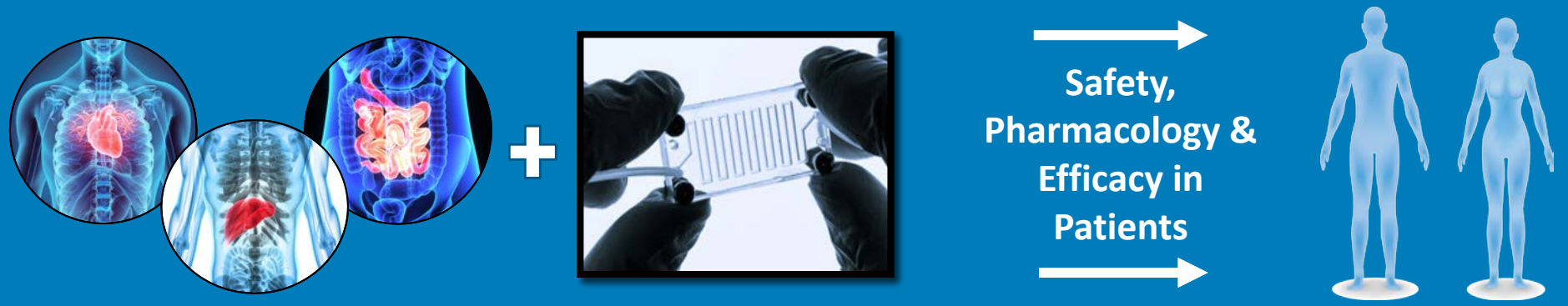
U.S. FOOD & DRUG ADMINISTRATION

Advancing Translational Models & Tools into the Drug Review Process: Opportunities for MPS



David Strauss, MD, PhD

Director, Division of Applied Regulatory Science
Office of Clinical Pharmacology | Office of Translational Sciences
Center for Drug Evaluation and Research

This presentation reflects the views of the author and should not be construed to represent FDA's view or policies

Translational Models and Tools to Advance Drug Development

Drug Development

← >10,000 Compounds

← Optimize Compounds

← Preclinical Safety

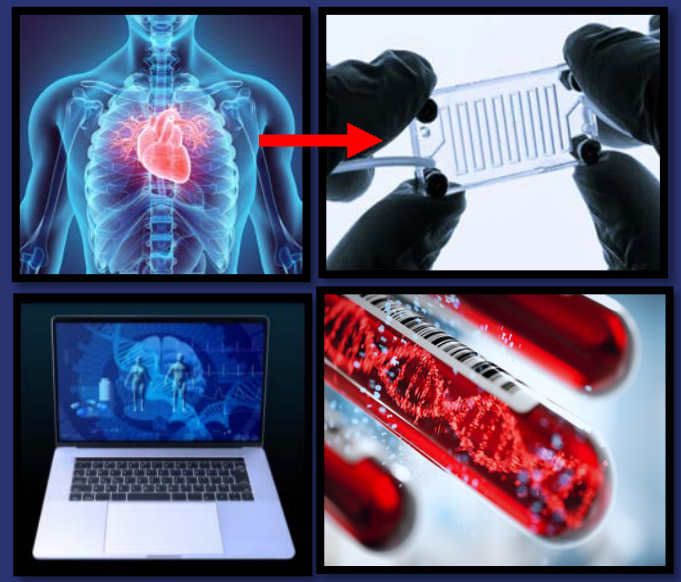
← Clinical Studies

← FDA Review

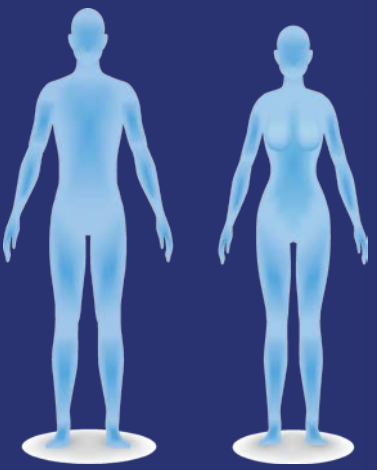
← 1 Approved Drug

Translational Models and Tools

New science can be used to overcome challenges and hurdles in drug development



Safety, Pharmacology & Efficacy in Patients



Including MPS

Translating New Science Into the Drug Review Process: FDA's Division of Applied Regulatory Science (DARS)

Regulatory Science: Review

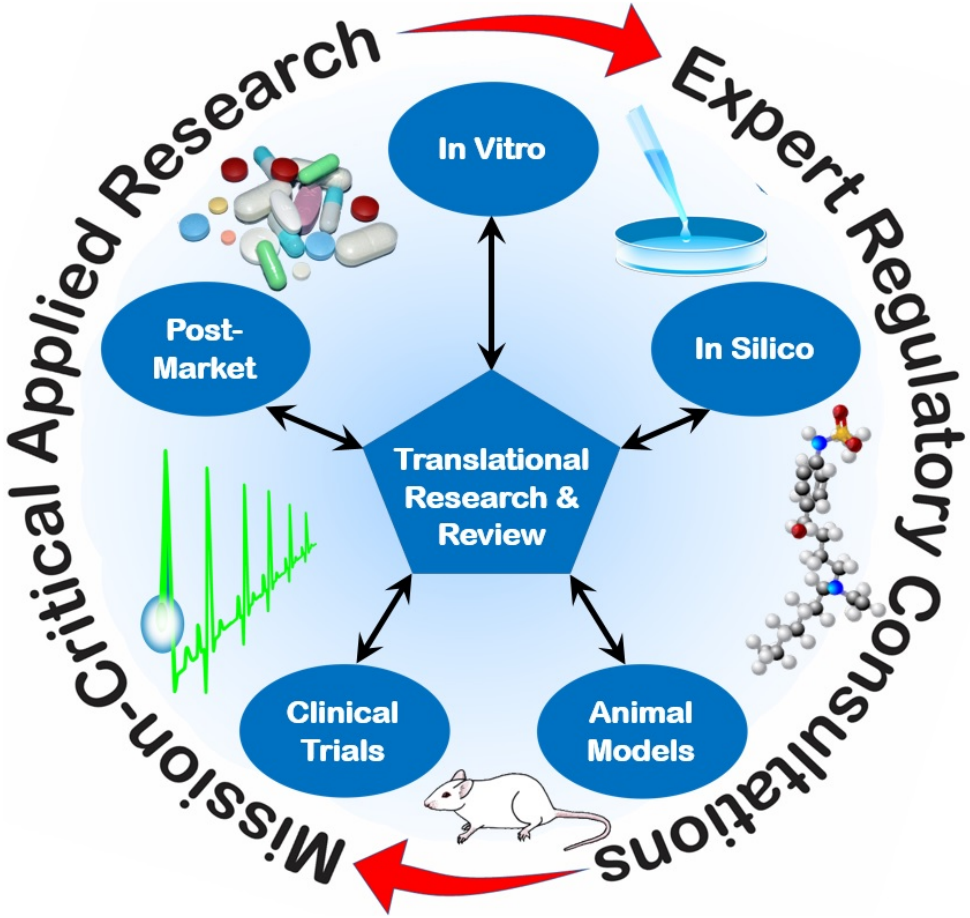
DIA

Translating New Science Into the Drug Review Process: The US FDA's Division of Applied Regulatory Science

Rodney Rouse, DVM, MBA, PhD[1], Naomi Kruhlak, PhD[1], James Weaver, PhD[1], Keith Burkhart, MD[1], Vikram Patel, PhD[1], and David G. Strauss, MD, PhD[1]

Therapeutic Innovation & Regulatory Science 2018.

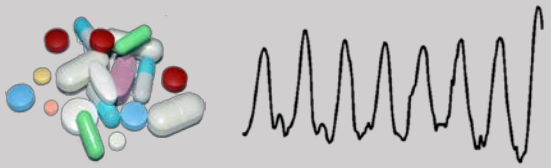
DARS was created to move new science into the drug review process and close the gap between scientific innovation and drug review



Learning from Our Recent Updates to the ICH Regulatory Guidelines for Cardiac Safety of New Drugs

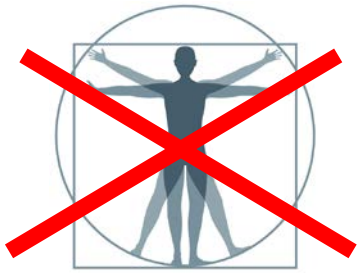
Normal Heart Rhythm

Drug-Induced ABNORMAL Heart Rhythm!



International Council for Harmonisation (ICH) Regulatory Guidelines implemented in 2005 have limitations

ICH S7B Nonclinical | ICH E14 Clinical



Unclear risk communication

GUIDANCE DOCUMENT

E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential--Questions and Answers

Draft Guidance for Industry

SEPTEMBER 2020

Nonclinical Models Reduce Number of Clinical Studies

Studies

Studies

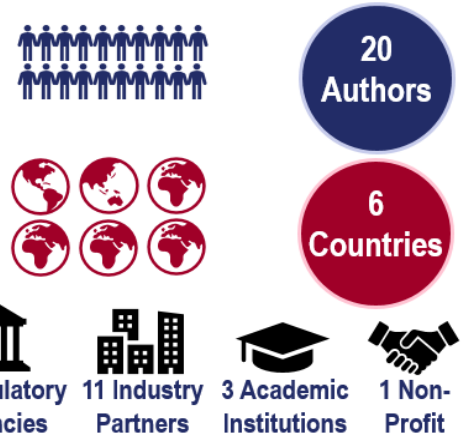
Nonclinical Models Inform Approval Decisions & Labeling

Possible Risk? → **Low Risk**

Example of Recent ICH Updates for Cardiac Safety: Collaborative Process to Increase the Role of Nonclinical Assays

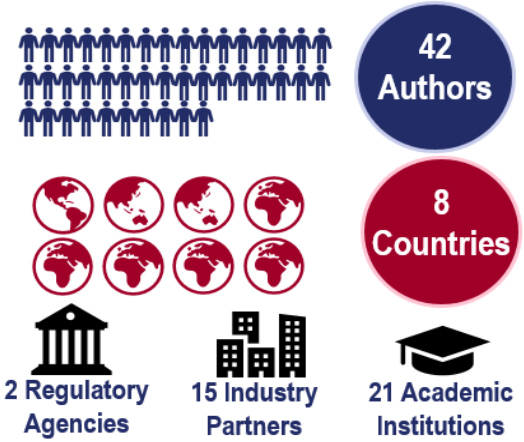
White Paper on Human Stem Cell-Derived Cardiomyocyte Assays

Regul Toxicol Pharmacol. 2020;117:104756.



White Paper on Proarrhythmia Model Validation

Clin Pharmacol Ther. 2020;107(1):102-111



ICH S7B Updates: Assay Standards and Best Practices

- Quality control criteria to document cell health
- Positive/negative controls
- Principles for proarrhythmia models (including qualification)
- How to report data to regulators to demonstrate quality

ICH E14/S7B Updates as a Potential Model for Other Safety Areas

Clinical Pharmacology & Therapeutics

FDA Perspective

REVIEW | Open Access

Translational Models and Tools to Reduce Clinical Trials and Improve Regulatory Decision-Making for QTc and Proarrhythmia Risk (ICH E14/S7B Updates)

David G. Strauss, Wendy W. Wu, Zhihua Li, John Koerner, Christine Garnett

First published: 17 December 2020 | https://doi.org/10.1002/cpt.2137

Clinical Pharmacology & Therapeutics

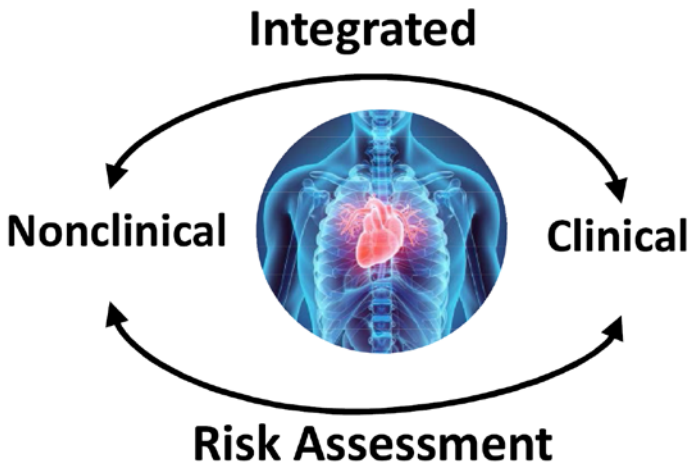
Industry Perspective

Review | Open Access

Time for a Fully Integrated Nonclinical–Clinical Risk Assessment to Streamline QT Prolongation Liability Determinations: A Pharma Industry Perspective

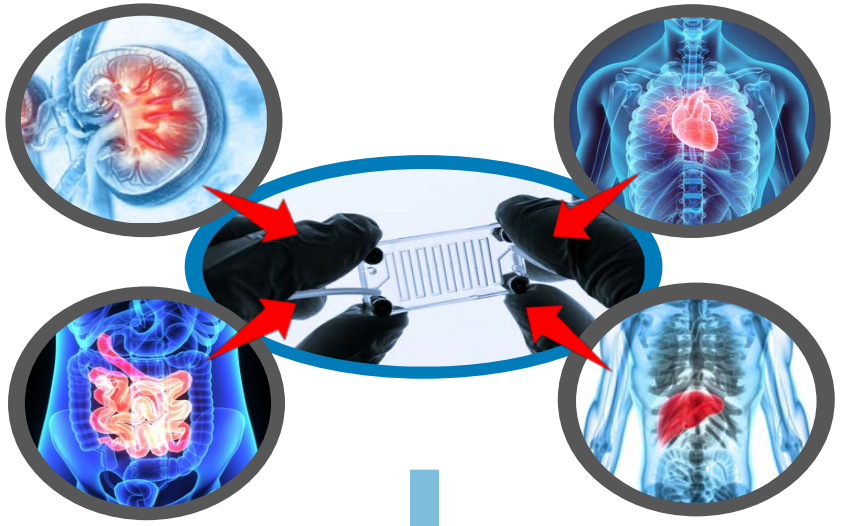
Hugo M. Vargas, Michael G. Rolf, Todd A. Wisialowski, William Achanzar, Anthony Bahinski, Alan Bass, Charles T Benson, Khuram W. Chaudhary, Nicolas Couvreur, Corina Dota ... See all authors

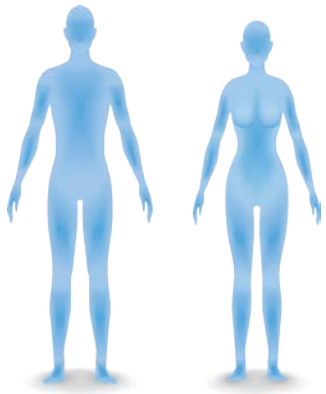
First published: 31 August 2020 | https://doi.org/10.1002/cpt.2029



"The integrated nonclinical-clinical assessment here can also serve as a model for other safety areas in drug development and regulatory evaluation."

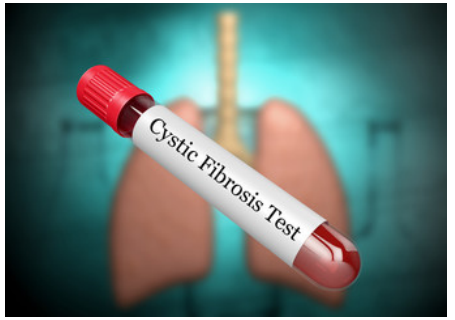
Opportunities for MPS to Impact the Regulatory Evaluation of Drugs





1. Predict Safety in Patients

2. Reduce Clinical Drug Interaction Studies



3. Predict Efficacy in Patients

Advance Drugs in Development with Potentially False-Positive Safety Signals

Safety need: IQ industry-wide survey for attrition of small molecules due to unacceptable toxicity in animal studies

- **Late discovery phase terminations:**
  - Cardiovascular (18%)
  - Liver (16%)
  - Gastrointestinal (GI) (12%)
  - Central nervous system (CNS) (13%)
- **IND-enabling phase terminations:**
  - Cardiovascular (27%)
  - Testis (11%)
  - CNS (11%)
  - Kidney (9%)
  - Liver (5%)

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

Lab Chip. 2020 Mar 17;20(6):1049-1057

Example of Complex In Vitro Model (CIVM) Data Submitted to FDA

New Drug Application

- Other drugs in class discontinued from clinical development due to liver toxicity
- Some liver enzyme elevations in rat studies
- **Complex *in vitro* models with 3D spheroids combined with *in silico* modeling**
  - Reproduced observed liver toxicity of other drugs
  - Suggested new drug has significantly reduced risk of liver toxicity
- **Regulatory Impact**: Data contributed to liver toxicity assessment as described in supervisory pharmacology-toxicology review for NDA

Nonclinical NDA Review

Reduce Clinical Drug Interaction Studies

- **Problem:** Impractical to evaluate every drug combination in clinical trials
- FDA Guidance documents describe how ***in vitro* studies** (in combination with PBPK modeling) inform the need for conducting clinical DDI studies
- However, there are limitations → opportunity for MPS

Limitations of Conventional *In Vitro* Models + PBPK

Physiologically Based Pharmacokinetic Modeling in Regulatory Science: An Update from the U.S. Food and Drug Administration's Office of Clinical Pharmacology
J Pharm Sci. 2019 Jan;108(1):21-25.

Underpredict Clinical CYP3A Induction

- Drug may induce multiple enzymes (not accounted for)
- Dual enzyme time-dependent inhibitor and inducer
- Effect of inhibitors for phase II enzymes

Difficulty with Transporter-Mediated DDI

- Incongruence between in vitro and in vivo transporter behavior
- Lack of correlation between transporters' abundance and activity
- Lack of knowledge about drug exposure at the site of action

Opportunities for MPS

Opportunities For MPS to Impact Clinical Studies

✓ **Reduce the need for clinical DDI studies**
✓ **Impact the timing of clinical DDI studies**

PBPK = physiologically-based pharmacokinetic modeling DDI = drug-drug interaction

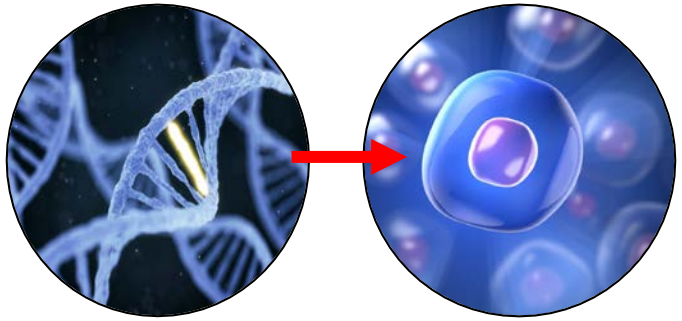
In Vitro Models to Expand Drug Approvals for Rare Diseases

Rare Disease Drug Development Challenges

- Small number of patients
- Thousands of genetic variants

Innovative Approach

Test drug efficacy in cell models with each genetic variant



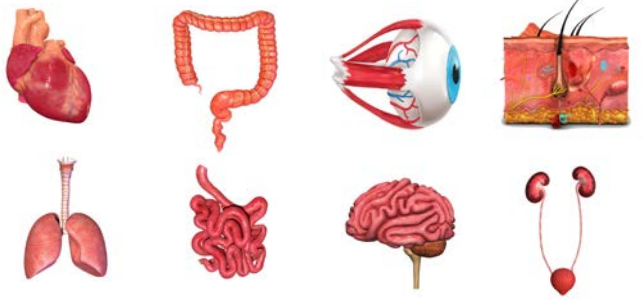
Cystic Fibrosis

✓Drug previously approved for 10 genetic variants

✓Expanded approval to 24 more based on cellular models

Fabry's Disease

Affects Many Organ Systems



✓Clinical trial included 63 patients with 40 genetic variants

✓Drug approved for 348 genetic variants based on cell model

----------INDICATIONS AND USAGE----------

KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 4 months and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor based on clinical and/or *in vitro* assay data. (12.1, 14)

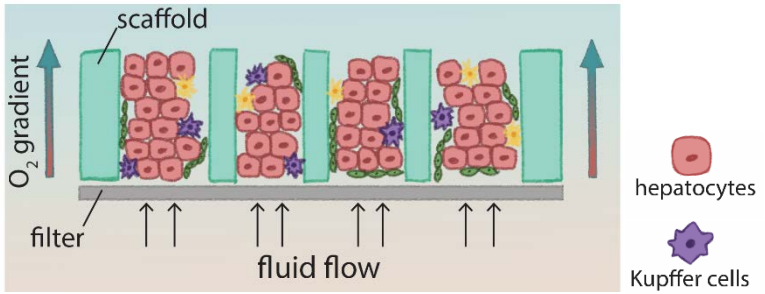
----------INDICATIONS AND USAGE----------

GALAFOLD is an alpha-galactosidase A (alpha-Gal A) pharmacological chaperone indicated for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene (*GLA*) variant based on in vitro assay data. (1, 12.1)

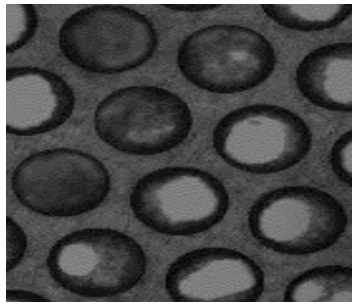
- **Extensive laboratory experience from FDA/CDER DARS staff with specific assays was critical to assess quality, reproduce results and gain confidence for *in vitro* data to serve as primary efficacy data for expanding indications**
- **Summary publication is forthcoming**

FDA/CDER DARS Research on Liver and Heart MPS

1. Liver MPS Using Primary Cells

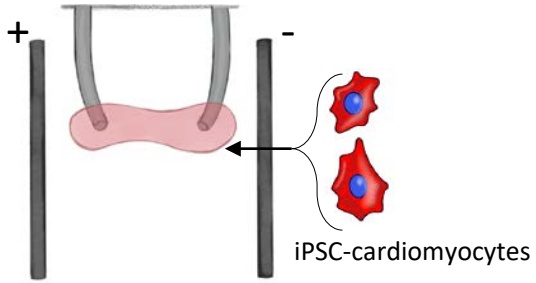


Assayed Output →

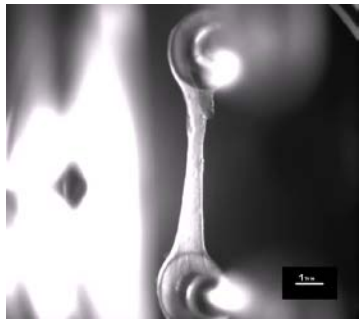


- Cell death
- Metabolism
- Biomarkers
- Gene expression
- Drug distribution

2. Engineered Heart Tissue (EHT)

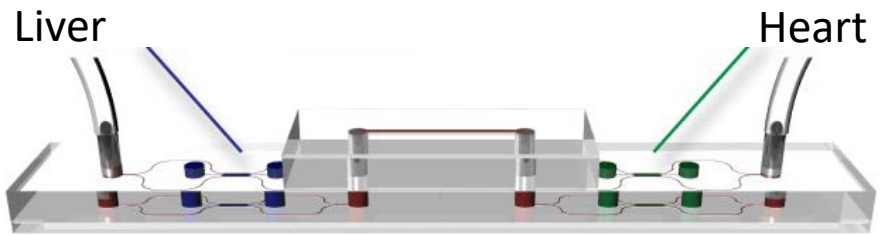


Assayed Output →



- Contractility
- Calcium cycling
- Length of contractions

3. Heart-Liver System



Connected system designed to use iPSC-derived cells

FDA/CDER Microphysiological Systems Laboratory

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

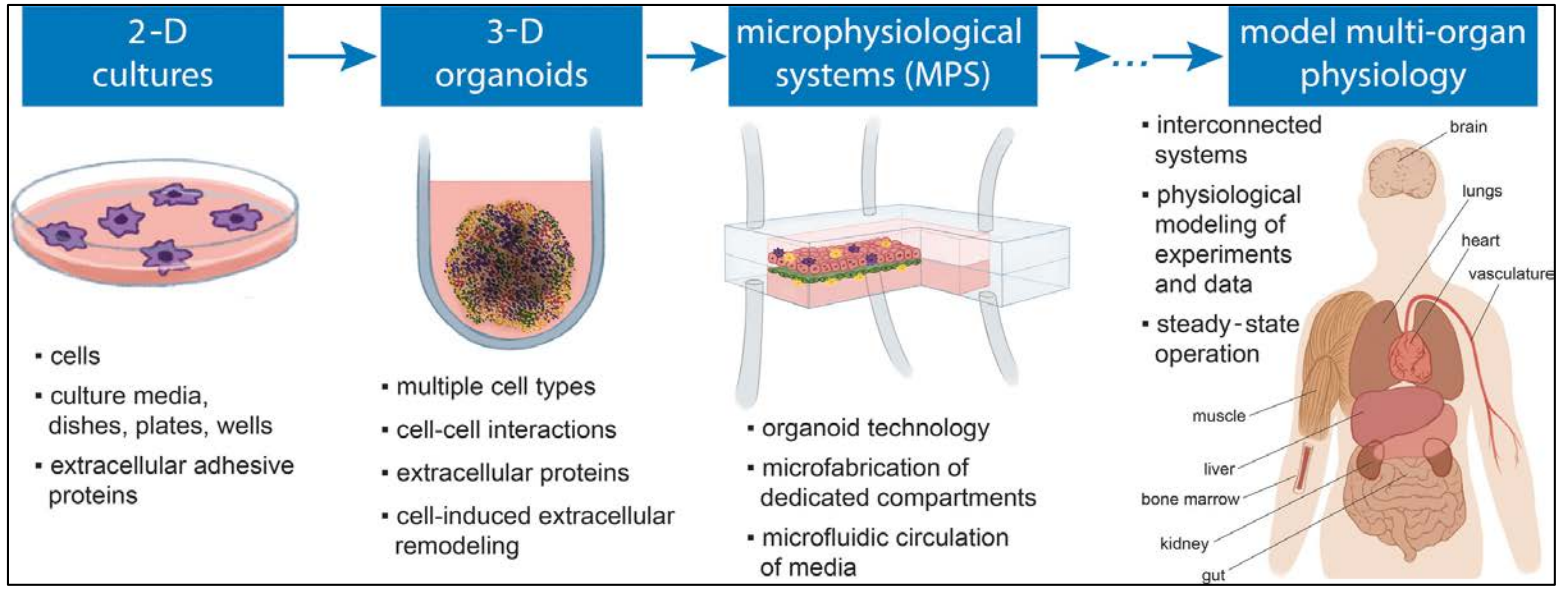
Clinical Pharmacology & Therapeutics 2019;106:139-47.

ARTICLE | Open Access

Characterizing the Reproducibility in Using a Liver Microphysiological System for Assaying Drug Toxicity, Metabolism and Accumulation

Andres Rubiano, Amruta Indapurkar, Ryosuke Yokosawa, Alina Miedzik, Barry Rosenzweig, Ayesha Arefin, Chloe M. Moulin, Keri Dame, Neil Hartman, Donna A. Volpe, Murali K. Matta, David J. Hughes, David G. Strauss, Tomasz Kostrzewski, Alexandre J.S. Ribeiro

Clinical & Translational Science 2020 [epub].

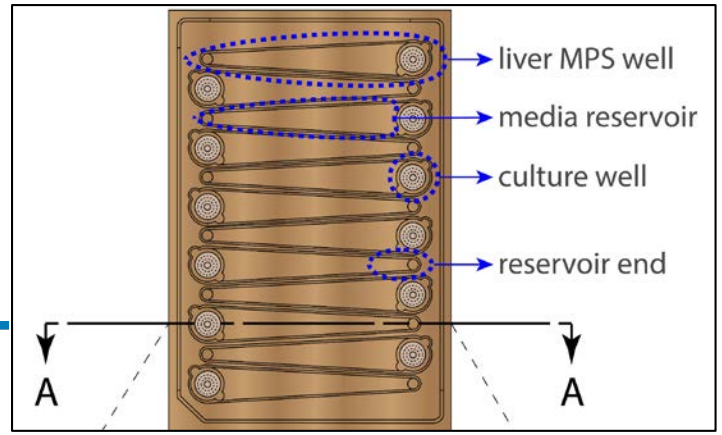


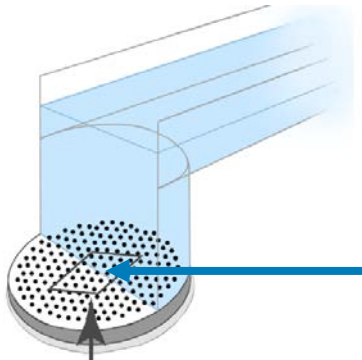
MPS Questions

- What is the performance of MPS compared to 2D cultures and 3D organoids?
- For MPS to be used for regulatory applications in drug development, can criteria to ensure reproducibility of results be developed?

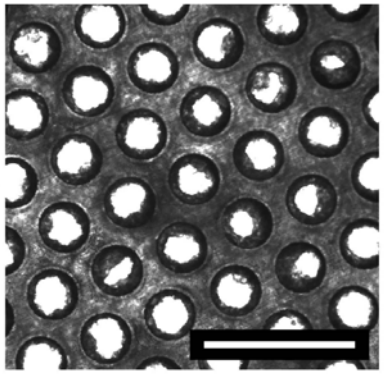
MPS Cultures Hepatic Cells in 3D with Fluid Flow

12-Well Plate

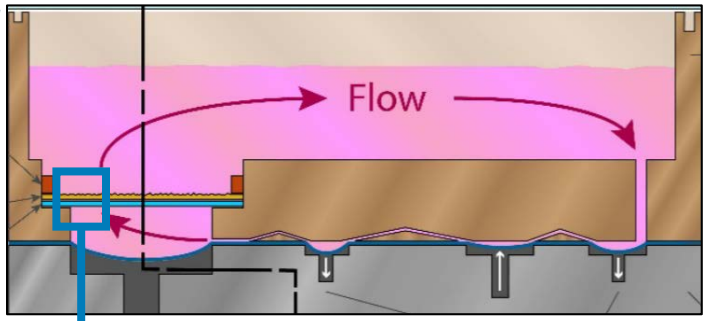




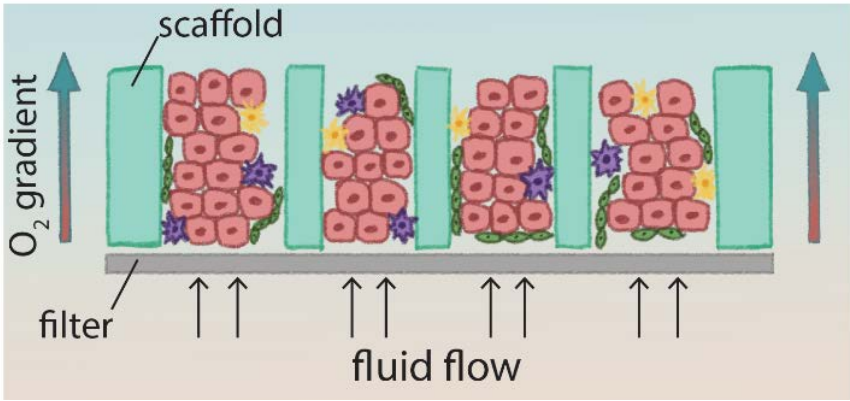
Cells cultured within scaffold exposed to flow



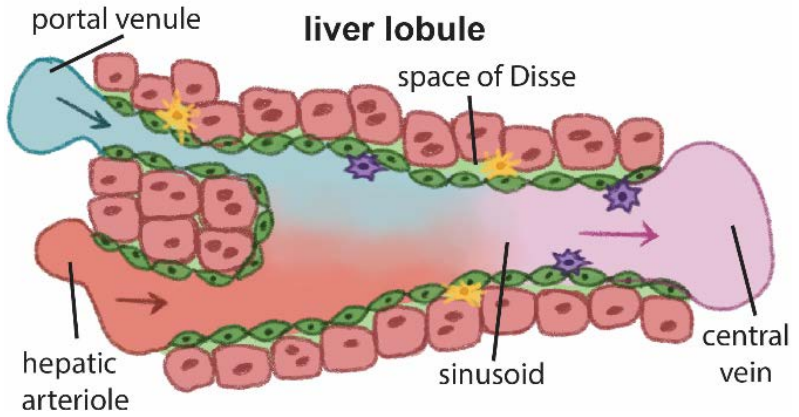
Flow



Enhances the Physiology of Cell Culture



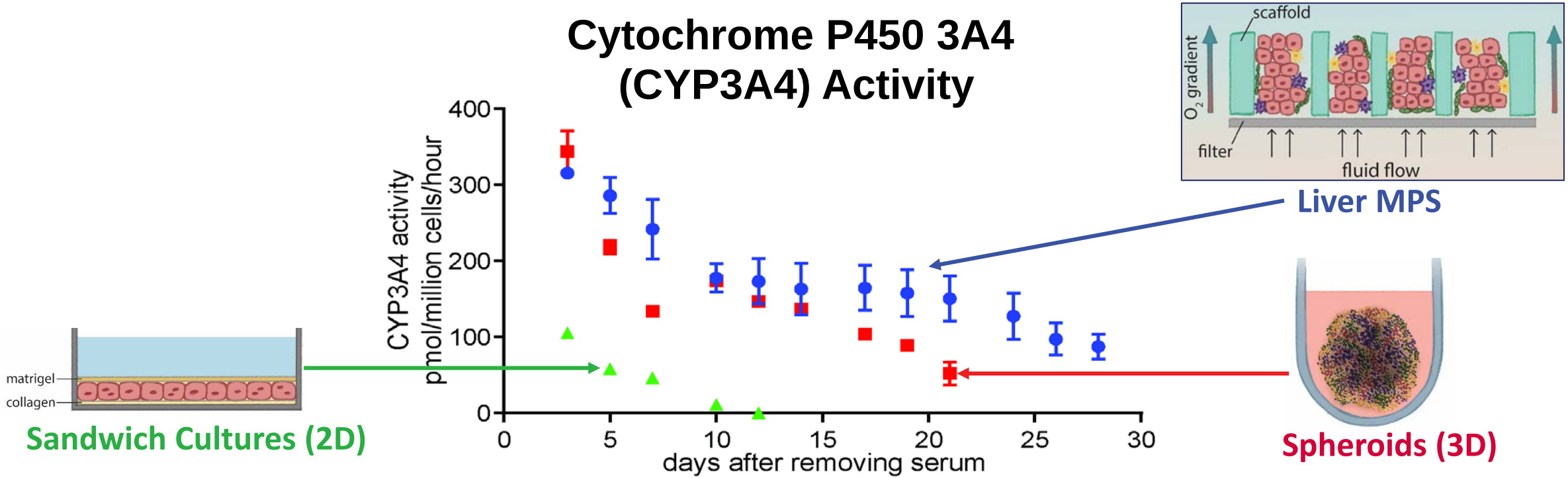
Physiologic Liver Lobule



Rubiano et al. Clinical and Translational Science 2020;
Ribeiro et al. Clinical Pharmacology and Therapeutics 2019

Kupffer cells = liver macrophages (immune cells) critical for liver function

Hepatocyte Function: 2D vs. Spheroid vs. MPS

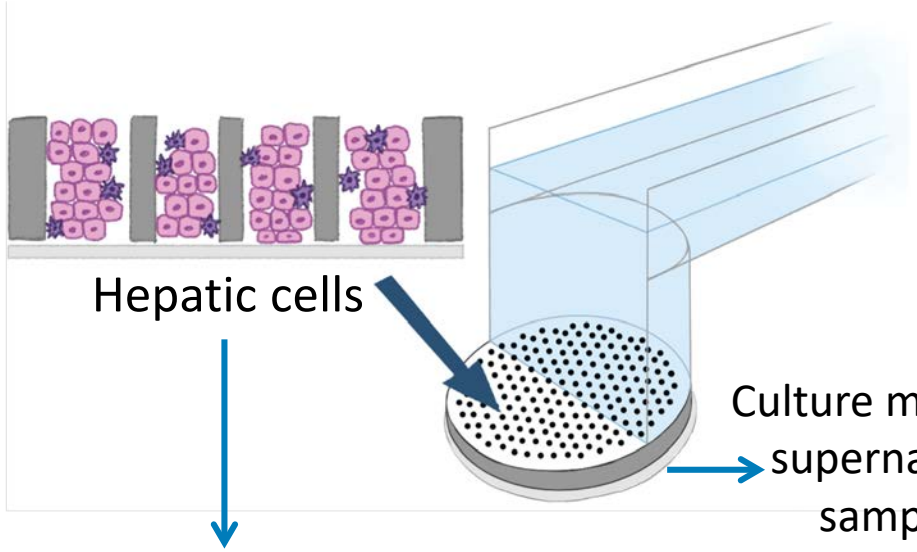


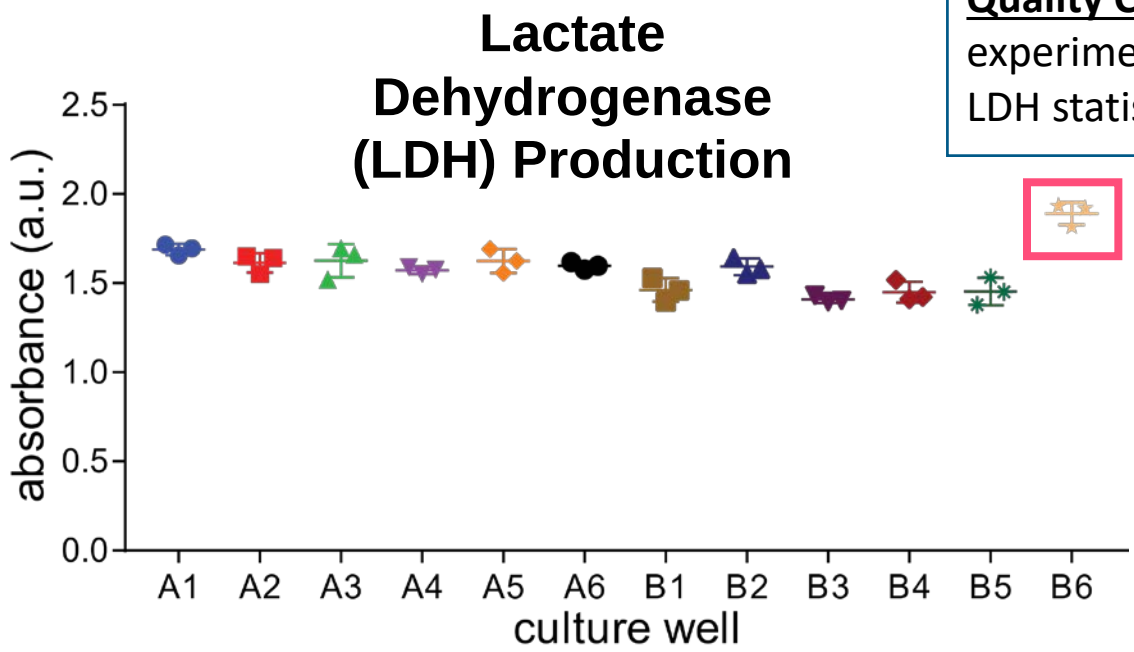
- **Hepatocytes in MPS were more functionally stable than those in other culture platforms**
  - CYP3A4 activity (above) and albumin secretion remained prominent for >18 days
  - Functional decline occurred earlier in spheroids (12 days) and sandwich cultures (7 days)

Rubiano et al. *Clinical & Translational Science* 2020.

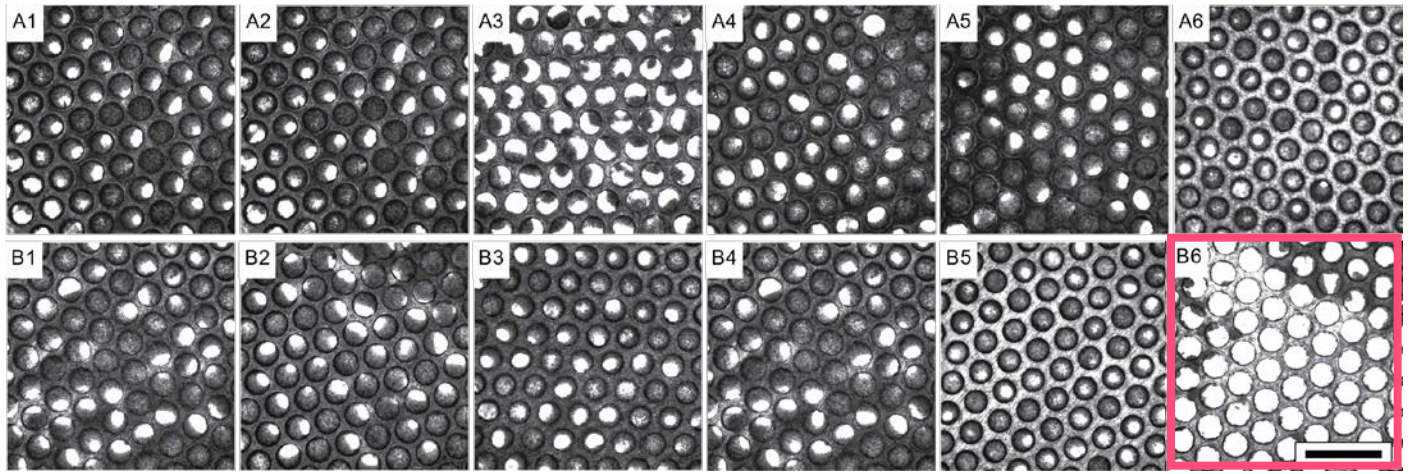
Proof of Principle: MPS Quality Control Based on Assaying Culture Media

Quality Control: Before experiments exclude LDH statistical outliers





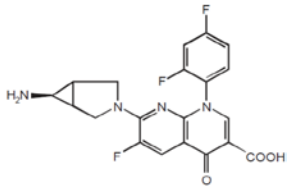
Microscopy After Disassembling System



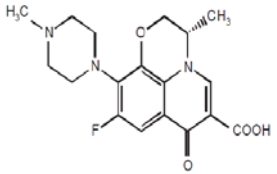
Rubiano et al. *Clinical & Translational Science* 2020.

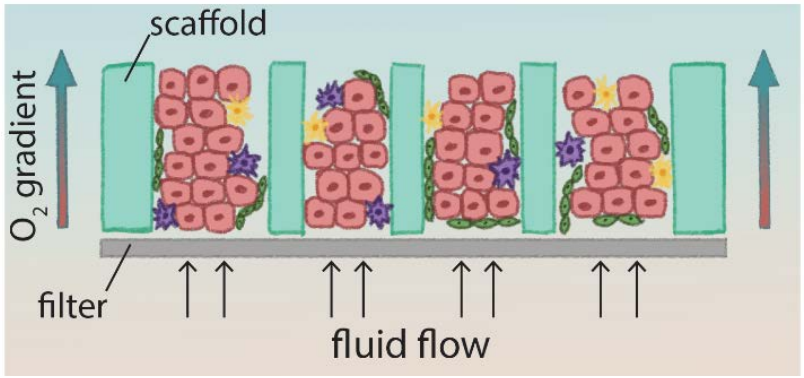
Liver MPS Reproduced Hepatotoxicity of Drug Withdrawn from Market Due to Causing Idiosyncratic Acute Liver Failure and Death

Trovafloxacin (Hepatotoxic)

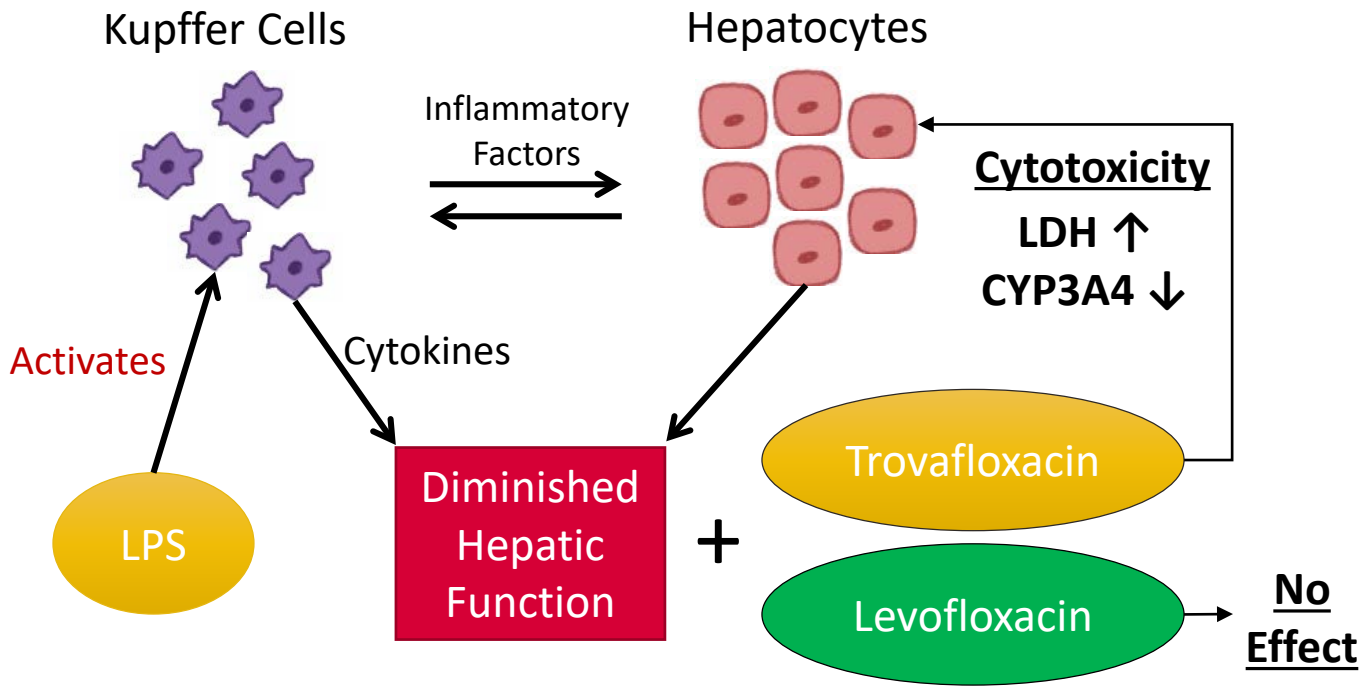


Levofloxacin (Not Hepatotoxic)





Co-dosing with lipopolysaccharides (LPS) to induce inflammatory signaling

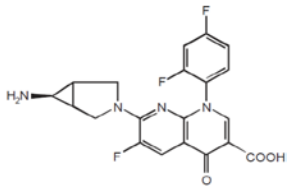


Liver MPS detects inflammatory-induced drug toxicity

Rubiano et al. *Clinical & Translational Science* 2020.

Liver Toxicity Reproducibility

Trovafloxacin (Hepatotoxic)



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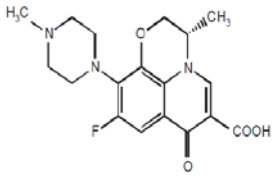
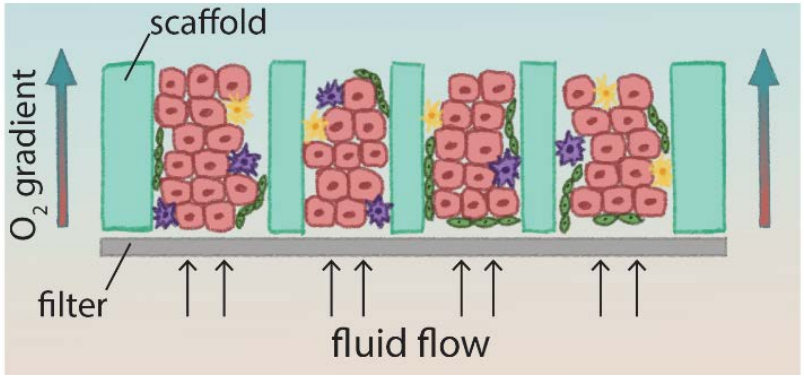
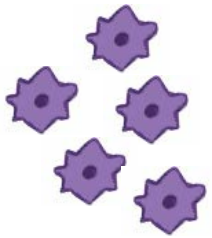




- **Similar Results Between Two Sites**

- **Similar Results Within a Site When Using Different Batches of Kuppfer Cells**

Batch 1

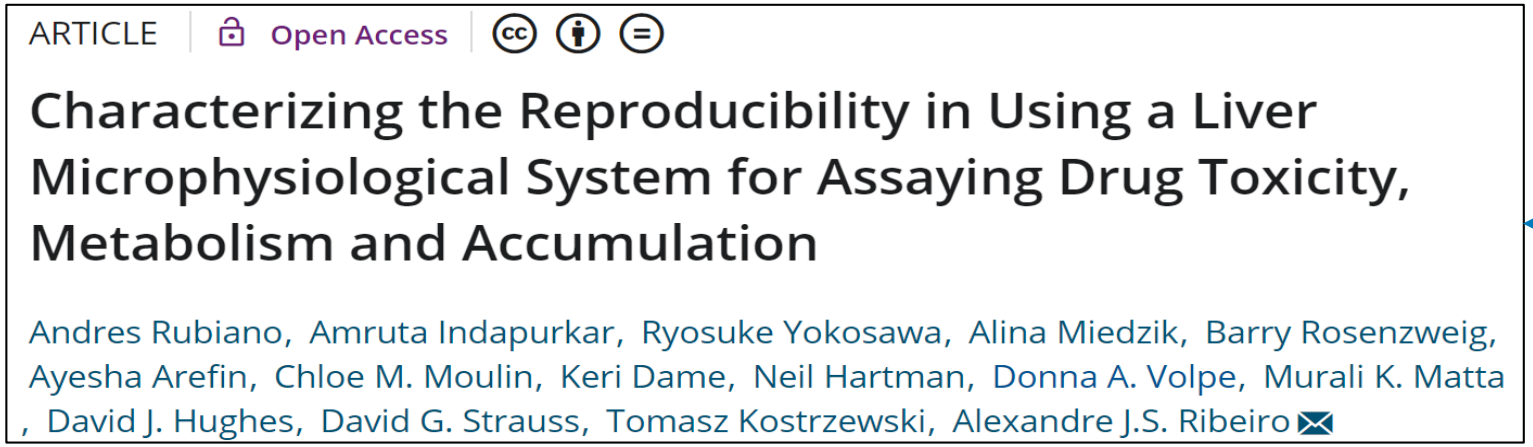


Batch 2

- **Identified Quality Control Criteria for Kuppfer Cells**

Rubiano et al. *Clinical & Translational Science* 2020.

General Considerations and 7 Recommendations: As Outlined In Supplement to



ARTICLE | Open Access

Characterizing the Reproducibility in Using a Liver Microphysiological System for Assaying Drug Toxicity, Metabolism and Accumulation

Andres Rubiano, Amruta Indapurkar, Ryosuke Yokosawa, Alina Miedzik, Barry Rosenzweig, Ayesha Arefin, Chloe M. Moulin, Keri Dame, Neil Hartman, Donna A. Volpe, Murali K. Matta , David J. Hughes, David G. Strauss, Tomasz Kostrzewski, Alexandre J.S. Ribeiro

Examples:

1. Establish quality control criteria that ensure proper assembly and preparation of functional systems
2. Test cellular properties to enable the intended system use

Rubiano et al. *Clinical & Translational Science* 2020.

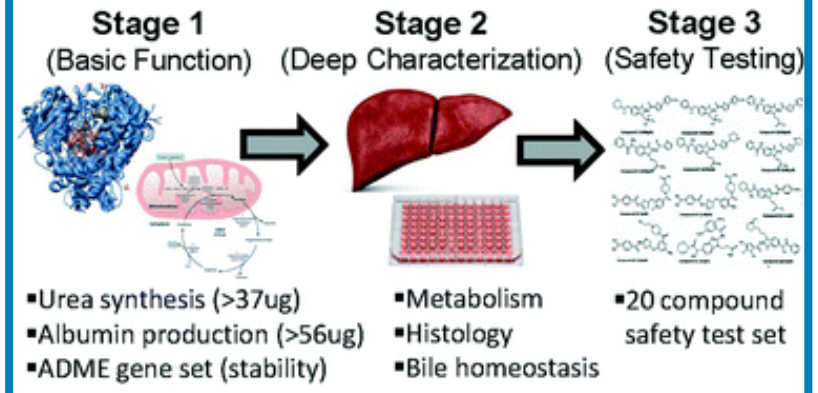
IQ MPS Organ-Specific and ADME Paper Recommendations

IQ-MPS has published dedicated papers on ADME, liver, kidney, GI, lung, skin & biologics (CNS/BBB & cardiovascular in development)

www.iqmps.org/publications

Example: Liver MPS Development Guidelines for Safety Risk Assessment

"… guidance on best approaches to benchmark liver MPS based on 3 stages of characterization …"



Stage 1: Characterize Basic Function

Measure	Function assessed	Specifications
Albumin production	Liver transcription, translation, processing, and export function	• >37 μg per day per 1 million hepatocytes • Daily production rates should remain stable across a 14 day time frame
Urea synthesis		
Baseline quantitative gene expression profiling		

Stage 2: Deep Characterization

Measure	Function assessed	Specifications
Alanine aminotransferase (ALT), lactate dehydrogenase (LDH), miR122, cytokines	Indications of cell damage and MPS stability over time	• ≤30% C.V. for mean daily baseline release levels across a 14 day time frame
Baseline and induced metabolic enzymes functional activity using a set of standard probe substrates	Liver phase I/II metabolizing enzymes capability (measure of CYP450 enzymatic capacity and induction) Benchmark levels specified for each enzyn compared to fresh hepatocytes and demonstrate <30% CV (as measure of stability of enzymatic activity rates over tir	
Transporter function and bile acid homeostasis: uptake, metabolism, and export	Measures of daily rates of transporter substrate and bile acid uptake, metabolisr conjugation, and export in media	
Histology of MPS	Allows comparison to that of normal hum *in vivo* liver architecture and cellular morphology	

Stage 3: Safety Testing

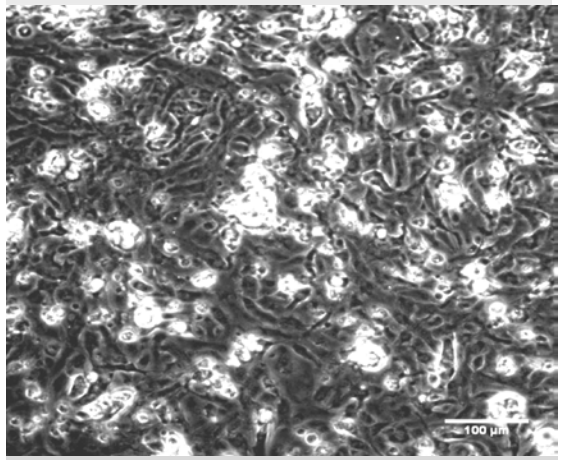
Tool liver toxicant	DILI presentation	Mechanism of toxicity	Appropriate less toxic comparator
Sitaxsentan	ALT elevations after 2 weeks	Reactive metabolites, mitochondrial toxicity, BSEP inhibition[76–78]	**Ambrisentan**
Clozapine	ALT elevations after 1 week	Reactive metabolite[80–82]	**Olanzapine**
Diclofenac	ALT elevations within 1 month	Reactive metabolites, mitochondrial dysfunction, bile acid dysfunction[84–87]	
Zileuton	ALT elevations after 6 weeks	Reactive metabolite formation[88,89]	
Fialuridine	Liver failure after 12 weeks of dosing	Mitochondrial toxicity as primary event causing lactic acidosis, microvesicular steatosis[90]	**FIRU [1-(2′-fluoro-2′-deoxy-D-ribofuranosyl)-5-iodouracil]**
Tolcapone	ALT elevations, acute liver failure	Reactive metabolite, mitochondrial toxicant, BSEP inhibition[45,91]	**Entacapone**
Asunaprevir	ALT elevations after 2 weeks[93]	Alterations in bile acids	
Troglitazone	ALT, bilirubin elevations after 18 weeks	Reactive metabolites, BSEP inhibition[94–96]	**Pioglitazone**
Telithromycin	ALT elevations after 1 day	Bile acid alterations[98,99]	
Trovafloxacin	Acute liver failure	Immune mediated[100]	**Levofloxacin**
Pemoline	Liver failure	Immune mediated[102]	
Mipomersen	Oligonucleotide, ALT elevations and hepatic steatosis	Lipid alterations[103]	
Nefazodone	Liver failure	Reactive metabolites, BSEP inhibitor, mitochondrial tox[54,104]	**Buspirone (or Trazodone)**

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

Lab Chip. 2020 Jan 21;20(2):215-225.

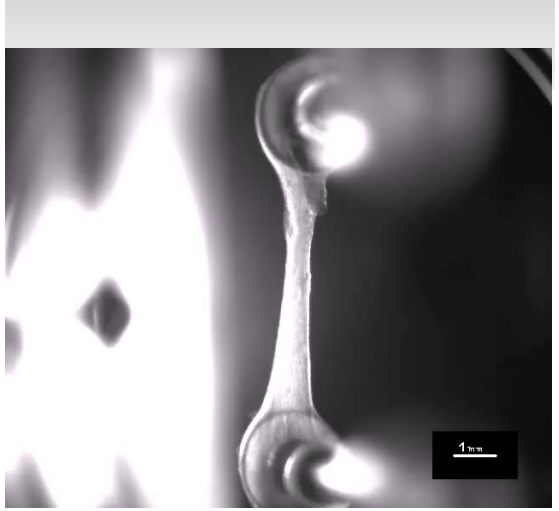
Additional FDA/CDER Research: Differences in Drug Response between 2D and 3D Approaches to Culturing iPSC-Cardiomyocytes

2D



Cardiomyocytes on Dish (2D)

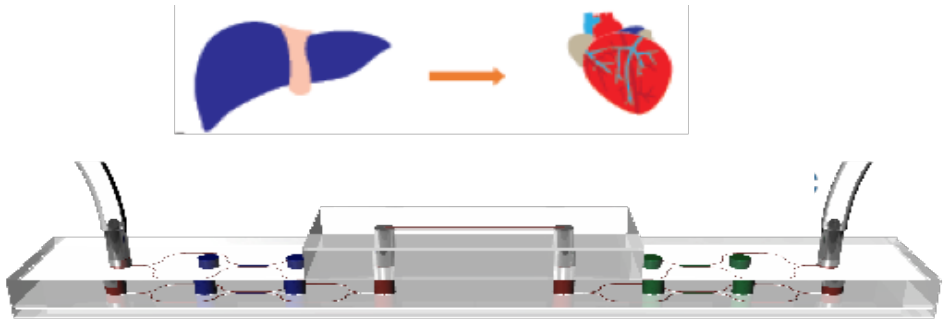
3D



Engineered Heart Tissue (3D)

- **Evaluating contractility endpoints:**
  - Reproducibility of distinct lines of iPSC-cardiomyocytes
  - Response to inotropic agents
  - Cardiotoxicity of oncology drugs
- **Evaluating calcium cycling endpoints:**
  - Concordance with contractility endpoints
  - How to dissect drug mechanism

Additional FDA/CDER Research: Characterization of Combined Heart-Liver System



Liver-chip **Heart-chip**

CERSI UCSF-Stanford

Berkeley UNIVERSITY OF CALIFORNIA

Kevin Healy

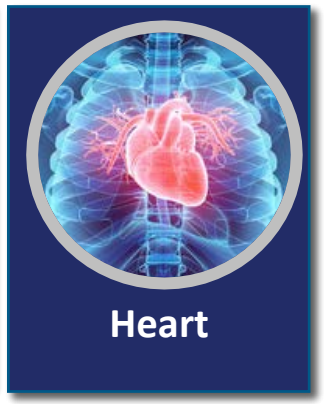
- **Characterize function reproducibility of additional liver and heart MPS that utilizes iPSC-differentiated cells:**

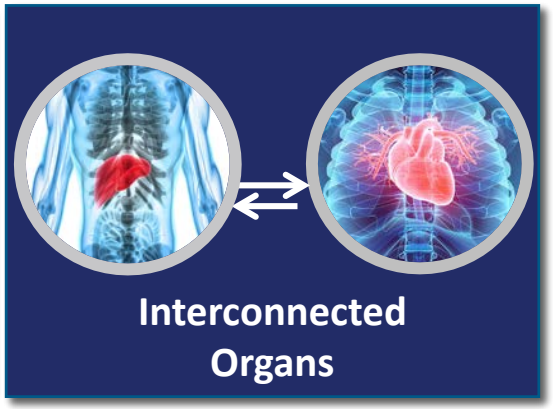
- **Test interconnecting heart-liver systems:**
  - Effects of liver metabolism/drug interactions on cardiotoxicity
  - Dual liver-heart drug toxicity

Lee-Montiel et al. BioRXiv 2020 doi.org/10.1101/2020.05.24.112771
Images: courtesy Dr. Kevin Healy (UC Berkeley)

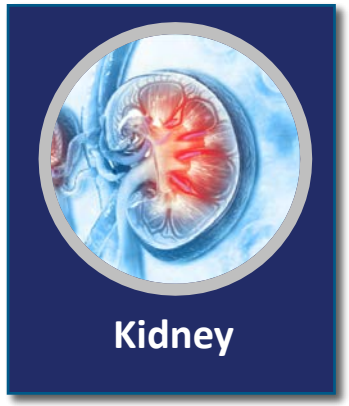
Translating MPS Into the Drug Review Process at FDA

FDA/CDER Research Discussed:





Planned FDA/CDER Research:



SUMMARY:

- MPSs can yield reproducible results if system preparation, drug administration and measurement schedules are carefully planned
  - Assess drug adsorption and stability of metabolites and specific endpoints
- Quality control criteria for cells and functional MPSs can be assessed prior to drug experiments to increase reproducibility
  - Similar principles have been implemented in ICH S7B Guideline updates
- Full characterization and qualification for use in drug development depends on the specific context of use

Thank You!

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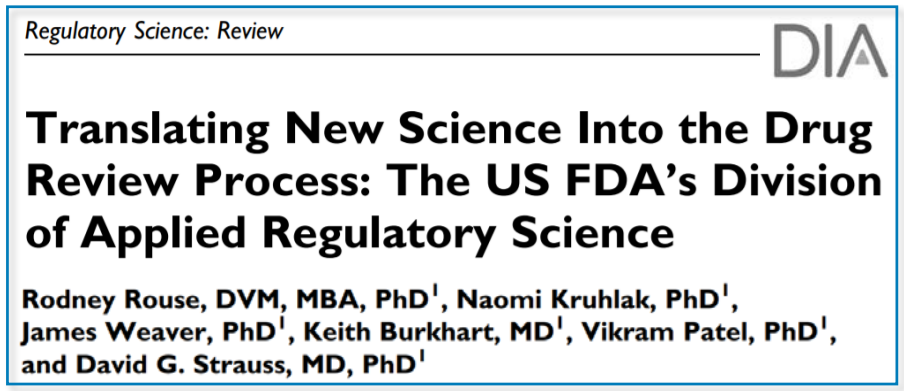
Links for Additional Information

Division of Applied Regulatory Science (DARS)

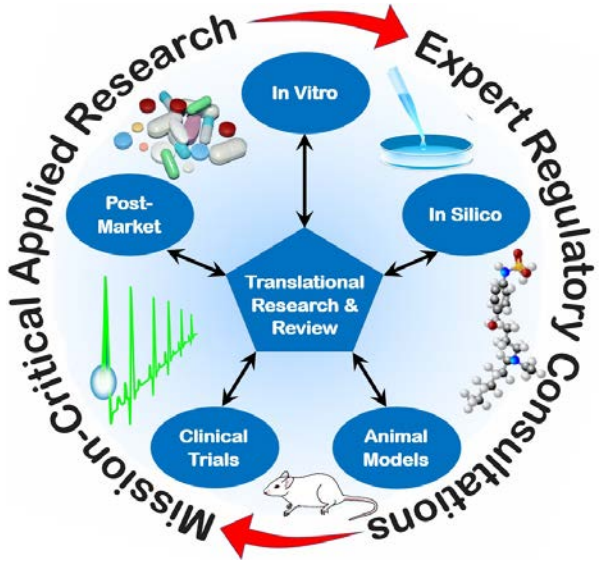

Regulatory Science: Review

DIA

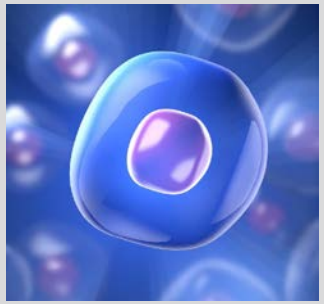
Translating New Science Into the Drug Review Process: The US FDA's Division of Applied Regulatory Science

Rodney Rouse, DVM, MBA, PhD[1], Naomi Kruhlak, PhD[1], James Weaver, PhD[1], Keith Burkhart, MD[1], Vikram Patel, PhD[1], and David G. Strauss, MD, PhD[1]

Therapeutic Innovation & Regulatory Science 2018.



Laboratory Cellular Models



- Organs-on-a-chip (workshop)
- Clinical pharmacology
- Cellular efficacy data (cystic fibrosis)

Publications link

Biomarkers

- Organ injury biomarkers
- Human immune system
- Respiratory depression

Publications Link

- Heart Safety Biomarkers
- Opioids Effects on Breathing Biomarkers
- Biologics and biosimilars

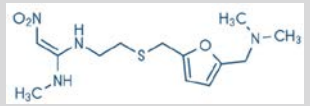
Publications link

Computer Models

- Systems pharmacology & heart safety
- Chemical & biomedical informatics

Publications link

Other Clinical Studies



- Sunscreen absorption studies (*2 JAMA publications*)
- Most read JAMA article of 2019
- Ranitidine metabolites (NDMA) *(1 ongoing study)*

DARS: Mission/Vision Research Overview Video Annual Report Clinical Trials DIA Podcast JAMA News Article