

## **Elucidating the Function of Cancer-related Histone Modifiers by Integrative Analysis**

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Abstract: Histone modifying enzymes are emerging as key players in normal physiology and disease. In particular, protein methyltransferases (PMTs) and demethylases are misregulated in many cancers and contain "druggable" catalytic domains, thus providing promising therapeutic targets. To understand the role of PMTs in cancer and the consequences of their inhibition, we must decipher their molecular and regulatory function. Recent developments in gene perturbation and epigenomic and proteomic profiling offer an extraordinary opportunity to dissect this circuitry. However, to date, most studies have been small-scale, focused on single PMTs, and emphasized specific functional aspects. This is largely due to the difficulty to integrate the diverse aspects of each PMT's mechanism and function, including its genomic binding sites, catalytic activity towards histone and non-histone proteins, and regulatory impact. Here, we will develop a multi-pronged approach harnessing biochemical, genomic, proteomic and computational methods to dissect the regulatory circuits in which PMTs function. We will leverage our complementary expertise in PMTs biochemistry (Luo) and circuit reconstruction (Regev) to: (1) Profile a large number (~20) of cancer-associated PMTs for both their catalytic functions and changes in gene expression following their perturbation in model cancer cell lines; (2) integrate these into a computational model for the function of each PMT; and (3) verify and refine the model by functional experiments including in a panel of cell lines with relevant "PMT-mutants". Our integrative analysis will advance the global understanding of the function and therapeutic potential of PMTs and will provide a general approach applicable to other epigenetic regulators.