"Molecular Dissection of Myelodysplastic Syndrome and Myeloproliferative Disease"

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Abstract: Large-scale studies of the cancer genome are currently underway that promise unprecedented insight into the full spectrum of somatic mutations in human malignancies. The next stage in this endeavor will be to identify the functional role of each mutation in the initiation and progression of tumors. We propose to develop high throughput functional assays to determine the functional consequences of molecular lesions in two paradigmatic hematologic malignancies: myelodysplastic syndrome (MDS) and myeloproliferative diseases (MPD).

Three critical cellular abnormalities in hematologic malignancies, and cancer in general, are defects in differentiation, increased proliferation, and expansion of a pool of cells capable of self-renewal. Our goal is to develop high throughput assays that delineate the effects of genetic lesions on these three traits. MDS and MPD represent the spectrum of hematologic malignancies with respect to these properties. MDS is defined by dysplastic and ineffective hematopoietic differentiation with relatively little change in proliferation; MPD is characterized by increased proliferation with relatively normal differentiation; and both diseases achieve clonal dominance of the bone marrow, indicating a selective advantage at the stem cell level.

Our groups have led efforts to identify key mutations in MPD and MDS, and we are currently pursuing large scale genomic characterizations of these diseases. The development of informative functional assays will provide an unprecedented opportunity for the rapid credentialing of candidate mutations and the correlation of genotype and phenotype in cancer. In addition, insights derived from these studies may inform novel targeted therapeutic agents for treatment of MDS and MPD.