Name: Katherine Savell
PI Name: Bruce Hope

Email: katherine.savell@nih.gov
PI Email: bhope@intra.nida.nih.gov

Identifying the Transcriptional Fingerprint of a Drug Reward Memory

Katherine E. Savell, Rajtarun Madangopal, Drake J. Thompson, Ava Holmes, Madeline Sagona, Olivia R. Drake, Diana Q. Pham, Megan B. Brenner, Kareem D. Woods, Padmashri Saravanan, Bruce T. Hope

NIDA IRP, Behavioral Neuroscience Research Branch, Baltimore MD

Environmental stimuli linked to drug use can trigger drug-seeking and relapse long after abstinence. Maladaptive cue-drug associations are thought to be encoded in specific patterns of neurons, known as neuronal ensembles, that are activated by drug-related cues. Previous studies have shown the medial prefrontal cortex (mPFC) plays a key role in cocaine-seeking and cue-induced relapse. However, the molecular encoding of these associations within mPFC ensembles remains unclear. To answer this question, we recently developed MultipleXed Population Selection and Enrichment single nucleus RNA-sequencing pipeline (XPoSE-seq) to perform targeted snRNA-seq on cocaine relapse ensembles, which provides an unbiased screen of ensemble-specific cell types and transcriptional changes during cocaine relapse at the individual animal level.

We trained male and female Fos-mRFP rats to self-administer cocaine during twice daily 3 h sessions. Following training and 21 days of abstinence, we tested rats for cocaine seeking and collected brains. We observed reliable cocaine self-administration during training and robust cue-induced cocaine seeking following abstinence. We applied the XPoSE-seq pipeline to identify which cell types comprise the cocaine relapse ensemble and characterize the cell-type specific transcriptional signatures of cocaine relapse. After confirming cell type identities of known cell types in the region, we found that ITL5 excitatory and Sst inhibitory cell types are preferentially engaged in cocaine seeking. We characterized ensemble-specific transcriptional signatures across cell types and highlight that there are shared and distinct targets. Future work will employ transcriptional modulators to assess causal roles for these cocaine memory-specific genes in relapse and determine relevant circuits.