CN-BIO

SUMMER WEBINAR SERIES

A regulators viewpoint

Establishing Strategies To Evaluate Microphysiological Systems for Drug Development

Q&A

A full rundown of questions & answers from our July 15th webinar

Abbreviations

AAV - Adeno-associated virus

ASO - Anti-streptolysin O

3D - three-dimensional

CRISPR - Clustered regularly interspaced short palindromic repeat

FDA - Food & Drug Administration

HLA - Human Leukocytes Antigen

IND - Investigational New Drug

MPS - Microphysiological system

OOC - Organ-on-chip

siRNA - small interfering Ribonucleic Acid

Q&A participants

Dr Alexandre Ribeiro
Staff Fellow & Biological Scientist, FDA

Dr Tomasz Kostrzewski
Director of Biology, CN Bio

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Questions

Q1

Q: How comparable are the results from microphysiological systems versus eventual outcomes in clinical trials?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

Microphysiological systems are fast developing technologies that are still being evaluated for various applications within the drug development process. The evaluation of these technologies is ongoing and involves comparison to preclinical and clinical data sets to understand translation between MPS models and humans.

Overall, a cellular microenvironment with physiological properties can prolong, enhance, enable or stabilize the function of tissue-specific cells relative to traditional culture systems. The next step is to evaluate to what extent organ-on-chip (OOC) systems can be predictive of clinical results. For this purpose, OOC systems should be tested for specific contexts of use using assays and compounds (with controls) that are related to each context of use.

Q2

Q: As far as lung-on-a-chip is concerned, is it critical to have an air-liquid interface 3D lung model?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

Yes. However, handling drugs in “gas” phase or dissolved in air is technically still very challenging. Currently, it may be more convenient to handle them in a solution that is added to the air side of the interface. This is something that we are currently considering.

Dr Tomasz Kostrzewski, Director of Biology, CN Bio:

MPS/OOC lung models can be configured for use with and without air-liquid interfaces and those that have this feature have been demonstrated to more closely mimic human lung physiology.

Q3

Q: How do you mimic the tissue microenvironment?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

Considerable advances have been made to culture cells in tissue-like properties at a microscale. The properties of cellular microenvironments *in vivo* vary from tissue to tissue and therefore different approaches are used for recreating the microenvironment of different tissue types *in vitro*.

Depending on tissue type, such approaches commonly aim to:

- enable 3D culture or co-culture of different cell types,
- expose cells to microfluidics and electromechanical cues,
- culture cells with polarity as tight barrier-like monolayers,
- deliver chemical signals,
- use engineered and functionalized extracellular matrices, among other techniques in the field of bio-microfabrication.

Q4

Q: Do you suggest using hydrogels specific to the target organ?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

Yes, if the hydrogels in question have properties that enhance the physiological relevance of cell culture relative to the *in vivo* organ.

Q5

Q: How do you deal with degradation or gel contraction over extended periods of cell culture?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

We tend to design experiments while considering such potential limitations. The properties of microphysiological devices, such as gel degradation over time, need to be well characterized prior to use.

Q6

Q: You mentioned that lung and kidney are the next targets after liver and heart. But what about the brain?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

I am aware of opportunities where brain-like models could be used to evaluate the safety and efficacy of oncological therapeutic agents. We are eager to learn more about these models to investigate how they can be used in drug development.

Q7

Q: Are all the cells used human in origin or are you also examining chips with animal cells to allow closer comparison with *in vivo* data?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

So far, we have only used human cells (primary or iPSC-derived). However, for some applications, such as developmental and reproductive toxicity testing, it would make sense to use animal cells since animal models are the gold standard for decision making.

Q8

Q: In the near term, do you anticipate that organ-on-chip supplemental data will be accepted within IND submissions to the FDA?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

I don't see why that is not a possibility. It is my understanding that all data is welcome in IND submissions if relevant to it.

Q9

Q: What would it take for the data from MPS systems to be solely considered (i.e.: purely *in vitro* data) in regulatory decision-making?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

I can think of several ways. The easiest way would be to obtain or publish experimental data showing that this is possible. The next step would be to involve different drug development stakeholders to ensure data reproducibility. After this, there are many options, including the development of guidance documents if needed.

Q10

Q: Is it possible to use this OOC system for therapeutic gene delivery?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

This is not my field of work; however, I believe these OOC systems could be useful for such an application. I know that Kupffer cells, for example, interact with several agents that have been proposed to be used in gene delivery strategies.

Dr Tomasz Kostrzewski, Director of Biology, CN Bio:

OOC/MPS can be used for testing genetic engineering therapeutic agents, including AAV and adenovirus, ASOs, siRNAs and CRISPR agents. The longevity of MPS cultures makes them particularly well suited to studying these agents which need some time to establish in cellular systems before having an efficacy or toxicological effect. Additionally, as most of these agents are human cell specific, they can be tested on primary human cells cultured in MPS/OOC.

Q11

Q: Regarding the scaffolds used for the PhysioMimix™ liver-on-a-chip model, how does the scaffold affects the cell phenotype?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

We have not investigated the effect of the scaffold on the cell phenotype. However, the scaffolds used in the PhysioMimix™ MPS-LC12 plate enable cell culture under microfluidics whilst maintaining a 3D organization, which is a game changer.

Dr Tomasz Kostrzewski, Director of Biology, CN Bio:

The MPS-LC12 scaffolds enable primary human liver cells to form 3D microtissues that mimic the microarchitecture of the human liver sinusoid. They are generated inside the scaffold and are consistently under flow which mimics the blood flow through the human liver.

Q12

Q: How important is it to have circulatory immune cells in these MPS systems? Is this something that can be achieved with the current set-up?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

It is my understanding that any cell types can be added to these MPS systems. However, it is important to keep in mind that difficulties keeping cells in a quiescent state can arise.

Q13

Q: Circulatory immune cells can be added to MPS platforms and flow into and out of microtissue structures, alternatively they can be housed in separate compartments to allow endocrine signalling between immune cells and other tissues. HLA matching and donor matching of material is a challenge when preparing these co-cultures and care should be taken to assess auto-activation of immune cells. Has data from any MPS system been used successfully in regulatory packages to replace data from animal models?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

I am not aware of any scenarios such as this.

Q14

Q: How do you evaluate a specialized *in vitro* system when a gold standard doesn't exist and animal/clinical data is limited?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

Firstly, I would try to find any published data that could be used as a reference point even if the number of studies available is limited.

Where gold standard disease models are not available, these MPS systems can be of great value. I know that, lately, several advances have been made in Academia to model rare conditions. This field would highly benefit from an MPS approach.

Q15

Q: Can we work with you? If we have existing *in vitro* model platforms with preliminary data, would the FDA be interested in testing them if we sent you some materials?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

As alluded to in the presentation, our research projects focus on critical research related to gaps or bottlenecks in drug development. With microphysiological systems, we would prefer to work with models that have already been tested and show promise for addressing these critical drug safety, efficacy and pharmacology gaps or bottlenecks.

Q16

Q: What does “operate robustly” and “originate reproducible results” mean? 90% of chips give data within 2 standard deviations?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

Our research shows that where specific quality control criteria (cell and device properties) can be followed, similar results were generated independently of laboratory location and time of experimental execution, therefore demonstrating reproducibility.

In our characterization studies, robustness relates to the durability of properties that define the quality of the system while it is operating. Changes in surface chemistry, drug adsorption to the materials, gel degradation, leaks, pressure drops, cracks and more operational defects can define low levels of system robustness all of which can affect the function of cultured cells and the results obtained from these MPS systems.

Q17

Q: What do you think are the biggest remaining hurdles for organ-on-chip adoption across the industry?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

- Lack of performance criteria and standards.
- Lack of specific contexts of use where systems can make a change relative to other methods and models. Applications in drug development need to be researched and established for microphysiological systems.
- The field needs the involvement of multiple drug development stakeholders to address these hurdles.

Q18

Q: In your presentation you discussed healthy liver and heart organ models, but do you see a need for diseased models (of these, or other organs)?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

Yes. In many fields: genetic disorders, rare diseases, oncology,

population differences, sex differences, etc.

Dr Tomasz Kostrzewski, Director of Biology, CN Bio:

Various disease models of the liver have already been generated, including those of metabolic liver disease (NAFLD/NASH), viral infection (HBV/HCV) and liver cancer. These provide tools to understand basic biology and underlying mechanisms of these disease states, understanding target ID and therapeutic efficacy.

Q19

Q: What do you think the future of organ-on-chip technology will be in terms of regulations for pre-clinical drug testing? Do you expect this to be a requirement before entering the clinic?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

To my knowledge, despite our optimism regarding this field, there are no data or published work that can lead me to confidently expect these OOC systems to become a requirement in regulatory applications. I do hope to see OOC systems being developed and qualified to eventually replace, refine or improve some of the current preclinical and clinical practices. For now, I am excited to investigate which gaps and bottlenecks in drug development can be addressed by these systems. As mentioned in earlier responses, there are unique needs and opportunities for microphysiological systems in areas lacking gold standard *in vitro* models.

Q20

Q: There are now commercially available organ-on-chip models for a range of organs. Are there any organs or models that haven't been created that you see a great need for in drug development?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

According to my colleagues who work in immunology, the immune component of these systems is still very underdeveloped. However, there is still a lot of work that can be achieved using currently available systems.

Dr Tomasz Kostrzewski, Director of Biology, CN Bio

Modelling the full human immune system is a huge challenge in the field. Innate immune cells and some subsets of adaptive immune cells have been added to MPS platforms but the full human immune system is yet to be recapitulated.

Q21

Q: What criteria are required for a great, robust and reliable organ-on-chip model?

A: Dr Alexandre Ribeiro, Staff Fellow & Biological Scientist, FDA:

This is a big question and very dependent on the system and on the intended use. The term “great” is subjective, but a system with well-defined and well-tested applications that delivers reproducible data predictive of clinical results would be “great”. An MPS system would be deemed reliable if it could be used in any lab in the world (with reproducible results), with cells that are easily accessible for purchase and with well-defined quality control criteria. An MPS system would be robust if its operational properties could be constantly maintained and if any malfunction could be comprehensively understood and fixed based on performance criteria.

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