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Human Postmortem-Derived Brain Models of Drug Exposure in Substance Use Disorders

Patient-derived brain cellular models have high potential to study human brain physiology and disease. The use of these models in substance use disorders (SUD) has been limited. While these studies shed light on effects of drugs in SUD, how well the models recapitulate the actual drug-induced brain alterations, genomic landscape and cell function remains to be determined.

We engineered a novel induced pluripotent stem cell (iPSC)-neuronal model derived from postmortem fibroblasts, and directly compared these to isogenic brain tissue from the donor source. We assessed the maturity of the neurons across differentiation using RNA cell type and maturity deconvolution analyses as well as DNA methylation epigenetic clocks trained on adult and fetal human tissue. Gene expression profiles in morphine- or cocaine-treated cells paralleled those observed in brain of the respective opioid and cocaine overdose subjects they were derived from, including alterations in cell communication and signaling transduction.

While extremely valuable to determine the effect of drugs in naïve-cells, the pluripotency induction process clears many disease-related epigenetic signatures that are acquired during life and that are important for understanding SUD mechanisms. As an alternative to iPSC-neurons, we are currently using direct conversion of postmortem fibroblasts into iNeurons to directly generate neurons with mature marker expression and functionality, thus maintaining many of the epigenetic signatures from the source tissue, including those related to drug-induced alterations. Using iNeurons, we are investigating mechanisms of opioid and cocaine-induced gene regulation and evaluating the extent to which iNeurons can recapitulate postmortem brain alterations, compared to iPSC-neurons.

Studies of human postmortem-derived brain models of drug exposure hold promise for both genetic (iPSC-derived) and epigenetic (direct differentiation) studies that shed light on the molecular mechanisms of drug effects and propagate discovery of novel therapies aimed at reversing the consequences of chronic toxicity and overdose.

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