ICR The Institute of Cancer Research

Collaboration opportunity

Targeting EXD2 for treating tumours with deficiencies in homologous recombination

The Institute of Cancer Research, London, is seeking commercial partners to exploit a synthetic lethal interaction between EXD2 and cancers with deficiencies in homologous recombination (HR), including mutations in BRCA1 or BRCA2.

Key points

- EXD2 inhibition increases cell killing in BRCA1/2 deficient tumours via synthetic lethality and suppression of resistance mechanisms.
- Targeting EXD2 could potentially be more potent than PARP or pol theta inhibition as a monotherapy for treating HR-deficient tumours.
- EXD2 inhibition used in combination with existing PARP inhibitors could boost the effectiveness of these drugs and reduce the likelihood of resistance.

Intellectual property

The Institute of Cancer Research (ICR) has filed a patent (WO-2020260870-A1) covering the targeting of EXD2 – including small molecule inhibitors of its nuclease activity – for treating BRCA1/2- or HR-deficient tumours.

About the programme

Repairing DNA double-strand breaks (DSBs) by HR is critical for maintaining genome stability during DNA replication. Defects in genes involved in the HR pathway, such as BRCA1, BRCA2, RAD51C, RAD51D and PALB2, are common in many different types of cancer – particularly ovarian, breast, prostate and pancreatic cancers.

Scientists at the ICR have made major advances in identifying and understanding synthetic lethal interactions – when a defect in one gene has a limited impact on a cell but causes cell death when combined with blocking the function of another gene product. Exploiting these vulnerabilities has led to novel therapeutic approaches, such as blocking the poly-ADP ribose polymerase (PARP) enzyme to target and kill cancer cells with a deficiency in HR (such as breast, ovarian, pancreatic and prostate tumours with BRCA1/2 deficiencies). But unfortunately, tumour resistance to PARP inhibitors can emerge via several routes – limiting the effectiveness of these drugs.

ICR researchers have recently discovered EXD2 exonuclease as a novel factor with a critical role in repairing of DSBs via two mechanisms: HR and an alternative DNA repair pathway called microhomology-mediated end joining (MMEJ). The loss of this enzyme increases cell death in BRCA1/2 deficient tumours – both via synthetic lethality and the suppression of resistance mechanisms via the MMEJ pathway such as the restoration of BRCA1/2 expression.

Inhibition of EDX2 nuclease is a viable strategy to kill HR-deficient tumours

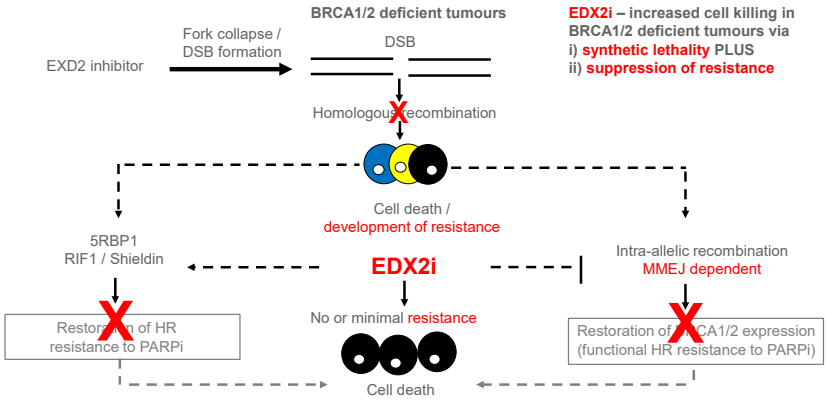

Figure 1: EXD2 inhibition as a novel strategy to treat HR-deficient tumours. EXD2 inhibition leads to increased cell death in BRCA1/2 deficient tumours via synthetic lethality plus the suppression of resistance mechanisms.

About the programme (continued)

Targeting EXD2 – for example, through the development of small molecule inhibitors of its nuclease activity – could be used either as a monotherapy for treating HR-deficient tumours, or in combination with existing PARP inhibitors to improve efficacy and prevent the development of drug resistance.

Lead scientist/inventor

Professor Wojciech Niedzwiedz heads the Genome Instability and Cancer team at the ICR.

He is studying the cellular mechanisms that prevent genomic instability, with a focus on understanding how DNA replication and repair mechanisms function to help prevent cancer development.

Key publications

1. Broderick R, et al. EXD2 promotes homologous recombination by facilitating DNA end resection. ***Nat Cell Biol.*** 2016 Mar;18(3):271-280.

2. Nieminuszczy J, et al. EXD2 Protects Stressed Replication Forks and Is Required for Cell Viability in the Absence of BRCA1/2. ***Mol Cell***. 2019 Aug 8;75(3):605-619.e6.

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