

Licensing and collaboration opportunity

BAF-complex gene defects as cancer biomarkers for ATR inhibitor (ATRi) sensitivity

The Institute of Cancer Research, London, is seeking a partner to continue the development of ARID1A and other BAF-complex genes as cancer biomarkers for predicting sensitivity to ATRi.

Key Features

- Strong pre-clinical evidence and mechanistic rationale supports the ATR-targeting strategy (both *in vitro* and *in vivo*)
- Potential to use clinical ATRi as single agents or in combination with chemotherapeutic agents or radiotherapy, in multiple tumour types
- Potential for an effective method for selecting patients for ATRi treatment by assessing cancers for defects in BAF-complex genes (especially ARID1A)
- Patent filed to cover use of ARID1A (and potentially other BAF-complex genes) as a biomarker for ATRi treatment in multiple tumour types.

Intellectual property

The ICR has filed an international patent application (PCT/EP2017/050270) to cover the use of these biomarkers with ATRi in multiple tumour types, which has now entered the National Phase in multiple territories. Professor Lord's team also has a wealth of know-how surrounding this biomarker, which will be made available to commercial partners.

Commercial Opportunity

The ICR has full commercialisation rights to this biomarker, and is seeking licensees and/or an industrial partner to collaborate on expanding the pre-clinical data and setting up biomarker-driven proof-of-concept clinical studies.

Background

Genes encoding subunits of the SWI/SNF complex (also known as the BAF complex) including ARID1A are potent tumour suppressors, and these subunits are estimated to be mutated in nearly 20% of all human cancers. However, therapeutic approaches that target SWI/SNF defects are not yet available for clinical use.

An alternative approach has been to identify novel synthetic lethal interactions, and develop therapeutic approaches that exploit them. A team led by Professor Chris Lord at The Institute

of Cancer Research (ICR) has discovered that defects in one or more BAF-complex genes, especially ARID1A, have the potential to be used as biomarkers for selecting patients whose tumours are likely to respond to treatment with inhibitors of ATR (Ataxia-Telangiectasia Mutated (ATM) and Rad3-related protein kinase).

Recently, potent and specific ATRi have been discovered, including VE-821 and VX-970 (aka VE-822) (Vertex), which are currently in early-phase clinical trials as cancer treatments.

Key publication

Williamson, C., Miller, R., Pemberton, H. et al. *ATR inhibitors as a synthetic lethal therapy for tumours deficient in ARID1A*. Nat Commun 7, 13837 (2016). <https://doi.org/10.1038/ncomms13837>

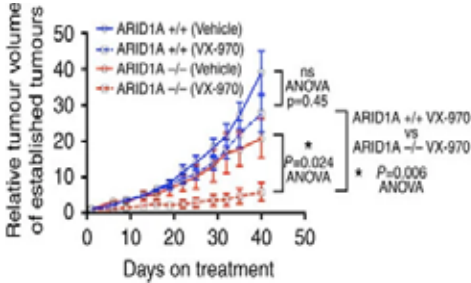


Fig. 3b. *In vivo* ARID1A/ATR synthetic lethality: Relative tumour volume plot showing efficacy of VX-970 and selectivity for ARID1A^{-/-} and ARID1A^{+/+} xenografts in mice.

Biomarker Identification

Using RNAi chemosensitisation screens involving a potent selective ATRi (VE-821), the team initially identified ARID1A as a synthetic lethal partner of ATR inhibition in a p53 mutant, triple negative breast tumour cell line, HCC1143.

Inhibition of ATR in ARID1A-deficient tumour cells triggered premature mitotic entry, genomic instability and apoptosis.

Validation and Mechanistic Insight

The *in vitro* data have been confirmed *in vivo*. In a xenograft tumour model, a clinical ATRi (VX-970) was shown to significantly inhibit ARID1A-deficient tumours (ARID1^{-/-}) as a single agent and impair their establishment and further growth.

Contact

The ICR's interactions with industry partners are managed by our Business and Innovation Office.

This UK-leading technology transfer hub oversees a large portfolio of partnership and licensing opportunities across a wide range of oncology research, from drug discovery and development to medical devices and artificial intelligence tools.

The team also has substantial experimental evidence to support a mechanism driving the sensitivity of ARID1A-deficient cells to ATRi, having shown ARID1A deficiency results in:

1. defective recruitment of the topoisomerase TOP2A to chromatin
2. cell cycle progression defects in both S and G2/M phases of the cell cycle.

They propose that these aberrations might render ARID1A-deficient cells sensitive to ATRi, as these inhibitors impair the ability of the cells to trigger adequate DNA damage responses, whilst accelerating mitotic entry.

Further work has shown that inhibition of other BAF tumour suppressor genes also causes ATRi sensitivity, suggesting this synthetic lethal approach could have wider clinical utility.

Combined with the pre-clinical evidence, this mechanistic rationale provides a strong basis for the assessment of cancers for defects in one or more BAF-complex genes, especially ARID1A, as biomarkers of ATRi response.

Lead scientist

Professor Christopher Lord is Deputy Head of our Division of Breast Cancer Research and leads the Gene Function Team, which applies concepts such as synthetic lethality and non-oncogene addition to identify novel approaches to treating cancer.



To find out more about this and other opportunities please contact:

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