Name of Institution: Garvan Institute of Medical Research

Project Title: Dual targeting of metabolic and immunological aberrations in Pancreatic Cancer

Principal Investigator: Dr David Herrmann

Grant: Round 4 Innovation Grant 2018

Background:

Pancreatic Cancer survival has remained at a standstill for the last four decades, partly due to resistance to standard treatment approaches. Immunotherapy has emerged as a powerful means to improve outcomes in several cancer types. However, there is a profound room for improvement for immunotherapy in Pancreatic Cancer. Cellular metabolic problems often found in Pancreatic Cancer may be caused, in part, by the dysfunction of a neuronal signalling axis involved in the regulation of satiety and energy expenditure. Dr Herrmann and his team have revealed that inhibiting this system can impair tumour growth in other cancer types. They also found that it is strongly linked to the tumour-associated immune system. In this study, Dr David Herrmann and the Garvan team aimed to dually target this signalling axis (called NPY) and the immune system, by establishing efficient treatment schedules in mouse models.

The Research:

1. **Optimisation of dual targeting regimen**: Dr Herrmann's team optimised the treatment of NPY targeting in combination with immunotherapy for long-term mouse survival studies.
2. **Long-term studies with optimised treatment regime, determined from Aim 1:** Long-term survival studies with optimised treatment regimen were completed. Dr Herrmann and his team then analysed the data, and the collection of samples is ongoing.

The Impact:

Pancreatic cancer is one of the most lethal cancer types. Dr Herrmann found that inhibition of NPY signalling reduces both pancreatic tumour growth and spread (liver metastasis), which both contribute to the dismal outcomes of pancreatic cancer patients. Future assessment in patient-derived models from the APGI cohort of pancreatic cancer patients, which have been stratified for their expression of NPY ligands and receptors (high versus low) will allow the

team to elucidate the therapeutic potential of NPY inhibition in personalised pancreatic cancer treatment approaches.

Further funding was obtained from Sydney Catalyst to assess the role of the NPY signalling axis in pancreatic cancer. Furthermore, the team has applied for larger-scale funding from NHMRC/Cancer Australia/Cancer Council NSW to determine the effect of NPY inhibition on pancreatic cancer growth, spread and progression in a stratified pancreatic cancer patient cohort (outcomes pending).

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

(a) Dr Herrmann was awarded the following additional research funding:

a. Dr Herrmann received a Pilot and Seed Funding Award from Sydney Catalyst from June 2019 to June 2020 for the amount of $46,875. The project is titled *"Intravital imaging to overcoming pancreatic cancer resistance to immunotherapy."*

(b) Dr Herrmann published the following journal articles:

a. Conway JR, **Herrmann D**, Evans TJ, Morton JP and Timpson P. Combating pancreatic cancer with PI3K pathway inhibitors in the era of personalised medicine. Gut. 2019 Apr;68(4):742-758. doi: 10.1136/gutjnl-2018-316822.
b. Vennin C, Mélénec P, Rouet R, Nobis M, Cazet AS, Murphy KJ, **Herrmann D**, Reed DA, Lucas MC, Warren SC, Elgundi Z, Pinese M, Kalna G, Roden D, Samuel M, Zaratzian A, Grey ST, Da Silva A, Leung W, Australian Pancreatic Genome Initiative (APGI), Mathivanan S, Wang Y, Braithwaite AW, Christ D, Benda A, Parkin A, Phillips PA, Whitelock JM, Gill AJ, Sansom OJ, Croucher DR, Parker BL, Pajic M, Morton JP, Cox TR and Timpson P. CAF hierarchy driven by pancreatic cancer cell p53-status creates a pro-metastatic and chemoresistant environment via perlecan. Nature Communications. 2019 Aug 12;10(1):3637. doi: 10.1038/s41467-019-10968-6.
c. Pereira BA, Vennin C, Papanicolaou M, Chambers CR, **Herrmann D**, Morton JP, Cox TR and Timpson P. CAF subpopulations: a new reservoir of stromal targets in cancer. Trends in Cancer. 2019 Nov;5(11):724741. doi: 10.1016/j.trecan.2019.09.010. Epub 2019 Oct 21.
d. Follain G*, **Herrmann D***, Harlepp S*, Hyenne V*, Osmani N*, Warren SC*, Timpson P and Goetz JG. Fluids and their mechanics in transit: shaping metastasis. Nature Reviews Cancer. 2019 Nov 28. doi: 10.1038/s41568-019-0221-x. [Epub ahead of print] *Co-

first authors.

(c) Dr Herrmann won the following awards:

a. 2019 Best Poster Award at the Sydney Catalyst Postgraduate Early Career Researcher Symposium
b. Sydney Catalyst Pilot and Seed Funding Award by Sydney Catalyst
c. F1000prime Poster Prize 2019 by Hunter Cell Biology

Feedback provided by Dr David Herrmann

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