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RACP Foundation Research Awards

PROGRESS REPORT

Project / Program Title		Cell Survival Pathways as Potential Targets in Breast Cancer
Name		Dr James Whittle
Award Received		2015 RACP NHMRC JJ Billings Scholarship
Report Date		29 March 2017
Chief Investigator / Supervisor		Supervisor: Professor Geoff Lindeman
Administering Institution		Walter and Eliza Hall Institute of Medical Research
Funding Period	Start Date:	1 March 2015
	Finish Date:	1 March 2018

PROJECT SUMMARY

Breast cancer is the most common cancer affecting Australian women and accounts for more than one quarter of all new cancers. Developing new strategies to treat breast cancer is complicated by the heterogeneity between cancers, which cannot be distinguished by current histopathological techniques that are used to make treatment decisions. Therefore, despite the unprecedented level of knowledge obtained from whole genome sequencing, we still face challenges in the clinic with respect to treatment resistance.

This research project is focussed on two subsets of breast cancer. Firstly, basal like (triple negative) breast cancer, which remains an aggressive form with no available targeted therapies. I have performed single gene and genome wide screens using CRISPR/Cas9 lentiviral delivery technology in models of basal like breast cancer to identify novel tumour suppressor genes. Novel targets have been identified and currently in the process of being validated.

Secondly, I am evaluating HER2 amplified breast cancer, harnessing recent insights into cancer cell resistance to cell death that represents a promising new area of breast cancer research. The observation that BCL-2 family members are overexpressed in the majority of HER2 positive breast cancer samples raises the prospect that breast cancer cells might be sensitive to an emerging class of BH3 mimetics targeting BCL-2 family proteins. Current work is focussed on the rational combination of BH3 mimetics with chemotherapy or targeted therapy for swift translation into clinical benefit.

PROJECT AIMS / OBJECTIVES

This work is divided into two separate projects

Project A - Using CRISPR/Cas9 lentiviral technology to identify novel tumour suppressor genes in basal like breast cancer. The specific objectives are:

1. Proof of principle in-vitro studies

- Use CRISPR/Cas9 to knockdown p53 in MCF-7 breast cancer cell lines
- Use CRISPR/Cas9 to -knockdown p53 in the basal (MaSC enriched) cells from MMTV-Wnt1 tumour model

2. In vivo mouse studies

- Determine if deletion of a single tumour suppressor (p53) will reduce latency of breast cancer onset in MMTV-Wnt1 and MMTV-Brca'1t-p53+I- mouse models

3. Genome wide-screen to identify novel regulators of tumour suppressor processes

- Use CRISPR/Cas9 lentiviral library to transduce basal (MaSC enriched) cells from BalbC p53+1-, MMTV-Wnt1 and other mouse models.

4. Validation of novel genes

- Novel genes ·will be validated in an in-vitro mouse organoid system and in-vivo.

Project B - Investigating the potential interaction between BCL-2 family member expression and tumour response in different breast cancer subtypes. The specific objectives are:

1. To test the efficacy of combining HER2 inhibitors with BCL-2 family inhibitors

2. Derive trastuzumab and T-DM1 resistant tumours and evaluate their response to BCL-2 inhibitors

3. Perform in vitro CRISPR/Cas9 screen in HER2 positive cancer cell lines to identify novel regulators of HER2 inhibitor resistance

4. Evaluate novel BH3 mimetics (drug XXXX) targeting other BCL- 2 family proteins in triple negative and HER2 positive breast cancer

5. Design rational clinical trials to evaluate the combination of BCL-2 family inhibitors with standard anti-cancer therapies in different breast cancer subtypes

SIGNIFICANCE AND OUTCOMES

This work has directly led to one manuscript in submission with the plan for a further two manuscripts evaluating BH3 mimetics in breast cancer. It in addition, this pre-clinical work has directly led to proposals for investigator initiated studies and we anticipate will provide the foundation for establishing these agents in solid organ cancers.

PUBLICATIONS / PRESENTATIONS