PANCREATIC CANCER EVOLUTION AND THERAPEUTIC DEVELOPMENT

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Pancreatic cancer is one of the most lethal cancers and will soon become the second cause of cancer death in the UK. Working at the interface between clinical care in the NHS and laboratory research, the overall aim of our research is to improve outcomes for pancreatic cancer patients by deepening our understanding of tumour-host interactions driving pancreatic cancer progression and response to therapy. To do this, we perform in-depth molecular and pathological studies of patient samples and use patient-derived preclinical models to create a solid platform of preclinical evidence to translate our discoveries into the clinic.

Pancreatic cancer is a cancer of unmet need that is fatal for most patients. In addition to late presentation, patients with pancreatic cancer develop rapid decline of their performance status, leading to ~60-70% of patients not receiving any anti-cancer treatment. Most patients succumb to the effects of metastatic disease imposed on the patient (host), including inappropriate inflammatory and immune response, and metabolic aberrations leading to muscle and fat wasting and functional decline. In addition, there are striking differences in outcomes based on other host factors such as age, gender, ethnicity and socioeconomic exposures. Interactions between the tumour and the patient (host) affected by pancreatic cancer are complex, from the formation of the very initial cancer cell to the ultimate demise of the host due to the overwhelming effect of the dissemination of metastatic disease. During this journey, the tumour and the host interacts and "co-evolve" in a symbiotic relationship. The trajectory and the outcomes of the co-evolution all depends on the tumour-host interactions temporally and spatially (Figure 1).

The overall aim of our research is to elucidate how tumour and host diversity drive co-evolution and outcome in order to develop better therapeutic strategies to improve the overall outcome of pancreatic cancer and to reduce cancer inequalities. To do so, we use routinely collected health care data, in-depth interrogation of patient samples using state of the art technologies (multiplex immunofluorescence, single cell and spatial sequencing, plasma proteomics) and preclinical patient-derived models for functional studies. Patient sample collection is ongoing as part of the national UK therapeutic development platform for pancreatic cancer (Precision-Panc), and the recently awarded Cancer Grand Challenge studying pancreatic cancer inequalities (SAMBAI, www.cancergrandchallenges.org/sambai).

We have identified systemic inflammation, host factors, and differential KRAS signalling as key drivers of rapid progression of the disease but with marked heterogeneity, which is being studied in more detail in our laboratory. In collaboration with the Le Quesne laboratory, we have developed a bespoke 50-plex immunofluorescence (mIF) protein expression panel using the Akoya Phenocyler system (Figure 2). The panel consists of antibodies targeting known molecular subtypes of pancreatic cancer (classical vs squamous/basal-like), cancer associated fibroblast (inflammatory, myofibroblastic-like, antigen presenting and metabolic), T cells (subtyping, checkpoints and functional state), B cells, and myeloid cells. Prognostically important spatial entropy, morphology and tumour microenvironment enrichment profiles have been identified and are being further evaluated. Moreover, in collaboration with the Yuan laboratory, we have identified the histomorphological landscape of pancreatic cancer using H&E images from multiple patient cohorts, using Histomorphological Phenotype Learning (a self-supervised learning network developed in the University of Glasgow).

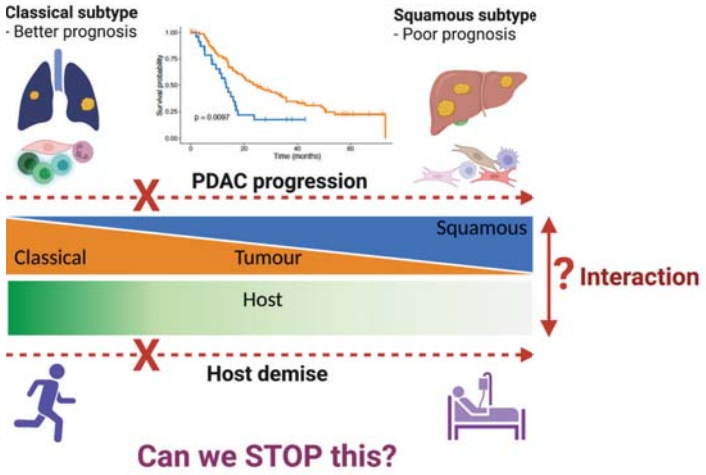

Figure 1. Co-evolution of tumour and host in pancreatic cancer. The overall goal of our research team is to understand tumour-host interactions driving distinct outcomes to develop better treatment strategies and reduce cancer inequalities.

As part of team SAMBAI, we will study how tumour-host interactions drive pancreatic cancer inequalities, with comprehensive measurements of social determinants of health, environmental, genetic and immunology factors that can help define the causes of disparate outcomes in patients of the African diaspora or those from deprived areas.

Clinically, I work as Consultant Medical Oncologist at the Beatson West of Scotland Cancer, am the pancreatic cancer lead of the Glasgow Experimental Cancer Medicine Centre, am principal investigator of multiple clinical trials and lead the molecular tumour board for Precision-Panc, the national therapeutic development platform for pancreatic cancer in the UK. Overall, this allows me to focus on developing personalised therapeutic strategies that emanate from discoveries in both basic science and reverse translation from clinical observation.

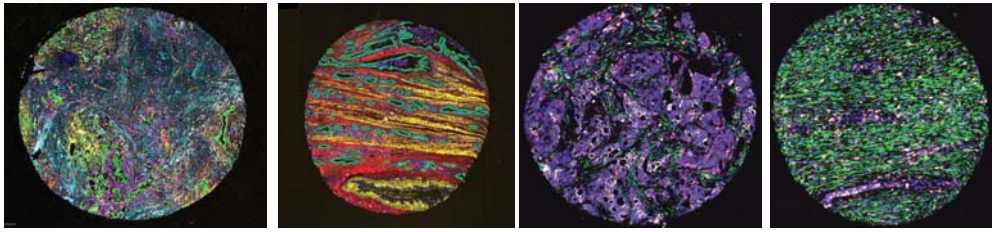

Figure 2. Representative multiplex immunofluorescence images of selected markers from bespoke 50-plex pancreatic cancer panel