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# PRECLINICAL PANCREATIC CANCER


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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 immuno-suppressive 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.

Pancreatic cancer kills over 430,000 people every year. It is one of the deadliest epithelial malignancies, and both incidence and mortality are rising. Indeed, it is predicted to be the second most common cause of cancer death within the next decade. In the UK alone, there are around 30 new cases every day. Less than 8% of those patients will survive their disease for five years, and only 1% are likely to survive beyond ten years. Despite improvements in surgical management and significant investment in clinical trials, cure rates have only minimally increased over the last 50 years, and current therapies are largely ineffective.

Research has helped improve our understanding of disease evolution, genetic alterations, transcriptional subtypes, and the tumour microenvironment. Activating mutations in KRAS are the most prevalent driver mutations, accompanied by loss of function of tumour suppressor genes. Some mutations found in subsets of patients may confer sensitivity to targeted therapies (Biankin *et al.*, 2012, *Nature*). For that reason, part of our work involves modelling gene mutations that are found in smaller subsets of human pancreatic cancer, with a view to understanding the biological consequences and therapeutic sensitivities associated with those mutations.

Another feature characteristic of PDAC is the dense fibrotic stroma that surrounds and supports the tumour cells and can account for up to 90% of the tumour volume. This microenvironment consists of fibroblasts and extracellular matrix proteins as well as significant inflammation but a dearth of effector T cells. Each component plays an important role in pancreatic cancer progression, influencing tumour cell proliferation and survival, metabolism, migration, and immune surveillance (Candido et al., 2018, Cell Reports; Steele *et al.*, 2016, *Cancer Cell*; Vennin *et al.*, 2018, *Gastroenterology*). Therefore, another aim of work in our lab is to investigate how stromal signalling impacts on the disease and how we might target it for therapeutic gain. Due to the complex nature of tumour-stromal interactions it is important to study this *in vivo*, in spontaneous tumours with a physiological microenvironment and immune response.

## PDAC Microenvironment

Tumour-associated macrophages (TAMs) and cancer-associated fibroblasts (CAFs), play a critical role in PDAC progression, but it has only recently been appreciated that significant heterogeneity exists in these cell populations (Yang *et al.*, 2020, *Front Cell Dev Biol*; Helms *et al.*, 2020, *Cancer Discov*). Moreover, the complex interplay between these populations in the tumour microenvironment (TME) is poorly understood. Rare populations of immune cells can also play a role in modulating the phenotype of these different populations, but these too have been under-studied. The stroma can have profound effects on therapeutic response (Beatty *et al.*, 2021, *Genes Dev*); however, therapeutic interventions may also have significant effects on the stroma. For example, radiotherapy causes CAFs and TAMs to alter their secretory output, remodelling the TME to favour tumour growth and treatment resistance (Krisnawan *et al.*, 2020, *Cancers*). By developing a clearer understanding of the complex signalling between different stromal cell subtypes, and the effects on individual signalling pathways on tumour progression and chemoresistance, we should be able to develop rational stromal targeting strategies for this disease. Thus, we are investigating how signalling between different cellular subsets and phenotypes can support fibrosis and tumour progression, how these phenotypes are controlled, and how therapy, particularly radiotherapy, can drive microenvironmental changes. Ultimately, we hope to identify signalling networks that could be exploited for therapeutic benefit, and test these concepts in tumour-bearing GEMMs (Figure 1).

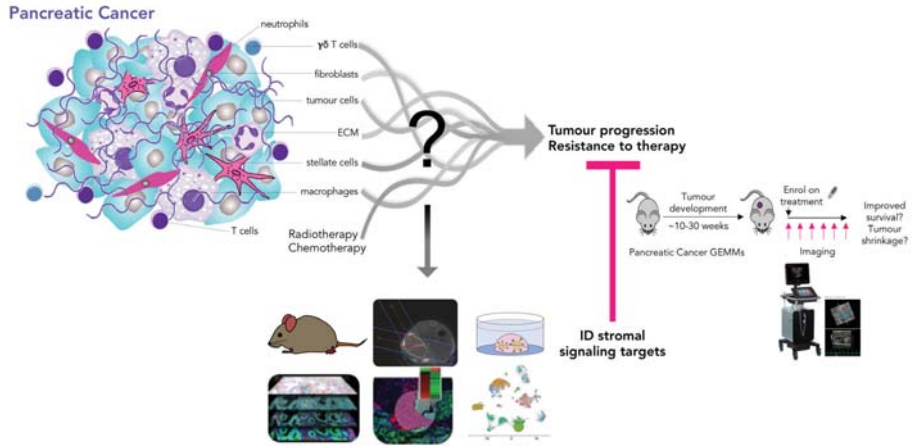


**Figure 1.** Schematic of workplan to investigate tumour-microenvironment signalling networks driving PDAC progression and therapeutic response and test newly identified therapeutic strategies.

## Therapeutic Resistance

By far the most common event driving pancreatic tumourigenesis is KRAS mutation. Previously believed to be "undruggable", the advent of mutant KRAS inhibitors could be transformative in this disease, particularly now that inhibitors have been developed for the most mutated form 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 (Driscoll *et al.*, 2016, *Cancer Research*). However, our recent data suggest that resistance can develop quickly. Indeed, most tumours relapse quickly, and display elevated fibrosis, enhanced extracellular matrix deposition, and a re-wiring of signalling, including metabolic pathways, in the microenvironment. We are now investigating how these factors can help tumour cells to adapt to therapeutic intervention and influence the response to treatment. Cancer-associated fibroblasts exhibit distinct expression profiles that 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 are investigating signalling within individual cell types. New technologies, such as spatial transcriptomic analysis and CODEX, are allowing us to spatially resolve mRNAs and proteins in individual tissue sections to visualize cells and signalling networks in their native tissue context (Figure 2A), but also spatially link molecular changes to therapeutic responses. Mass spectrometry imaging has also revealed significant metabolic plasticity in response to therapy (Figure 2B). Visualising this in spatial context and longitudinally across treatment experiments is crucial to observe metabolic rewiring/resistance mechanisms in situ. Building a comprehensive understanding of the signalling pathways and metabolic features in tumour cells and the tumour microenvironment following therapeutic intervention will allow us to identify the best strategies to overcome resistance.

Publications listed on page 117

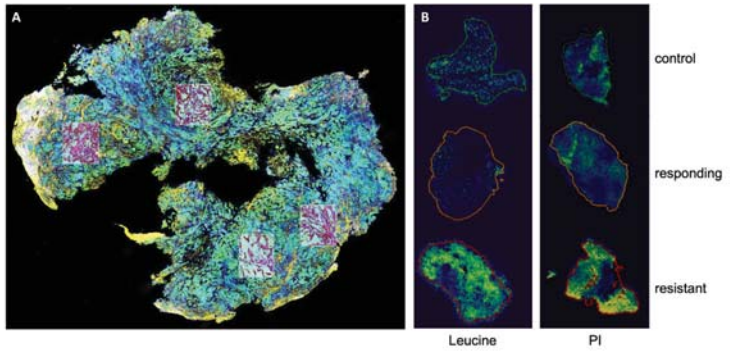


**Figure 2. A** Region selection and cell type masking for spatial transcriptomic analysis. PDAC tissue immuno-stained for CK19 (cyan, tumour cells), PDPN (yellow, CAFs) and DAPI (blue, CK19-PDPN- cells). **B** Mass spec imaging showing metabolic plasticity in PDAC response to therapy.