Name: Derek Hui, B.S. Email: mhui3@jh.edu

Epigenetic mechanisms of information storage after acute cocaine exposure

The midbrain Ventral Tegmental Area (VTA) is a pivotal brain structure in the dopamine circuitry, and a main source of dopaminergic neurons (DNs). VTA-DNs are the primary mediators of reward processing and reinforcement learning which are triggered upon a single drug exposure. VTA-DNs undergo synaptic long-term potentiation (LTP) for up to ten days, entering an altered functional state. Several drugs with distinct pharmacological sites such as cocaine and fentanyl are known to induce this LTP-like state in VTA-DNs by inhibiting the dopamine transporter (DAT) and disinhibiting mu opioid receptor-mediated GABA disinhibition. We have shown that acute cocaine exposure induces extensive rewiring of 3D chromatin structures in VTA-DNs that are altered at 14 days and affects immediate early genes and genes previously associated with chronic addiction. To gain insights into the mechanisms underlying the long-term memory of single cocaine exposure in the VTA, we generated single-cell multiome (RNA-ATAC-seq) datasets at various time points post-exposure (up to 14 days). We found lasting changes in gene expression, involving key genes for cocaine-induced behavior (e.g., Cartpt, Npy, Gad1). We identified differential chromatin accessibility of binding sites like NR4A1 (regulator of Cartpt) and a methylation-sensitive AP-1 variant. We are currently investigating whether other cell types in the VTA also retain long-lasting changes in gene expression after single exposure, including astrocytes, which play significant roles in brain homeostasis and synapse formation. Astrocytes also retain long-lasting changes in gene expression upon single cocaine exposure, involving key genes for addiction behavior (e.g., Pdk4, Fkbp5), and genes involved in neurodegeneration pathology (e.g., Ctsd, Tm4sf1). These findings suggest that single cocaine exposure induces specific molecular signatures on VTA cell types at a transcriptomic and epigenetic level which provide mechanistic insights about the long-term memory that follows the initial exposure to drugs of addiction.

Authors:
Submitter: Derek Hui, Graduate Student, Johns Hopkins University, Baltimore
Altuna Akalin, Ph.D., Max-Delbrück Centre for Molecular Medicine, Berlin Institute for Medical Systems Biology, Bioinformatics and Omics Data Science Platform
Laura Arguedas-Jimenez, Ph.D., Max-Delbrück Centre for Molecular Medicine, Berlin Institute for Medical System Biology, Epigenetic Regulation and Chromatin Architecture Group
Brigitte Bouman, Ph.D., Max-Delbrück Centre for Molecular Medicine, Berlin Institute for Medical Systems Biology, Computational Methodologies and Omic Analytics Group
Caroline Braeuning, Ph.D., Max-Delbrück Centre for Molecular Medicine, Berlin Institute for Medical Systems Biology, Genomics Technology Platform
Vedran Franke, Ph.D., Max-Delbrück Centre for Molecular Medicine, Berlin Institute for Medical Systems Biology, Bioinformatics and Omics Data Science Platform
Laleh Haghverdi, Ph.D., Max-Delbrück Centre for Molecular Medicine, Berlin Institute for Medical Systems Biology, Computational Methodologies and Omic Analytics Group
Alexander Kukalev, Ph.D., Max-Delbrück Centre for Molecular Medicine, Berlin Institute for Medical System Biology, Epigenetic Regulation and Chromatin Architecture Group
Oscar Marin, Ph.D., Center for Developmental Neurobiology, Institute of Psychiatry, Psychology and Neuroscience, King's College London
Eleanor Paul, Ph.D., Center for Developmental Neurobiology, Institute of Psychiatry, Psychology and Neuroscience, King's College London
Ana Pombo, Ph.D., Department of Biology, Johns Hopkins University
Mark Ungless, Ph.D., MRC Laboratory of Medical Sciences, Imperial College London

DRAFT