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RACP Foundation Research Awards

FINAL REPORT

Project / Program Title		Application of a novel 'degron'-based approach of protein degradation to study mechanisms of oncogene addiction in myeloid malignancy
Name		Dr Andrew Guirguis
Award Received		2017 Astra-Zeneca Research Establishment Fellowship
Report Date		26 July 2018
Chief Investigator / Supervisor		Professor Benjamin Ebert
Administering Institution		Harvard Medical School
Funding Period	Start Date:	1 May 2017
	Finish Date:	1 May 2018

PROJECT SUMMARY

Acute myeloid leukaemia is a rapidly progressive blood cancer that occurs with increasing frequency with age. Genetic analysis of patient samples has revealed leukaemia results from the acquisition of a series of genetic mutations. While we understand which mutations contribute to leukaemia development, it is less clear what role each of these mutations plays once the leukaemia has fully developed. One issue at present, is that we don't have drugs that specifically target each of these individual mutations.

In this project, we have generated a system that allows us to determine what role a mutation of interest plays in sustaining the leukaemia once it is formed. We are generating various models of leukaemia to determine how early or late-acquired mutations contribute to the ongoing survival of the leukaemic cell.

This work will enable us to determine which mutation should be targeted in various patients to achieve long-term disease control.

PROJECT AIMS / OBJECTIVES

1. To develop a system that allows us to degrade proteins of interest using a 'degron' sequence - achieved by appropriate cloning.

2. To validate this system in an in-vitro setting - achieved by performing western blot analyses in the presence of compound; functional assays also performed

3. To generate in-vivo models of myeloid leukemia in which sequentially acquired mutations can be individually targeted - will be achieved through mouse transplantation of various mutations of interest

SIGNIFICANCE AND OUTCOMES

The proposed work will highlight two key points of significance:

1. Using this 'degradation' approach - we will be able to determine the contribution of various 'undruggable' proteins in the ongoing maintenance of acute myeloid leukemia. This has not been previously possible for this set of mutations. This work will answer the key question of whether targeting an early-acquired mutation is associated with better disease control long-term.

2. We envisage the 'degron' system developed can ultimately be applied in various other disease contexts - particularly in situations where no therapy currently exists for a specific target. This system is highly adaptable, rapidly- acting and reversible and allows greater control over degradation kinetics - with changes in protein expression occurring within hours of drug treatment.

Once we have validated key proteins responsible for AML maintenance, longer-term goals will involve determining how these mutations can be therapeutically targeted.

PUBLICATIONS / PRESENTATIONS

Blood. 2018 Jul 31. pii: blood-2018-05-852798. doi: 10.1182Jblood-2018-05-852798. [Epub ahead of print]

Crbn1391 v is sufficient to confer in vivo sensitivity to thalidomide and its derivatives in mice