Submitter Name: Zhuzhu Zhang Submitted Email: zhuzhuzhang@uchicago.edu

Single-Cell Resolution and Circuit-Level Dissection of Epigenomic Remodeling in Addiction

Zhuzhu Zhang[1], Lin Yang[1]

[1]Department of Human Genetics, The University of Chicago

The reward circuitry comprises a vast diversity of cell types, each defined by specific molecular and anatomical properties, including their locations and neuronal projections. These cell types perform distinct functions and respond differently to exposure to substances of abuse in the context of addiction. Thus, dissecting these cellular molecular responses, particularly gene expression alterations mediated by epigenomic remodeling, at cell-type resolution and within the context of connections between brain regions and cell types in the reward circuitry, is crucial for understanding the molecular underpinnings of addiction. To tackle this challenge, my lab adopts an interdisciplinary approach that combines the mouse model of intravenous self-administration (IVSA) of cocaine with innovative single-cell epigenomics assays. Specifically, I have developed Epi-Retro-Seq, a cutting-edge single-cell epigenomics method that merges retrograde tracing with single-cell DNA methylome and RNA sequencing. This approach allows for the simultaneous investigation of epigenetic and gene regulation in individual cells and their connectivity within the reward circuitry. We have proven the effectiveness of this strategy in exploring the principles that link neuronal projections to transcriptomics and epigenomics in the mouse brain. Moreover, we have enriched Epi-Retro-Seq with spatial transcriptomics, including multiplexed error-robust fluorescence in situ hybridization (MERFISH), to further refine the precise spatial locations of the cell types of interest. Applying these methodologies in concert to the IVSA mouse model promises to reveal cell type-specific epigenetic mechanisms in addiction and to provide essential insights for subsequent targeted functional studies of key epigenomic regulators.