"Fit for Purpose" for Organotypic Models in Environmental Health Protection

Ivan Rusyn, MD, PhD

University Professor, Texas A&M University

Research funding from US EPA/ORD:

R832720	Carolina Environmental Bioinformatics Center (co-Investigator)	2005-2010
R833825	Carolina Center for Computational Toxicology	2008-2012
R835166	Carolina Center for Computational Toxicology: Assays, models and tools for NextGen safety assessments	2012-2016
R835612	Toxicogenetics of tetrachloroethylene metabolism and toxicity	2014-2017
R835802	Cardiotoxicity Adverse Outcome Pathway	2015-2021
RD840032	Integrating tissue chips, rapid untargeted analytical methods and molecular modeling for toxicokinetic screening	2020-2023

US EPA/ORD/NCEA Faculty Fellow (ORISE): 2011-2013

Other government funding sources: NIH (NIEHS, NTP, NCATS, NIAAA, NIGMS, NCI), CalEPA, Environment Agency Abu-Dhabi

Other private funding sources: Concawe, Foundation for Chemistry Research and Initiatives, ACC, BMS, Sanofi-Aventis

Tissue Chips Landscape (NCATS perspective)

Establishment of NCATS
December 2011

IQ Consortium MPS Affiliate: AbbVie, Alnylam, Amgen, Astellas, AstraZeneca, Biogen, Bristol-Myers Squibb, Company, Celgene, Eisai, Eli Lilly, Genentech, GlaxoSmithKline, Janssen Pharmaceuticals, Merck & Co., Merck KGaA, Mitsubishi Tanabe, Novartis, Pfizer, Sanofi, Seattle Genetics, Takeda, Theravance, Vertex

US Food and Drug Administration

2010 – 2012
Regulatory Science

NIH – FDA Joint Leadership Council on Advancing Regulatory Science

RFA-RM-10-006
- Heart and Lung Micromachine was one of 4 awards

NIH $18 M
FDA $2.25 M

2012 - 2017
Toxicity Studies

* DARPA $75 M

* AstraZeneca, GlaxoSmithKline and Pfizer Reference Set Compounds *(2014-2017)*

NCATS Tissue Chips for Drug Screening

RFA-RM-11-022
- 10 awards

RFA-RM-12-001
- 8 awards

NCATS $50 M

Common Fund, NIBIB, NCI, NICHD, NIEHS, ORWH $25 M

2016 - 2021
Accelerated Aging Models

* Center for Advancement of Science in Space (CASIS) or International Space Station – National Laboratory
$8 M in kind per launch
* NASA task orders with implementation partners

Tissue Chips in Space

RFA-TR-16-019
- 5 awards $12 M

RFA-TR-18-001 (joined by NIBIB)
- 4 awards $10 M

2018 – 2022 Disease Models for Efficacy Testing

Nociception, Addiction, and Overdose
RFA-TR-19-003
- 5 awards ($25 M HEAL)

Alzheimer's Disease-Related Dementias
RFA-NS-19-027
- 1 award $7.5 M

Disease Models
RFA-TR-16-017
NHLBI, NIAMS, NIBIB, NICHD, NIDCR, NIDDK, NIEHS, NINDS, ORWH
- 13 awards $75 M

RFA-DK-17-035 Type 2 Diabetes
- 3 awards $15 M

2016 – 2020 Building Confidence in MPS

Tissue Chips Testing Centers and Database Center
RFA-TR-16-006, RFA-TR-18-005, RFA-TR-18-006
- 2 TCTCs and 1 MPS Database Center $24 M

Self-sustaining beyond NCATS support

Slide courtesy of Danilo Tagle (NIH/NCATS)

National Center for Advancing Translational Sciences

Tissue Chips are *already* in use for internal portfolio decision-making by Pharma

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 (screening)	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

Target identification

Lead optimization

PK/TK

Preclinical safety

Preclinical efficacy

Marx et al., ALTEX 37(3):364-394, 2020. doi: 10.14573/altex.2001241

U.S. FOOD & DRUG ADMINISTRATION

US FDA Office of Chief Scientist, Office of Commissioner:

Alternative Methods Working Group https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda

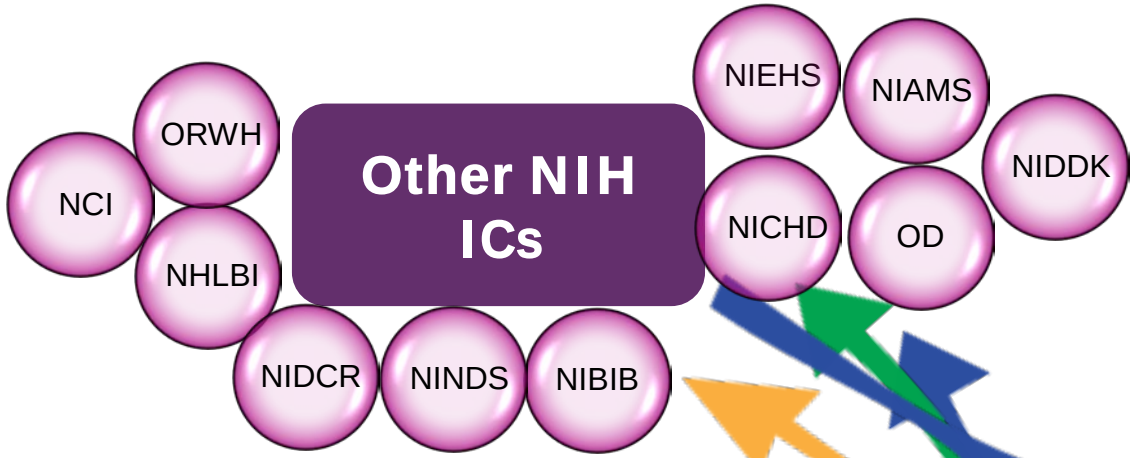
Objectives of FDA's Alternative Methods Working Group

- Discuss FDA-wide new in vitro, in vivo, and in silico methods, including research, training, and communication.
- Interact with U.S. Federal partners and other global stakeholders to facilitate discussion and development of draft performance criteria for such assays.
- Establish a dialogue and develop partnerships with FDA stakeholders to explore regulatory science applications for such technologies.
- Identify the performance criteria of microphysiological systems by engaging with FDA experts and FDA stakeholders through public-private partnerships.

Research projects using “tissue chips” at US FDA (examples):

- CDER: Division of Applied Regulatory Science – testing commercial **liver**, **heart**, **liver-heart** platforms
- CBER: Developing/improving test methods for **cell-based product** characterization (safety and effectiveness)
- CTP: Using organo-mimetic human **lung airway**-on-a-chip to test various tobacco and related products

Growing Partnerships and Investments in MPS beyond NCATS



- Cancer Biomimetics (NCI)
- Microphysiological Systems (MPS) for Modeling Diabetes (NIDDK)
- ImmuneChip: Engineering Microphysiological Immune Tissue Platforms (NIBIB)
- Nervous system MPS (NIMH)
- Human Three-Dimensional Cell Model Systems for Alzheimer's Disease-Related Dementias (NINDS)
- Trans-agency Blood-Brain Barrier Interface (NHLBI)
- Biomimetics for Infectious diseases (NIAID)

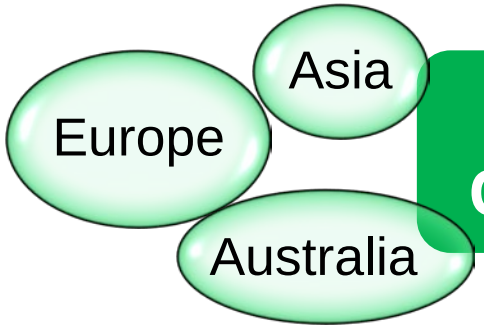
NCATS

NASA and HHS

- NCATS-NASA State of the Science Workshop: 3D Tissues and Microphysiological Systems
- NIH ICs, FDA, NASA, BARDA, CDC, ISS-NL

Other Interests

- BARDA
- Translational Research Institute for Space Health
- NASA Human Research Program
- **EPA – *animal-free testing by 2035***
- USGS
- VA



Other Countries

Slide courtesy of Danilo Tagle (NIH/NCATS)

National Center for Advancing Translational Sciences

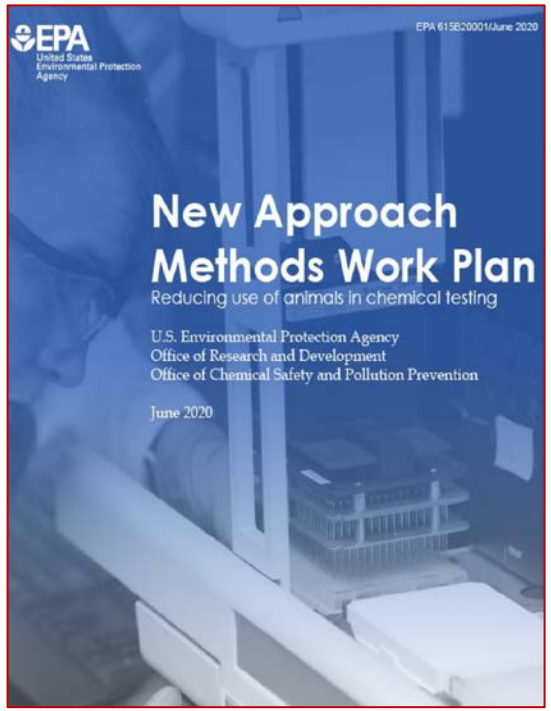
US EPA "Safer Chemicals Research Grants"

Organotypic Culture Models for Predictive Toxicology Center (2013) - $18 million			
R835736	Vanderbilt - Pittsburgh resource for organotypic models for predictive toxicology	University of Pittsburgh Vanderbilt University	2014-2019
R835737	Human models for analysis of pathways (H-MAPs) center	University of Wisconsin - Madison	2014-2019
R835738	Predictive toxicology center for organotypic cultures and assessment of AOPs for engineered nanomaterials	University of Washington	2014-2020
R835802	Cardiotoxicity adverse outcome pathway	Texas A&M University North Carolina State University	2015-2021

Advancing Actionable Alternatives to Vertebrate Animal Testing for Chemical Safety Assessment (2018) - $4.25 million			
R839501	Instrumenting phenotypic immunological responses to toxicants that threaten human reproduction	Vanderbilt University	2019-2022
R839502	Skeletal teratogenicity of industrial and environmental chemicals predicted with human pluripotent stem cells *in vitro*	University of California - Riverside	2019-2022
R839503	Reducing the reliance on early-life stage testing with relevance to euryhaline fishes	Oregon State University Louisiana State University	2019-2022
R839504	A Neurovascular Unit on Chip for reducing animals in organophosphate neurotoxicology	Vanderbilt University	2019-2020
R839505	Multiplexed human BrainSphere developmental neurotoxicity test for 6 key events of neural development	The Johns Hopkins University	2019-2022

https://www.epa.gov/research-grants/safer-chemicals-research-grants

What is "Fit for Purpose" for Organotypic Models at EPA?



- *"Most of the statutes and regulations surveyed include statements such as the necessity of upholding scientific standards and using "**the best available science**," which may include NAMs"* – **Animal tests used by the EPA are NOT always required!**
- *"The authority for EPA's research programs arising from these statutes is broadly written and does not constrain the Agency from developing or advancing the use of NAMs"* – **Non-animal tests that are "the best available science" CAN be used!**
- *"The Administrator's directive and similar text in section 4(h)(1) of TSCA note the need for information of "equivalent or better" scientific quality and relevance to animal test-based results"* – **The comparator for NAMs at EPA is ANIMAL data!**
- Need to *"Develop a scientific confidence framework to evaluate the quality, reliability, and relevance of NAMs"* – **How do we know it is "best available science"?**

Table 2. Initial Selection of On-Going EPA Case Studies for Potential Incorporation into Work Plan

Title	Description
Refining Inhalation Risk Assessment with NAMs	Refine inhalation risk assessment for point of contact toxicity using a three-dimensional *in vitro* test system of human respiratory tissues to derive a point of departure, in conjunction with computational fluid dynamic modeling.
Integrating *In Vitro* Assay and Toxicokinetic Data in Read Across	Use of *in vitro* toxicity and toxicokinetic testing to refine/support read across categories for per- and polyfluoroalkyl substances (PFAS).
Application of *In Vitro* Bioactivity for Screening-Level Risk Decisions	Use of bioactivity from *in vitro* assays and *in vitro* toxicokinetics to prioritize chemical contaminants in biosolids.
Application of NAMs for Chronic and Carcinogenicity Testing	Integration of NAMs to identify chronic toxicity and non-genotoxic carcinogenicity modes-of-action and quantitative points-of-departure for regulatory decisions

EMERGING SCIENCE FOR ENVIRONMENTAL HEALTH DECISIONS

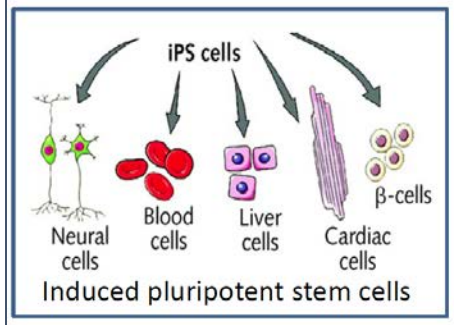
http://nas-sites.org/emergingscience/meetings/bioplatform/

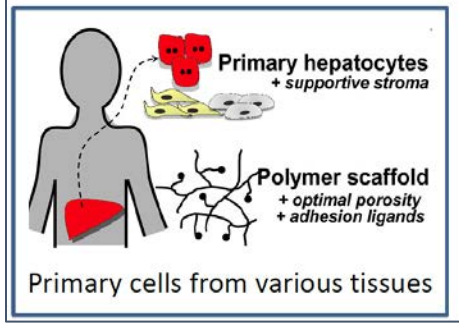
The Potential of the Tissue Chip for Environmental Health Studies

JULY 21–22*, 2014 ▪ MONDAY ~8:30–5:00, TUESDAY 8:30–NOON

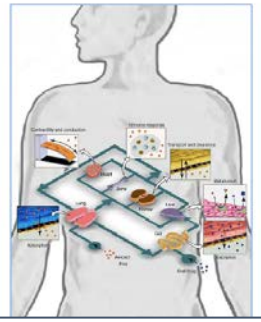
NATIONAL ACADEMY OF SCIENCES, ROOM 120 ▪ 2101 CONSTITUTION AVENUE, NW ▪ WASHINGTON, DC

The "biology"





The "plumbing"



The "nails"

Human health assessment of chemicals

"Tissue Chips will not be used in isolation, just like any other piece of evidence in regulatory decision-making is not being used in isolation to arrive at the ultimate decision"

Moving forward ("convince me!")

- Validation/qualification of the tissue chip systems
- Making tissue chips widely available so that the database is broad and robust
- The research and application of these models has to be transparent even though this area is in a "highly competitive state"
- Tissue chip technologies should be evaluated collectively so that the technology does not fall individually
- Inter-species extrapolation and exploiting of the animal to *in vitro* to human extrapolations

Texas A&M University Tissue Chip TESTING Center (TEX-VAL)

Tier -1:
Collaborative research and technology transfer agreements
- Execution of all legal agreements
- Sharing of the protocols
- TAMU staff training with developers

Tier 0:
Tissue chip testing without cells
- Assembling of tissue chips
- Testing of the flow and operation
- Testing drug binding to devices
- Development of LC-MS methods

Tier 1:
Reproducibility testing of tissue chips
- Replicating published studies
- Evaluation of key findings
- Detailed protocols and SOPs

Tier 2:
Extending the utility of the tissue chips
- Defining the "context of use"
- Conducting additional studies
- Depositing data into MPS-Db

4-8 months period of testing for each tissue chip/microphysiological system (MPS)

Oct. 2016 – Sept. 2019 (TEX-VAL 1.0)

Proximal kidney tubule	Himmelfarb/Kelly (Univ. Washington)
Neurovascular unit (BBB)	Wikswo (Vanderbilt)
Bone +/- tumor	Vunjak-Novakovic (Columbia)
Gut enteroid	Donowitz/Estes (JHU/BCM)
Skin from iPS cells	Christiano (Columbia)
Heart	Healy (UC-Berkeley)
Vasculature +/- tumor	Hughes (UC-Irvine)/George (UC-Davis)
Skeletal muscle	Truskey (Duke)
Liver (multi-cell)	Taylor (University of Pittsburgh)
Liver	Healy (UC-Berkeley)
White fat	Healy (UC-Berkeley)

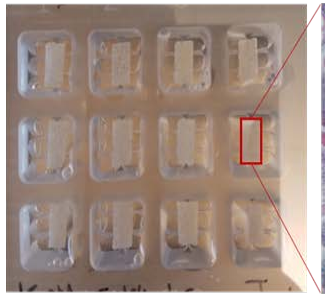
Oct. 2018 – Sept. 2021 (TEX-VAL2.0)

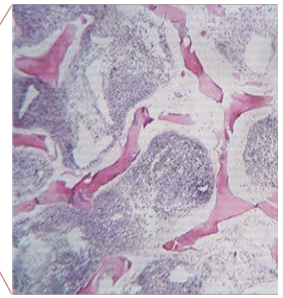
Arteriole-scale vessel	Truskey (Duke)
Salivary gland	Benoit (U-Rochester)
Vascularized kidney	Himmelfarb/Kelly (Univ. Washington)
Atria on a chip	George (UC-Davis)
Bone joint & cartilage	Tuan (University of Pittsburgh)
Small Airway	Huh (University of Pennsylvania)
Vascularized Liver (vLAMPS)	Taylor (University of Pittsburgh)
Vascularized micro-Liver	Hughes (UC-Irvine)

TEX-VAL Tissue Chip Testing: Diversity of experience with MPS

Static cultures

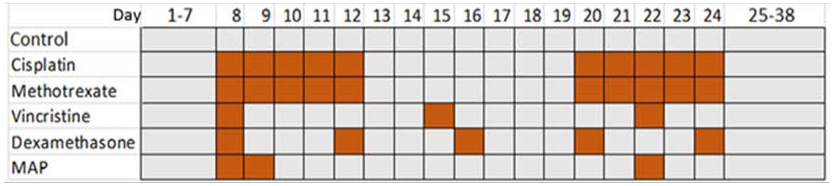
Columbia Univ.: Bone +/- Tumor Model



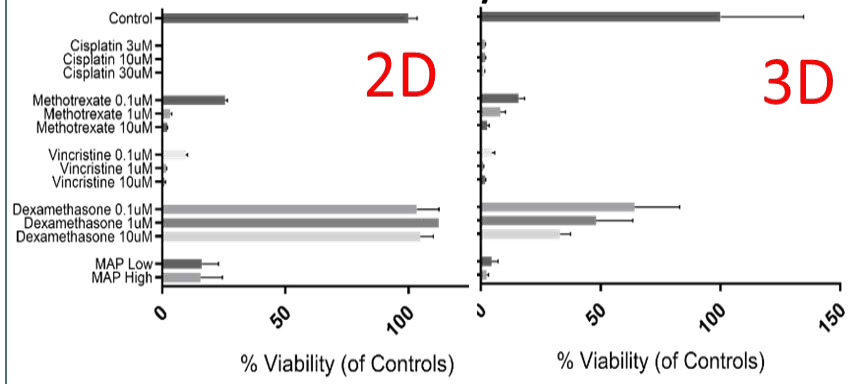


- De-cellularized bovine trabecular bone
- Human osteoblasts and Ewing's sarcoma cells

Simulating cancer treatments *in vitro* (3D and 2D)

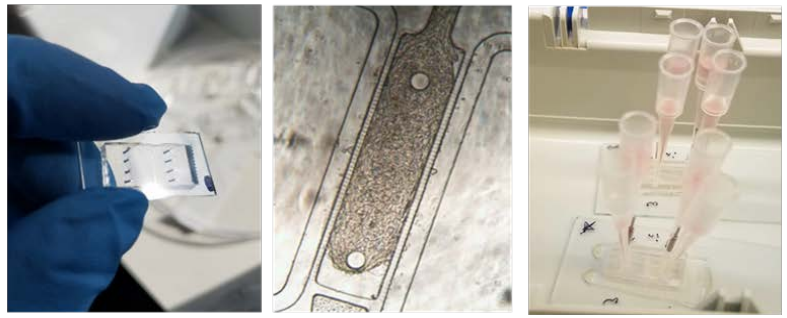


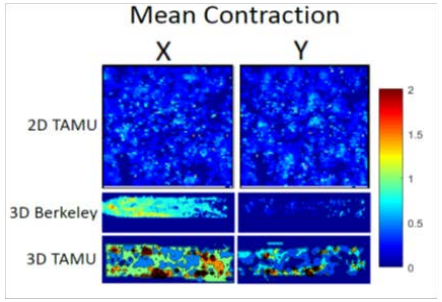
Cancer cell viability after treatment



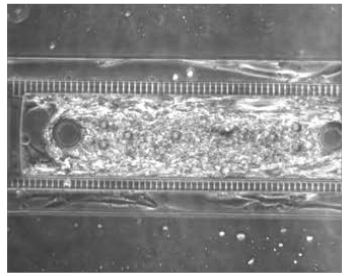
"Gravity Flow" cultures

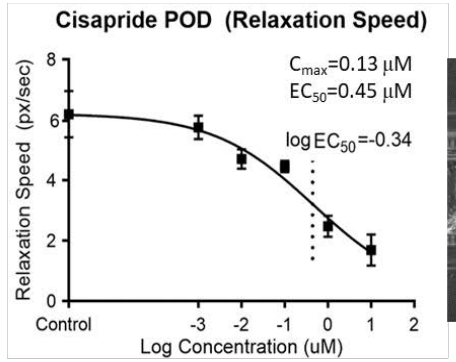
Univ. Cal.-Berkeley: Cardiac Model



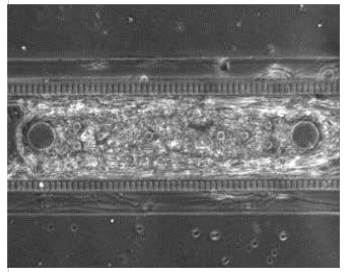


Vehicle





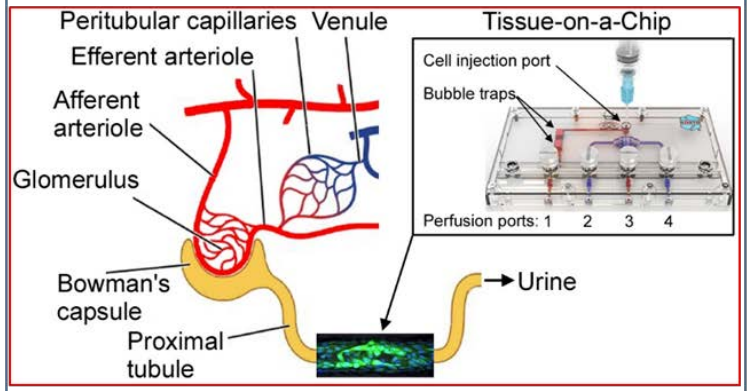
10µM Cisapride



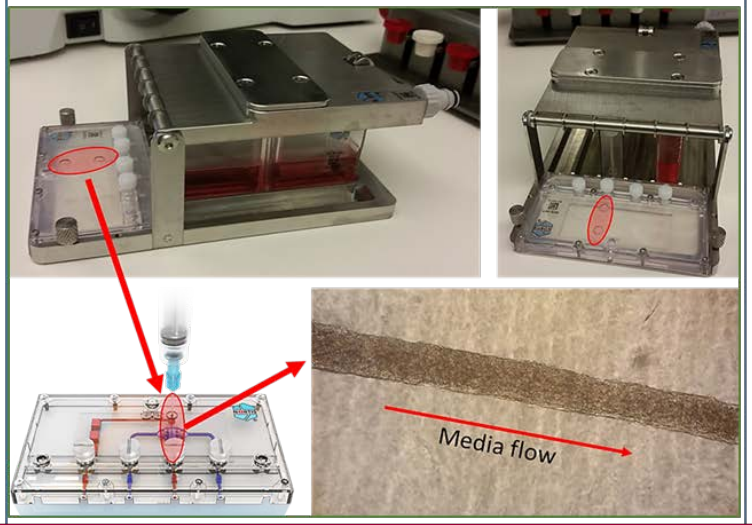
"Forced Flow" cultures

Univ. Wash.: Proximal Tubue

"Microphysiological" system



Bioengineer's "rendering"



TEX-VAL Status of Depositing Data to U-Pitt MPS Db (Oct. 2020)

https://upddi.pitt.edu/microphysiology-systems-database/

Tissue Chip Model	# Wells/Chips	
	2D	3D
Proximal Tubule, *U-Washington*	500	91
Blood-Brain Barrier, *Vanderbilt*	-	9
Bone/Tumor, *Columbia*	462	234
Skin, *Columbia*	-	224
Cardiac Tissue, *UC-Berkeley*	1091	141
Gut Enteroid, *Baylor College Med*	4,488	1,382
Vascularized Tumor, *UC-Irvine*	320	69
Liver, *UC-Berkeley*	90	81
Liver (multi-cell), *U-Pitt*	220	90
White Adipose, *UC-Berkeley*	626	104
Skeletal Muscle, *Duke*	-	192
Atrial Cardiomyocyte (2.0), *UC-Davis*	178	6
Kidney (2.0), *U-Washington*	-	21
TOTAL	**7,975**	**2,638**

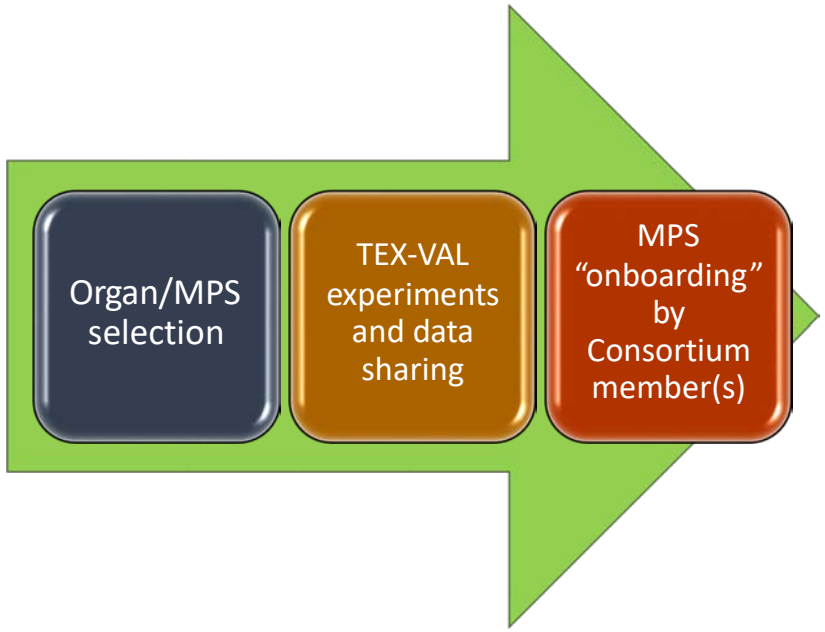
TEX-VAL Tissue Chip Testing Consortium (2020 - …)

Industry

- Bristol-Myers Squibb
- Sanofi-Aventis
- American Chemistry Council

Government

- NIH-NCATS
- NIH-NIEHS-NTP
- **EPA-NCCTE**



2020 Work Plan:

(including the "fit for purpose")

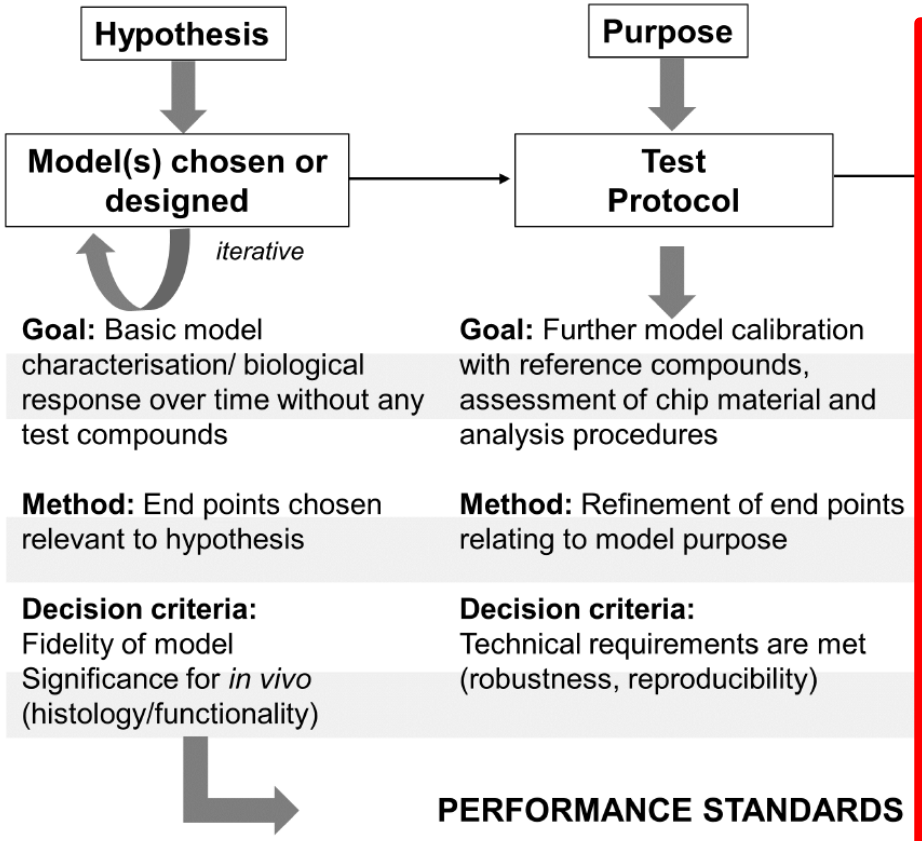
- Kidney (glomerulus and tubule)
- Liver (multicellular)
- Gut (different gut sections)
- Lung (air-liquid interface)

About that… “FIT FOR PURPOSE” again…

“Chemical _____ is NOT a hazard for _____”

Replace animal test _____ with cell-based test _____

“Best available science”?



Parameter	Explanation
Compounds	Commercially available compounds
Context of use	A clear definition of the relevance of the test method, where relevance describes the relationship of the test method to the effect of interest and whether it is meaningful and useful for a particular purpose (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-principles-regulatory-acceptance-3rs-replacement-reduction-refinement-testing-approaches_en.pdf). This includes the endpoints which are to be investigated with reference to the conventional animal or human endpoint, e.g. if the MPS is used to detect DILI, it needs to be specified whether it covers all kinds of liver damage (cholestasis, steatosis, inflammation, fibrosis, …) and how these are specified (biomarkers, morphology, histopathology, …).
Historical reference data	Data describing morphological and physiological outcome (e.g., histopathology, clinical chemistry) in MPS for defined reference compounds (positive and negative controls). Concentration ranges tested should be included. Endpoints measured in the MPS might include genomics markers, biomarker changes, etc.
Cell material & quality	Description of cell or tissue source, including potential quality checks (e.g., viability, functional performance tests, metabolic activity)
Specification of materials & media	Detailed description of materials with regard to biocompatibility, potential leachables, surface adsorption (drug binding), composition of media (protein content and source, growth factors included in the medium or added, flow rates, etc.)
Exposure	Drug stability data and determination of exposure (total/unbound, ideally also intracellular)
Exposure modeling	Description of the model that was used to compare exposure in the MPS with the *in vivo* situation (animal or human)
General documentation	Will Good Laboratory Practice (GLP) need to be met for such studies? A workshop on this topic, perhaps in partnership with the OECD, would be advisable as it will inform any decisions on performance standards. Alternatively, the regulatory agencies could brainstorm on what context of use situation would require these systems to be performed under GLP.
Robustness	Intra-assay (repeatability) and inter-laboratory comparative result data. The need for the latter may be decided on a case-by-case basis.

Marx et al., ALTEX 37(3):364-394, 2020.
doi: 10.14573/altex.2001241

EMERGING SCIENCE FOR ENVIRONMENTAL HEALTH DECISIONS

The Potential of the Tissue Chip for Environmental Health Studies

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NATIONAL ACADEMY OF SCIENCES, ROOM 120 ■ 2101 CONSTITUTION AVENUE, NW ■ WASHINGTON, DC

EPA United States Environmental Protection Agency

Prototypical Hazard ID and Dose-Response Assessment

July 21, 2014

Weihsueh Chiu (EPA)

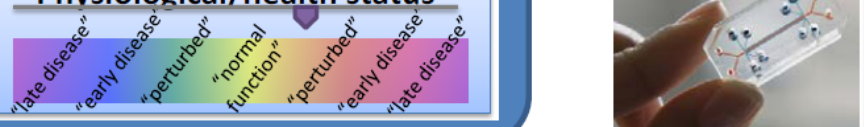
"Questions and Needs in Environmental Health and Risk Assessment Communities"

https://youtu.be/byaodNMCjf8

Data, models, theories, concepts

Source-to-Outcome Continuum

- Source/media concentrations
- Exposure
- External doses
- Toxicokinetics
- Internal concentrations
- Toxicodynamics
- Biological response measurements
- Systems dynamics
- Physiological/health status



Identify, evaluate, & integrate evidence
- Epidemiology
- Rodent bioassays
- Mechanistic data

Identify health effects, e.g.,
- Developmental effects
- Carcinogenicity

Estimate points of departure (PODs) from suitable studies, e.g.,
- LOAEL or NOAEL
- Benchmark dose at 10% response

Calculate toxicity values
- Reference dose = POD/Uncertainty factors
- Cancer slope factor = 10%/POD

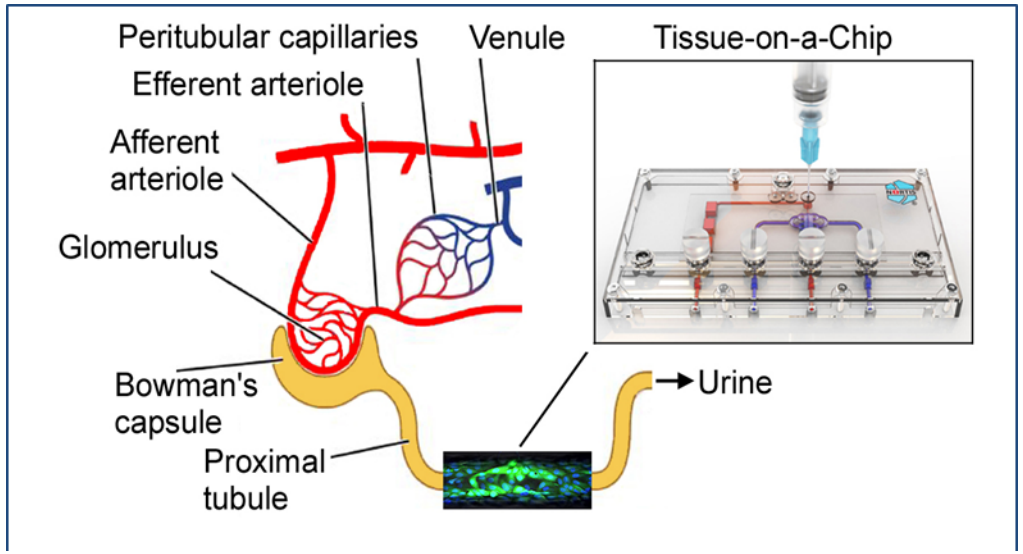
????

How could Tissue Chips be used in each step?

Environmental Health Decisions

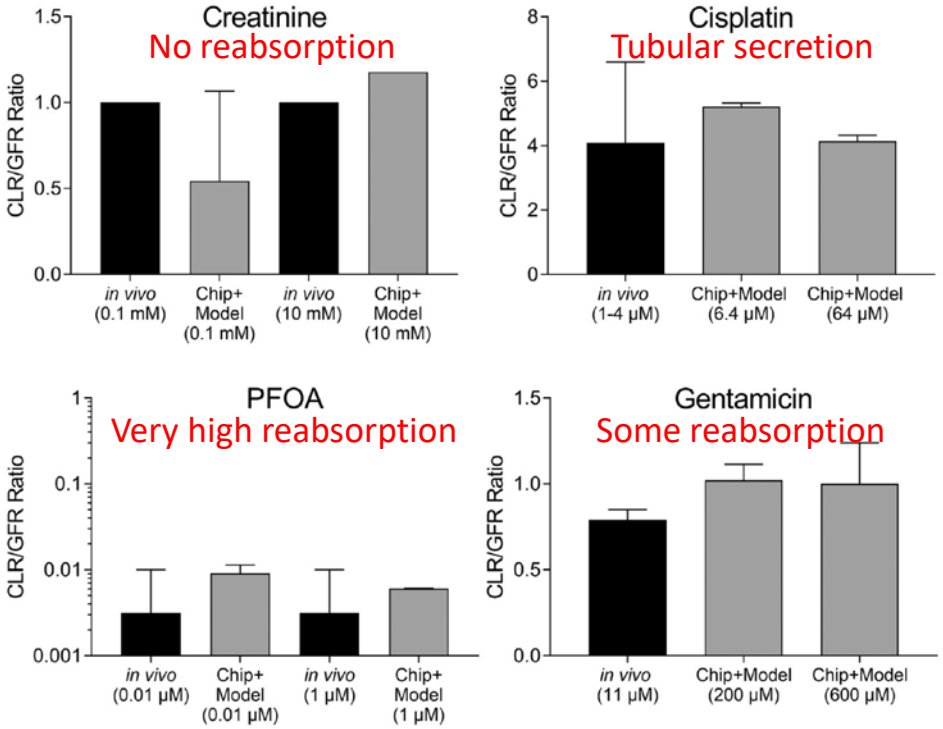
- Screening and/or prioritization
- Case example 1: Setting levels of exposure concentrations or intakes
- Case examples 2-3: Population-level analyses
- Risk-risk comparison

Case #1: Understanding kidney TK using *in vitro* NAM [reabsorption]

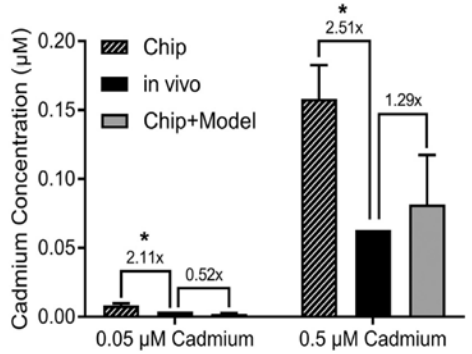


What is needed (experimental or from the literature):

- Free fraction of tested compounds in buffer and cell media
- Recovery from proximal tubule devices seeded with RPTECs
- Recovery from blank tissue chips
- Chip-to-human extrapolation model (dimension and flow)
- Knowledge of human kinetics for tested compounds (f_u)



Measured and predicted cadmium concentrations in chip effluent and human urine

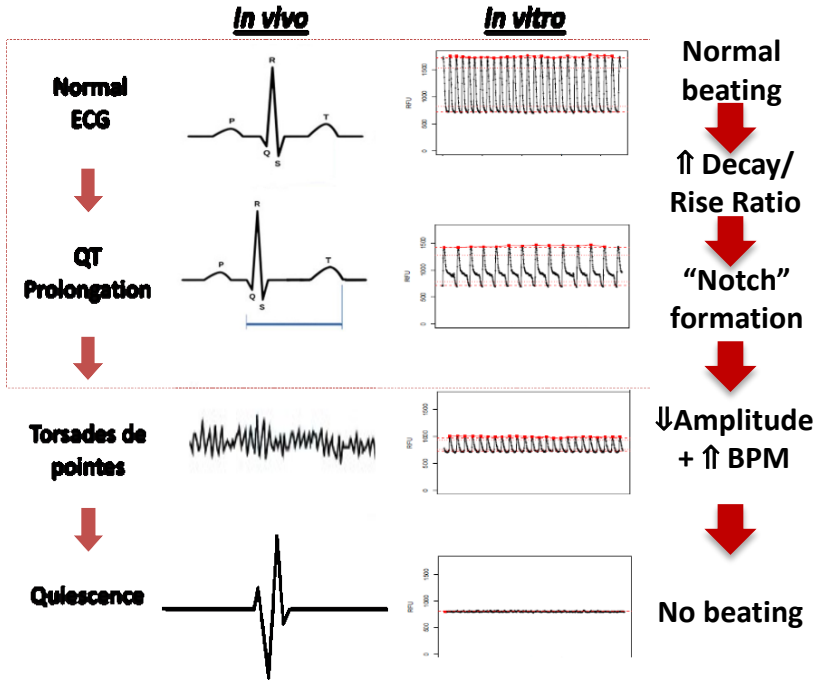


It's a tissue chip! Of only <u>one</u> part of <u>one</u> organ…
Plus, there is no vascular channel, only renal reabsorption and no tubular secretion…

Sakolish *et al*. Toxicol In Vitro. 63:104752, 2020. doi: 10.1016/j.tiv.2019

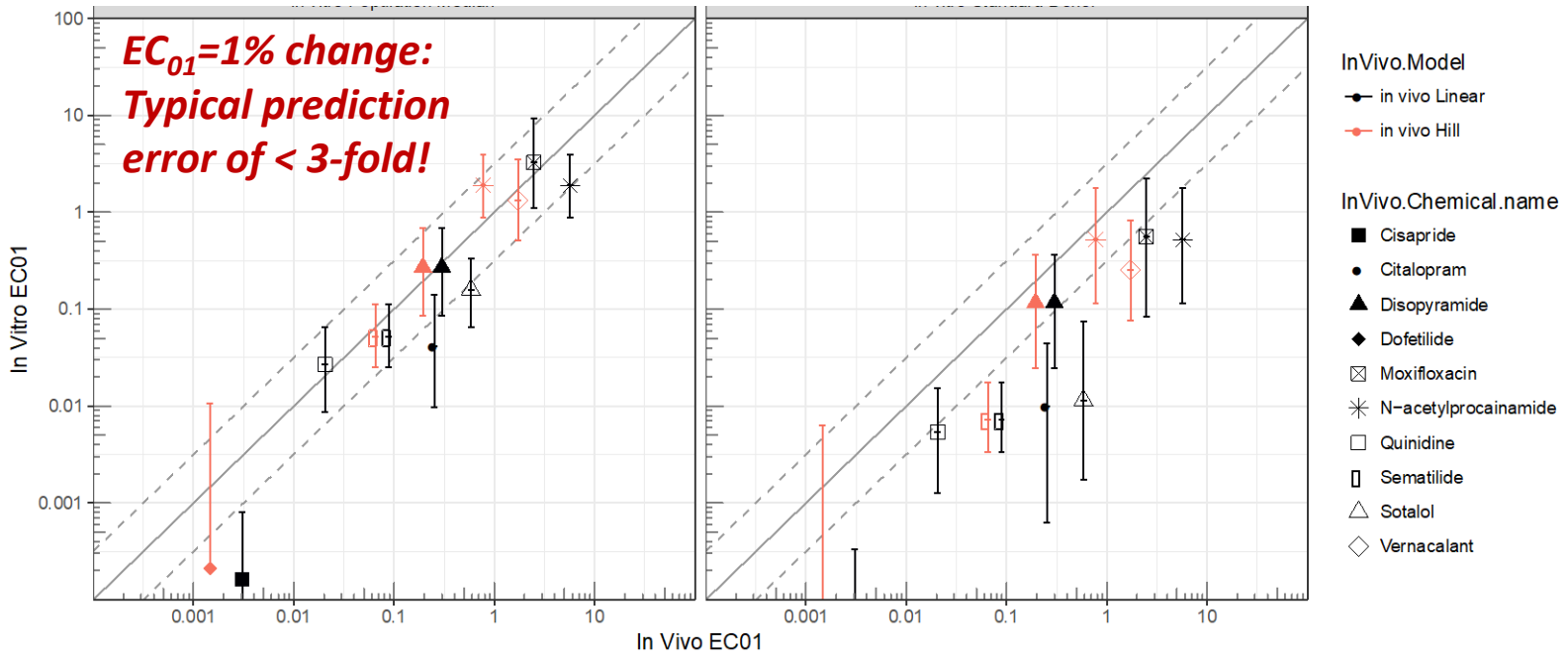
Case #2: Deriving a "safe dose" using NAMs [iPSC-CM, cardiac rhythm]

Qualitative Comparison:



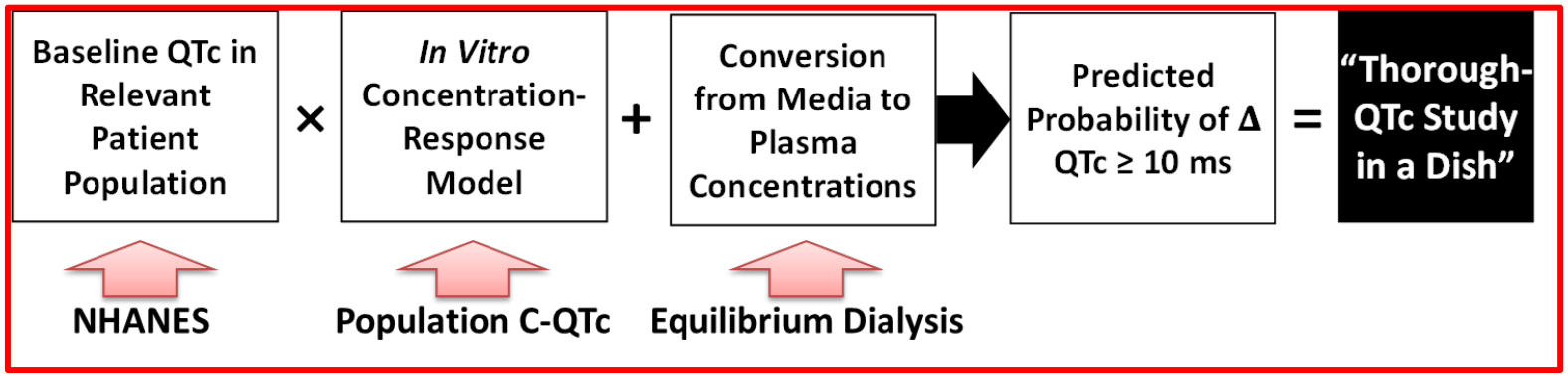
Clinical guidance: 95% for 10 ms change → Mean change of 5 ms → **1.2% change** from baseline (NHANES)

Population of iPSC-CM [27 donors] "Standard" donor iPSC-CM



Quantitative Comparison:

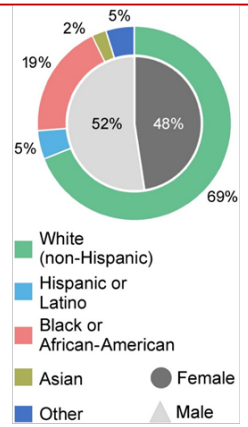
- ***In vivo***: use published PD modeling data for concentration-response relationships for QTc
- ***In vitro***: conduct Bayesian population PD modeling (Chiu et al. 2017) of decay-rise ratio
- **Compare *in vivo* and *in vitro*** concentration-response relationships (e.g., median and CIs)



Blanchette *et al*. Clin Pharmacol Ther. 105(5):1175-1186, 2019. doi: 10.1002/cpt.1259

Case #3: Risk characterization (population variability) [cardiac rhythm]

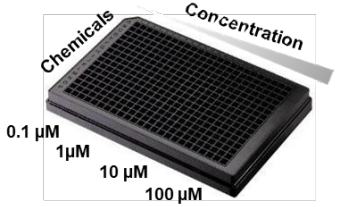
Population-Based iPSC-Derived Cardiomyocyte Model (n = 43 individuals)



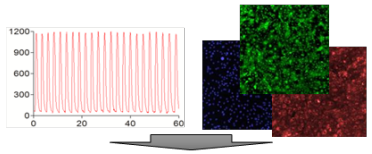
Compounds from Multiple Chemical Classes (n=136)

Chemical Class:	n
CiPA Pharmaceuticals	15
Other Pharmaceuticals	39
Environmental Chemicals (e.g., pesticides, PAHs, industrial chemicals, flame retardants)	82

***In Vitro* Concentration-Response Screening**

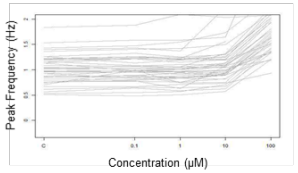


Function *[Ca^{2+}-Flux Imaging]* | ***Cytotoxicity*** *[HC-Imaging]*



Peak / Image Processing

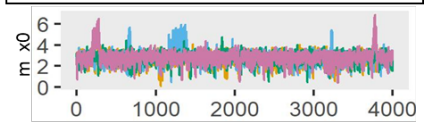
Population Concentration-Response Data



Bayesian Population Concentration-Response Modeling

Data | Likelihood | Hill Model | Priors

Markov Chain Monte Carlo Sampling



Posterior Distributions

Model Evaluation and Predictions

Population-Based Hazard and Risk Characterization

Hazard Characterization
- Active/inactive for each chemical and endpoint
- Critical endpoint for each chemical
- Point of departure (POD) for each endpoint
- Population variation in toxicodynamic sensitivity

Risk Characterization
- Margin of safety for pharmaceuticals
- Margin of exposure for environmental chemicals
- Separate estimates for population median and sensitive individual

See Burnett et al. (2019) for details

Population median POD

Active for chemical/endpoint
- Adequate Convergence
- Model error < 10%
- Population median POD < max tested concentration

Population variation in individual PODs

Sufficient for population variability analysis
- Active for population median
- 90% CI for population median POD < 100-fold
- At least 20 individuals with data at 3 concentrations + control

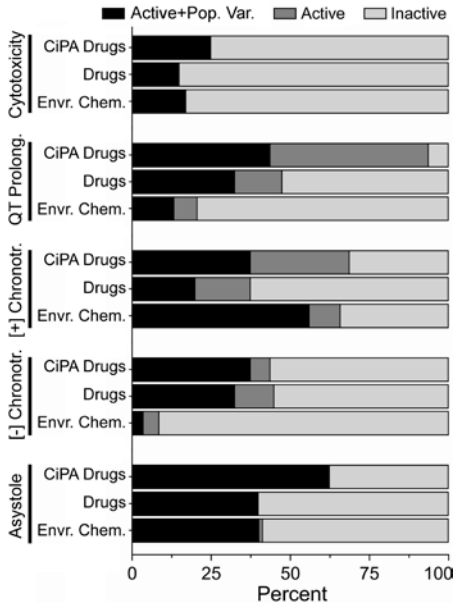
Critical Endpoint
- Endpoint with lowest population median or random individual POD

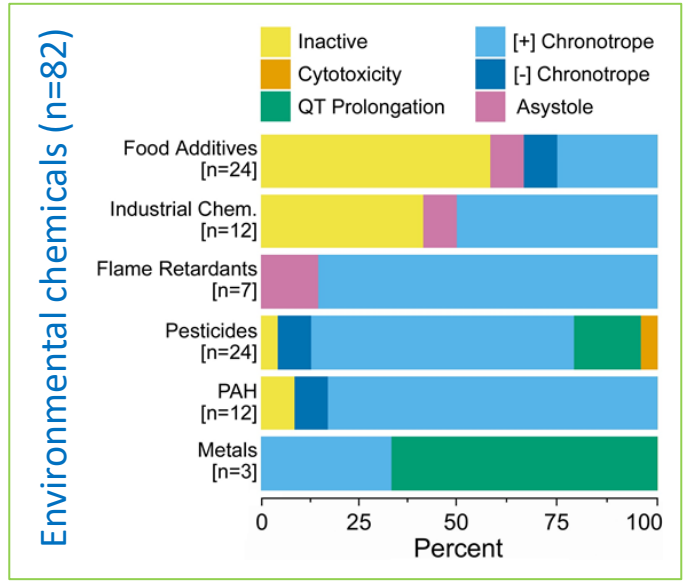
Plasma concentration estimates
- Pharmaceutical Cmax values
- Environmental chemical steady state concentrations [Expocast exposure estimates + httk-based reverse toxicokinetics]

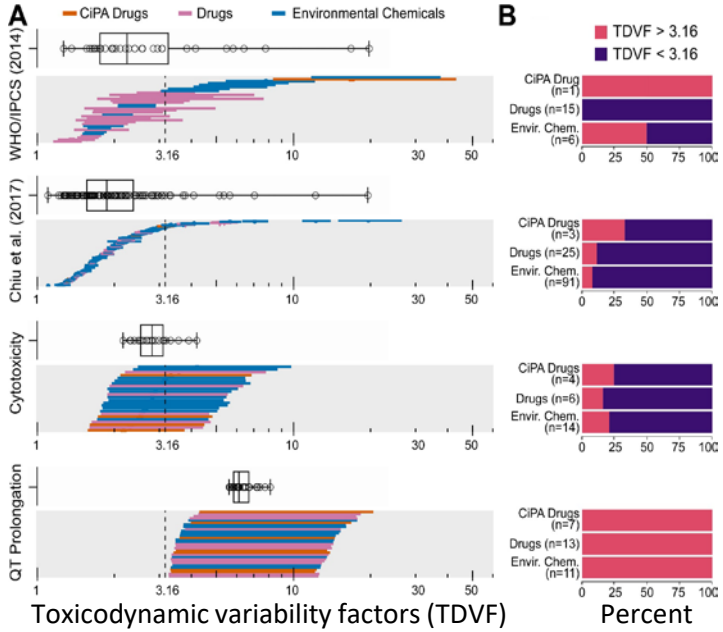
Population variation in toxicodynamic sensitivity
- Toxicodynamic variability factor for 5th percentile = $TDVF_{05}$ = POD[Population median] / POD[5th percentile individual]
- Chemical-to-chemical variation and heterogeneity (random effects meta-analysis)

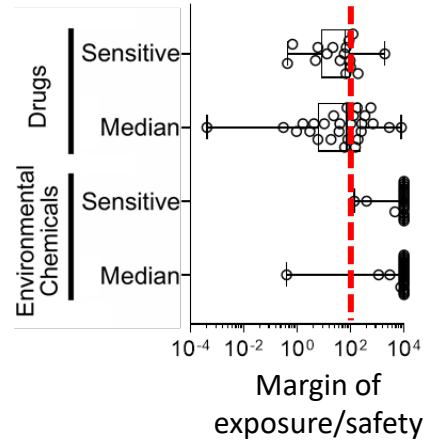
Critical Endpoint POD Posterior Samples

Margin of safety or margin of exposure
- Ratio of POD to plasma concentration estimates









Blanchette *et al*. Toxicol Sci. 2020 (Accepted)

Chemical Watch

US Society of Toxicology urges EPA to be flexible over testing

19 September 2019

Concerns over 2035 deadline for ending mammalian testing

…Some academics also gave a note of caution. *"As a toxicologist who is passionate about replacement of animal testing with cell-based models, I welcome this announcement*," said Ivan Rusyn, director of the Superfund Research Center at Texas A&M University. *"However, a clear plan and milestones for how this vision will be implemented by the agency is needed to ensure that solid foundation exist for replacement of certain animal tests with alternative methods and that human health protection is not diluted by reducing the regulatory requirements on chemical safety*," he told Chemical Watch.

- Are we ready to stop using animals for evaluating safety of EPA-regulated chemicals? **NOT immediately**
- When will we be ready to stop using animals for evaluating safety of EPA-regulated chemicals? **NOT soon**
- Is there a promise for organotypic models as NAMs? **YES!! but EPA needs to define fit(s) for purpose**
- Why not use "human on a chip" to replace animal tests? **A combination of PBK modeling and organotypic model-derived hazard, mechanistic, TK and other data is likely to pave the way forward**
- How can Administrator's directive to reduce/eliminate animal testing benefit from organotypic models? **The Agency shall continue supporting targeted research on the application of these models to EPA's purpose(s) and to develop intramural capacity in the use of these new models**

Tissue Chip Testing Experiments:

Courtney Sakolish Leoncio Vergara
Yizhong Liu Clifford Stephan

Analytical Chemistry Experiments:

Yu-Syuan Luo Kyle Ferguson
Alan Valdiviezo

In Vitro Experiments & Modeling:

Fabian Grimm Sarah Burnett
Zunwei Chen Alex Blanchette
William Klaren Nan-Hung Hsieh

Faculty Collaborations:

Weihsueh Chiu Fred Wright
Arum Han

Special Thanks to Tissue Chip Developers:

University of Washington: Elijah Weber, Edward Kelly, and Jonathan Himmelfarb

Duke University: Xu Zhang and George Truskey

University of Pittsburgh: Celeste Reese, Richard DeBiasio, Larry Vernetti and Lans Taylor

Baylor College of Medicine: Xi-Lei Zeng and Mary Estes

Johns Hopkins University: Mark Donowitz

Columbia University: Zongyou Guo, Yanne Doucet, Alan Chramiec, Sue Halligan, Angela Christiano and Gordana Vunjak-Novakovic

UC-Berkeley: Nikhil Deveshwar, Nathaniel Huebsch, Felipe Montiel, Brian Siemons and Kevin Healy

UC-Irvine: Duc Phan, Hugh Bender and Chris Hughes

Vanderbilt University: Jackie Brown and John Wikswo

University of Washington: Tomoki Imaoka, Edward Kelly, and Jonathan Himmelfarb

University of Pittsburgh: Celeste Reese, Richard DeBiasio, Larry Vernetti and Lans Taylor

University of Pittsburgh: Zhong Li, Hang Lin

University of Rochester: Azmeer Sharipol, Lindsay Piraino, Hitoshi Uchida, Yuanhui Song, Catherine Ovitt, Lisa DeLouise and Danielle Benoit

University of Pennsylvania: Andrei Georgescu and Dan Huh

UC-Davis: Bhupinder Shergill, Sergey Yechikov, Steven George

Duke University: Xu Zhang and George Truskey