HepaRG spheroid models for predicting liver toxicity

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Organisation

Name of the organisation Vrije Universiteit Brussel (VUB)
Department Department of Pharmaceutical and Pharmacological Sciences
Country Belgium
Geographical Area Flemish Region

SCOPE OF THE METHOD

The Method relates to	Human health
The Method is situated in	Translational - Applied Research
Type of method	In vitro - Ex vivo
Species from which cells/tissues/organs are derived	Human
Type of cells/tissues/organs	Immortalized hepatic cell line

DESCRIPTION

Method keywords

HepaRG
spheroids
liver cells
hepatic cell line
3D in vitro model
liver model

Scientific area keywords

Cholestatic drug-induced liver injury
cDILI
Drug-induced cholestasis index
DICI
predictive toxicology

Method description

Cholestatic drug-induced liver injury (cDILI) is a frequent reason for drug failure and withdrawal during premarketing and postmarketing stages of drug development. Strategies for reliable detection of cDILI in early drug development are therefore urgently needed. The drug-induced cholestasis index (DICI) concept was previously introduced as

a tool for assessing the cholestatic potential of drug candidates. DICI is calculated as the ratio between the viability values obtained in drug-treated liver cells in the presence and absence of bile acids. The present in vitro study was set up to investigate the applicability of DICI in a novel high-throughput and large sample setting. Furthermore, the improvement of the predictivity of the DICI by introduction of advanced modeling was explored. Fifty-eight well-documented drugs were selected and categorized as drugs inducing cDILI, non-cholestatic DILI (ncDILI), and not inducing DILI (non-DILI). Differentiated HepaRG cells were handled according to the manufacturer's instructions. Briefly, thawed cells were centrifuged and resuspensed in MHTAP medium. Cells were seeded in ultra-low attachment plates. Plates were maintained for 1?day on a tilting stand to facilitate the aggregation of the cells and improve uniform spheroid formation at 37 °C under a humidified atmosphere containing 5?% CO2. Cell culture medium was replaced with MHPIT medium and cultured for 7 additional days with cell culture medium renewal every 2–3 days until spheroid formation and maturation. Morphological features and viability of the fully formed spheroids were assessed by phase-contrast imaging at days 0 following spheroid generation (i.e., 8 days after seeding). The average diameter of the spheroids at day 0 after spheroid generation was 189.1 ± 9.4 µm. HepaRG spheroids showed BSEP protein expression as an indicator of their suitability to investigate cholestatic liability.

Lab equipment

Centrifuge, Incubator, Confocal imaging system.

Method status

Published in peer reviewed journal

PROS, CONS & FUTURE POTENTIAL

Advantages

- The 3D culturing has shown to increase the similarities in metabolic activities and functional characteristics to the human liver,
- HepaRG cells in 3D spheroid culture show increased sensitivity to DILI drugs compared to 2D cultures, showing high potential to detect cholestatic drugs, based on cytotoxicity and DICI,
- HepaRG spheroids have showed to improve hepatic functionality and metabolism compared to 2D, exhibiting liver specific functions and increasing the sensitivity to hepatotoxic compounds, ultimately allowing for accurate toxicity testing,
- Possibility for chronic exposure up to 14 days compared to the commonly assessed 24–72 hours in monolayer models addressing drug-induced cholestasis index (DICI).

REFERENCES, ASSOCIATED DOCUMENTS AND OTHER INFORMATION

Links

Optimization of the drug-induced cholestasis index based on advanced modeling f…
Prof. Mathieu Vinken - Team
IVTD - VUB

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