PhD DEFENCE – Monday, July 13th, 2015

Student: **Jithendra (Jay) Gunawardana**

Title: **IDENTIFICATION AND CHARACTERIZATION OF NOVEL RECURRENT MUTATIONS IN PRIMARY MEDIASTINAL LARGE B CELL LYMPHOMA AND HODGKIN LYMPHOMA**

Time and Location: 09:00 am, Room 200, Graduate Student Centre, UBC Campus

Supervisor: Dr. Christian Steidl

ABSTRACT

Classical Hodgkin lymphoma (HL) and primary mediastinal large B cell lymphoma (PMBCL) are related lymphomas sharing pathological, molecular and clinical characteristics. Here we discovered by next-generation sequencing recurrent somatic coding-sequence mutations in the protein tyrosine phosphatase *PTPN1* and the cytokine receptor *IL4R*. Mutations in *PTPN1* were found in 6 of 30 (20%) HL cases, in 6 of 9 (67%) HL–derived cell lines, in 17 of 77 (22%) PMBCL cases and in 1 of 3 (33%) PMBCLderived cell lines, consisting of nonsense, missense and frameshift mutations. We demonstrate that *PTPN1* mutations lead to reduced phosphatase activity and increased phosphorylation of JAK-STAT pathway members. Moreover, silencing of *PTPN1* by RNA interference in HL cell line KM-H2 resulted in hyperphosphorylation and overexpression of the downstream oncogenes *BCL6* and *MYC*.

Mutations in *IL4R* were found in 18 of 65 (28%) PMBCL cases confirming a 'hotspot' missense mutation I242N in exon 8 in 11 of 18 (61%) mutated cases. Ectopic expression of the mutant I242N in HEK 293 cells showed increased activated STAT6-dependent *SEAP* reporter gene expression without interleukin-4 stimulation. Introduction of the mutant into Hodgkin lymphoma cell line DEV showed cytokineindependent hyperphosphorylation of JAK-STAT pathway members and upregulation of the T cell regulatory chemokine TARC (CCL17) and the B cell activation marker CD23.

Our data suggest loss-of-function *PTPN1* and gain-of-function *IL4R* mutations leading to oncogenic JAK-STAT activation as new driver alterations in lymphomagenesis with implications for future treatment strategies.