CBR Virtual Summer Seminar Series

Wednesday, August 4 | 11:00am - 12:00pm PT

Dr. Ali Karsan, *Professor*
Centre for Blood Research
Department of Pathology and Laboratory Medicine
Michael Smith Genome Sciences Centre & BC Cancer Agency

Topic: "Elucidating the mechanisms of leukemogenesis driven by FBXO11 loss"
Presented by: Angela Mo, PhD Candidate

Acute myeloid leukemia (AML) is the most common adult leukemia, and AML patients have a 5-year survival rate of <30%. We found frequent somatic mutations in ubiquitin proteasome system (UPS) genes by exome and RNA-seq of 140 clinical AML samples, with recurrent inactivating mutations in *FBXO11*, which codes the substrate-recognizing component of the SKP1-CUL1-F-BOX (SCF) ubiquitin E3-ligase complex. In our mouse marrow transplant model, *Fbxo11* knockdown cooperates with *AML1-ETO* expression to initiate AML. These AMLs were serially transplantable, indicating the presence of leukemic stem cells (LSC). We found that *FBXO11* loss in human cells promoted stem cell maintenance and myeloid differentiation in vivo, and also in xenotransplanted mice. Mass spectrometric analysis of FBXO11 co-immunoprecipitating proteins in K562 *FBXO11* CRISPR/Cas9 knockout and control clones and identified mitochondrial protease LONP1 as a top interacting protein. We found that *FBXO11* loss enriches primitive HSPC populations in our human model, identified novel candidate targets of FBXO11, and identified a novel link between the UPS and mitochondrial function. We are investigating mechanisms and effects of LONP1 regulation by FBXO11.