CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180826

Project Title:
Integrative Analysis of Structural Variants in Cancer Genomes

Award Mechanism:
High Impact/High Risk

Principal Investigator:
Xu, Jian

Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Acute myeloid leukemia (AML) accounts for 90% of all acute leukemias in adults and 15-20% of those in children. AML is a genetically heterogeneous blood cancer and its disease development is associated with a variety of genomic structural variants (SVs) such as chromosomal translocations, large sequence insertions and deletions. The discovery of recurrent AML-associated SVs has provided successful targets for diagnosis, prognosis and therapeutics; however, due to major limitations of conventional SV detection tools, recurrent SVs were not identified or characterized in the majority of AML cases. This represents a major challenge in risk stratification and clinical management of these patients. Therefore, there is a critical need to characterize new genomic SVs associated with these uncategorized AMLs in order to study disease pathophysiology and to design novel targeted treatments. In this project, we aim to overcome current challenges of SV analysis by developing new experimental and computational tools. We will establish a “first-of-the-kind” integrative approach to comprehensively identify pathogenic SVs and their molecular consequences by combining three methods with distinct sensitivity and resolution, including next-generation optical genome mapping (NGM), whole genome sequencing (WGS), and chromosome conformation capture (Hi-C). The identified SVs will be validated and prioritized for subsequent molecular and functional analyses in AML development in vitro and in vivo. Our studies will not only identify de novo SVs as new drivers of leukemogenesis, but also provide innovative strategies to characterize the causal mechanisms underlying recurrent SVs, altered genome structures and gene expression in cancer development. These results will help translate findings from cancer genetic studies to mechanism-based therapies for blood cancers, which can be easily extended to other types of human cancers.