November 2018

Project editorial piece for public release

Round 3 – Innovation Grant 2017

Name of Grant Recipient / Institution: The Garvan Institute of Medical Research

Project Title: *Harnessing a novel 'tunable' immune check point to enhance the immunogenicity of anti-pancreatic ductal adenocarcinoma*

Principal Investigator: Assoc. Prof Shane Grey

1. Summarise the aim of your research

SUMMARY OF RESEARCH QUESTION

Pancreatic cancer remains one of the most lethal of all human malignancies and we desperately need new therapies to improve patient outcomes. We are proposing to develop a novel immune "checkpoint" regulator to allow immune-mediated killing of pancreatic cancer.

In recent times the clinical development of novel immunotherapies has revolutionised the way many cancers are being treated. Immune checkpoint inhibitors including drugs that target anti-PD-1/PD-L1 and anti-CTLA-4, or immune activators like anti-CD40, have shown great improvements in patient outcomes for several types of cancers including melanoma of the skin, bladder cancer and Hodgkin's lymphoma. These results highlight the key principle that boosting the natural immune response either by removing immune suppressive pathways, or by directly enhancing the immune response, is a promising new approach to improve patient outcomes that could be applied to pancreatic cancer.

Our studies focus on new ways to directly enhance the immune response. In work unrelated to cancer, but in the field of immunology, we have discovered a novel immune 'checkpoint' regulator gene, which we have called "*Voldemort*" (The genes real identity is under embargo pending a current patent application). We are investigating whether we can increase the ability of a T cell to kill a cancer cell by manipulating Voldemort.

WHAT WE HOPE TO ACHIEVE

Our vision is to CRISPR engineer variants of Voldemort into patient T cells, these engineered cells would be transferred back to the patient where they would show enhanced tumour infiltration and cancer killing, most likely synergising with current chemotherapy with or without current checkpoint inhibitors.

HYPOTHESIS

Enhancing a patient's natural immunity to the pancreatic cancer will synergise with current therapies and improve patient survival and overall outcomes.

2. What have the outcomes been to date?

To address our aims we have achieved the following outcomes:

(1)We have identified a series of Voldemort gene variants in the human genome that exhibit graded changes in their biochemical function to tune immunity.
(2)We have used genome editing methods to generate unique mouse lines that each harbour a specific Voldemort gene variant. We have generated two such lines with a third in progress.
(3)We have tested these novel engineered mouse lines in various immune models that assess the speed, veracity, and sensitivity of the immune system to different [infectious] challenges. These data show that specific genetic 'versions' of Voldemort can tune the immune system to a more aggressive setting.
(4)We have tested the anti-pancreatic cancer activity of the "Voldemort activated" immune system using the Pdx1-Cre; KrasLSL.G12D/+; p53R172H/+; (KPC) orthotopic model of pancreatic cancer. In this aggressive model we found that there is less spread (metastasis) in mice harbouring one specific Voldemort variant.
(5) We have established an in vitro human CAR T cell model to test whether engineering a specific human CAR T cell will enhance its ability to target and kill a cancer cell. We have generated the CAR T cell model and successfully engineered human T cells to express different Voldemort gene variants.

3. What are the next steps?

The data we have attained so far is consistent with our hypothesis that we can enhance immunity, and therefore we predict cancer killing, by genome editing of Voldemort. In an exciting but still preliminary study we showed that mice harbouring a more aggressive Voldemort gene variant showed a reduced number of METS in the liver.

Future Experiments: With these data in hand we will continue to test the different Voldemort mouse lines in orthotopic model. We will also move to test our approach using human CAR T cells. Human CAR T cells engineered to express specific Voldemort variants will be assessed for increased pathogenesis towards their target cancer cell.

Future Funding: We will continue to seek funding from relevant agencies using the data already gathered and supported by Avner.

Future Commercial Development: We believe the promising results from our studies could be rapidly translated to the clinic and provide a potential breakthrough therapeutic approach for the treatment of patients with pancreatic cancer. We are currently preparing IP that covers this invention. We have initiated discussions with big Pharma regarding potential translation of our findings.

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

Avner funding has been crucial for our research. By funding our research at a very early stage Avner have enabled the development of significant proof of concept data. This data will be leveraged to obtain more funding, support our patent application, and support continuing discussions with Pharma as we continue to test and develop our technology towards clinical translation.