

Investigating Cancer-associated Structural Genomic Rearrangements Using *in vivo* Genome Editing

Principal Investigator:

- Lukas Dow, PhD – Weill Cornell Medicine

Co-Principal Investigators:

- Andrea Ventura, MD, PhD – Memorial Sloan Kettering Cancer Center

Abstract: Cancer genomes are complex, often harboring recurrent large-scale chromosomal rearrangements that can result in the generation of therapeutically actionable gene fusions. Such cancer-specific changes present new opportunities to design targeted therapeutic approaches, tailored to individual patients. However, identifying from the vast pool of genetic lesions those that actively drive tumorigenesis requires *in vivo* systems that recapitulate the biology of the human disease. Mouse models offer an ideal setting to dissect the genetic factors that influence cancer progression and treatment, but conventional approaches are not suited for modeling chromosomal rearrangements. Here we propose to use *in vivo* CRISPR/Cas9-based somatic genome editing to define the consequences of recurrent, cancer-associated chromosomal rearrangements. We will establish experimental pipelines to rapidly model newly discovered chromosomal alterations and generate a series of preclinical mouse models of colon, brain, and lung tumors that can be used to validate new targeted therapies. This work will define the contribution of numerous novel and recurrent genomic aberrations to tumor development, and establish new systems to explore the role of structural rearrangements in tumorigenesis.