“Oncogenic Regulation of B-Lymphomagenesis by the Chromatin Modulator DOT1L”

Principal Investigators:
Bing Ren, PhD (Moores Cancer Center)
Aniruddha Deshpande, PhD (Sanford Burnham Prebys)

SCIENTIFIC ABSTRACT
MYC is one of the most frequently misregulated oncogenes in human cancer. Despite this, therapeutic MYC targeting has remained elusive. One way of overcoming the intractability of direct pharmacologic MYC inhibition is by identifying actionable dependencies that cooperate with oncogenic MYC. MYC dysregulation by way of chromosomal translocation, aberrant activation, or genomic amplification is a key oncogenic event in diverse sub-types of B-cell lymphoma and is often correlated with poor survival outcomes. Using mouse and human models of B-lymphoma, we observe that MYC-driven proliferation of B-lymphoma cells is dependent on the epigenetic regulator DOT1L.

This collaborative C3 proposal aims to identify effectors of DOT1L-inhibitor sensitivity in B-cell lymphoma and investigate the mechanisms by which histone 3 lysine 79 (H3K79) methylation by DOT1L regulates oncogenic transcription. Small molecule DOT1L inhibitors are currently in clinical trials for acute myeloid leukemia with MLL–rearrangements. A successful outcome of this C3 proposal will provide a rationale for using DOT1L inhibitors in lymphoma and perhaps other malignancies where novel therapies targeting the MYC oncotranscriptome are urgently needed. Our preliminary findings reveal a novel, actionable dependency in B-cell lymphoma and is therefore of potentially high translational relevance – consistent with the goals of the C3 award.

LAY ABSTRACT
The epigenome is an exciting new frontier for therapeutic intervention in human disease, because unlike genomic abnormalities that are difficult to reverse therapeutically, abnormal epigenetic changes are amenable to reversal using chemical compounds. Our collaborative proposal aims to identify and characterize a novel, actionable, epigenetic vulnerability in B-lymphomas where safer curative treatment options are needed.