If you build it, will they come?

Testing the "value proposition" for tissue chips in drug and chemical safety assessments

Ivan Rusyn, MD, PhD

University Professor, Texas A&M University

Research funding from NIH/NCATS: U24 TR001950, U24 TR002633

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TEX-VAL Tissue Chip Testing Consortium is funded by:

- American Chemistry Council
- US EPA
- National Toxicology Program
- Bristol Myers Squibb
- Sanofi-Aventis
- Unilever

Tissue Chips Landscape (NIH funding)

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)

NIH National Center for Advancing Translational Sciences

What type of “validation” will help NIH move tissue chips into practice?

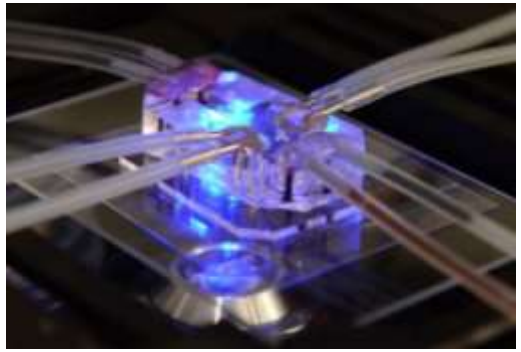
Option 1: “Real” validation

OECD GD 34 – *Guidance document on the validation and international acceptance of new or updated test methods for hazard assessment*

European Union Network of Laboratories for the Validation of Alternative Methods:

37 EU-NETVAL Test Facilities

Option 2: “Organic” validation [*a.k.a.* “if we build it, they will come”???]



Technology transfer

Some basic truths about onboarding remain the same since the dawn of technology…

Option 3: “Fit for purpose” validation [an *END USER*-directed activity]

- Tissue chip technologies are are rapidly developing (*what do you test??*)
- Potential users (*e.g.*, pharmaceutical companies) are weary of “placing all eggs into one basket”
- Tissue chip development “market” is still highly fragmented which makes it difficult to establish strategic partnerships
- Are MPS a “commodity” or “advantage”?
- The users and regulators need a “safe place” consortium to select and test most promising technologies and to gain confidence through an independent third-party testing

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)

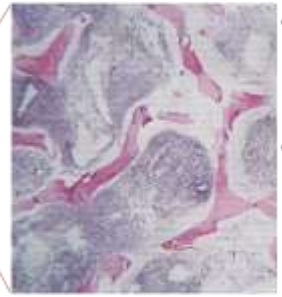
Oct. 2018 – Sept. 2021 (TEX-VAL2.0)

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

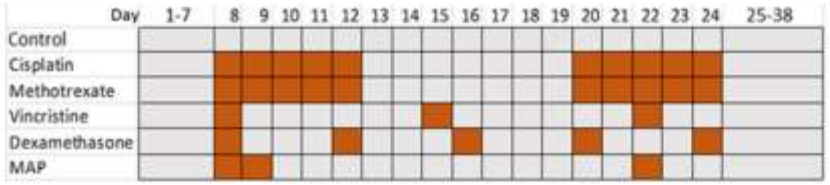
Static cultures

Columbia Univ.: Bone +/- Tumor Model

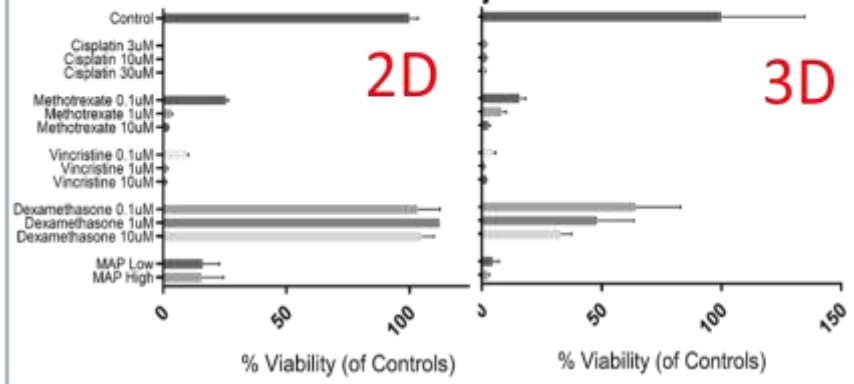


- De-cellularized bovine trabecular bone
- Human osteoblasts and Ewing's sarcoma cells

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

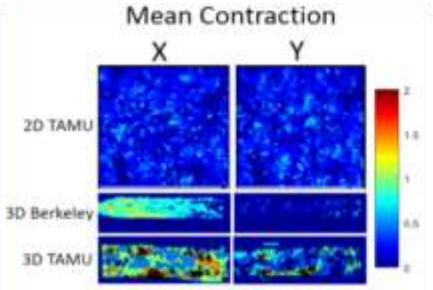


Cancer cell viability after treatment

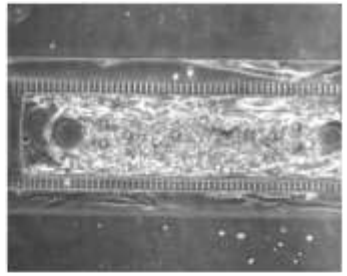


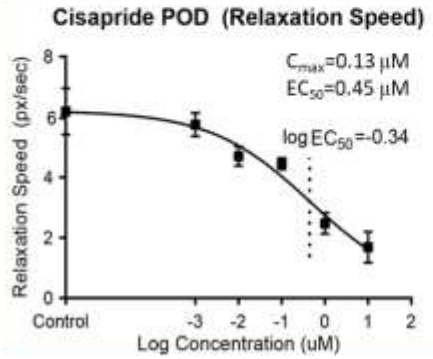
"Gravity Flow" cultures

Univ. Cal.-Berkeley: Cardiac Model

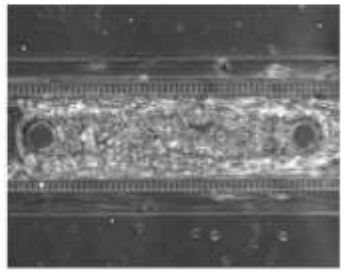


Vehicle





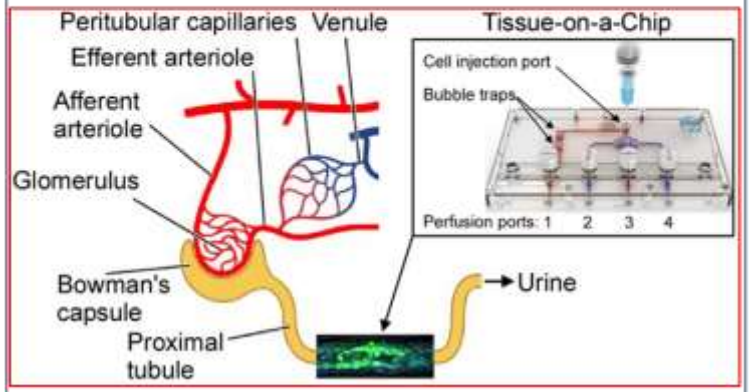
10µM Cisapride



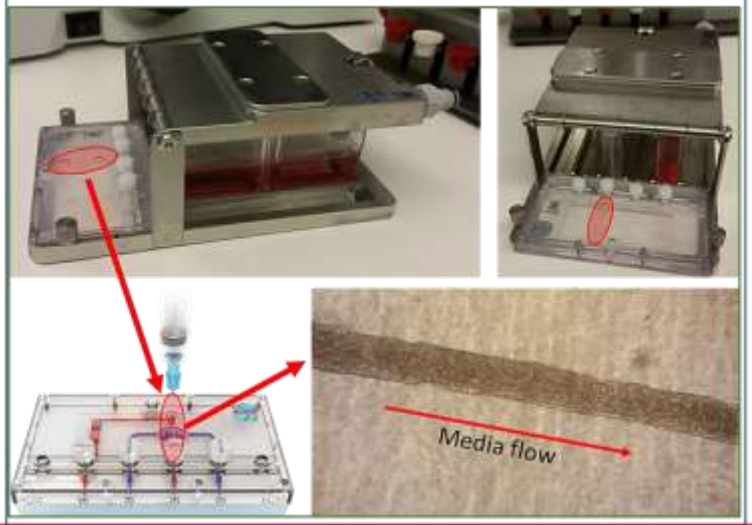
"Forced Flow" cultures

Univ. Wash.: Proximal Tubue

"Microphysiological" system



Bioengineer's "rendering"



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

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

Tissue Chip Model	# Wells/Chips		# Data Points in MPS Database		# Images in MPS Database		# Videos in MPS Database		Data Upload	Data Availability
	2D	3D	2D	3D	2D	3D	2D	3D		
Proximal Tubule, *U-Washington*	500	91	4,057	2,878	151	1,254	-	-	Complete	**Available**
Blood-Brain Barrier, *Vanderbilt*	-	9	-	1,289	-	-	-	-	Complete	Available
Bone/Tumor, *Columbia*	462	234	1495	7,669	256	114	-	-	Complete	**Available**
Skin, *Columbia*	-	224	-	1,512	-	157			Complete	**Available**
Cardiac Tissue, *UC-Berkeley*	1091	141	9,084	9,456	1,069	1,164	146	124	Complete	**Available**
Gut Enteroid, *Baylor College Med*	4,488	1,382	4,488	6,656	-	-	-	-	Complete	**Available**
Vascularized Tumor, *UC-Irvine*	320	69	320	3,370	-	1,596	-	-	Complete	**Available**
Liver, *UC-Berkeley*	90	81	2,736	6,509	180	126	-	-	Complete	**Available**
Liver (multi-cell), *U-Pitt*	220	90	5,985	7,279	565	224	-	-	Complete	**Available**
White Adipose, *UC-Berkeley*	626	104	4,736	600	32	32	-	-	Complete	**Available**
Skeletal Muscle, *Duke*	-	192	-	21,568	-	2,758	-	-	Complete	**Available**
Atrial Cardiomyocyte (2.0), *UC-Davis*	178	6	2,624	3,768	-	-	-	-	In progress	-
Kidney (2.0), *U-Washington*	-	21	-	796	-	167	-	-	In progress	-
TOTAL	**7,975**	**2,638**	**35,525**	**73,350**	**2,253**	**7,435**	**146**	**124**		

Deliverables of TEX-VAL:

- ~20 Tissue chips tested in 4+ years
- All data from testing deposited into the University of Pittsburgh MPS-Db
- Detailed protocols for technology transfer and experiments (also in U-Pitt MPS-Db)
- Detailed descriptions of all phenotypic endpoints and guidance for their interpretation
- List of all equipment necessary for use of each MPS (*e.g.*, syringe pumps vs specialized equipment)
- Detailed description of the experimental throughput for each tested MPS
- Publications and reports describing the outcome of testing and comparison between 3D and 2D versions

Challenges:

- Developers sometimes are not ready and/or willing to test their devices in another lab
- The quality of the non-commercial MPS devices
- Poor quality of the cells that are used in the MPS devices
- Lack of immediate availability of the necessary cells and/or cell culture media
- Technical challenges associated with the complexity of some tissue chip models

Opportunities:

- Developers work to improve/streamline MPS
- End-users are very engaged and supportive of independent testing of MPS before “onboarding”
- The regulatory agencies have begun developing internal capacity in MPS research

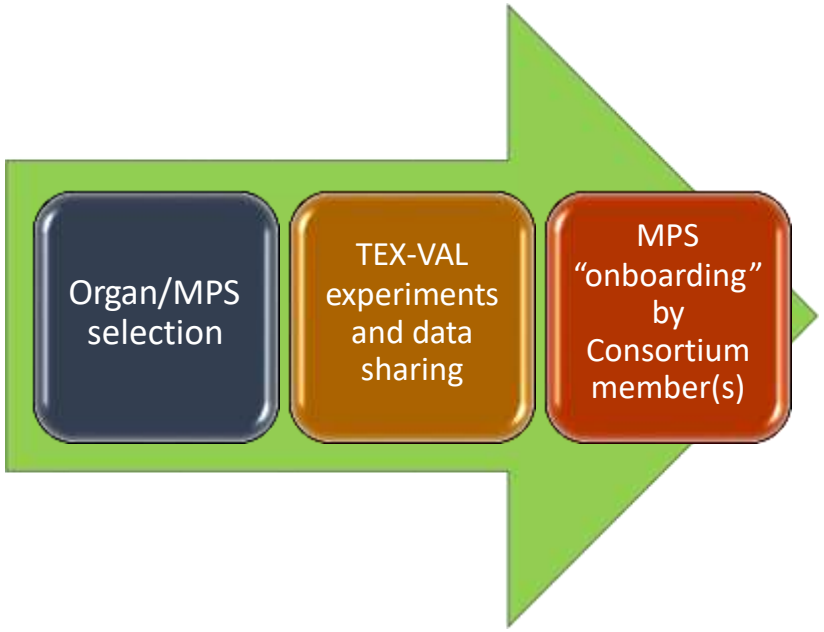
TEX-VAL Tissue Chip Testing Consortium (2020 - …)

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)

How does the "Consortium" work?

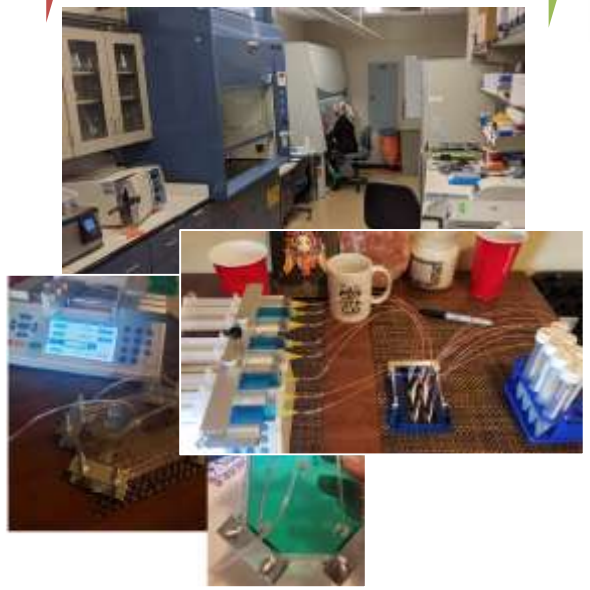
Kick-off Face-to-Face brainstorming session:

All members came in with the "ask" for the Consortium

February 12, 2020
Washington, DC (ACC)

- List of models of interest to **ALL** members
- Platforms for consideration (commercial vs academic)
- Cell sources
- Basic parameters that should be replicated – **"context of use"**

1. Experiments on each model: lab-based or "*kitchen science*"
2. Data deposit into MPS-Db



Monthly webinars with **ALL** members to discuss results and next steps

"On-demand" small group meetings to refine detailed experiments

Consortium members decide on the suitability of each model to their "context(s) of use"

TEX-VAL staff will assist members with platform on-boarding and provide all necessary SOPs and other information

Tissue Chips in decision-making: An end-user's perspective

- The MPS technology is very useful and promising and bioengineering research and development need support
- The applications of "tissue chips" in the real world will be highly "fit for purpose"
- The developers need to appreciate the need for portability, as well as reasonable "ease of use" and "cost" for their devices

Lab on a Chip

ROYAL SOCIETY OF CHEMISTRY

PERSPECTIVE

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

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

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

Table 2 Examples of commonly requested information by pharmaceutical companies for models being evaluated

Duration
- Set up time including cells
- Viability
- Activity/metabolic functionality
System
- Capacity
- Maintenance level
- Throughput
- Space requirements
- Equipment requirements
- Material properties (compound binding)
- Level of training/expertise required
Abilities
- Sampling
- Frequency (some systems do not allow for daily sampling)
- Type (liquid, histology)
- Imaging
- *In situ*
Testing parameters
- Cell sourcing including commercial *versus* non-commercial
- Media sourcing including commercial *versus* non-commercial
- Reproducibility level
- Comparisons
- 2D systems
- *In vivo* models
- Baseline function assays
- Toxicity assays
- Appropriate positive/negative controls
Restrictions
- In house only
- Limited cell types
Business model
- For customer use
- Contractual (in house only)

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/human scaling	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 pharmacodynamics	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

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 the regulated chemicals? **NOT immediately**
- ***When*** will we be ready to stop using animals for evaluating safety of the regulated chemicals? **NOT soon**
- Are MPS useful "new approach methodologies" (NAMs)? **YES!! but "fit(s) for purpose" needs to defined**
- Why not use "human on a chip" to replace animal tests? **A combination of PK modeling and organotypic model-derived hazard, mechanistic, kinetic and other data is more likely to be of "value"**
- How can the efforts to reduce/eliminate animal testing benefit from the MPS? **The end-users (government or companies) shall continue supporting targeted research on the application of these models to their purpose(s) while developing intramural capacity in the use of these 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:

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Duke University: Xu Zhang and George Truskey