ICR The Institute of Cancer Research

CANCER RESEARCH HORIZONS

Discovering and developing small-molecule inhibitors of ERAP1

The Institute of Cancer Research, London, and Cancer Research Horizons are seeking a collaborative partner to accelerate the development of an ERAP1 programme in the Centre for Cancer Drug Discovery at The Institute of Cancer Research (ICR).

The research team has discovered a series of novel compounds which are now at the lead optimisation stage, having shown potent activity against ERAP1 in preclinical studies.

Targeting ERAP1 has particular potential to enhance the effectiveness of checkpoint inhibitors or radiotherapy, in patients who do not currently respond to those treatments.

About the programme

The development of immunotherapies has created a paradigm shift in the treatment of some cancers. Monoclonal antibodies that modulate the activity of T-cells through pathways such as CTLA-4, PD-1 and PD-L1 have become a standard treatment and have made an enormous impact in several cancer types. However, patients do not respond to these drugs in a wide range of settings.

Scientists are now searching for new therapeutic agents that could enhance the effectiveness of immunotherapies. One promising avenue of investigation is the discovery and development of small molecule cancer drugs that could increase the availability of immunogenic neo-antigens on the surface of tumour cells – increasing the engagement of T-cells with tumours and making cancer cells 'more visible' to the immune system.

ERAP1 is an aminopeptidase that plays an important role in antigen generation, trimming peptides for presentation to Major Histocompatibility Complex (MHC) proteins and subsequent immune response to pathogens.

Scientists in the ICR's Centre for Cancer Drug Discovery believe that an ERAP1 inhibitor could modulate tumour antigen presentation on the surface of tumour cells to elicit an increased T-cell response, and tumour regression. In addition, ERAP1 inhibition can change the configuration of antigens presented to MHC protein HLA-E, and in turn result in the activation of natural killer cells.

ICR scientists at the Centre for Cancer Drug Discovery have developed a series of ERAP1 inhibitors which are at the early Lead Optimisation stage. The most potent compounds have pIC50 > 8 against both human and mouse ERAP1 (unpublished data).

Lead scientists/inventors

Dr Gary Newton is Team leader in Medicinal Chemistry at the ICR's Centre for Cancer Drug Discovery. His team is particularly involved in collaborative research with internal and external partners.

Dr Esther Arwert is an ICR Fellow based across our Divisions of Breast Cancer and Cancer Therapeutics. Dr Arwert is aiming to therapeutically exploit the complex interactions between cancer cells and their microenvironment.

Dr Olivia Rossanese is Director of the Centre for Cancer Drug Discovery and Head of the Division of Cancer Therapeutics, and has substantial experience of leading and contributing to discovery and target validation programmes.

Key points

- A lead-stage series of small molecule inhibitors of human ERAP1*
- Potent, orally-available inhibition of mouse and human ERAP1*
- Highly selective (>100-fold) for ERAP1 over other M1 aminopeptidases*
- Good oral absorption and microsomal stability*
- Positioned as a combination therapy in diverse cancers, with particular focus on colorectal cancer*
- Compounds modulate tumour antigen expression*
- Further studies are planned, including combination analyses with existing modalities and efficacy studies using in vivo and in vitro cancer models

* unpublished data

Our Centre for Cancer Drug Discovery

The ICR's Centre for Cancer Drug Discovery is one of the world's most successful academic drug discovery centres. made up of around 180 scientists in a wide variety of disciplines – including cell and molecular biology, pharmacology, tumour modelling, computational and structural biology, and medicinal chemistry – who have discovered 21 drug candidates since 2005, of which 13 have progressed to clinical trials.

Our scientists in drug discovery also work closely with colleagues in the Drug Development Unit at the ICR and our partner hospital, The Royal Marsden NHS Foundation Trust, which is one of the most successful phase I oncology units in the world. We are particularly well known for our expertise in small-molecule therapeutics and recently launched new Centres for Protein Degradation and for Target Validation.

Our Business and Innovation Office

Our Business and Innovation Office oversees a portfolio of partnership opportunities across a wide range of oncology research.

Contact
Dr Jonathan Beech
Business Development Manager
The Institute of Cancer Research
E jonathan.beech@icr.ac.uk
T +44 20 8722 4226

CANCER RESEARCH HORIZONS

Cancer Research Horizons is a specialist oncology drug discovery, development and commercialisation company that fast tracks scientific breakthroughs for patient benefit.