CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP160022

Project Title:
Role of Cohesin in Hematopoiesis and Myeloid Leukemia in Children with Down Syndrome

Award Mechanism:
Individual Investigator Research Awards for Cancer in Children and Adolescents

Principal Investigator:
Pati, Debananda

Entity:
Baylor College of Medicine

Lay Summary:

Children with Down syndrome (DS) are at an increased risk of developing leukemia. Nearly half of the DS leukemia in children is classified as acute megakaryoblastic leukemia (AMKL), a relatively rare subtype of acute myeloid leukemia (AML) with dismal prognosis - median overall survival is 6 months. A myelodysplastic phase known as transient myeloproliferative disorder (TMD) frequently precedes development of AML in these children, and the spectrum of both myelodysplastic syndrome (MDS) and AML have been known collectively as myeloid leukemia of Down syndrome (ML-DS). Children with ML-DS represent approximately 15% of the pediatric AML cases. Over 95% of ML-DS cases are diagnosed in children younger than 4 years old. Three quarters of children with ML-DS harbor mutations in chromosomal cohesin components in their bone marrow cells, but how myeloid leukemia arises from these mutations and whether cohesins have a physiological role in hematopoiesis are poorly understood. In this proposal, we will use a novel mouse model to study how cohesion mutations perturb normal hematopoiesis and contribute to the multistep process of leukemic transformation in DS associated AML. The proposed work has the potential to significantly impact the future care of infants and children with DS and advance our scientific understanding of the driver mutations and genetic alterations that contribute to leukemogenesis in children. This work will address several key gaps in current scientific knowledge and may lead to genomic-proteomic biomarkers predictive of subsequent leukemia in infants with TMD. Our work may also provide an in vivo model system for testing potential biologically targeted therapies aimed at preventing leukemic transformation in patients with TMD or overcoming treatment resistance, especially in patients older than 4 years with high-risk forms of DS-acute myeloid leukemia.