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

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

How can we manipulate cells therapeutically to alter this balance?