Evolving the Paradigm: In Vivo to In Vitro Extrapolation
Microphysiological Systems-Enabled 'Virtual Human' Hazard Assessment: A Concept

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Overview

Animal hazard assessment studies have effectively identified many noxious agents in our environment enabling us to protect the public's health. That protection has come at a significant price including the use of animals in studies that intentionally cause them harm, an inability to keep up with the pace of production of those agents, and the challenges of extrapolating animal effects to potential human effects. Efforts to develop high-throughput mechanistic bioactivity screening approaches have been successful at generating lots of interesting data but marginally effective at changing contemporary approaches to hazard assessment. The current approach could benefit from a paradigm that qualifies and bridges mechanistic bioactivity to human in vivo outcomes with a physiologically and human-derived assessment platform.

The emergence and rapid progress of more in vivo-relevant microphysiological systems (MPS) using human-derived cells presents an unprecedented opportunity to build that virtual human platform. A rapid proliferation of target tissue and organ-based systems populated by iPSC-derived human cells that replicate dynamic in vivo biology is enabling the application of translational measures in genetically diverse backgrounds over timespans that rival animal studies. A portfolio of these systems used strategically could increase confidence in the human in vivo relevance of high-throughput bioactivity screens.

No one MPS or even a collection of existing MPS can replicate the biological integration and complexity of a living mammalian system (e.g., an animal or a human patient). Accordingly, we need to rationalize the most important biological systems to model in a portfolio of MPS that would capture important liabilities for patients. That rationalization is a unique exercise in 'in vivo to in vitro extrapolation'. We will explore approaches to that exercise in this discussion.