TELOMERI E COMPLESSI DEL TELOMERO

Telomeres are the terminal nucleoprotein structures located at the ends of eukaryotic chromosomes.

These structures function as

A guardians of genome stability by limiting unwanted DNA repair activity at chromosome ends, and in human cells,

B by controlling the total number of times a cell can divide, thereby limiting the accumulation of genomic instability in actively cycling cells

2015 -1260 pubblicazioni !!

Send to:

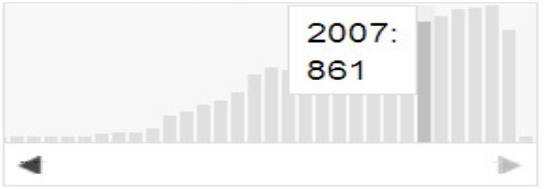
Results: 1 to 20 of 19058

<< First < Prev Page 1 of 705 Next > Last >>

1. **Telomere** length and LINE1 methylation is associated with chromosomal aberrations in peripheral blood.
   Li H, Hilmarsen HT, Hossain MB, Björk J, Hansteen IL, Albin M, Furu Skjelbred C, Broberg K.
   Genes Chromosomes Cancer. 2012 Sep 21. doi: 10.1002/gcc.22000. [Epub ahead of print]
   PMID: 22997064 [PubMed - as supplied by publisher]
   Related citations

2. Understanding the molecular pathways associated with seed vigor.
   Ventura L, Donà M, Macovei A, Carbonera D, Buttafava A, Mondoni A, Rossi G, Balestrazzi A.
   Plant Physiol Biochem. 2012 Sep 1;60C:196-206. doi: 10.1016/j.plaphy.2012.07.031. [Epub ahead of print]

Results by year

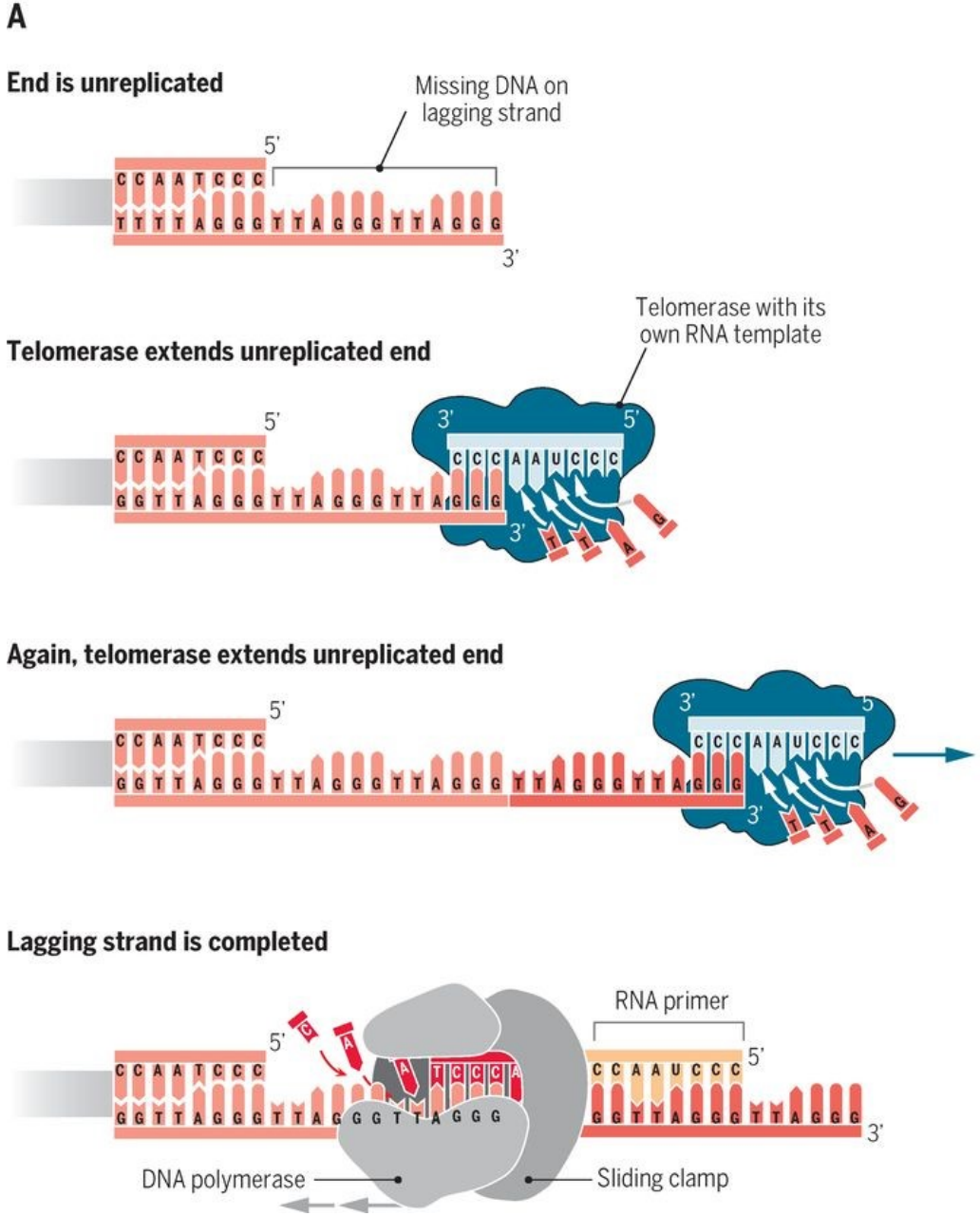


Related searches

- **telomere** shortening
- **telomere** dysfunction
- **telomere** review
- **telomere** aging
- **telomere** cancer

PMC Images search for telomere

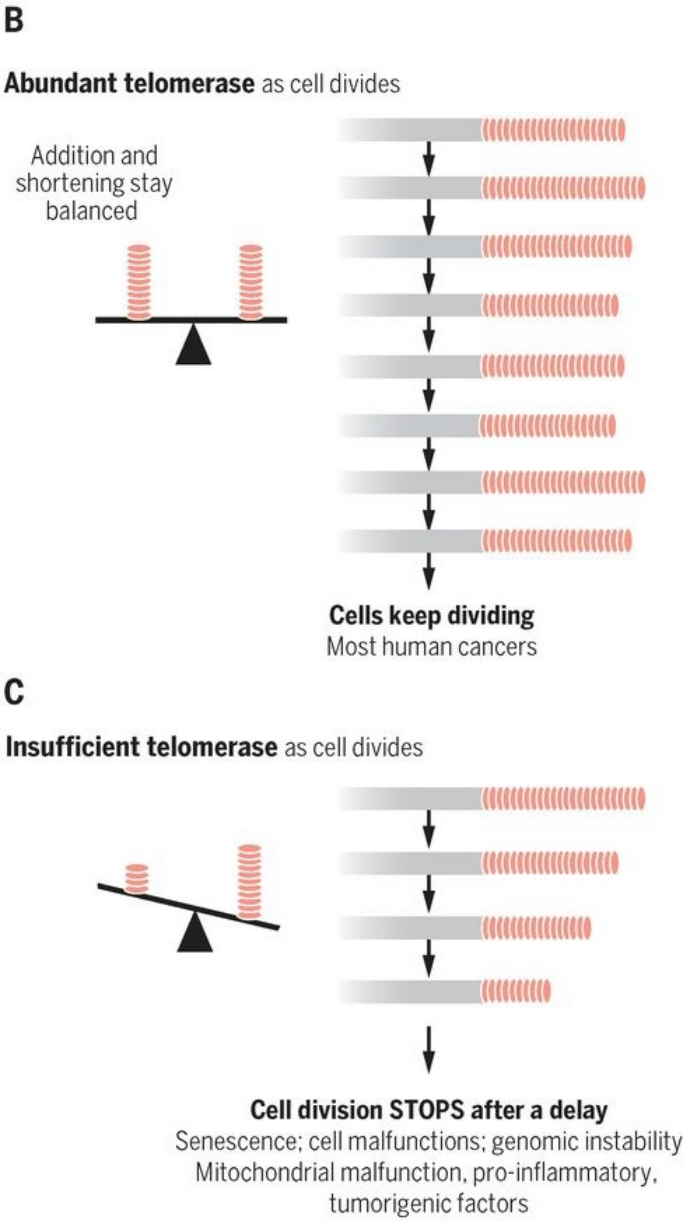
Long-term maintenance of telomeric DNA length requires telomerase.



Published by AAAS

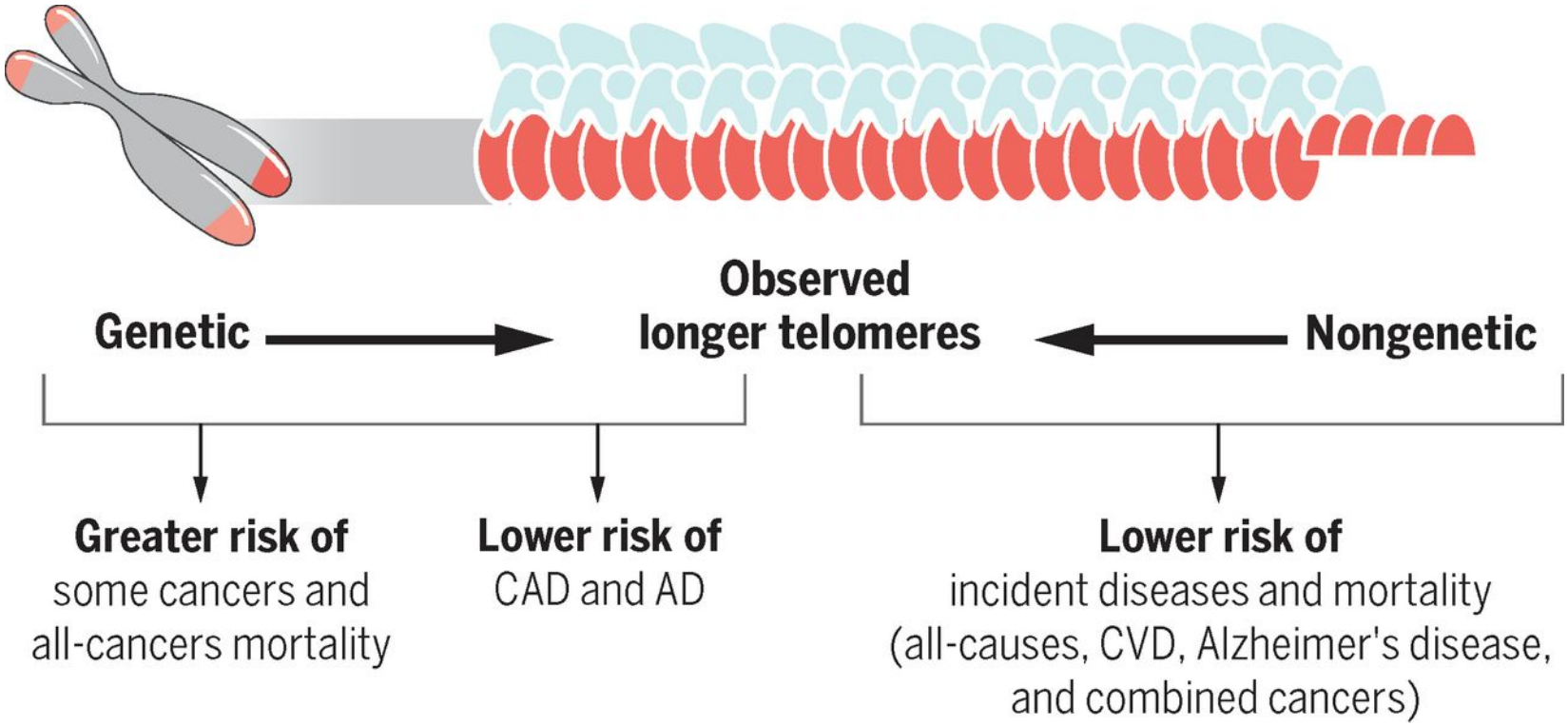
Elizabeth H. Blackburn et al. Science 2015;350:1193-1198

Long-term maintenance of telomeric DNA length requires telomerase.



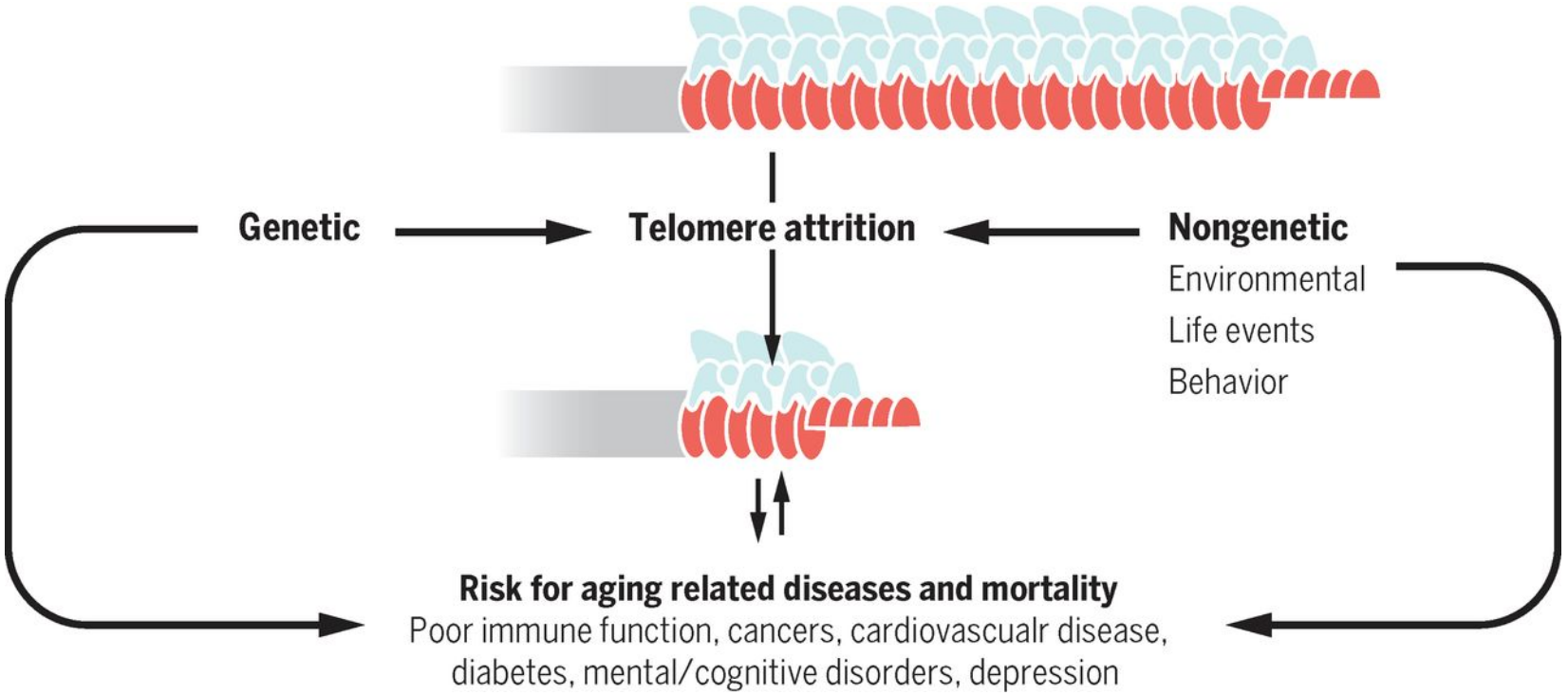
Published by AAAS **Elizabeth H. Blackburn et al. Science 2015;350:1193-1198**

Different inputs to telomere maintenance have disease-specific consequences.



Elizabeth H. Blackburn et al. Science 2015;350:1193-1198

Relationship of telomere attrition to human aging-related diseases.



Elizabeth H. Blackburn et al. Science 2015;350:1193-1198

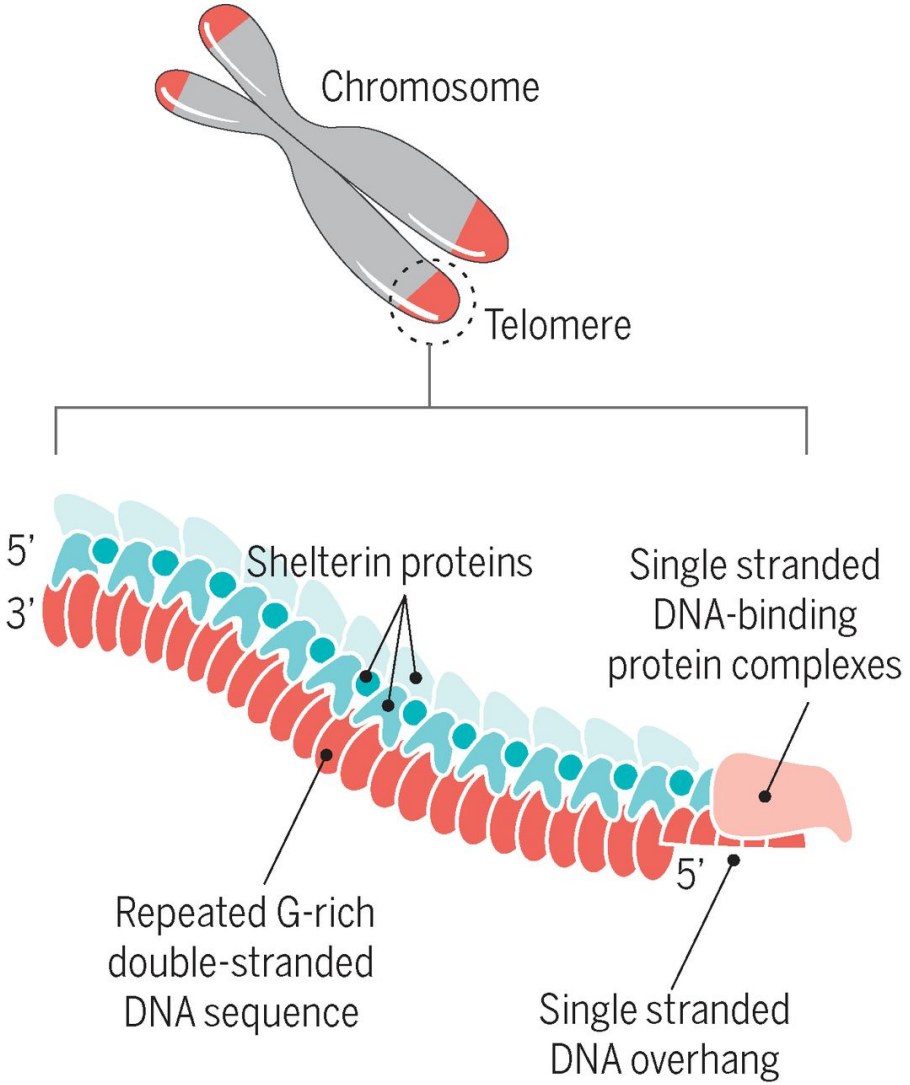
IL DNA Telomerico e le sue strutture alternative

SEQUENZA TELOMERICA

5–15 kb in humans, ~48 kb in mice

Watson et al., BIOLOGIA MOLECOLARE DEL GENE, Zanichelli editore S.p.A.

Telomere general structure.

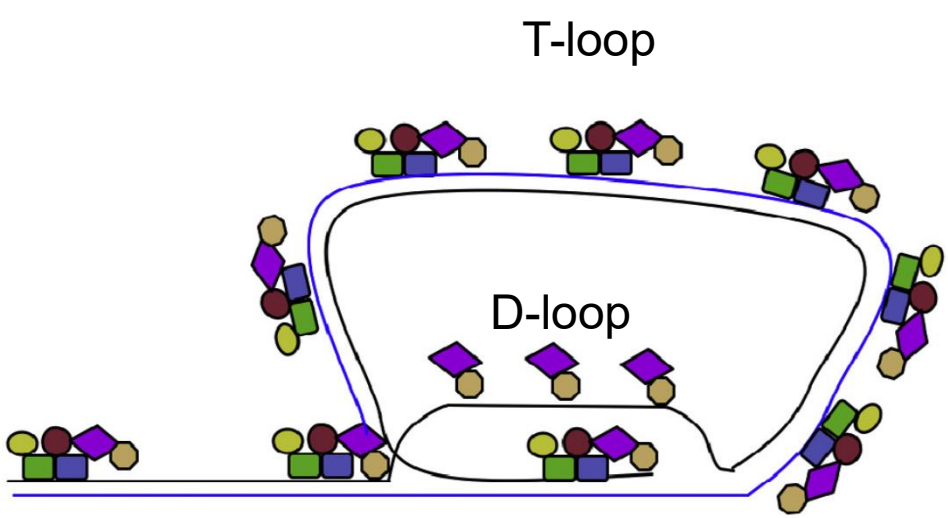


Elizabeth H. Blackburn et al. Science 2015;350:1193-1198

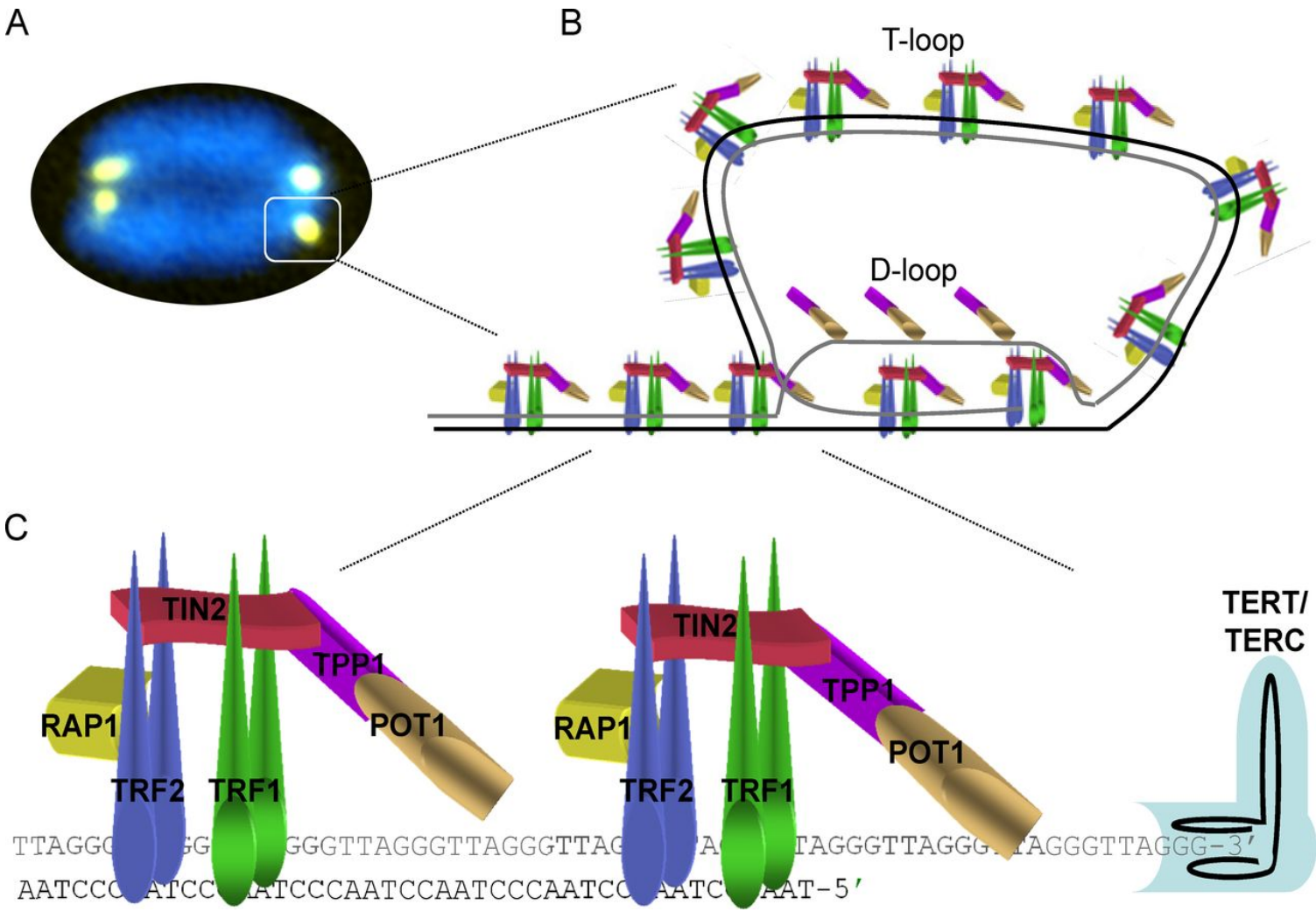
The single-stranded 3′ overhang folds back into the telomeric DNA, invades the double-helix, and anneals with the C-rich strand, forming a loop known as T-loop, thus hiding the very ends of chromosomal DNA.

TTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGG-3′

AATCCCAATCCCAATCCCAATCCAATCCCAATCCCAATCCCAATC-5′



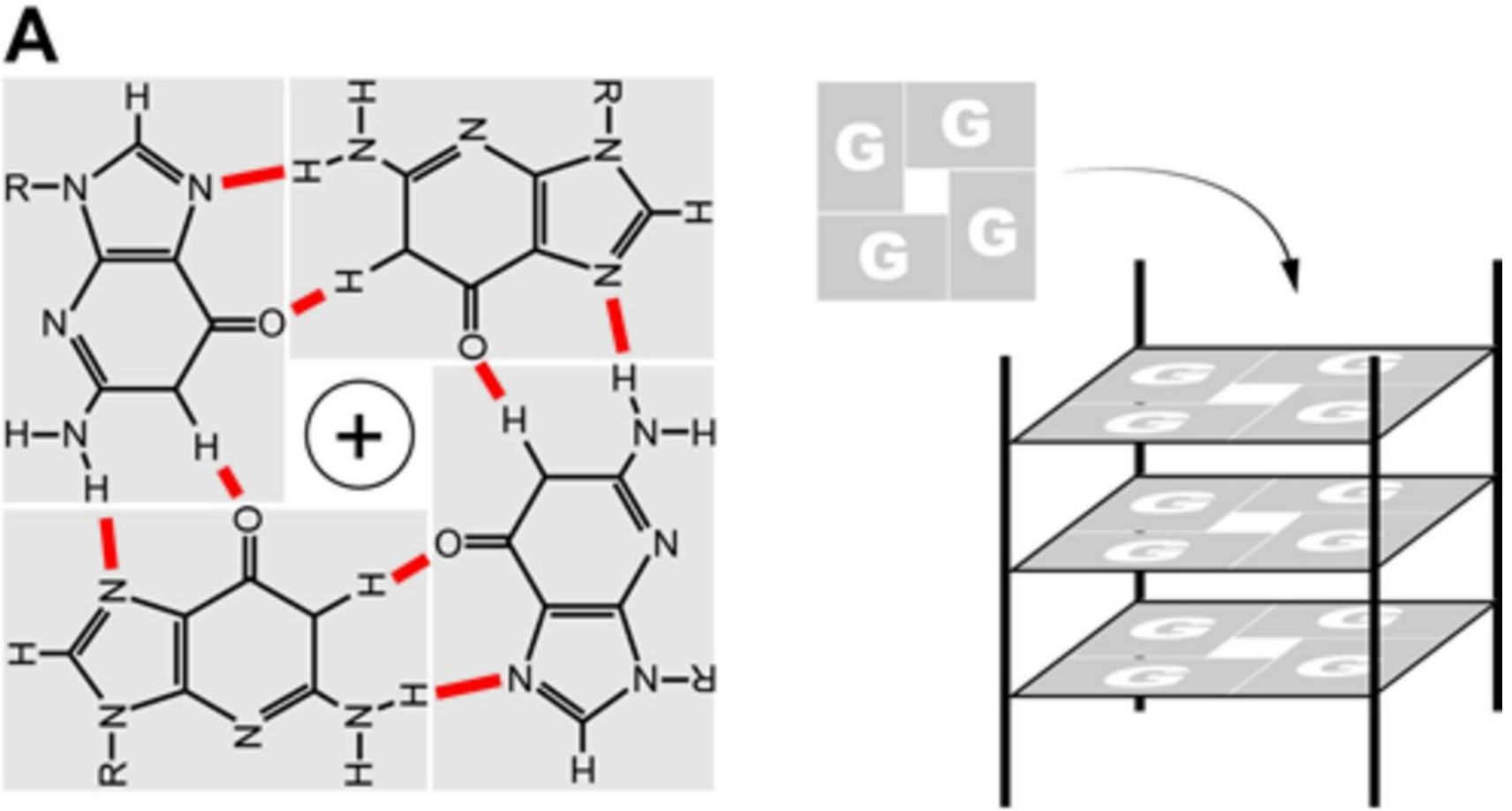
The shelterin complex and the structure of telomeres.



Paula Martínez, and Maria A. Blasco J Cell Biol
doi:10.1083/jcb.201610111

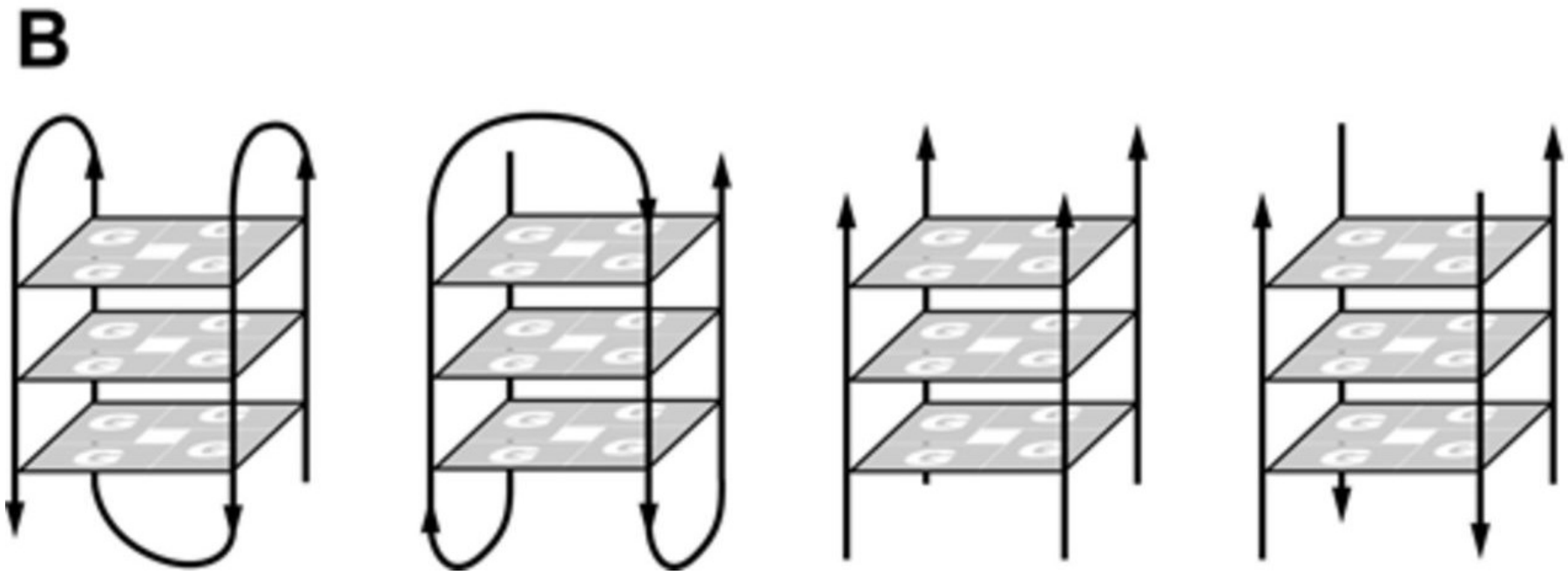
JCB

Structure of G-quadruplexes.



Daniela Rhodes, and Hans J. Lipps Nucl. Acids Res. 2015;nar.gkv862

Structure of G-quadruplexes.

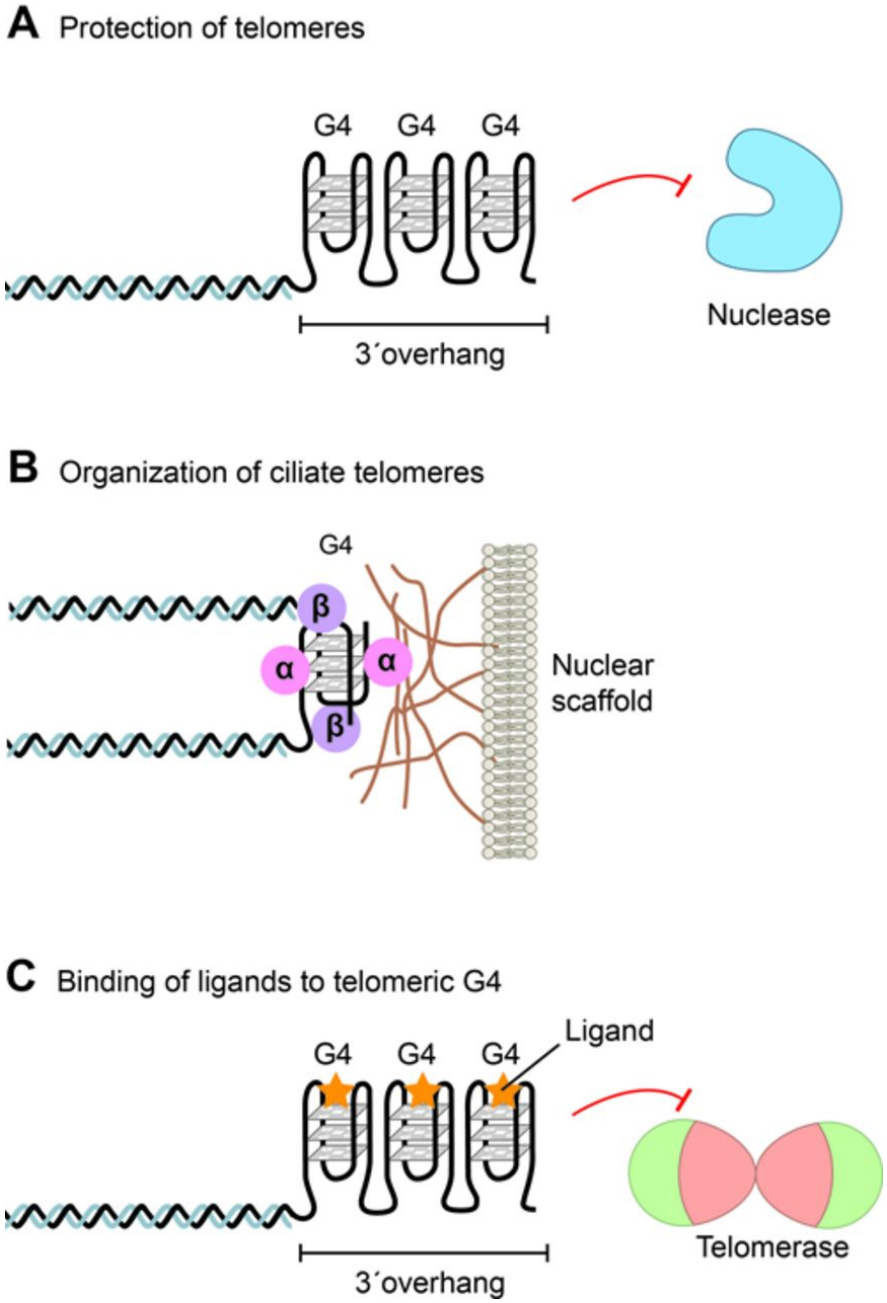


Daniela Rhodes, and Hans J. Lipps Nucl. Acids Res. 2015;nar.gkv862

G-quadruplexes at telomeres.

G-quadruplex structures involving two telomeres promoted by the telomere-end binding protein TEBPβ

G-quadruplexes binding ligands (yellow stars) impairs telomere repeat synthesis by the telomerase enzyme and lead to telomere shortening



Daniela Rhodes, and Hans J. Lipps Nucl. Acids Res. 2015;nar.gkv862

G-quadruplexes at telomeres?

For human telomeres, the first indication that G-quadruplexes may be present came from the observation that G-quadruplex stabilizing ligands impaired telomere metabolism and lead to telomere shortening

A number of G-quadruplex stabilizing ligands are now available and it has become evident that many do not target the telomerase enzyme but the telomere itself

A structure-specific antibody against human G-quadruplexes detect signals at the ends of chromosomes, albeit not all ends.

A number of helicases that are known to unwind G-quadruplex in vitro (such as WRN) localize at telomeres. WRN is required for telomere integrity and physically interacts with the critical telomere binding proteins TRF2 and POT1.
This suggests that G-quadruplexes form at telomeres and if not resolved result in DNA damage.

The resolution of light microscopy is insufficiently high to decipher whether binding occurred at the very end of the chromosome or at subtelomeric regions

whether G-quadruplexes are present at human telomeres remains to be established.

Daniela Rhodes and Hans J. Lipps Nucl. Acids Res. 2015;nar.gkv862

La cromatina telomerica e la sua modificazione

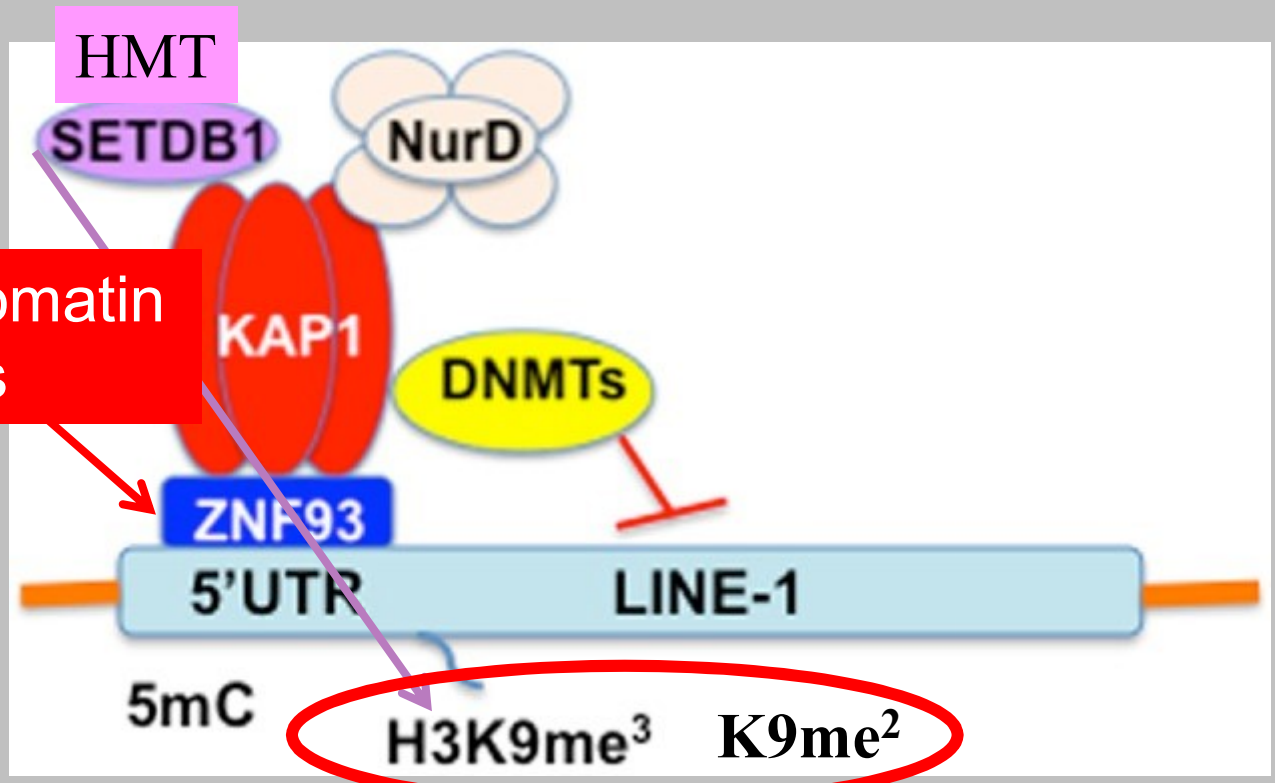
Telomeres also bind to nucleosomes, which are rich in modified histones.

Major histone modifications *found in telomeres are*

*-H3K9 and H4K20 trimethylatio*n

-low abundance of acetylated H3 and H4

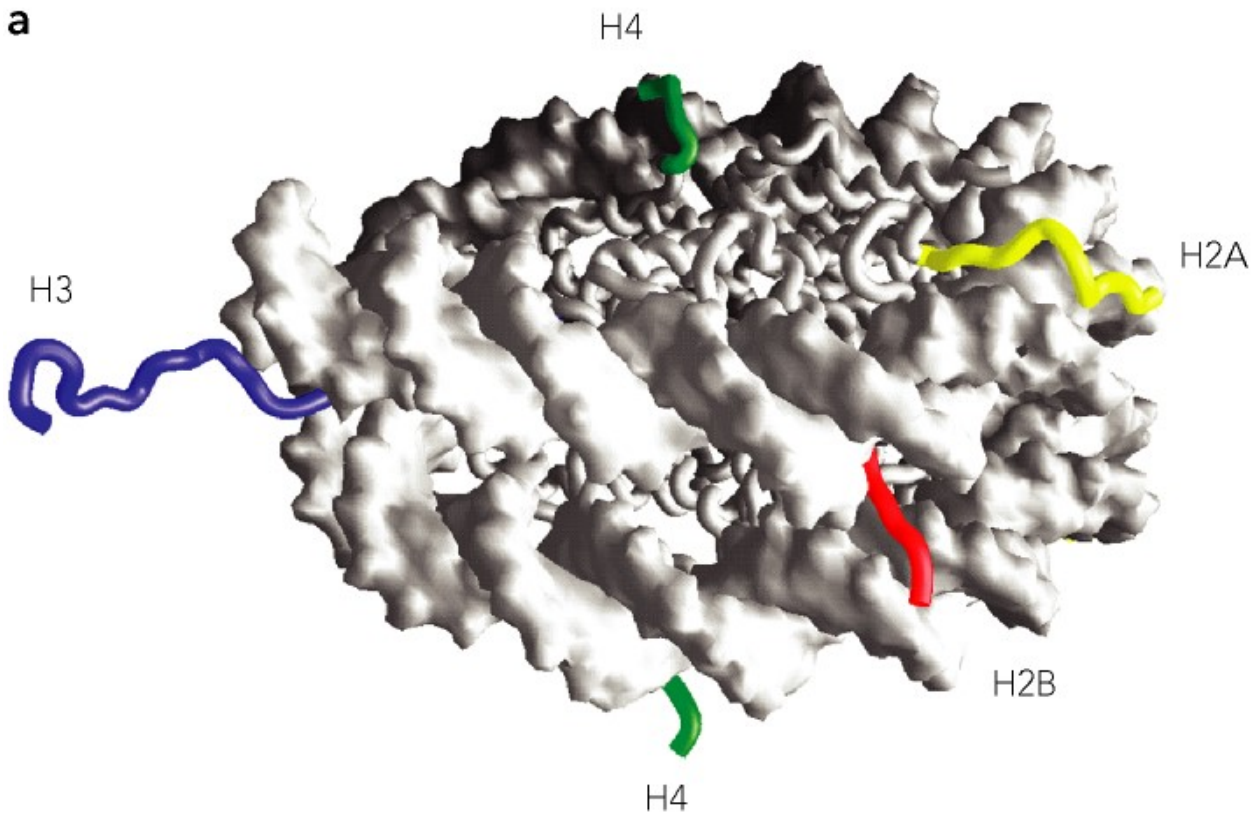
Negative Control of the transcriptional activity of L1 in ES cells



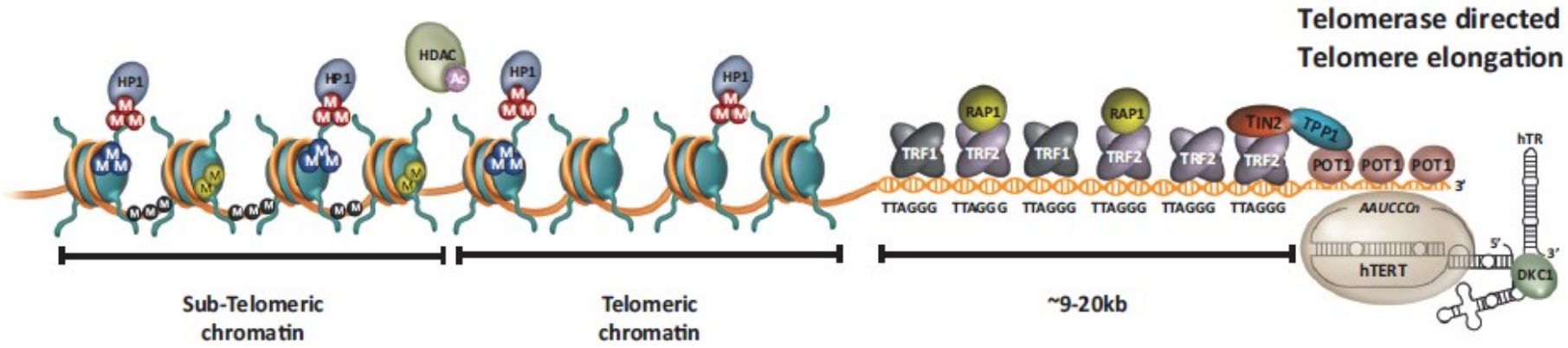
heterochromatin complexes

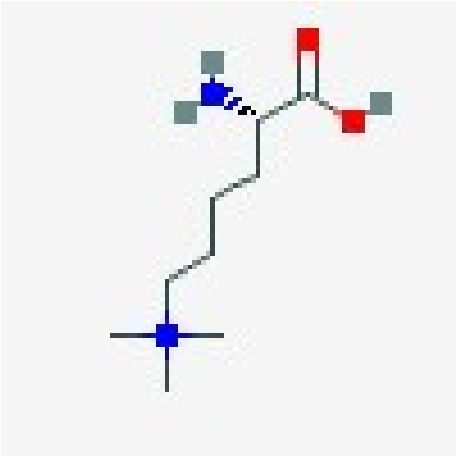
Riconoscimento

HMT istone metiltransferasi

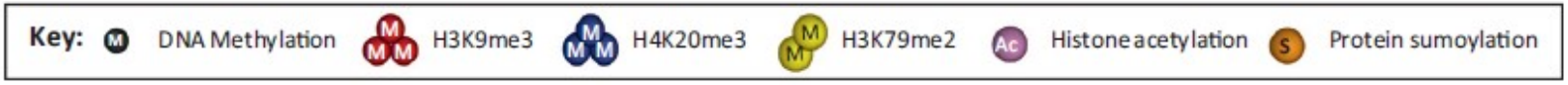


Telomeres in germ and stem cells





Kme3 =trimetillisina



Riconoscimento acetilisina bromodominio

Un enzima deacitilante specifico: SIRT6

SIRT6 is a histone H3 lysine 9 deacetylase that modulates telomeric chromatin

The Sir2 deacetylase regulates chromatin silencing and lifespan in Saccharomyces cerevisiae.

In mice, deficiency for the Sir2 family member SIRT6 leads to a shortened lifespan and a premature ageing-like phenotype.

SIRT6 is a chromatin-associated NAD+-dependent, histone H3 lysine 9 (H3K9) deacetylase that modulates telomeric chromatin.

SIRT6 is a histone H3 lysine 9 deacetylase that modulates telomeric chromatin

SIRT6 associates specifically with telomeres, and SIRT6 depletion leads totelomere dysfunction with end-to-end chromosomal fusions and premature cellular senescence. Moreover, SIRT6-depleted cells exhibit abnormal telomere structures

We propose that SIRT6 contributes to the propagation of a specialized chromatin state at mammalian telomeres, which in turn is required for proper telomere metabolism and function.

Our findings link chromatin regulation by SIRT6 to telomere maintenance and a human premature ageing syndrome

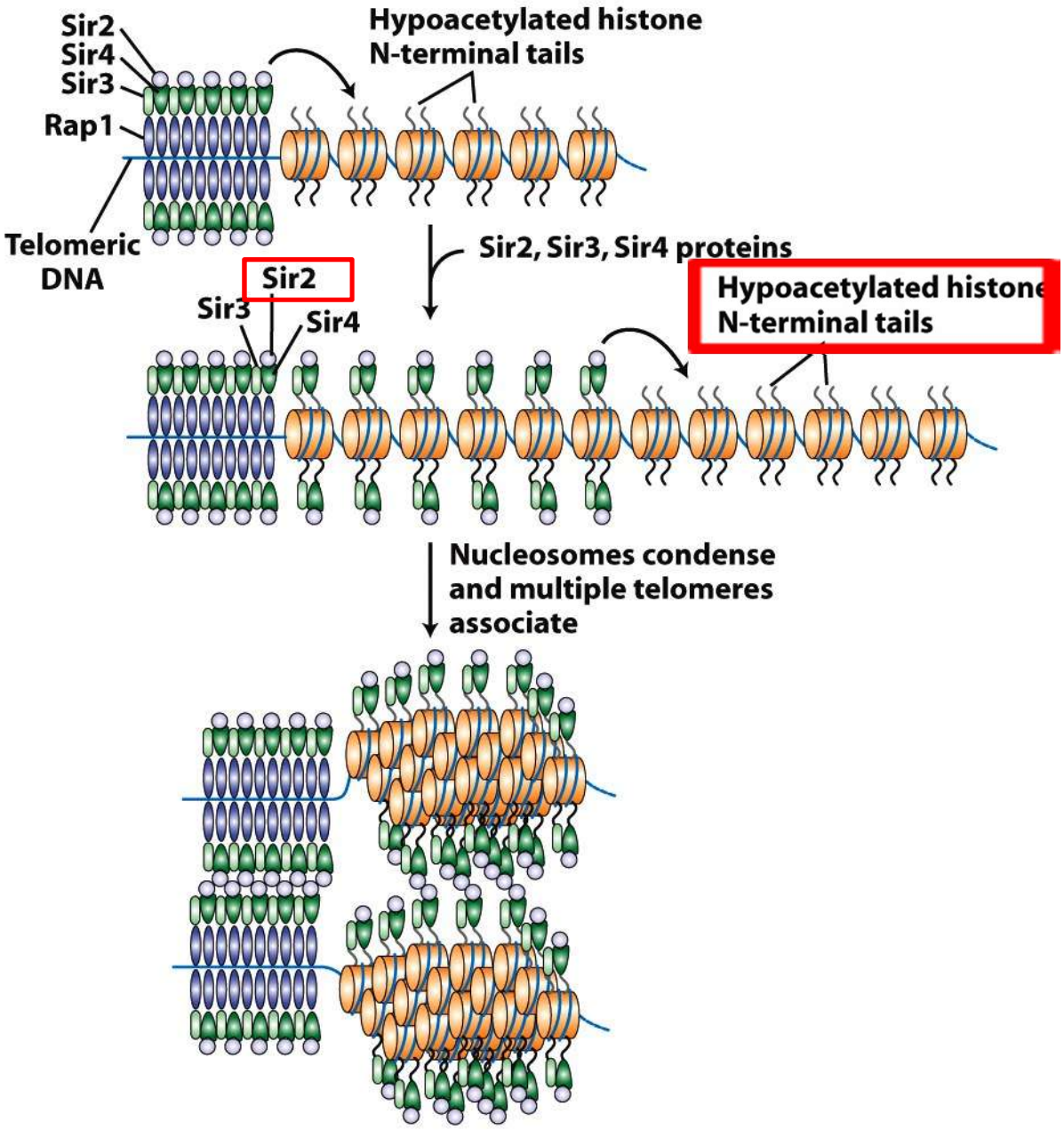
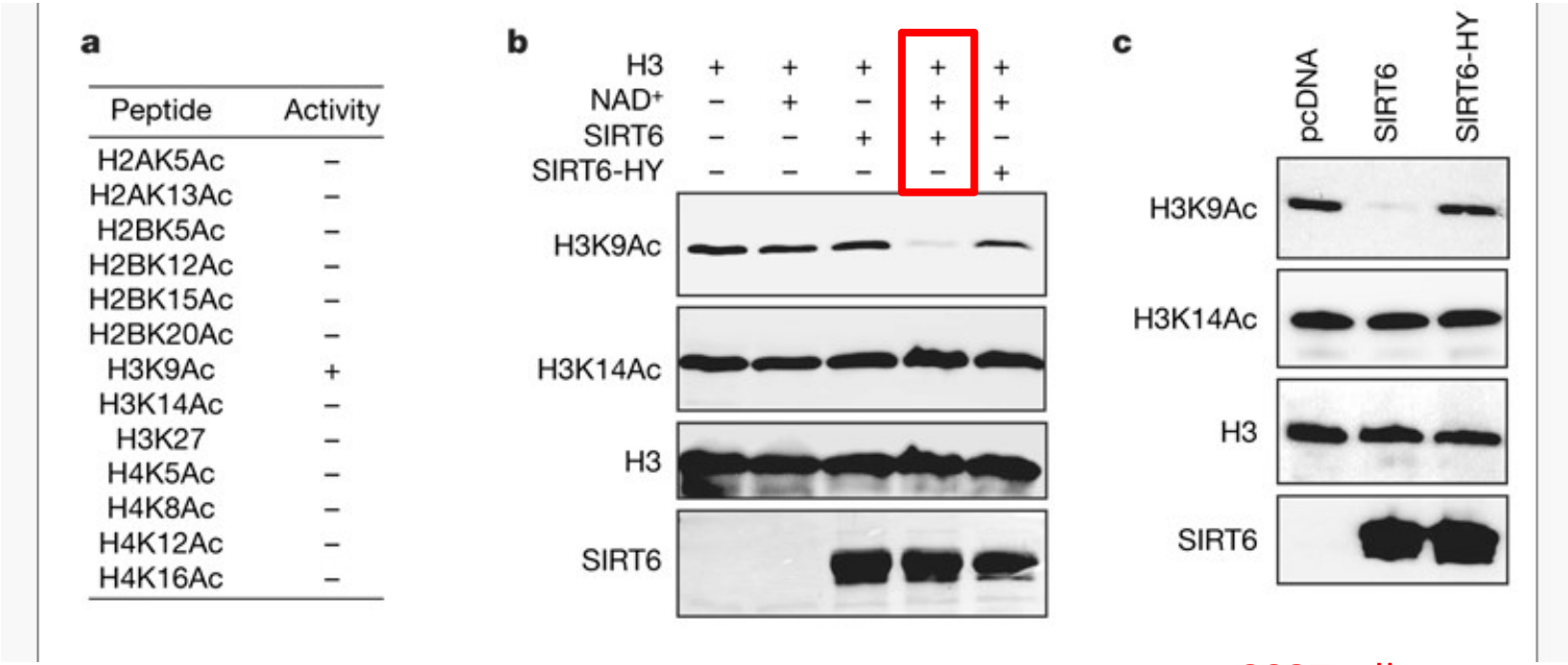


Figure 7-35
Molecular Cell Biology, Sixth Edition

SIRT6 (sir 2) deacetylates lysine 9 of histone H3 at telomeric chromatin



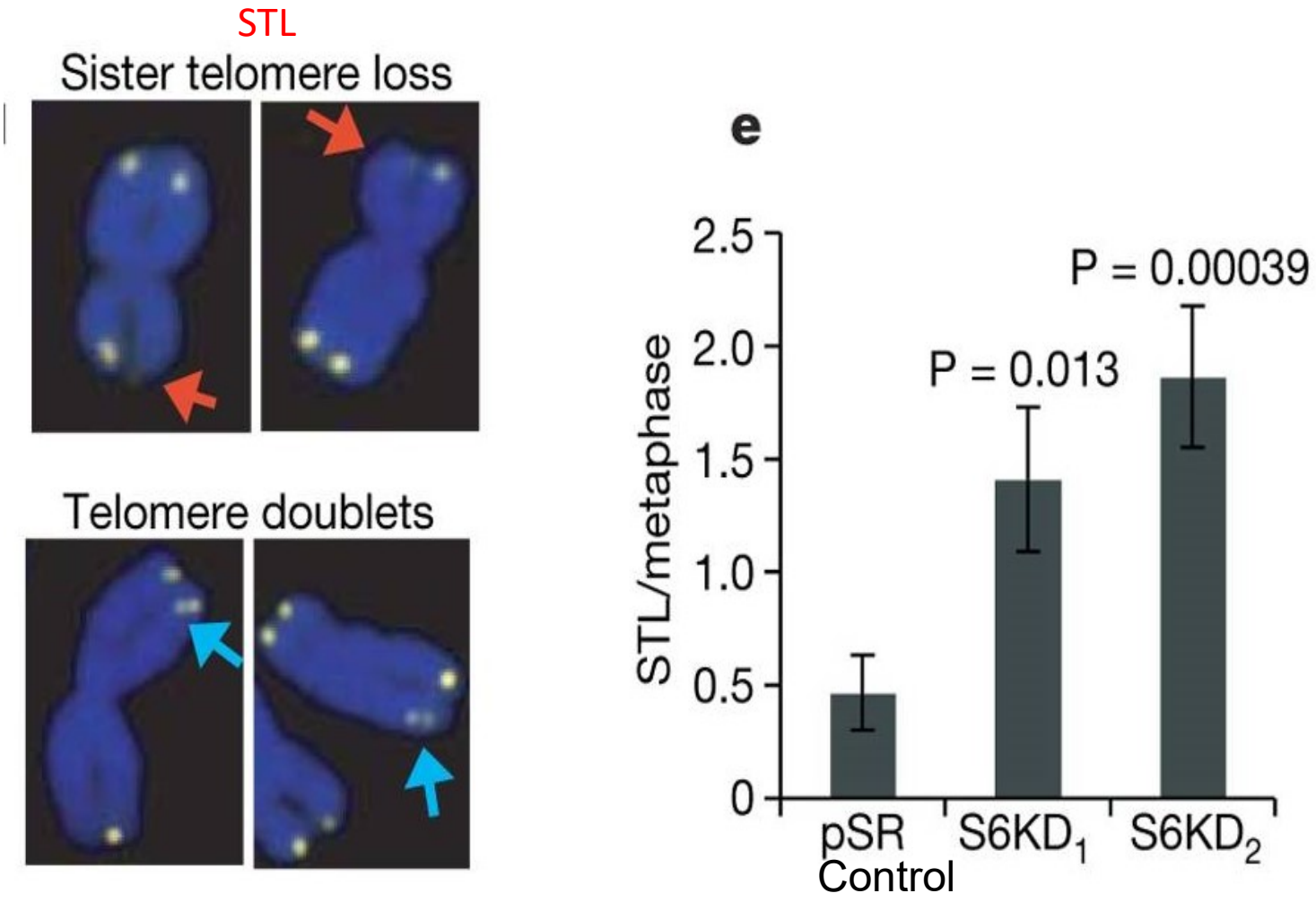
histone tail peptides

full-length histone H3

293Tcells overexpressing SIRT6

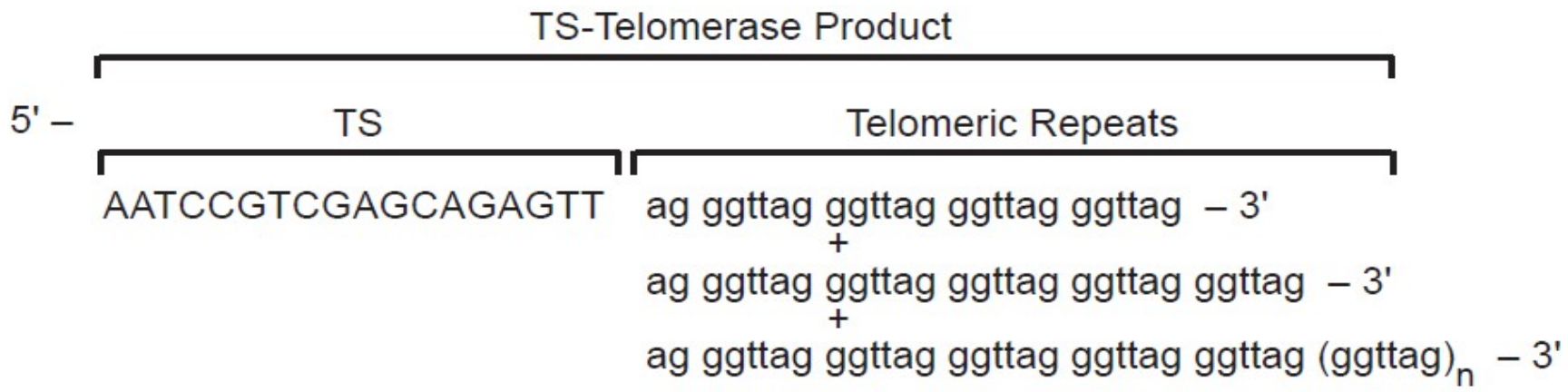
SIRT6-HY: *catalytic H133Y SIRT6 mutant protein*

SIRT6 knockdown (S6KD) cells

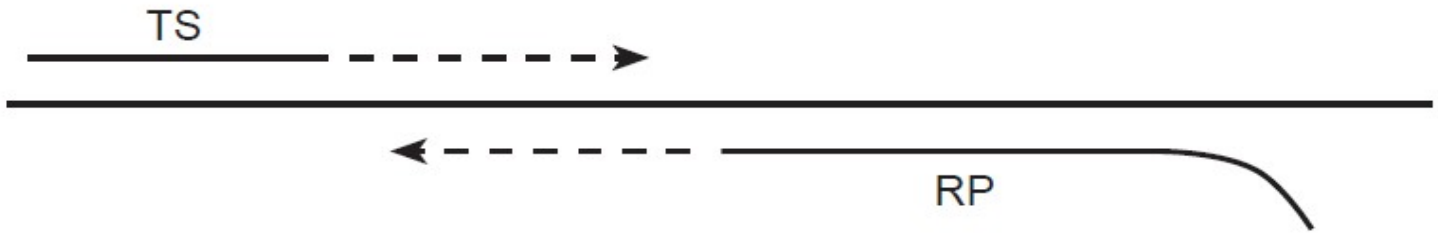


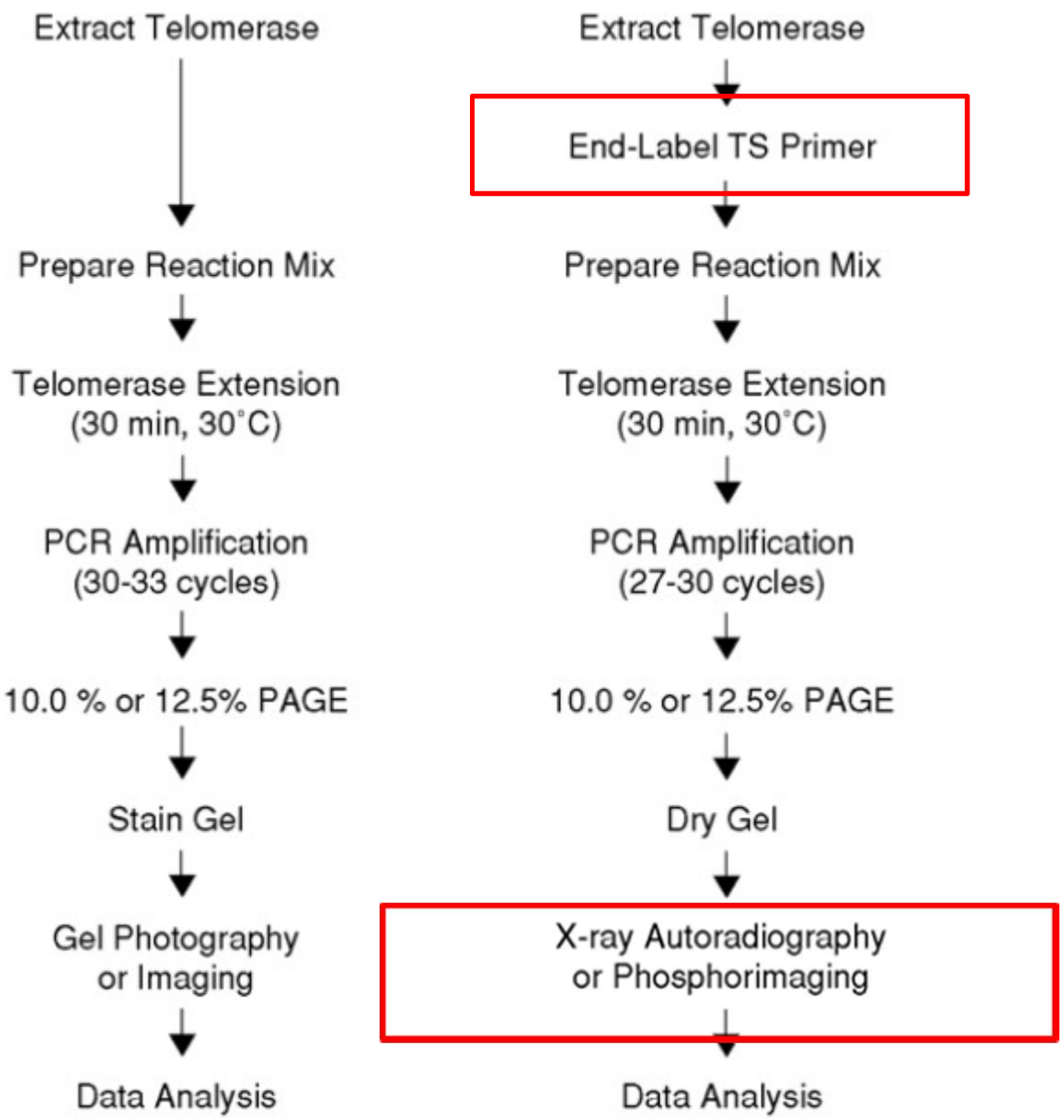
d, Representative S6KD metaphases showing aberrant telomere signals. Red arrows, sister telomere loss; blue arrows, telomere doublets. e, Quantification of sister telomere loss

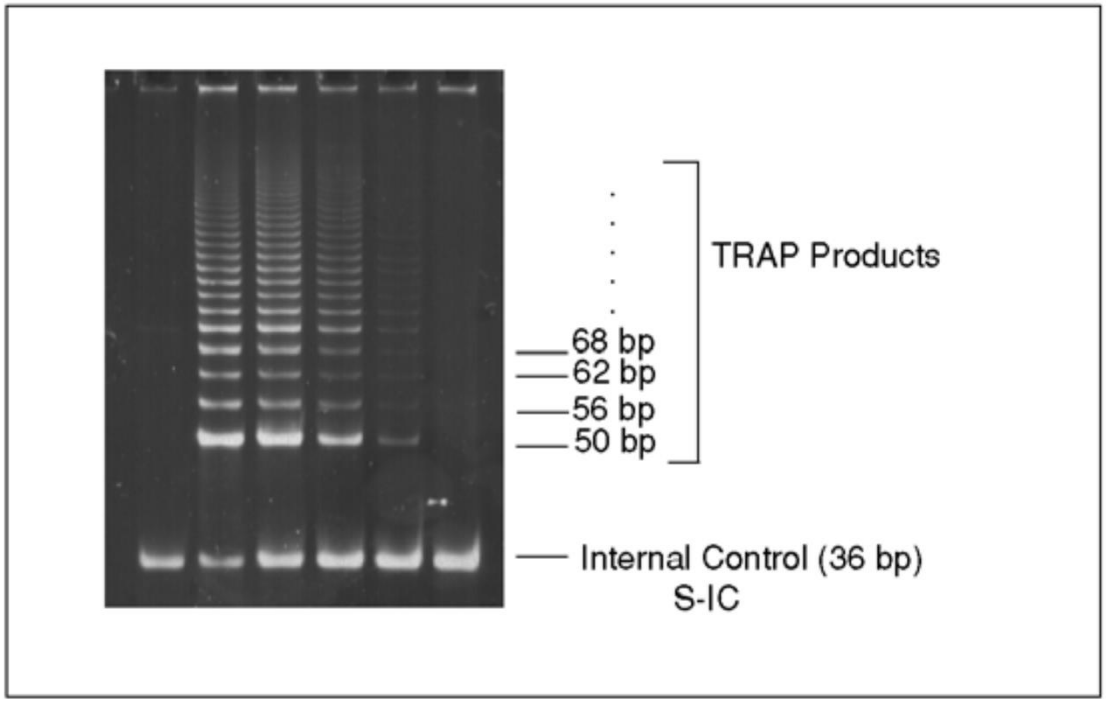
Metodi per lo studio dell’attività telomerasica



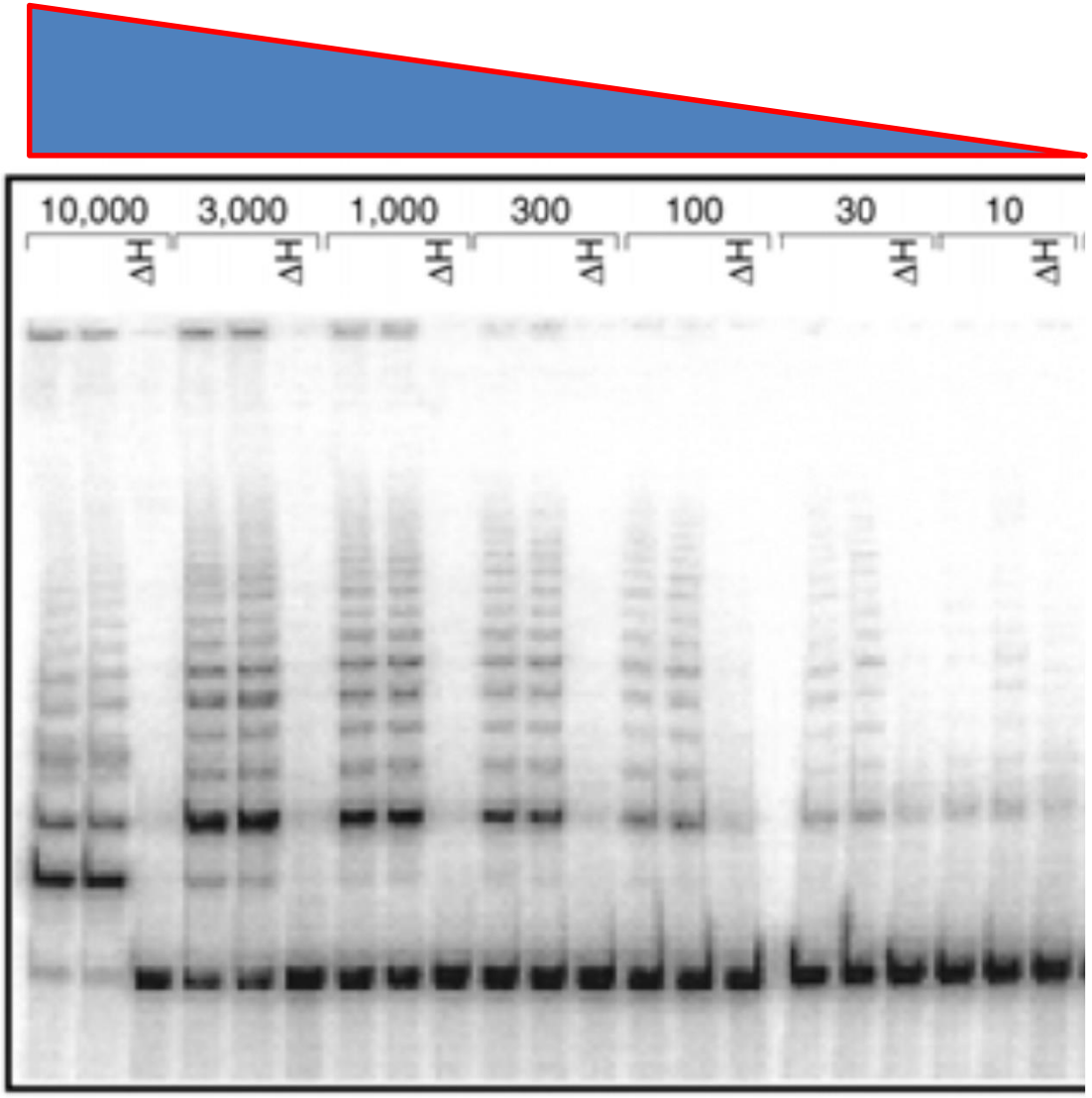
STEP 2. Amplification of TS-Telomerase Product By PCR




Extract Telomerase
Prepare Reaction Mix
Telomerase Extension
(30 min, 30˚C)
PCR Amplification
(30-33 cycles)
10.0 % or 12.5% PAGE
Stain Gel
Gel Photography
or Imaging
Data Analysis
Extract Telomerase
End-Label TS Primer
Prepare Reaction Mix
Telomerase Extension
(30 min, 30˚C)
PCR Amplification
(27-30 cycles)
10.0 % or 12.5% PAGE
Dry Gel
X-ray Autoradiography
or Phosphorimaging
Data Analysis

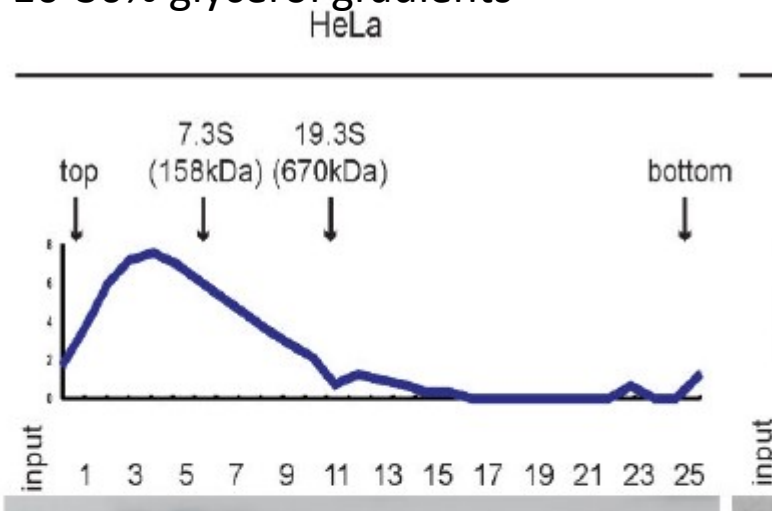


Telomeric Repeat Amplification Protocol

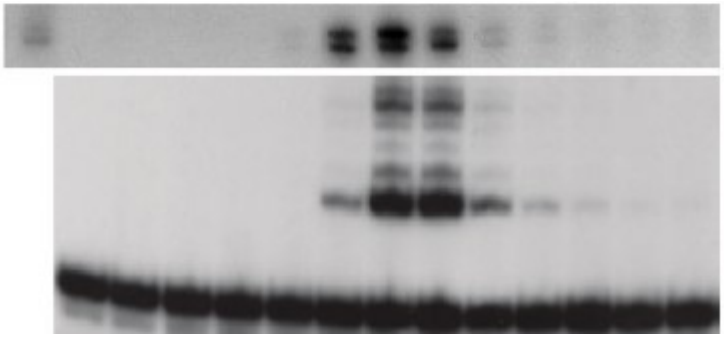

10,000
3,000
1,000
300
100
30
10
ΔH
ΔH
ΔH
ΔH
ΔH
ΔH
ΔH

COMPLESSI TELOMERICI

10-30% glycerol gradients



Total protein



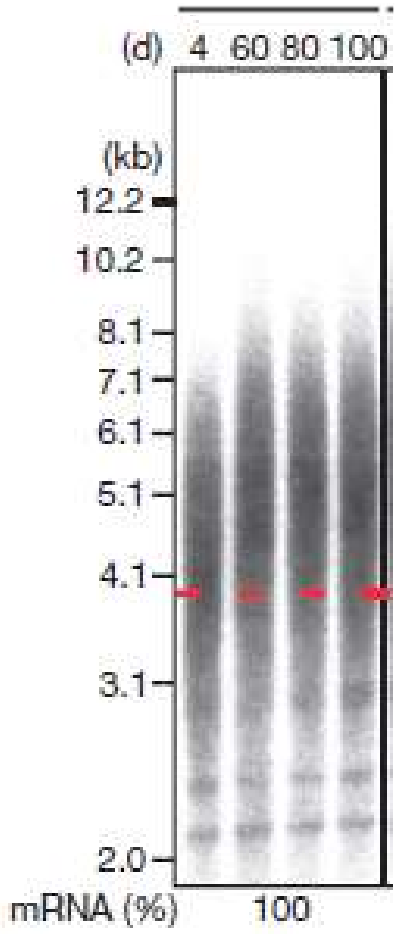
NB: TERC

TRAP

Telomeric Repeat Amplification Protocol

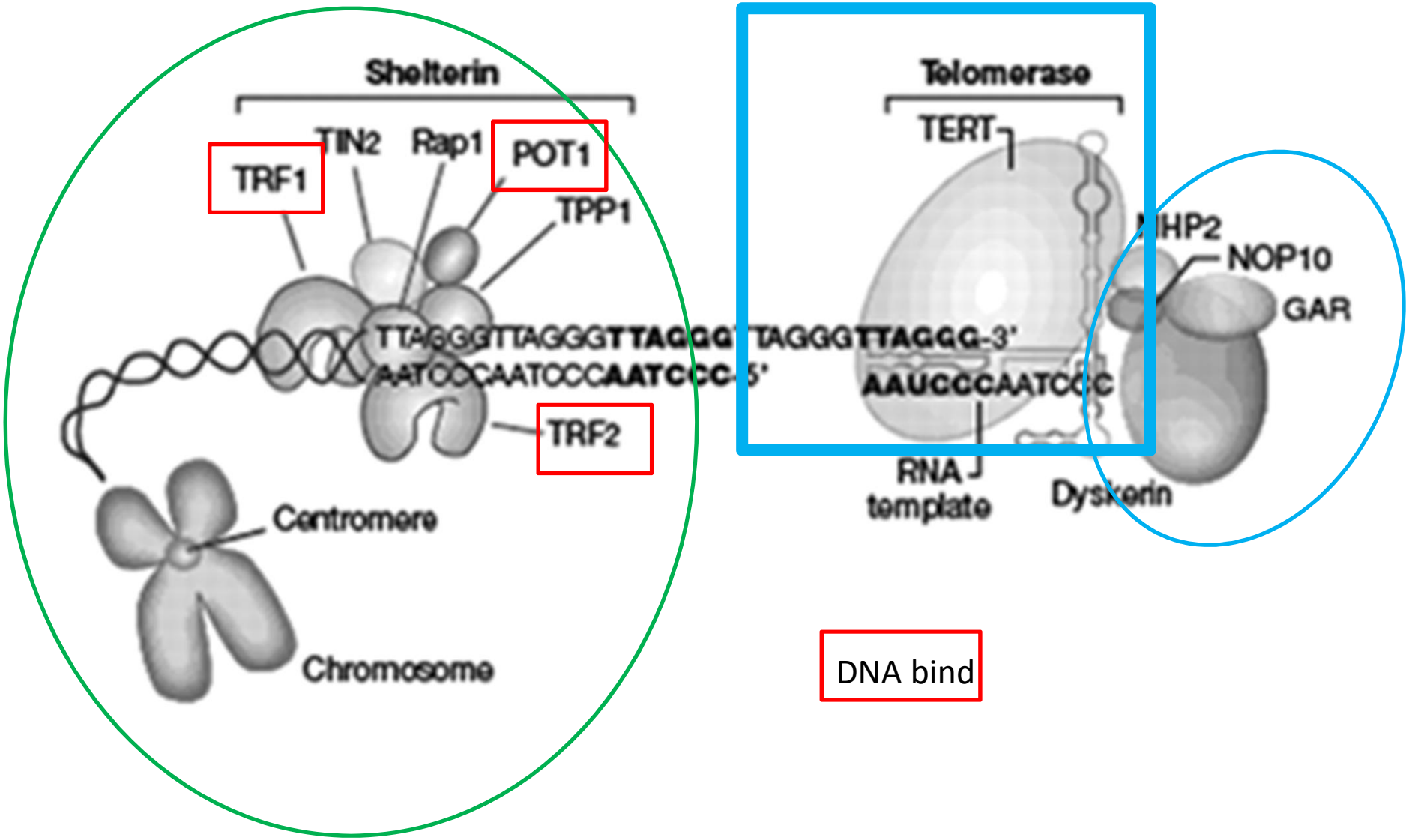
Metodi per lo studio dello stato dei telomeri

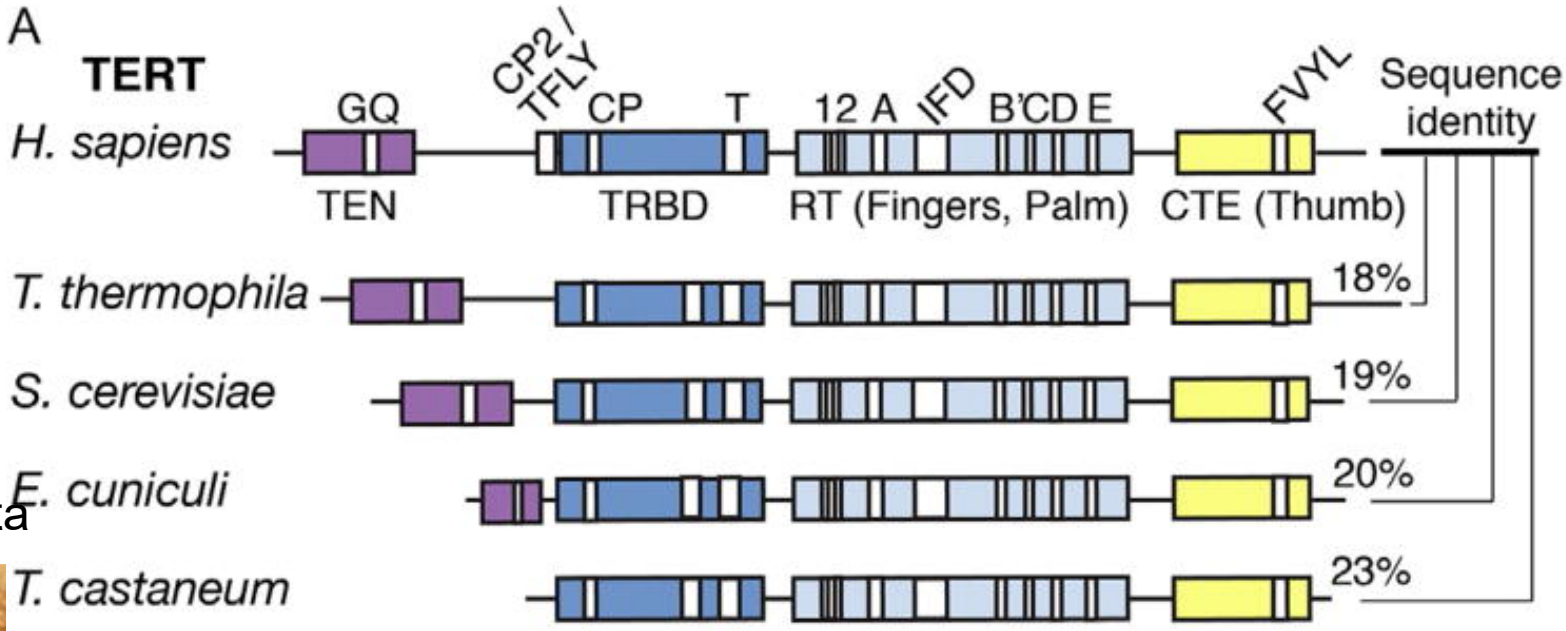
DNA TELOMERICO



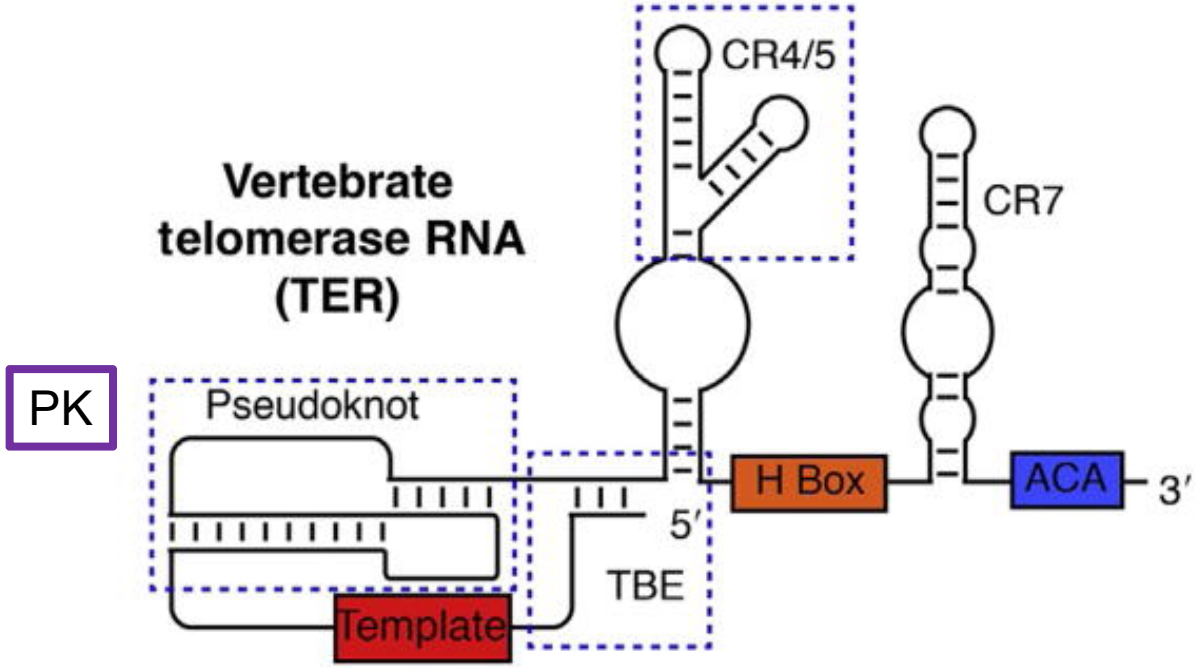
Complessi macromolecolari associati al Telomero: funzioni

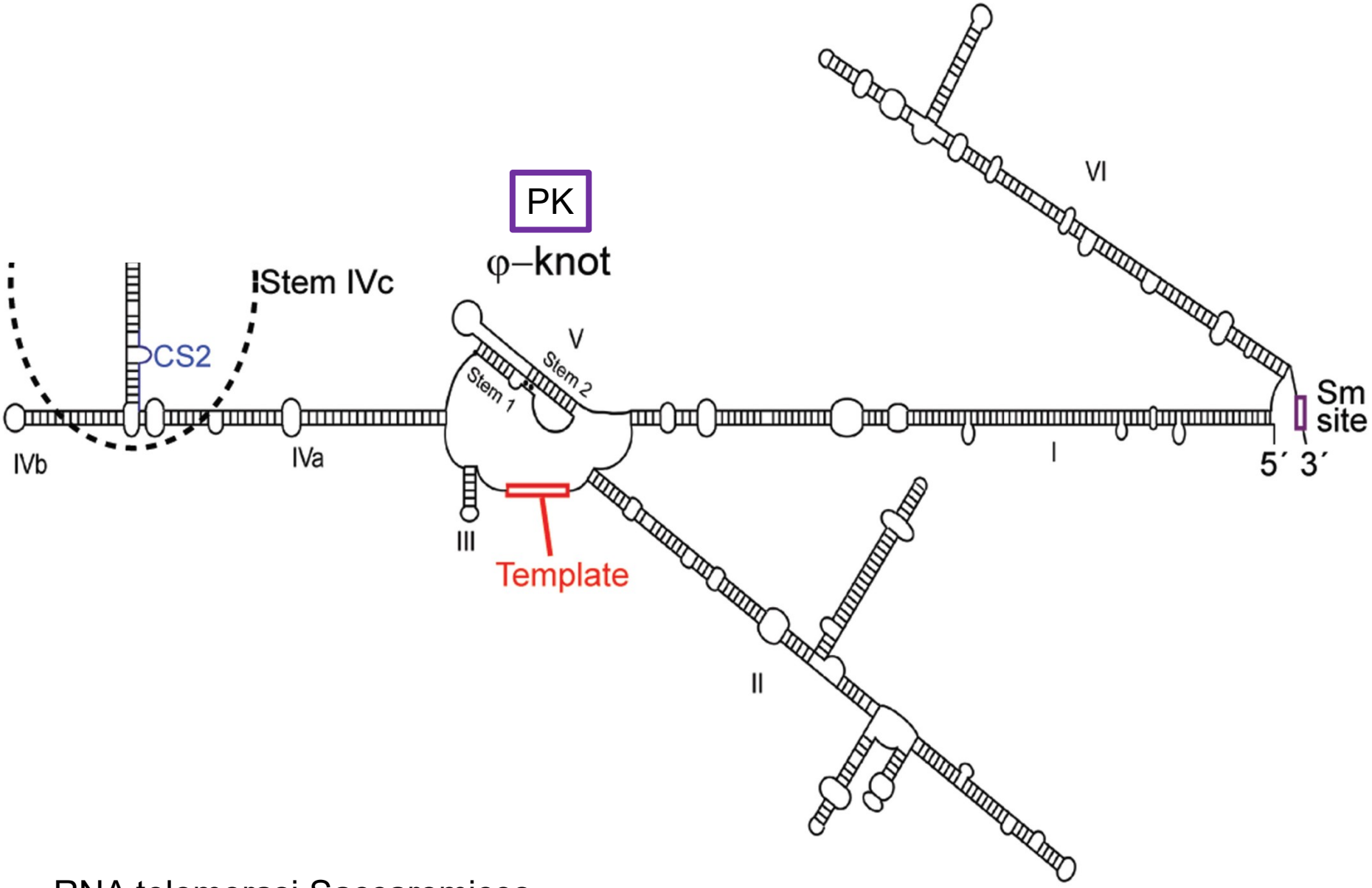
Complessi macromolecolari associati al Telomero ed alla Telomerasi





Fungo parassita

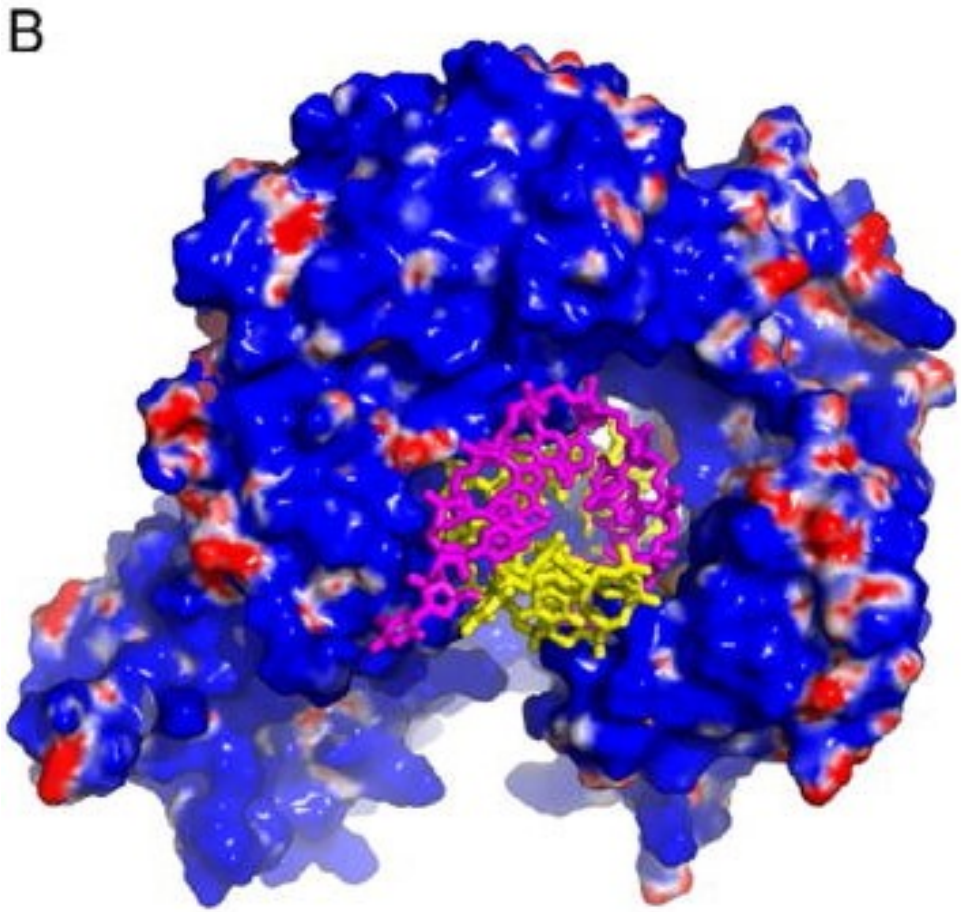




RNA telomerasi Saccaromices

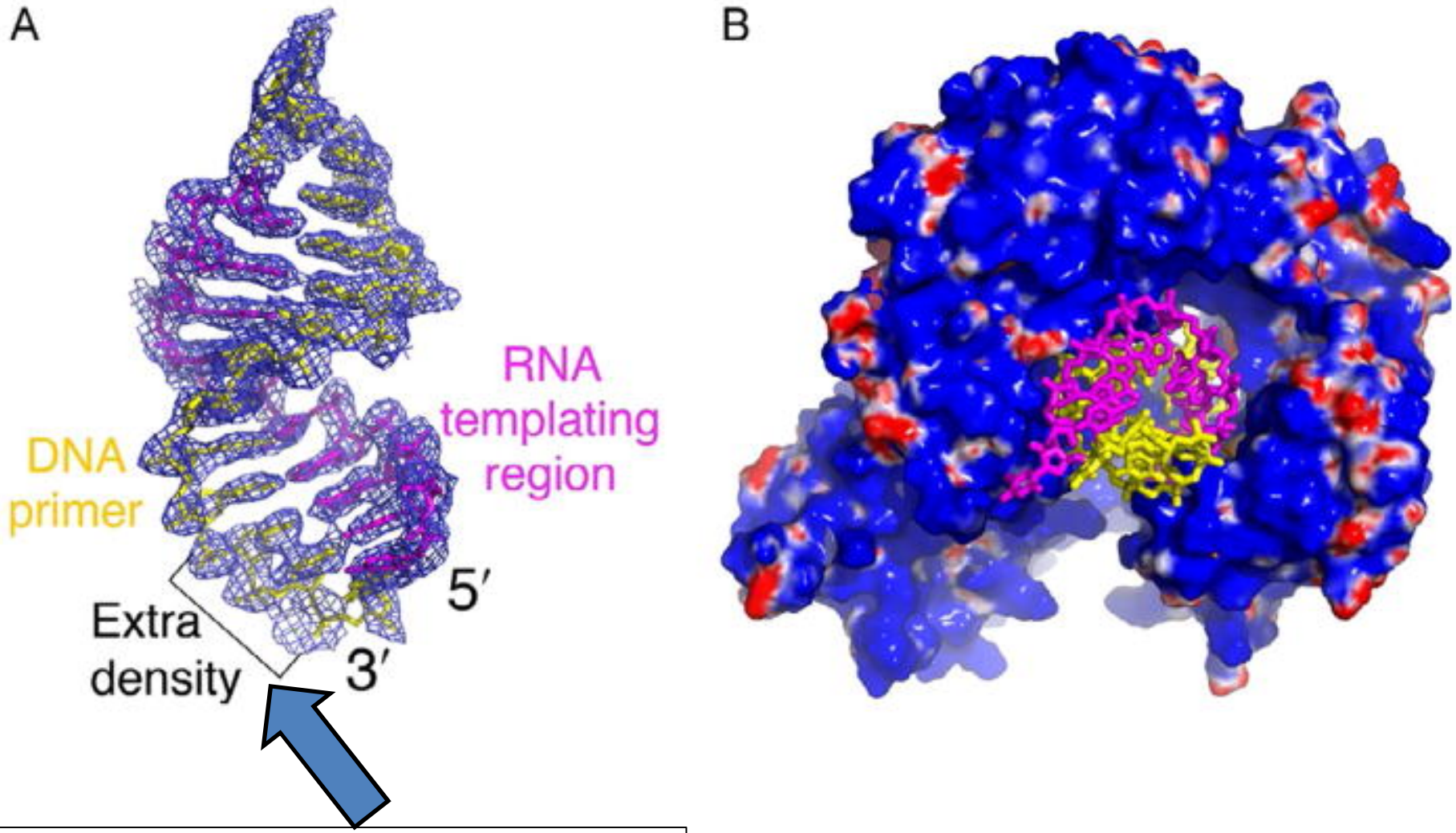
hTR is a 451-nucleotide RNA which contains a box H/ACA motif at its 3 end.
The box H/ACA motif is essential for hTR stability and for its assembly with hTERT.
These functions are mediated by the presence of the box H/ACA-binding dyskerin complex, which is composed of four proteins:
dyskerin, NOP10, NHP2 and GAR1.

RNA (magenta stick)–DNA (yellow stick) hairpin cocrystallized with tcTERT



tcTERT surface charge representation,
the RNA–DNA hybrid (stick) docked in the
interior cavity of the TERT ring

RNA (magenta stick)–DNA (yellow stick) hairpin cocrystallized with tcTERT

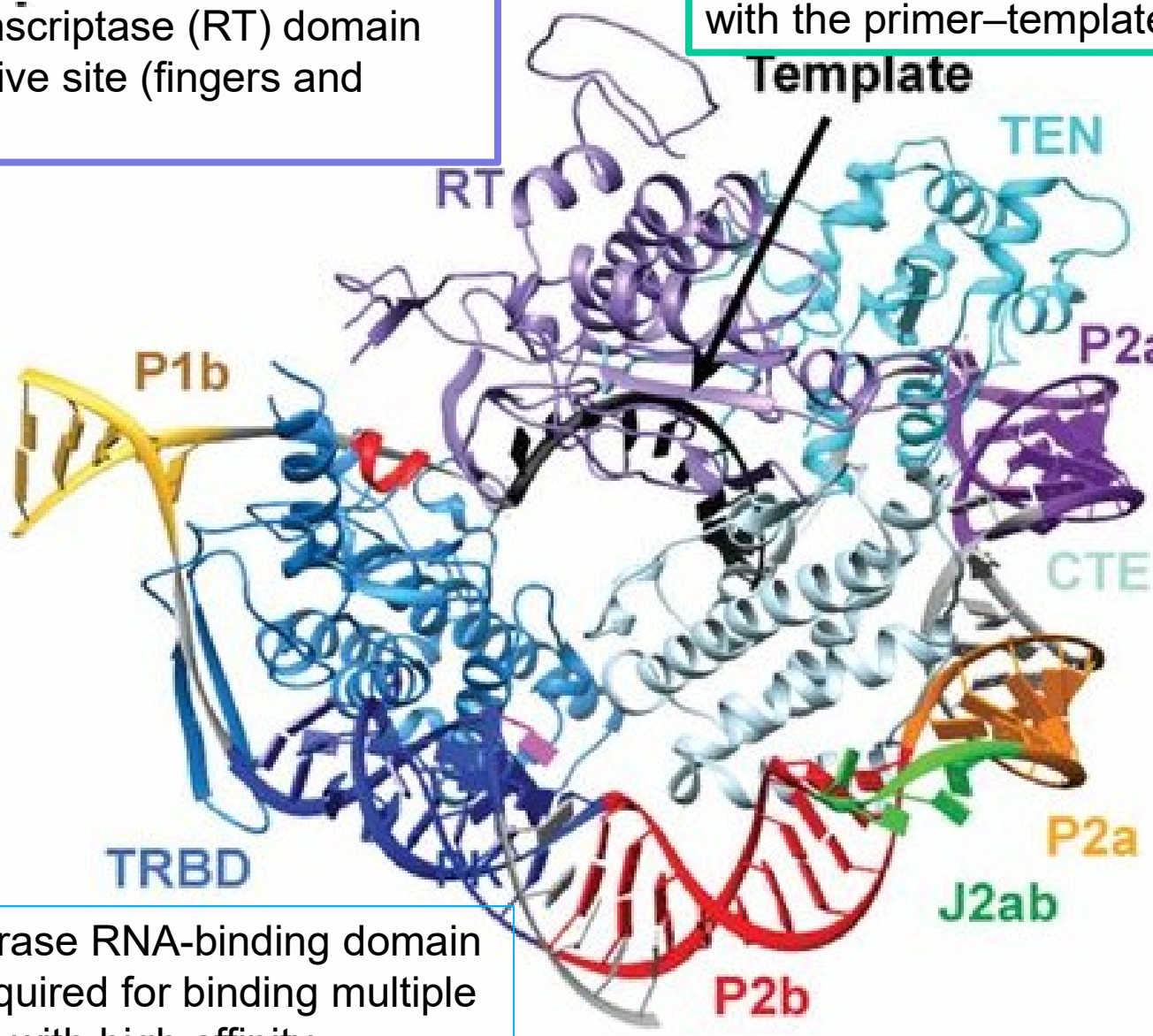


three additional nucleotides at the 3′-end of the telomeric DNA !!

Models of human TERT–t/PK.

reverse transcriptase (RT) domain enzyme active site (fingers and palm)

N-terminal (TEN) domain interacts with the primer–template duplex



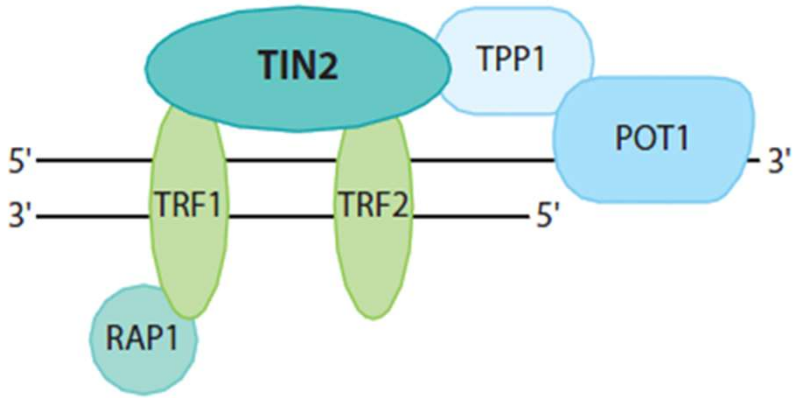
C-terminal extension (CTE) (thumb) processivity

the telomerase RNA-binding domain (TRBD) required for binding multiple sites of TR with high affinity

Yaqiang Wang et al. PNAS 2016;113:E5125-E5134

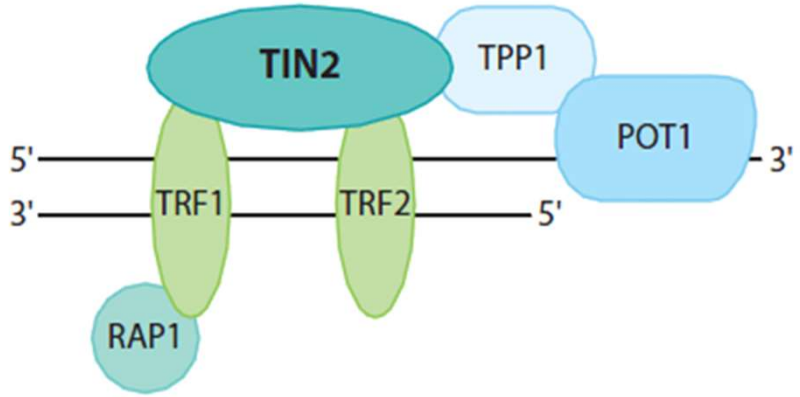
MUTATIONS IN TELOMERIC PROTEINS AND CANCER

Protein	Cancer(s)
Shelterin	
TRF1/TRF2	Gastric
POT1	Leukemia (CLL) Melanoma Glioma
TPP1	DC Melanoma
TIN2	DC
RAP1	Melanoma

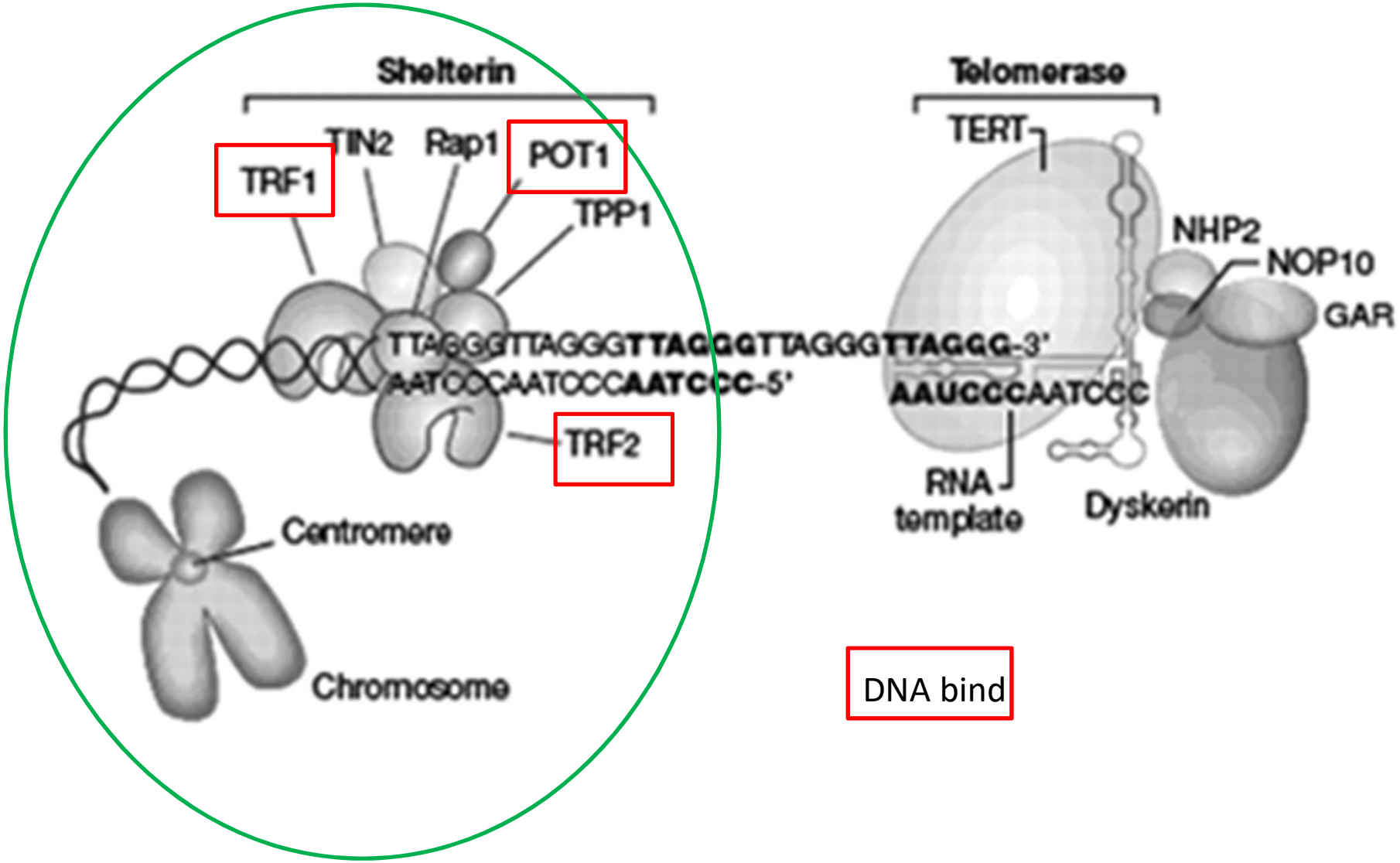


MUTATIONS IN TELOMERIC PROTEINS AND CANCER

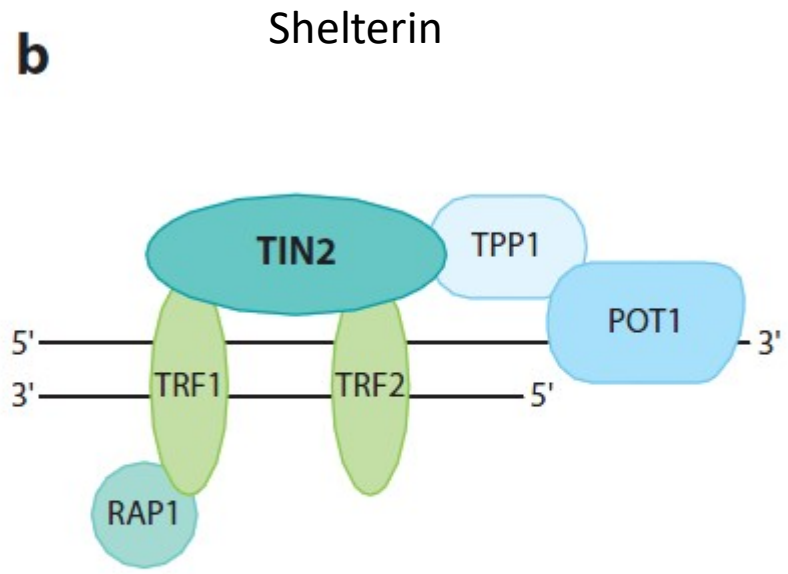
Protein	Cancer(s)
Shelterin	
TRF1/TRF2	Gastric
POT1	Leukemia (CLL) Melanoma Glioma
TPP1	DC Melanoma
TIN2	DC
RAP1	Melanoma
Telomere elongation	
TERT	Glioma Bladder Thyroid Melanoma Breast/ovarian
TERC	MDS



Complessi macromolecolari associati al Telomero ed alla Telomerasi



Complessi macromolecolari associati al Telomero

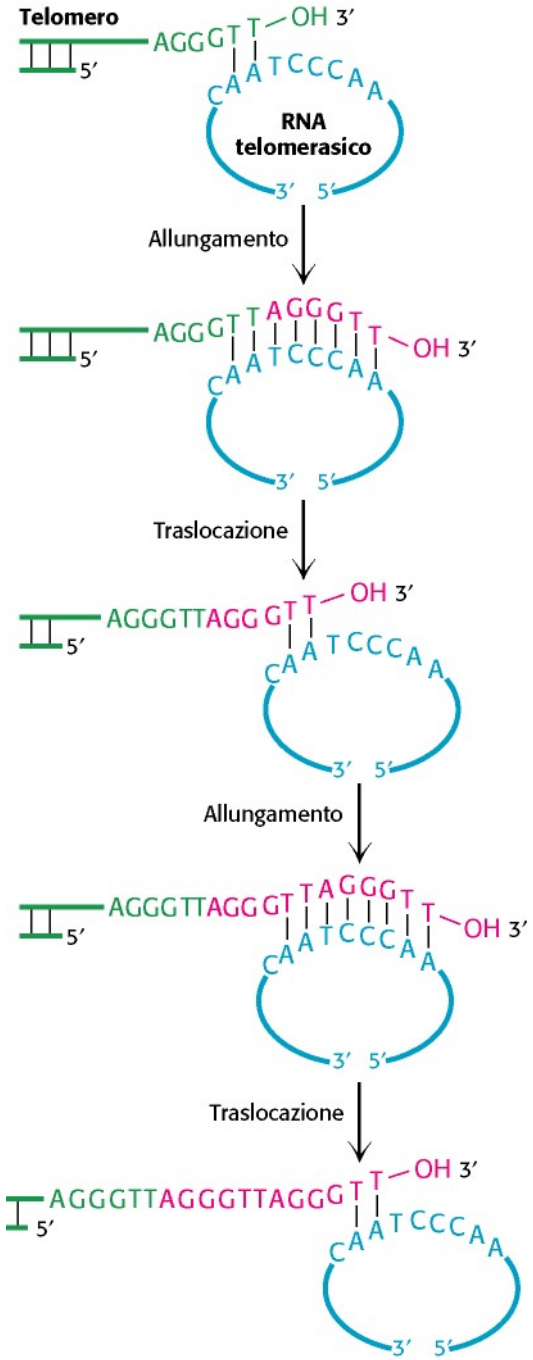


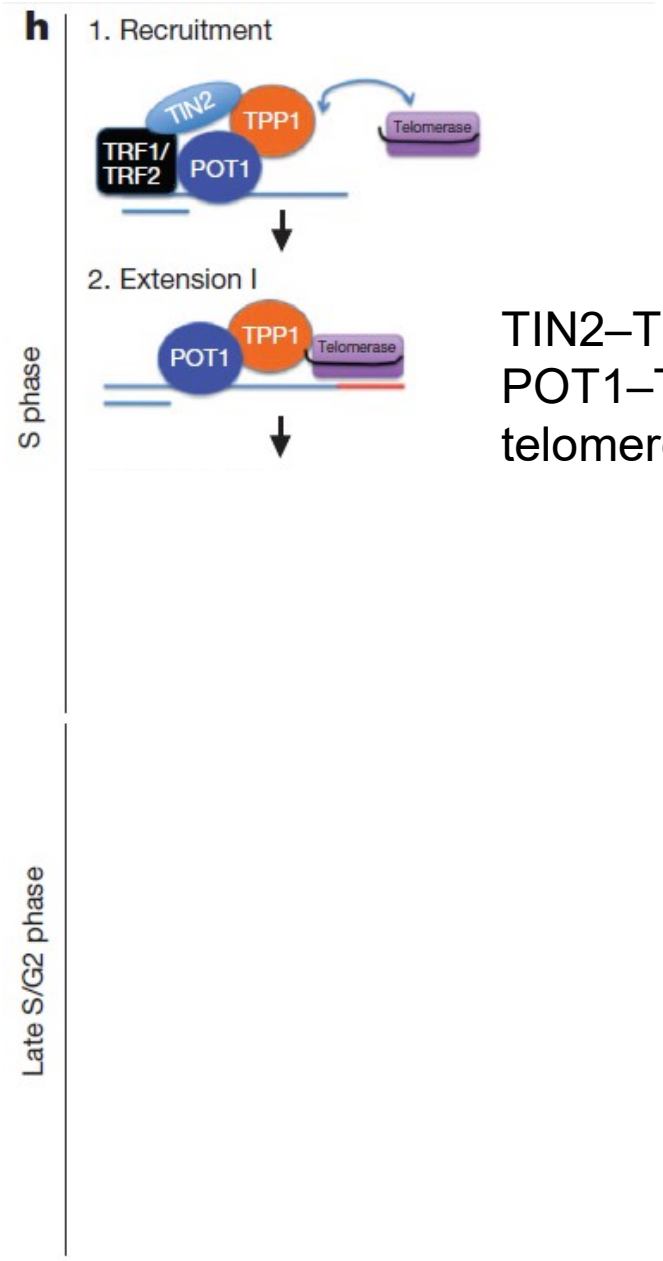
Telomeres are coated by a group of at least six proteins, collectively called **shelterin**
Three proteins, TRF1, TRF2, and POT1(single-stranded repeats) directly recognize and bind to TTAGGG repeats
TIN2 TPP1, and Rap1, interconnect the telomere-binding proteins to form the entire complex

Shelterin serves as a signal that allows the cellular DNArepair machinery to distinguish telomeres from DNA double-stranded breaks

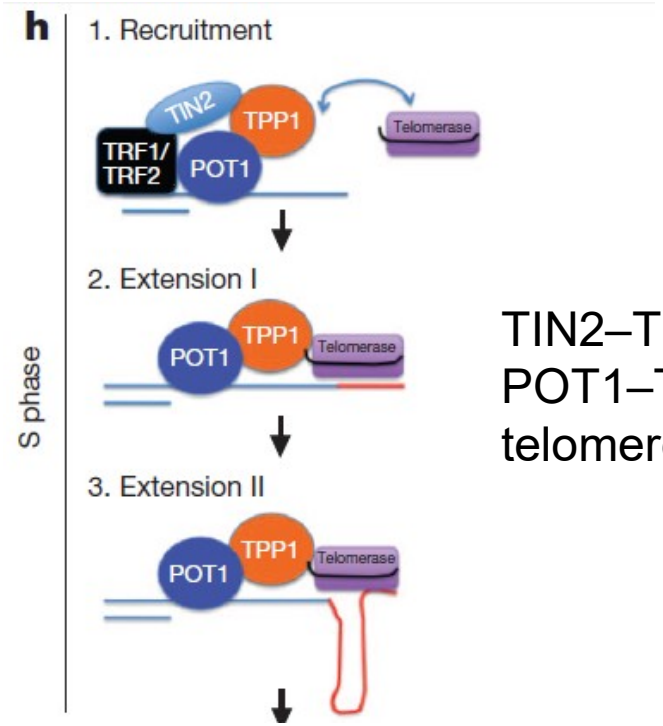
L’allungamento del telomero modello riassuntivo

During every cell division, telomeres are potentially shortened by 50–200 bp due to the end replication problem





TIN2–TPP1 recruits telomerase and POT1–TPP1 promotes processive telomere elongation



TIN2–TPP1 recruits telomerase and POT1–TPP1 promotes processive telomere elongation

IL RECLUTAMENTO DELLA TELOMERASI

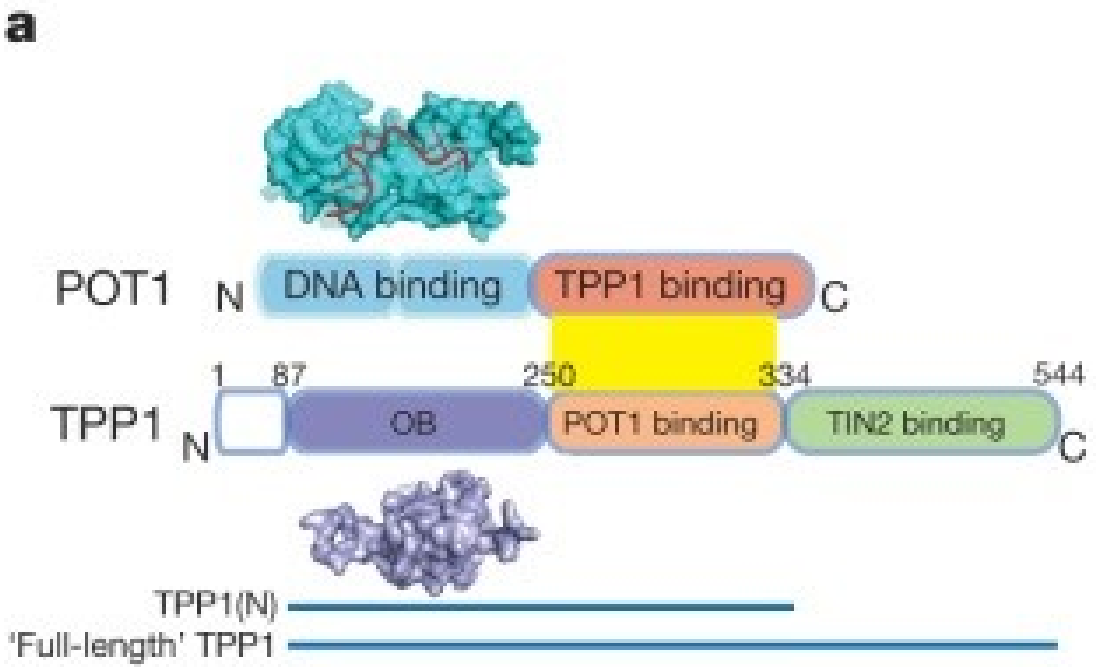
TPP1 recruits telomerase to telomeres

Telomere synthesis involves trafficking of telomerase and telomerase is thought to be recruited to telomeres through interactions with telomere-binding proteins.

The OB-fold domain of the telomere-binding protein TPP1 recruits telomerase to telomeres through an association with the telomerase reverse transcriptase, TERT.

The TPP1 OB-fold domain is sufficient to recruit telomerase to a heterologous chromatin locus.
A minimal TPP1 OB-fold inhibits telomere maintenance by blocking access of telomerase to its binding site at telomeres.

A specific loop residues within the TPP1 OB-fold is necessary for association with critical residues in TER Telomerase, including those mutated in pulmonary fibrosis patients, which defines the interface required for telomerase-TPP1 interaction.



nature

J Nandakumar *et al. Nature* **000**, 1-5 (2012) doi:10.1038/nature11648

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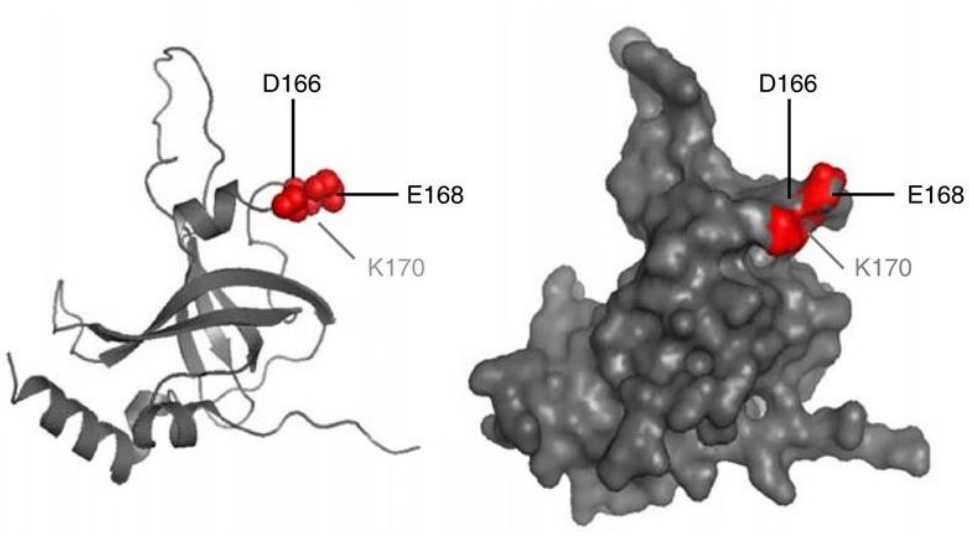
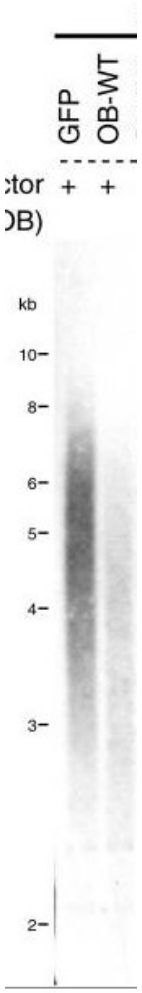


Structural representation of TPP1-OB domain (PDB 2i46).
Residues required for telomerase interaction shown in red

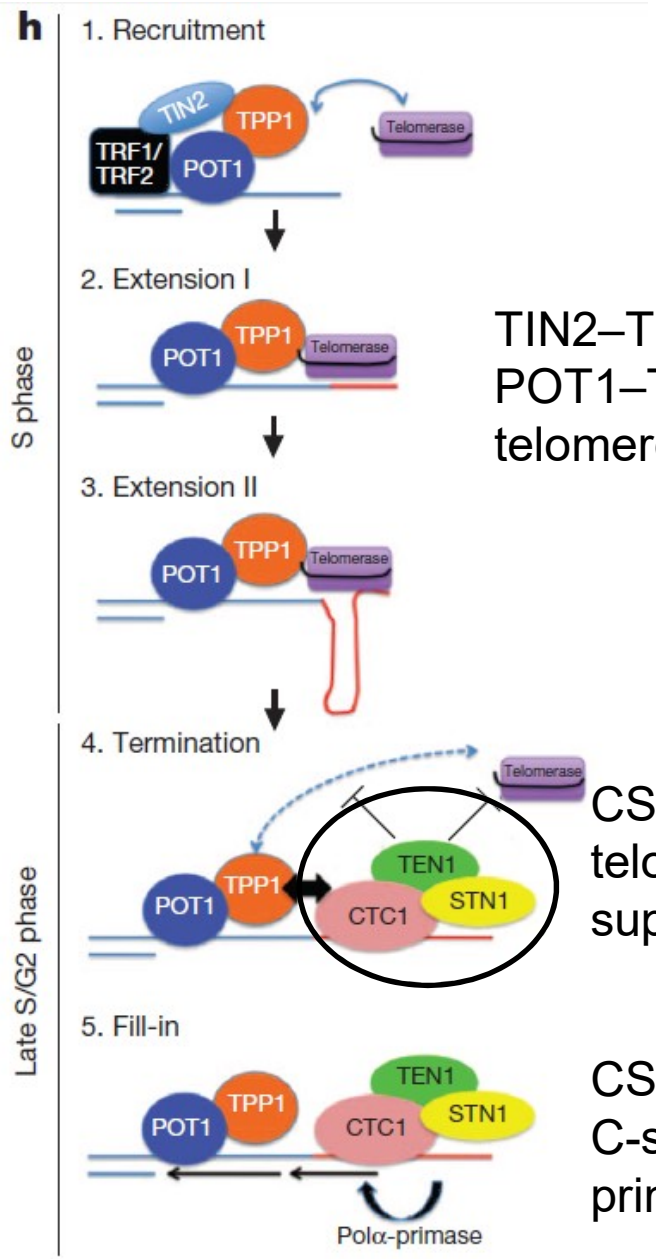
Direct telomerase activity assay with primer of lysates from cells co-transfected with a TR plasmid and POT1, TPP1 MUTANTS and TERT.

J Nandakumar *et al. Nature* **000**, 1-5 (2012) doi:10.1038/nature11648

TPP1-OB inhibits telomere length maintenance by telomerase and blocks endogenous telomerase recruitment



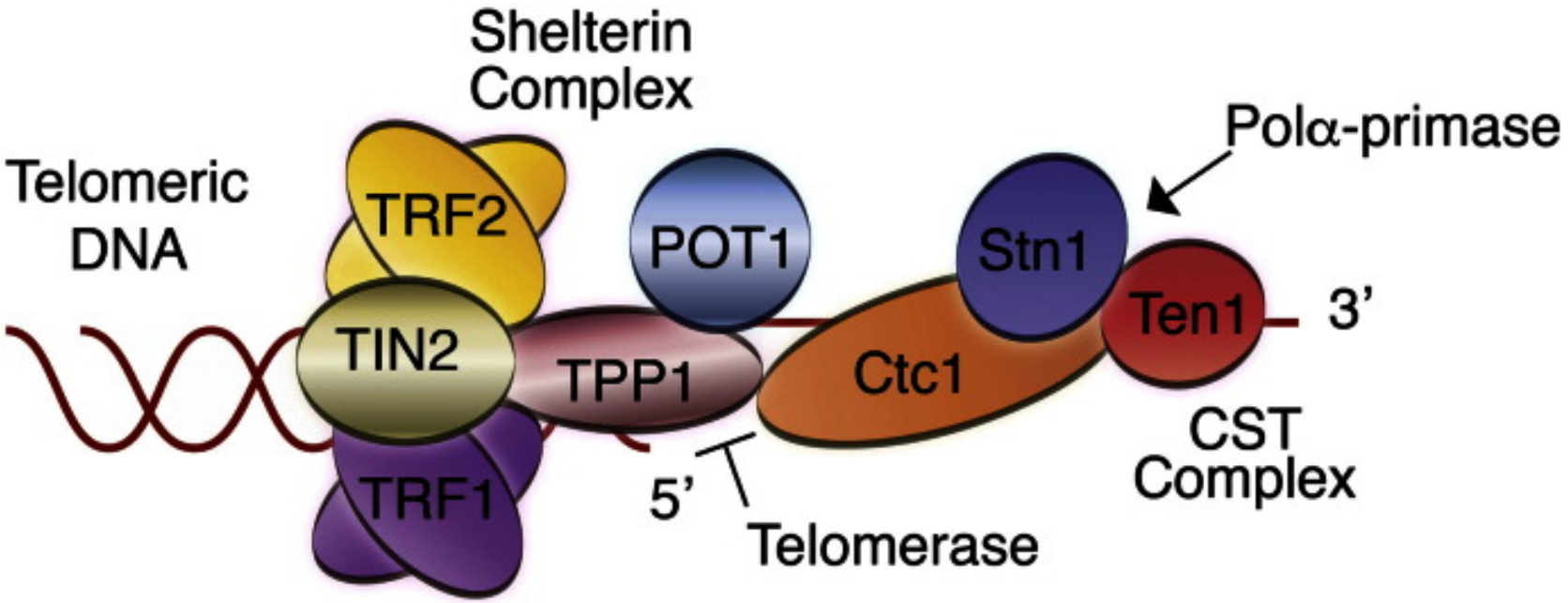
The CST complex is a terminator of telomerase activity



TIN2–TPP1 recruits telomerase and POT1–TPP1 promotes processive telomere elongation

CST binds to the telomerase-extended telomere end
suppressing telomerase access.

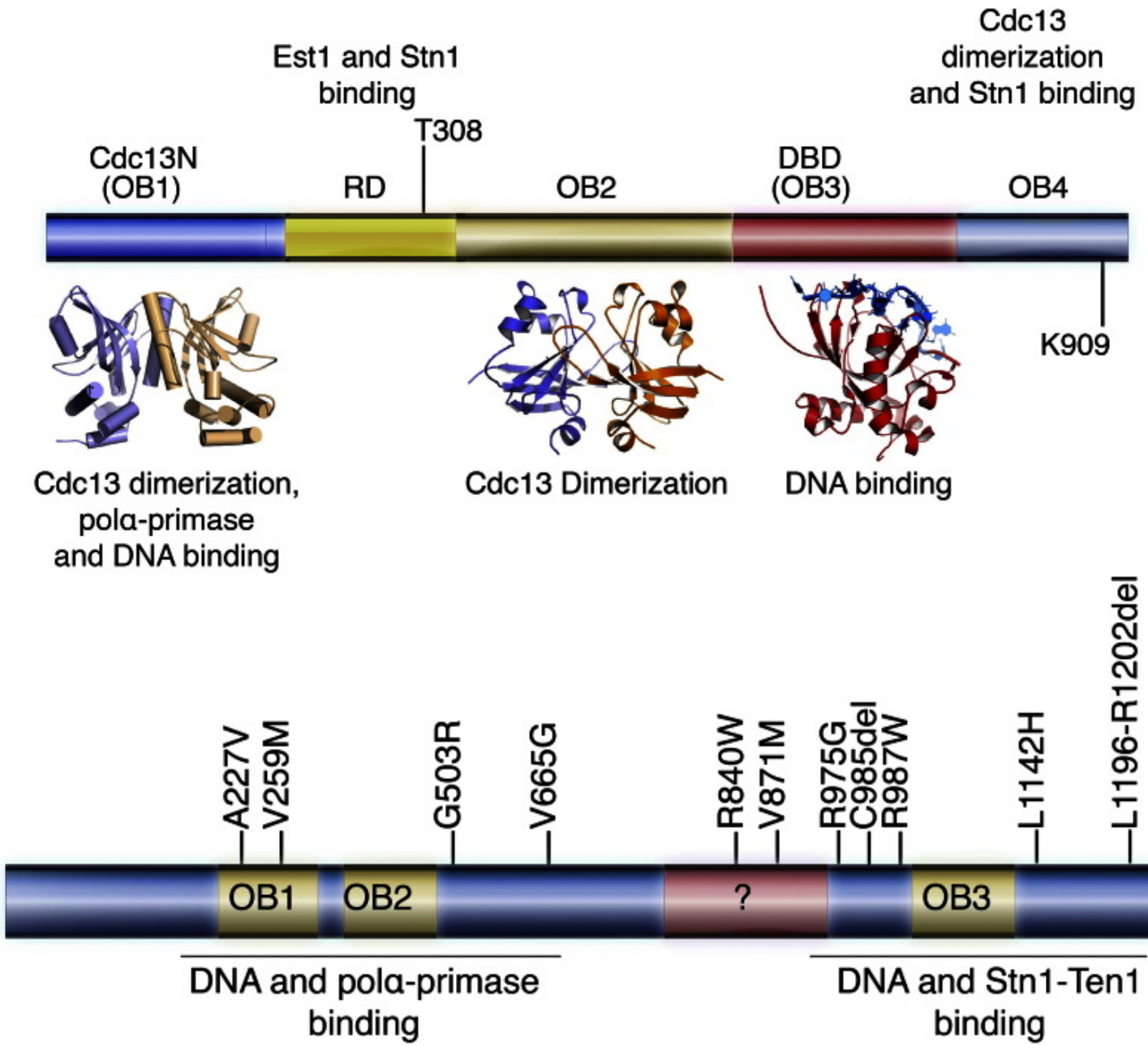
CST promotes fill-in synthesis of the C-strand stimulating DNA polymerase a-primase



CST localizes specifically to the single-stranded telomeric DNA

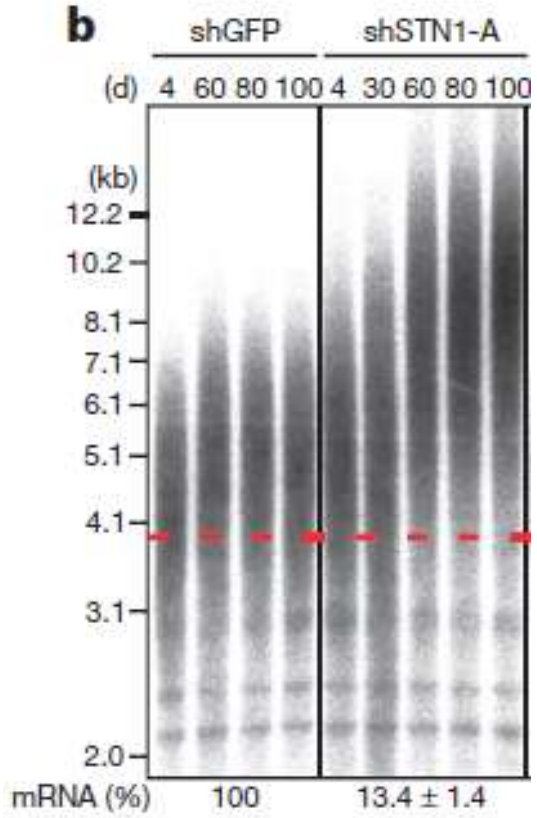
chromosome end capping and telomere length regulation

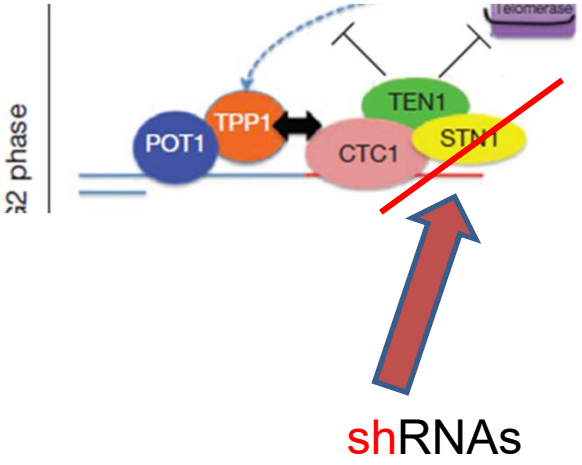
Primary structures of Cdc13 / CTC) indicating domain organization



The CST complex limits telomere elongation

HT1080
human cancer cells





shRNAs

GLI STATI DEL TELOMERO

Telomeric nucleosomes

Telomeric nucleosomes are hypersensitive to micrococcal nuclease.

Reconstituted nucleosomes on TTAGGG repeats show higher mobility than on other sequences.

Telomeric chromatin is enriched for heterochromatin modification, such as tri-methylation of H3K9 and H4K20, and loss of these marks affects telomere length regulation.

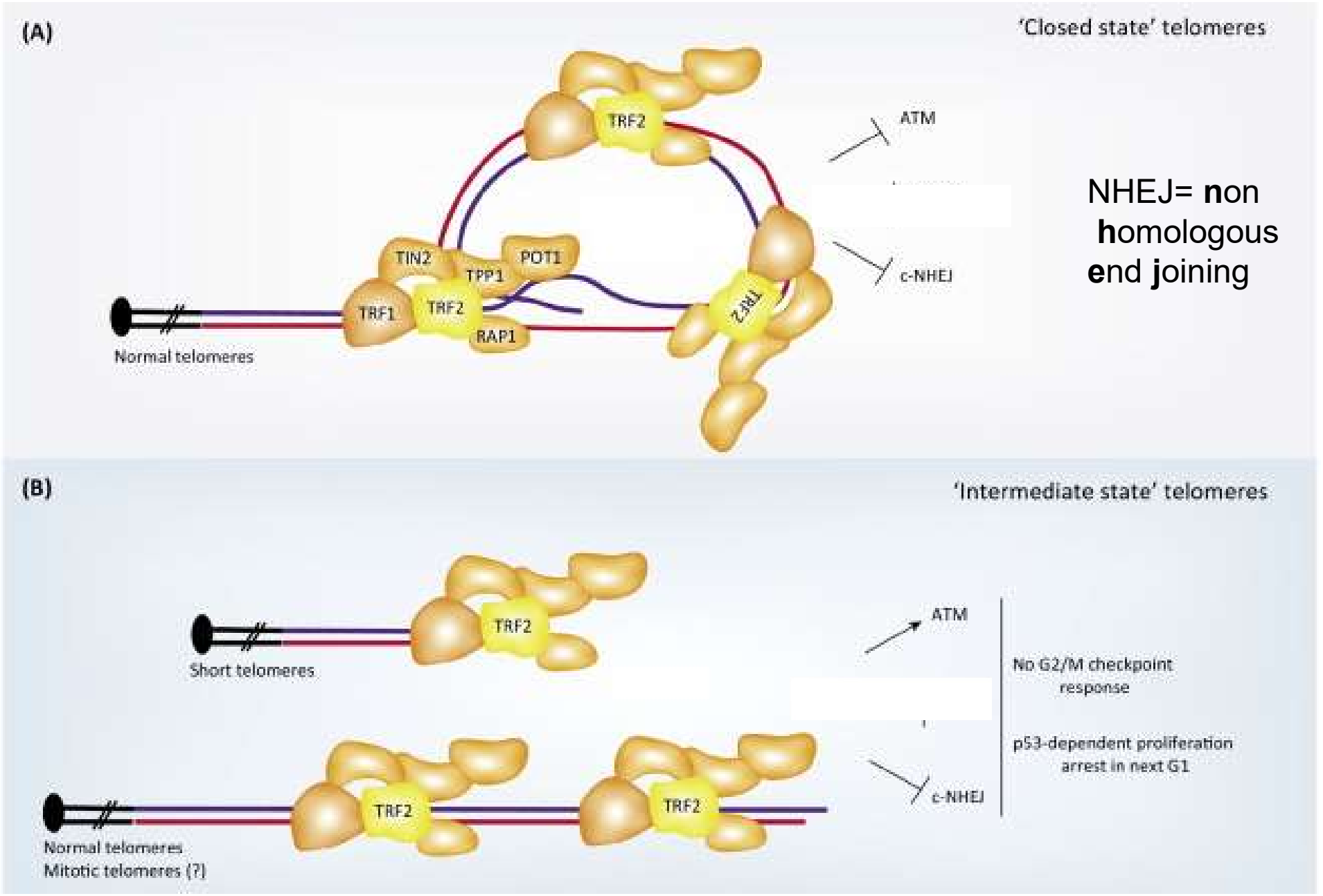
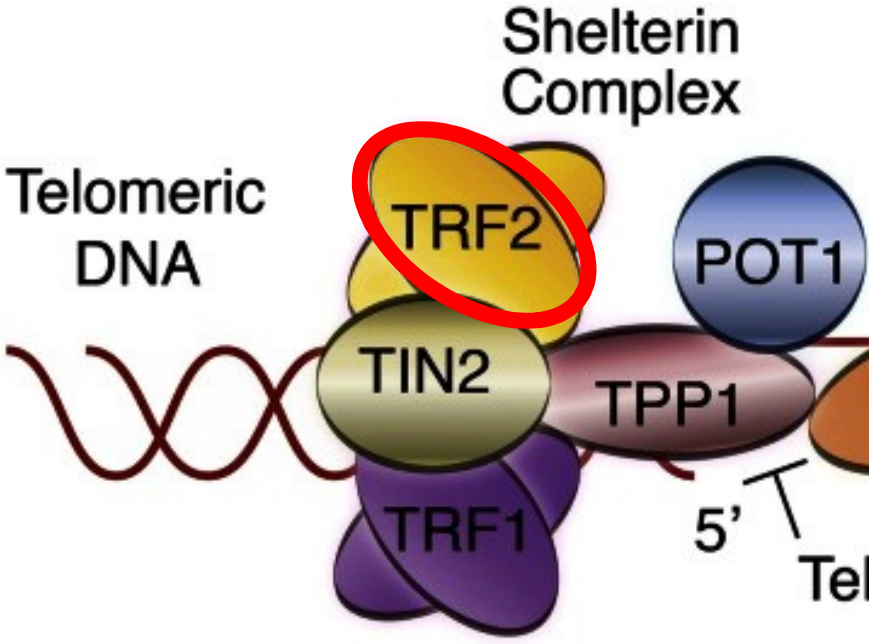


Figure 2. The different states of telomeres: from the physiological 'closed state' to the pathological 'uncapped state

No DDRama at chromosome ends: TRF2 takes centre stage, Sascha Feuerhahn, Liuh-yow Chen, Brian Luke, Antonio Porro

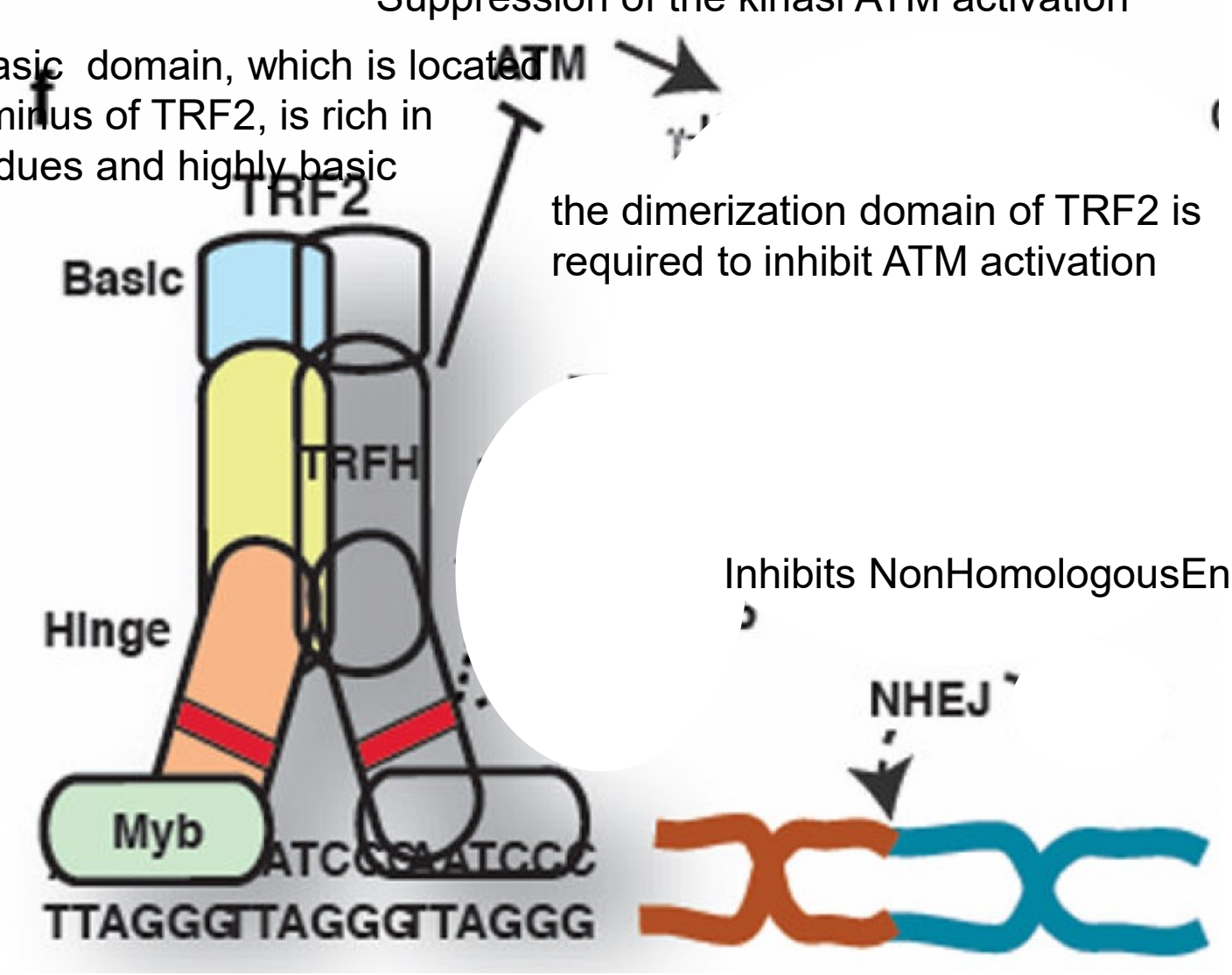

Shelterin
Complex
Telomeric
DNA
TRF2
POT1
TIN2
TPP1
TRF1
5’
Tel

mechanism for TRF2-mediated chromosome end protection

Suppression of the kinasi ATM activation

The GAR/Basic domain, which is located at the N terminus of TRF2, is rich in Gly/Arg residues and highly basic

the dimerization domain of TRF2 is required to inhibit ATM activation

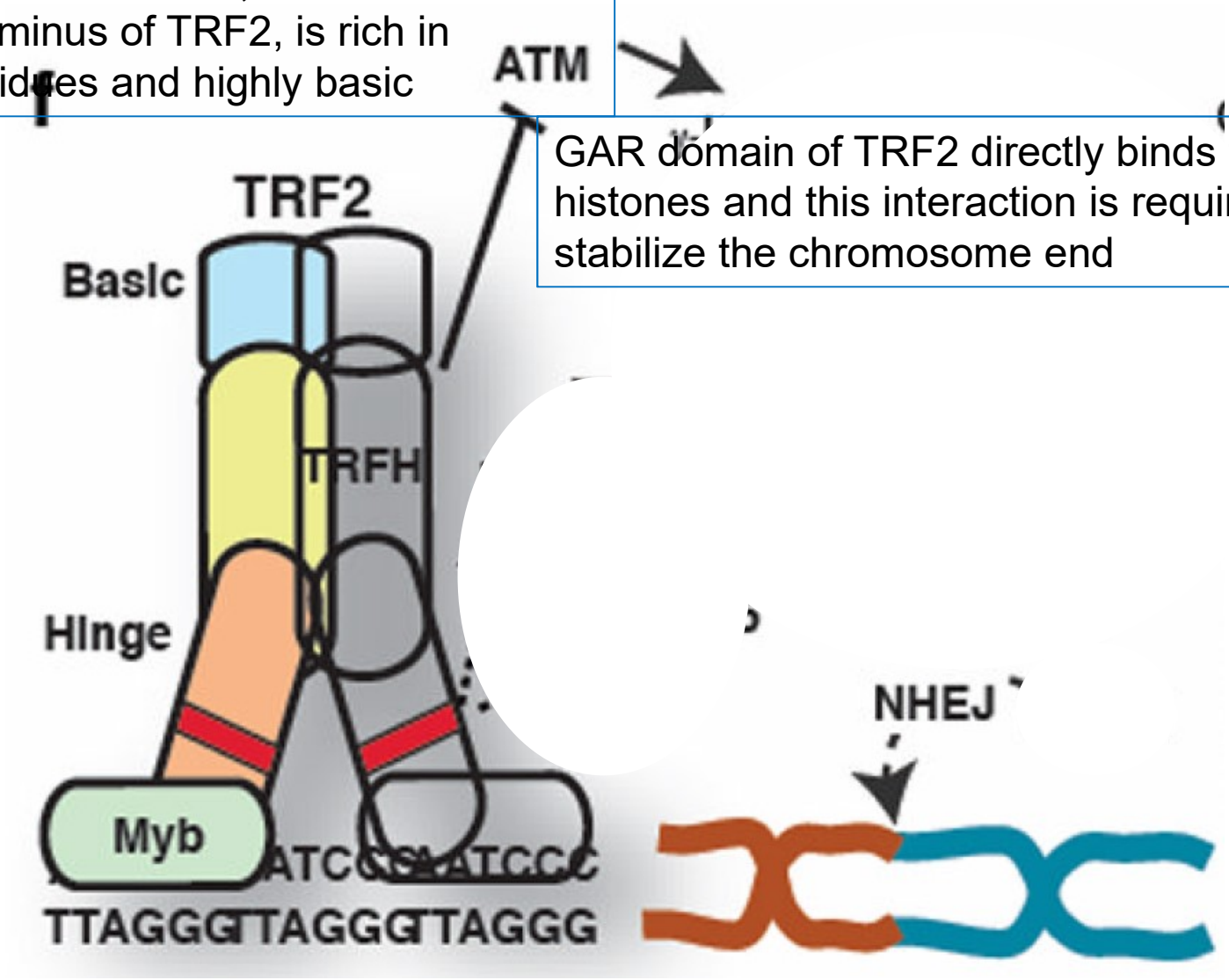


Inhibits NonHomologousEndJoining

mechanism for TRF2-mediated chromosome end protection

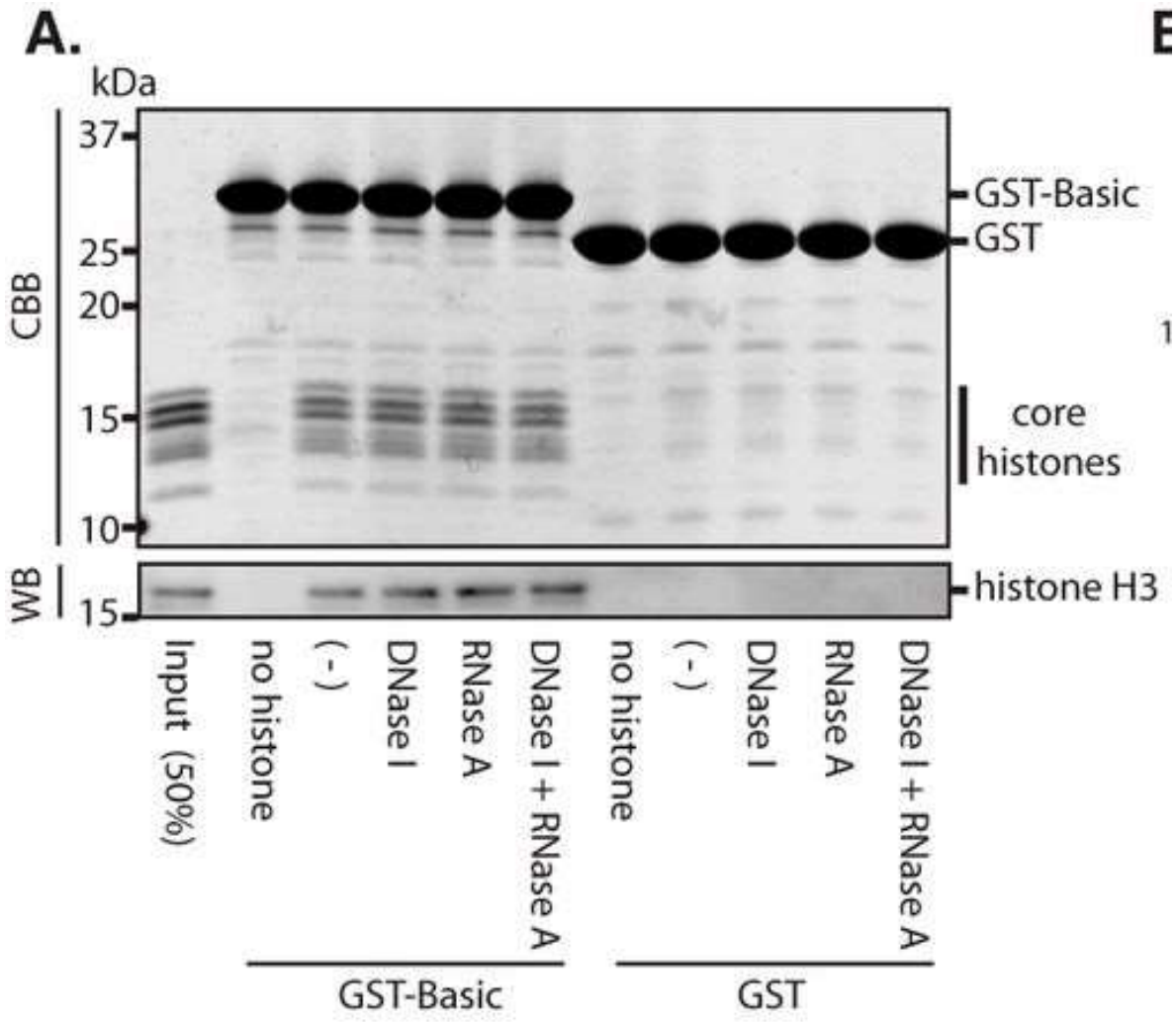
The GAR/Basic domain, which is located at the N terminus of TRF2, is rich in Gly/Arg residues and highly basic

GAR domain of TRF2 directly binds to core histones and this interaction is required to stabilize the chromosome end



Direct binding of the GAR domain of TRF2 and core histones.

Coomassie Brilliant Blue



GAR domain fused with GST

Core histones: mono-nucleosomes were purified using from HeLa cell nuclei digested with micrococcal nuclease- mono-nucleosome peaks were collected and partially digested with trypsin to generate the tailless histones

Akimitsu Konishi et al. J. Biol. Chem. 2016;291:20798-20810

jbc

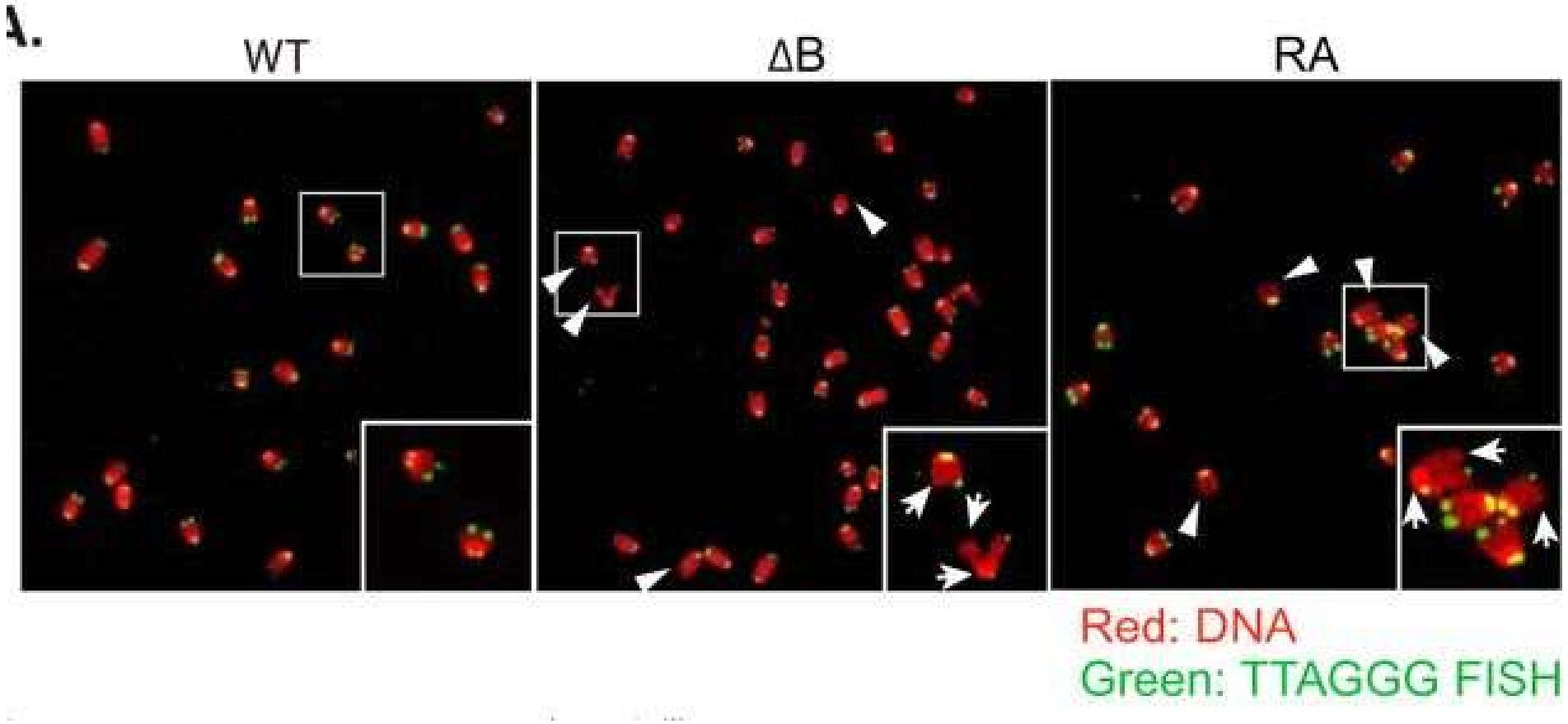
Direct binding of the GAR domain of TRF2 and core histones.

latency-associated nuclear antigen (LANA)
viral element essential for the DNA replication and genome maintenance during latency

Akimitsu Konishi et al. J. Biol. Chem. 2016;291:20798-20810

jbc

Rapid telomere DNA loss and t-circle generation by loss of histone binding of TRF2.



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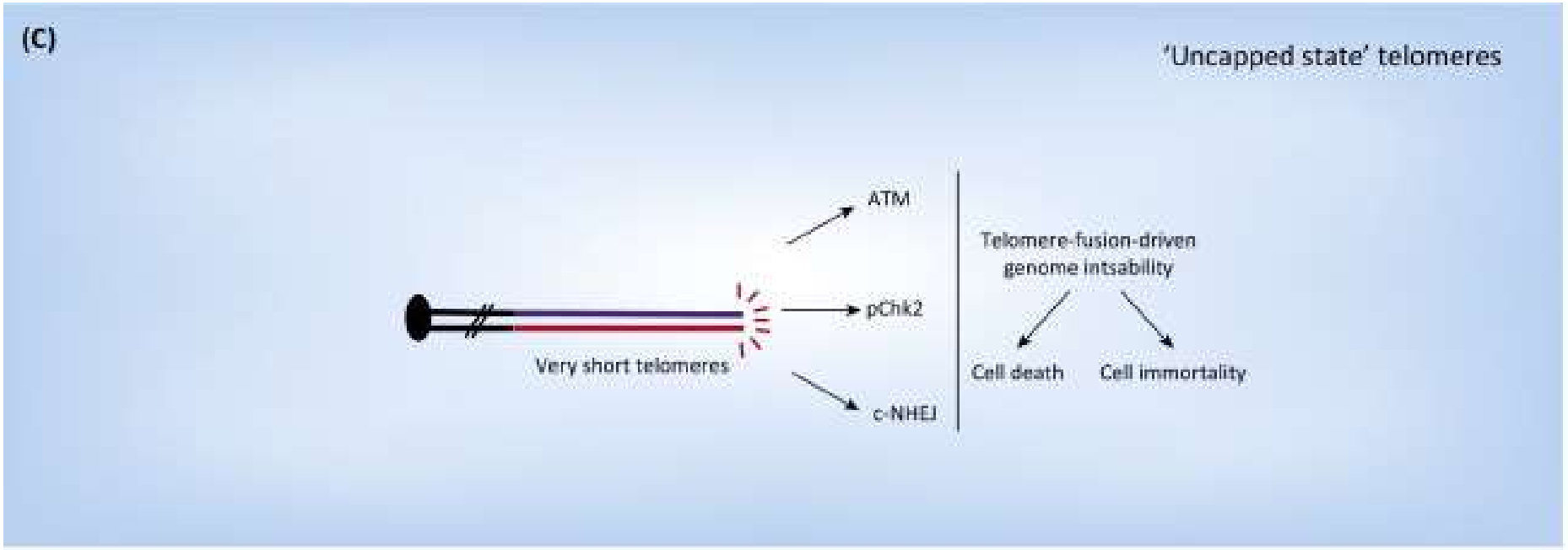

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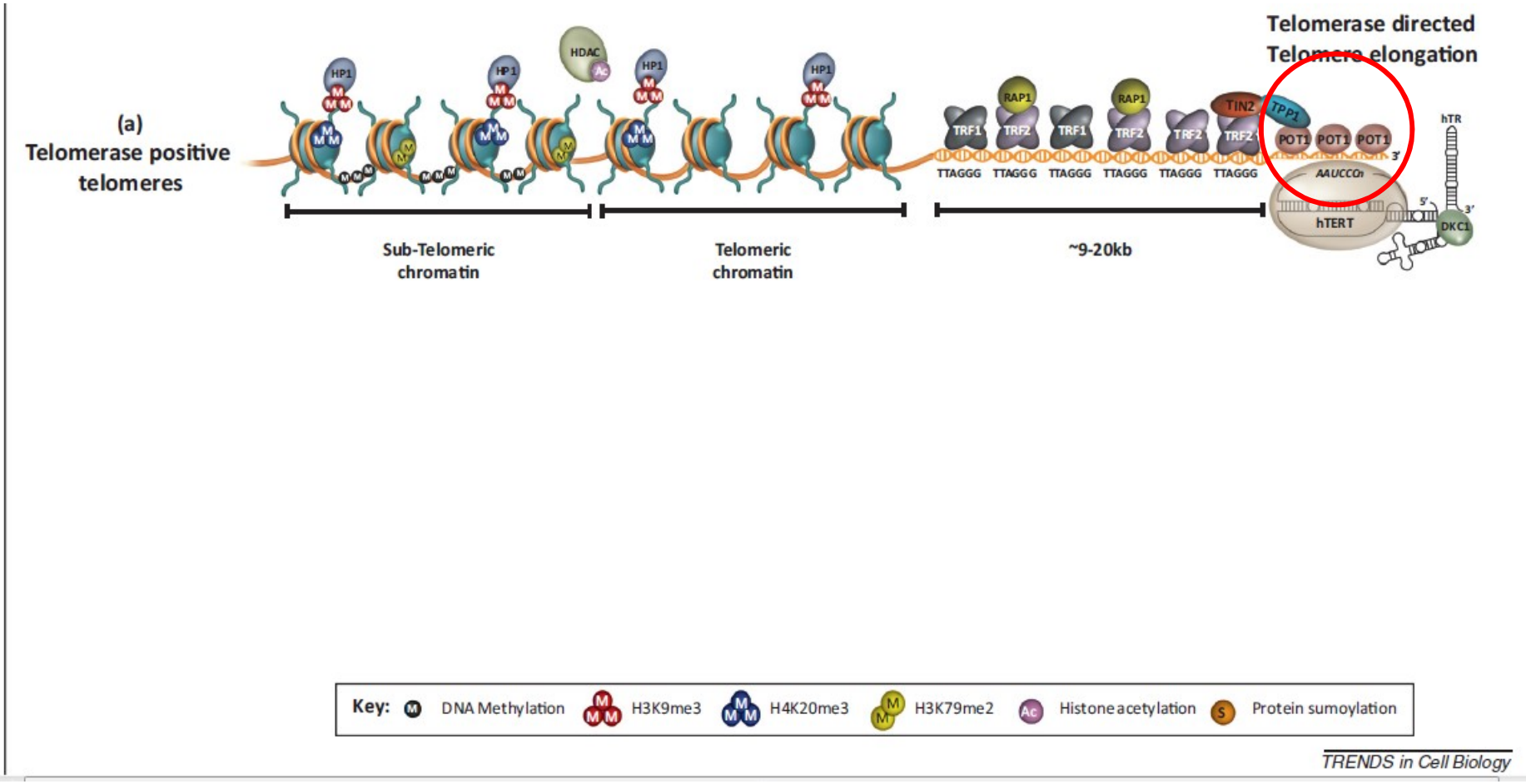
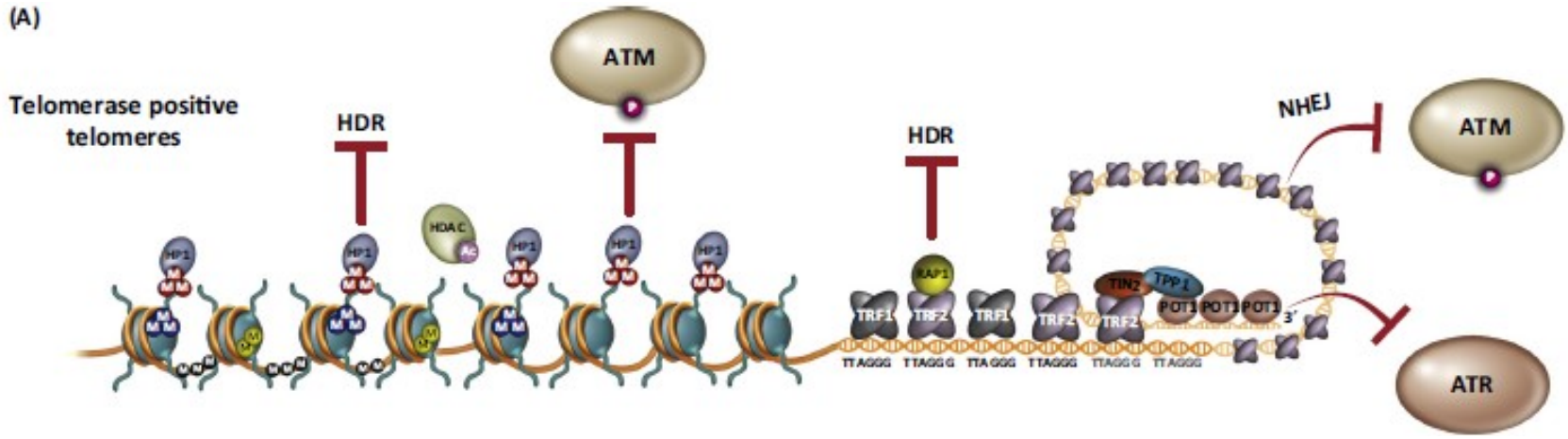
Telomeres in germ and stem cells





DNA damage suppression at mammalian telomeres in the T-loop structure blocks the association of ATM) and ATR kinases to prevent non-homologous end joining (NHEJ)-mediated fusion of telomeres