

PI Name: Ming-Fen Ho, Ph.D.

Email: ho.mingfen@mayo.edu

PI Name: Richard Weinshilboum, M.D.

Email: Weinshilboum.richard@mayo.edu

Single cell transcriptomics reveals distinct transcriptional response to oxycodone and buprenorphine by iPSC-derived brain organoids from patients with opioid use disorder

Ming-Fen Ho¹, Cheng Zhang¹, Irene Moon¹, Brandon Coombes², Joanna Biernacka², Michelle Skime³, Tyler Oesterle³, Victor Karpyak³, Kristen Schmidt⁴, Kate Gliske⁴, Quyen Ngo⁴, Cedric Skillon⁴, Marvin Seppala⁴, Hu Li¹, and Richard M. Weinshilboum¹

¹Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, MN 55905, USA; ²Department of Health Sciences Research, Mayo Clinic, Rochester, MN 55905, USA; ³Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN 55905, USA; ⁴Hazelden Betty Ford Foundation, Center City, MN 55012, USA

Background: The opioid epidemic represents a national crisis. Oxycodone is the most prescribed opioid medication in the United States, whereas buprenorphine is currently the most used drug for opioid use disorder (OUD) pharmacotherapy. Given the extensive use of prescription opioids and the global opioid epidemic, it is important to understand how these drugs modulate brain cell types at the single cell level.

Methods: We performed single nucleus RNA-seq (snRNA-seq) for iPSC-derived forebrain organoids from three male OUD subjects in response to oxycodone, buprenorphine or vehicle for seven days. The snRNA-seq data were utilized to identify differentially expressed genes following drug treatment using the Seurat integrative analysis pipeline.

Results: We used iPSC-derived forebrain organoids and single cell sequencing technology as an unbiased tool to study cell-type-specific and drug-specific transcriptional response. We analyzed 25787 cells after quality control filtering. Sixteen clusters were identified using unsupervised clustering analysis. Our results showed that oxycodone and buprenorphine displayed distinct gene expression profiles. Specifically, buprenorphine displayed significant influence on transcription regulation in astroglial cells. However, oxycodone induced type I interferon signalling in many cell types, including neural cells, in brain organoids. Finally, we used ELISA to confirm that oxycodone could induce interferon gamma concentrations in both iPSC-derived brain organoids and neurons. However, buprenorphine had no effect on interferon gamma concentrations.

Conclusions: Oxycodone induced type I interferon signalling was most pronounced in glutamatergic neurons, while buprenorphine affected transcriptional response primarily in glial cells. These results provide novel mechanistic insight into drug action at single cell resolution.