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Building a cellular platform to model addiction stages in the context of psychiatric genetic risk

Substance use disorders (SUDs) are clinically heterogeneous conditions characterized by substantial genetic overlap with psychiatric disorders. Cellular models provide a powerful approach for dissecting the contributions of genetic and environmental factors to these complex disorders. This project aims to characterize molecular and cellular signatures associated with different stages of SUD, including acute use, chronic dependence, remission, and relapse, using multimodal phenotypic profiling (e.g., multielectrode arrays and microscopy-based biomarkers). In parallel, we will integrate patient-derived cellular models with genetic and clinical data, focusing on risk for psychiatric disorders to identify molecular and cellular subtypes of SUDs. Currently, we are developing a high-throughput pipeline for multimodal phenotypic analyses for iPSC-derived brain cell types. At the same time, we are building a cohort based on existing data and biospecimens from the NIDA Genetics Consortium. We will generate induced pluripotent stem cell (iPSC)-derived neurons and profile native lymphocytes from individuals with SUDs and matched controls. We will test the hypothesis that distinct SUDs are associated with specific genetic risk profiles for neuropsychiatric traits and cellular phenotypes, including differences in epigenetic state, gene expression, and functional responses to drug exposure. Integrated molecular and functional assays will be combined with polygenic risk scores and clinical data. Machine learning approaches will be used to define molecular subtypes and link cellular phenotypes to genetic variation and clinical features. Together, these studies will establish a framework connecting genetic risk to neuronal function and clinical heterogeneity in SUDs, supporting the development of targeted strategies to co-treat SUDs and co-occurring psychiatric disorders.

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