PRECISION-Panc: the next generation therapeutic development platform for Pancreatic Cancer

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Introduction

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With the development of next generation sequencing (NGS) technology, there has been an enormous increase in our knowledge and understanding of the molecular pathology of various cancer types, including pancreatic cancer (PC). PC remains the most lethal solid tumour type in our population. There has been little improvement in overall outcomes, with few effective therapies available for patients with advanced disease. PC is a disease of low incidence, being the 11th most common cancer, yet the persisting high mortality will see it become the 2nd leading cause of cancer death in the West by 2025[1]. The relative low incidence and low surgical resection rates (only ~15%) makes meaningful tissue acquisition to enable substantial advances in scientific research extremely difficult for most institutions, which has further compounded slow progress. To tackle these issues, *PRECISION-Panc* was established, it is a pan-UK multi-centre, therapeutic development platform which aims to rapidly translate pre-clinical molecular advances into clinical practice for patients with PC. Crucial to the success of this endeavour is molecular profiling of tumours from patients with all stages of PC to enable biomarker driven therapeutic testing within molecularly selected subgroups to improve response rates and development of therapeutic biomarkers. In addition, molecular profiling for all patients with PC will enable viable and attractive clinical trial options, thereby finding the right trial for the patient, rather than finding the right patient for the trial. By combining molecular profiling with clinical response data, rapid forward and backward translation between the laboratory and clinic is facilitated and allows the discovery of therapeutic response and resistance mechanisms.

Challenges of Therapeutic Development

With the increasing understanding of the molecular pathology of PC and other cancers, it is becoming clear that the disease is no longer seen as a single, homogenous entity. Instead, it should be viewed as a collection of individually uncommon, molecularly heterogeneous

tumours that are histologically undistinguishable[2]. It makes sense, thus, that PC should not be treated with the same strategy in all patients. Current therapeutics for the disease, especially in the advanced setting, offer only modest survival improvement overall, however, significant and sometimes exceptional responders are seen in undefined subgroups of patients. Currently, large groups of patients are treated for potential benefits in small, undefined patient subgroups. This may lead to significant treatment related morbidity in a large proportion of patients who gain little or no benefit from these therapies. Developing new therapies for molecular aberrations of low prevalence is extremely challenging. It requires hundreds or even thousands of patients, at great cost, to demonstrate clinical benefit in a small proportion of patients, with the potential of high clinical trial failure rates. To overcome these challenges, we need to shift therapeutic development, to adaptive clinical trials and enrich for molecular subgroups that are more likely to respond. However, identifying and characterising individual molecular subgroups in the real world in a clinically relevant time-frame presents a significant challenge, especially using next generation sequencing (NGS) technology.

A number of studies which attempted real-time molecular profiling to facilitate stratified clinical trials were unfortunately met with high sample or technical failure rates frequently due to insufficient DNA yields [3-7]. Utilising archival, diagnostic material is also fraught with difficulties including wide variation of tissue collection techniques employed and time in preservatives such as formalin which may directly affect NGS results leading to false positives if not accounted for in the sequencing analysis pipeline. In addition, PC has high stromal and low tumour epithelial content, further influencing the accuracy of mutation detection. The challenges are further magnified by the difficulty in obtaining PC samples, due to anatomical location and low resection rates in a relatively low incidence cancer. To address this, some precision medicine initiatives in PC have relied on biopsies of metastatic

lesions or surgical resection specimens in patients who have developed recurrence and large sequencing projects to date have almost exclusively utilised resected samples of early disease[3,8]. This approach unfortunately excludes a significant proportion of patients from the full spectrum of disease stages. Patients with metastatic disease do not always have lesions amenable to percutaneous biopsy, resulting in the exclusion of large proportions of patients from precision oncology initiatives and a scenario that fits poorly within the ethos of finding a trial option for all patients with PC.

The *PRECISION-Panc* Master Protocol

To overcome these issues, we have developed the *PRECISION-Panc* Master-Protocol, a dynamic and flexible tissue acquisition and molecular profiling pathway to screen and enrol all patients with PC, regardless of disease stage or pattern. The process is initiated at presentation to the specialist unit, even prior to a formal cancer diagnosis being established. Patients who are referred for Endoscopic Ultrasound (EUS) or radiologically guided diagnostic biopsy are counselled and provide consent for participation in the *PRECISION-Panc* Master Protocol (stage 1 consent) (Figure 1). This involves extra passes of biopsies (in the case of EUS) and peripheral venous sampling of blood to enable molecular profiling. Extra biopsy samples are processed in unison with the diagnostic sample into a single tissue block. This maximises diagnostic yield and allows rapid histological assessment, whilst minimising tissue wastage and other resources. Once the diagnosis is confirmed and tumour epithelial content is assessed, the molecular profiling process begins after stage 2 consent has been obtained (Figure 1). This involves DNA and RNA extraction from the surplus diagnostic tissue and venous blood sample as the source for germline DNA, followed by sequencing using Illumina® NGS technology. Targeted capture sequencing is performed using the *Glasgow Precision Oncology Laboratory (GPOL) Clinical Cancer Genome (CCG)*

™, a bespoke PC specific multiplex assay accompanied by a purposely built analysis pipeline (termed HOLMES), using publicly available and proprietary software developed in house. By targeting specific genomic regions and performing a collection of sub-assays; point mutations, copy number and structural changes, as well as tumour mutational signatures can be determined. Importantly, the *GPOL CCG* ™ and analysis pipeline is specifically designed to overcome the challenges of molecular profiling low cellularity samples, a hallmark of PC. Analysis output is then summarised into a molecular report with clinically relevant genomic aberrations. This process takes around 2 - 3 weeks for patients from the day of presentation at the EUS clinic, until generation of a molecular report. Thus, patients are able to be molecularly profiled within current National Health Service clinical pathways with no extra visits or procedures, within a clinically acceptable timeframe (Figure 1).

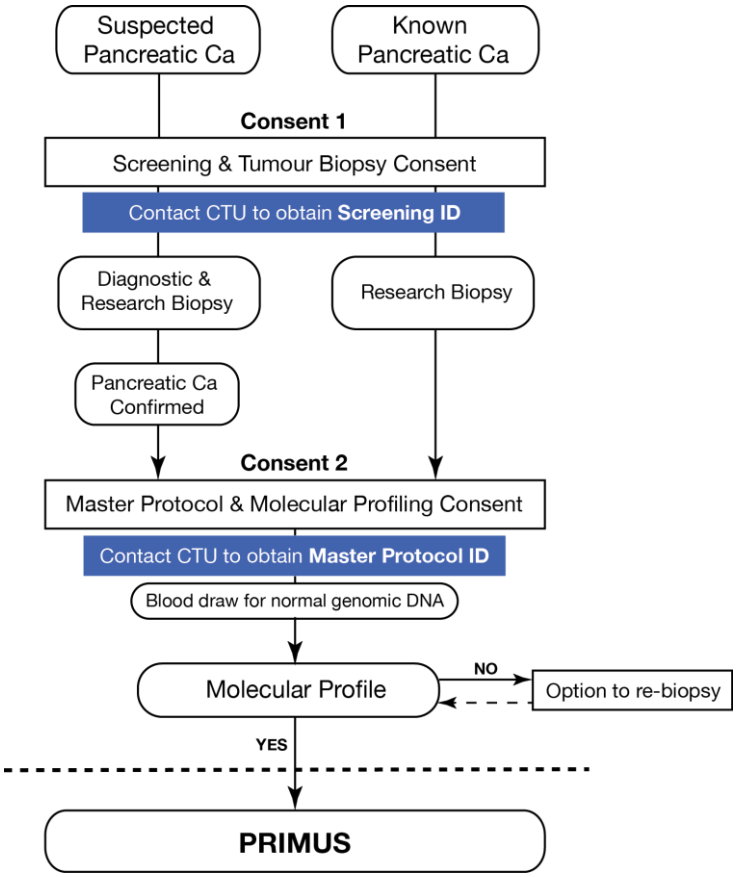

Figure 1 The *PRECISION-Panc* Master Protocol. Patients can enter the master protocol even prior to a diagnosis of PC, provided they have a suspicious lesion and potentially suitable for any of the clinical trials that are open. Molecular profiling is done using the diagnostic biopsy, and thus leads to rapid diagnosis and proceed to DNA extraction and sequencing. Patients can re-enter the master protocol pathway at any stage of their treatment journey, provided there is a suitable trial option available.

To increase the enrolment to the *PRECISION-Panc* Master Protocol, especially capturing those patients with low volume metastatic disease, who may not be amenable to radiologically guided biopsy, we optimised and endoscopic ultrasound (EUS) guided biopsy pathway and sample processing protocol. Patients presenting with PC *de novo* have a primary lesion that is almost always amenable for EUS biopsy. Thus, this makes a perfect solution for

obtaining tissue in all stages of PC. Traditionally, EUS samples are taken using fine needle aspirates with low tissue yield that is not suitable for NGS. However, with the development of modern EUS core biopsy needles in recent years, this problem is mitigated by the much-improved quality and volume of tissue obtained. Increasing the number of biopsy passes from 2 - 3 to 4 - 5 per patient, achieves extremely low sample failure rates[9]. We did not observe any increased morbidity in our experience of over 100 patients with additional EUS tissue taken[9].

Integral to the design and ethos of *PRECISION-Panc* is the rapid and dynamic sharing of data between the clinic and the laboratory. This allows rapid translation into clinical trial, whilst backward translation further refines therapeutic targets and resistance mechanisms (Figure 2). This provides a unique opportunity to perform multiple small, signal seeking clinical trials (~20 - 40 patients) of novel agents, or repurposing effective therapies from other cancer types[10]. This is of particular importance in the advanced, second line setting where there is currently no standard effective therapy. The parallel generation of clinical, molecular and relevant pre-clinical data allows for potential advances into identifying therapeutic responses and resistance mechanisms, even in small groups of patients. The key to this umbrella of clinical trials, is enrichment of molecular and therapeutic responsive subgroups in each trial (see accompanying Editorial)[10] to enable a positive signal, but more importantly give patients a viable and attractive trial option with the best chance of benefit. For example, in patients that develop resistance to platinum but are deemed homologous recombination deficient (see accompanying editorial), testing of a PARP inhibitor would provide the best chance of success based on pre-clinical data and responses in other tumour types[11].

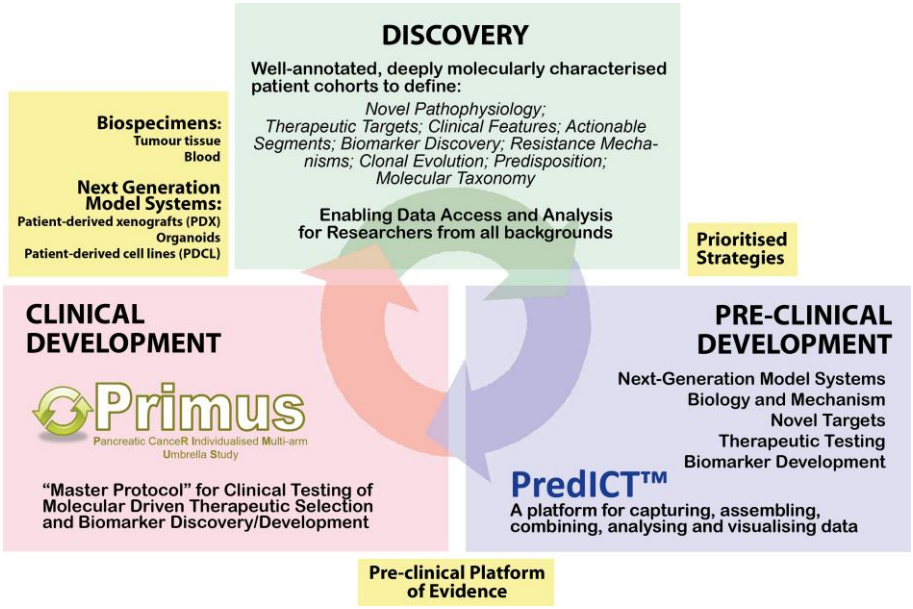

Figure 2: The *PRECISION-Panc* therapeutic development platform. Integrating Discovery, with pre-clinical development and clinical trial design allows forward and backward translation. This allows refinement of therapeutic segments in PC and development of novel therapeutics.

Conclusions

The progression to precision oncology is a natural evolution of cancer medicine that has been on the horizon for a decade or more. The major obstacle to implementing the scientific advances into practice for many cancer types is the significant challenge in molecularly profiling patients of all disease stages in a clinically meaningful timeframe, using a clinically relevant molecular assay with a low failure rate. The *PRECISION-Panc* Master Protocol was designed to overcome these challenges and is demonstrating its initial success, enabling patients with PC the opportunity to participate and potentially enter an attractive clinical trial option with maximal chance of success.

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