**Name of Institution:** The Garvan Institute of Medical Research, The Kinghorn Cancer Centre, Cancer Division

**Project Title:** *Immunology and Anti-Invasive Treatments for Pancreatic Cancer: a New Therapeutic Partnership*

**Principal Investigator:** Dr Marina Pajic

**Grant:** Round 1 Innovation Grant 2015

**Background:**
Pancreatic cancer is a diverse disease, with quite distinct subtypes and the current "one drug fits all" treatment approach is not effective. Dr Pajic's 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", which prior to funding received by the Avner Pancreatic Cancer Foundation was 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. Dr Pajic's team has recently shown that JAK/STAT-3 signalling is deregulated in up to a third of pancreatic cancers.

The Avner Pancreatic Cancer Foundation has funded early career researcher Dr Pajic to find out if specifically targeting these tumours with a combination of drugs to disrupt the JAK/STAT-3 signalling pathway would have significant anti-cancer effects. The overall goal of Dr Pajic's research was to develop a more efficient strategy for personalised testing of new therapies and to accelerate progress into clinical trials.

**The Research:**

1. **Define the JAK/STAT-3/Src molecular subtype in pancreatic cancer**. Dr Pajic analysed potential biomarkers of interest and key regulators of the Src/JAK/STAT-2 signalling network, potentially identifying several key biomarkers of interest that may have prognostic relevance and may directly define pathway activation, an important step towards the identification of pancreatic tumours that may respond to the dual treatment combination.

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2. **Systematically examine individualised therapeutic strategies based on targeting Src/JAK/STAT-3 and functionally interrogate biological mechanisms of efficacy of dual targeting with Ruxolitinib/Dasatinib in extensively characterised model systems of pancreatic cancer, patient-derived cell lines and patient-derived xenografts (PDCL and PDX).** Dr Pajic conducted in vitro drug synergy screening on the TKCC PDCL panel and proof-of- principle in vivo studies, one PDX of interest. As a result, Dr Pajic has demonstrated significant efficacy of the two drug combination, Dasatinib and Ruxolitinib, specifically in models characterised by an "activated" Src/JAK/STAT-3 pathway which is defined by measuring protein levels of key components of this signalling network.

   Dr Pajic's team has also shown that Ruxolitinib alone efficiently induced apoptosis and decreased proliferation in selected PDCLs of interest and this effect was significantly increased following addition of Dasatinib. These effects were also observed in the genetically- engineered KPC model of pancreatic cancer.

   Dr Pajic has also been able to show that a different JAK2 inhibitor, AZD1480, when combined with Dasatinib, is similarly synergistic, highlighting that the observed response is robust. Moreover, this efficacy appears to be specific to JAK1/2 inhibition, as Tofacitinib, which predominantly targets JAK3, did not synergise with Dasatinib, but showed interesting anti-invasive and anti-proliferative effects in one JAK3-mutated PDCL.

3. **Investigate in real-time how altering the tumour microenvironment and immune cell signalling (Ruxolitinib) may improve anti-invasive drug targeting in vivo (Dasatinib).** Dr Pajic conducted organotypic, (Src) biosensor investigations and in vivo survival analysis using patient-derived and genetically-engineered (KPC) models which produced interesting data on the activity of tailored treatment combinations in more complex 3D and live settings.

   Dr Pajic observed significant anti-invasive effects of the Dasatinib/Ruxolitinib combination in a phenotype-specific manner in PDCL- derived or KPC-driven organotypic models, significant decrease in primary tumour growth in KPC tumours, and significant improvement in chemoresponsiveness of the KPC model compared to gemcitabine/Abraxane being standard-of- care therapy in pancreatic cancer.

   Dr Pajic's immunological studies revealed interesting effects on the tumour infiltrate profiles i.e. a decreased presence of immunosuppressive populations, such as regulatory T cells and tumour-associated macrophages and is now pursuing the possibility that Dasatinib/Ruxolitinib may help sensitise otherwise "cold" pancreatic cancers to immunotherapy.

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Dr Pajic's important findings were incorporated into a successful application for a grant awarded in 2017 by the NHMRC, Cancer Australia and Cancer Council NSW.

**The Impact:**
The key findings of this study include identification of a potentially targetable molecular pathway Src/JAK/STAT-3 network in pancreatic cancer with clinically-used or clinically-available agents, Dasatinib and Ruxolitinib.

Dr Pajic's team identified several ways in which these agents modify the pancreatic tumour and its microenvironment, with the goal to further exploit these effects by combining their approach with either chemotherapy or immunotherapy, ultimately to identify the right drug combination for the right patient and improve survival of patients with pancreatic cancer.

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

**(a) Dr Pajic has been awarded additional research funding for this or related studies:**

- Cancer Australia (co-funded by Cancer Council NSW), APP:1143699 *"Dual Targeting of Src and JAK/STAT3 Signalling as a Novel Personalized Treatment Strategy for Pancreatic Cancer*". 2018-December 2020 (three years) - **$600,000**

**(b) Dr Pajic and her team have presented their findings:**

- Avner Pancreatic Cancer Foundation Symposium (2017), Pajic M. *Immunology and Anti-Invasive Therapies in Pancreatic Cancer: A New Therapeutic Partnership;*
- Sydney and Cell Signalling and its Therapeutic Implications Meeting (2017), Victoria, Morgan A. *Targeting the Src/JAK/STAT3 Signalling Pathway: A Novel and Promising Therapeutic Strategy for Pancreatic Cancer;*
- Sydney Catalyst International Symposium (2017), Morgan A. *Targeting the Src/JAK/STAT3 Signalling Pathway: A Novel and Promising Therapeutic Strategy for Pancreatic Cancer;*
- Sydney Catalyst Post- Graduate and Early-Career Researcher (PG&ECR) Symposium (2017), Sydney, Morgan A, *Pancreatic Tumours with Activated Src/JAK/STAT-3 Signalling are a Novel and Targetable Tumour Subtype That are yet to be Examined;*
- Sydney Catalyst Post- Graduate and Early-Career Researcher (PG&ECR) Symposium (2016), Sydney, Morgan A. *Examining Pancreatic Tumours with Activated Src/JAK/STAT- 3 Signalling as a Novel and Targetable Tumour Subtype.*

**In addition, Dr Pajic and her team have leveraged funding provided by the Avner Pancreatic Cancer Foundation and:**

**(a) published the following two journal articles:**

- *Tailored First- and Second-Line CDK4-Targeting Treatment Combinations in Mouse Models of Pancreatic Cancer*. Gut 2017 [Epub ahead of print]. IF 16.7 Study further highlighted by articles in Nature Reviews Gastroenterology and Hepatology, iflscience.com, The Australian, SMH and Daily Telegraph. Chou A, Froio D, Nagrial AM, Morgan A, Murphy KJ, Chin VT, Wohl D, Steinmann A, Stark R, Drury A, Walters SN, Vennin C, Burgess A, Pinese M, Chantrill LA, Cowley M, Molloy TJ, Australian Pancreatic Cancer Genome Initiative (APGI), Waddell N, Johns A, Grimmond SM, Chang DK, Biankin AV, Sansom OJ, Morton J, Grey ST, Cox TR, Turchini J, Samra J, Clarke SJ, Timpson P, Gill AJ, Pajic M. Senior/ corresponding author.
- *Study further highlighted by Cancer Discovery*, Nature Reviews Gastroenterology and Hepatology, Nature Reviews Clinical Oncology and article in New Scientist magazine. Study made front cover of Science Translational Medicine Issue 9. Vennin C, Chin VT, Warren S, Lucas MC, Herrmann D, Melenec P, Walters SN, Magenau A, Allam AH, McCloy RA, Conway JRW, Pinese M, Boulghourjian A, Zaratzian A, Heu C, Nagrial AM, Chou A, Steinmann A, Drury A, Froio D, Giry-Laterriere M, Harris NLE, Mcghee EJ, Whan R, Grey S, Johns AL, Samra JS, Chantrill L, Gill AJ, Biankin AV, APGI, Wang Y, Evans TRJ, Anderson KI, Samuel MS, Burgess A, Sansom OJ, Morton JP, Pajic M*, Timpson P*. * Senior and co- corresponding authors.

**(b) won the following awards:**

- Sydney Catalyst, Won Best T1/T2 talk, Prize, 2017;
- Sydney Catalyst, Won Best T1/T2 talk, Prize, 2016;
- Cell Signalling and its Therapeutic Implications (CSTI) Meeting, Best overall poster (Ashleigh Morgan, now Parkin); and
- Cancer Institute NSW, Premier's Awards for Outstanding Cancer Research: 2017 Outstanding Cancer Research Fellow, Marina Pajic.

**Feedback *provided by Dr Marina Pajic*:**

*I would like to thank the Avner Pancreatic Cancer Foundation for understanding the need to fund and foster development of the early ideas, and I hope this continues into the future, as without this funding it would be very difficult to generate strong preliminary data and be competitive for other forms of grants.*