Putting Science into Standard - “Organ-on-chip: toward standardization”

Assays and Biomarkers

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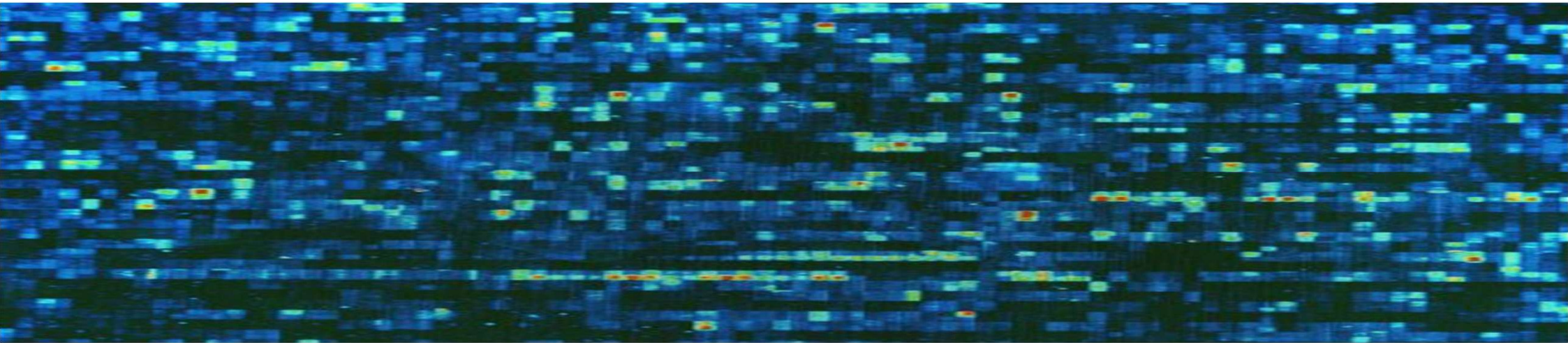
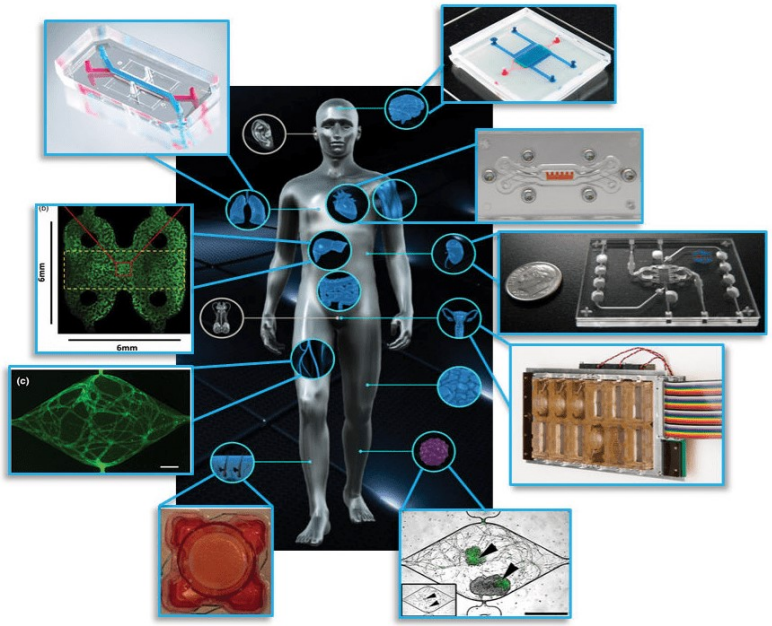


Introduction: OoaC is a wide field that has just started

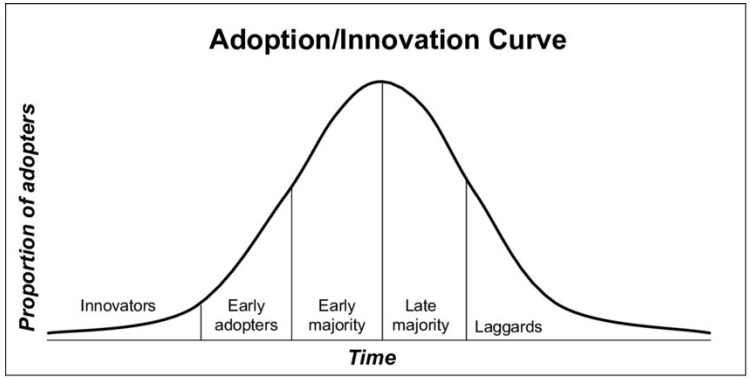
- ***Organ on a Chip (or Microphysiological Systems) <u>is not «a» technology</u>, but rather a concept, an ambition to better recapitulate aspects of human physiology***
- ***It builds on the use of human tissue in combination with e.g. 3D architecture, microfluidics, mechanical movements and other aspects to achieve this goal***
- ***There is currently <u>a burst of different approaches</u> – some with more, some with less potential for application***
- ***The best and most convincing way for application is to <u>demonstrate compelling evidence for defined use cases</u> – rather than directly aiming for a universal model that solves all questions***
- ***It is currently not clear which cells, which materials, which set-ups, which assays or which endpoints are «the right ones» - but the more research is published and the more use cases are built, the more we learn a) what doesn't work at all, b) what works in a defined context of use and and c) what has broader applicability***



Can standardization support safe, widescale deployment ?

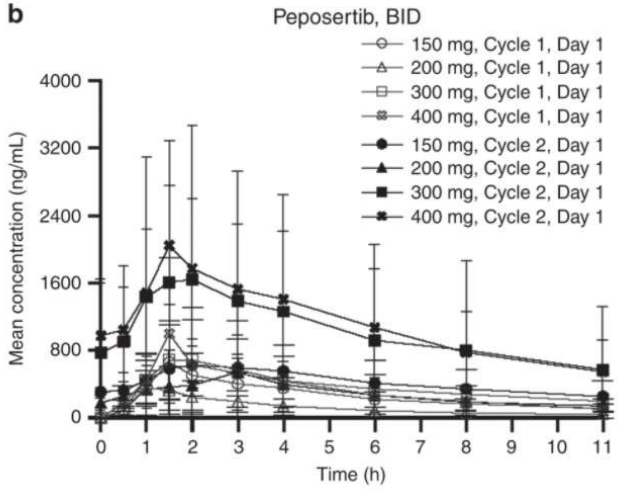
Given the novelty of the concept of «Organ on Chip»

- ***is it the right time to discuss standardization ?***
- ***does standardization help or hamper driving it's application forward ?***



Humans are hugely variable (i.e. not «standardized») and to be able to accurately predict human variability, technical variability must be controlled

Peposertib pharmacokinetics in Phase 1 clinical study
(British Journal of Cancer volume 124, pages728–735(2021))



Important for future development of Organs on Chips: View from a stakeholder

The context of use is key

- Complexity not always needed
- Make sure not trying to solve a problem that doesn't exist – many pre-clinical tests work beautifully
- «3D is better than 2D» is not enough to justify the use of OoaC
- The 1 universal system that is best suited for all questions does not exist

Don't re-invent the wheel

- To assess a clinically relevant endpoint in an OoaC model, consider using the current standard measurement used in clinic
- Additional, novel endpoints can add value

Statistics, propoer controls, reference to published data

- Robustness of data over time is key
- Continuous measurements in technical repeats & a set of different donor samples (-> human diversity!)
- Variability in data not necessarily bad, but you need to demnonstrate it reflects true human variability and is not due to lack of robustness of the model

Context of use examples for OoaC Liver models

Context of use	Micropatterned hepatocytes	3D primary hepatocyte spheroids	Stem cell-derived organoids	3D bioprinted liver	Liver-on-a-chip
Assessing toxicity endpoints	✓	✓	✓	✓	✓
Advanced architectural integration of nonparenchymal cells			✓	✓	✓
High throughput formats		✓	✓		
Donor-matched cells to study immune-mediated DILI, specific patient populations, or disease with long term consistent supply			✓		
Bile acid homeostasis				✓	✓
Studying transporter mechanisms and biliary clearance of drugs	✓			✓	✓
Histopathology with microscopic processing/tissue staining		✓	✓	✓	
Regulated fluidic flow for sampling of media flow-through for metabolites and biomarkers					✓
Oxygen gradients and metabolic zonation for studying zone specific toxicities					✓

Assays and Biomarkers: relevant endpoints, reference drugs, measurement methods, parameters to assess organ functionality and benchmarking

Assess organ functionality

Key as first step **to demonstrate relevance of chosen model** – must be done **over whole period of measurement**

For a number of organs, such **parameters exist and should be included**, ideally several

Benchmarking may be trickier for organs and endpoints where there is sparse clinical reference data

Should also include assessing **different cell types** and **composition over time**

Measurement methods have to be **described in detail** – recommended to **start with what is considered standard** – otherwise will be hard to convince community

Relevant Endpoints

are mostly **model-independent**, exist for most Drug-Development related questions and are well established

Endpoints used in **regulatory assays** can be used, though one should not be limited to these as they are typically **within a very narrow defined area** (e.g. hERG)

As OoaC aim to recapitulate a human relevant situation, it is recommended to **use endpoints similar to those used in clinic** (e.g. ALT for DILI)

These & potential novel endpoints should be **validated in a context of use by using reference drugs** that have a well documented clinical outcome

Most of thesed points are general to any kind of in vitro assay used in a drug development context and not specific to OoaC

Assays and Biomarkers: relevant endpoints, reference drugs, measurement methods, parameters to assess organ functionality and benchmarking

Validation guidelines to assess a multitude of different OoaC approaches

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Recommendations to assess over time defined set of endpoints:

- **Functional parameters**
- **Liver specific enzyme activities**
- **Tissue integrity**
- **Reference Drugs**

Cardiovascular microphysiological systems (CVMPS) for safety studies – a pharma perspective

Amy Pointon, Jonathan Maher, Myrtle Davis, Thomas Baker, Joseph Cichocki, Diane Ramsden, Christopher Hale, Kyle L. Kolaja, Paul Levesque, Radhakrishna Sura, David M. Stresser and Gary Gintant

Microphysiological systems for ADME-related applications: current status and recommendations for system development and characterization

Stephen Fowler, Wen Li Kelly Chen, David B. Duignan, Anshul Gupta, Niresh Hariparsad, Jane R. Kenny, W. George Lai, Jennifer Liras, Jonathan A. Phillips and Jinping Gan

Drug-induced skin toxicity: gaps in preclinical testing cascade as opportunities for complex *in vitro* models and assays

Rhiannon N. Hardwick, Catherine J. Betts, Jessica Whritenour, Radhakrishna Sura, Maike Thamsen, Elad H. Kaufman and Kristin Fabre

Microphysiological lung models to evaluate the safety of new pharmaceutical modalities: a biopharmaceutical perspective

Garrett R. Ainslie, Myrtle Davis, Lorna Ewart, Linda A. Lieberman, David J. Rowlands, Andrew J. Thorley, Gorm Yoder and Anne M. Ryan

Developing *in vitro* assays to transform gastrointestinal safety assessment: potential for microphysiological systems

Matthew F. Peters, Allison L. Choy, Carmen Pin, Derek J. Leishman, Annie Moisan, Lorna Ewart, Peggy J. Guzzie-Peck, Radhakrishna Sura, Douglas A. Keller, Clay W Scott and Kyle L. Kolaja

A pharmaceutical industry perspective on microphysiological kidney systems for evaluation of safety for new therapies

Jonathan A. Phillips, Taraka Sai Pavan Grandhi, Myrtle Davis, Jean-Charles Gautier, Niresh Hariparsad, Douglas Keller, Radhakrishna Sura and Terry R. Van Vleet

Doing now what patients need next