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SUMMARY OF THE VIDEO ON THE

MECHANISM OF ACTION (MOA) OF PARP INHIBITORS AND TARGETING DNA DAMAGE RESPONSE (DDR)

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MoA of PARP inhibitors and targeting DDR

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DNA DAMAGE RESPONSE REPAIRS DNA DAMAGE

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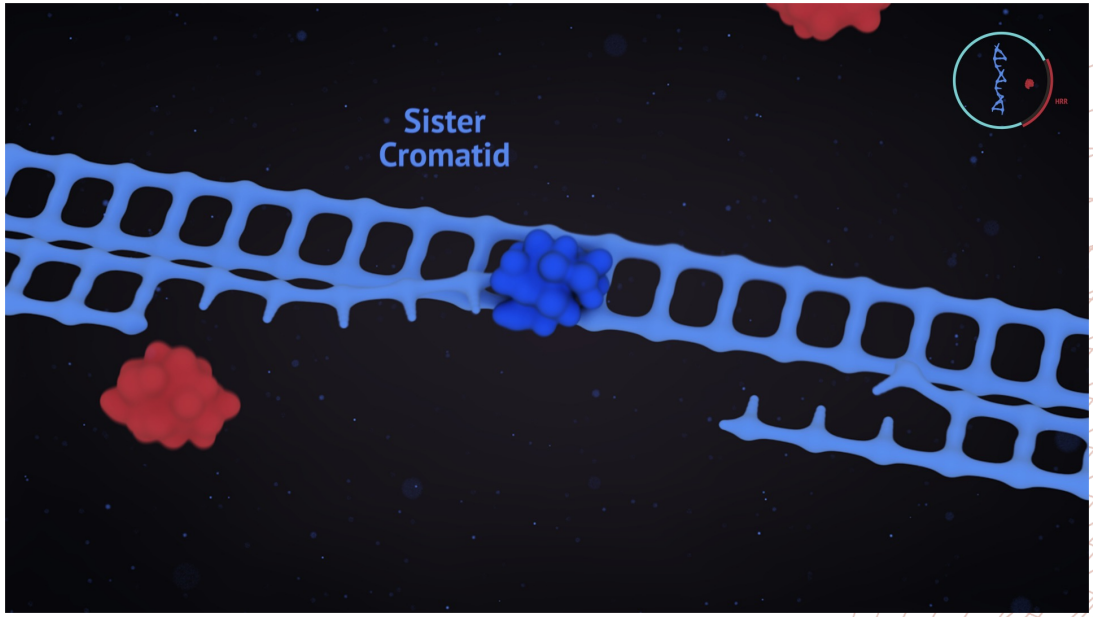

DNA is under **constant risk of damage** by endogenous and exogenous factors. Multiple repair systems, collectively referred to as **DNA damage response** (DDR), can repair this damage.

Homologous recombination repair (HRR) repairs **double-strand breaks**:

1. The broken DNA is trimmed back
2. One of the broken strands invades a sister chromatid
3. The missing information is copied
4. The break is repaired

DDR, DNA damage response; HRR, homologous recombination repair

Gourley C, et al. J Clin Oncol 2019 May 3:JCO1802050

HRR DEFICIENCY LEADS TO INACCURATE DNA REPAIR

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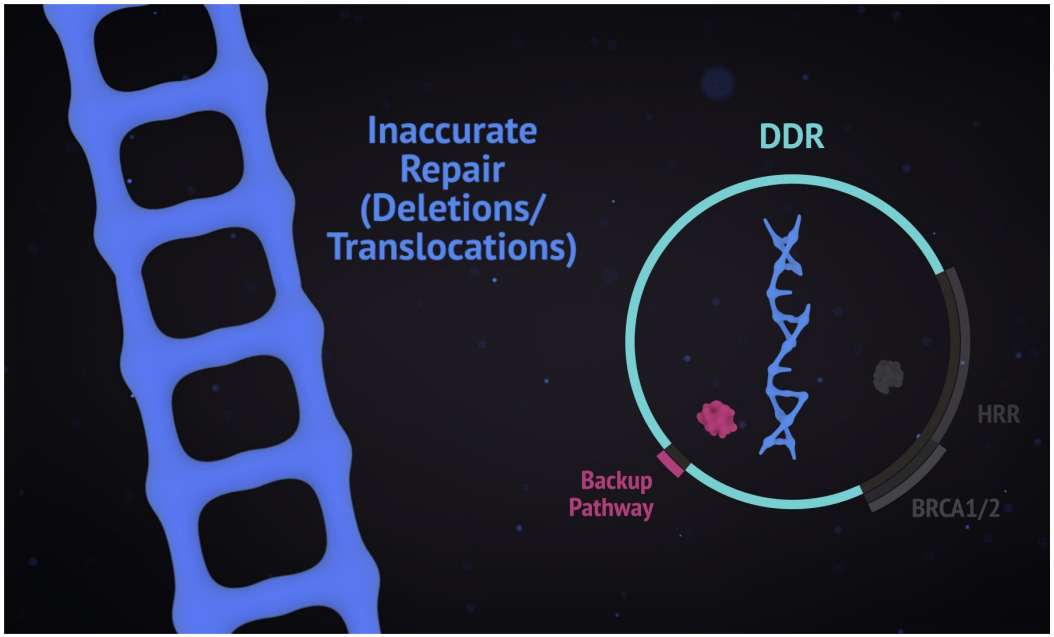

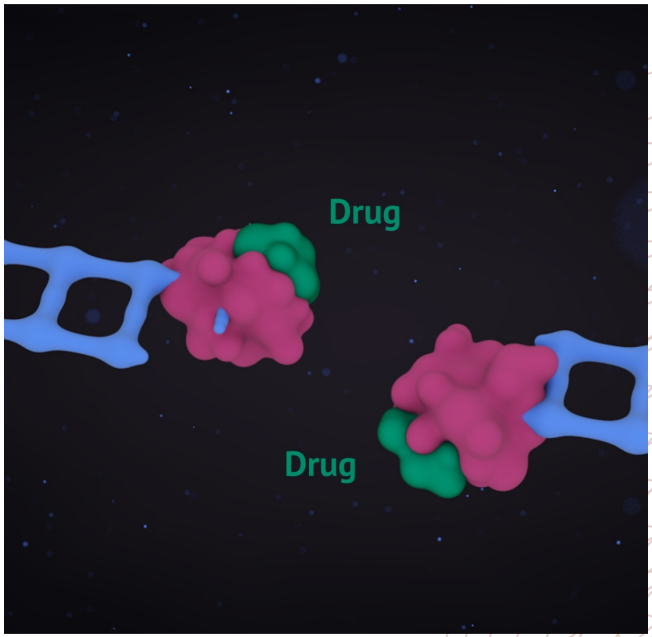

In **HRR deficient cells**, DNA damage is **repaired inaccurately** by a backup pathway. Persistent damage leads to genome instability, so defects in DDR pathways **drive cancer progression.**

BRCA1 and *BRCA2* mutations are the most well-known HRR mutations.

Targeting DDR is an approach that can be applied in **cancer treatment**.

DDR, DNA damage response; HRR, homologous recombination repair

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PARP INHIBITORS ARE THE PROOF OF CONCEPT OF TARGETING DDR

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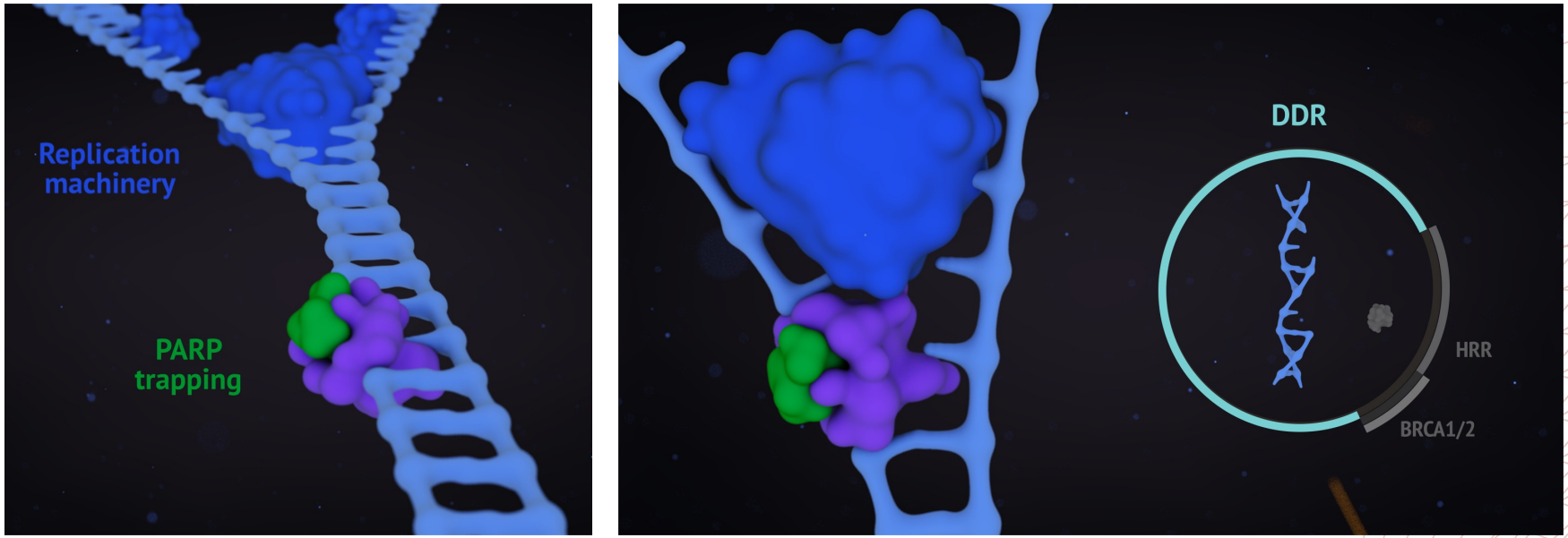

PARP inhibitors **trap PARP on the DNA**, where the complex then presents a **physical obstacle** to the DNA replication machinery, resulting in a double-strand break. The HRR pathway is essential for repairing this type of DNA damage.

In HRR deficient cancer cells, PARP trapping by a PARP inhibitor results in:

1. Replication-fork collapse
2. Accumulation of double-strand breaks
3. Cell death

DDR, DNA damage response; HRR, homologous recombination repair; PARP, poly (ADP-ribose) polymerase

Gourley C, et al. J Clin Oncol 2019 May 3:JCO1802050

PARP INHIBITORS IN CLINICAL PRACTICE

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PARP inhibitors have shown clinical benefit in **ovarian and breast cancer**, with clinical data supporting the use of PARP inhibitors in patients with an **HRR deficiency**.

Platinum also exploits HRR defects, so **platinum sensitivity** serves as a **surrogate** for HRR deficiency.

HRR, homologous recombination repair; PARP, poly (ADP-ribose) polymerase
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THE FUTURE OF PARP INHIBITION AND TARGETING DDR

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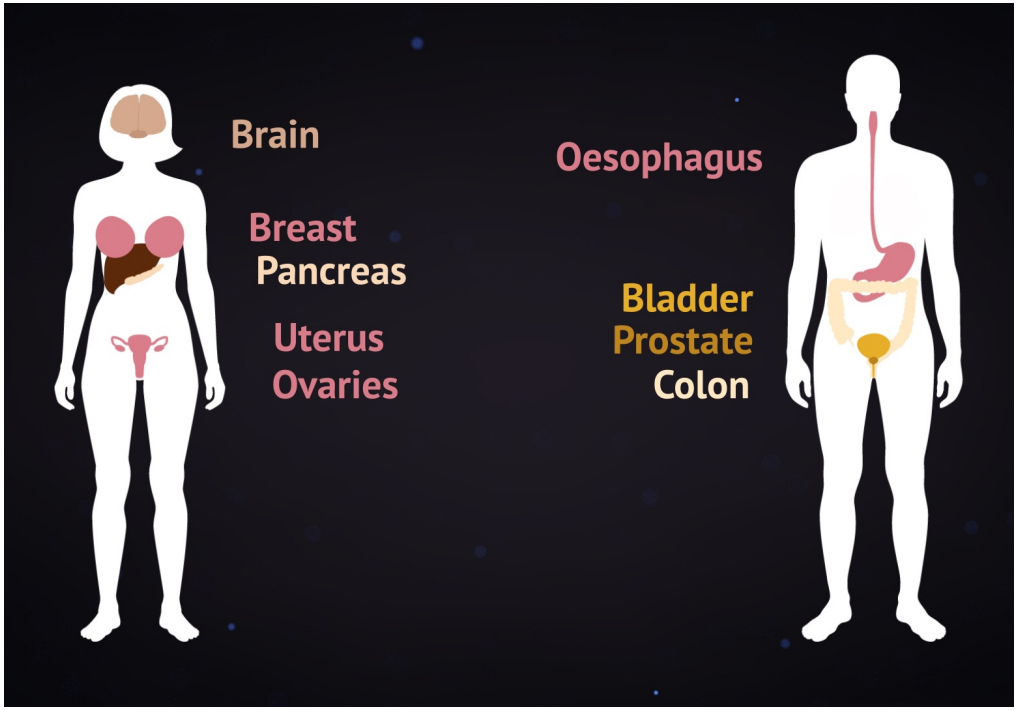

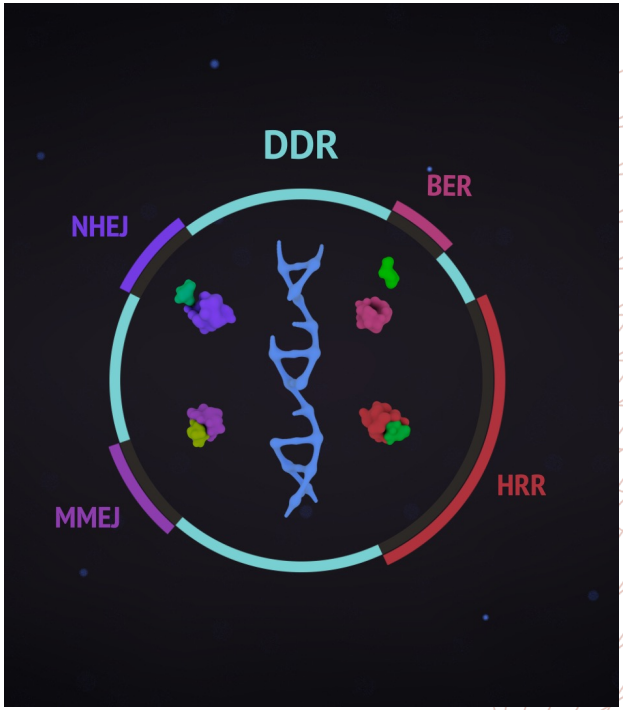

HRR deficiency is seen in a range of cancers, so it is anticipated PARP inhibitors will be effective in various tumour types.

Various **other compounds targeting DDR** are currently under investigation.

BER, base excision repair; DDR, DNA damage response; HRR, homologous recombination repair; MMEJ, microhomology-mediated end joining; NHEJ, nonhomologous end joining; PARP, poly (ADP-ribose) polymerase

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