Hepatocyte-based in vitro model for drug-induced cholestasis

Commonly used acronym: *DICI-MODEL*

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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	Human liver tissue (from resections during surgery)

DESCRIPTION

Method keywords

bile acids

sandwich-cultured human hepatocytes

in vitro model

Scientific area keywords

Hepatotoxicity

Drug-induced liver injury (DILI)

Drug-induced cholestasis

Method description

Sandwich-cultured hepatocytes are exposed to test compounds (e.g. drug candidates) or known hepatotoxicants (as controls) both in the absence and in the presence of a mixture of physiologically relevant bile acids. After 24h, decreased hepatocyte viability and functionality in the presence of bile acids is expressed as a drug-induced cholestasis index (DICI) value. DICI values < 0.8 are indicative of possible cholestatic liabilities and a safety margin can be calculated provided *in vivo* therapeutic exposure data (or estimates) are available.

Lab equipment

Biosafety cabinet ;

Plate reader (absorbance) ;

Incubator.

Method status

Internally validated

Published in peer reviewed journal

PROS, CONS & FUTURE POTENTIAL

Advantages

Early detection of cholestasis potential of medicines and environmental toxicants.

Challenges

Availability and characterisation of plateable human hepatocytes.

Modifications

Additional endpoints (ATP instead or urea, bile acid profiles) are under development.

Future & Other applications

Could extrapolate concept of co-incubation with endogenous compounds to other organs / tissues.

REFERENCES, ASSOCIATED DOCUMENTS AND OTHER INFORMATION

References

Chatterjee S, Richert L, Augustijns P, Annaert P. Hepatocyte-based in vitro model for assessment of drug-induced cholestasis. Toxicol Appl Pharmacol. 2014 Jan 1;274(1):124-36. doi: 10.1016/j.taap.2013.10.032. Epub 2013 Nov 7. PubMed PMID: 24211272.

Chatterjee S, Richert L, Augustijns P, Annaert P. Hepatocyte-based in vitro model for assessment of drug-induced cholestasis. Toxicol Appl Pharmacol. 2014 Jan 1;274(1):124-36. doi: 10.1016/j.taap.2013.10.032. Epub 2013 Nov 7. PubMed PMID: 24211272.

Oorts M, Baze A, Bachellier P, Heyd B, Zacharias T, Annaert P, Richert L. Drug-induced cholestasis risk assessment in sandwich-cultured human hepatocytes. Toxicol In Vitro. 2016 Aug;34:179-186. doi: 10.1016/j.tiv.2016.03.008. Epub 2016 Apr 2. PubMed PMID: 27046439.

Links

Link to initial publication on this topic

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