Name: Julie Blendy Email: blendy@pennmedicine.upenn.edu

Spatial Transcriptomics Reveals Distinct Cell Type Dynamics Following the Development of Opioid Dependence

Yihan Xie[1],
Omar Guessoum[2],
Adrienne Jo[1],
Johnathan Schug[2],
Gunnar Hoogerwerf[2],
Klaus H. Kaestner[2],
Julie A. Blendy[1]

[1]Departments of System Pharmacology and Translational Therapeutics and [2]Genetics,
Perelman School of Medicine, University of Pennsylvania

Opioid Use Disorder (OUD) is a multifaceted neuropsychiatric disorder that can arise from genetic, environmental, and neurobiological factors. Genetic variants, such as the relatively common A118G SNP in the μ-opioid receptor gene (OPRM1), have been linked to susceptibility to OUD. Mice with the equivalent Oprm1 variant, A112G, demonstrate sex-specific alterations in the rewarding properties of morphine and heroin. Females with the minor G- allele exhibit distinct patterns of functional connectivity in the opioid dependent state which is less stable compared to other groups. How this SNP specifically alters brain function, network dynamics, and structural adaptations at a transcriptional level is unknown. Single-cell RNA sequencing and other transcriptomic approaches lack the spatial resolution to appreciate regional specificity and cell-cell interactions within the opioid dependent brain. Therefore, we leverage spatial transcriptomics to identify and map gene expression patterns within the brain of A112 or G112 mice to identify region-specific molecular changes associated with genetic variance and opioid dependence. To accomplish this we developed a systematic, cross-modality, open platform to assess the cell dynamics of spatial transcriptomics (CellDynamicsST). This platform provides the analytical framework to study underlying spatial, molecular and cellular function, cell state dynamics, cellular and network connectivity. By mapping gene expression changes within the precise anatomical context of the mouse brain following opioid dependence, we provide a comprehensive view of how opioid exposure affects different regions across the brain landscape in mice with genetic variants in Oprm1 and provide a novel molecularly defined and spatially resolved opioid-dependent mouse brain atlas.