2017 Progress Report

Name of Grant Recipient:	**University of Sydney**
Project Title:	***Development of Novel Agents that target P-glycoprotein resistant pancreatic cancer***
Principal Investigator:	**Dr Des Richardson** **Professor of Cancer Cell Biology** **NHMRC Senior Principal Research Fellow**

1. Summarise the aim of your research

Over the last 40 years, there has been little progress in improving the survival of pancreatic cancer patients. This project aims to attack this problem "head-on" by developing novel frontier chemotherapeutics that strategically target drug-resistant pancreatic cancer. This is achieved by directly taking advantage of their own drug detoxifying pumps (*i.e.,* the P-glycoprotein; Pgp drug-pump) to transport agents into their site of action (the lysosome).

Indeed, 80-93% of pancreatic cancer tumour specimens express the multi-drug resistant protein, Pgp. Our proposal describes an innovative new mechanism for the development of drugs that take advantage of elevated levels of the drug detoxifying pump Pgp within the lysosomal membrane and the high levels of copper inside lysosomes of drug-resistant pancreatic cancer tumours to kill the cancer. This strategy is an exciting new paradigm for utilising a drug resistance pump against the tumour itself to target drug-resistant pancreatic cancer tumours that are intractable to treat.

2. What have the outcomes been to date?

We have now established the optimal structural features for the agents to overcome drug resistance. These type of agents need to maintain the basic active pharmacophore with the 3 key molecular signatures that are: (1) being a P-glycoprotein substrate; (2) becoming charged and trapped in lysosomes; and (3) binding copper and inducing lysosomal membrane permeabilisation and cancer cell death.

Notably, our lead agent, DpC utilise this mechanism of action and has entered multi-centre clinical trials in Australia (NCT02688101) for advanced cancer.

3. What are the next steps?

Notably, we found that our lead agent, DpC become only partially trapped in lysosomes (16 %). Hence, despite the impressive efficacy of this drug, new agents will be developed to optimise Pgp transport and lysosomal trapping to maximise their efficacy against drug-resistant cancers. As such, we are now focussing on designing new libraries of agents that take advantage of Pgp and the high levels of copper in pancreatic cancer to overcome cancer resistance based on our findings how agents need to be optimised.

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

The poor clinical response of pancreatic cancer is due to its highly metastatic phenotype and the rapid development of resistance to conventional chemotherapies. Indeed, 80-93% of pancreatic cancer patient tumour specimens (solid or metastatic) express the multidrug-resistant drug pump, Pgp.

This funding from Avner Pancreatic Cancer Foundation has enabled us to take an unexplored route of attacking drug-resistant pancreatic cancer. Other research investigations are currently trying to overcome drug resistance in cancer by development of inhibitors of Pgp to block drug efflux from cancer cells and enhance the efficacy of clinical chemotherapeutics. Unfortunately, these drug pump inhibitors have shown very little clinical success in overcoming resistance to standard chemotherapies.

The use of inhibitors to block Pgp transport is totally opposite and unrelated to our drugs that directly utilise lysosomal Pgp to their advantage to kill resistant tumours.

It's our hope that by using our discovered frontier strategy to utilise Pgp to treat drug-resistant pancreatic cancer, will result in translation of effective clinical therapies that will directly impact the survival rate of pancreatic cancer patients. Hence, the funding from Avner Pancreatic Cancer Foundation has enabled us to explore a paradigm shifting strategy to "trick" the drug detoxifying pump, Pgp, to target the most advanced and drug-resistant pancreatic cancer tumours that are currently a major intractable problem in the clinics.