“Chemical Biology Approaches to Dissect Protein Methylation in Hematopoietic Cancer”

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Abstract: Lysine methyltransferases (KMTs) orchestrate epigenetics through posttranslational methylation and their dysregulation has been frequently implicated in cancer. Recent evidence showed that KMTs function through methylating both histones and nonhistone targets. However, few tools are available to dissect the nonhistone targets of designated KMTs. Such a situation significantly limits our ability to define and manipulate the epigenetic roles of KMTs in cancer. We recently formulated a novel technology, Bioorthogonal Profiling of Protein Methylation or BPPM, for profiling the targets of designated protein methyltransferases. The objective of this proposal is to implement the BPPM to elucidate SET7/9 nonhistone targets in the context of hematopoietic cancer models. In the BPPM approach, SET7/9 will be engineered to utilize S-adenosyl-*L*-methionine analogue cofactors and thus label SET7/9 targets with distinct chemical groups. The distinctly-modified targets will be enriched and profiled with the function/antibody-based probes developed under this proposal. The impact of this proposal is further strengthened by the general applicability of our approach to over 50 biologically- or cancer-relevant KMT enzymes.