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Identification of disease signatures and discovery of novel therapeutics in schizophrenia and bipolar disorder using patient induced pluripotent stem cell (iPSC)-derived neurons

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Recent advances in stem cell biology and chemical biology provide unique opportunities to investigate cellular processes that are aberrant in schizophrenia and bipolar disorder. The ability to generate induced pluripotent stem cells (iPSCs) from patient fibroblasts enables the generation of neuronal cells with patients' genotypes. Phenotypic and gene-expression studies of these neuronal cells in the presence of annotated small-molecule perturbagens will allow for a systematic investigation to elicit disease-related phenotypes. In addition, signaturebased high-throughput screens can identify novel probes to investigate disease biology and provide leads for therapeutic development. We are reprogramming iPSCs from patients with schizophrenia and bipolar disorder as well as from matched controls. We derive neural progenitor cells (NPCs) from the iPSCs, and then furtherdifferentiate them along the neuronal lineage. We will acquire high-content images of NPC-derived neuronal cells and label them with neuronal subtype-specific markers as well as a range of cellular stains. We will analyze the high-content images using algorithms that quantify a range of cellular and sub-cellular features (e.g. numbers, lengths, branching patterns of dendrites, quantity/localization of mitochondria etc.). In addition to acquiring high-content images of neuronal cells under normal conditions, we will analyze images of neuronal cultures treated with small-molecule perturbagens. We will use an annotated library of 300 small molecules comprised of known inhibitors/activators of various signaling pathways as well as small molecules/drugs that modulate neuronal and glial biology. While disease-related phenotypic features may not be apparent at baseline, perturbation of specific signaling pathways may expose cellular deficits inherent to the biology of the disease neurons. We will use machine-learning algorithms to identify features that distinguish schizophrenia and bipolar disorder neurons from those derived from healthy controls. If a specific small molecule elicits a different phenotypic response in disease neuronal cells vis-àvis control cells, we will carry out RNAi knockdown of the target to recapitulate the different effects observed with small molecules. The identification of differential responses to small molecule/RNAi will give important clues on the underlying pathways that may be aberrant in the disease neuronal cells. When we identify robust disease signatures using this methodology, we will carry out high-throughput screens to find small molecules that "normalize" or modulate the disease signature. These signature-based screens can generate new tools to investigate the disease biology and provide leads for therapeutic development.