“Functional Genetic and Proteomic Analysis of Sensitivity and Resistance to Targeted Therapies”

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Abstract: Hematologic malignancies have provided a testing ground for the development of targeted therapies for cancer, and in some cases these therapies have fundamentally altered patient outcomes. Although targeted therapies have already had significant clinical impact, the emergence of resistant clones has become a central problem for successful treatment of human malignancies. Moreover, in some cases new therapies have been demonstrated to have significant clinical benefit for specific hematopoietic malignancies without detailed knowledge of mechanisms of drug sensitivity or drug resistance. We therefore propose to use state-of-the-art genomic and proteomic platforms to elucidate mechanisms of sensitivity and resistance to a set of drugs for the treatment of myeloid malignancies: lenalidomide for the treatment of myelodysplastic syndrome (MDS), JAK2/HSP90 inhibitors for the treatment of myeloproliferative neoplasms (MPN), and SYK inhibitors for the treatment of acute myeloid leukemia (AML). We will use RNAi to perform functional genetic studies of drug sensitivity and resistance, and SILAC profiling to identify proteins which serve as targets for specific drugs and which mediate resistance to targeted therapies. We will next functionally validate target sensitivity and resistance in both cell lines and primary samples. These experiments have the potential to inform the development of novel therapies, to delineate the optimal clinical setting for use of these agents, and to develop combinations of drugs that circumvent key mechanisms of resistance to therapy.