275 FIRST-IN-CLASS IKK ALPHA SELECTIVE COMPOUNDS

Asset Overview

Product Type	Small Molecule
Indication	Oncology
Current Stage	Lead discovery/optimization
Target (MoA)	IKK ALPHA Selective Compounds
Brief Description	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.
Organization	Cancer Research UK

Differentiation

□ **Unmet Needs**

- For castrate reisistant prostate cancer, current therapies exert inadequate therapeutic benefit, Of 1 in 8 men diagnosed with prostate cancer, 25 will die of metastatic disease. Despite the approval of four new agents (abiraterone, enzalutamide and provenge) that have been shown to prolong life for up to 3-9 months in advanced PC patients, it remains an incurable disease

□ **Innovations**

- A mutation that prevents IKK α activation slows down prostate cancer growth and inhibits metastasis in TRAMP mice
- Suppression of IKK α by siRNA delays the appearance of CRPC in the murine myc CaP allograft model of PC
- The amount of active nuclear IKK α in mouse and human prostate cancer correlates with metastatic progression
- Nuclear IKK α appears to provide a mechanism for hormone resistance in the development of CRPC
- Deletion of BAG 3 which is required for IKK α nuclear translocation delays development of castrate resistant disease

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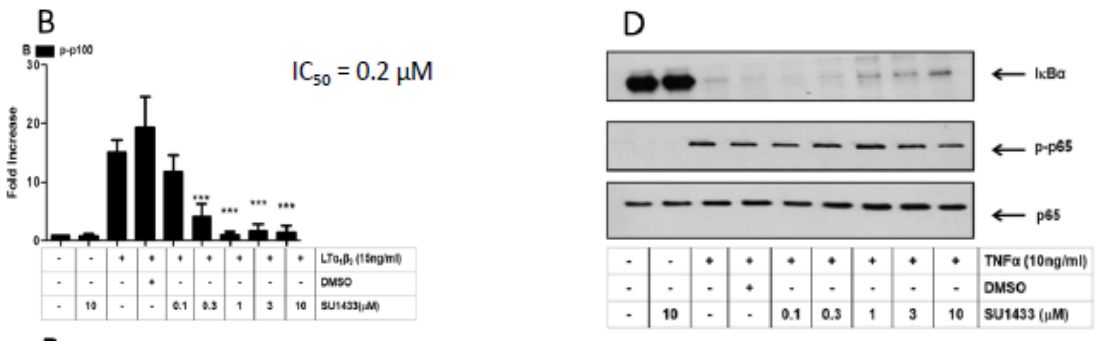
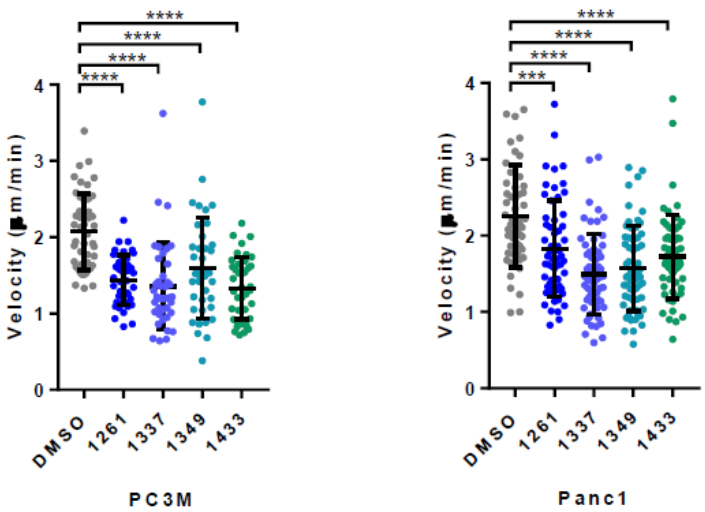
Key Data

SU1433 inhibits IKKαPD markers in the non-canonical NF-kB pathway in pancreatic cancer cells



SU 1433 inhibits LTα 1 β 2 induced phosphorylation of p p 100 and had no effect on TNFα mediated IkB α degradation and phosphorylation of p 65 NF kB in Panc 1 cells

SU1433 inhibits migration of pancreatic cancer cells



SU1433 (and SU1349) inhibits PC3M and Panc1 cell migration at 1 µM as assessed by timelapse microscopy

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Studies in nude mice bearing PC3M xenografts show SU1433 inhibits tumour growth by 60%

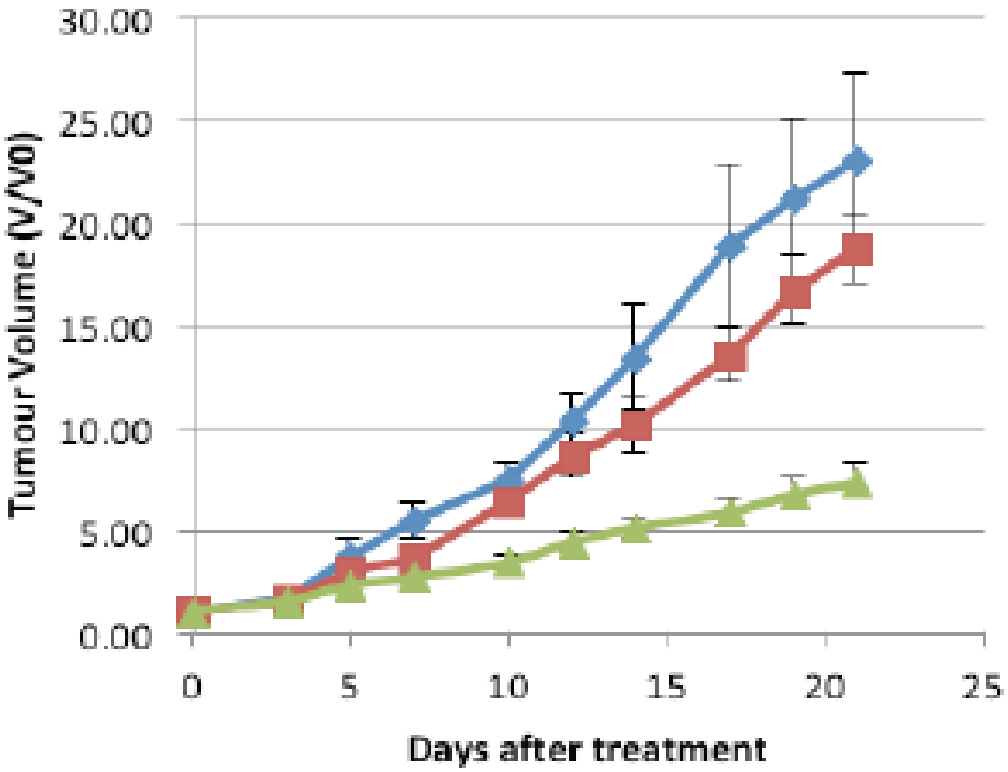

Figure 1. Tumour efficacy in metastatic prostate cancer model: The three groups were control no-treatment group (diamonds), vehicle alone treatment (squares) and treatment group (triangles) which were treated with once daily I.P. injection of lead compound at 50mg/kg. Tumours were established in nude mice for 8 days following subcutaneous injection of PC3MLuc-c6 cells before mice were randomized into three treatment groups of 8 mice in each.

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Intellectual Property

Patent No.	
Application Date	
Status	
Country	

Contact Information

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