Name of Institution: Curtin University of Technology

Project Title: A novel therapeutic target in pancreatic cancer: implications for therapy and diagnosis

Principal Investigator: Professor Marco Falasca

Grant: Round 2 Accelerator Grant 2016

Background:

This research, led by Professor Marco Falasca from the Curtin Health Innovation Research Institute, aimed to find novel treatments for Pancreatic Ductal AdenoCarcinoma (PDAC) by analysing specific mechanisms involved in cancer progression. Targeting these mechanisms could have the potential to increase the efficacy of treatments.

Lipids are essential in pancreatic cancer metabolism. This team found that one of these molecules, lysophosphatidylinositol (LPI), binds to a specific receptor, GPR55, and contributes to pancreatic cancer progression. LPI is produced by the cancer cells and transported outside by specific transport proteins called ABC transporters, in particular ABCC3. Once outside the cells, LPI can bind GPR55 in the neighbouring cells as well as in the same cells where it has been produced, activating signalling cascades that promote cancer growth. This creates a strong connection between ABCC3, transporting LPI and GPR55, binding LPI to activate cancer proliferation.

Therefore, Professor Falasca aimed to validate the ABCC3-GPR55 axis as a potential target for PDAC therapies and analyse the effect of different inhibitors of ABCC3 and GPR55 on PDAC cell proliferation and progression, both in a laboratory setting and in animal models of PDAC. The overall objective of this research project was to develop more effective and less toxic treatments for pancreatic cancer. The plan was to test in pre-clinical mouse models the most promising drug combination identified in a laboratory setting.

This study had the potential to validate innovative drugs in combination with traditional drugs as successful treatments for PDAC, with the ultimate aim being to provide strong pre-clinical data for its progression to clinical trials with pancreatic cancer patients.

The Research:

During this grant, Professor Falasca and his team achieved the following research objectives:

1. **Investigation of the effect of novel cannabidiol (CBD) combination in vitro**: Identification of a synergistic combination CBD and Gemcitabine.
2. **Investigation of the effect of novel CBD combinations in KPC mice:** The combination CBD and Gemcitabine have been successfully tested in KPC mice.
3. **Investigation of the effect of novel CBD combinations in PDX model**: The combination CBD and Gemcitabine has been successfully confirmed in PDX model
4. **Investigation of the mechanism of action of the GEM+CBD combination:** The mechanism of action has been identified, and the result publishes (Ferro et al Oncogene 2018).
5. **Investigation of LPI production in pancreatic cancer cell lines:** The production of LPI in pancreatic cancer cell lines has been tested (Adamska et al. ABR 2019).
6. **Investigation of LPI production in plasma and urine samples from a transgenic mouse model of PDAC:** One complication in this analysis is the presence of lipids in exosomes. This elicited a novel field of investigation on the role of exosomes in pancreatic cancer (Emmanouilidi et al. Proteomics 2019).
7. **Investigation of LPI production in plasma and urine samples from normal and pancreatic cancer patients:** LPI and exosomes analysis in patients material is ongoing.

The Impact:
In this research, the team identified a synergistic combination of gemcitabine and cannabidiol on pancreatic cancer models in vitro and in vivo. In addition, they have a stronger effect on tumorspheres compared to the corresponding parental tumour cells.

The implications of these key discoveries are that a combination of cannabidiol and gemcitabine can be used in clinical trials and the major effect of extracts on pancreatic cancer tumorspheres suggests that they could be more efficacious in resistant tumours.

The major objective of Professor Falasca's work is to bring these discoveries to the clinical trial stages. The team is very close to reaching this outcome and are discussing with clinicians and a pharmaceutical company the details of the trials. In addition, this research stimulated many other research avenues such as the investigation of exosomes role in pancreatic cancer and the identification of novel targets such as ABCC3.

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

Foundation:

(a) Professor Falasca has published the following journal articles:

1. Elaskalani O, Domenichini A, Razak NB, Dye DE, **Falasca M**, Metharom P. Antiplatelet Drug Ticagrelor Enhances Chemotherapeutic Efficacy by Targeting the Novel P2Y12-AKT Pathway in Pancreatic Cancer Cells. Cancers 2020.
2. Paternoster S, **Falasca M.** The intricate relationship between diabetes, obesity and pancreatic cancer. Biochim Biophys Acta Rev Cancer. 2019 Nov 9;1873(1):188326. doi: 10.1016/j.bbcan.2019.188326. [Epub ahead of print]
3. Casari I, Domenichini A, Sestito S, Capone E, Sala G, Rapposelli S, **Falasca M.** Dual PDK1/Aurora Kinase A Inhibitors Reduce Pancreatic Cancer Cell Proliferation and Colony Formation. Cancers (Basel). 2019 Oct 31;11(11). pii: E1695. doi: 10.3390/cancers11111695.
4. Begicevic RR, Arfuso F, **Falasca M.** Bioactive lipids in cancer stem cells. World J Stem Cells. 2019 Sep 26;11(9):693-704. doi: 10.4252/wjsc.v11.i9.693. Review.
5. Paternoster S, **Falasca M.** Targeting the adipose tissue to fight prostate cancer. Transl Androl Urol. 2019 Jul;8(Suppl 3):S229-S231. doi: 10.21037/tau.2019.01.13. No abstract available.
6. Adamska A, Domenichini A, Capone E, Damiani V, Akkaya BG, Linton KJ, Di Sebastiano P, Chen X, Keeton AB, Ramirez-Alcantara V, Maxuitenko Y, Piazza GA, De Laurenzi V, Sala G, **Falasca M.** Pharmacological inhibition of ABCC3 slows tumour progression in animal models of pancreatic cancer. J Exp Clin Cancer Res. 2019 Aug 5;38(1):312. doi: 10.1186/s13046-019-1308-7.
7. Emmanouilidi A, Fyffe CA, Ferro R, Edling CE, Capone E, Sestito S, Rapposelli S, Lattanzio R, Iacobelli S, Sala G, Maffucci T, **Falasca M.** Preclinical validation of 3-phosphoinositide-dependent protein kinase 1 inhibition in pancreatic cancer. J Exp Clin Cancer Res. 2019 May 14;38(1):191. doi: 10.1186/s13046-019-1191-2.
8. Adamska A, Ferro R, Lattanzio R, Capone E, Domenichini A, Damiani V, Chiorino G, Akkaya BG, Linton KJ, De Laurenzi V, Sala G, **Falasca M.** ABCC3 is a novel target for the treatment of pancreatic cancer. Adv Biol Regul. 2019 Aug;73:100634. doi: 10.1016/j.jbior.2019.04.004. Epub 2019 Apr 24.
9. Emmanouilidi A, Paladin D, Greening DW, **Falasca M.** Oncogenic and Non-Malignant Pancreatic Exosome Cargo Reveal Distinct Expression of Oncogenic and Prognostic Factors Involved in Tumor Invasion and Metastasis. Proteomics. 2019 Apr;19(8):e1800158. doi: 10.1002/pmic.201800158. Epub 2019 Apr 9.
10. Domenichini A, Edmands JS, Adamska A, Begicevic RR, Paternoster S, **Falasca M.** Pancreatic cancer tumorspheres are cancer stem-like cells with increased chemoresistance and reduced metabolic potential. Adv

Biol Regul. 2019 May;72:63-77. doi: 10.1016/j.jbior.2019.02.001. Epub 2019 Feb 23.
11. Simpson PV, Desai NM, Casari I, Massi M, **Falasca M.** Metal-based antitumor compounds: beyond cisplatin. Future Med Chem. 2019 Jan;11(2):119-135. doi: 10.4155/fmc-2018-0248. Epub 2019 Jan 15. Review.
12. Adamska A, **Falasca M.** Epithelial plasticity is crucial for pancreatic cancer metastatic organotropism. Ann Transl Med. 2018 Nov;6(Suppl 1):S53. doi: 10.21037/atm.2018.10.16. No abstract available.
13. Domenichini A, Adamska A, **Falasca M.** ABC transporters as cancer drivers: Potential functions in cancer development. Biochim Biophys Acta Gen Subj. 2019 Jan;1863(1):52-60. doi: 10.1016/j.bbagen.2018.09.019.
14. Adamska A, **Falasca M.** ATP-binding cassette transporters in progression and clinical outcome of pancreatic cancer: What is the way forward? World J Gastroenterol. 2018 Aug 7;24(29):3222-3238. doi: 10.3748/wjg.v24.i29.3222. Review.
15. Ferro R, Adamska A, Lattanzio R, Mavrommati I, Edling CE, Arifin SA, Fyffe CA, Sala G, Sacchetto L, Chiorino G, De Laurenzi V, Piantelli M, Sansom OJ, Maffucci T, **Falasca M.** GPR55 signalling promotes proliferation of pancreatic cancer cells and tumour growth in mice, and its inhibition increases effects of gemcitabine. Oncogene. 2018 Dec;37(49):6368-6382. doi: 10.1038/s41388-018-0390-1. Epub 2018 Jul 30.
16. Adamska A, Elaskalani O, Emmanouilidi A, Kim M, Abdol Razak NB, Metharom P, **Falasca M.** Molecular and cellular mechanisms of chemoresistance in pancreatic cancer. Adv Biol Regul. 2018 May;68:77-87. doi: 10.1016/j.jbior.2017.11.007. Epub 2017 Nov 22. Review.
17. Begicevic RR, **Falasca M.** ABC Transporters in Cancer Stem Cells: Beyond Chemoresistance. Int J Mol Sci. 2017 Nov 8;18(11). pii: E2362. doi: 10.3390/ijms18112362. Review.
18. Emmanouilidi A, **Falasca M.** Targeting PDK1 for Chemosensitization of Cancer Cells. Cancers (Basel). 2017 Oct 24;9(10). pii: E140. doi: 10.3390/cancers9100140. Review.
19. Elaskalani O, **Falasca M**, Moran N, Berndt MC, Metharom P. The Role of Platelet-Derived ADP and ATP in Promoting Pancreatic Cancer Cell Survival and Gemcitabine Resistance.Cancers (Basel). 2017 Oct 24;9(10). pii: E142. doi: 10.3390/cancers9100142.
20. Emmanouilidi A, Lattanzio R, Sala G, Piantelli M, **Falasca M**. The role of phospholipase Cγ1 in breast cancer and its clinical significance. Future Oncol. 2017 Aug 22. doi: 10.2217/fon-2017-0125. [Epub ahead of print]
21. Elaskalani O, Berndt MC, **Falasca M**, Metharom P. Targeting Platelets for the Treatment of Cancer. Cancers (Basel). 2017 Jul 22;9(7). pii: E94. doi: 10.3390/cancers9070094. Review.

22. Adamska A, Domenichini A, **Falasca M**. Pancreatic Ductal Adenocarcinoma: Current and Evolving Therapies. Int J Mol Sci. 2017 Jun 22;18(7). pii: E1338. doi: 10.3390/ijms18071338. Review.
23. Marat AL, Wallroth A, Lo WT, Müller R, Norata GD, **Falasca M**, Schultz C, Haucke V. mTORC1 activity repression by late endosomal phosphatidylinositol 3,4-bisphosphate.Science. 2017 Jun 2;356(6341):968-972. doi: 10.1126/science.aaf8310.
24. Simpson PV, Casari I, Paternoster S, Skelton BW, **Falasca M**, Massi M. Defining the Anti-Cancer Activity of Tricarbonyl Rhenium Complexes: Induction of G2/M Cell Cycle Arrest and Blockade of Aurora-A Kinase Phosphorylation. Chemistry. 2017 May 11;23(27):6518-6521. doi: 10.1002/chem.201701208. Epub 2017 Apr 12.
25. Elaskalani O, Razak NB, **Falasca M**, Metharom P. Epithelial-mesenchymal transition as a therapeutic target for overcoming chemoresistance in pancreatic cancer. World J Gastrointest Oncol. 2017 Jan 15;9(1):37-41. doi: 10.4251/wjgo.v9.i1.37. Review.

26. Professor Falasca won the following awards:

a. Australasian Pancreatic Club 2016 Lord Williams Award
b. National University of Singapore Best Oral Scientific Presentation Award

27. Professor Falasca has presented findings in major conferences worldwide throughout this grant.