CN-BIO

2022 WEBINAR SERIES

Every breath you take

Predicting Inhaled Drug ADME Using Lung-on-a-Chip

Q&A

A full run down of questions & answers from our 28th June webinar

Acronyms

ALI
Air-liquid interface

ATI
Alveolar epithelial type I cells

ATII
Alveolar epithelial type II cells

CDER
Center for Drug Evaluation and Research

FDA
Food and Drug Administration

MPS
Microphysiological system

OOC
Organ-on-a-chip

TEER
Transepithelial electrical resistance

Q&A participants

Dr Emily Richardson

Lead Scientist - Assay Development, CN Bio

Another question?

Drop an email to one of our experts

sales@cn-bio.com

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recording of the webinar here

Questions

Q1

Q: You mentioned in-house verification of the primary cells used for your models. What does a good cell lot look like and what qualifies it as good for microphysiological system work?

A: Dr Emily Richardson, Lead Scientist – Assay Development, CN Bio.

That's a really important question. Ensuring we have a good supply of quality primary cells for use with **PhysioMimix™ organ-on-a-chip (OOC) systems** is something that we focus a lot of time and effort on at CN Bio. As I mentioned in the presentation, we use commercially available primary cells. When primary cells arrive, the first thing we do is to carefully look at the structures that they form in our lung microphysiological system (MPS), otherwise known as lung-on-a-chip. Firstly, we ensure they can form a good barrier by looking at transepithelial electrical resistance (TEER) over several weeks. We also focus on the cell phenotypes formed after differentiation at air-liquid interface (ALI), particularly the alveolar and bronchial epithelial cell phenotypes, to ensure they are forming lung tissues that resemble the human lung. For example, when thinking about the alveolar model we ensure that the cell population remains at a good ratio of alveolar epithelial type I (ATI) to alveolar epithelial type 2 (ATII) cells. In other model systems this balance is often skewed towards an ATI alone population which is not representative of *in vivo* alveoli.

Q2

Q: Can any commercially available aerosoliser or nebuliser systems be used with your system?

A: Dr Emily Richardson, Lead Scientist – Assay Development, CN Bio.

As I mentioned in the conclusion of the webinar, our next steps are to think about the best ways of administering aerosolised drugs onto our system. This will be a fairly simple transition because the standard size Transwell® inserts used for culturing liver tissue in **PhysioMimix Barrier model (MPS-T12) consumable plates** can be transferred into commercially available aerosolizers or nebulizers, such as VitroCell.

By using aerosoliser/nebulisers, future studies will be useful for understanding the real physiological application of inhaled

medications. Obviously, in the studies I presented in the webinar, we used liquid dosing. That's because we wanted to really focus on the absorption and the permeability of the drugs, rather than the extra dimension of the dissolution of the drugs, which adds another layer of complexity. Now we have a base layer of knowledge, we can now move on to making experiments more complex to understand the full picture.

Q3

Q: What applications will you use your lung and liver models for, and can bioavailability studies be done with it?

A: Dr Emily Richardson, Lead Scientist – Assay Development, CN Bio.

Generated using the **Dual-organ (MPS TL6) consumable plate,** our lung-liver model is very exciting, and it's something that we can apply to (more or less!) anything people are interested in. In the first instance we designed this dual organ system for COVID-19 research as funded by our Innovate UK grant. In particular, we looked at the crosstalk between the lung and liver when we infected the lung with COVID-19 pseudoparticles. Through this we've been able to elucidate over time how the liver responds to inflammatory signals given by the lung during the challenge.

In the future this could also be applied to drug studies, whether that be ADME, toxicity, bioavailability or pharmacology – there's a whole host of different applications that could be applied to the multi-organ system.

Q4

Q: How are the cells used to make MPS chips representative of a broad group of humans or the general population? Are the cells from one source or human, or are they available with a range of source cells? What's being done to get a broader representation of the general population?

A: Dr Emily Richardson, Lead Scientist – Assay Development, CN Bio.

I think that's an interesting and important point. It's something the OOC/MPS community are really focused on right now. Being able to perform individual "patient-on-a-chip" assays and broaden out the scope of assays to better represent the variety of responses we'd see within a population in the clinic is possible using an OOC approach.

What we've done so far is to use a range of healthy donors from commercial cell suppliers. We work very closely with our cell providers to ensure we have access to a large range of donors with different properties. This is something we will continue to focus on and strive for further diversity as our suppliers' technology and donor banks increase. I think it is important to get a range of genders, ages and ethnicities to ensure that when you're making predictions using lung MPS you are representing a whole population, not just a single person. I believe this is a vital step for technology providers to get right in support of OOC/MPS use for regulatory purposes.

Q5

Q: Is it possible to link the gut and lung model to evaluate bioavailability of oral therapeutics?

A: Dr Emily Richardson, Lead Scientist – Assay Development, CN Bio.

Currently, we do not have an insert-to-insert based plate capable of linking the gut and lung. Our **Dual-organ (MPS TL6) consumable plate,** links an insert-based chip to a liver MPS (or liver-on-a-chip), which has been used to evaluate the bioavailability of oral therapeutics.

To learn more, click the link to download an application note entitled "**Improved prediction of oral bioavailability using a gut-liver microphysiological system**". Alternatively, the results of this study were presented in a short (20 mins) webinar "**From dose to circulation**".

However, if there is sufficient market demand for a dual-organ gut-lung model, this is a project that we could potentially undertake by adapting either the Barrier (MPS-T12) plate, or our Dual-organ (MPS-TL6) plate. In the past we have built insert-linked systems using technology from MIT, so we have prior experience. A possible short-term option would be to balance an insert in the current liver compartment of the Dual-organ (MPS-TL6) plate.

Q6

Q: How long can these be under culture? Can we expose them to repeated test articles over a period of 28 days for e.g., genetoxicity assays?

A: Dr Emily Richardson, Lead Scientist – Assay Development, CN Bio.

Currently the longest we have cultured these lung MPS is 21 days, however we are currently undertaking experiments to understand how far/long we can push the systems and retain optimal cell phenotypes. The lung MPS cultures are very stable once differentiated, as we see steady barrier integrity and maintenance of key cell types (e.g. AT2 cells in alveolar cultures). Furthermore, as our MPS system is an open-well format, repeat dosing over a long period is straight-forward to do experimentally.

Q7

Q: Have your chips been to the International Space Centre etc? Which ones? How did the fare?

A: Dr Emily Richardson, Lead Scientist – Assay Development, CN Bio.

This is an exciting question! We haven't focussed on any space exploration to date, it is likely that some areas of our system would work well, and some areas would require small adaptations. For example, as we use recirculating flow, liquids would not need to be replenished as frequently (other than when the cells need it), which is a positive. To keep cells perfused, we use a pump-based system (like our own hearts) rather than relying on gravity, which would also suit conditions in space. However, the system's weight (~25kg) may need to be trimmed down for space flight (which obviously is less of a consideration on Earth). We haven't made the journey yet... but watch this space!

Q8

Q: What impact do you think these projects will have as we step away over time from animal testing? Do you think if these systems get FDA approval it will push the field?

A: Dr Emily Richardson, Lead Scientist – Assay Development, CN Bio.

An excellent question. It's a very exciting time to be in the OOC/MPS field. As we speak, regulators are acknowledging that animal testing for the sake of animal testing is not the way forward. The US House recently approved the Food and Drug Administration's (FDA) **Modernization Act of 2021** to allow manufacturers and sponsors of a drug to use alternative testing methods to animal testing to investigate the safety and effectiveness of a drug, and for other

purposes. Last year the European Parliament resoundingly **passed a resolution** to phase out animal testing in research, regulatory testing and education.

The regulators themselves are exploring novel alternative methods for evaluating drugs. As I mentioned in the webinar, we are already collaborating with FDA's Center for Drug Evaluation and Research (CDER) group who are independently evaluating our lung MPS for use in preclinical studies. Once the FDA approve a method for preclinical testing and mandate it, those who develop therapies will follow. Especially if it's cheaper, quicker and more predictive than animal studies! Our immediate vision is for MPS to be used alongside animal testing, but as trust and confidence in the translatability of MPS technology increases, our end goal is for OOC/MPS technology to replace their use.

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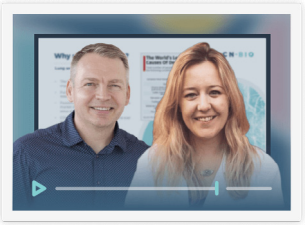

A Breath of Fresh Air:
Novel approaches to human lung disease modelling for accelerated drug discovery

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