Pharma Perspective on Animal Microphysiological Systems

Innovation and Quality consortium
IQ Microphysiological Systems (MPS) Affiliate

PJ Devine, Senior Principal Scientist
Novartis Institutes for BioMedical Research
Jan 19-20, 2020

Who I am

Current Position

- Patrick “PJ” Devine
- Senior Principal Scientist
- **Discovery and Investigative Safety/Preclinical Safety**
- **Novartis Institutes for Biomedical Research**
- patrick.devine@novartis.com

Background

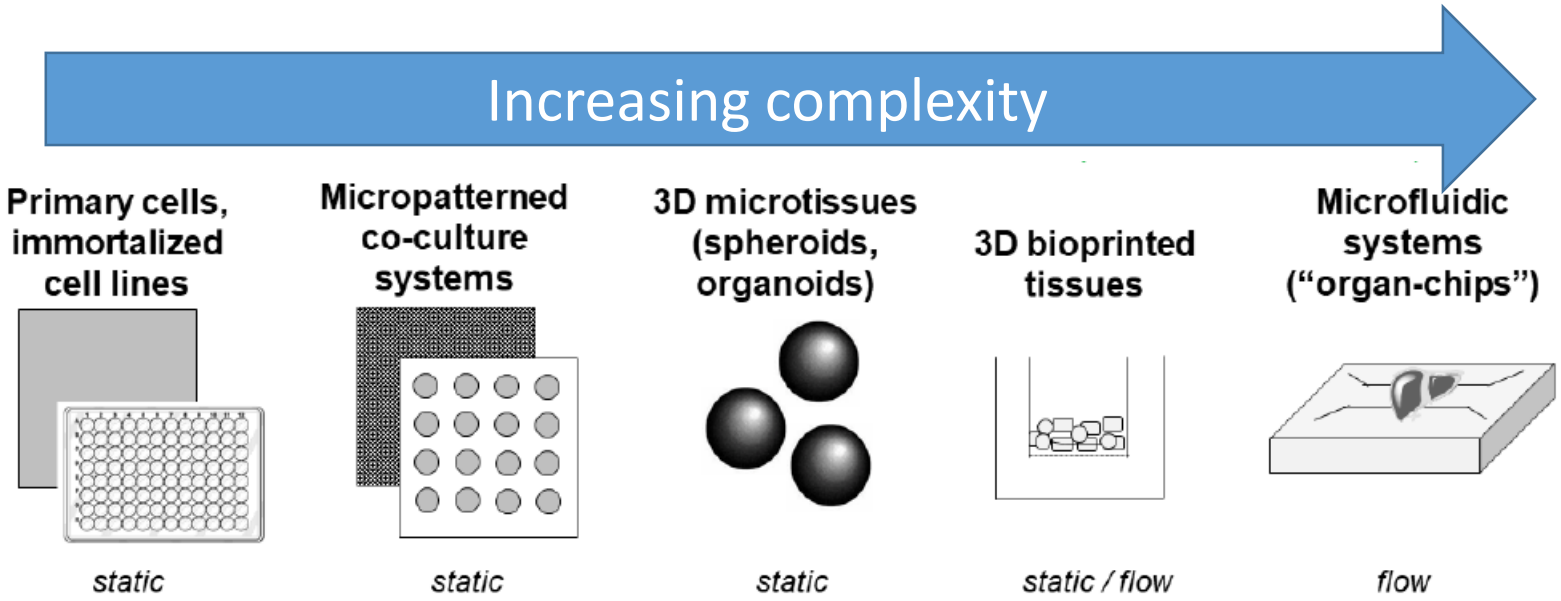
- Studying drug safety at Novartis (2010-current)
- Studied reproductive toxicology and safety as Professor, INRS-Institut Armand-Frappier (2003-2010)
- Studied reproductive toxicology as post-doc, U of Arizona (1999-2003)
- Studied toxicology at U of Maryland, Baltimore (1992-1999)

All stages involved both *in vivo* and *in vitro* safety studies, investigative toxicology

Definition of MPS from IQ MPS Affiliate

The IQ MPS affiliate defines MPS as going beyond traditional 2D culture models by including several of the following design aspects: a multicellular environment within biopolymer or tissue-derived matrix; a 3D structure; the inclusion of mechanical cues such as stretch or perfusion for breathing, gut peristalsis, flow; incorporating primary or stem cell derived cells; and/or inclusion of immune system components.

*- Fabre et al. **Lab Chip** (2020) 20:1049-1057*



- Adapted from Dash and Proctor (2019) Hepatic microphysiological systems: Current and future applications in drug discovery and development. In Micro and Nano Technologies, microfluidic Cell Culture Systems (2nd Ed) Elsevier, 2019.

IQ MPS Members and Overview

- **Current Membership**

AbbVie	BMS	Merck	Takeda
Alnylam	Eisai	Merck Healthcare KGaA	Theravance
Amgen	Eli Lilly	Novartis	Vertex
Astellas	Genentech	Pfizer	
AstraZeneca	GSK	Sanofi	
Biogen	Janssen	Seattle Genetics	

- Diverse representation from **Drug Safety, Pharmacology**, **3Rs**, **ADME**, and **PK/PD**
- **Leadership**
  - *Chair* - Jason Ekert (GlaxoSmithKline)
  - *Vice Chair* - Szczepan Baran (Novartis)
  - *Vice Chair-Elect* – Rhiannon Hardwick (Theravance)
  - *Past Chair* - Terry Van Vleet (AbbVie)

IQ Microphysiological Systems Affiliate Evolution

2014

Established MPS Working Group

(11 member companies)

2015

Signed MOU with NCATS

2016

MPS WG represented at NCATS Tissue Chip Workshops and 3D Tissue Models Summit

2017

Published position paper on tissue chip development in Exp Bio Med. *-Navigating tissue chips from development to dissemination: A pharmaceutical industry perspective..*

Developed poster presentations on 5 sets of organotypic standards

Hosted an MPS Industrialization Strategy Worskshop

2018

Established MPS Affiliate

IQ MPS Affiliate Aims

Serve as a thought leader for both MPS developers and stakeholder organizations in the industry implementation and qualification of MPS models.

Provide a venue for appropriate cross-pharma collaboration and data sharing to facilitate industry implementation and qualification of MPS models.

Create focused engagement between industry and regulatory agencies on the current status and evolving field of MPS in an industry setting.

Develop external partnerships and collaborations to help enhance the inclusion of industry priorities.

Thought Leadership/Partnerships

Organotypic Standards

- 8 Manuscripts Series 1.0 complete (9th submitted) - *Lab on a Chip (JIF 6.914)*
- 9 teams established for manuscript series 2.0 - *Altex (JIF 6.183)*
- Summary presented at the PREDiCT: 3D Oncology & Tissue Models Summit

Public Presentations

- PREDiCT: 3D Oncology & Tissue Models Summit
- 16th NCATS Tissue Chip Consortium Meeting
- NICEATM / NIEHS Town Hall Meeting on Development of New Approach Methodologies to Reduce Animal Use in Toxicity Testing
- World Pharma Week – Drug Discovery & Preclinical Webinar Series

FDA - Dialogue & Collaboration

- Feb 26 Case Study Workshop and Webinar presentations (Aug 12 & Jan 29)
- Invited to comment on FDA definitions
- Presented at Oct 21 FDA Office of Clinical Pharmacology / IQ Consortium Scientific Exchange Meeting with the Translational ADME and Clinical Pharmacology Leadership Groups

NCATS - Continued Relationship

- Presented at Annual Tissue Chip Workshop
- Opportunity to contribute to MPS World Congress Planning

Organotypic Manuscripts

Evolved from “guidance” posters presented at NCATS Tissue Chip Consortium Meetings

Serve as a focal point for stakeholder engagements with vendors and regulators

Manuscripts address 3 overarching questions:

1. What are the challenges/gaps in current *in vitro* and *in vivo* models?
2. What data and capabilities would be needed to demonstrate a meaningful improvement over standard 2D systems?
3. What are the industry suggested endpoints, online readouts, test compounds, etc. for “MPS qualification” studies?

- CNS/BBB
- IMMUNE
- OCULAR
- REPRO
- CNS/PNS
- MPS for OLIGOS
- MPS for GENE EDITING
- MPS for CELL THERAPIES
- DISEASE MODELS
- CARDIOVASCULAR
- INTRO
- LUNG
- SKIN
- LIVER
- ADME
- BIOLOGICS
- KIDNEY
- GI

https://www.iqmps.org/publications

Cross-Pharma Collaboration And Data Sharing

GI RFI[1]

- Goal: evaluate available GI MPS
- Released RFI for GI MPS
- 11 responses received from 8 organizations

Kidney RFI

- Goal: evaluate available kidney MPS
- RFI for Kidney MPS being prepared

Organ/COU[2]-Specific Discussion Groups

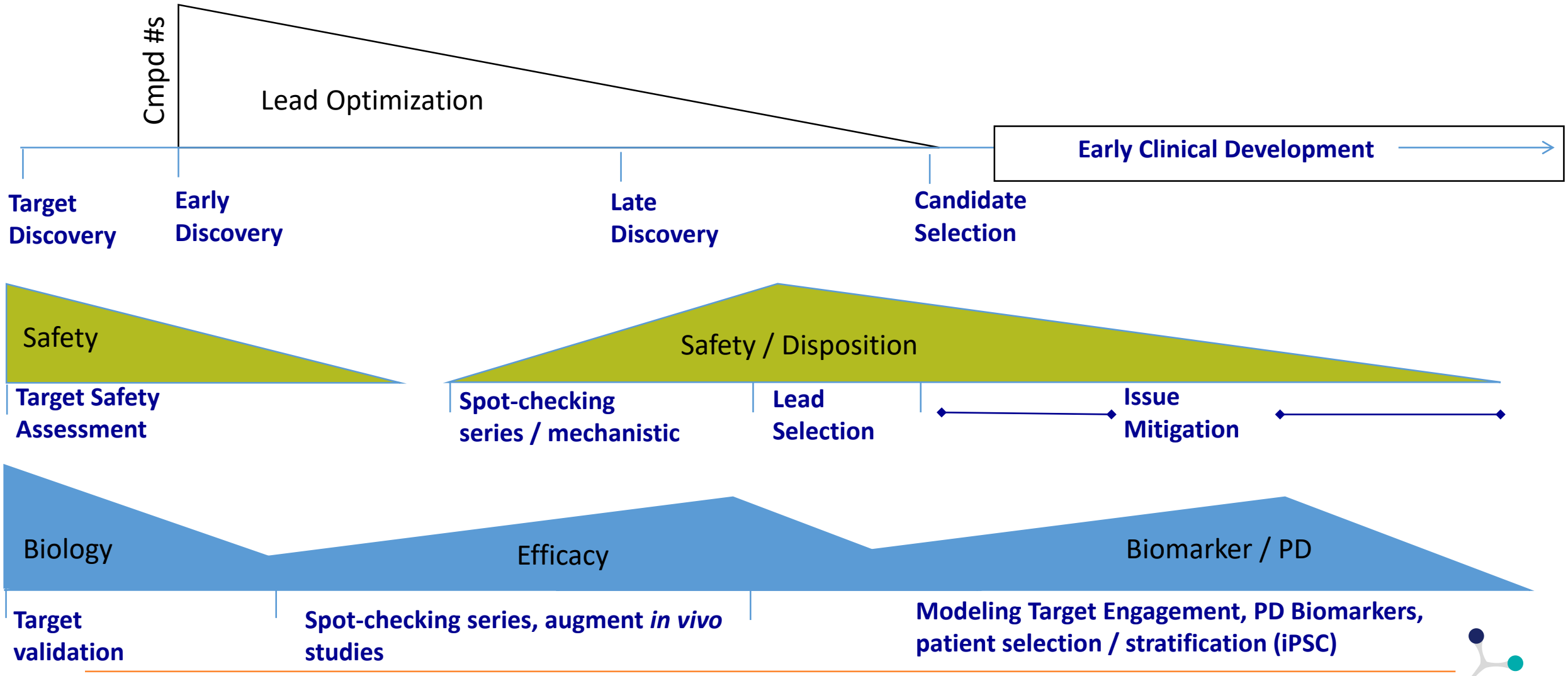
- Goal: coordinate cross-pharma sharing of MPS data and collaborations
- Formed 10 organ specific discussion groups to explore collaboration opportunities outside of the IQ MPS

Landscape / Gap Analysis Survey

- Goal: characterize MPS use and gaps in Pharma
- Redesigned Survey (version 2.0) and incorporated FDA feedback
- Collecting responses through mid-Jan

[1]Request for information; [2]Context of Use

Positions in Drug Discovery/Development for MPS Entry and Impact



Fabre et al. ***Lab Chip*** (2020) **20**:1049-1057

IQ MPS statement on animal MPS (1/3)

- The IQ MPS Affiliate recognizes the importance, impact, and the need for animal models as well as the opportunity for new approach methodologies to enhance/reimagine drug discovery and development (DDD).
- The exclusive utilization of human cell-based systems however would make it challenging to:
  - support the investigation of species-specific mechanisms
  - demonstrate that a model recapitulates histopathological findings
  - validate predictivity for toxicities that only occur above feasible clinical exposures in humans
- Therefore, MPS composed of cells from animal species are also important to the advancement of MPS development and use.

IQ MPS statement on animal MPS (2/3)

The IQ MPS Affiliate supports the development and utilization of animal cell based MPS in addition to human cell based MPS in order to:

- cross-reference animal cell based MPS data with in vivo animal data to accelerate the development and validation of novel MPS technologies and applications
- leverage animal in vivo data with animal MPS data to gain confidence in predictivity of human MPS
- Identify species-specific differences for selection of translational models through MPS species comparisons, especially for rare diseases
- develop transgenic and disease-specific MPS models with cells derived from transgenic mice/rats
- carry out structure-activity relationship (SAR) and mechanistic studies in instances where there are nonclinical toxicological issues that need resolution, e.g. nephrotoxicity, CNS toxicity
- compare ADME in nonclinical species and human

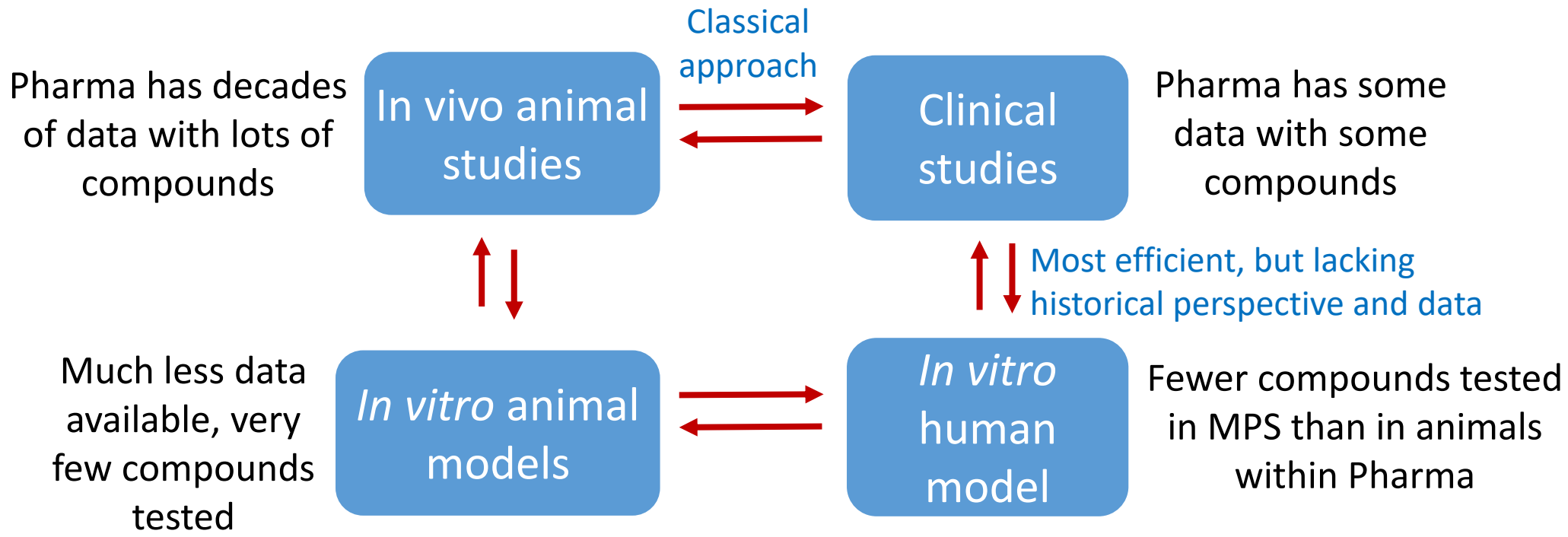
IQ MPS statement on animal MPS (3/3)

- The IQ MPS Affiliate supports the 3Rs (Refinement, Reduction and Replacement) concept described by Russell and Rex Burch in The Principles of Humane Experimental Technique (Russell & Burch, 1959). The current use of MPS has already a direct impact on the Refinement and Reduction in Drug Discovery and Development, with a long-term goal of animal Replacement in the future.

From statements to …
My thoughts: Why Pharma needs animal *MPS*

Translating preclinical models to the clinic and reverse translation from clinic

- We don't always have models we need, and we don't always know what models we need
- We don't always know how well *in vitro* models predict humans



14

My further thoughts and predictions

- Critical needs for animal MPS (even though we are developing drugs for humans)
  - Animal MPS needed for Pharma over the next few decades (at least)
  - Consistent cell sources from various tissues from various species (diverse sources)
  - Experience/expertise in rapidly establishing new robust MPS of multiple species
  - Comparison of human and animal MPS and *in vivo* data - translatability
- Where animal models may still be needed further in the future:
  - Final confirmation of efficacy or safety before going into humans
  - Carcinogenicity studies
  - Fertility, embryofetal development, reproductive safety
  - Understanding clinical issues of unknown mechanism

Acknowledgements

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- IQ MPS secretariat
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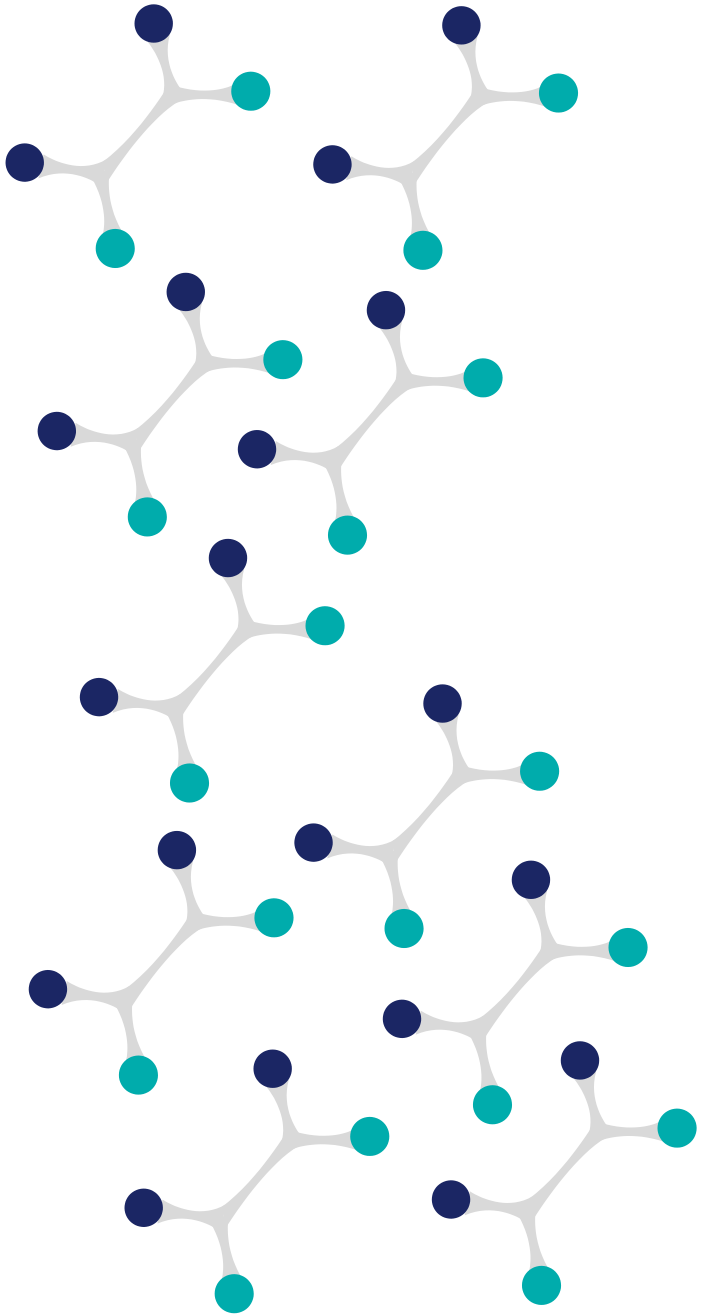
  - Catherine Graveline
  - Reed Abrahamson
- Szczepan Baran (Novartis)
- Francois Pognan (Novartis)



THANK YOU

Organotypic Manuscript Series

Lab on a Chip

ROYAL SOCIETY OF CHEMISTRY

PERSPECTIVE

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Cite this: *Lab Chip*, 2020, **20**, 1049

Introduction to a manuscript series on the characterization and use of microphysiological systems (MPS) in pharmaceutical safety and ADME applications

Kristin Fabre,[ab] Brian Berridge,[c] William R. Proctor,[d] Sherry Ralston,[e] Yvonne Will,[f] Szczepan W. Baran,[g] Gorm Yoder[h] and Terry R. Van Vleet *[e]

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Cite this: *Lab Chip*, 2019, **19**, 3152

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

Garrett R. Ainslie, *[a] Myrtle Davis,[b] Lorna Ewart,[c] Linda A. Lieberman,[d] David J. Rowlands,[e] Andrew J. Thorley, [e] Gorm Yoder[f] and Anne M. Ryan[g]

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Cite this: *Lab Chip*, 2020, **20**, 697

Application of microphysiological systems in biopharmaceutical research and development

Norman C. Peterson, *[a] Prathap Kumar Mahalingaiah,[b] Aaron Fullerton[c] and Matteo Di Piazza[d]

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Cite this: *Lab Chip*, 2020, **20**, 215

Liver microphysiological systems development guidelines for safety risk assessment in the pharmaceutical industry

Andreas R. Baudy, *[a] Monicah A. Otieno,[b] Philip Hewitt,[c] Jinping Gan, [d] Adrian Roth,[e] Douglas Keller, [f] Radhakrishna Sura,[g] Terry R. Van Vleet[g] and William R. Proctor[h]

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Cite this: *Lab Chip*, 2020, **20**, 199

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

Rhiannon N. Hardwick, *[a] Catherine J. Betts,[b] Jessica Whritenour,[c] Radhakrishna Sura,[d] Maike Thamsen,[e] Elad H. Kaufman[f] and Kristin Fabre†[g]

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Cite this: *Lab Chip*, 2020, **20**, 468

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

Jonathan A. Phillips, [a] Taraka Sai Pavan Grandhi,[b] Myrtle Davis,[c] Jean-Charles Gautier,[d] Niresh Hariparsad,[a] Douglas Keller, [e] Radhakrishna Sura[f] and Terry R. Van Vleet*[f]

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Cite this: *Lab Chip*, 2020, **20**, 446

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

Stephen Fowler, [a] Wen Li Kelly Chen,[b] David B. Duignan,[c] Anshul Gupta,[b] Niresh Hariparsad,[d] Jane R. Kenny,[e] W. George Lai,[f] Jennifer Liras, [g] Jonathan A. Phillips [h] and Jinping Gan *[i]

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Cite this: *Lab Chip*, 2020, **20**, 1177

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

Matthew F. Peters, *[a] Allison L. Choy,[b] Carmen Pin,[c] Derek J. Leishman,[d] Annie Moisan,[e] Lorna Ewart, ‡[a] Peggy J. Guzzie-Peck,[f] Radhakrishna Sura,[g] Douglas A. Keller, [h] Clay W Scott[a] and Kyle L. Kolaja [i]

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