CN-BIO

2021 WEBINAR SERIES

Liver-on-Chip and *in Silico* Modeling for Quantitative Drug Metabolism Studies

Q&A

A full run down of questions & answers from our September 16th webinar

Abbreviations

IVIVE - *in vitro* to *in vivo* extrapolation

OOC - Organ-on-a-chip

PK - Pharmacokinetic

FM - Fraction metabolised

Q&A participants

Dr Nicolo Milani

Postdoc Scientist
Hoffmann-La Roche

Dr Audrey Dubourg

Product Manager
PhysioMimix™ OOC, CN Bio

Another question?

Drop an email to one of our experts - **sales@cn-bio.com**

Missed the webinar?

Watch an on demand - **recording of the webinar here**

Questions

Q1

Q: What biological improvements does Liver-on-a-chip provide to improve IVIVE (*in vitro* to *in vivo* extrapolation)?

A: Dr. Nicolo Milani, Postdoc Scientist, Hoffmann-La Roche.

The PhysioMimix™ Single-Organ microphysiological system creates a more physiological-like environment in the Liver-on-a-chip through the use of cell perfusion. This leads to a better drug clearance, therefore improving our IVIVE.

Another big and potentially important advantage of the liver-on-a-chip system is the long-term incubation and cell longevity that it offers. Here the experimental set-up requires the liver tissue to be viable and functional for four days and more, which traditional liver models do not allow. Using CN Bio's liver-on-a-chip system makes it possible and the study of low clearance compounds *in vitro* achievable.

Q2

Q: What are the advantages of using *in silico* modelling in combination with Organ-on-a-chip?

A: Dr. Nicolo Milani, Postdoc Scientist, Hoffmann-La Roche.

In my opinion, there are 3 key points to consider:

1. Organ-on-a-chip (OOC) systems are complex and require application of sophisticated modelling to realise their full benefit. This is particularly important for multi-organ systems where mathematical deconvolution of the system is necessary to get the pharmacokinetic (PK) parameters.

2. The second point relates to highly metabolically stable compounds. As I demonstrated here, it is possible to reduce the impact of evaporation in our clearance estimation (using *in silico* modelling) for more reliable data interpretation.

3. The last point relates to the use of modelling to better understand the system, and potentially help with new experimental design.

Q3

Q: Why did you choose this OOC system over others available? What are its benefits?

A: Dr. Nicolo Milani, Postdoc Scientist, Hoffmann-La Roche.

When we first started this project, the CN Bio PhysioMimix System was already in use by another group within Roche for qualitative applications. However, to me, this kind of system should be utilised for quantitative applications which is why we moved towards this kind of studies.

In my experience, one of the advantages of this system is the large volume of sampling media (1 mL) available in each well. This enables the user to repeat sample many times, potentially delivering more informative results than our *in silico* models, whilst still maintaining a relatively reasonable cell-volume ratio.

Importantly, I also found it easy to prepare and run incubations using this system.

Q4

Q: What are the advantages of using OOC to study low clearance compounds versus traditional approaches?

A: Dr. Nicolo Milani, Postdoc Scientist, Hoffmann-La Roche.

As I mentioned before, one of the main advantages of OOC using the PhysioMimix is the possibility to extend incubation times to increase the accuracy of clearance estimations, as liver tissues remain viable and functional for longer. The standard approach can only maintain the viability of suspended hepatocytes for a few hours, making it impossible to run an experiment anywhere near as long as our three compound PhysioMimix study.

Q5

Q: Why do you think the data for compounds with high liver transport exhibited lower hepatic clearance predictivity?

A: Dr. Nicolo Milani, Postdoc Scientist, Hoffmann-La Roche.

This is a hard question to answer because we used a single hepatocyte donor for all experiments. It is therefore difficult to conclude the reason why the clearance of Telmisartan and Repaglinide in particular, were under predicted by more than ten-

fold. This could be explained by the low expression of transporter in the system that we used, but without investigating other lots we don't know if this is by chance or if this is a trend.

Q6

Q: From this study, do you foresee OOC models being used more frequently for low clearance compounds and other pharmacokinetics studies?

A: Dr. Nicolo Milani, Postdoc Scientist, Hoffmann-La Roche.

Yes – I think that *in silico* modelling in combination with organ-on-a-chip will become routine in the future, but not just for low clearance compounds or FM (fraction metabolised) estimations, but also for many other applications such as drug-drug interactions.

Q7

Q: Is 4 days the maximum length of time that the experiment can run for?

A: From Dr Audrey Dubourg, Product Manager, CN Bio:

The length of time a Liver-on-a-chip experiment can be run for greatly depends on the end goal and application. Here, four days were necessary to study the metabolization of known low clearance compounds. We routinely use the PhysioMimix to culture liver microtissues in a flow perfused microenvironment for over four weeks. Their phenotype, function and viability are maintained, without primary liver cell dedifferentiation throughout.

To learn more about additional Liver-on-a-chip applications, the following on-demand webinars may be of interest:

Q8

Q: Are the cells in suspension or on a collagen matrix in your Liver-on-a-chip System?

A: From Dr Audrey Dubourg, Product Manager, CN Bio:

Each well in the Liver-MPS (LC12) Consumable Plate contains a proprietary collagen-coated 3D scaffold that is continually perfused by cell culture medium during experiments. This scaffold enables the formation of a liver tissue with polarised hepatocytes and the

formation of bile canaliculi that resembles the microarchitecture observed *in vivo*.

To learn more about how the PhysioMimix OOC creates a lab-grown organs and tissues whose phenotype and function resembles that *in vivo* , **watch the on-demand webinar: The rhythm of life**

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+44 (0) 1223 737941 | **sales@cn-bio.com**

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