PANCREATIC CANCER EVOLUTION AND THERAPEUTIC DEVELOPMENT

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 an average survival of less than a year after diagnosis, pancreatic cancer (PC) 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 genomic medicine, one of the challenges for therapeutic development for pancreatic cancer is its heterogeneity and large cellular plasticity. Research within the field has however 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 PC 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 PC progression with the overall goal to develop novel, biomarker directed therapies. To do so, we use 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.

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 informed consent for biopsy and molecular profiling with subsequent enrolment into multiple PRIMUS clinical trials. Within the Precision-Panc consortium, we are starting the PRIMUS-004 platform trial with the aim to offer a range of signal seeking second-line studies with extensive molecular profiling and evaluation of candidate selection biomarkers. This not only provides a clear pathway for translation of preclinical discoveries into scientifically driven clinical trials, it also allows reverse translation of clinical observations into the laboratory to keep advancing our knowledge and refine therapeutic approaches.

With thanks to the patients, translational research samples will be taken at baseline, at 2 weeks, at 10 weeks and at progression. Additional blood samples for pharmacokinetic and pharmacodynamic analysis will also be collected. The molecularly characterised, clinically well-annotated, data collected as part of PRIMUS-004 and the Precision-Panc Master Protocol, enable us to perform further in-depth studies to understand pancreatic cancer progression and treatment response.

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