Understanding and Targeting Spliceosomal-Mutation Hematopoietic Malignancies

Principal Investigator:

- Omar Abdel-Wahab, MD, Memorial Sloan Kettering Cancer Center

Co-Principal Investigators:

- Benjamin Ebert, MD, PhD, The Broad Institute of MIT & Harvard
- Adrian Krainer, PhD, Cold Spring Harbor Laboratory

Abstract: Dysregulated gene expression occurring partly at the level of alternative splicing (AS) of tumor suppressors and oncogenes is a critical feature of malignancies. Recently, recurrent somatic mutations in genes encoding key members of the tightly regulated spliceosomal complex have been identified across various human leukemias, potentially linking specific somatic mutations with altered cancer-associated splicing. Recurrent spliceosomal mutations in leukemias most commonly occur in *SF3B1*, *U2AF1*, and *SRSF2*, and the significant frequency of these mutations and their recurrence across diverse malignancies suggest a functional role as leukemia drivers. Mutations in each of these genes conspicuously occur as heterozygous point mutations at highly restricted residues and are mutually exclusive, suggesting that these could be oncogenic gain-of-function alterations. At the present time, the mechanisms by which mutations in spliceosomal components exert their putative driver function are unknown. We hypothesize that spliceosomal mutations impact the transcriptome in a manner that promotes hematopoietic transformation and that these alterations may be targeted therapeutically. By forging a collaborative effort between Drs. Abdel-Wahab, Krainer, and Ebert, we will leverage our expertise in genomics, RNA splicing biochemistry, mouse models of hematologic malignancies, therapeutic modulation of splicing, and experience in genetically manipulating primary human cells to dissect the biological impact of these key mutations. We aim (I) to identify the impact of *SRSF2* and *SF3B1* mutations on the transcriptome of human and murine leukemias and (II) to develop novel therapeutic strategies targeting splicing-factor mutant cancers.