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Studying Synaptic Transmission Under Opioid Exposure Using hiPSC-derived Midbrain Model and Hyperspectral Fluorescence Lifetime Imaging

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There is an urgent need to address the current public health crisis of opioid abuse and overdose deaths through development of effective treatments for opioid use disorder (OUD) and non-addictive therapeutics to manage pain. Ultimately, achievement of these goals would be greatly facilitated by the existence of novel ex-vivo models that recapitulate key features of neurobiology underlying the addictive process using human cells and advanced imaging systems that can monitor the interactions between multiple neurotransmitter actions driving opioid responses and reward pathways. We have been developing methods to recapitulate neuronal pathways in the ventral tegmental area (VTA) and nucleus acccumbens core (NAc), which have long been recognized to form the basis of substance abuse disorders. Specifically, we used an additive manufacturing approach based on 3D bioprinting of human induced pluripotent stem cells (hiPSCs) to establish 3D cultures within brain-mimetic scaffolds. Moreover, use of an innovative, self-healing biomaterial as a printing medium and 3D culture scaffold enables “stitching” of unique neuronal tissues constructs into integrated, yet regionally defined, complex networks. In the future, we aim to develop a TIRF (Total Internal Reflection Fluorescence) microscopy technique to probe agonist-dependent dimerization of MOR (human μ-opioid receptor) at the single-molecule level and a hyperspectral and lifetime imaging system to monitor the dynamics of dopamine, GABA, glutamate and Ca2+ simultaneously. Together, these new imaging methods will enable dynamic monitoring of the effects of opioids, and other small-molecule therapeutics, on the neuronal circuitry underlying addictive processes. Overall, we expect these technological innovations to provide crucial tools for development of new therapeutics which can effectively combat the opioid crisis.