# SIgN Immunology Seminar

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## Themis sets the signalling threshold between positive and negative selection in T-cell development by regulating SHP1 activity

*Host*
Prof Laurent Renia
Singapore Immunology Network, A*Star

*Date*
**Wednesday 22 January 2014**

*Time*
11am – 12pm

*Venue*
SIgN Seminar Room
Immunos Building
Level 4
Biopolis

Themis was recently described as a T lineage-specific protein that is important for positive selection in the thymus. It is now known to be part of the LAT signalosome but its mode of action in regulating positive selection is obscure. Positive selection of thymocytes requires a lower affinity TCR interaction than negative or agonist selection, and results in development of the naïve T cell populations. We find that Themis acts as a negative regulator of TCR signaling in pre-selection thymocytes, but that its effect is only manifest in responses to relatively weak ligands, such as those that cause positive selection. Thus, in Themis-deficient thymocytes, there is a normal (strong) calcium flux in response to strong agonist ligands that induce negative selection, but also a strong response to an antagonist, positive selecting, ligand that normally induces a weak calcium flux. Similar results were found for Erk phosphorylation and for other TCR-proximal signaling molecules. This overly strong response of Themis-deficient thymocytes to positive-selecting ligands induces Bim expression and caspase 3 activation, markers characteristic of activation-induced cell death. Thus the defect in positive selection is due to a change in signal threshold that reduces the proportion of cells able to undergo positive selection in response to self pMHC, while negative and agonist selection occurs in response to what should be positive-selecting self pMHC. We have now found that Themis interacts with the protein tyrosine phosphatase SHP1 (PTPN6), and that in Themis-deficient cells, SHP1 is not phosphorylated and therefore not activated in response to TCR signals. Thus, Themis acts through SHP1 to reduce the strength of signaling in response to low-affinity ligands. Targeting Themis in mature T cells could be a means to induce stronger responses to weak ligands such as tumor antigens.