Institute of Molecular and Cell Biology
A*STAR

SEMINAR ANNOUNCEMENT

We would like to invite you to attend this seminar hosted by Prof Vinay Tergaonkar:

Date: 3 April 2019, Wednesday
Time: 11:00AM – 12:00PM
Venue: Level 3, IMCB Seminar Room 3-46, Proteos, Biopolis

Speaker: Prof Stuart Pitson, NHMRC Senior Research Fellow and Research Professor at the Centre for Cancer Biology, Adelaide, Australia
Title: Targeting sphingolipid metabolism in acute myeloid leukemia

Pro-survival Bcl-2 family proteins such as Mcl-1 and Bcl-2 have garnered significant interest as therapeutic targets due to their up-regulation in many cancers, including acute myeloid leukaemia (AML), leading to enhanced cancer cell survival. Small molecule inhibitors such as the selective Bcl-2 inhibitor, Venetoclax, are very effective in some cancers that are highly on Bcl-2, but have demonstrated poor single agent efficacy in AML due to these cells being highly dependent on Mcl-1, which is not targeted by this agent. Sphingosine kinase 1 (SK1) is a signalling enzyme with established roles in oncogenesis and has recently emerged as a potential therapeutic target in leukaemia. We recently demonstrated that SK1 inhibitors exhibit anti-leukemic activity in vitro and in vivo using patient-derived AML xenograft models. Mechanistically, SK1 inhibition induced increases in ceramide levels which activates the integrated stress response. This results in ATF4 mediated transcriptional upregulation of BH3-only protein, Noxa and formation of Noxa/Mcl-1 complexes, leading to Mcl-1 degradation and AML cell death. Combinational therapies with SK1 inhibitors and Venetoclax induced synergistic cell death in AML cell lines and AML patient samples, including isolated patient leukemic stem/progenitor cells. Furthermore, we demonstrated that SK1 inhibition and Venetoclax treatment exhibits anti-leukemic activity in vivo providing pre-clinical evidence to target SK1 and Bcl-2 in AML.

Biography:
Stuart Pitson is a NHMRC Senior Research Fellow and Research Professor at the Centre for Cancer Biology, Adelaide, Australia. His research interests are in examining cell signalling pathways controlled by sphingolipids, and how they contribute to cancer, fibrosis and wound healing. His laboratory has made a number of notably contributions to the field, including the cloning of the first human sphingosine kinase, and identification of key regulatory mechanisms regulating the sphingolipid metabolism that have (patho)physiological significance, as well as the development of novel inhibitors with potential clinical application. He is also Co-Founder and Chief Scientific Officer of Cincera Therapeutics, a spin-out company established in 2018 through investment by the Australian Medical Research Commercialisation Fund.

ALL ARE WELCOME *(No registration required)*

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