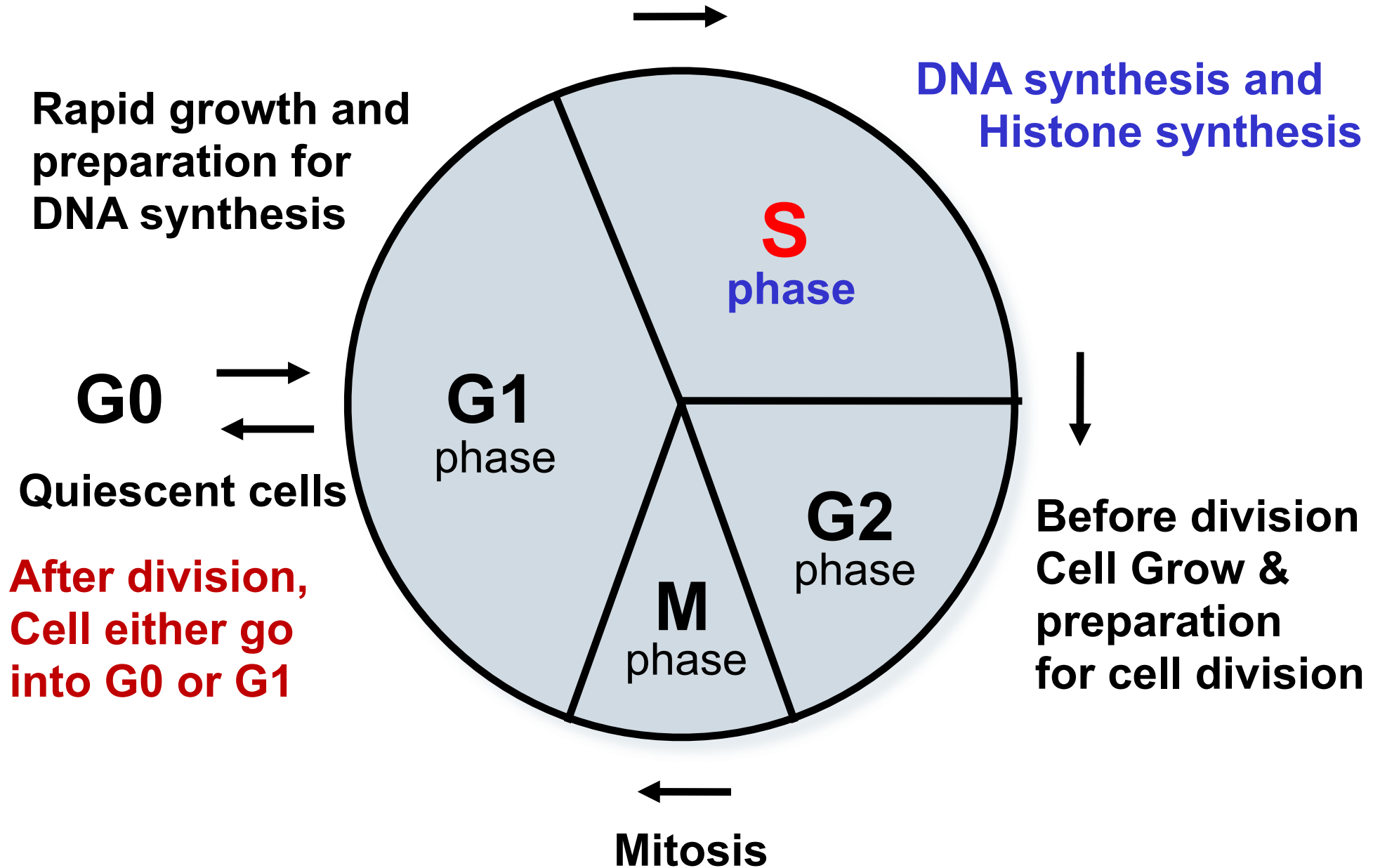


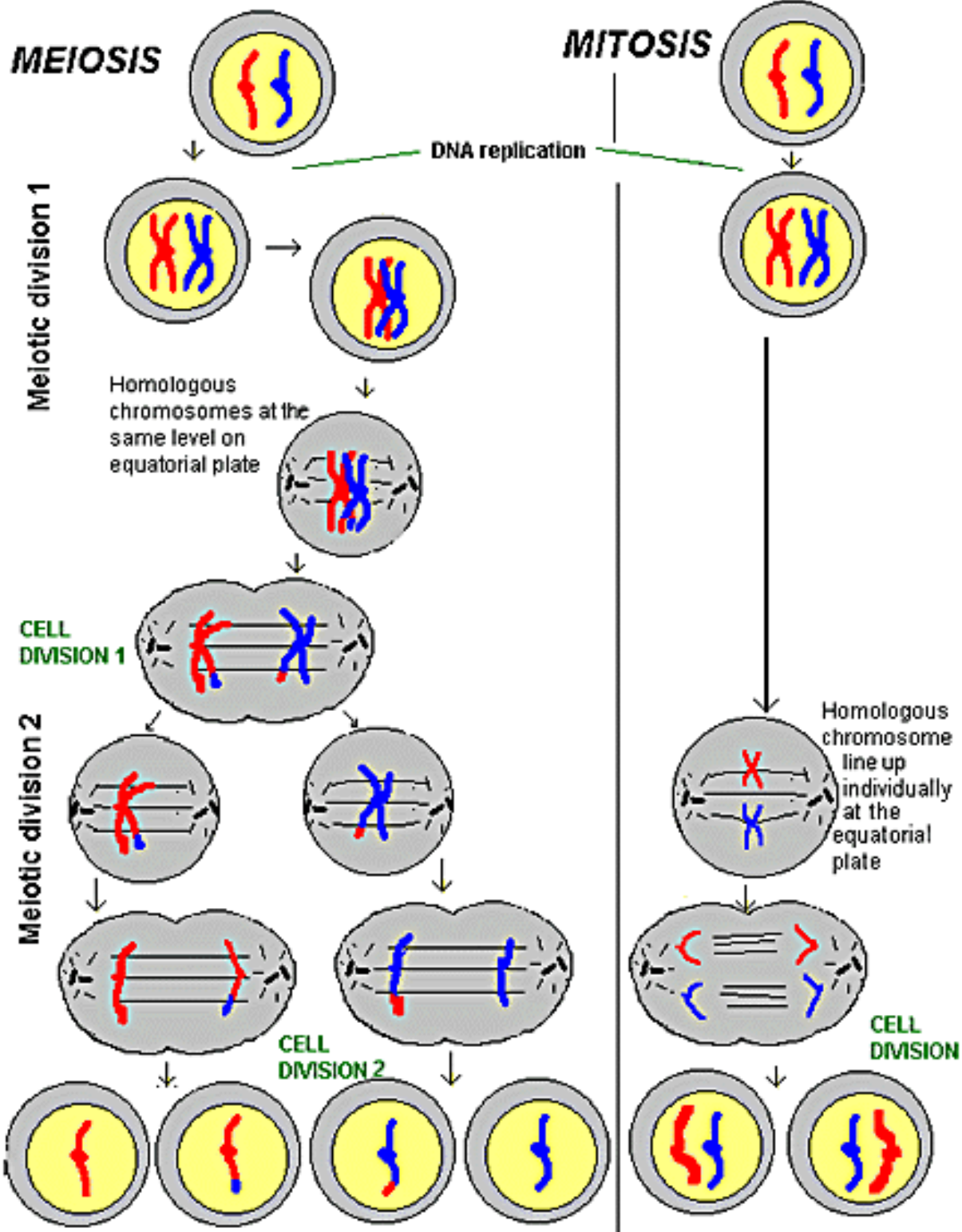
DNA Replication
Mutation during Replication
&
It's Repair

DR PIYUSH B. TAILOR

Professor & Head
Department of Biochemistry
Govt. Medical College
Bhavnagar

The mammalian cell cycle





Meiosis vs Mitosis

Purpose:

Production of gametes (sperm and egg) for sexual reproduction.

Location:

Germ cells in the gonads (ovaries and testes).

Daughter Cells:

Four haploid (n) daughter cells, unique from the parent.

Divisions:

Two divisions (Meiosis I and Meiosis II).

Genetic Variation:

High variation due to crossing over and independent assortment.

Purpose:

Growth, tissue repair, and asexual reproduction

Location:

Somatic (body) cells.

Daughter Cells:

Two diploid (2n) daughter cells, identical to the parent.

Divisions:

One division (Prophase, Metaphase, Anaphase, Telophase).

Genetic Variation:

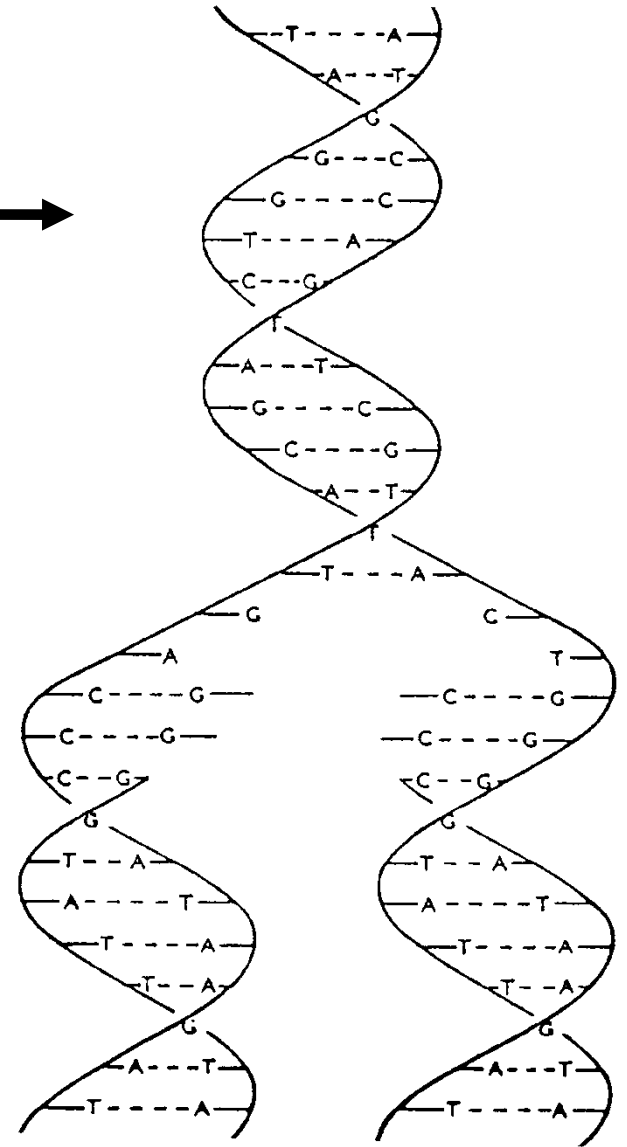
No variation; cells are clones.

DNA replication is semi-conservative

Parental DNA strands →

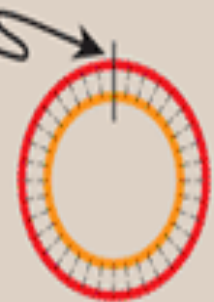
Each of the parental strands serves as a template for a daughter strand

Daughter DNA strands →

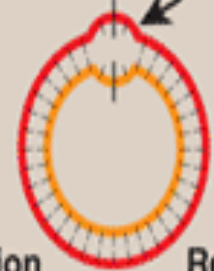


A

Origin of replication



Local opening of double helix

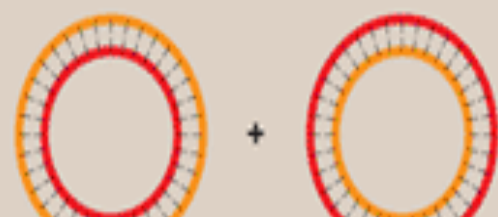


Replication fork

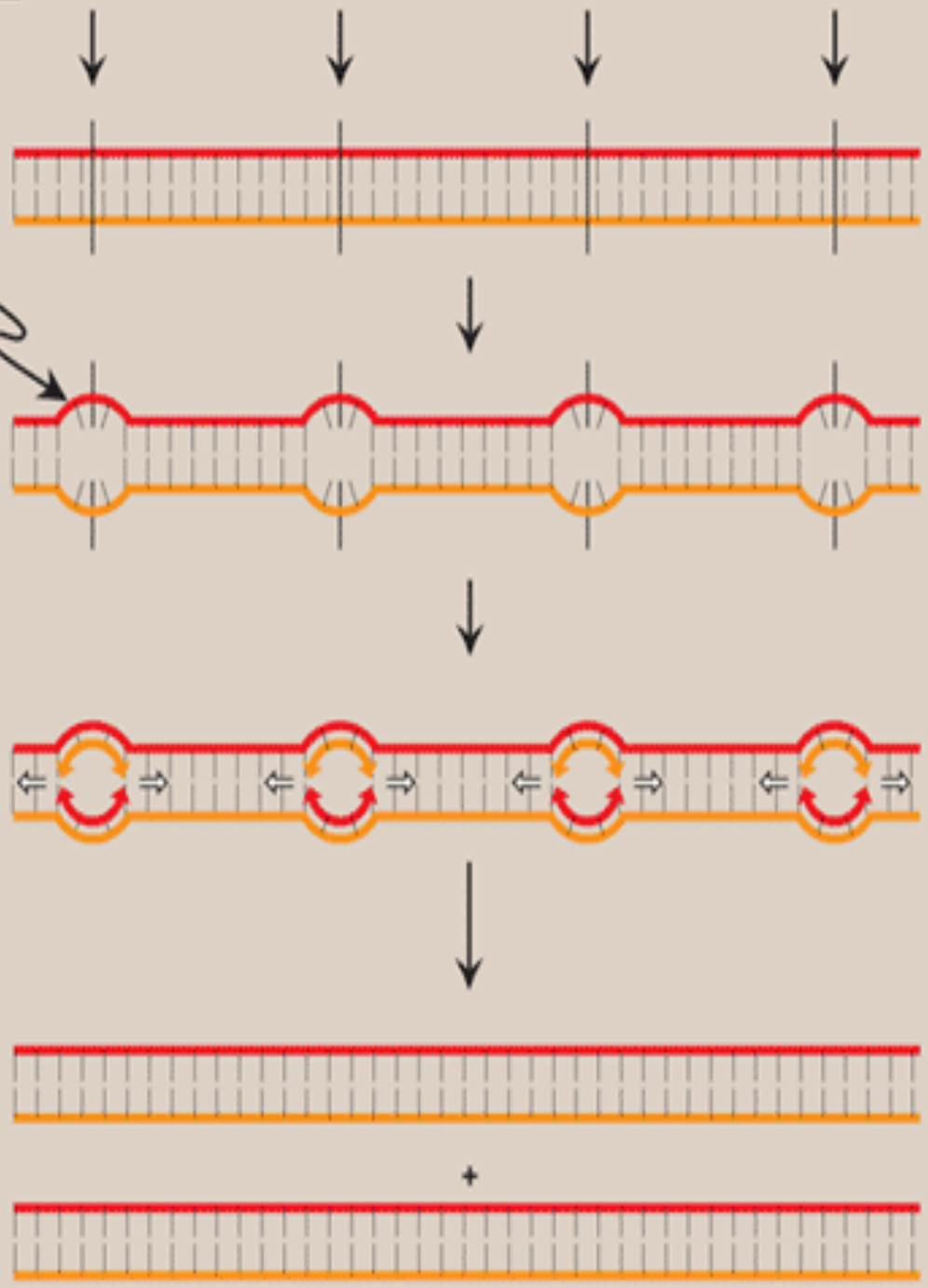
Replication fork



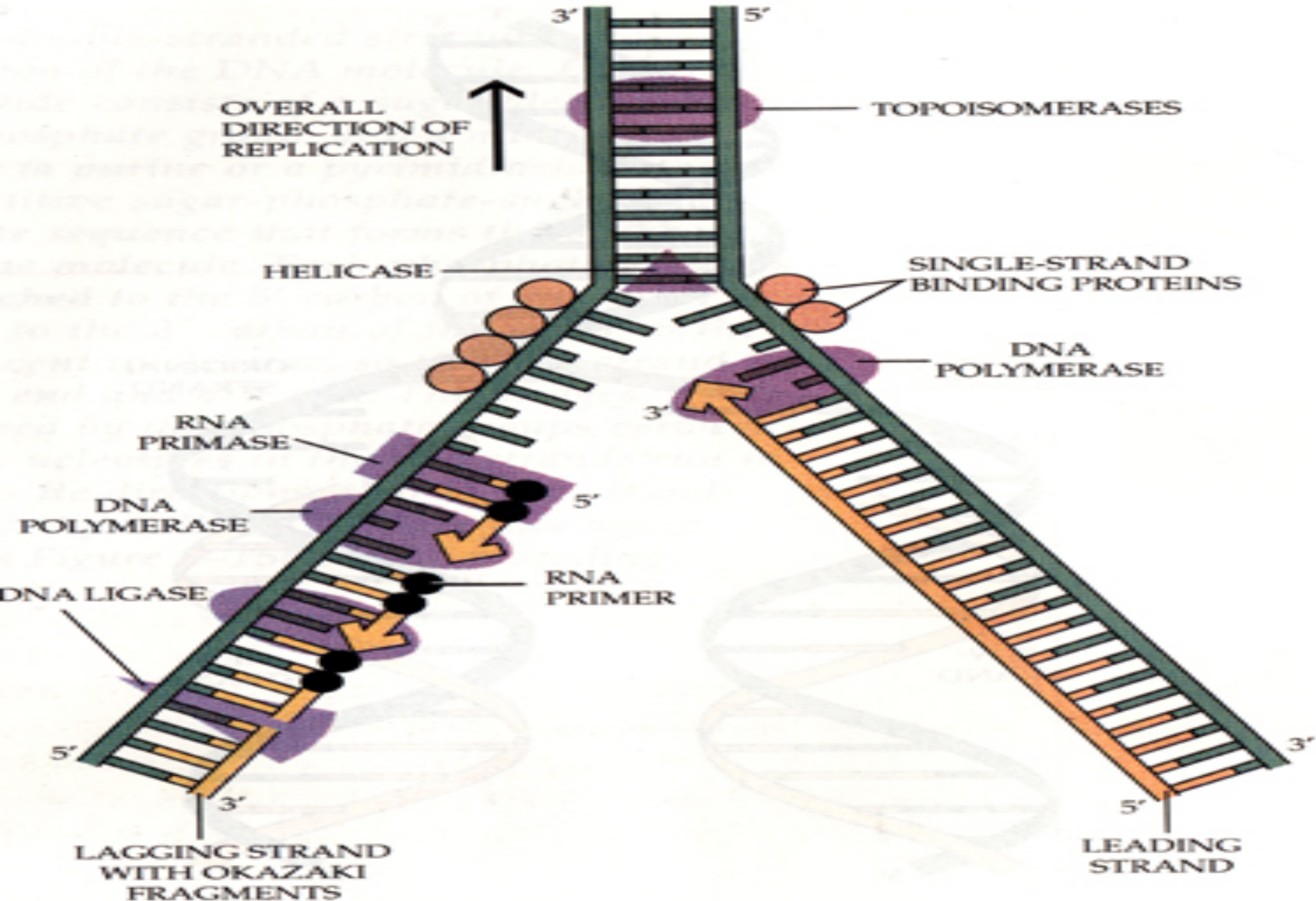
Bidirectional replication continues

**B**

Multiple origins of replication

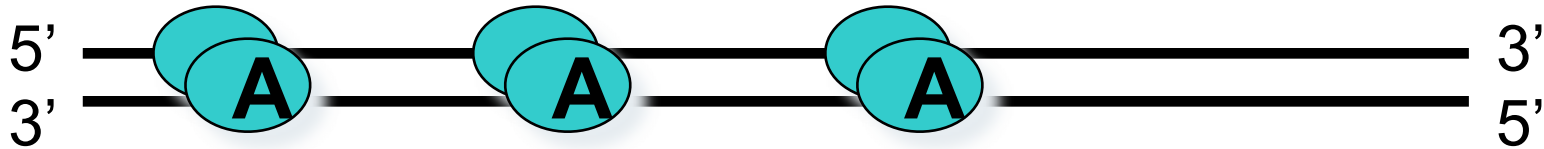


Replication



Initiation of DNA synthesis at the *E. coli* origin (ori)

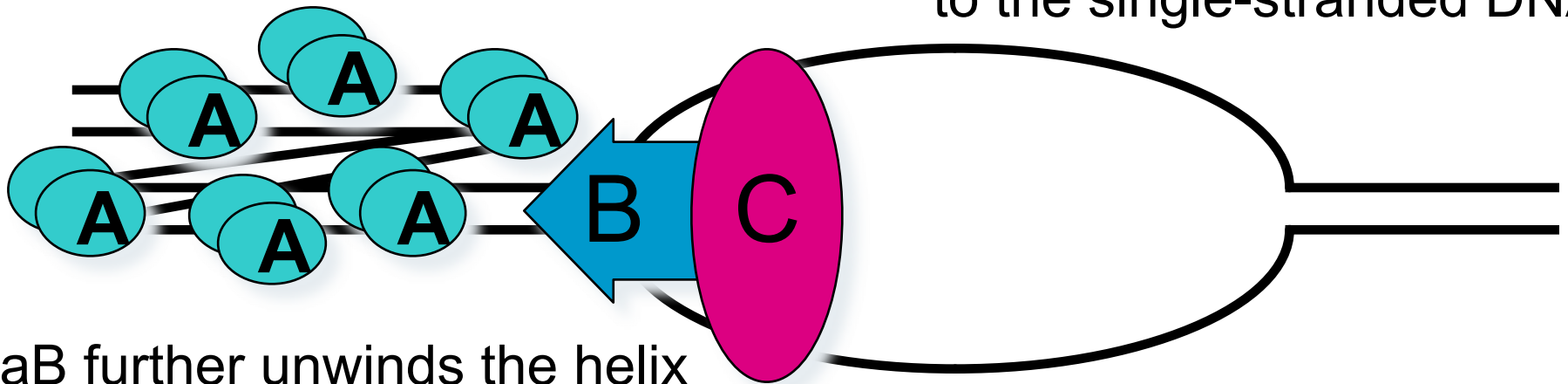
origin DNA sequence



binding of dnaA proteins



dnaB and dnaC proteins bind to the single-stranded DNA



dnaB further unwinds the helix

Dna A protein:

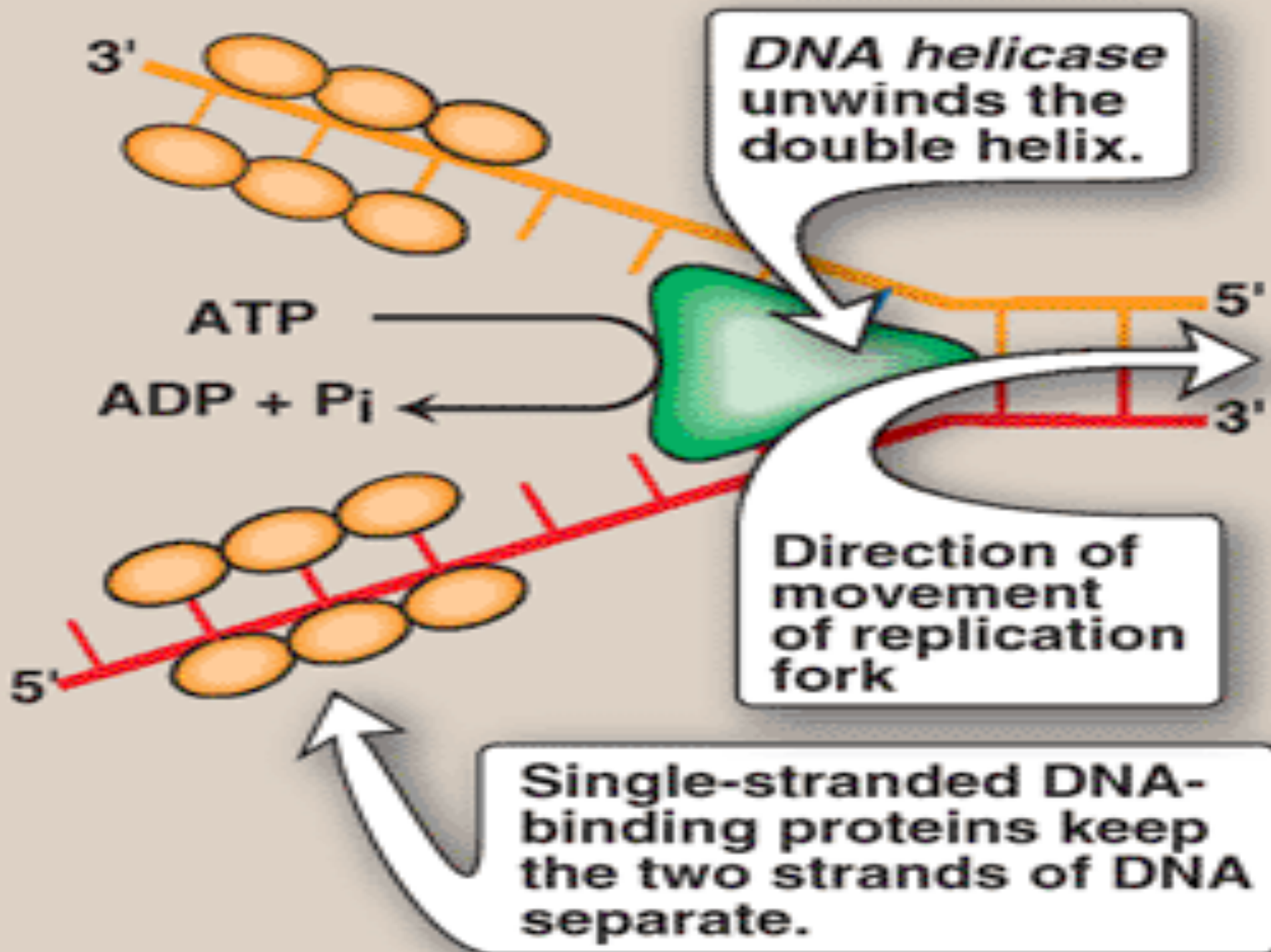
- Bind at the origin of replication
- Binds to specific nucleotide sequences
 - at AT-rich regions.
- ATP-dependent
- Strand separation
- Formation of localized ssDNA.

DNA helicases:

- Bind to ssDNA near replication fork
- Unwind double helix.
- ATP energy dependent

Single-stranded DNA-binding (SSB) proteins:

- Bind to the ssDNA
- Bind cooperatively
 - binding of one SSBP makes easier for another SSBP to bind tightly .
- Keep two strands of DNA separated
- Protect DNA from nucleases activity that cleave ssDNA.



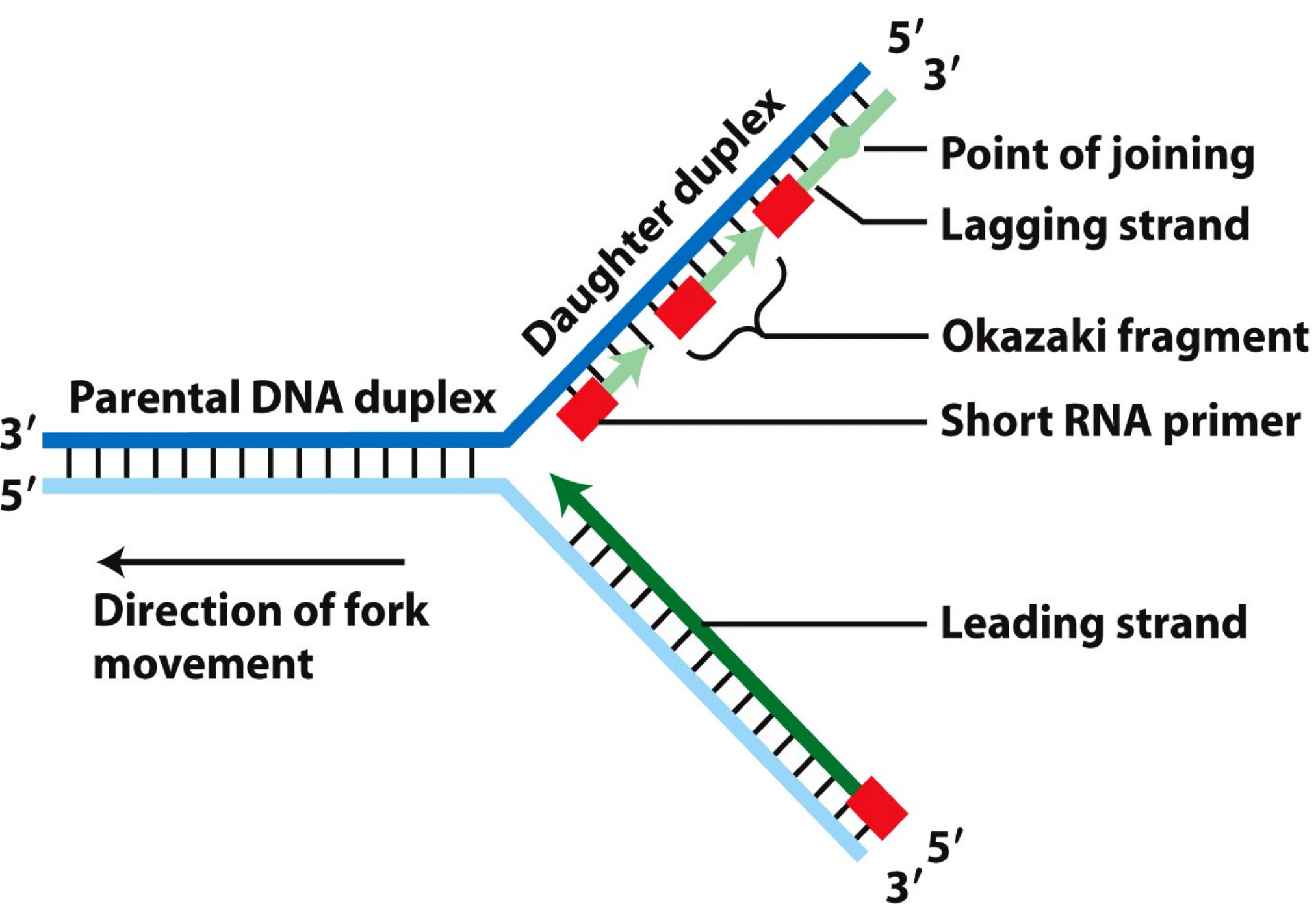
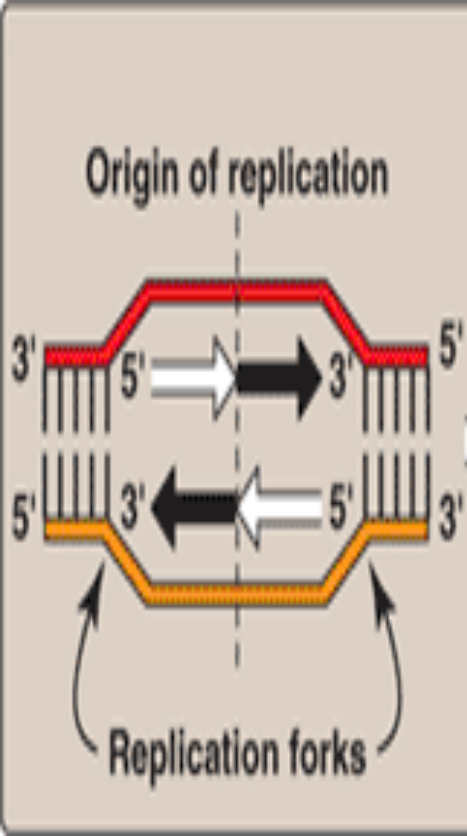


Figure 4-30
Molecular Cell Biology, Sixth Edition
 © 2008 W. H. Freeman and Company

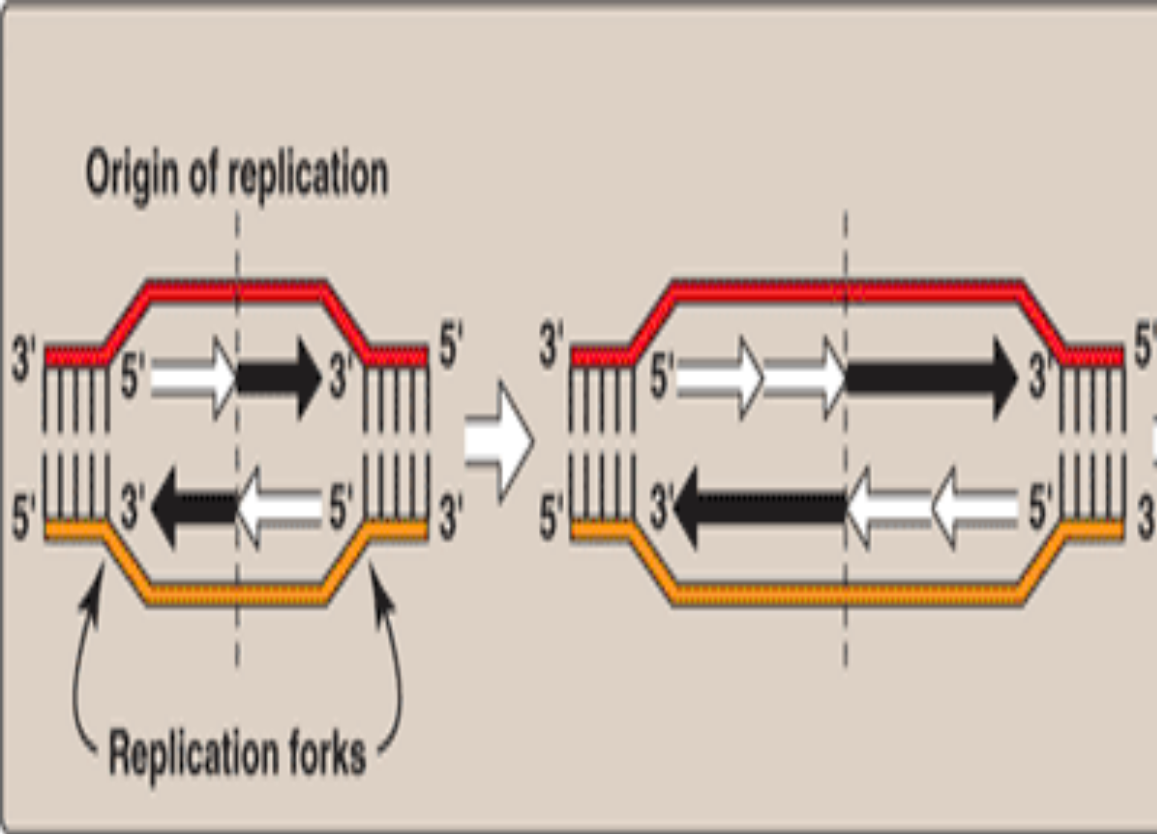


The DNA polymerases

= Copying the DNA templates

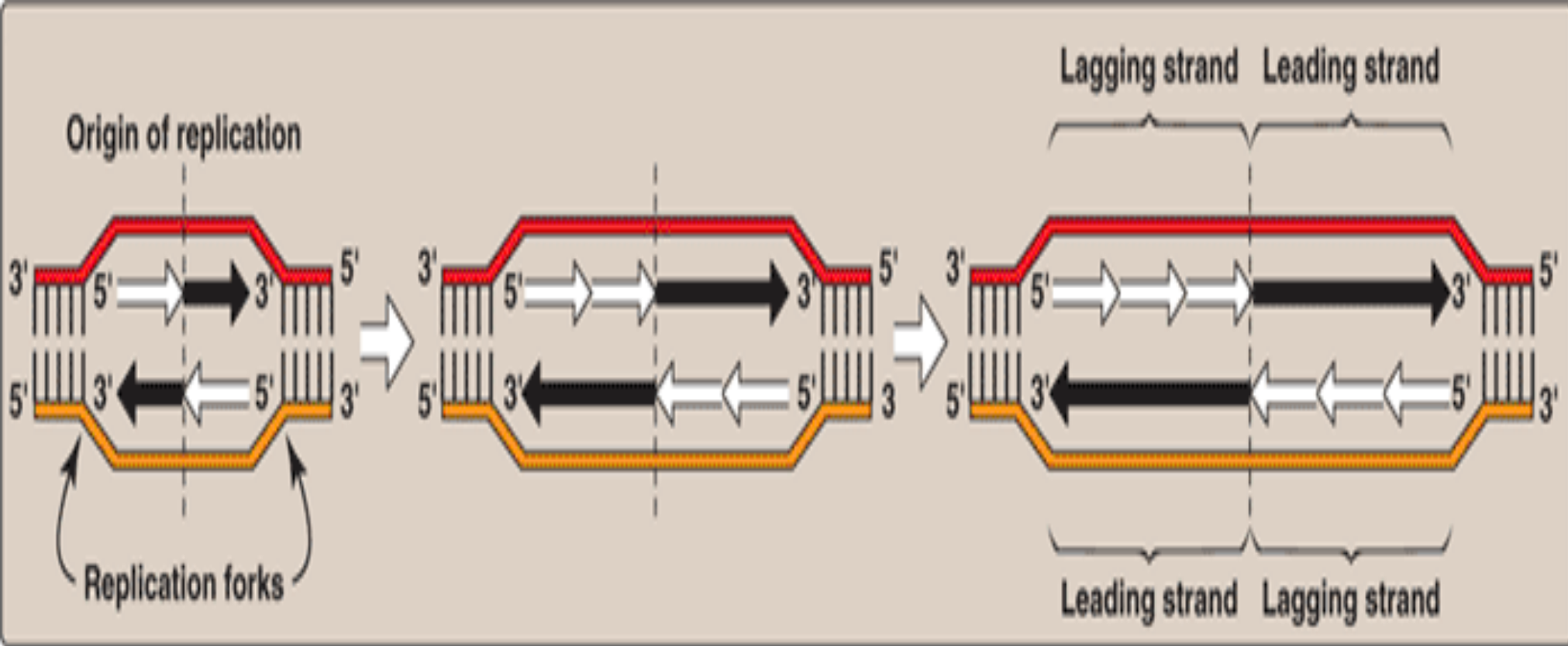
= Read parental sequences in the $3' \rightarrow 5'$ direction

= Synthesize new DNA strands in the $5' \rightarrow 3'$ (antiparallel)



The DNA polymerases

- = Copying the DNA templates
- = Read parental sequences in the 3'→5' direction
- = Synthesize new DNA strands in the 5'→3' (antiparallel)



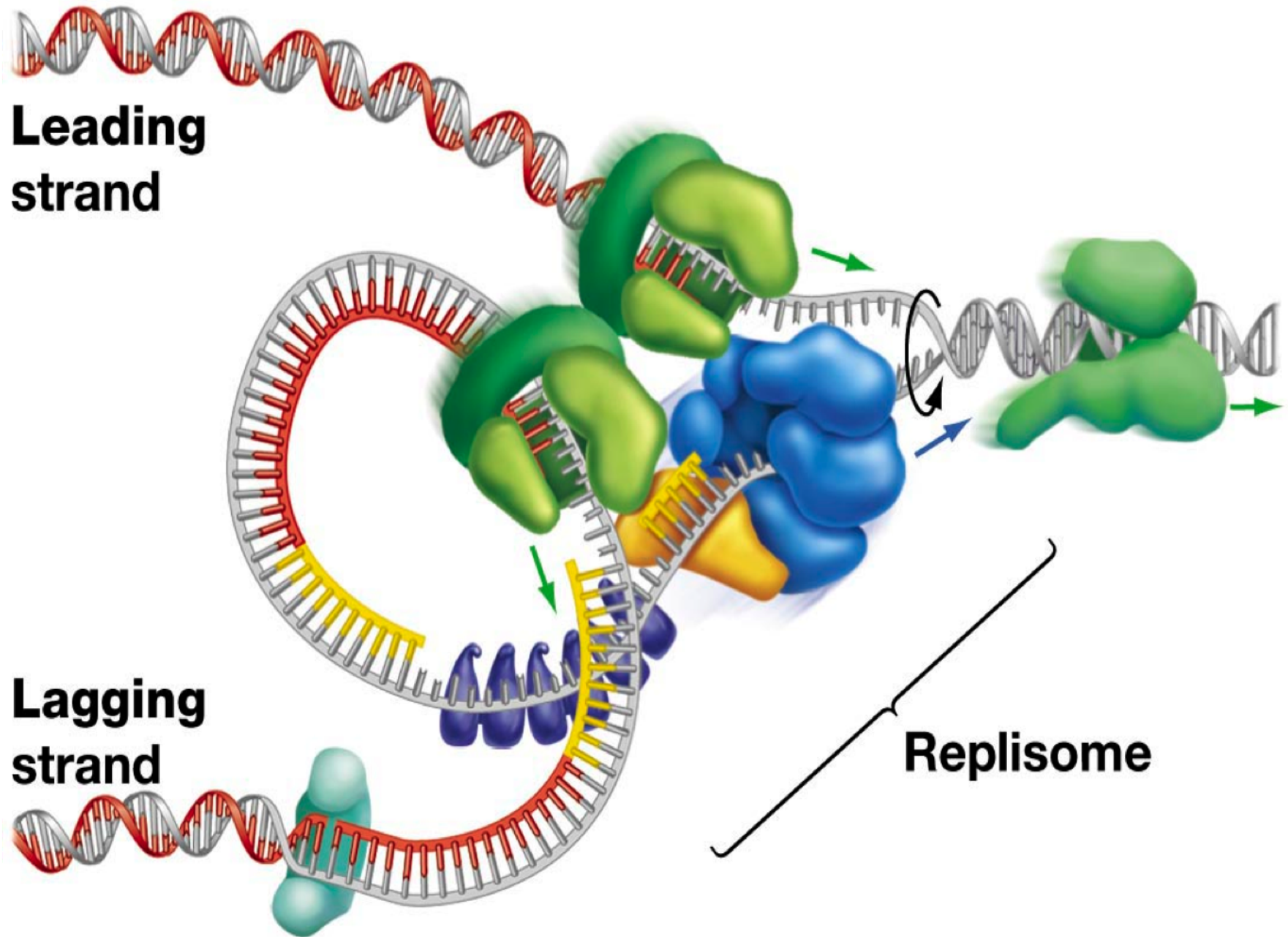
The DNA polymerases

= Copying the DNA templates

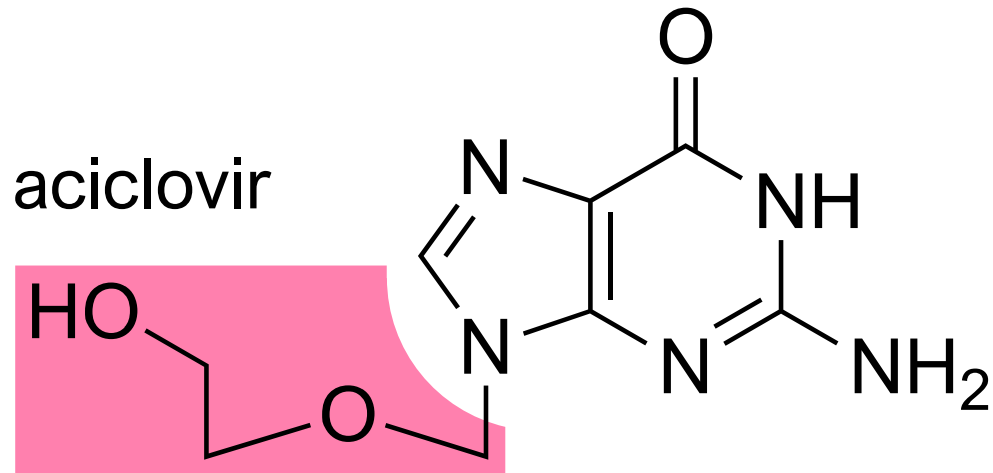
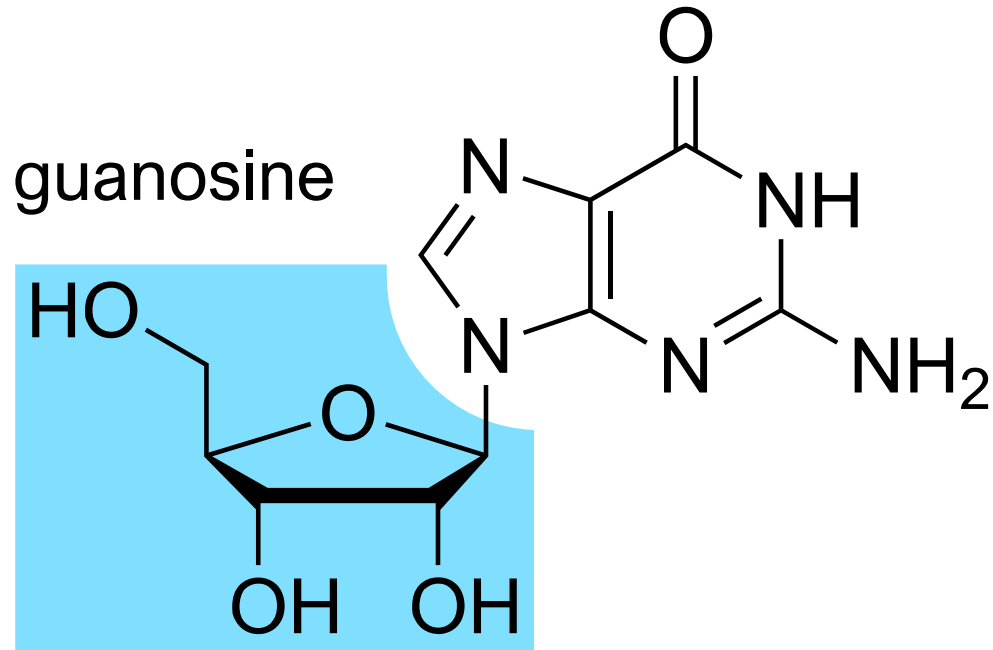
= Read parental sequences in the 3'→5' direction

= Synthesize new DNA strands in the 5'→3' (antiparallel)

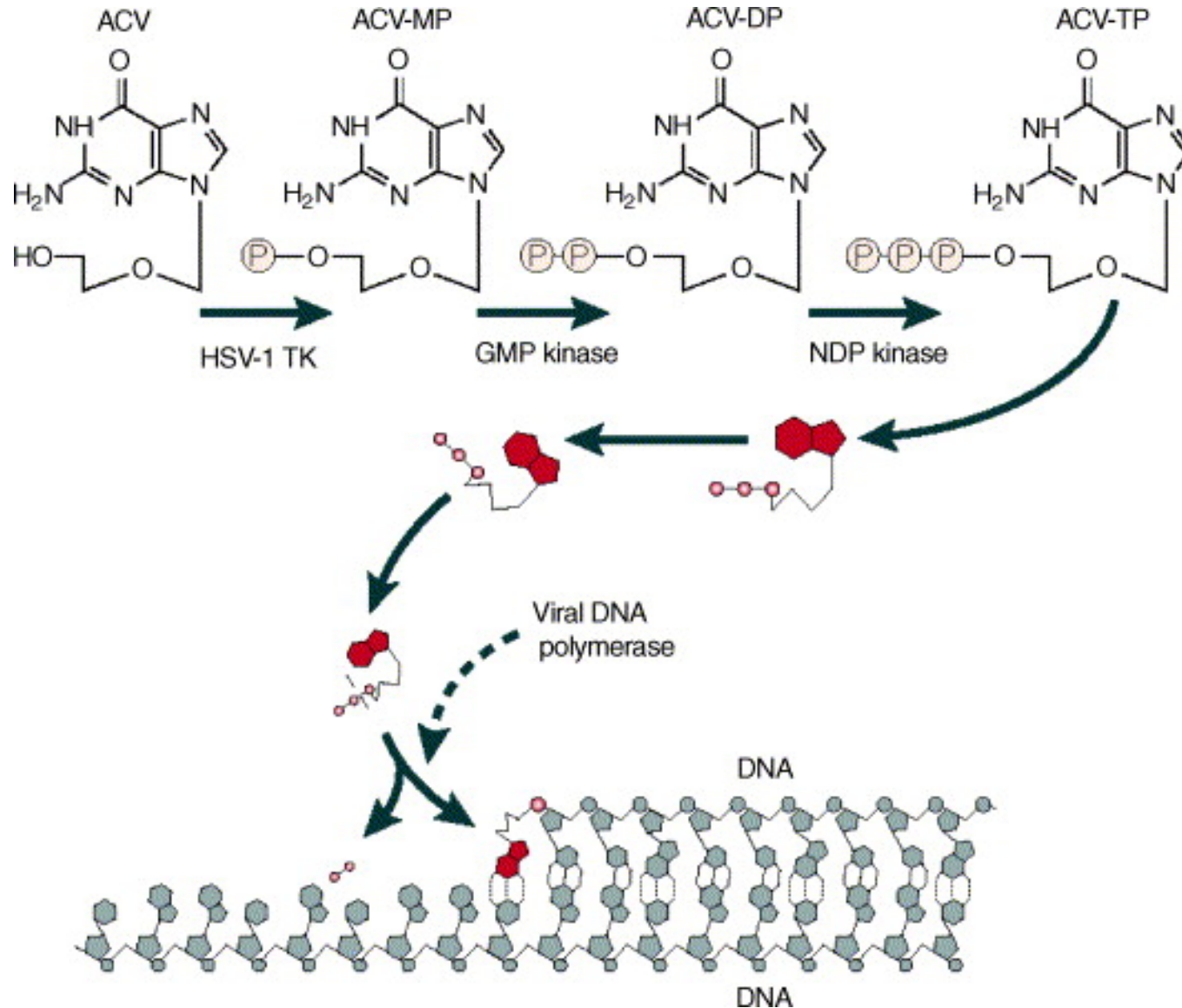
Replication - DNA Polymerase



Acyclovir - Anti Viral Drug

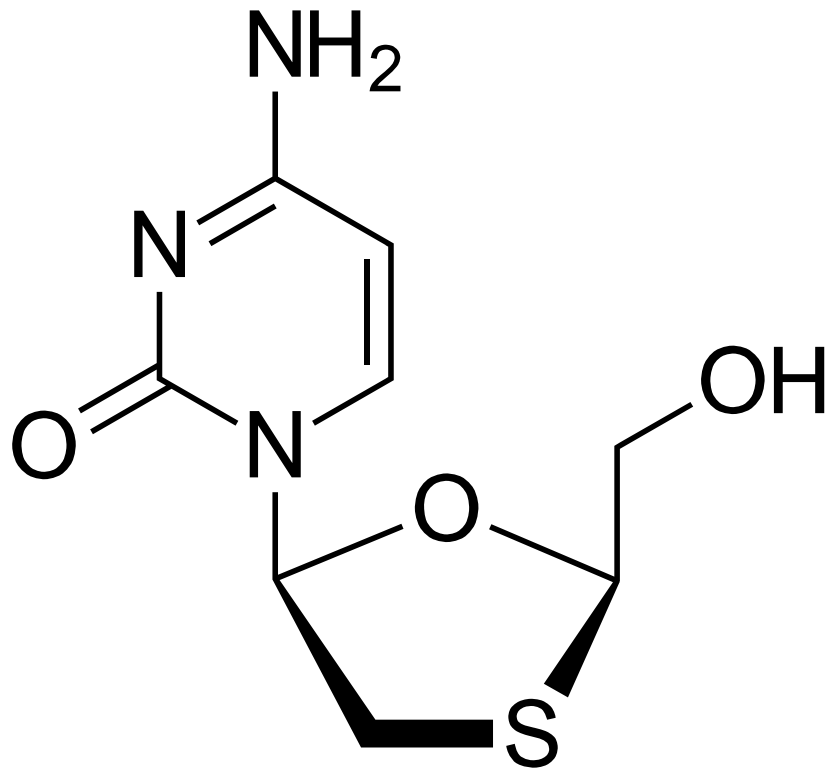


Acyclovir - DNA Polymerase Inhibitor



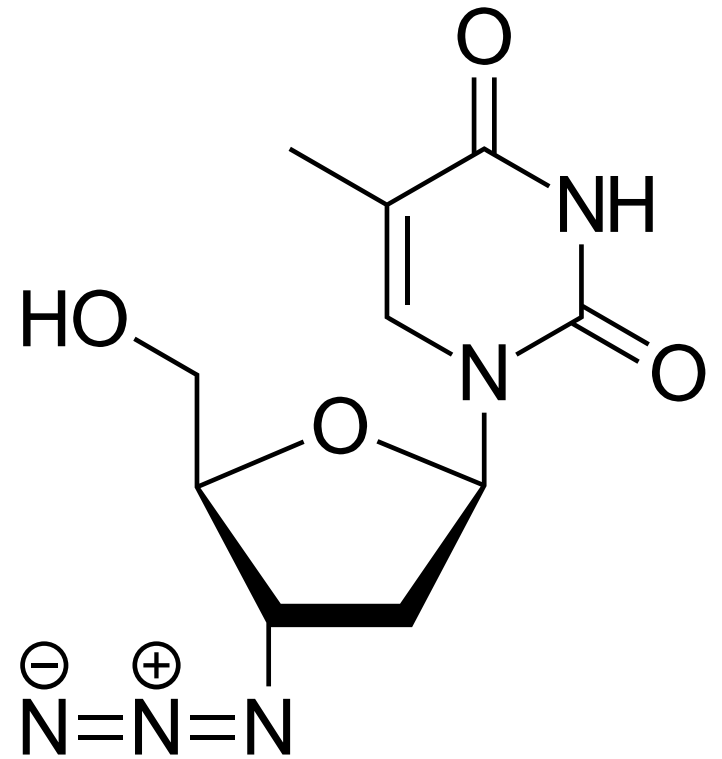
Acyclovir - DNA Polymerase Inhibitor

- Virus - DNA Polymerase Inhibitor
- Competitive Inhibition
- Analogues to Guanosine
- Use in
 - ✓ Herpes Simplex
 - ✓ Chicken Pox
 - ✓ Viral Encephalitis - Herpes
- Can it affect human cell ?
- If Yes,
- What can be effect on Human Cell ?



Lamivudine

Analogues
to
Cytidine



Zidovudine

Analogues
to
Cytidine

- **Leading strand:**

- Synthesized in direction of replication fork.
- Synthesized *continuously*.

- **Lagging strand:**

- Strand that synthesized in the direction away from the replication fork.
- Synthesized *discontinuously*
- Synthesized in small fragments of DNA
- “*Okazaki fragments*”
- joined to become a single, continuous strand.

● RNA primer

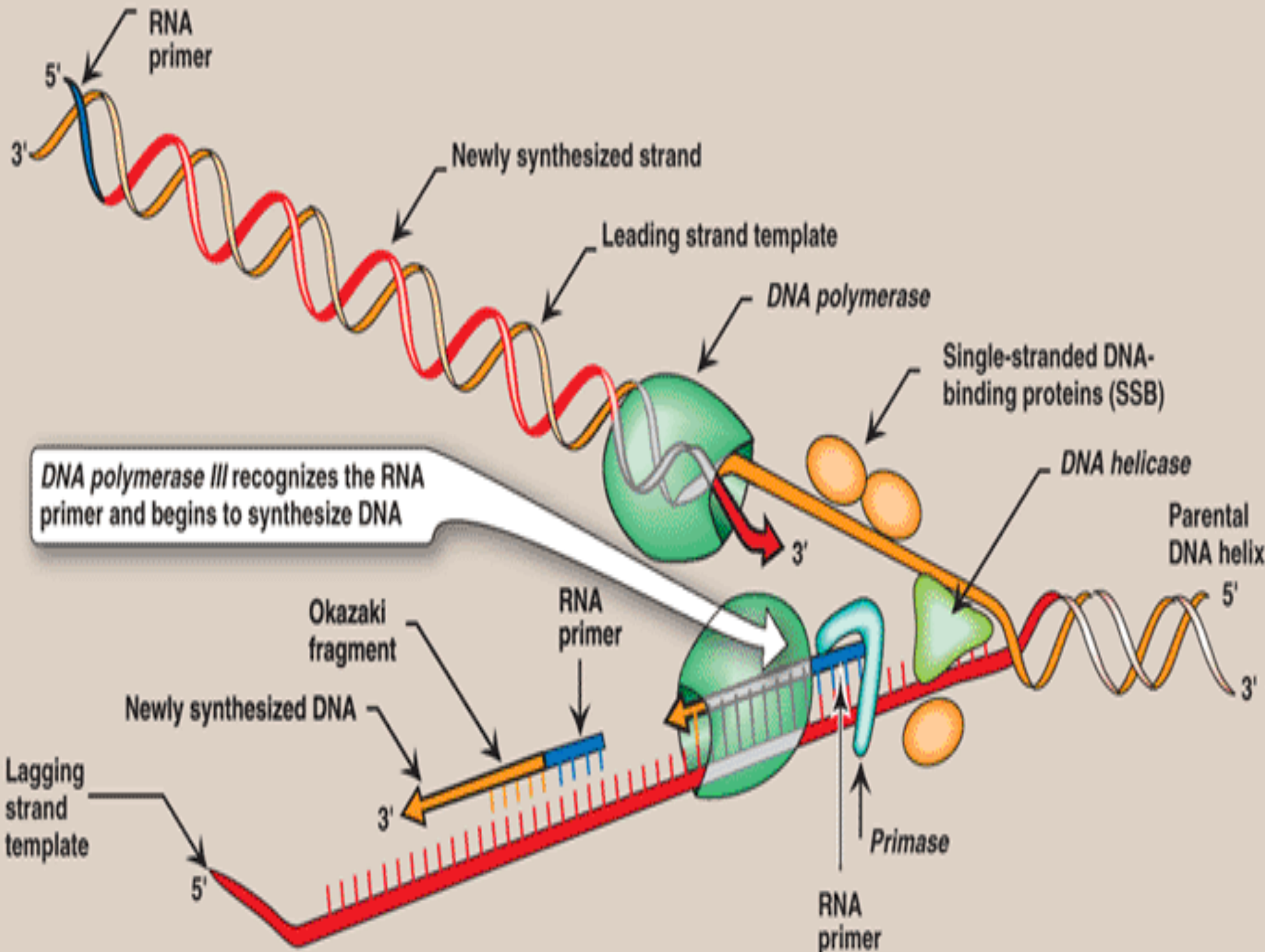
- DNA polymerases cannot initiate replication on a totally single-stranded template.
- Require an RNA primer
- Short chain of RNA base-paired.
- With free hydroxyl group on 3'-end of RNA strand.
- This hydroxyl group serves as the first acceptor of a nucleotide by action of DNA polymerase.

- **Primase:**

- Synthesizes short of RNA (approx. 10 nucleotides)
- Complementary and antiparallel to DNA template.
- U in RNA pairs with A in DNA.
- On lagging strand = Multiple RNA primers
- On leading strand = Only one RNA primer require.

- **Primosome:**

- The primosome makes the RNA primer.
- As with DNA synthesis, the direction of synthesis of the primer is 5' → 3' (antiparallel to the template strand).



Chain Elongation

- DNA polymerases $5' \rightarrow 3'$ direction elongate a new DNA strand
- Add deoxyribonucleotides, one at a time, to the 3'-end .
- New strand grows in the $5' \rightarrow 3'$ direction, antiparallel
- DNA polymerase III is a highly “processive” enzyme
 - Remains bound to template strand as it moves along
 - β subunit forming a ring with template strand
 - As a sliding DNA clamp.
- With each nucleotide addition, Pyrophosphate (PP_i) is released
- All four deoxyribonucleoside triphosphates (dATP, dTTP, dCTP, and dGTP) are require.

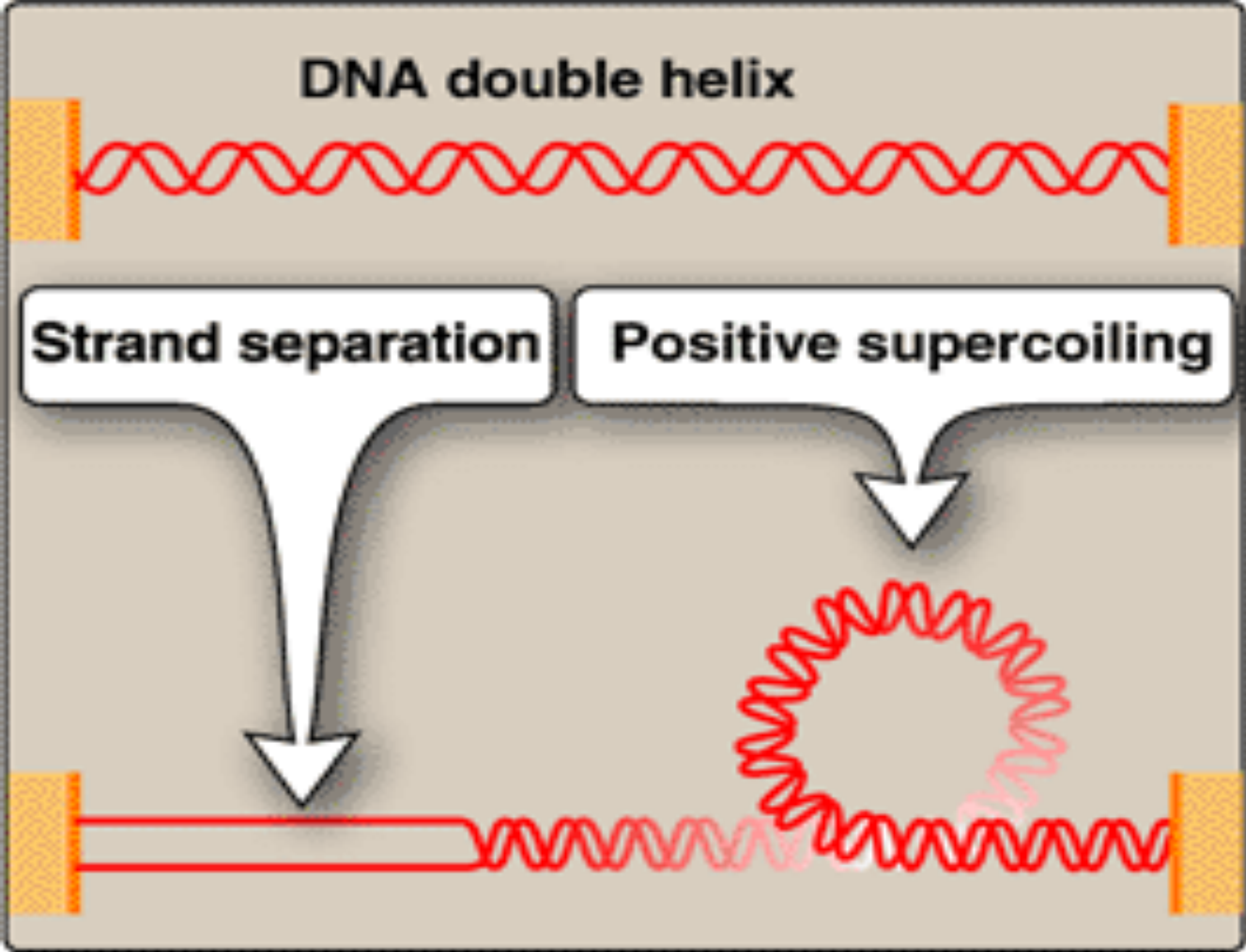
Proof-Reading of new DNA

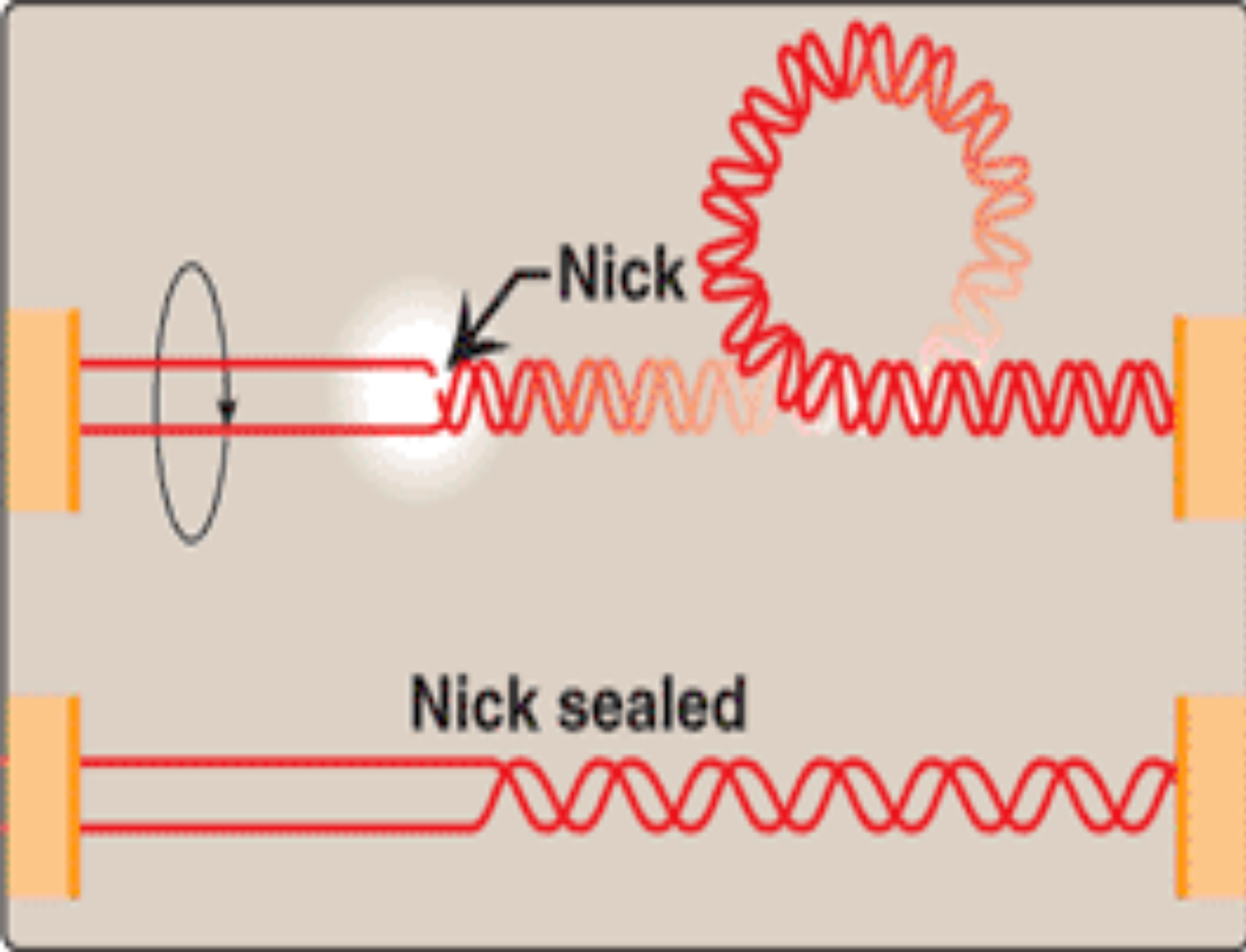
- Misreading of template sequence make in deleterious or mutations.
- To ensure replication fidelity,
- DNA polymerase III $3' \rightarrow 5'$ exonuclease has addition “Proofreading” activity.
- $3' \rightarrow 5'$ exonuclease removes misplaced nucleotide.
- Than $5' \rightarrow 3'$ polymerase then replaces it with correct nucleotide.

DNA double helix

Strand separation

Positive supercoiling





Properties of Topo-isomerase (Gyrase)

- Relieve supercoiling in downstream of DNA during replication by making break in strand & again reseal it.
- Have both action of Nuclease & Ligase
- **Type – I** = act by making break in one strand
= Break require energy, resealing does not require energy
- **Type – II** = act by making break in both strands.
= Breaking & Resealing both require energy.
- **Antibiotics = Ciprofloxacin, Nalidixic acid** inhibits bacterial Gyrase.
- **Anti-tumour agents = Etoposide, Adriamycin ,Doxorubicin** inhibits eukaryotics topo-isomerase.



Relaxed
circle



1

The left half of the circle folds over the right half.

2

The back half of the helix is cleaved.



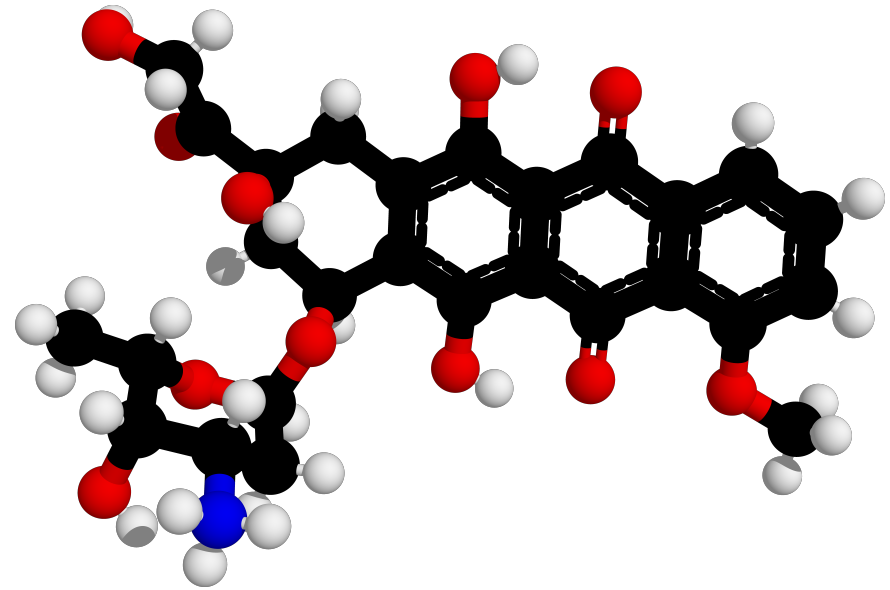
Negatively
supercoiled
DNA

3

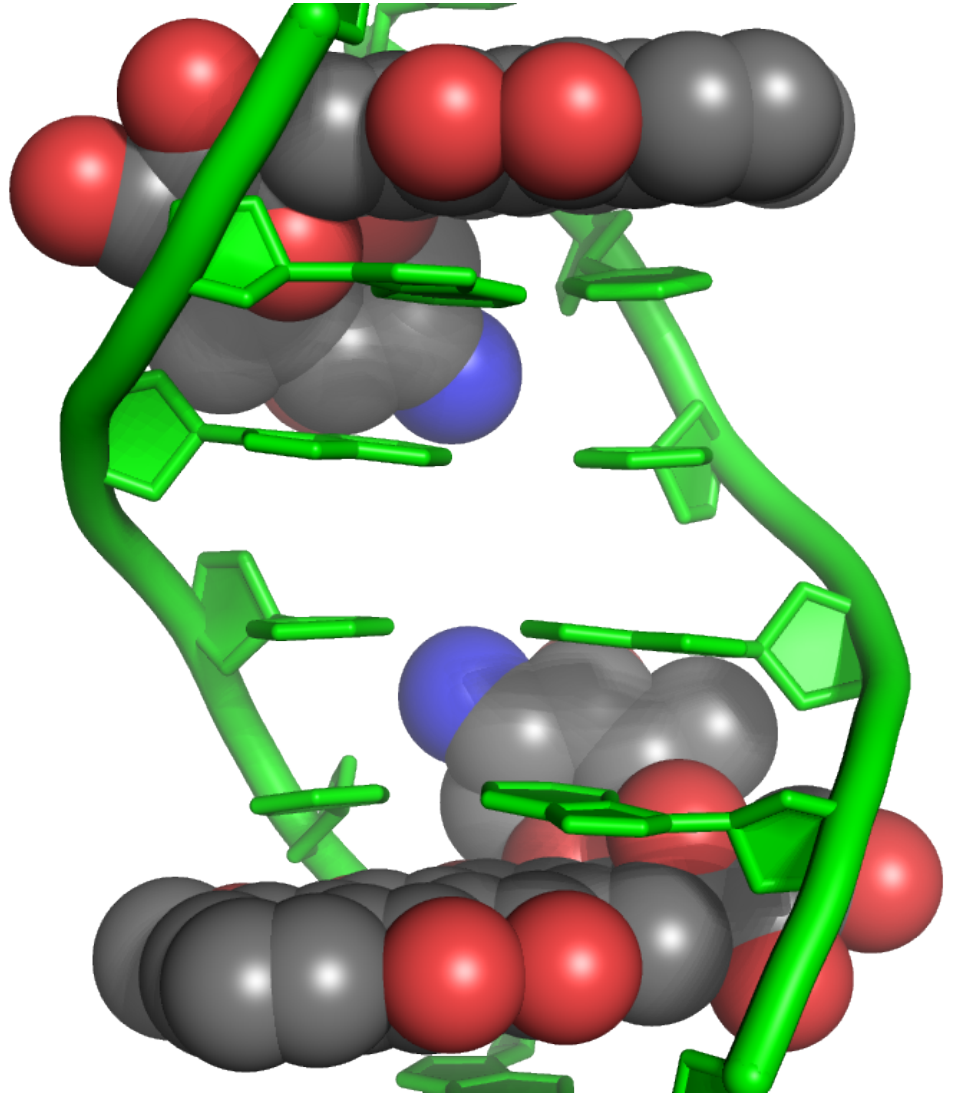
The front half of the helix passes through the break, which is resealed.



Doxorubicin bound with DNA

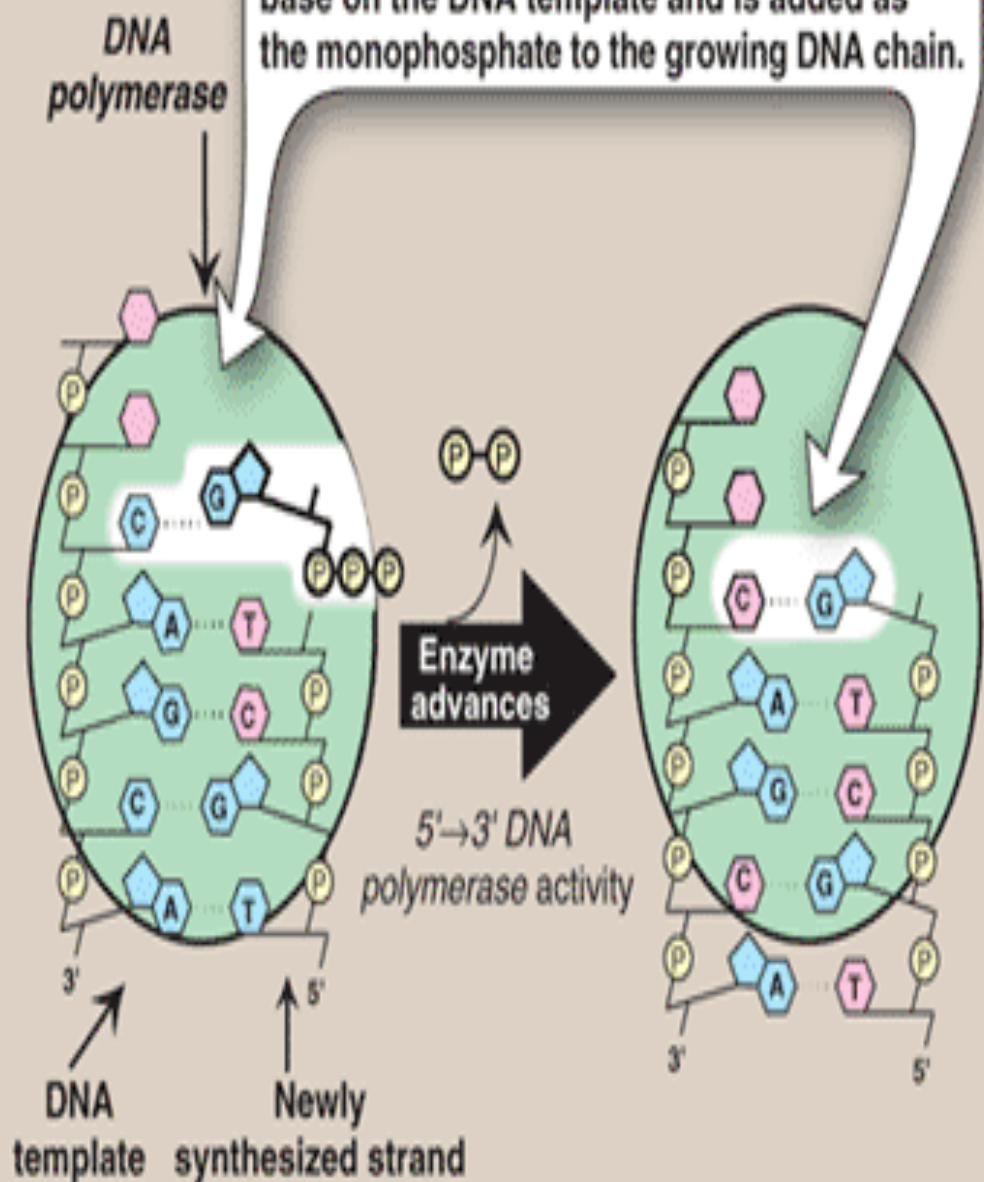


Doxorubicin



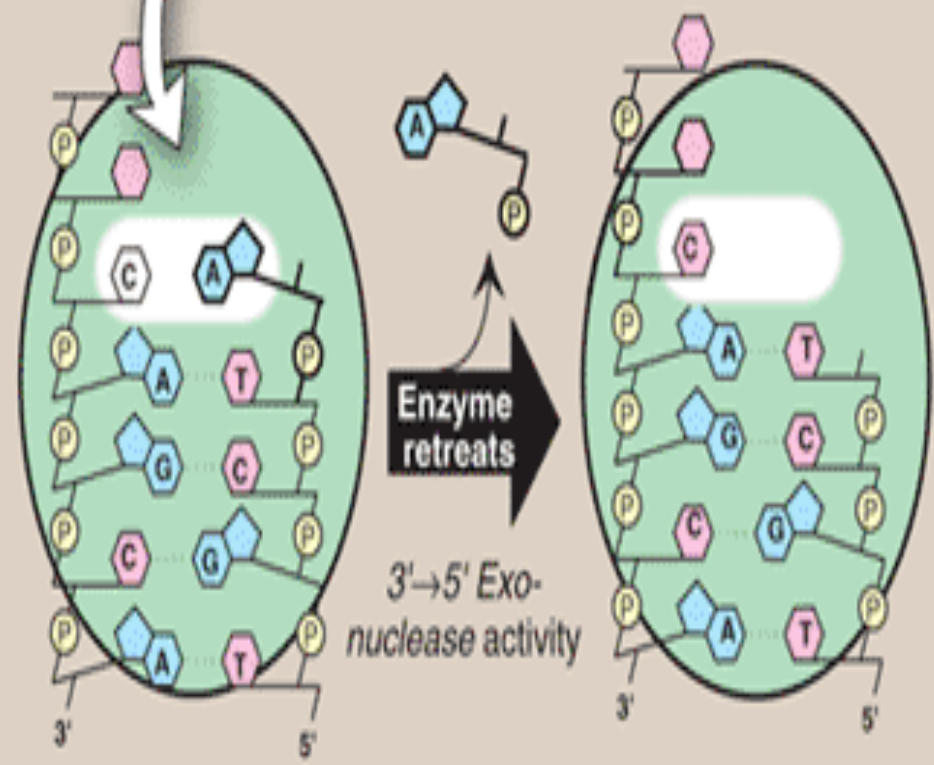
A POLYMERASE FUNCTION

An incoming nucleoside triphosphate is correctly matched to its complementary base on the DNA template and is added as the monophosphate to the growing DNA chain.



B PROOFREADING FUNCTION

If DNA polymerase mismatches a nucleotide with the template, it uses its 3'→5' exonuclease activity to excise the mismatched nucleotide.



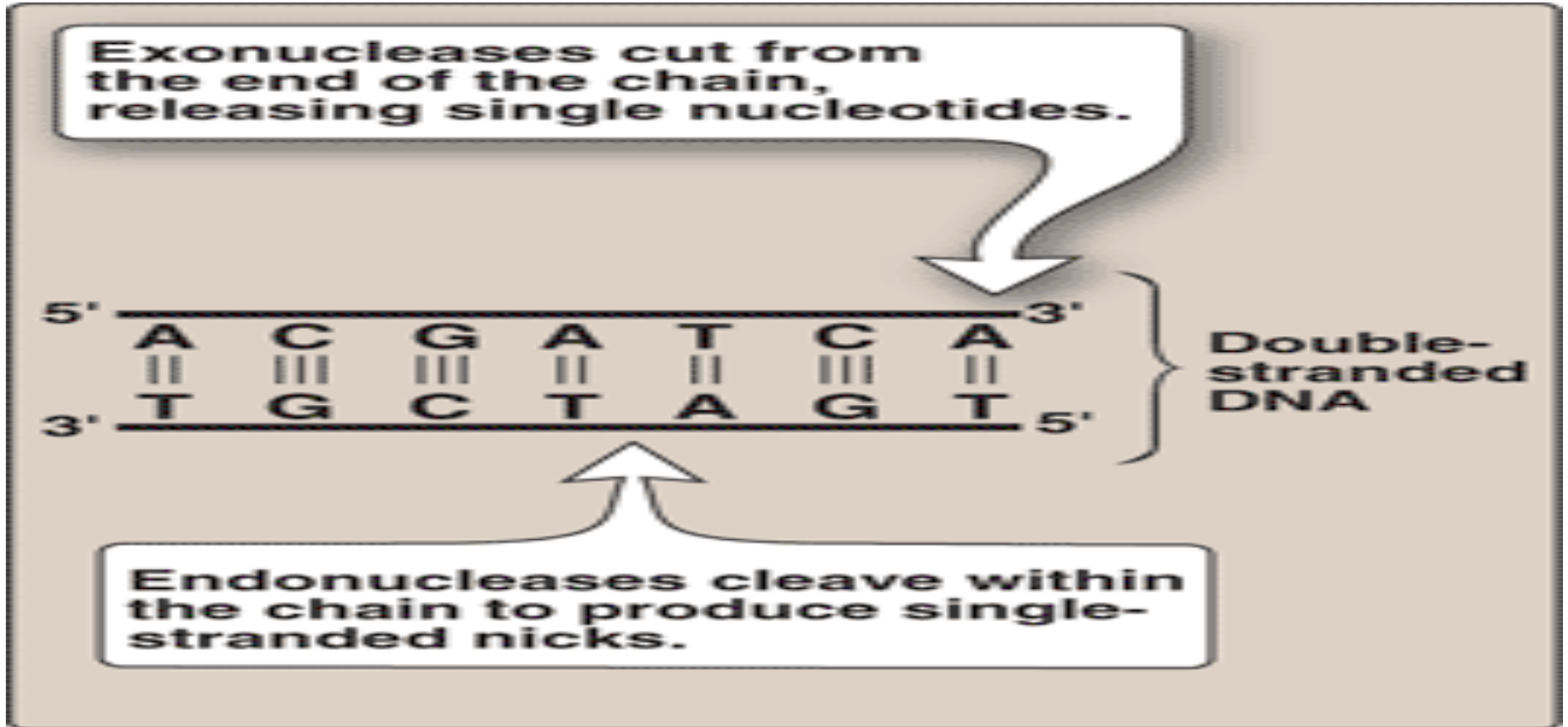
Excision of RNA primers and their replacement by DNA

- DNA polymerase III continues to synthesize DNA on the lagging strand until it is blocked by proximity to an RNA primer.
- DNA polymerase I excise RNA and fill the gap.
- **DNA polymerase III** = $5' \rightarrow 3'$ polymerase activity that synthesizes DNA
= $3' \rightarrow 5'$ exonuclease activity that proofreads
- **DNA polymerase I** = $5' \rightarrow 3'$ polymerase activity.
= $3' \rightarrow 5'$ exonuclease activity that proofreads
= $5' \rightarrow 3'$ exonuclease activity, hydrolytically remove the RNA primer.

- ***DNA polymerase I***

- locates space
- Between 3'-end of New DNA & 5'-end of adjacent RNA primer.
- Hydrolytically removes RNA .
- Make **5'→3' exonuclease activity**.
- Than, **5'→3' polymerase activity** to fill Gap by synthesis of new DNA.
- **3'→5' exonuclease** activity to make “proofreads” .

Endonuclease versus exonuclease activity

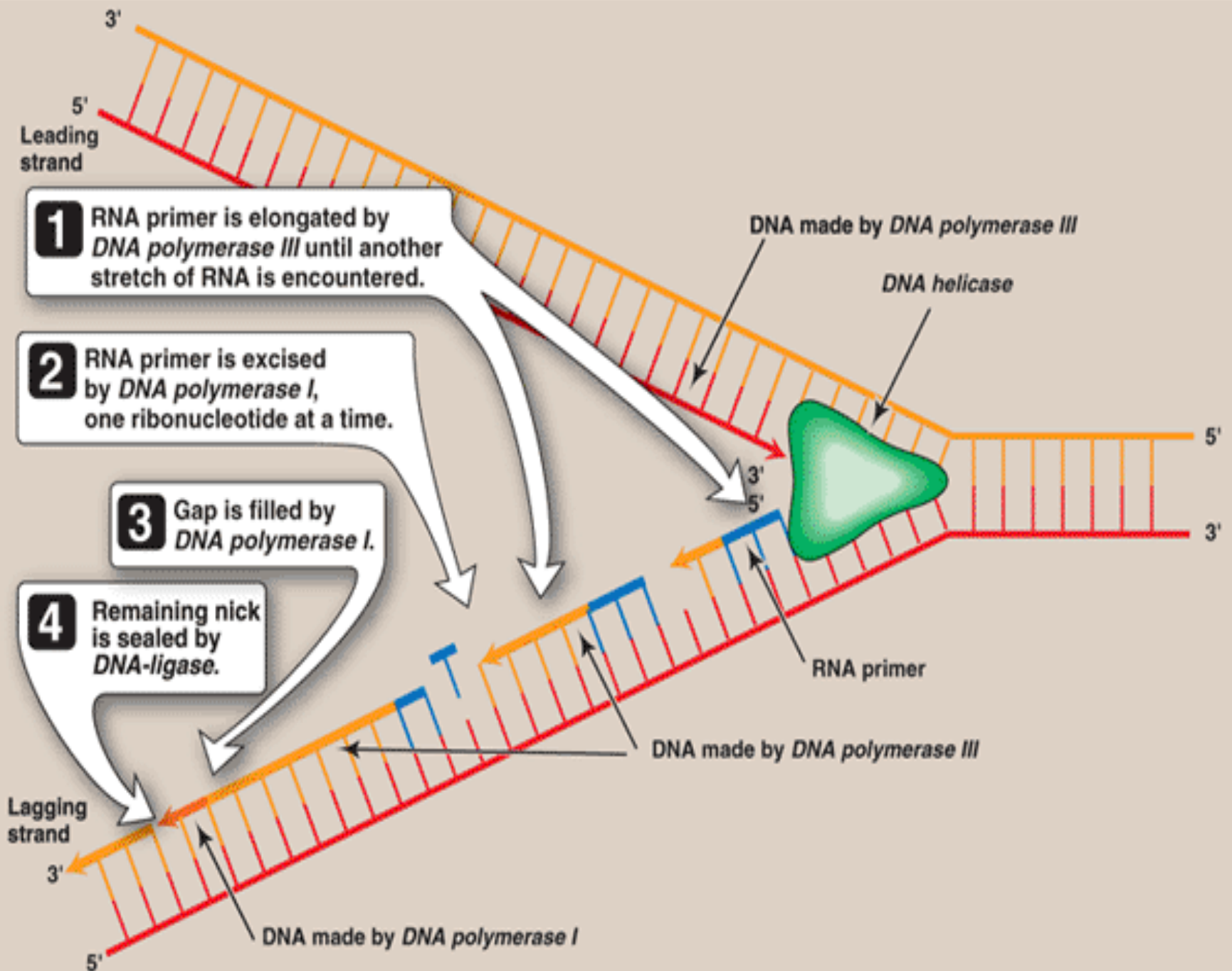


- Exonuclease = Remove one nucleotide at a time from the end of the DNA chain
- Endonuclease = Remove the chain Internally.

Differences between $5' \rightarrow 3'$ & $3' \rightarrow 5'$ exonucleases

- $3' \rightarrow 5'$ exonuclease
 - Remove nucleotides in the $3' \rightarrow 5'$ direction
 - Remove **one nucleotide at a time.**
 - Important in proof reading
- $5' \rightarrow 3'$ exonuclease
 - Remove groups of altered nucleotides in the $5' \rightarrow 3'$ direction
 - Removing from **one to ten nucleotides at a time.**
 - Important in repair of damaged DNA

Removal of RNA primer and filling of the resulting “gaps” by DNA polymerase I.



- The RNA polymerase that produces the primer necessary for DNA synthesis is called
 - a. polymerase
 - b. helicase
 - c. primase
 - d. ligase

- The RNA polymerase that produces the primer necessary for DNA synthesis is called
 - a. polymerase
 - b. helicase
 - c. primase**
 - d. ligase

- An enzyme that form a covalent bond between adjacent 5'-P and 3'-OH terminal of separate fragments of DNA is
 - a. convertase
 - b. primase
 - c. ligase
 - d. topoisomerase

- An enzyme that form a covalent bond between adjacent 5'-P and 3'-OH terminal of separate fragments of DNA is
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 - b. primase
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- An enzymes that breaks & than seal the break of DNA strand to remove underwinding or overwinding of the DNA helix is
 - a. helicases
 - b. DNA polymerase
 - c. topoisomerases
 - d. ligases

- An enzymes that breaks & than seal the break of DNA strand to remove underwinding or overwinding of the DNA helix is
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 - b. DNA polymerase
 - c. topoisomerases**
 - d. ligases

- Proof reading activity of DNA polymerase refers to
 - a. 5' to 3' exonuclease activity
 - b. 5' to 3' polymerase activity
 - c. 3' to 5' exonuclease activity
 - d. 3' to 5' polymerase activity

- Proof reading activity of DNA polymerase refers to
 - a. 5' to 3' exonuclease activity
 - b. 5' to 3' polymerase activity
 - c. 3' to 5' exonuclease activity**
 - d. 3' to 5' polymerase activity

- What is false about DNA Polymerase I?
 - a. 5' to 3' polymerase activity
 - b. 5' to 3' exonuclease activity
 - c. 5' to 3' proof reading activity
 - d. None.

- What is false about DNA Polymerase I?
 - a. 5' to 3' polymerase activity
 - b. 5' to 3' exonuclease activity
 - c. 5' to 3' proof reading activity**
 - d. None.

- Which activity is belong to only DNA Polymerase I ?
 - a. 5' to 3' polymerase activity
 - b. 5' to 3' exonuclease activity
 - c. 3' to 5' exonuclease activity
 - d. 5' to 3' proof reading activity

- Which activity is belong to only DNA Polymerase I ?
 - a. 5' to 3' polymerase activity
 - b. 5' to 3' exonuclease activity**
 - c. 3' to 5' exonuclease activity
 - d. 5' to 3' proof reading activity

- DNA Polymerase I and III does not have activity of,
 - a. 5' to 3' proof reading & 3' to 5' polymerase
 - b. 5' to 3' polymerase & 5' to 3' exonuclease
 - c. 5' to 3' polymerase & 3' to 5' exonuclease
 - d. 3' to 5' proof reading & 3' to 5' exonuclease

- DNA Polymerase I and III does not have activity of,
 - 5' to 3' proof reading & 3' to 5' polymerase**
 - 5' to 3' polymerase & 5' to 3' exonuclease
 - 5' to 3' polymerase & 3' to 5' exonuclease
 - 3' to 5' proof reading & 3' to 5' exonuclease

- Which molecule prevent re-annealing of the denatured DNA strand?
 - a. DNA topoisomerase
 - b. DNA helicase
 - c. Single Stranded Binding Protein
 - d. All of Above.

- Which molecule prevent re-annealing of the denatured DNA strand?
 - a. DNA topoisomerase
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- What could be different between replication process of eukaryotes and prokaryotes ?
 - a. Number of site of replication process
 - b. Number of replication fork at time
 - c. Number of enzyme requirements
 - d. All of above.

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 - a. Number of site of replication process
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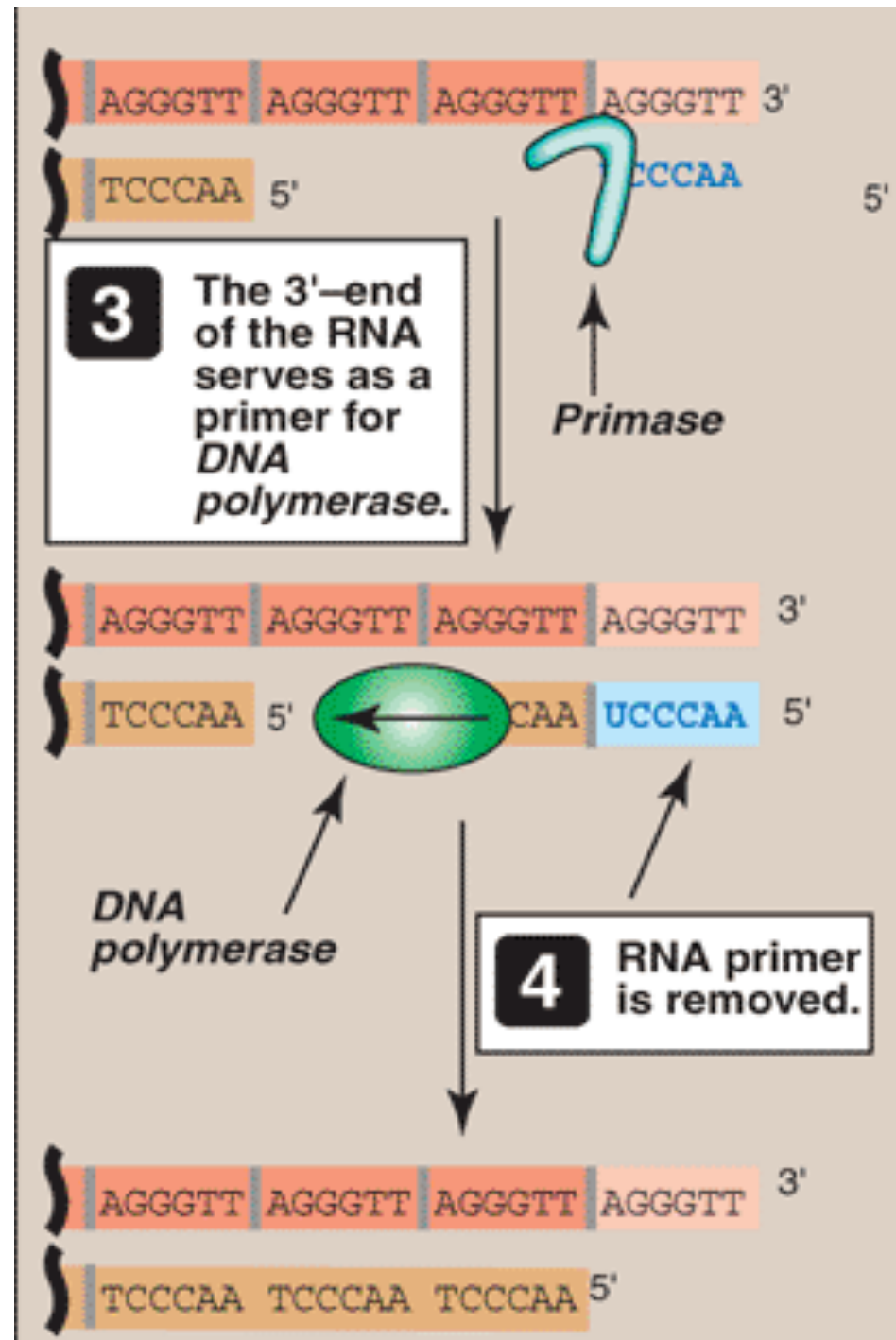
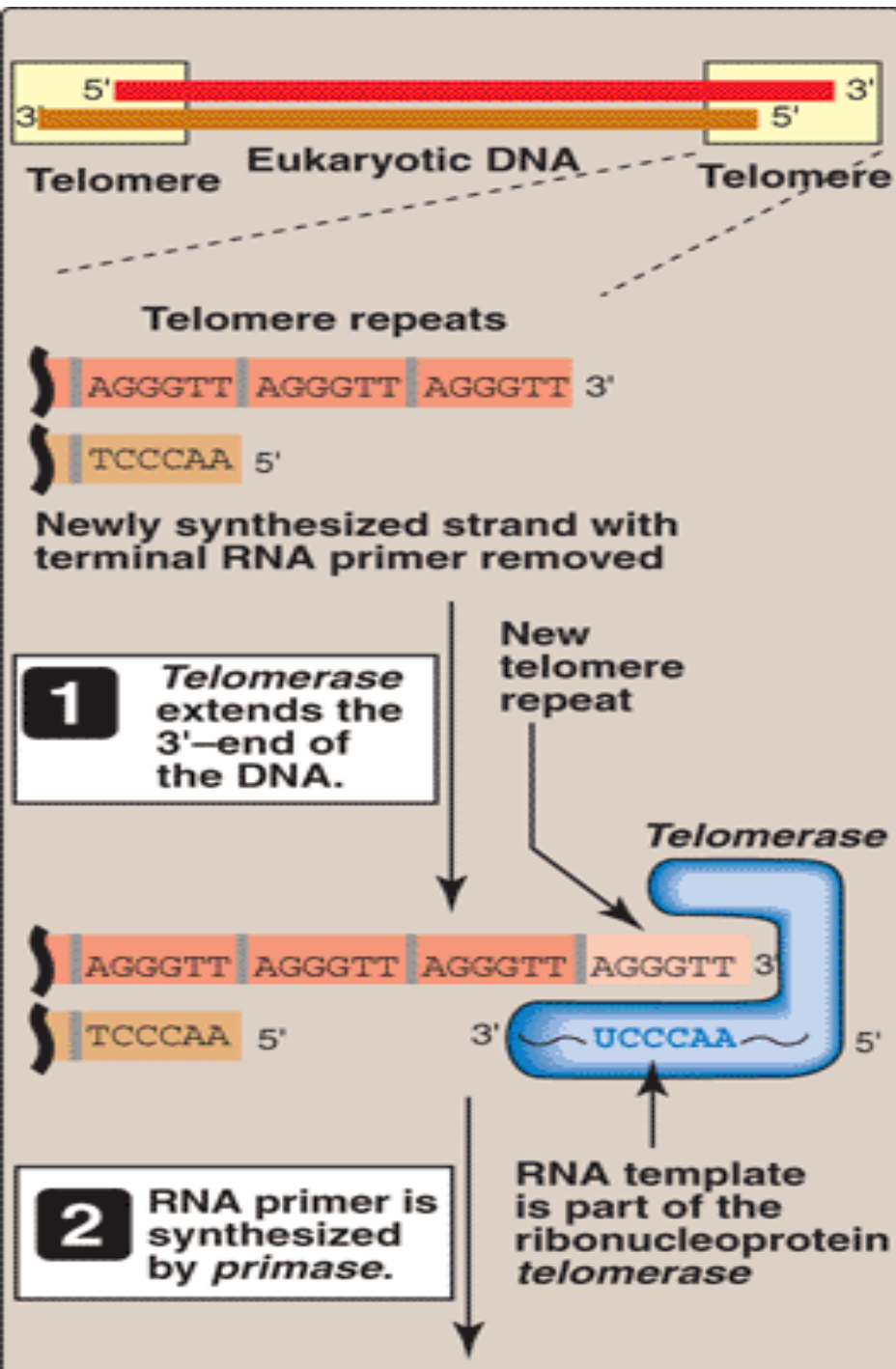
- What is require for elongation of DNA chain during replication process?
 - a. dNTP
 - b. dNDP
 - c. dNMP
 - d. dNADP

- What is require for elongation of DNA chain during replication process?
 - a. dNTP**
 - b. dNDP
 - c. dNMP
 - d. dNADP

- Which enzyme can not does 5' to 3' polymerase activity ?
 - a. DNA Polymerase -1
 - b. DNA Ligase
 - c. DNA Polymerase - 3
 - d. RNA primase

- Which enzyme can not does 5' to 3' polymerase activity ?
 - a. DNA Polymerase -1
 - b. DNA Ligase**
 - c. DNA Polymerase - 3
 - d. RNA primase

Telomere & Telomerase



Telomere

- **Gap at extreme 5'-end of the leading strand**
- After removal of RNA primer
- This End is protect with proteins.
- **The DNA–protein complex is termed “Telomere”.**
- Consists of tandem repeats of **AGGGTT**.

Telomere

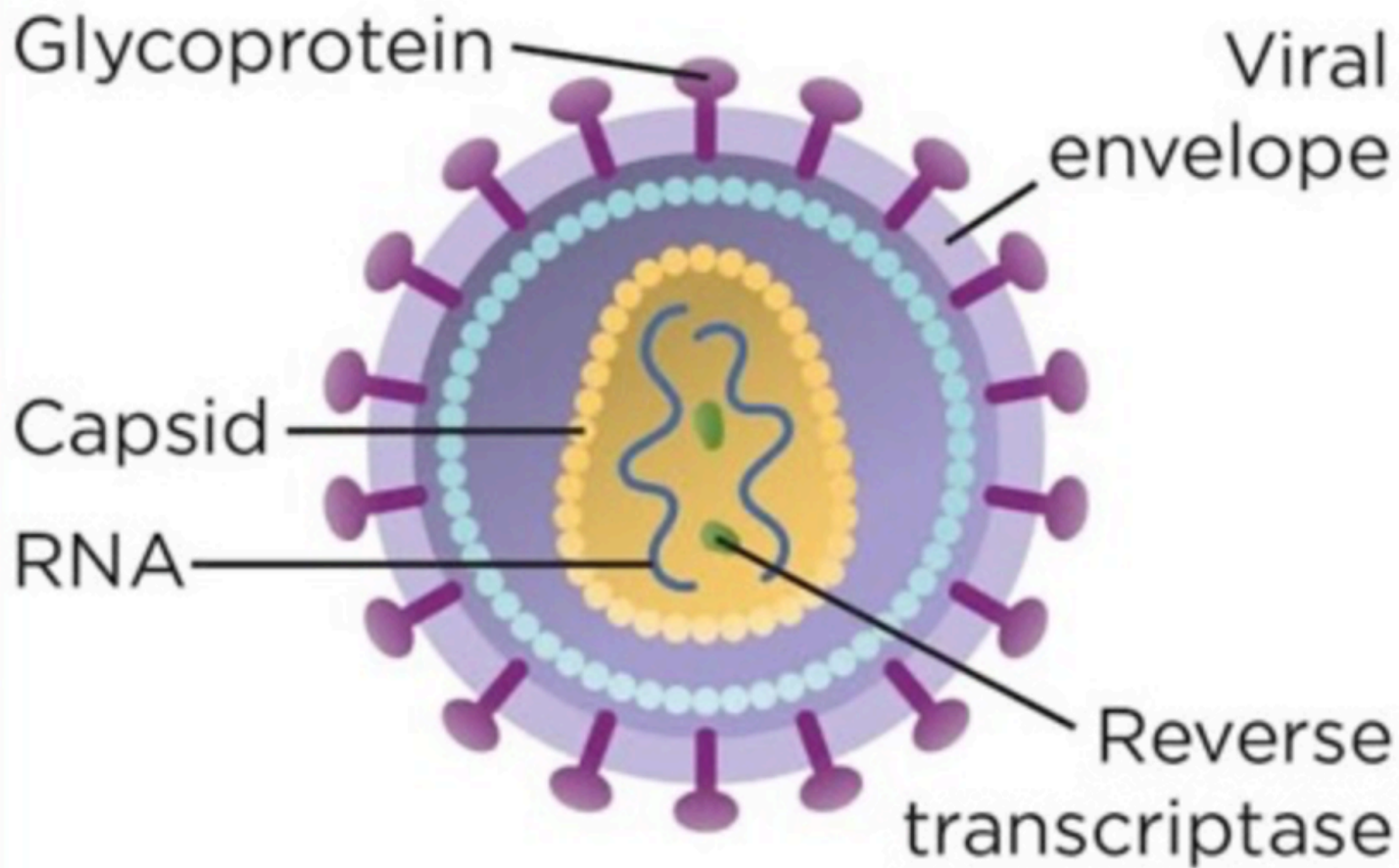
- In normal somatic cells, telomeres shorten with each successive cell division.
- if shortened beyond some critical length, the cell can not survive.
- In germ cells, other stem cells & in cancer cells
 - telomeres do not shorten
 - so the cells survival is longer.

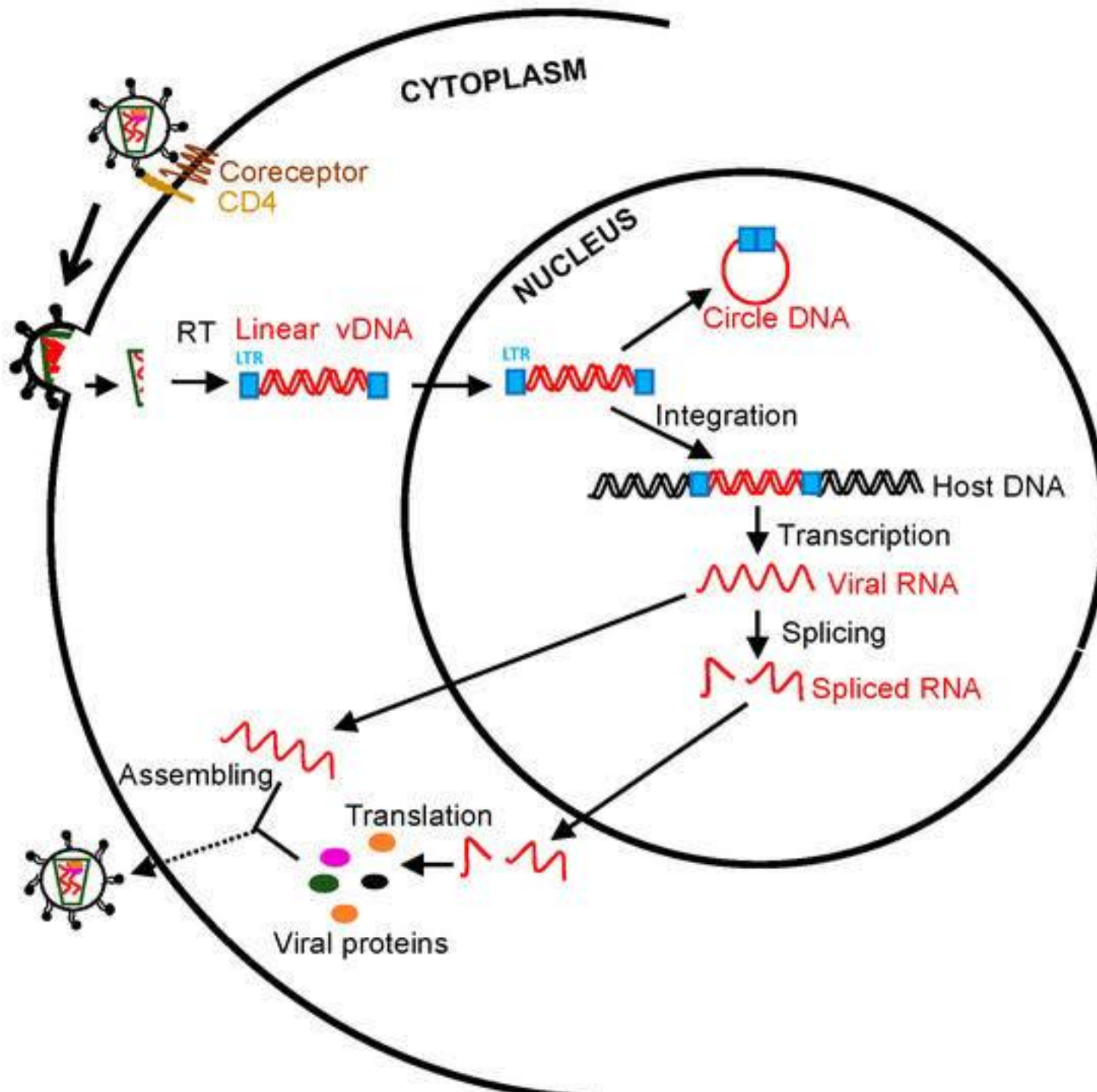
Telemerase

- Enzyme = Ribonucleoprotein (Telomerase)
- Maintain length.
- Reverse transcriptase.
- Make RNA template to DNA 5'→3'
- Lengthen GT-rich strand
- Than Primase can synthesize an RNA primer.
- Than RNA primer is extended by DNA polymerase and make de novo DNA synthesis

Telomere Significant

- Mitotic clock.
- Providing information of aging and cancer.





Reverse transcriptase

- Replication of retroviruses
- Human Immunodeficiency Virus (HIV).
- Viruses carry their genome in form of ssRNA.
- Following infection of a host cell,
- Viral enzyme, uses the viral RNA as a template for the 5'→3' synthesis of viral DNA
- Than Viral DNA integrated into host chromosomes.
- In eukaryotes, such elements are transcribed to RNA.



Tenolam E - Tenofovir 300 Mg + Lamivudine 300 Mg + Efavirenz 600 Mg Tablet

Post - Exposure Prophylaxis

Tenofovir 300 mg
+
Lamivudine 300 mg
+
Efavirenz 600 mg
once daily
for
28 days.

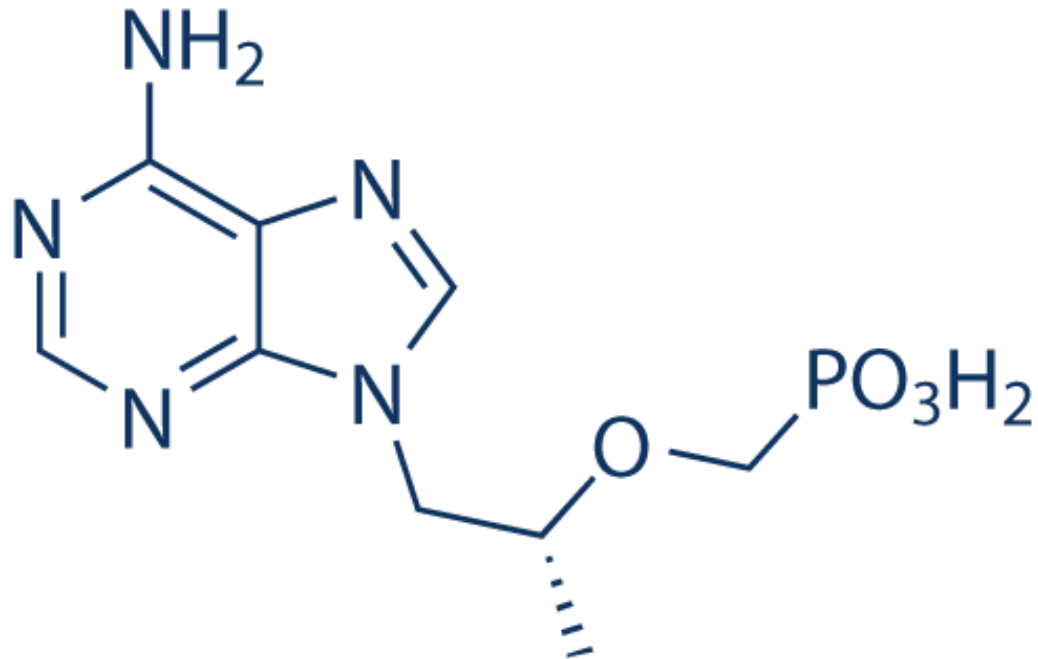
Post - Exposure Prophylaxis

Tenofovir 300 mg

Structure Similar to

Deoxyadenosine 5'-monophosphate (dAMP)

Reverse Transcriptase Inhibitor



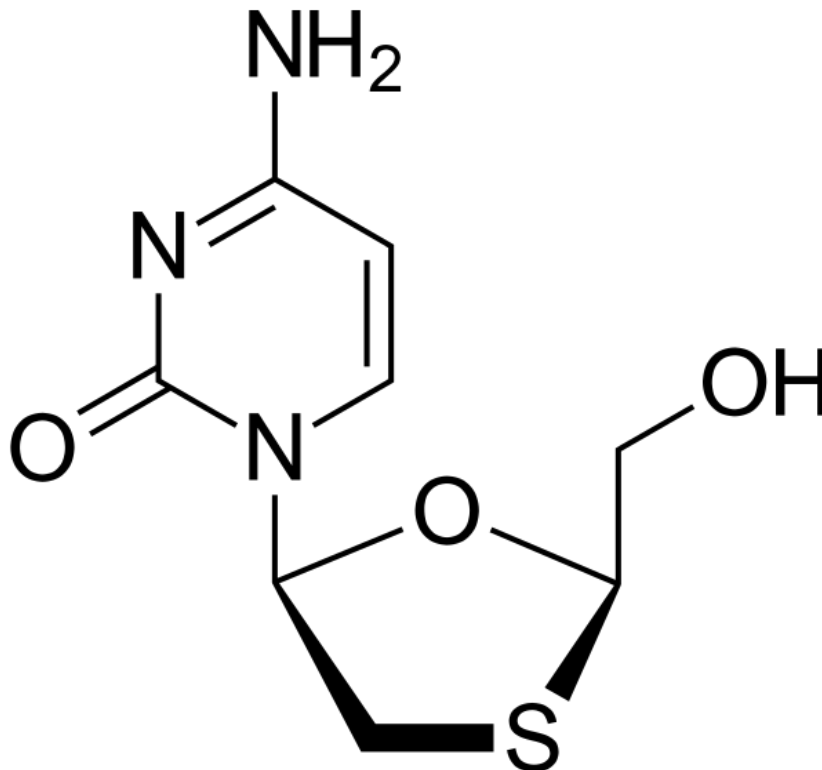
Post - Exposure Prophylaxis

Lamivudine 300 mg

Structure Similar to

(Cytidine)

Reverse Transcriptase Inhibitor

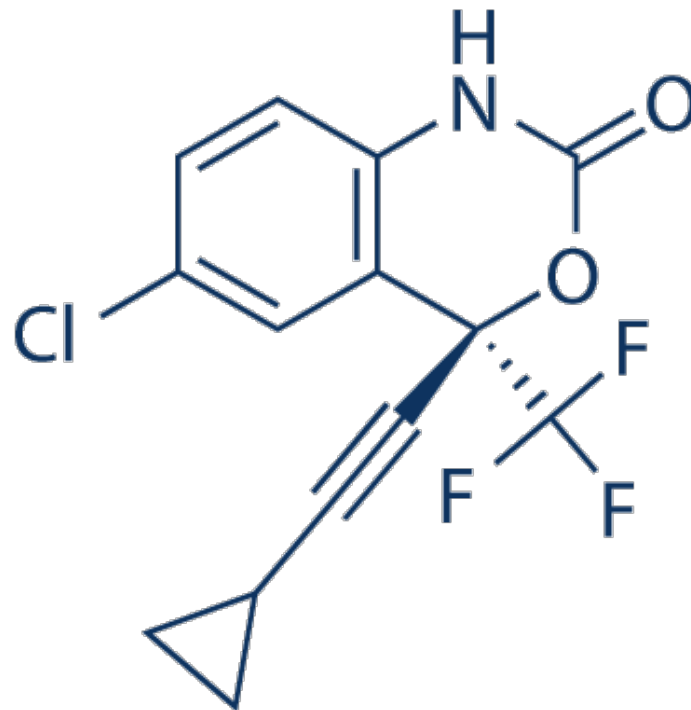


Post - Exposure Prophylaxis

Efavirenz 600 mg

Non-Nucleoside Structure

Reverse Transcriptase Inhibitor



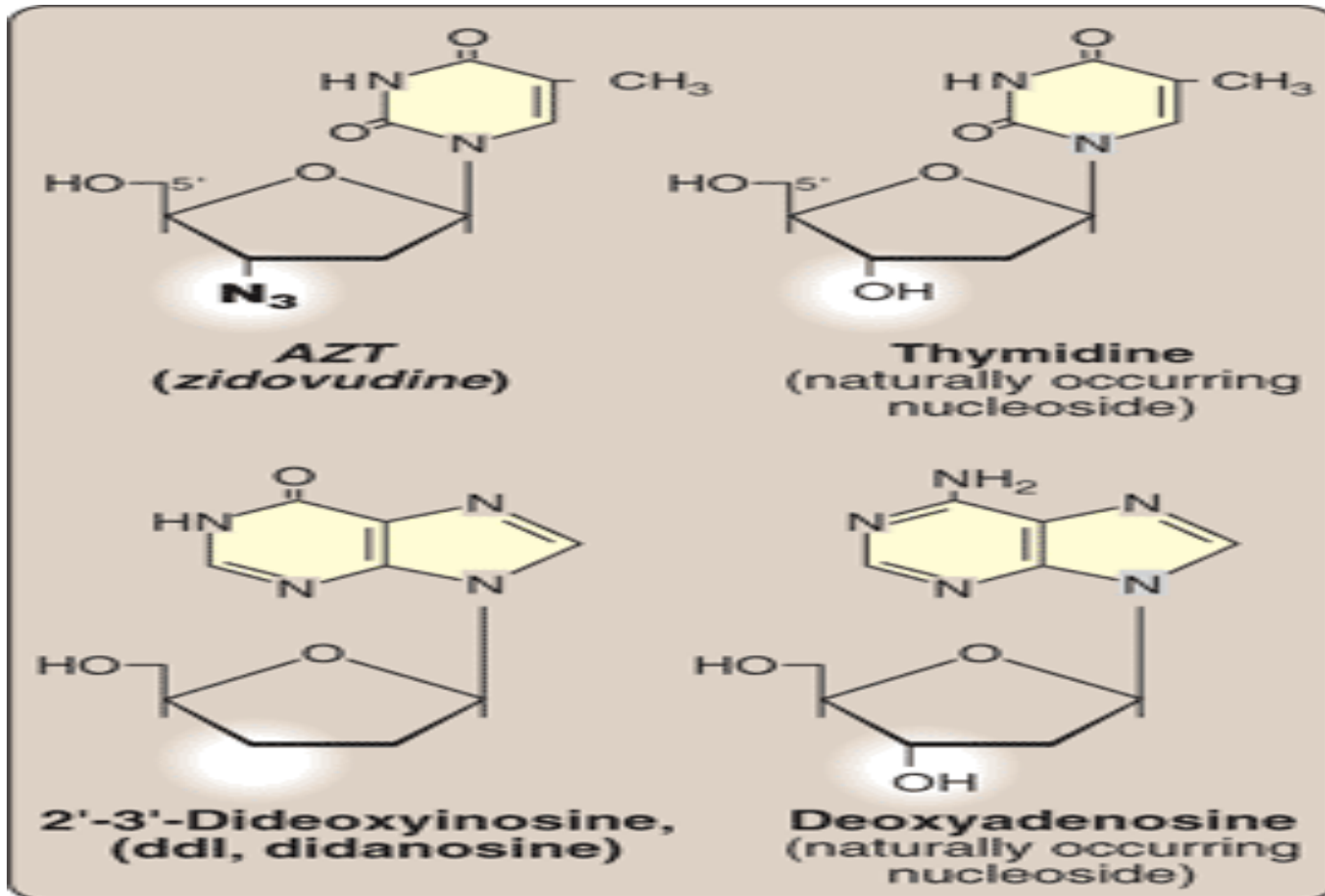
Eukaryotic DNA polymerases

- Five key eukaryotic DNA polymerases identified.
- Pol α and pol Δ :
- **Pol α** is a multisubunit enzyme.
 - One subunit has **primase activity**,
- **Pol Δ**
 - **Elongation** of DNA on the leading strand and elongate
 - **3'→5' exonuclease** activity to proofread the newly synthesized DNA.
 - Associates with the protein, proliferating cell nuclear antigen, which serves as a sliding DNA clamp in much the same way the **β subunit of DNA polymerase III** does in E. coli.
- **Pol β** and **pol ϵ** are involved in **DNA repair**.
- **Pol γ** replicates **mitochondrial DNA**.

Inhibition of DNA synthesis by nucleoside analogs

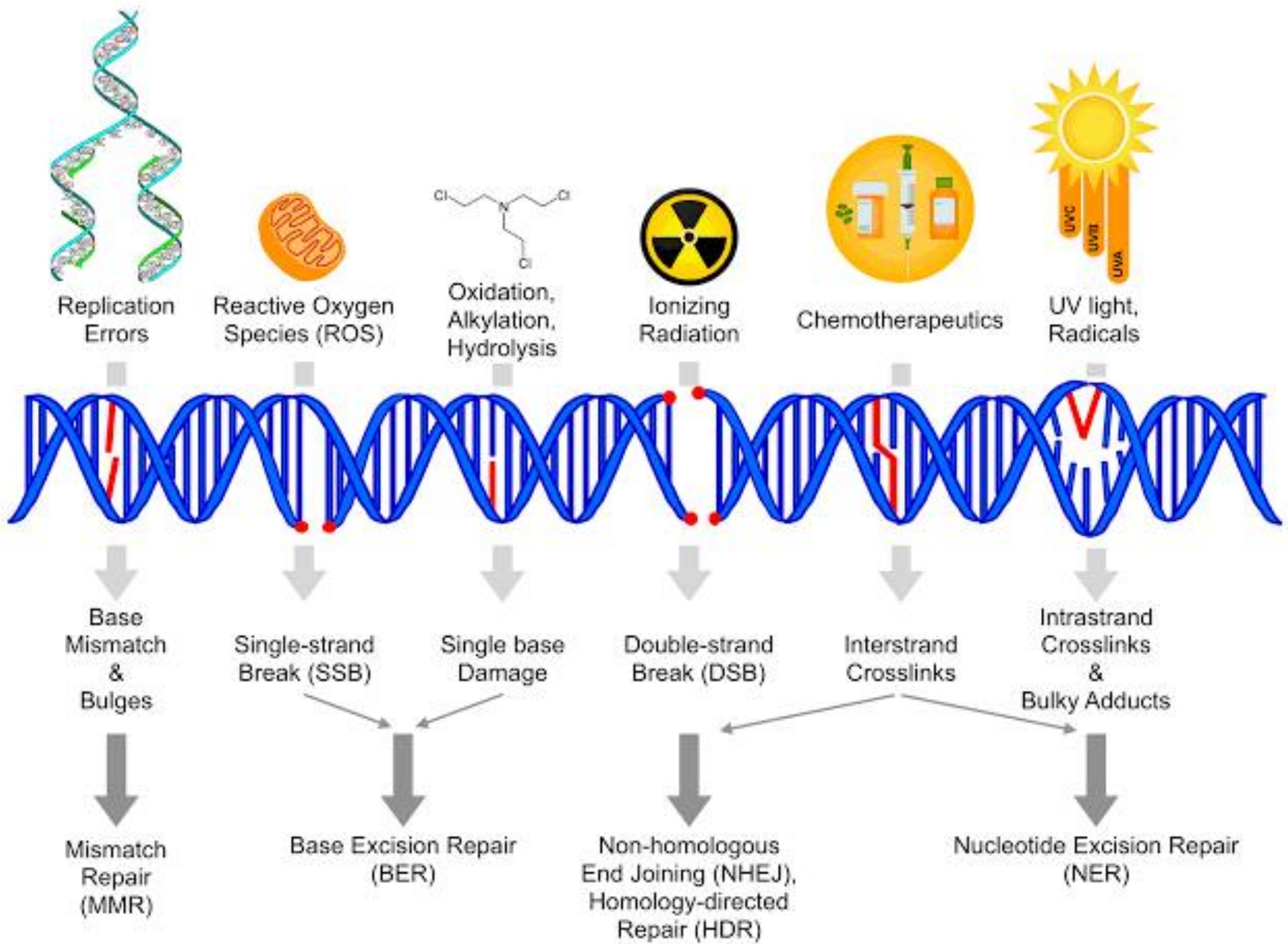
- Arabinose - Analogues of the deoxyribose
- Cytosine arabinoside
 - Anticancer chemotherapy.
- Adenine arabinoside
 - Antiviral agent.
- Zidovudine (AZT)
 - Analogues to Thymidine
 - Use in AIDS
- Didanosine
 - Analogues to Deoxy-adenosine
 - Use in AIDS

Drugs Structural Analogue to Nitrogen base



*Can Zidovudine affect
human cellular DNA
replication ?*

DNA Damage & DNA Repair



Replication Errors

Reactive Oxygen Species (ROS)

Oxidation, Alkylation, Hydrolysis

Ionizing Radiation

Chemotherapeutics

UV light, Radicals

Base Mismatch & Bulges

Single-strand Break (SSB)

Single base Damage

Double-strand Break (DSB)

Interstrand Crosslinks

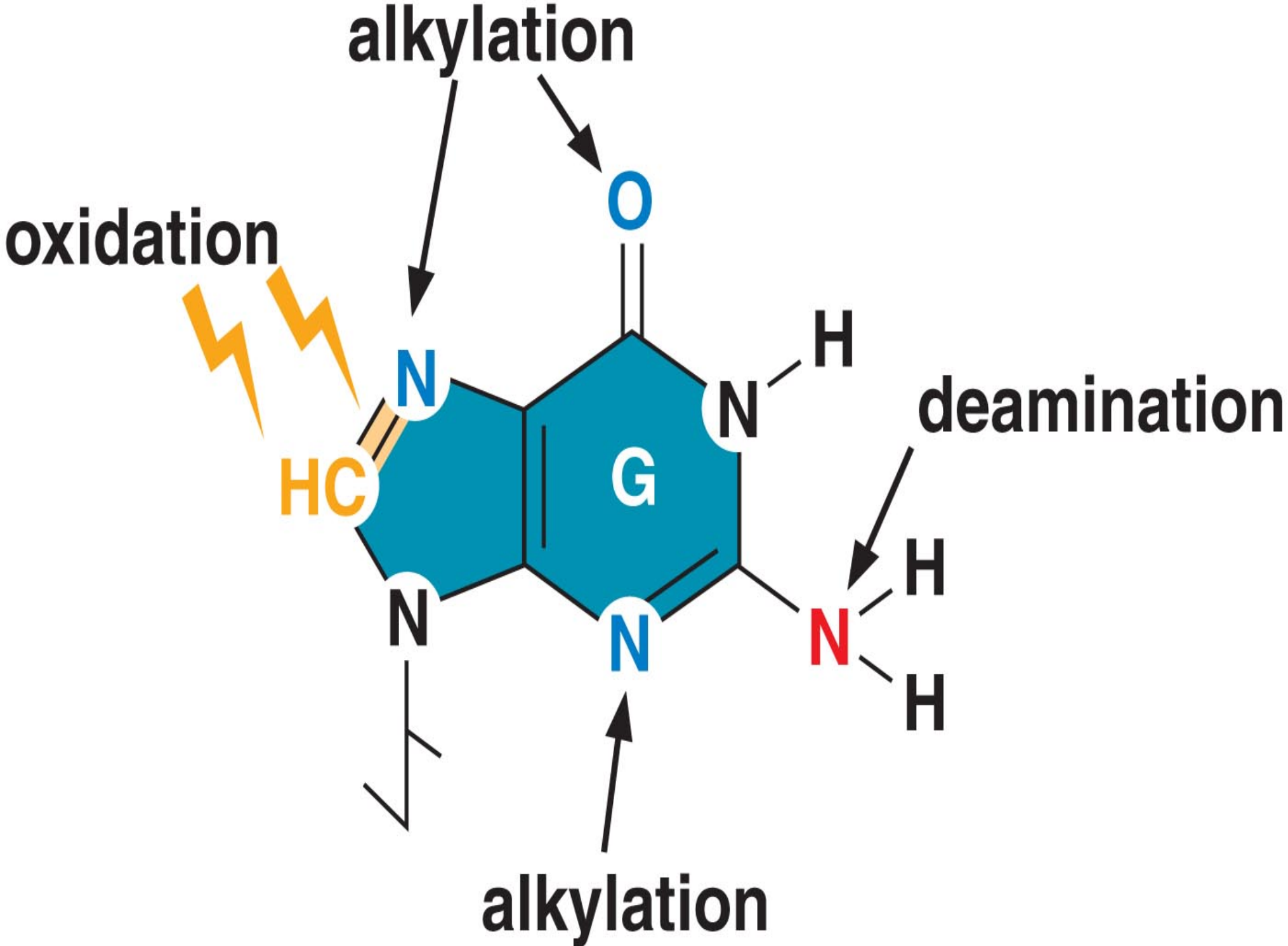
Intrastrand Crosslinks & Bulky Adducts

Mismatch Repair (MMR)

Base Excision Repair (BER)

Non-homologous End Joining (NHEJ), Homology-directed Repair (HDR)

Nucleotide Excision Repair (NER)

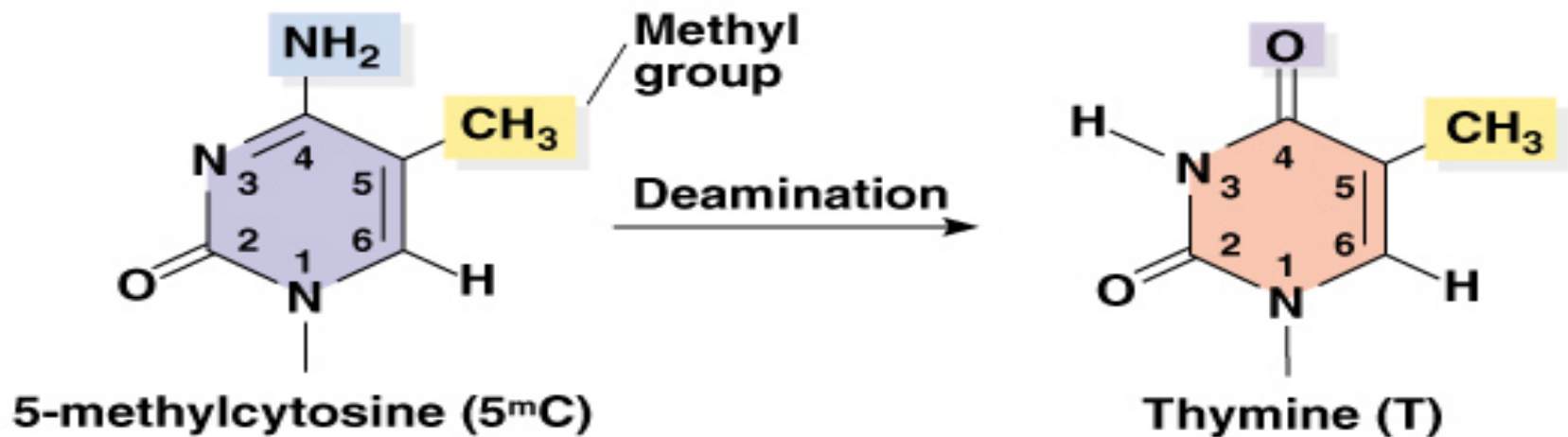


Deamination

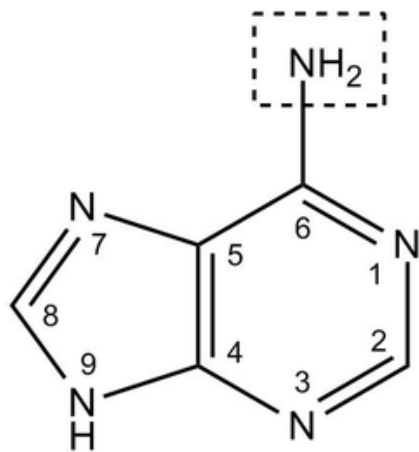
a)



b)

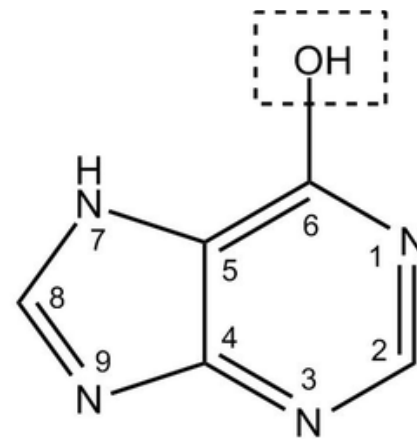


Deamination

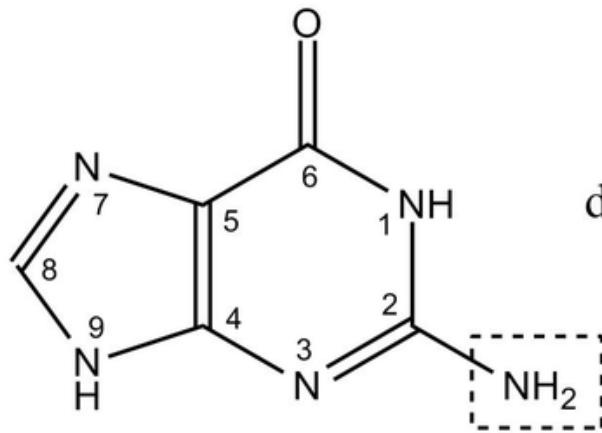


Adenine

deamination

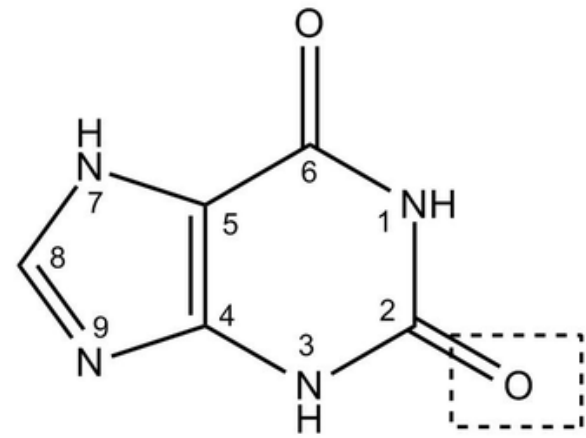


Hypoxanthine



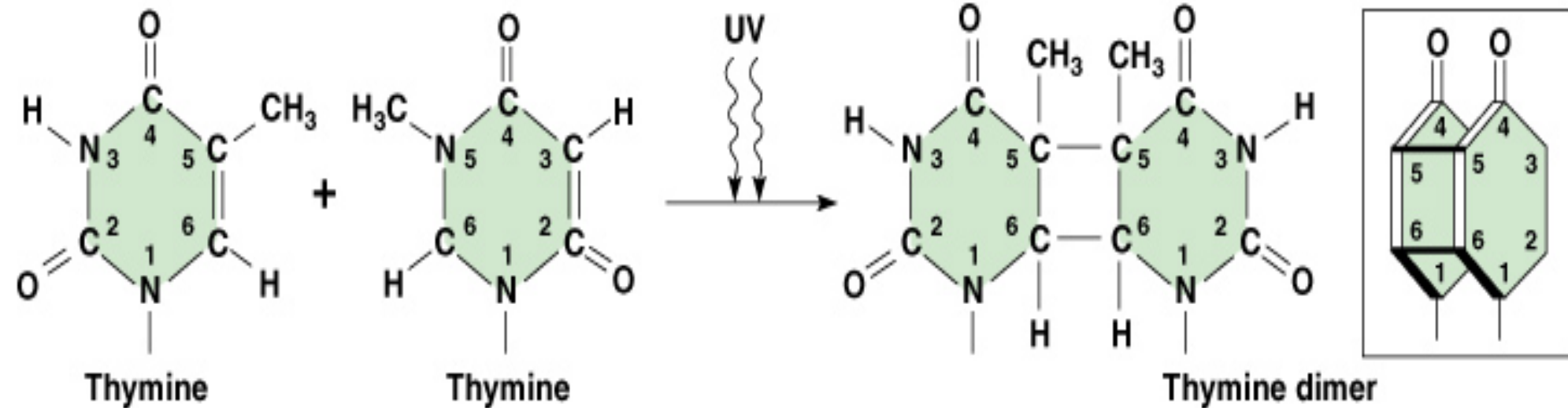
Guanine

deamination



Xanthine

Thymine Dimer



DNA Damage

I. Single-base alteration

- A. Depurination
- B. Deamination of cytosine to uracil
- C. Deamination of adenine to hypoxanthine
- D. Alkylation of base
- E. Insertion or deletion of nucleotide
- F. Base-analog incorporation

II. Two-base alteration

- A. UV light–induced thymine-thymine (pyrimidine) dimer
- B. Bifunctional alkylating agent cross-linkage

DNA Damage

III. Chain breaks

- A. Ionizing radiation
- B. Oxidative free radical

IV. Cross-linkage

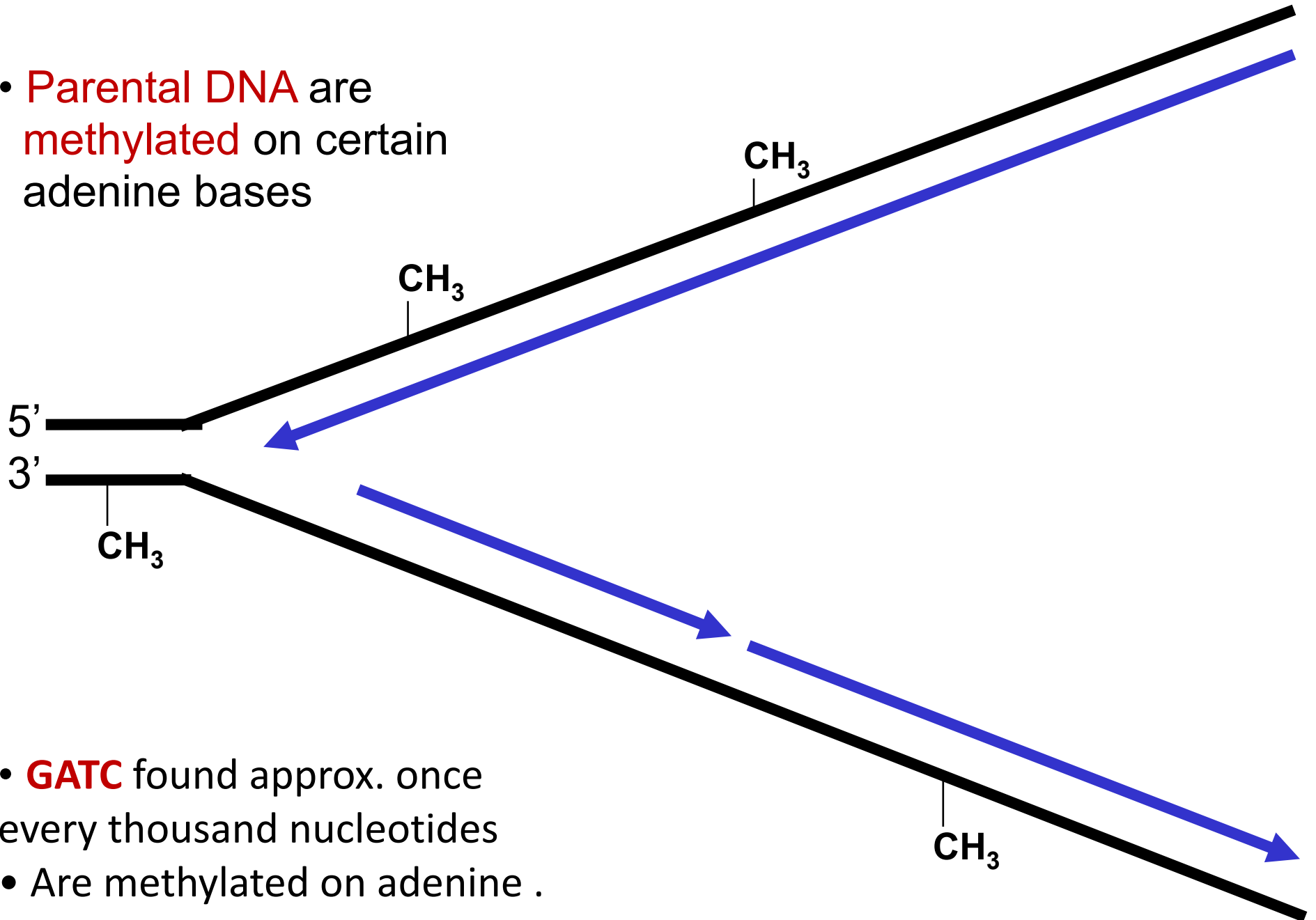
- A. Between bases in same or opposite strands
- B. Between DNA and protein molecules (eg histones)

Mechanisms of DNA Repair

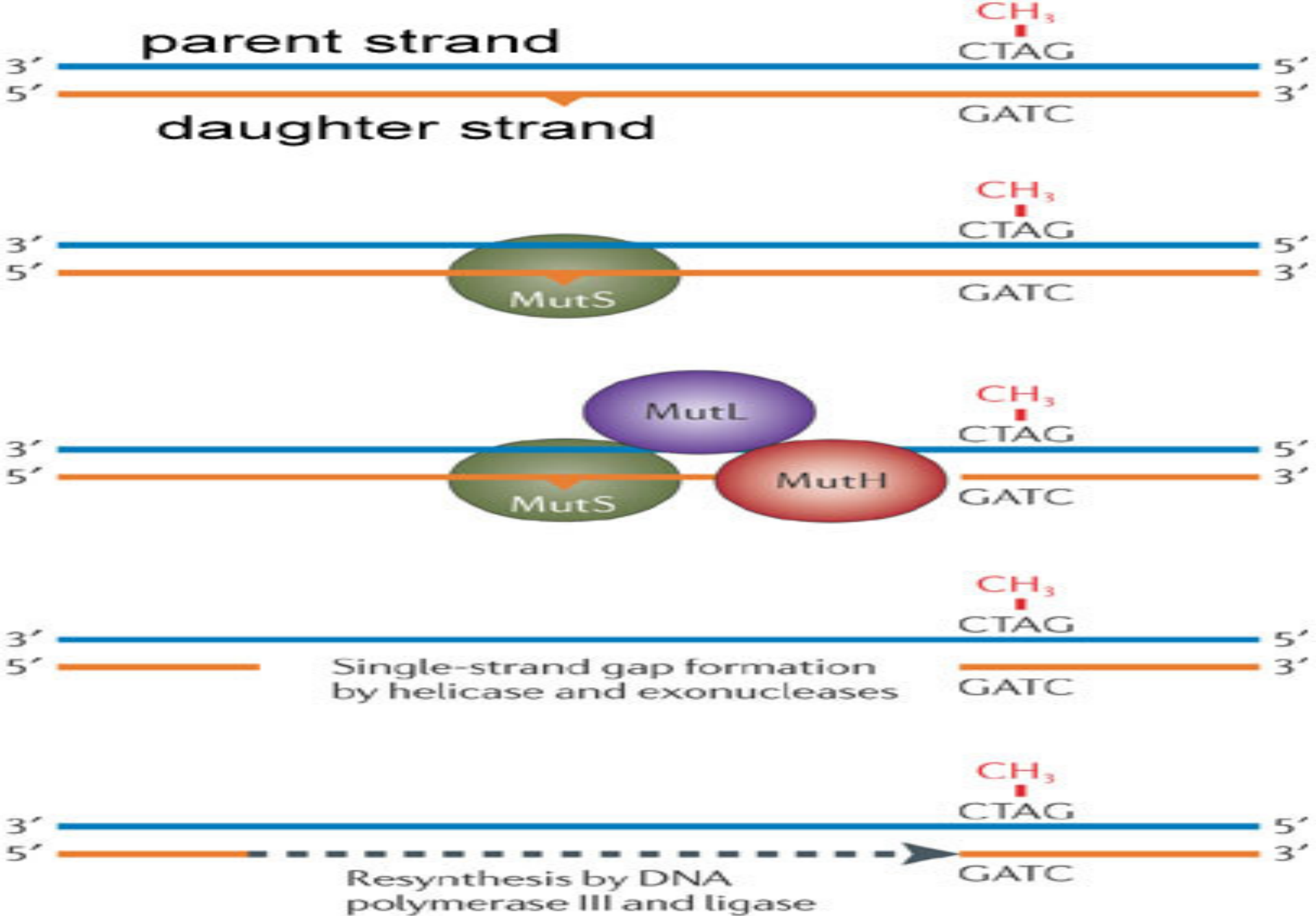
- 1. Proofreading by the DNA polymerases**
- 2. Mismatch (post-replication) repair (MMR)**
- 3. Base Excision repair**
- 4. Nucleotide Excision repair (NER)**

Mismatch (Post-replication) repair

- Parental DNA are methylated on certain adenine bases



- **GATC** found approx. once every thousand nucleotides
- Are methylated on adenine .



Mut proteins

```
graph TD; Mut[Mut proteins] --> MutS[Mut S]; Mut --> MutL[Mut L]; Mut --> MutH[Mut H]; MutS --- SList["• Scans DNA<br>• Recognize mismatch base"]; MutL --- LList["• Links Mut S & Mut H<br>• Activates Mut H"]; MutH --- HList["• Binds to hemi methylated<br>• GATC sequence"];
```

Mut S

- Scans DNA
- Recognize mismatch base

Mut L

- Links Mut S & Mut H
- Activates Mut H

Mut H

- Binds to hemi methylated
- GATC sequence

Mismatch Repair

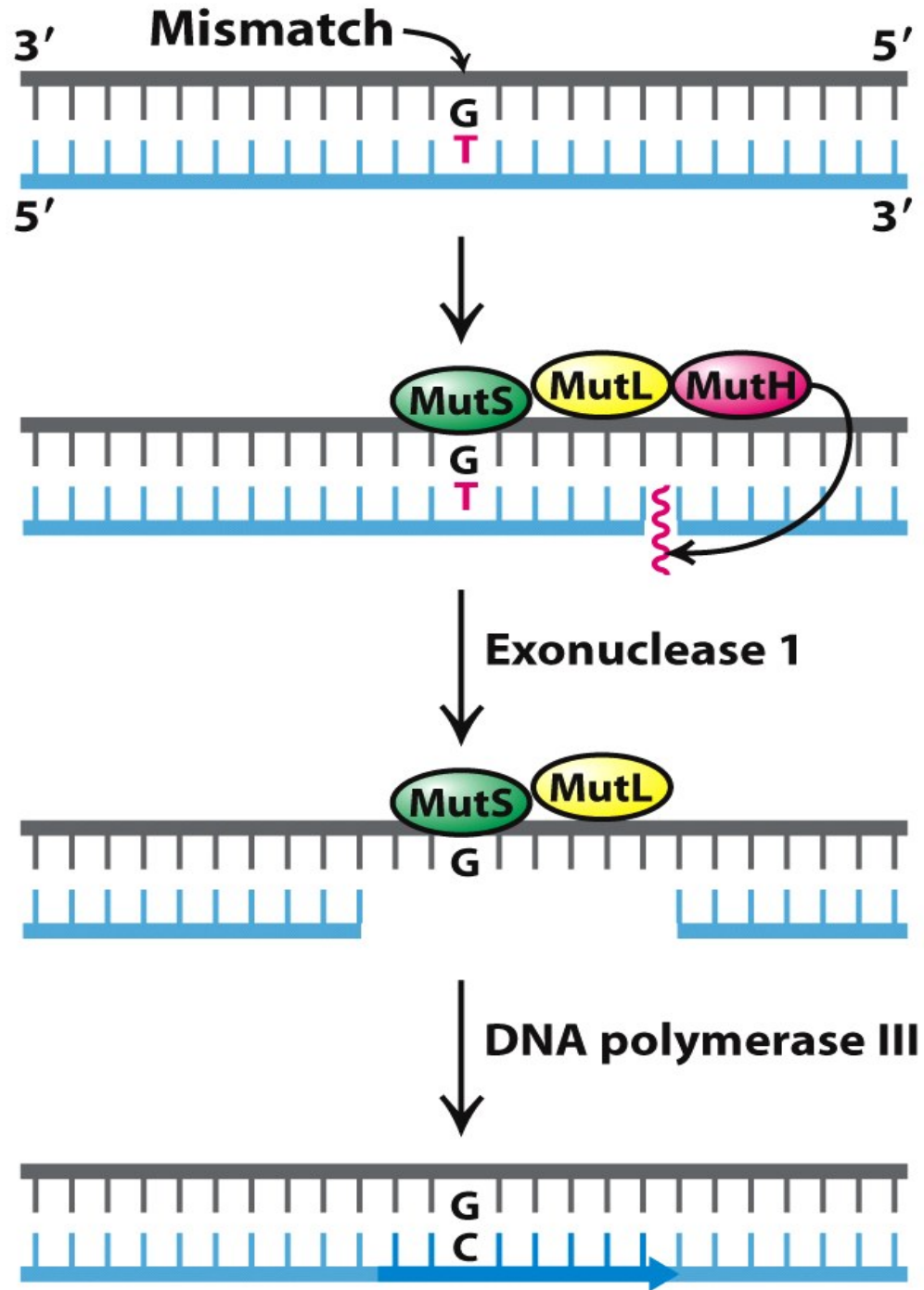


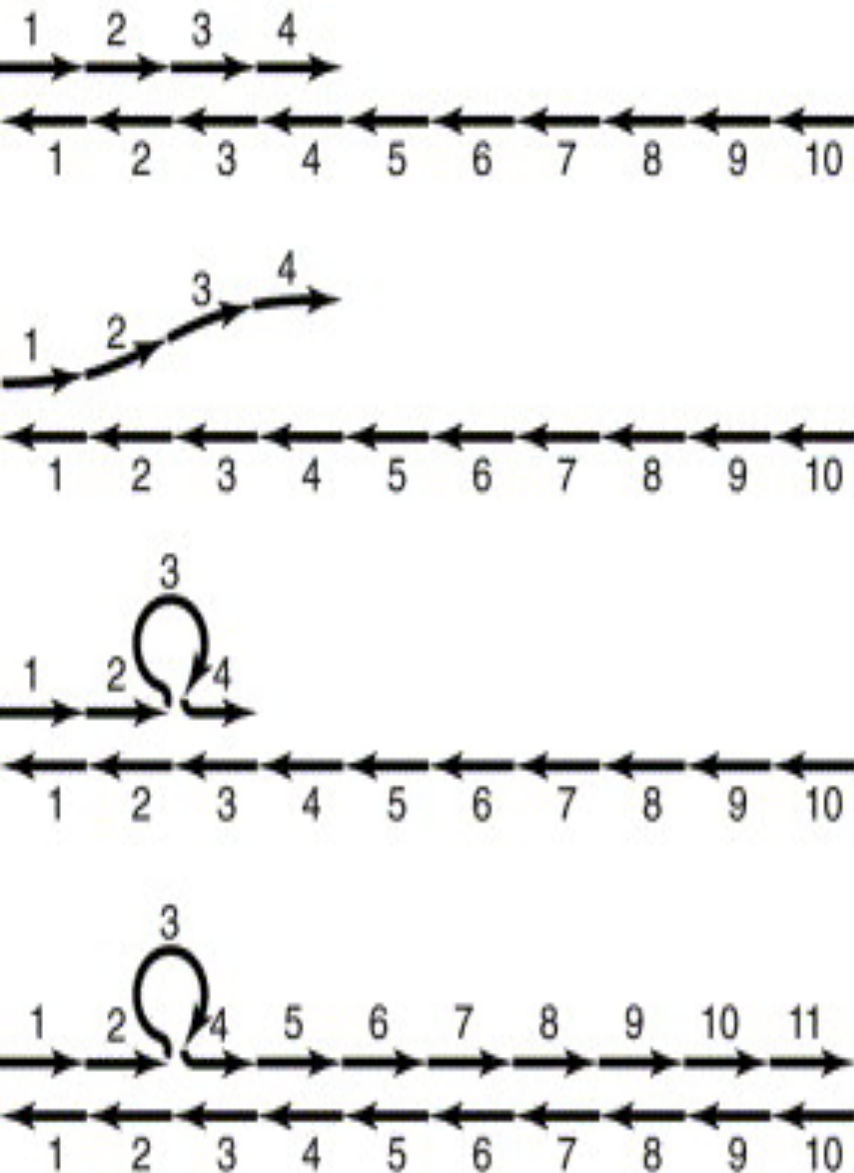
Figure 28.36
Biochemistry, Seventh Edition
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Repair of Mismatch DNA damage

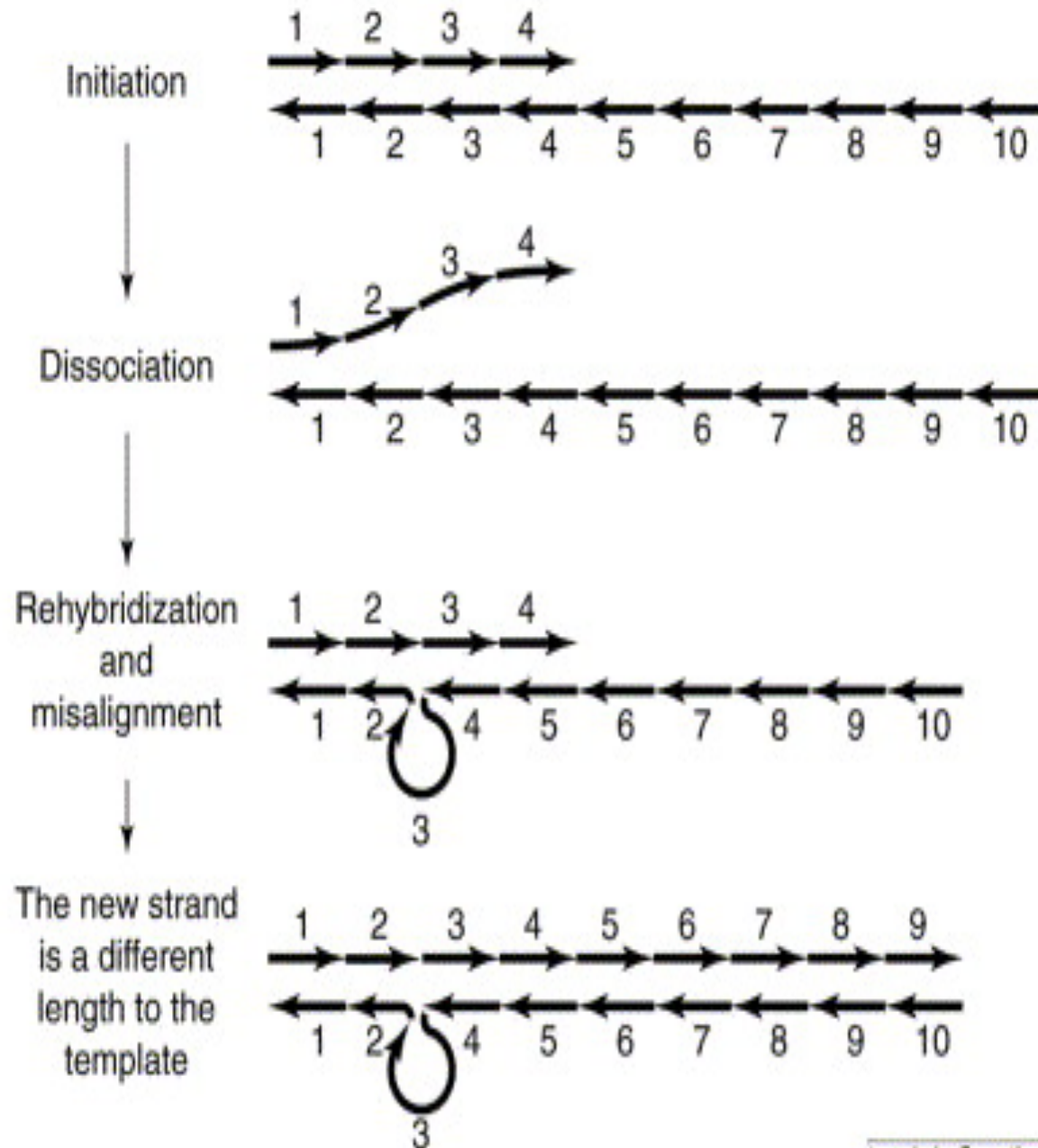
- Mismatch is **identified**
- **Endonuclease** nicks the strand
- **Exonuclease** remove Mismatched nucleotide(s).
- Additional nucleotides at the 5'- and 3'-ends are also removed.
- **DNA polymerase & DNA ligase** fill the gap.
- **Hereditary Nonpolyposis Colorectal Cancer (HNPCC)**
(Lynch syndrome).
 - Mutation in Mut-S, Mut-L & Mut-H

Microsatellite instability (MSI)

(a) Increase in repeat length



(b) Decrease in repeat length

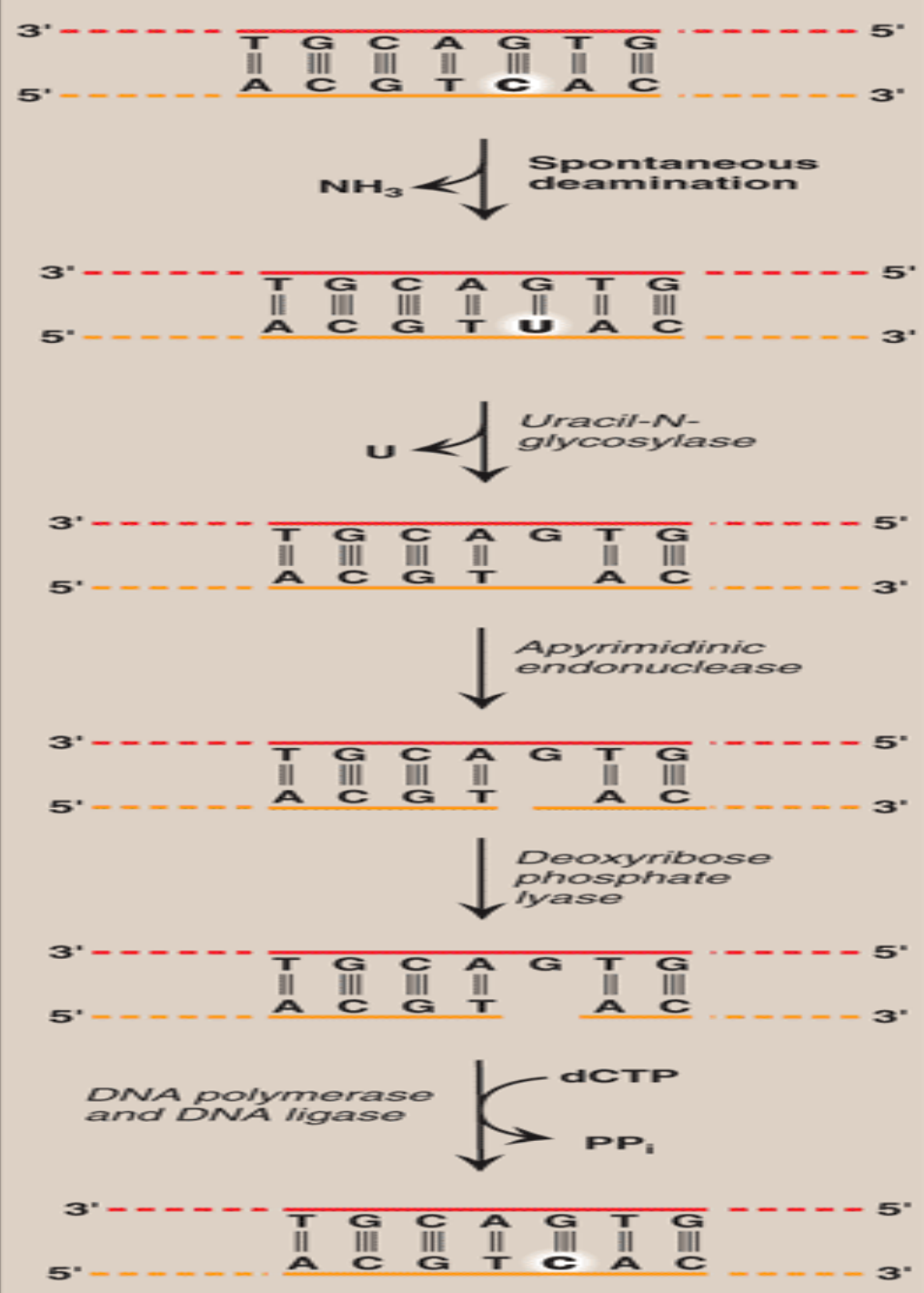


Mismatch Repair for Microsatellite instability (MSI)

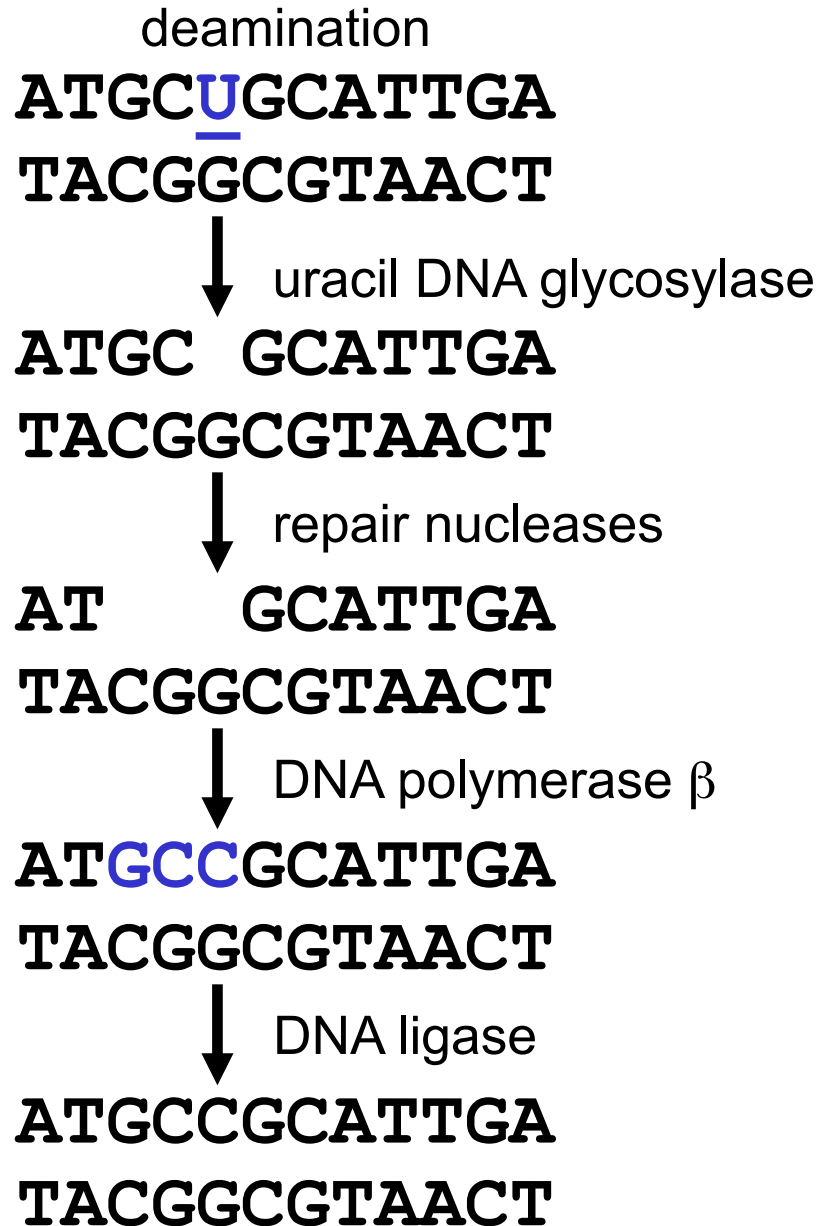
- Micro-satellites = Repeated Di-nucleotide “CA”
- DNA polymerase slips out these sequences
- Forms loop
- If defects in MMR repair process
 - Increase in length of DNA
 - Decrease In length of DNA
- **Corrected by MMR and NER mechanism**

Base Excision Repair

- **Deamination** type of damage is repaired by Base excision repair .
- **Removal of abnormal bases only :**
 - Deamination convert Cytosine = Uracil
 - **N-Glycosidic bond break** first
 - **Specific AP-endonucleases**
 - Recognition AP site = Missing base
 - Hydrolytically cleave nitrogen base.
 - Initiate the process of excision.
 - Remove **Deoxyribose phosphate**
 - Than Polymerase & Ligase complete repair



Find Difference BER vs NER



Base excision repair

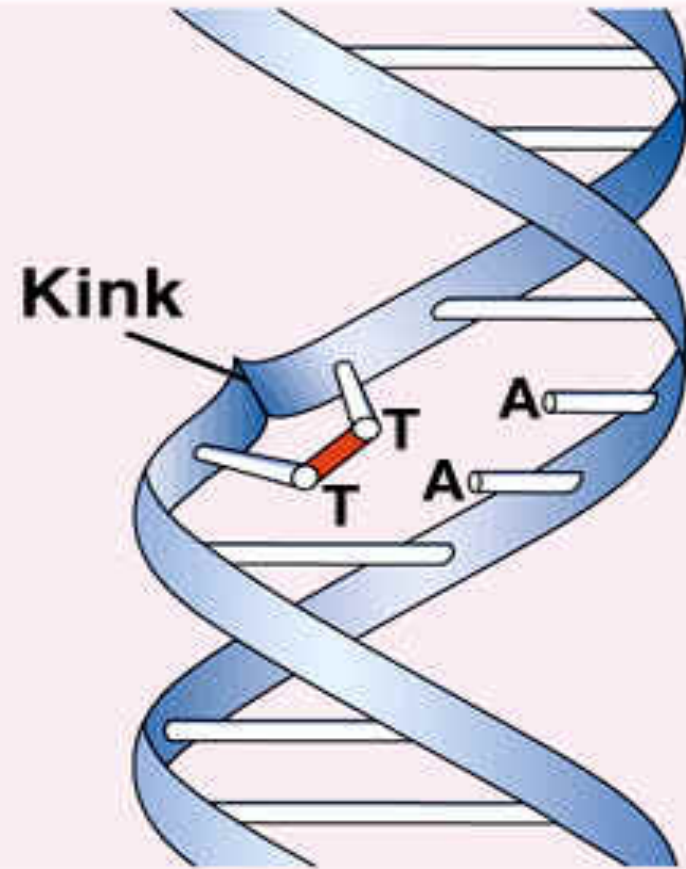
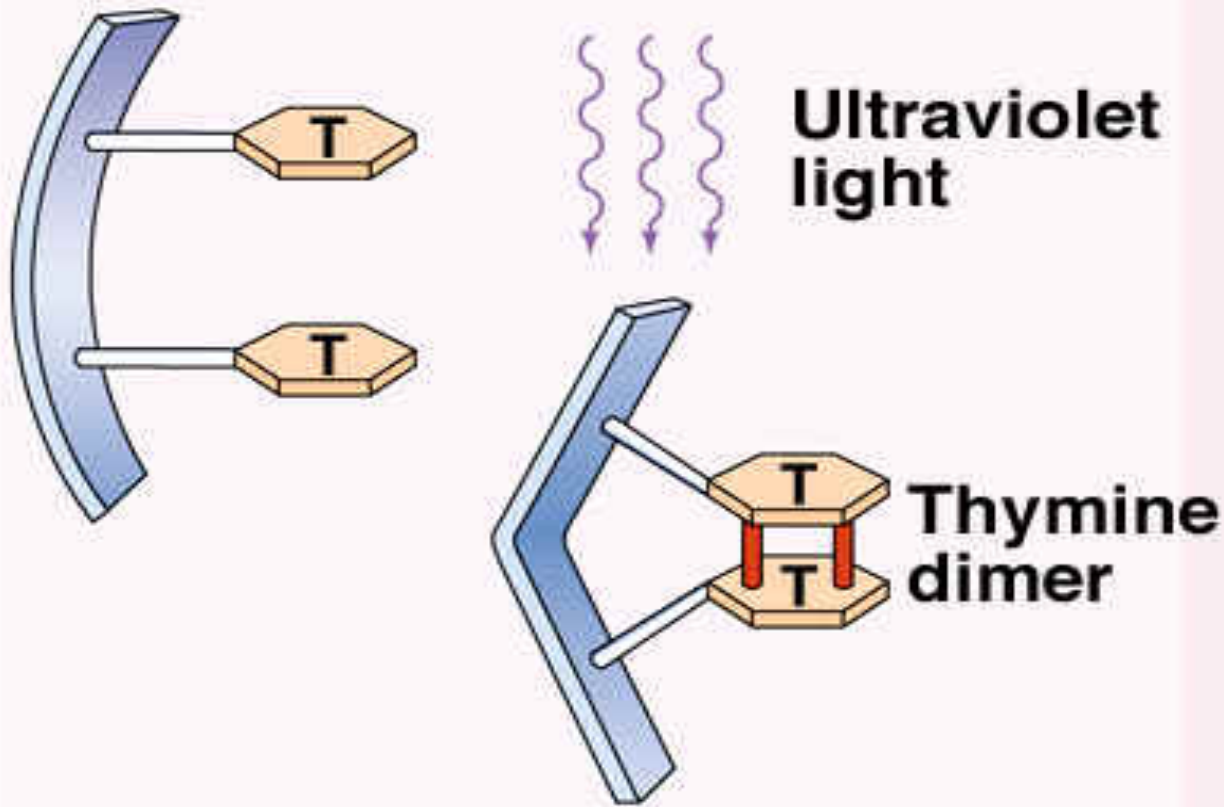


Nucleotide excision repair

Thymine Dimer due to UV light

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Pyrimidine Dimer



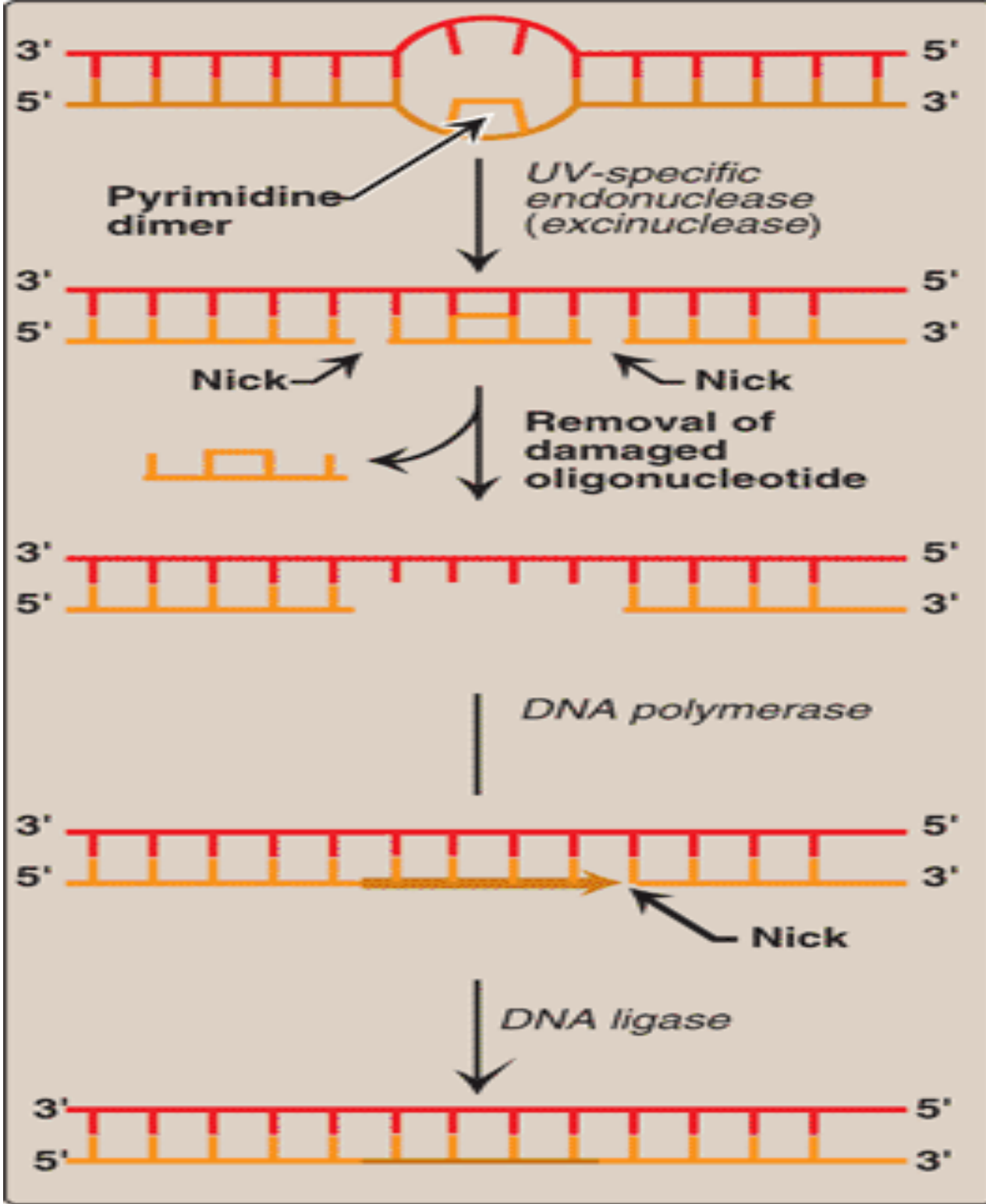
Mismatch Repair for Thymine Dimer due to UV light

- **Dimer = Thymine dimer**
- Obstruct DNA polymerase
- Inhibit DNA replication
- **UV-specific endonuclease (uvrABC excinuclease)**
- **Recognition and excise dimer**
- **Dimer containing short oligonucleotide removed.**
- Gap is filled same repair as mismatch repair.

UV radiation and cancer

- **Xeroderma Pigmentosum**
- **Skin cancer**
- Due to exposure to unfiltered sunlight.
- Defect in “UV-damage repair mechanism.

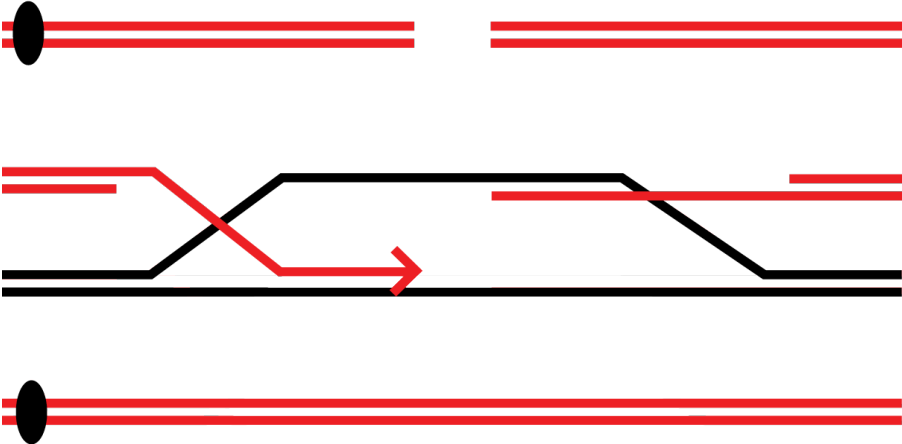




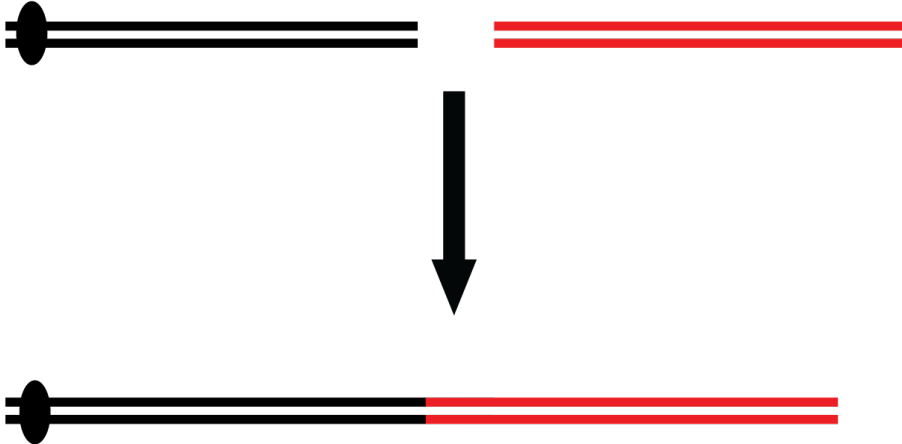
Repair Of Double Strand Break (DSB)

- Occur due to High-energy radiation or oxidative free radicals
- Potentially lethal
- Non-Homologous End-joining Repair (NHER)
 - Error prone and mutagenic.
 - Very low fidelity (less faithful - More Error)
 - Defects in this repair system
 - Severe immunodeficiency syndromes & Cancer
- Homologous recombination repair (HR)
 - Less error
 - Higher fidelity (More Faithful - Less Error)

Homologous recombination



Non-homologous end-joining



BRCA Gene 1 & 2

(BR^east CAⁿcer)

- » BRCA - 1
- » BRCA - 2
- » Both - Tumour Suppressor Gene
- » Good For Human - Prevent Cancer
- » Help in DNA Repair Mechanism

Transcriptional regulation
or coupled repair



BRCA-1



BRCA-1



DNA break
or other
lesion



DNA repair by
homologous
recombination

mRad51

BRCA-2



mRad52 epistasis group molecules



Tumour Suppressor Gene

- » **ATM - Ataxia Telangiectasia Mutated**
- » **mRad 51**
- » Both - Tumour Suppressor Gene
- » Good For Human - Prevent Cancer
- » Help in DNA - DSB- Repair Mechanism



Progeria

Hutchinson–Gilford syndrome

Hutchinson–Gilford progeroid syndrome - HGPS

LMNA (Lemin A protein)

- **Function :**

- ✓ Provide Stability of Genetic Material for Double Stand Repair

- **Pathogenesis of Progeria**

- ✓ Mutation in Gene for LMNA (Lemin A protein)

- ✓ Single Base Replacement

- ✓ Position 1824

- ✓ Cytosine with Thymine

p53

Function

- Role in apoptosis, genomic stability
- Anti-cancer role

Mechanism

- Activate DNA repair proteins
- Arrest growth by holding the cell cycle at G_1/S
- Hold cell here for long enough
- DNA repair proteins get time to repair
- Otherwise
- Initiate apoptosis, the programmed cell death, if DNA damage proves to be irreparable.

- Arabinose (analogue of deoxyribose) is
 - a. Use as antiviral and anticancer drug
 - b. Use to inhibit replication.
 - c. Use as anti- diabetic agent.
 - d. a & b.

- Which of the following is true about DNA topoisomerase
 - a. It unwinds DNA.
 - b. It always break both strand of DNA
 - c. It produces positive supercoiling.
 - d. None

- The 3' end of each Okazaki fragment is joined to the 5' end of the next fragment by
 - a. DNA Polymerase I & DNA ligase
 - b. DNA Polymerase III & DNA ligase
 - c. DNA ligase
 - d. DNA Polymerase I

- Topo isomerase enzyme is inhibited by antibiotic
 - a. Ciprofloxacin
 - b. Adriamycin
 - c. Doxorubicin
 - d. Amoxycillin

- During mismatch repair , parent DNA strand is identify by it's
 - a. Ribosylation
 - b. Hydroxylation
 - c. methylation
 - d. phosphorylation

- Error during DNA replication can be corrected by
 - a. DNA ligase
 - b. Primase
 - c. DNA Polymerase
 - d. Topoisomerase

- All of the following is a tumor suppressor protein, EXCEPT
 - a. p53
 - b. mdm2
 - c. BRCA
 - d. UV specific endonuclease

- About “Non homologous end joining”, what is incorrect out of following?
 - a. higher chance of gene loss.
 - b. higher fidelity of fidelity
 - c. higher chance of gene exchange
 - d. higher chance of immunodeficiency syndrome.