Elucidating Mechanisms of Histone H3.3 Mutants-Mediated Oncogenesis in Pediatric Brain Cancers

Principal Investigator:
• C. David Allis, PhD, The Rockefeller University

Co-Principal Investigators:
• Cameron Brennan, MD, Memorial Sloan-Kettering Cancer Center
• Yu Chen, MD, PhD, Memorial Sloan-Kettering Cancer Center
• Ping Chi, MD, PhD, Memorial Sloan-Kettering Cancer Center
• Jeff P. Greenfield, MD, PhD, Weill Cornell Medical College
• Viviane Tabar, MD, Memorial Sloan-Kettering Cancer Center

Abstract: An emerging literature documents an increasing number of mutations affecting chromatin-modifying enzymes in human cancer, suggesting that aberrant chromatin modifications can lead to oncogenesis. In particular, genes affecting the post-translational modifications of histone H3 Lys27 and H3 Lys36 are frequently mutated. Whole-exome sequencing of pediatric gliomas led to the discovery of mutations at Lys27 and Gly34 of the "variant" histone H3.3A gene that may directly affect post-translational modifications of Lys27 and Lys36. Moreover, pediatric gliomas also harbor mutations of the ATRX and Daxx machinery that functions to 'chaperone' histone H3.3 to heterochromatin. The goal of our collaborative effort is to understand how histone H3.3 mutations affect the epigenetic landscape to mediate pediatric gliomagenesis and to identify novel therapeutic strategies for pediatric gliomas. We will determine the biochemical mechanisms of how H3.3 mutations affect recruitment and activity of histone-modifying enzymes, which in turn affects the modifications of nearby histones and correlate these results with the effect of H3.3 mutations on the epigenetic landscape and transcriptome (Aim1). We propose to generate accurate model systems of H3.3 mutant-mediated pediatric gliomas, using both mouse models and human neural progenitor cells derived from pluripotent stem cells (Aims 2&3). As one of the largest referral centers for this rare and deadly disease, we further propose to determine the effect of histone H3.3 mutations on the epigenetic landscape of tumor samples and correlate with clinicopathologic variables (Aim 4). We anticipate that our collaborative multidisciplinary effort will generate novel insight of pediatric gliomagenesis and streamline clinical translation of pediatric glioma treatment.