



2019 Final Report

Name of Institution: The University of Sydney, Faculty of Medicine and Health

Project Title: Therapeutic Targeting of the Potent Metastasis Suppressor, NDRG1, in Pancreatic Cancer

Principal Investigator: Dr Zaklina Kovacevic

Grant: Round 3 Innovation Grant 2017

Background:

Dr Kovacevic's research findings identified, for the first time, a potential strategy to inhibit both arms of cross-talk between pancreatic cancer cells and the surrounding stroma. Targeting NDRG1 inhibits the ability of pancreatic cancer cells to activate the stroma, while also de-sensitising pancreatic cancer cells to the oncogenic cytokines and growth factors being secreted by the stroma. This approach potentially overcomes the desmoplasia that is associated with pancreatic cancer and which forms a major barrier to current therapeutics, thus sensitising pancreatic cancer cells to current treatments.

Dr Kovacevic and her team will continue to develop this project to understand how their findings can be used to develop more effective treatments for pancreatic cancer, including assessing potential combination treatments to enhance response to current therapies.

The Research:

1. Characterise the effect of NDRG1 on HGF/c-MET and IGF-1/IGF-1R β signalling in PC cells co-cultured with pancreatic stellate cells. Dr Kovacevic extensively characterised how NDRG1 affects these signalling pathways using both 2D and 3D culture conditions and coculture with pancreatic stellate cells. This work is currently being prepared for publication.
2. Assess the efficacy of a novel anti-cancer agent to inhibit PC progression and overcome stromal cross-talk in vitro and in vivo. Dr Kovacevic found that that this agent can indeed inhibit the cross-talk between pancreatic cancer cells and the stroma in vitro using both 2D and 3D co-culture models as well as in vivo. This work is being prepared for publication



3. Preparation of research manuscript. Dr Kovacevic will prepare two research manuscripts as a result of these studies, with the first expected to be submitted in December 2019 and the second in early 2020.

The Impact:

Dr Kovacevic's research findings identified, for the first time, a potential strategy that can inhibit both arms of cross-talk between pancreatic cancer cells and surrounding stroma. Targeting NDRG1 inhibits the ability of pancreatic cancer cells to activate the stroma, while also de-sensitising pancreatic cancer cells to the oncogenic cytokines and growth factors being secreted by the stroma. This approach potentially overcomes the desmoplasia (the growth of connective tissue) that is associated with pancreatic cancer and which forms a major barrier to current therapeutics, thus sensitising pancreatic cancer cells to current treatments.

Dr Kovacevic and her team will continue to develop this project to understand how these findings can be used to develop more effective treatments for pancreatic cancer, including assessing potential combination treatments to enhance response to current therapies.

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

- (a) Dr Kovacevic was awarded additional research funding for this or related studies:
 - Dr Kovacevic has received an NHMRC Project Grant from 2019 to 2020 for the amount of \$200,000. The project title is Inhibiting the Oncogenic CrossTalk between Cancer Cells and Surrounding Stroma by Targeting the Metastasis Suppressor NDRG1 in Pancreatic Cancer.
 - Dr Kovacevic has also received a University of Sydney Equity Fellowship for the amount of \$60,000 starting in 2019, for the same above project.
- (b) Dr Kovacevic has won the following awards:
 - Dr Kovacevic was awarded the Sydney Medical School Carer Travel Assistance Award to enable attendance at the AACR Pancreatic Cancer Conference for the amount of \$2,500. The awarding body was the University of Sydney.
- (c) Dr Kovacevic gave the following presentations to present her findings:
 - An oral presentation titled A Promising New Therapy for Pancreatic Cancer for The Avner Pancreatic Cancer Foundation.
 - Two oral presentations titled Molecular Pharmacology and Cellular Targets for Cancer Treatment, both for the University of Sydney.



- A poster presentation titled Targeting the Metastasis Suppressor NDRG1 to Re-tune Oncogenic Cell Signalling Pathways in Pancreatic Cancer for the AACR Pancreatic Cancer conference.
- A poster presentation titled Targeting the Metastasis Suppressor NDRG1 to Re-tune Oncogenic Cell Signalling Pathways in Pancreatic Cancer for the Sydney Cancer Conference.
- An oral presentation titled The metastasis suppressor NDRG1: A promising therapeutic target for the Bioscience Reports Editorial Symposium.

Feedback provided by Dr Kovacevic

I think the Avner Pancreatic Cancer Foundation is doing fantastic work in terms of raising the profile of pancreatic cancer research in Australia. Further, by funding innovation grants into pancreatic cancer research, the Foundation is enabling the development of novel research directions and enabling them to be competitive for larger government grants that can ultimately deliver significant new benefits for patients.