



**BİLKENT UNIVERSITY  
MOLECULAR BIOLOGY AND GENETICS  
DEPARTMENTAL SEMINAR**

**"Functional genomics of NK and  $\gamma\delta$  T cell lymphomas: therapeutic and diagnostic implications"**

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Lymphomas arising from NK or  $\gamma\delta$  T cells are rare and clinically aggressive diseases with little insight into its pathogenesis. In three different next-generation sequencing (NGS) based projects, we have investigated genomic or epigenomic aberrations with therapeutic or diagnostic potential. In the first project, we have identified recurrent STAT5B and STAT3 mutations in natural killer cell lymphomas (NKCL) and in a variety of different lymphomas of gamma delta type using RNA-Seq, whole exome sequencing or Sanger sequencing. We also showed that these mutations are associated with constitutive JAK-STAT pathway activation through stronger STAT dimer formation and better regulation of its target genes. In the second project, we have investigated global promoter methylation levels in NKCLs, which revealed 95 epigenetically-silenced tumor suppressor gene candidates including BCL2L11 (BIM), DAPK1, PTPN6 (SHP1), TET2, SOCS6, and ASNS. Ectopic expression of BIM or SOCS6 showed tumor suppressor effect in NK cell lines. In addition, reconstitution of BIM expression sensitized cell lines to chemotherapy-induced apoptosis. In addition, NK-cell lines with no ASNS expression showed increased sensitivity to treatment with l-asparaginase. In the third project, we investigated the diagnostic and biological significance of killer-cell immunoglobulin-like receptor (KIR) gene expression through RNA-Seq. Interestingly, we have identified selective expression KIR2DL4 whereas all other KIR genes were silenced in NKTCLs. In contrast, normal NK-cells expressed most KIR genes. This finding suggests that exclusive expression of KIR2DL4 may be used as a clonal diagnostic marker for NKTCL as no good clonal biomarker has been defined to date although B and T cell lymphomas can be diagnosed by assessing B or T cell receptor rearrangements. Altogether these results show the potential of NGS based functional genomics approaches in identification of novel diagnostic biomarkers or therapeutic targets in NK and T-cell lymphomas.

**Date-Time : Wednesday, 17 , 2016 – at 15:40**

**Location : SBZ-14**

**Host : Çağlar Çekiç**