DNA Recombinase Proteins, their Function and Structure in the Active Form, a Computational Study.

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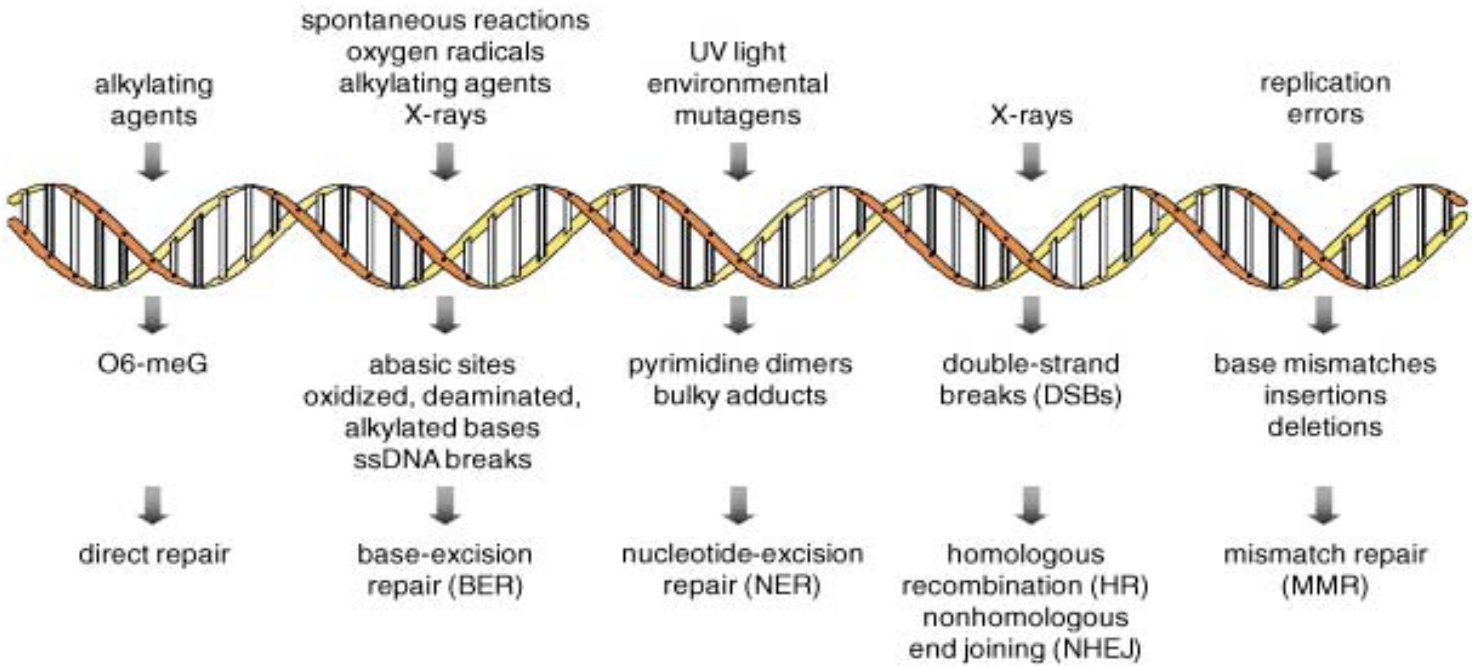
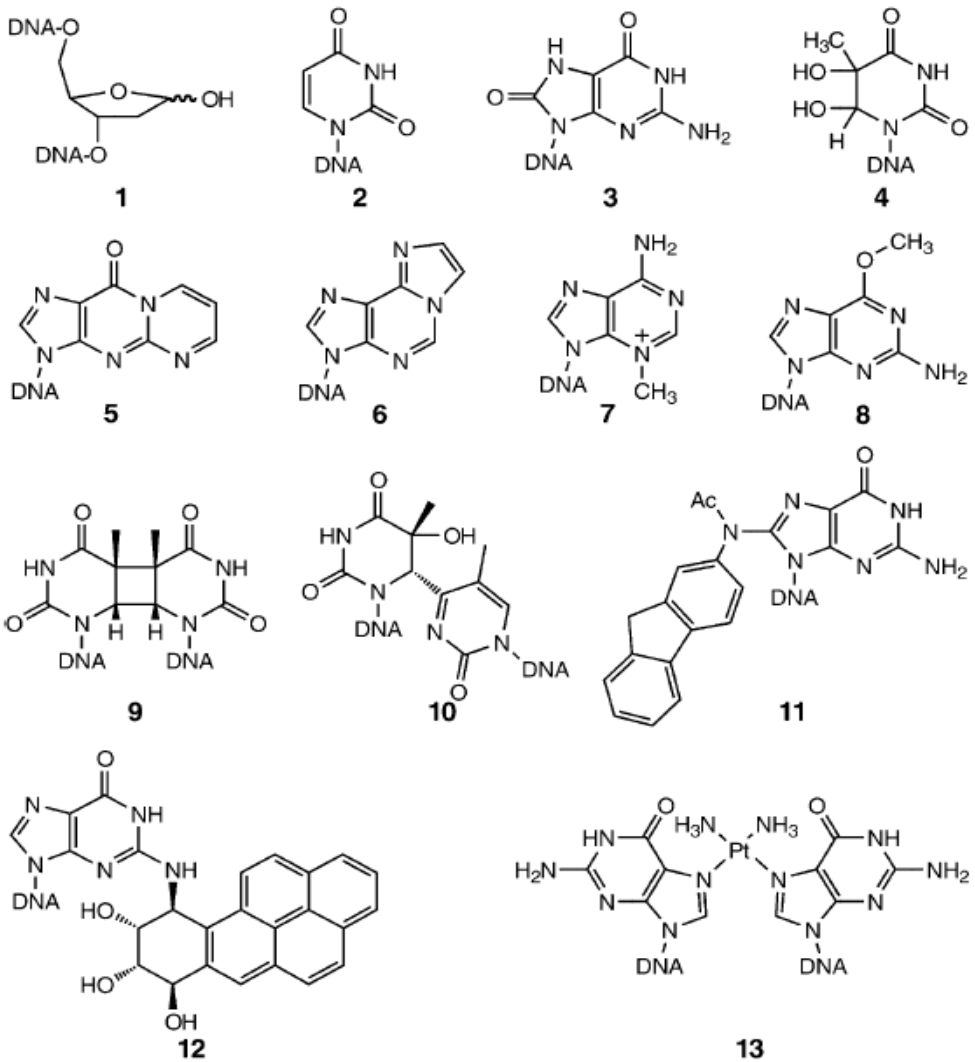
Introduction:



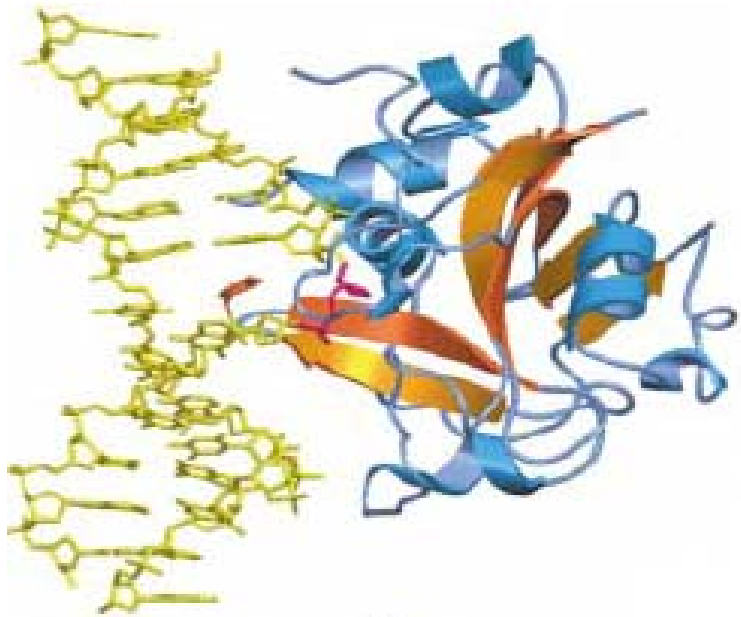
Common DNA damages:

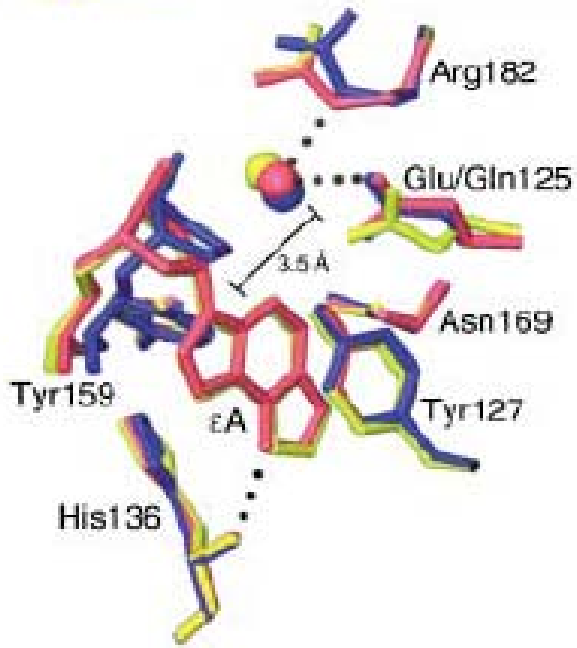


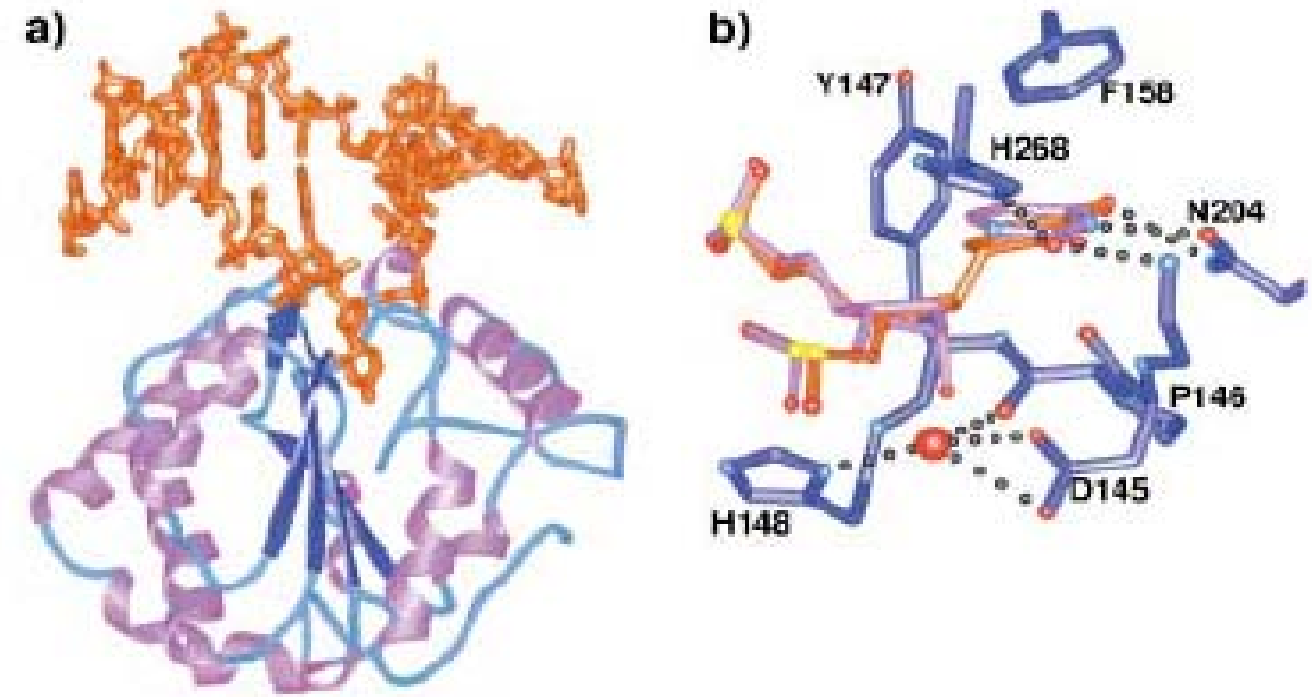
Structure of AAG bound to DNA

a. overview of the crystal structures

b. structure of the active site:







Structure of UDG bound to an uncleavable analogue substrate

a. overview of the crystal structures

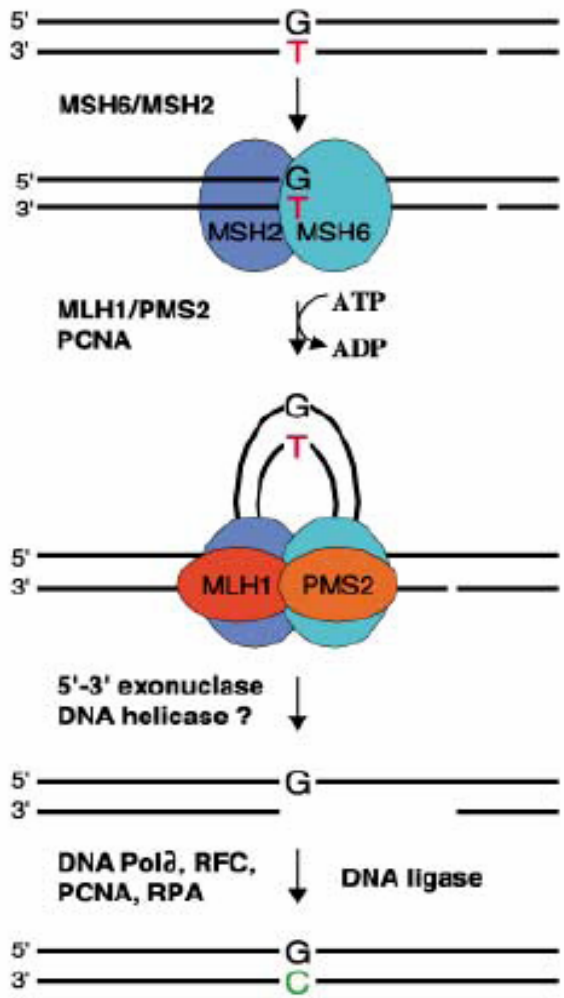
b. structure of the active site

Human mismatch repair pathway.

The nicked strand contains the erroneous base. A base/base mismatch resulting from faulty replication is recognized by the MSH6–MSH2 heterodimer (MutSa).

ATP drives the bidirectional threading of DNA through MutSa. Recruitment of MLH1/PMS2 (MutLa) and PCNA leads to the formation of a loop structure with the MMR proteins at the base and mismatch in the loop.

One or several exonucleases and helicases are then recruited to degrade the error-containing strand. The gap is subsequently filled by the replication machinery, and DNA ligase I seals the nick.



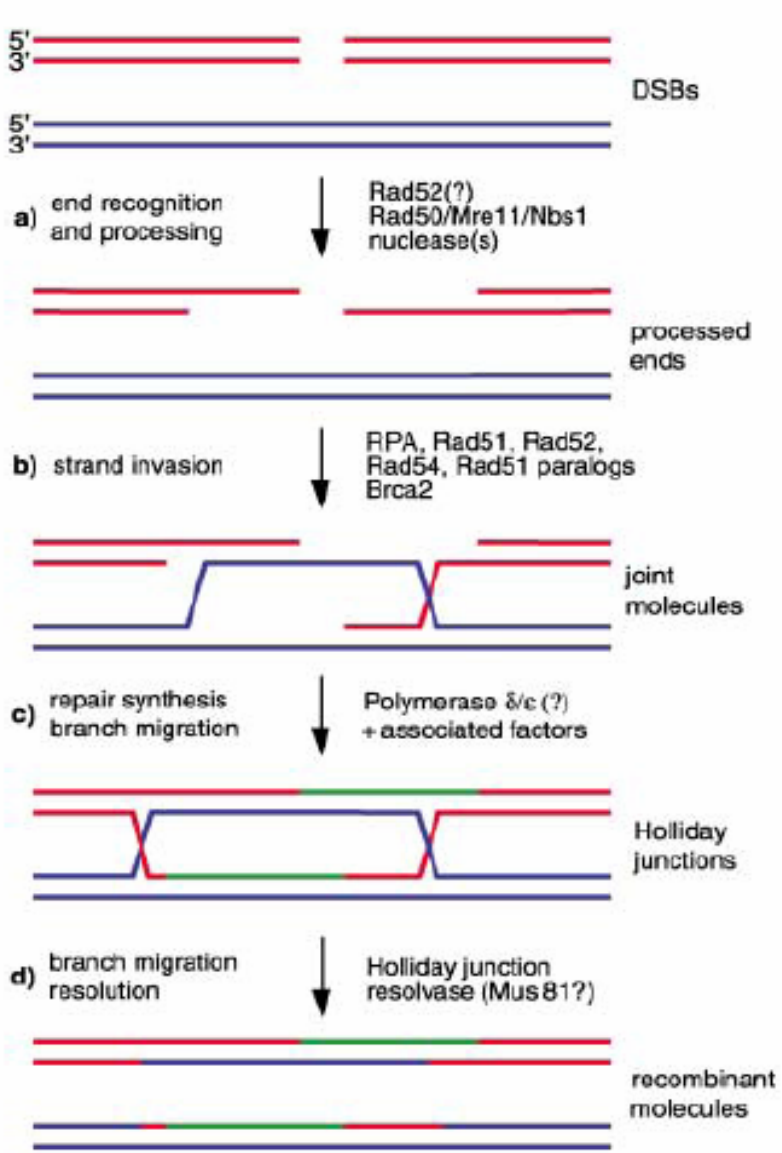
Double-strand break (DSB) repair by homologous recombination.

a) Initial recognition of a DSB may involve binding of the Rad52 protein. Nucleolytic processing of the DNA ends to form 3'- ssDNA overhangs involves the Rad50/Mre11/Nbs1 complex, probably in conjunction with another nuclease.

b) The ssDNA ends are bound by the ssDNA-binding protein RPA and with the help of Rad52 and the **Rad51** paralogs (Rad51B,C,D and XRCC2,3), Rad51 is loaded onto the ssDNA to form a nucleoprotein filament. The BRCA2 protein has a role in regulating Rad51 activity and may directly stimulate the formation of the nucleoprotein filament. This nucleoprotein filament searches for homologous duplex DNA, and a strand-exchange reaction generates a joint molecule between the damaged and undamaged DNA, a step stimulated by Rad54.

c) In a process that is not ellunderstood, DNA polymerases and their associated factors carry out repair synthesis and Holliday junctions are formed.

d) Holliday junctions are resolved by endonucleolytic cleavage and rejoining in a reaction that may involve the Mus81 protein and in which two intact DNA molecules are formed.

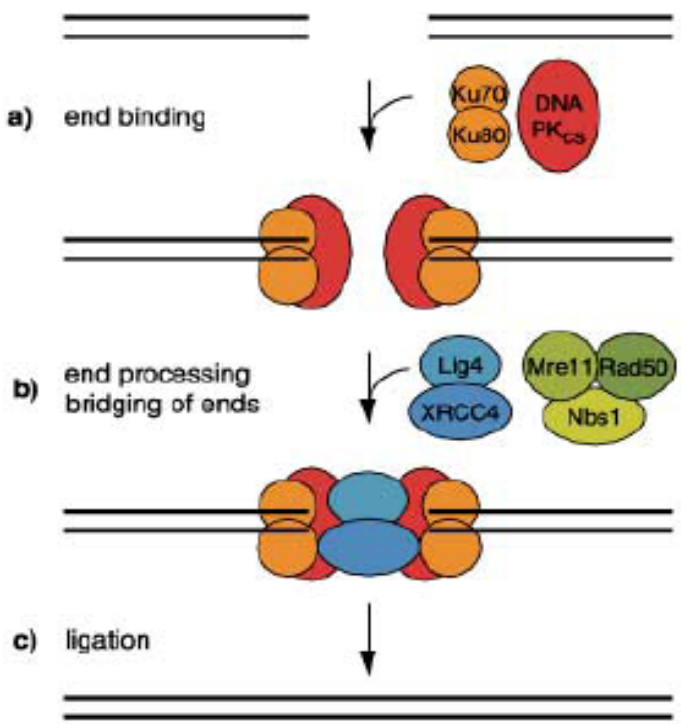


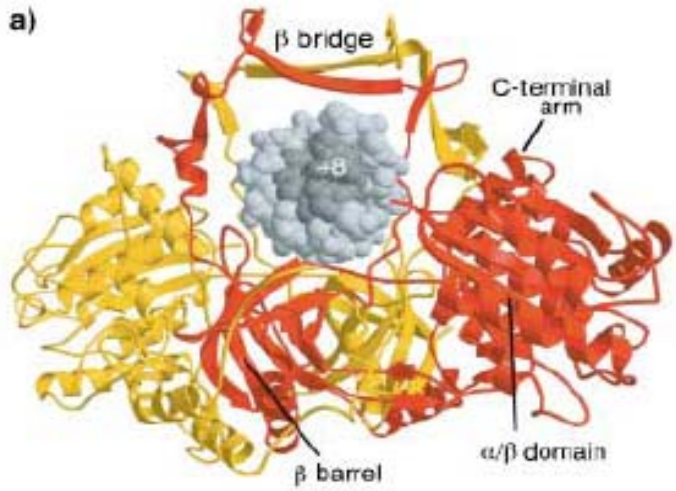
DSB repair by nonhomologous end joining (NHEJ).

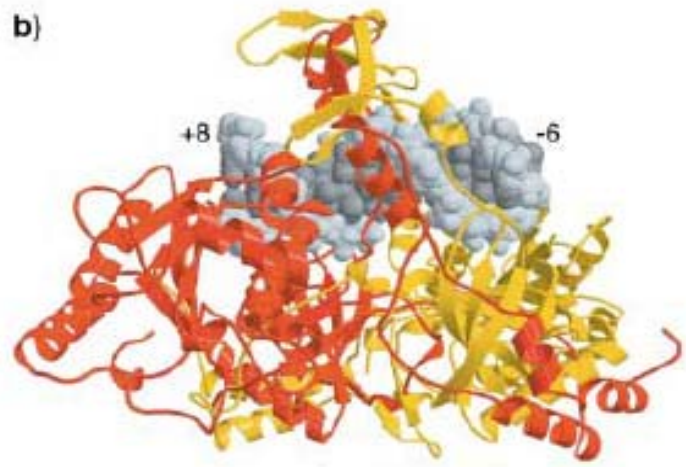
a) DSBs are recognized by the Ku70 and Ku80 proteins, which specifically bind to DNA ends and form a complex withth e DNA-dependent protein kinase catalytic subunit (DNA-PKCS).

b) The ends of the break may be processed in a step involving Rad50/Mre11/Nbs1 and a furthe nuclease; a few base pairs may be removed in this step. The Rad50/Mre11/Nbs1 and Xrcc4/DNA ligase IV complexes have structura features that suggest that they are involved in the bridging of the DNA ends.

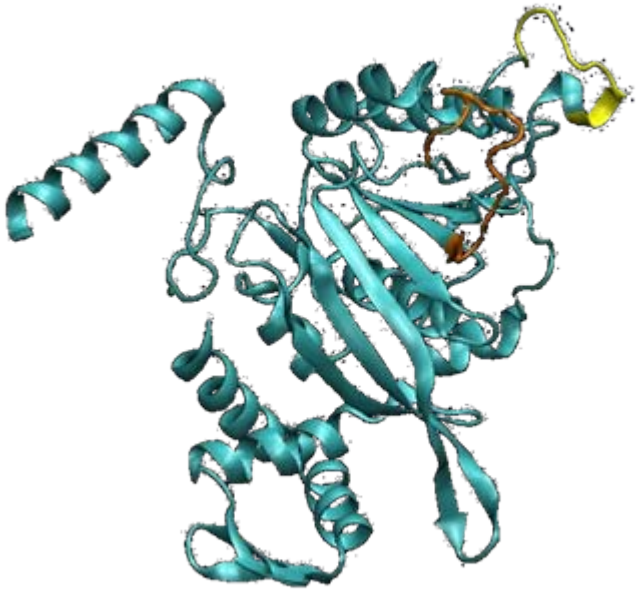
c) The two ends are ligated by Xrcc4/DNA ligase IV to restore a continuous DNA molecule. NHEJ is not intrinsically error-free and may result in the loss of a few nucleotides



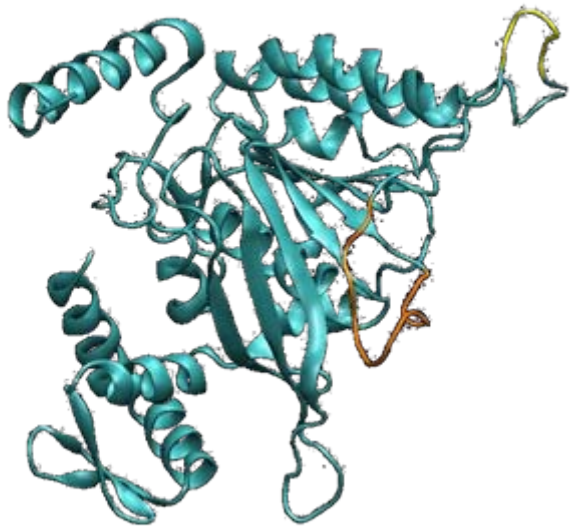




Structure of Ky70/Ku80

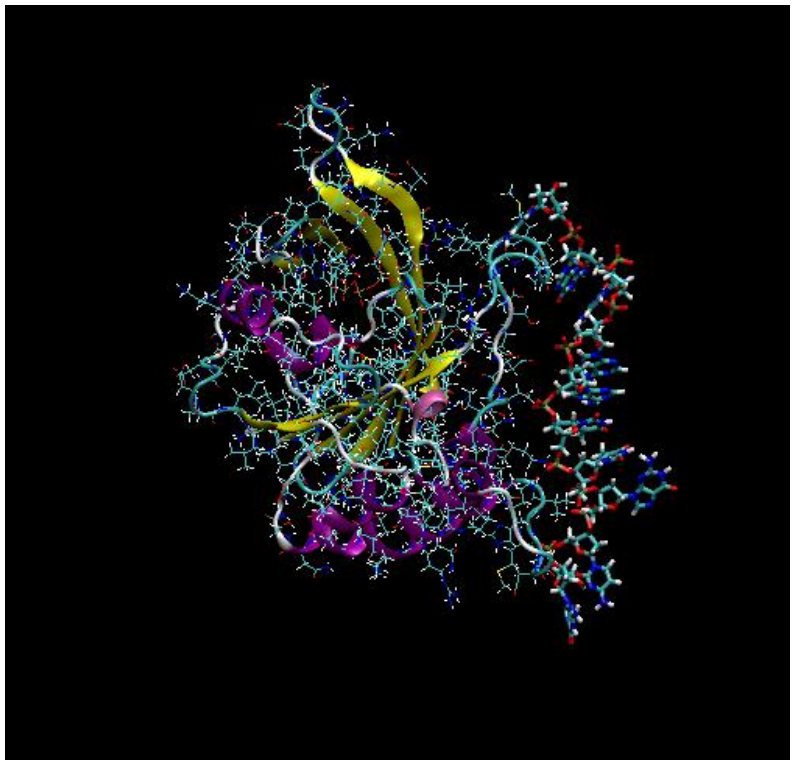


EcRecA

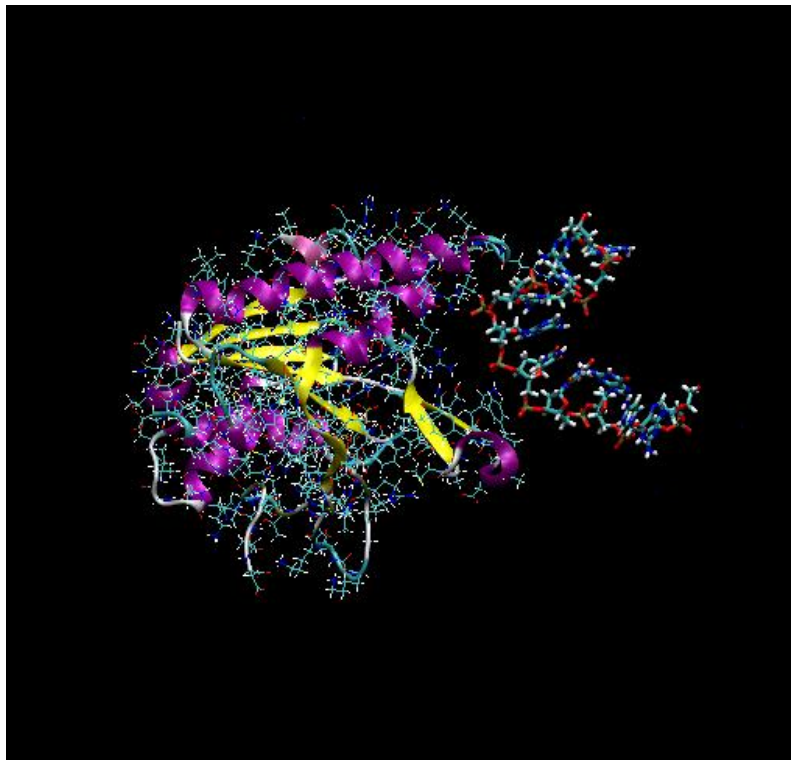


MvRadA

with ssDNA:



EcRecA



MvRadA

Conclusions

- We can provide unique insights on the mechanism of the reconbinases processes
- importance of the computational chemistry approach
- relevance on the long term space flights