Lineage Tracing of Human Exosomal microRNAs to Brain Regions Impacted by Cocaine Use Disorder to Develop a Mechanistic Biosignature for Pharmacotherapy Response

An Ye1, Emily Mendez2, Brandon J. Mistretta3, Micah Castillo3, Sakuni Rankothgedera3, Laura Stertz2, David A. Nielsen1, Gabriel R. Fries2, Katherine Najera2, Thomas D. Meyer2, Consuelo Walss-Bass2, Preethi Gunaratne3, Cristian Coarfa4, Thomas R. Kosten1

1Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, and Michael E. DeBakey VAMC, Houston, Texas; 2Department of Psychiatry and Behavioral Sciences, University of Texas Health Science Center at Houston, Houston, Texas; 3Department of Biology and Biochemistry, University of Houston, Houston, Texas; 4Department of Molecular & Cellular Biology, Baylor College of Medicine, Houston, Texas

Background: Rodent brain epigenetics show abnormal microRNA (miRNA) levels following chronic cocaine, which also releases exosomal (EXO) miRNAs into the blood. Rationale: Brain-derived EXO miRNAs in blood of cocaine use disorder (CUD) patients may reflect changes in their targets genes underlying brain abnormalities induced by CUD, and provide biosignatures for changes in brain proteins associated with brains regions impacted by CUD. These proteins can become new medication targets for reversing abnormalities in the brain’s gene pathways.

Methods/Hypothesis: To identify miRNAs relevant to CUD we matched post-mortem brain mRNAs to brain miRNAs that significantly distinguished CUD from normal controls (NC) in cocaine-disrupted brain areas (e.g., nucleus accumbens (putamen) and cortical BA9). We developed a “biosignature” by matching post-mortem blood EXO miRNAs back to these “distinguishing” BRAIN miRNA. Results/Discussion: We have completed post-mortem miRNA and mRNA bulk sequencing analyses on BA9 (12 CUD vs 15 NC) and Putamen (3 CUD vs 3 NC). We found a post-mortem miRNA biosignature of three down-regulated (miR-424-5p, miR-376a-3p, miR-126-5p) and two up-regulated (miR_211_5p and miR_1305) blood EXO miRNAs. We also found that in an independent sample, these five miRNA biosignature distinguished 50 CUD patients from 50 NC. By integrating the miRNA biosignature’s target genes with the Broad Institute Connectivity Map (CMap), we found four previously tested CUD medications that could show greater success, if targeted to CUD patients showing abnormal levels of these five biosignature miRNAs, and, furthermore, uncovered several new druggable targets for repurposing of FDA approved drugs.