FDA Division of Applied Regulatory Science

Bridging the gap between scientific innovation and drug regulation

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- Disclaimer: The opinions expressed in this presentation are mine and do not necessarily reflect the official views of the U.S. Food and Drug Administration (FDA)

- No conflicts of interest

Presentation goals

- Describe the FDA and its mission
- General interest of the FDA in bioengineering research
- The Center for Drug Evaluation and Research (CDER)
- The Division of Applied Regulatory Science
- Applications in Regulatory Science: liver and cardiac cellular systems
- Q&A

FDA Mission

- Protect the public health by ensuring the safety, efficacy, and security of:
  - Human and veterinary drugs
  - Biological products
  - Medical devices

- Ensure the safety of the U.S.:
  - Food supply
  - Cosmetics
  - Products that emit radiation

FDA Organization

- **Office of the Commissioner**
  - FDA Commissioner
  - Immediate Office of the Commissioner
  - National Center for Toxicological Research
- **Office of Foods and Veterinary Medicine**
  - Center for Food Safety and Applied Nutrition
  - Center for Veterinary Medicine
- **Office of Global Regulatory Operations and Policy**
  - Office of International Programs
  - Office of Regulatory Affairs
- **Office of Medical Products and Tobacco**
  - Center for Biologics Evaluation and Research
  - Center for Devices and Radiological Health
  - Center for Drug Evaluation and Research
  - Center for Tobacco Products
  - Office of Special Medical Programs
  - Oncology Center of Excellence
- **Office of Operations**
  - Office of Equal Employment Opportunity
  - Office of Finance, Budget and Acquisitions
  - Office of Information Management and Technology

FDA Interest in Tissue Engineering, Microfabrication and Biomechanics

- The regulatory use of novel technologies

- Regulation of medical products involving biomanufacturing and tissue regeneration:
  - Center for Biologics Evaluation and Research (CBER)
  - Center for Devices and Radiological Health (CDRH)

- Tools for drug development or predicting human/clinical effects of products:
  - Center for Drug Evaluation and Research (CDER)
  - National Center for Toxicological Research (NCTR)
  - Center for Biologics Evaluation and Research (CBER)
  - Center for Devices and Radiological Health (CDRH)
  - Center for Food Safety and Applied Nutrition (CFSAN)

What is Regulatory Science?

- Regulatory Science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products.

Published Reports on Regulatory Science

Focus on the Center for Drug Evaluation and Research (CDER)

- Critical Path Opportunity List - 2006
- FDA's Regulatory Science Strategic Plan - 2011
- 2011 CDER's Science Needs Report→
- Food and Drug Administration Safety Innovation Act (FDASIA) of 2012
- 2015 CDER's Safety Research Priorities
- 2018 FDA Division of Applied Regulatory Science Annual Report

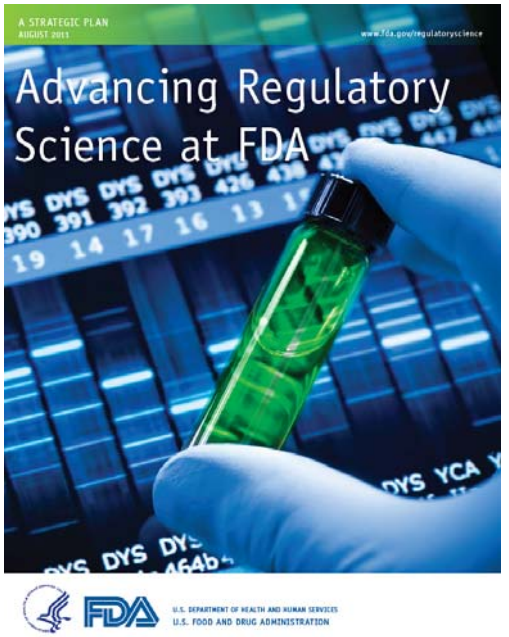
"In all cases, we look to FDA reviewers and scientists to identify the most pressing problems and scientific issues, so that we can recruit partners to help us address them."
Janet Woodcock, 2007

http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm076689.htm
http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm267719.htm
http://www.fda.gov/drugs/scienceresearch/ucm264327.htm
http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FDASIA/ucm356316.htm
https://www.fda.gov/files/about%20fda/published/Division-of-Applied-Regulatory-Science-Annual-Report-2018_5.pdf

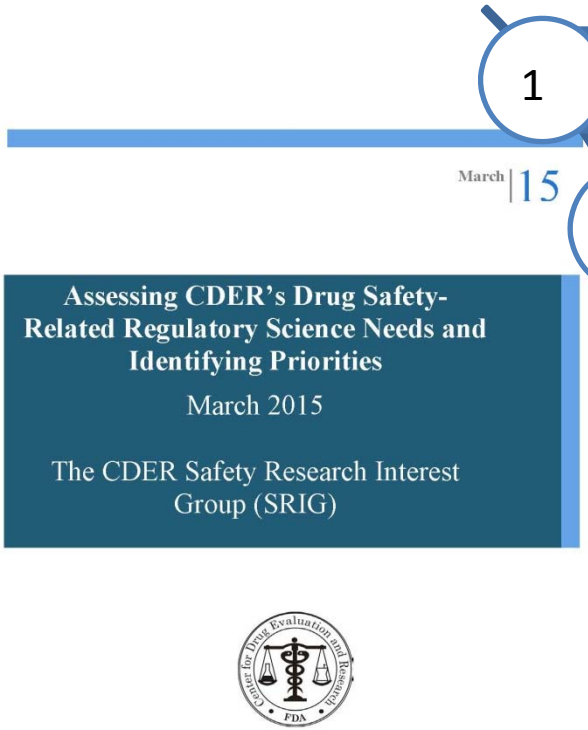
Slide modified from Ruth Barratt and Alexandre Ribeiro, FDA/CDER

FDA Regulatory Science Priorities

1. Modernize Toxicology to Enhance Product Safety: Strategic Plan for Regulatory Science
2. Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes: Strategic Plan for Regulatory Science
3. Support New Approaches to Improve Product Manufacturing and Quality: Strategic Plan for Regulatory Science
4. Ensure FDA Readiness to Evaluate Innovative Emerging Technologies
5. Harness Diverse Data through Information Sciences to Improve Health Outcomes: Strategic Plan for Regulatory Science
6. Implement a New Prevention-Focused Food Safety System to Protect Public Health: Strategic Plan for Regulatory Science
7. Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security
8. Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Products: Strategic Plan for Regulatory Science



CDER: 7 Safety-Related Research Topics



1. Improve Access to Post-market Data Sources and Explore Feasibility of Their Use in Safety Signal Analyses
2. Improve Risk Assessment and Management Strategies to Reinforce the Safe Use of Drugs
3. Evaluate and Improve Risk Communication
4. Focus on Product Quality Attributes, Manufacturing Processes, and Product Performance relating to Safety
5. Develop and Improve Predictive Models of Safety in Humans, including Non-Clinical Biomarkers
6. Improve Clinical Trial Statistical Analyses for Safety and Benefit Risk
7. Investigate Clinical Biomarkers of Safety, Including Standards for Qualification

http://www.fda.gov/drugs/scienceresearch/ucm264327.htm

Slide modified from Ruth Barratt, FDA/CDER

What We Do in OTS and OCP

- **Office of Translational Sciences**
  - Promote innovation in drug regulatory review
  - Assure the validity of clinical trial design and analysis
  - Develop and apply quantitative approaches
  - Promote scientific collaboration
  - Ensure alignment of CDER research with CDER goals

- **Office of Clinical Pharmacology**
  - Evaluate pharmacokinetics and pharmacodynamics
  - Understand inter-patient variabilities
  - Optimize dose and dose regimen to balance benefit and risk
  - Conduct research to advance clinical pharmacology and better evaluate benefit and risk

Division of Applied Regulatory Science (DARS)

Vision

- To move new science into the CDER review process and close the gap between scientific innovation and product review

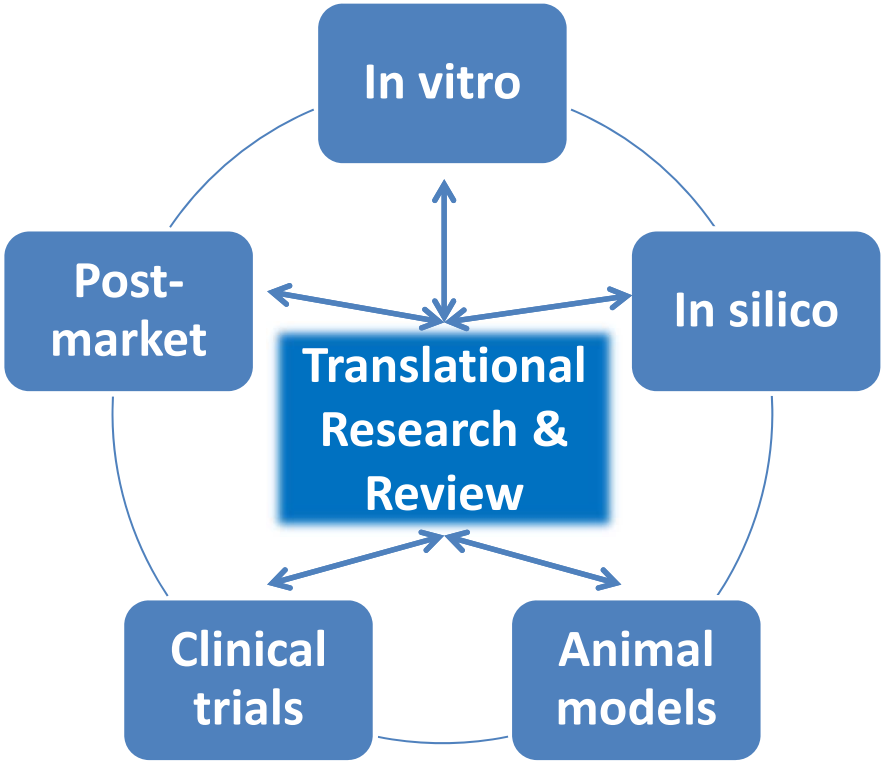
What does DARS do?

- Performs mission-critical applied research to develop and evaluate tools, standards and approaches to assess the safety, efficacy, quality and performance of drugs

- Performs expert regulatory review consultations for mechanistic safety evaluation for immediate regulatory needs combining
  - Critical review of existing knowledge
  - Computational analyses with informatics tools and disease-pharmacology models
  - In vitro and in vivo laboratory studies
  - Translational analysis of preclinical studies, clinical trials and post-market data

Division of Applied Regulatory Science Priority Areas

- Translational research
- Collaboration and interdisciplinary team approaches
- Implementation of new regulatory review methods and programs



Collaboration: OSE, OND, OGD, OTS, CDRH, CBER, NCTR, NIH, industry, universities

- Kevin Healy: UC Berkeley
- Ed Hsiao: UCSF

General Research Areas

1) Mechanistic safety assessment with humanized assays, genomics and biomarkers (nonclinical and clinical)
   - Model-informed, mechanistic-based cardiac safety
   - Genomic (microRNA) biomarkers for tissue injury
   - Humanized mouse models (immune and liver)

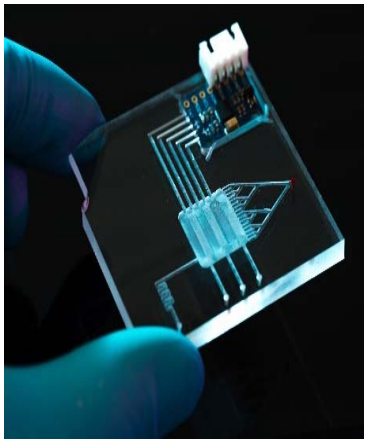
2) Bioanalytical, pharmacokinetics and drug-drug interactions (DDI)
   - In vivo biodistribution studies
   - Bioequivalence of topical ophthalmic products
   - In vitro + in vivo assessment of combination therapy to prevent antibacterial resistance

3) Chemical and Biomedical Informatics tools for research and regulatory review
   - Chemical informatics
   - Biomedical informatics
   - Mechanistic safety and pharmacology consults

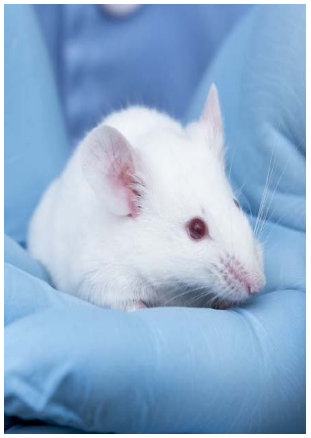
Current Research projects

1. Modeling & Simulation

2. In Vitro Models



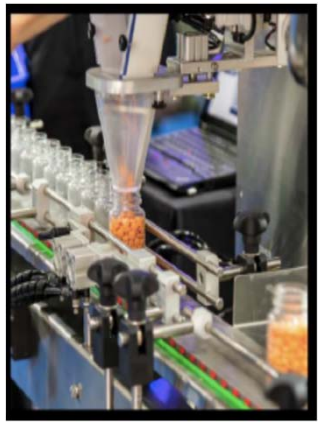
3. In Vivo Models



4. Biomarkers

5. Innovative Clinical Trial Designs

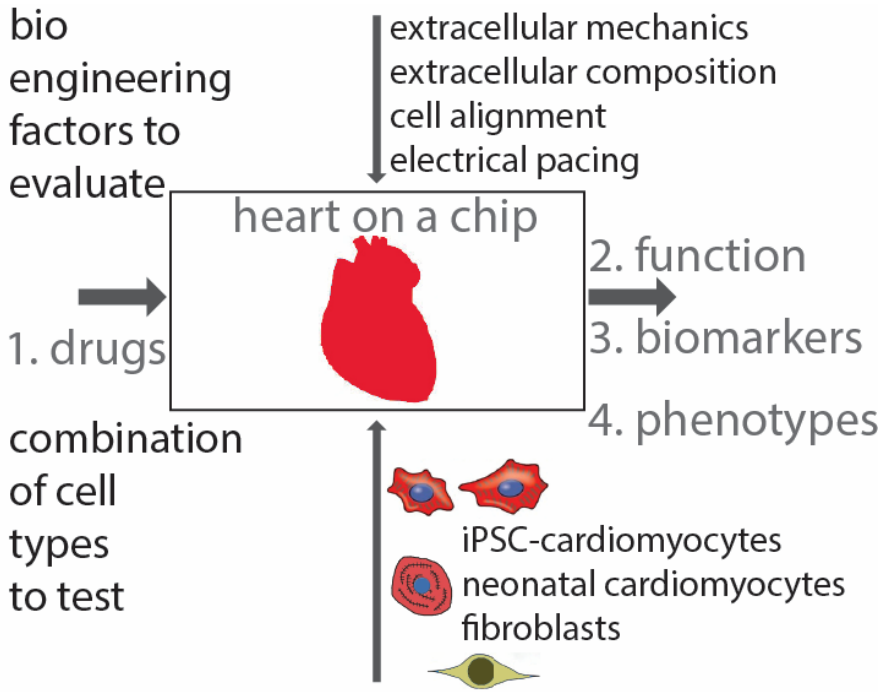
6. Advanced Manufacturing

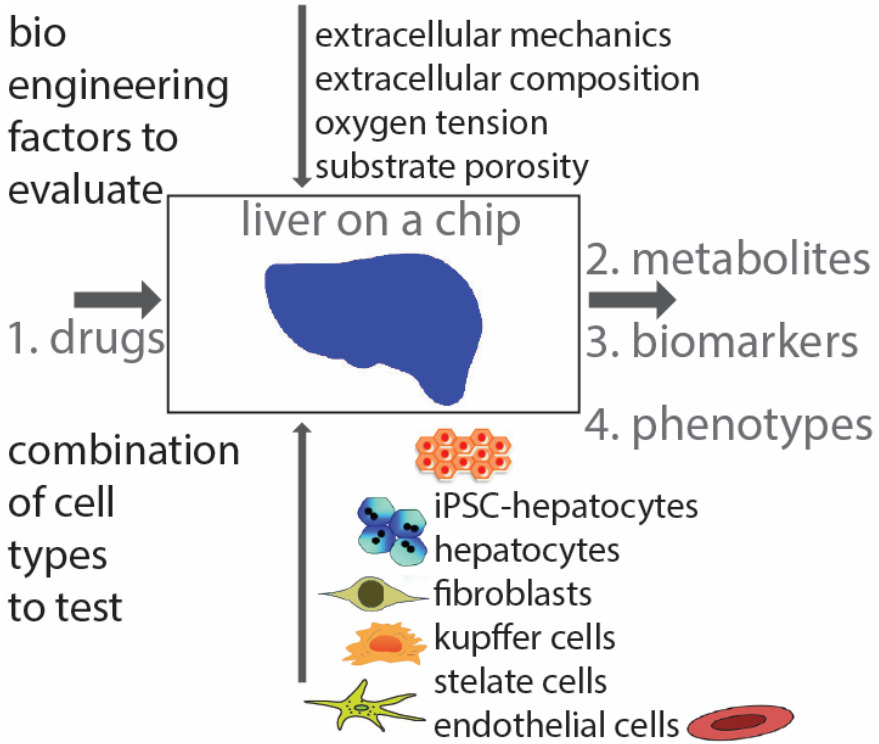


7. Real World Data

8. Complex Generics & Biosimilars

Cellular systems are *in vitro* platforms to assay organ-specific function





- Combining cells in an engineered microenvironment originates in vitro settings with higher physiological relevance
- How important is physiological relevance for regulatory contexts of use?

We evaluate the regulatory use of cellular systems in drug development

building confidence

analytical validation

translational qualification

Key Enablers

- replicate biology
- demonstrate pharmacology and toxicology
- test for analytical reproducibility
- comparative studies
- evolution of use
- learn to make decisions
- clinical outcomes
- tincture of time/experience

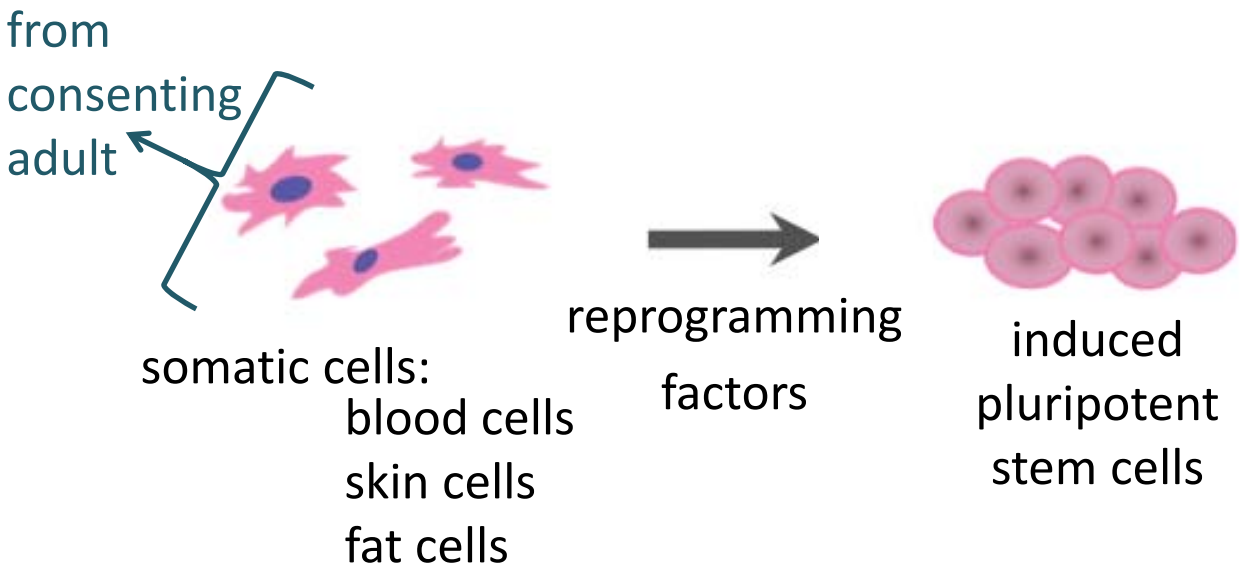
Our Lab

- investigates critical technology for drug development
- complements work done by other researchers
- collaborates with different stakeholders

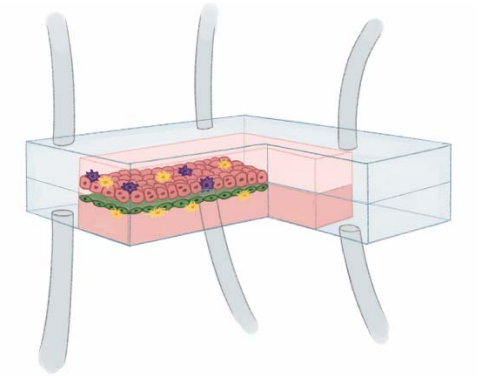
Provided by Brian Berridge (National Toxicology Program - NIH)

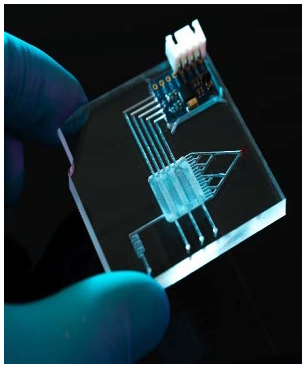
Emerging technologies evaluated in our laboratory

induced pluripotent stem cells (iPSCs)



microphysiological systems (MPS)





Heart and Liver toxicity is the main cause for drug attrition

Phase	Preclinical		Phase I-III		Post-Approval
Information	**Attrition**	**Attrition**	**Attrition**	**Attrition**	**Withdrawal**
Source:	ABPI(2008)	Car (2006)	ABPI(2000)	Olson et al (2000)	Stevens & Baker (2008)
Sample size:	156 CDs stopped	88 CDs stopped	63 CDs stopped	82 CDs stopped	47 drugs
Cardiovascular	**24%**	**27%**	**35%**	**21%**	**45%**
Liver	**15%**	**8%**	**29%**	**21%**	**32%**
Hematology	3%	7%	3%	4%	9%
Neuro	**12%**	**14%**	2%	**21%**	2%
Immuno	7%	7%	**10%**	**11%**	2%
GI	5%	3%	2%	5%	2%
Reproductive	9%	**13%**	5%	1%	2%
Musculo-Skeletal	8%	4%	5%	1%	2%
Respiratory	1%	2%	2%	0%	2%
Renal	6%	2%	5%	**9%**	0%
Genetic tox	5%	5%	0%	0%	0%
Carcinogenicity	0%	3%	3%	0%	0%
Other	4%	0%	2%	4%	1%

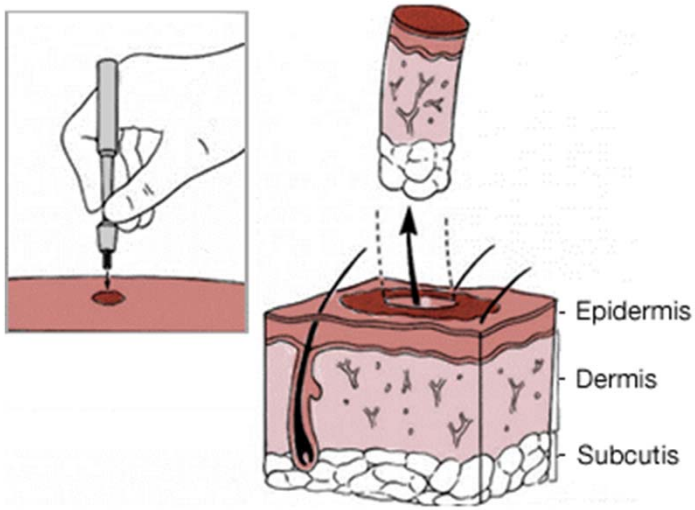
Adapted from Redfern et al (2010) and provided by Tim Hammond (AstraZeneca) and Kristina Howard (FDA-CDER)

Hypothesis that motivates this focus:

- Physiological and human-specific cellular systems can better predict clinical drug effects and reduce drug attrition in clinical trials

Human-specific cellular systems have higher potential to predict clinical drug effects

- Tissues/ biopsies isolated from humans/ patients



- primary hepatocytes
- primary Kupffer cells

- Induced pluripotent stem cells (iPSCs)

somatic cells:
- blood cells
- skin cells
- fat cells

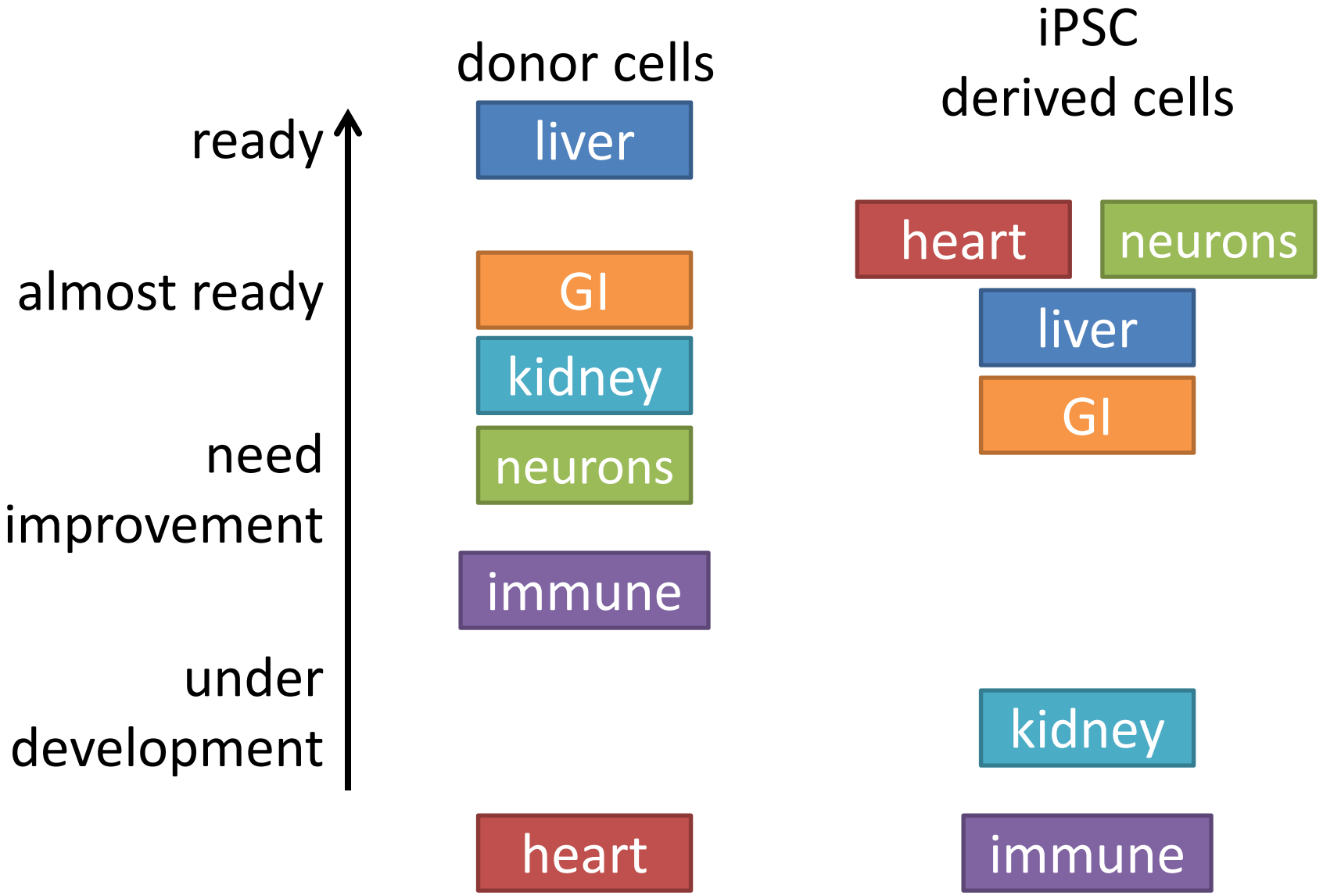
reprogramming factors

induced pluripotent stem cells (iPSCs)

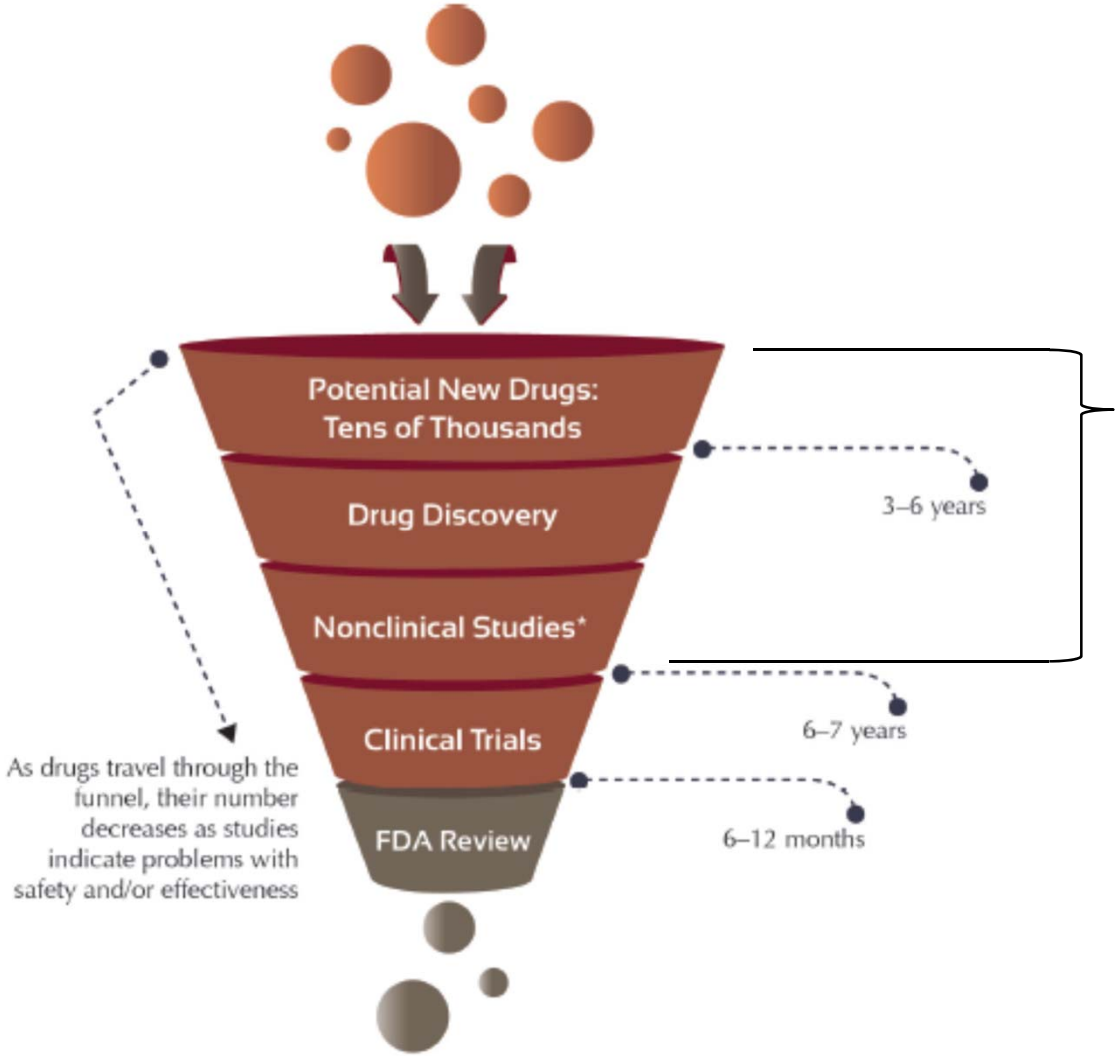
Potential to differentiate into any human cell type

- iPSC-derived cardiomyocytes

Use of human cellular system depends on readiness of cellular materials



In vitro systems are used early in drug development



- Biochemical and molecular assays
- High throughput and low sensitivity assays
- Cell types for different contexts of use
- Mechanistic assays

Throughput, sensitivity, mechanistic relevance and cost dictate the use of cellular systems

large screens in early testing:

- high throughput
- cheap
- low sensitivity
- phenomenological
- cover broad mechanisms

focused screens in late testing:

- sufficient high end
- benefit must compensate cost
- focused on mechanism
- sensitive and accurate
- more physiological
- measure chronic effects

liver as an example

endpoints: metabolism, transport, cell death mechanisms

HepG2 cells
HepaRG cells

iPSC-hepatocytes

primary hepatocytes

microphysiological systems

HL-1 cells
H9C2 cells
AC16 cells
HEK cells

isogenic iPSC-cardiomyocytes

isolated tissue/cardiomyocytes

engineered cardiac microsystems with iPSC-cardiomyocytes

time of *in vitro* testing in drug development

for cardiac

endpoints: electrophysiology, calcium, contractility, mitochondria, energetics, biomarkers, cell death mechanisms

Cellular systems should be designed for a context of use of drug evaluation

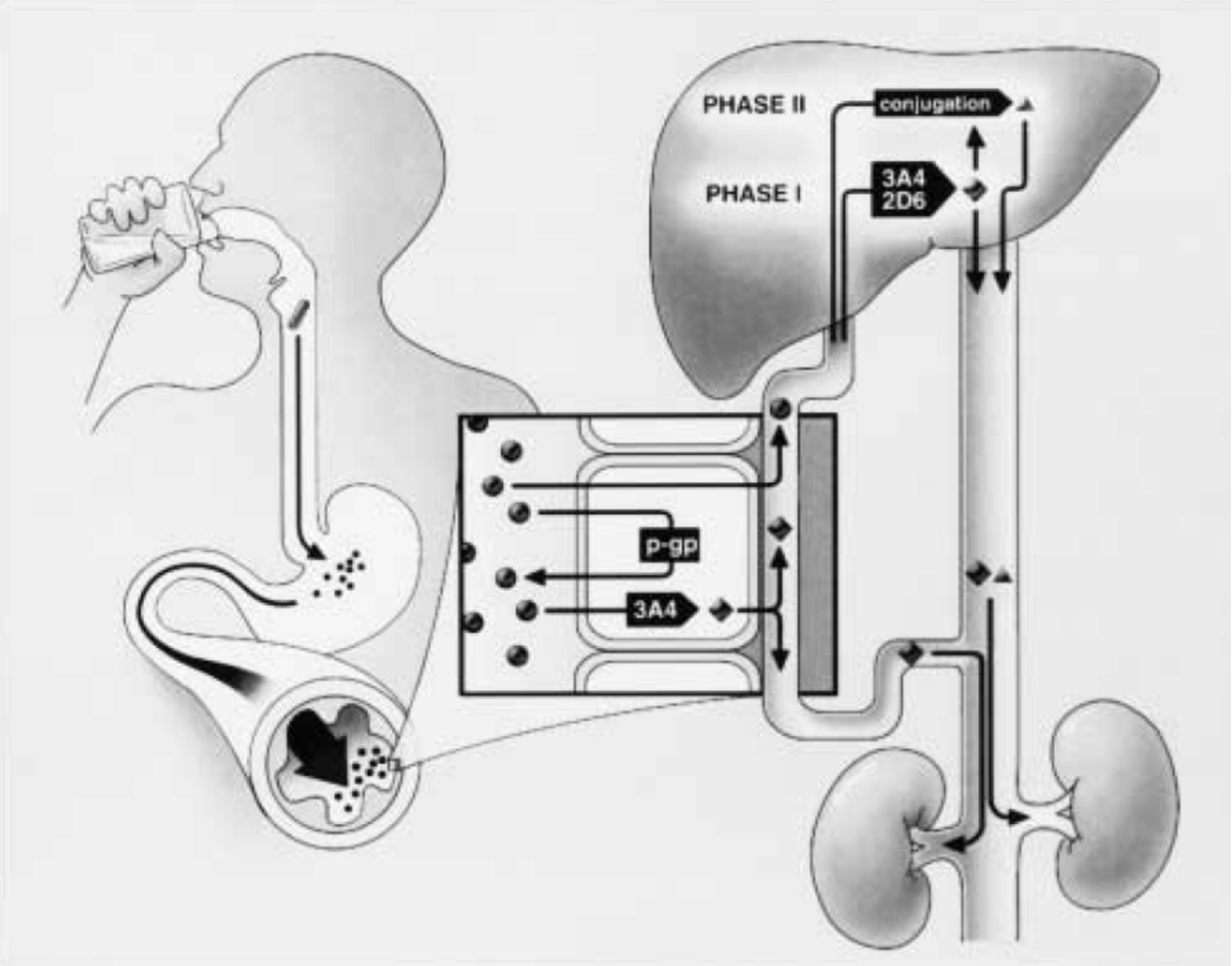
- Organ-specific properties? cell types, co-cultures, expression of specific receptors
- Human-specific properties? human mechanisms that differ from animals or data showing human-animal differences
- Physiological experimental settings/microenvironment? nutrients, hormones, other organ systems, mechano-electrical factors
- The example of iPSC-cardiomyocytes? human-specific cells that can be engineered to predict different contexts of drug toxicity
- When to use them in the drug development route? early, late, reliability and robustness matter

- Evaluation of microphysiological systems: LiverChip
- Contractility of iPSC-cardiomyocytes
- Future: multi-organ systems and compare with *in vivo* data

In addition to toxicity, the liver is a key organ to model metabolism and pharmacokinetics

Liver:

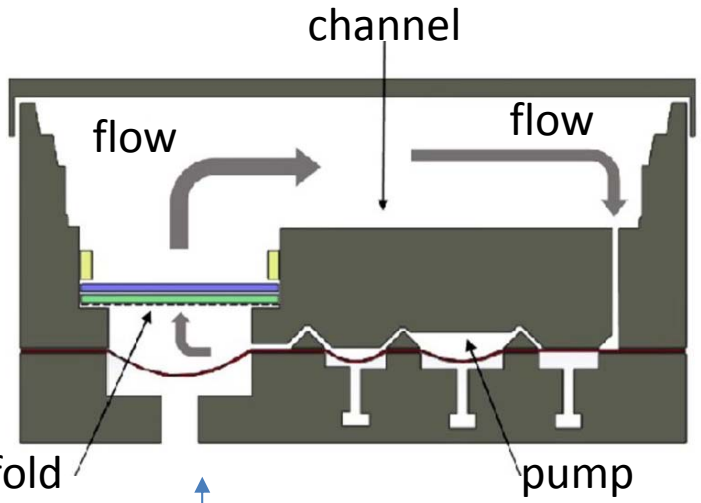
- generation of toxic drug metabolites
- drug metabolism
- drug clearance
- drug-drug interactions
- data needed for physiologically-based pharmacokinetic and pharmacodynamic models

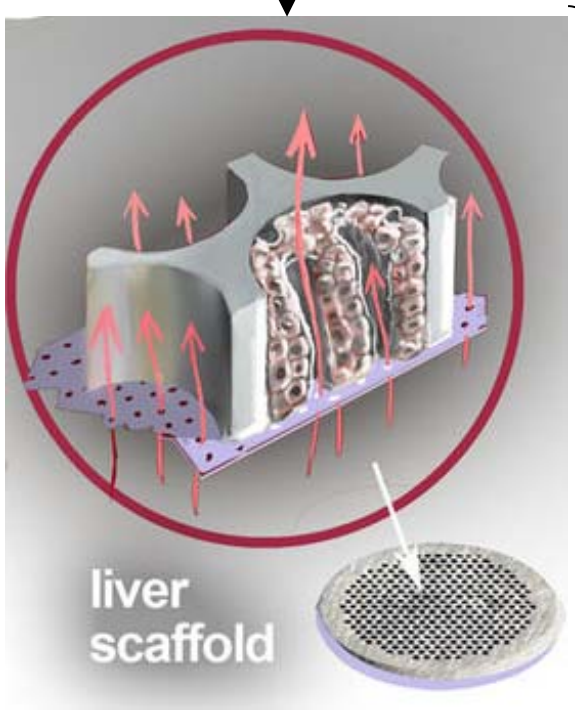


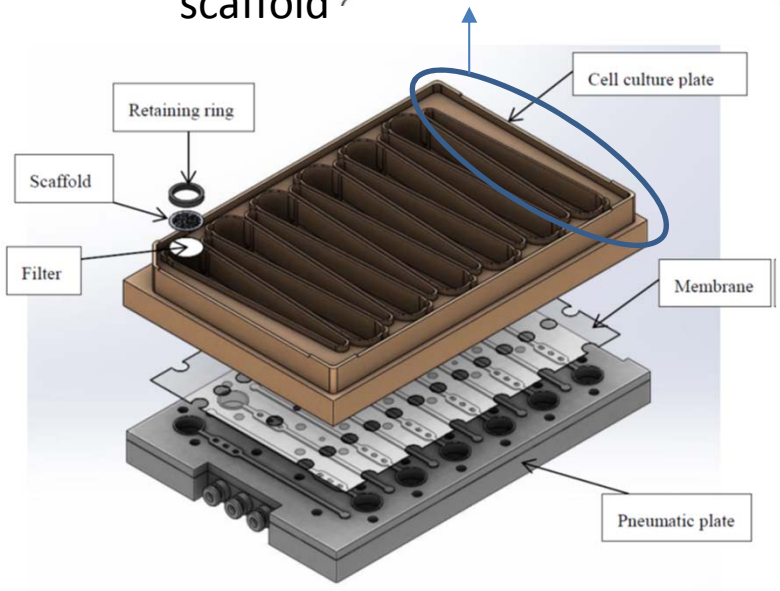
Bauman JL *European Heart Journal Supplements* 2001

LiverChip cultures hepatic cells in 3D and exposed to flow

- Perfusate: media in contact with cells
- Cells: tissue within the scaffold







Criteria for evaluating LiverChip system

- Site-to-site variability: the developers repeat experiments

- Chip-to-chip variability: how different chip batches (device + cells) affect results

- Focus on PTMS protocols: Preparation, Treatment and Measurement Schedules

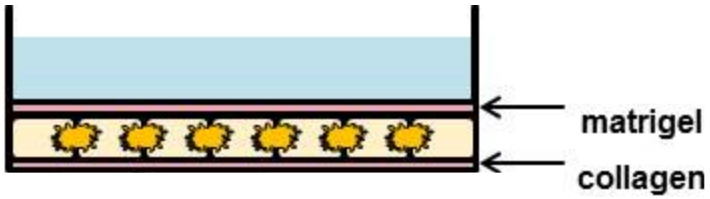
Project evaluation goals

1. assemble, operate and assay the LiverChip
   a) variability: chip-to-chip and well-to-well.
   b) endpoints: cell viability, cytochrome P4503A (CYP3A4) activity, gene expression and structural organization.
   c) contexts of evaluation: use of known toxicants.

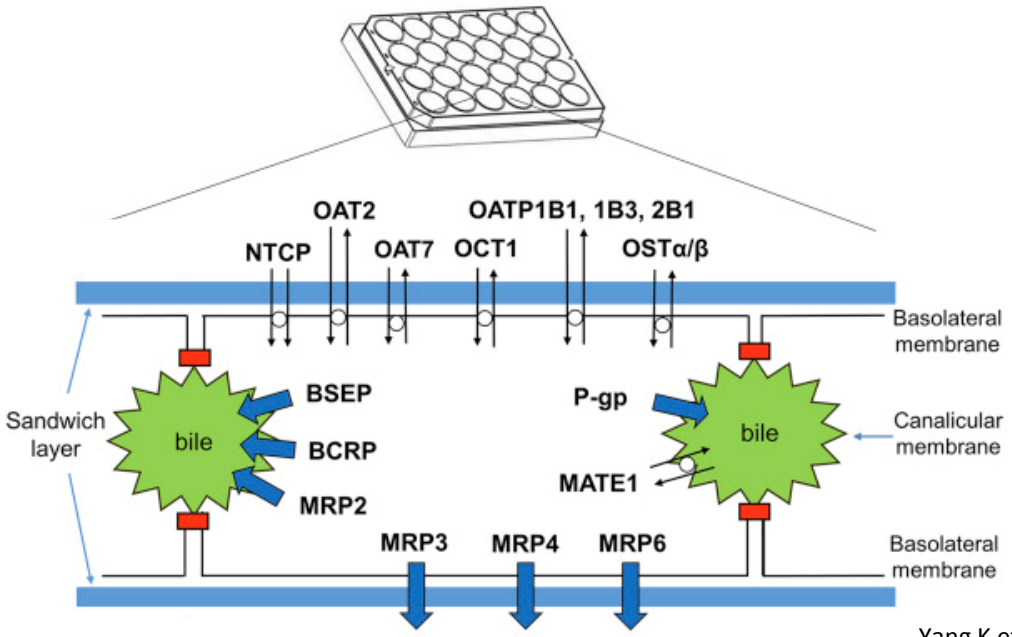
2. different drug contexts of use for measuring hepatic properties
   a) detect **phase II metabolism** by analyzing drug bioprocessing
   b) test predictability of **differential toxicity** of drugs.

3. human-specific metabolism
   a) drugs with human-specific metabolism

This evaluation compares the LiverChip with other *in vitro* systems: ***sandwich culture***



- induces cell polarity
- allows metabolism studies
- transport activity

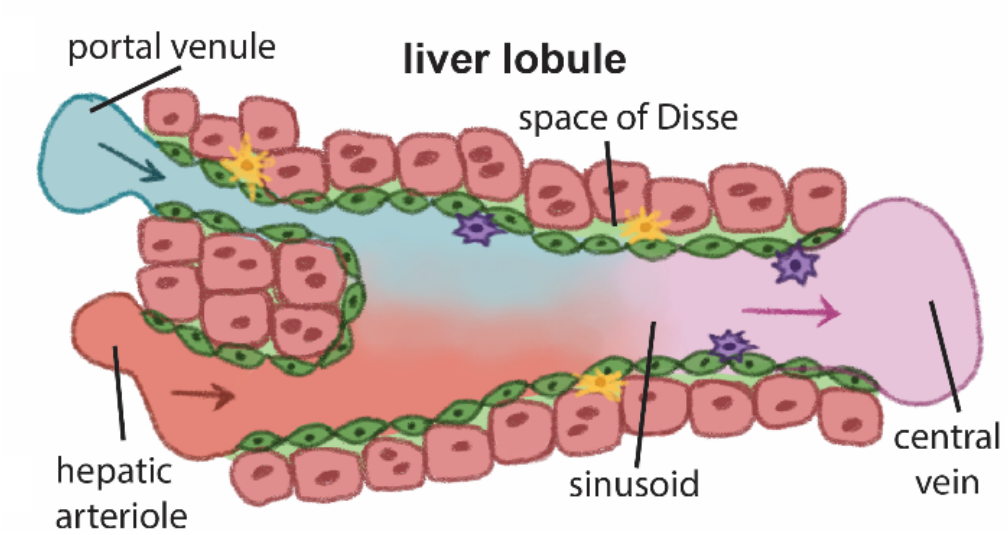


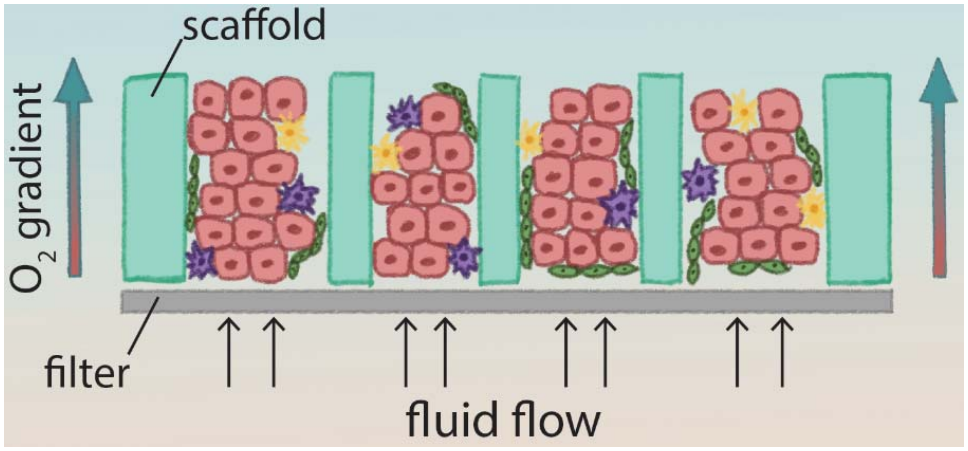
Limitations:

- Hepatic properties do not last beyond day 4
- Other hepatic cells are absent
- Absence of a physiological microenvironment: 3D + flow

Yang K et al. *J Pharm Sci* 2016

The liver microenvironment is 3D, under fluid flow and multicellular

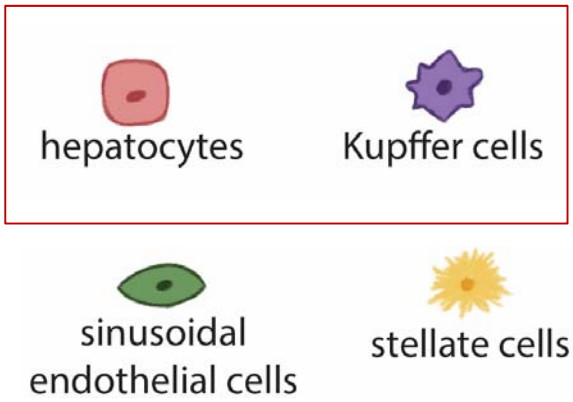




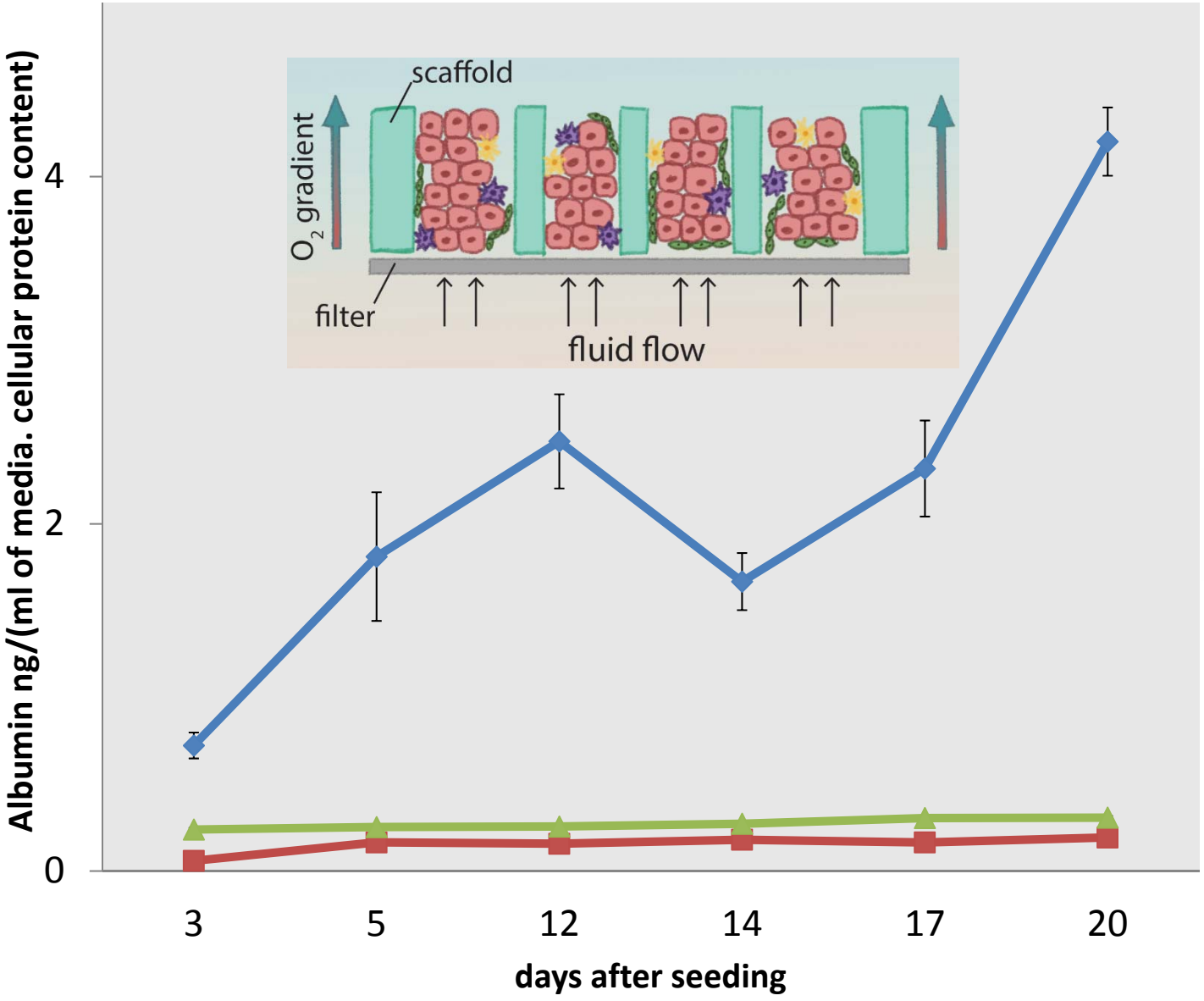
LiverChip

LiverChip:

- long-lasting hepatic properties
- heterogeneity of cell types
- universally reliable and robust properties

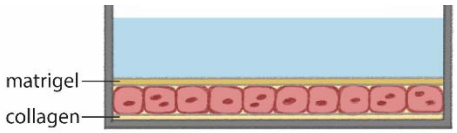


Albumin production is higher in cells cultured in the LiverChip than in other platforms

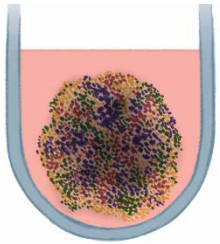


LiverChip

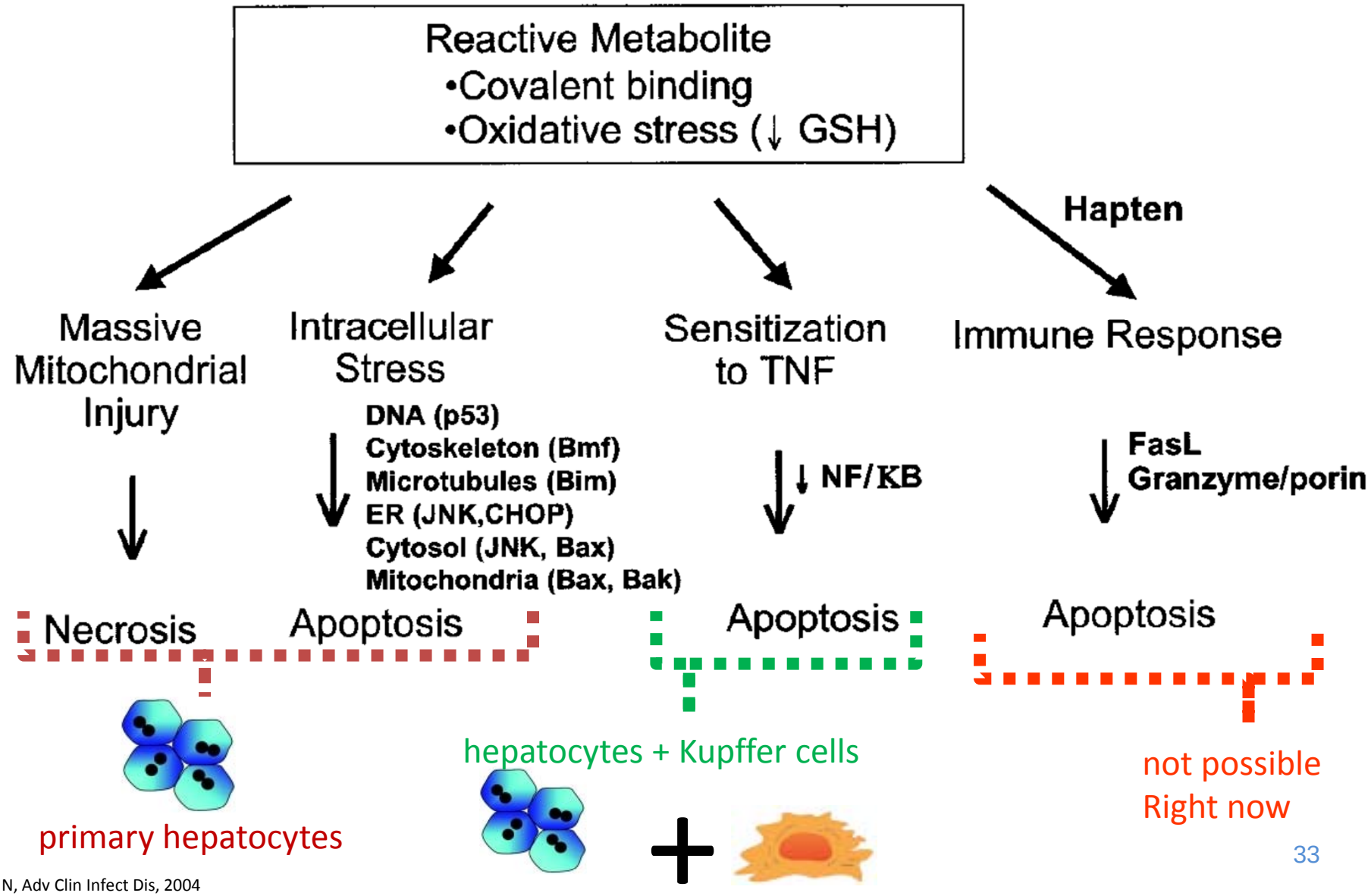
sandwich culture



spheroids



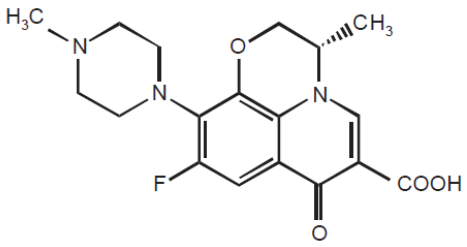
Adding multiple cell types improves the ability to predict different mechanisms



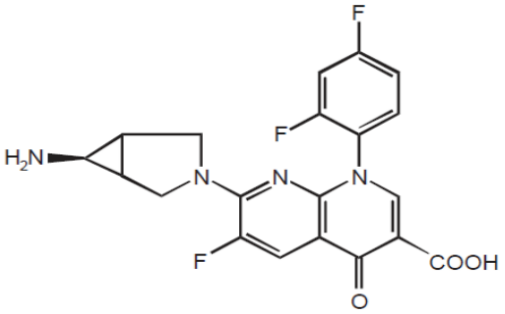
Kaplowitz, N, Adv Clin Infect Dis, 2004

We tested the use of co-cultures to screen drug toxicity with known drugs

levofloxacin (FDA-approved)



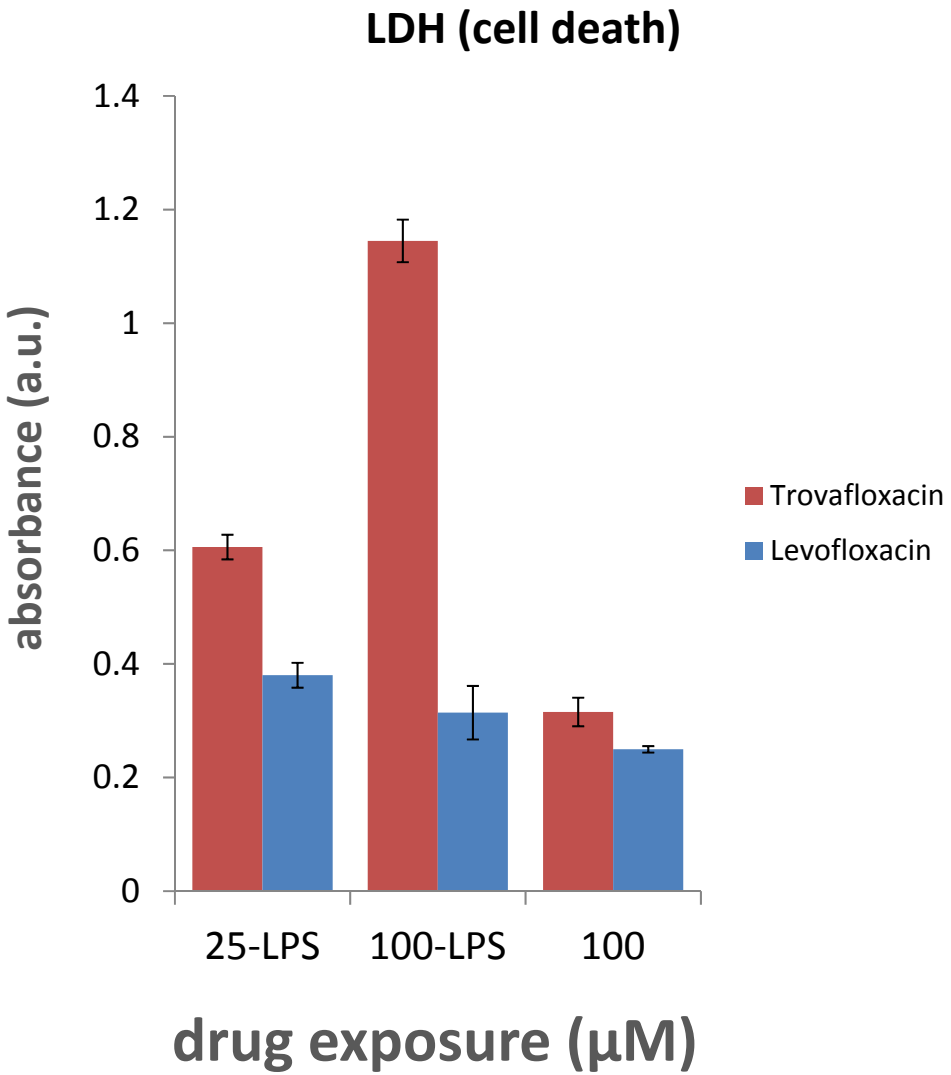
trovafloxacin (restrictions for use due to hepatotoxicity)

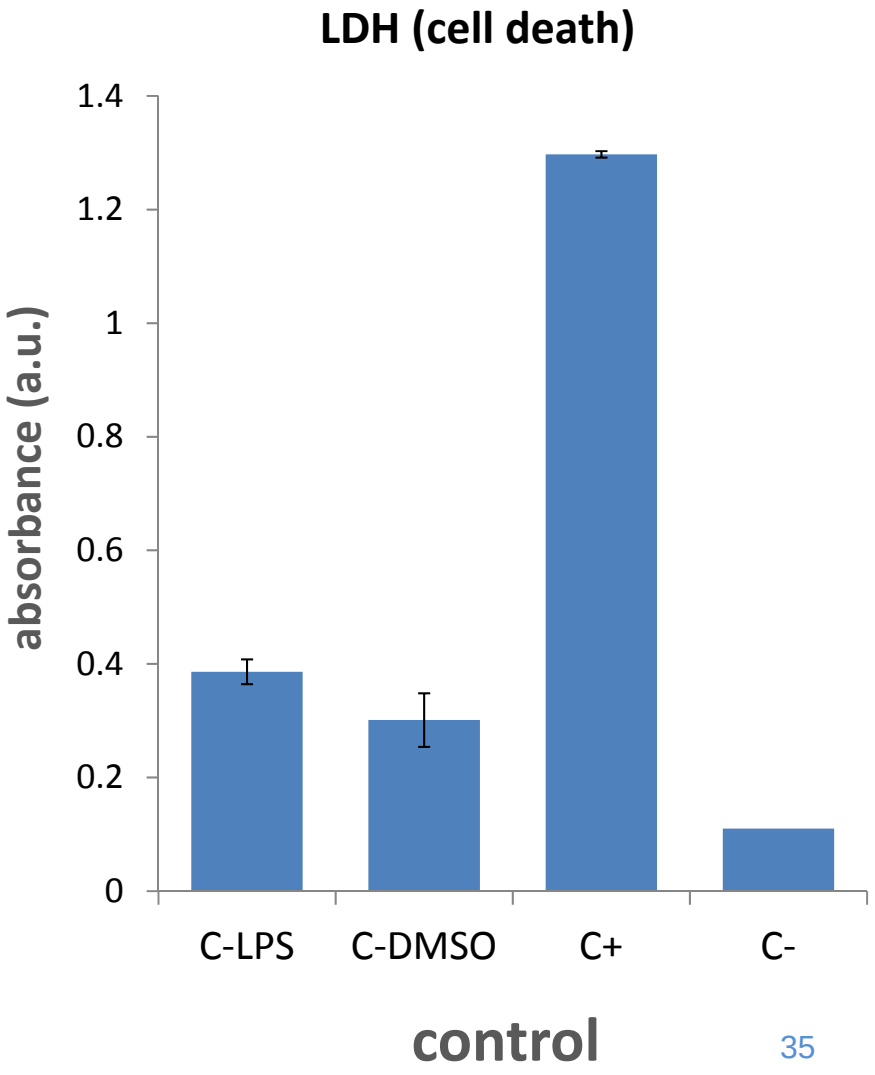


We developed a protocol:

- Defined treatment schedules
- Co-dosing with (Lipopolysaccharides) LPS: induce inflammatory signaling
- Concentrations (0, 25, 100) µM

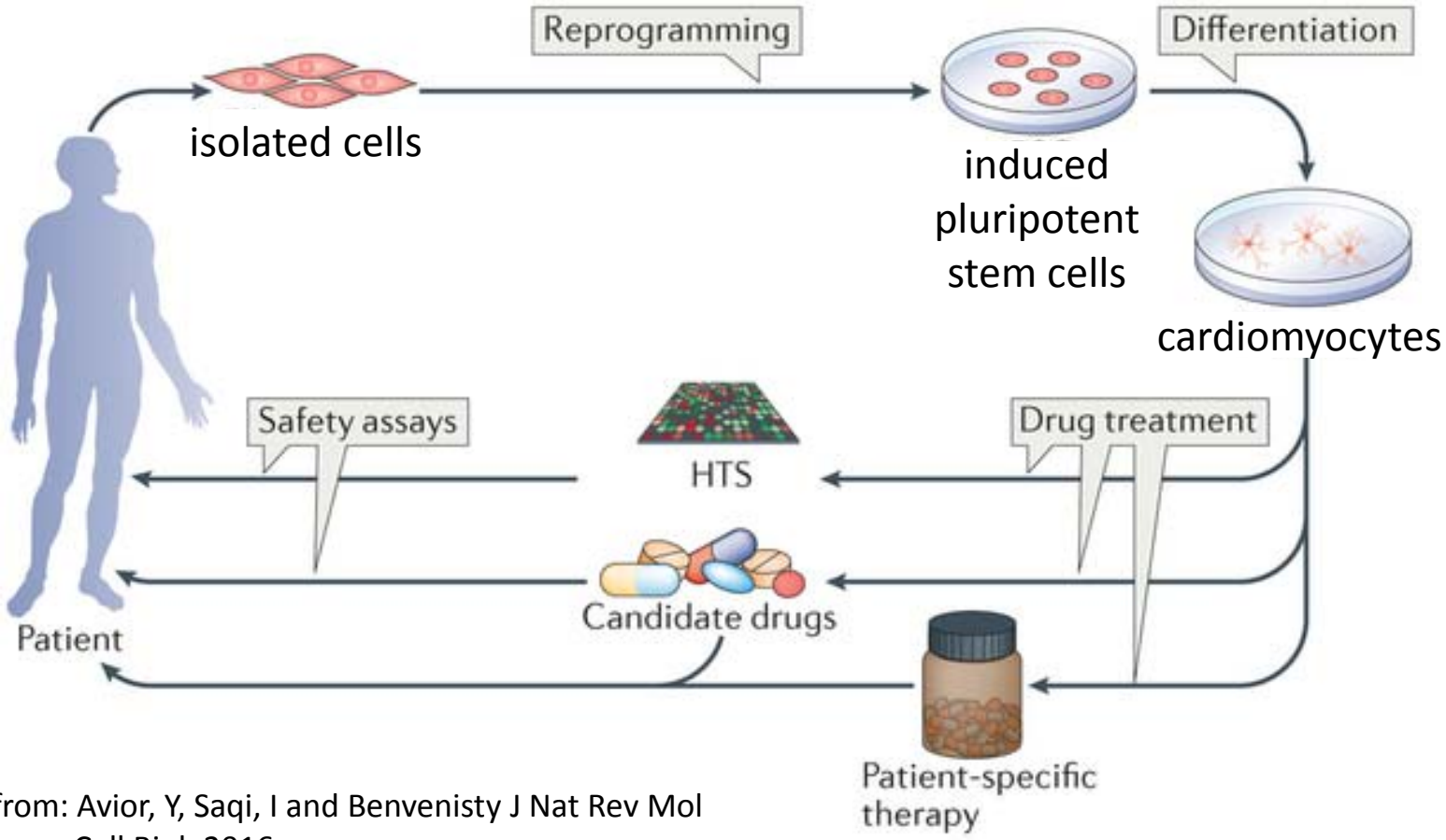
We observed toxicity induced by trovafloxacin and enabled by inflammation





- Contractility of iPSC-cardiomyocytes
- Towards multi-organ systems

iPSC-cardiomyocytes: assay human heart function in a dish



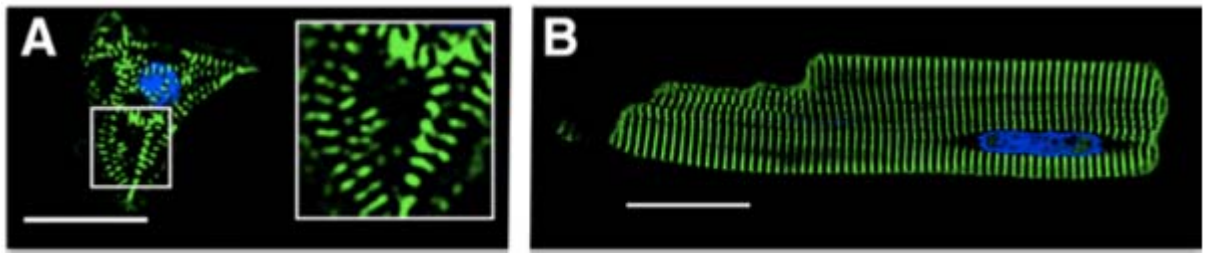
Adapted from: Avior, Y, Saqi, I and Benvenisty J Nat Rev Mol Cell Biol. 2016

Our goal is to evaluate drug toxicity assays

The use of iPSC-cardiomyocytes is limited by their fetal-like properties

Parameters		Immature CMs	Mature CMs	Methods / Metrics
Sarcomere	Structure / Length / Stability	Disarrayed / 1.6 µm / fluid	Organized / 2.2 µm / fixed	FFT / measure length / dynamic of myofibrils
Mitochondria	Distribution	Occupies a small fraction	≈ 40% of cell	Mitochondria Dies
Binucleation	Number	Mononucleated	≈ 25% binucleated	Counting
Electrophysiology	Upstroke velocity / Resting potential	≈ 50 V/s / -60mV	≈ 250 V/s / -90 mV	Patch clamp
Excitation-Contraction Coupling	Pacing of Cells	Partially Developed - relate to calcium	Mature	Calcium imaging
Contractile Force	Biomechanical Phenotypes	≈ nN range/cell	≈ µN range/cell	Traction Force Microscopy

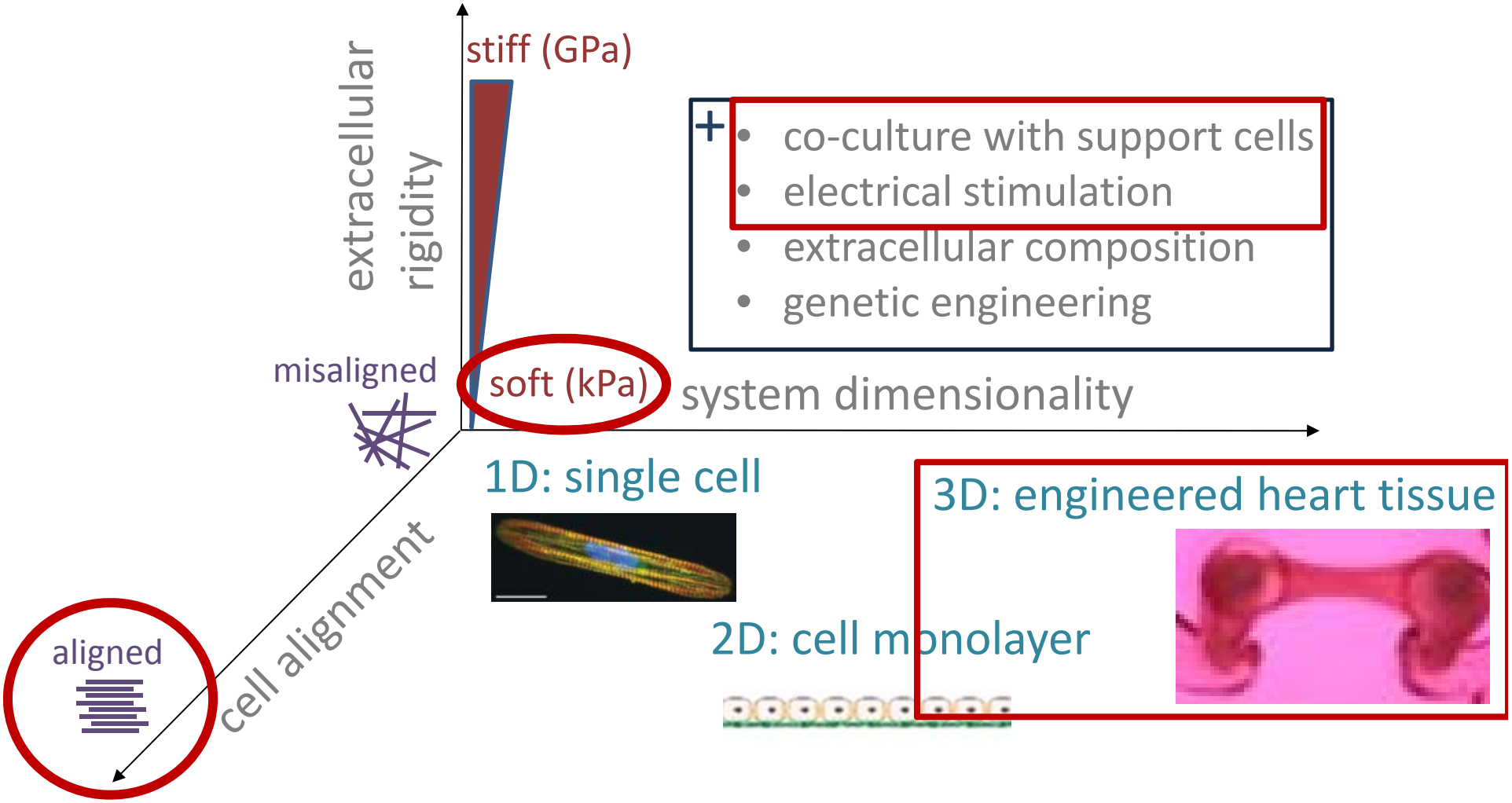
Stem Cell – CM
Fetal-like



Adult CM
Mature

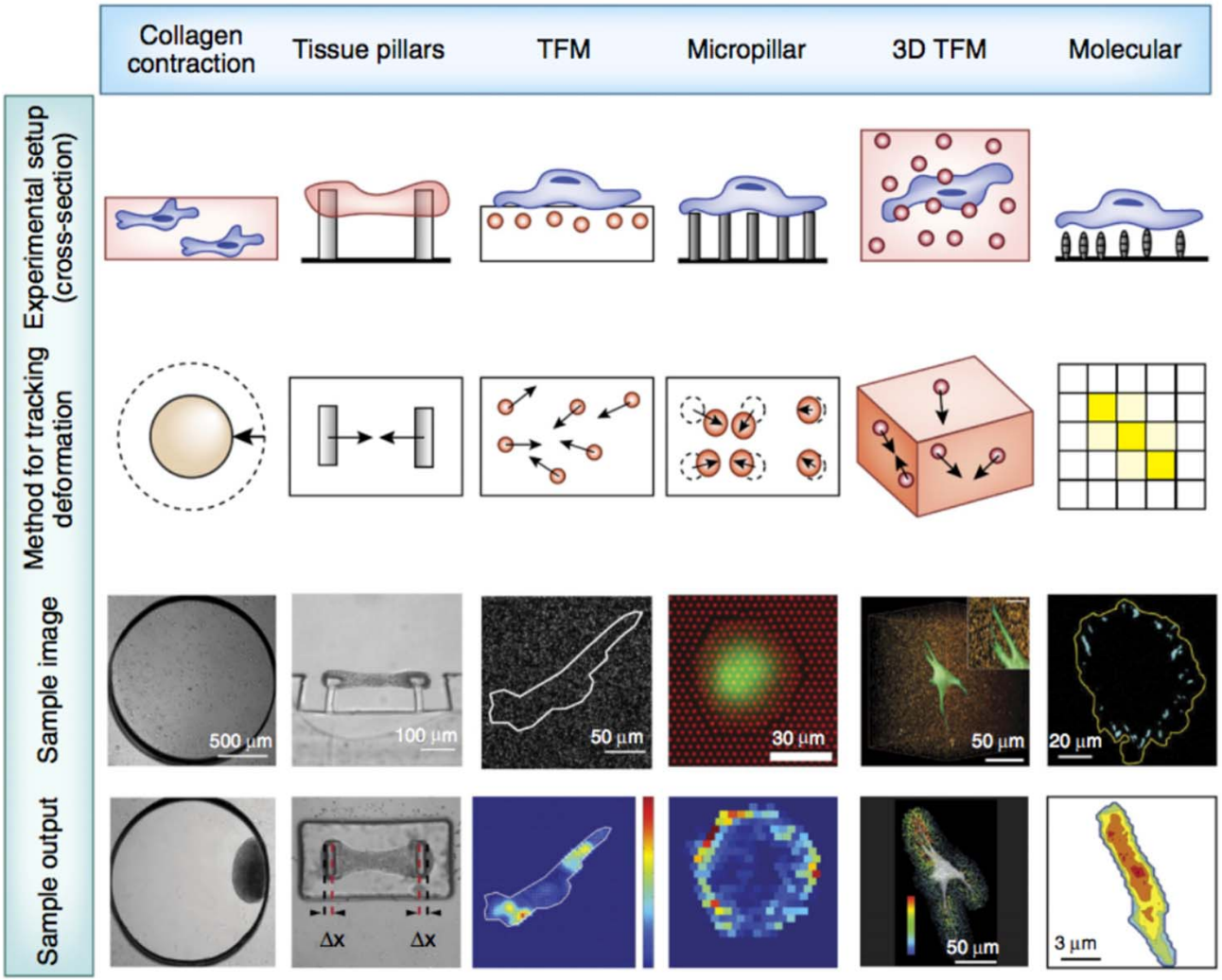
Yang, X et al., Circ Res. 2014

Cellular systems are also used to improve maturity of iPSC-cardiomyocytes



- Evaluate the effects of these approaches on drug response
- Focus on contractility endpoints: non-destructive and minimally invasive

iPSC-cardiomyocytes can be cultured in microfabricated platforms to measure contractility

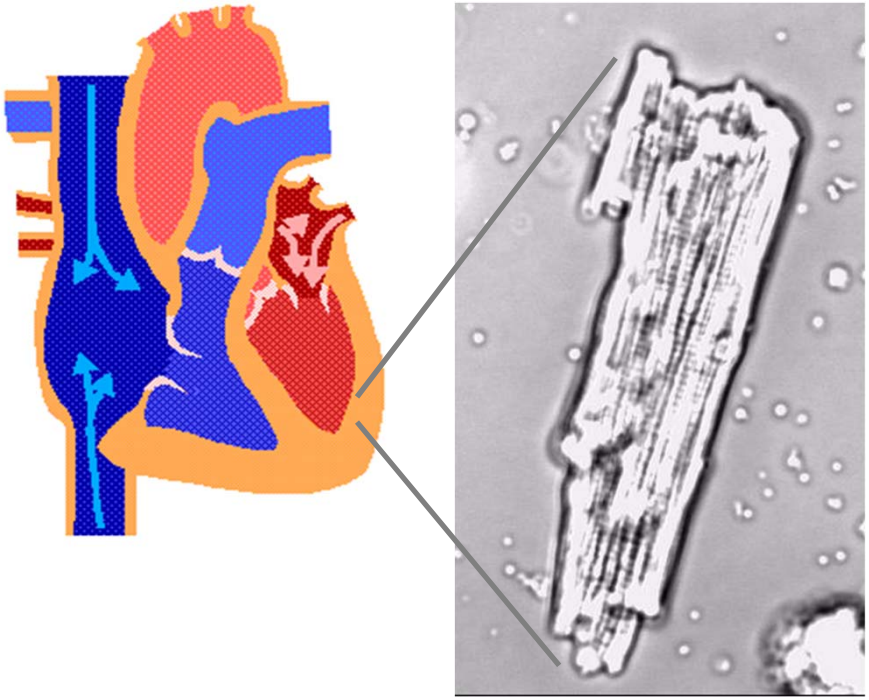


Polacheck et al., Nature Methods, 2016

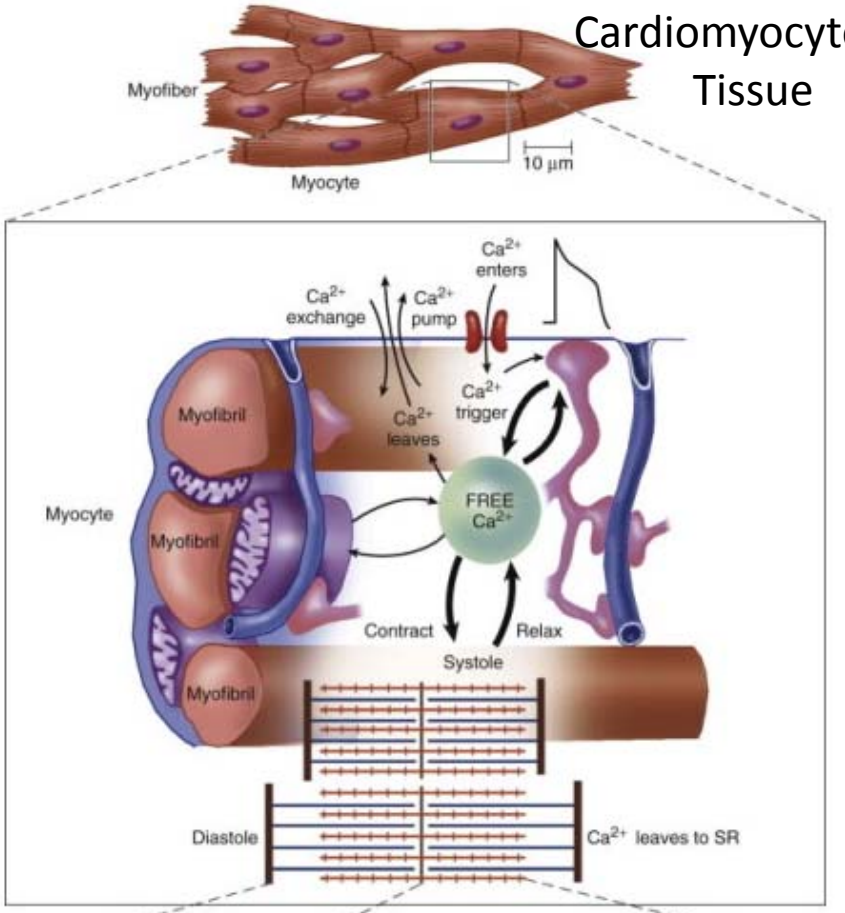
- methods must be feasible, robust and reliable
- physiologic relevance must be ensured

Cardiac contractility results from actin-myosin interactions

Cardiomyocyte
Isolated from a Mouse

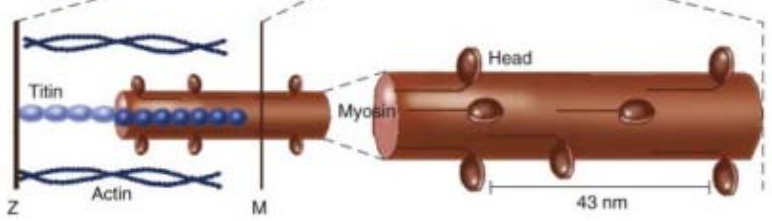


Cardiomyocytes In Tissue

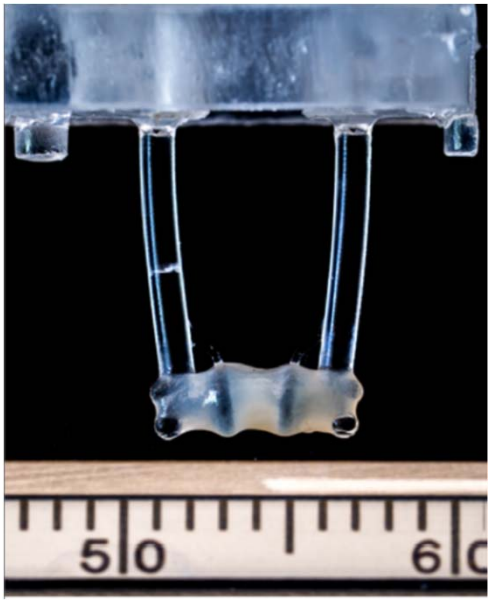


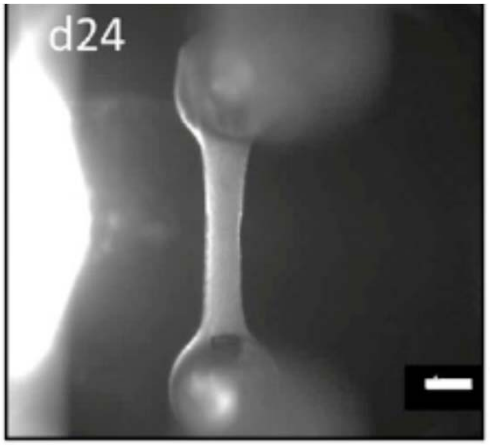
Braunwald's Heart Disease - A Textbook of Cardiovascular Medicine, 9th ed. - 2011

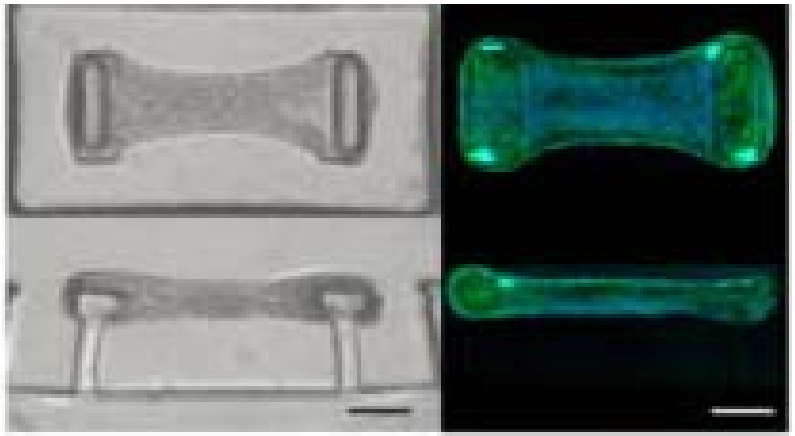
Actin-myosin interactions →

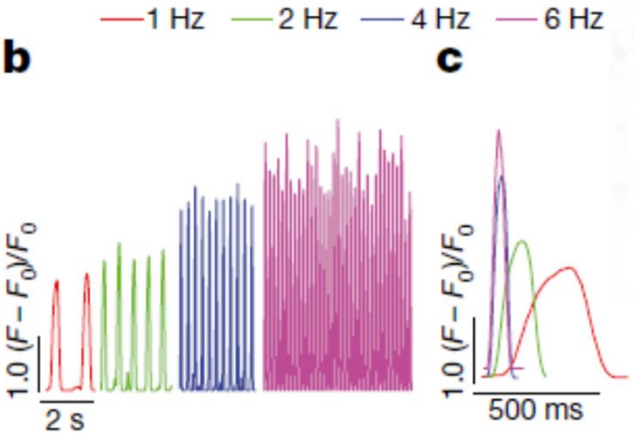


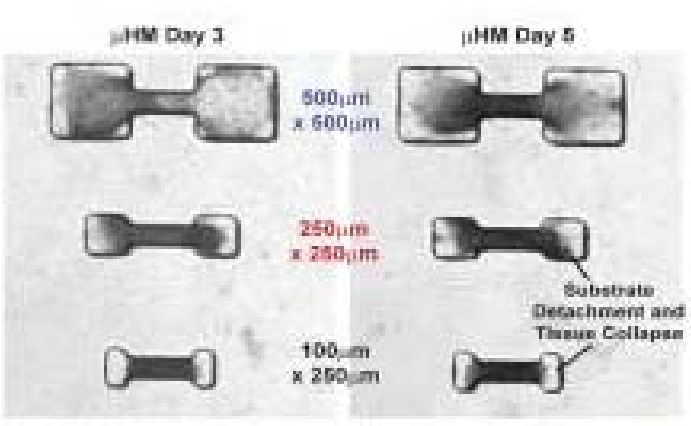
Engineered heart tissues

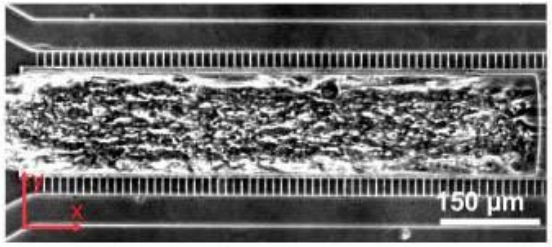






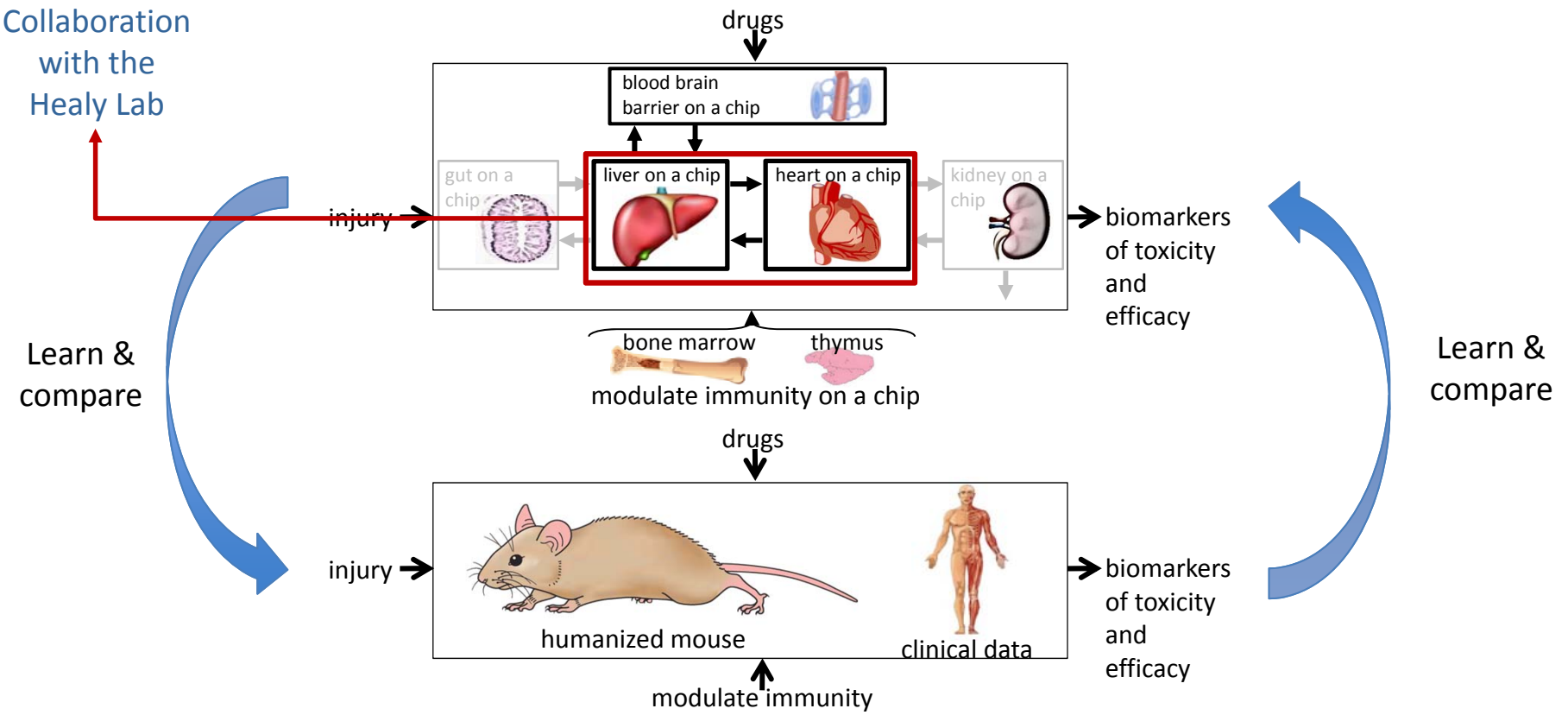






Ronaldson-Bouchard et al. Nature 2018
Mannhardt et al. Stem Cell Rep 2016
Huebsch et al. Sci Rep 2016
Hinson, Chopra et al. Science 2015
Mathur et al. Sci Rep 2015

Ultimate Goal: Evaluate More Systems and Compare Different Platforms

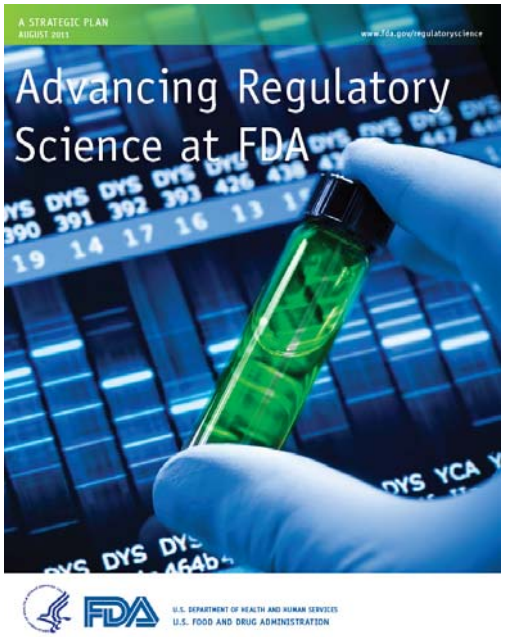


Key takeaways

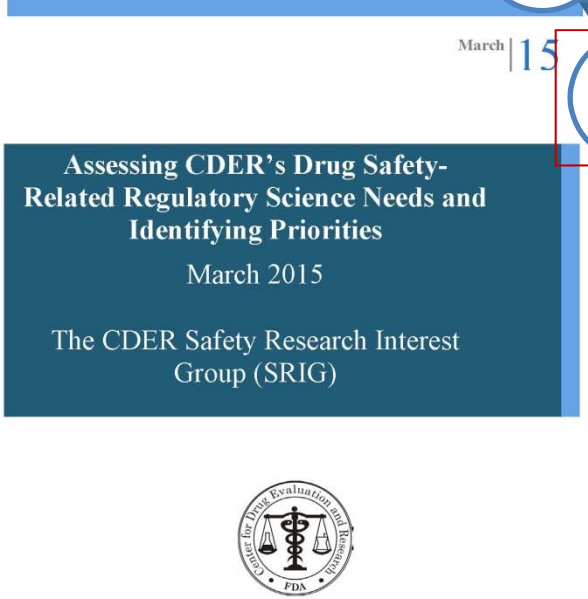
- FDA CDER laboratories are heavily invested in evaluating novel technologies to better predict clinical drug effects
- Human cellular systems should answer focused mechanistic questions
- Design of systems should be focused on physiological relevance and validation of functional endpoints to measure
- Efforts must be developed to set contexts of use of different systems:
  - what types/ classes of drugs?
  - what mechanism(s) of drug effects?
  - how predictable functional endpoints are?

FDA Regulatory Science Priorities

1. Modernize Toxicology to Enhance Product Safety: Strategic Plan for Regulatory Science
2. Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes: Strategic Plan for Regulatory Science
3. Support New Approaches to Improve Product Manufacturing and Quality: Strategic Plan for Regulatory Science
4. Ensure FDA Readiness to Evaluate Innovative Emerging Technologies
5. Harness Diverse Data through Information Sciences to Improve Health Outcomes: Strategic Plan for Regulatory Science
6. Implement a New Prevention-Focused Food Safety System to Protect Public Health: Strategic Plan for Regulatory Science
7. Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security
8. Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Products: Strategic Plan for Regulatory Science



CDER: 7 Safety-Related Research Topics



1. Improve Access to Post-market Data Sources and Explore Feasibility of Their Use in Safety Signal Analyses
2. Improve Risk Assessment and Management Strategies to Reinforce the Safe Use of Drugs
3. Evaluate and Improve Risk Communication
4. Focus on Product Quality Attributes, Manufacturing Processes, and Product Performance relating to Safety
5. Develop and Improve Predictive Models of Safety in Humans, including Non-Clinical Biomarkers
6. Improve Clinical Trial Statistical Analyses for Safety and Benefit Risk
7. Investigate Clinical Biomarkers of Safety, Including Standards for Qualification

http://www.fda.gov/drugs/scienceresearch/ucm264327.htm

Slide modified from Ruth Barratt, FDA/CDER

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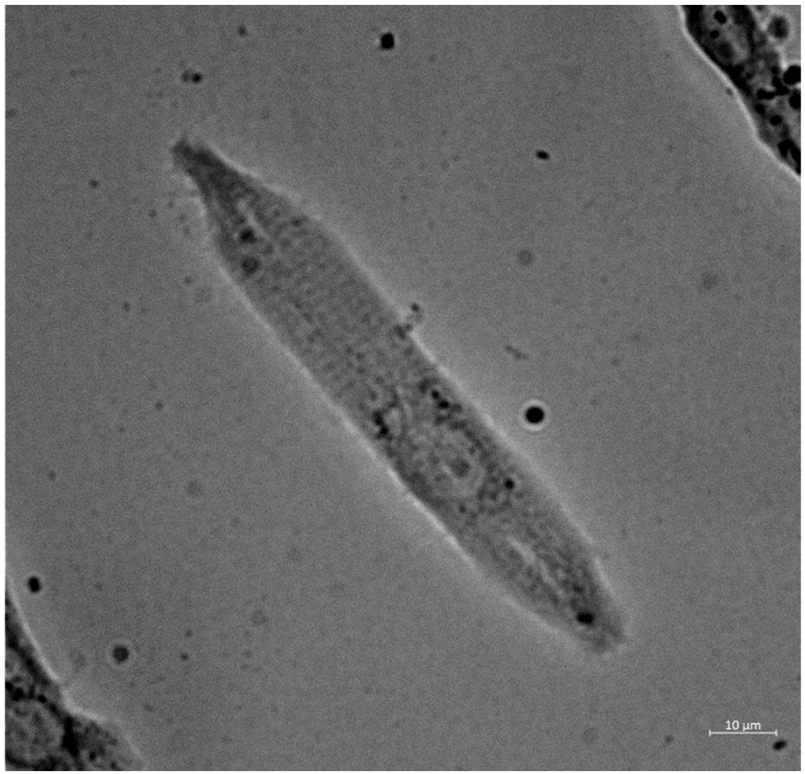
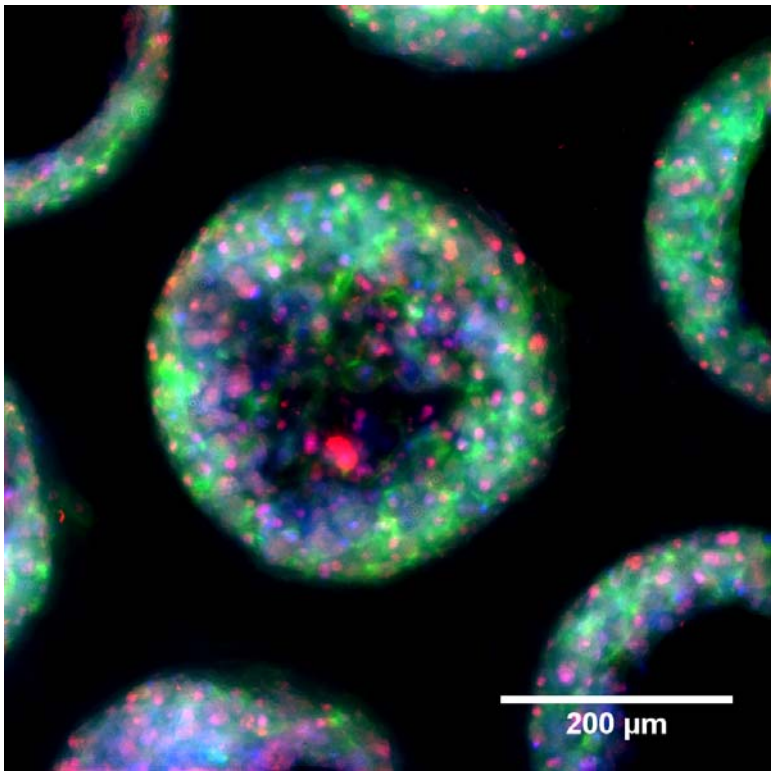
- Disclaimer: The opinions expressed in this presentation are mine and do not necessarily reflect the official views of the U.S. Food and Drug Administration (FDA)

- No conflicts of interest

Thanks!



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