Development and Validation of a Highly Efficient Multi-Battery in vitro Testing Platform for the Assessment of Developmental Neurotoxicity

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INTRODUCTION

Humans are exposed to a multitude of potentially harmful pesticides and chemicals. Only a small percentage of the more than 350 000 chemicals marketed globally have been extensively tested on human physiology. Traditional approaches for assessing the risks of pesticides and chemicals reply primarily on animal models and are very expensive, time-consuming, ineffective and non-predictive of the effects on humans. There is an urgent need for an improved animal-free risk assessment methods for testing. Ananda Devices develops and manufactures nervous system-on-a-chip technologies deployed by pharmaceutical, chemical and cosmetics (PCC) industries for in vitro safety and efficacy testing during compound development. We have developed the NeuroHTSTM device, a high-throughput screening nervous system on-a-chip platform that provides predictive insights on the effect of compounds on the neuronal system. The new platform accommodates 3000 neurons per plate, enables generation of 7-10 quantitative readouts per sample and possible high-powered top-down screening approaches for risk assessment.

METHODOLOGY

Recently, we have developed a battery of 10 tests (astrocyte differentiation, oligodendrocyte differentiation, neuronal differentiation, neurite outgrowth, NS/PC proliferation, NPC apoptosis, dendrite formation, synaptogenesis, neuronal maturation and neuronal subtype differentiation) to comprehensively describe effects of compounds on key adverse event pathways in the neurodevelopmental processes. More importantly, all of the 10 tests can be conducted on one single platform, which enables high levels of standardisation as well as improved comparability across tests. This approach simplifies key user experiences and streamlines compound testing processes. In this research, we validated the 10 tests using human neurons exposed to methylmercury in the NeuroHTSTM platform.

RESULTS

We observed highly sensitive and significant changes to neuronal morphological measures and comprehensively characterised the neurodevelopmental toxicities. We measured neurite length, thickness, straightness, viability, neuron developmental types along with 10+ other parameters. With the data generated, we clearly identified the most influential adverse outcome pathway affected by mercury.

DISCUSSION

This testing workflow can be applied to any future compound development for predictive testing of neurodevelopmental toxicity. The developmental neurotoxicology tests performed with the NeuroHTSTM device are highly cost-effective and generate relevant and predicative results to derisk compound development early on during the process. The platform fulfils a major need for neurodevelopment testing as an alternative to animal testing.