Chemical disruption of kinase-to-chromatin signaling in chemotherapy-refractory leukemia

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Abstract: In acute myeloid leukemia (AML), chemotherapy resistance remains enigmatic and prevalent. Convergent studies from Kentsis, Vakoc, and Gray have led to a hypothesis that disruption of kinase-to- chromatin signaling by small molecule inhibitors will restore sensitivity to chemotherapy in AML. This proposal builds upon recent studies by our team that validate MARK and SIK kinases as dysregulating the function of MEF2C, a transcription factor that confers chemotherapy resistance in a significant fraction of AML patients. In addition, we have developed tool compounds that allow for selective SIK/MARK modulation in tissue culture and in animals. The first Aim of this proposal will investigate the anti-leukemia activity of SIK/MARK inhibitors in faithful animal models of chemotherapy-refractory AML to understand mechanisms of response. The second Aim will employ medicinal chemistry to produce drug-like inhibitors and degraders of SIK and MARK for definitive preclinical assessment and as candidates for clinical investigation in humans. The final Aim of this proposal will identify novel kinase-to-chromatin signaling pathways that confer chemotherapy resistance in AML using an innovative chemical-genetic-proteomic strategy. This proposal has a strong translational focus, which is justified by a wealth of basic mechanistic science and the advanced stage of tools and compounds already developed by our team. For this reason, a two-year period of collaborative research support will have a strong potential to motivate clinical studies of SIK/MARK inhibitors in AML, as well as provide a broadly applicable paradigm for pharmacological targeting of oncogenic transcription factors in human cancer.