

Name: Jonathan Gewirtz, Ph.D.

Email: jgewirtz@asu.edu

Repurposing drugs for opioid use disorder (OUD) through multiomics network analysis

Despite our growing understanding of neural mechanisms underlying opioid use disorder (OUD), current pharmacological treatment options either have limited clinical utility (e.g., naltrexone) or are themselves subject to abuse (e.g., methadone and buprenorphine). Given the protracted time course of novel drug discovery, development, and approval, an alternative avenue is to repurpose existing medications. In a proof-of-concept study, we first used the gene network analysis tool Mergeomics2.0 to synthesize epigenetic (RNA-seq and ATAC-seq) and GWAS datasets from Sprague-Dawley (SD) and Heterogenous Stock (HS) rats, respectively, to identify gene networks and their key drivers associated with several rodent behavioral phenotypes of vulnerability to OUD. We next integrated these networks with a large knowledgebase of tissue- and species-specific drug gene signatures using PharmOmics to derive a list of potentially repurposable drugs. Of the top 10 candidates, five have anti-inflammatory properties and of the latter group, two are antidiabetics that increase insulin sensitivity. Finally, one of these antidiabetic drugs, metformin, also affects myelination, a process that was implicated in differential OUD vulnerability through Weighted Gene Network Analysis of our RNA-seq data. Metformin's functional profile, therefore, makes it a viable candidate for repurposing to treat OUD. To begin to test this hypothesis, we evaluated metformin's effects on morphine self-administration in male and female SD rats. Repeated s.c. injections of metformin reduced morphine self-administration (0.4 mg/kg/infusion) in females (200-mg/kg metformin) and males (275-mg/kg metformin). Metformin (200 mg/kg) also reduced subsequent economic "demand" for morphine, a measure of the persistence of seeking a drug as its "cost" is increased, in females. These findings are consistent with recent preclinical findings that metformin reduces the addiction-related effects of cocaine and ethanol. More broadly, these data demonstrate the potential utility of this approach in identifying novel putative treatments for OUD with safe profiles and a faster path to translation.

Authors:

Submitter: Jonathan Gewirtz, Professor, Arizona State University, Tempe, AZ
Montgomery Blencowe, Ph.D., University of California, Los Angeles
Andrew Harris, Ph.D., Hennepin Healthcare Research Institute
Brittany Kuhn, Ph.D., Baylor University, TX
Shirelle Liu, Ph.D., University of Minnesota, Minneapolis, MN
Peter Muelkin, B.S., Hennepin Healthcare Research Institute, Minneapolis, MN
Abraham Palmer, Ph.D., University of California, San Diego
Aarthi Ramakrishnan, M.S., Icahn School of Medicine at Mount Sinai, New York, NY
Li Shen, Ph.D., Icahn School of Medicine at Mount Sinai, New York, NY
Phu Tranh, Ph.D., University of Minnesota, Minneapolis, MN
Xia Yang, Ph.D., University of California, Los Angeles