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Biomarker Discovery in Peripheral Blood Demonstrating Brain Relevant Mechanistic Convergence in Opioid Exposure

This talk will describe a biomarker discovery strategy that leverages peripheral blood to index brain-relevant mechanisms and predict treatment response in methamphetamine use disorder. As an example of this broader strategy, we present our work on recent opioid exposure, which leaves measurable biological signatures, yet clinically scalable biomarkers of such exposure remain limited. DNA methylation (DNAm) in peripheral blood is a well established marker of environmental and substance related exposures, motivating our investigation into its utility as a biomarker of recent opioid medication use.

We conducted ancestry and sex stratified epigenome wide association studies (EWAS) in two cohorts with whole blood DNAm and harmonized medication data (Sister Study: N = 2,749; GuLF Study: N = 1,479), and integrated published summary statistics from two additional cohorts (ALHS and FHS). Meta analysis of 10,684 participants identified 15 CpG sites associated with recent opioid use at FDR < 0.05, mapping to genes including SUSD5, NOTCH1, PARVA, MGRN1, and NACC1.

To evaluate biological relevance, we compared these DNAm associations with a multi omic gene network derived from GWAS of opioid use disorder and opioid misuse, coupled with transcriptomic, proteomic, and epigenetic data from postmortem dorsolateral prefrontal cortex (DLPFC) of individuals who died of opioid overdose and matched controls. Remarkably, 37 of the top 50 high confidence network genes contained CpGs with nominal blood based EWAS associations ($p < 0.05$), and permutation testing confirmed that this overlap was unlikely by chance ($p = 0.0017$).

These findings demonstrate strong cross tissue coherence between peripheral DNAm and central molecular pathways implicated in opioid exposure, supporting DNAm biomarkers as scalable clinical tools for monitoring drug use and aligning with the symposium's focus by informing treatment response assessment and future trial design.

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