Name: Christopher Baker Email: christopher.baker@jax.org

Genetic variation influences cell specific cis-regulatory landscape in the mouse striatum

Oliver Poirion[1], Catrina Spruce[1], Wulin Zuo[1], Ashley Wilson[1,2], Sandy Daigle[1], Dan Skelly[1], Brian White[1], Vivek M. Philip[1,2], Lisa M. Tarantino[2,3], Elissa J. Chesler[1,2], Christopher L. Baker[1,2]

[1]The Jackson Laboratory, [2]Center for Systems Neurogenetics of Addiction, [3]The University of North Carolina at Chapel Hill

Addiction is highly heritable, but our mechanistic understanding of the link between genetics and predisposition to addiction is limited. Genetic variation impacts all aspects of addiction, drug response, and drug seeking behavior and most variants are expected to function through epigenetic mechanisms. Here we applied single-cell approaches to the mouse striatum to 1) determine the cell-type specific chromatin landscape linking cis-regulatory elements (CREs) to gene expression; 2) delineate how genetic variation impacts CREs; and 3) integrate existing addiction-related phenotypes to identify critical CREs. We profiled chromatin accessibility and gene expression in both sexes across the eight inbred founders of the Collaborative Cross and Diversity Outbred genetic reference populations. All major striatal cell types, including *Drd1* and *Drd2* expressing medium spiny neurons (MSNs), were identified. To integrate data modalities, we developed a new computational approach to leverage single-cell signals to infer linkages between CREs and their cognate genes, termed Enhlink. Enhlink incorporates features lacking in current methods accounting for technical or biological covariates such as batch, sex, or genetic background, and demonstrates superior performance at identifying biologically relevant enhancer-promoter interactions. Focusing on D1 and D2 MSNs we predicted cis- and trans-regulatory linkages, indicating coordinated transcription factor regulation. Integrating these links with expression QTL, we predict association of a CRE with expression of *Me3* and *Eed*, two genes which are behavioral QTL positional candidates and transcript correlates of reward seeking behavior in mice from the same population. Future directions will apply this framework to identifying epigenomic changes upon repeated exposure to cocaine.