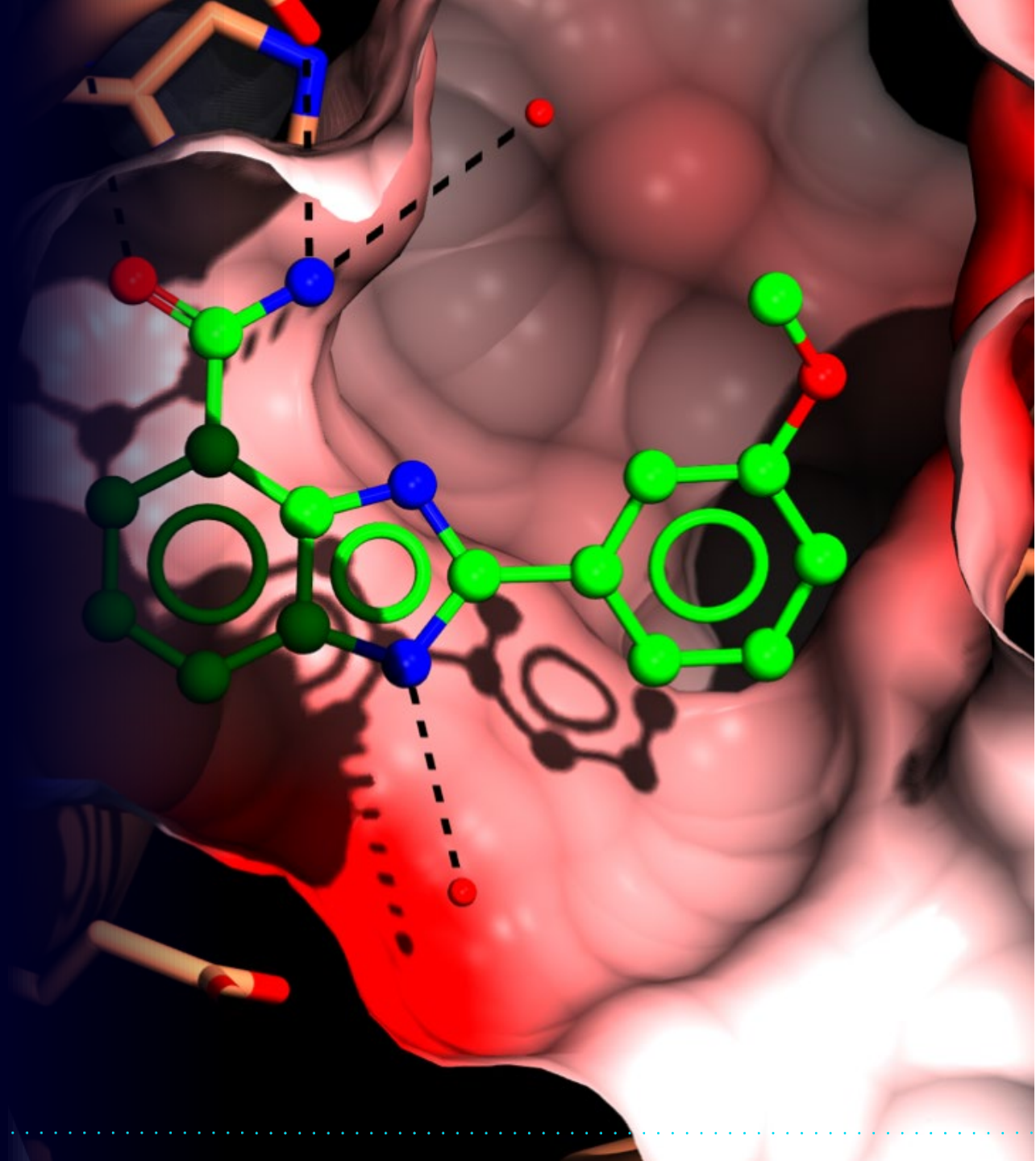
CANCER RESEARCH HORIZONS

FURTHER FASTER TOGETHER

LICENSING OPPORTUNITY:

IKK ALPHA-SELECTIVE SMALL MOLECULE INHIBITORS



June 2022

OPPORTUNITY OVERVIEW

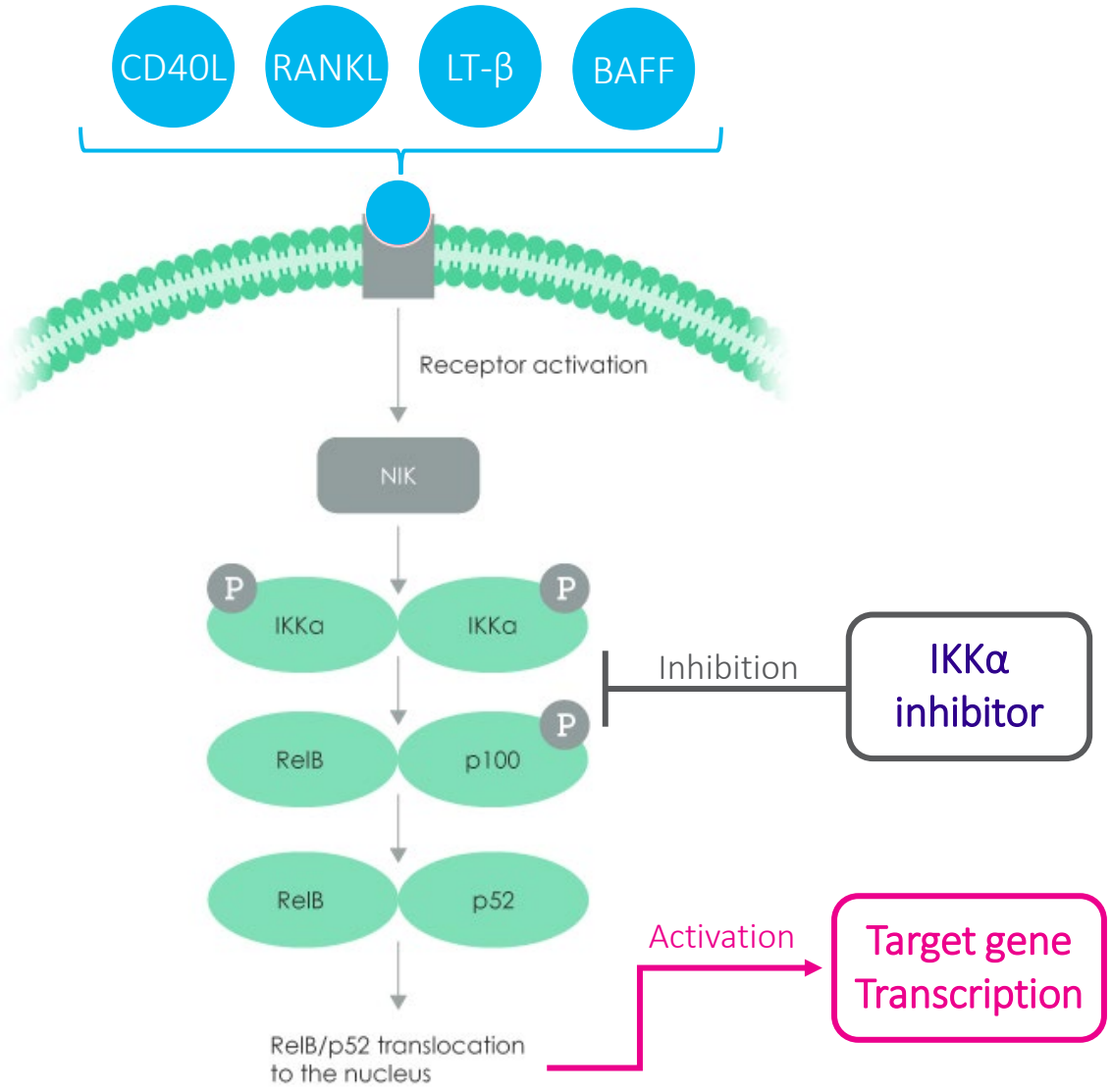
- IKKα is key kinase in the non-canonical NF-κB signalling pathway, which drives signalling from TNF family receptors such as CD40, lymphotoxin Beta, RANK and BAFFR. Lead investigator is Professor Simon Mackay, professor of medicinal chemistry at Strathclyde University
- Compounds in lead-optimisation show no engagement with IKKβ markers in cells
- In-vivo efficacy demonstrated in prostate cancer model
- Primary clinical hypothesis: use of IKKα inhibitors for the treatment of castrate resistant prostate cancer (CRPC) and resistance to androgen ablation therapies (e.g. abiraterone, enzalutamide etc)
- Additional targeted indications: pancreatic cancer, multiple myeloma, CLL, colorectal cancer, triple negative breast cancer
- Scaffold/series in clear chemical space and priority patent application filed (May 2022)

NF-κB PATHWAY

NON-CANONICAL

Non-canonical NF-κB pathway relies on phosphorylation-induced p100 processing.

This pathway is dependent on NIK and IKKα, but not on the trimeric IKK complex (canonical NF-κB pathway), and mediates the persistent activation and nuclear translocation of RelB/p52 heterodimer.



Adapted from www.abcam.com/research-areas/overview-of-nf-kb-signaling

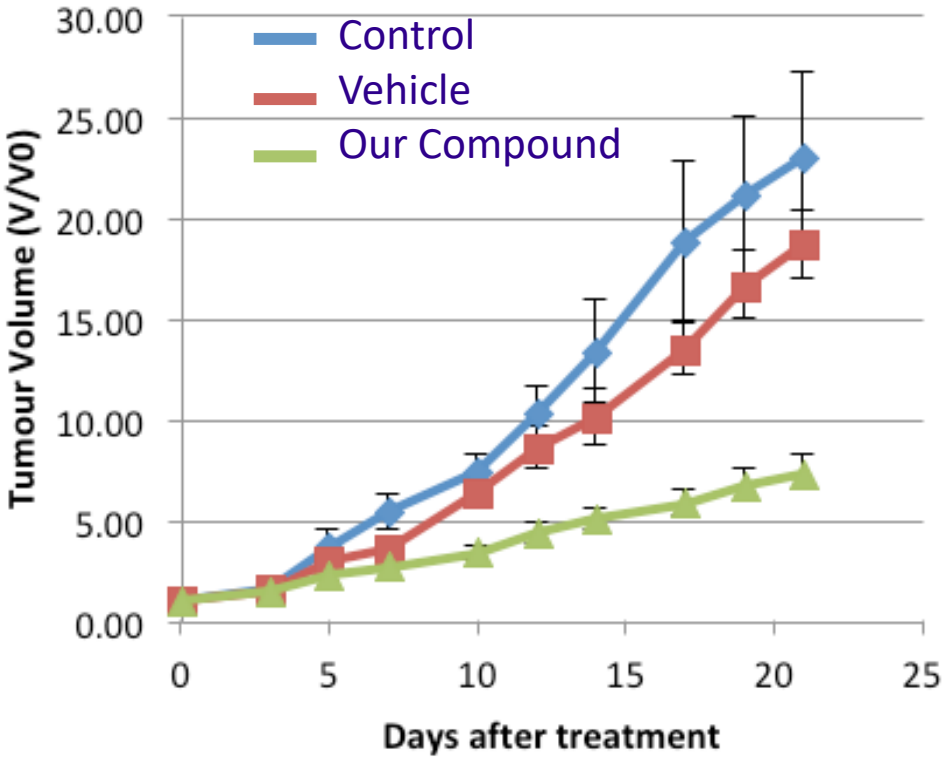
TARGET VALIDATION AND CLINICAL POSITIONING

- **Target validation in prostate cancer:**
  - IKKα inhibitor compound shows no engagement with IKKβ markers in cells
  - Selective IKKα compound inhibits tumour growth in-vivo in PC3M prostate cancer model
  - Mutational inactivation (or siRNA) of IKKα reduces prostate tumour growth/metastasis in multiple models
  - IKKα phosphorylates androgen receptor and p52 heterodimerises with AR increasing AR activity
  - p52 activity promotes prostate cancer cell growth, survival and activation of androgen receptor
- **Clinical positioning data in prostate cancer:**
  - TNF family receptors which act via IKKα pathway linked to prostate cancer progression
  - - β-lymphotoxin stimulates IKKα enhancing androgen independent growth
  - - RANK inhibits expression of the metastasis suppressor maspin
  - Levels of activated nuclear IKKα correlate with metastatic progression
  - Unpublished data on relevant prognostic biomarkers indicate poor outcome related to IKKα
- Mutational activation of IKKα pathway seen in several cancer types (TRAF2 in pancreatic, multiple pathway mutations in multiple myeloma, p100 rearrangements in leukaemia, IKKα truncation in colorectal)

PROJECT STATUS: IN VITRO DATA

- **Small molecule IKK alpha inhibitors series**
  - Low nM IKKα inhibitors with high selectivity over IKKβ. Scaffold shows good kinome selectivity
  - Potently inhibit direct IKKα PD biomarker (P-p100) in cells (~100nM IC50) and don't inhibit IKKβ PD biomarkers (IC50's typically >10uM)
  - Compounds reduce prostate cancer cell viability, colony formation and induce apoptosis with cellular IC50's typically in the 0.2-0.4uM range
  - Strong in-vivo efficacy demonstrated (>50% TGI) in prostate cancer model using tool compound despite only maintaining coverage above cellular PD marker IC50 for estimated 6hrs per day
- **Selectivity over IKKβ:**
  - Highly selective over IKKβ at biochemical level and also at pathway PD marker level in cells
  - Historic IKK inhibitors have been pan inhibitors or IKKβ selective
  - IKKβ linked to range of toxicities hence need for selective IKKα inhibitor for clinical use

PROJECT STATUS: IN VIVO DATA



Studies in nude mice bearing PC3M xenografts show our compound inhibits tumour growth by **60%**

Figure: Tumour efficacy in PC3M metastatic prostate cancer model using tool compound.

The three groups were control no-treatment group (diamonds), vehicle alone treatment (squares) and treatment group (triangles) which were treated with once daily I.P. injection of lead compound at 50mg/kg. Tumours were established in nude mice for 8 days following subcutaneous injection of PC3M-Luc-c6 cells before mice were randomized into three treatment groups of 8 mice in each.

FURTHER DEVELOPMENT PLANS

- Continue to optimise lead compound's in-vivo PK profile before expanding in-vivo testing
- Increase compound half-life and improve solubility
- With grant funding or a licensee onboard estimate **12-18 months to clinical candidate**

We are seeking an industry co-development partner and/or licensee to help drive the programme to clinical candidate and into the clinic.

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THANK YOU

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