Pancreatic cancer is a major healthcare challenge, predicted to become the second most common cause of cancer death in the Western world within the decade. The focus of our research is to better understand the disease and identify and test more effective therapies. We use genetically engineered models that recapitulate human tumours, in terms of both driving mutations and the immunosuppressive tumour microenvironment and adapt them to mirror heterogeneous subsets of the disease. These models provide a clinically relevant platform in which we trial novel tumour and microenvironment targeting therapies.

Modelling genetic subsets of patients
We have developed several models to mimic patients with mutations that may be actionable, to identify and to test therapeutic targets. Our collection of models covers many genes/pathways identified in the patient tumours. For example, RAF43a, the gene encoding ubiquitin E3 ligase ring finger 43, has been shown to be mutated in 10-15% of cases of metastatic pancreatic cancer (Jiang et al., 2013, PNAS). Using KPC mice as a backbone (Hingorani et al., 2005, Cancer Cell), we have developed a genetically engineered mouse model of Rnf43 deletion and found that RNF43 deletion is a strong driver of pancreatic cancer progression, with loss of even a single copy sufficient to significantly accelerate tumour progression. Mutations in DNA damage repair genes have also been reported in 15% of pancreatic cancers (Aguirre et al., 2018, Cancer Discovery). We have developed models of these patients, by deleting Atm or Brca1 in KPC mice, to provide an opportunity to explore how signalling within the tumour microenvironment (TME) can drive drug resistance, and we have found that drugs targeting RAS signalling can cause microenvironmental changes associated with acquired resistance. Indeed, most tumours relapsed quickly, and displayed elevated fibrosis, tumorigenic immune responses while inhibiting pro-tumorigenic immune and fibrotic responses.

Therapeutic Resistance
By far the most common event driving pancreatic tumorigenesis is KRAS mutation. Previously believed to be "undruggable", the advent of mutant KRAStargets has the potential to be transformative in this disease, particularly now that inhibitors are in development for the most mutated forms in pancreatic cancer (Hallin et al., 2022, Nature Medicine). We have already observed that inhibition of multiple signalling pathways downstream of Kras can have significant efficacy in tumour-bearing mice (Discolli et al., 2016, Cancer Research). However, our recent data, together with results using KRAS inhibitors in other tumour types, suggested that resistance can develop quickly. In pancreatic cancer, the stromal cells can drive drug resistance, and we have found that drugs targeting RAS signalling can cause microenvironmental changes associated with acquired resistance. Indeed, most tumours relapsed quickly, and displayed elevated fibrosis, enhanced extracellular matrix deposition, and intriguingly, a re-wiring of signaling in the microenvironment (Figure 1). We are now investigating how signaling within the TME can help tumour cells to adapt to therapeutic intervention and influence the response to treatment. Tumour and stromal compartments display both significant heterogeneity in terms of gene expression and function, for example, discrete populations of cancer-associated fibroblasts with distinct expression profiles can either support or restrict tumour growth (Hutton et al., 2021, Cancer Cell). Therefore, to fully understand how best to target different cell types for therapeutic effect, we need to investigate signaling within individual cell types (e.g., Figure 2), but also spatially link molecular changes to therapeutic responses. Building a comprehensive understanding of the relationships between signaling pathways, tumour cells and the TME following therapeutic intervention will allow us to identify the best strategies to overcome resistance.

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Figure 1
Representative Haematoxylin & Eosin (H&E) staining, cytoation, immunohistochemistry (IHC) for tumour cells, podoplanin (D2-40) staining for collagen I, and podoplanin IHC for fibroblasts, in vehicle or inhibitor treated pancreatic tumour bearing kpc (kras;G12D, p53R172H, Pdx1-Cre) mice, demonstrating increased fibrosis in treated tumours.

Figure 2
Example of Uniform Manifold Approximation and Projection (UMAP) of single cell RNA-Seq data from control and treated tumour-bearing KPC mice.