



“Role of ubiquitin system mutations in AML”

Date & Time: Wednesday, August 10 | 1:00PM - 2:00PM PT

Hybrid: Life Sciences Centre Room 1003 (LSC3) & Zoom

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Presented by: Dr. Aly Karsan and Hayle Kincross

Analysis of multiple AML sequencing datasets comprising 1,627 unique patient samples revealed frequent loss-of-function mutations in ubiquitin ligase family genes, and particularly in the Skp1/Cul1/Fbox (SCF) E3 ubiquitin ligase complex genes. In particular, we have found recurrent mutations or reduced expression of FBXO11. In synthetic mouse and human models, FBXO11 knockdown in hematopoietic stem/progenitor cells cooperates with AML1-ETO and activated KRAS to generate serially transplantable AML. FBXO11 mediates K63-linked polyubiquitination of the LONP1 mitochondrial protease, and Loss of FBXO11 impairs LONP1 function thereby reducing mitochondrial membrane potential, imparting stem cell properties and driving leukemogenesis. Our findings suggest that loss of FBXO11 function primes HSPC for self-renewal through attenuation of LONP1-mediated regulation of mitochondrial function.