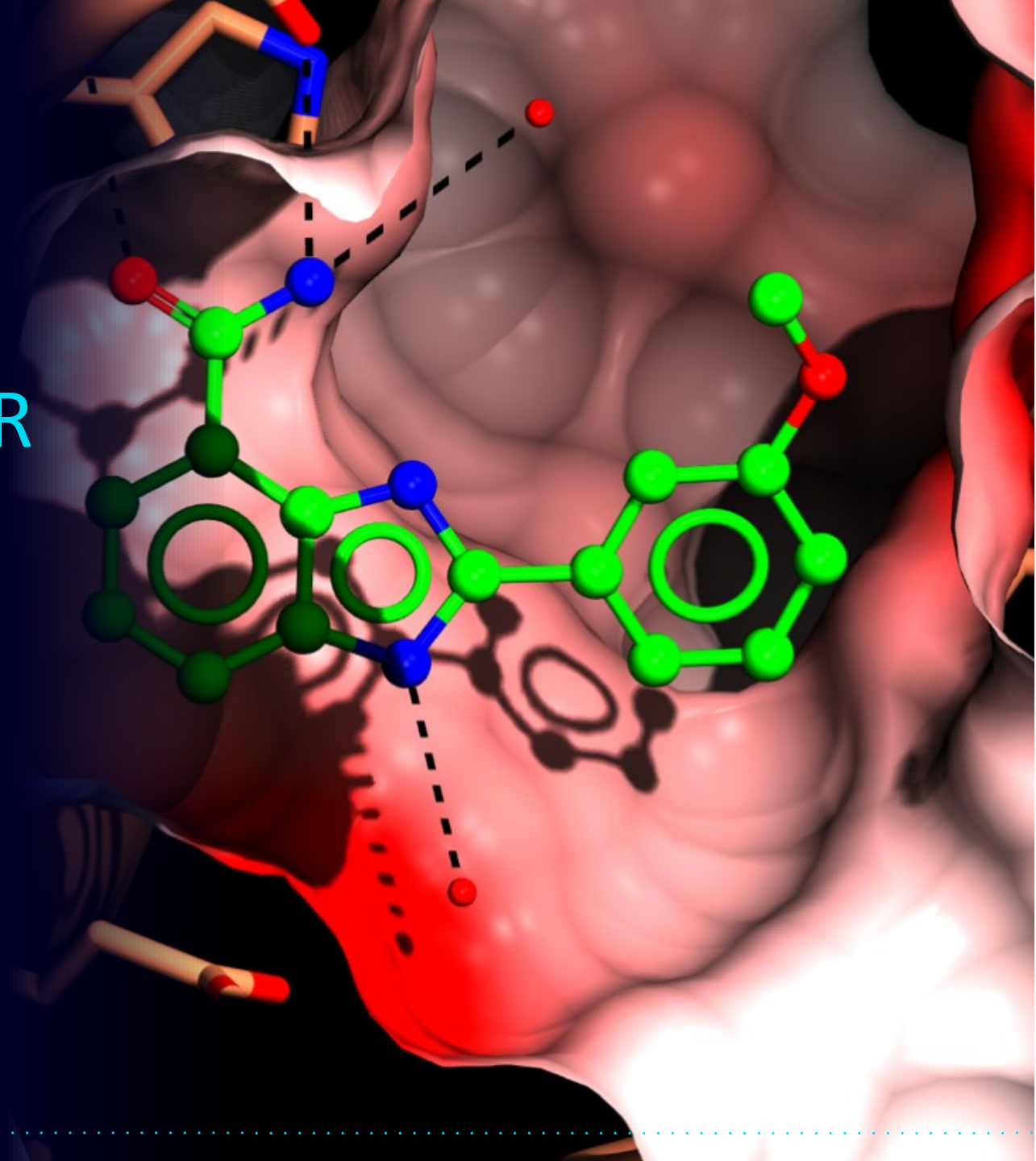
CANCER RESEARCH HORIZONS

FURTHER FASTER TOGETHER

ICR The Institute of Cancer Research

ERAP1 INHIBITORS FOR ENHANCING TUMOUR ANTIGEN PRESENTATION



Non-confidential overview

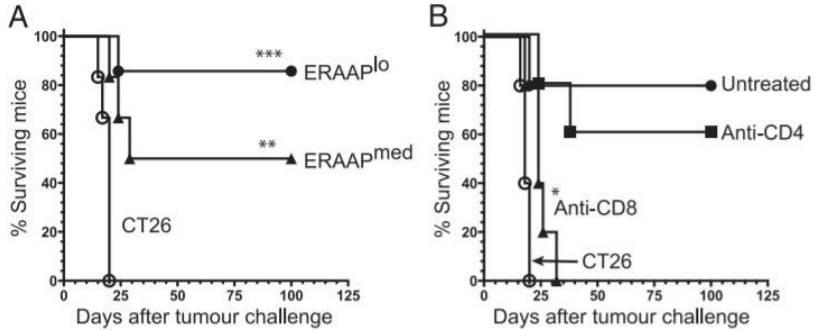
December 2022

OPPORTUNITY OVERVIEW

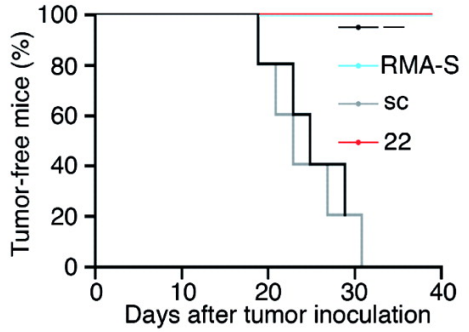
- A lead-optimisation stage series of small molecule inhibitors of ERAP1 has been developed at the Institute of Cancer Research in London
- Compounds have been shown to increase the variety of tumour antigen expressed and are positioned as a combination therapy in diverse cancers, with particular focus on colorectal cancer
- Potent, orally-available inhibition of mouse and human ERAP1 enzyme
  - *hERAP1 and mERAP1 pIC50 > 8*
  - Highly selective (>100-fold) for ERAP1 over other M1 aminopeptidases
- Priority GB patent application filed in on novel chemical series in April 2022
- **Available for collaborative development partnership to accelerate preclinical and clinical studies**

ERAP1 – TARGET HYPOTHESIS

- Checkpoint inhibitors are effective in only in a small subset of cancers, typically presenting with:
  - Sufficient antigen presentation on tumour cell surface,
  - Adequate T-Cell activation to engage the immune response.
- ERAP1 is a M1 Aminopeptidase that plays a major role in determining which antigens are expressed on the surface of cells.
- shRNA KD or KO of ERAP1 prolongs survival in immunocompetent mouse cancer models (see Figures.).
- Inhibiting ERAP1 changes antigen presentation in tumour cells, making tumours more visible to the immune system.
- **It is hypothesised that ERAP1 inhibition, in particular in combination with checkpoint inhibitors or radiotherapy, will lead to enhanced T cell and NK cell responses and therefore significantly increase tumour cytotoxicity.**



Mice with subcutaneous injection of CT26 colorectal cancer with shRNAKD of mERAP1 *(James et al, J. Immunol, 2013)*



Mice with subcutaneous injection of RMA lymphoma cells with shRNA KD mERAP1 *(Cifaldiet al Cancer Research 2011)*

ERAP1 INHIBITION IN CANCER CELL LINES

- The identified ERAP-1 inhibitors effectively modulated the immunopeptidome in cancer cell lines:
  - Immunopeptidome studies revealed lengthening of peptides in response to inhibition of ERAP1 in HCT116 cells, which is a characteristic phenotype observed in ERAP1 KO cells (Fig 1)
  - Known ERAP1-driven surface antigens (SIINFEKL and LV9) are modulated by ERAP1 inhibition (Fig 2).

Fig 1

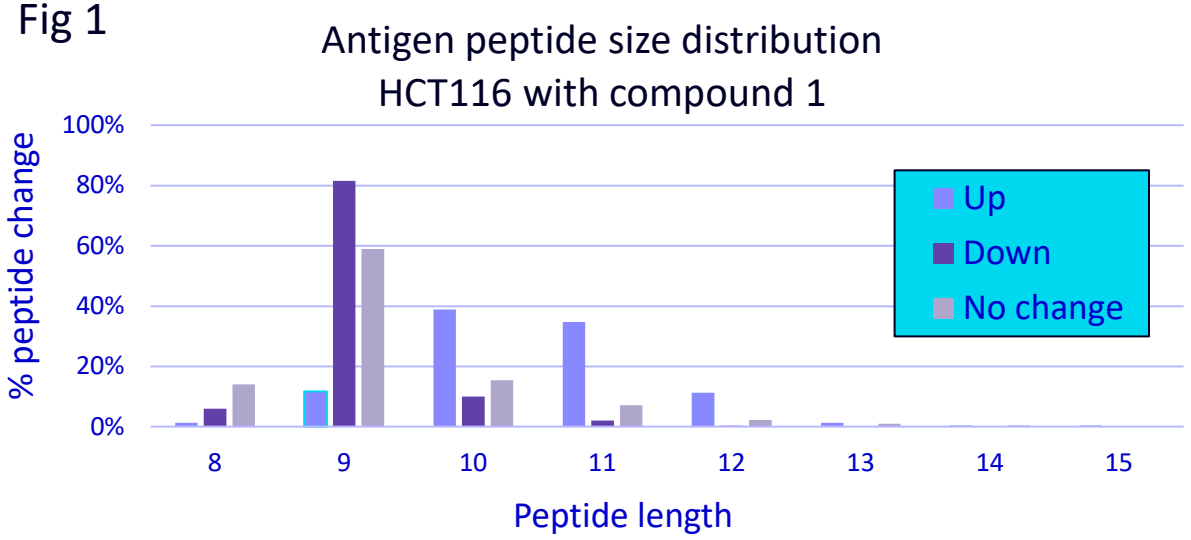
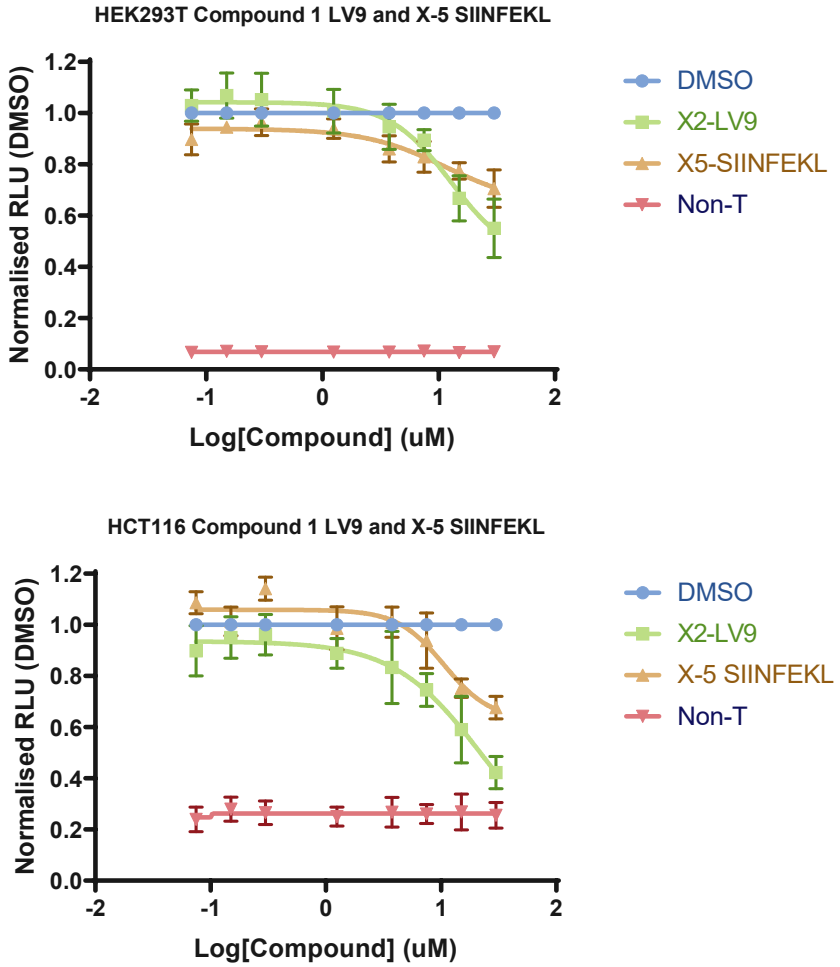


Fig 2



PROGRAM STATUS

ICR has developed a series of ERAP1 inhibitors with good oral absorption and microsomal stability.

Current efforts are focused on structure-guided lead optimisation using X-ray crystallography, with a view toward in vivo efficacy studies to support confirmation of disease positioning and combination analyses with existing modalities.

	Lead Compound 1	Lead Compound 2
hERAP1 IC_{50}	**5.1 nM**	**1.6 nM**
mERAP1 IC_{50}	**19 nM**	**4.5 nM**
hERAP1 target engagement Free EC_{50}	52 nM	45 nM
Kinetic Solubility	>500 µM	460 µM
MLM Clint (NADPH)	< 10 µl/min/mg/protein	117 µl/min/mg/protein
CACO2	A:B: $3.7x10^6$ cm/s ER: 6.9	A:B: $7.4x10^6$ cm/s ER: 0.9

CANCER RESEARCH HORIZONS

FURTHER FASTER TOGETHER

SUMMARY

- Potent, lead optimisation stage chemistry
- Deep in-house biology expertise to support collaborative studies
- Priority, Composition-of-Matter GB patent application filed
- Available for partnering for preclinical and clinical studies

THANK YOU

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