Assessment of the cholestatic potential of drugs using primary human hepatocyte spheroids

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Organisation

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Department Pharmaceutical and Pharmacological Sciences

Specific Research Group or Service In Vitro Toxicology and Dermato-Cosmetology

Country Belgium

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
Specify the type of cells/tissues/organs	Primary human hepatocytes

DESCRIPTION

Method keywords

primary human hepatocytes

spheroids

ATP quantification

cholestatic index

Scientific area keywords

cholestasis
in vitro toxicology
hepatology
cholestatic liability

Method description

This method describes a very reliable and robust *in vitro* model for the screening of the cholestatic liability of drugs and other chemical entities. The 3D spheroids generated from primary human hepatocytes can be cultivated up to 28 days, allowing long-term exposures which can depict otherwise undetectable toxicity. After spheroid generation, these are exposed to the test drug in the presence or in the absence of a 30x concentrated mixture of the 5 most relevant bile acids (BA) up to 28 days, with medium renewal every 2 days. At the pre-established time-points, cell viability is checked using an ATP quantification kit and the cholestatic potential of the studied drug is determined by means of the Cholestatic Index (CIx). This is calculated as the ratio between the ATP content in spheroids treated with drug plus BA and the spheroids treated only with the drug. A CIx equal or below 0.8 suggests increased cholestatic liability for the tested drug.

Lab equipment

Biosafety cabinet ;
Centrifuge with rotor for plates ;
Microscope ;
Incubator at 37ºC with controlled atmosphere ;
Plate reader for bioluminescence.

Method status

Still in development

PROS, CONS & FUTURE POTENTIAL

Advantages

Increased similarity to the *in vivo* situation ;

Allows studying long-term effects.

Challenges

Expensive methodology.

Future & Other applications

The method has not yet been tested with chemicals other than drugs, so the IVTD group is further studying this possibility.

REFERENCES, ASSOCIATED DOCUMENTS AND OTHER INFORMATION

References

Characterization of primary human hepatocyte spheroids as a model system for drug-induced liver injury, liver function and disease. Bell CC et al. Sci Rep. 2016 May 4;6:25187. doi: 10.1038/srep25187

Three-Dimensional Spheroid Primary Human Hepatocytes in Monoculture and Coculture with Nonparenchymal Cells. Baze AC et al. Tissue Eng Part C Methods. 2018 Sep;24(9):534-545. doi: 10.1089/ten.TEC.2018.0134

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