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Prediction of Metabolism-Induced Neurotoxicity on a 384PillarPlate

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Abstract

Metabolism of compounds including neurotoxins primarily occurs in the liver by a variety of drug-metabolizing enzymes (DMEs) followed by a series of downstream responses. Unmodified (or parent) neurotoxins are transported into human hepatocytes through several influx transporters or via passive diffusion and undergo Phase I and Phase II biotransformation by DMEs before they are cleared. Neurotoxins and their metabolites generated from human hepatocytes could potentially lead to the toxic effects on neural stem cells (NSCs) as the reactive metabolites have potential for producing reactive oxygen species (ROS), which can lead to irreversible oxidative damage to NSCs via lipid peroxidation, DNA, mitochondrial and protein damage, and endoplasmic reticulum (ER) stress. Our goal is to evaluate molecular actions of compounds and their metabolites within NSCs and their cellular consequences by a suite of high-content toxicology assays. A 3D NSC culture on a 384PillarPlate will be combined with human liver cell aggregates expressing cytochrome P450s in an ultralow attachment (ULA) 384-well plate to demonstrate metabolism-induced neurotoxicity. Model compounds will be added in the 384-well plate containing liver cells and sandwiched with 3D NSCs on the 384PillarPlate. High-content imaging assays will be performed to evaluate the effect of compounds and their metabolites in NSCs to analyze the metabolism-induced neurotoxicity.