Define Oncogenic Mechanisms of Protein Methyltransferases SETDB1 and SUV39H1 in Melanoma

Principal Investigator:

- Minkui Luo, PhD, Memorial Sloan-Kettering Cancer Center

Co-Principal Investigators:

- Steven Gross, PhD, Weill Cornell Medical College
- Yariv Houvras, MD, PhD, Weill Cornell Medical College
- Ari Melnick, MD, Weill Cornell Medical College

Abstract: Protein lysine methyltransferases (PKMTs) orchestrate epigenetics through posttranslational methylation and their dysregulation has been frequently implicated in multiple cancers. Two PKMTs SETDB1 and SUV39H1 were recently identified as key players in BRAF(V600E) melanoma. However, how the oncogenic roles of the two PKMTs remain unclear, a situation significantly restricting our ability to manipulate the downstream epigenetic targets of PKMTs for novel diagnosis and cancer therapy. Strongly supported by our preliminary results and the evidence that PKMTs can function through methylating both histones and nonhistone targets, we hypothesized that the two PKMTs recognize a subset of targets, which render SETDB1/SUV39H1-driven melanoma malignancy. The objective of this proposal is to define and validate these downstream oncogenic events. Here we will leverage the novel Bioorthogonal Profiling of Protein Methylation (BPPM) technology, developed by the Luo laboratory, to profile nonhistone targets (Aim 1) and map histone modification sites of SETDB1 and SUV39H1 (Aim 2). The putative oncogenic methylation events will be examined with rigorous *in vitro* cell-based and novel *in vivo* zebrafish melanoma models, developed by the Houvras laboratory (Aim 3). This proposal aims at developing an innovative screening platform to define PKMTs' downstream oncogenic pathways in general and revealing the methylation events essential for BRAF melanoma in particular. These findings are expected to have direct impact on diagnosis, early intervention, treatment or even prevention of melanoma. The broad contributions of this proposal to cancer and epigenetic research lie in its cutting-edge technological advancement to define epigenetic functions of cancer-addicted PKMTs.