THESIS DEFENSE – PUBLIC SEMINAR

MANIPULATING CELL STATES FOR LEUKAEMIA DIFFERENTIATION THERAPY USING NETWORK PHARMACOLOGY

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IBM PHD PROGRAM (INTAKE 2016)

ABSTRACT:

Acute myeloid leukaemia (AML) is a rapidly fatal blood cancer which is characterized by the accumulation of immature myeloid cells in the blood and bone marrow as a result of blocked differentiation. Methods which identify master transcriptional regulators of AML subtype-specific leukaemia cell states and their combinations could be critical for differentiation-inducing therapy. In this proof-of-concept study, we demonstrate a novel utility of the MOGRIFY® algorithm in identifying combinations of transcription factors (TFs) and drugs which recapitulate granulocytic differentiation of the NB4 acute promyelocytic leukaemia (APL) cell line. Connectivity Map (CMAP) analysis of these TFs and their target networks identified dimaprit and mebendazole as a drug combination which induces myeloid differentiation. Alternatively, we show that genetic and pharmacologic manipulation of MOGRIFY-identified TFs, specifically MYC and IRF1, also leads to co-operative induction of APL differentiation. We also outline potential mechanisms by which MYC down-regulates IRF1 expression in NB4 cells whereby MYC recruits PML-RARa, the major fusion oncoprotein in APL cells, and represses the IRF1 promoter. Finally, we demonstrate that these drug combinations can also induce differentiation of primary patient-derived APL cells. Thus, we anticipate that MOGRIFY could be used to discover TF-based differentiation therapies for other subtypes of leukaemia or cancers.

Date :
04 Oct 2021 (Monday)

Time :
9.00 - 10.00 am

Thesis Advisor :
Asst. Prof. Jean-Paul Kovalik and A/Prof. Ong Sin Tiong

Venue :
Amphitheatre, Level 2, Duke-NUS

This Seminar is part of the fulfillment of his PhD requirements

GRADUATE STUDIES DEPARTMENT