

Project Title: “Characterising determinants of therapeutic response in reconstituted patient models of PDA.”

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Research Group: Systems Oncology

This 4-year PhD studentship will be funded by the NIHR Manchester Biomedical Research Centre and based in CRUK Manchester Institute’s new world class research building next to the Christie NHS Foundation Trust, Withington, Manchester, UK.

Pancreatic Ductal Adenocarcinoma (PDA) is currently the 4th leading cause of cancer-related deaths and projected to be the 2nd leading cause by 2030. There are several reasons for this, but late detection and therapeutic resistance are main clinical challenges that needs urgent attention.

The remodelled desmoplastic reaction, which takes up more than 80% of the tumour volume on average, is a key feature of PDA and a major cause of therapeutic resilience. Specifically, tumour cells co-opt stromal cells, such as fibroblasts and macrophages, which in turn remodel the extracellular matrix and increase tissue stiffening while simultaneously providing nutritional support and cell survival signals to the tumour cells, ultimately leading to therapeutic resilience and progression (Tape et al Cell 2016, Lee et al Nat Comm 2021).

A major barrier to determining how interactions between tumour and stromal cells drive therapeutic resistance is a lack of contemporary models which recapitulate salient features of the tumour ecosystem. We have recently developed and implemented a synthetic scaffold supporting direct co-cultures of tumour and stromal cells while also allowing tuning of the tissue stiffening (Below et al Nat Materials 2022). We now aim to use this model in a systematic effort to determine how stromal cell populations drive therapeutic resistance.

The project involves use of human patient-derived 3D models, which will be analysed by a combination of proteomics (mass spectrometry), single cell analysis (CyTOF) and functional genetic manipulation (CRISPR).