September 2018

Project editorial piece for public release

Round 3 – Innovation Grant 2017

Name of Grant Recipient / Institution: Monash University, Hudson Institute of Medical Research

Project Title: *A novel translational pipeline for the introduction of new immune-based therapies targeting localised and metastatic pancreatic ductal adenocarcinoma*

Principal Investigator: Prof Brendan Jenkins

1. Summarise the aim of your research

This project aims to evaluate the anti-cancer activity of a novel series of immune-based therapies in models for human pancreatic tumours that have been genetically screened to predict responsiveness to specific treatments. The use of immune-based therapies in precision medicine for pancreatic cancer has great potential to enhance patient outcomes.

2. What have the outcomes been to date?

Using endoscopic ultrasound guided fine needle aspiration (EUS FNA), a relatively non-invasive procedure (compared to surgery) that is available to virtually all pancreatic cancer patients, we have collected cancer (tumour) biopsies for whole exome sequencing (genomic DNA) and transcriptome RNASeq profiling (RNA).

Analysis of the data generated thus far (by bioinformatics) indicates that in pancreatic cancer tumour biopsies, there is an enrichment in the expression of gene networks and signalling pathways that are involved in the (innate) immune system, which supports our hypothesis that deregulated innate immunity contributes to the pathogenesis of pancreatic cancer. Further analyses confirm that our candidate genes of interest, in particular TLR2, are over-expressed in pancreatic cancer at all stages of disease.

Using patient-derived xenografts (PDXs), we have identified a high TLR2-expressing PDX (from EUS FNA) that responds to a clinical grade inhibitor against TLR2. Specifically, the growth of this tumour xenograft (selection based on high TLR2 expression in the primary biopsy) was significantly impaired upon treatment with the inhibitor, therefore providing preclinical

evidence that EUS FNA can be used to identify tumours in a timely manner that respond to specific therapy against innate immunity regulators.

3. What are the next steps?

We aim to verify the cellular processes (eg proliferation, survival) and molecular pathways that are affected by TLR2 inhibition, and which are associated with its anti-cancer activity.

Ongoing analysis of whole exome sequencing data from EUS FNA tumour biopsies is underway to identify whether potential "driver" gene mutations are also present in TLR2 and other innate immune candidates in pancreatic cancer.

Additional PDXs for other innate immune targets are being identified to determine if targeting such candidate with specific inhibitors will also yield anti-cancer activity.

We are also developing an *in vivo* system to "humanise" PDXs to determine whether the presence of a competent immune system will impact on the anti-cancer activity of the TLR2 inhibitor.

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

To the best of our knowledge, our results thus far provide strong evidence for the first time that EUS FNA can be used to inform precision medicine (targeted therapy) in pancreatic cancer. In addition, we reveal that specific regulators of innate immunity (eg TLR2) have the potential to serve as new targets for therapy in pancreatic cancer. These discoveries provide a critical platform to introduce targeted therapy against innate immune regulators in pancreatic cancer into the clinic, and would not have been possible without the invaluable funding provided by the Avner Pancreatic Cancer Foundation.