Award ID:
RP180177

Project Title:
Novel Small Molecule Probes Targeting Histone Acetyltransferase p300/CBP

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

Human genome is composed of double-stranded DNA wrapped around millions of protein histone cores. Acetylation of histones plays critical roles in gene transcription, DNA replication and repair. In addition, aberrant histone acetylation often occurs in many diseases such as cancer. In this project, we aim to discover and develop novel small molecule inhibitors of histone acetyltransferases (HAT) p300 and CBP, which are proteins that can acetylate histones and are co-activators of gene transcription. Previous studies have shown HAT activity of p300/CBP is essential for many transcription factors mediated gene transcription as well as oncogene driven cancers, including ~15% acute myeloid leukemia (AML). In the US, ~15,000 people are newly diagnosed with AML each year. The incidence rate of the malignancy increases dramatically with age and the prognosis is poor, with 5-year survival rates being <40% for patients younger than 65 years and only 5.2% for older patients. Potent, selective and cell-permeable compounds targeting p300/CBP-HAT are therefore needed. To date, only a limited number of p300/CBP-HAT inhibitors have been disclosed. However, these compounds do not have potent, low nM activity and are either non-cell-permeable or contain unfavorable structures for drug development or cell biology. Success of this project would lead to the discovery of useful chemical probes of p300/CBP for cancer biology studies as well as potential therapeutics for p300/CBP associated cancers.