ICR The Institute of Cancer Research

Licensing and collaboration opportunity

Immunotherapy and vaccine-based targeting of drug resistance in HR-defective cancers

The Institute of Cancer Research, London, is seeking a partner to collaborate on the development of anti-cancer vaccines and/or immunotherapeutic approaches to help overcome resistance to PARP inhibition or platinum-based chemotherapy.

Key Features

- PARP inhibitors (PARPi) are used for the treatment of cancers with deficiencies in the homologous recombination (HR) DNA repair pathway, which can be due to defects in certain genes such as BRCA1 and BRCA2. However, resistance restricts clinical utility.
- The Institute of Cancer Research (ICR) has filed a patent for vaccine-based therapy and immunotherapy for the prevention or treatment of certain drug-resistant cancers, following the discovery of neoantigens encoded by reversion mutations in HR genes that drive resistance to therapies such as PARPi.
- We are now seeking a commercial partner to further develop the approach collaboratively for the prevention or treatment of drug resistance in HR-defective cancers.

Intellectual property

The ICR has filed an international patent application (PCT/EP2021/061184) covering anti-cancer vaccines and immunotherapies that mediate immune system-targeting to neoantigens encoded by reversion mutations that drive resistance to therapies such as PARPi or platinum-based chemotherapy.

Commercial Opportunity

We are seeking a commercial partner to further develop the approach collaboratively for the prevention or treatment of drug resistance in HR-defective cancers.

About the programme

PARP inhibitors (PARPi) are used for the treatment of cancers with deficiencies in the homologous recombination (HR) DNA repair pathway, which can be due to defects in genes such as BRCA1, BRCA2, RAD51C, RAD51D and PALB2. Such defects are common in many different types of cancer – particularly ovarian, breast, prostate and pancreatic cancers. Four PARP inhibitors are now approved for treating certain types of cancers – with the potential to expand to more patients in the future. But drug resistance can emerge via several routes, including via reversion mutations that restore the function of HR genes.

Scientists at ICR are studying the emergence, prevention and treatment of resistance to PARPi or platinum-based chemotherapy in HR-defective cancers using established human and mouse T-cell priming assays, novel mouse models available in the group, clinical samples from cancer patients with reversion mutations, and mass-spectrometry approaches.

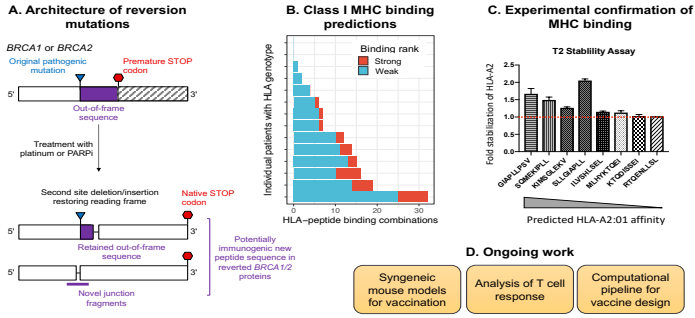

***Figure 1**. A. Common architecture of reversion mutations. A pathogenic frameshift mutation (blue) is compensated for in resistant tumours. This can happen by a second mutation restoring the reading frame, or an in-frame deletion removing the pathogenic mutation. Each of these outcomes introduces new, potentially antigenic, protein sequence (purple). B. Prediction of class I MHC binding affinity for reversions where patient HLA type available. C. Experimental confirmation of binding, assessed via surface HLA-A2 stabilisation in T2 cells exposed to the indicated synthetic peptides observed in clinical reversions. Red line indicates no binding. D. Approaches being taken towards development of immunotherapy and/or vaccination approaches to target reversion-mediated drug resistance.*

Reversion mutuations

The team has discovered that drug-resistant cancers arising through reversion mutations that restore the function of defective HR genes often encode a new protein sequence (neoantigen) that could potentially be targeted using immunotherapy and/or vaccination approaches.

Unlike most other neoantigens under investigation for targeting in cancer, neoantigens associated with reversions offer the advantage that there is a tumour dependency on the reverted protein for survival.

Key publication

Pettitt, SJ et al, *Clinical BRCA1/2 Reversion Analysis Identifies Hotspot Mutations and Predicted Neoantigens Associated with Therapy Resistance*. Cancer Discovery 2020;10(10).
DOI: 10.1158/2159-8290.CD-19-1485

Lead scientists

Dr Stephen Pettitt (*right*) is Deputy Team Leader of the Gene Function Team at the ICR.

He maintains reversions.icr.ac.uk, a comprehensive database of analysis of published reversion mutations.

Professor Christopher Lord is Deputy Head of the Breast Cancer Now Toby Robins Research Centre and Leader of the Gene Function Team at the ICR.

Professor Alan Melcher leads the Centre for Translational Immunotherapy, which brings together experts from the ICR and our partner hospital, The Royal Marsden Hospital NHS Foundation Trust.

Our Business and Innovation Office

The ICR's interactions with industry partners are led by our Business and Innovation Office, which oversees a large portfolio of partnership and licensing opportunities across a range of oncology research.

Contact the Business & Innovation Office for more information on our licensing and partnering opportunities.

Read more about our commercialisation work and sign up for our industry email newsletter at icr.ac.uk/partnerships

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