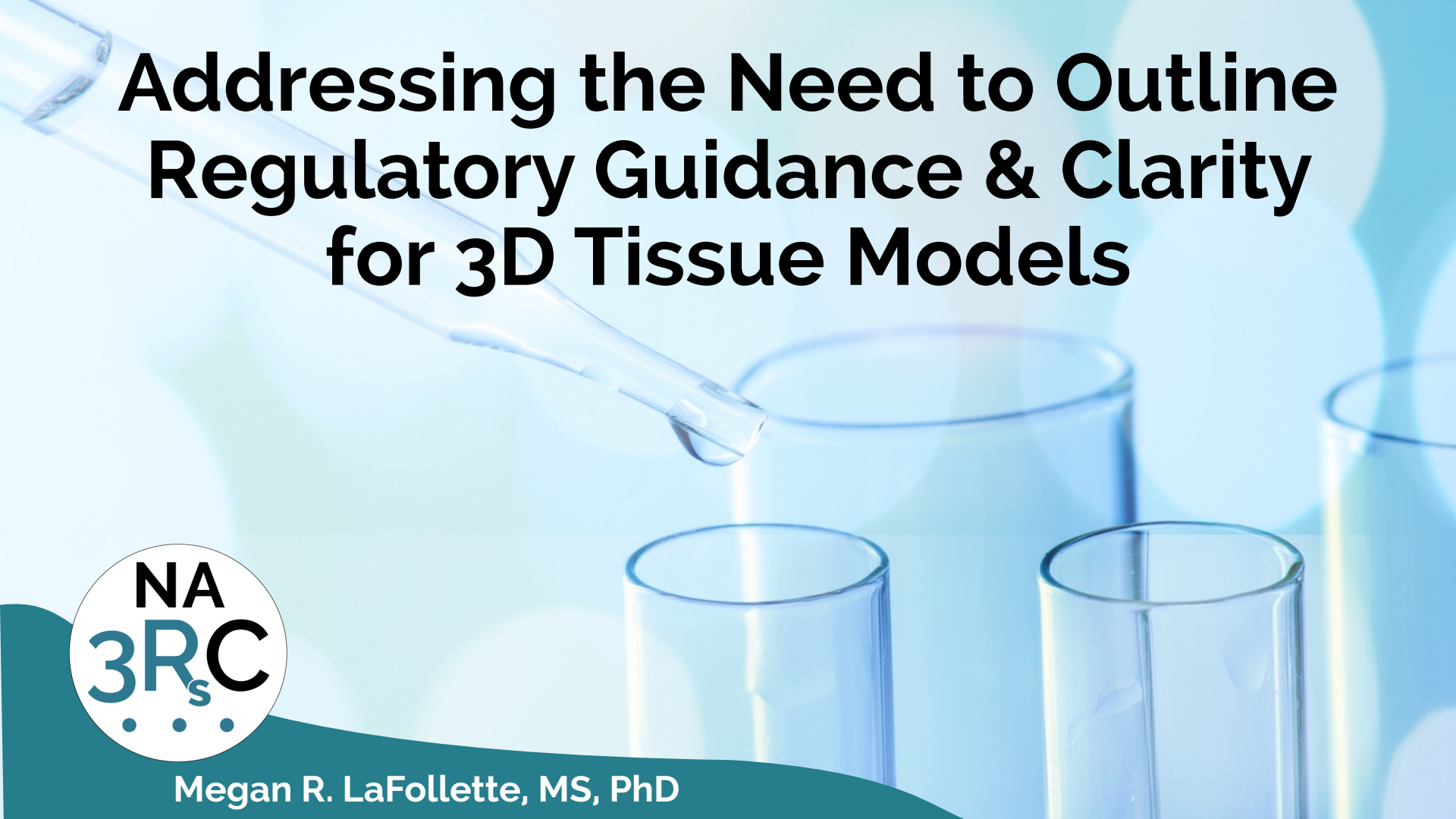
Addressing the Need to Outline Regulatory Guidance & Clarity for 3D Tissue Models



NA 3RsC

Megan R. LaFollette, MS, PhD

Acknowledgements

Abigail Martin (ImmuONE)
Albert Li (In Vitro ADMET Laboratories)
Anjali Venkateswaran (FlowCell Inc.)
Anne Dickinson (Alcyomics)
Barb Jones (Stemonix/Vyant)
Ben Cappiello (AxoSim)
Bill Thelin (Altis Biosystems)
Blake Anson (Stemonix/Vyant)
Bonnie Berry (Curi Bio)
Brian Manning (CN-Bio)
Carolina Lucchesi (Emulate)
Cecilia Sanchez (Obatala)
Chelsea Richardson (AxoSim)
Chris Hughes (Aracari Biosciences)
Clive Roper (Roper Toxicology)
Colin Brown (Newcells Biotech)
Connie Lebakken (Stem Pharm)
David Bode (Obatala Sciences)
David O'Dowd (Draper)
Dharaminder Singh (CN-Bio)
Doreen Miao (Ananda devices)
Elliott Johns (Emulate)
Ewelina Hoffman (ImmuONE)
Garrett Bennett (Nortis, Inc.)
Gwen Fewell (SynVivo)
Heejoon Choi (Curi Bio)
Henning Mann (Nortis)
Hossein Eslami Amirabadi (Azar Innovations)
James Hickman (Hesperos)
James Shoemaker (Lena Biosciences)
Jan Lichtenberg (InSphero)
Janick Stuck (Alveolix)
Jelena Vukasinovic (Lena Biosciences)
Jonathan Welch (Independent)
Joseph Charest (Biogen)
Kapil Pant (SynVivo)
Katie Zander (Standards Coordinating Body)
Krista Durney (Tara Biosystems)
Liz Boazak (Altis Biosystems)
Lowry Curley (AxoSim)
Marco Rasponi (BiomimX S.r.l)
Margaret-Anne Craig (Newcells Biotech)
Matthew Gevaert (Kiyatec)
Maurizio Aiello (React 4 Life)
Max Narovlyanksy (FlowCell Inc.)
Michael Biron (Altis Biosystems)
Mike Hendrickson (BrainXell)
Ming-i Huang (Aracari Biosciences)
Misti Ushio (Tara Biosystems)
Monica Metea (AxoSim/Preclinical Electrophysiology Consulting, LLC)
Nate Post (Hesperos)
Nick Geisse (Curi Bio)
Niki Heinz (Altis Biosystems)
Nina Hobi (Alveolix)
Norman Peterson (Seagen)
Olivier Frey (InSphero)
Paola Occhetta (BiomimX S.r.l)
Pelin Candarlioglu (GSK)
Ping Yeh (Independent Scientist)
Prathap Kumar Mahalingaiah (AbbVie)
Reyk Horland (Tissuse)
Rhys Powell (Newcells Biotech)
Roberta Visone (BiomimX S.r.l)
Ruth Plummer (MicroMatrices Associates Ltd)
Ryan Gordon (Stem Pharm)
Sarah Payne (CN-Bio)
Sepand Bafti (Nortis)
Silvia Scaglione (React 4 Life)
Simon Plummer (Micro Matrices)
Steven Visuri (Stem Pharm)
Sue Grepper (InSphero)
Suzanne Fitzpatrick (FDA)
Szczepan Baran (VeriSim)
Terry Van Vleet (AbbVie)
Tessa Desrochers (Kiyatec)
Thomas Neumann (Nortis)
Tomasz Kostrezewski (CN-Bio)
Trivia Frazier (Obatala Sciences)
Victoria Hutter (ImmuONE)
Ville Kujala (Emulate)
Wes Hatfield (Aracari Biosciences)
Wouter Striker (Mimetas)
Liv Brancato-Buentello (NA3RsC)
Natalia Ozimo (React4Life)
Michael Johnson (Visikol)

TODAY'S AGENDA

Existing Guidance & Standards

Importance of COU

Consensus-Based Guidance & Best Practices

NA3RsC mission is to advance science, innovation, & research animal welfare.

NA3RsC collaborates with experts across the field.

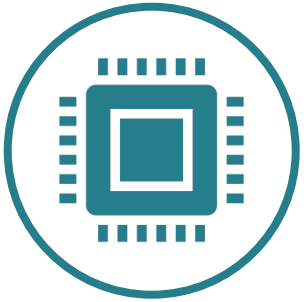
Lilly
scientist.com
USDA
Stanford University
3 R C C
zoetis
Roper Toxicology Consulting Limited
abbvie
EMORY
W
NC 3Rs

NA3RsC's strategy is to identify initiatives with

- Strong Evidence
- Big Impact
- Real-World Practicality

We currently have six key 3Rs initiatives.

Rodent Health Monitoring



Microphysiological Systems

Translational Digital Biomarkers

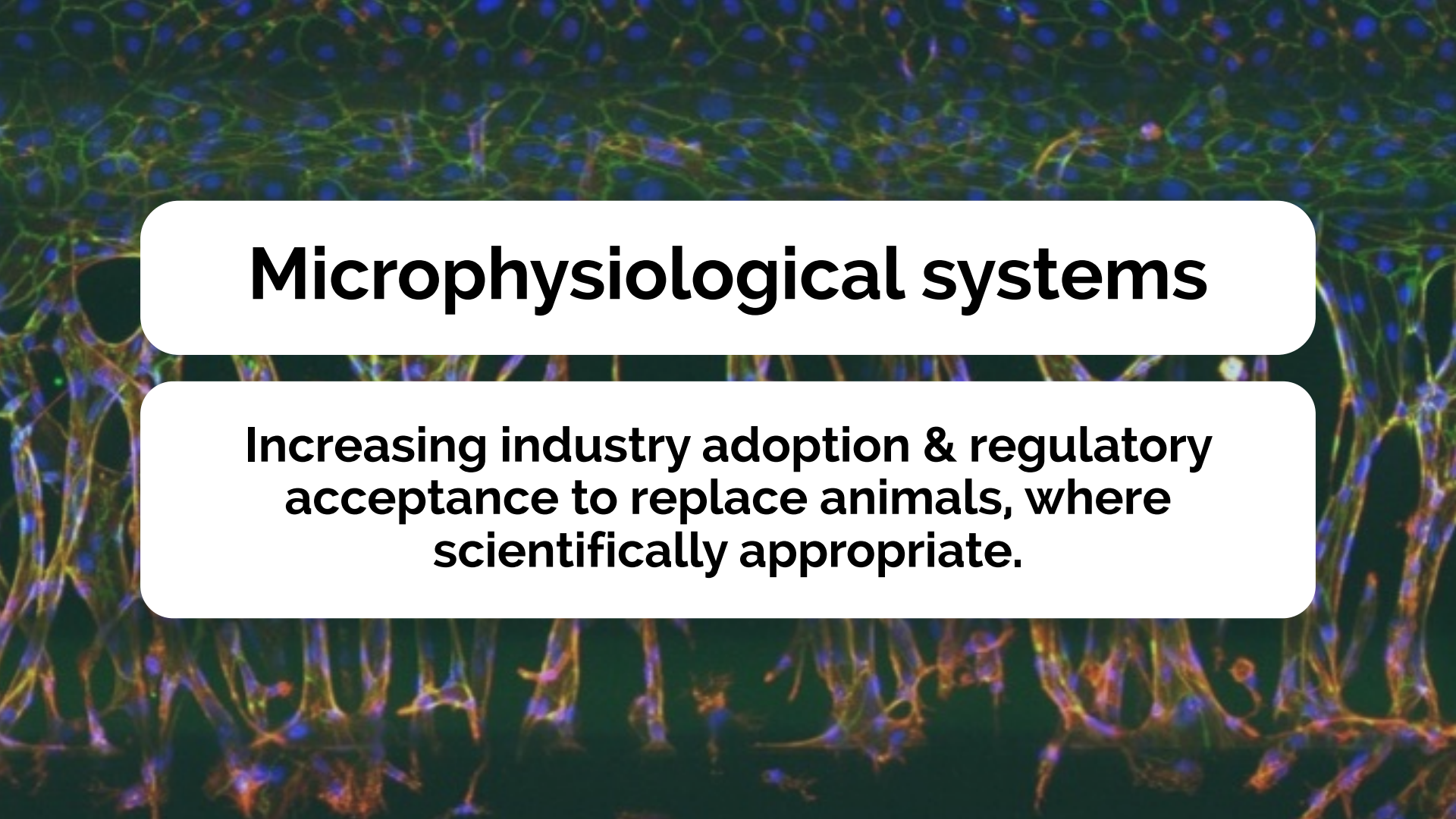
Refinement

3Rs Certification Course

Compassion Fatigue Resiliency

Our MPS group is unique because it's situated in an organization that recognizes the value and necessity of animal research.

We are committed to advancing all three "Rs."

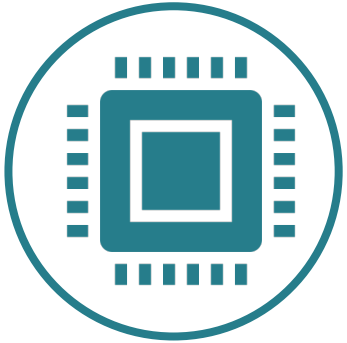


Microphysiological systems

Increasing industry adoption & regulatory acceptance to replace animals, where scientifically appropriate.

There are 3 key stakeholders for MPS.

Regulators



Developers

End-Users

Our group is unique because it's focused on developers with commercially-available systems.

Developers are in a key position to guide & assist MPS use & acceptance.

Promise

Limitations

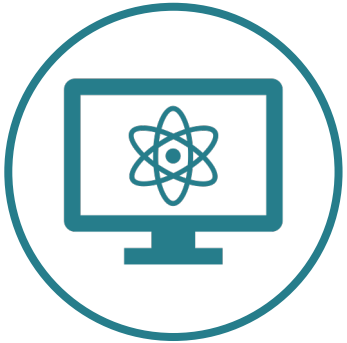
Tailored R&D

40 institutions (28 developers) are members.

Our initiative focuses on four key efforts.

End-user Interfacing

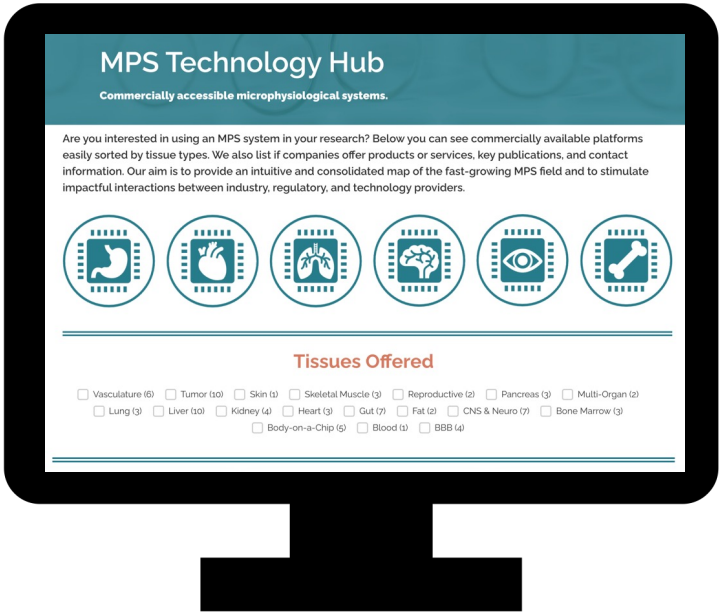
Regulatory Acceptance



Technology Expo

Education

NA3RsC has created a user-friendly technology hub

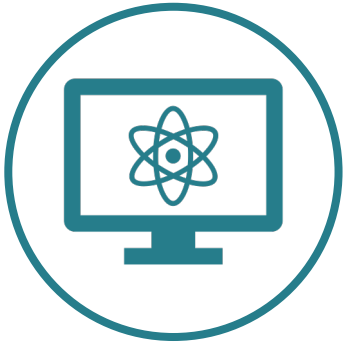


NA3RsC.org/mps-tech-hub/

Our initiative focuses on four key efforts.

End-user Interfacing

Regulatory Acceptance



Technology Expo

Education

TODAY'S AGENDA

Existing Guidance & Standards

Importance of COU

Consensus-Based Guidance & Best Practices

Regulatory guidance on acceptance criteria is lacking.

Historically, alternative methods have been evaluated based on comparison with *in vivo* test methods

MPS data currently complements traditional methods, rather than replacing it.

Regulatory agencies (FDA/CDER) generally support the development of & are receptive to MPS.

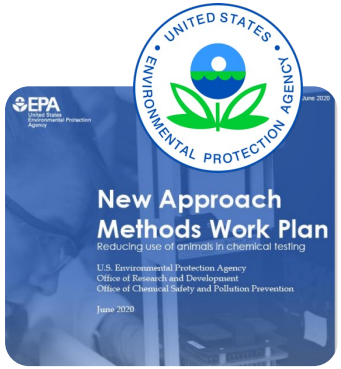
There are current regulatory efforts to advance the MPS field which may be applied to development of guidance & standards.

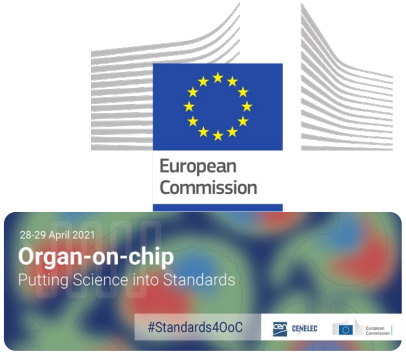
FDA

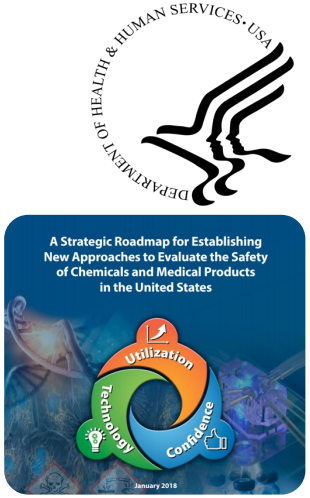
FDA U.S. FOOD & DRUG ADMINISTRATION

Advancing New Alternative Methodologies at FDA

FDA Webinar Series on Alternative Methods: Showcasing cutting-edge technologies for disease modeling, efficacy, and safety

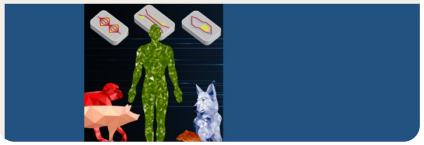






NATIONAL ACADEMY OF SCIENCES

Microphysiological Systems: Bridging Human and Animal Research - A Workshop



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Meeting Report:
First EMA workshop on non-animal approaches in support of medicinal product development – challenges and opportunities for use of micro-physiological systems (EMA/CHMP/SWP/250438/2018)
5 October 2017, European Medicines Agency, London

NIH

MPSCoRe Spring Workshop
April 1, 2021
Session 1: MPS Models for Testing Therapeutics

FDA's Innovative Science & Technology Approaches for New Drugs (ISTAND) can be used for MPS.

- Allow developers to pre-qualify a new drug development tool (e.g., MPS) for a broad context of use
- Removes responsibility from end-user
- Once qualified, the tool will be seen as reliable for specific application and context of use within regulatory review

Launched in December 2020

There are current regulatory efforts to advance the MPS field which may be applied to development of guidance & standards.

Publications (NAMS, etc.)

Research

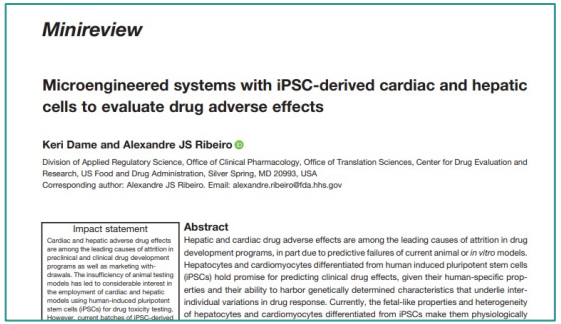
ICH Guideline Revision

Existing qualification & Pilot initiatives

Conferences & Meetings NAS, NIH, FDA, MS, PSIS, etc.

Clippinger et al., 2018

The FDA is actively evaluating MPS for a number of contexts of use.



Minireview

Microengineered systems with iPSC-derived cardiac and hepatic cells to evaluate drug adverse effects

Keri Dame and Alexandre JS Ribeiro

Division of Applied Regulatory Science, Office of Clinical Pharmacology, Office of Translation Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD 20993, USA
Corresponding author: Alexandre JS Ribeiro. Email: alexandre.ribeiro@fda.hhs.gov

Impact statement

Cardiac and hepatic adverse drug effects are among the leading causes of attrition in preclinical and clinical drug development programs as well as marketing withdrawals. The insufficiency of animal testing models has led to considerable interest in the employment of cardiac and hepatic models using human-induced pluripotent stem cells (iPSCs) for drug toxicity testing. However, current batches of iPSC-derived

Abstract

Hepatic and cardiac drug adverse effects are among the leading causes of attrition in drug development programs, in part due to predictive failures of current animal or *in vitro* models. Hepatocytes and cardiomyocytes differentiated from human induced pluripotent stem cells (iPSCs) hold promise for predicting clinical drug effects, given their human-specific properties and their ability to harbor genetically determined characteristics that underlie inter-individual variations in drug response. Currently, the fetal-like properties and heterogeneity of hepatocytes and cardiomyocytes differentiated from iPSCs make them physiologically

Received: 13 August 2020 | Revised: 2 December 2020 | Accepted: 7 December 2020
DOI: 10.1111/cts.12969

ARTICLE

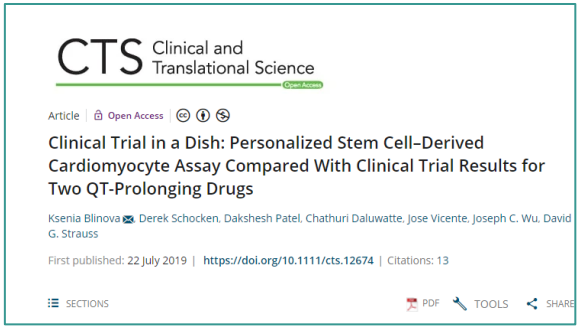
Characterizing the reproducibility in using a liver microphysiological system for assaying drug toxicity, metabolism, and accumulation

Andrés Rubiano[1] | Amruta Indapurkar[1] | Ryosuke Yokosawa[1] | Alina Miedzik[2] | Barry Rosenzweig[1] | Ayesha Areffin[1] | Chloe M. Moulin[1] | Keri Dame[1] | Neil Hartman[1,†] | Donna A. Volpe[1] | Murali K. Matta[1] | David J. Hughes[2] | David G. Strauss[1,3] | Tomasz Kostrzewski[2] | Alexandre J. S. Ribeiro[1]

[1]Center for Drug Evaluation and Research, Office of Translational Sciences, Office of Clinical Pharmacology, Division of Applied Regulatory Science, US Food and Drug Administration, Silver Spring, Maryland, USA
[2]CN Bio Innovations Limited, Cambridge, UK

Abstract

Liver microphysiological systems (MPSs) are promising models for predicting hepatic drug effects. Yet, after a decade since their introduction, MPSs are not routinely used in drug development due to lack of criteria for ensuring reproducibility of results. We characterized the feasibility of a liver MPS to yield reproducible outcomes of experiments assaying drug toxicity, metabolism, and intracellular accumulation. The ability of the liver MPS to reproduce hepatotoxic effects was assessed using troglitazo



CTS Clinical and Translational Science

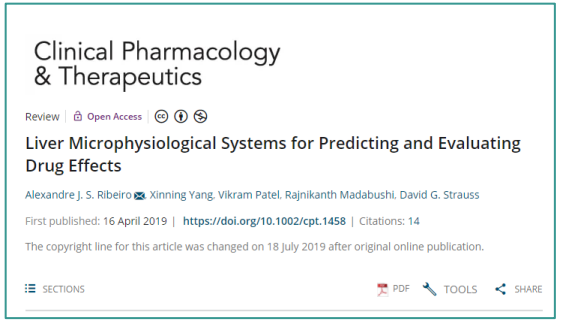
Article | Open Access

Clinical Trial in a Dish: Personalized Stem Cell–Derived Cardiomyocyte Assay Compared With Clinical Trial Results for Two QT-Prolonging Drugs

Ksenia Blinova, Derek Schocken, Dakshesh Patel, Chathuri Daluwatte, Jose Vicente, Joseph C. Wu, David G. Strauss

First published: 22 July 2019 | https://doi.org/10.1111/cts.12674 | Citations: 13

SECTIONS PDF TOOLS SHARE



Clinical Pharmacology & Therapeutics

Review | Open Access

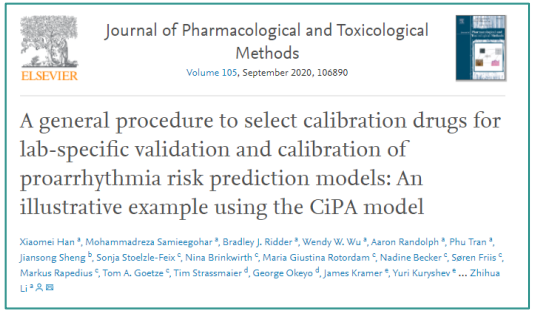
Liver Microphysiological Systems for Predicting and Evaluating Drug Effects

Alexandre J. S. Ribeiro, Xinning Yang, Vikram Patel, Rajnikanth Madabushi, David G. Strauss

First published: 16 April 2019 | https://doi.org/10.1002/cpt.1458 | Citations: 14

The copyright line for this article was changed on 18 July 2019 after original online publication.

SECTIONS PDF TOOLS SHARE



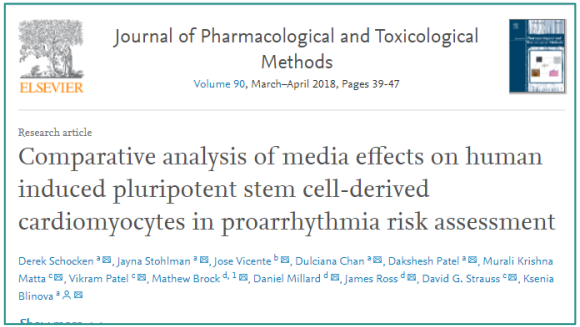
ELSEVIER

Journal of Pharmacological and Toxicological Methods

Volume 105, September 2020, 106890

A general procedure to select calibration drugs for lab-specific validation and calibration of proarrhythmia risk prediction models: An illustrative example using the CiPA model

Xiaomei Han [a], Mohammadreza Samieegohar [a], Bradley J. Ridder [a], Wendy W. Wu [a], Aaron Randolph [a], Phu Tran [a], Jiansong Sheng [b], Sonja Stoelzle-Feix [c], Nina Brinkwirth [c], Maria Giustina Rotordam [c], Nadine Becker [c], Søren Friis [c], Markus Rapedius [c], Tom A. Goetze [c], Tim Strassmaier [d], George Okeyo [d], James Kramer [e], Yuri Kuryshev [e] ... Zhihua Li [a]



ELSEVIER

Journal of Pharmacological and Toxicological Methods

Volume 90, March–April 2018, Pages 39-47

Research article

Comparative analysis of media effects on human induced pluripotent stem cell-derived cardiomyocytes in proarrhythmia risk assessment

Derek Schocken [a], Jayna Stohlman [a], Jose Vicente [b], Dulciana Chan [a], Dakshesh Patel [a], Murali Krishna Matta [c], Vikram Patel [c], Mathew Brock [d, 1], Daniel Millard [d], James Ross [d], David G. Strauss [c], Ksenia Blinova [a]

Current MPS use is far from its full potential.

In-House Screening: End-Users are already being used for internal portfolio decision making.

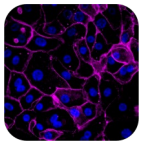
MPS-based organ/tissue model	No. of cases	Area of use (drug development phase)	MPS-supplier	End user	Reference (if available)
Blood vessel, vasculature	5	Target identification, validation and compound selection	AIST	Daiichi-Sankyo	Satoh et al., 2016
		Discovery (scleroderma)	Mimetas	Galapagos	–
		Systems toxicology for consumer products	Mimetas	Philip Morris	Poussin et al.,2020
		Pharmacokinetics and pharmacology	Mimetas	undisclosed	–
		Target identification and validation	Mimetas	NovoNordisk	–
Bone marrow	4	Preclinical safety	TissUse	AstraZeneca	Sieber et al., 2018
		Preclinical safety	Emulate	AstraZeneca	Chou et al., 2018
		Preclinical safety	TissUse	Roche	–
		Preclinical safety	TissUse	Bayer	–
Gut epithelium	4	Discovery (inflammatory bowel disease)	Mimetas	Galapagos	Beaurivage et al., 2019
		Discovery	Mimetas	Roche	–
		Clinical development	Mimetas	Roche	–
		Preclinical safety	Emulate	Roche	–
Lung	3	Discovery (alveolus)	Wyss	undisclosed	Huh et al., 2012
		Drug efficacy (epithelium)	Wyss	Pfizer, Merck USA	Benam et al., 2016b
		Preclinical safety	Emulate	Roche	–
Liver	2	Pharmacological and toxicological effects	Emulate	AstraZeneca	Foster et al., 2019
		Preclinical safety – assessment of species (rat, dog & human)	Emulate	J&J, AstraZeneca	Jang et al., 2019
Ocular compartment	1	Discovery	Fh IGB / EKUT	Roche	Achberger et al., 2019
Kidney epithelium	1	Pharmacokinetics and pharmacology	Mimetas	undisclosed	Vormann et al., 2018
Liver-Pancreas	1	Target validation / identification	TissUse	AstraZeneca	Bauer et al., 2017
Liver-Thyroid	1	Preclinical safety – assessment of species-specificity (rat and human)	TissUse	Bayer	Kühnlenz et al., 2019
Skin-Tumor	1	Preclinical safety & efficacy	TissUse	Bayer	Hübner et al., 2019

Abbreviations: Wyss, Wyss Institute at Harvard, Boston, MA, USA; AIST, National Institute of Advanced Industrial Sciences, Tokyo, Japan; Fh IGB, Fraunhofer Institute for Interfacial Engineering and Biotechnology, Stuttgart, Germany; EKUT, Eberhard Karls University, Tübingen, Germany

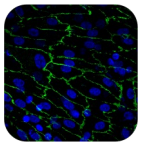
Marx et al. Altex. 2021

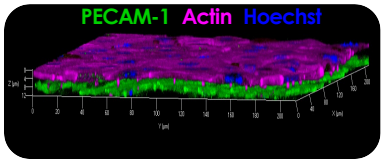
MPS have successfully been used in several IND studies for large/small molecules & immunotherapeutics safety assessment

Primary lung epithelial cells

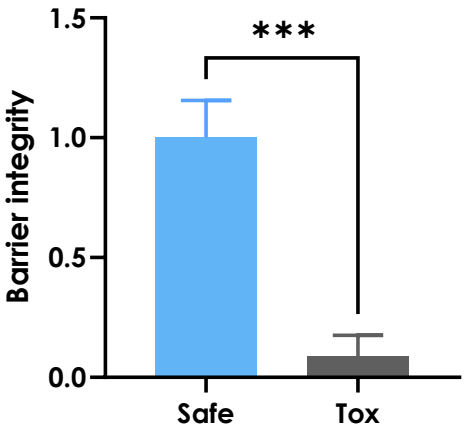


Primary lung endothelial cells

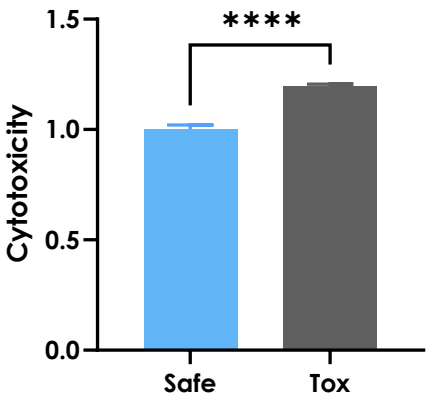




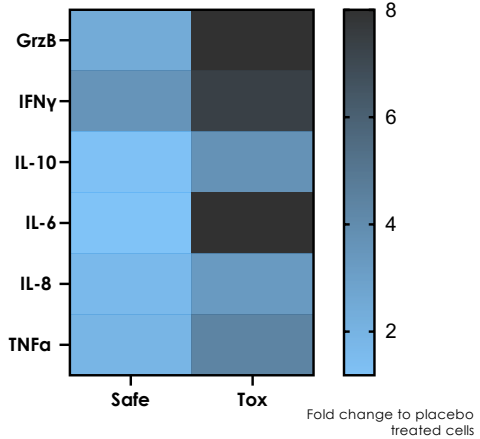
Barrier integrity



Cytotoxicity



Inflammation



In these cases, animal tests are not useful due to species specificity

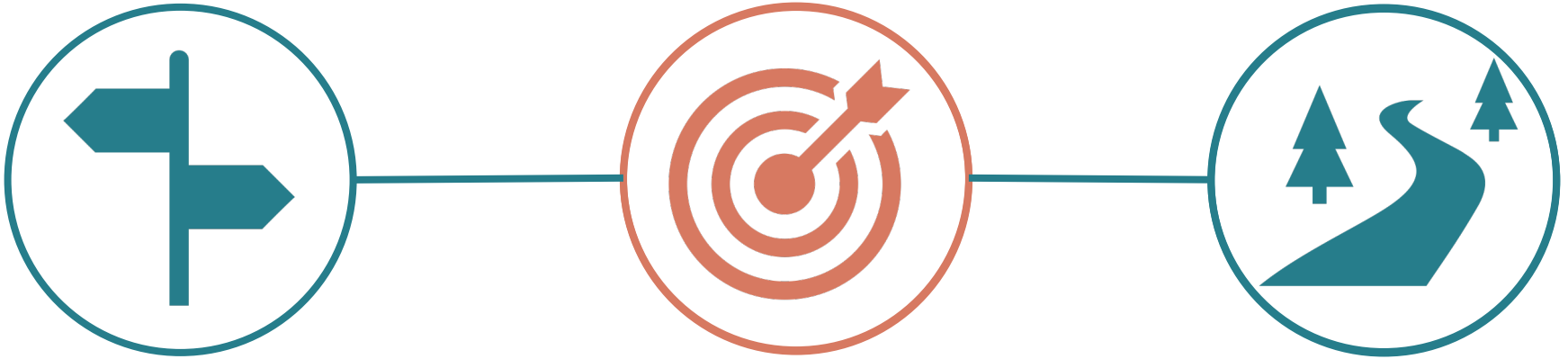
(AlveoliX Alveoloar Barrier Model, Stucki et al 2018 Sci Report, Raggi et al 2020 ERJ)

Case by Case: The FDA accepted label expansion using only MPS Data

- Vertex Pharmaceuticals
- Treatment of cystic fibrosis
- Qualification for new genotypes of patients with mutations in the cystic fibrosis transmembrane conductance regulatory (CFTR) gene
- MPS were used in a focused assay with defined electrophysiological alterations to evaluate efficacy of a drug

Gaining consistent & clear regulatory acceptance is critical for the field.

TODAY'S AGENDA



Existing Guidance & Standards

Importance of Contexts of Use (COU)

Consensus-Based Guidance & Best Practices

Context of use is a concise definition of the manner & purpose of a MPS use.

- Determines how much "validation/qualification" is needed for a particular assay
- Defines the domain, boundaries, & limitations for acceptable use as justified by data

Manner

Purpose

Boundaries

(Amy Avila on MPS: Bridging human & Animal Research as NAM for Improving Predictability & Helping 3Rs, FDA/CDER, 2021)

Defining context of use is essential for regulatory acceptance of MPS.

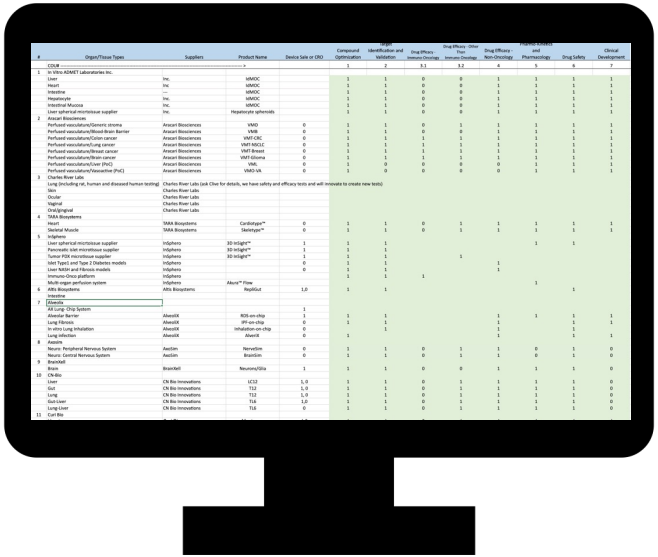
- MPS are drug development tools
- As such, MPS could be qualified for a specific context of use across drug development programs which would…

Increase availability of effective drugs

Accelerate the drug development cycle

Enhance knowledge of developed drugs

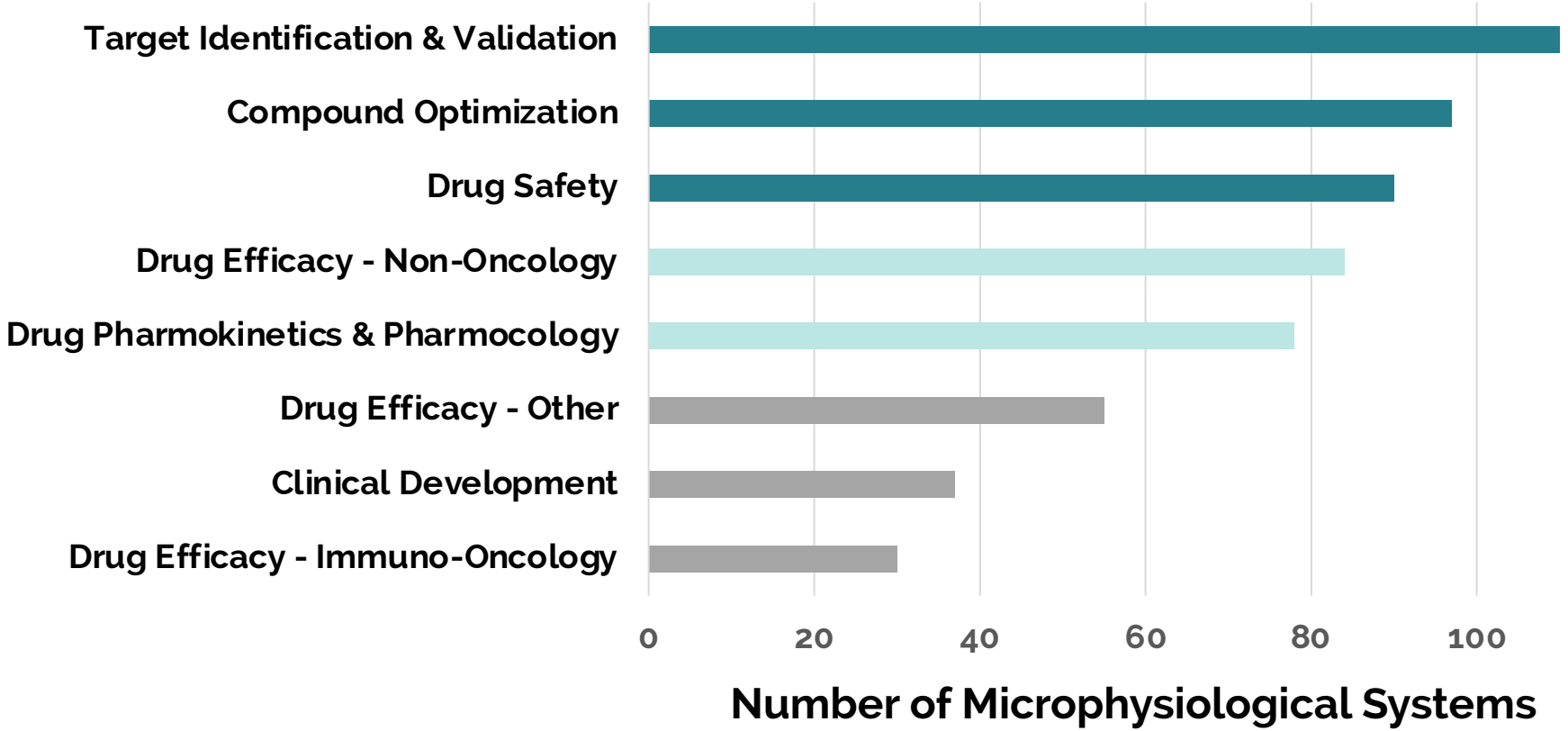
NA3RsC is collecting data on commercially available technologies.



#	Organ/Tissue Types	Suppliers	Product Name	Device Sale or CRO	Compound Optimization	Target Identification and Validation	Drug Efficacy - Immuno-Oncology	Drug Efficacy - Other Than Immuno-Oncology	Drug Efficacy - Non-Oncology	Preclinical Safety and Pharmacology	Drug Safety	Clinical Development
	COU# →				1	2	3.1	3.2	4	5	6	7
1	In-Vitro ADMET Laboratories Inc.											
	Liver	Inc.	MMOC		1	1	0	0	1	1	1	1
	Heart	Inc	MMOC		1	1	0	0	1	1	1	1
	Intestine	Inc	MMOC		1	1	0	0	1	1	1	1
	Hepatocyte	Inc.	MMOC		1	1	0	0	1	1	1	1
	Intestinal Mucosa	Inc.	MMOC		1	1	0	0	1	1	1	1
	Liver spherical microtissue supplier	Inc.	Hepatocyte spheroids		1	1	0	0	1	1	1	1
2	Avacet Biosciences											
	Perfused-vasculature/Genomic stroma	Avacet Biosciences	VMO	0	1	1	0	1	1	1	1	1
	Perfused-vasculature/Blood-Brain Barrier	Avacet Biosciences	VMB	0	1	1	0	0	1	1	1	1
	Perfused-vasculature/Colon cancer	Avacet Biosciences	VMT-CRC	0	1	1	1	1	1	1	1	1
	Perfused-vasculature/Lung cancer	Avacet Biosciences	VMT-NSCLC	0	1	1	1	1	1	1	1	1
	Perfused-vasculature/Breast cancer	Avacet Biosciences	VMT-Breast	0	1	1	1	1	1	1	1	1
	Perfused-vasculature/Brain cancer	Avacet Biosciences	VMT-Glioma	0	1	1	1	1	1	1	1	1
	Perfused-vasculature/Liver (PoC)	Avacet Biosciences	VML	0	1	0	0	0	0	1	1	1
	Perfused-vasculature/Vasoactive (PoC)	Avacet Biosciences	VMO-VA	0	1	0	0	0	0	1	1	1
3	Charles River Labs											
	Lung (including rat, human and diseased human testing)	Charles River Labs (ask Clive for details, we have safety and efficacy tests and will innovate to create new tests)										
	Skin	Charles River Labs										
	Ocular	Charles River Labs										
	Vaginal	Charles River Labs										
	Oral/gingival	Charles River Labs										
4	TARA Biosystems											
	Heart	TARA Biosystems	Cardiotype™	0	1	1	0	1	1	1	1	1
	Skeletal Muscle	TARA Biosystems	Skeletype™	0	1	1	0	1	1	1	1	1
5	InSphero											
	Liver spherical microtissue supplier	InSphero	3D InSight™	1	1	1				1	1	
	Pancreatic islet microtissue supplier	InSphero	3D InSight™	1	1	1						
	Tumor PDX microtissue supplier	InSphero	3D InSight™	1	1	1		1				
	Islet Type1 and Type 2 Diabetes models	InSphero		0	1	1			1			
	Liver NASH and Fibrosis models	InSphero		0	1	1			1			
	Immuno-Onco platform	InSphero			1	1	1					
	Multi-organ perfusion system	InSphero	Akura™ Flow							1		
6	ARIs Biosystems	ARIs Biosystems	RegiMGut	1,0	1	1					1	
	Intestine											
7	Alveolix											
	Alt Lung -Chip System			1								
	Alveolar Barrier	AlveoliX	With-on-chip	1	1	1			1	1	1	1
	Lung Fibrosis	AlveoliX	IPF-on-chip	0	1	1			1		1	1
	In-vitro Lung Inhalation	AlveoliX	Inhalation-on-chip	0		1			1		1	
	Lung Infection	AlveoliX	AlveoliX	0	1				1		1	1
8	Axiom											
	Neuro: Peripheral Nervous System	AxoSim	NerveSim	0	1	1	0	1	1	0	1	0
	Neuro: Central Nervous System	AxoSim	BrainSim	0	1	1	0	1	1	0	1	0
9	BrainXell											
	Brain	BrainXell	Neurons/Glia	1	1	1	0	0	1	1	1	0
10	CN-Bio											
	Liver	CN Bio Innovations	LC12	1, 0	1	1	0	1	1	1	1	0
	Gut	CN Bio Innovations	T12	1, 0	1	1	0	1	1	1	1	0
	Lung	CN Bio Innovations	T12	1, 0	1	1	0	1	1	1	1	0
	Gut-Liver	CN Bio Innovations	TL6	1,0	1	1	0	1	1	1	1	0
	Lung-Liver	CN Bio Innovations	TL6	0	1	1	0	1	1	1	1	0
11	Cori Bio											

Context of Use Document

Commercial contexts of use are diverse



NA3RsC MPS Initiative Internal Data

MPS Need
By COU

Urgent Drug
Development Areas

Gaps in Animal
Models

Our goal is to identify a few greatly needed COUs from end-users that developers can commercially provide & regulators support.

Drug-Induced Liver Toxicity may be a key context of use to focus on (1) Due to high species-specific physiology

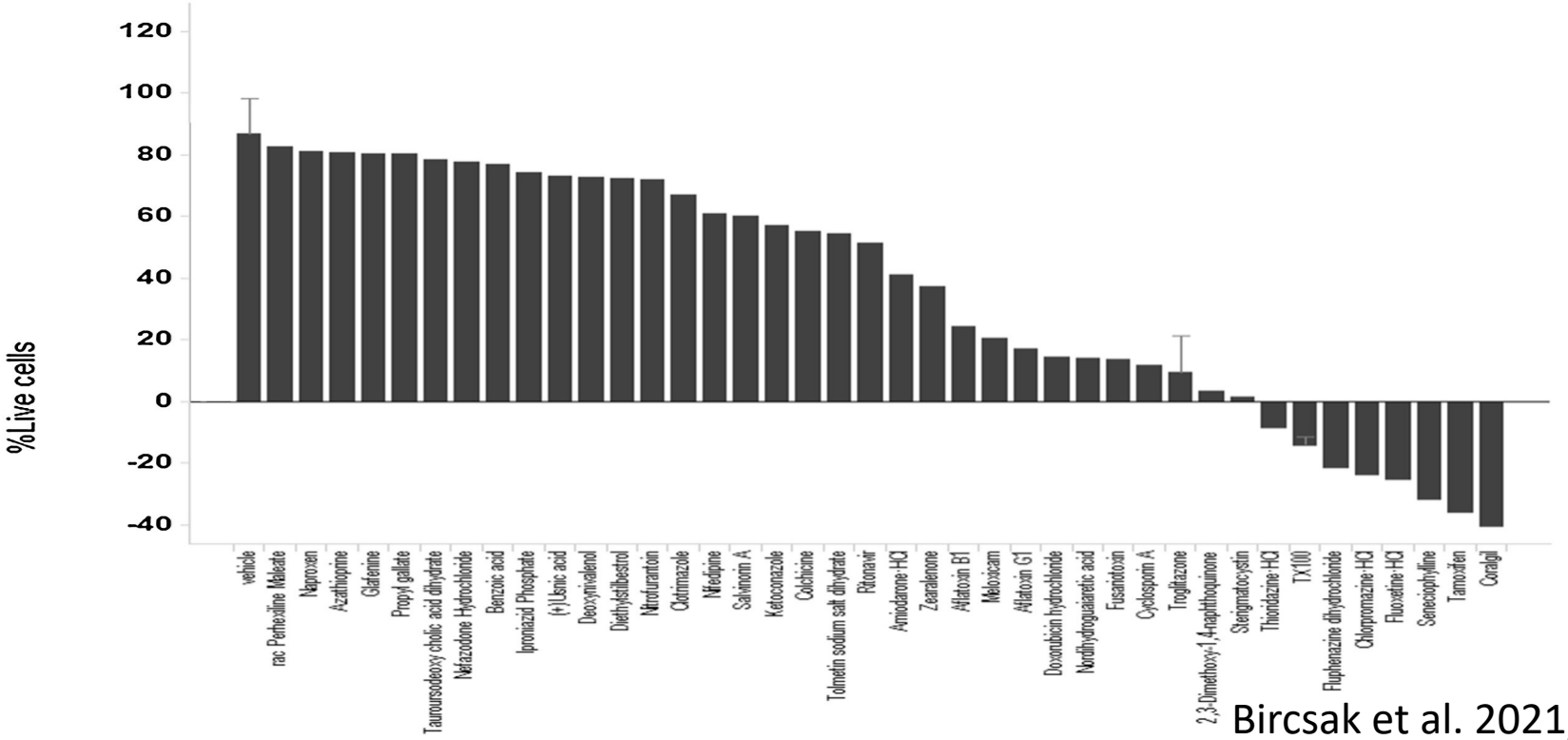
5 of 7 of the most important drug metabolizing enzymes are different between humans & animal models

The two that are the same only metabolize

5% of drugs

Jang et al. 2019.

Drug-Induced Liver Toxicity may be a key context of use to focus on (2) developers can provide fully human, highly complex, predictive MPS liver models



Bircsak et al. 2021, Toxicology

TODAY'S AGENDA

Existing Guidance & Standards

Importance of COU

Consensus-Based Guidance & Best Practices

This is an opportunity to create clinically relevant, built for purpose guidance that ultimately replaces some animal research.

Write an opinion paper to guide regulators from the developers point of view.

MPS can learn from animal models

- Animal model systems include variability between labs (species, strain, housing, husbandry, diet, measures, etc.) but little variability within labs (unlike a human population).
- Animal models are not necessarily reproducible or translational to humans. In part, reflects species-specific physiology
- Therefore, our stance is that animal model systems should not necessarily be held as the gold standard. Rather the gold standard should be response in human patients.

Animal models can be qualified via the FDA AMQP

- It is **voluntary**
- Needs to support multiple IND programs
- Need to show it is a suitable system with regards to the drugs mechanism of action and translatability to human
- Ideally follows GLP regulations (good practice/QC aspect)

There are two key areas to consider when qualifying MPS models.

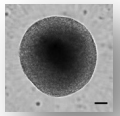
- **Replicability & Reproducibility** = consistent results within and between laboratories
- **Translation** = extent that test method correctly predicts in vivo effects
  - Animal MPS to animal *in vivo*
  - Human MPS to human *in vivo*
  - Mechanistically relevant human specific endpoints/biomarkers that allow for accurate prediction of human *in vivo* effects
  - Recapitulation of important in vivo physiological (e.g., morphology, function, proteome, metabolome) & pathophysiological conditions

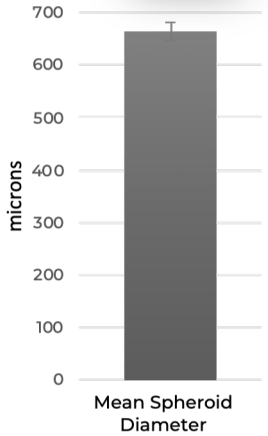
MPS systems can have robust reproducibility.

Quality control results from 17 months of manufacturing batches (thousands of organoids)

Structural Reproducibility

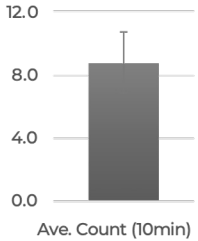
Spheroid diameter

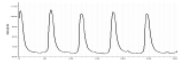




665 +/- 17.2mM

Consistent baseline activity

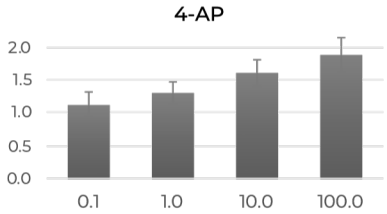




9+/-2 peaks
- **384 wells/plate**
- **17 months of mfg**

Consistent Pharmacology I

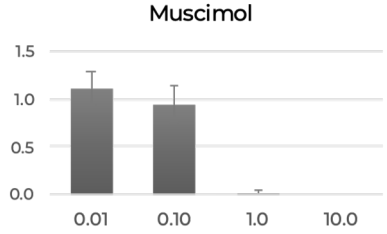
Ion channel activity

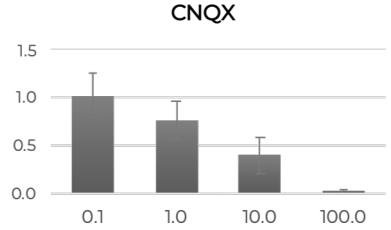


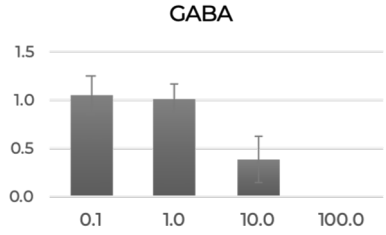
***All compound tests are peak count normalized to DMSO controls**

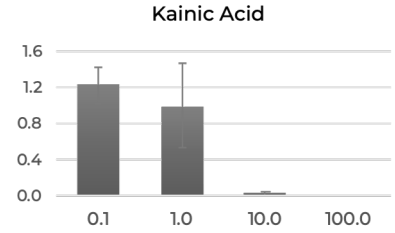
Consistent Pharmacology II

Key neurotransmitter responses







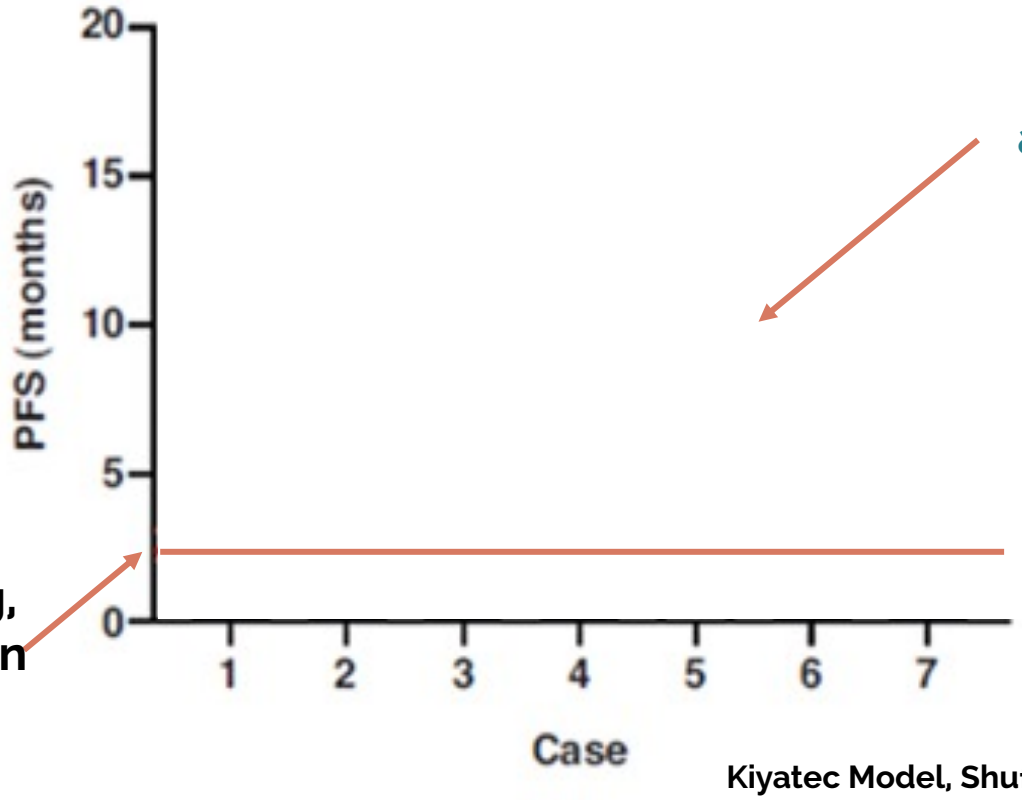


Concentration (mM)

Reproducible longitudinal structural and functional QC demonstrate stable cellular processes across manufacturing batches

(Vyant Bio Data)

Human MPS to Human In Vivo translation has increased patients' progression free survival (PFS) time



With MPS-aided decision making, all patient's PFS time more than doubled

With traditional decision making, historical median PFS is ~2.5 months

Kiyatec Model, Shuford et al. Neurooncol Adv. 2021

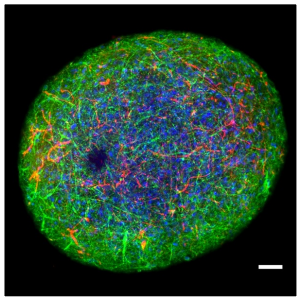
Recapitulation of important in vivo physiological & pathophysiological conditions with human specific endpoints

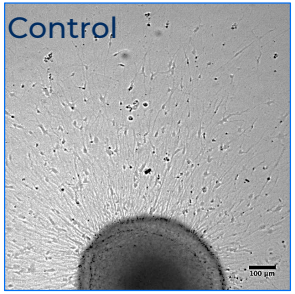
Neurite Outgrowth

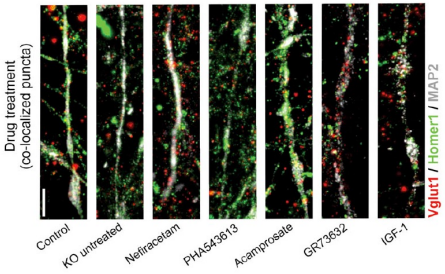
Synapse Formation

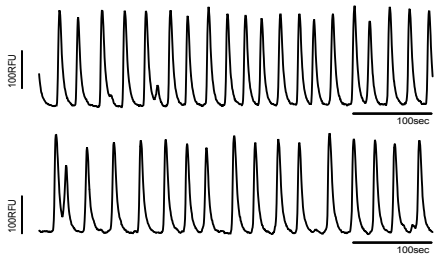
Neural Function

Control

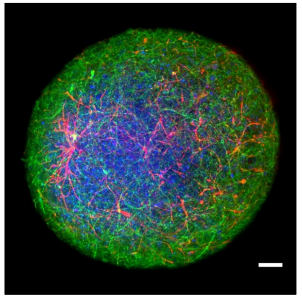


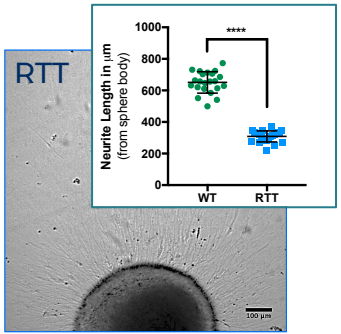


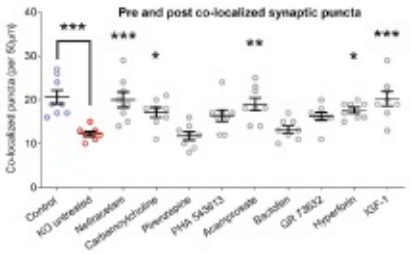


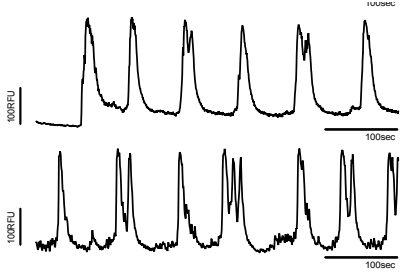


Rhett Disease







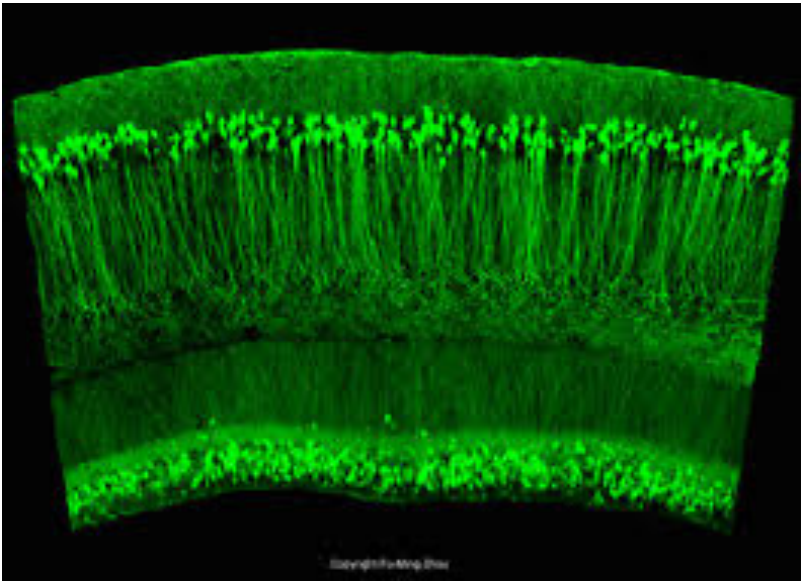


(Vyant Bio Model, Trujillo et al., 2020)

Qualification of MPS models

- Biological characterization by structural and functional integrity. Define and evaluate criteria for physiological relevance and pathophysiology (identification of plausible biomarker)
- Qualification by reference compounds. Testing of in vivo positive and negative compounds. Comparison with in vitro data.
- Technical feasibility
- Testing assays for specific biomarker (e.g., clinical)

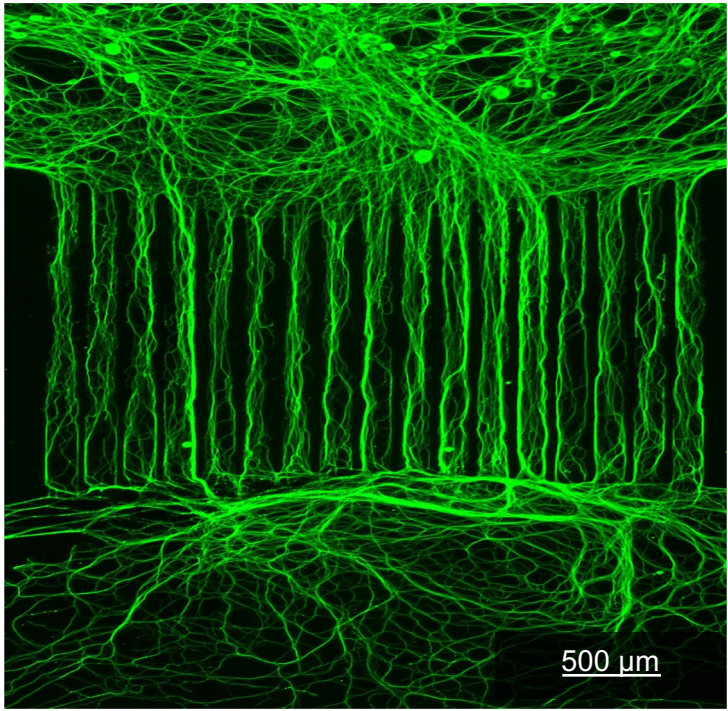
Biological characterization by structural and functional integrity.



Brain Slice

Soma

Axon



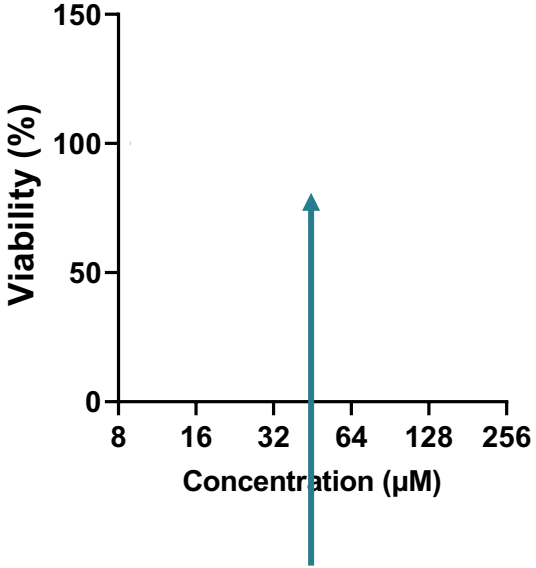
Cortical neurons on-a-chip

(Ananda Devices Model)

Qualification by reference compounds

Non-Cytotoxic

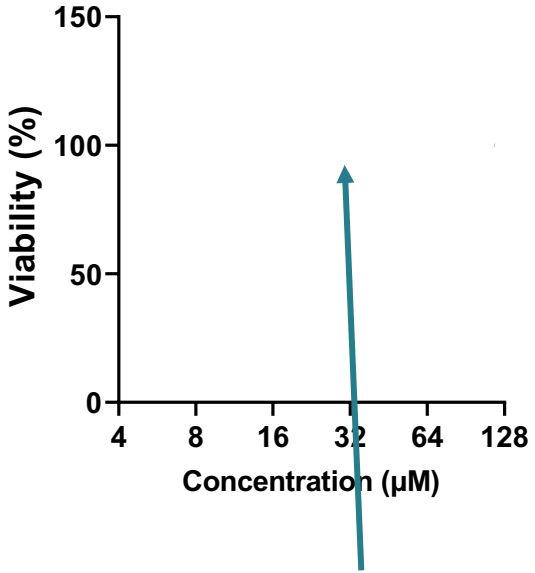
Ketorolac Tromethamine - 72 h



Cells remain viable at all concentrations even after 72 hours of incubation

Cytotoxic

Doxorubicin - 24 h



Cells viability decreases in a dose-dependent manner to known toxins

(Newcell Bio Model, Dr Valeria Chichagova & Dr. Carol de Santis)

While qualifying MPS models, the following should be considered:

- High scalability enables pragmatic industrial application and data production
- Validation by consortium (stakeholder from industry and/or academia)
- Early Involvement of regulatory bodies/stakeholders (FDA, EMA, JRC ECVAM, NIEHS, etc)

Guidance should follow
the *in vivo* model qualification criteria,
discussing best practices, &
MPS should be held to the
same standard as animal models.

Next Step

Collaborate with current initiatives to reach harmonized global guidance.

Ultimately, our aim is to create global harmonized guidance for MPS to make this technology as regulatory accepted as in vivo methods.

NA 3RsC

Thank you to our current sponsors

Thank you to our MPS initiative members.

Visit NA3RsC.org to learn more & join us to further the 3Rs.

Email me: meglafollette@na3rsc.org