Name: Amrit Koirala, PhD

Email: amritkoirala@bcm.edu

PI Name: Thomas Kosten, MD

PI email: kosten@bcm.edu

Deconvolution of microRNA/mRNA Networks in Brain Regions Impacted by Cocaine Use Disorder to Develop a Mechanistic Biosignature for Pharmacotherapy Response

Amrit Koirala[1,2], Sandra L. Grimm[1], Preethi Gunaratne[3], David A. Nielsen[2], Consuelo Walss-Bass[4], Cristian Coarfa[1], Thomas R. Kosten[2]

[1]Dept. of Molecular and Cellular Biology, Baylor College of Medicine;
[2]Department of Neuroscience and Dept. of Psychiatry, Baylor College of Medicine;
[3]Department of Biology and Biochemistry, University of Houston;
[4]Louis A. Faillace, MD, Department of Psychiatry and Behavioral Sciences, The McGovern Medical School of University of Texas Health Science Center at Houston

Cocaine use disorder (CUD) is a major public health problem, yet we lack FDA-approved pharmacotherapies or biosignatures for predicting treatment response. CUD significantly alters gene expression in the brain, most notably in the striatum and prefrontal/cingulate cortex. Brain-derived exosomal microRNAs (miRNAs) in blood are thought to reflect changes in brain gene networks, acting as biosignatures distinguishing CUD and control subjects. We analyzed miRNA-Seq and RNA-Seq from BA9 (13 CUD, 16 controls), miRNA-Seq from post-mortem blood of the same subjects, and miRNA-Seq from a live donor blood cohort (100 cases, 100 controls). At FDR<0.2 significance we identified 136 differentially expressed mRNAs, controlling for age, gender, PMI, RIN, and pH. Differential miRNAs were also identified from the three tissues and SigTerms software was used to infer miRNA/mRNA networks underlying CUD. Using BA9 miRNAs, we inferred networks with 7 induced miRNAs targeting 38 suppressed genes and 9 suppressed miRNAs targeting 5 increased genes. Interestingly, miR-138 was commonly induced in all three tissue sources, targeting four down-regulated genes in BA9 (*ADAMTSL3, EGFLAM, PAPPA, INHBB*). Using these 43 miR-targeted mRNAs, top pathways enriched using Gene Ontology include neurogenesis and glia differentiation. Compounds targeting these genes which could be repurposed to treat CUD include benzodiazepine, acetylcholine, and adrenergic receptor agonists. Using the live donor blood miRNAs, we built a machine classifier using Support Vector Machines that distinguished CUD vs control subjects with over 99% accuracy. Our study showcases the potential of miRNAs as both biosignatures and as a guide for repurposing of pharmacotherapies for CUD.