



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

**"Autophagy repression: A novel anti-leukemic function of histone deacetylase inhibitors in myeloid leukemias"**

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Histone deacetylase (HDAC) inhibitors (HDACis) are well-characterized anti-cancer agents with promising results in clinical trials. However, mechanistically little is known regarding their selectivity in killing malignant cells while sparing normal cells. Gene expression-based chemical genomics identified HDACis as being particularly potent against Down syndrome-associated myeloid leukemia (DS-AMKL) blasts. Investigating the antileukemic function of HDACis revealed their transcriptional and post-translational regulation of key autophagic proteins, including ATG7. This leads to suppression of autophagy, a lysosomal degradation process that can protect cells against damaged or unnecessary organelles and protein aggregates. DS-AMKL cells exhibit low baseline autophagy due to mammalian target of rapamycin (mTOR) activation. Consequently, HDAC inhibition repressed autophagy below a critical threshold, which resulted in accumulation of mitochondria, production of reactive oxygen species, DNA damage and apoptosis. Those HDACi-mediated effects could be reverted upon autophagy activation or aggravated upon further pharmacological or genetic inhibition. Our findings were further extended to other major acute myeloid leukemia subgroups with low basal level autophagy. The constitutive suppression of autophagy due to mTOR activation represents an inherent difference between cancer and normal cells. Thus, via autophagy suppression, HDACis deprive cells of an essential pro-survival mechanism, which translates into an attractive strategy to specifically target cancer cells.

**Date-Time : Wednesday, November 23, 2016 – at 15:40**  
**Place : SBZ-14**  
**Host : Serkan İsmail Göktona**