Project title: **"Characterising tumour -promoting and -restrictive functions of the microenvironment"**
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Pancreatic Ductal Adenocarcinoma (PDAC) is a highly lethal disease with limited options for treatment. Despite being the 11th most frequent occurring cancer, PDAC is currently the 4th leading cause of cancer-related deaths and projected to be the 2nd leading cause by 2030. Patients with PDAC are commonly diagnosed with locally advanced or metastatic disease and are not offered surgery. Even in the cases where surgery is offered, more than 2/3rds of patients return with local or metastatic disease. Importantly however, surgery at early stages (Stage I) offers much improved benefit and a 5-year survival >40%, which starkly contrasts a 5-year survival of only 3% in the metastatic setting.

Thus, improved clinical management of patients with PDAC rely on a combination of early detection and interception and/or improved treatment in the metastatic setting.

A characteristic feature of PDAC is the conscripted and pathologically remodelled tumour microenvironment (TME), which takes up more than 80% of the tumour volume on average. Here, host cells such as fibroblasts and immune cells are co-opted by tumour cell-derived signals to permit tumour growth and immune escape. Moreover, a remodelled extracellular matrix alters tissue biophysics resulting in a stiff, poorly perfused, nutrient depleted environment. While the tumour stroma largely has been viewed as tumour promoting, emerging data have demonstrated that stromal subsets also may act in a tumour-restrictive manner. The mechanisms whereby individual stromal subsets regulate tumour progression or restriction is less well understood.

The Systems Oncology lab has a long-standing interest in understanding tumour-stroma interactions and how these interactions regulate tumour cell function (Tape et al Cell 2016, Lee et al Nat Comm 2021, Below et al Nat Materials 2022, Hutton et al Cancer Cell 2022).

This project aims to functionally identify and molecularly characterise tumour cell dependencies on the microenvironment.

Using a combination of murine in vivo models and human patient samples we have amassed a series of data sets describing changes in the microenvironment associated with tumour development. The aim of this project is to identify, functionally interrogate and molecularly characterise a subset of these interactions. Experimental approaches will include but not be limited to CRISPR engineering of murine and patient derived cells, in vivo modelling, human tissue analysis, single cell analysis and mass spectrometry. The project will also leverage our recently developed fully synthetic model to culture human and murine organoids. You will benefit from established models, expertise, clinical and computational collaborations as well as access to state-of-the-art infrastructure.