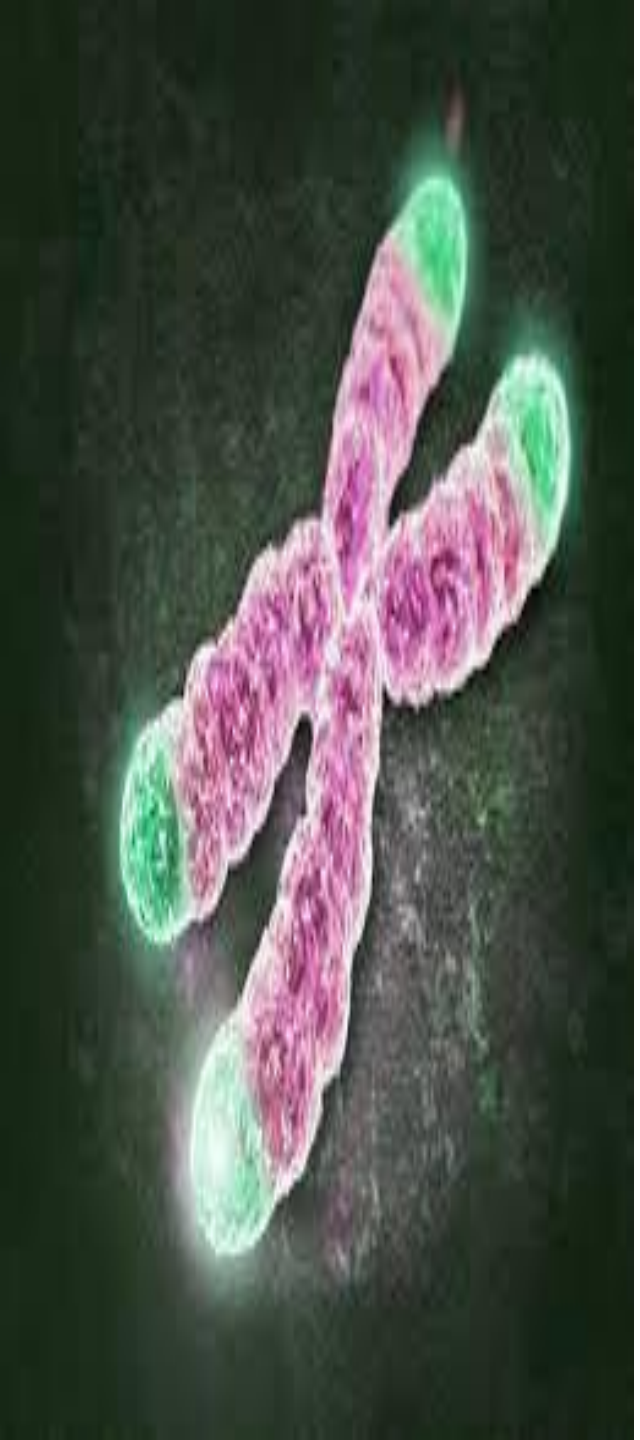


Telomere , Telomerase & End Replication Problem

Learning outcomes

- Define telomeres
- Identify functions of telomeres
- Recognize the End replication problem
- Understand how Telomerase enzyme solve the problem
- Detect the linkage between telomeres and aging
- Outline the relationship between telomerase and cancer

Aging is a natural process that all living beings undergo

What comes to your mind when you hear the word aging?

Wrinkles, white hair and becoming weak.

Ever you wonder why we age?

Let’s take a look at it to see what happens at the molecular level.

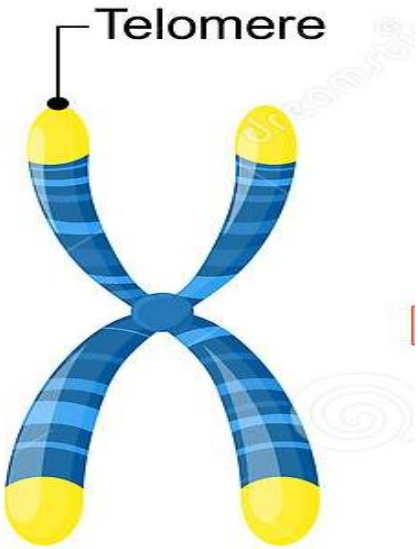
What are telomeres?

Telomeres are…

- Repetitive DNA sequences at the ends of all human chromosomes

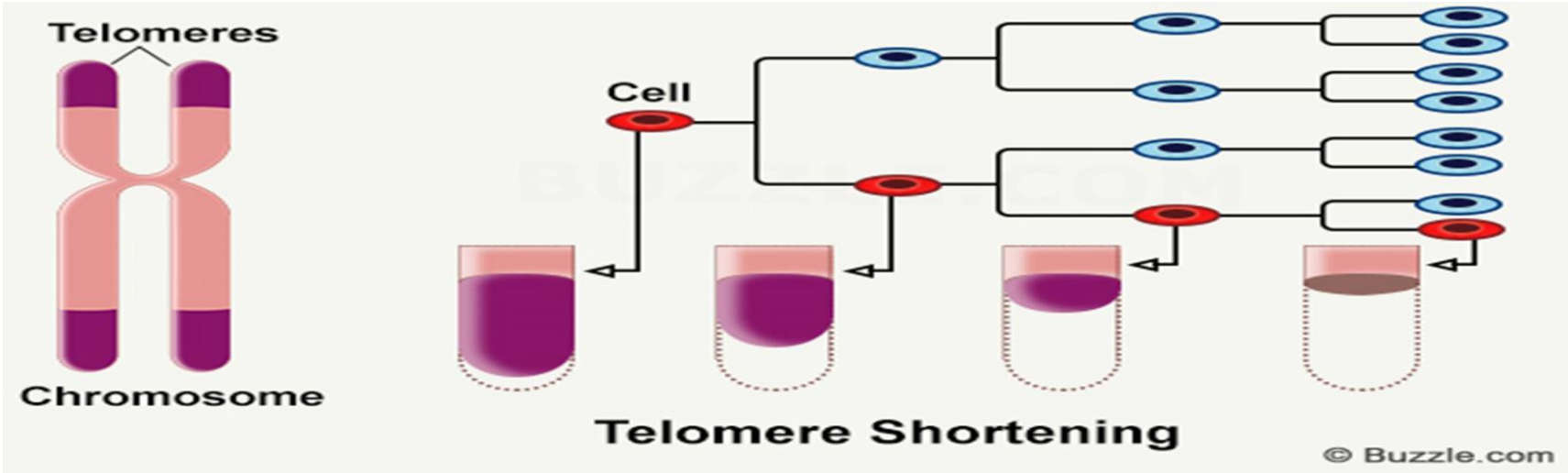
- Its name is derived from the Greek nouns telos ='end' and meros = 'part'.

- They contain thousands of repeats of the six-nucleotide sequence TTAGGG.



What do telomeres do?

1) They protect the end of chromosomes (capping) as shoelaces.
2) Prevent chromosome fusion
3) Enable a complete replication of DNA.
4) Telomeric sequences shorten each time the DNA replicates the mechanism that counts the number of times a cell has divided "molecular clock"



How does telomeres get shorter each time a cell divides?

- During DNA replication, the DNA replicating enzymes cannot replicate the sequences present at the end of chromosomes.
- Hence, these sequences and the information they carry may get lost and this is called "End- replication problem".
- Telomeres cap the end sequences and themselves get lost in the process of DNA replication.

Telomere: Animation

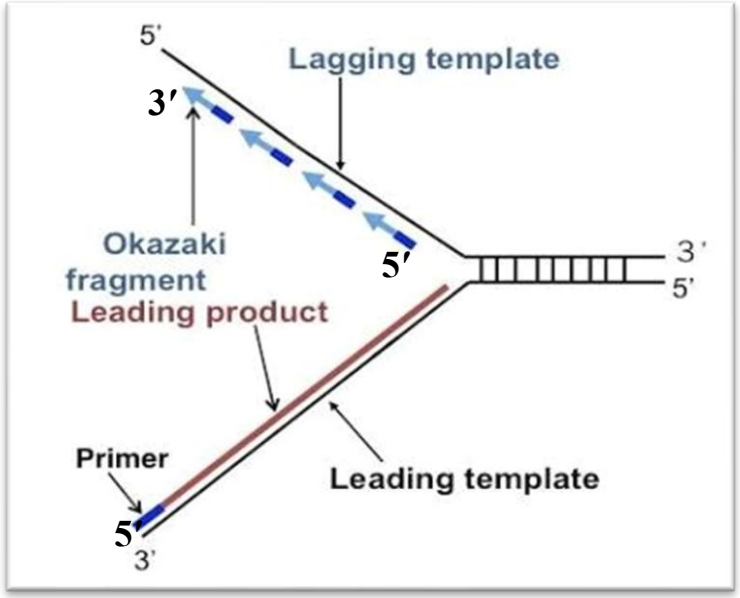
The end replication problem

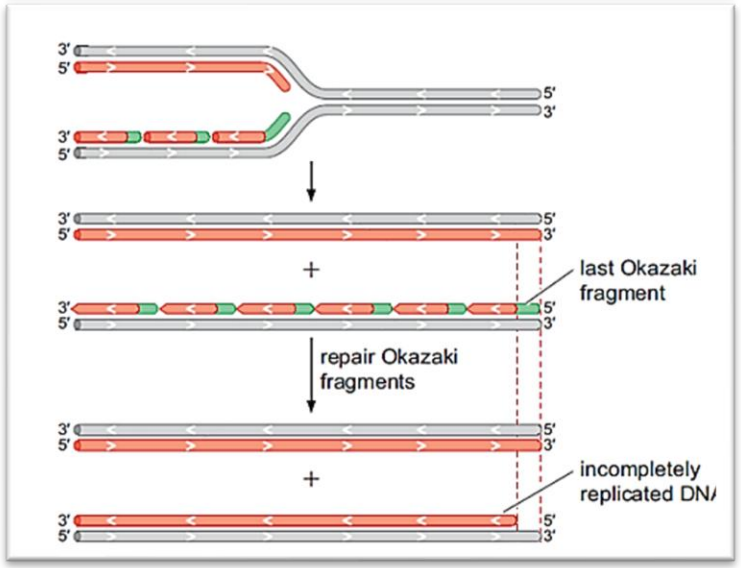
- **Definition: It is the inability of DNA polymerase to completely replicate the ends of linear chromosomes, leading to progressive shortening of telomeres after each cell division.**

➢ During DNA replication, DNA polymerase can only add nucleotides in the 5′ → 3′ direction and it requires an RNA primer to start synthesis.

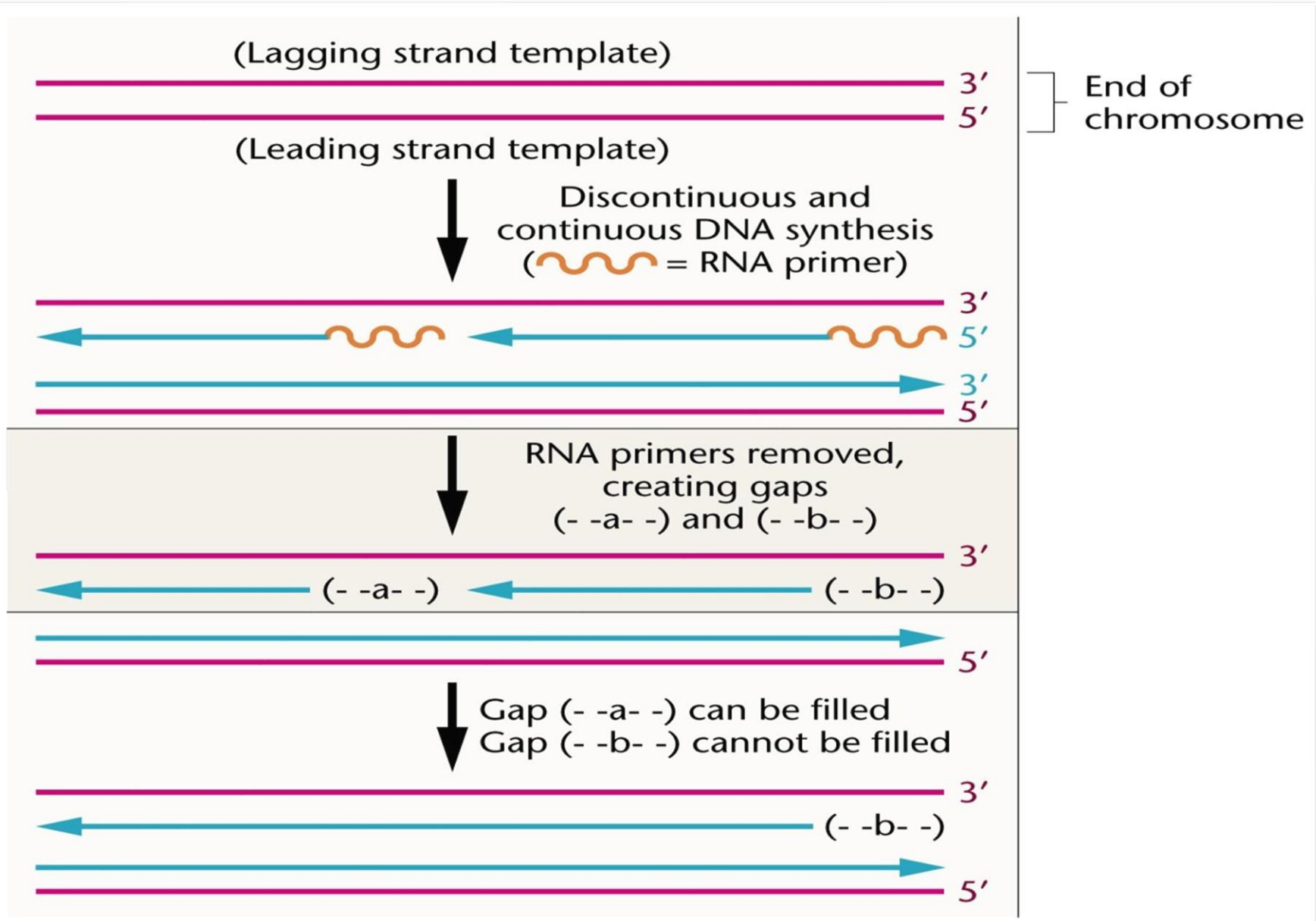
➢ Leading strand is synthesized continuously & completely to the end of the chromosome.

➢ On the lagging strand, DNA is synthesized in short fragments called Okazaki fragments.



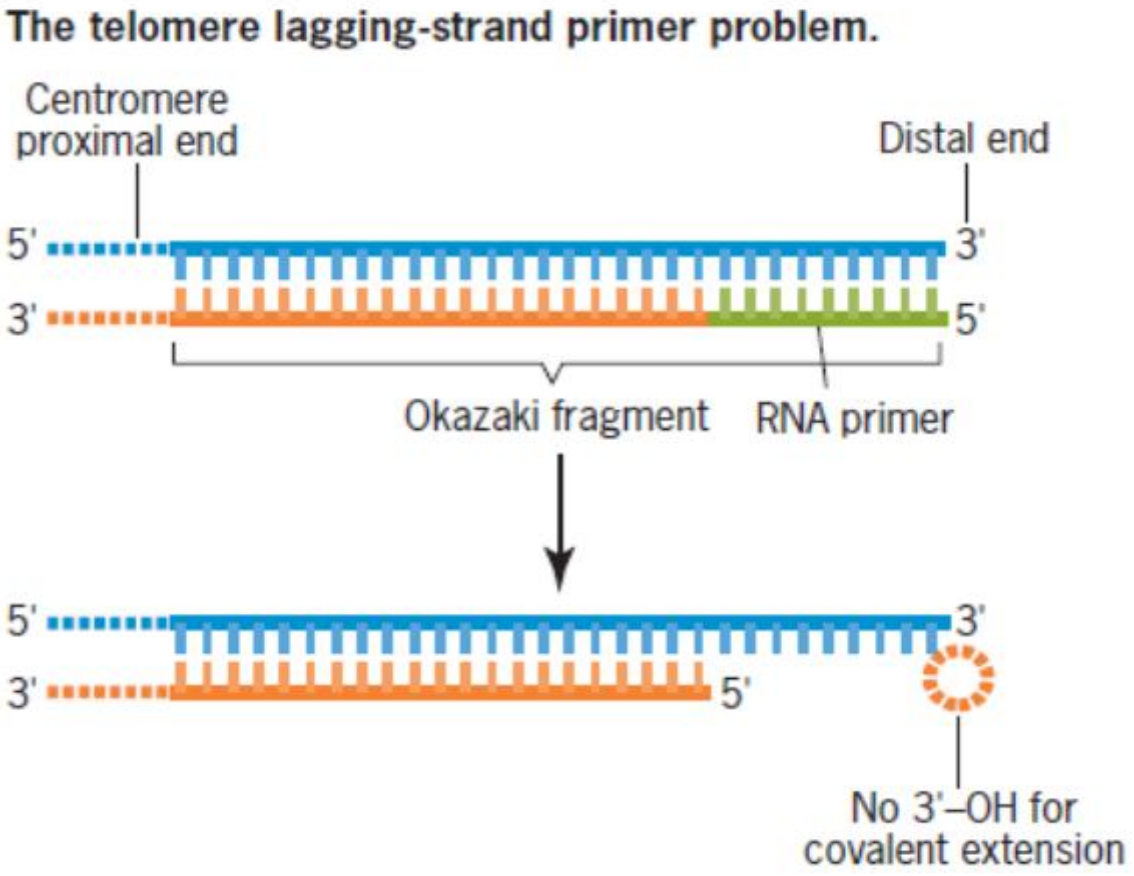


The end replication problem



When replication reaches the end of the chromosome, the last RNA primer is removed, but DNA polymerase cannot replace it with DNA because there is no upstream 3′-OH group available for extension.

The end replication problem



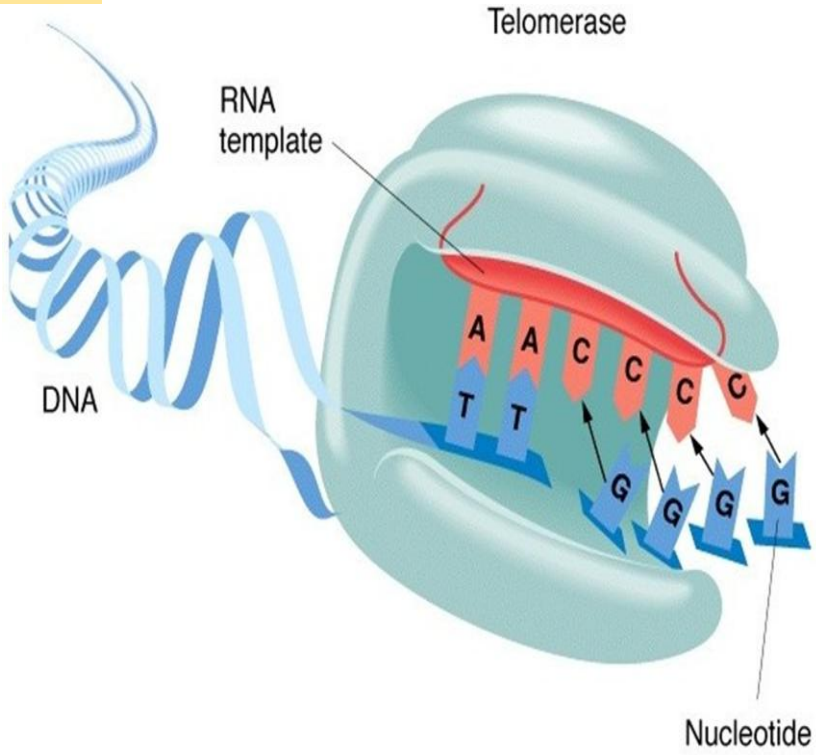
Thus, the lagging strand is shortened at each cell division

Solution to the End replication problem:

Telomerase

What is telomerase?

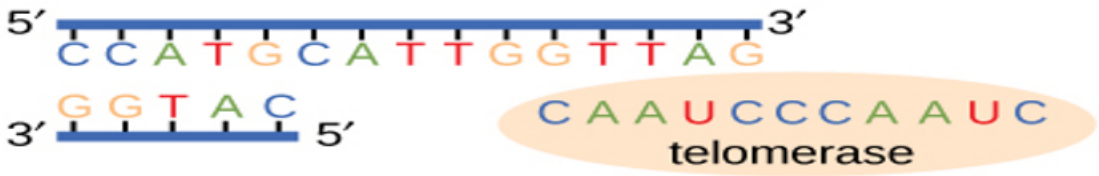
- Telomerase is a ribonucleoprotein enzyme complex (reverse transcriptase)
- It carries its own RNA template, which is complementary to telomeric repeat sequences.



- It stabilizes telomere length by adding hexameric (TTAGGG) repeats onto the telomeric ends of the chromosomes, thus compensating for the loss of telomeres that occurs as cells divide.

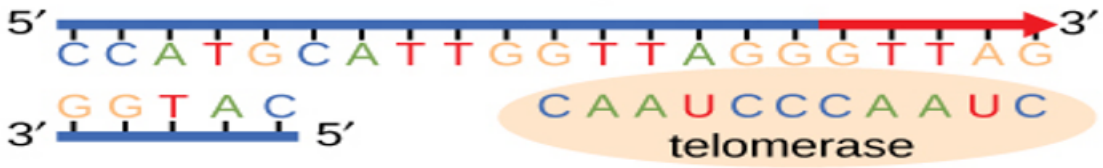
How does telomerase work?

1) Recognition and binding



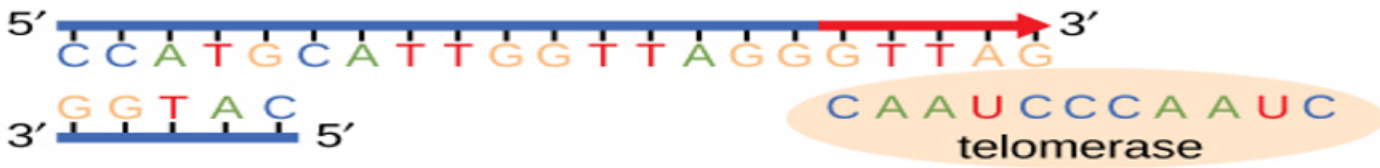
Telomerase has an associated RNA that complements the 3′ overhang at the end of the chromosome.

2) Elongation

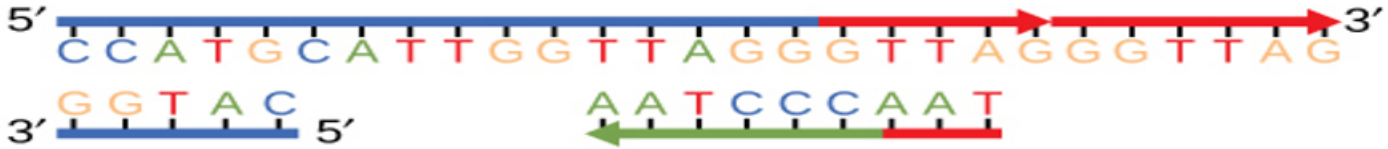


The RNA template is used to synthesize the complementay strand.

3) Translocation

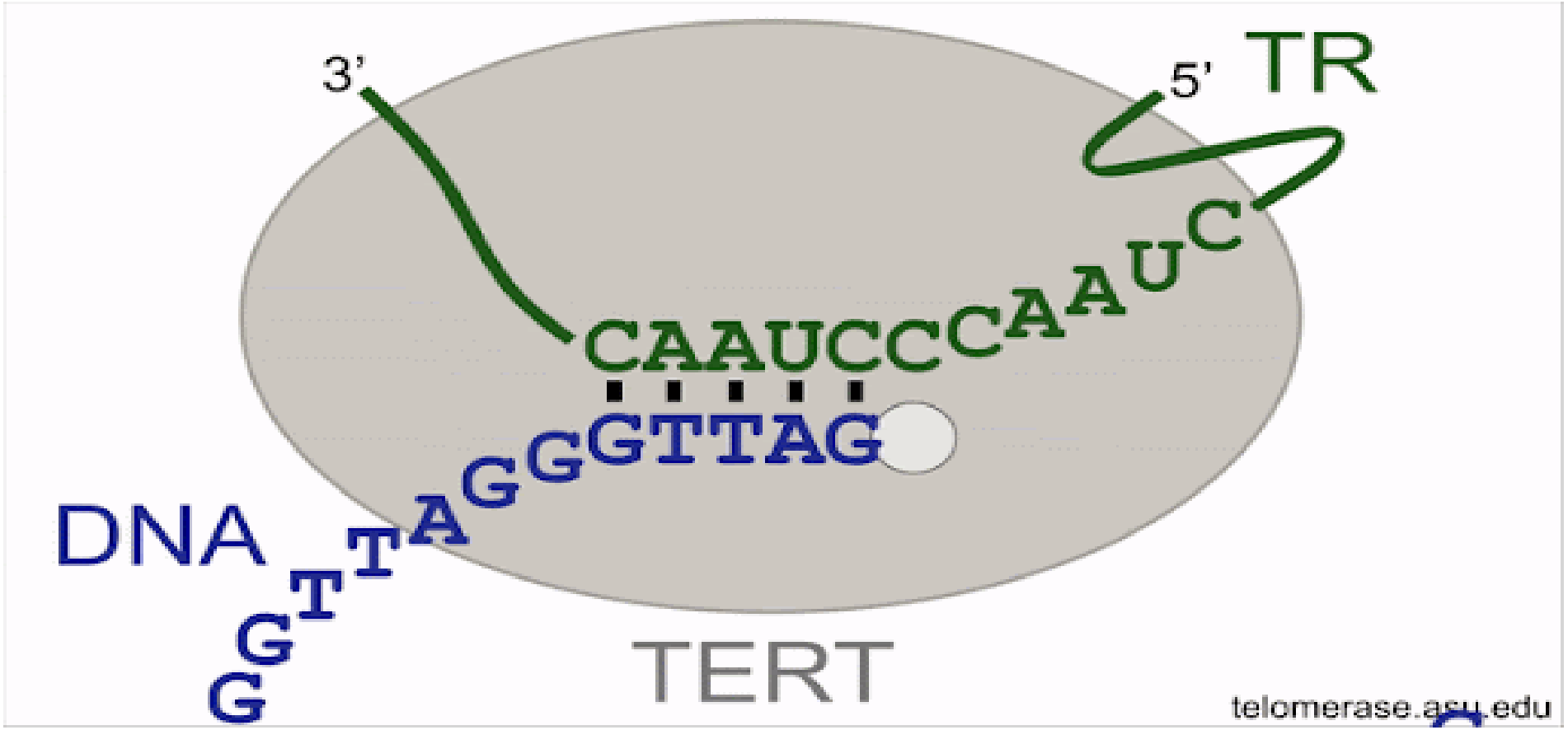


Telomerase shifts, and the process is repeated.

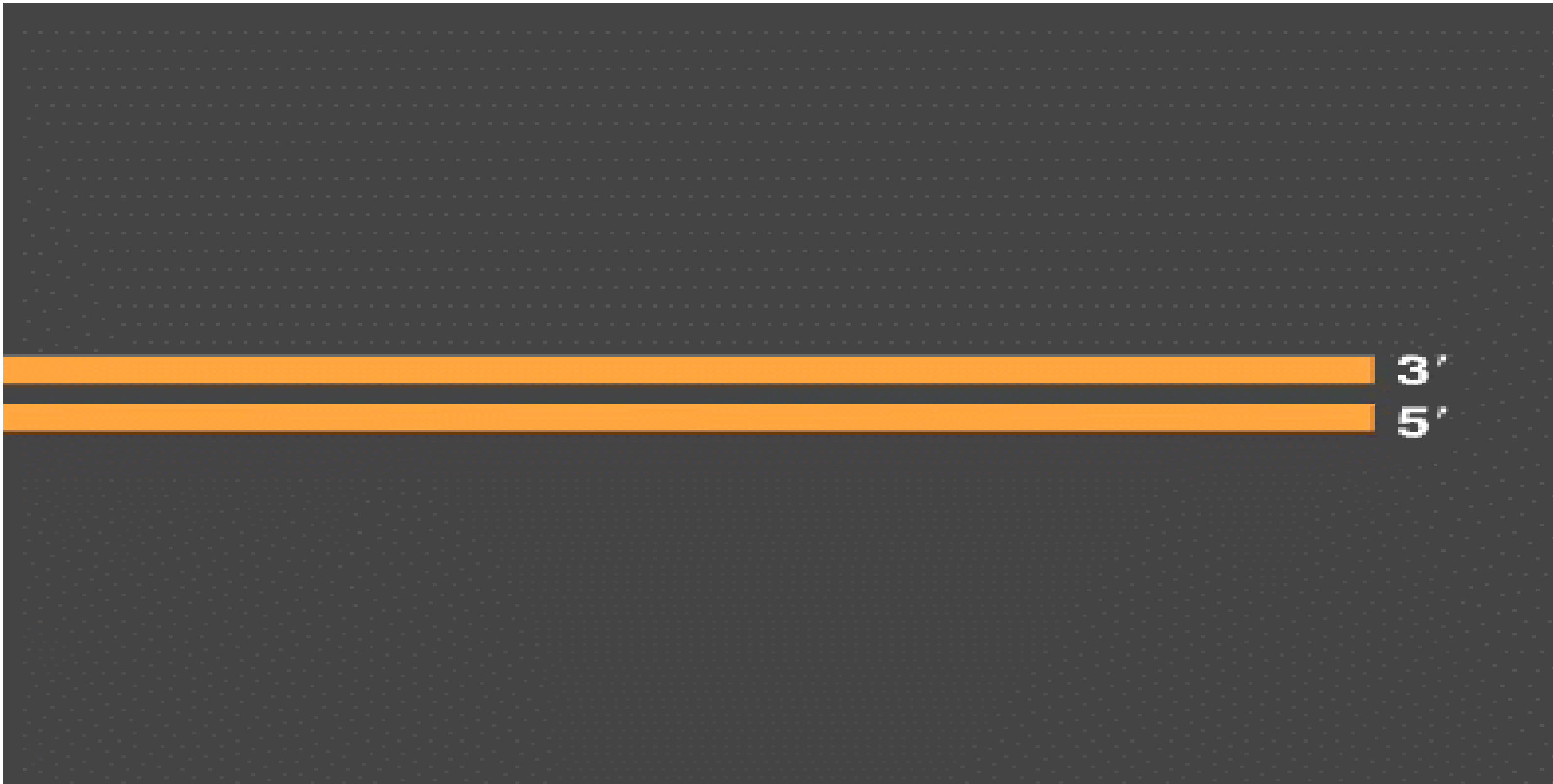


Primase and DNA polymerase syntesize the complementary strand.

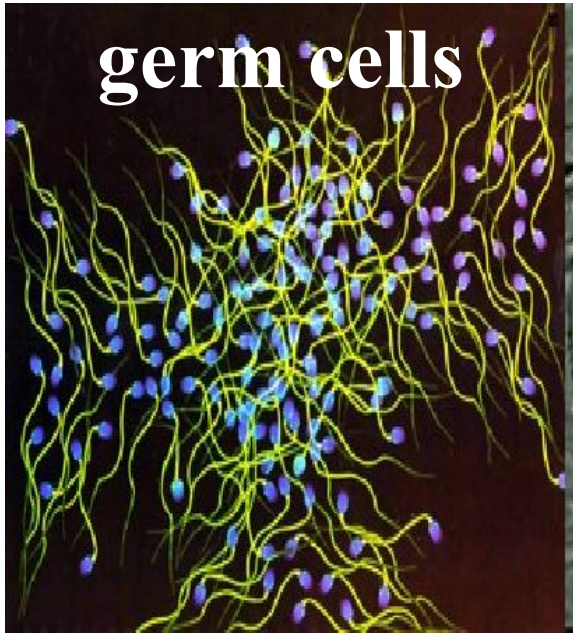
Telomerase

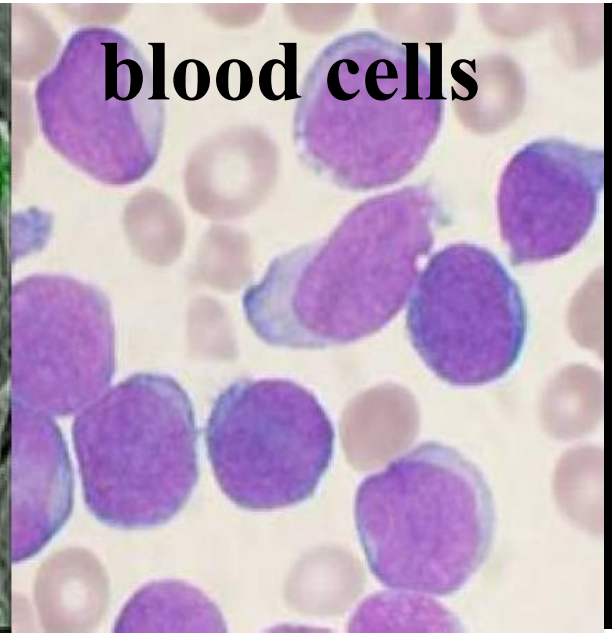

3'
5'
TR
CAAUCCCAAUC
GGGTTAG
DNA
GGTTAG
TERT
telomerase.asu.edu

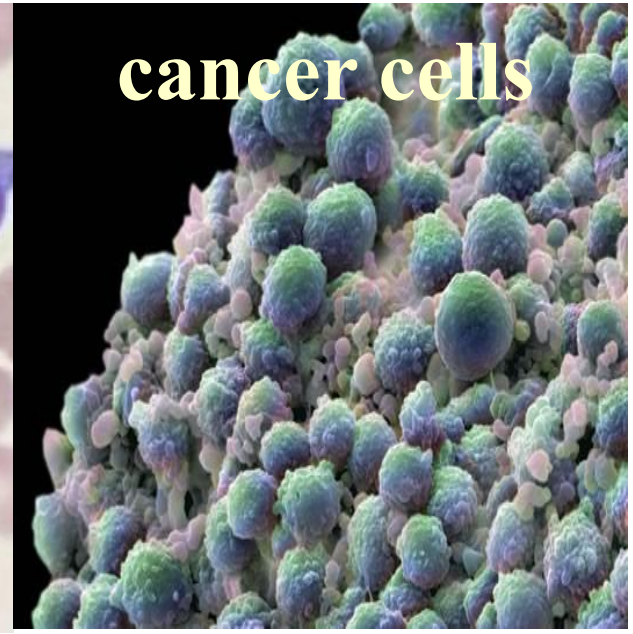
The end replication problem: Animation



- Most normal somatic cells do not have active telomerase and thus they lose telomeres with each division.
- In humans, telomerase is active in germ cells, stem cells, blood cells and cancer cells.

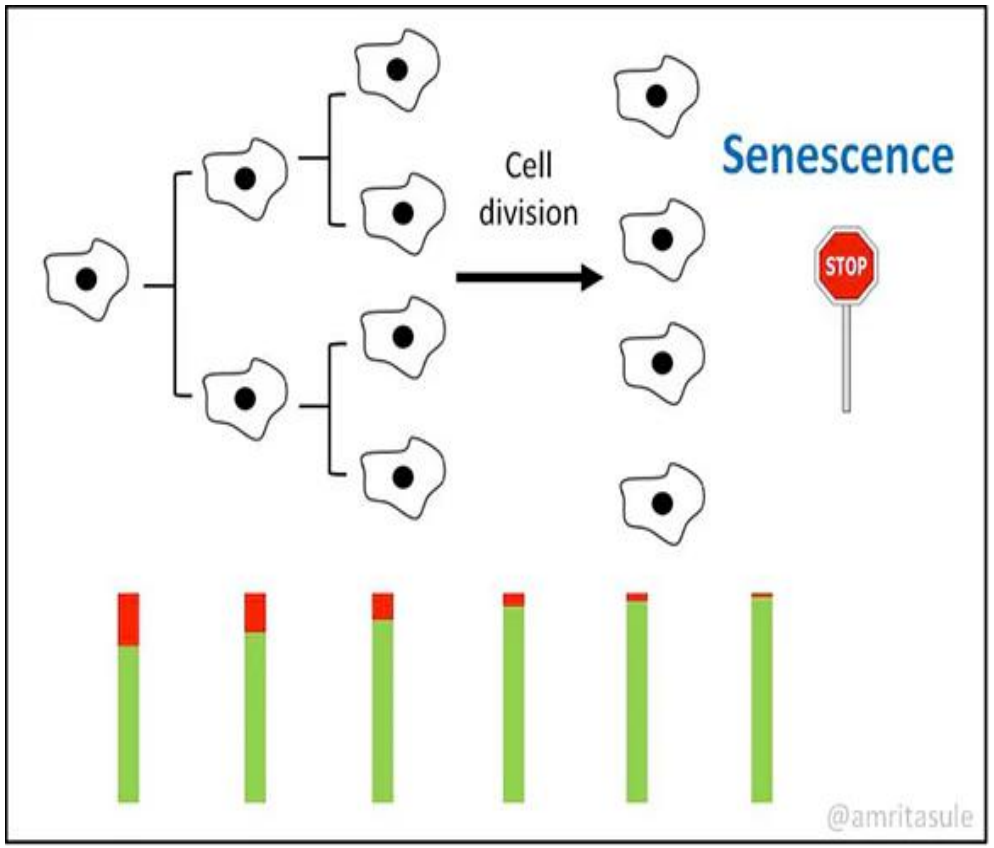


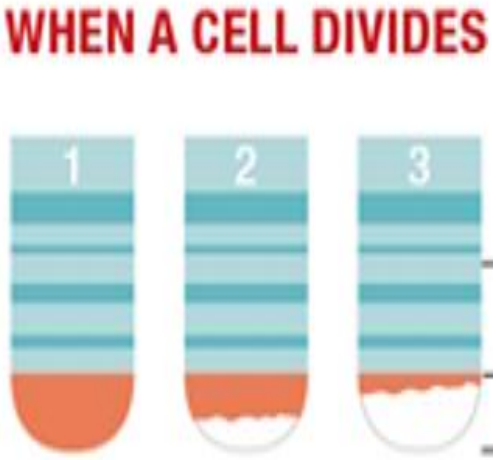




Cells with telomerase vs cells without telomerase

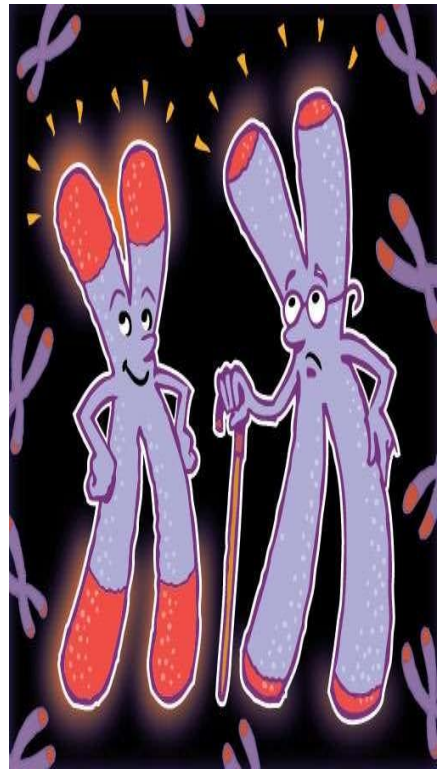
Cells without telomerase





Telomeres & Aging

- Healthy human cells are mortal because they can divide only a finite number of times (about 40-60 times), growing older each time they divide.
- Cells in an elderly person are much older with shorter telomeres than cells in an infant.
- When telomeres become too short, cellular senescence (growth arrest) occurs.



Telomerase & cancer

- **Most human somatic cells lack telomerase activity leading to:**

-Telomere shortening

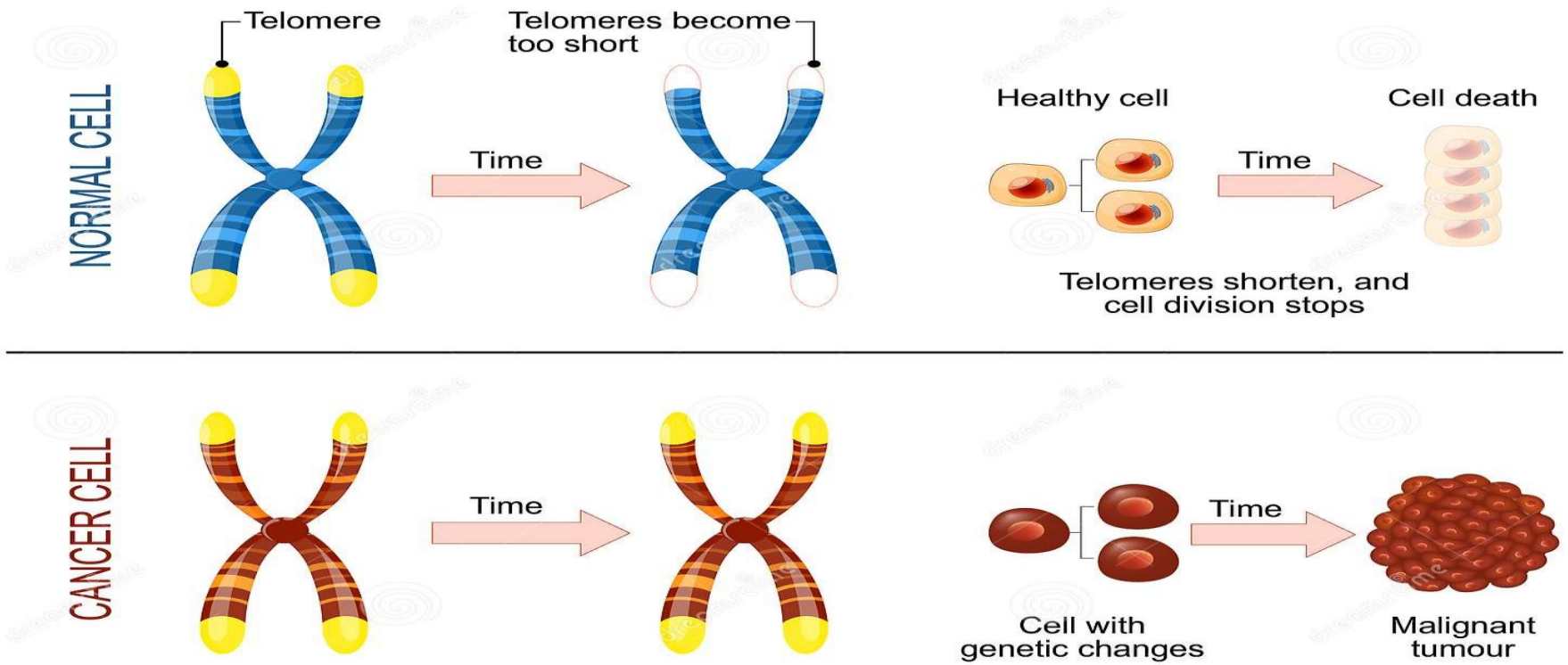
- Senescence (growth arrest)

- **Most tumors regain the ability to produce telomerase so:**

- Cells become immortal

- Telomerase is up-regulated (switched on) in the ~90% of human cancers

TELOMERE and CANCER



Thank you