June 2017 – Final Report

Name of Institution: Pancreatic Cancer Translational Research Group, Lowy Cancer Research Centre, UNSW Australia

Project Title: Elucidating the mechanism by which MutY-Homolog knockdown kills pancreatic cancer cells

Principal Investigator: Dr George Sharbeen

Background:

Pancreatic cancer is a deadly disease with a 5-year survival rate of just 8%. Our current best treatments extend life by only 8-16 weeks, making it imperative that we design more effective therapeutic approaches to tackle this disease. It is incredibly hard to treat due to chemoresistance and metastatic spread. A major contributor to this poor outcome is the extensive scar tissue that encapsulates pancreatic tumours. The scar tissue forms a physical barrier to conventional cancer drugs and distorts blood vessels in the tumour, hindering drug access and creating conditions that drive tumour progression. This environment also imposes a type of stress on cancer cells that can compromise their DNA, leading to cell death, yet these cells manage to thrive. In 2016, the Avner Pancreatic Cancer Foundation funded early career researcher Dr Sharbeen's investigation into a mechanism that helps pancreatic cancer cells survive this stress, as a potential therapeutic target in pancreatic cancer. This work built on Dr Sharbeen's expertise in DNA repair, gained during his PhD, and in translational pancreatic cancer researcher, gained during his current post-doctoral work with A/Prof Phoebe Phillips, at the Lowy Cancer Research Centre, University of New South Wales (UNSW) Sydney. In addition, he contributed to the development of a novel nanomedicine capable of inhibiting this target.

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The Research:

1. **Identification of a new therapeutic target for pancreatic cancer.** As a result of funding from the Avner Foundation, Dr Sharbeen was able to complete and publish research that has identified a novel therapeutic target for pancreatic cancer (**Publication:** Oncotarget. 2017 8[6]:9216-9229). Inhibition of this target reduced pancreatic cancer cell survival, sensitised them to a broad range of cancer drugs and reduces their potential to spread throughout the body.

2. **Development of a novel nanomedicine for pancreatic cancer.** This funding has also allowed Dr Sharbeen to help develop a novel nanoparticle called STAR-PEG, capable of overcoming the physical barriers to drug delivery in pancreatic cancer (**Publication:** Biomacromolecules. 2016 17[7]:2337-51).

The Impact: If translated to the clinic, inhibition of the target identified by Dr Sharbeen has the potential to improve pancreatic cancer patient survival by reducing tumour growth and metastatic spread, and by increasing the efficacy of a variety of existing cancer drugs. The nanoparticle work will help facilitate the translation of the targets identified through this fellowship, to the clinic. This work continues to build on Dr Sharbeen's track record of high-impact research publications, which is critical for his development as a future research leader. The funding from the Avner Foundation was also instrumental in developing preliminary data that resulted in Dr Sharbeen's acquisition of competitive research funding (Cure Cancer Australia: $200,000, 2017-2019; Tour de Cure: $80,000, 2018) that will help continue this work.

Feedback: Dr Sharbeen says "*This was an excellent initiative and provided invaluable support for myself as an early career researcher in pancreatic cancer. Without this seed funding, I would not have been able to continue development of a potential therapeutic approach for the treatment of this devastating disease. This funding was also critical in helping me build a critical track record of competitive funding acquisition as an early career researcher, which has now allowed me to acquire another 2 years of category 1 funding to continue this research.*"