Institute of Molecular and Cell Biology
A*STAR

SEMINAR ANNOUNCEMENT

We would like to invite you to attend this seminar hosted by Dr. Ernesto Guccione:

Date: 5 August 2014, Tuesday
Time: 11:00AM – 12:00PM
Venue: Level 3, IMCB Seminar Room 3-46, Proteos, Biopolis

Speaker: Dr. Tan Ying Xim, Post-Doctorate, University of California, San Francisco, USA
Title: A chemical genetic approach to inhibit Csk reveals insights into the regulation of T cell receptor signaling

C-terminal Src kinase (Csk) is the primary negative regulator of the Src family kinase (SFK) Lck in T cells. Proper control of Lck activity is necessary for appropriate T cell receptor (TCR) activation. Phosphorylation of a conserved tyrosine in the C-terminal tail of Lck inhibits its kinase activity and is reciprocally regulated by the protein tyrosine kinase, C-terminal Src kinase (Csk), and the protein tyrosine phosphatase, CD45. To investigate how Csk activity regulates basal and ligand-induced TCR signaling in T cells, we have generated mice in which wild-type Csk has been replaced by an analog-sensitive mutant of Csk (Csk^{AS}) that can be specifically and rapidly inhibited by a small molecule. Inhibition of Csk^{AS} in thymocytes and CD4+ T cells, without engagement of the TCR, induced potent activation of Lck and proximal TCR signaling up to phospholipase C-γ1 (PLC-γ1). Unexpectedly, increases in inositol phosphates, intracellular calcium and phosphorylation of the kinase ERK were impaired. Altering the actin cytoskeleton pharmacologically or providing costimulation via CD28 in thymocytes 'rescued' those defects. On the other hand, inhibition of Csk^{AS} during TCR stimulation by both anti-CD3 antibodies and peptide-MHC tetramers led to stronger and prolonged TCR signaling that in turn induced increased cellular proliferation. Our data suggest that by controlling Lck activity, Csk plays an important role in preventing aberrant TCR signaling, setting the TCR signaling threshold and a partial role in TCR signal termination. However, our studies also revealed a requirement for actin remodeling, initiated by costimulation, for full TCR signaling. Manipulating Csk activity may enable control of T cell activation.

Biography:
Dr. Tan obtained her Ph.D. in Immunology from the University of California, San Francisco under the supervision of Dr. Arthur Weiss. Her Ph.D. thesis work on the negative regulation of T cell receptor signaling has led to several publications, including in the journal Nature Immunology. She obtained her bachelor's degree in Molecular and Cell Biology from the University of California, Berkeley, where she was the top graduate in the division of Immunology.

ALL ARE WELCOME *(No registration required)*