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[1-3]

1. Jackson SP. Biochem Soc Trans 2001;29:655-661
2. Lindahl T. Nature 1993;362:709-715
3. Jackson SP, Bishop CL. Drug Discovery World 2003;(Fall):41-45

Types of DNA damage and repair

Type of damage:

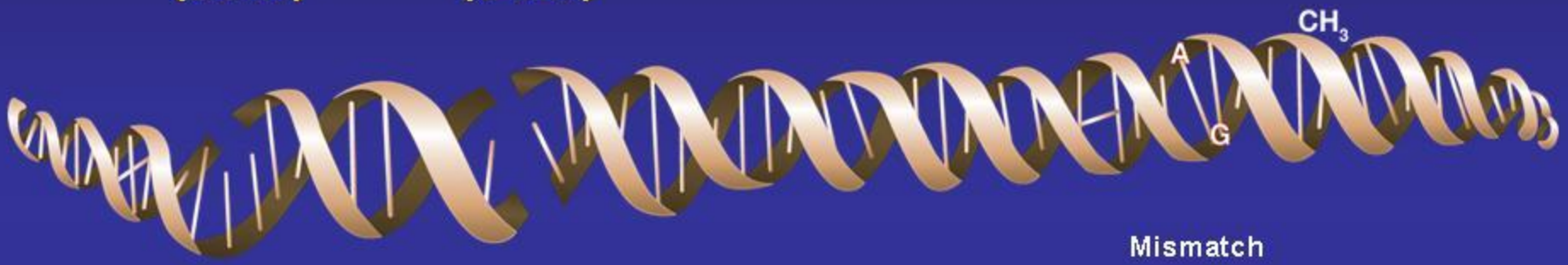
Single-strand breaks (SSBs)

Double-strand breaks (DSBs)

Bulky adducts

O6-alkylguanine

Insertions & deletions



Repair pathway:

Base excision repair

Recombinational repair

HR

NHEJ

Mismatch repair

Nucleotide-excision repair

Direct reversal

Repair enzymes:

PARP

ATM

DNA-PK

XP, poly-merases

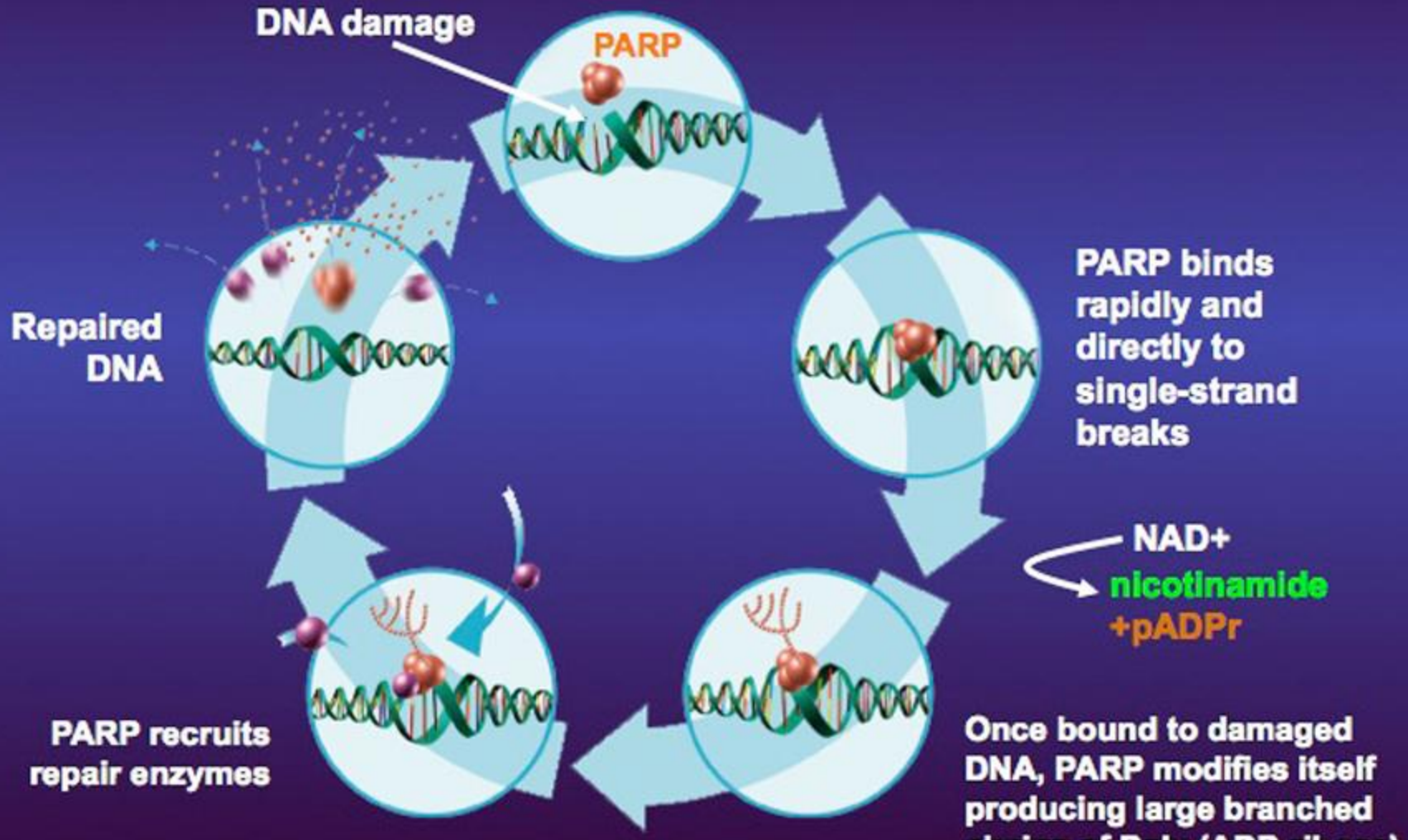
MSH2, MLH1

AGT

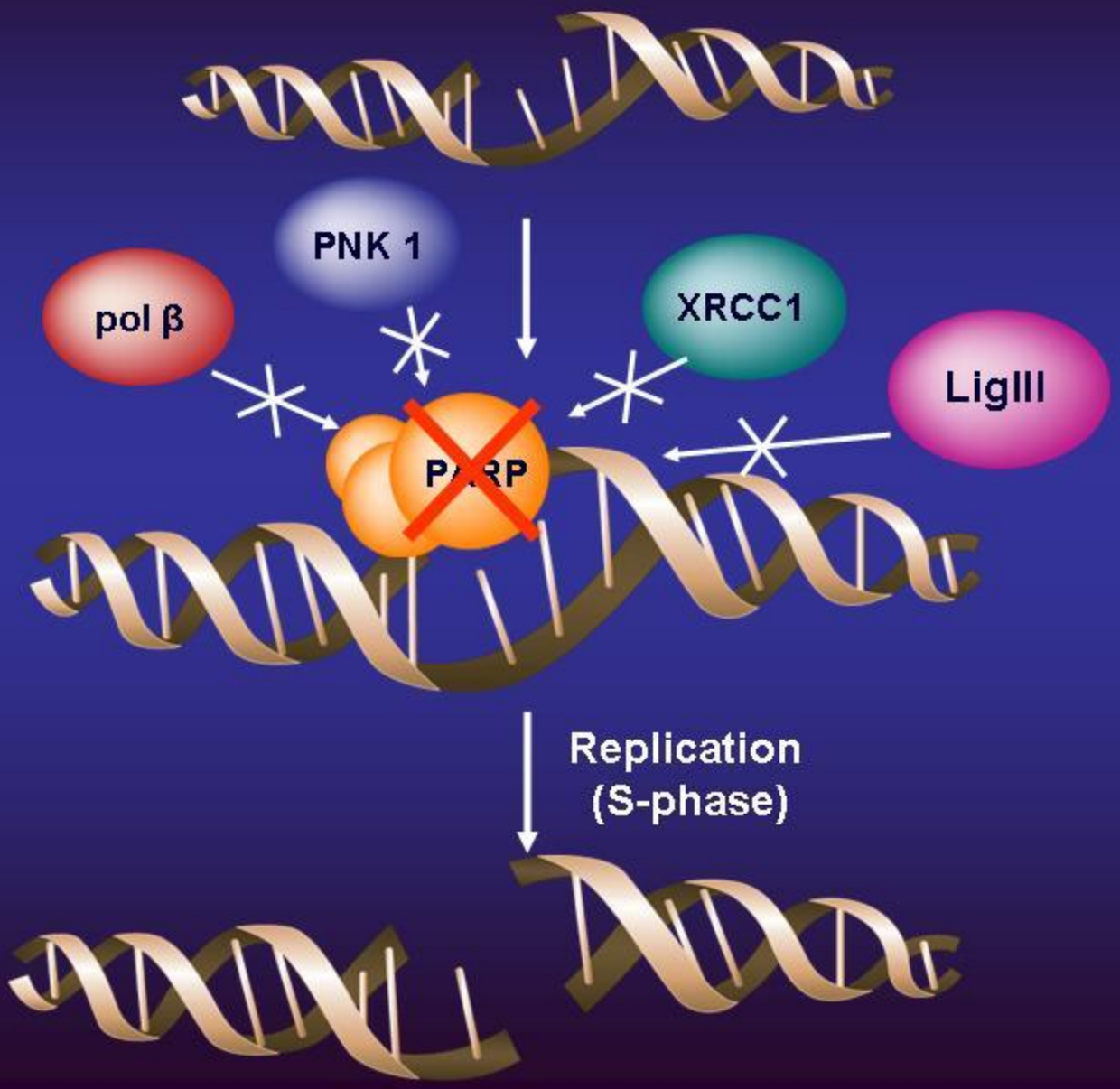
Cancer cells are highly susceptible to DNA repair inhibition

- 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



Inhibiting PARP-1 increases double-strand DNA damage



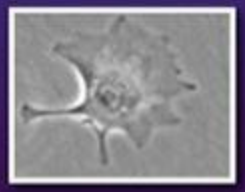
Selective effect of PARP-1 inhibition on cancer cells with BRCA1 or BRCA2 mutation (an example of HR-deficient cells)

DSB in DNA

Normal cell

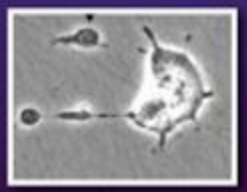
DSB repaired effectively via HR pathway

Cell survival



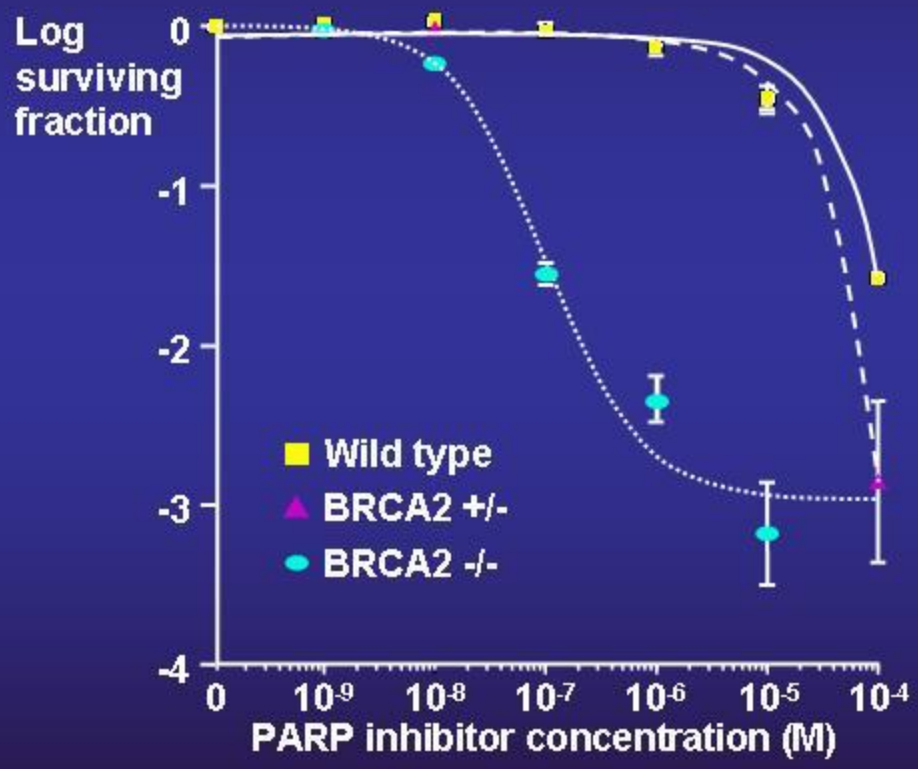
BRCA-deficient cancer cell

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

Control

+ PARP inhibitor

Wild type

Control

+ PARP inhibitor

BRCA2 -/-

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
2. Ratnam K, Low JA. Clin Cancer Res 2007; 13: 1383-1388
3. Fong PC et al. New Engl J Med 2009; 361: 123-134
4. Tutt A et al. J Clin Oncol 2009; 27(18S): Abstr CRA502
5. Audeh MW et al. J Clin Oncol 2009; 27(15S): Abstr 5500