ONBOARDING AND TESTING OF MICROPHYSIOLOGICAL SYSTEMS: EXPERIENCE OF THE TEX-VAL CONSORTIUM

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Background and Rationale

The NCATS Tissue Chip Testing Centers (TCTC) program promotes a systematic approach to testing the feasibility of the technology transfer of microphysiological systems (MPS) from developers to end-users. From 2016 to 2020, the TCTC at Texas A&M University tested approximately two dozen MPS that represented a wide variety of tissues/organs developed by academic researchers based in the United States. Since 2020, this NIH-funded testing center has evolved into a university-based collaboration of diverse end-user stakeholders to establish the TEX-VAL Tissue Chip Testing Consortium (TEX-VAL Consortium). The TEX-VAL Consortium brought together pharmaceutical companies – Sanofi-Aventis US (Framingham, MA), Bristol-Myers Squibb (Princeton, NJ), F. Hoffmann-La Roche (Switzerland) and Merck KGaA (Germany); a consumer goods company Unilever (UK); a trade association of chemical manufacturers – The American Chemistry Council (Washington, DC); and government agencies that develop, promote and use various in vitro methods – US EPA (RTP, NC) and Division of Translational Toxicology at NIEHS (RTP, NC). The overall framework for TEX-VAL Consortium involves equitable monetary contributions from the members, while Texas A&M University provides in-kind support in the form of facilities and equipment use. Member organizations collectively decide on the annual work plan and the research staff at Texas A&M University conduct experiments and share their findings through bi-weekly meetings with TEX-VAL Consortium members. All data generated by TEX-VAL is deposited into the MPS-Database and made public one year after it has been finalized for each study. Since 2020, the TEX-VAL Consortium tested several commercial models for the liver, proximal kidney tubule, gut, blood brain barrier, lung and other tissues. Each model was evaluated with different commercially-available primary and iPSC-derived cell types and benchmarked to appropriate 2D models as well as other MPS. The robustness, reproducibility and fit for both drug development and regulatory decision-making are evaluated based on the feedback received from all participating stakeholders. Results are shared with the wider community through peer-reviewed publications, the MPS database, and presentations. Overall, we conclude that TEX-VAL Consortium efforts towards building consensus and promoting the gradual incorporation of MPS models into tiered approaches for safety assessment and decision-making is the sensible path to their wider adoption.

TEX-VAL Consortium Member Organizations

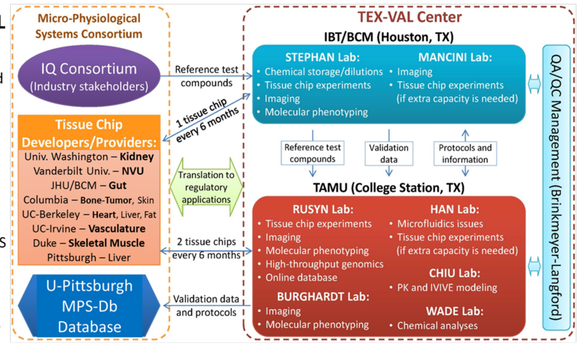
2020	2021	2022	2023	2024
sanofi	sanofi	sanofi	sanofi	sanofi
Bristol Myers Squibb	Bristol Myers Squibb	Bristol Myers Squibb	Bristol Myers Squibb	abbvie
American Chemistry Council	American Chemistry Council	American Chemistry Council	American Chemistry Council	American Chemistry Council
National Toxicology Program	National Toxicology Program	National Toxicology Program	National Toxicology Program	National Toxicology Program
	Unilever, Merck	Unilever, Merck	Unilever, Merck, Roche	Unilever, Merck, Roche

The TEX-VAL Consortium has grown to include 7-8 member organizations since its establishment in 2020. Member organizations are asked to volunteer 2-3 investigators who participate in bi-weekly calls and provide recommendations for testing conditions, treatments, analyses, etc. for tissue chip testing and evaluation.

Texas A&M Tissue Chip Testing Center (TCTC; 2016-2020)

Core principles for TEX-VAL Center tissue chip testing:

- Inclusion of faculty/staff with broad relevant technical and scientific expertise
- Experience with using "new alternative methods" in regulatory decision-making
- Full independence from NCATS-funded tissue chip development
- Side-by-side comparison of the MPS with *in vitro* (2D) and *in vivo* data
- Transparency and communication of the outcomes of testing to the developers, and other stakeholders



TEX-VAL Workflow

Tier -1: Collaborative research and technology transfer agreements	Tier 0: Tissue chip testing without cells	Tier 1: Reproducibility testing of tissue chips	Tier 2: Extending the utility of the tissue chips
•Execution of all legal agreements •Sharing of the protocols •TAMU staff training with developers	•Assembling of tissue chips •Testing of the flow and operation •Testing drug binding to devices •Development of LC-MS methods	•Replicating published studies •Evaluation of key findings •Detailed protocols and SOPs	•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)

Models tested as part of Tissue Chip Testing Centers

Oct. 2016 – Sept. 2018 (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, LAMPS)	Taylor (University of Pittsburgh)
Liver	Healy (UC-Berkeley)
White fat	Healy (UC-Berkeley)

11 academic tissue chip models tested

Oct. 2018 – Sept. 2020 (TEX-VAL 2.0)

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)

7 academic tissue chip models tested

Texas A&M TEX-VAL Consortium (2020 – Current)

TEX-VAL Tissue Chip Testing Center → Consortium

Aim 3: To establish revenue-generating activities for MPS validation beyond NIH funding:

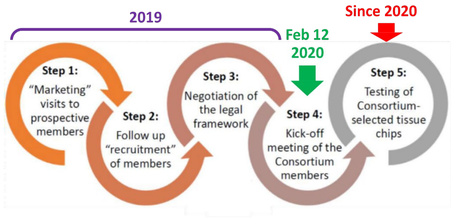
- conduct site visits and seminars with stakeholders,
- identify interested parties for Consortium membership,
- negotiate a consortium agreement, and
- conduct tissue chip testing "*happily ever after… NCATS*"

Goals of the Consortium:

- Bring together industry, trade association and government agencies to define a work plan and deliverables
- Defining a ***work plan***: identifying ***common*** needs for "tissue chips": organs, platforms, cells, chemicals (+/- controls), phenotypes, etc.

Texas A&M University role:

- Execute on a Consortium's ***work plan***:
  - Procuring equipment and consumables
  - Establishing the models in the lab
  - Verifying reproducibility of cell sourcing
  - Replicating key published findings
  - Refining the models based on feedback



How did TEX-VAL Consortium begin (2020)?

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"**

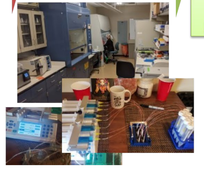
1. Experiments on each model: lab-based or "*kitchen science*„
2. Data uploaded into MPS-Db

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

"On-demand" monthly small group meetings to focus on a particular model

Consortium members decide on the "fit for [their] purpose" and "context(s) of use"

TEX-VAL assists members with platform on-boarding and troubleshooting



Workplans Evolve as Interests Change

TEX-VAL Consortium Members' Organs/Tissues of Interest

2020		2021		2022		2023		2024	
Organ	# Asks	Organ	# Asks	Organ	# Asks	Organ	# Asks	Organ	# Asks
Liver	4	Liver	5	Liver	5	Liver	7	Liver	7
BBB	1	BBB	4	BBB	4	BBB	6	BBB	2
Kidney	3	Kidney	4	Kidney	4	Kidney	4	Kidney	5
GI	2	GI	5	GI	5	GI	4	GI	2
Repro	2	Repro	4	Repro	4	Repro	4	Repro	3
Cardio	1	Cardio	1	Cardio	1	Cardio	2	Cardio	1
Vascular	0	Vascular	0	Vascular	0	Vascular	1	Vascular	1
Lung	2	Lung	1	Lung	1	Lung	1	Lung	1

From 2020 to 2023, our workplans primarily involved surface-level testing of Tissue Chip models, including activities such as technology transfer, cell selection (testing multiple vendors, lots, etc.), baseline function, and toxicity testing. In 2024, we have reduced the number of models being tested, but we are now conducting more in-depth characterization of these models.

The "Value Proposition"

TEX-VAL's Contributions to the MPS-Database (Studies, Chips, Data Uploaded)

2020

		Studies	Chips
Kidney	Glomerulus (Mimetas 3-lane)	6	360
	Proximal Tubule (Mimetas 3-lane)	7	320
Liver	NortisBio (LAMPS)	11	90
Gut	Mimetas 3-lane (caco-2)	8	206
	Mimetas 3-lane (enteroids)	4	405
Lung	Small airway (U-Penn Model)	6	115
Total:		**42**	**1,500**

2021

		Studies	Chips
Kidney	Glomerulus (Mimetas 3-lane)	4	160
	Proximal Tubule (Mimetas 3-lane, CN-Bio TC12, Transwells)	7	524
Liver	Mimetas 2-lane CNBio LC12	12 11	1,072 110
Gut	Transwells (Caco-2)	4	96
	Transwells (Enteroids)	5	216
	CNBio T12 (Caco-2)	3	147
	CNBio T12 (Enteroids)	6	240
BBB	Transwells	3	32
Total:		**55**	**2,600**

2022

		Studies	Chips
Kidney (PT)	Mimetas 3-lane	6	431
	CNBio T12	4	216
	Transwells	2	24
Liver	CNBio LC12	14	526
Gut	Transwells (Caco-2)	2	23
	Transwells (Enteroids)	5	91
	CNBio T12 (Enteroids)	1	18
	Mattek (Epiintestinal)	1	24
	Mimetas (caco2)	1	14
	Mimetas (enteroids)	1	25
	2D culture (caco2)	1	96
BBB	Transwells	5	58
FMI	FMi-OOC (Arum Han)	4	120
Total:		**47**	**1,700**

2023

Platform	# Studies	Chips/wells	Data points	Images
CNBio TC12	4	252	2861	*TBA*
Transwells	3	240	2837	*TBA*
Mimetas 3-lane plate	1	160	960	*TBA*
CNBio LC12	3	216	1728	216
Mimetas 2-lane plate	2	288	*TBA*	*TBA*
96-well Transwell	11	1014	7104 +	*TBA*
96-well Transwell	4	529	5030	324
24-well Transwell	9	249	2321	100
TOTAL for 3D	**37**	**3,000**	**23,000+**	**640+**
	2	576	1915	*TBA*
96-well plate	5	1266	2298 +	3450 +
384-well plate	3	300	*TBA*	*TBA*
	2	222	426	0
TOTAL for 2D	**12**	**2,400**	**4,600+**	**3450+**

Personnel	Annual Effort
Faculty	
Rusyn, Ivan	0%
Chiu, Weihsueh	0%
Stephan, Clifford	9.2%
Staff	
Sakolish, Courtney	75%
Vergara, Leoncio	50%
Jin, Unho	50%
Trainees	
Lin, Alicia	66.6%
Moyer, Haley	16.7%
Barlow, Nikki	40%
Total effort "charged" to TEX-VAL	**~3 full-time research staff**

Conclusions

- A robust collaboration of diverse stakeholders who continue their participation each year
- The "value proposition" exists for "**try before you buy**" operations through TEX-VAL
- Example "LEARNINGS" of the Consortium:
  a. How to select the models for testing (organs/tissues of interest)
  b. ADME/PK is a common need (single chemicals and mixtures)
  c. Barrier function challenges (gel layer is an un-physiological barrier)
  d. Finding the right cells and device configuration combinations
  e. Understanding the "cost" for increased technical complexity
  f. The range of phenotyping methods to test "performance"
  g. Understanding the "true" cost and throughput
  h. Defining the needs for equipment (in addition to the "tissue chips")