Targeting DNA repair through PARP inhibition
Sources of DNA damage

- Ultraviolet light
- Ionizing radiation
- Man-made and natural chemicals
- Reactive oxygen species
  - most are generated “endogenously”
- ~100,000,000,000,000,000 DNA lesions in a human body every day

Cancer cells are highly susceptible to DNA repair inhibition

- Cancer cells
  - undergo deregulated proliferation
    - less time for DNA repair than in normal cells
  - grow under stress, which causes ongoing DNA damage
  - have DNA repair defects
    - mutator phenotype
    - allow growth despite ongoing genome instability
  - are reliant on the DNA repair pathways they still retain
PARP-1 is a key enzyme involved in the repair of single-strand DNA breaks.

1. DNA damage
2. PARP binds rapidly and directly to single-strand breaks
3. PARP recruits repair enzymes
4. Once bound to damaged DNA, PARP modifies itself producing large branched chains of Poly (ADP-ribose)
Inhibiting PARP-1 increases double-strand DNA damage

DNA SSB

Inhibition of PARP-1 prevents recruitment of repair factors to repair SSB

DNA DSB

Replication (S-phase)
Selective effect of PARP-1 inhibition on cancer cells with BRCA1 or BRCA2 mutation (an example of HR-deficient cells)

DSB in DNA

Normal cell
- DSB repaired effectively via HR pathway
- Cell survival

BRCA-deficient cancer cell
- Deficient HR pathway - DSB not repaired
- Cancer cell death
BRCA1 and BRCA2 -/- embryonic stem cells are very sensitive to PARP inhibition.

Increased levels of chromosomal aberrations in PARP inhibitor treated BRCA2 -/- cells.

Log surviving fraction

Wild type

Control + PARP inhibitor

Wild type

Control + PARP inhibitor

Farmer H et al. Nature 2005;434:917-920
Personal communication, Alan Ashworth
PARP inhibition research at AstraZeneca

- AstraZeneca is evaluating the PARP-1 inhibition approach to cancer treatment.
- AstraZeneca is investigating a personalized healthcare approach in this area.
- Earlier clinical trial results have been reported and Phase II clinical trials are underway\(^1-5\).

1. Plummer ER. Curr Opin Pharmacol 2006; 6: 364-368