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RACP Foundation Research Awards

FINAL REPORT

Project / Program Title		Inducing apoptosis to improve the efficacy of CDK4/6 inhibitors in breast cancer
Name		Dr Shom Goel
Award Received		2020 Fellows Research Establishment Fellowship
Report Date		11/02/2021
Funding Period	Start Date:	06/01/2020
	Finish Date:	04/01/2021

PROJECT SUMMARY

Recently, a new class of medicines known as the CDK4/6 inhibitors has been developed as a treatment for breast cancer, and the use of these agents has markedly improved outcomes for many patients. These drugs were designed to stop breast cancer cells from dividing and although they do this very well, we recently discovered that they also render these cells harder to kill. In this project, we have uncovered a key reason for this observation. CDK4/6 inhibitors cause breast cancer cells to make high levels of a protein (called Bcl-xL) that protects them from dying. We have uncovered the reasons behind this, and also show that this can be overcome by using drugs that inhibit the effect of Bcl-xL.

PROJECT AIMS / OBJECTIVES

Aim 1: To determine whether CDK4/6 inhibitors increase Bcl-xL levels in breast cancer cells by activating an enhancer spanning the BCL2L1 locus.

This has been achieved through western blotting, RNA-seq and H3K27Ac ChIP-seq for a variety of cell lines after CDK4/6i treatment.

Aim 2: To determine whether Bcl-xL is functionally implicated in mediating apoptosis resistance after CDK4/6 inhibitor treatment.

This has been completed with the use of dynamic BH3 profiling experiment and in vitro studies as proposed.

Aim 3: To determine whether Bcl-xL inhibitors improve the efficacy of CDK4/6 inhibition in mouse models of luminal breast cancer.

This has been completed as proposed. The primary output was apoptosis as measured by a panel of IHC markers.

Aim 4: To determine whether CDK4/6 inhibitors increase tumour cell Bcl-xL levels in breast cancer patients.

This is ongoing, in collaboration with colleagues at the Dana-Farber Cancer Institute,

SIGNIFICANCE AND OUTCOMES

Collectively, our results clearly show that:

1. CDK4/6 inhibitors increase Bcl-xL levels in breast cancers

2. This is driven by RB-dependent chromatin remodelling which activates a superenhancer over Bcl-xL

3. This results in priming of tumour cells away from apoptosis, which can be reversed with a Bcl-xL inhibitors

4. CDK4/6 pretreated cancers are more susceptible to Bcl-xL inhibition.

The results of this project have shed new insight into mechanisms of apoptosis resistance after CDK4/6 inhibition and as a part of therapy-induced senescence more broadly.

PUBLICATIONS / PRESENTATIONS

The work has been published in Nature Cancer (Watt et al, 2021).

ACKNOWLEDGEMENTS

The RACP is acknowledged in the Nature Cancer paper mentioned above.