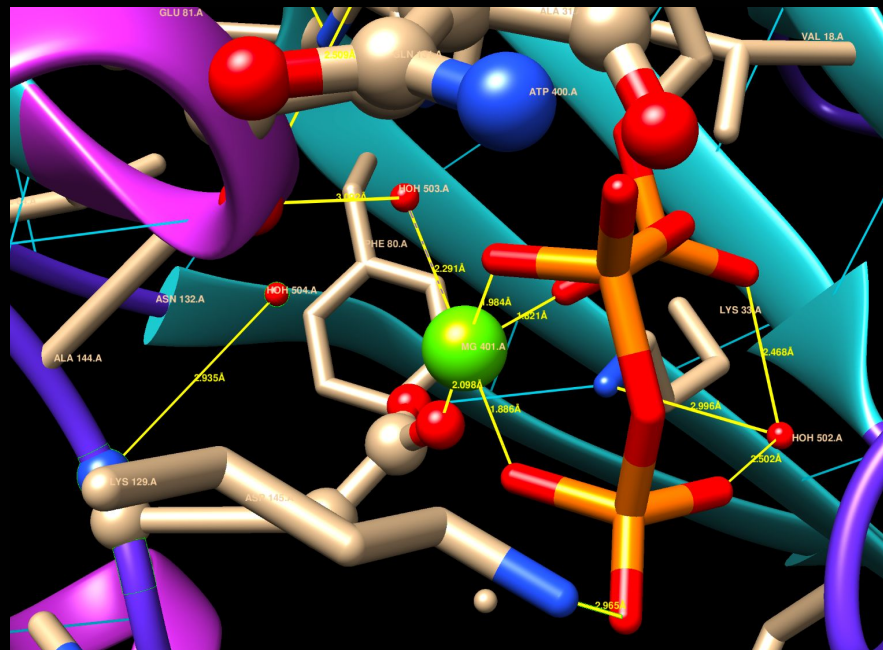
Interaction with H₂O

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

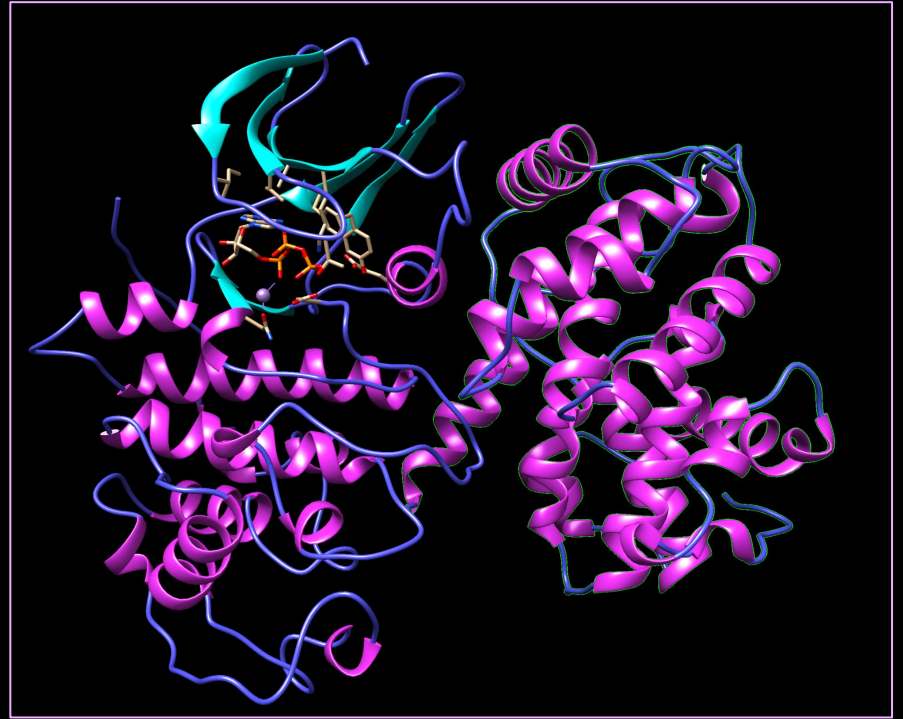
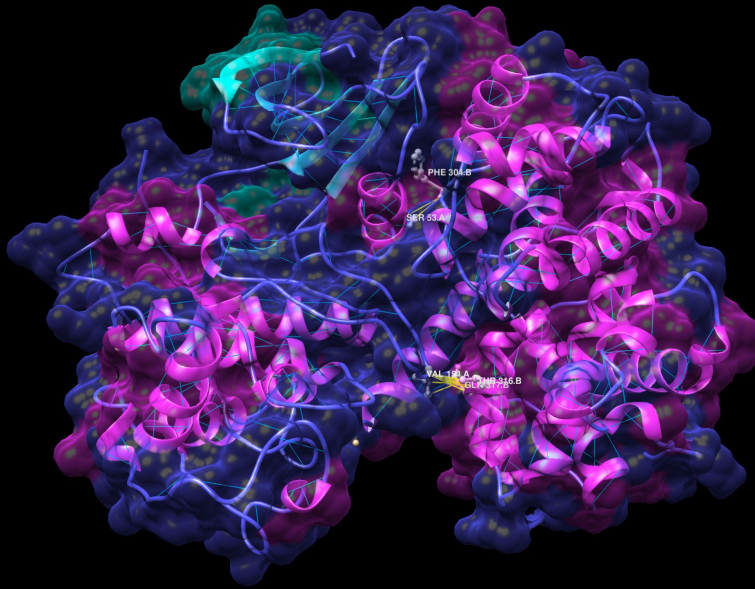
} Hbonds

Active site, proton acceptor

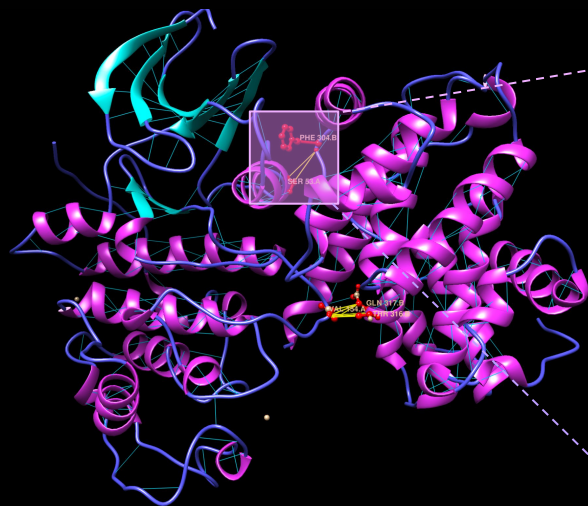
MENFQKVEKIGEGTYGVVYKARNKLTGEVVALKKIRLDTETEGVPSTAIREISLLKELNHPNIVKLLDVIHTENKLYLVFEFLHQDLKKFMDASALTGI
 PLPLIKSYLFQLLQGLAFCHSHRVLHRD LKPQNLLINTEGAIKLADFGRLARAFGVPVRTYTHEVVT LWYRAPEILLGCKYYSTAVDIWLSLGCIFAEMV
 TRRALFPGDSEIDQLFRIFRTLGTGPDEVVWPGVTSMPDYKPSFPKWARQDFSKVVPPLDEDGRSLLSQMLHYDPNKRISAKAALAHPPFQDVTKP
 VPHLR



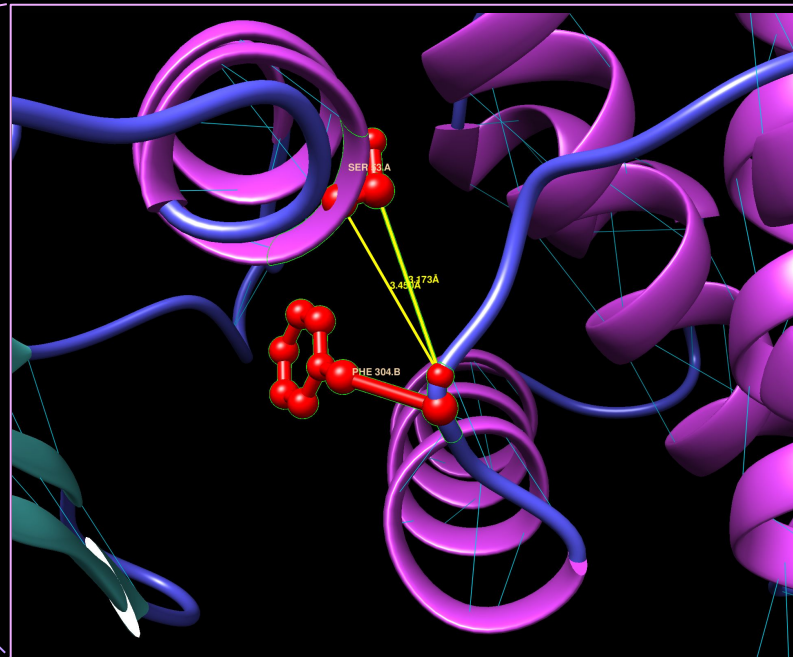
CDK2/Cyclin A Complex



CDK2/Cyclin A Complex

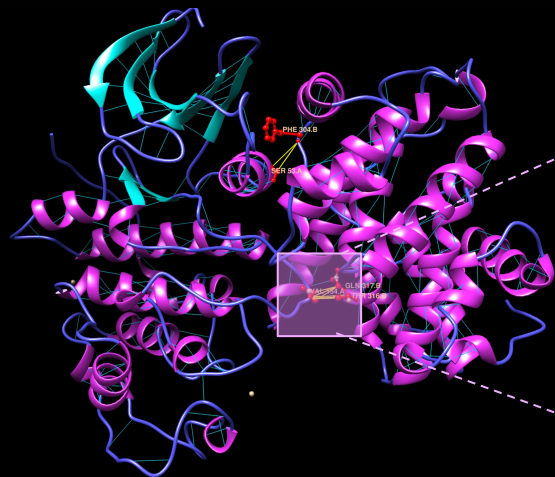


Hydrophobic interactions

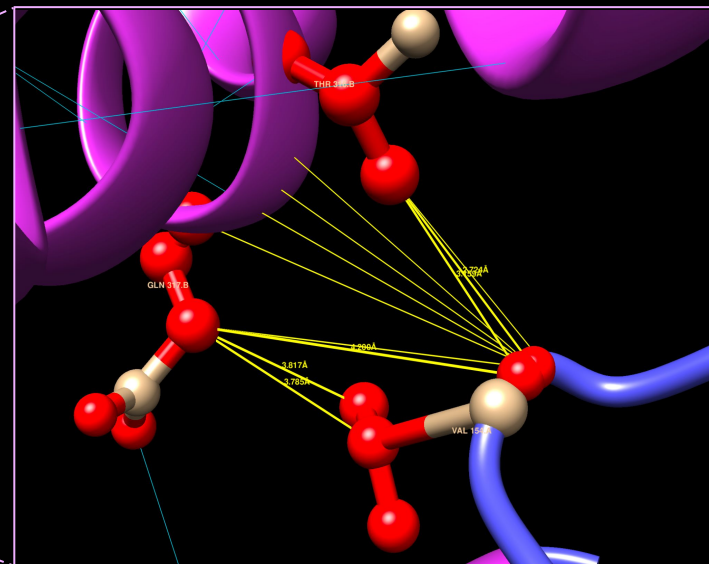


CDK2	Cyclin A	Distance
SER 53.A (CB)	PHE 304.B (CA)	3.173 Å
SER 53.A (CA)	PHE 304.B (CA)	3.450 Å

CDK2/Cyclin A Complex



Hydrophobic interactions



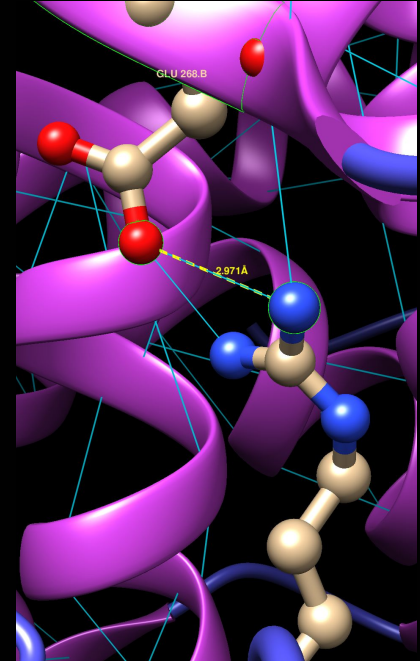
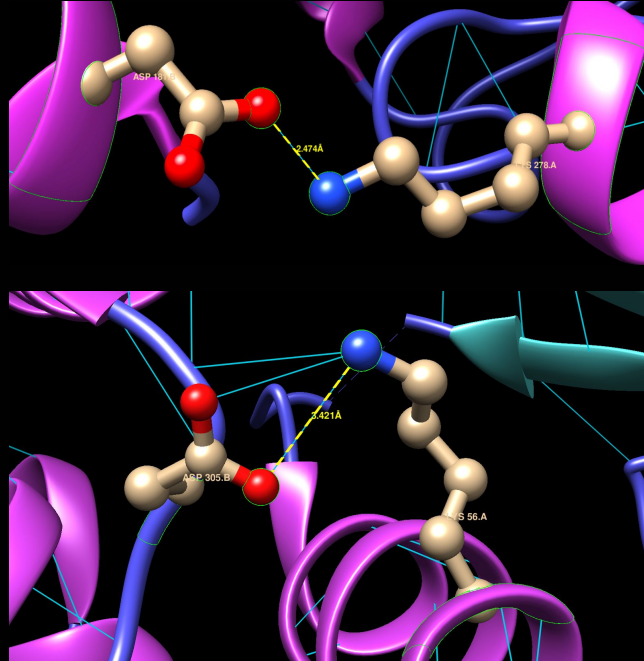
CDK2	Cyclin A	Distance
VAL 154.A (CB)	GLN 317.B (CG)	3.785 Å
VAL 154.A (CG1)	GLN 317.B (CG)	3.817 Å
VAL 154.A (C)	GLN 317.B (CG)	4.200 Å

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

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]

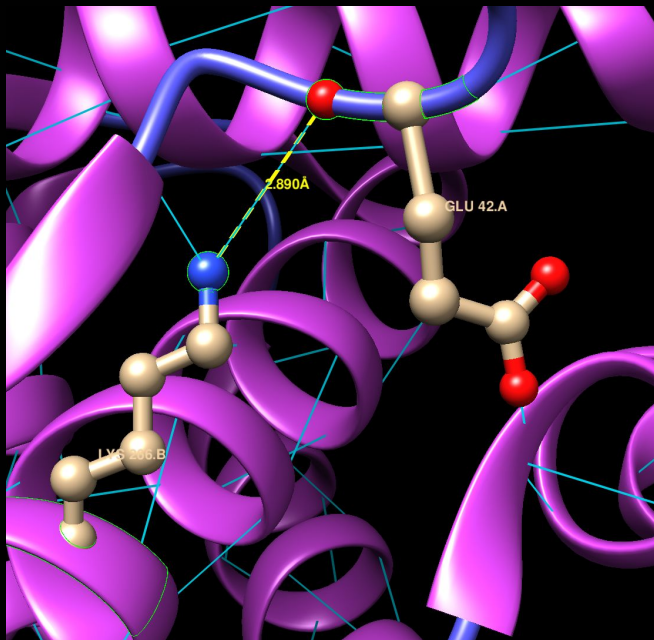
CDK2/Cyclin A Complex

Hydrogen bonds

B:LYS 266[NZ]

2.89

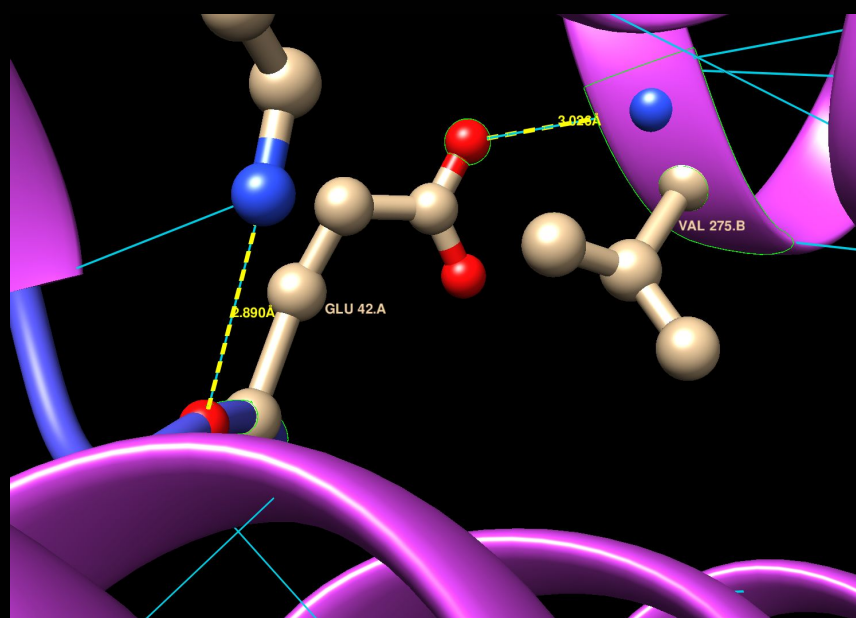
A:GLU 42[O 1]



B:VAL 275[N 1]

3.03

A:GLU 42[OE1]



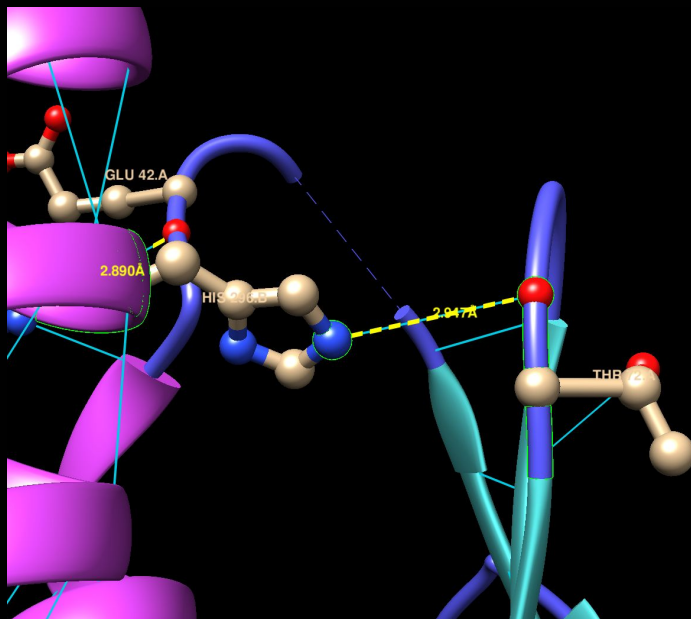
CDK2/Cyclin A Complex

Hydrogen bonds

B:HIS 296[NE2]

2.95

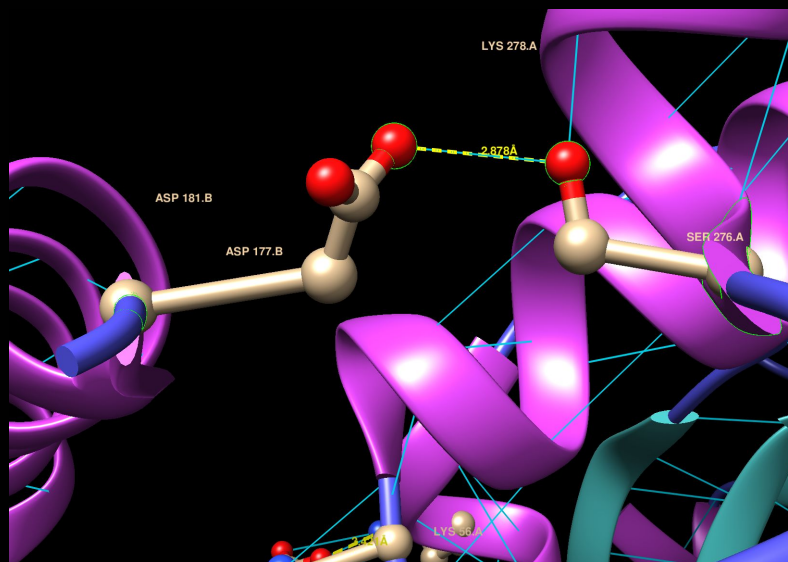
A:THR 72[O]



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

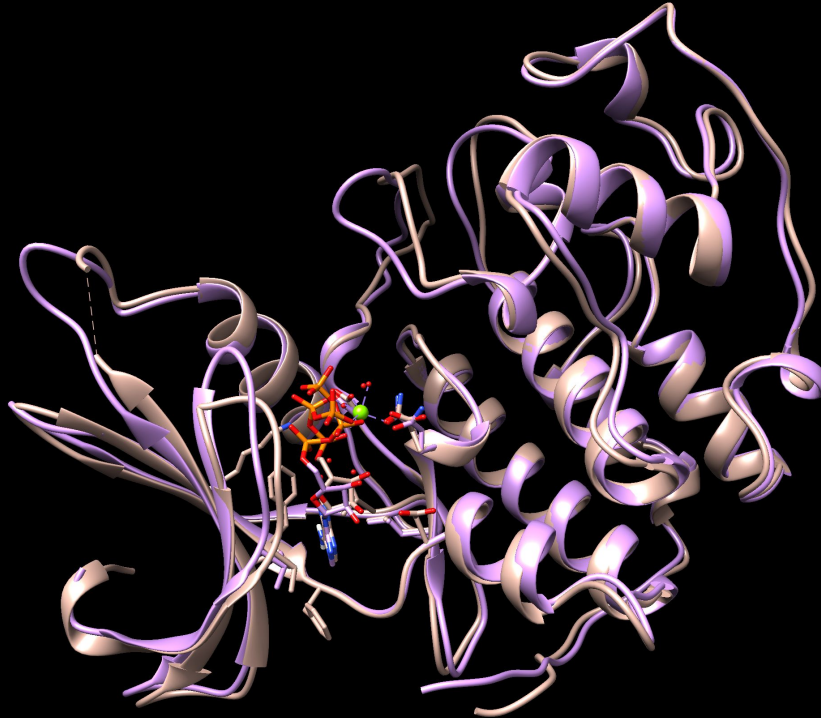
Main differences:

- a helix & β -sheet reorientation
- PSTAIRE against the β -sheet
- Reorientation of Ile49 and Glu51 (Lys33)
- α 12 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:

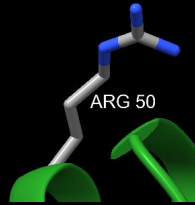
- Glu162 → P-Thr160 (active site cleft)
- Arg50, 126 & 150 CDK interactions (T loop, N and C lobes)
- P-Thr160 → No Glu12-Thr14 interactions in the activation site

CDK2/Cyclin A

Organizing center

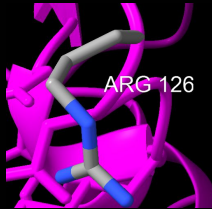
PSTAIRE
(residues 45-51)

Arg50



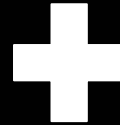
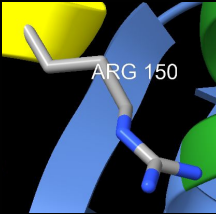
C terminal lobe
(residues 86-298)

Arg126

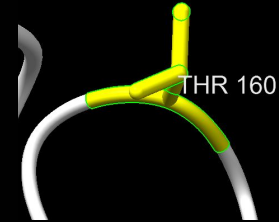


T loop
(residues 150-158)

Arg150



Thr160



Is phosphorylated

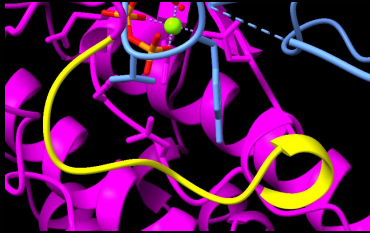


Complete activation of CDK2

CDK2/Cyclin A

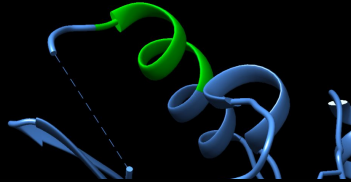
Changes

T loop
(residues 150-158)



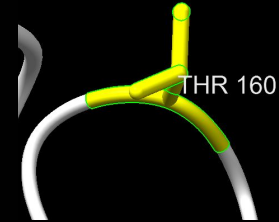
It's exposed to the solvent

PSTAIRE
(residues 45-51)



Rotates 90°

Thr160

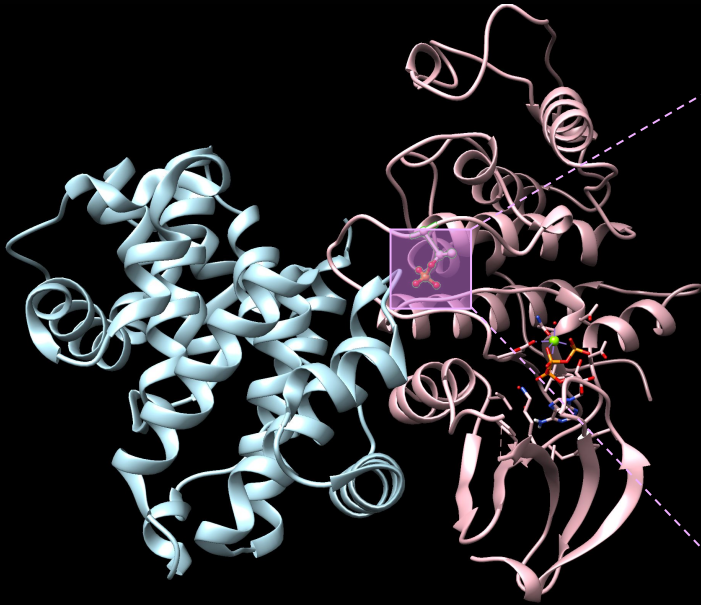


Is phosphorylated

Complete activation of CDK2

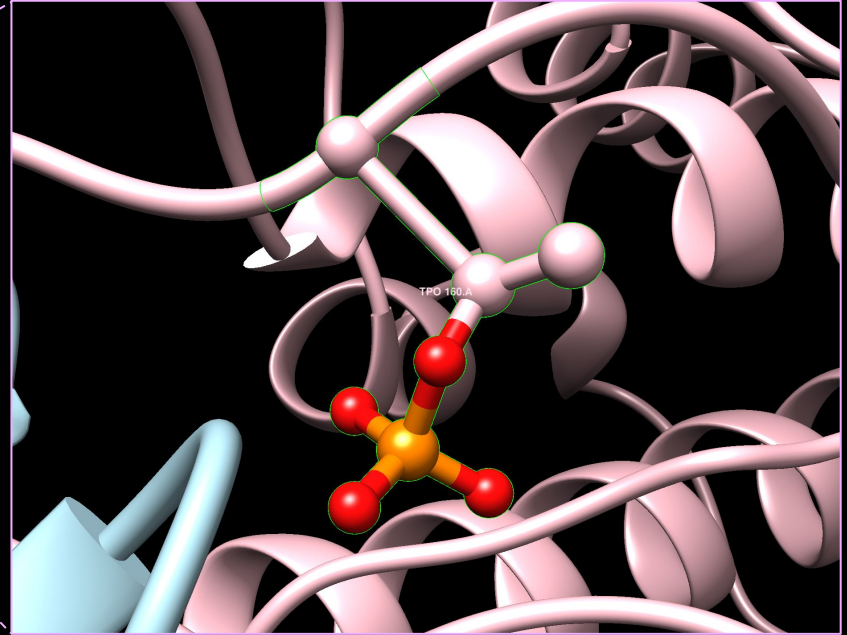
CDK2 activation

Fully activated state + cyclin A



Fully activated cdk2

Cyclin A



Phosphorylated Thr 160

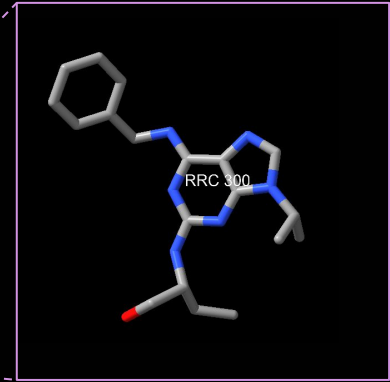
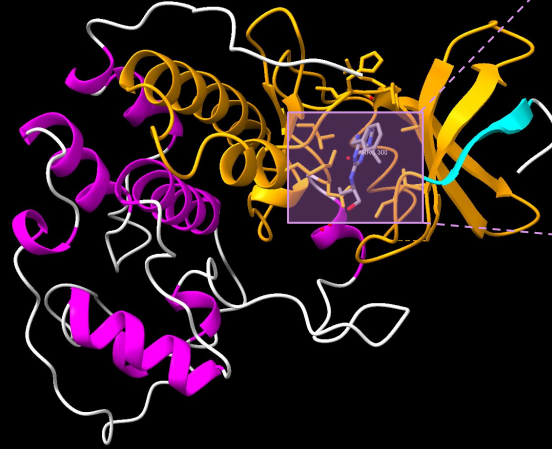
CDK2 interactions with inhibitors

ATP-competitive

Non ATP-competitive

CDK2 interactions with inhibitors

ATP-competitive:
Roscovitine



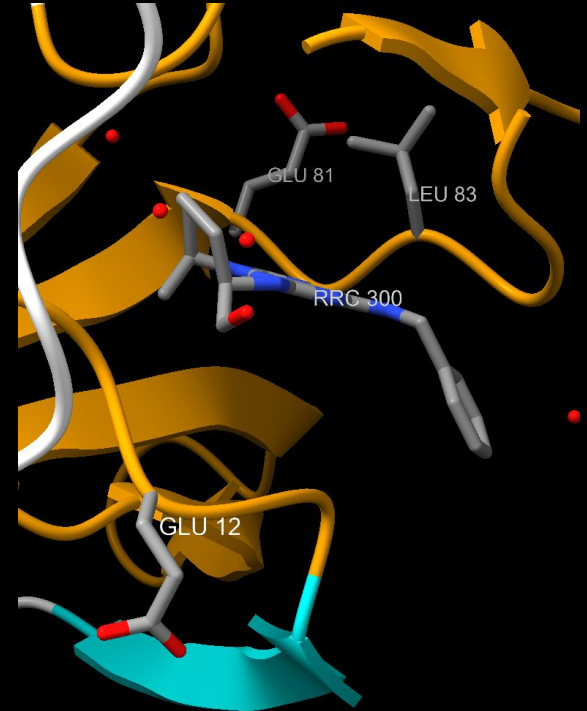
Roscovitine
PDB ID: 2A4L

CDK2 interactions with inhibitors

ATP-competitive: Roscovitine

Hydrogen bonds

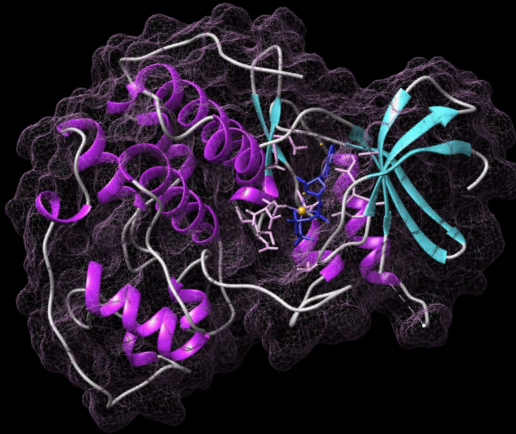
- Leu83 - N7
- Leu83 - NH position 6
- Glu12 - Hydroxybutylamine C2



03

CONSERVATION

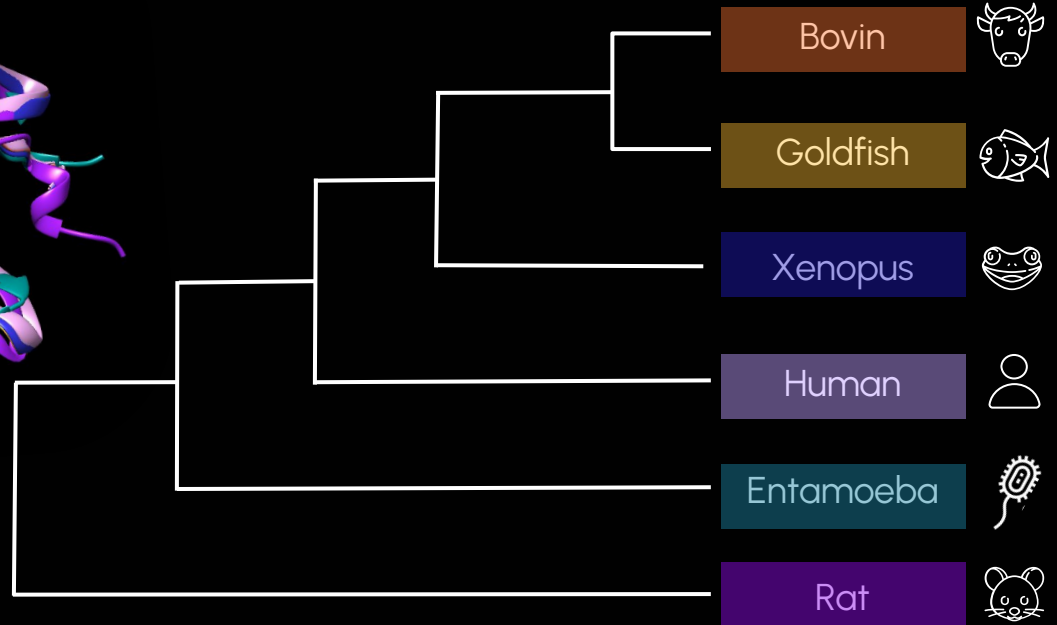
With cyclins and inhibitors



CDK2 between species



Score	9.03
RMSD	1.18



CDK2 between species

Consensus Conservation Q63699 CDK2_RAT Q5E9Y0 CDK2_BOVIN P24941 CDK2_HUMAN P43450 CDK2_CARAU P23437 CDK2_XENLA Q04770 CDK2_ENTH1	1 ME n FQKVEK I MENFQKVEK I MENFQKVEK I MENFQKVEK I MESFQKVEK I MENFQKVEK I MTRYKKKQQL	11 GEGTYGVVYK GEGTYGVVYK GEGTYGVVYK GEGTYGVVYK GEGTYGVVYK GEGTYGVVYK GEGTYGVVCK	21 A k n k I TGE v V AKNKLTGEVV AKNKLTGEVV AKNKLTGEVV AKNKVTGETV ARNRETGEIV AWD TVCNRYV	31 ALKKIRLDTE ALKKIRLDTE ALKKIRLDTE ALKKIRLDTE ALKKIRLDTE ALKKIRLDTE ALKKIKQER	41 TEGVPSTAIR TEGVPSTAIR TEGVPSTAIR TEGVPSTAIR TEGVPSTAIR TEGVPSTAIR DGGIPVTSVR
Consensus Conservation Q63699 CDK2_RAT Q5E9Y0 CDK2_BOVIN P24941 CDK2_HUMAN P43450 CDK2_CARAU P23437 CDK2_XENLA Q04770 CDK2_ENTH1	51 E I S L L K E L N H E I S L L K E L N H E I S L L K E L N H E I S L L K E L N H E I S L L K E L N H E I S L L K E L N H E I A V L L E L K H	61 P N I V K L I D V I PNIVKLLDVI PNIVKLLDVI PNIVKLLDVI PNIVKLLDVI PNIVKLLDVI PNVVDLYDIY	71 H T E N K L Y L V F HTENKLYLVF HTENKLYLVF HTENKLYLVF HTENKLYLVF HTENKLYLVF LEDKFLYLVF	81 E F L h Q D L K K F EFLHQDLKKF EFLHQDLKKF EFLHQDLKKF EFLHQDLKKF EFLHQDLKKF EFCDEDLYQF	91 M D a S a l t G l p MDASALTGLP MDASALTGLP MDASALTGLP MDASALTGLP MDSSVTGTS MDSNIGIS MSRS - - SKIP
Consensus Conservation Q63699 CDK2_RAT Q5E9Y0 CDK2_BOVIN P24941 CDK2_HUMAN P43450 CDK2_CARAU P23437 CDK2_XENLA Q04770 CDK2_ENTH1	101 L p L i K S Y L F Q LPLIKSYLFQ LPLIKSYLFQ LPLIKSYLFQ LPLIKSYLFQ LPLIKSYLFQ LNE TRSIVYQ	111 L L Q G L A F C H S LLQGLAFCHS LLQGLAFCHS LLQGLAFCHS LLQGLAFCHS LLQGLAFCHS LLQGLAFCHY	121 H R V L H R D L K P HRVLHRDLKP HRVLHRDLKP HRVLHRDLKP HRVLHRDLKP HRVLHRDLKP HQILHRDMKP	131 Q N L L I N a e G a QNLLINAEga QNLLINAEga QNLLINAEga QNLLINAEga QNLLINAEga QNLLINKNGT	141 I K L A D F G L A R IKLADFGLAR IKLADFGLAR IKLADFGLAR IKLADFGLAR IKLADFGLAR IKLADFGLAR
Consensus Conservation Q63699 CDK2_RAT Q5E9Y0 CDK2_BOVIN P24941 CDK2_HUMAN P43450 CDK2_CARAU P23437 CDK2_XENLA Q04770 CDK2_ENTH1	151 A F G V P V R T Y T AFGVVVRTYT AFGVVVRTYT AFGVVVRTYT AFGVVVRTYT AFGVVVRTYT LTTINDRKYT	161 H E V V T L W Y R A HEVVTLWYRA HEVVTLWYRA HEVVTLWYRA HEVVTLWYRA HEVVTLWYRA SEVVTLWYRA	171 P E I L L G C K Y Y PEILLGCKYY PEILLGCKYY PEILLGCKYY PEILLGCKYY PEILLGCKYY PEILLGATQY	181 S T A V D I W S L G STAVDIWSLG STAVDIWSLG STAVDIWSLG STAVDIWSLG STAVDIWSLG GGAIDIWSTA	191 C I F A E M i T R r CIFAEMITRR CIFAEMITRR CIFAEMITRR CIFAEMITRR CIFAEMITRR AIFGELINKE

Proton acceptor
conserved in all species

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

CDK2 between species

ATP-binding site

Consensus Conservation Q63699 CDK2_RAT Q5E9Y0 CDK2_BOVIN P24941 CDK2_HUMAN P43450 CDK2_CARAU P23437 CDK2_XENLA Q04770 CDK2_ENTH1	1 M E n F Q K V E K I 51 E I S L L K E L N H 101 L p L i K S Y L F Q 151 A F G V P V R T Y T	11 G E G T Y G V V Y K 61 P N I V K L I D V I 111 L L Q G L A F C H S 161 H E V V T L W Y R A	21 A k n k i T G E v v 71 H T E N K L Y L V F 121 H R V L H R D L K P 171 P E I L L G C K Y y	31 A L K K I R L D T E 81 E F L h Q D L k k F 131 Q N L L I N a e G a 181 S T A V D I W S L G	41 T E G V P S T A I R 91 M D a S a l t G l p 141 I K L A D F G L A R 191 C I F A E M i T r r
Q63699 CDK2_RAT Q5E9Y0 CDK2_BOVIN P24941 CDK2_HUMAN P43450 CDK2_CARAU P23437 CDK2_XENLA Q04770 CDK2_ENTH1	M E N F Q K V E K I M E N F Q K V E K I M E N F Q K V E K I M E S F Q K V E K I M E N F Q K V E K I M T R Y E K K Q Q E I S L L K E L N H E I S L L K E L N H E I S L L K E L N H E I S L L K E L N H E I S L L K E L N H E I A V L L E L K H L P L I K S Y L F Q L P L I K S Y L F Q L P L I K S Y L F Q L P L V K S Y L F Q L A L V K S Y L F Q I N E T R S I V Y Q A F G V P V R T Y T A F G V P V R T Y T A F G V P V R T Y T A F G V P V R T Y T A F G V P V R T F T L T T I N D R K Y T	G E G T Y G V V Y K G E G T Y G V V Y K G E G T Y G V V Y K G E G T Y G V V Y K G E G T Y G V V Y K G E G T Y G V V C K P N I V K L I D V I P N I V K L L D V I P N I V K L L D V I P N I V K L L D V I P N I V K L L D V I P N V V D L Y D I Y L L Q G L A F C H S L L Q G L A F C H S L L Q G L A F C H S L L Q G L A F C H S L L Q G L A F C H S I L Q G L A F C H Y H E V V T L W Y R A H E V V T L W Y R A H E V V T L W Y R A H E V V T L W Y R A H E V V T L W Y R A S E V V T L W Y R A	A k n k i T G E v v A K N K L T G E V V A K N K L T G E V V A R N K V T G E T V A R N R E T G E I V A W D T V C N R Y V H T E N K L Y L V F H T E N K L Y L V F H T E N K L Y L V F H T E N K L Y L V F H T E N K L Y L V F L E D K F L Y L V F H R V L H R D L K P H R V L H R D L K P H R V L H R D L K P H R V L H R D L K P H R V L H R D L K P H Q I L H R D M K P P E I L L G C K Y y P E I L L G C K Y Y P E I L L G C K Y Y P E I L L G C K Y Y P E I L L G C K F Y P E I L L G A T Q Y	A L K K I R L D T E A L K K I R L D T E A L K K I R L D T E A L K K I R L D T E A L K K I R L D T E A L K K I K Q E R E E F L h Q D L k k F E F L h Q D L K K F E F L h Q D L K K F E F L h Q D L K K F E F L h Q D L K K F E F D E D L Y Q F Q N L L I N a e G a Q N L L I N A E G S Q N L L I N A D G S Q N L L I N T E G A Q N L L I N A Q G E Q N L L I N S D G A Q N I L I N K N G T S T A V D I W S L G S T A V D I W S L G S T A V D I W S L G S T A V D I W S L G S T A V D I W S L G G G A I D I W S T A	T E G V P S T A I R T E G V P S T A I R T E G V P S T A I R T E G V P S T A I R T E G V P S T A I R D D G I P V T S V R M D a S a l t G l p M D A S A L T G L P M D A S A L T G L P M D A S A L T G I P M D S S T V T G I S M D G S N I S G I S M S R S - - S K I p I K L A D F G L A R I K L A D F G L A R I K L A D F G L A R I K L A D F G L A R I K L A D F G L A R I K L G D F G L A R C I F A E M i T r r C I F A E M V T R R C I F A E M V T R R C I F A E M V T R R C I F A E M I T R K C I F A E M I T R R A I F G E L I N K E

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

Consensus Conservation Q63699 CDK2_RAT Q5E9Y0 CDK2_BOVIN P24941 CDK2_HUMAN P43450 CDK2_CARAU P23437 CDK2_XENLA Q04770 CDK2_ENTH1	1 ME n FQKVEK I MENFQKVEK I MENFQKVEK I MENFQKVEK I MESFQKVEK I MENFQKVEK I MTRYKKKQQL	11 GEGTYGVVYK GEGTYGVVYK GEGTYGVVYK GEGTYGVVYK GEGTYGVVYK GEGTYGVVYK GEGTYGVVYK	21 A k n k I T G E v V AKNKLTGEVV AKNKLTGEVV AKNKLTGEVV AKNKVTGETV ARNRETGEIV AWDTVCNRYV	31 ALKKIRLDTE ALKKIRLDTE ALKKIRLDTE ALKKIRLDTE ALKKIRLDTE ALKKIRLDTE ALKKIKQER	41 TEGVPSTAIR TEGVPSTAIR TEGVPSTAIR TEGVPSTAIR TEGVPSTAIR TEGVPSTAIR DGGIPVTSVR
Consensus Conservation Q63699 CDK2_RAT Q5E9Y0 CDK2_BOVIN P24941 CDK2_HUMAN P43450 CDK2_CARAU P23437 CDK2_XENLA Q04770 CDK2_ENTH1	51 E I S L L K E L N H EISLLKELNH EISLLKELNH EISLLKELNH EISLLKELNH EISLLKELNH EIAVLLLELKH	61 P N I V K L I D V I PNIVKLLDVI PNIVKLLDVI PNIVKLLDVI PNIVKLLDVI PNIVKLLDVI PNVVDLYDIY	71 H T E N K L Y L V F HTENKLYLVF HTENKLYLVF HTENKLYLVF HTENKLYLVF HTENKLYLVF LEDKFLYLVF	81 E F L h Q D L K K F EFLHQDLKKF EFLHQDLKKF EFLHQDLKKF EFLHQDLKKF EFLHQDLKKF EFCDEDLQF	91 M D a S a l t G l p MDASALTGLP MDASALTGLP MDASALTGLP MDASALTGLP MDSSSTVTGIS MDSNISGIS MSRS - - SKIP
Consensus Conservation Q63699 CDK2_RAT Q5E9Y0 CDK2_BOVIN P24941 CDK2_HUMAN P43450 CDK2_CARAU P23437 CDK2_XENLA Q04770 CDK2_ENTH1	101 L p L i K S Y L F Q LPLIKSYLFQ LPLIKSYLFQ LPLIKSYLFQ LPLIKSYLFQ LPLIKSYLFQ LNETRSIVYQ	111 L L Q G L A F C H S LLQGLAFCHS LLQGLAFCHS LLQGLAFCHS LLQGLAFCHS LLQGLAFCHS LLQGLAFCHY	121 H R V L H R D L K P HRVLHRDLKP HRVLHRDLKP HRVLHRDLKP HRVLHRDLKP HRVLHRDLKP HQILHRDMKP	131 Q N L L I N a e G a QNLLINAEga QNLLINAEga QNLLINAEga QNLLINAEga QNLLINAEga QNLLINKNGT	141 I K L A D F G L A R IKLADFGLAR IKLADFGLAR IKLADFGLAR IKLADFGLAR IKLADFGLAR IKLADFGLAR
Consensus Conservation Q63699 CDK2_RAT Q5E9Y0 CDK2_BOVIN P24941 CDK2_HUMAN P43450 CDK2_CARAU P23437 CDK2_XENLA Q04770 CDK2_ENTH1	151 A F G V P V R T Y T AFGVVVRTYT AFGVVVRTYT AFGVVVRTYT AFGVVVRTYT AFGVVVRTYT LTTINDRKYT	161 H E V V T L W Y R A HEVVTLWYRA HEVVTLWYRA HEVVTLWYRA HEVVTLWYRA HEVVTLWYRA SEVVTLWYRA	171 P E I L L G C K Y Y PEILLGCKYY PEILLGCKYY PEILLGCKYY PEILLGCKYY PEILLGCKYY PEILLGATQY	181 S T A V D I W S L G STAVDIWSLG STAVDIWSLG STAVDIWSLG STAVDIWSLG STAVDIWSLG GGAIDIWSTA	191 C I F A E M i T R r CIFAEMITRR CIFAEMITRR CIFAEMITRR CIFAEMITRR CIFAEMITRR AIFGELINKE

Hinge region mostly
conserved in all species

CDK2 between species

Activation of CDK2

Consensus Conservation Q63699 CDK2_RAT Q5E9Y0 CDK2_BOVIN P24941 CDK2_HUMAN P43450 CDK2_CARAU P23437 CDK2_XENLA Q04770 CDK2_ENTH1	1 M E n F Q K V E K I M E N F Q K V E K I M E N F Q K V E K I M E S F Q K V E K I M E N F Q K V E K I M T R Y E K K Q Q L	11 G E G T Y G V V Y K G E G T Y G V V Y K G E G T Y G V V Y K G E G T Y G V V Y K G E G T Y G V V Y K G E G T Y G V V C K	21 A k n k i T G E v v A K N K L T G E V V A K N K L T G E V V A K N K L T G E V V A K N K V T G E T V A W D T V C N R Y V	31 A L K K I R L D T E A L K K I R L D T E A L K K I R L D T E A L K K I R L D T E A L K K I R L D T E A L K K I K Q E R E	41 T E G V P S T A I R T E G V P S T A I R T E G V P S T A I R T E G V P S T A I R T E G V P S T A I R D D G I L V T S V R
Consensus Conservation Q63699 CDK2_RAT Q5E9Y0 CDK2_BOVIN P24941 CDK2_HUMAN P43450 CDK2_CARAU P23437 CDK2_XENLA Q04770 CDK2_ENTH1	51 E I S L L K E L N H E I S L L K E L N H E I S L L K E L N H E I S L L K E L N H E I S L L K E L N H E I A V L L E L K H	61 P N I V K L I D V I P N I V K L L D V I P N I V K L L D V I P N I V K L L D V I P N I V K L L D V I P N V V D L Y D I Y	71 H T E N K L Y L V F H T E N K L Y L V F H T E N K L Y L V F H T E N K L Y L V F H T E N K L Y L V F L E D K F L Y L V F	81 E F L h Q D L K k F E F L H Q D L K K F E F L H Q D L K K F E F L H Q D L K K F E F L H Q D L K K F E F C D E D L Y Q F	91 M D a S a l t G l p M D A S A L T G L P M D A S A L T G L P M D A S A L T G L P M D S S T V T G I S M D G S N I S G I S M S R S - - S K I P
Consensus Conservation Q63699 CDK2_RAT Q5E9Y0 CDK2_BOVIN P24941 CDK2_HUMAN P43450 CDK2_CARAU P23437 CDK2_XENLA Q04770 CDK2_ENTH1	101 L p L i K S Y L F Q L P L I K S Y L F Q L P L I K S Y L F Q L P L I K S Y L F Q L P L V K S Y L F Q I N E T R S I V Y Q	111 L L Q G L A F C H S L L Q G L A F C H S L L Q G L A F C H S L L Q G L A F C H S L L Q G L A F C H S I L Q G L A F C H Y	121 H R V L H R D L K P H R V L H R D L K P H R V L H R D L K P H R V L H R D L K P H R V L H R D L K P H Q I L H R D M K P	131 Q N L L I N a e G a Q N L L I N A E G S Q N L L I N A D G S Q N L L I N T E G A Q N L L I N A Q G E Q N L L I N S D G A Q N I L I N K N G T	141 I K L A D F G L A R I K L A D F G L A R I K L A D F G L A R I K L A D F G L A R I K L A D F G L A R I K L G D F G L A R
Consensus Conservation Q63699 CDK2_RAT Q5E9Y0 CDK2_BOVIN P24941 CDK2_HUMAN P43450 CDK2_CARAU P23437 CDK2_XENLA Q04770 CDK2_ENTH1	151 A F G V P V R T Y T A F G V P V R T Y T A F G V P V R T Y T A F G V P V R T Y T A F G V P V R T Y T L T I N D K K	161 H E V V T L W Y R A H E V V T L W Y R A H E V V T L W Y R A H E V V T L W Y R A H E V V T L W Y R A S E V V T L W Y R A	171 P E I L L G C K Y Y P E I L L G C K Y Y P E I L L G C K Y Y P E I L L G C K Y Y P E I L L G C K F Y P E I L L G A T Q Y	181 S T A V D I W S L G S T A V D I W S L G S T A V D I W S L G S T A V D I W S L G S T A V D I W S L G G G A I D I W S T A	191 C I F A E M i T R r C I F A E M V T R R C I F A E M V T R R C I F A E M V T R R C I F A E M I T R K C I F A E M I T R R A I F G E L I N K E

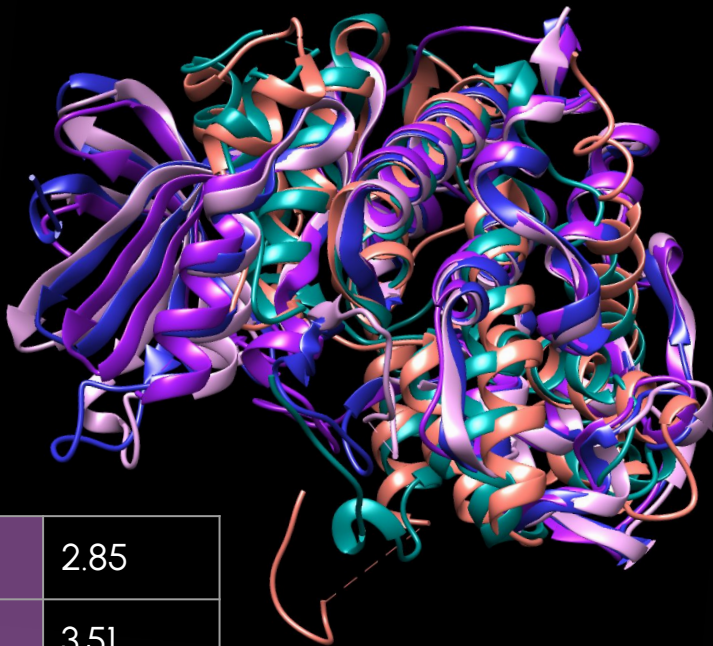
PSTAIRE Domain mostly conserved in all species

T loop mostly conserved

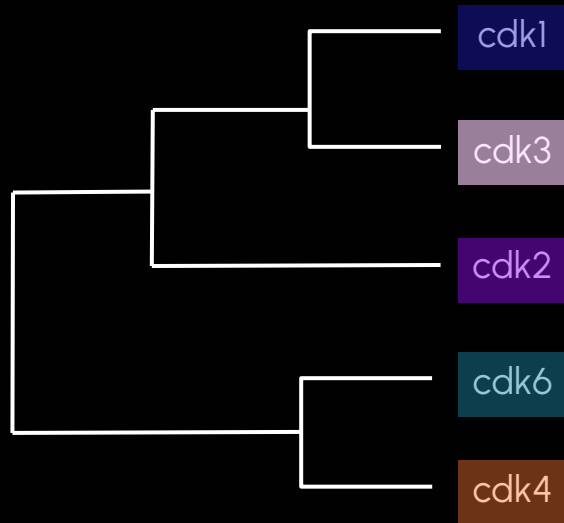
DFG motif conserved in all species

Thr 160 conserved in all species

Cell Cycle CDK's



Score	2.85
RMSD	3.51



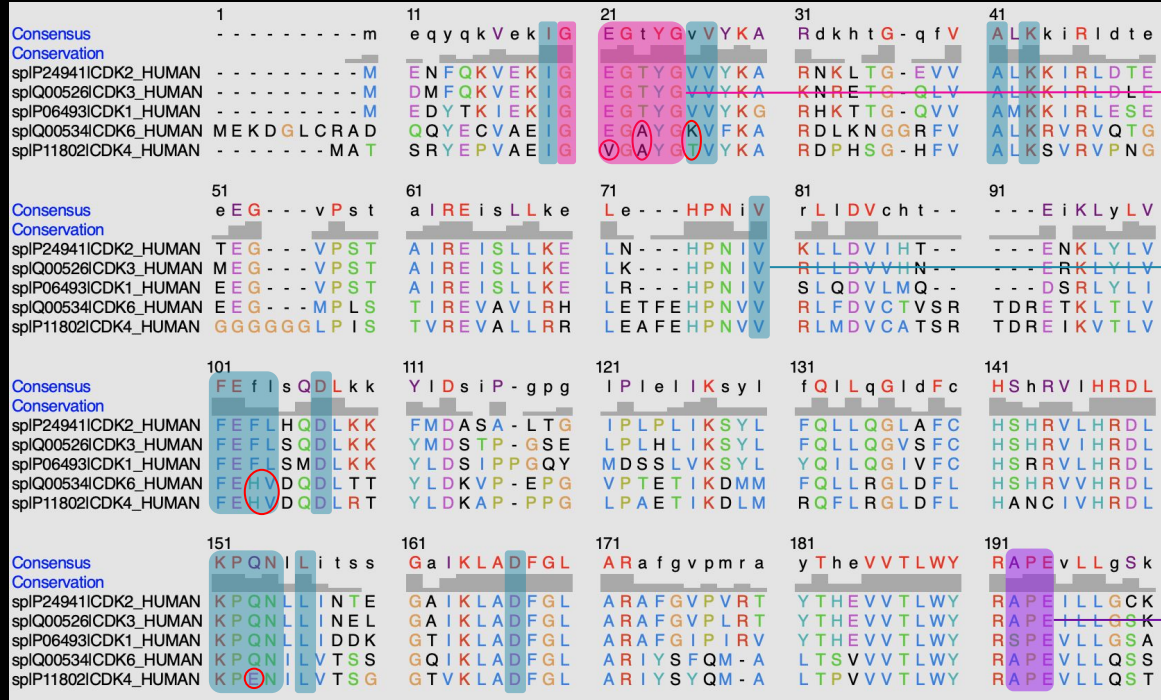
Cell Cycle CDK's

Consensus Conservation splP24941CDK2_HUMAN splQ005261CDK3_HUMAN splP064931CDK1_HUMAN splQ005341CDK6_HUMAN splP118021CDK4_HUMAN	1 - - - - - m e E G - - - v P s t T E G - - - V P S T M E G - - - V P S T E E G - - - V P S T E E G - - - M P L S G G G G G G L P I S	11 e q y q k V e k I G E N F Q K V E K I G D M F Q K V E K I G E D Y T K I E K I G Q Q Y E C V A E I G S R Y E P V A E I G	21 E G t Y G v V Y K A E G T Y G V V Y K A E G T Y G V V Y K A E G T Y G V V Y K G E G A Y G K V F K A V G A Y G T V Y K A	31 R d k h t G - q f v R N K L T G - E V V K N R E T G - Q L V R H K T T G - Q V V R D L K N G G R F V R D P H S G - H F V	41 A L K k i R l d t e A L K K I R L D T E A L K K I R L D L E A M K K I R L E S E A L K R V R V Q T G A L K S V R V P N G
Consensus Conservation splP24941CDK2_HUMAN splQ005261CDK3_HUMAN splP064931CDK1_HUMAN splQ005341CDK6_HUMAN splP118021CDK4_HUMAN	51 e E G - - - v P s t T E G - - - V P S T M E G - - - V P S T E E G - - - V P S T E E G - - - M P L S G G G G G G L P I S	61 a I R E i s L L k e A I R E I S L L K E A I R E I S L L K E A I R E I S L L K E T I R E V A V L R H T V R E V A L L R R	71 L e - - - H P N i v L N - - - H P N I V L K - - - H P N I V L R - - - H P N I V L E T F E H P N V V L E A F E H P N V V	81 r L l D V c h t - - K L L D V I H T - - R L L D V V H N - - S L Q D V L M Q - - R L F D V C V S R R L M D V C A T S R	91 - - - E i K L y L V - - - E N K L Y L V - - - E R K L Y L V - - - D S R L Y L I T D R E T K L T L V T D R E I K V T L V
Consensus Conservation splP24941CDK2_HUMAN splQ005261CDK3_HUMAN splP064931CDK1_HUMAN splQ005341CDK6_HUMAN splP118021CDK4_HUMAN	101 F E f l s Q D L k k F E F L H Q D L K K F E F L S Q D L K K F E F L S M D L K K F E H V D Q D L T T F E H V D Q D L R T	111 Y l D s i P - g p g F M D A S A - L T G Y M D S T P - G S E Y L D S I P P G Q Y Y L D K V P - E P G Y L D K A P - P P G	121 l P l e l i K s y l I P L P L I K S Y L I P L H L I K S Y L M D S S L V K S Y L V P T E T I K D M M L P A E T I K D L M	131 f Q l l q G l d F c F Q L L Q G L A F C F Q L L Q G V S F C Y Q I L Q G I V F C F Q L L R G L D F L R Q F L R G L D F L	141 H S h r V l H R D L H S H R V L H R D L H S H R V I H R D L H S R R V L H R D L H S H R V V H R D L H A N C I V H R D L
Consensus Conservation splP24941CDK2_HUMAN splQ005261CDK3_HUMAN splP064931CDK1_HUMAN splQ005341CDK6_HUMAN splP118021CDK4_HUMAN	151 K P Q N l l i t s s K P Q N L L I N T E K P Q N L L I N E L K P Q N L L I D D K K P Q N I L V T S S K P E N I L V T S G	161 G a I K L A D F G L G A I K L A D F G L G A I K L A D F G L G T I K L A D F G L G Q I K L A D F G L G T V K L A D F G L	171 A R A f g v p m r a A R A F G V P V R T A R A F G V P L R T A R A F G I P I R V A R I Y S F Q M - A A R I Y S Y Q M - A	181 y T h e V V T L W Y Y T H E V V T L W Y Y T H E V V T L W Y Y T H E V V T L W Y L T S V V V T L W Y L T P V V V T L W Y	191 R A P e v L L g S k R A P E I L L G C K R A P E I L L G S K R S P E V L L G S A R A P E V L L Q S S R A P E V L L Q S T

Proton acceptor
conserved in all cell
cycle CDKs

Coordination of the
 Mg^{2+} ion conserved

Cell Cycle CDK's



Cell Cycle CDK's

Consensus Conservation 1 - - - - - m splP24941CDK2_HUMAN splQ005261CDK3_HUMAN splP064931CDK1_HUMAN splQ005341CDK6_HUMAN splP118021CDK4_HUMAN	11 e q y q k V e k I G ENFQKVEKIG DMFQKVEKIG EDYTKIEKIG QQYECVAEIG SRYPEPVAEIG	21 EGtYGVVYKA EGTYGVVYKA EGTYGVVYKA EGTYGVVYK EGAYGVVYKA VGAYGVVYKA	31 RdkhtG-qfv RNKLTG-EVV KNRETG-QLV RHKTG-QVV RDLKNGGRFV RDPHSG-HFV	41 ALKkiRldte ALKKIRLDTE ALKKIRLDLE AMKKIRLSE ALKRVRVQTG ALKSVRVPNG
51 eEG--vPst splP24941CDK2_HUMAN splQ005261CDK3_HUMAN splP064931CDK1_HUMAN splQ005341CDK6_HUMAN splP118021CDK4_HUMAN	61 aIREisLLke AIREISLLKE AIREISLLKE AIREISLLKE TIREVAVLRH TVREVALLR	71 Le--HPNiV LN--HPNIV LK--HPNIV LR--HPNIV LETFEHPNVV LEAFEHPNVV	81 rLLDVcht-- KLLDVIHT-- RLLDVVHN-- SLQDVLMQ-- RLFDVCTVSR RLMDVCA TSR	91 --EiKLyLV --ENKLYLV --ERKLYLV --DSRLYLI TDRKTCLTLV TDREIKVTLV
101 FEflsQDLkk splP24941CDK2_HUMAN splQ005261CDK3_HUMAN splP064931CDK1_HUMAN splQ005341CDK6_HUMAN splP118021CDK4_HUMAN	111 YlDsiP-gpg FMDASA-LTG YMDSTP-GSE YLDSPGGQY YLDKVP-EPG YLDKAP-PPG	121 lPlleIKsyI lPLPLIKSYL lPLHLIKSYL MDSSLVKSYL VPTETIKDMM LPAETIKDLM	131 fQLLqGldFc FQLLQGLAFC FQLLQGVVFC YQILQGVVFC FQLLRGLDFL RQFLRGLDFL	141 HShRVlHRDL HSHRVLHRDL HSHRVVHRDL HSHRVVHRDL HSHRVVHRDL HANCIVHRDL
151 KPQNIllitss splP24941CDK2_HUMAN splQ005261CDK3_HUMAN splP064931CDK1_HUMAN splQ005341CDK6_HUMAN splP118021CDK4_HUMAN	161 GaIKLADFGL GAIKLADFGL GAIKLADFGL GTIKLADFGL GQIKLADFGL GTVKLADFGL	171 ARa fgvpmra ARAFGVVVRT ARAFGVPLRT ARAFGIPIRV ARIYSFQM-A ARIYSYQM-A	181 yTheVVT LWY YTHEVVTLWY YTHEVVTLWY YTHEVVTLWY LTSVVVTLWY LTPVVVTLWY	191 RAPEvLLgSk RAPEILLGCK RAPEILLGSK RSEPVLLGSA RAPEVLLQSS RAPEVLLQST

Hinge region
conserved in CDK1,
CDK2 and CDK3

Cell Cycle CDK's

Activation of CDK

Consensus Conservation 1 - - - - - m splP24941CDK2_HUMAN splQ005261CDK3_HUMAN splP064931CDK1_HUMAN splQ005341CDK6_HUMAN splP118021CDK4_HUMAN	11 e q y q k V e k I G ENFQKVEKIG DMFQKVEKIG EDYTKIEKIG QQYECVAEIG SRYEPVAEIG	21 E G t Y G v V Y K A EGTYGVVYKA EGTYGVVYKA EGTYGVVYKQ EGAYGKVFKA VGAYGTVYKA	31 R d k h t G - q f v RNKLTG-EVV KNRETG-QLV RHKTG-QVV RDLKNGGRFV RDPHSG-HFV	41 A L K k i R l d t e ALKKIRLDTE ALKKIRLDLE AMKKIRLSE ALKRVRVQTG ALKSVRVFNG
51 e E G - - - v P s t splP24941CDK2_HUMAN splQ005261CDK3_HUMAN splP064931CDK1_HUMAN splQ005341CDK6_HUMAN splP118021CDK4_HUMAN	61 a I R E i s L L k e AIREISLLKE AIREISLLKE AIREISLLKE AIREVAVLRH AIREVALLRR	71 L e - - - H P N i v LN--HPNIV LK--HPNIV LR--HPNIV LETFEHPNVV LEAFEHPNVV	81 r L L D V c h t - - KLLDVIHT-- RLLDVVHN-- SLQDVLMQ-- RLFDVCTVSR RLMDVCA TSR	91 - - - E i K L y L V --ENKLYLV --ERKLYLV --DSRLYLI TDRKTCLTV TDREIKVTLV
101 F E f l s Q D L k k splP24941CDK2_HUMAN splQ005261CDK3_HUMAN splP064931CDK1_HUMAN splQ005341CDK6_HUMAN splP118021CDK4_HUMAN	111 Y I D s i P - g p g FMDASA-LTG YMDSTP-GSE YLDSPGGQY YLDKVP-EPG YLDKAP-PPG	121 I P l e l i K s y l IPLPLIKSYL LPLHLIKSYL MDSSLKSYL VPTETIKDMM LPAETIKDLM	131 f Q L L q G l d F c FQLLQGLAFC FQLLQGV SFC YQLLQGVVFC FQLLRGLDFL RQFLRGLDFL	141 H S h r V I H R D L HSHRVLHRDL HSHRVIHRDL HSRRVLHRDL HSHRVVHRDL HANCIVHRDL
151 K P Q N I L l t s s splP24941CDK2_HUMAN splQ005261CDK3_HUMAN splP064931CDK1_HUMAN splQ005341CDK6_HUMAN splP118021CDK4_HUMAN	161 G a I K L A D F G L GAIKLADFGL GAIKLADFGL GTIKLADFGL GQIKLADFGL GTVKLADFGL	171 A R a f g v p m r a ARAFGVVVRT ARAFGVPLRT ARAFGVPLRT ARISYFQM-A ARISYQMA	181 y T h e V V T L W Y YTHEVVTLWY YTHEVVTLWY YTHEVVTLWY LTSVVVTLWY LTPVVVTLWY	191 R A P E v L L g S k RAPEVLLGCK RAPEVLLGSK RSEVLLGSA RAPEVLLQSS RAPEVLLQST

PSTAIR domain
partially conserved

DFG motif conserved

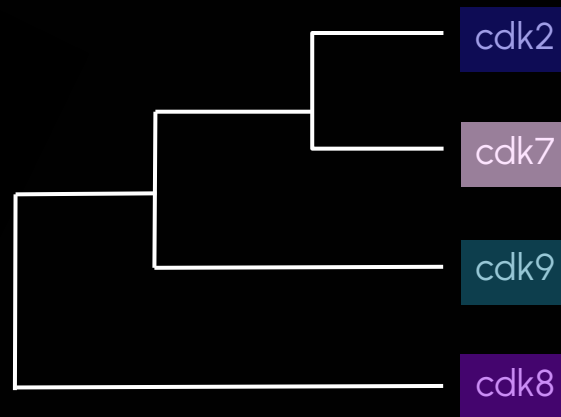
T loop partially
conserved in CDK2,
CDK3 and CDK1

Thr 160 conserved

Transcriptional CDK's



Score	1.43
RMSD	4.22



Transcriptional CDK's

Consensus	1	11	21	31	41
Conservation	-----	---rvekye	kle--kiGeG	tyghVyKARh	kkttgqivalk
splP24941CDK2_HUMAN	-----	---MENFQ	KVE--KIGEG	TYGVVYKARN	KLTFEVVALK
splP50613CDK7_HUMAN	-----MAL	DVKSRRAKRYE	KLD--FLGEG	QFATVYKARD	KNTNQIVAIK
splP50750CDK9_HUMAN	MAKQYDSVEC	PFCDEVSKYE	KLA--KIGGG	TFGEVFKARH	RKTGGKVALK
splP49336CDK8_HUMAN	MDYDFVKVLS	SERERVEDLF	EYEGCKVGRG	TYGHVYKAKR	KDGKDKDYA
Consensus	51	61	71	81	91
Conservation	k i q l e h --- e	keGipitAIR	E i k l L q e L k h	pNiikLldvf	htka-----
splP24941CDK2_HUMAN	K I R L D T --- E	T E G V P S T A I R	E I S L L K E L N H	P N I V K L L D V I	H T E N --- --
splP50613CDK7_HUMAN	K I K L G H R S E A	K D G I N R T A L R	E I K L L Q E L S H	P N I I G L L D A F	G H K S --- --
splP50750CDK9_HUMAN	K V L M E N --- E	K E G F P I T A L R	E I K L L Q L L K H	E N V V N L I E I C	R T K A S P Y N R C
splP49336CDK8_HUMAN	L K Q I E G ---	- T G I S M S A C R	E I A L L R E L K H	P N V I S L Q K V F	L S H A D R ---
Consensus	101	111	121	131	141
Conservation	--k i y L v F d f	a e h D L a h i i k	-----na	l v q i p l - h i k	s y m q q l L q G I
splP24941CDK2_HUMAN	--K L Y L V F E F	L H Q D L K K F M D	A --- -- -- S A	L T G I P L L I K	S Y L F Q L L Q G L
splP50613CDK7_HUMAN	--N I S L V F D F	M E T D L E V I I K	D --- -- -- N S	L V L T P S - H I K	A Y L M T L Q G L
splP50750CDK9_HUMAN	K G S I Y L V F D F	C E H D L A G L L S	-----N V	L V K F T L S E I K	R V M Q M L L N G L
splP49336CDK8_HUMAN	--K V W L L F D Y	A E H D L W H I I K	F H R A S K A N K K	P V Q L P R G M V K	S L L Y Q I L D G I
Consensus	151	161	171	181	191
Conservation	a y l H q h w i L H	R D I K p a N I L I	m r e G --- v l	K I A D f G I A r a	F g s p k r ---
splP24941CDK2_HUMAN	A F C H S H R V L H	R D I K P Q N L L I	N T E G --- A I	K L A D F G L A R A	F G V P V R ---
splP50613CDK7_HUMAN	E Y L H Q H W I L H	R D L K P N L L L I	D E N G --- V L	K L A D F G L A K S	F G S P N R ---
splP50750CDK9_HUMAN	Y Y I H R N K I L H	R D M K A A N V L I	T R D G --- V L	K L A D F G L A R A	F S L A K N S Q P N
splP49336CDK8_HUMAN	Y Y L H A N W V L H	R D L K P A N I L V	M G E G P E R G R V	K I A D M G F A R L	F N S P L K P - L A
Consensus	201	211	221	231	241
Conservation	a y t h q V V T I W	Y R A P E I L L G a	t r y y g p a i D i W	a a G C I f A E m l	t r s p i f p g d s
splP24941CDK2_HUMAN	T Y T H Q V V T L W	Y R A P E I L L G C	K Y Y S T A V D I W	S L G C I F A E M V	T R R A L F P G D S
splP50613CDK7_HUMAN	A Y T H Q V V T R W	Y R A P E L L F G A	R M Y G V G V D M W	A V G C I L A E L L	L R V P F L P G D S
splP50750CDK9_HUMAN	R Y T N R V V T L W	Y R D E L L L L G E	R D Y G P P I D L W	G A G C I M A E M W	T R S P I M Q G N T
splP49336CDK8_HUMAN	D L D V V V T F W	Y R A P E L L L G A	R H Y T K A I D I W	A I G C I F A E L L	T S E P I F H C R Q

G-G-G motif
(GLoop)

Proton acceptor

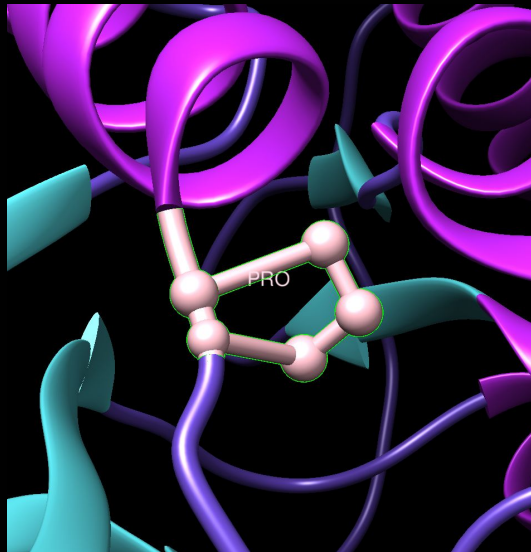
Coordination of
the Mg²⁺ ion

APE motif

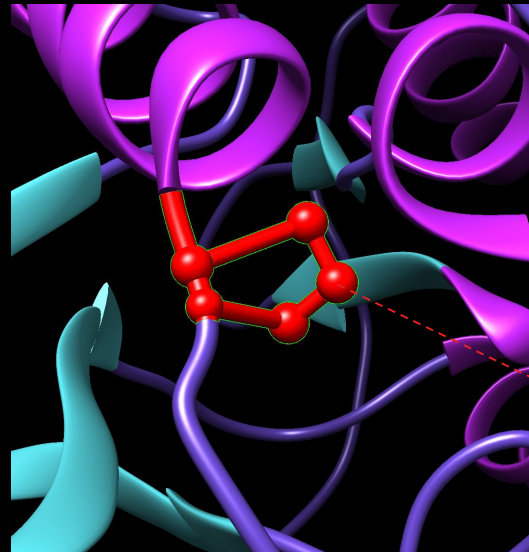
Thr 160

CDK2 mutant variant: P45 → L45

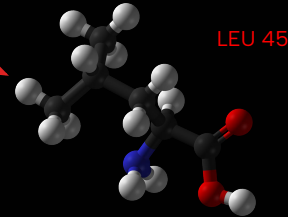
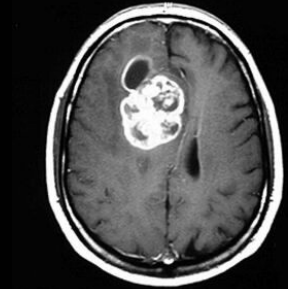
In a Glioblastoma multiforme sample somatic mutation



TEGV**P**STAIRE



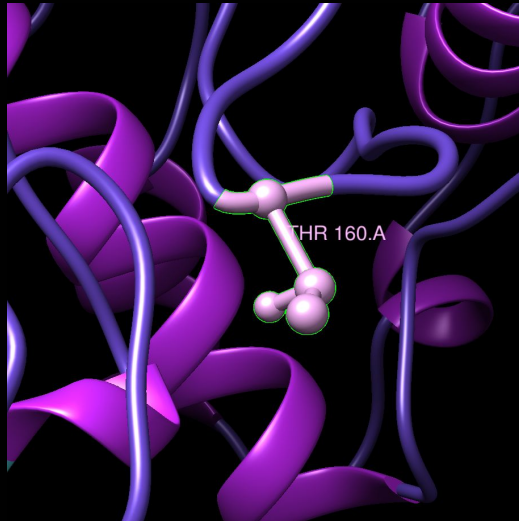
TEGV**L**STAIRE



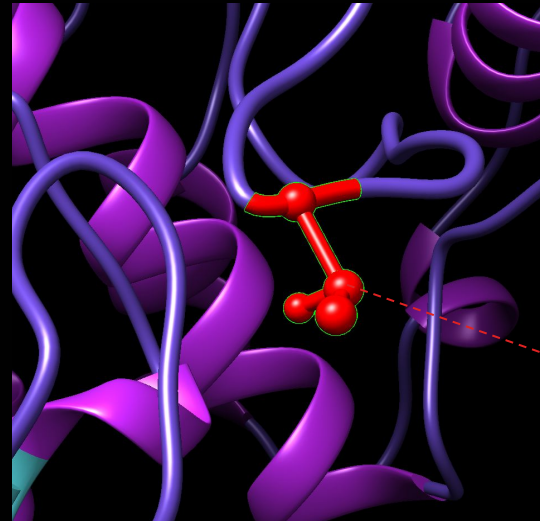
LEU 45

CDK2 mutant variant: T160 → A160

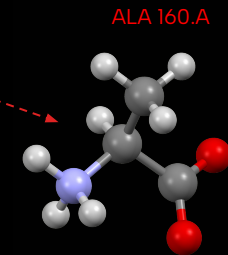
Abolishes activity



PVRTY**T**HEVVT



PVRTY**A**HEVVT



FINAL REMARKS

01

Biological importance of CDK2

02

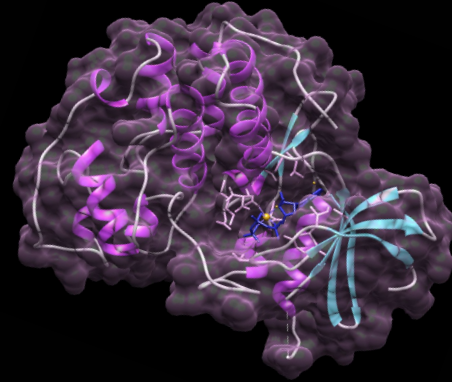
Structure-function relationship

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 Mg^{2+} 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) K_{cat} decreases and K_M 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 helices 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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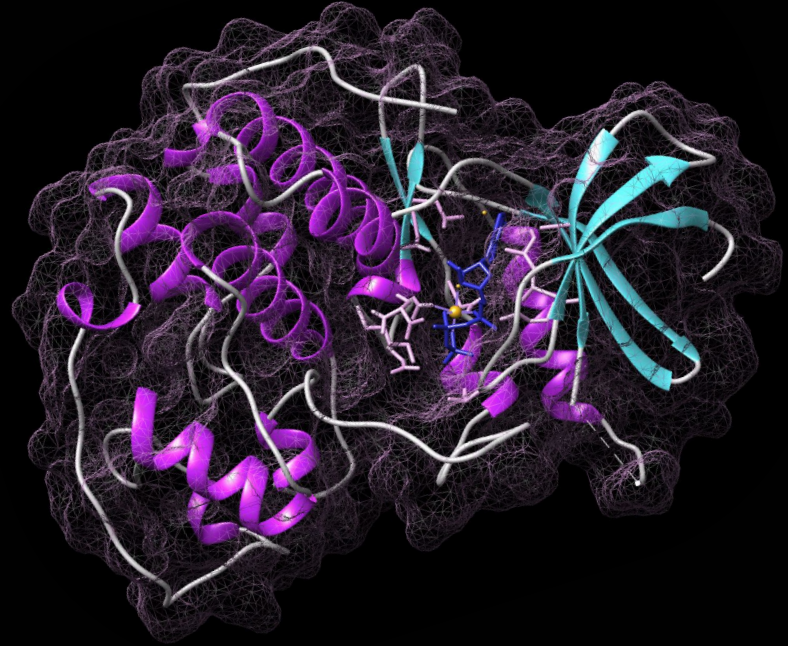
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A study on CDK2

Thanks!



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Structural Biology 2023/2024