CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150006

Project Title:
Defining and Treating Targetable Lesions in AYA Acute Lymphoblastic Leukemia

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

Principal Investigator:
Konopleva, Marina

Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

Acute lymphoblastic leukemia (ALL) is the most common form of cancer in children. Despite tremendous improvements in the outcomes, a subset of children relapses and often succumbs to their disease. In adults, the outcomes remain vastly inferior, and most patients are expected to die either of their disease or of treatment-related toxicities. The need for novel therapies is thus unquestioned. A major recent advance in understanding the biology of ALL was the discovery of a novel category of “Ph-like” ALL which exhibit gene expression signatures similar to patients with “Philadelphia (Ph)” chromosome but are lacking Ph-chromosome. Further discoveries have demonstrated that the tumors in these patients with ALL are driven by alterations in oncogenic kinases amenable to therapy with FDA-approved tyrosine kinase inhibitors (TKIs). Depending on the underpinning genetics, these patients may respond to ABL/PDGFR inhibitor dasatinib, which has recently improved survival in Ph(+) ALL; or JAK2 inhibitor ruxolitinib, approved for therapy of JAK2-driven myeloproliferative neoplasms. This concept, developed in pre-clinical leukemia models, was validated in reports of the success of TKIs in refractory EBF1-PDGFRB Ph-like ALL patients. Recent studies with our collaborator from St. Jude’s Charles Mullighan have shown that the frequency of “Ph-like” ALL increases with age, whereby one-third of young adults with ALL have actionable genetic lesions and very poor outcomes. In this study, we will (1) design and validate the genetic platform that can rapidly identify high-risk Ph-like ALL patients; (2) treat relapsed or refractory Ph-like ALL patients with TKI matched against patients’ specific genetic make-up, alone or in combination with salvage chemotherapy in a clinical trial setting; and (3) perform deep RNA sequencing and proteomic analyses to characterize novel actionable targets. We will test novel therapies in immunodeficient mice engrafted with human leukemia samples.