

# BDR SEMINAR in Yokohama

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**Monday, May 27, 2019**

15:00-16:00, Koryu-to Hall, Main office Bldg.

## Chemical control of chromatin signaling in cancer

\* This seminar is a part of the Epigenetics Seminar Series 2019-2020.

### Summary

Pathogenic transcriptional regulatory networks sustain malignant cell phenotypes in human cancers. We have previously identified that the transcriptional co-activator, ENL, is essential for the survival of diverse acute leukemia in both cellular and animal models of the disease but is dispensable for the survival of hematopoietic stem and progenitor cells. Thus, we predict that ENL-targeted anti-cancer agents will possess favorable therapeutic windows and have therefore endeavored to discover small-molecule inhibitors of ENL. The ENL YEATS domain recognizes acylated lysine residues within amino-terminal histone tails and this function is essential for both the localization of ENL to chromatin and for its ability to sustain leukemic proliferation.

We developed an ultra-high-throughput screening (uHTS) assay that reports on the association of a synthetic histone peptide to recombinant ENL YEATS domain and screened a collection of 250,000 small molecules. Validated hits were identified among false positives using a novel target engagement assay, resulting in the classification of two structurally distinct chemical scaffolds as ENL YEATS inhibitors. Hits were optimized via hit expansion studies and iterative medicinal chemistry to yield selective ENL YEATS inhibitors. These data will support the development of ENL YEATS antagonists as in vivo chemical probes and targeted anti-cancer agents.



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