Project Title: "Defining regulators of early-stage PDAC tumour development"

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Pancreatic Ductal Adenocarcinoma (PDAC) is a dismal disease with limited treatment options. Despite being the 11th most frequent occurring cancer, PDAC is currently the 4th leading cause of cancer-related deaths and is projected to be the 2nd leading cause by 2030. ~ 80% of patients with PDAC are diagnosed with incurable locally advanced or metastatic disease and are offered palliative systemic chemotherapy treatment. Even in the cases where surgery with curative intent is offered (~20% of newly diagnosed patients), more than 2/3rds return with local or metastatic disease within months. Importantly, surgery at early stages (Stage I) offers much improved benefit and a 5-year survival >40%, which contrasts a 5-year survival of only 3% in the metastatic setting. Despite the introduction of novel KRAS inhibitors, resistance develops rapidly and progression is inevitable. Thus, improved clinical management of patients with PDAC rely on a combination of early detection and improved treatment.

Precursors of PDAC are common and uniformly carry the mutationally activated oncogene KRAS. As disease progress, activated KRAS is typically accompanies by loss of CDKN2A, TP53 and SMAD4 tumour suppressor function. Notably, pre-cancerous precursors of PDAC are very common and can even be identified in young otherwise healthy individuals. However, despite a high prevalence, precursors only rarely progress to form PDAC.

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. The microenvironment is conscripted already at the earliest stages of tumour development, exhibiting clear signs of fibroblast activation, immune escape and remodelling of the extracellular matrix. Moreover, studies in animal models have demonstrated that a normal microenvironment can limit PDAC progression, but that inflammation alleviate this otherwise restrictive effect. How the tumour cells are functionally regulated by signals from the microenvironment to progress is currently poorly understood.

This project aims to identify and mechanistically interrogate signals from the tumour microenvironment that regulate early stages of malignant tumour cell progression. You will use human patient samples and our recently developed fully synthetic organoid model in combination with CRISPR engineering, Mass Spectrometry based protein analysis and in vivo modelling to unpick the tumour cell response to the host cell signals that drive early tumour progression. See Tape et al Cell 2016, Lee et al Nat Comm 2021, Below et al Nat Materials 2022, Hutton et al Cancer Cell 2022. You will benefit from established models, expertise, clinical and computational collaborations as well as access to state-of-the-art infrastructure.