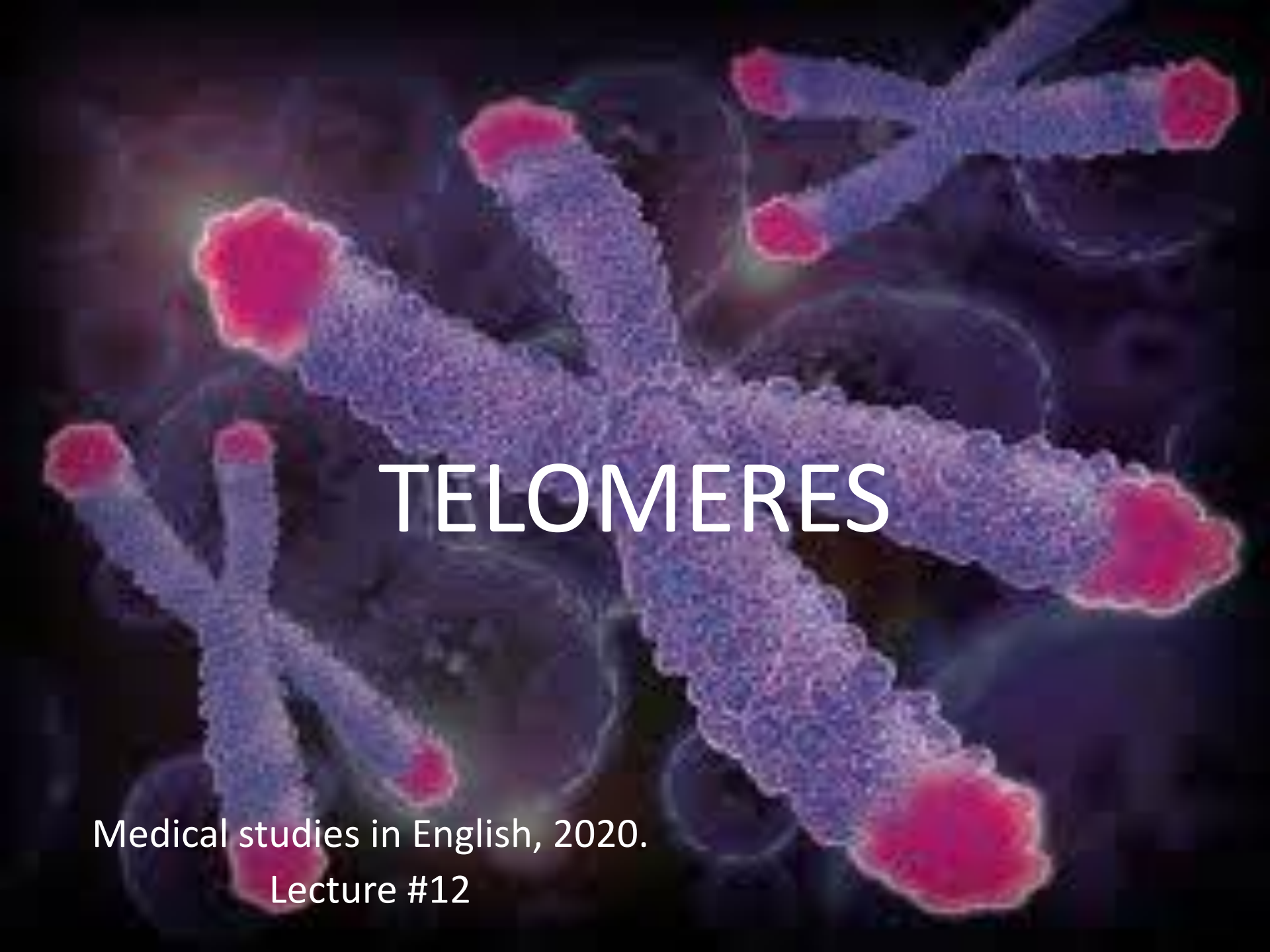


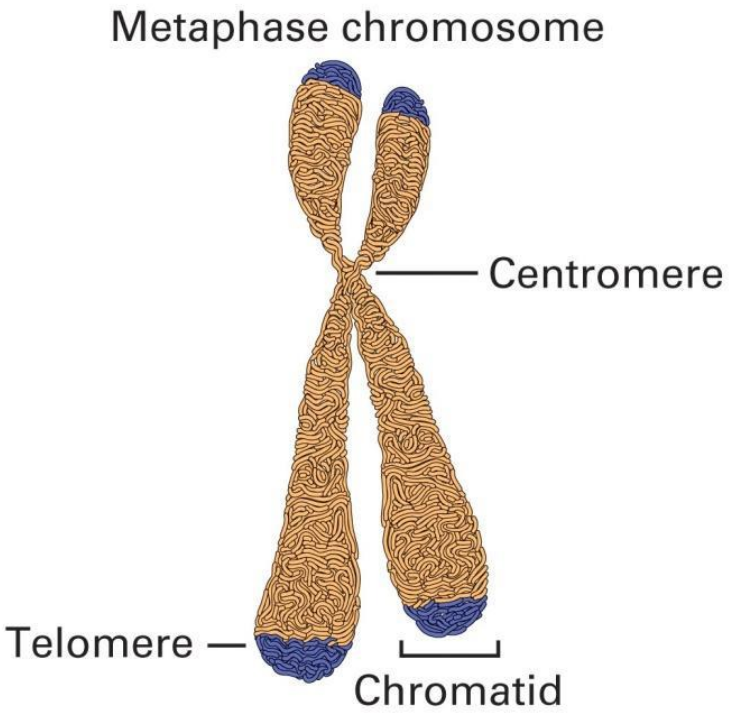
TELOMERES

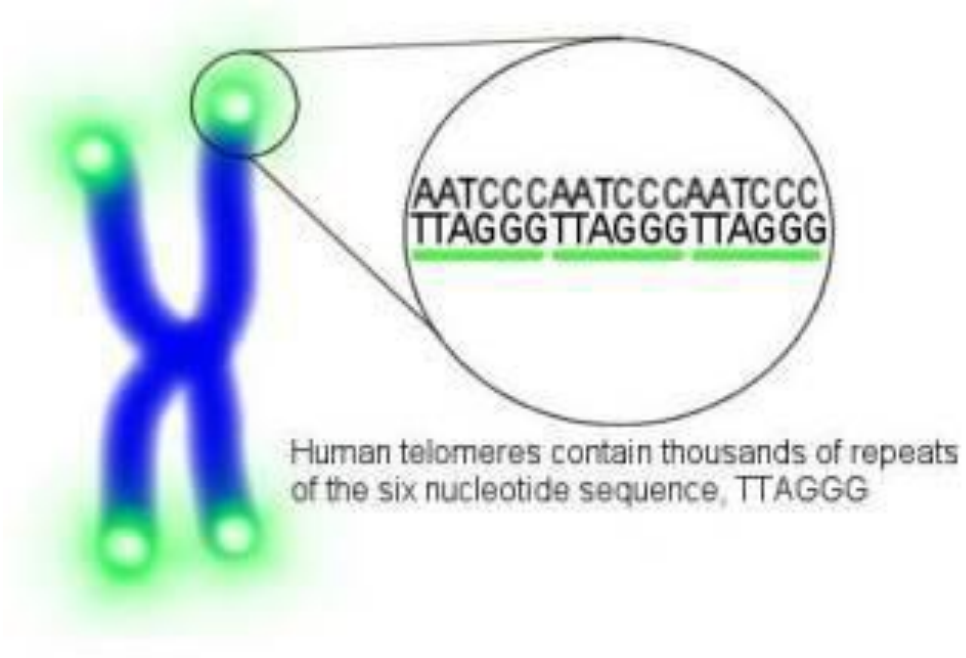
Medical studies in English, 2020.

Lecture #12

Telomere structure

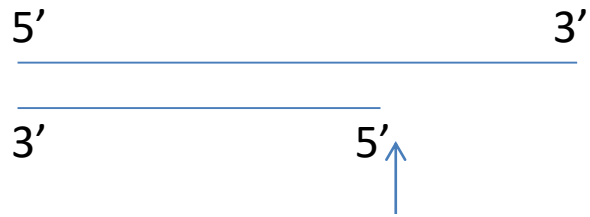
- Telomeres - region of repetitive TTAGGG nucleotide sequences at each end of a chromosome; protect chromosome from deterioration
- Non coding cequence



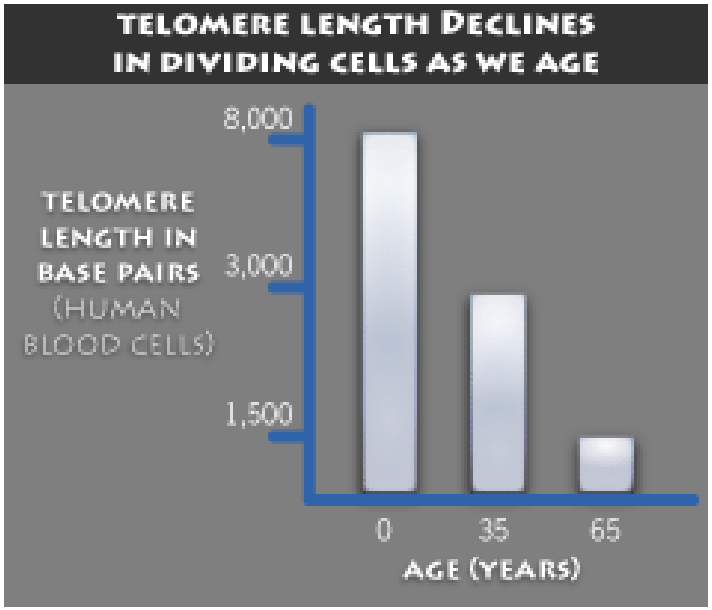


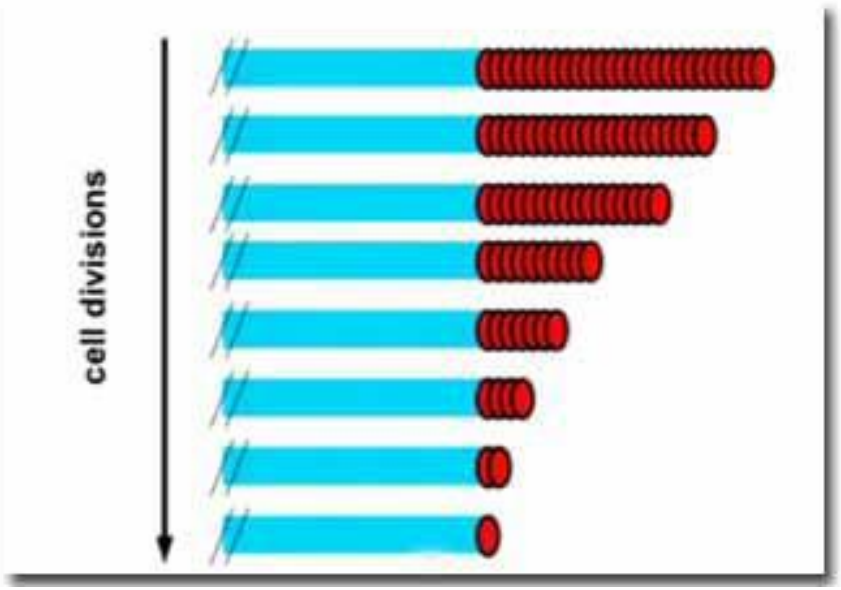
Shortening of telomeres

- During replication, DNA polymerase is unable to replicate the whole length of a lagging strand (5’ end)
- Consequence: after every DNA replication telomeres are shorter for 50-100 bp
- Telomere length in humans: form 8000 bp in newborns to 1500 bp in elderly



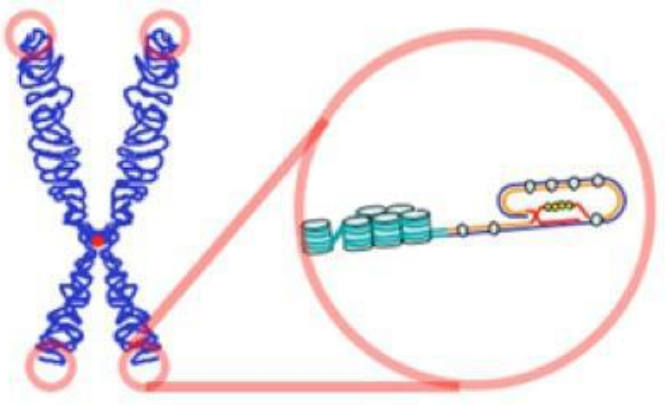
Lagging strand is shortened

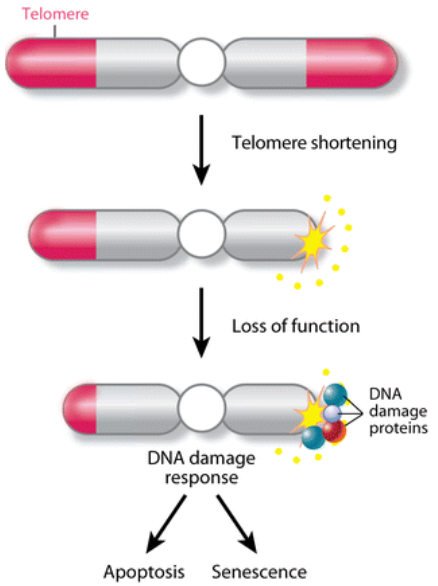


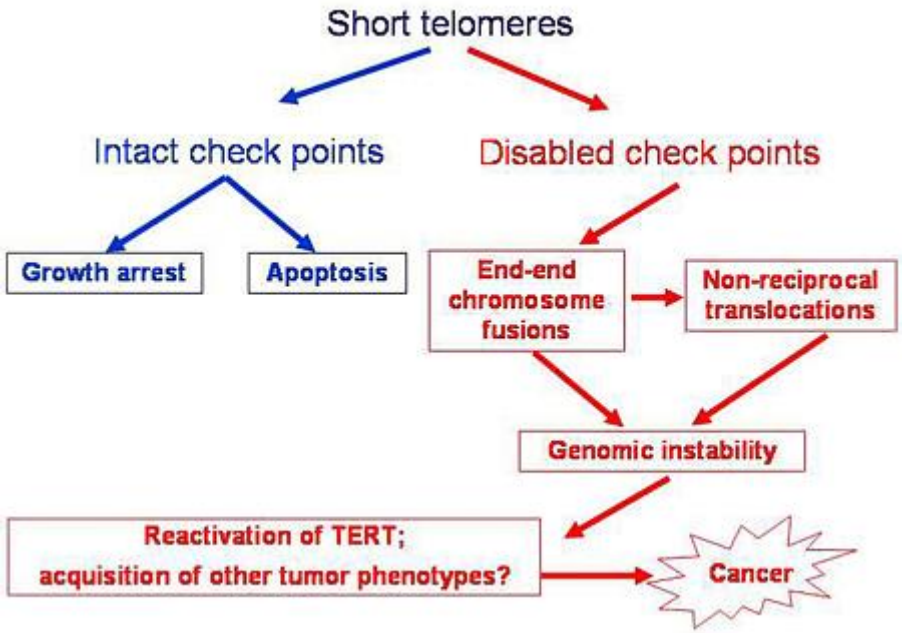


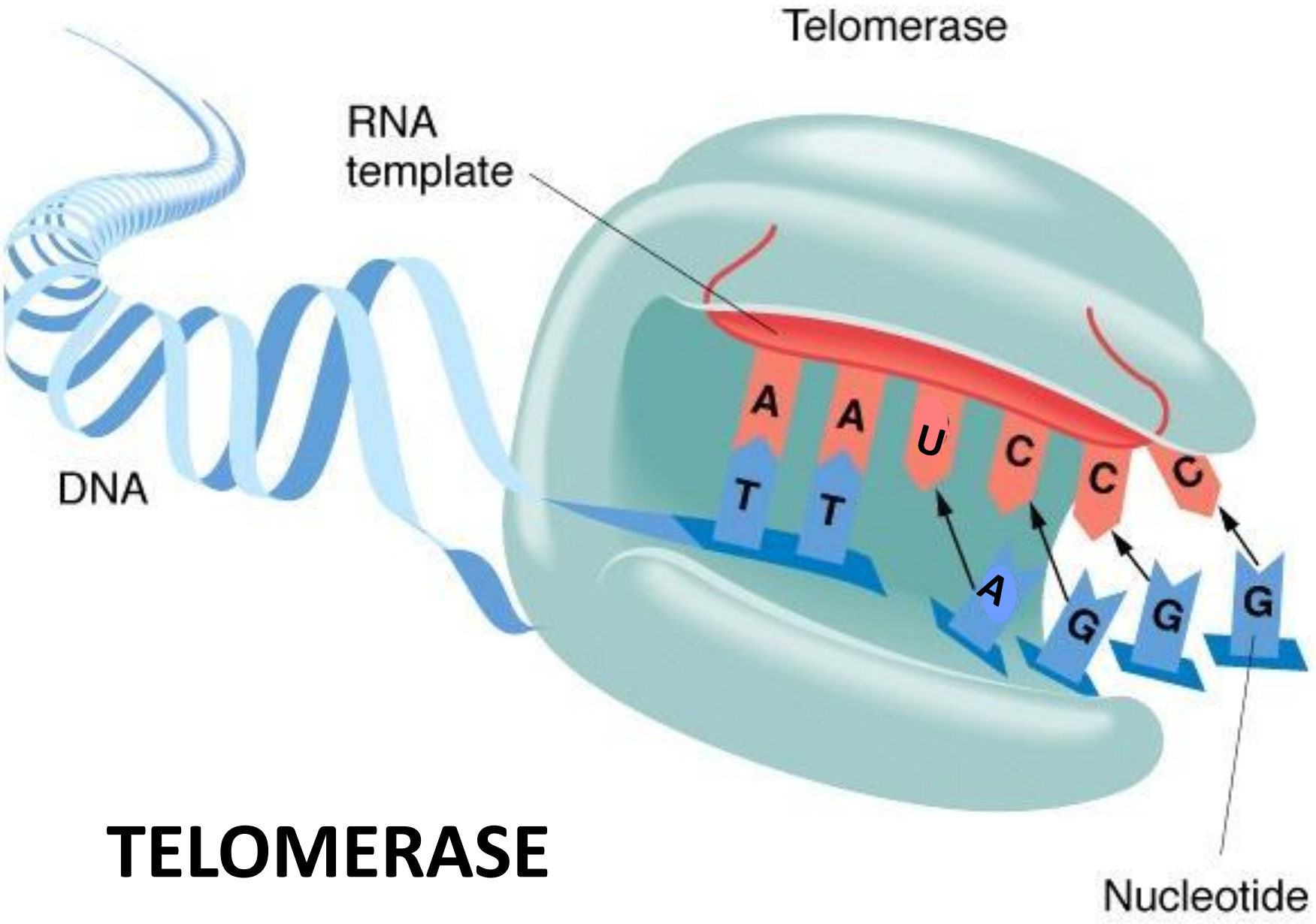
Telomere shortening

- Criticaly short telomeres are unable to form T-loop and are unable to protect chromosomal ends
- Cell recognises such telomeres as double stranded DNA breaks, and recruits DNA repair
- Such cells are aged, senescent, they die or develop tumors





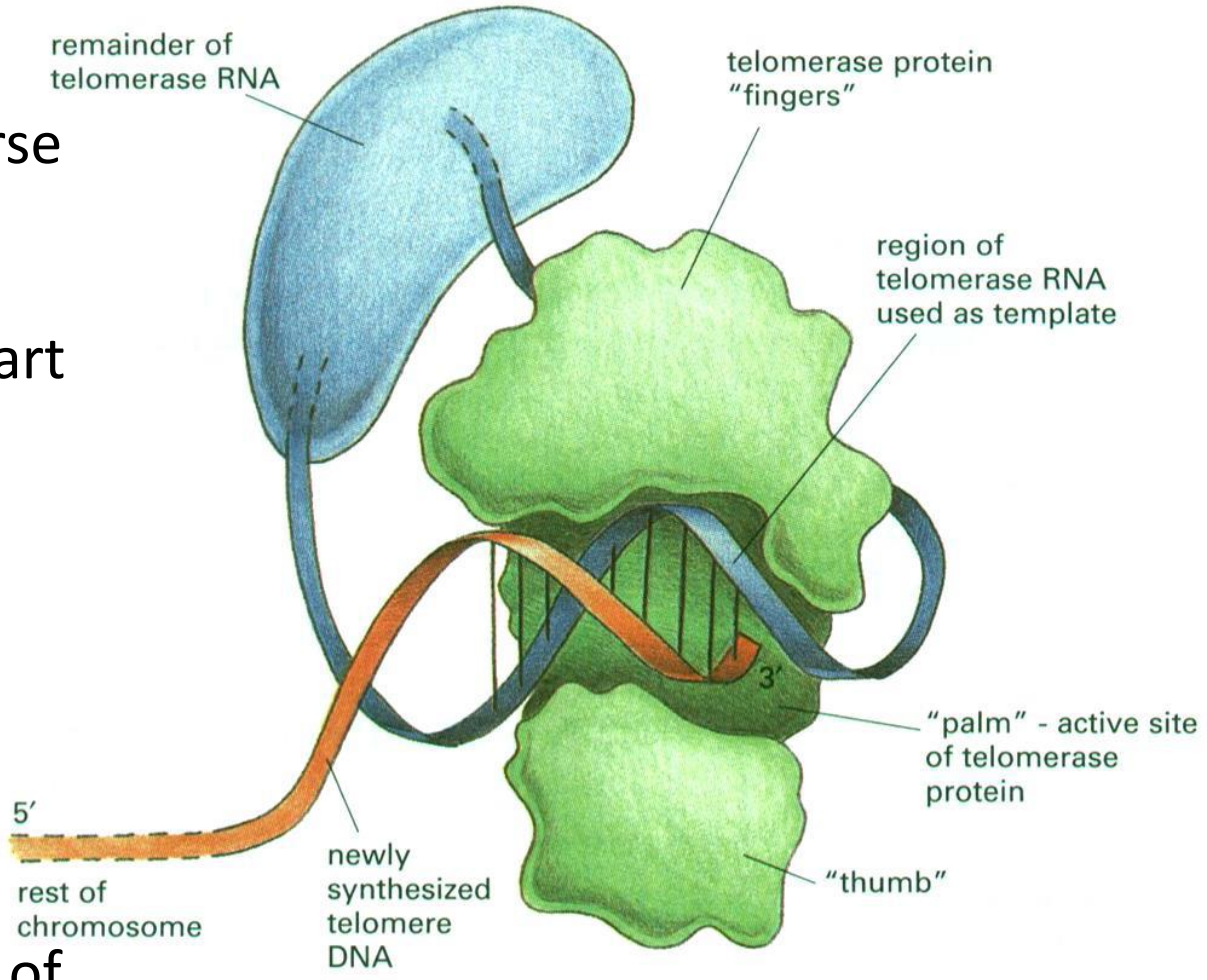




TELOMERASE

Telomerase

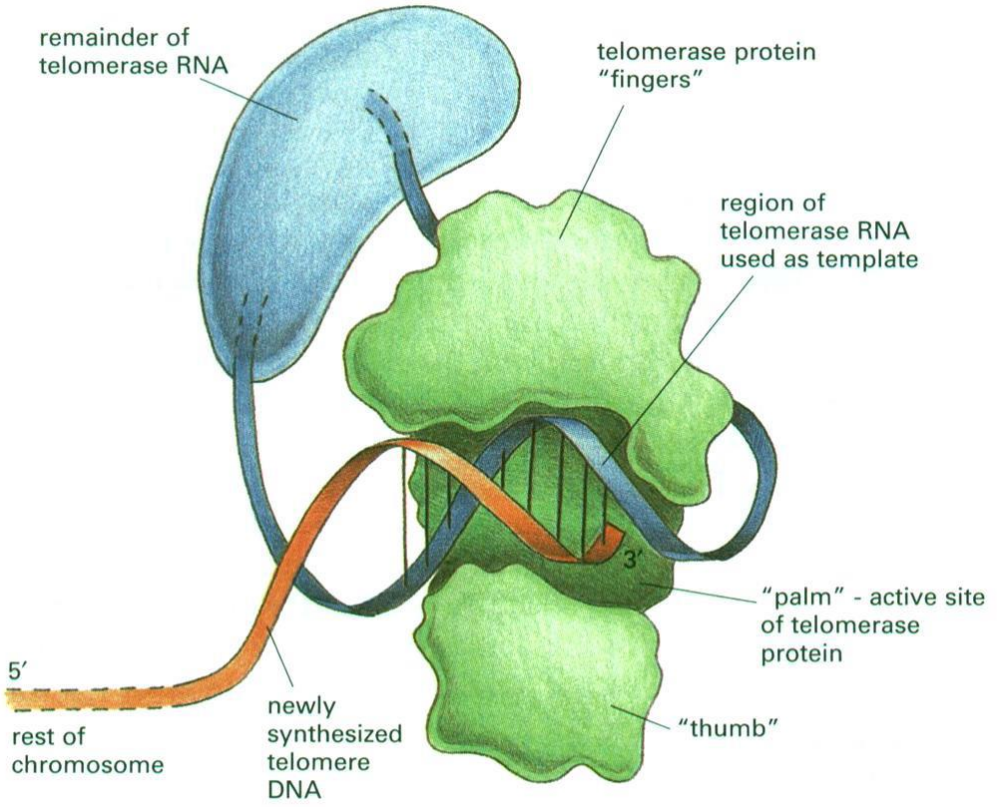
- Telomerase is a reverse transcriptase (TERT)
- Consists of protein part and telomerase RNA (template)
- RNA template is complementary with telomeric sequence repets
- Function: elongation of telomeres



Telomere replication

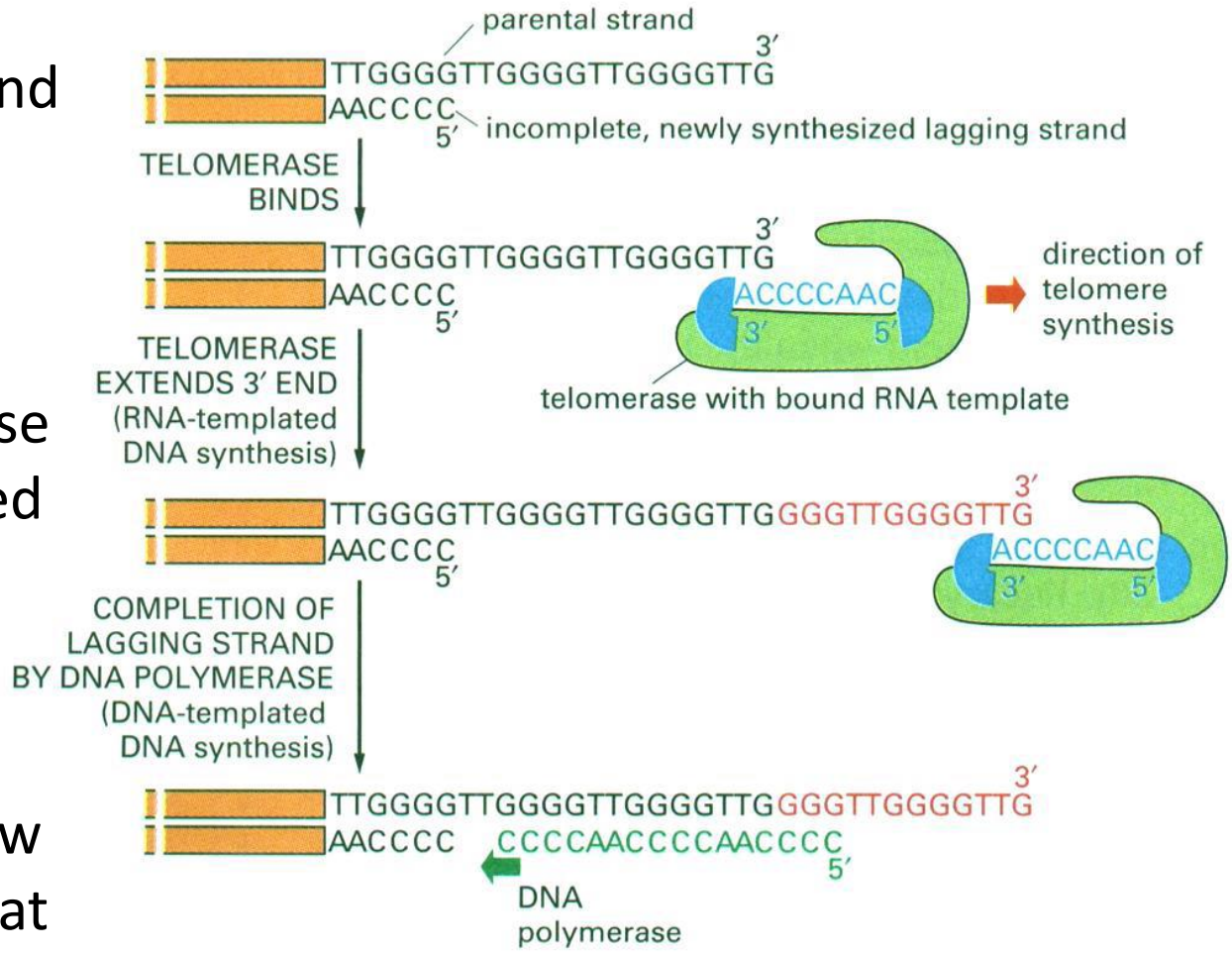
- In majoriti of somatic cells telomerase is inactive

- Telomerase is active in:
  - Sex cells (gametes)
  - Bone marrow cells
  - Stem cells
  - Tumor cells



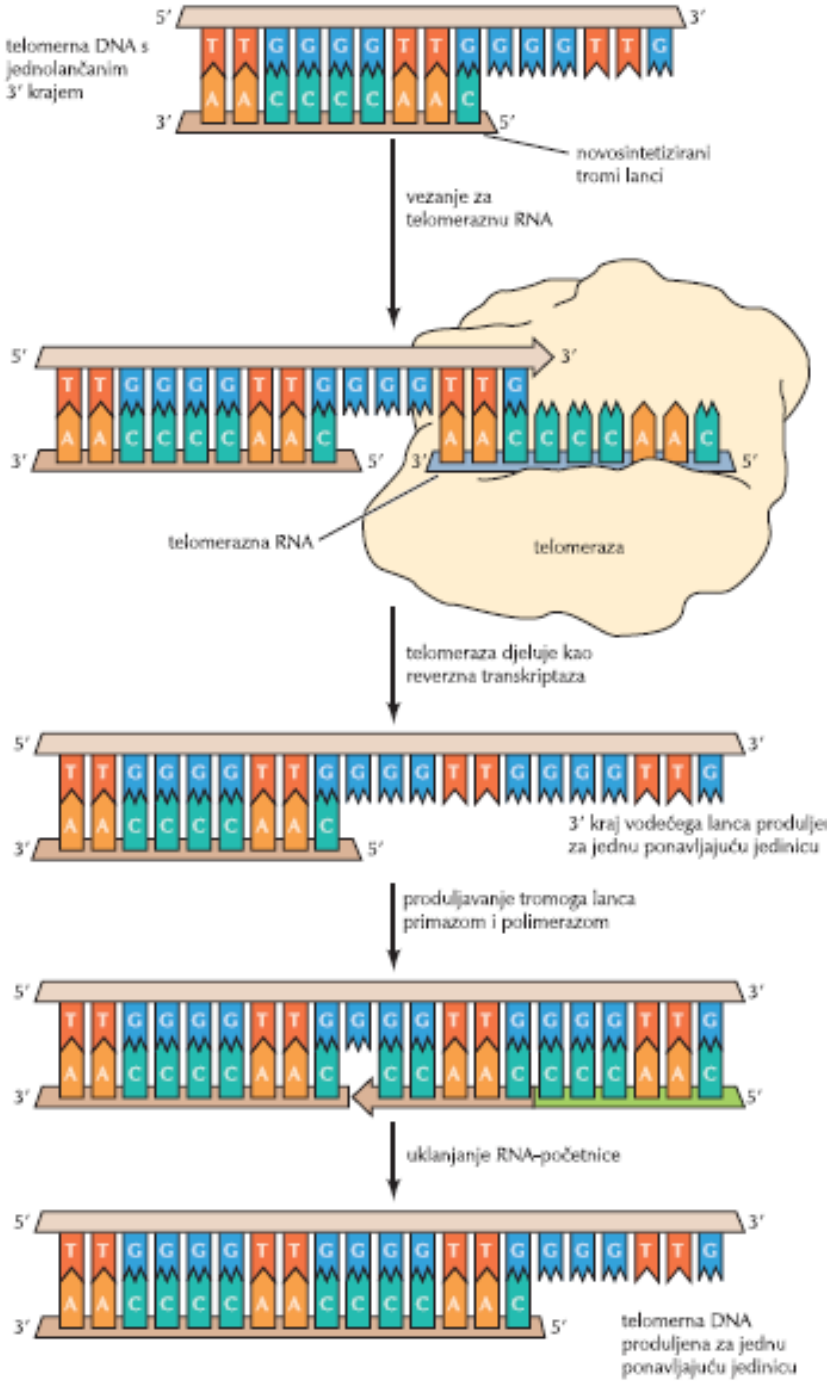
Telomere replication

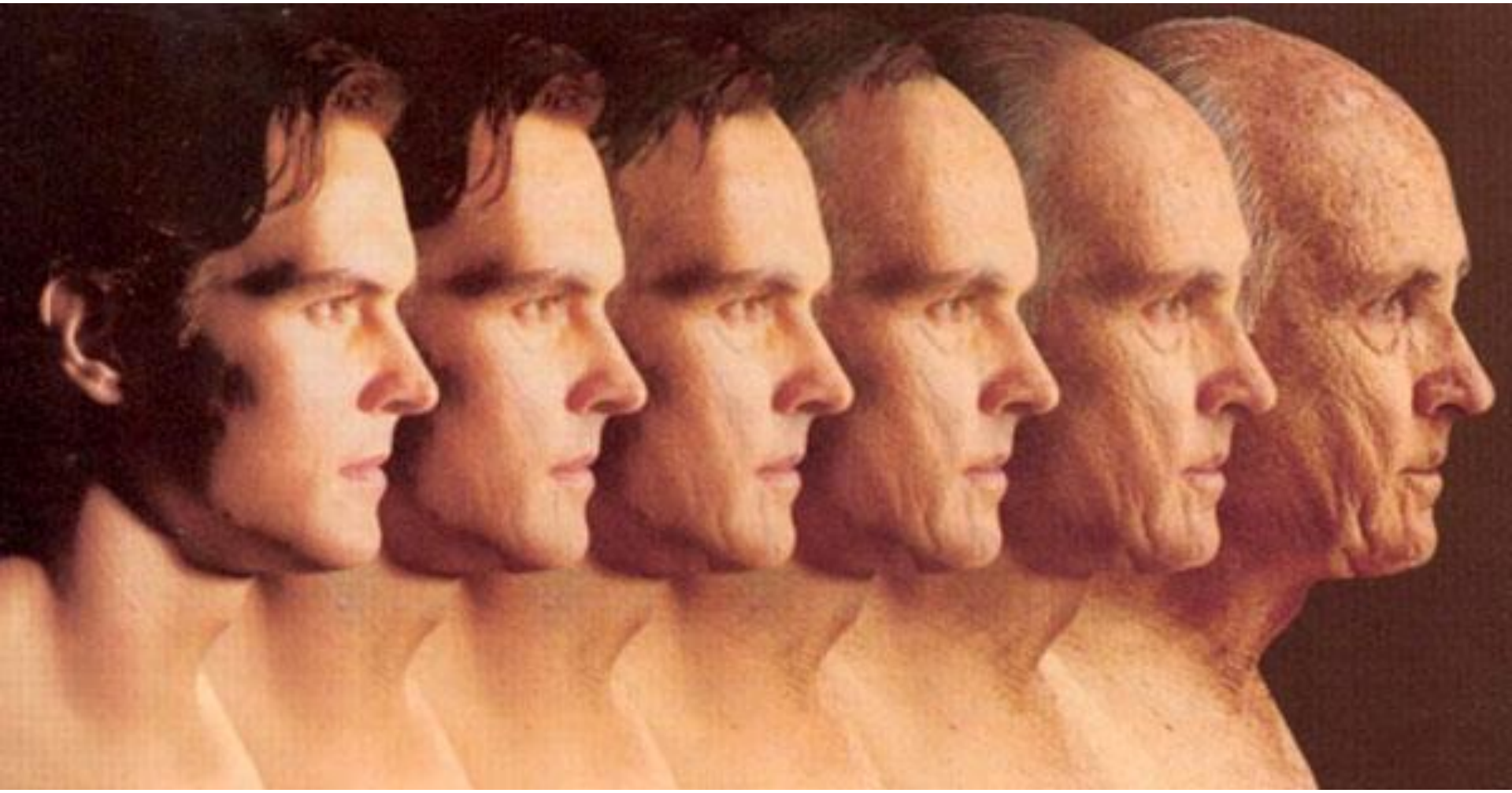
- Telomerase binds to longer 3’ end of chromosomes, with it’s RNA template, and further elongates 3’ end
- Now DNA polymerase can bind to elongated longer strand of chromosome
- DNA polymerase now elongates telomere at 5’ end (lagging strand)



Telomerase activity

At each cycle of telomerase activity, 6 nucleotides are added to the telomere:





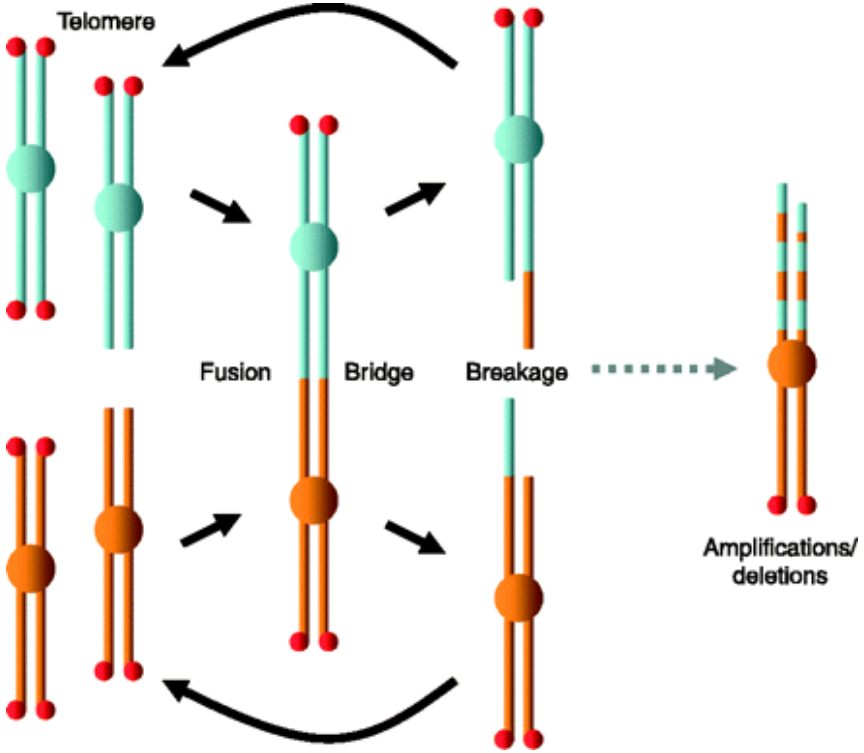
TELOMERE, CELL AGING AND CANCER

Telomeres and cell aging

- Hayflick limit (phenomenon) – a number of divisions before cell stops dividing
  - 40-60 in awerage, intercellular variability
  - Previous notion was that this number is unlimited
- Experiment: Hayflick and Moorhead mixed equal number of male fibroblasts (divided 40x) with female fibroblasts (divided 10x). Male cells stop dividing and mix culture only had female cells
- This is atributed to telomere shortening after every mitosis
- TELOMERES = biological clock of the cell

Telomerase and cancer

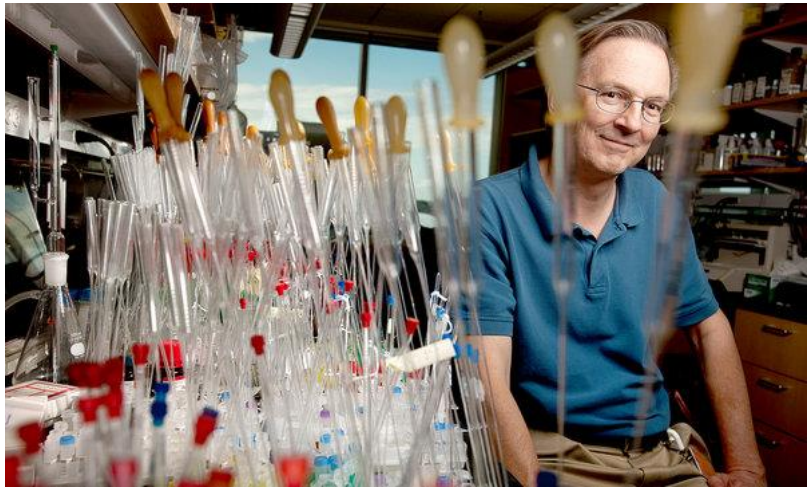
- Telomerase is active in many cancer cells
- Cancer cell imortalisation ⇒ telomeres do not become shorter
- Telomerase inhibitors – possible anti-cancer treatment
- Unfortunately, alternative mechanisms are activated in cancer cells:



Telomerase experiments

- "In vitro" experiment with human fibroblasts:
  - Cultured cells can divide up to 60 times
  - Culture than becomes old – quiescence state
  - By activation of telomerase in fibroblasts
    - Telomeres elongate
    - Fibroblasts divide unlimitedly (imortalised culture)
- "In vivo" experiment with C. elegans
  - By activating telomerase, old worm "rejuvenates"
- Popular name for telomerase is "Immortality enzyme"
- Diatery influence on telomeres and telomerase activity

Telomerase discovery – Nobel price 2009



Carol Greider,
Elizabeth Blackburn,
Jack Szostak