"Cancer Epigenetics: Understanding the "Writers", "Readers" and Functional Readout of Histone Lysine and Arginine Methylation Marks in Human Cancer"

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Abstract: The ultimate goal of this program is to determine how histone lysine and arginine methyl marks are installed, recognized, interpreted and possibly removed on gene promoters for the purpose of regulating or modulating critical biological processes that are strongly involved in cancer development, such as progenitor differentiation versus proliferation in hematopoietic malignancies (Allis lab) and p53-induced transcriptional response upon DNA damage (Roeder lab). Notably, both the H3K4me "writer", MLL, and the "eraser," JARID1, contain several PHD fingers that "read" H3K4me marks, and the dysregulation of either of these enzymes causes blood cancers in humans (Hess, 2004; van Zutven et al., 2006). The "reader" that recognizes histone arginine methylation marks will be identified using approaches that were proven successful for identified H3K4me binding modules, PHD fingers (Wysocka et al., 2005; Wysocka et al., 2006)(Allis lab). Structural analyses (Li et al., 2006) (Patel lab) will yield valuable insights into how these marks are "read" by key effectors to bring about downstream events. A complete understanding of these mechanisms will require access to defined "designer" nucleosomal arrays with these modifications pre-installed in a controlled, homogeneous manner (Muir lab). Emphasis will be placed on *in vitro* transcription assays as a functional readout for histone lysine/arginine methylations, as co-activators such as MLL, CARM1 and PRMT1, catalyze robust transcription via methylation on target lysine/arginine sites using a pure transcription system with defined chromatin templates of p53 target promoters (Roeder lab) (An et al., 2004; Dou et al., 2005).