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Genomic and Transcriptomic Characterization of Pancreatic Cancer

Our laboratory combines next generation sequencing of human pancreatic cancer, xenograft and organoid models, and retrospective and prospective clinical and pathological databases to better understand and manage this highly lethal malignancy. The etiology of pancreatic ductal adenocarcinoma (i.e. “pancreatic cancer”) and the relationship between the primary tumour and its characteristic dense, encroaching stroma are still poorly understood. In addressing this, my work has focused on integrating DNA- and RNA-based features of resected pancreatic cancer samples.

Using whole genome sequencing in two large cohorts, we showed that there are predominantly four major mutational processes active in pancreatic cancer. With expression data, we found that the interaction between tumour and stroma varied with the type of mutational process in the primary tumour. Tumours defective in either homologous recombination or mismatch repair (~10% of all pancreas cancers) were associated with active cytotoxic immune cells in the stroma, likely due to adaptive immune responses to the relatively high numbers of “neoantigens” in these tumours. Hopefully, this will inform both future investigations of heterogeneous tumour-stroma interactions and clinical trials of immunotherapy in pancreatic cancer, with has previously not benefited from biomarker guidance. We’ve now started a prospective trial for patients with locally advanced and metastatic pancreatic cancer at the Princess Margaret Cancer Centre, performing whole genome and transcriptome sequencing of biopsies taken at the time of diagnosis. This may inform second-line therapies and will provide both an unprecedented “knowledge bank” with which to develop personalized medicine approaches to pancreatic cancer and an opportunity to study differences between primary and metastatic disease.