“Mechanisms Determining Disease Relapse in Older Patients with Acute Myeloid Leukemia”

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Abstract: Acute myeloid leukemia (AML) remains almost universally fatal, especially in adults older than 60 yrs in whom the disease is most common. Although patients often initially respond to treatment, most quickly relapse. Recent studies from our group and others suggest that subsets of leukemia repopulating "stem" cells mediate relapse. Understanding and overcoming the molecular basis of relapse is a significant biomedical challenge. We formed a multidisciplinary "AML Relapse Consortium" to address this challenge. We hypothesize that sub-clones of leukemia cells, potentially representing a small minority of the cells present at diagnosis, are genetically and epigenetically programmed to survive chemotherapy and re-establish the disease. We will therefore determine at single-base pair resolution the distribution of genetic mutations and aberrant DNA methylation, and precisely measure the abundance and splicing of mRNA transcripts in 50 paired leukemia specimens at diagnosis and relapse. We will validate these findings using germline DNA and other controls, and will confirm the significance of our findings in an independent cohort of 400 patients. We will also identify the biological pathways affected by these alterations, and determine their contribution to malignant transformation and resistance to therapy. This will be accomplished by combining and integrating state of the art deep-sequencing and computational genomics approaches with leukemia stem cell functional and experimental therapeutics methods. We expect to discover important mechanisms of leukemia relapse, identify clinically useful biomarkers of resistant AML, and provide the basis for targeted therapy clinical trials to eradicate resistant cells.