Inhibition of CDK8/CDK19 as a Therapeutic Strategy for MPNs

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Abstract: The majority of patients with myeloproliferative neoplasms (MPNs) harbor activating somatic mutations in *JAK2* (V617F) leading to activated JAK-STAT, PI-3 kinase and ERK signaling. JAK2 inhibitor therapy (ruxolitinib) demonstrates clinical efficacy however it does not significantly reduce mutant allele burden or improve survival due to persistent JAK2 activation. In some cases, patients with MPN progress onto acute myeloid leukemia (post-MPN AML). CDK8 phosphorylates the transactivation domains of STATs 1,3 and 5, suggesting that CDK8 inhibitors might modulate expression of STAT target genes and thereby inhibit the growth of *JAK2* mutant leukemia cells which are resistant to JAK inhibitor therapy. In support of such an outcome, we have discovered that cortistatin A (CA), a potent natural product inhibitor of CDK8 and its paralog CDK19, suppresses the growth of JAK inhibitor-resistant MPN cell lines, demonstrates synergy with ruxolitinib and is efficacious in a murine model of MPN at doses that are well-tolerated. However, CA has poor pharmacokinetics and is only available in small quantities, preventing its clinical development. We have identified potent synthetic analogs of CA and the site of metabolism. Herein, we propose to: 1) prepare CA analogs with acceptable drug properties for future advancement to MPN and post-MPN AML clinical trials and 2) to investigate why MPN cell proliferation requires CDK8/CDK19. This project will leverage the Shair lab's chemistry and chemical biology expertise with the Levine lab's preclinical and clinical experience in MPNs to catalyze the development of a CDK8/CDK19 inhibitor for treatment of MPNs and post-MPN AML.