

**Title: Investigating Hypomethylation of Transposable Elements and Their Effects on Karyotype Stability in Chronic Lymphocytic Leukemia (CLL)**

**IRB# 2010-021**

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**Synopsis:**

Drawing upon the resources of CHORI and our expertise in human genetics, cytogenetics and genomics, this project aims to study the relationship between **global hypomethylation, activation of Transposable elements, and chromosomal rearrangements in cancer**. Transposable elements are sequences of DNA that can move and change location within the genome and cause mutations, including large-scale chromosomal rearrangements. CpG methylation is the main mechanism to repress these elements and limit genomic damage. Because both reduction of methylation (hypomethylation) and chromosomal rearrangements are common in cancer, it has been suggested that the two phenomena are connected. Although this hypothesis has convincing theoretical bases, **currently there is no evidence of a 'cause - effect' relationship**. The proposed project builds on our recent observations on evolutionary chromosomal breakpoints in gibbon species, which are characterized by a high rate of evolutionary chromosomal rearrangements. Using this model, we were able to show an association between a class of undermethylated TEs (Alus) and chromosomal breakpoints. We want to explore the possibility that a similar association exists in cancer cells. In this pilot project, we will implement and test an approach to measure CpG methylation of transposable elements in cancer cells by using massively parallel sequence. In particular, we will compare Chronic Lymphocytic Leukemia patients to healthy controls. Furthermore we will characterize the association between hypomethylated elements and chromosomal rearrangements. The **translational application** of this research program will be the establishment of a high-throughput method to measure global CpG methylation of TEs in cancer patients, which may be applied to diagnosis, staging, and monitoring of progression and treatment response.