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RACP Foundation Research Awards

YEAR 1 PROGRESS REPORT

Project Title		Combinatorial Therapeutics in High-Risk Infant Acute Lymphoblastic Leukaemia
Name		Dr Rishi S Kotecha
Award Received		2018 The Kids' Cancer Project Research Establishment Fellowship
Report Date		5 February 2019
Chief Investigator / Supervisor		Chief Investigator: Dr Rishi S Kotecha Supervisor: Terrance Johns
Administering Institution		Telethon Kids Institute
Funding Period	Start Date:	1 January 2018
	Finish Date:	31 December 2020

PROJECT SUMMARY

Leukaemia is the most common form of cancer in children. The most common form of leukaemia in children is acute lymphoblastic leukaemia or ALL. Remarkable improvements have been made to therapy over the past sixty years and modern treatment protocols for children achieve cure rates in more than 90% of patients. In contrast, survival for infants less than one year of age at the time of diagnosis is less than 50%. Better therapies are desperately needed. From laboratory testing we have discovered effective novel cancer drugs, which are not currently used for treatment of babies with leukaemia. We will evaluate novel drug combinations and test them in model systems, such that they can be fast-tracked to the clinic.

PROJECT AIMS / OBJECTIVES

Aim 1 Systematic identification of synergistic novel drug combinations

The in vitro synergistic effect of novel drugs identified from our pilot data, will be tested with each of the nine standard chemotherapeutic drugs currently used to treat infant ALL. The most effective combinations will be selected for Aim 2.

Aim 2 Efficacy of novel drug combinations in vivo using infant ALL xenograft models

The novel drugs will be tested in patient derived xenograft models as single agents and in combination with currently used drugs.

SIGNIFICANCE AND OUTCOMES

Infant ALL has an extremely poor outcome and novel therapeutic strategies are desperately needed. We provide key findings to highlight the potential for the histone deacetylase inhibitor, romidepsin, to be integrated into clinical trials for infants with ALL. We provide strong in vivo evidence that romidepsin can be combined to augment the effect of the conventional chemotherapeutic agent, cytarabine, in infants with ALL. We show a reduction in leukemic burden and significantly enhanced event-free survival using combination therapy in three independent infant ALL xenograft models harbouring distinct KMT2A translocation partners. Importantly, this combination did not cause myelosuppression, which is a toxic side effect of high-dose chemotherapy to which infants are particularly vulnerable and contributes to the increased mortality as shown in collaborative international trials. Further in vitro studies demonstrate that romidepsin enhanced the DNA-damage response of cytarabine. Romidepsin was also shown to synergize with several other conventional chemotherapeutic agents in vitro, providing evidence as to where it could be scheduled within the standard chemotherapy backbone that is currently used to treat infants with ALL.

PUBLICATIONS / PRESENTATIONS

1. Cheung LC, Cruickshank MN, Hughes AM, Singh S, Chua GA, Ford J, Ferrari E, Oommen J, Malinge S, Lock RB, Kees UR, Kotecha RS. Romidepsin enhances the efficacy of cytarabine in vivo, revealing histone deacetylase inhibition as a promising therapeutic strategy for KMT2Arearranged infant acute lymphoblastic leukemia. Haematologica 2019.