KDDF
Korea Drug Development Fund

Asset #45
Dana-Farber Cancer Institute

Selective Disruption of Histone Deacetylase Complexes by Protein Interaction Inhibitors to Treat Cancer and Neurological Disorders

Therapeutic Area	Oncology, Neurology	**Indications**	Haematological Cancers
Modality	Small Molecule	**Development Stage**	Hit to Lead/Lead Optimization

Overview

Background

- Enzymes collaborate with other proteins to form complexes, as seen with histone deacetylases (HDACs) involved in gene regulation by modifying histone tails. HDACs are implicated in diseases like cancer, Alzheimer's, and Parkinson's. While FDA-approved inhibitors target HDAC pockets, achieving specificity remains a challenge.
- Dana-Farber researchers have discovered novel inhibitors binding to the PAH domain of SIN3, an HDAC complex scaffold protein. These inhibitors disrupt interactions with transcription factors or DNA binding proteins, showing potential for targeted therapy with fewer gene perturbations in mammalian cells and mouse models.

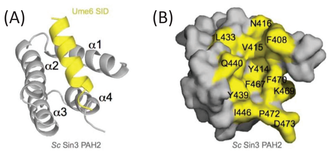
Technology Advantages

- This new class of HDAC inhibitors disrupts the transcriptome of cancer cells more specifically than enzymatic inhibitors like trichostatin A
- Compared to trichostatin A (an establish HDAC inhibitor) there was a 20-fold drop in the number of genes perturbed in neuroblastoma cells
- There was also a 50-fold drop in the number of genes perturbed in HDAC2 knockout mice

Key Data

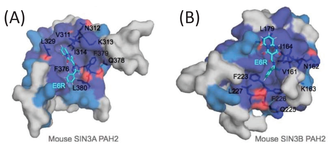
E6R perturbs transcription by binding to the SIN3 PAH2 domain and inhibiting the PAH2 -SID interaction

A



(A) Ribbon diagram of the Sc Sin3 PAH2-Ume6 SID structure with alpha helices indicated.
(B) Surface representation of the Sc Sin3 PAH2 domain with residues in contact with the Ume6 SID peptide indicated in yellow.

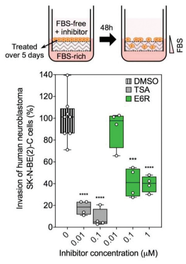
B



Docking of E6R into the mouse SIN3A PAH2 (PDB: 2L9S) (A), and SIN3B PAH2 (PDB: 2F05) (B) domains where deep blue corresponds to residues conserved across all SIN3 PAH2 homologs and sky blue to semi-conserved residues. Amino acids shown as sticks correspond to NMR perturbed residues by E6R in yeast and their mouse pendants.

E6R reduces neuroblastoma cell invasion and tumor growth with restricted transcriptomic change

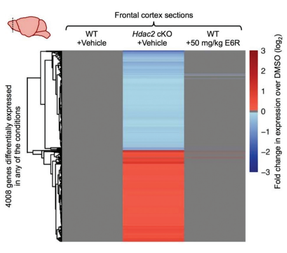
C



Models of the human Sin3 HDAC18 and yeast S. cerevisiae Sin3/Rpd3L HDAC32 complexes with some protein domains indicated. The synthetic URS-URA3 reporter gene in yeast is represented.

E6R reduces head-twitch response with restricted transcriptomic changes in the frontal cortex

D



Genes differentially expressed (RNA-seq) in FC sections of WT or Hdac2 cKO mice chronically treated with E6R or vehicle, respectively (n ≥ 5 biologically independent samples per group). For each condition, a row represents a gene log2(fold change).

IP Status & Publication(s)

Intellectual Property

Patent Number
PCT-US2022-034043 (2022.06.17)

Patent Family
PCT, US

Publication(s)

- Olivet at al. (2022). Expanding the HDAC druggable landscape beyond enzymatic activity. bioRxiv (Cold Spring Harbor Laboratory)