2019 Final Report

Name of Institution: The University of Melbourne, Centre for Cancer Research

Project Title: The Australian Pancreatic Cancer Organoid BioBank

Principal Investigator: Professor Sean Grimmond

Grant: Round 2 Accelerator Grant 2016

Background:

There are still very few therapeutic options for pancreatic cancer patients. For other diseases, there is the option to try a variety of drugs on a patient until they respond. However, as most pancreatic cancers are diagnosed late, this type of treatment is not viable for most suffering from pancreatic cancer.

Professor Sean Grimmond and his team aimed to address this issue by pioneering personalised genome analysis and broad-scale drug screening outside the patient using organoids. Organoids are copies made by taking a biopsy of a tumour and growing the cells outside of the body to be a model for drug testing.

Professor Grimmond aimed to develop the means to create organoids of patients tumours quickly, and to sequence the genome of these tumours. He also aimed to survey the drug responses each organoid had to dozens of anti-cancer drugs.

The Research:

1. **Complete organoid generation and molecular characterisation of 60 additional lines.** One hundred and twenty nine patients were recruited and consented for the program from which tumour tissue and matched blood, and an organoid was generated. The overall success rate for organoid generations was 55% . Patient-matched models for nine patients were rescued after failure to generate organoids from the primary tissue by the expansion of their tumour in mouse xenografts instead. An additional eight pancreatic cancer organoids were recently expanded and are undergoing analysis. Molecular profiling was used to confirm the tissue of origin of the tumour and to quantify the level of mutational fidelity between the organoid and its matched tumour. It was also used to identify the driver mutations

present in each tumour and its matched model.

2. **Compile data to confirm the responsiveness of targeted agents.** The data from generating the first organoids was used to identify druggable driver mutations and other vulnerabilities present in the cohort. Before drug screening, the data for the organoids and their matched tumour profiles and ICGC and TCGA atlases were compiled . The study identified potentially druggable mutations in patients or their organoids that may influence sensitivity to specific inhibitors (PARP, CDK4/6, MEK, EDFR, , EZH2, WEE1, PRMT5, RET, FGFR and ATR). The largest druggable segment present in the cohort was patients bearing mutated CDKN2A, TP53 and KRAS who lack mutations in the RB1 pathway, which acts to supress tumour cells. Patients with this mutation profile are considered targets for CDK4/6 inhibition. These results and comparison revealed that pancreatic organoid culturing methods will not successfully expand for certain mutations in the tumours (BRCA deficient and KRAS wildtype). The detection of these results was referred to the VCCC molecular tumour board and returned to patients and their clinicians to assist in future management of their disease.
3. **Screen for recurrent defects in all organoids that respond to specific agents.** Determining the inhibitory potency of these agents provided the foundations to assess the specificity of response and overall sensitivity. The responsiveness to the standard agents approved for pancreatic cancer treatment have been assessed, both as single agents and in the standard combinations used in the clinic.The responses the organoids had to specific drugs was compared to the treatments given to their matching patient. In terms of targets agents, CDK4/6 inhibitor, MEK inhibitor and anti-apoptotic inhibitor (birinapant) were performed on the organoid panel. Additional studies are continuing.

4. **Test combination drug screening on organoids involving non-targeted and genomically targeted drug combinations for individual lines.** Both single agent and combination CDK4/6 inhibitors have been performed on the organoid bank to assess synergistic killing of potentially sensitive tumours.

The Impact:

This study by Professor Grimmond has revealed a wealth of important findings. It enabled the team to establish a workflow of consenting patients, collection of samples, genomically characterising these samples and the generation of patient-matched models. This study also gave the researchers the ability to systemically screen these models for druggable targets.

Professor Grimmond will continue the recruitment of pancreatic cancer patients and produce organoids to complete their molecular profiles for potential drug targets. Further recruitment will increase the patient numbers required to confirm the responsiveness of targeted agents.

As a result of this project funded by the Avner Pancreatic Cancer Foundation:

(a) Professor Grimmond was awarded additional research funding for this or related studies:

- An NHMRC Project Grant titled Dissecting the mutational landscapes and cellular ecosystems of pancreatic cancer. This grant started in 2019 for the amount of $854,384.

(b) Professor Grimmond gave oral presentations at the following events and organisations:

- 2017 VCCC Symposium on Pancreatic Cancer
- Gastroenterological Society of Australia during Australian Gastroenterology Week in 2017
- The 2017 Annual Scientific Meeting of the Australasian Gastro-Intestinal Trial Group
- 2017 Victorian Comprehensive Cancer Centre Molecular Tumour Board Educational Meeting
- 2017 Cutting Edge Science Symposium on Genome Engineering for Cancer Treatment
- 8th Barossa Meeting for Cell Signalling in Cancer Medicine
- The 17th Annual Conference of the Australasian Genomic Technologies Association
- 2018 Walter and Eliza Hall Institute Educational Talk
- 2018 International Summit on Population & Medical Genomics, UK
- 2018 Australian Precision Oncology Symposium
- 2018 East-West Alliance Symposium & Shantou University Medical College Research Day, China
- Bio Connections Australia, 2018
- 49th International Symposium Princess Takamatsu Cancer Research Fund, Japan
- 2018 Avner Pancreatic Cancer Foundation Researcher Symposium
- Victorian Comprehensive Cancer Centre Molecular Tumour Board Education meeting 2019