

A mechanistically-anchored and human stem cell-based in vitro test battery for assessing liver steatogenic potential of chemicals

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Organisation

Name of the organisation Vrije Universiteit Brussel (VUB)

Specific Research Group or Service

In Vitro Toxicology and Dermato-Cosmetology (IVTD)

Country Belgium

Geographical Area Brussels 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
Specify the type of cells/tissues/organs	human skin-derived precursor cells differentiated into hepatic cells (hSKP-HPC)

DESCRIPTION

Method keywords

adult stem cells
in vitro
test battery
Adverse outcome pathway
AOP
NAM
new approach methodologies
Stem cells
tiered approach

Scientific area keywords

chemical toxicity
Steatosis
hepatic cells
safety assessment
fatty liver disease

Method description

Fatty liver disease, which can result from various factors including chemical exposure, is an increasing clinical concern. A key event in its development is steatosis, referring to the accumulation of lipids within hepatocytes. To enable early detection of chemical-induced liver steatosis, we developed a mechanistically-anchored, human-relevant new approach methodology (NAM). This NAM consists of a 2-tiered *in vitro* test battery, aligned with the adverse outcome pathway (AOP) network for steatosis, and utilizes human skin-derived precursor cells differentiated into hepatic cells (hSKP-HPC), previously shown to be responsive to steatogenic triggers. In total, 6 well-known steatogenic compounds, including 3 pharmaceuticals, a pesticide, and 2 plasticizers alongside 2 non-steatogenic chemicals were tested over a 72-hour period. Tier 1 evaluated transcriptional changes in key lipid metabolism pathways, and modulations were observed in nuclear receptors (peroxisome proliferator-activated receptor), fatty acid uptake (fatty acid translocase), de novo lipogenesis (diacylglycerol acyl transferase 2, fatty acid synthase and stearoyl-CoA desaturase 1), as well as in VLDL secretion (apolipoprotein B100). Tier 2 assays assessed and confirmed downstream functional disruptions in fatty acid uptake and lipid accumulation as ultimate specific key events for steatogenic chemicals. Overall, this human stem cell-based NAM offers a promising tool for supporting early hazard identification of steatogenic chemicals across diverse sectors, bridging mechanistic insights to outcomes relevant to the initiation of fatty liver disease.

Lab equipment

- Cell culture facilities,
- CellTiter-Glo kit,
- Flow cytometer,
- Microscope.

Method status

Published in peer reviewed journal

PROS, CONS & FUTURE POTENTIAL

Advantages

- Human stem cell-derived hepatic cell models offer an unlimited cell source, capture population diversity, and show the ability to detect idiosyncratic liver toxicities, making them valuable tools for both academic research and regulatory safety assessments.
- Among them, hSKP-HPC cells have previously demonstrated to be able to express typical fatty liver markers and accumulate intracellular lipid droplets upon exposure to steatogenic pharmaceuticals.
- hSKP-HPC cells possess the necessary cellular machinery required to recapitulate steatosis, supporting their application in NAMs for hazard identification of steatogenic chemicals.
- This strategy offers a targeted and mechanistically informed approach for supporting the early detection of a chemical's steatogenic potential. Tier 1 serves as an initial screening to identify potential pathways that contribute to a chemical's steatogenic properties. Tier 2 quantifies functional changes in steatogenic-associated anabolic pathways, adding weight to the evidence and enhancing the predictive performance of the *in vitro* test battery.

Challenges

While hSKP-HPC cells have previously been shown to be suitable for liver toxicity assessments, these may have certain limitations in fully reproducing the intricacies of

mitochondrial function and regulation.

Future & Other applications

The NAM holds promise for supporting early hazard screening in the safety assessment of pharmaceuticals, industrial chemicals and environmental contaminants, bridging mechanistic insights to outcomes relevant to the initiation of fatty liver disease.

REFERENCES, ASSOCIATED DOCUMENTS AND OTHER INFORMATION

Links

[A mechanistically-anchored and human stem cell-based in vitro test battery for ...](#)
[Prof. Mathieu Vinken - Team](#)
[IVTD Research Group](#)

Other remarks

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