Table Discussion Leader Instruction Guide

2017 *In Vitro* Lecture: Human Organs-on-Chips Testing—Strengths and Challenges

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Timeline

11:30 am-12:00 pm Lunch
11:40 am Participants Cue Up Poll Everywhere Audience Response System
Knowledge Inventory Questions

12:00 pm-12:10 pm Welcome from Dr. Barb Kaplan, Education Committee Chair
Dr. John Morris, SOT President
Thank you to Colgate-Palmolive
Recognition of Guests and Awardees
Introduction of Dr. Anthony Bahinski

12:10 pm-12:20 pm Lecture: Dr. Bahinski

12:20 pm-12:45 pm Discussion at Tables

12:45 pm-1:00 pm Discussion Summary
Knowledge Inventory Questions

A. Knowledge Inventory (Poll Everywhere–respondents answer to the best of their ability)

1. How many tissue types do you think can be in a 3D organ model?
2. What two things do you think are critical to establish a 3D organ model?
3. What disease states can be modeled with a 3D organ model?

B. Focus of the Discussion

In vitro systems are important models for identifying effects and mechanisms by which xenobiotics produce toxicity. The complexity of *in vitro* culture systems can be increased with addition of a relevant cell type, which might help identify mechanisms more similar to that observed *in vivo*.

Background for Dr. Bahinski's Presentation

Organs-on-Chips are microfluidic cell culture devices that recreate the specialized multicellular architectures, tissue-tissue interfaces, physicochemical microenvironments and vascular perfusion necessary to recapitulate organ-level physiology *in vitro*.

These microsystems could potentially fill the critical need for improved model systems to predict human efficacy, safety, bioavailability, and toxicology outcomes.

Organ-on-a-chip Models

- Recreate tissue-tissue interface that define organ structure
- Provide mechanical cues necessary for relevant physiology
- Precisely orient cells for high-resolution real-time imaging
- Control fluid flow through microfluidic channels
- Incorporate endothelium-lined vascular channels
  - To enable physiological vascular coupling between different organ chips
  - Permits real-time analysis of inflammation (recruitment of circulating immune cells)

C. Thought Questions (provided at the tables for the students)

1. What considerations are needed to adapt the lung-on-chip to another organ (for example, the liver)?

Cell types: hepatocytes, hepatic stellate cells, Kupffer cells, endothelial cells
Ratios of various cell types
Mechanics of blood flow, bile flow
Understanding of differential oxygenation throughout the liver
Increased metabolism capacity
If linking to other organs, ratio of liver tissue (mass) to other organs

2. As a group, design a lung-on-chip system to evaluate a toxicant. Select a toxicant. What are the considerations as you design and set up the experiment to test the effect of the toxicant in this system?

Deliver toxicants either directly or via inhalation (i.e., smoking)
Examine endpoints in the various cell types
Considerations: Vehicle of toxicant, concentrations–comparable to human exposures, use of parent compound or metabolite

3. Using the lung-on-chip system, what kinds of different scenarios can you envision that might influence the effect of toxicant?

Healthy versus disease
Disease state (pneumonia versus asthma)
Using various genetic backgrounds
Male versus female-derived cells (or in the presence of sex steroids)
Acute versus chronic exposures
High versus low toxicant concentrations

4. **How do the principles of the 3Rs apply to the lung-on-chip model?**

   Refine the model
   Reduce animal use by using the model instead and/or gain insight on species differences
   Ultimately replace animals

D. Use these additional questions if time allows (not provided to the students).

5. What are the advantages of a 3D organ model over other *in vitro* models?

   Better predictors
   More accurate
   Models 3D aspects/micro changes in interactions
   Use of human cells
   Interactions with blood, pressure, oxygen

6. Would you expect inter-study variability to be high or low? Why?

   Human sourced cells would produce inter-individual variability
   Highly controlled system would limit variability across replicates

7. If you were designing a multi-tissue 3D organ model for smoking, what tissues might you include?

   Cells from lung
   Cells from mouth, throat
   Heart
   Vascular cells
   Immune cells

8. Do you think 3D models will replace current *in vitro* models? Why?

   Not yet - Expense
   Not yet - Availability limited currently
   Not yet – Complexity

9. What type of work do you think needs to be done to characterize these models to understand their predictivity to human diseases?

Understanding sex differences
Understanding developmental influence on disease incidence
Genetic differences
Epigenetic differences
Level of oxygenation to target tissue
Level of blood flow
Capability of metabolism
Role of inflammation – either in target tissue or from distant site

E. Take home message to provide to the students near end of discussion

In vitro systems are important models for identifying effects and mechanisms by which xenobiotics produce toxicity. With testing advances, we continue to refine, replace, and reduce experimentation with animal models.

F. Knowledge Polling Questions are Repeated

1. How many tissue types do you think can be in a 3D organ model?
2. What two things do you think are critical to establish a 3D organ model?
3. What disease states can be modeled with a 3D organ model?

We thank the table hosts for encouraging and supporting the discussion and facilitating networking during this event.