FIRST-IN-CLASS
IKK ALPHA SELECTIVE INHIBITORS
FEBRUARY 2020
FIRST-IN-CLASS IKK ALPHA SELECTIVE INHIBITORS

PROJECT SUMMARY

- 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 with 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 and lymphoma.

- Scaffold/series in clear chemical space and discussions with patent agents underway re filing on series.
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.
IKK ALPHA INHIBITORS
TARGET VALIDATION AND CLINICAL POSITIONING

- Target validation in prostate cancer:
  - 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  - Unpublished data on relevant prognostic biomarkers indicate poor outcome related to IKKα.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)
IKK ALPHA INHIBITORS
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.
IKK ALPHA INHIBITORS  
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.
- Making good progress to increase compound half-life and improve solubility.
- With grant funding or a licensee/collaborator onboard, it’s estimated to be 12-18 months to clinical candidacy.

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