

## **Pankind 2026 Scientific Meeting**

### **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 which allow cancer cells to exhibit immortal proliferative 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 (ECM) deposition, which drives resistance and restricts treatment efficacy. We have identified Focal Adhesion Kinase (FAK) as a critical regulator of matrix organisation and thus as an important contributor to PC progression.

**Methods:** We assessed FAK/KRAS inhibitor synergy against tumour cells in a three-dimensional cell assay and used organotypic matrices to optimise drug timing. A subcutaneous syngeneic PDAC mouse model was used to determine how KRAS inhibition influences the ECM by quantifying the expression of picrosirius red, alpha-smooth muscle actin, and FAK activity.

**Results:** PDAC mouse models demonstrated that our KRAS inhibitors have efficacy, increase fibrosis, and activate fibroblasts. Synergy response was heterogeneous across a panel of patient cell lines, suggesting context-specific determinant of combination response. Priming the ECM with a FAK-inhibitor reduced cancer cell invasion and rendered them vulnerable to subsequent KRAS inhibition in vitro.

**Conclusion:** Combined, this suggests that subtle stromal manipulation via FAK inhibition may allow us to overcome resistance mechanisms to KRAS inhibition.