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A Multi-omics Perspective on Substance Use Disorders

Dr. Cristian Coarfa is currently an Associate Professor in the Molecular and Cellular Biology, and Co-Director for Multi-Omics Data Analysis in the Biostatistics and Informatics Shared Resource (BISR) of the Dan L Duncan Comprehensive Cancer Center and the Advanced Technology Cores at Baylor College of Medicine. His research focuses on achieving biological insight via integrative analysis, interpretation, and visualization of deep multi-omics profiling data. He has developed methods for integration of genetic and epigenetic variation, reference pipelines for epigenetic assays, and bioinformatic tools for high-throughput reads mapping and structural variants detection.

Dr. Coarfa earned his B.Sc in 1998 from POLITEHNICA University in Bucharest in Computer Science, and a Ph.D. in 2007 in Computer Science from Rice University, with additional Postdoctoral training from Baylor College of Medicine. He co-authored over 250 publications in the field of computational biology and high-performance computing. His work yielded new insights into the prostate cancers transcription regulators SPOP and GATA2, CPT1B as a driver of metabolic dysregulation in bladder cancer, regions of systemic methylation in human genome, and disease endotypes with clinical relevance in Tuberculosis.

Abstract: To understand mechanisms and identify potential targets for intervention in the current crisis of opioid use disorder (OUD), postmortem brains represent an under-utilized resource. To refine previously reported gene signatures of neurobiological alterations in OUD from the dorsolateral prefrontal cortex (Brodmann Area 9, BA9), we explored the role of microRNAs (miRNA) as powerful epigenetic regulators of gene function. Building on the growing appreciation that miRNAs can cross the blood-brain barrier, we carried out miRNA profiling in same-subject postmortem samples from BA9 and blood tissues. miRNA-mRNA network analysis showed that even though miRNAs identified in BA9 and blood were fairly distinct, their target genes and corresponding enriched pathways overlapped strongly. Among the dominant enriched biological processes were tube development and morphogenesis, and pathways related to endothelial cell function and vascular organization. Using correlation network analysis we identified cell-type specific miRNA targets, specifically in astrocytes, neurons, and endothelial cells, associated with OUD transcriptomic dysregulation. Our

miRNA-mRNA networks enabled identification of novel pharmacotherapeutic interventions for OUD, particularly targeting the TGFß-p38MAPK signaling pathway. Leveraging a collection of control brain transcriptomes from the Genotype-Tissue Expression (GTEx) project, we identified correlation of OUD miRNA targets with TGFß, hypoxia, angiogenesis, coagulation, immune system and inflammatory pathways. These findings support previous reports of neurovascular and immune system alterations as a consequence of opioid abuse and shed new light on miRNA network regulators of cellular response to opioid drugs. Single nuclei analysis in postmortem BA9 tissue revealed a global reduction in cell-cell communication in opioid users, with NRXN-NLGN identified as a common decreased L/R pair. Interestingly, endothelial cells appeared to be the only cell type gaining communication as revealed by incoming ligand/receptor pairs (Figure 6B), with APP-CD74 identified as a L/R pair gained from multiple source cell types. Overall, our work reveals the discovery potential of combining post-mortem brains as a biological source with rich multi-omic profiling in elucidating dysregulation mechanisms and potential interventions in OUD.