

## “Bromodomain Inhibition as Targeted Therapy in Acute Myeloid Leukemia”

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**Abstract:** In cancer, epigenetic proteins are among the most promising and intently pursued targets in drug discovery. This relates to the growing appreciation that malignant gene regulatory pathways are centrally influenced by proteins which modify chromatin. Already, inhibitors of DNA methyltransferases and histone deacetylases have demonstrated substantial clinical efficacy leading to regulatory approval for use in hematologic malignancies. These events have triggered intense competition to develop inhibitors of chromatin modifying enzymes, or so-called epigenetic "writers" and "erasers". Perhaps owing to perceptions regarding the feasibility of targeting protein:protein interactions, small-molecule inhibitors of chromatin-binding modules or epigenetic "readers" have not been described. Recently, the Bradner laboratory has reported a first-in-class chemical inhibitor of one such histone binding module, namely the acetyl-lysine binding bromodomain of an epigenetic memory and transcriptional elongation factor, BRD4 (*Nature*, 2010). Convergent advances in the cancer biology programs of the Vakoc and Nimer laboratories have identified critical mechanistic roles of bromodomain proteins in epigenetic regulation of oncogenic transcriptional networks in two genetically-defined sub-types of human acute myeloid leukemia (AML). This proposal seeks research support for a highly collaborative program directed at the chemical optimization, mechanistic characterization and pre-clinical development of BRD4 and EP300 inhibitors in Mixed Lineage Leukemia (MLL) and t(8;21)-positive AML.