PANCREATIC CANCER FOUNDATION

Name of Institution: Centenary Institute

Project Title: *A new therapy for pancreatic cancer that improves tumour microenvironment and immune cell penetration*

Principal Investigator: Prof Jennifer Gamble

Grant: Round 1, Accelerator Grant 2015

Background:

Blood vessels provide the body with key nutrients and energy, they also regulate the passage of immune cells from the blood stream into tissues. Blood vessels within a tumour are highly abnormal and their expansion is needed to support the growing tumour mass. Furthermore, these abnormal blood vessels inhibit the infiltration of immune cells into the tumour which is a reason for the failure of the body to use its immune system to fight against tumour growth.

Prof Gamble and her team have developed a new drug, CD5-2, that targets the endothelial cells that line all vessels and renders these cells in disease more "normal". Experimental results have shown CD5-2 significantly inhibits the growth of tumours in a number of different types of animal models. The objective of this Project was to gather preclinical data to assist with procuring the funds necessary to progress CD5-2 to a phase I oncology study that may ultimately lead to a new therapy to treat pancreatic cancer.

The Research:

Determine whether CD5-2 is effective in a pancreatic neuroendocrine tumour model.

Prof Gamble and her team have demonstrated that CD5-2:

- is effective in a pancreatic neuroendocrine tumour model to promote changes in the vasculature;
- promotes tumour specific CD8+ T cell infiltration into the tumour:
- inhibits the migration of neutrophils into tumours, neutrophils in the tumour are associated with a poor prognosis and poor response to immunotherapy.

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The Impact:

This Project demonstrated that CD5-2 is a first-in-class drug that has therapeutic potential especially to enhance immunotherapy.

Prof Gamble's research demonstrated that CD5-2 is able to substantially alter the immune cell infiltrate by targeting the endothelial cells in the vasculature. The research suggests that CD5-2 may function in conjunction with immunotherapies, enhancing the number and activity of the immune cells to increase their ability to fight and destroy the tumour cells. Future studies in pancreatic cancer studies will involve CD5-2 in combination with anti-PD-1, a checkpoint inhibitor that is now widely used in other cancers but fails to have a significant effect in pancreatic cancer.

Prof Gamble is currently in discussions with pharmaceutical and funding companies regarding the clinical development of CD5-2, including potential Phase I human studies of CD5-2. This Project provided the preclinical studies required to obtain data on the pharmacokinetics, toxicology and pharmacodynamics of CD5-2 to progress to phase I clinical trials

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

(a) Prof Gamble has been awarded additional research funding for this and related studies:

The NHMRC has awarded Prof Gamble a Project Grant, *Modulation of Endothelial Junctions as Selective Immunotherapy*, worth **$911,000**

(b) Prof Gamble and her team have published the following journal article:

Targeting vascular VE-cadherin in tumors promotes T cell-mediated Immunotherapy. Cancer Research 77(16); 1–14. 2017. Yang Zhao, Ka Ka Ting, Jia Li, Victoria C. Cogger, Jinbiao Chen, Anna Johansson- Percival, Shin Foong Ngiow, Jeff Holst, Georges Grau, Shom Goel, Thorleif Muller, Elisabetta Dejana, Geoff McCaughan Mark J. Smyth, Ruth Ganss, Mathew A. Vadas, and Jennifer R. Gamble

(c) Prof Gamble has presented her findings

- *A Novel Oligonucleotide Based Drug Against Vascular Leak*, presented at:
  - Immunotherapy in Brisbane, 2016;
  - Queensland Medical Meeting, New Zealand, 2017;
  - International Vascular Biology Meeting, Finland, 2018; and
  - Second JCS Forum on Basic Cardiovascular Research, Japan, 2018.

Feedback provided by Prof Gamble:

The grant awarded to us by the Avner Foundation has provided a boost in our efforts to determine whether our novel drug will be clinically useful. It has allowed us to focus on this devastating and hard to treat cancer, pancreatic cancer, where patients have little hope. Further it has been a catalyst to secure more funding for the development of the drug. Thus, we hope to contribute to the vision of the Foundation, to double the number of people surviving pancreatic cancer by 2020.