Project title: **"Computational annotation of the evolutionary relationship between metastatic tumour and host environment"**

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Research Group: **Systems Oncology**

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 is a computational project focusing on delineating the evolutionary landscape of tumour and host interactions in metastatic PDAC. Most of the current appreciation of interactions between tumour and host emerges from studies of primary PDAC. However, available, but limited, data suggests that distinct tissue environments establish differential interactions with tumour cells. Whether these interactions elicit functionally distinct responses in tumour cells and, in turn, impose divergent therapeutic sensitivity is not yet known. Thus, strategies to target interactions between tumour and host cannot be extrapolated from current knowledge from studies in primary disease but depend on a detailed mechanistic appreciation of the evolving interdependency of tumour and host across both primary and metastatic disease.

Using a combination of genomics and spatial imaging and transcriptional analysis you will discern the evolutionary pattern of tumour metastasis and the resulting response of the microenvironment. This project is predominantly computational and a strong interest in the use of computational analysis of genomics, transcriptomics and spatial imaging data would be beneficial. You will benefit from an existing collaboration with local oncologists, geneticists and pathologists (Jamie Weaver, Emma Woodward, Lucy Foster) and computational geneticists (David Wedge).

This position has been generously funded by donations to The University of Manchester from The Ian Harty Charitable Trust. The successful candidate will work with the University's development team to help keep the donor up-to-date on their progress. This could include providing written updates and photographs, appearing in video content, attending events, or meeting donors. By doing this, you'll help show donors the difference they are making and inspire them to continue their support for our cancer research.