Human hepatic organoid model to test for drug-induced liver fibrosis

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Organisation

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SCOPE OF THE METHOD

The Method relates to	Human health
The Method is situated in	Basic Research, Translational - Applied Research
Type of method	In vitro - Ex vivo
Specify the type of cells/tissues/organs	Hepatocytes

DESCRIPTION

Method keywords

Hepatic organoid
spheroids
drug-induced liver injury
DILI
Hepatic stellate cell
HepaRG
HSC co-culture

Scientific area keywords

Liver fibrosis
liver disease
hepatocytes
Toxicity testing

Method description

This model is a 3D human co-culture model where both hepatocyte functionality and HSC quiescence can be maintained for at least 21 days. This novel system allows hepatotoxicity testing and can detect drug-induced as well as hepatocyte-dependent HSC

activation, thereby representing an important step forward towards *in vitro* compound testing for drug-induced liver fibrosis.

Lab equipment

- Incubator,
- Orbital shaker,
- Confocal fluorescent microscope.

PROS, CONS & FUTURE POTENTIAL

Advantages

- The spheroid formation procedure is highly reproducible.
- The model can be used for single or repeated dose exposure.
- The hepatic organoids are sensitive to the nature of the compounds.
- The model can be used to identify compounds that induce fibrosis, a drug-induced liver injury (DILI) rarely addressed *in vitro.*
- The model represents a substantial improvement in terms of cost, animal use and prediction of liver fibrosis in human.

Challenges

- The culture depends on primary human HSCs, although also hiPSC-HSCs can be used.
- Only one cellular source of hepatocyte-like cell is used.
- One needs to test the cell repellent plates before use since HSCs do attach to many cell-repellent or low cell attachment plates

Modifications

Similar ratios can be used for primary liver cells as well (for mouse Hepatocyte/HSC cultures see Mannaerts, I., Eysackers, N., Anne van Os, E., Verhulst, S., Roosens, T., Smout, A., Hierlemann, A., Frey, O., Leite, S.B., and van Grunsven, L.A. (2020). The fibrotic response of primary liver spheroids recapitulates *in vivo* hepatic stellate cell activation. Biomaterials 261, 120335.)

Future & Other applications

- The model could be used to further optimize the AOP of liver fibrosis.
- The model could stimulate the development of culture models representative of fibrosis in other organs such as lung and kidney, since these share common mechanisms.

REFERENCES, ASSOCIATED DOCUMENTS AND OTHER INFORMATION

References

S.B. Leite, T. Roosens, A. El Taghdouini, I. Mannaerts, A.J. Smout, M. Najimi, E. Sokal, F. Noor, C. Chesne, L.A. van Grunsven Novel human hepatic organoid model enables testing of drug-induced liver fibrosis *in vitro*. Biomaterials, 78 (2016), pp. 1-10

Links

Liver cell biology research group

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