ICR The Institute of Cancer Research

Collaboration opportunity

CAR-T therapy development for breast cancer and other solid tumours

- **The Institute of Cancer Research, London, is seeking a partner to continue the development of CAR-T technology targeted against transmembrane glycoprotein Endosialin – also known as CD248 – in breast cancer and other solid tumours.**
- **No patents have been filed to date, but there is significant know-how within the research team.**

About the programme

There are around 55,900 new breast cancer cases in the UK every year and it is the fourth most common cause of cancer death in the UK, accounting for 7% of all cancer deaths. The majority of breast cancer deaths are due to metastatic disease.

Breast cancer metastasis is a multi-step process influenced by many factors, including the tumour microenvironment (TME). Key interactions between the TME and tumour cells have been identified as promoting metastasis, thus presenting novel clinical targets.

One such target is endosialin, a transmembrane glycoprotein expressed in both developing and adult tissues that are undergoing active physiological or pathological angiogenesis. Endosialin has limited expression in healthy tissues but is strongly upregulated on tumour-associated pericytes and fibroblasts in most solid cancers, including breast cancer.

Using endosialin knockout mice, which show no overt phenotypic abnormalities, the research team has demonstrated that expression of endosialin in the tumour stroma promotes tumour cell intravasation into blood vessels, thereby promoting metastatic dissemination. Endosialin-expressing cells present an interesting target for CAR T-cell therapy as they are relatively accessible to infiltrating CAR T-cells.

Based on an in-house generated monoclonal antibody a CAR construct that recognises both mouse and human endosialin was generated. Experiments comparing the effects of endosialin-directed CAR T-cells (Endo3 CARs) and mock transduced T-cells (mock T-cells) in a spontaneously metastatic BALB/c breast cancer mouse model revealed that Endo3 CAR treatment significantly reduces the number of metastatic deposits in the lungs.

Endo3 CARs expanded by at least two-fold in tumour-bearing mice, with endosialin staining confirming that Endo3 CAR treatment resulted in the depletion of endosialin-positive cells in the tumour stroma, without affecting normal tissue.

Strikingly, Endo3 CAR treatment also resulted in significant growth inhibition and necrosis of the primary tumour. No off-target or on-target/off-tumour activity was observed in experiments with non-tumour bearing wildtype mice, in wounding models which display an activated stroma or tumour-bearing endosialin knockout mice.

The proof-of-concept results show that targeting endosialin via CAR-T therapy could be a viable option to treat not only breast cancer but also other solid tumours and metastatic cancers.

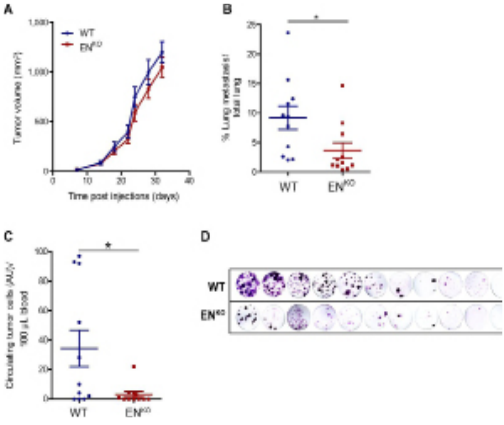

Fig.5 from *Viski C et al*. Stromal endosialin promotes tumor cell dissemination. 4T1-Luc-RFP cells (1 × 104) were injected orthotopically into BALB/c WT or ENKO mice (n = 11 mice per group). **A**, primary tumor growth. **B,** quantification of lung metastasis by digital droplet PCR (ddPCR). Data shown are the percentage of RFP+ droplets relative to TFRC+. Each data point represents one mouse. *, P < 0.05. **C**, quantification of circulating tumor cells from 14 days cultured blood. Data are mean number of tumor colonies per 100 µL whole blood from two independent samples per animal. *, P < 0.05. Equivalent results were obtained in two independent experiments. **D**, representative images of tumor cell colonies.

Breast cancer research

Scientists in the ICR's Division of Breast Cancer Research have been global pioneers in exploiting the concept of synthetic lethality in cancer research and treatment, after also first discovering the BRCA2 gene.

They discovered how to use PARP inhibitors to target cancer with BRCA 1/2 mutations, then led early clinical trials using these drugs. PARP inhibitors are now established as a widely used treatment for BRCA-positive breast and ovarian cancers.

Our Faculty has also led the development of molecular biomarkers for prognosis and therapy prediction, as well as driving the development of aromatase inhibitors and CDK4/6 inhibitors in oestrogen receptor positive (ER+) breast cancer.

Our researchers work closely with industry to develop novel treatments for breast cancer using a multidisciplinary approach that spans clinically relevant fundamental biology, through to therapy discovery and development.

We develop molecular biomarkers, discover novel drivers of cancer phenotypes, and test new therapy approaches in proof-of-concept clinical trials.

Lead scientist

Professor Clare Isacke

Professor Isacke is an international leader in the study of breast cancer metastasis. She has held several senior positions at the ICR.

Key publications

Viski C, et al. *Endosialin-Expressing Pericytes Promote Metastatic Dissemination.* Cancer Res September 15 2016 (76) (18) 5313-5325; DOI: 10.1158/0008-5472.CAN-16-0932.

Ash S et al. *Targeting the tumor stroma using CAR T-cells.* Cancer Res August 15 2020 (80) (16 Supplement) 3241; DOI: 10.1158/1538-7445. AM2020-3241.

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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