Unraveling Chromatin Complexes with Small Molecules

Abstract: The orchestrated interactions of chromatin complexes and transcription factors shape the cell's epigenome to control gene expression and cell state. Dysregulation of these complexes and their interactions underlie human disease, and new therapeutic approaches to modulate them by blocking or even creating interactions are transforming paradigms for drug discovery. Beyond their potential as therapeutics, these small molecules are powerful tools to dissect the function and regulation of chromatin complexes. By combining genome-editing with chemical inhibitor profiling in an approach called CRISPR-suppressor scanning, we describe the systematic identification of drug resistance alleles across protein targets, including chromatin complexes. These drug resistance alleles not only confirm on-target engagement but can be used as powerful discovery tools to uncover new principles and aspects of chromatin complex biology. In this seminar, I will describe how the application of these approaches in combination with deeper mechanistic investigation has led to unexpected biological discoveries that reshape our views on targeting chromatin modifying enzymes for therapeutics.