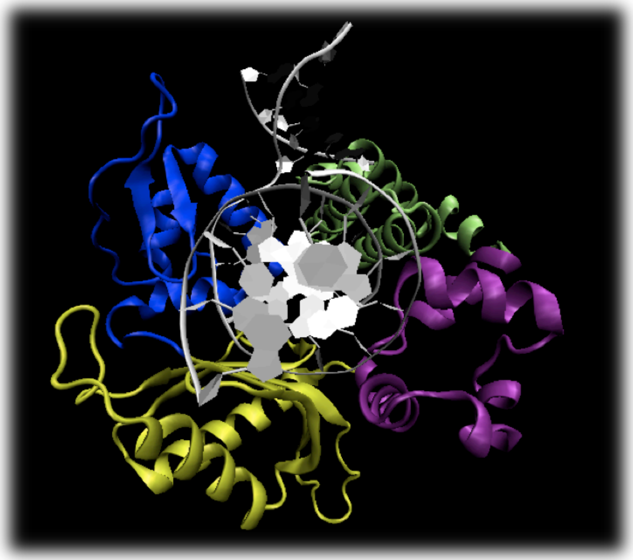
DNA REPLICATION MACHINERY: DNA POLYMERASES



SILVIA FRIAS

CRISTINA GARCÍA

LARA RUBIO

OUR AIMS

- To understand the **DNA polymerases mechanism**
- To analyse the **structural relationship** between the members of DNA polymerases families.
- To study **mechanism of interaction** between DNA and DNA polymerases.
- To comprehend **evolutionary relationships** of DNA polymerases.

MATERIAL AND METHODS

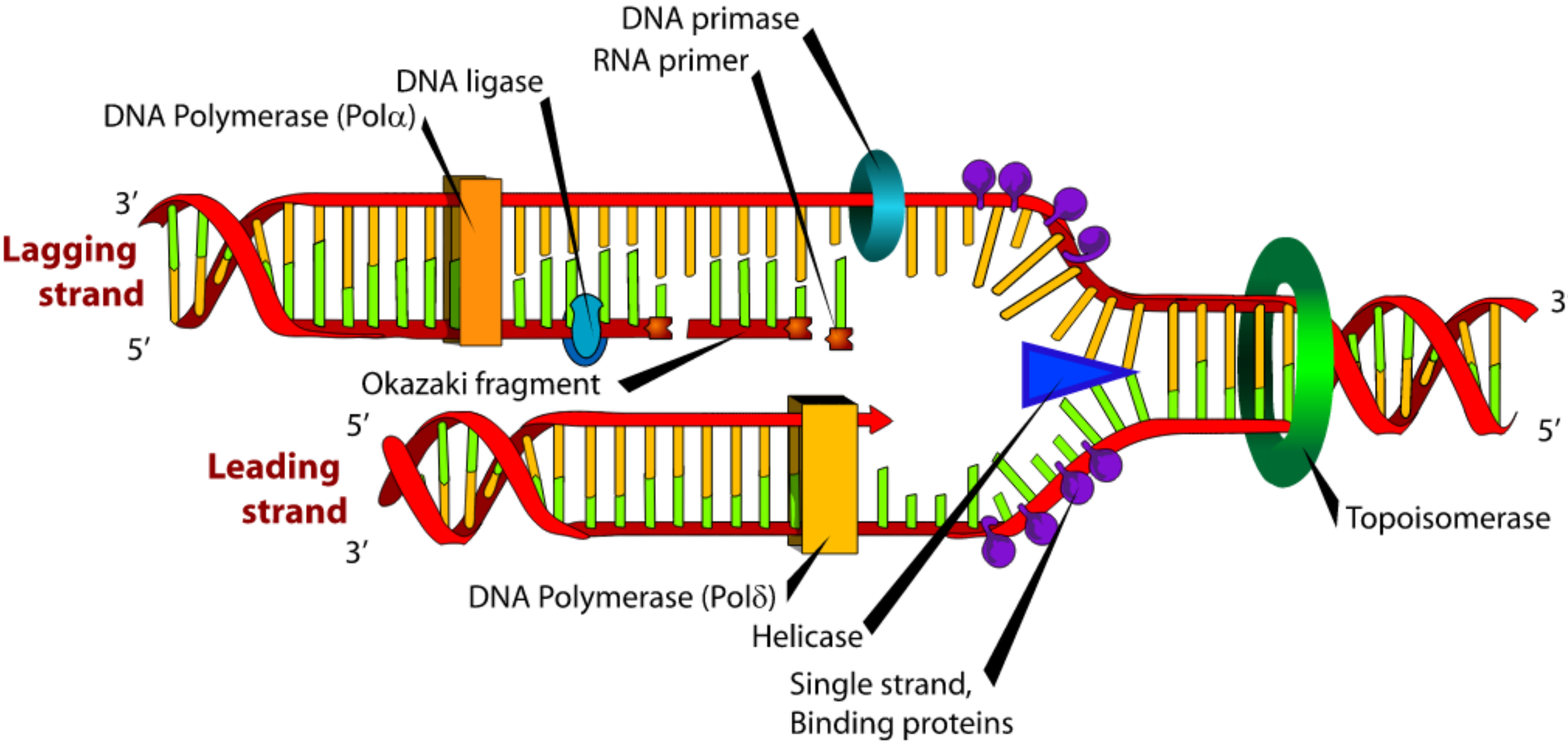
- Bibliographic research
- Blast against PDB and Swissprot databases
- Sequence alignment: Clustalw and T_Coffee
- Structural alignment: Stamp
- Molecular visualization: RasMol , VMD, Jmol and Pymol
- Databases: PDB, PFAM and SCOP

INDEX

DNA-polymerase mu

1. DNA replication components
2. Families of DNA polymerases
3. Structure of DNA polymerases
4. General mechanism of DNA polymerases
5. Different families of DNA polymerases
    1. Family A
    2. Family X
    3. Family C
6. Evolutionary relationships between DNA polymerases families

DNA REPLICATION COMPONENTS



FAMILIES OF DNA POLYMERASES

Families	Features	Members
Family A	Replicative and repair enzymes	T7 polymerase E. coli polymerase I Taq polymerase I B. stearothermophilus
Family B	DNA replication and 3’-5’ exonuclease activity	Eukaryotic replicative DNA polymerase α, δ, Ɛ
Family C	DNA replication	DNA polymerase III
Family D	DNA replication and a 3’-5’ exonuclease activity	Furiosus DNA polymerase II
Family X	Base excision repair (BER)	DNA polymerase β, TdT, μ and λ
Family Y	Low fidelity on undamaged DNA	E. Coli polymerases IV and V
RT family	Conversion of ssRNA into dsDNA	RT HIV-1,2

STRUCTURE OF DNA POLYMERASES

SUBDOMAINS

Common architecture likened to a right hand:

- **FINGERS** subdomain: interacts with the incoming nucleotide
- **THUMB** subdomain: binds the duplex DNA product
- **PALM** subdomain: contains the catalytic residues
- **CLEFT**

DNA-polymerase I

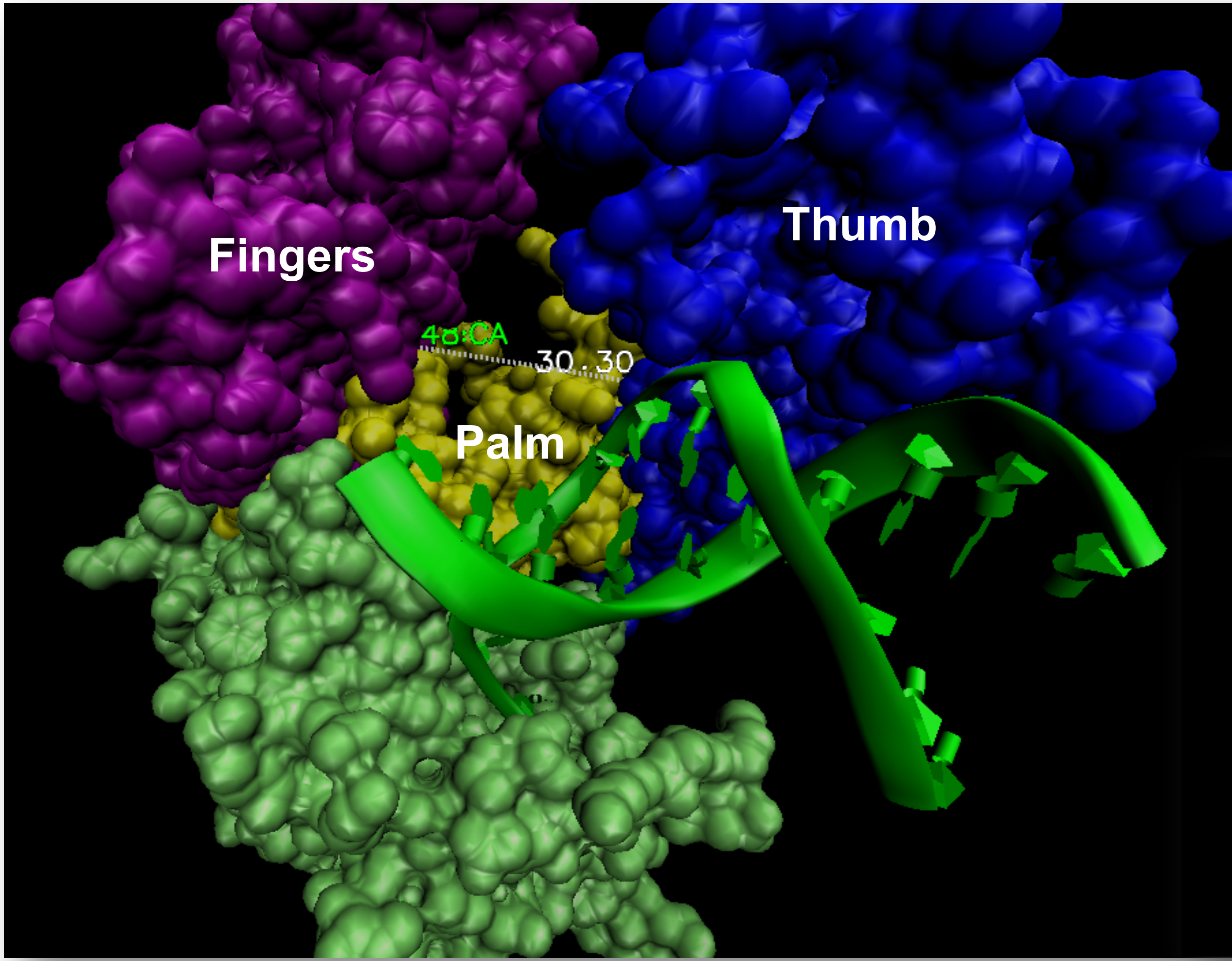
GENERAL MECHANISM OF DNA POLYMERASES

$$\mathrm{E + p/t \rightleftharpoons E\text{-}p/t \overset{\textbf{dNTP}}{\rightleftharpoons} E\text{-}p/t + dNTP \rightleftharpoons E\text{-}p/t_{n+1} - PPi \overset{\textbf{PPi}}{\rightleftharpoons} E{-}t/p_{n+1}}$$

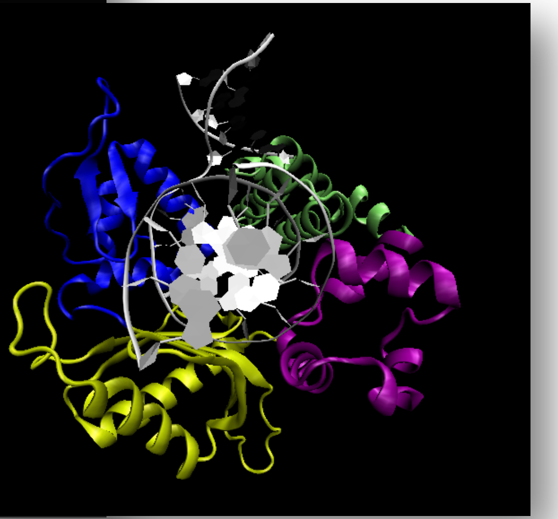
E: DNA polymerase
p: primer
t: template
PPi: pirophosphate

GENERAL MECHANISM OF DNA POLYMERASES

BINDING OF POLYMERASE TO DNA



DNA-polymerase I



DNA-polymerase beta

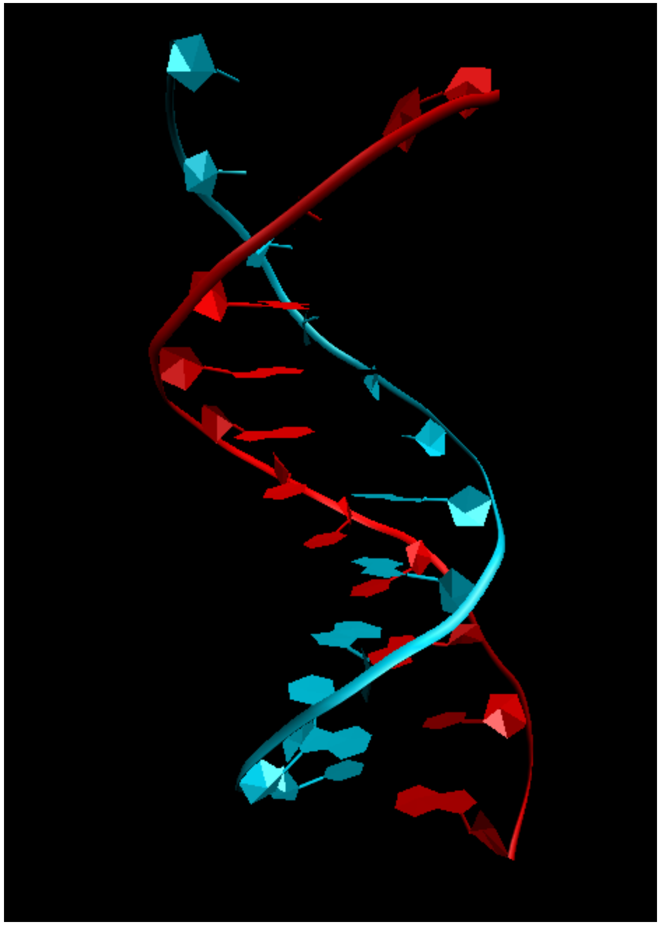
GENERAL MECHANISM OF DNA POLYMERASES

dNTP BINDING

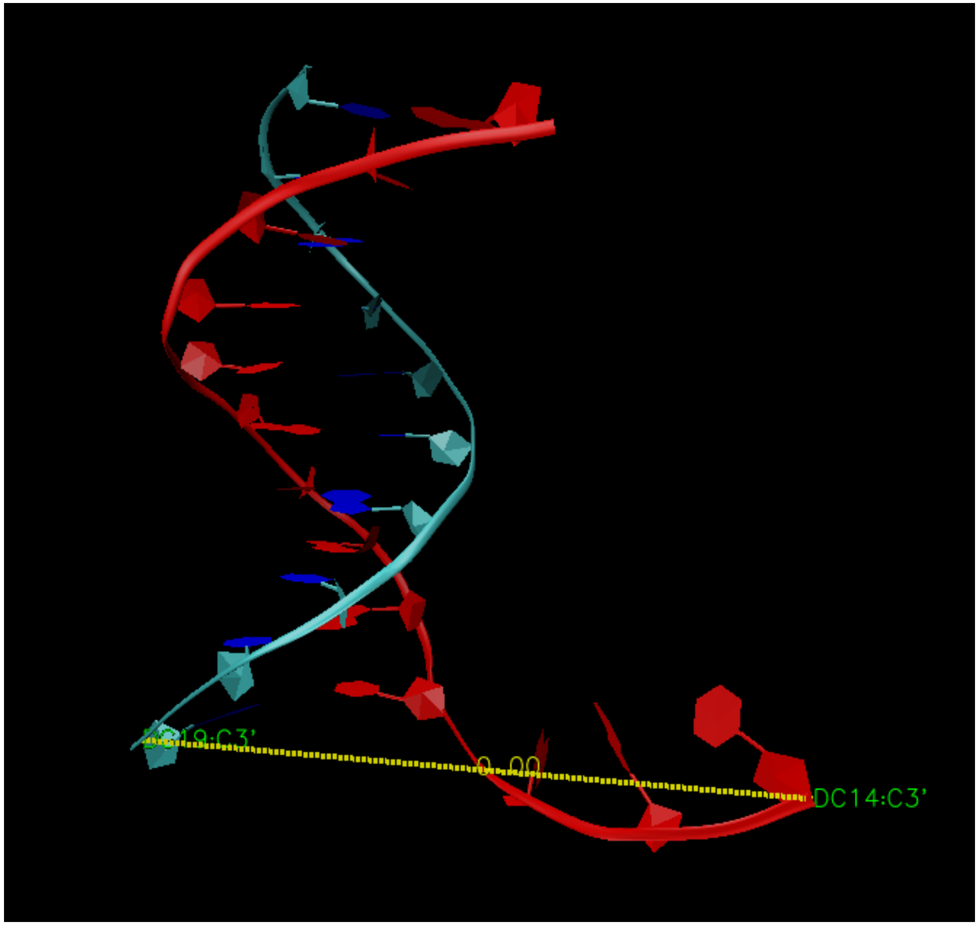
1. Finger domain rotates resulting in a “closed” structure
2. Base- flipping mechanism
3. The bases of incoming nucleotide interacts with the template (Watson-Crick base- pair)
4. Metal mediated ionic interactions between amino acid residues of the active site and triphosphate portion the dNTP

GENERAL MECHANISM OF DNA POLYMERASES

BASE- FLIPPING MECHANISM



B- DNA



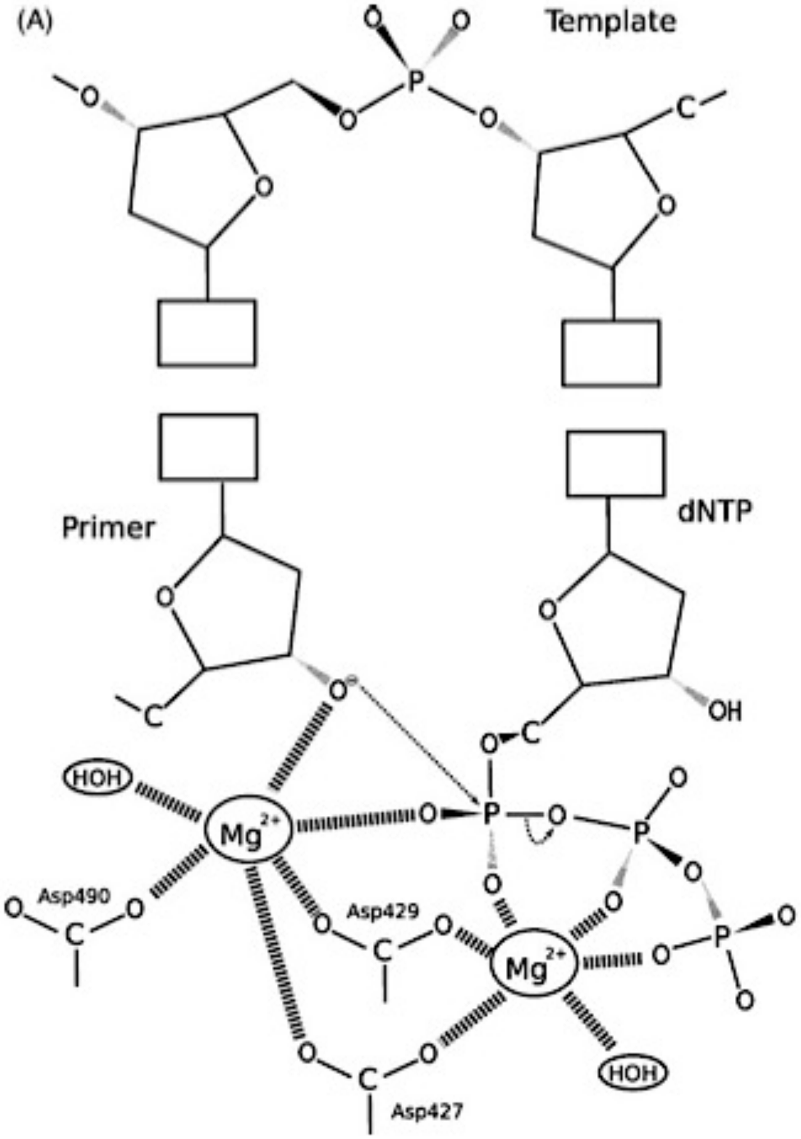
Rotated B-DNA

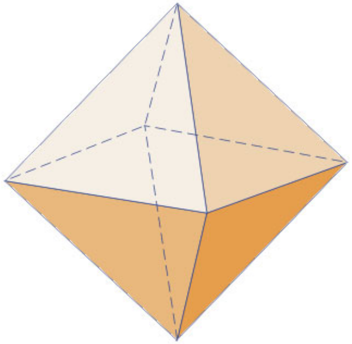
GENERAL MECHANISM OF DNA POLYMERASES

TWO METAL ION MECHANISM

Two metal ion coordinate the reactive groups: **octahedral coordination**

- **Metal A**: is coordinated by 3’-OH (primer), the α-phosphate dNTP and oxigen atoms of Asp side chains.
- **Metal B**: is coordinated by α,β,γ-phosphate groups of dNTP and carboxylates of Asp.





GENERAL MECHANISM OF DNA POLYMERASES

NUCLEOPHILIC ATTACK

Metal A coordination

⬇

3’-OH and α-phosphate in close proximity

⬇

Phosphoryl transfer reaction

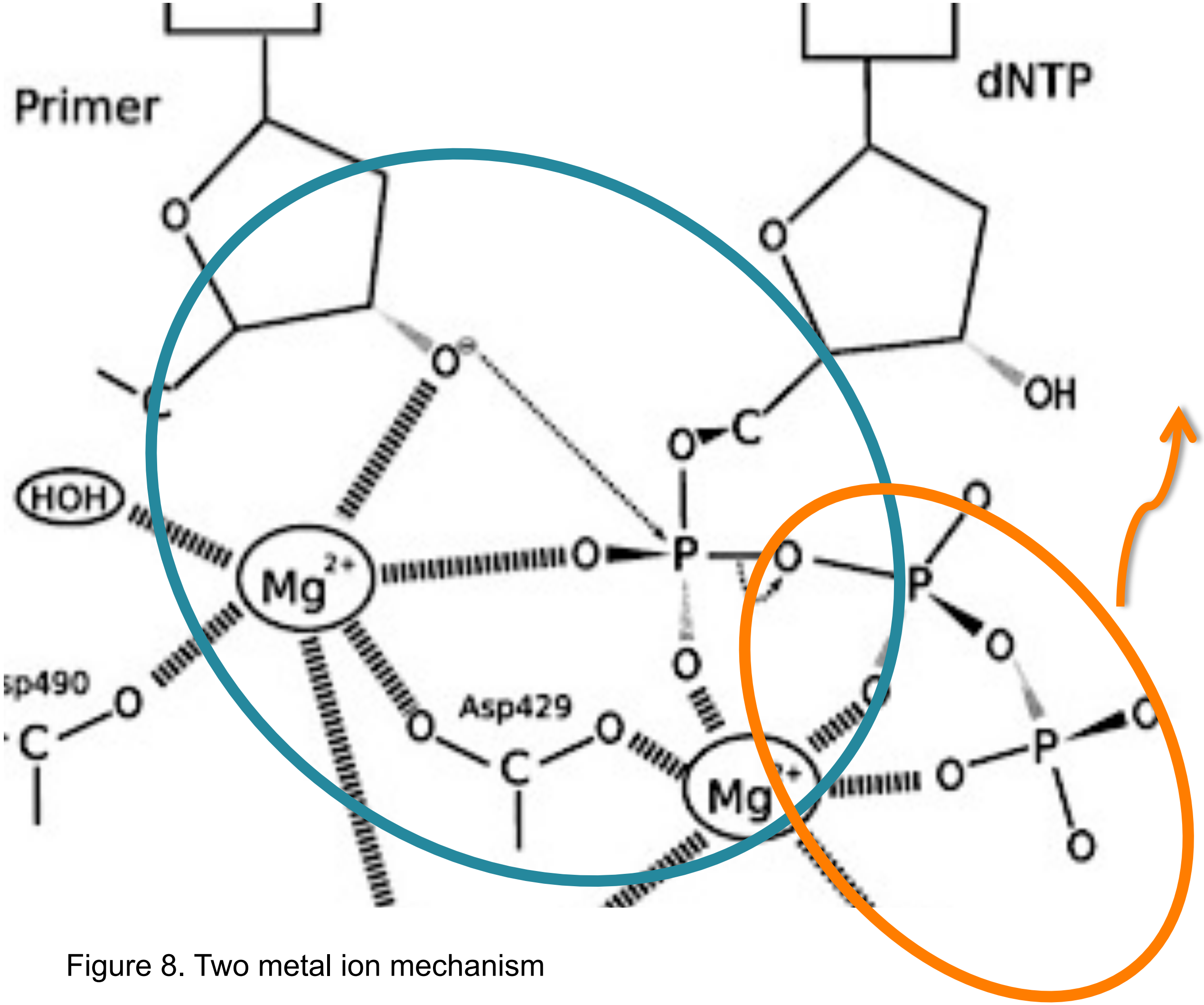


Figure 8. Two metal ion mechanism

FAMILY A

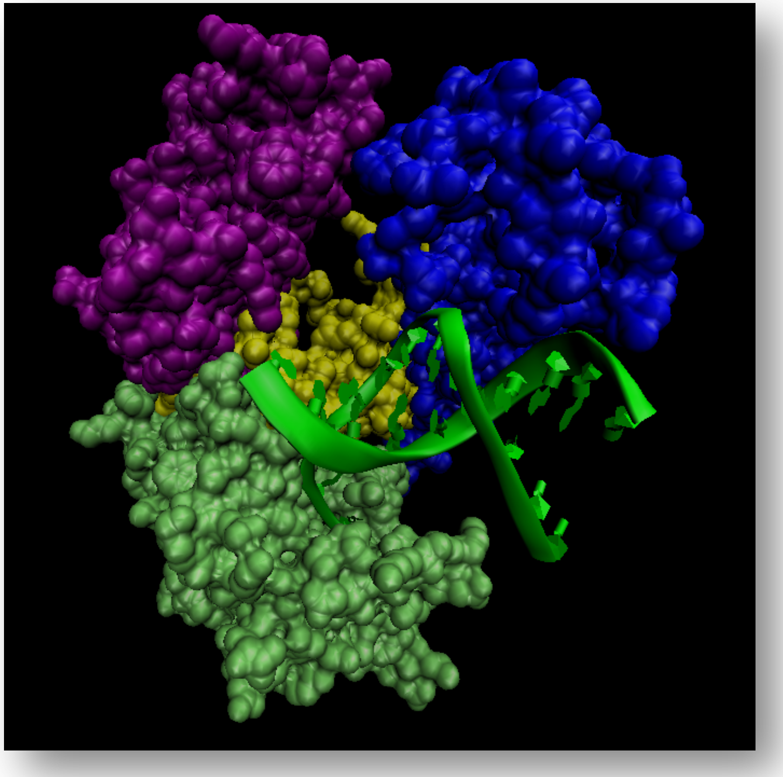
MEMBERS

Replicative enzymes:

- Bacteriophages T3, T5 and T7
- Mitocondrial polymerases: γ

Repair enzymes:

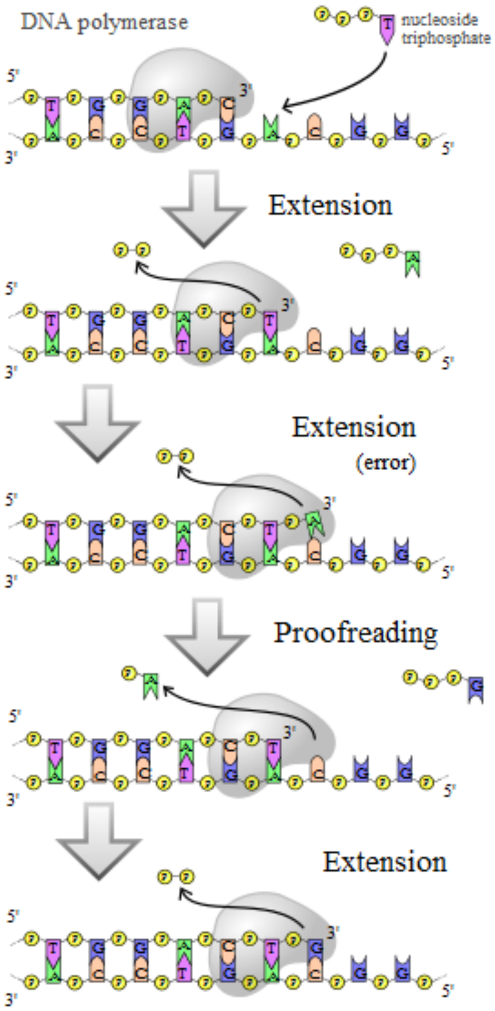
- *E.coli* polymerase I
- *Taq* polymerase I
- *Bacillus stearothermophilus* polymerase I



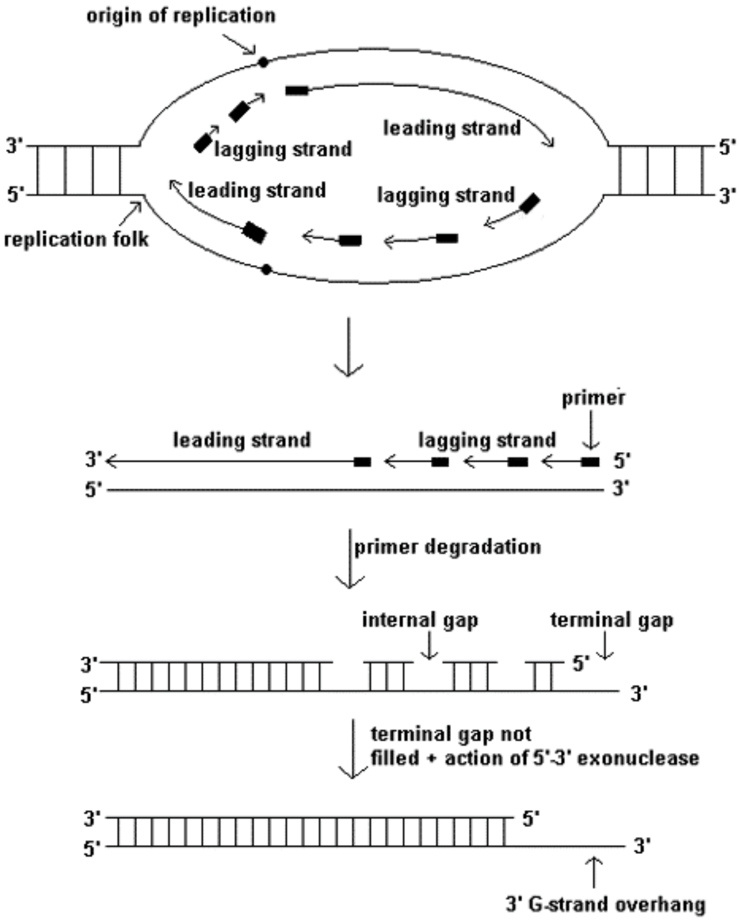
1KLN, 3,20Å

FAMILY A

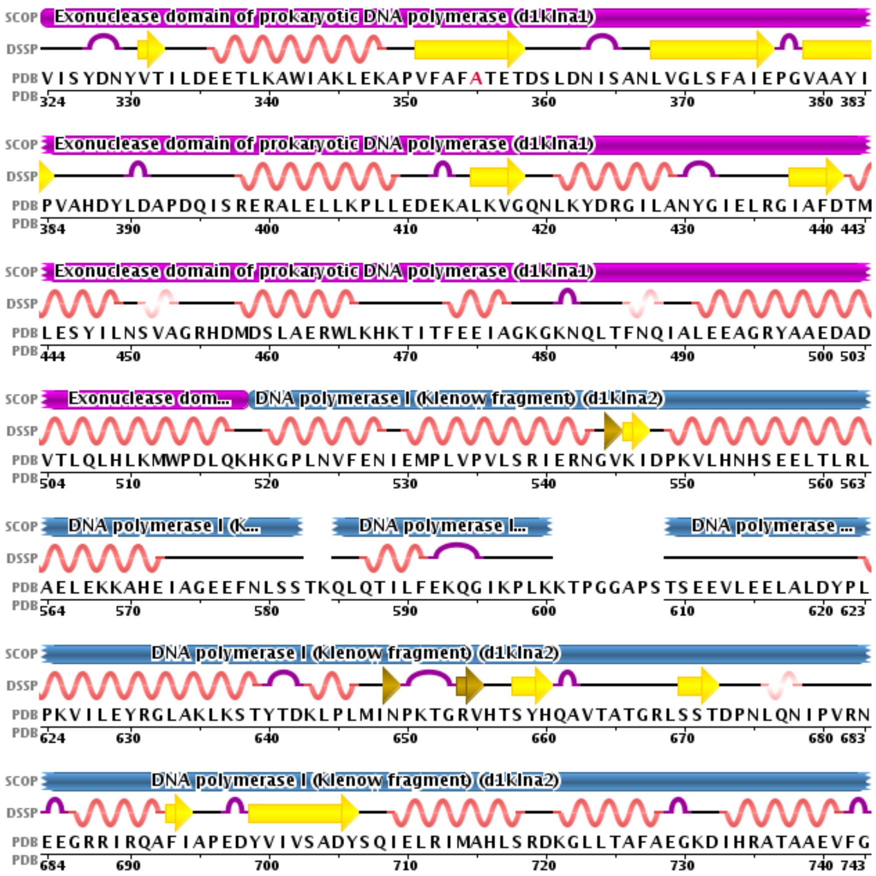
3' - 5' exonuclease activity

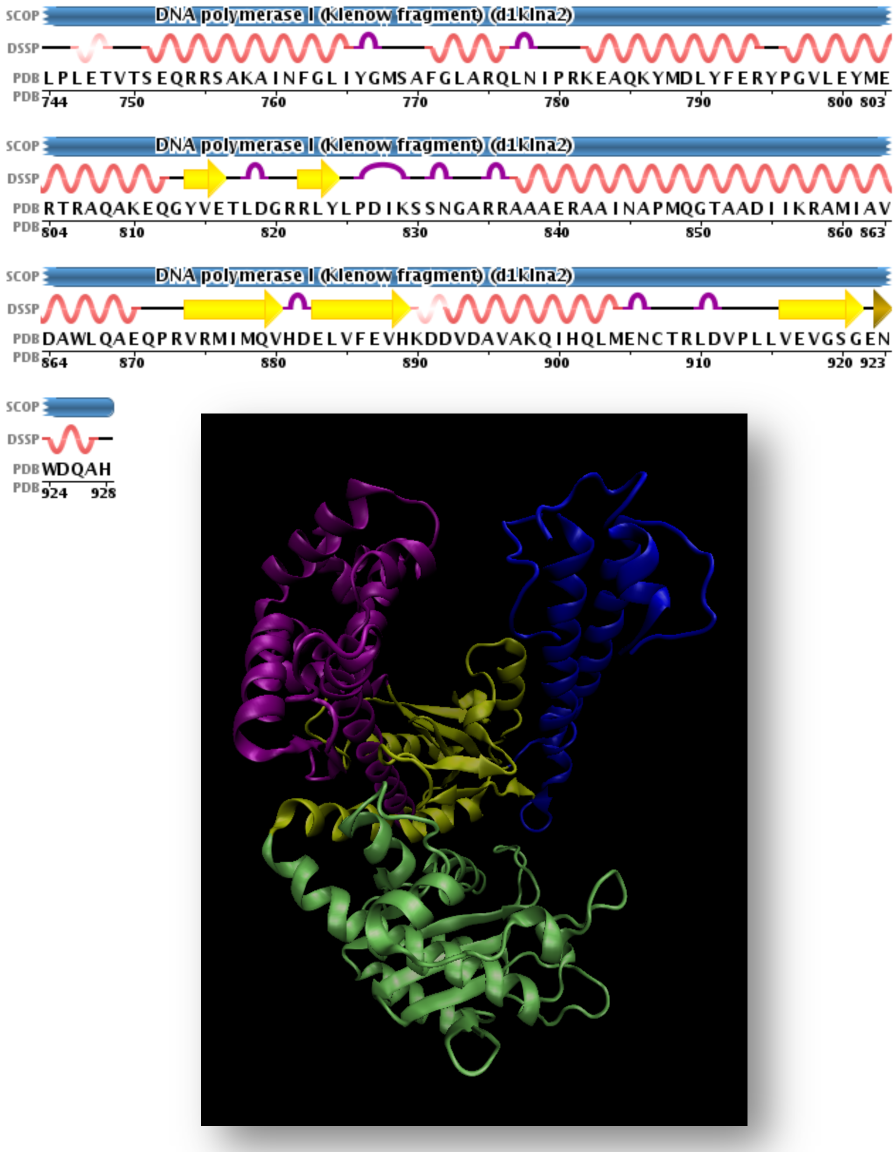


5' - 3' exonuclease activity



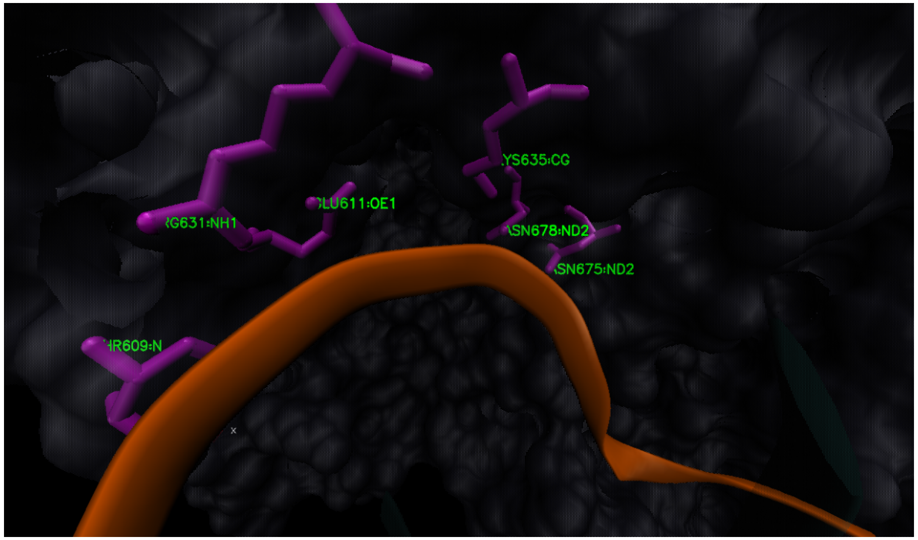
POL I E.COLI: STRUCTURAL CHARACTERISTICS



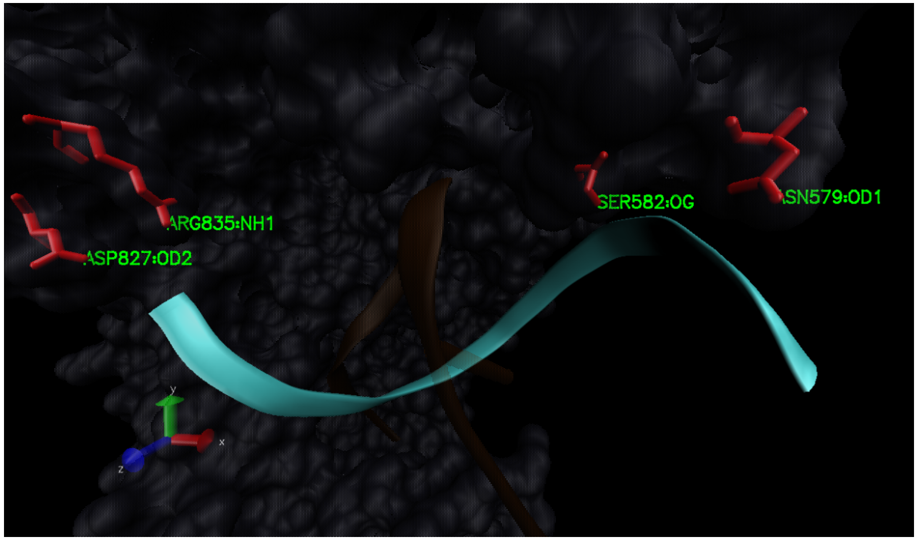


PRIMER AND TEMPLATE INTERACTON WITH DNA POLYMERASE

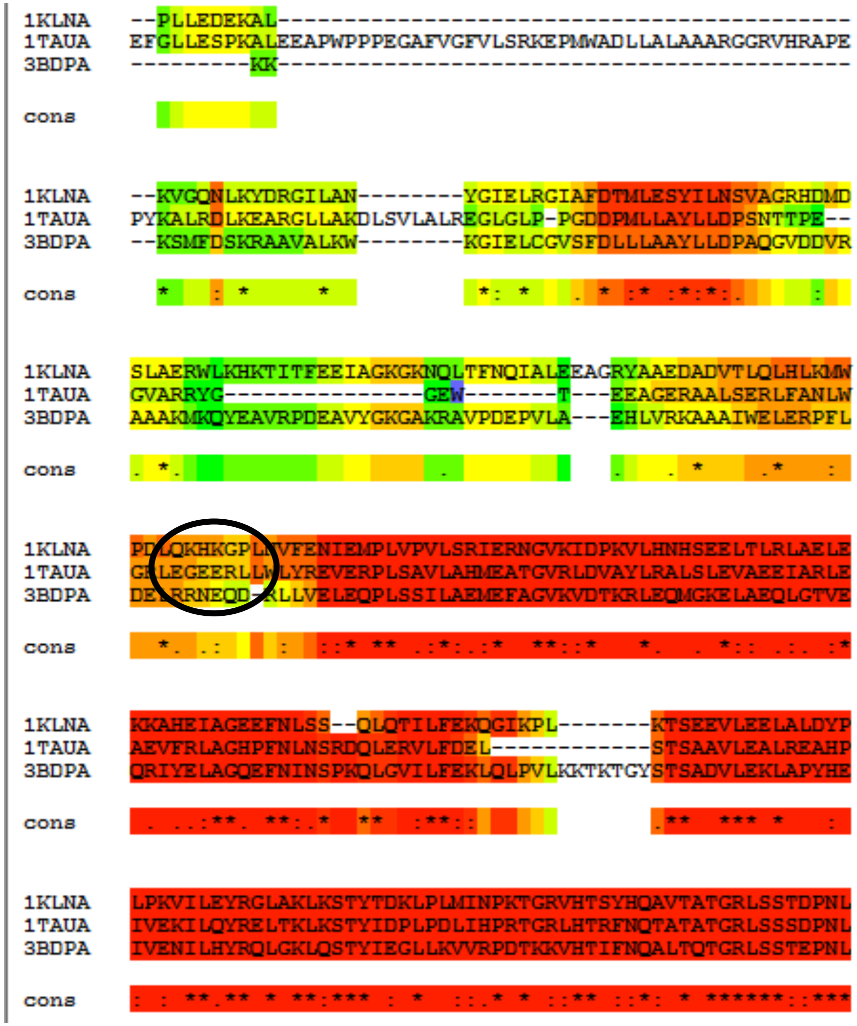
PRIMER STRAND INTERACTION



TEMPLATE STRAND INTERACTION



FAMILY A SEQUENCE ALIGNMENT



```
1KLNA   --PLLEDEKAL-------------------------------------------
1TAUA   EFGLLESPKALEEAPWPPPEGAFVGFVLSRKEPMWADLLALAAARGGRVHRAPE
3BDPA   ---------KK-------------------------------------------

cons


1KLNA   --KVGQNLKYDRGILAN--------YGIELRGIAFDTMLESYILNSVAGRHDMD
1TAUA   PYKALRDLKEARGLLAKDLSVLALREGLGLP-PGDDPMLLAYLLDPSNTTPE--
3BDPA   --KSMFDSKRAAVALKW--------KGIELCGVSFDLLLAAYLLDPAQGVDDVR

cons      *   : *     *           *: *   . * :* :*:*:.     :


1KLNA   SLAERWLKHKTITFEEIAGKGKNQLTFNQIALEEAGRYAAEDADVTLQLHLKMW
1TAUA   GVARRYG---------------GEW-------T---EEAGERAALSERLFANLW
3BDPA   AAAKMKQYEAVRPDEAVYGKGAKRAVPDEPVLA---EHLVRKAAAIWELERPFL

cons    . *.                   .            .   . *    .*   :


1KLNA   PDLQKHKGPLNVFENIEMPLVPVLSRIERNGVKIDPKVLHNHSEELTLRLAELE
1TAUA   GRLEGEERLLWLYREVERPLSAVLAHMEATGVRLDVAYLRALSLEVAEEIARLE
3BDPA   DELRRNEQD-RLLVELEQPLSSILAEMEFAGVKVDTKRLEQMGKELAEQLGTVE

cons      *. .:    :  ::* ** .:*:.:*  **::*   *.  .  *:: .:. :*


1KLNA   KKAHEIAGEEFNLSS--QLQTILFEKQGIKPL-------KTSEEVLEELALDYP
1TAUA   AEVFRLAGHPFNLNSRDQLERVLFDEL------------STSAAVLEALREAHP
3BDPA   QRIYELAGQEFNINSPKQLGVILFEKLQLPVLKKTKTGYSTSADVLEKLAPYHE

cons     . ..:**. **:.*  **  :**::             .**  *** *   :


1KLNA   LPKVILEYRGLAKLKSTYTDKLPLMINPKTGRVHTSYHQAVTATGRLSSTDPNL
1TAUA   IVEKILQYRELTKLKSTYIDPLPDLIHPRTGRLHTRFNQTATATGRLSSSDPNL
3BDPA   IVENILHYRQLGKLQSTYIEGLLKVVRPDTKKVHTIFNQALTQTGRLSSTEPNL

cons    : : **.** * **:*** : *  ::.* * ::** ::*: * ******::***
```

Bst pol I
E.Coli pol I
Taq pol I

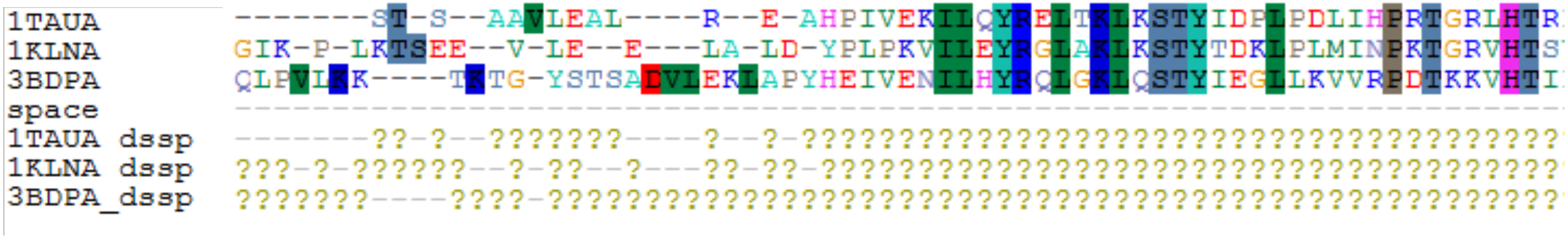
SCORE=82

FAMILY A STRUCTURAL ALIGNMENT: PRIMER INTERACTION RESIDUES

Thr
609

Arg
631

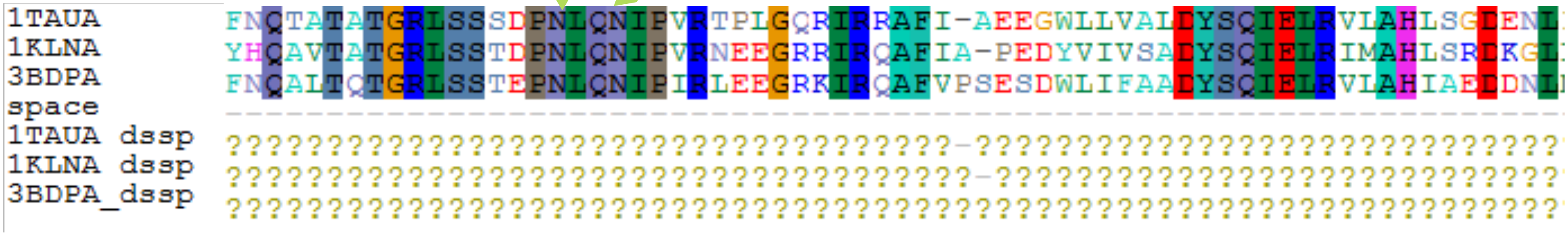
Lys
635



```
1TAUA        -------ST-S--AAVLEAL----R--E-AHPIVEKILQYRELTKLKSTYIDPLPDLIHPRTGRLHTR
1KLNA        GIK-P-LKTSEE--V-LE--E---LA-LD-YPLPKVILEYRGLAKLKSTYTDKLPLMINPKTGRVHTS
3BDPA        QLPVLKK----TKTG-YSTSADVLEKLAPYHEIVENILHYRQLGKLQSTYIEGLLKVVRPDTKKVHTI
space        --------------------------------------------------------------------
1TAUA dssp   -------??-?--???????----?--?-???????????????????????????????????????
1KLNA dssp   ???-?-??????--?-??--?---??-??-??????????????????????????????????????
3BDPA_dssp   ???????----????-????????????????????????????????????????????????????
```

Asn
675

Asn
678

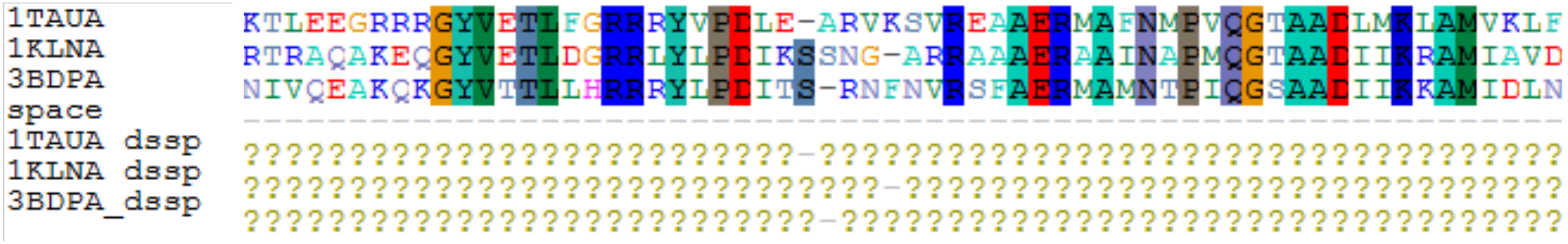


```
1TAUA        FNQTATATGRLSSSDPNLQNIPVRTPLGQRIRRAFI-AEEGWLLVALDYSQIELRVLAHLSGDENL
1KLNA        YHQAVTATGRLSSTDPNLQNIPVRNEEGRRIRQAFIA-PEDYVIVSADYSQIELRIMAHLSRDKGL
3BDPA        FNQALTQTGRLSSTEPNLQNIPIRLEEGRKIRQAFVPSESDWLIFAADYSQIELRVLAHIAEDDNL
space        ------------------------------------------------------------------
1TAUA dssp   ????????????????????????????????????-?????????????????????????????
1KLNA dssp   ?????????????????????????????????????-????????????????????????????
3BDPA_dssp   ??????????????????????????????????????????????????????????????????
```

FAMILY A STRUCTURAL ALIGNMENT: TEMPLATE INTERACTION RESIDUES

Asp 827

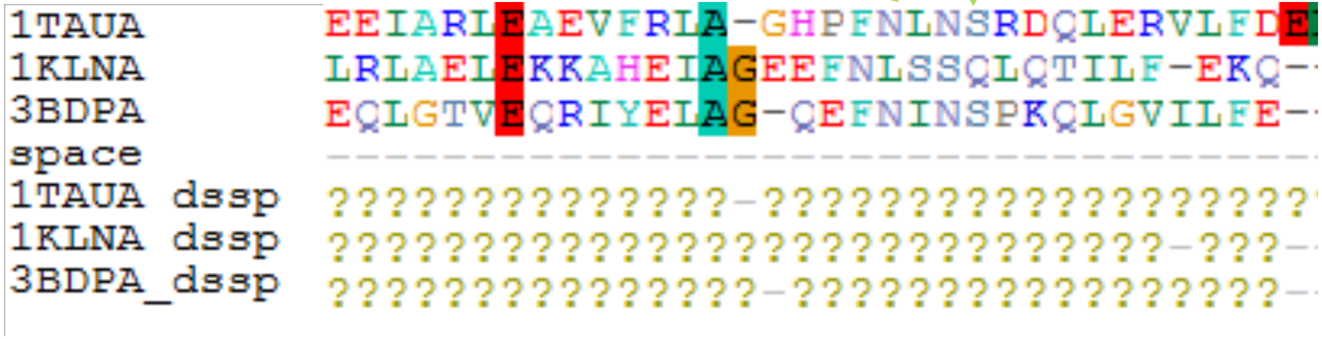
Arg 835



```
1TAUA        KTLEEGRRRGYVETLFGRRRYVPDLE-ARVKSVREAAERMAFNMPVQGTAADLMKLAMVKLF
1KLNA        RTRAQAKEQGYVETLDGRRLYLPDIKSSNG-ARRAAAERAAINAPMQGTAADIIKRAMIAVD
3BDPA        NIVQEAKQKGYVTTLLHRRRYLPDITS-RNFNVRSFAERMAMNTPIQGSAADIIKKAMIDLN
space        --------------------------------------------------------------
1TAUA dssp   ??????????????????????????-???????????????????????????????????
1KLNA dssp   ??????????????????????????????-???????????????????????????????
3BDPA_dssp   ???????????????????????????-??????????????????????????????????
```

Asn 579

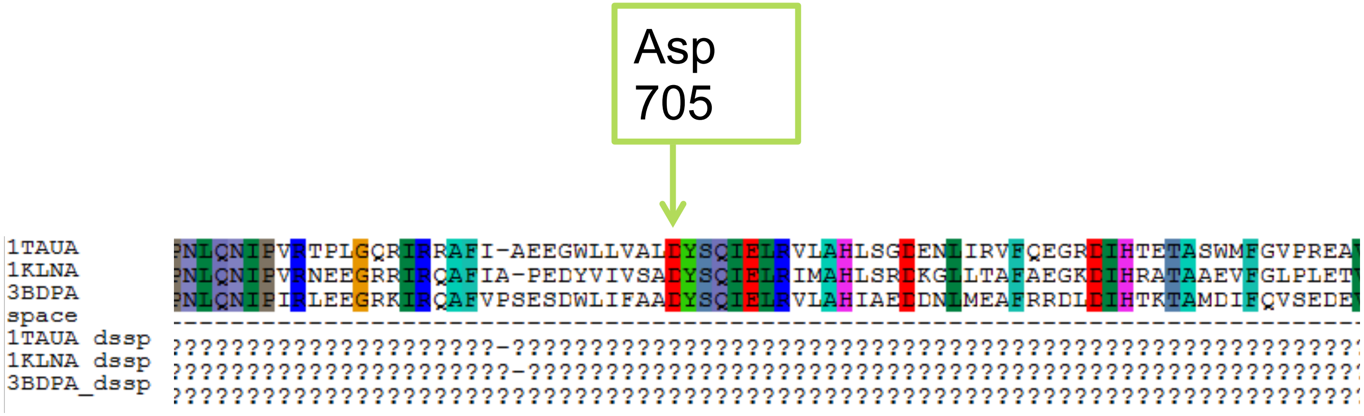
Ser 582



```
1TAUA        EEIARLEAEVFRLA-GHPFNLNSRDQLERVLFDE
1KLNA        LRLAELEKKAHEIAGEEFNLSSQLQTILF-EKQ-
3BDPA        EQLGTVEQRIYELAG-QEFNINSPKQLGVILFE-
space        ----------------------------------
1TAUA dssp   ??????????????-???????????????????
1KLNA dssp   ?????????????????????????????-???-
3BDPA_dssp   ???????????????-?????????????????-
```

FAMILY A TWO METAL ION MECHANISM: CONSERVED RESIDUES

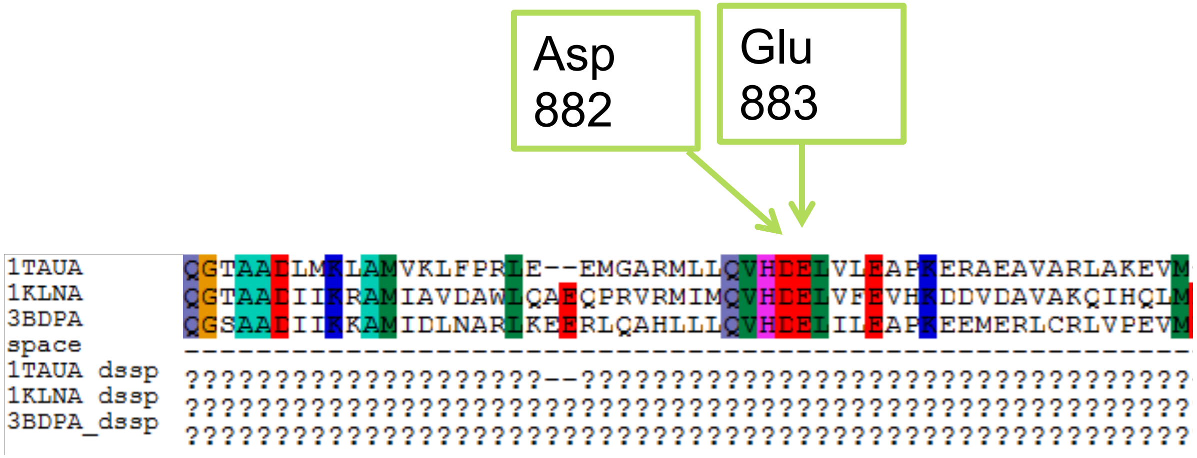
Asp 705



```
1TAUA       PNLQNIPVRTPLGQRIRRAFI-AEEGWLLVALDYSQIELRVLAHLSGDENLIRVFQEGRDIHTETASWMFGVPREA
1KLNA       PNLQNIPVRNEEGRRIRQAFIA-PEDYVIVSADYSQIELRIMAHLSRDKGLLTAFAEGKDIHRATAAEVFGLPLET
3BDPA       PNLQNIPIRLEEGRKIRQAFVPSESDWLIFAADYSQIELRVLAHIAEDDNLMEAFRRDLDIHTKTAMDIFQVSEDE
space       ----------------------------------------------------------------------------
1TAUA dssp ?????????????????????-??????????????????????????????????????????????????????
1KLNA dssp ??????????????????????-?????????????????????????????????????????????????????
3BDPA_dssp ????????????????????????????????????????????????????????????????????????????
```

Asp 882

Glu 883



```
1TAUA       QGTAADLMKLAMVKLFPRLE--EMGARMLLQVHDELVLEAPKERAEAVARLAKEVM
1KLNA       QGTAADIIKRAMIAVDAWLQAEQPRVRMIMQVHDELVFEVHKDDVDAVAKQIHQLM
3BDPA       QGSAADIIKKAMIDLNARLKEERLQAHLLLQVHDELILEAPKEEMERLCRLVPEVM
space       --------------------------------------------------------
1TAUA dssp ????????????????????--??????????????????????????????????
1KLNA dssp ????????????????????????????????????????????????????????
3BDPA_dssp ????????????????????????????????????????????????????????
```

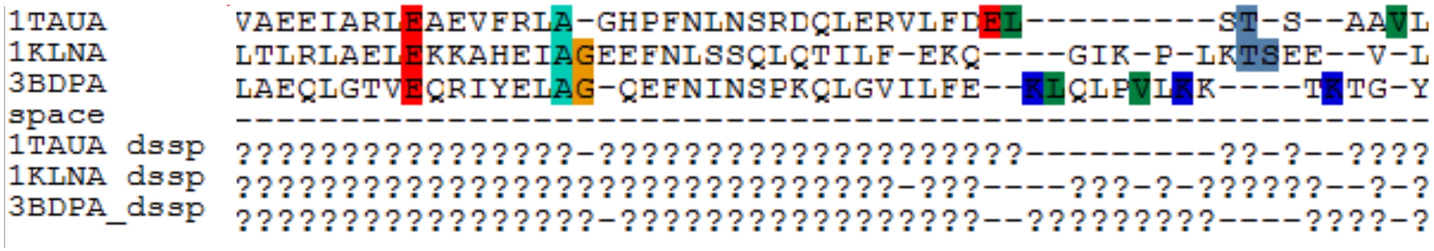
FAMILY A CONSERVED MOTIFS


Pol I *E.coli*


Pol I *Taq*


Pol I *B. Stearothermophillus*

Region 1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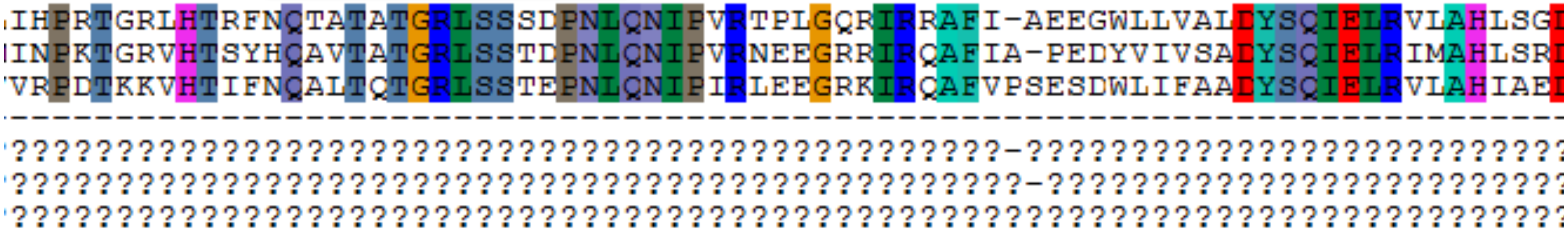
1TAUA        VAEEIARLEAEVFRLA-GHPFNLNSRDQLERVLFDEL---------ST-S--AAVL
1KLNA        LTLRLAELEKKAHEIAGEEFNLSSQLQTILF-EKQ----GIK-P-LKTSEE--V-L
3BDPA        LAEQLGTVEQRIYELAG-QEFNINSPKQLGVILFE--KLQLPVLKK----TKTG-Y
space        --------------------------------------------------------
1TAUA dssp   ????????????????-????????????????????---------??-?--????
1KLNA dssp   ???????????????????????????????-???----???-?-??????--?-?
3BDPA_dssp   ?????????????????-?????????????????--?????????----????-?
```

Region 2

Region 3 (A)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IHPRTGRLHTRFNQTATATGRLSSSDPNLQNIPVRTPLGQRIRRAFI-AEEGWLLVALDYSQIELRVLAHLSG
INPKTGRVHTSYHQAVTATGRLSSTDPNLQNIPVRNEEGRRIRQAFIA-PEDYVIVSADYSQIELRIMAHLSR
VRPDTKKVHTIFNQALTQTGRLSSTEPNLQNIPIRLEEGRKIRQAFVPSESDWLIFAADYSQIELRVLAHIAE
-------------------------------------------------------------------------
???????????????????????????????????????????????-?????????????????????????
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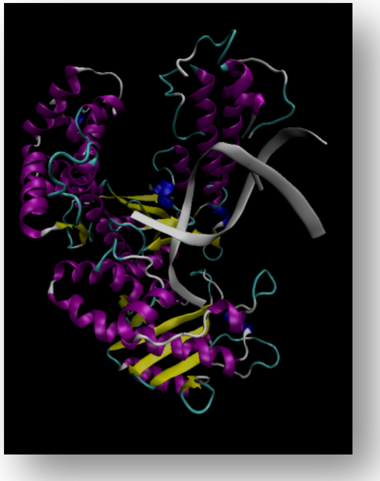
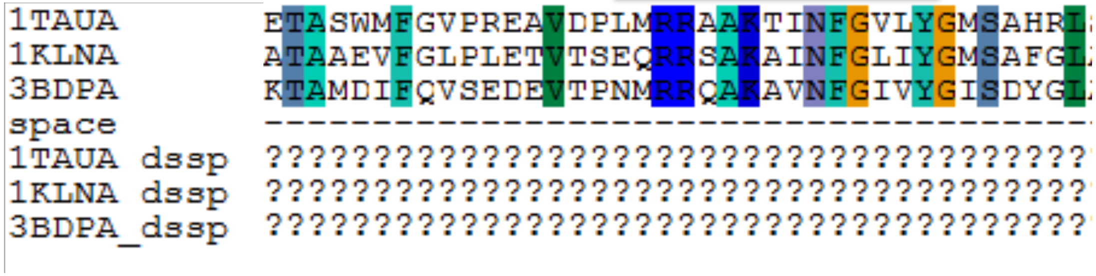


Pol I E.coli

Pol I Taq

Pol I B. Stearothermophillus

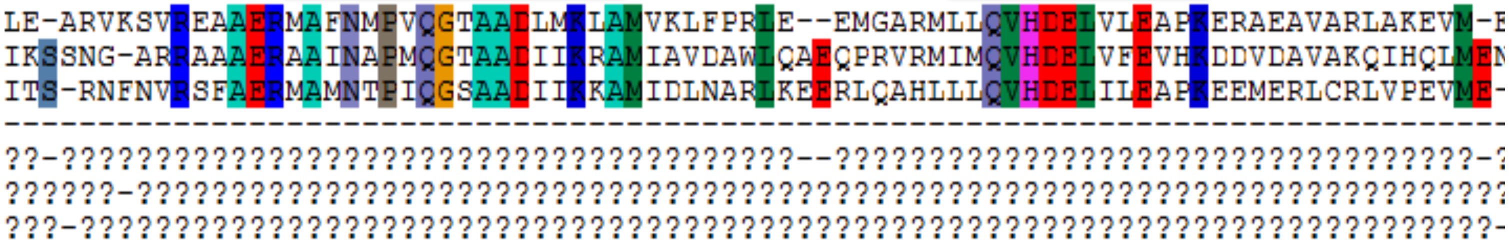
Region 4 (B)



```
1TAUA       ETASWMFGVPREAVDPLMRRAAKTINFGVLYGMSAHRL
1KLNA       ATAAEVFGLPLETVTSEQRRSAKAINFGLIYGMSAFGL
3BDPA       KTAMDIFQVSEDEVTPNMRRQAKAVNFGIVYGISDYGL
space       --------------------------------------
1TAUA dssp  ??????????????????????????????????????
1KLNA dssp  ??????????????????????????????????????
3BDPA_dssp  ??????????????????????????????????????
```

Region 6

Region 5 (C)



```
LE-ARVKSVREAAERMAFNMPVQGTAADLMKLAMVKLFPRLE--EMGARMLLQVHDELVLEAPKERAEAVARLAKEVM-E
IKSSNG-ARRAAAERAAINAPMQGTAADIIKRAMIAVDAWLQAEQPRVRMIMQVHDELVFEVHKDDVDAVAKQIHQLMEN
ITS-RNFNVRSFAERMAMNTPIQGSAADIIKKAMIDLNARLKEERLQAHLLLQVHDELILEAPKEEMERLCRLVPEVME-
--------------------------------------------------------------------------------
??-???????????????????????????????????????--??????????????????????????????????-?
??????-?????????????????????????????????????????????????????????????????????????
???-???????????????????????????????????????????????????????????????????????????-
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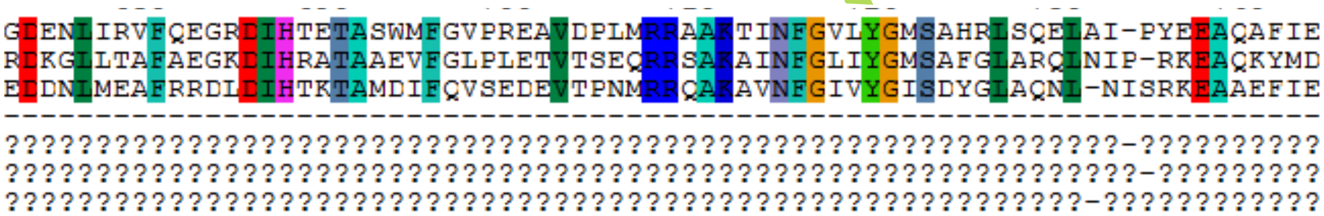
FAMILY A PREINSERTION SITE

Tyr 714



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GDENLIRVFQEGRDIHTETASWMFGVPREAVDPLMRRAAKTINFGVLYGMSAHRLSQELAI-PYEEAQAFIE
RDKGLLTAFAEGKDIHRATAAEVFGLPLETVTSEQRRSAKAINFGLIYGMSAFGLARQLNIP-RKEAQKYMD
EDDNLMEAFRRDLDIHTKTAMDIFQVSEDEVTPNMRRQAKAVNFGIVYGISDYGLAQNL-NISRKEAAEFIE
------------------------------------------------------------------------
?????????????????????????????????????????????????????????????-??????????
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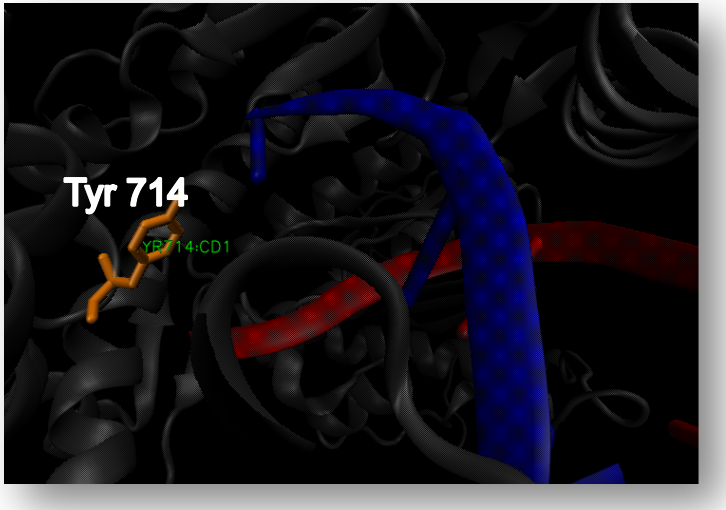
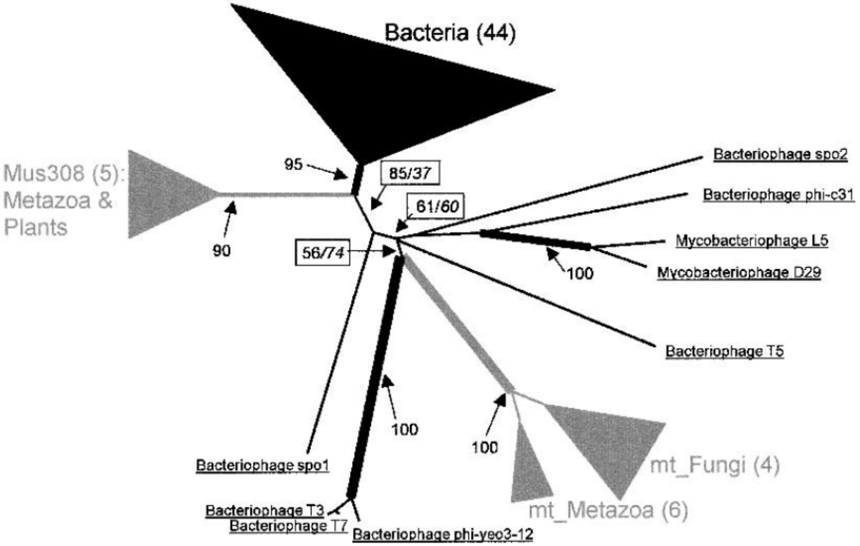
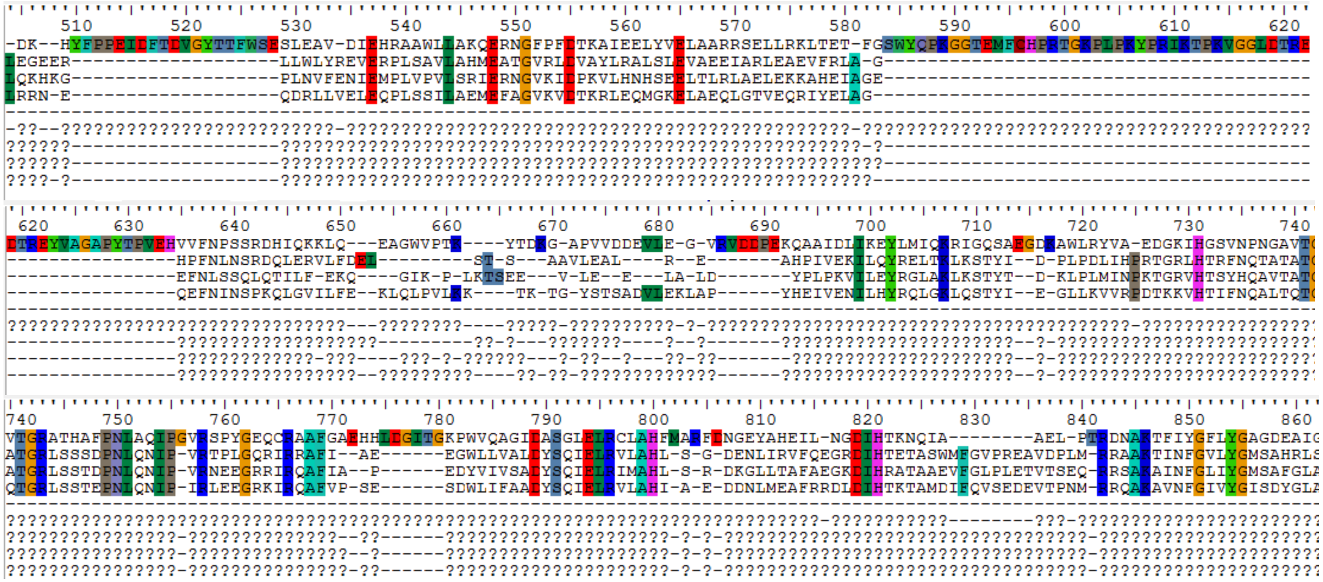

Tyr 714

FAMILY A EVOLUTION





```
      510         520         530         540         550         560         570         580         590         600         610         620
-DK--HYFPPEIDFTDVGYTTFWSESLEAV-DIEHRAAWLLAKQERNGFPFDTKAIEELYVELAARRSELLRKLTET-FGSWYQPKGGTEMFCHPRTGKPLPKYPRIKTPKVGGLDTRE
LEGEER-------------------LLWLYREVERPLSAVLAHMEATGVRLDVAYLRALSLEVAEEIARLEAEVFRLA-G---------------------------------------
LQKHKG-------------------PLNVFENIEMPLVPVLSRIERNGVKIDPKVLHNHSEELTLRLAELEKKAHEIAGE---------------------------------------
LRRN-E-------------------QDRLLVELEQPLSSILAEMEFAGVKVDTKRLEQMGKELAEQLGTVEQRIYELAG----------------------------------------
-----------------------------------------------------------------------------------------------------------------------
-??--?????????????????????????-??????????????????????????????????????????????-?????????????????????????????????????????
??????-------------------????????????????????????????????????????????????????-?---------------------------------------
??????-------------------???????????????????????????????????????????????????????---------------------------------------
????-?-------------------??????????????????????????????????????????????????????----------------------------------------

 620         630         640         650         660         670         680         690         700         710         720         730         740
DTREYVAGAPYTPVEHVVFNPSSRDHIQKKLQ---EAGWVPTK----YTDKG-APVVDDEVLE-G-VRVDDPEKQAAIDLIKEYLMIQKRIGQSAEGDKAWLRYVA-EDGKIHGSVNPNGAVT
----------------HPFNLNSRDQLERVLFDEL---------ST-S---AAVLEAL----R--E-------AHPIVEKILQYRELTKLKSTYI--D-PLPDLIHPRTGRLHTRFNQTATAT
----------------EFNLSSQLQTILF-EKQ----GIK-P-LKTSEE---V-LE--E---LA-LD-------YPLPKVILEYRGLAKLKSTYT--D-KLPLMINPKTGRVHTSYHQAVTAT
----------------QEFNINSPKQLGVILFE--KLQLPVLKK----TK-TG-YSTSADVLEKLAP------YHEIVENILHYRQLGKLQSTYI--E-GLLKVVRPDTKKVHTIFNQALTQT
---------------------------------------------------------------------------------------------------------------------------
????????????????????????????????---????????----?????-??????????-?-????????????????????????????????????????-????????????????
----------------???????????????????---------??-?---???????----?--?-------??????????????????????--?-????????????????????????
----------------?????????????-???----???-?-??????---?-??--?---??-??-------?????????????????????--?-????????????????????????
----------------?????????????????--?????????----??-??-?????????????------??????????????????????--?-????????????????????????

740         750         760         770         780         790         800         810         820         830         840         850         860
VTGRATHAFPNLAQIPGVRSPYGEQCRAAFGAEHHLDGITGKPWVQAGIDASGLELRCLAHFMARFLNGEYAHEIL-NGDIHTKNQIA--------AEL-PTRDNAKTFIYGFLYGAGDEAIG
ATGRLSSSDPNLQNIP-VRTPLGQRIRRAFI--AE------EGWLLVALDYSQIELRVLAHL-S-G-DENLIRVFQEGRDIHTETASWMFGVPREAVDPLM-RRAAKTINFGVLYGMSAHRLS
ATGRLSSTDPNLQNIP-VRNEEGRRIRQAFIA--P------EDYVIVSADYSQIELRIMAHL-S-R-DKGLLTAFAEGKDIHRATAAEVFGLPLETVTSEQ-RRSAKAINFGLIYGMSAFGLA
QTGRLSSTEPNLQNIP-IRLEEGRKIRQAFVP-SE------SDWLIFAADYSQIELRVLAHI-A-E-DDNLMEAFRRDLDIHTKTAMDIFQVSEDEVTPNM-RRQAKAVNFGIVYGISDYGLA
---------------------------------------------------------------------------------------------------------------------------
????????????????????????????????????????????????????????????????????????????-???????????--------???-???????????????????????
????????????????-??????????????--??------?????????????????????-?-?-??????????????????????????????????-?????????????????????
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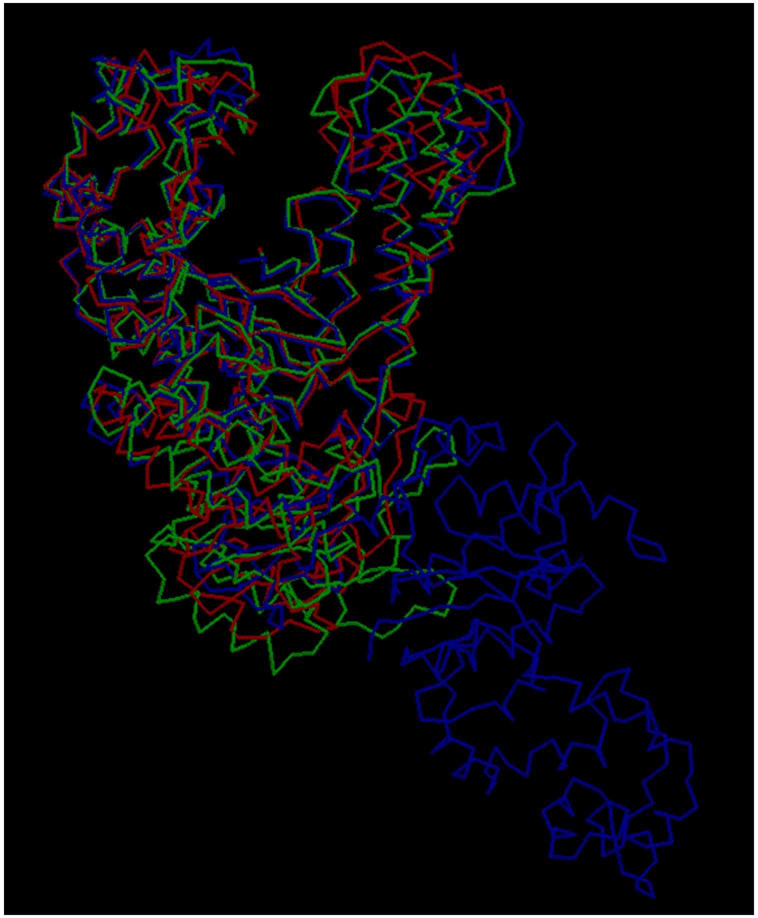
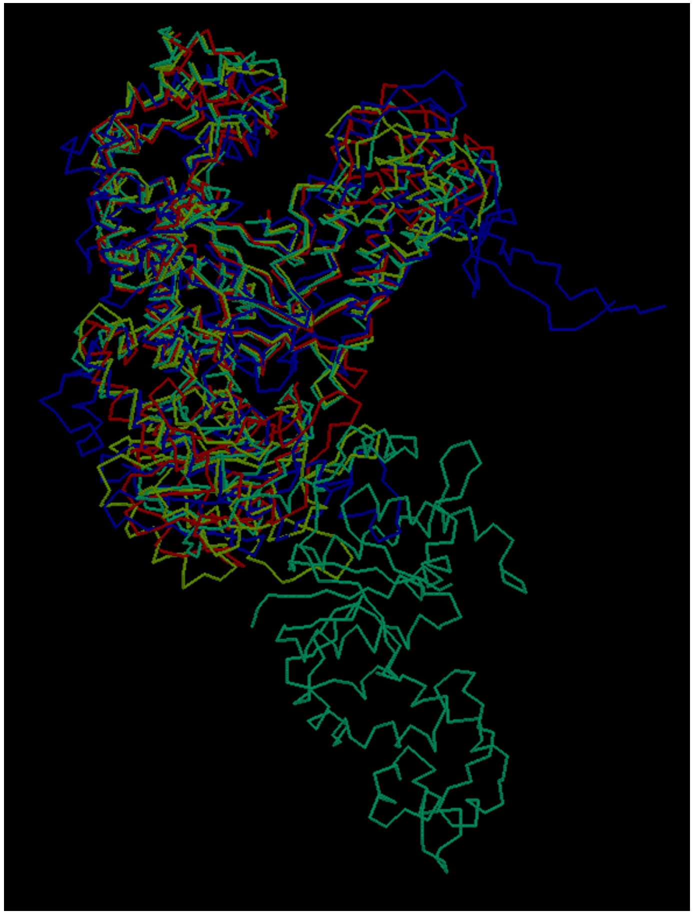
FAMILY A STAMP



Taq pol I, Bst pol I and E.coli pol I

Sc 6.00 RMS 1.61



Taq pol I, Bst pol I, E.coli pol I and T7 pol

Sc 4.82 RMS 2.40

FAMILY X

Members:

- DNA polymerase beta
- DNA polymerase lambda
- DNA polymerase mu
- TdT

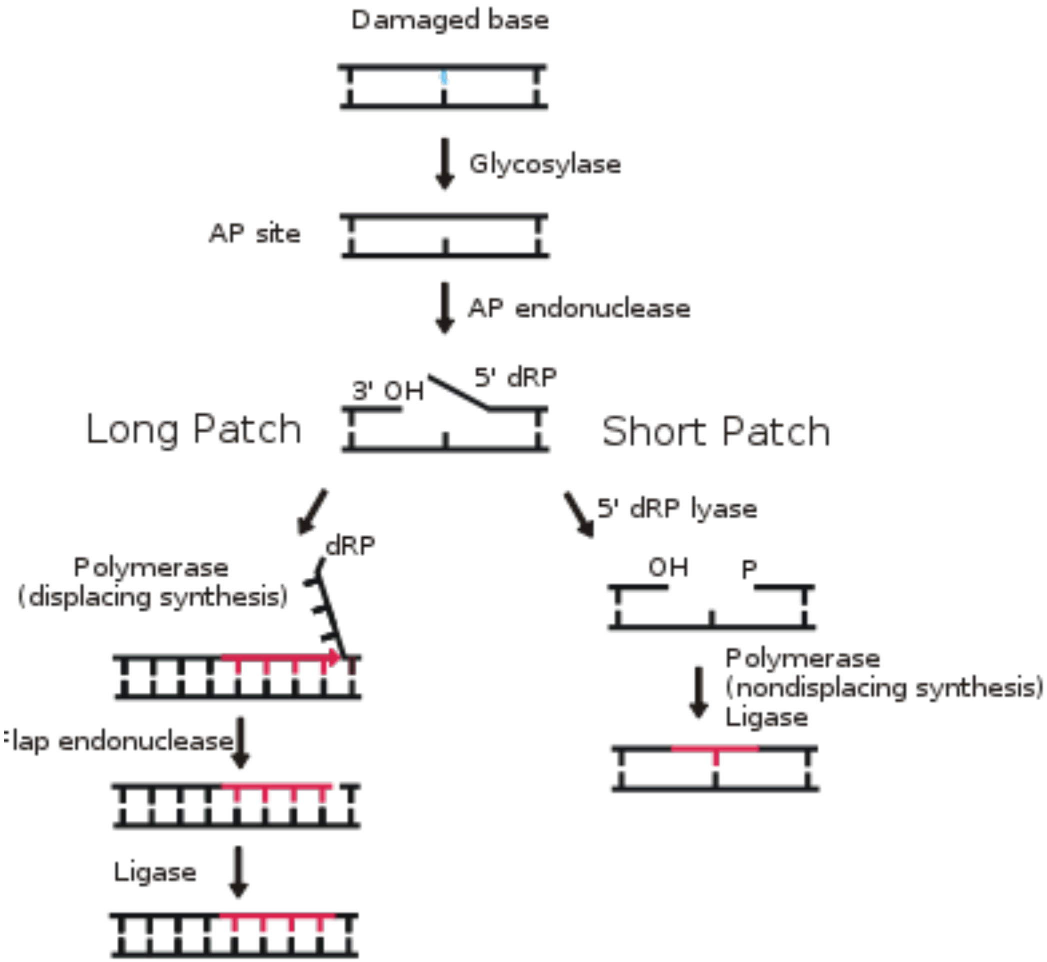
DNA-polymerase lambda

All family members being found in vertebrates

Function: involved in **base excision repair (BER)**

FAMILY X

BASE EXCISION REPAIR (BER)



Removal of damage base

Incision of the sugar-phosphate backbone 5’ of the AP site

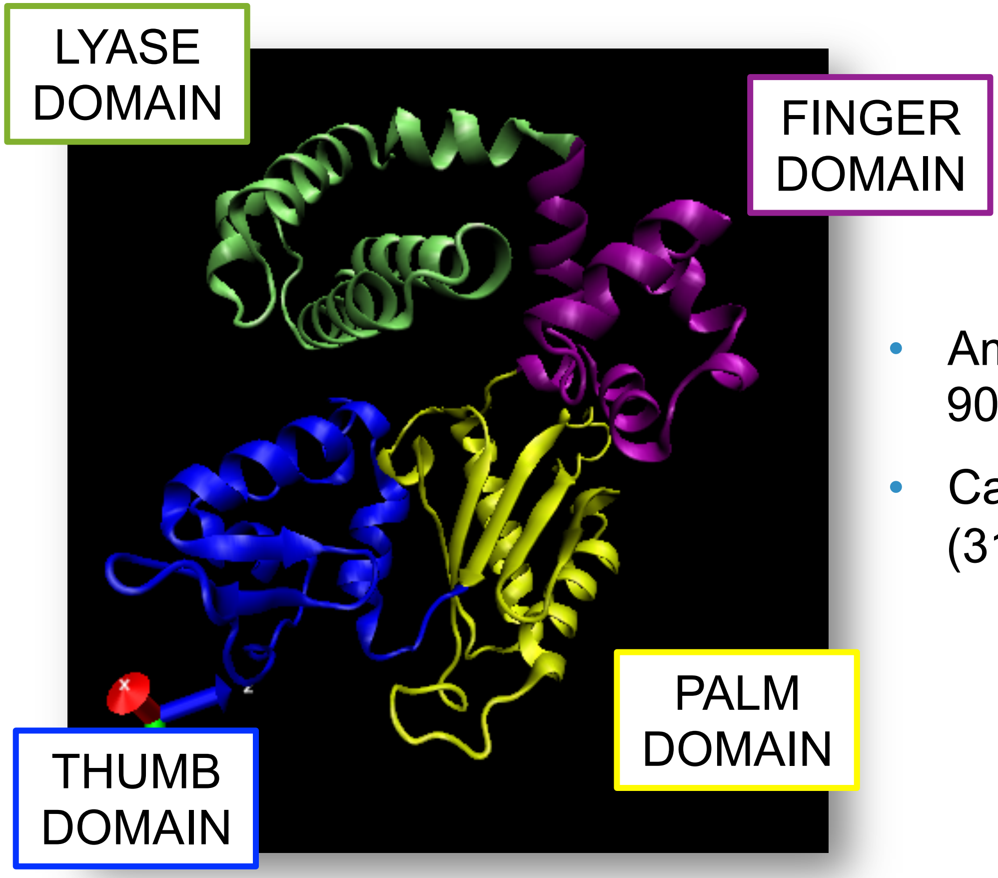
5’ terminal dRP site

Replace the missing nucleotide

dRP group is removed

The gap is ligated

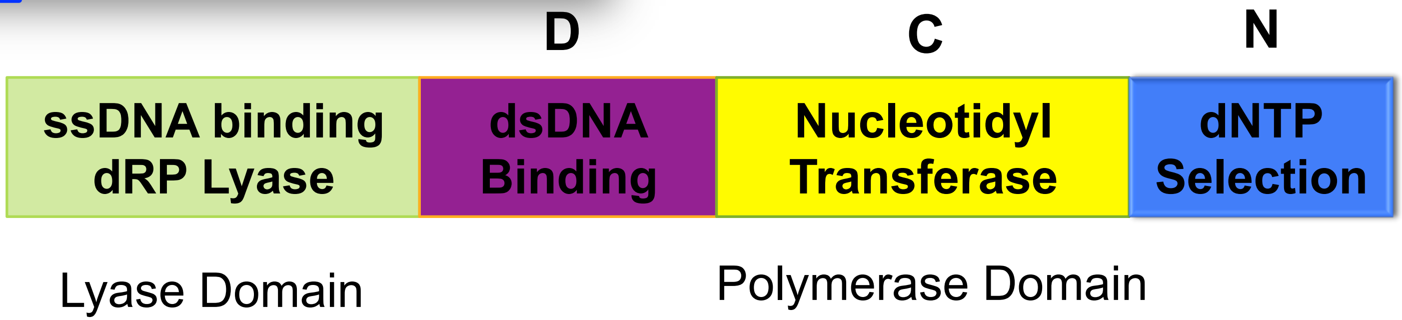
DNA POLYMERASE BETA



DOMAINS

- Amino- terminal lyase domain (8 kDa ≈ 90 residues)
- Carboxyl- terminal polymerase domain (31 kDa ≈ 250 residues)

1BPY, 2.20Å



D C N

ssDNA binding dRP Lyase

dsDNA Binding

Nucleotidyl Transferase

dNTP Selection

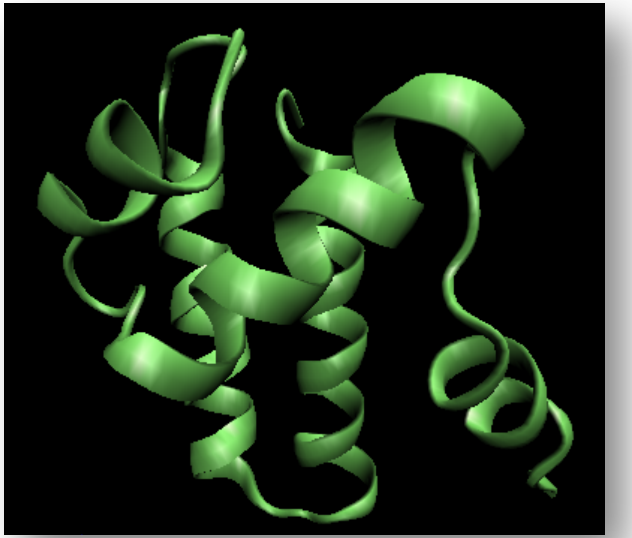
Lyase Domain

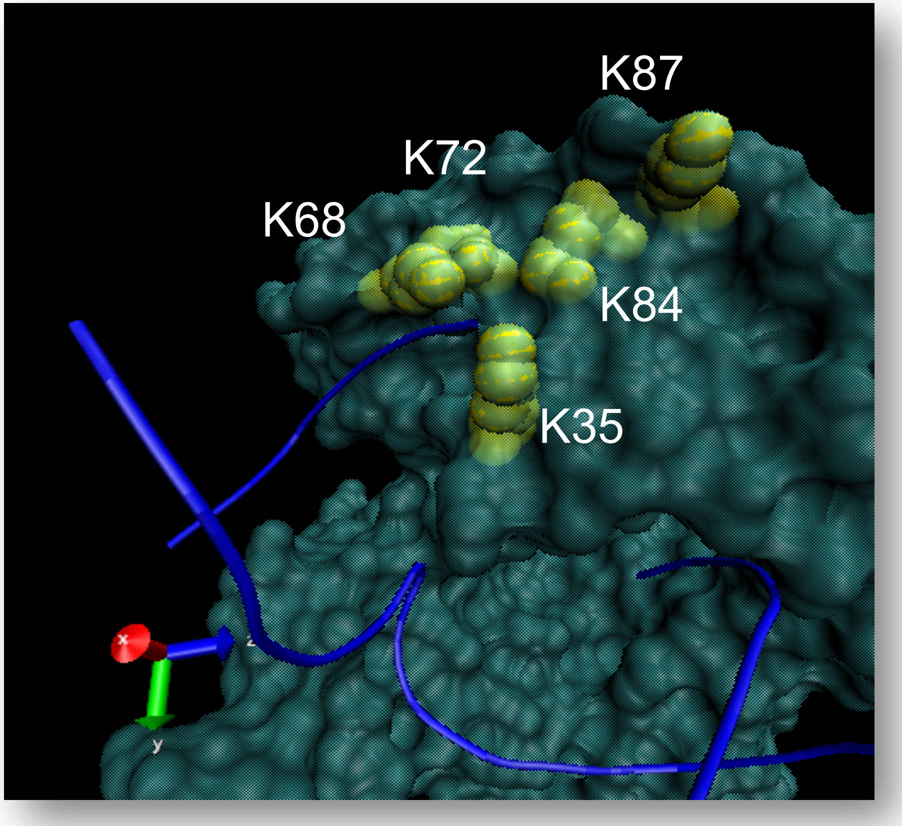
Polymerase Domain

DNA POLYMERASE BETA

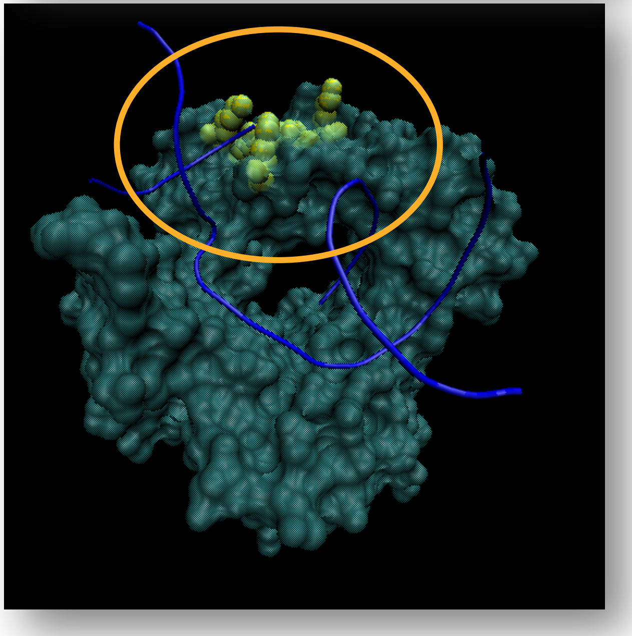
LYASE DOMAIN

The dRP lyase active site (Lys72) is observed to be a part of **a lysine-rich pocket** on the surface of the 8kDa domain



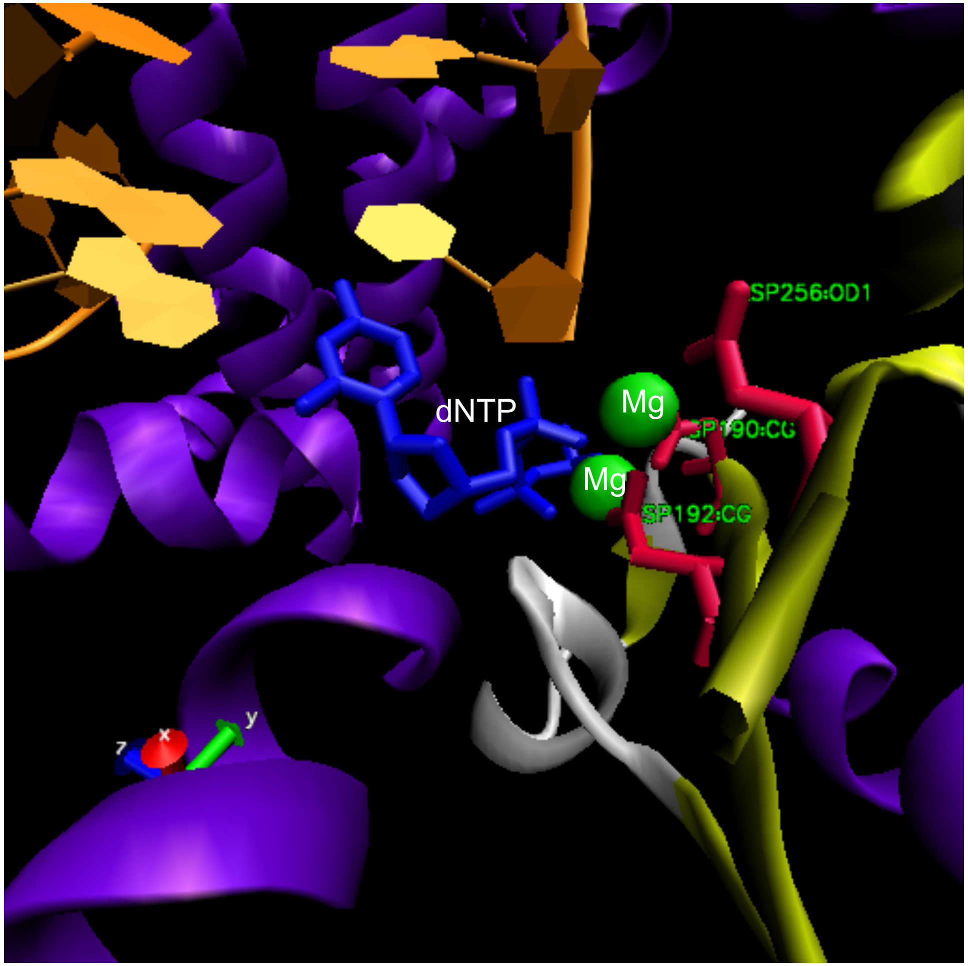


Lysine-rich pocket on the surface of 8-kDa domain



DNA POLYMERASE BETA

PALM DOMAIN

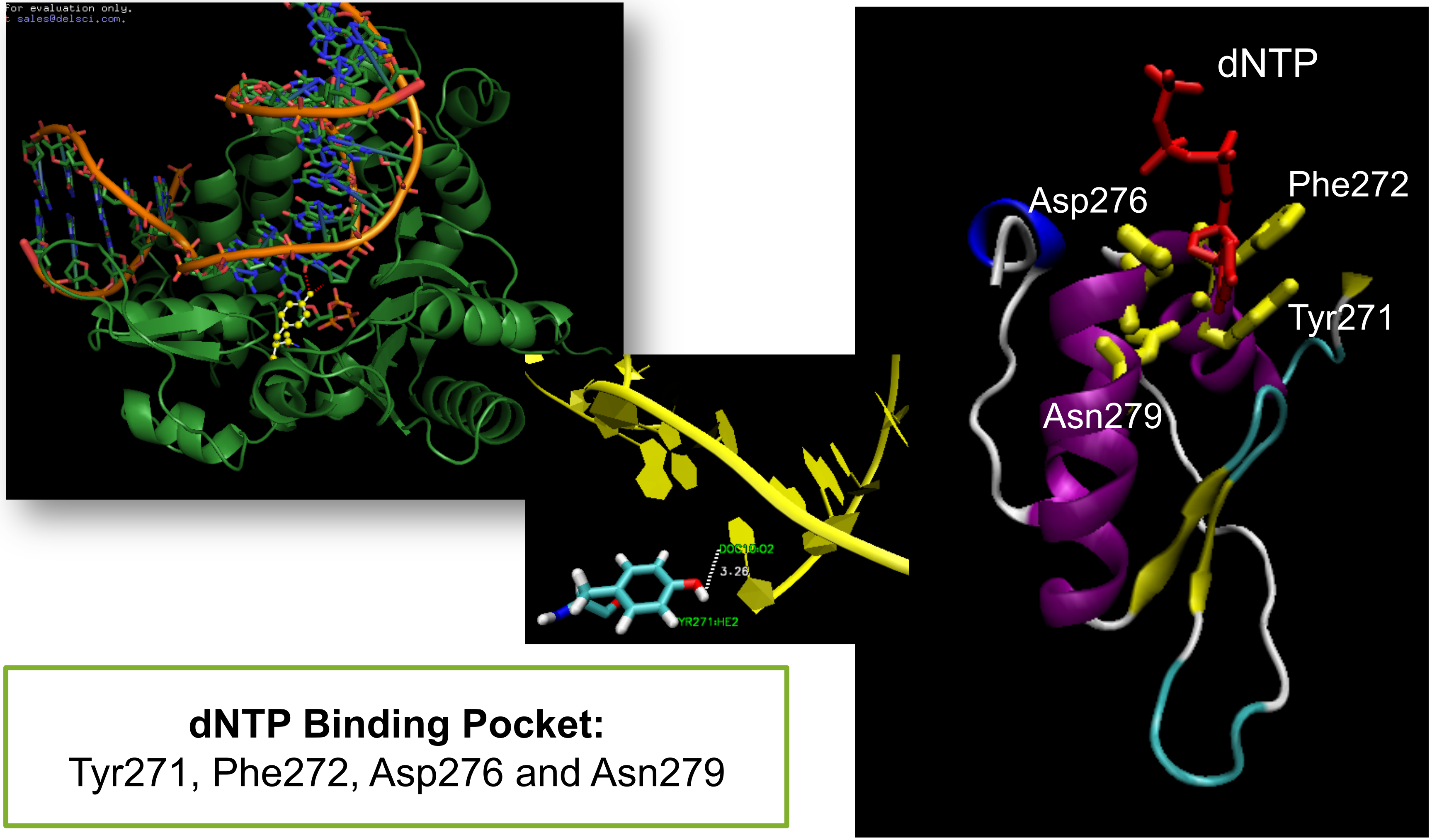


There are three aspartates that coordinate two divalent cations (Mg 2^+), that assist the nucleotydil transferase reaction.

Asp 190
Asp 192
Asp 256

DNA POLYMERASE BETA

NUCLEOTIDE SELECTIVITY DURING dNTP BINDING



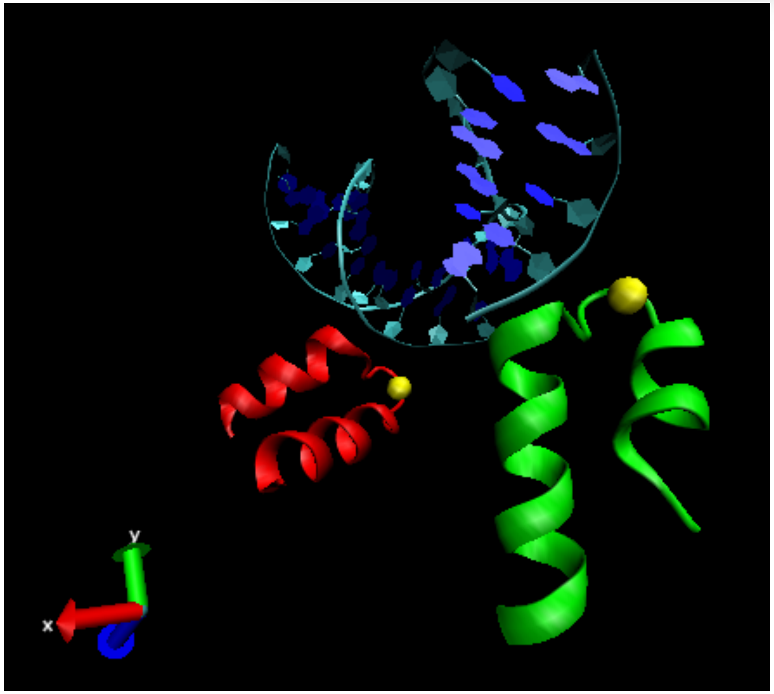
dNTP Binding Pocket:
Tyr271, Phe272, Asp276 and Asn279

HELIX-HAIRPIN-HELIX (HhH) MOTIF

- Involved in non-sequence-specific DNA binding
- Structurally, the motif forms into a pair of anti-parallel α-helices connected by a hairpin-like loop
- Sequence pattern: glycine-hydrofobic residue- glycine

There are two HhH in the structure of DNA polymerase beta:

- **Lyase domain**
- **Fingers domain**



DNA POLYMERASE BETA

SEQUENCE ALIGNMENT

```
CLUSTAL FORMAT for T-COFFEE Version_7.54 [http://www.tcoffee.org] [MODE:  ], CPU=0.22 sec, SCORE=87, Nseq=3, Len=383

1BPY_A|PDBID|CHAIN|SEQUENCE  -----MSKRKAP-QETLNGGITDMLTELAN---FEKNVSQAIHKYNAYRKAASVIAKYPH
1XSN_A|PDBID|CHAIN|SEQUENCE  -----MAQPSSQKATNHNLHITEKLEVLAKAYSVQGDKW----RALGYAKAINALKSFHK
2IHM_A|PDBID|CHAIN|SEQUENCE  SMPAYACQRPSP-LTHHNTLLSEALETLAEAAGFEANEG----RLLSFSRAASVLKSLPC
                                   .:  :      *  ::: *  **:   .: :      :  .: :* ..: .

1BPY_A|PDBID|CHAIN|SEQUENCE  KIKSGAEAKKLPGVGTKIAEKIDEFLATGKLRKLEKIRQDDTSSSINFLTRVSGIGPSAA
1XSN_A|PDBID|CHAIN|SEQUENCE  PVTSYQEACSIPGIGKRMAEKIIEILESGHLRKLDHI--SESVPVLELFSNIWGAGTKTA
2IHM_A|PDBID|CHAIN|SEQUENCE  PVASLSQLHGLPYFGEHSTRVIQELLEHGTCEEVKQVRCSERYQTMKLFTQVFGVGVKTA
                              : *  :   :* .* : :. * *:*  *  .::.::  .:    :::::.: * * .:*

1BPY_A|PDBID|CHAIN|SEQUENCE  RKFVDEGIKTLEDLRKNEDKLNHHQRIGLKYFGDFEKRIPREEMLQMQDIVLNEVKKVDS
1XSN_A|PDBID|CHAIN|SEQUENCE  QMWYQQGFRSLEDIRSQA-SLTTQQAIGLKHYSDFLERMPREEATEIEQTVQKAAQAFNS
2IHM_A|PDBID|CHAIN|SEQUENCE  NRWYQEGLRTLDELREQPQRLTQQQKAGLQYYQDLSTPVRRADAEALQQLIEAAVRQTLP
                             . : ::*:::*:::*.:   *. :*  **::: *:   : * :   ::: :   .:   .

1BPY_A|PDBID|CHAIN|SEQUENCE  EYIATVCGSFRRGAESSGDMDVLLTHPSFTSESTKQPKLLHQVVEQLQKVHFITD-----
1XSN_A|PDBID|CHAIN|SEQUENCE  GLLCVACGSYRRGKATCGDVDVLITHPDGRSHRGIFSRLL----DSLRQEGFLTD-----
2IHM_A|PDBID|CHAIN|SEQUENCE  GATVTLTGGFRRGKLQGHDVDFLITHPEEGQEVGLLPKVM----SCLQSQGLVLYHQYHR
                                 .  *.:***     *:*.*:***.  ..    .:::    . *:.  ::

1BPY_A|PDBID|CHAIN|SEQUENCE  -TLS----K----------------------GETKFMGVCQLPSKNDEKEYPHRRIDIRL
1XSN_A|PDBID|CHAIN|SEQUENCE  -DLVSQEENG---------------------QQQKYLGVCRLPGPG----RRHRRLDIIV
2IHM_A|PDBID|CHAIN|SEQUENCE  SHLADSAHNLRQRSSTMDVFERSFCILGLPQPQQAALAGALPPCPT----WKAVRVDLVV
                               *     :                       :   :. .  *           *:*: :

1BPY_A|PDBID|CHAIN|SEQUENCE  IPKDQYYCGVLYFTGSDIFNKNMRAHA-LEKGFTINEYTIRPLGVT------GVAGEPLP
1XSN_A|PDBID|CHAIN|SEQUENCE  VPYSEFACALLYFTGSAHFNRSMRALA-KTKGMSLSEHALSTAVVRNTHGAKVGPGRVLP
2IHM_A|PDBID|CHAIN|SEQUENCE  TPSSQFPFALLGWTGSQFFERELRRFSRQEKGLWLNSHGLFDPE----------QKRVFH
                              * .::  .:* :***  *::.:*  :   **: :..: :                .  :

1BPY_A|PDBID|CHAIN|SEQUENCE  VDSEKDIFDYIQWKYREPKDRSE
1XSN_A|PDBID|CHAIN|SEQUENCE  TPTEKDVFRLLGLPYREPAERDW
2IHM_A|PDBID|CHAIN|SEQUENCE  ATSEEDVFRLLGLKYLPPEQRNA
                             . :*:*:*  :   *  * :*.
```

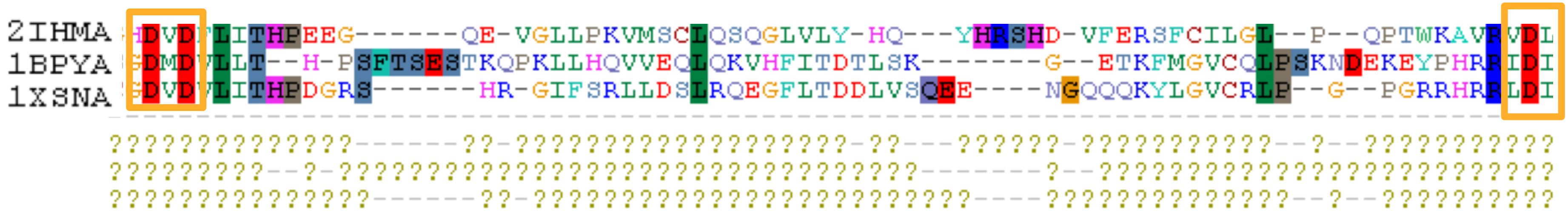
DNA polymerase beta (1BPY,2.20Å)
DNA polymerase lambda (1XSN,1.95Å)
DNA polymerase mu (2IHM, 2.40Å)

SCORE: 87

X FAMILY

STRUCTURAL ALIGNMENT

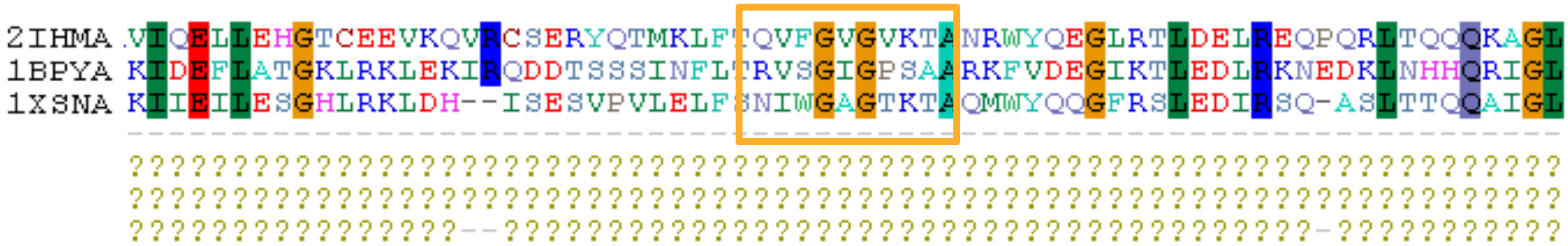
Asp of catalytic domain



```
2IHMA HDVDTLITHPEEG------QE-VGLLPKVMSCLQSQGLVLY-HQ---YHRSHD-VFERSFCILGL--P--QPTWKAVRVDL
1BPYA GDMDVLLT--H-PSFTSESTKQPKLLHQVVEQLQKVHFITDTLSK-------G--ETKFMGVCQLPSKNDEKEYPHRRIDI
1XSNA GDVDVLITHPDGRS------HR-GIFSRLLDSLRQEGFLTDDLVSQEE----NGQQQKYLGVCRLP--G--PGRRHRRLDI
      ??????????????------??-???????????????????-??---??????-???????????--?--???????????
      ?????????--?-????????????????????????????????-------?--??????????????????????????????????
      ???????????????------??-?????????????????????????----??????????????--?--??????????
```

DNA polymerase beta (1BPY)
DNA polymerase lambda (1XSN)
DNA polymerase mu (2IHM)

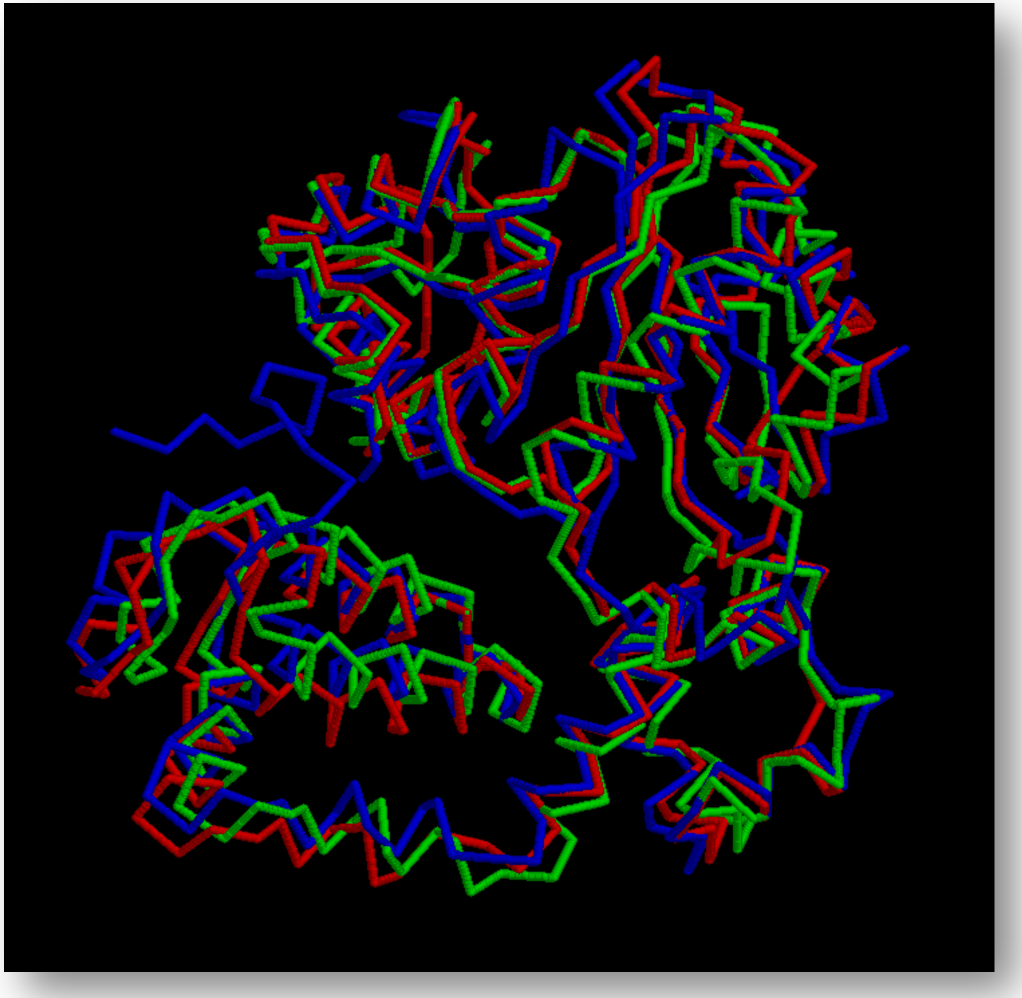
Helix-hairpin-helix motif



```
2IHMA VIQELLEHGTCEEVKQVRCSERYQTMKLFTQVFGVGVKTANRWYQEGLRTLDELREQPQRLTQQQKAGL
1BPYA KIDEFLATGKLRKLEKIRQDDTSSSINFLTRVSGIGPSAARKFVDEGIKTLEDLRKNEDKLNHHQRIGL
1XSNA KIIEILESGHLRKLDH--ISESVPVLELFSNIWGAGTKTAQMWYQQGFRSLEDIRSQ-ASLTTQQAIGL
      ?????????????????????????????????????????????????????????????????????
      ?????????????????????????????????????????????????????????????????????
      ??????????????????--???????????????????????????????????????-???????????
```

X FAMILY

STRUCTURAL ALIGNMENT



DNA polymerase beta (1BPY)
DNA polymerase lambda (1XSN)
DNA polymerase mu (2IHM)

RMSD:1,89
SCORE: 8,50

X FAMILY

EVOLUTIONARY RELATIONSHIP BETWEEN FAMILY X

1360 *M. Garcia-Diaz et al. / DNA Repair 4 (2005) 1358–1367*

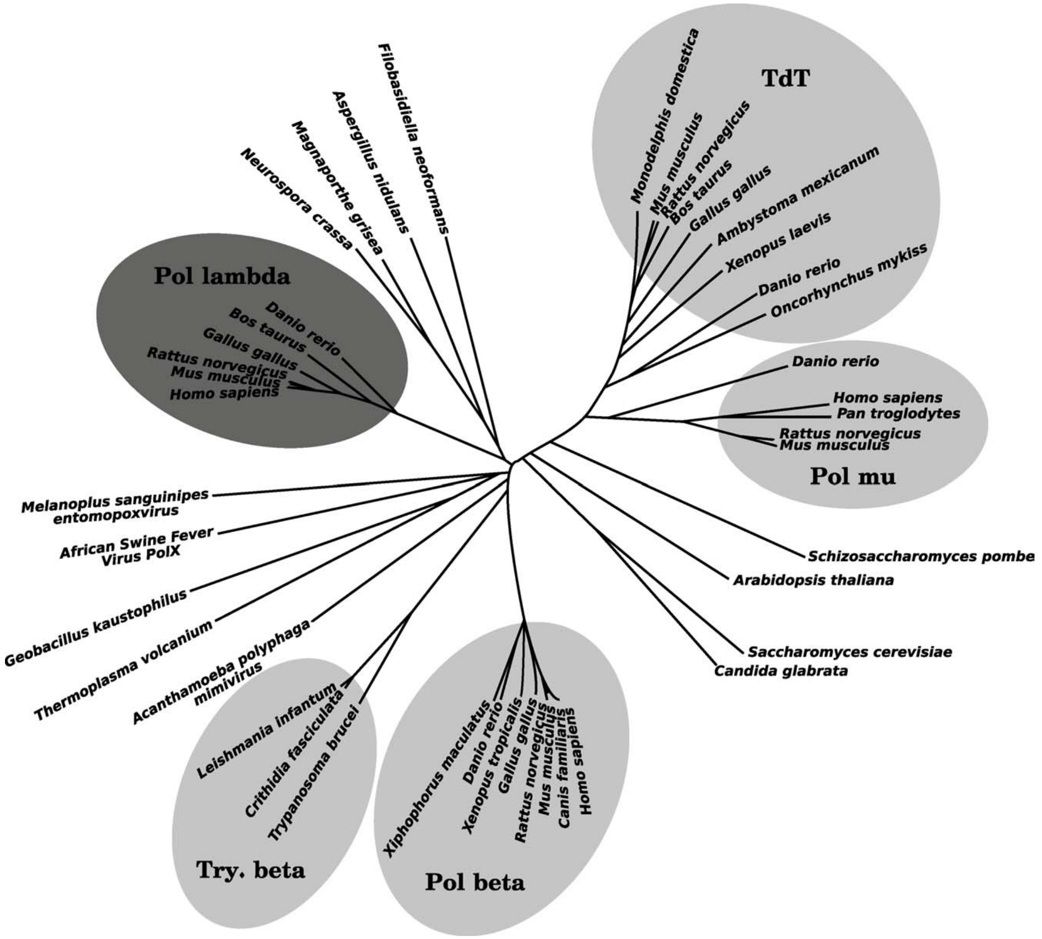


Fig. 1. Evolutionary relationships between family X members. An unrooted phylogenetic tree built using a primary sequence alignment of a segment of the catalytic domain. Different enzymes are grouped (shaded areas) into the five main enzyme classes in the family: Pol β, Pol λ, Pol μ, TdT, and trypanosomatid (Try) Pol β-like enzymes.

DNA polymerase lambda and DNA polymerase beta have a less evolutionary distant than DNA polymerase mu

FAMILY C

Members:

- **DNA polymerase III**

The main eubacterial DNA polymerases that is responsible for the **replication of DNA duplex**

Organisms studied

- ***E. Coli***: 2HNH (2.30Å)
- ***T. aquaticus***
  2HPI (3 Å)
  3EOD (4.5 Å)

Figure 9. Subunit alpha of *E. coli* DNA polymerase III

DNA POLYMERASE III

DNA polymerase III holoenzyme is composed of 10 subunits

- The core polymerase: α, Ɛ, θ.

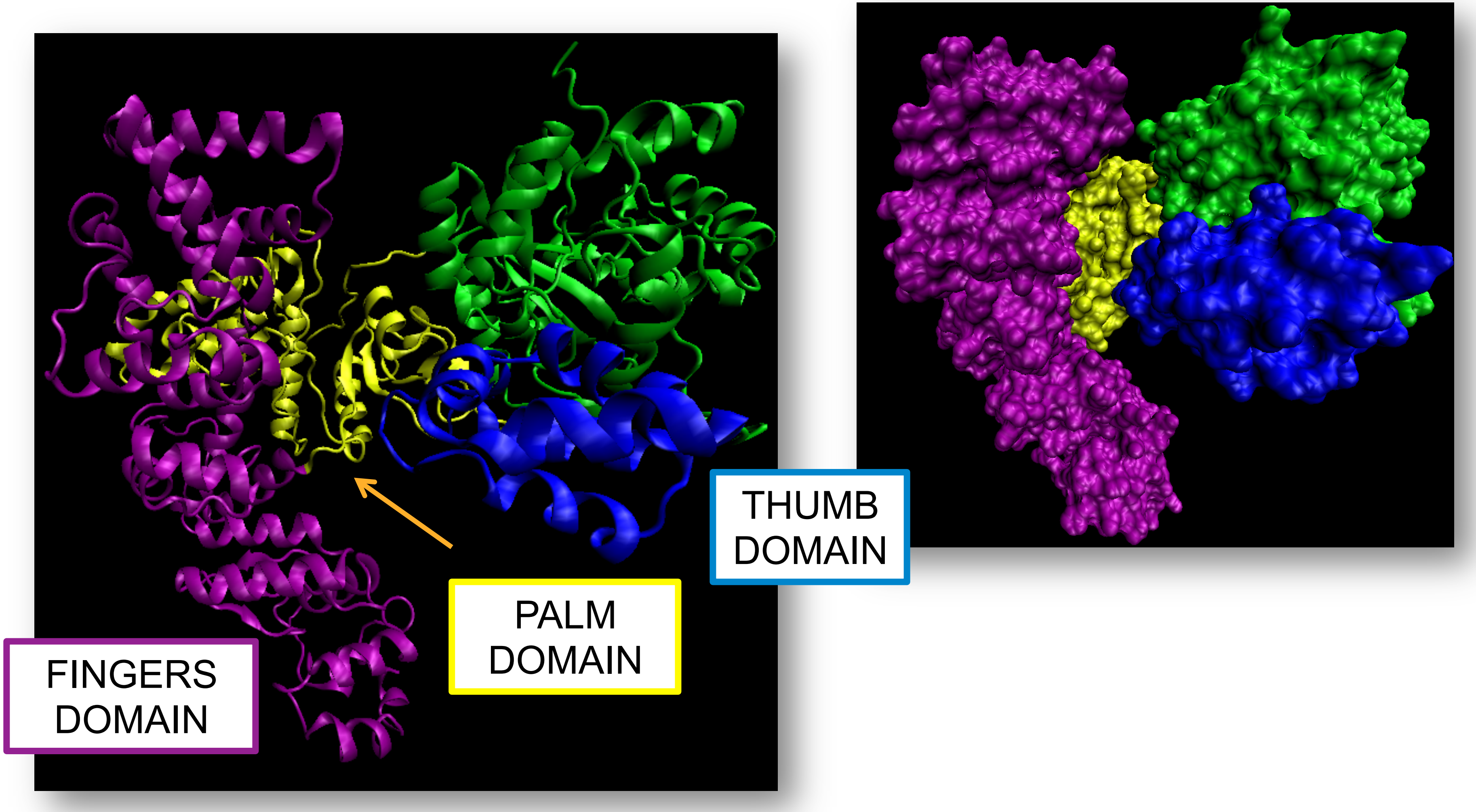
α
catalytic subunit

Ɛ
3’-5’ proofreading exonuclease

Θ
Minor stimulation of Ɛ

- The clamp loader complex (γ complex): multisubunit ATPase.
- The β-sliding clamp: encircles duplex DNA.

ALPHA SUBUNIT OF DNA POLYMERASE III



Subunit alpha of *E. coli* DNA polymerase III

ALPHA SUBUNIT OF DNA POLYMERASE III

PHP | Palm | Thumb | Fingers | β-binding | C-terminal

Subunit alpha of *T. aquaticus* DNA polymerase III

DOMAINS

- PHP domain (N-terminal)
- β binding domain
- C-terminal domain

STRUCTURE OF ALPHA SUBUNIT OF DNA POL III

PALM DOMAIN

Palm domain of *E.coli* DNA pol III

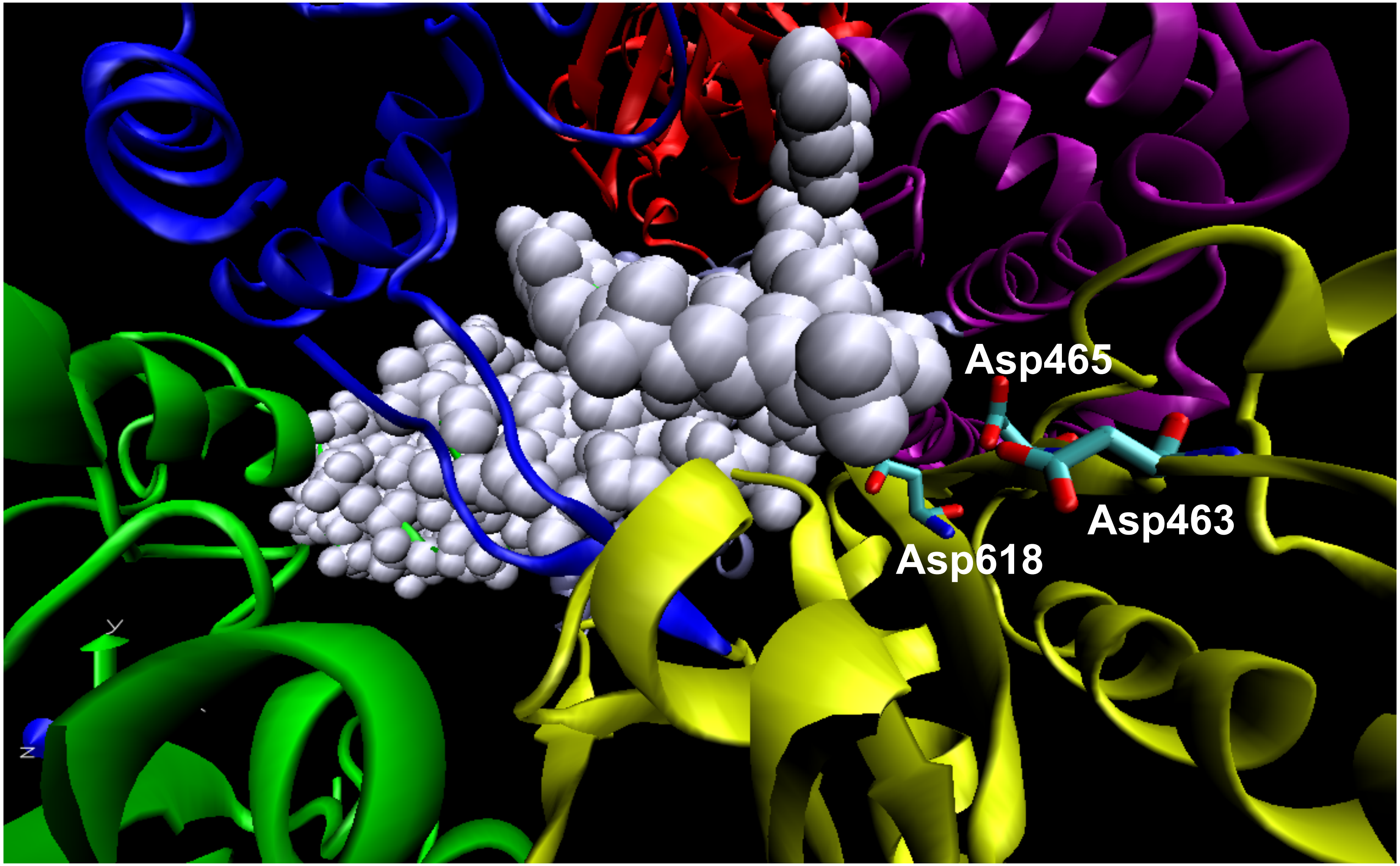
βNT fold: 5 stranded mixed βsheet

3 catalytic conserved aspartate residues in *T. aquaticus*
Asp463, Asp465 and Asp618

Equivalent residues in *E.coli*
Asp401, AspD403, and Asp555

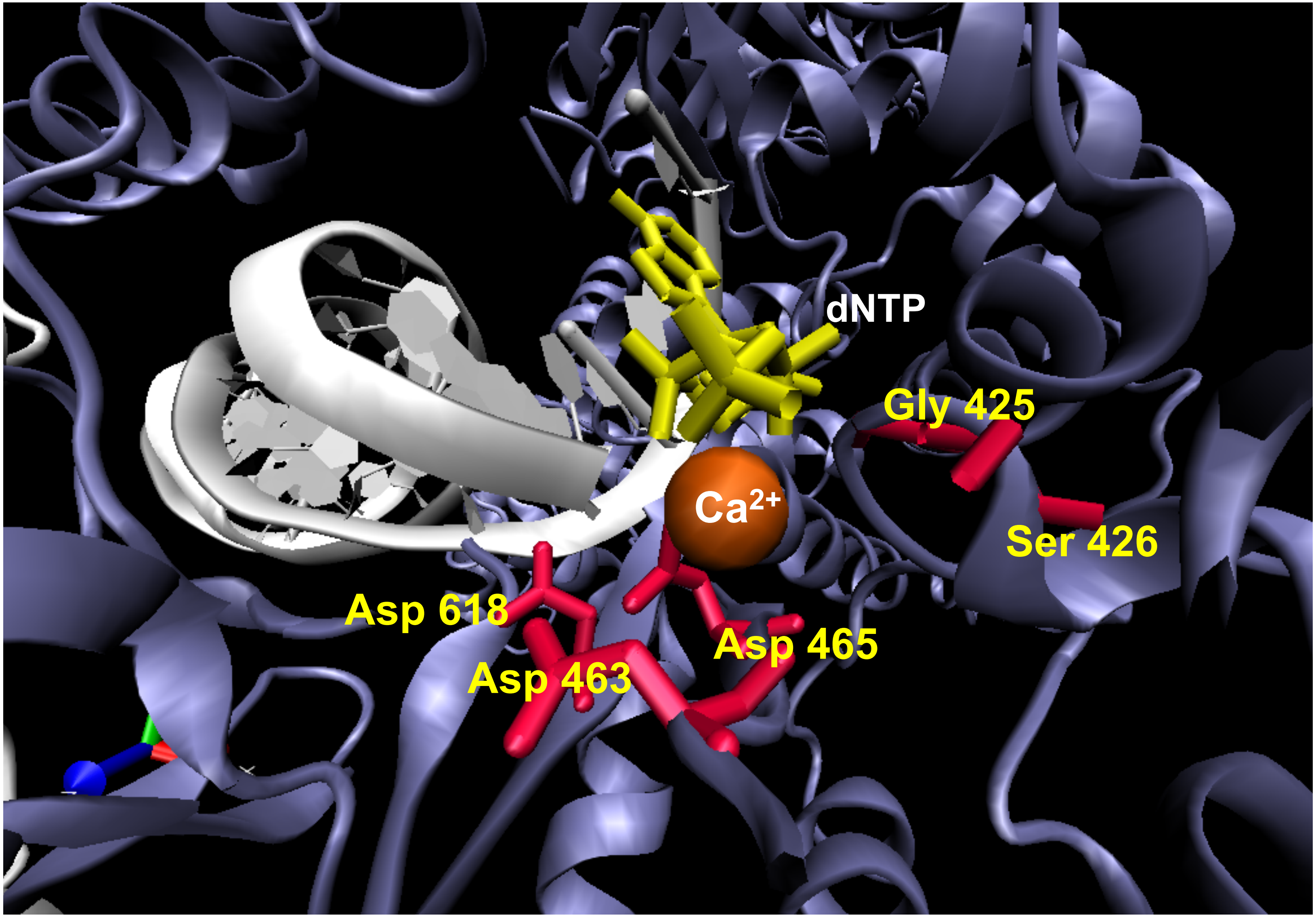
STRUCTURE OF ALPHA SUBUNIT OF DNA POL III: *T. aquaticus*

PALM DOMAIN



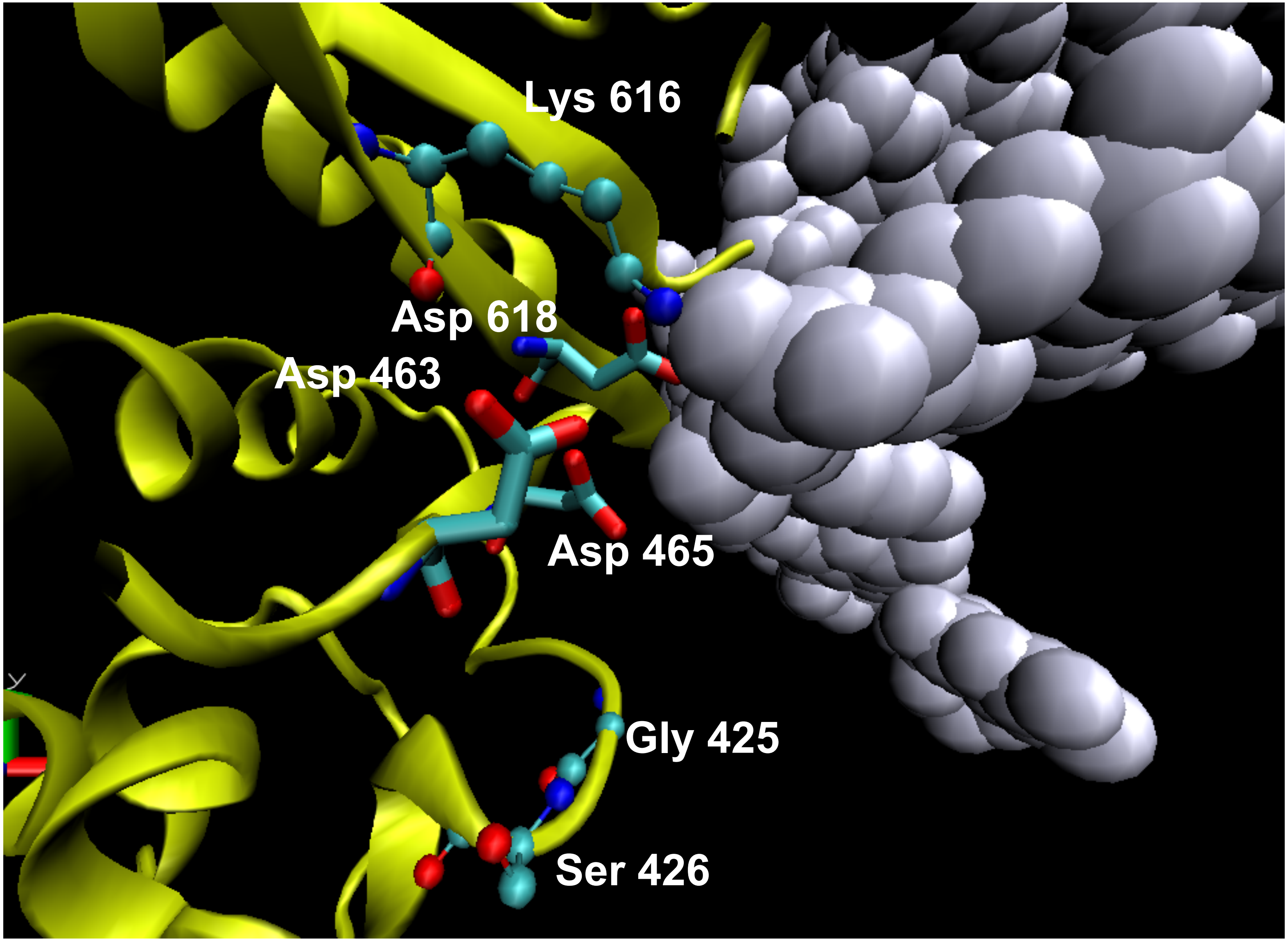
Palm domain of *E.coli* DNA pol III

PALM DOMAIN

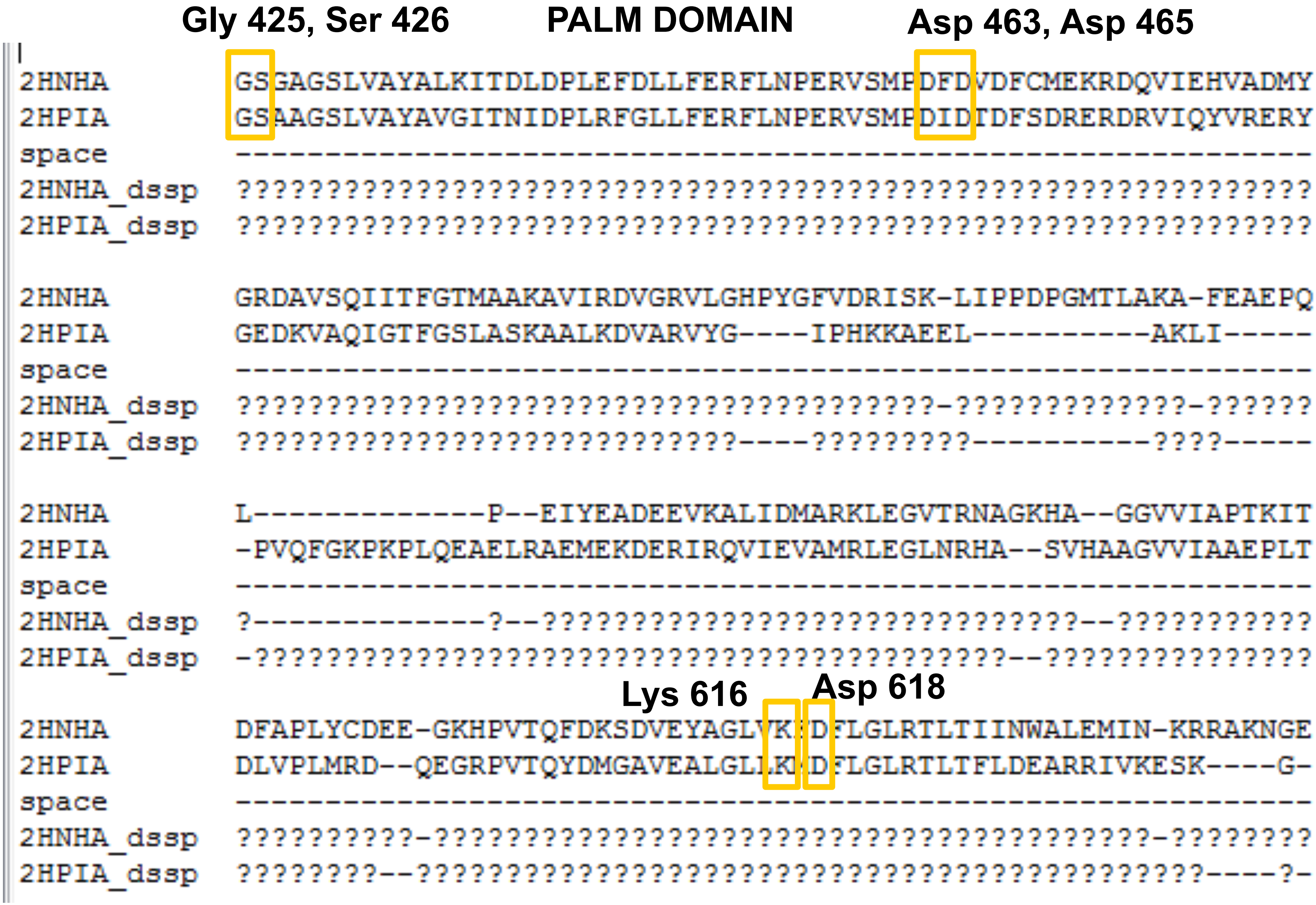


Palm domain of *E.coli* DNA pol III

PALM DOMAIN



T. aquaticus vs. *E. coli*



Gly 425, Ser 426

PALM DOMAIN

Asp 463, Asp 465

Lys 616

Asp 618

```
2HNHA        GSGAGSLVAYALKITDLDPLEFDLLFERFLNPERVSMPDFDVDFCMEKRDQVIEHVADMY
2HPIA        GSAAGSLVAYAVGITNIDPLRFGLLFERFLNPERVSMPDIDTDFSDRERDRVIQYVRERY
space        ------------------------------------------------------------
2HNHA_dssp   ????????????????????????????????????????????????????????????
2HPIA_dssp   ????????????????????????????????????????????????????????????

2HNHA        GRDAVSQIITFGTMAAKAVIRDVGRVLGHPYGFVDRISK-LIPPDPGMTLAKA-FEAEPQ
2HPIA        GEDKVAQIGTFGSLASKAALKDVARVYG----IPHKKAEEL----------AKLI-----
space        ------------------------------------------------------------
2HNHA_dssp   ???????????????????????????????????????-?????????????-??????
2HPIA_dssp   ????????????????????????????----?????????----------????-----

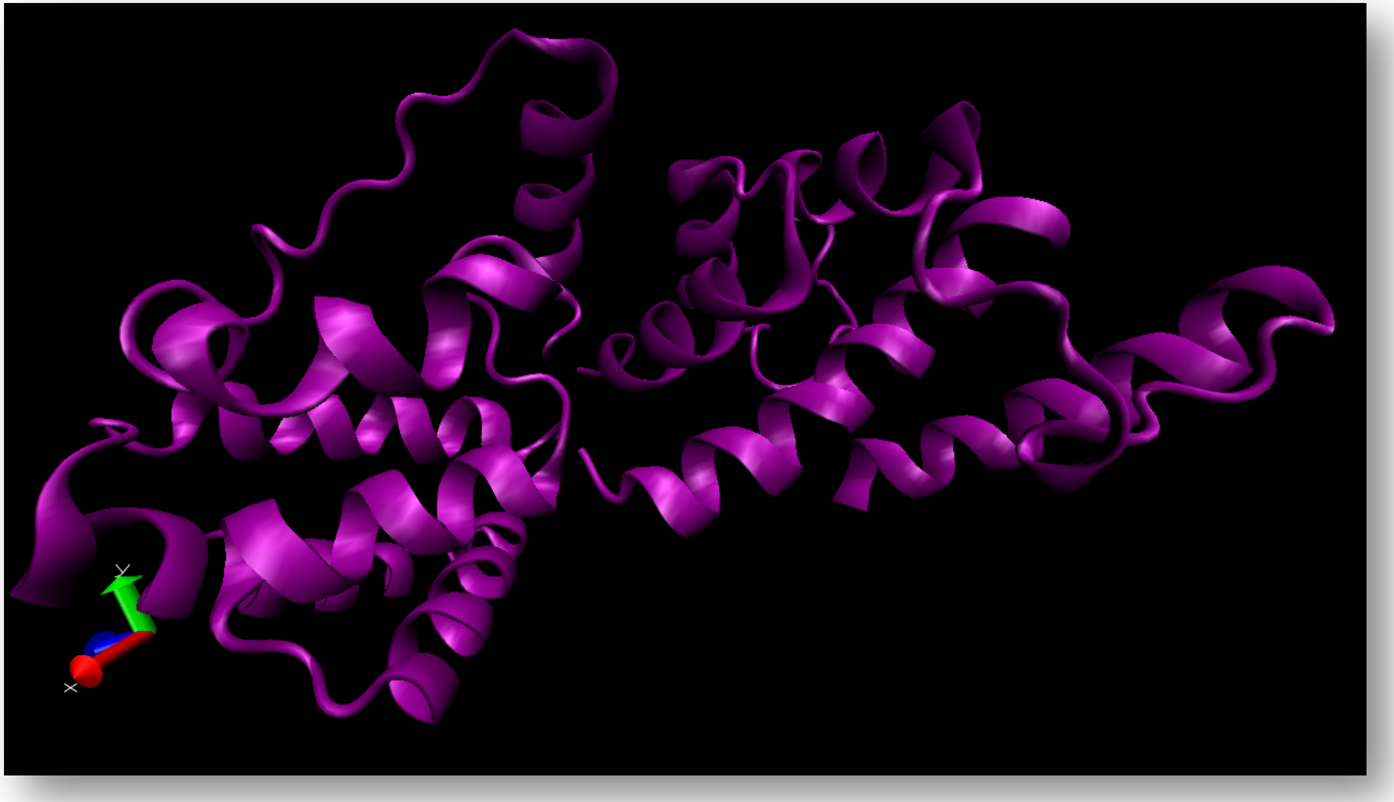
2HNHA        L-------------P--EIYEADEEVKALIDMARKLEGVTRNAGKHA--GGVVIAPTKIT
2HPIA        -PVQFGKPKPLQEAELRAEMEKDERIRQVIEVAMRLEGLNRHA--SVHAAGVVIAAEPLT
space        ------------------------------------------------------------
2HNHA_dssp   ?-------------?--?????????????????????????????--???????????
2HPIA_dssp   -???????????????????????????????????????????--???????????????

2HNHA        DFAPLYCDEE-GKHPVTQFDKSDVEYAGLVK[illegible]DFLGLRTLTIINWALEMIN-KRRAKNGE
2HPIA        DLVPLMRD--QEGRPVTQYDMGAVEALGLLK[illegible]DFLGLRTLTFLDEARRIVKESK----G-
space        ------------------------------------------------------------
2HNHA_dssp   ??????????-???????????????????????????????????????-????????
2HPIA_dssp   ????????--??????????????????????????????????????????----?-
```

STRUCTURE OF DNA POL III:
T. aquaticus

FINGERS DOMAIN

A large crescent-shaped structure composed **exclusively of alpha helixes**

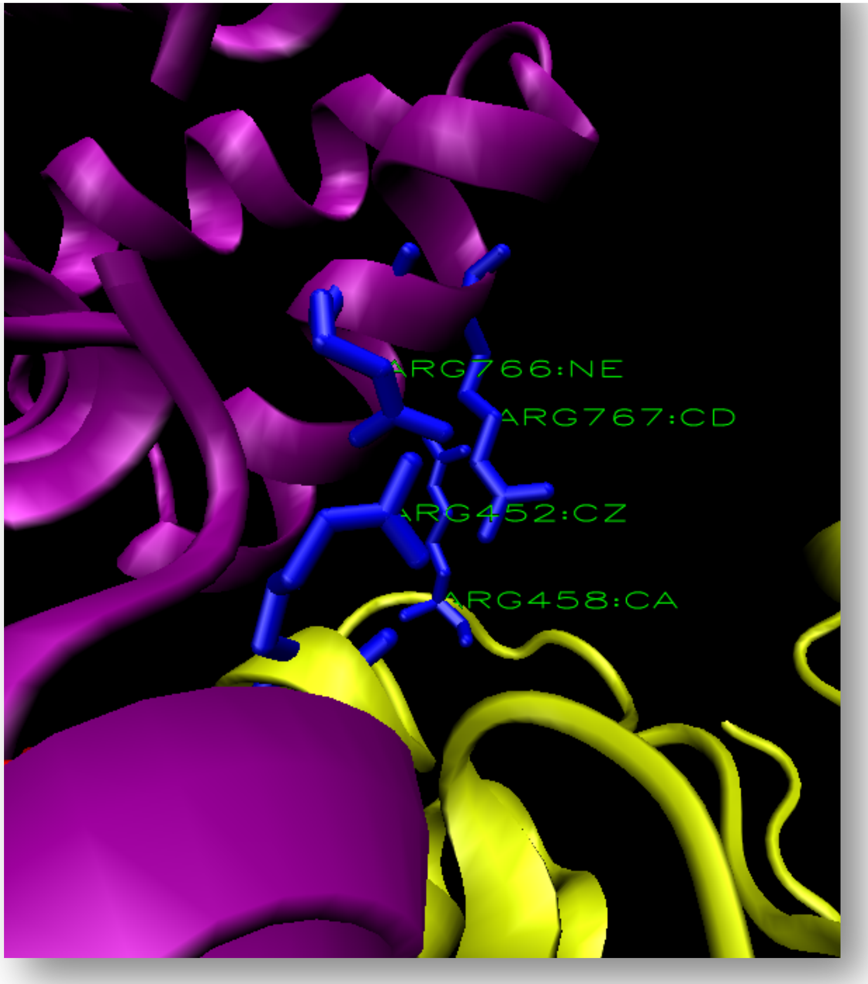


Fingers domain of *T.aquaticus* DNA pol III

STRUCTURE OF DNA POL III

T. aquaticus

FINGERS DOMAIN



The triphosphate interacts with a cluster of 4 highly conserved arginine residues:

- Arg452 and Arg458 from the **palm**
- Arg766 and Arg767 from **fingers domain**

```
2HNHA         GSGAGSLVAYALKITDLDPLEFDLLFERFLNPERVSMPDFDVDFCMEKRDQVIEHVADMY
2HPIA         GSAAGSLVAYAVGITNIDPLRFGLLFERFLNPERVSMPDIDTDFSDRERDRVIQYVRERY
space         ------------------------------------------------------------
2HNHA_dssp    ????????????????????????????????????????????????????????????
2HPIA_dssp    ????????????????????????????????????????????????????????????

2HNHA         GRDAVSQIITFGTMAAKAVIRDVGRVLGHPYGFVDRISK-LIPPDPGMTLAKA-FEAEPQ
2HPIA         GEDKVAQIGTFGSLASKAALKDVARVYG----IPHKKAEEL----------AKLI-----
space         ------------------------------------------------------------
2HNHA_dssp    ???????????????????????????????????????-?????????????-??????
2HPIA_dssp    ????????????????????????????----?????????----------????-----

2HNHA         L-------------P--EIYEADEEVKALIDMARKLEGVTRNAGKHA--GGVVIAPTKIT
2HPIA         -PVQFGKPKPLQEAELRAEMEKDERIRQVIEVAMRLEGLNRHA--SVHAAGVVIAAEPLT
space         ------------------------------------------------------------
2HNHA_dssp    ?-------------?--??????????????????????????????--???????????
2HPIA_dssp    -??????????????????????????????????????????--???????????????

2HNHA         DFAPLYCDEE-GKHPVTQFDKSDVEYAGLVKFDFLGLRTLTIINWALEMIN-KRRAKNGE
2HPIA         DLVPLMRD--QEGRPVTQYDMGAVEALGLLKMDFLGLRTLTFLDEARRIVKESK----G-
space         ------------------------------------------------------------
2HNHA_dssp    ??????????-????????????????????????????????????????-????????
2HPIA_dssp    ????????--????????????????????????????????????????????----?-

2HNHA         PLQSGMVDNFIDRKHGREEISYPDVQWQ---H-ESLKPVLEPTYGIILYQEQVMQIAQVL
2HPIA         P--MEHIPTYIRRHHGQEPVS--YA--EFPHAEKYLRPILDETYGIPVYQEQIMQIASQV
space         ------------------------------------------------------------
2HNHA_dssp    ????????????????????????????---?-???????????????????????????
2HPIA_dssp    ?--??????????????????--??--?????????????????????????????????

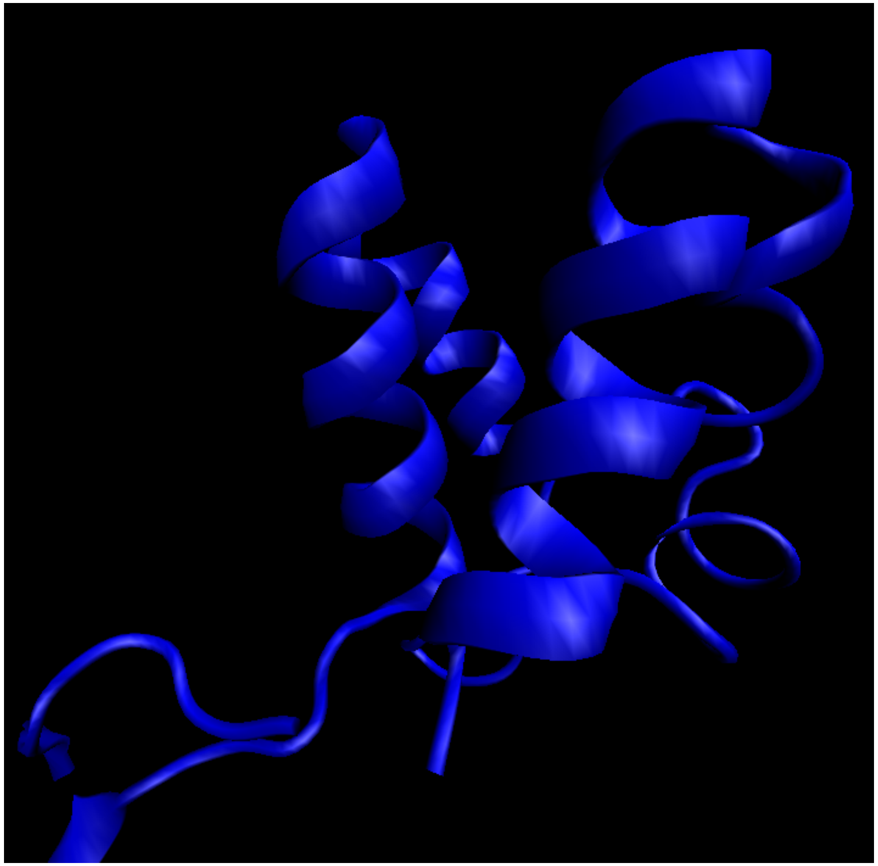
2HNHA         SGYTLGGADMLRRAMGKKKPEEMAKQRSVFAEGAEKNGINAELAMKIFDLVEKFAGYGFN
2HPIA         AGYSLGEADLLRRAMGKKRVEEMQKHRERFVRGAKERGVPEEEANRLFDMLEAFANYGFN
space         ------------------------------------------------------------
2HNHA_dssp    ????????????????????????????????????????????????????????????
2HPIA_dssp    ????????????????????????????????????????????????????????????
```

Conserved residues in palm and fingers domain

STRUCTURE OF DNA POL III

T. aquaticus

THUMB DOMAIN



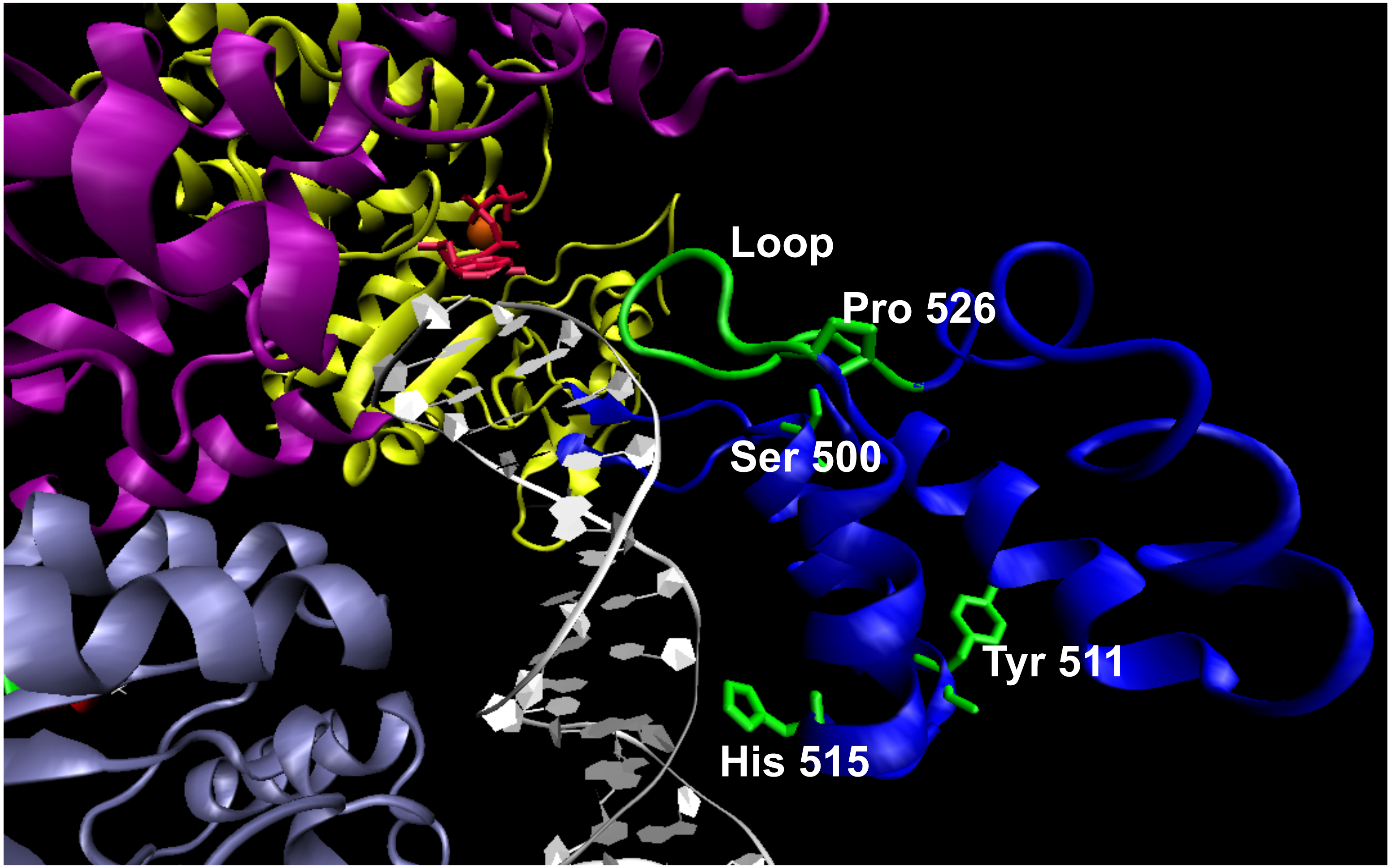
It is **4 helix** bundle

It binds to the primer/template DNA

STRUCTURE OF DNA POL III

T. aquaticus

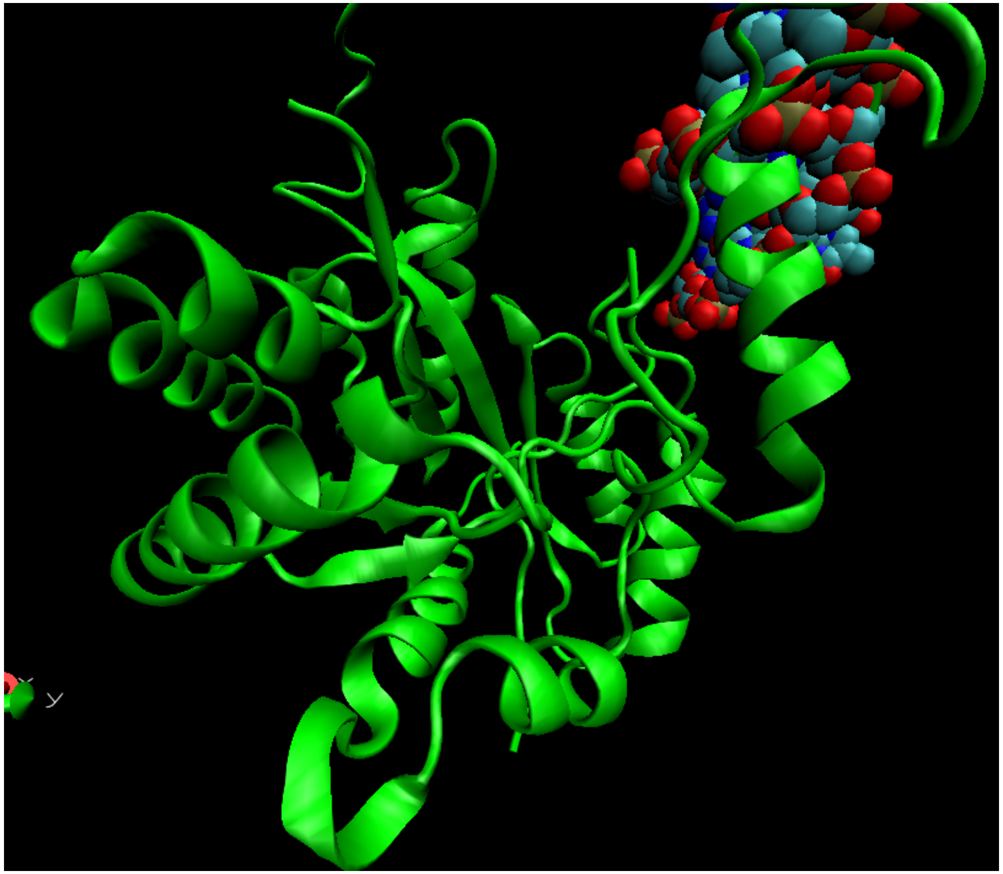
THUMB DOMAIN



STRUCTURE OF DNA POL III

T. aquaticus

PHP DOMAIN



A **TIM barrel-like fold** with seven-stranded β-barrel surrounded by seven helices

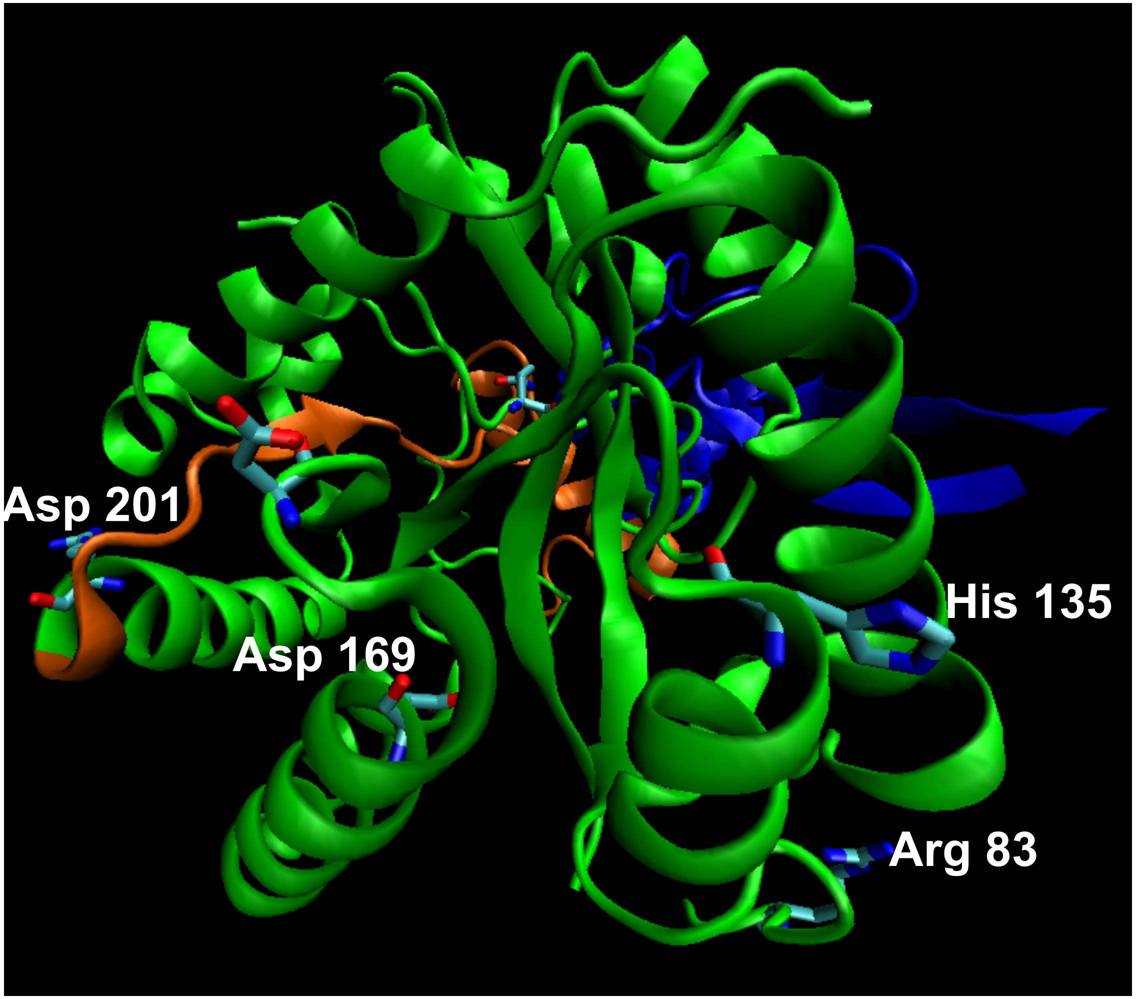
Function

It exhibits a zinc ion-dependent 3’-5’ exonuclease activity

STRUCTURE OF DNA POL III

T. aquaticus

PHP DOMAIN

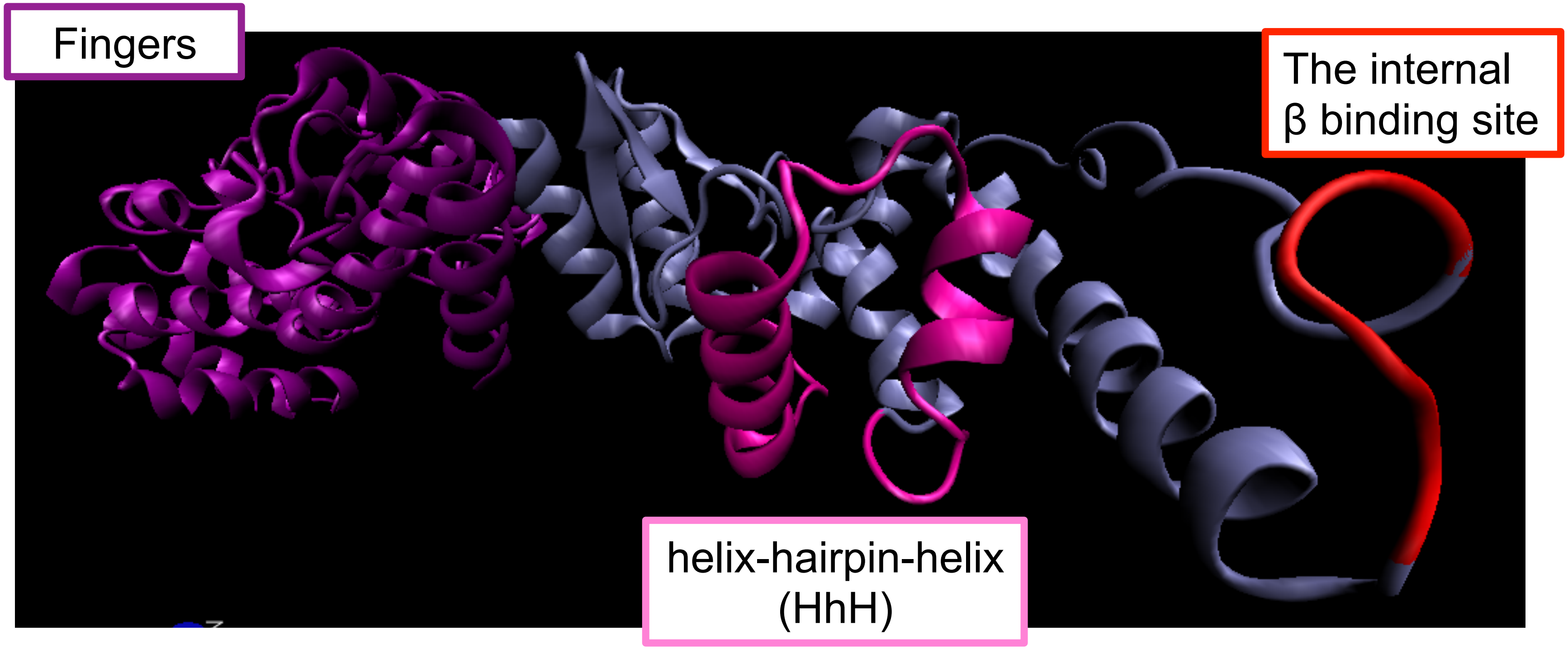


STRUCTURE OF DNA POL III

T. aquaticus

BETA BINDING DOMAIN

The β binding domain has an αβ fold and interacts extensively with the fingers domain



Fingers

The internal β binding site

helix-hairpin-helix (HhH)

BETA BINDING DOMAIN

```
2HNHA        PLQSGMVDNFIDRKHGREEISYPDVQWQ---H-ESLKPVLEPTYGIILYQEQVMQIAQVL
2HPIA        P--MEHIPTYIRRHHGQEPVS--YA--EFPHAEKYLRPILDETYGIPVYQEQIMQIASQV
space        ------------------------------------------------------------
2HNHA_dssp   ????????????????????????????---?-???????????????????????????
2HPIA_dssp   ?--??????????????????--??--?????????????????????????????????

2HNHA        SGYTLGGADMLRRAMGKKKPEEMAKQRSVFAEGAEKNGINAELAMKIFDLVEKFAGYGFN
2HPIA        AGYSLGEADLLRRAMGKKRVEEMQKHRERFVRGAKERGVPEEEANRLFDMLEAFANYGFN
space        ------------------------------------------------------------
2HNHA_dssp   ????????????????????????????????????????????????????????????
2HPIA_dssp   ????????????????????????????????????????????????????????????

2HNHA        KSHSAAYALVSYQTLWLKAHYPAEFMAAVMTADMDNTEKVVGLVDECWRMGLKILPPD-I
2HPIA        KSHAAAYSLLSYQTAYVKAHYPVEFMAALLSVERHDSDKVAEYIRDARALGIP-VLPPDV
space        ------------------------------------------------------------
2HNHA_dssp   ??????????????????????????????????????????????????????????-?
2HPIA_dssp   ?????????????????????????????????????????????????????-??????

2HNHA        NSGLYHFHVNDDGEIVYGIGAIK-GVGEGPIEAIIEARNK-GGYFRELFDLC--A---RT
2HPIA        NRSGFDFKV-VGEEILFGLSA-VKNVGEMAARAILEERERGGP-FKSLGDFLKRLPEQVV
space        ------------------------------------------------------------
2HNHA_dssp   ???????????????????????-????????????????-???????????--?---??
2HPIA_dssp   ?????????-???????????-?????????????????????-????????????????

2HNHA        -DTKKLNRRVLEKLIMSGAFDRLGPHRAALMNSLGDAL-KAAD-----------------
2HPIA        NK-RA-LESLVK----AGALDAFG----D-RARLLASLEPLLRWAAETRERGRSGLVGLF
space        ------------------------------------------------------------
2HNHA_dssp   -?????????????????????????????????????-????-----------------
2HPIA_dssp   ??-??-??????----????????----?-??????????????????????????????

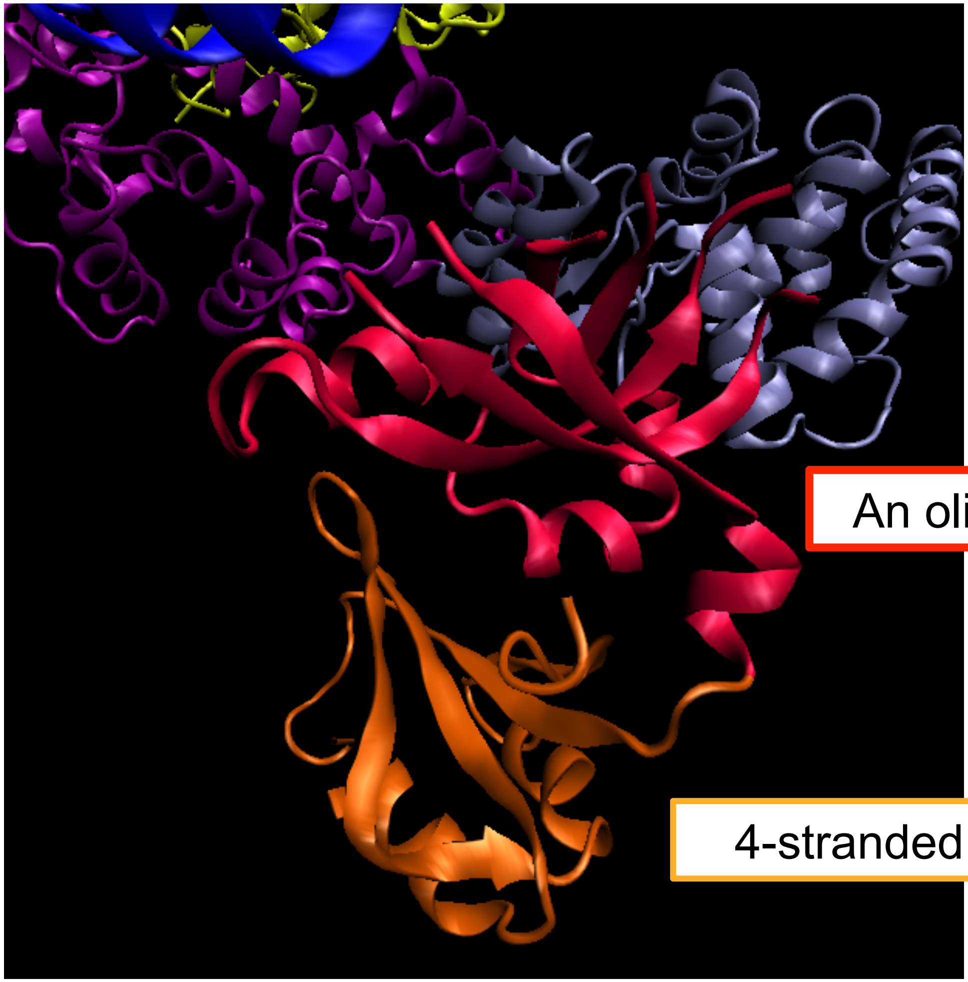
2HNHA        ------------------------------------------------------------
2HPIA        AEVEEPPLVEASPLDEITMLRYEKEALGIYVSGHPVLRYPGLREVASCTIEELSEFVREL
space        ------------------------------------------------------------
2HNHA_dssp   ------------------------------------------------------------
2HPIA_dssp   ????????????????????????????????????????????????????????????
```

helix-hairpin-helix
(HhH)

STRUCTURE OF DNA POL III

T. aquaticus

C- TERMINAL DOMAIN



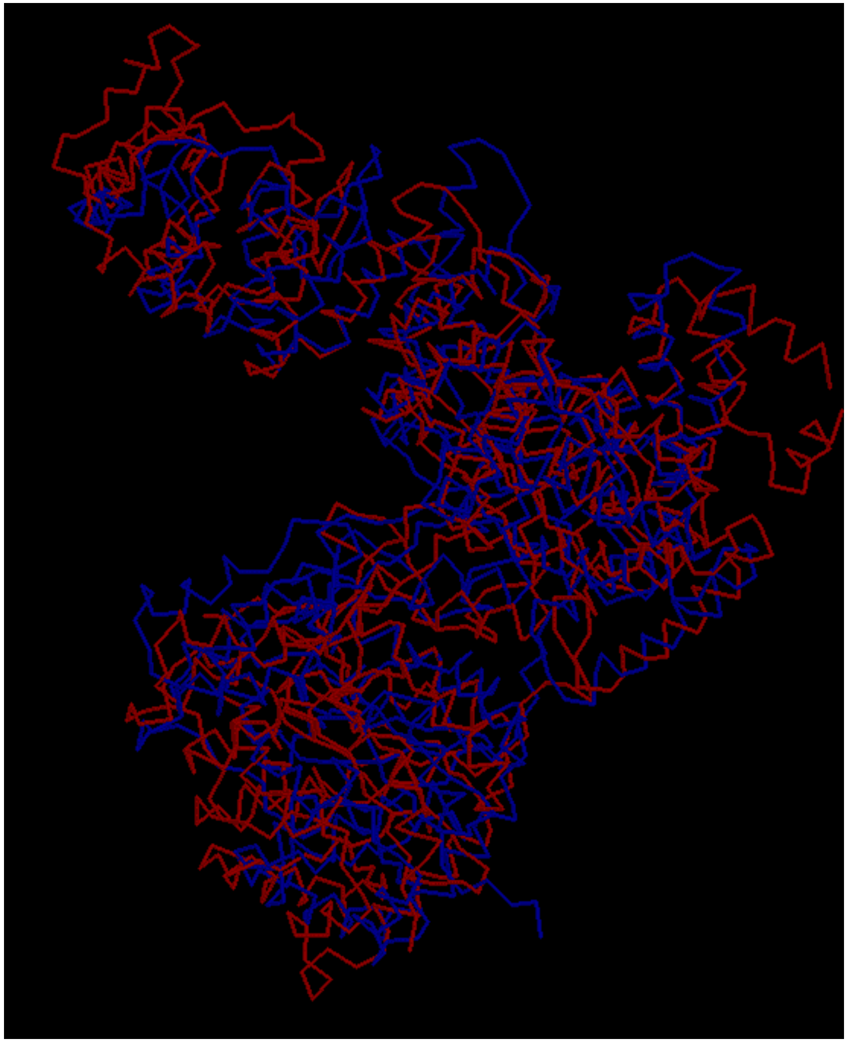
2 subdomains of C-terminal

An oligonucleotide binding (OB) fold

4-stranded β sheet

STRUCTURAL ALIGNMENT

T. aquaticus vs. E. coli



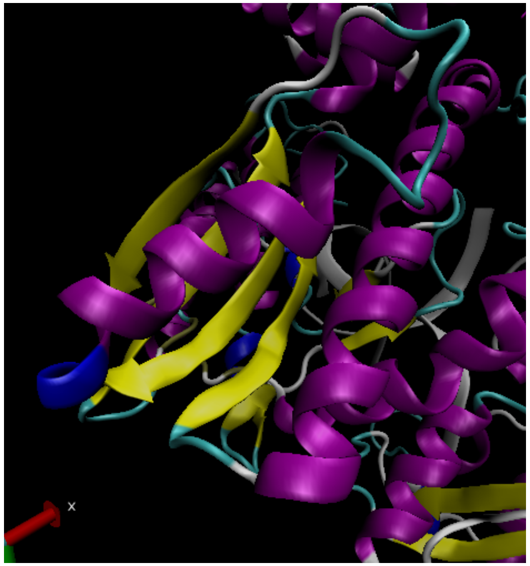
DNA polymerase III of T. aquaticus

DNA polymerase III of E. coli

Score 4.58
RMSD 2.59

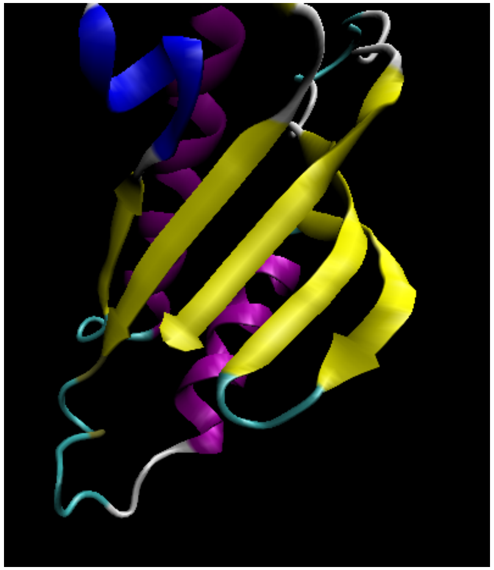
COMPARISON BETWEEN FAMILIES

PALM DOMAIN



DNA POLYMERASE I

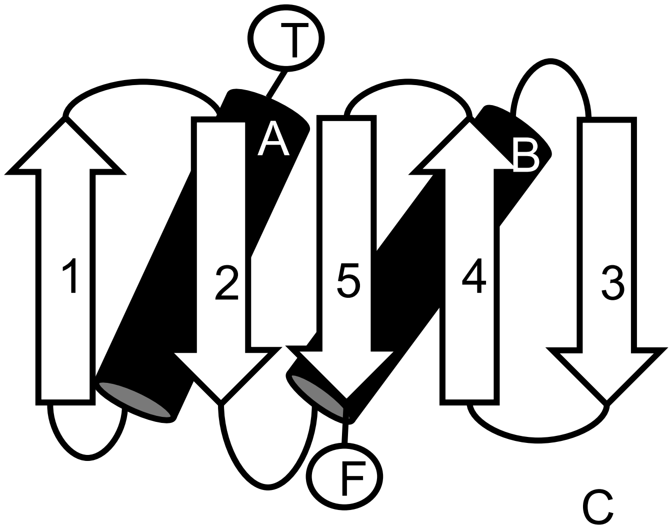
DNA POLYMERASE III



DNA POLYMERASE BETA

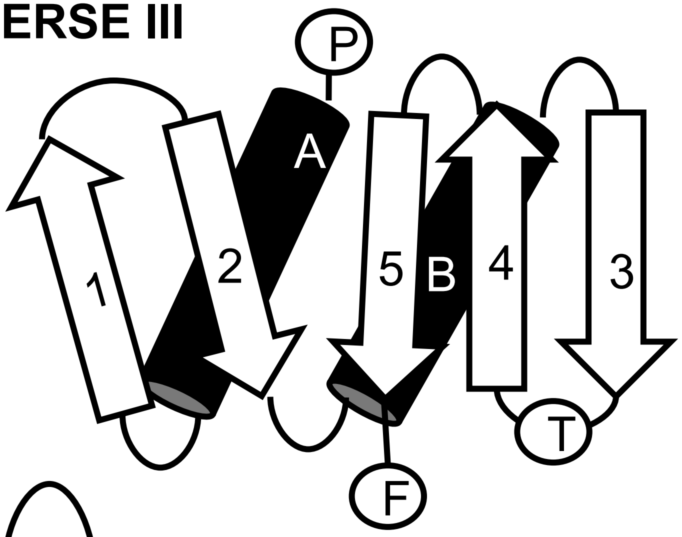
COMPARISON BETWEEN FAMILIES

PALM DOMAIN

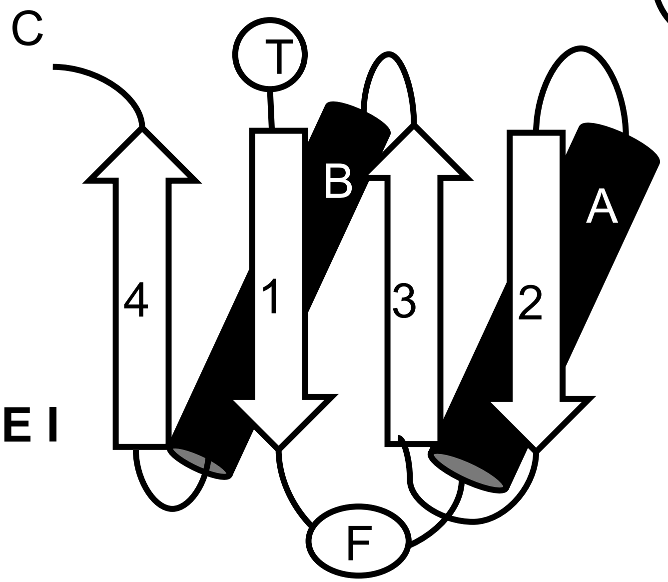


DNA POLYMERSE BETA

DNA POLYMERSE III

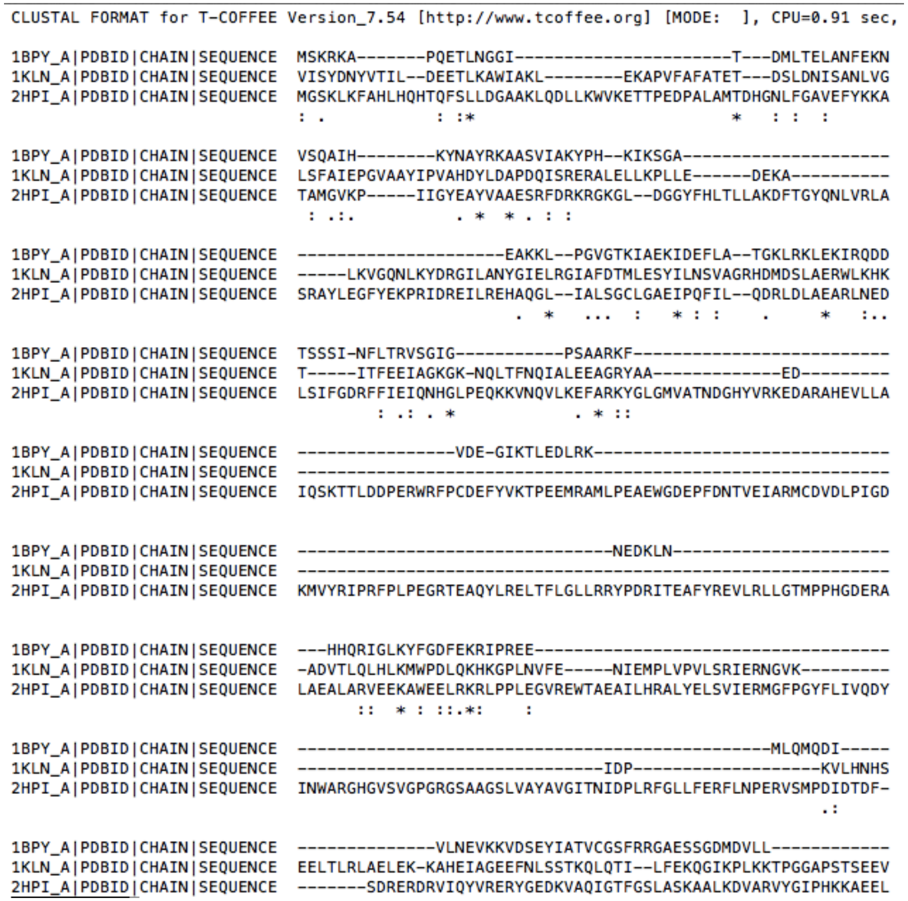


DNA POLYMERSE I



COMPARISON BETWEEN FAMILIES

SEQUENCE ALIGNMENT vs. STRUCTURAL ALIGNMENT



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CLUSTAL FORMAT for T-COFFEE Version_7.54 [http://www.tcoffee.org] [MODE:  ], CPU=0.91 sec,

1BPY_A|PDBID|CHAIN|SEQUENCE  MSKRKA-------PQETLNGGI----------------------T---DMLTELANFEKN
1KLN_A|PDBID|CHAIN|SEQUENCE  VISYDNYVTIL--DEETLKAWIAKL--------EKAPVFAFATET---DSLDNISANLVG
2HPI_A|PDBID|CHAIN|SEQUENCE  MGSKLKFAHLHQHTQFSLLDGAAKLQDLLKWVKETTPEDPALAMTDHGNLFGAVEFYKKA
                             : .           : :*                          *   : :  :

1BPY_A|PDBID|CHAIN|SEQUENCE  VSQAIH--------KYNAYRKAASVIAKYPH--KIKSGA---------------------
1KLN_A|PDBID|CHAIN|SEQUENCE  LSFAIEPGVAAYIPVAHDYLDAPDQISRERALELLKPLLE------DEKA----------
2HPI_A|PDBID|CHAIN|SEQUENCE  TAMGVKP-----IIGYEAYVAAESRFDRKRGKGL--DGGYFHLTLLAKDFTGYQNLVRLA
                              : .:.          . *  * . : :

1BPY_A|PDBID|CHAIN|SEQUENCE  ---------------------EAKKL--PGVGTKIAEKIDEFLA--TGKLRKLEKIRQDD
1KLN_A|PDBID|CHAIN|SEQUENCE  -----LKVGQNLKYDRGILANYGIELRGIAFDTMLESYILNSVAGRHDMDSLAERWLKHK
2HPI_A|PDBID|CHAIN|SEQUENCE  SRAYLEGFYEKPRIDREILREHAQGL--IALSGCLGAEIPQFIL--QDRLDLAEARLNED
                                                   .  *   ...  :   * : :    .     *   :..

1BPY_A|PDBID|CHAIN|SEQUENCE  TSSSI-NFLTRVSGIG-----------PSAARKF--------------------------
1KLN_A|PDBID|CHAIN|SEQUENCE  T-----ITFEEIAGKGK-NQLTFNQIALEEAGRYAA-------------ED---------
2HPI_A|PDBID|CHAIN|SEQUENCE  LSIFGDRFFIEIQNHGLPEQKKVNQVLKEFARKYGLGMVATNDGHYVRKEDARAHEVLLA
                                     : .: . *            . * ::

1BPY_A|PDBID|CHAIN|SEQUENCE  ----------------VDE-GIKTLEDLRK------------------------------
1KLN_A|PDBID|CHAIN|SEQUENCE  ------------------------------------------------------------
2HPI_A|PDBID|CHAIN|SEQUENCE  IQSKTTLDDPERWRFPCDEFYVKTPEEMRAMLPEAEWGDEPFDNTVEIARMCDVDLPIGD


1BPY_A|PDBID|CHAIN|SEQUENCE  --------------------------------NEDKLN----------------------
1KLN_A|PDBID|CHAIN|SEQUENCE  ------------------------------------------------------------
2HPI_A|PDBID|CHAIN|SEQUENCE  KMVYRIPRFPLPEGRTEAQYLRELTFLGLLRRYPDRITEAFYREVLRLLGTMPPHGDERA


1BPY_A|PDBID|CHAIN|SEQUENCE  ---HHQRIGLKYFGDFEKRIPREE------------------------------------
1KLN_A|PDBID|CHAIN|SEQUENCE  -ADVTLQLHLKMWPDLQKHKGPLNVFE-----NIEMPLVPVLSRIERNGVK---------
2HPI_A|PDBID|CHAIN|SEQUENCE  LAEALARVEEKAWEELRKRLPPLEGVREWTAEAILHRALYELSVIERMGFPGYFLIVQDY
                                   ::  * : ::.*:    :

1BPY_A|PDBID|CHAIN|SEQUENCE  ------------------------------------------------MLQMQDI-----
1KLN_A|PDBID|CHAIN|SEQUENCE  -------------------------------IDP-------------------KVLHNHS
2HPI_A|PDBID|CHAIN|SEQUENCE  INWARGHGVSVGPGRGSAAGSLVAYAVGITNIDPLRFGLLFERFLNPERVSMPDIDTDF-
                                                                                  .:

1BPY_A|PDBID|CHAIN|SEQUENCE  --------------VLNEVKKVDSEYIATVCGSFRRGAESSGDMDVLL------------
1KLN_A|PDBID|CHAIN|SEQUENCE  EELTLRLAELEK-KAHEIAGEEFNLSSTKQLQTI--LFEKQGIKPLKKTPGGAPSTSEEV
2HPI_A|PDBID|CHAIN|SEQUENCE  -------SDRERDRVIQYVRERYGEDKVAQIGTFGSLASKAALKDVARVYGIPHKKAEEL
```

```
2HPIA      ------------------TVEIAR-----MCDVDLPIGDKMVYRIPRFPLGRTEAQYLRE
1BPYA      PKLLHQVVEQLQKVHFITD-TL-SKGETKFMGVCQ-------------------------
1KLNA      -------------------YHQAVT---ATGR---LSSTDPNLQNIPVRNEEGRRIRQAF
space      ------------------------------------------------------------
2HPIA_dssp ------------------??????-----???????????????????????????????
1BPYA_dssp ???????????????????-??-????????????-------------------------
1KLNA_dssp -------------------??????---????---?????????????????????????

2HPIA      LTFLGLLRRYPDRITEAFYREVLRLLDERALAEALARVEEKAWEELRKREWTAEAILHRA
1BPYA      ------LPSKND------------------------------------------------
1KLNA      IAPEDYVI----VSADYSQIELRIMAHLSRDKGLLTAFAEGKDIHRATAAEVFGLPLETV
space      ------------------------------------------------------------
2HPIA_dssp ????????????????????????????????????????????????????????????
1BPYA_dssp ------??????------------------------------------------------
1KLNA_dssp ????????----????????????????????????????????????????????????

2HPIA      LYELSVIERMGFPGYFLIVQDYINWARGHGVSVGPGRGSAAGSLVAYAVGITNIDPLRFG
1BPYA      ------------------------------------------------------------
1KLNA      TSEQRRSAKAINFGLIYGMSAFGLARQLNIPRKEAQKYMDLYFERYPGVLEYMERTRAQA
space      ------------------------------------------------------------
2HPIA_dssp ????????????????????????????????????????????????????????????
1BPYA_dssp ------------------------------------------------------------
1KLNA_dssp ????????????????????????????????????????????????????????????

2HPIA      LLFERFLNPERVSMPDIDTDFSDRERDRVIQYVRERYGEDKVAQIGTFGSLASKAALKDV
1BPYA      ------------------------------------------------------------
1KLNA      KEQGYVETLDGRRLYLPDIKSSNGARRAAAERAAINAPMQGTAADIIKRAMIAVDAWLQA
space      ------------------------------------------------------------
2HPIA_dssp ????????????????????????????????????????????????????????????
1BPYA_dssp ------------------------------------------------------------
1KLNA_dssp ????????????????????????????????????????????????????????????

2HPIA      ARVYGIPHKKAEELAKLIPVQFGKPKPLQEAELRAEMEKDERIRQVIEVAMRLEGLNRHA
1BPYA      --EKEYPHRRIDIRLIPKDQYYCGVLYFTGSDIFNKNMRAHALEKGFTINEYTIRPLGVT
1KLNA      EQPRVRMIMQVHDELVFEVHKDDVDAVAKQIHQLMENCTRLDVPLLVEVGSGENWDQAH-
space      ------------------------------------------------------------
2HPIA_dssp ????????????????????????????????????????????????????????????
1BPYA_dssp --??????????????????????????????????????????????????????????
1KLNA_dssp ???????????????????????????????????????????????????????????-

2HPIA      SVHAAGVVIAAEPLTDLVPLMRDQEGRPVTQYDMGAVEALGLLKMDFLGLRTLTFLDEAR
1BPYA      GVAGEPLPVDSEKDIFDYIQWKYREPKDRSE-----------------------------
1KLNA      ------------------------------------------------------------
space      ------------------------------------------------------------
2HPIA_dssp ????????????????????????????????????????????????????????????
```

CONCLUSIONS

- To sum up we have seen that there is a common mechanism that takes place during DNA replication in different families of DNA polymerases
- We can conclude that the structure is well conserved in DNA polymerase families
- We have observed different conserved residues that are involved in interactions between DNA polymerases and DNA
- We have done an approximation of evolutionary relationships between DNA polymerases

BIBLIOGRAPHY

Eom SH, Wang J, Steitz TA. Structure of Taq polymerase with DNA at the polymerase active site. Nature. 1996 Jul 18;382(6588):278-81.

Patel PH, Suzuki M, Adman E, Shinkai A, Loeb LA.Prokaryotic DNA polymerase I: evolution, structure, and "base flipping" mechanism for nucleotide selection. J Mol Biol. 2001 May 18;308(5):823-37.

Steitz TA. A mechanism for all polymerases. Nature. 1998 Jan 15;391(6664):231-2.

Kiefer JR, Mao C, Braman JC, Beese LS.Visualizing DNA replication in a catalytically active Bacillus DNA polymerase crystal. Nature. 1998 Jan 15;391(6664):304-7.

Beese LS, Derbyshire V, Steitz TA. Structure of DNA polymerase I Klenow fragment bound to duplex DNA. Science. 1993 Apr 16;260(5106):352-5.

Johnson SJ, Taylor JS, Beese LS. Processive DNA synthesis observed in a polymerase crystal suggests a mechanism for the prevention of frameshift mutations. Proc Natl Acad Sci U S A. 2003 Apr 1;100(7):3895-900. Epub 2003 Mar 20.

BIBLIOGRAPHY

DeRose EF, Clarkson MW, Gilmore SA, Galban CJ, Tripathy A, Havener JM, Mueller GA, Ramsden DA, London RE, Lee AL. Solution structure of polymerase mu's BRCT Domain reveals an element essential for its role in nonhomologous end joining. Biochemistry. 2007 Oct 30;46(43):12100-10. Epub 2007 Oct 4.

Rothwell PJ, Waksman G. Structure and mechanism of DNA polymerases. Adv Protein Chem. 2005;71:401-40.

Joubert AM, Byrd AS, LiCata VJ. Global conformations, hydrodynamics, and X-ray scattering properties of Taq and Escherichia coli DNA polymerases in solution. J Biol Chem. 2003 Jul 11;278(28):25341-7. Epub 2003 May 3.

Yamtich J, Sweasy JB. DNA polymerase family X: function, structure, and cellular roles.Biochim Biophys Acta. 2010 May;1804(5):1136-50. Epub 2009 Jul 23.

BIBLIOGRAPHY

Beard WA, Wilson SH. Structural design of a eukaryotic DNA repair polymerase: DNA polymerase beta. Mutat Res. 2000 Aug 30;460(3-4):231-44.
Shao X, Grishin NV. Common fold in helix-hairpin-helix proteins. Nucleic Acids Res. 2000 Jul 15;28(14):2643-50.

Beard WA, Wilson SH. Structure and mechanism of DNA polymerase Beta. Chem Rev. 2006 Feb;106(2):361-82.

Lamers MH, Georgescu RE, Lee SG, O'Donnell M, Kuriyan J.
Crystal structure of the catalytic alpha subunit of E. coli replicative DNA polymerase III. Cell. 2006 Sep 8;126 (5): 881-92.

Bailey S, Wing RA, Steitz TA.
The structure of T. aquaticus DNA polymerase III is distinct from eukaryotic repli cative DNA polymerases. Cell. 2006 Sep 8;126 (5): 893-904.

BIBLIOGRAPHY

Wing RA, Bailey S, Steitz TA. Insights into the replisome from the structure of a ternary complex of the DNA polymerase IIIalpha-subunit. J Mol Biol. 2008 Oct 17;382(4): 859-69.

Garcia-Diaz M, Bebenek K, Gao G, Pedersen LC, London RE, Kunkel TA. Structure-function studies of DNA polymerase lambda. DNA Repair (Amst). 2005 Dec 8;4(12):1358-67. Epub 2005 Oct 4.