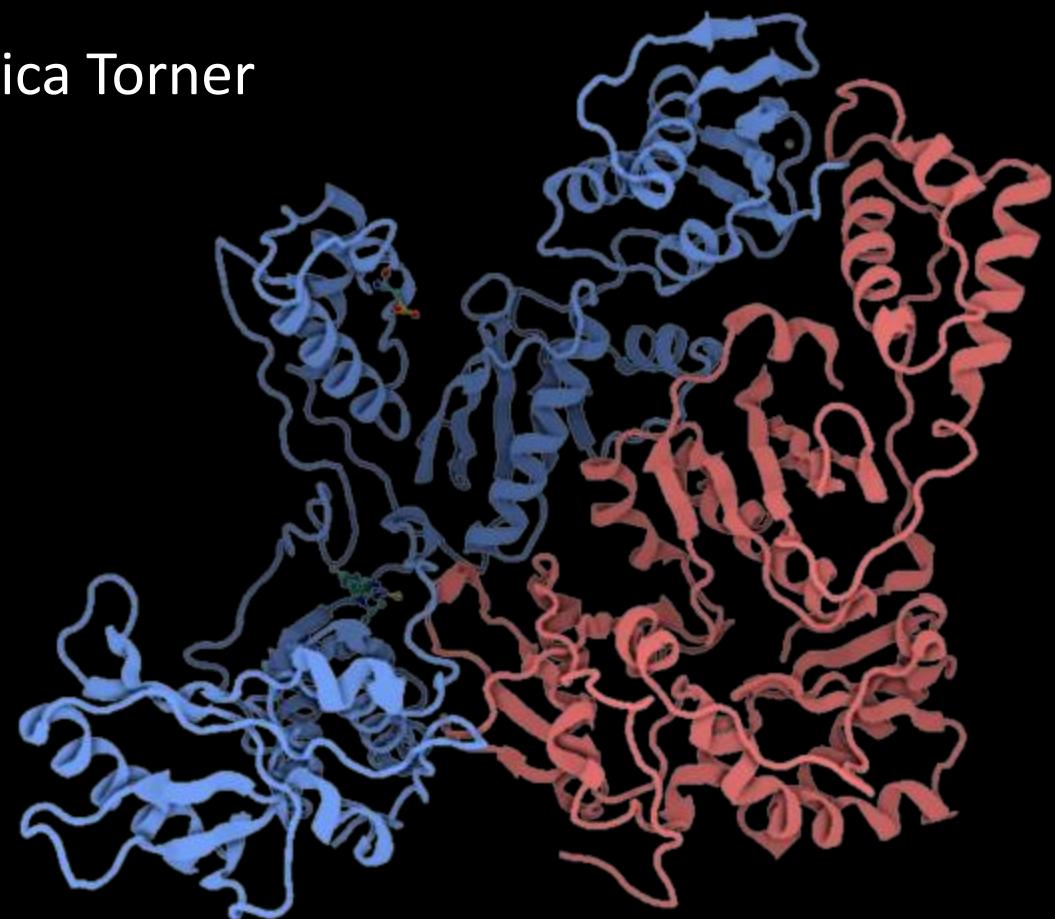
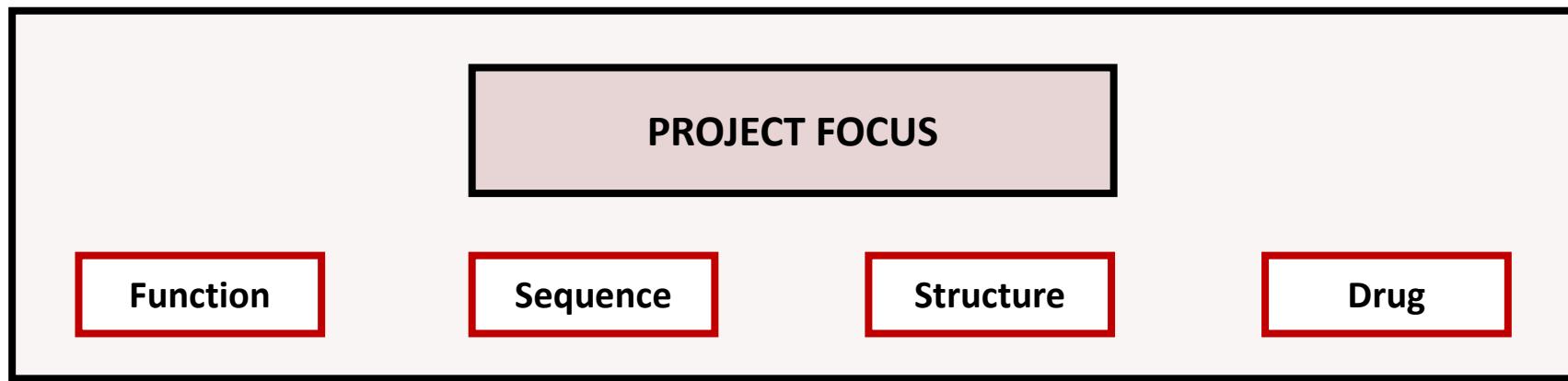
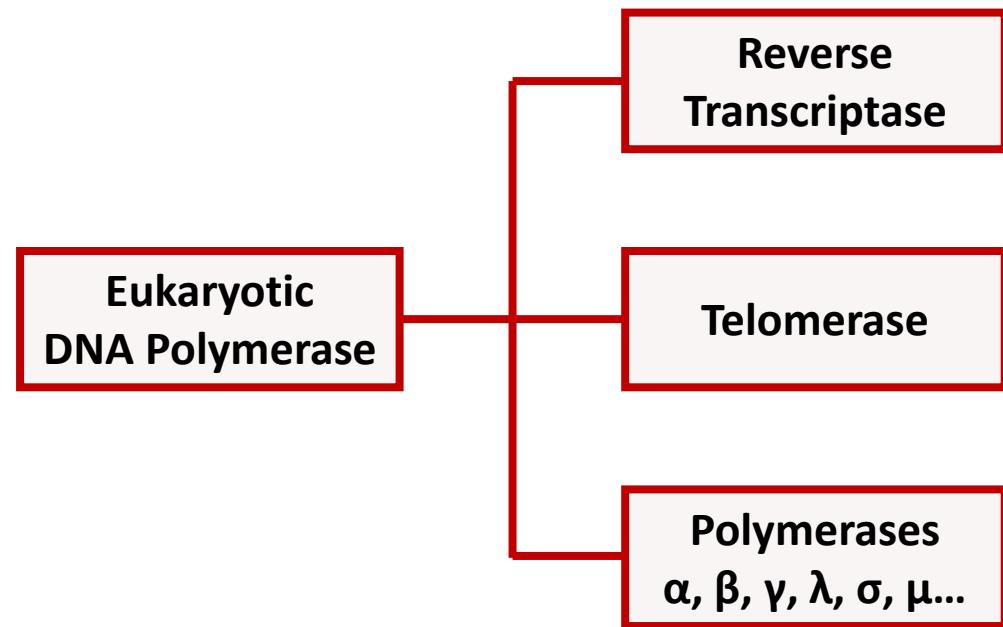
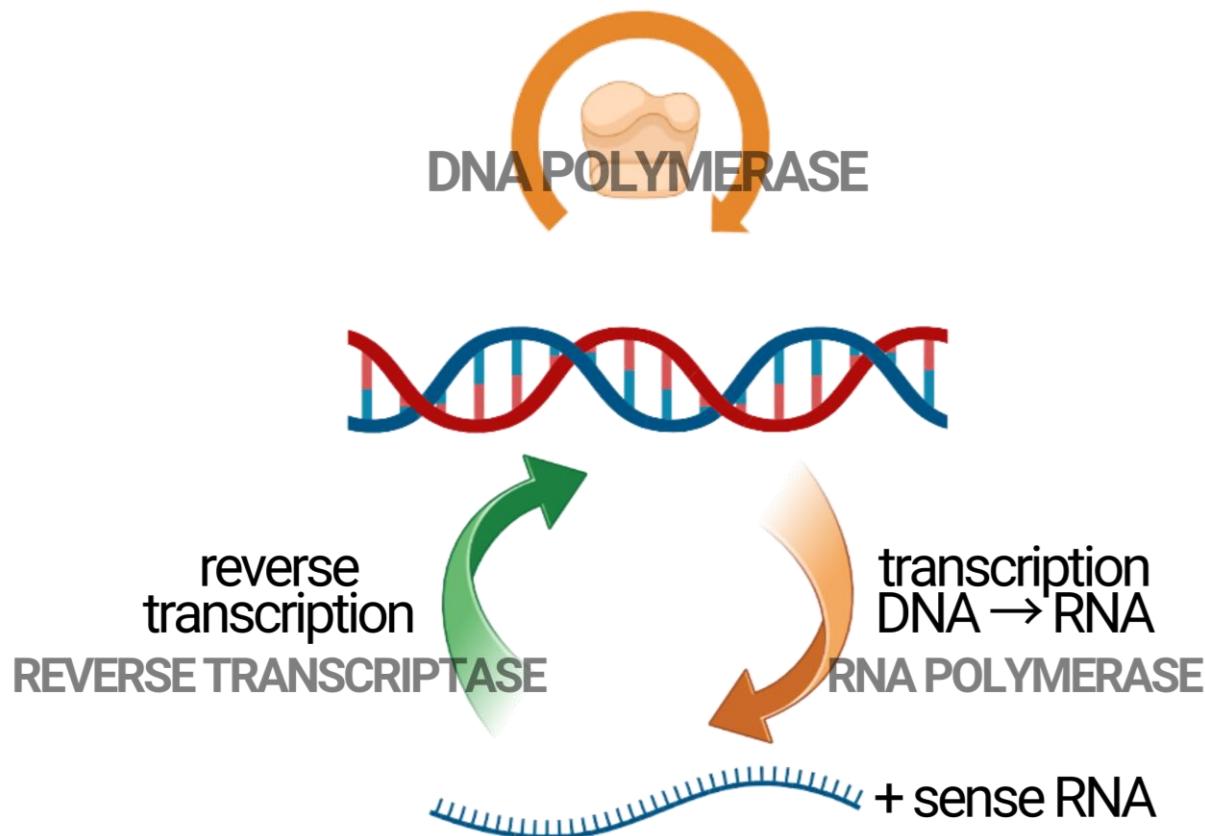


HIV: Reverse transcriptase

Marta Ortigas, Xavier Crespo, Núria Mitjavila & Mònica Torner
Structural Bioinformatics (2022/2023)







- **Binding proteins**
- **DNA topoisomerase**
- **DNA polymerase**
- **Cellular eukaryotic elongation factor 1 complex**

DNA Polymerase (active site)

Copy a DNA or RNA template

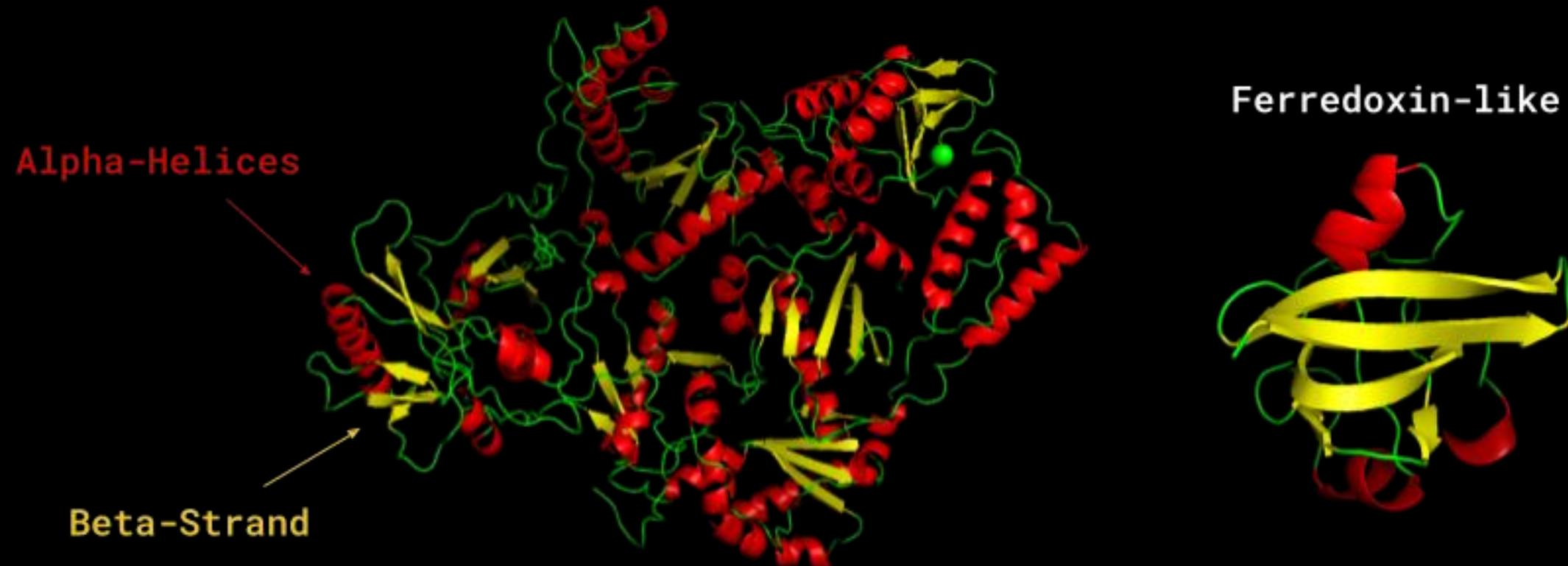


RNase H (active site at the opposite end)

Removes the original RNA strand by cleaving it into pieces.

Reverse transcriptase (cytoplasm)

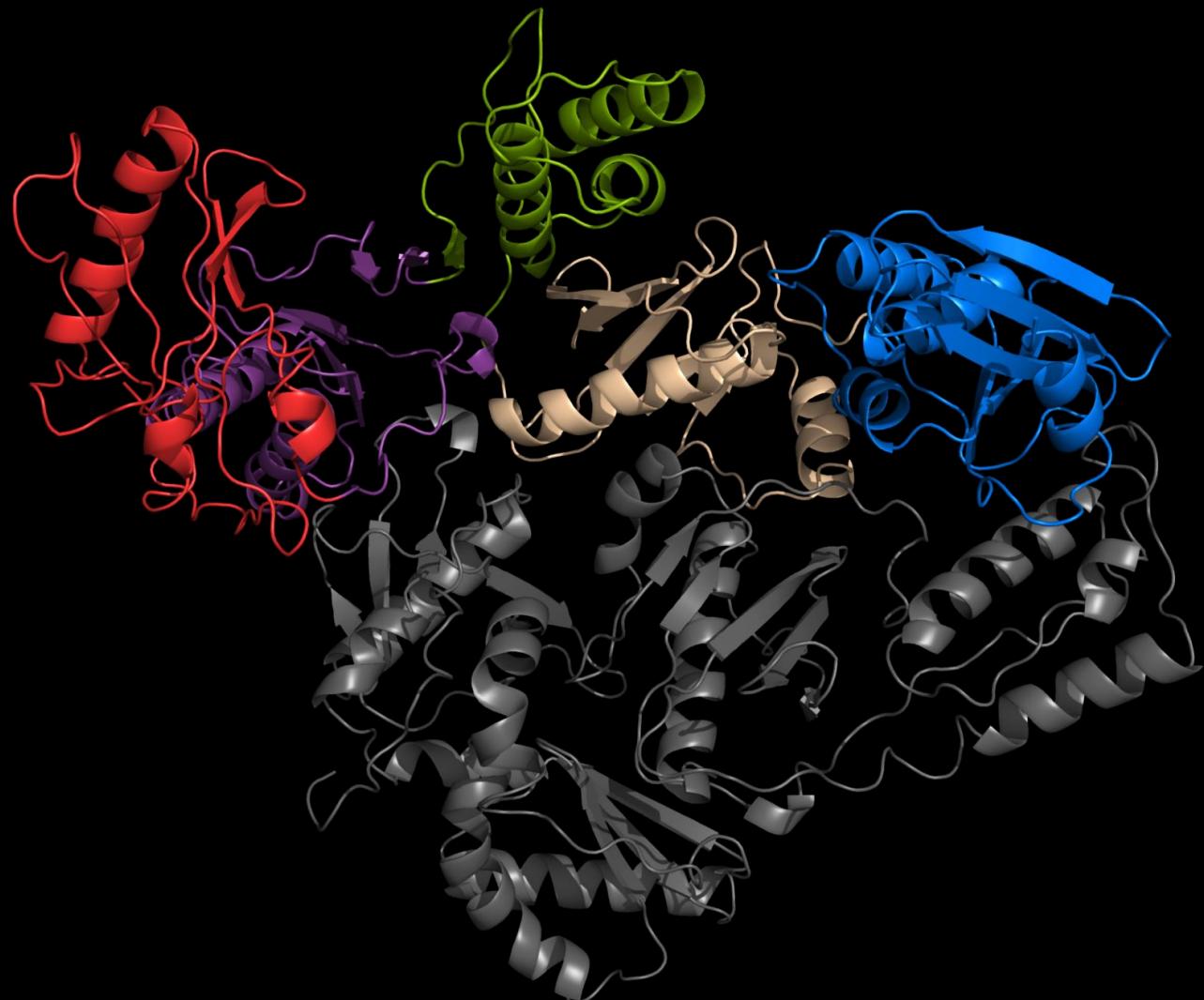
Cooperating together to convert the RNA into a double-stranded linear DNA. It builds a second DNA strand matched to the one that was just created to form the final DNA double helix. This reaction is also performed by the polymerase site.



Ferredoxin-like

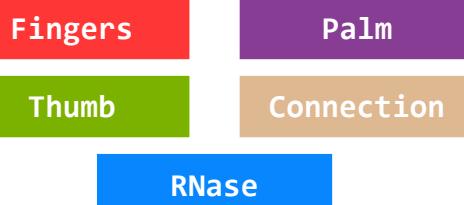


HIV Reverse Transcriptase structure



1REV

Two distinct subunits
P66 – Main coloured subunit



P51 – Gray subunit

Query: sp|P04585|POL_HV1H2 [L=1435]

Description: Gag-Pol polyprotein OS=Human immunodeficiency virus type 1 group M subtype B (isolate HXB2) OX=117

Scores for complete sequence (score includes all domains):

--- full sequence ---			--- best 1 domain ---			-#dom-		Model	Description
E-value	score	bias	E-value	score	bias	exp	N		
9.5e-80	266.8	0.0	2.5e-79	265.4	0.0	1.8	1	Gag_p24	gag gene protein p24 (core nucleocapsid protein)
2.3e-65	218.5	1.6	4.9e-65	217.4	0.6	2.2	2	Gag_p17	gag gene protein p17 (matrix protein)
5.9e-45	151.2	10.2	5.9e-45	151.2	10.2	2.7	2	RVT_connect	Reverse transcriptase connection domain
2e-37	126.4	1.2	2e-37	126.4	1.2	2.5	2	RVT_thumb	Reverse transcriptase thumb domain
3.5e-34	117.8	0.6	2.1e-33	115.3	0.1	2.5	2	RNase_H	RNase H
5e-33	112.8	0.3	1.9e-32	111.0	0.3	2.1	1	RVP	Retroviral aspartyl protease
9.4e-32	109.9	0.0	2.2e-31	108.7	0.0	1.7	1	RVT_1	Reverse transcriptase (RNA-dependent)

Query: Gag_p24 [M=206]

Accession: PF00607.15

Description: gag gene protein p24 (core nucleocapsid protein)

Scores for complete sequences (score includes all domains):

--- full sequence ---			--- best 1 domain ---			-#dom-		Sequence	Description
E-value	score	bias	E-value	score	bias	exp	N		
9.1e-81	275.4	0.0	1.8e-80	274.4	0.0	1.5	1	sp Q02843 GAG_SIVG1	Gag polyprotein OS=Simian immunodeficiency virus
4.5e-80	273.1	0.0	1.2e-79	271.7	0.0	1.8	1	sp Q02836 POL_SIVG1	Gag-Pol polyprotein OS=Simian immunodeficiency virus
1.6e-79	271.3	0.5	4.3e-78	266.6	0.0	2.1	2	sp P03349 GAG_HV1A2	Gag polyprotein OS=Human immunodeficiency virus type 1 group A
5.8e-79	269.5	0.2	1.4e-78	268.2	0.0	1.7	1	sp P04591 GAG_HV1H2	Gag polyprotein OS=Human immunodeficiency virus type 1 group M
6e-79	269.4	0.2	1.4e-78	268.2	0.0	1.7	1	sp Q0622 GAG_HV1LW	Gag polyprotein OS=Human immunodeficiency virus type 1 group M
6e-79	269.4	0.2	1.5e-78	268.1	0.0	1.7	1	sp P03347 GAG_HV1B1	Gag polyprotein OS=Human immunodeficiency virus type 1 group M



1. Introduction

2. Function

3. Sequence

4. Structure

5. Drug

6. Conclusions

sp|Q02843|GAG_SIVG1 knettappggesrnypvvnqnnawvhqplsPRTLNAVKCCEE-KRWGAEVVPMFQALSE
 sp|Q02836|POL_SIVG1 knettappggesrnypvvnqnnawvhqplsPRTLNAVKCCEE-KRWGAEVVPMFQALSE
 sp|P03349|GAG_HV1A2 aagtgnssqvsqnyipivqnllqqm vhqaisPRTLNAVKVVEE-KAFSPEVIPMFSALSE
 sp|P04591|GAG_HV1H2 aadtghsnqvsqnyipivqniiqqm vhqaisPRTLNAVKVVEE-KAFSPEVIPMFSALSE
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 sp|P03347|GAG_HV1B1 aadtghssqvsqnyipivqniiqqm vhqaisPRTLNAVKVVEE-KAFSPEVIPMFSALSE
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 sp|P03347|GAG_HV1B1 GTTSTLQEQUIGWMTNn-ppIPVGEIYKRWIILGLNKIVRMSPT-SILDIRQGPKEFRD
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sp|Q02843|GAG_SIVG1 YVDRFYKALRAEQAPQDVKNWMTQTLLIQNANPDCKLILKGLGMNPTLEEMLIACQGVGG
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 sp|P03347|GAG_HV1B1 PGHKARVLaeamsqvttatimmqrgnfrnqrkivkcfncgkeghtarncraprkkgcwk
 sp|P04585|POL_HV1H2 PGHKARVLaeamsqvtsatimmqrgnfrnqrkivkcfncgkeghtarncraprkkgcwk

HIV Reverse Transcriptase structure



1REV

sp|Q02843|GAG_SIVG1 knettappggesrnypvvnqnnawvhqpllsPRTLNAWVKCVEE-KRWGAEVVPMFQALSE
 sp|Q02836|POL_SIVG1 knettappggesrnypvvnqnnawvhqpllsPRTLNAWVKCVEE-KRWGAEVVPMFQALSE
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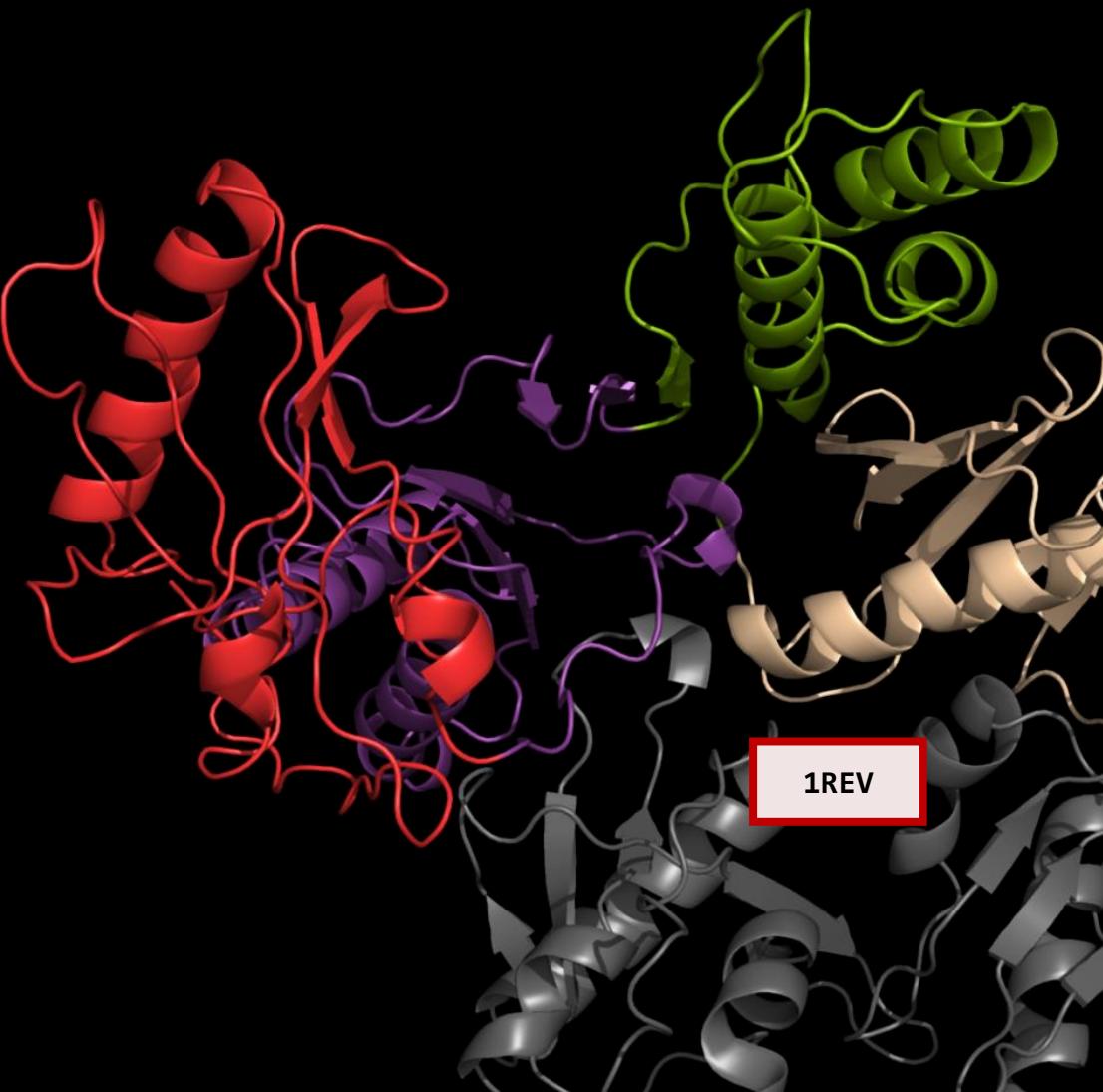
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HIV Reverse Transcriptase structure



Query: RVT_1 [M=214]

Accession: PF00078.22

Description: Reverse transcriptase (RNA-dependent DNA polymerase)

Scores for complete sequences (score includes all domains):

--- full sequence ---			--- best 1 domain ---			-#dom-		Sequence	Description
E-value	score	bias	E-value	score	bias	exp	N		
3.1e-32	114.7	0.1	9.8e-32	113.1	0.0	1.8	1	1jkh_B	mol:protein length:440 HIV-1 RT, B-CHAIN
3.1e-32	114.7	0.1	9.8e-32	113.1	0.0	1.8	1	1jla_B	mol:protein length:440 HIV-1 RT B-chain
3.1e-32	114.7	0.1	9.8e-32	113.1	0.0	1.8	1	1jlb_B	mol:protein length:440 HIV-1 RT B-chain
3.1e-32	114.7	0.1	9.8e-32	113.1	0.0	1.8	1	1jlc_B	mol:protein length:440 HIV-1 RT B-chain
3.2e-32	114.7	0.1	1e-31	113.1	0.0	1.8	1	3drr_B	mol:protein length:443 p51 RT
4.6e-32	114.2	0.1	1.5e-31	112.5	0.0	1.8	1	2iaj_B	mol:protein length:447 Reverse transcriptase/ribon
4.6e-32	114.2	0.1	1.5e-31	112.5	0.0	1.8	1	2ic3_B	mol:protein length:447 Reverse transcriptase/ribon
5.1e-32	114.0	0.0	1.6e-31	112.4	0.0	1.8	1	3dmj_B	mol:protein length:440 p51 RT
5.6e-32	113.9	0.1	1.6e-31	112.4	0.0	1.8	1	1jkh_A	mol:protein length:560 HIV-1 RT, A-CHAIN
5.6e-32	113.9	0.1	1.6e-31	112.4	0.0	1.8	1	1jla_A	mol:protein length:560 HIV-1 RT A-chain
5.6e-32	113.9	0.1	1.6e-31	112.4	0.0	1.8	1	1jlb_A	mol:protein length:560 HIV-1 RT A-chain
5.6e-32	113.9	0.1	1.6e-31	112.4	0.0	1.8	1	1jlc_A	mol:protein length:560 HIV-1 RT A-chain
5.7e-32	113.9	0.1	1.6e-31	112.4	0.0	1.8	1	3drr_A	mol:protein length:563 Reverse transcriptase/ribon
...									
1.1e-29	106.4	0.0	1.4e-29	106.0	0.0	1.1	1	1n4l_A	mol:protein length:255 Reverse Transcriptase
7.9e-06	28.5	0.3	1.9e-05	27.2	0.3	1.7	1	3du5_A	mol:protein length:596 Telomerase reverse transcri

Query: RVT_1 [M=214]

Accession: PF00078.22

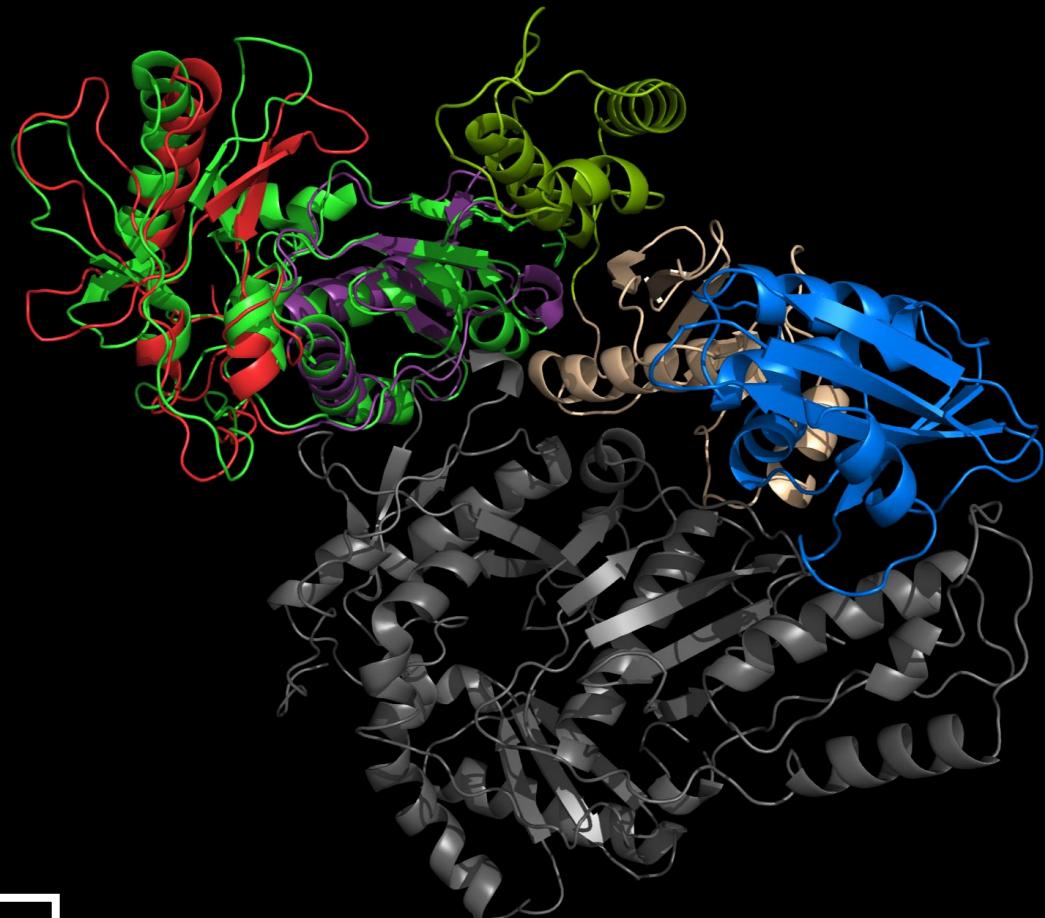
Description: Reverse transcriptase (RNA-dependent DNA polymerase)

Scores for complete sequences (score includes all domains):

--- full sequence ---			--- best 1 domain ---			-#dom-		exp	N	Sequence	Description
E-value	score	bias	E-value	score	bias						
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
3.1e-32	114.7	0.1	9.8e-32	113.1	0.0	1.8	1	1jkh_B		mol:protein length:440	HIV-1 RT, B-CHAIN
3.1e-32	114.7	0.1	9.8e-32	113.1	0.0	1.8	1	1jla_B		mol:protein length:440	HIV-1 RT B-chain
3.1e-32	114.7	0.1	9.8e-32	113.1	0.0	1.8	1	1jlb_B		mol:protein length:440	HIV-1 RT B-chain
3.1e-32	114.7	0.1	9.8e-32	113.1	0.0	1.8	1	1jlc_B		mol:protein length:440	HIV-1 RT B-chain
3.2e-32	114.7	0.1	1e-31	113.1	0.0	1.8	1	3drr_B		mol:protein length:443	p51 RT
4.6e-32	114.2	0.1	1.5e-31	112.5	0.0	1.8	1	2iaj_B		mol:protein length:447	Reverse transcriptase/ribon
4.6e-32	114.2	0.1	1.5e-31	112.5	0.0	1.8	1	2ic3_B		mol:protein length:447	Reverse transcriptase/ribon
5.1e-32	114.0	0.0	1.6e-31	112.4	0.0	1.8	1	3dmj_B		mol:protein length:440	p51 RT
5.6e-32	113.9	0.1	1.6e-31	112.4	0.0	1.8	1	1jkh_A		mol:protein length:560	HIV-1 RT, A-CHAIN
5.6e-32	113.9	0.1	1.6e-31	112.4	0.0	1.8	1	1jla_A		mol:protein length:560	HIV-1 RT A-chain
5.6e-32	113.9	0.1	1.6e-31	112.4	0.0	1.8	1	1jlb_A		mol:protein length:560	HIV-1 RT A-chain
5.6e-32	113.9	0.1	1.6e-31	112.4	0.0	1.8	1	1jlc_A		mol:protein length:560	HIV-1 RT A-chain
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...											
1.1e-29	106.4	0.0	1.4e-29	106.0	0.0	1.1	1	1n4l_A		mol:protein length:255	Reverse Transcriptase
7.9e-06	28.5	0.3	1.9e-05	27.2	0.3	1.7	1	3du5_A		mol:protein length:596	Telomerase reverse transcri

Moloney murine
leukemia virus

1N4L → 1REV



RMSD: 1.534

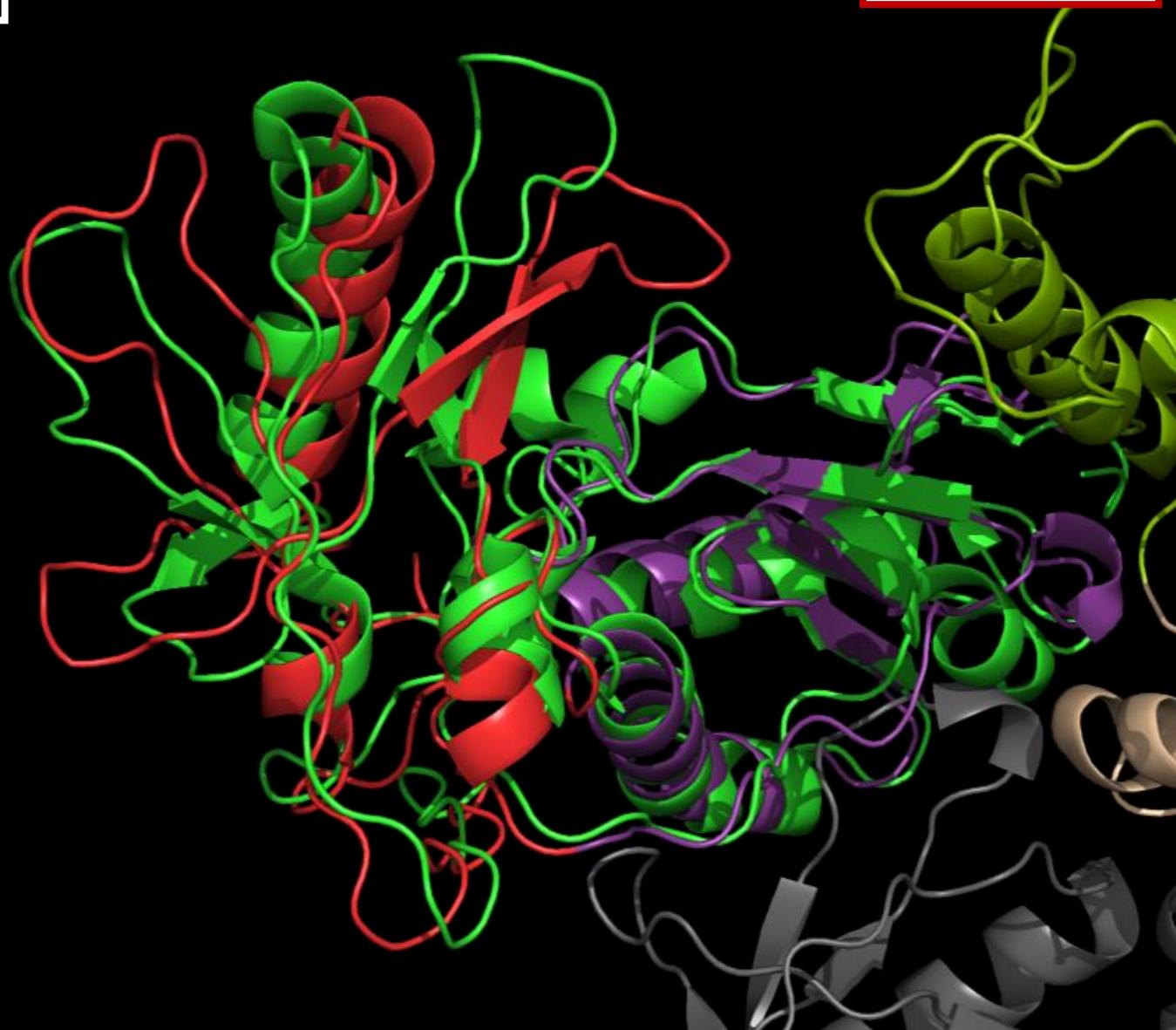
1N4L

This structure comes Moloney murine leukemia virus. A retrovirus that causes leukemia in murine (mouse).

The whole structure of the reverse transcriptase of this virus is not the same as HIV. Such structures are very different from protein to protein.
Superimposing the important regions makes more sense.

Moloney murine
leukemia virus

1N4L → 1REV



RMSD: 1.534

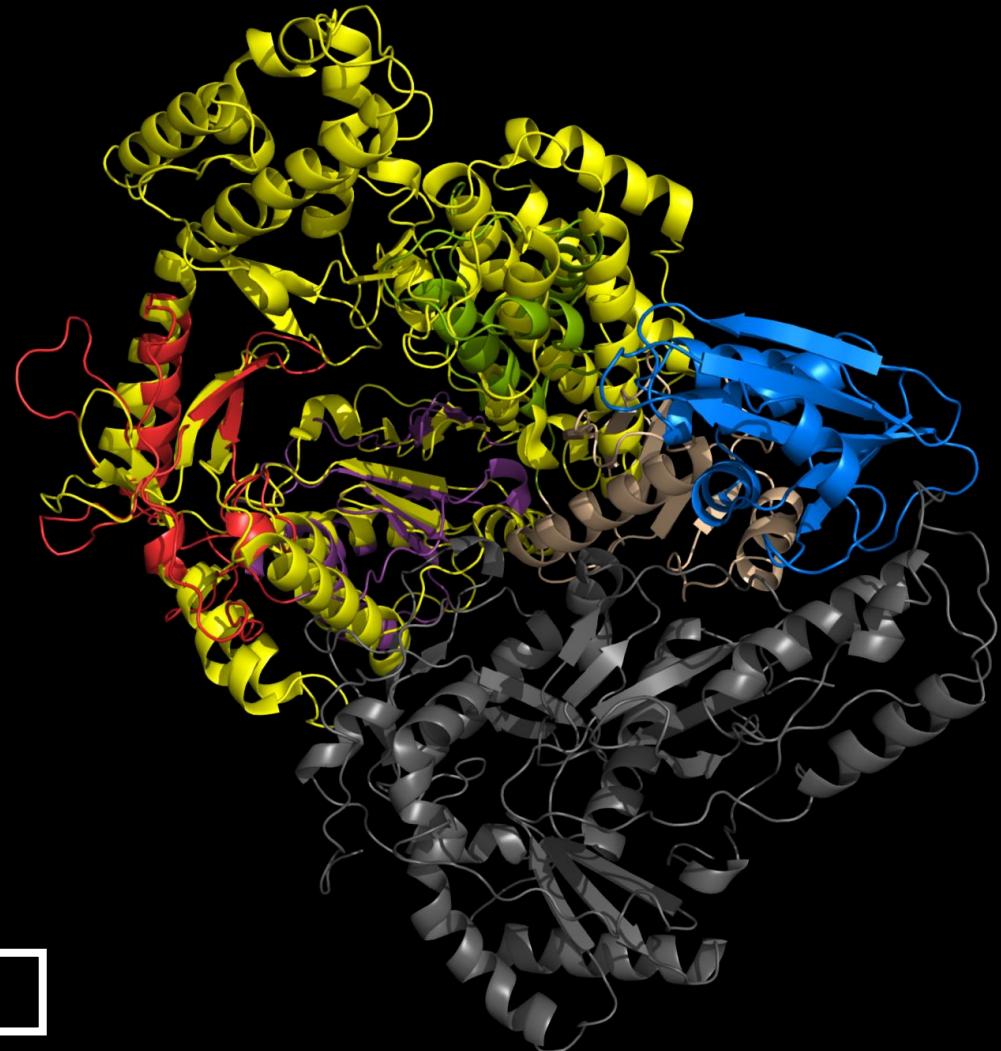
1N4L

This structure comes Moloney murine leukemia virus. A retrovirus that causes leukemia in murine (mouse).

The whole structure of the reverse transcriptase of this virus is not the same as HIV. Such structures are very different from protein to protein.
Superimposing the important regions makes more sense.

Catalytic subunit
of Telomerase

3DU5 → 1REV



RMSD: 6.504

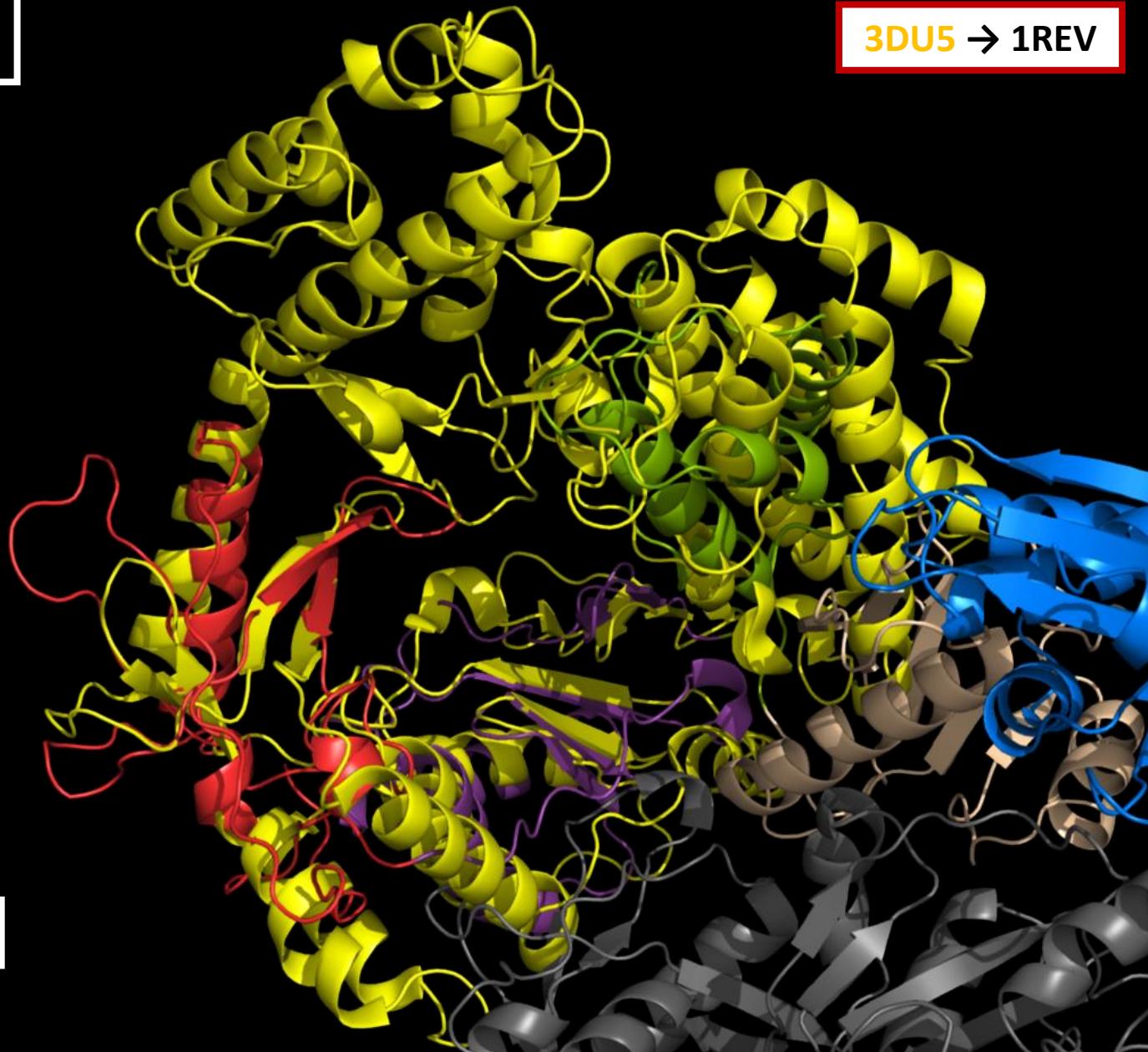
3DU5

The telomerase is an essential enzyme that keeps cells alive by adding DNA to telomeres, being the reverse transcriptase, the most important part of it.

Catalytic subunit
of Telomerase

3DU5 → 1REV

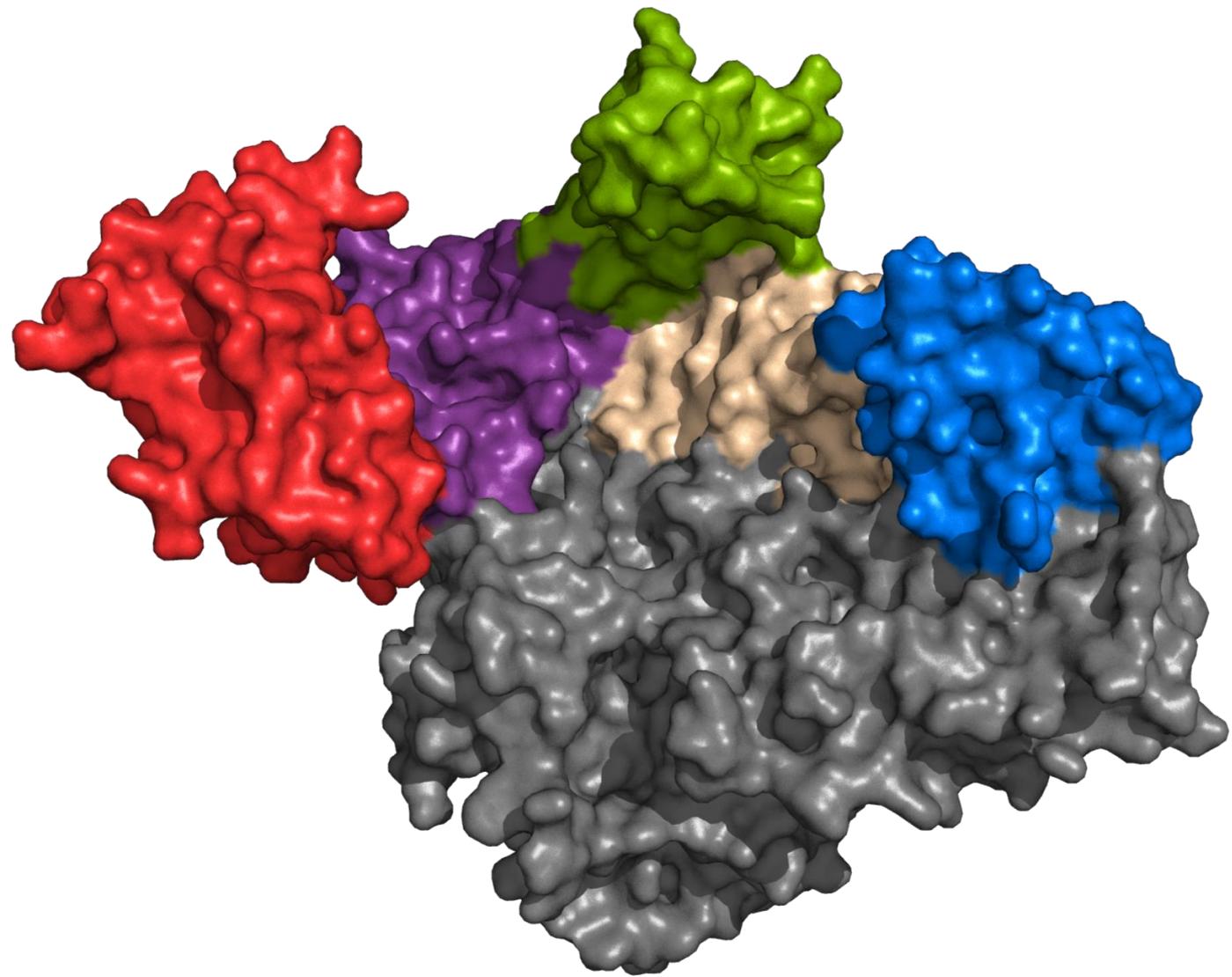
RMSD: 6.504



3DU5

The telomerase is an essential enzyme that keeps cells alive by adding DNA to telomeres, being the reverse transcriptase, the most important part of it.

HIV Reverse Transcriptase structure



1REV

Two disctint subunits

P66 – Main coloured subunit

Fingers

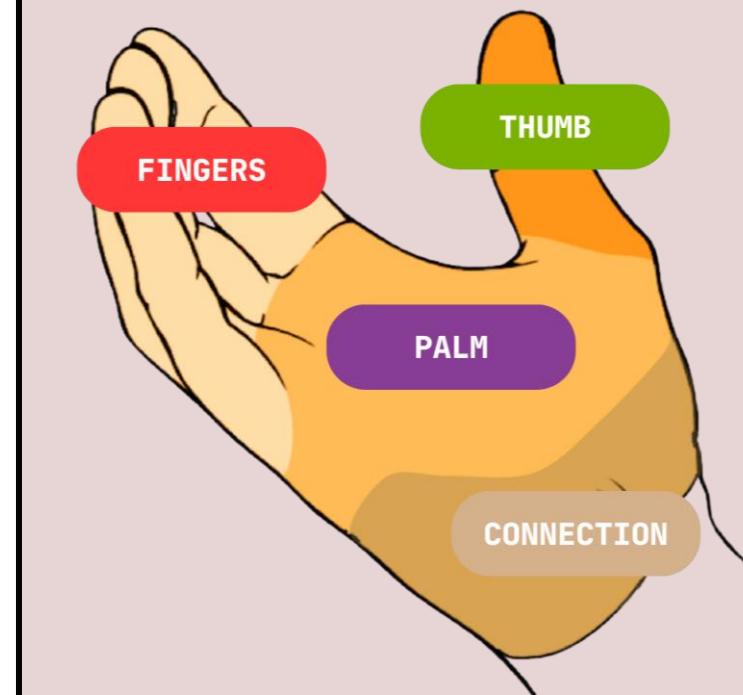
Palm

Thumb

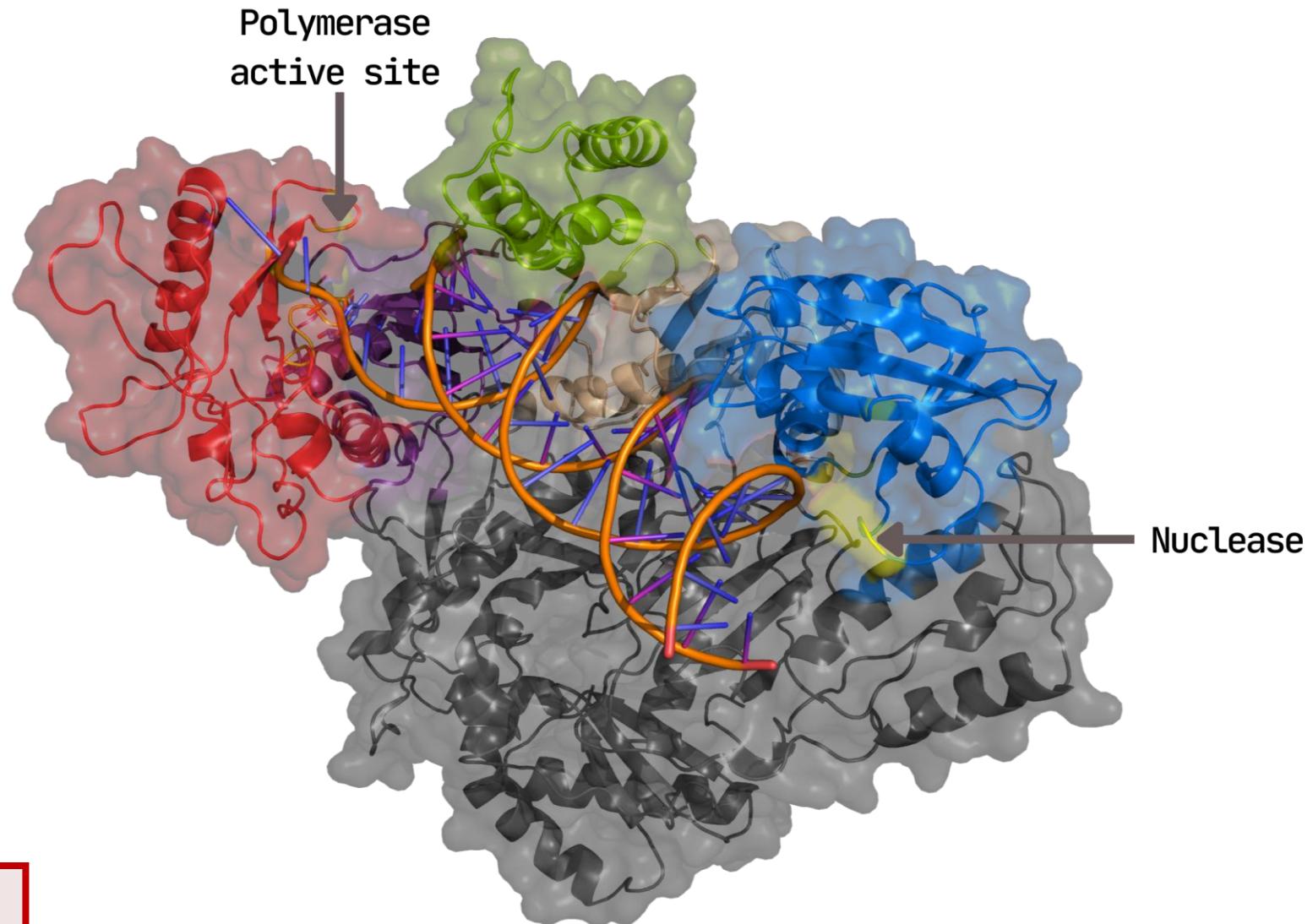
Connection

RNase

P51 – Gray subunit



HIV Reverse Transcriptase structure in complex with DNA



ACTIVE SITES

Polymerase active site

Fingers Palm
Thumb

Located in P66 subunit

Nuclease active site

RNase

Helps to degrade the RNA template that the enzyme is copying, allowing the reverse transcription to proceed.

Polymerase active site

Fingers

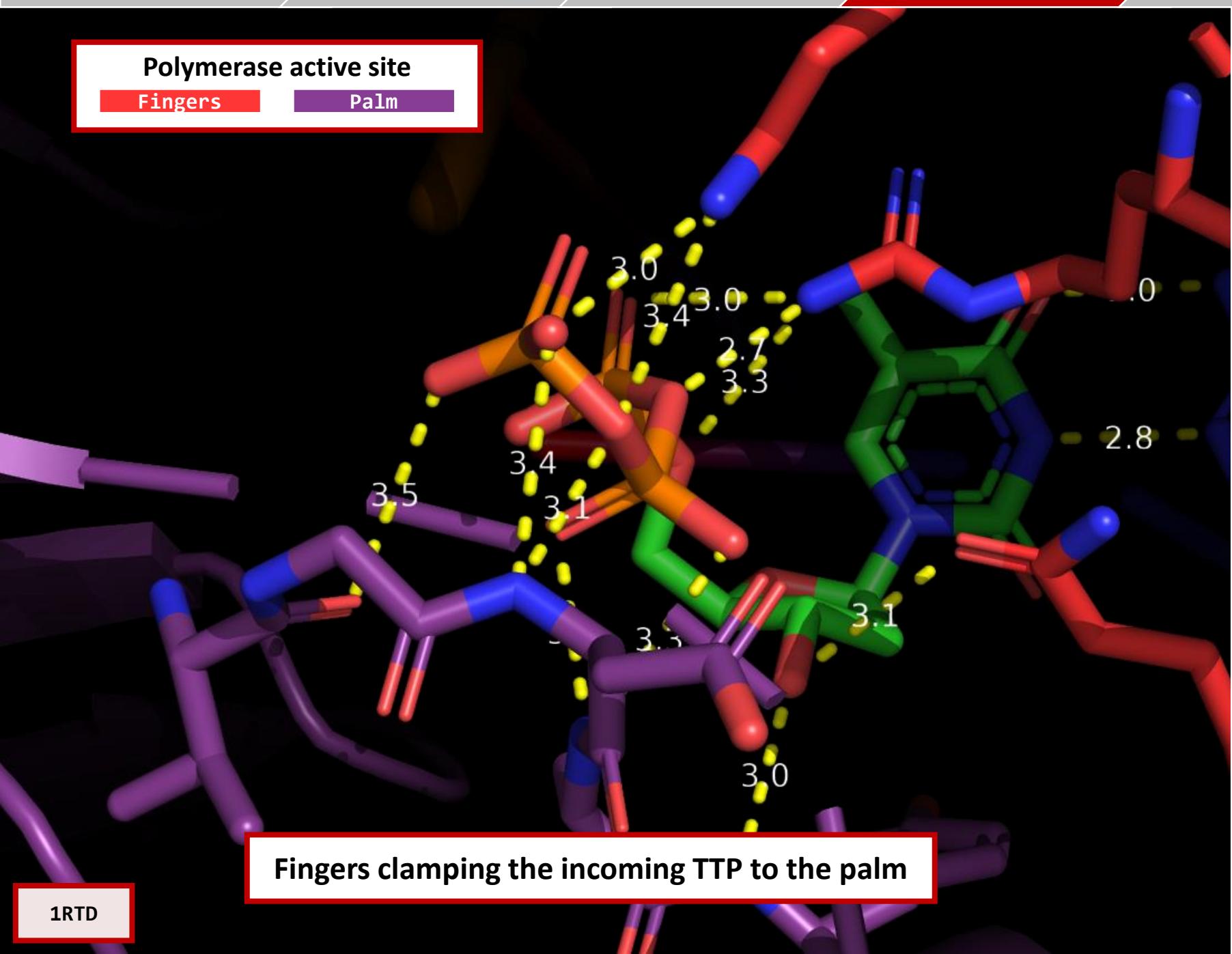
Palm

Fingers clamping the incoming TTP to the palm

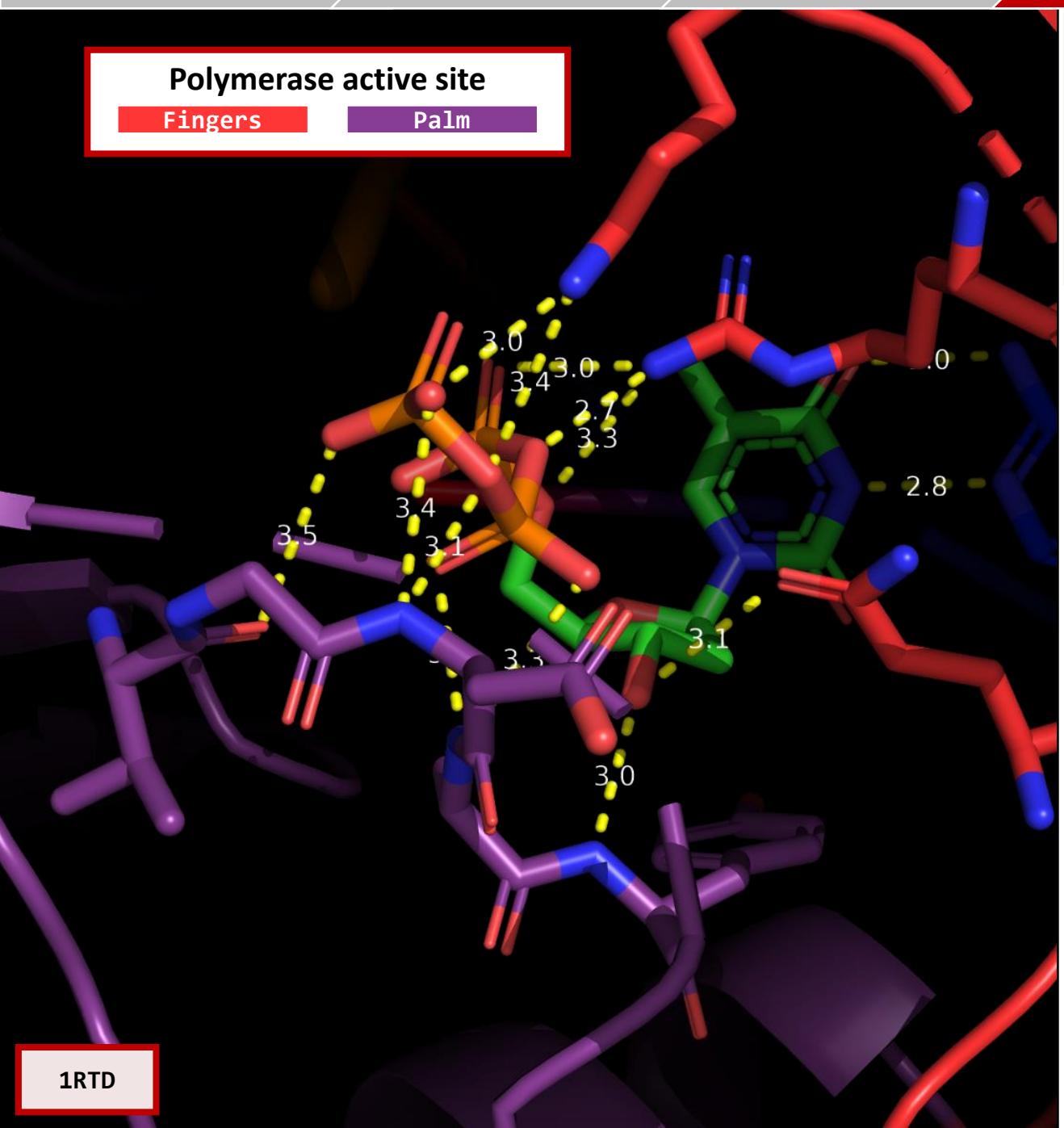
Polymerase active site

Fingers

Palm

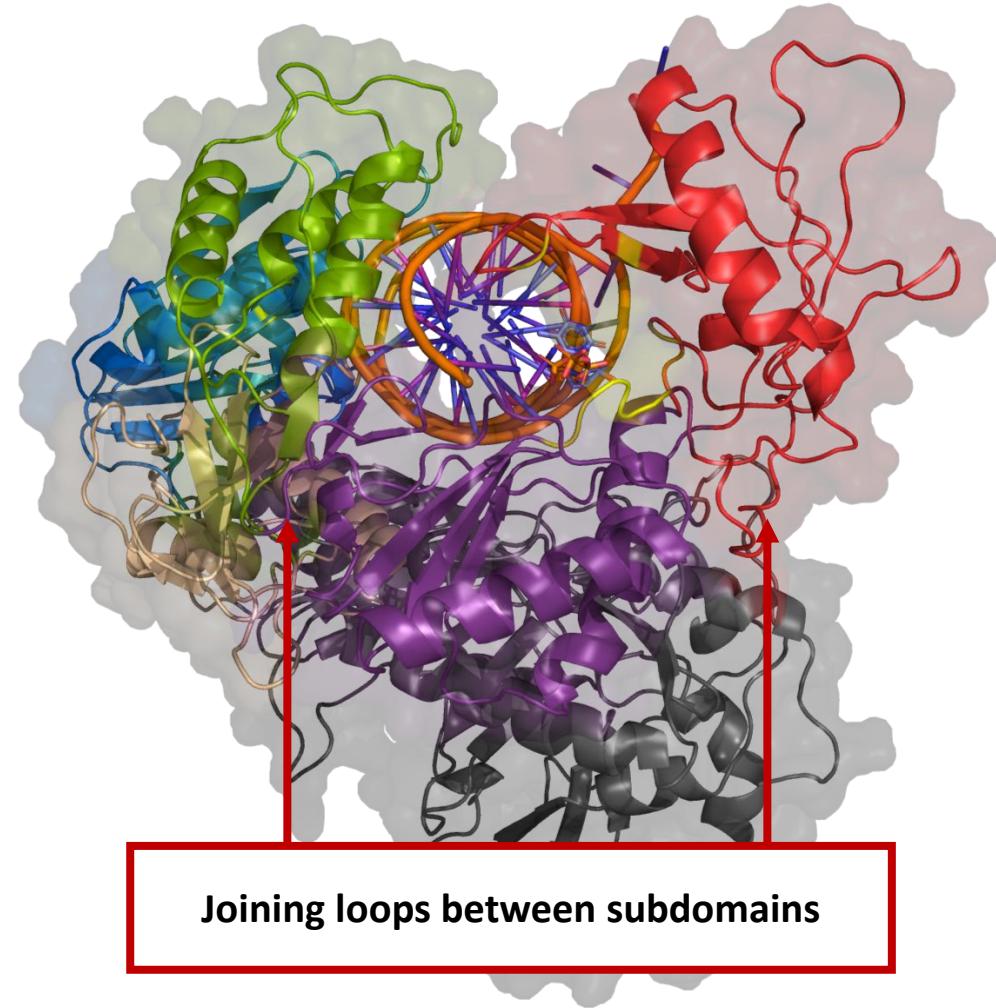
**Fingers clamping the incoming TTP to the palm****FUNCTION**

Its main function is to clamp incoming nucleosides and to catalyze the polymerization reaction, linking nucleotides together to form the cDNA strand



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Main types of drugs available

Nucleoside Reverse Transcriptase Inhibitors

NRTIs

These, mimic nucleosides with an important difference that stops transcription.

For example: Not having a 3'-hydroxyl group, which is necessary for the next nucleoside to be added to the chain. For this, transcription of the virus stops.

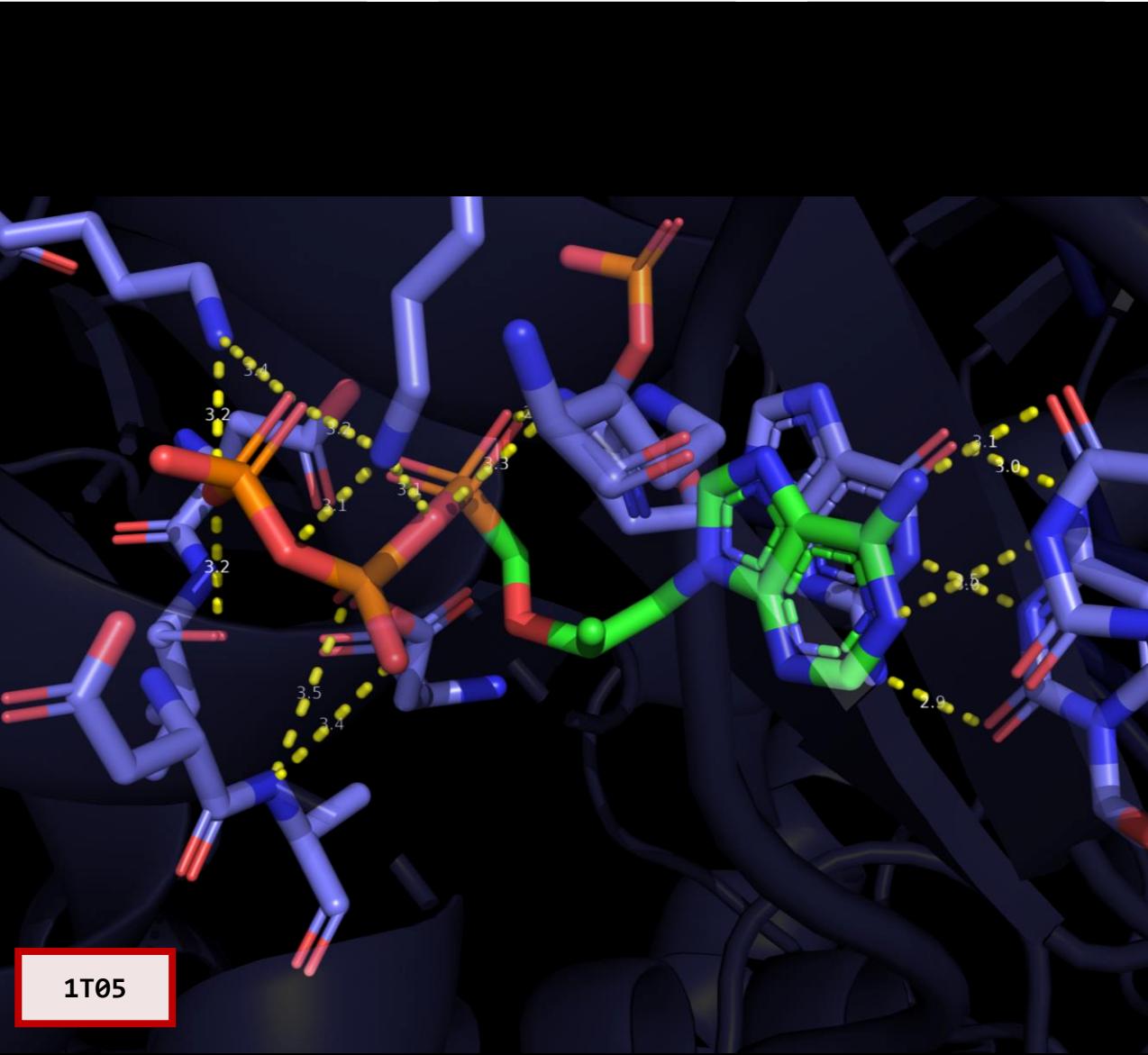
Examples: Emtricitabine, Tenofovir

Non-Nucleoside Reverse Transcriptase Inhibitors

NNRTIs

These drugs bind directly to the reverse transcriptase. They work by changing the shape of the reverse transcriptase enzyme, making it unable to function properly.

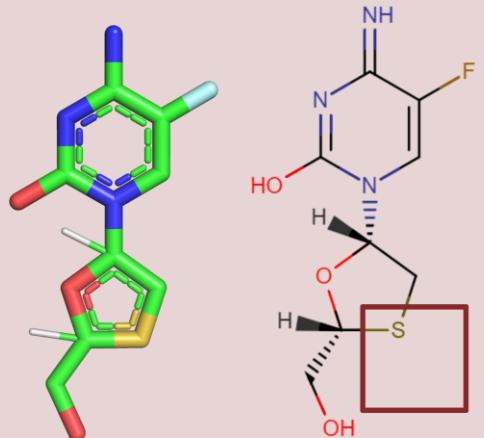
Examples: Efavirenz



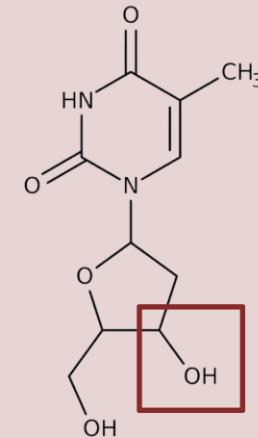
Tenofovir entering transcription
as incoming nucleoside

Nucleoside Reverse Transcriptase Inhibitors

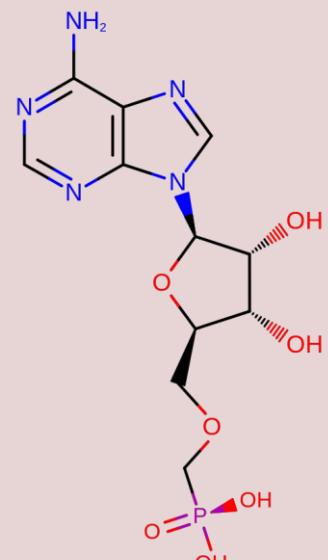
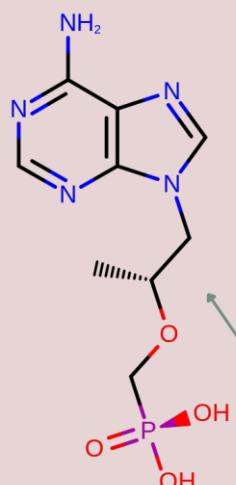
Emtricitabine



Thymidine



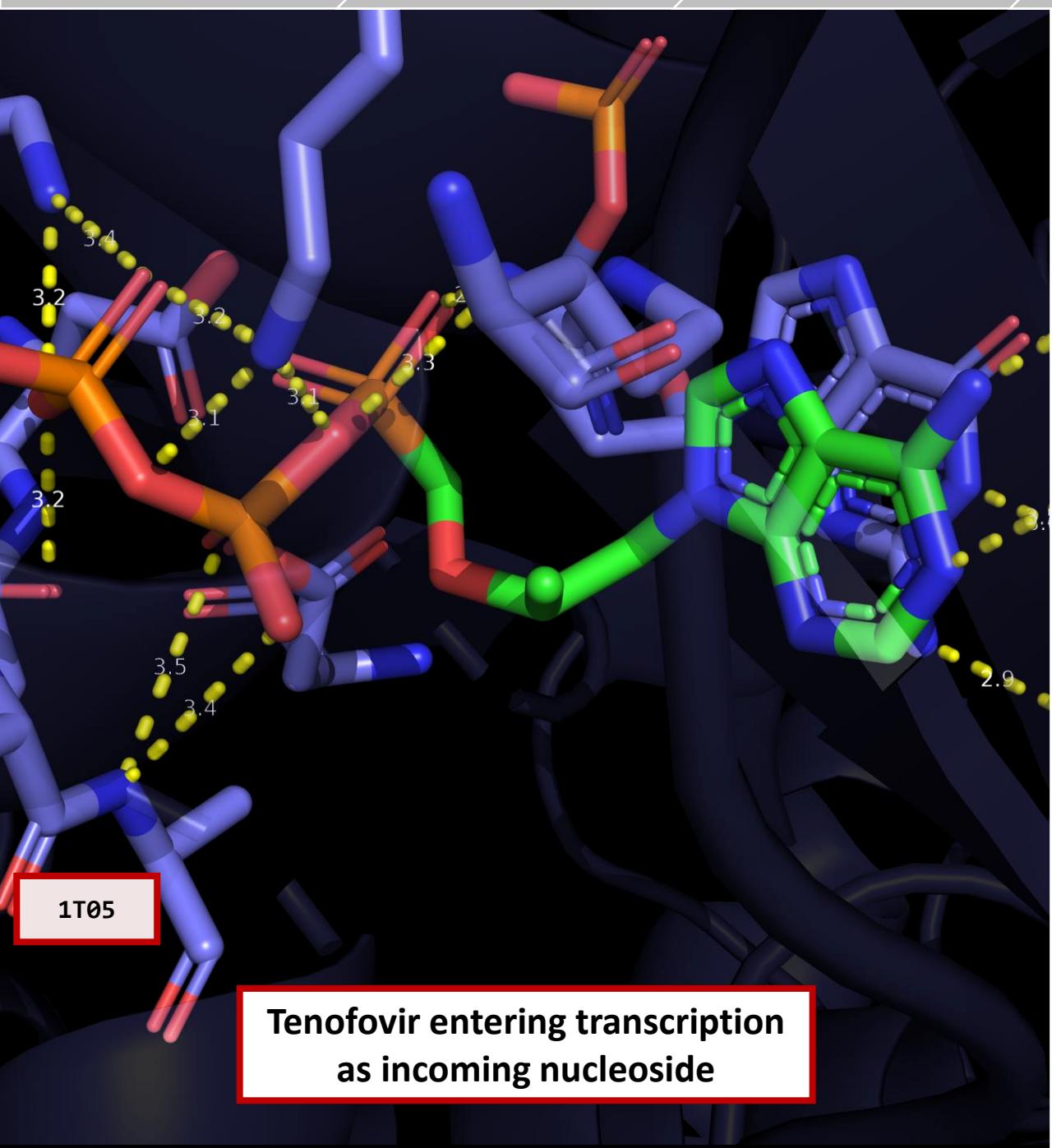
Emtricitabine



Tenofovir

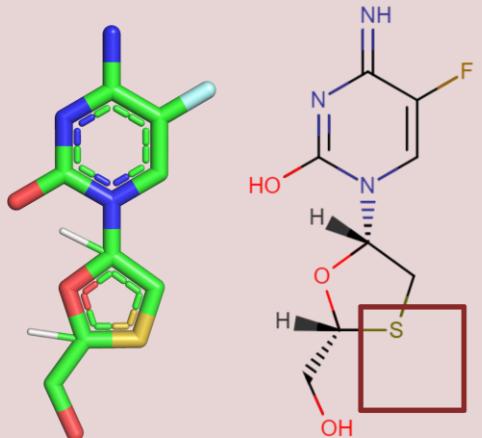
Tenofovir

Adenosine

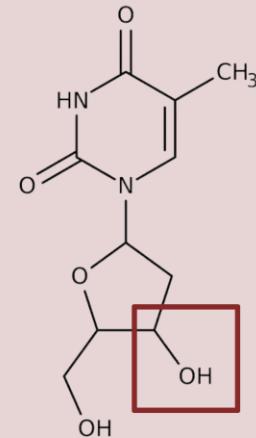


Nucleoside Reverse Transcriptase Inhibitors

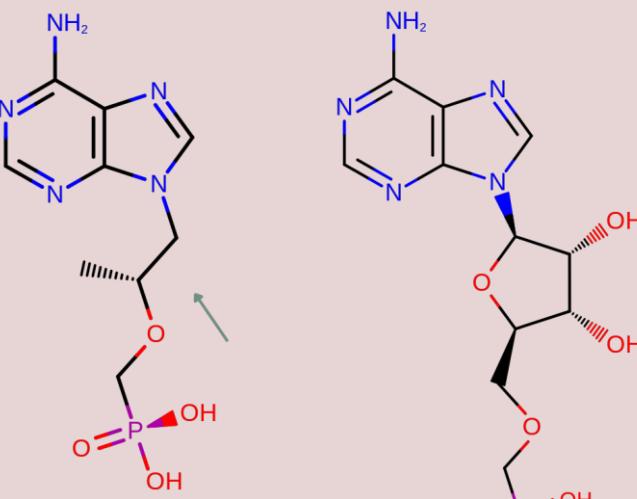
Emtricitabine



Thymidine



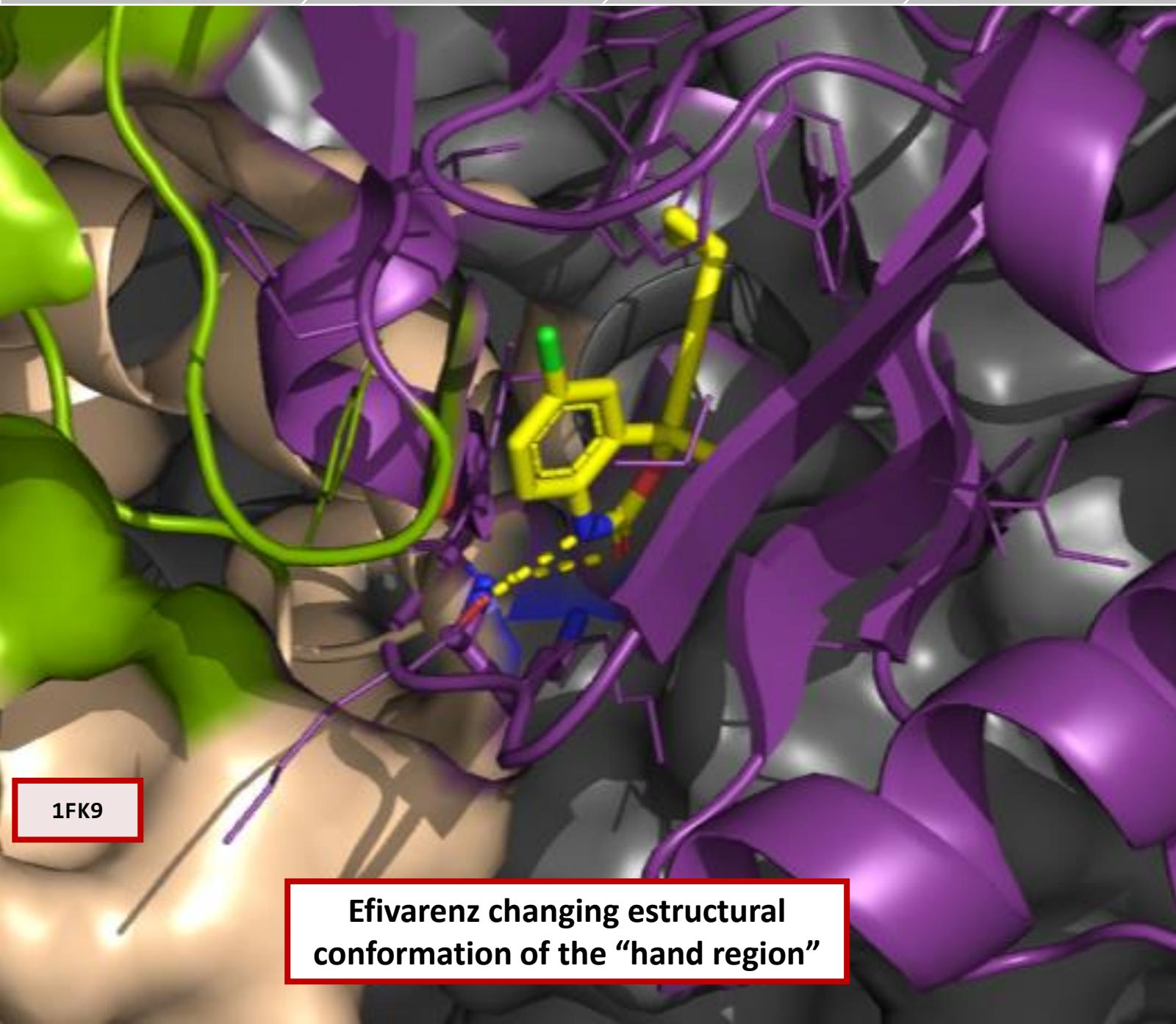
Emtricitabine



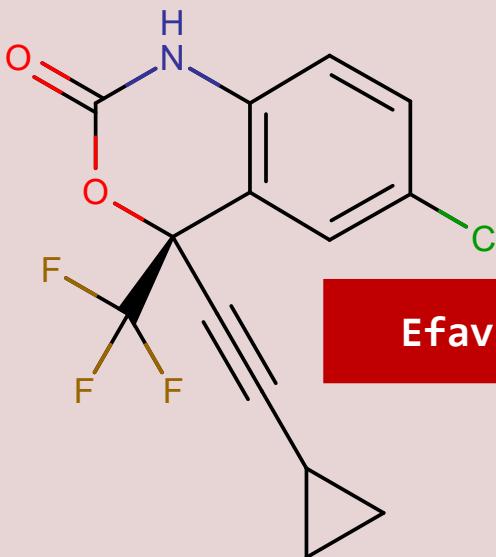
Tenofovir

Tenofovir

Adenosine



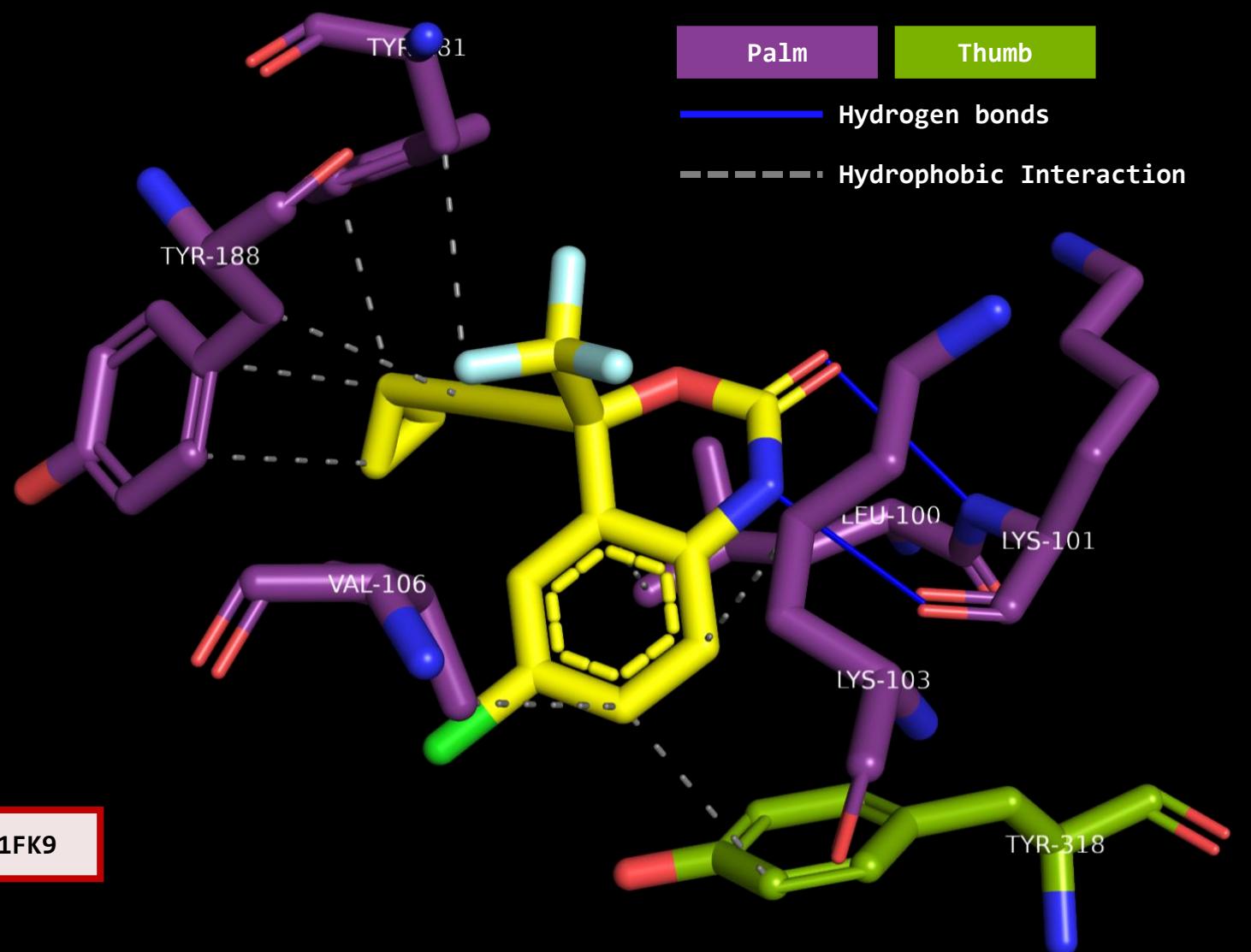
Non-Nucleoside Reverse Transcriptase Inhibitors



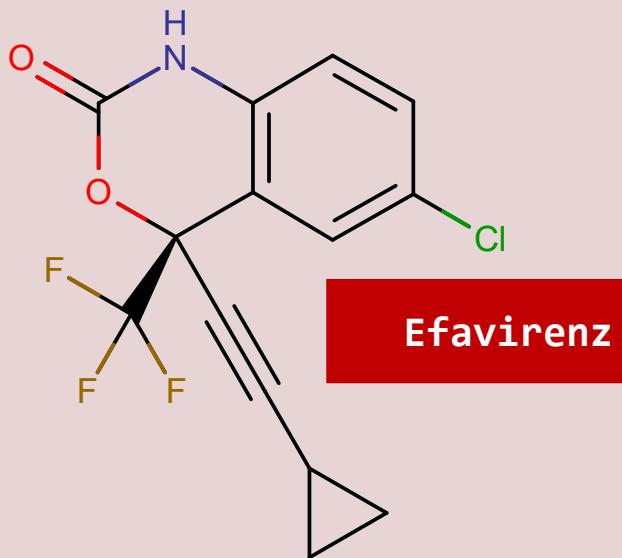
Efavirenz

Efavirenz binds to LYS-101 with hydrogen bonds, so it is fixed there.

For the other residues, hydrophobic interactions are the key. These interactions quickly change the overall conformation of this region and its effects affect the thumb and fingers making them adopt an open conformation.

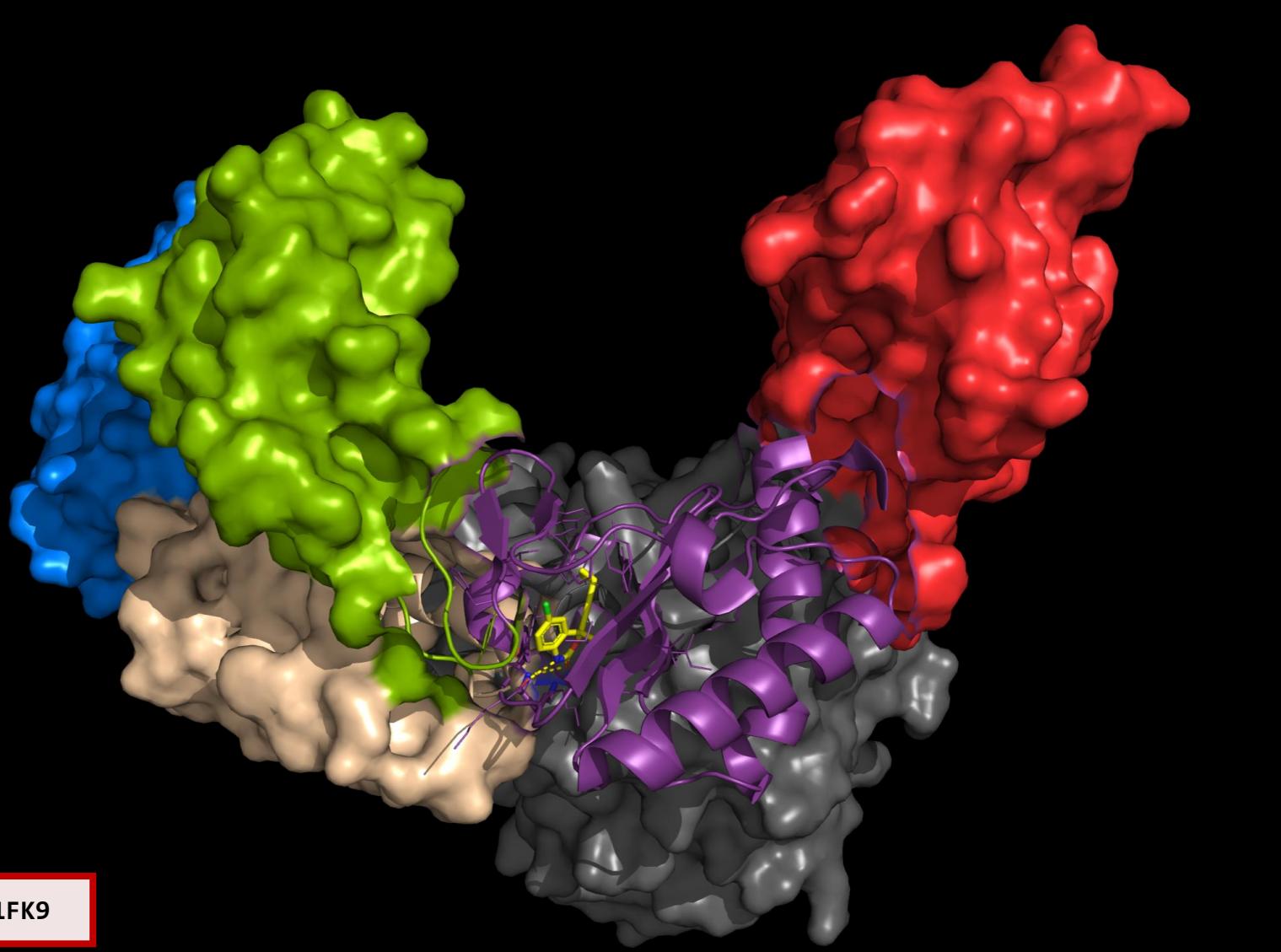


Non-Nucleoside Reverse Transcriptase Inhibitors



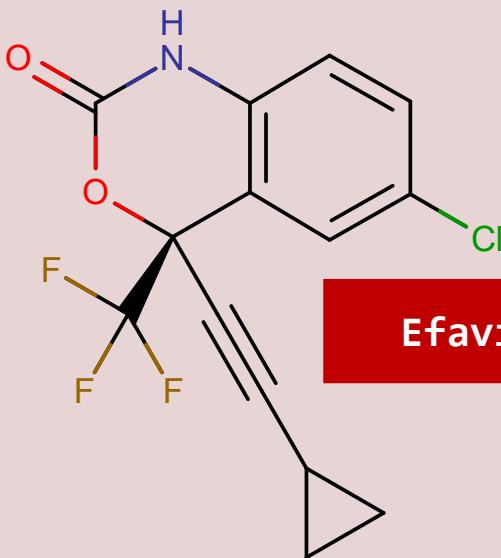
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Gets inside the hydrophobic site of the palm

Non-Nucleoside Reverse Transcriptase Inhibitors



Efavirenz

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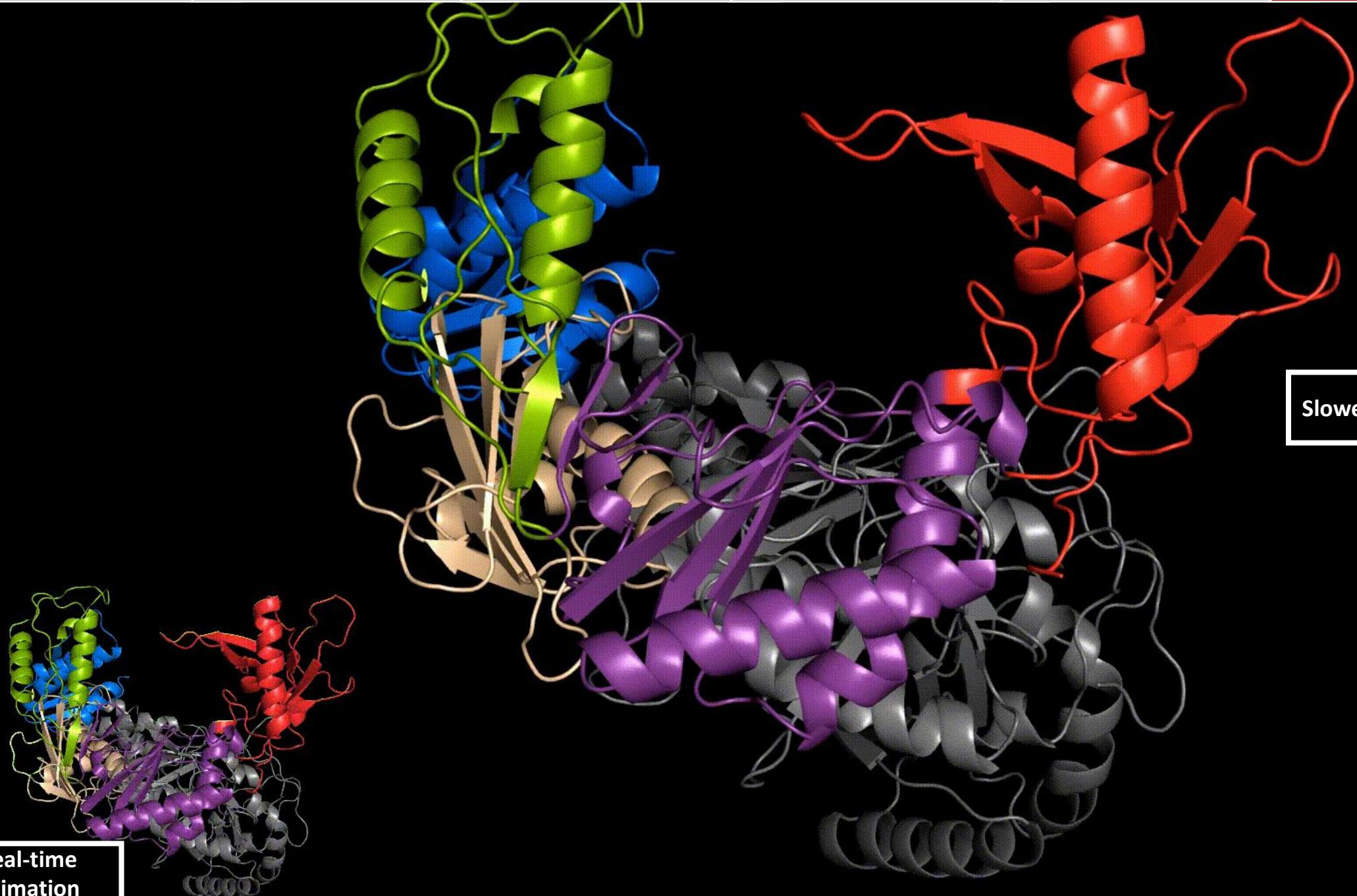
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MAIN CONCLUSIONS

Sub-domain conservation

**Flexible dependent
structure on hand region**

**Drugs attack flexibility
dependency among others**



Real-time
animation

Slowed animation