Name of Institution: Garvan Institute of Medical Research – The Kinghorn Cancer Centre

Project Title: Immunology and anti-invasive treatments for pancreatic cancer: a new therapeutic partnership

Principal Investigator: Dr Marina Pajic

1) Summarise what the aim of your research was.

Research from our lab has shown that pancreatic cancer is a diverse disease, with quite distinct subtypes, where unfortunately the currently used "one drug fits all" treatment approach is not effective. Our previous work highlights the need for a personalised treatment strategy, where pancreatic cancer patients receive optimal therapy tailored to their molecular "fingerprint" or subtype. One of these molecular "fingerprints" yet to be examined involves abnormal signalling through a specific cellular pathway called the JAK/STAT-3 pathway. Signalling via this pathway controls cancer cell growth, mediates communication between tumour cells and immune cells in the body, and promotes pancreatic cancer spreading or metastasis, which is ultimately fatal. Our team has recently shown that JAK/STAT-3 signalling is deregulated in up to a third of pancreatic cancers. Our main aim in this study was therefore to find out if specifically targeting these tumours with a combination of drugs able to disrupt the JAK/STAT-3 signalling pathway would have significant anti-cancer effects. The overall goals of our research are to develop a more efficient strategy for personalised testing of new therapies and to accelerate progress into clinical trials.

2) What has the outcomes been to date?

In this novel concept project, our analyses of tumours from pancreatic cancer patients have revealed that abnormal JAK/STAT-3 signalling is associated with worse patient prognosis and with chemoresistance, highlighting the urgent need to develop better treatment options for this disease subtype. Moreover, we have demonstrated for the first time that the combination of Ruxolitinib (an immune cell modulating agent) and Dasatinib (an anti-cancer drug currently used to treat blood cancers) may be an effective treatment option for this subtype of pancreatic cancers. With this drug combination, we saw significant anti-cancer effects in models of pancreatic cancer derived from patient tumours and in genetically engineered models of pancreatic cancer. Importantly, this treatment stopped both the growth of the cancer cells and decreased their ability to spread.

Finally, using innovative techniques including state-of-the-art 3D imaging of live cancer cells and tumours we are beginning to unravel previously unknown biological mechanisms that may explain why the combination of Ruxolitinib and Dasatinib is so effective. These early studies demonstrate that targeting not just tumour cells directly, but also multiple components of the surrounding tumour

tissue or “microenvironment”, including immune cells, could be a promising new approach for the treatment of pancreatic cancer.

3) What are the next steps?

Given the promising preliminary data we have generated, the next step is to expand our study to examine the effects of Ruxolitinib and Dasatinib in combination in a larger number of JAK/STAT-3 tumour models derived from pancreatic cancer patient tumours. To facilitate this, we have brought together a multidisciplinary, multi-institutional team led by Dr Pajic to test these findings in an advanced preclinical setting, with the next steps being progression into clinical trials and ultimately, real-world clinical application. We are hopeful that our promising data will ultimately lead to effective clinical application of the Ruxolitinib and Dasatinib, to treat chemoresistant and aggressive JAK/STAT-3 pancreatic cancers. These exciting preliminary findings will be used to submit a new Project Grant application to the NHMRC, Cancer Australia and Cancer Council NSW in 2017. Given our strong track record in translational research, and the quality of the data generated so far, we are confident we will be able to secure substantial funding support and continue to drive this research forward and thereby effectively leverage the initial Avner Foundation grant award.

4) What has it meant to have grant funding from the Avner Pancreatic Cancer Foundation?

While Dr Pajic has been very successful in attracting competitive funding from the NHMRC and Cancer Australia, the government funding bodies unfortunately do not support some of our most critical research needs, including seed funding for novel and highly innovative projects, which is why we are particularly grateful to the Avner Pancreatic Cancer Foundation. The Avner Foundation is making crucial, early-stage research happen!

The “Woolies on Wheels” Innovation grant has enabled testing of a completely novel concept for the treatment of pancreatic cancer. Our findings are contributing to and directly improving our understanding of pancreatic tumour biology and importantly, we are using this information to develop new and improved treatment approaches for this highly lethal disease. Finally, with the support from the Avner Foundation, we have been able to grow our scientific collaborations and to continue to increase capacity in pre-clinical and clinical pancreatic cancer research through recruitment and training of individuals from both clinical and scientific backgrounds.