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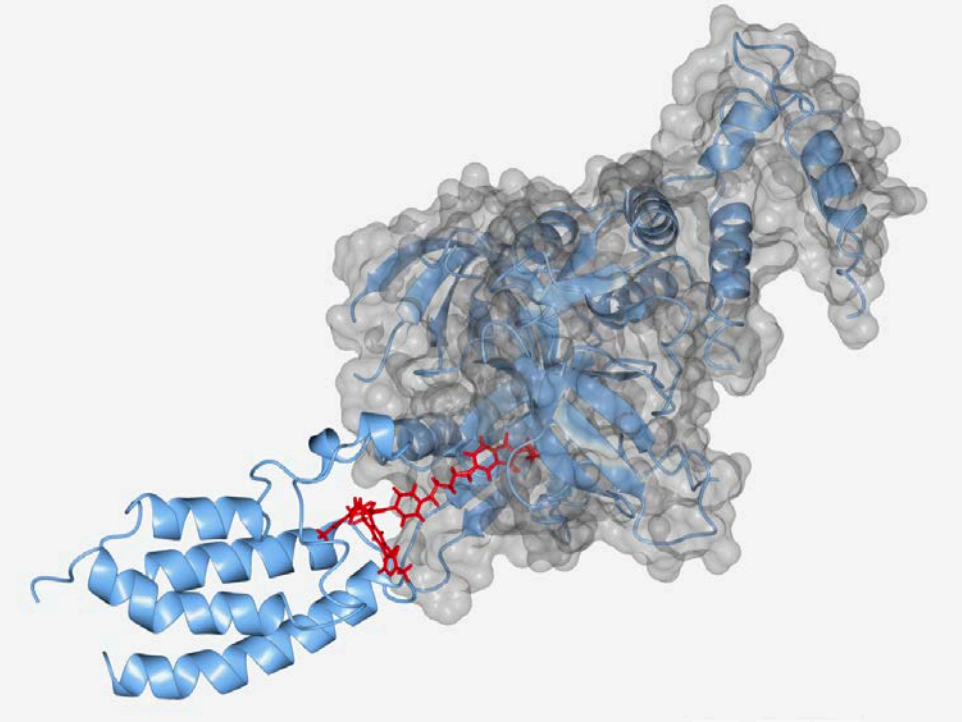
Mutations in cancer cells lead to malfunctioning control of gene expression. **The Ott laboratory** is dedicated to discovering the gene expression control factors that are essential for cancer cell survival. Discovery of these factors prompts further efforts in our group to design chemical strategies that directly target aberrant mechanisms of gene control. Biologically, gene control factors represent compelling therapeutic targets for cancer treatment as they are master regulators of cell identity. Yet despite this clear rationale, many are perceived as intractable drug targets owing to their large size, disordered shapes, and orchestration of complex cellular circuits. Recent advances in discovery chemistry, high-throughput assay technology, and gene editing technologies have advanced our capability to identify targetable components of gene control machinery. We use these chemical and genetic tools to probe cancer cells for new vulnerabilities ripe for therapeutics development.

Chemical modulation of bromodomains

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 protein modules called bromodomains. Recently, novel chemical compounds have been advanced that selectively target bromodomains. These compounds efficiently displace these proteins from enhancers, and we and others have found them to be active agents in models of acute leukemia, lymphoma, and several solid tumor types (Ott et al, *Blood* 2012; Ott et al, *Cancer Cell* 2018). Using a suite of genome-wide chromatin and transcriptomic assays, we aim to understand principles of bromodomain dependency in cancer. 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*. 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 or focal amplification. We have generated high-resolution enhancer landscapes derived from primary patient samples, including a large cohort of chronic lymphocytic leukemia samples (Ott et al, *Cancer Cell* 2018). 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



Structural model of the ternary complex formed by a novel chemical degrader of the CBP/p300 (dCBP-1) developed by the Ott laboratory. dCBP-1 (in red) induces degradation of CBP/p300 by acting as a 'molecular glue' between an E3 ubiquitin ligase and the bromodomain of CBP/p300 (structural model generated by J. Sayilgan).

for maintaining leukemia and lymphoma cell states.

Expanding the chromatin chemical probe toolbox

The successful discovery chemistry efforts that yielded bromodomain inhibitors have revealed chromatin reader domains broadly, and bromodomains specifically, as protein modules amenable for small molecule ligand development. Used experimentally, enhancer-targeting compounds enable precise and acute modulation of chromatin factors 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 elucidate fundamental aspects of epigenome 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 in cancer cells. Our recent efforts have led us to describe the first chemical degrader of the enhancer lysine acetyltransferases CBP and p300 (Vannam et al, *Cell Chemical Biology* 2021). Ongoing projects seek to expand our current toolbox of enhancer-targeting small molecules, and to develop these compounds into prototype cancer therapies.

Selected Publications:

Vannam R, Sayilgan J, Ojeda S, Karakyriakou B, Hu E, Kreuzer J, Morris R, Herrera Lopez XI, Rai S, Haas W, Lawrence M, **Ott CJ**. Targeted degradation of the enhancer lysine acetyltransferases CBP and p300. *Cell Chemical Biology*. 2021; 28:503-514.

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Ott CJ*^, Federation AJ*, Schwartz LS, Kasar S, Klitgaard JL, Lenci R, Li Q, Lawlor M, Fernandes SM, Souza A, Polaski D, Gadi D, Freedman ML, Brown JR^, Bradner JE^. Enhancer architecture and essential core regulatory circuitry of chronic lymphocytic leukemia. *Cancer Cell*. 2018; 34: 982-995.

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Koblan LW*, Buckley DL*, **Ott CJ***, Fitzgerald ME*, Ember S, Zhu J-Y, Lui S, Roberts JM, Remillard D, Vittori S, Zhang W, Schonbrunn E, Bradner JE. Assessment of bromodomain target engagement by a series of BI2536 analogues with miniaturized BET-BRET. *Chem Med Chem*. 2016; 11: 2575-2581.

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