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Project editorial piece for public release

Round 2 – Accelerator Grant 2016

Name of Grant Recipient / Institution: The University of Melbourne

Project Title: *The Australian Pancreatic Cancer Organoid Biobank*

Principal Investigator: Prof Sean Grimmond

1. Summarise the aim of your research

While we have made significant in-roads into understanding the root causes of Pancreatic Cancer, translating potential opportunities into improved therapeutic options and better outcomes is proving very slow. One major impediment against progress is the aggressive nature of the disease. In the case of other more indolent diseases (e.g. colorectal cancer), patients are cycled through multiple lines of therapy, until one is found. Sadly, learning and testing drug responsiveness in this manner is not a viable opportunity for most suffering from this disease.

This study seeks to pioneer personalized genome analysis and broad-scale drug screening outside the patient, using organoids as a model. We aim to build the means to rapidly expand cancer cells from a patient's tumour biopsy, decode its root cause by genome and transcriptome sequencing and then survey drug responses to dozens of anti-cancer drugs (far more than can ever be done or endured within the clinic). These studies will evaluate whether specific mutations influence drug responsiveness and measure how closely drug responsiveness of these lab models match the patient's experience. The bank of Pancreatic Cancer organoid models created by this study will provide us with a valuable resource to scale up and accelerate drug discovery in the future, something that is badly needed for this disease.

2. What have the outcomes been to date?

The program has built much of the foundations needed for routine prospective recruiting, organoid generation, cancer genome analysis and organoid drug screening with approximately 10 new cases being recruited per month. The methodologies necessary for screening drug responsiveness in organoids has been optimised against "standard of care drugs" currently approved for treating Pancreatic Cancer. Crucially, the responses of patients to drugs versus their organoid response have shown close concordance. As the efficiency of organoid generation has improved (currently 65% success rate and an 8 week turnaround), we have started to obtain lab-based, drug sensitivity profiles fast enough to be clinically useful. To that end, we have commenced piloting the return of drug response data for patients with extreme sensitivities to known agents. Genomic analysis (DNA and RNA sequencing) has been carried out on all organoids generated and mined for driver mutations and potential druggable vulnerabilities. More than a dozen different recurrent gene mutations have been found. The final phase of this program involves testing whether any of these mutations do in fact promote specific drug sensitivities in the organoid models.

3. What are the next steps?

This study is providing valuable foundations to drive new activities in both basic and clinical cancer research. From the basic science point of view, the bank of organoids provides a resource for studying how individual mutation patterns influence cancer biology beyond just drug response (e.g. how do cancer cells with different mutation profiles interact with supporting cells, how do they allow cancer cells to evade the immune system). From a clinical point of view, we are keen to see how these SOPS can be used to create a platform for genome and organoid directed trials in the future.

4. What has it meant to receive funding from the Avner Pancreatic Cancer Foundation?

This funding has proven crucial for three reasons. The first is that it has allowed us to rapidly roll out the means for ex-vivo (outside the body) drug screening and parallel genomic testing for Pancreatic Cancer in a timely manner. Such endeavours are notoriously difficult to fund through traditional mechanisms as they do not value the need to accelerate the pace of research and capacity building in pancreatic research as greatly as the Avner Pancreatic Cancer Foundation. Secondly, this grant provided a golden opportunity for a new collaboration to fight Pancreatic Cancer. It has brought together a dynamic set of clinicians and translational researchers across the University of Melbourne, Walter & Eliza Hall Institute, Victorian Comprehensive Cancer Centre alliance and other collaborative institutions to focus on Pancreatic Cancer. Finally it has rapidly created the know-how to survey and confirm for druggable vulnerabilities in the future and provided a bioresource for future drug discovery.