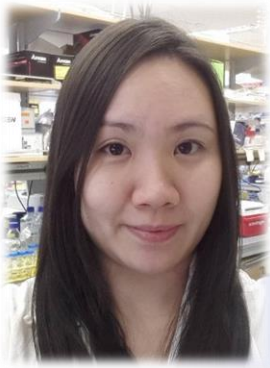
CANCER SCIENCE INSTITUTE OF SINGAPORE

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Kelly ONG Ooi Kee

PhD Candidate

(Supervisor: A/Prof Chng Wee Joo)

CSI Graduate Programme

PH.D ORAL DEFENSE

CeLS Seminar Room 1

Centre for Life Sciences (CeLS)
28 Medical Drive, Singapore 117456

No registration required. All are welcome.

Wed, 13 May 2015
3:00 – 4:00 PM

Role of Notch and JAK-STAT signaling pathways in acute megakaryoblastic leukemia

Children of Down syndrome (DS), the most common congenital disease, are at high risk of developing a specific subtype of acute myeloid leukemia, acute megakaryoblastic leukemia (AMKL). According to Malaysia-Singapore multicenter leukemia studies for childhood acute leukemia, the prevalence of AMKL in Singapore and Malaysia is strikingly high as compared to those in the worldwide populations, and its prognosis is unfavorable. Despite such widespread and local relevance, the mechanistic basis for AMKL remains elusive. To discover currently unknown genetic alterations associated with AMKL, an AMKL mouse model was developed employing retroviral insertional mutagenesis (RIM) on the genetically engineered mouse with alterations in *Gata-1* and *Runx1* genes, both of which are well documented to be critical for normal megakaryopoiesis and deregulated in AMKL. As RIM enables easy identification of affected genes potentially involved in leukemogenesis, we readily identified potential AMKL genes, which are classified into two signaling pathways, namely JAK-STAT and Notch pathways. We also employed targeted deep sequencing strategy in 51 AMKL patient samples and 7 AMKL cell lines and identified genetic mutations in Notch and JAK-STAT pathways besides known AMKL-related genetic changes such as GATA-1 point mutation and trisomy 21 causing an extra copy of RUNX1. *In vitro* cell based drug testing assays using Notch agonist and JAK inhibitor significantly suppressed AMKL cell proliferation by inducing apoptosis individually as a single agent and synergistically as a combination therapy. This potent inhibition holds a potential of therapeutic application of Notch agonist alone or in combination with JAK-STAT inhibitor for AMKL.