

BEYOND THE GOLDILOCKS ZONE: A NEW APPROACH TO TREATMENT OF CANCER IN CHILDREN AND YOUNG ADULTS

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Telomeres & immortality

- Telomeres protect the end of every chromosome
- Every time a cell divides, the telomeres **shorten**
- In old cells, telomeres become critically short, the cell **stops dividing** and undergoes **cell death**
- Cancer cells** develop strategies to **lengthen telomeres**
- This process is called **immortalisation**, as it allows cancer cells to **divide indefinitely**



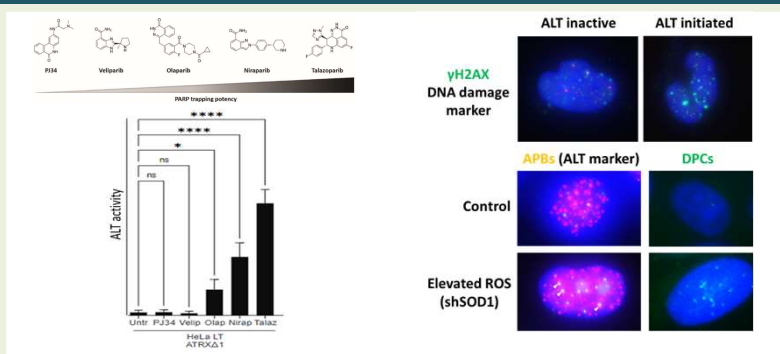
ALT cancers

- Some cancers use the **Alternative Lengthening of Telomeres (ALT)** pathway for immortalisation
- Cancers affecting **children, teenagers** and **young adults** are frequently ALT-cancers
- ALT-cancers have a **very poor outcome**

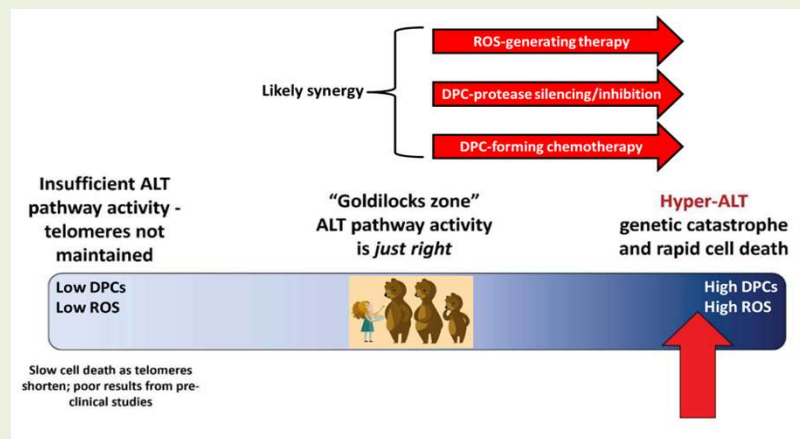


DNA damage: an essential factor

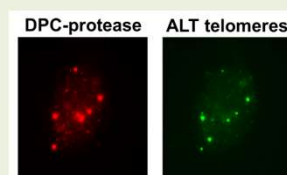
- The ALT pathway relies on **DNA damage** and formation of **DNA double-strand breaks**
- We have identified two types of DNA damage which drive ALT pathway activity
 - DNA-protein complexes (**DPCs**)
 - Reactive oxygen species (**ROS**)
- ALT pathway activity can be **initiated** by elevating DPC and ROS levels
- ROS levels and DPC formation appear linked



The Goldilocks zone: where ALT activity is just right



- ALT cells exist in a **precarious balance**
- Optimal ALT-activity vs. DNA instability
- They must carefully control of anti-oxidant genes
- They express enzymes to regulate DPC



How can we manipulate cells therapeutically to alter this balance?

Gene therapy

- Silencing of anti-oxidant genes
- Silencing of DPC-protease genes
- Viral & nanomolecule delivery of silencing RNA

Chemotherapy

- Test *SETD2* inhibitor
- Development of DPC-protease inhibitor
- Optimization of current DPC-forming drugs

Combination approach

- We have observed **synergistic effect** when the different approaches are combined, indicating **combination therapy** might be most effective

