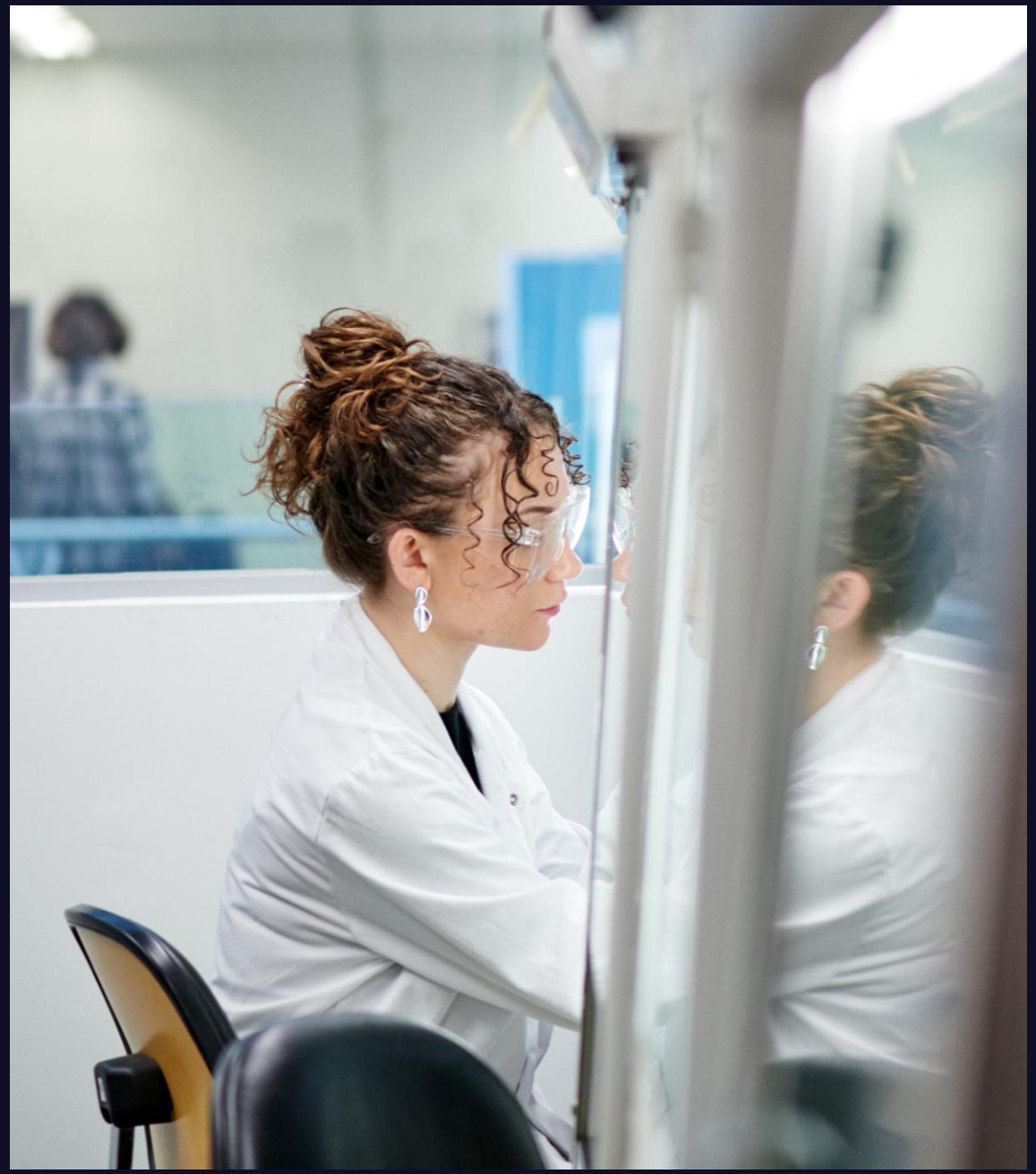


CANCER RESEARCH HORIZONS

MANCHESTER 1824
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ERK5-targeted PROTAC

Collaboration and licensing opportunity

Non-confidential overview

FURTHER FASTER TOGETHER
We are beating cancer

First-in class, ERK5-PROTAC

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CANCER RESEARCH HORIZONS

Early lead

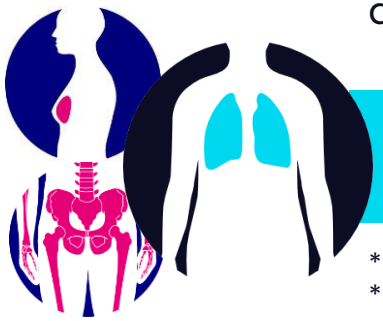
Asset: First in class, highly specific, ERK5/MAPK7 degrader molecules with effective target degradation *in vivo*, and preliminary evidence of efficacy in multiple tumour models. Mesothelioma current target indication.

Landscape: Additional immune-oncology mechanism complements non-immune impacts and unlocks ERK5 as a promising cancer target through modulation of the tumour microenvironment, differentiated from ERK5 inhibition. Our ERK5-PROTAC is the most specific and most advanced* (only one with *in vivo* efficacy data*

Commercial: Composition of matter patent filing (2021) in national phase with broad regions covered. Seeking licensing or collaboration partner to drive the asset through preclinical development and beyond.

Key Qualities:

- Highly selective (no BRD4/AurA liabilities)
- Potent degradation *in vitro* (DC50 <1 nM) and *in vivo*
- Novel immuno-oncology mechanism
- No clinical competition, and superior profile vs preclinical competition
- Team: experts in ERK5 (K. Finnegan) and medicinal chemistry (S. Butterworth)
- Composition of matter patent with high likelihood of granting

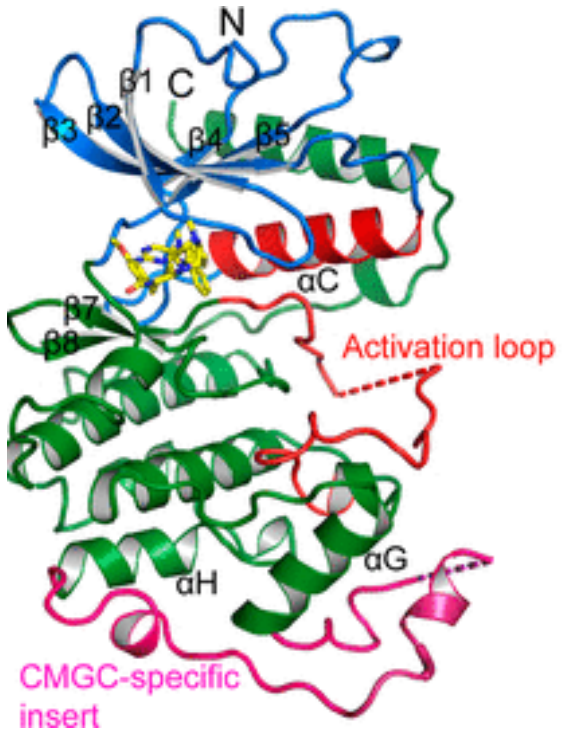


in vivo PoC underway in mesothelioma: MoA studies, biomarker identification, efficacy and tox. Supporting data also in TNBC, osteosarcoma, GBM**

*Based upon publicly disclosed information
**Under funding from CRH and University of Manchester

First in Class ERK5 PROTACs

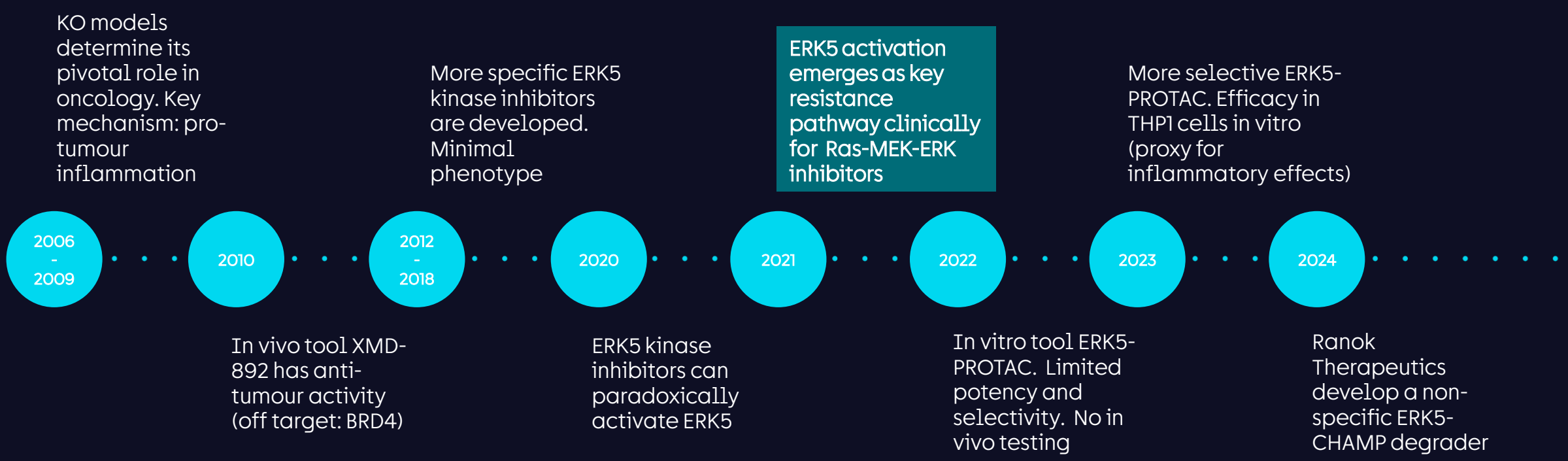
- ERK5 is a kinase upregulated in multiple cancers of high unmet-need and is linked to poor survival, metastasis and treatment resistance.
- Non-kinase function of ERK5 drives pro-tumour signalling through both immune dependent and independent pathways.
- We have discovered novel ERK5-PROTACs that outperform all other ERK5 inhibitors - with *in vivo* efficacy across TNBC, mesothelioma and osteosarcoma models.
- These tools have also facilitated target validation studies in non-oncology indications such as wound healing and fibrosis.
- We are now seeking licensing or collaboration partners to drive these asset through preclinical development and beyond.



ERK5 landscape timeline

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CANCER RESEARCH HORIZONS



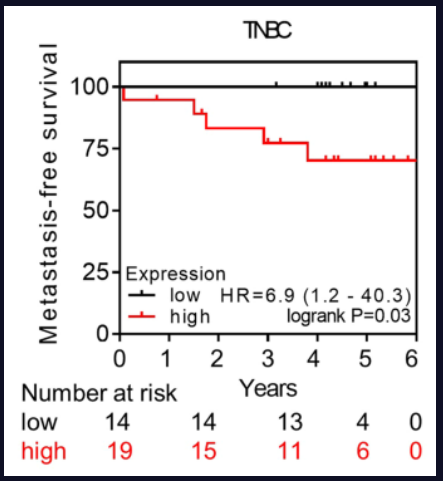
The challenge

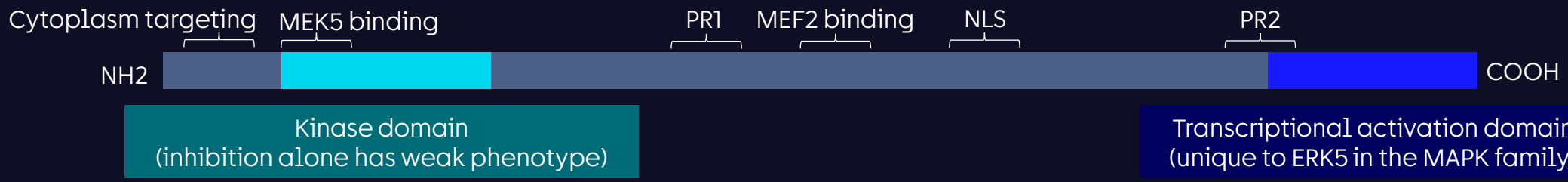
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CANCER RESEARCH HORIZONS

Targeting ERK5 demands fresh thinking to leverage the great potential shown by KO phenotypes

- ERK5 is a known driver of many hallmarks of cancer, and has few homeostatic functions making it an ideal drug target, unlike other targets in the ERK1/2 pathway
- ERK5 is a kinase upregulated in multiple unmet-need cancers and is linked to poor survival, metastasis and treatment resistance (TNBC, mesothelioma, sarcoma)
- ERK5 loss (KO) elicits strong anti-tumour and anti-metastatic phenotypes, concordant with clinical correlations
- Despite this, ERK5 inhibitors have not progressed to clinical trials
  - Minimal phenotype from specific kinase inhibitors
  - Some inhibitors cause paradoxical activation
- ERK5 is unique among the MAPK family as it contains both a kinase domain and a C-terminal transcriptional activation domain.
- ERK5's kinase-independent functions are the real driver of tumour growth. Kinase inhibition does not target the tumour-driving non-kinase functions of ERK5.





Solution:

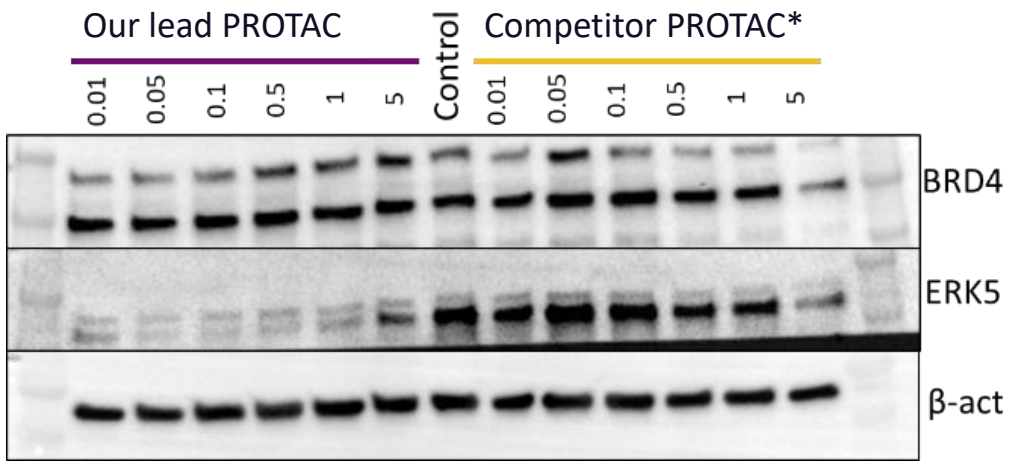
ERK5-PROTACs targeting non-kinase functions of ERK5 to replicate KO phenotype

Lead ERK5-PROTAC profile

- PROTAC designed based upon a known, highly selective ERK5 inhibitor with a cereblon type E3 ligase binder
- Current lead PROTAC has **DC50 <1 nM**
- **Effective degradation of ERK5 *in vivo*** with promising TGI and impact on immune contexture
- **PROTAC-ERK5 dosing has no observable adverse effects**: heart size, function and vessel patency

Competitive positioning

- Other ERK5 PROTACs that failed to demonstrate anti-proliferative effect have solely been tested *in vitro* (Nathaniel Gray, Harvard – NG7)
- Furthest development of ERK5-degrader by Ranok Therapeutics – preclinical stages, HSP90 chaperone mediated degradation, non-specific
- We have shown that the effect of ERK5-degradation is profound when observed *in vivo* and *in vitro,* using relevant assays
- Our PROTAC has demonstrated superior specificity (no BRD4/AurA interaction) and potency compared to NG7* (DC50 21 nM) and Ranok Therapeutics



24h treatment in MDA468 (TNBC) cell lines

*Competitor PROTAC – NG7, Nathaniel Grey lab, Stanford

ERK5-PROTAC prevents the growth and spread of TNBC tumours

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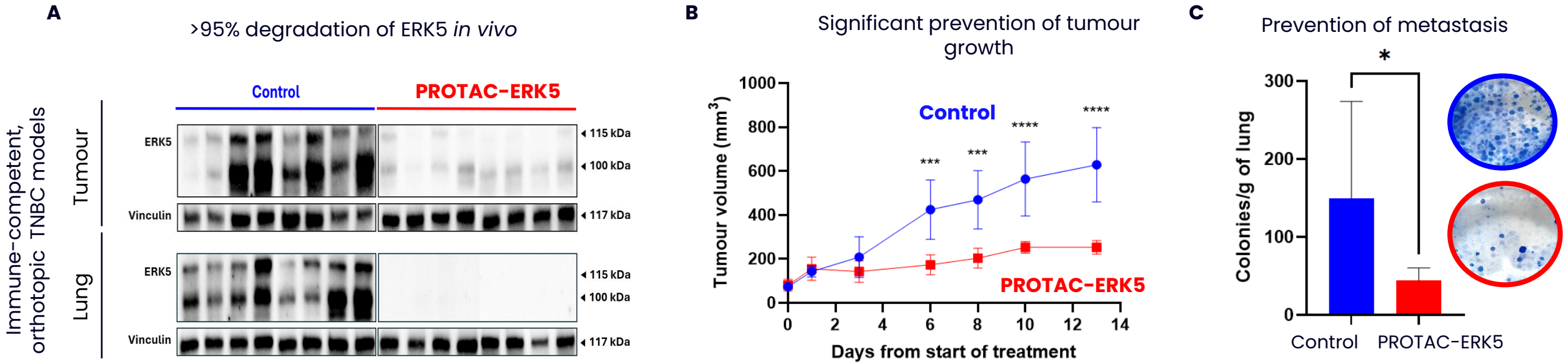
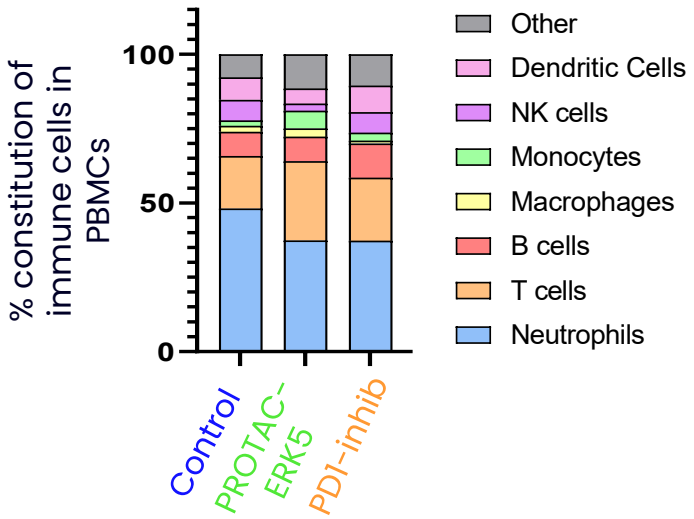


Figure 5 ERK5-PROTAC prevents tumour growth and spread in vivo. A. ERK5-PROTAC degrades ERK5 protein in tumour and lung. **B.** ERK5-PROTAC treatment significantly ($p<0.0001$) prevents tumour growth. **C.** ERK5-PROTAC treatment prevents metastatic spread to the lung (clonogenics).

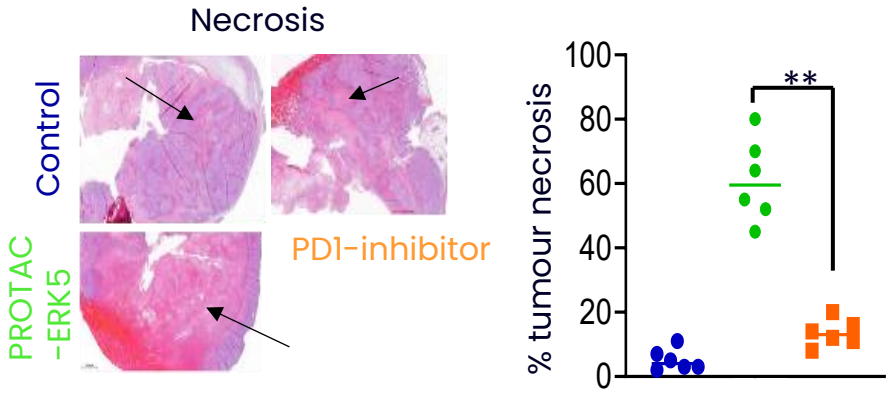
PROTAC-ERK5 is an immune modulatory agent and out-performs PD1 inhibitors

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A ERK5-PROTAC delivers PD1-inhibitor-like immune changes



B Multi-modal ERK5-PROTAC outperforms PD-1 inhibitors in tumour necrosis



C ERK5-PROTAC stops metastatic spread—PD-1 inhibition does not

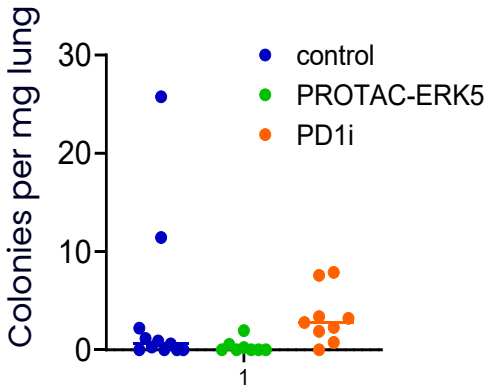


Figure 5 PROTAC-ERK5 inhibits the growth and prevents the metastatic spread of syngeneic, orthotopic TNBC tumours (EMT6) and outperforms PD1 inhibitors. A second model of immune-competent, orthotopic (mammary fat-pad, EMT6 cells) syngeneic TNBC tumours was used to complement the data in 4T1 TNBC models (Figures 1-5) and rigorously confirm ERK5-PROTAC efficacy in two independent TNBC tumour models and evaluate underpinning mechanisms.

Development Status

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LEAD ERK5-PROTAC identified. Efficacy proven in cancers of unmet need.

1. Creating a TPP

- Lead indication
- Comparison to standard-of-care
- MOA determination
- Patient Selection criteria

2. Expanding indications

- Osteosarcoma
- TNBC
- Comparison to and combination with standard-of-care



The June Hancock Mesothelioma Research Fund

LifeArc

CANCER RESEARCH UK

UKRI Medical Research Council

Progressing ERK5-PROTAC to FIH trials

- Developing our putative pharmacodynamic and patient-selection biomarkers to GLP standard
- Optimising oral bioavailability to final clinical candidate
- Established links with clinicians running international trials in lead indications

Commercial opportunity

Market Advantage

ERK5-PROTAC sits at the intersection of a proven MAPK market and a rapidly scaling PROTAC market, giving it a strong chance to define and lead the category

- No ERK5-directed therapies have reached the clinic, yet, despite strong tumour and immune genetic
- MEK-ERK inhibitors generate ~$2.1B today, projected to reach ~$4.6–7.6B by 2034, demonstrating strong demand (durability is limited by ERK5-driven resistance mechanisms)
- PROTAC market growing from ~$0.4–1.2B today to ~$4–6B+ by early 2030s

IP

Patent WO2023156791A1 covers lead and related heterocyclic compounds targeting ERK5-mediated diseases.

- Includes oncology and non-oncology uses e.g. fibrosis, and inflammatory diseases.
- Filed 17 February 2022. Now in national phase in the US, Europe, China, Japan, Canada, and Australia

Seeking partnerships

Licensing partners, collaborators and investors interested in advancing this first-in-class ERK5-PROTAC programme toward the clinic for a range of oncology and non-oncology indications.

Further data available under CDA

- Studies demonstrating cardiac safety
- Efficacy in models of TNBC, osteosarcoma and mesothelioma
- Synergistic efficacy with standard of care in TNBC models
- Profile of effects on immune contexture in immune competent osteosarcoma and TNBC models
- Biomarker studies
- Further preclinical studies in select lead oncology indications ongoing



Thanks from the Team



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World-leading expert in ERK5

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BONE CANCER RESEARCH TRUST
UNTIL THERE'S A CURE

Sarcoma UK
The bone & soft tissue cancer charity



The June Hancock Mesothelioma Research Fund

LifeArc

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