Name of Institution: University of Sydney, Kolling Institute

Project Title: *Harnessing the Power Within to Conquer Pancreatic Cancer*

Principal Investigator: Dr Emily Colvin

Grant: Round 1 Innovation Grant 2015

Background:

Stimulating the immune system so that a patient can mount an immune response to reject their tumour is considered to be the holy grail of cancer therapy. Several immunotherapies are already being applied as a clinical treatment for other cancer types with excellent results. However, these therapies have not been effective in pancreatic cancer. Evidence suggests that using a vaccine may help to boost the response to these immunotherapies.

The aim of Dr Colvin's research was to test a novel cancer vaccine developed in her laboratory in preclinical models of pancreatic cancer. Dr Colvin's team had developed a process to make a vaccine from a patient's own tumour, and therefore provide a personalised immune response. This Project aimed to test the novel tumour vaccine methodology when combined with current standard of care treatment as well as other immunotherapies.

The Research:

1. **Can the efficacy of standard of care chemotherapy for pancreatic cancer be improved by the addition of an autologous anticancer vaccine developed by Dr Colvin's team?** Dr Colvin and team determined that the cancer vaccine can be safely combined with standard of care chemotherapy in a mouse model of pancreatic cancer. In addition, survival was improved in mice treated with the vaccine plus chemotherapy compared to control, vaccine alone or chemotherapy alone groups.
2. **Can the efficacy of the vaccine for pancreatic cancer be improved by combination therapy with immune checkpoint inhibitors?** Dr Colvin and team tested three immune checkpoint inhibitors and found that only PD-1 antibody was able to improve the efficacy of the vaccine.
3. **What are the tumour and systemic immune responses in pancreatic cancer to the immune therapies trialled?** The immune therapies tested by Dr Colvin altered the pattern of immune cell infiltration within the tumour, with greater numbers of lymphocytes present compared to control mice. Systemically, there were increases in some immunosuppressive cytokines, which may be limiting the efficacy of immune therapies in pancreatic cancer and warrant further investigation.

The Impact:

This Project demonstrated that chemotherapy combined with the vaccine developed by Dr Chris Weir, also an investigator on the grant significantly prolonged survival in the mice and was superior to chemotherapy alone. The longest survivors were mice who were also treated with an anti-PD1 antibody as well as chemotherapy and the vaccine, suggesting that the addition of an immune checkpoint inhibitor may boost response to the vaccine.

The most important research findings as a result of this Project came from the ongoing characterisation of the tumours and blood collected from each of the treatment groups. While this vaccine has previously been shown to result in a >30% complete response in rodent models of aggressive brain cancers, Dr Colvin did not see any complete responses in any of the mice with pancreatic tumours. Despite this, histological analysis of pancreatic tumours demonstrated that the vaccine is having an effect on tumours, with tumours displaying changes in morphology compared to both controls and chemotherapy groups. In addition, there is an increase in infiltrating immune cells present in vaccine treated groups, with immune cells moving deeper into the tumour when PD-1 antibody is administered along with the vaccine. Flow cytometry analysis demonstrated that vaccine treatment increased the number of lymphocytes within the tumour, with increases in T cells, natural killer cells and macrophages seen.

Interestingly, cytokine profiling suggested that some immunosuppressive cytokines are upregulated in some of the treatment groups and this may explain why response to the vaccine hasn't been as strong as had previously been observed in rodent models of brain cancer.

Dr Colvin had also begun proteomic profiling in order to identify potential targets that will improve efficacy of the vaccine in pancreatic cancer. Dr Colvin found that the most differentially expressed proteins in treated mice are involved in regulation of inflammatory processes and immune response, protein and phospholipid transport, as well as activating signalling cascades involved in cell growth, survival, proliferation, motility and morphology.

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

(a) Dr Chris Weir (co-investigator of this Project) has been awarded additional research funding.

Specifically, Dr Weir successfully gained financial support from Vaxine Pty Ltd and the South Australian Government to continue developing and improving the vaccine for pancreatic cancer developed as a result of this Project and will continue to collaborate with Dr Colvin on this Project.

Further researching this Project is important given the vaccine developed as a result of this Project was able to prolong survival in a mouse model of pancreatic cancer however was less effective than the vaccine when tested in

models of brain cancer. Dr Weir's further research will involve using the characterisation of the immune response to further refine Dr Colvin's treatment regime in order to tailor it to the unique immune microenvironment present in pancreatic tumours.

(b) Dr Colvin presented her findings

- *Vaccines in Mouse Models of Pancreatic Cancer* at the Royal North Shore Hospital to the Hepatobiliary Research Group on 15 August 2016
- *Harnessing the power within to conquer pancreatic cancer* at the inaugural Avner Pancreatic Cancer Foundation Symposium, November 2017

Feedback *provided by* Dr Colvin:

The research undertaken as part of this Innovation Grant has been extremely useful in generating multiple hypotheses as to why pancreatic cancer is so resistant to immunotherapies. We anticipate that we will be able to present findings from this Project at scientific conferences in 2018 as well as publish a manuscript.

We hope that the Avner Pancreatic Cancer Foundation continues to distribute these Innovation Grants. They are really worthwhile for encouraging not only early career researchers to keep pursuing a career in pancreatic cancer research but also as a way to attract other high quality scientists into the area.