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 its 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.

With a median survival of less than a year after diagnosis, pancreatic cancer is a cancer of unmet need that is fatal for most patients. To date, there has been little improvement in these poor outcomes, with very few effective therapies available. We do, however, see exceptional tumour responses, where patients derive significant benefits and have better outcomes. Thus, there is an urgent need to personalise our patient care and better identify the right treatment for each patient.

In an era of precision medicine, one of the challenges for therapeutic development for pancreatic cancer is its heterogeneity and large cellular plasticity. Research within the field has shown two biologically different and prognostically important transcriptomic subtypes, or lineages: a relatively better "classical" and a poorer prognostic "squamous/basal-like" subtype (Figure 1A). Recent single-cell analyses have demonstrated the coexistence of squamous and classical lineages within a single tumour, and the presence of "hybrid" cells that co-express markers of both. These data suggest that molecular subtypes of pancreatic cancer exist as a continuum, with a classical tumour that has more indolent biology on one end, a highly aggressive squamous/basal-like tumour on the other, and a range of cellular states in between (Fig. 1B).

The cell-to-cell differences that drive this cellular plasticity are determined by a complex interplay of multiple genetic and non-genetic factors (Fig. 1B). Our research aims to better understand the dynamics and evolution of pancreatic cancer progression with the overall goal to develop novel, biomarker directed therapies. To do so, we use routine clinical health care data and patient samples for in-depth analysis, preclinical patient-derived models for functional studies and, in collaboration with the School of Computing Science, methods of deep learning techniques and artificial intelligence. 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.

Within the UK, the Precision-Panc consortium has been established to accelerate therapeutic development for pancreatic cancer and overcome challenges of delivering precision medicine for this disease. By means of a "Master Protocol", patients provide their informed consent for biopsy and molecular profiling with subsequent enrolment into multiple PRIMUS clinical trials. Within the Precision-Panc consortium, different studies are in development we have started a national molecular tumour board to enable a more personalised approach and possible treatment within second line or early phase clinical trials. Overall, the goal is to provide a clear pathway for translation of preclinical discoveries into scientifically driven clinical trials and allows reverse translation of clinical observations into the laboratory to keep advancing our knowledge and refine therapeutic approaches.

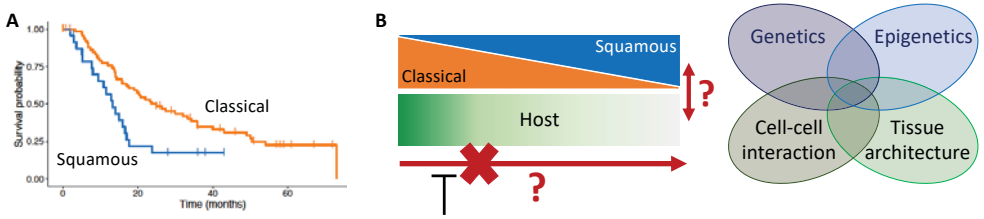

Figure 1. A) Two consensus subgroups, or lineages, of pancreatic cancer (PC) are a "classical" and a poorer prognostic "squamous/basal-like" subtype. Overall survival by subtype is shown. **B)** Recent research is indicating subtypes of PC exist as a continuum, with co-evolution of tumour and host cells driving the progression from a classical tumour into a highly aggressive squamous/basal-like tumour. By investigating and integrating key determinants of cellular state, our research aims to identify the key steps involved in PC progression, and how to therapeutically target these.

We are currently working as part of Team SAMBAI, which in 2023, was selected to receive a Cancer Grand Challenges award of up to £20m over five years to build an unprecedented resource, which will comprise a comprehensive measurement of social, environmental, genetic and biological factors that can be used to help define the causes of disparate outcomes in the selected populations. The team will focus on prostate, breast and pancreatic cancers spanning diverse cohorts of African descent from regions of Africa, the UK and the US.

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