COMMERCIAL PARTNERSHIP OPPORTUNITY
Small Molecules - Lead Optimisation
March 2018

FIRST-IN-CLASS IKK ALPHA SELECTIVE COMPOUNDS

OVERVIEW

- First reported potent and selective IKK alpha inhibitors.
- Efficacy in prostate cancer xenografts demonstrated.
- Selective modulation of IKKα PD marker demonstrated in cancer cells.
- Well placed for progression to candidate selection.

IKKα LEAD SERIES

- Lead compounds show stringent selectivity for IKKα PD marker over IKKβ PD markers in cancer cells.
- Nanomolar potency, selective and chemically tractable lead series identified.
- Selectivity has been demonstrated against a wide kinome panel.
- Low Mwt (250 - 350) and good ligand efficiency.
- Appropriate ADME properties with clear med-chem strategy to candidate.

THE OPPORTUNITY

Cancer Research UK is seeking a co-development or licensing partner to drive candidate selection and entry into formal pre-clinical studies. The programme is led by Professor Simon Mackay at the University of Strathclyde.

The team has developed the first IKKα selective inhibitors and have shown robustly that these compounds can selectively and potently inhibit the IKKα pathway without significant inhibition of IKKβ in multiple cancer cell lines using a panel of pharmacodynamic markers for the two pathways.

In addition, the team has recently generated in-vivo efficacy data in a metastatic prostate cancer model and shown robust tumour growth inhibition using the current IKKα selective lead compound (see figure 1). Further optimisation of the current leads are underway with the expectation of improved PK and even greater in-vivo efficacy in the near future.

Based on both published studies and the team's cancer cell line testing, inhibition of IKKα has potential utility in a wide range of leukaemias and other tumours of high unmet need such as pancreatic cancer.

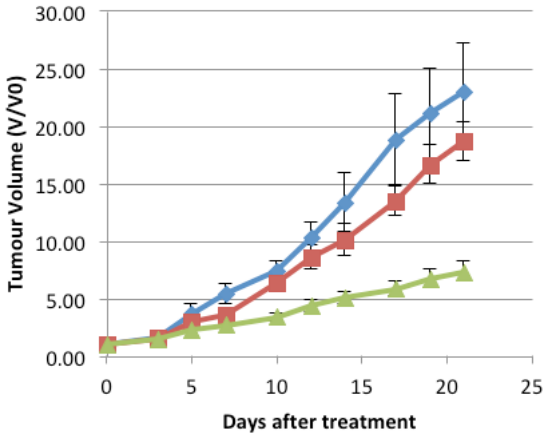

Figure 1. Tumour efficacy in metastatic prostate cancer model: The three groups were control no-treatment group (diamonds), vehicle alone treatment (squares) and treatment group (triangles) which were treated with once daily I.P. injection of lead compound at 50mg/kg. Tumours were established in nude 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.

Read more overleaf

BACKGROUND AND THERAPEUTIC RATIONALE

The pharmaceutical industry has devoted considerable effort to generating NF-κβ pathway inhibitors and a leading approach has been to target the IκB kinases (IKK). Reported inhibitors have either been pan-IKK inhibitors or IKKβ selective and to date there have been no reports of IKKα selective compounds. Despite being proposed as a target for treating inflammation, inhibition of IKKβ has more recently been associated with a number of side effects including development of inflammatory skin disease and sensitisation of colonic epithelium to a range of insults (1). In addition, IKKβ knockout mice display severe liver toxicity (2) and reports suggest intestinal and liver toxicity has been an issue in clinical trials of IKKβ inhibitors. Given the growing evidence that IKKα has an important role in a number of cancers, the development of selective IKKα inhibitors is an attractive approach and selectivity over IKKβ will facilitate the use of such compounds clinically.

Recent data has indicated that Lymphotoxin B, which activates the alternative NF-κβ pathway via IKKα, is an important driver of castrate resistant prostate cancer and may stimulate tumour progression/proliferation following androgen deprivation therapy (3). Androgen independent prostate cancer lines such as PC3 and DU-145 have also been shown to have constitutive activation of IKKα (4) and the presence of activated nuclear IKKα has been reported to correlate with more advanced cases of prostate cancer and have a role in driving metastasis (5). siRNA studies have also confirmed a role for IKKα in the survival and proliferation of androgen independent prostate cancer cell lines further highlighting the attractiveness of this target in castrate resistant prostate cancer. Furthermore, our efficacy data now provides in-vivo proof of principle data for the target using a selective pharmacological inhibitor compound.

In addition to prostate cancer, there is strong evidence in the literature that in a number of further cancers that the IKKα driven alternative NF-κβ signalling pathway is constitutively active and plays an important role. In a number of leukaemias and lymphomas oncogenic rearrangement of the nfkb2 gene (p100) has been reported and its constitutive activation requires IKKα (6). Similarly, constitutive activation of the alternative IKKα pathway has been reported in pancreatic cancer (7) and mutations in the non-canonical NF-κβ pathway are frequent in multiple myeloma (8).

REFERENCES

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2. Pubmed ID No: 10195897
3. Pubmed ID No: 20220849
4. Pubmed ID No: 10602496
5. Pubmed ID No: 17377533
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