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Poster Abstract Form

Enhancing the efficacy of and overcoming resistance to Kras Inhibitors in Pancreatic Cancer

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Introduction

Pancreatic cancer (PC) is a genetically complex and treatment-refractory malignancy. PC is predominantly driven by mutations in the Kras oncogene (90%) which allow cancer cells to exhibit immortal proliferation potential. Whilst PC has shown resistance to standard-of-care chemotherapy, new approaches to target mutated Kras show promise. However, pre-clinical investigations have revealed that Kras inhibition leads to enhanced extracellular matrix deposition, which drives resistance and restricts treatment efficacy. We have identified Focal Adhesion Kinase (FAK) – a critical regulator of matrix organisation – as an important contributor to PC progression. Thus, the aim is to determine whether anti-fibrotic FAK targeting can improve the delivery and longevity of Kras Inhibitors in PC.

Methods

An ERK/Kras-biosensor was developed and introduced via lenti-viral transduction, into PC cells to monitor **Kras inhibition,** allowing us to fine-tune drug response. Using three-dimensional in vitro organotypic matrices we optimised combinations and drug timing of antifibrotic FAK/Kras inhibition. Additionally, a panel of unique patient-derived xenografts (PDX) with high versus low FAK/ECM content/organisation was utilised to assess response to Kras inhibition by quantifying expression of pERK **(downstream effector of Kras signalling)**,Ki67 (**proliferation**), cleaved caspase-3 (**apoptosis**).

Results

We successfully established stable ERK-biosensor cell lines. In parallel, a short-term PDX pilot study demonstrated that our Kras inhibitor treatment has efficacy and increases fibrosis. Furthermore, priming the ECM with an antifibrotic FAK-inhibitor reduced cancer cell invasion and rendered them vulnerable to subsequent Kras inhibition in vitro.

Conclusion

Stromal manipulation via FAK inhibition may allow us to maximise the anti-tumour effect of Kras inhibition.