Hassan Rashidi, UCL Great Ormond Street Institute of Child Health, University College London, London, UK

"Pros and cons of adding an extra dimension to predict drug-induced hepatotoxicity".

There is a high attrition rate of promising drug candidates in post marketing stages due to adverse drug reactions (ADRs) [1-2]. While animal safety tests have been introduced as a mandatory requirement before a compound can proceed into clinical development, such animal models are often poor predictors for human toxicity events due to interspecies differences in liver-specific function [3].

The use of primary human hepatocytes (PHHs) is considered the gold standard *in vitro* model for drug toxicity testing [4], however, their availability and transient *ex vivo* phenotype has limited their wide-spread application in predicting toxicity in pre-clinical drug development [5]. Consequently, a variety of alternative 2-dimensional (2D)-models have been developed including platforms based on hepatoma cell lines [6,7] and human pluripotent stem cell (hPSC)-derived hepatocyte-like cells [8]. Although these models have allowed for the *in vitro* analysis of several mechanisms of DILI such as oxidative and endoplasmic reticulum stress and mitochondrial toxicity, none has been able to accurately predict drug-induced liver injury (DILI).

Recently, we developed a novel platform to generate hPSC-derived 3D hepatospheres under *xeno*-free and GMP-ready conditions [9]. Unlike their 2D counterpart, the 3D hepatospheres downregulate expression of alpha-fetoprotein as a foetal marker and remained metabolically active and drug-inducible for over a year in culture providing a better *in vitro* platform to evaluate long-term effect of new lead compounds in more physiologically relevant setup. In addition, hPSC-derived 3D hepatospheres showed higher sensitivity to drug toxicity compare to 2D counterparts.

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