



Christopher Ott, PhD

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Ott Laboratory

Matthew Lawlor
Christopher Ott, PhD
Logan Schwartz
Sharon Wu

Mutations in cancer cells lead to malfunctioning control of gene expression. **The Ott laboratory** is dedicated to discovering the gene expression control factors that are essential for leukemia and lymphoma cell survival. Discovery of these factors prompts further efforts in our group to design chemical strategies for the synthesis and deployment of prototype drugs targeting the aberrant mechanisms of gene control. Biologically, gene control factors represent compelling therapeutic targets for these cancers, as they are master regulators of cell identity. Yet despite this clear rationale, most are perceived as intractable drug targets owing to their large size, disordered shapes, and involvement in complex cellular circuits. Recent advances in gene editing technologies and discovery chemistry have advanced our capability to rapidly identify targetable aspects of gene control and methods to disrupt their function. We use these genetic and chemical tools to probe cancer cell circuitry and inform therapeutic hypotheses.

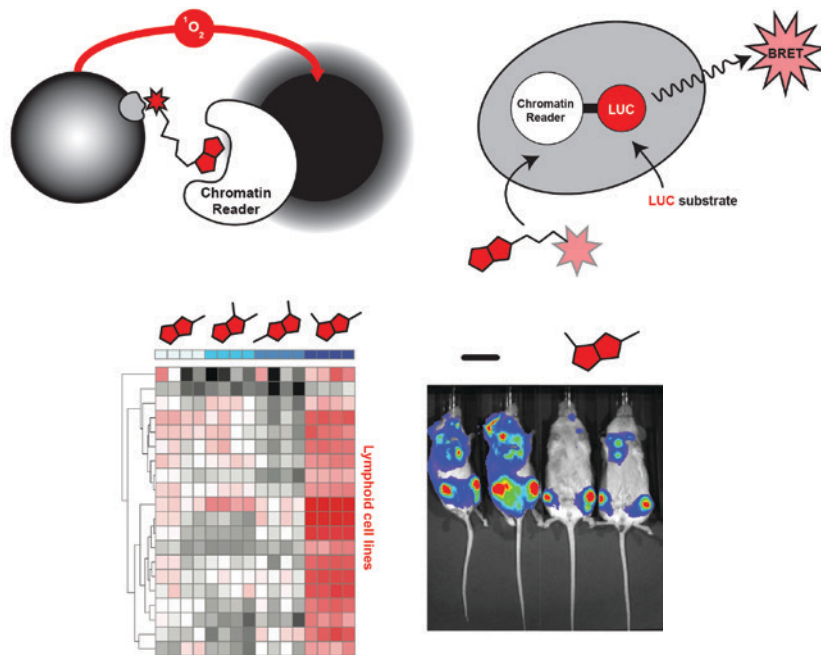
Chemical BET inhibition

Gene control factors bind to regions of transcriptionally active chromatin called enhancers. Enhancers are critical for driving cell-type specific gene expression, and their chromatin structures are typically marked with specific histone modifications. Among the most distinctive is lysine side-chain acetylation, recognized (or 'read') by histone modules called bromodomains. Recently, novel chemical compounds have been advanced that selectively target the bromodomains of the bromodomain and extra terminal domain (BET) family. These compounds efficiently displace BET proteins from active enhancer chromatin, and we and others have found them to be active agents in models of acute leukemia, lymphoma, and several solid tumor types. Using a suite of genome-wide chromatin and transcriptomic assays, we aim to understand principles of BET protein

dependency in leukemia and lymphoma cells. Efforts are ongoing to establish biomarkers for response and resistance, and realize promising rationales for combination therapies with other targeted agents.

Essential enhancers

Classic studies have described oncogenic enhancers in leukemia and lymphoma cells. This aberrant enhancer activity can occur by chromosomal translocation of proto-oncogenes such as *MYC* and *BCL2* to the transcriptionally active immunoglobulin locus, T-cell receptor rearrangements in T cell tumors, and the *EV11-GATA2* rearrangement in an aggressive subtype of acute myeloid leukemia. In addition to chromosomal translocations, cancer-specific enhancers have been described at proto-oncogene loci like *TAL1* and *MYC*, which are aberrantly bound by transcription factors through direct somatic mutation of enhancer DNA elements



Expanding the chromatin chemical probe toolbox with high throughput bead-based proximity assays, cellular target engagement assessment, cell line viability profiling, and in vivo pharmacology.

or focal amplification. We have generated high-resolution enhancer landscapes derived from primary patient samples, including a large cohort of chronic lymphocytic leukemia samples. Current projects include construction of core regulatory transcription factor circuitries, and the discovery of inherited and somatic variants leading to aberrant gene expression. Using genetic and epigenetic genome editing techniques, we are functionally dissecting malfunctioning enhancers and their cognate bound factors to derive mechanistic understanding of the essential enhancers principally responsible for maintaining leukemia and lymphoma cell states.

Expanding the chromatin chemical probe toolbox

The successful discovery of chemistry efforts that yielded efficient BET bromodomain inhibitors has revealed chromatin reader domains broadly, and bromodomains specifically, as protein modules amenable for small molecule ligand development.

Used experimentally, enhancer-targeting compounds enable precise disruption of chromatin features and can be used to identify and validate discrete biophysical and biochemical functions of target proteins. Paired with an understanding of integrated epigenomics, these probes enable the elucidation of fundamental insights into genome structure and function. We use high-throughput protein-protein interaction assays and cellular assays of chromatin reader activity to identify reader domain inhibitors. Lead compounds are iteratively optimized for potency and selectivity, followed by functional assessments on epigenome structure. Leukemia and lymphoma cell viability profiling and in vivo pharmacokinetic and pharmacodynamic studies enable the nomination of next-generation inhibitors of essential chromatin readers. Ongoing projects seek to expand our current toolbox of bromodomain inhibitors, with a particular focus on 'orphan' factors for which selective compounds have yet to be developed.

Selected Publications:

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*Co-corresponding authors