The NIH Microphysiological Systems Program:
Tissue-on-chips for Safety and Efficacy Studies in Drug Development

Interagency Coordinating Committee on
the Validation of Alternative Methods
Public Forum
May 23, 2019

Bo Yeon Lee, Ph.D.
Scientific Program Manager
Office of the Director, NCATS, NIH
National Center for Advancing Translational Sciences

Mission: To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.

• NCATS focuses on the scientific and organizational problems in translation

NCATS is all about getting more treatments to more patients more quickly.
Current Challenges in Drug Development

- Average time to develop (and bring it to market) a drug 10-15 years

- Average cost to develop a drug to market, including cost of failures, $2.6 billion (phRMA, Biopharmaceutical Research Industry Profile, 2016)

- The current drug discovery paradigm has a failure rate of 90%:
  - 55% due to lack of efficacy
  - 28% due to toxic effects in humans

- Need for new technologies in risk assessment that are more efficient and sustainable over current paradigms

The highest rates of true positives (36%) in animal-human translation is observed for dogs (cardiac & GI) and rats (renal & respiratory)

Arrowsmith and Miller, Nature Reviews Drug Discovery, Volume 12, 569 (2013)
Cook et al., Nature Reviews Drug Discovery, Volume 13, 419 (2014)
Clark and Steger-Hartmann, Regulatory Toxicology and Pharmacology, Volume 96, 94 (2018)

Most animal models are poor predictors of human response

3,290 approved drugs
1,637,449 adverse events
70 years
Microphysiological Systems Program: Tissue Chips for Drug Screening

GOAL: Develop an *in vitro* platform that uses human cells and tissues, and combine with advances in stem cell biology, microfluidics and bioengineering to evaluate the efficacy, safety and toxicity of promising therapies.

- All 10 human physiological systems will be functionally represented by human tissue constructs:
  - Circulatory
  - Endocrine
  - Gastrointestinal
  - Immune
  - Skin
  - Musculoskeletal
  - Nervous
  - Reproductive
  - Respiratory
  - Urinary

- Physiologically relevant, genetically diverse, and pathologically meaningful
- Modular, reconfigurable platform
- Tissue viability for at least 4 weeks
- Community-wide access
- Collaboration between NIH, FDA and DARPA
NIH Tissue Chips for Disease Modeling and Efficacy Testing

- Kam Leong, Columbia U
  Proteus Syndrome and DiGeorge Syndrome

- Danielle Benoit, Lisa Delouise, Catherine Ovitt, U Rochester
  Radiation-induced xerostomia

- Kevin Kit Parker, William Pu, Harvard U
  Barth syndrome, catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic cardiomyopathy

- Steven George, David Curiel, Stacey Rentschler, UC Davis and WashU
  atrial fibrillation

- Joseph Vincent Bonventre, Luke Lee, Brigham and Women’s
  autosomal dominant/recessive models of polycystic kidney disease, Focal segmental glomerulosclerosis

- Christopher Hughes, UC Irvine
  Hereditary hemorrhagic telangiectasia, Port Wine stain, Sturge-Weber syndrome

- Rocky Tuan, U Pittsburgh
  Osteoarthritis, inflammatory arthritis, adipose-mediated diabetic joint complications

- Clive Svendsen, Cedars-Sinai
  ALS; Parkinson’s Disease

- Aaron Bowman, Kevin Ess, John Wikswo, Vanderbilt U
  tuberous sclerosis complex (TSC) epilepsy, DEPDC5-associated epilepsy, & associated cardiac dysfunction

- Gordana Vunjak-Novakovic, Columbia U
  Dox induced cardiomyopathy; multi-system pathologies involving heart, liver, skin, bone and vasculature

- George Truskey, Duke U
  rheumatoid arthritis, atherosclerosis

- Donald Ingber, Harvard U
  influenza infection, COPD

- Jonathan Himmelfarb, U Washington
  apolipoprotein L1 mediated kidney disease, drug induced and host-pathogen interaction induced renal thrombotic microangiopathies

- Teresa Woodruff, Northwestern U
  Polycystic Ovarian Syndrome

- Kam Leong, Columbia U
  Type-2 Diabetes Mellitus
  - Andreas Stahl, Kevin Healy, Matthias Hebrok, Edward Hsiao, Holger Willenbring, UC Berkeley - Pancreatic islet, liver, adipose
  - Lansing Taylor, U Pittsburgh – Vascularized liver and pancreatic islets
  - James Wells, Moo-Yeal Lee, Cincinnati Children’s Hospital - Liver, pancreatic islet and intestine
Microphysiological Systems: *In Vitro* Mimics of Human Organ Function

Diversity of Bioengineered Platforms
## Commercial Activities around Organ-on-chip Technologies

### Body on-a-Chip

**Hesperos**
- Scientific founders: Michael Shuler, James Hickman
- Selected products: Multi-Organ Chip (2-4 organs), (6-10 organs)

**TISSUSE**
- Scientific founders: Uwe Marx
- Selected products: 2-Organ-Chip (2-OC), 4-Organ-Chip (4-OC), Human-on-a-chip (HOC)

**emulate**
- Scientific founders: Donald Ingber, Olivier Guenet, Thomas Neumann, Axel Gruenther
- Selected products: Lung on-a-chip, Airway on-a-chip, Gut on-a-chip, Kidney on-a-chip, Bone Marrow on-a-chip, Lung-on-a-chip array, Kidney on-a-Chip Vessel on-a-Chip, Artery on-a-Chip

### Tissue interface on-a-Chip

**CNBio Innovations**
- Scientific founders: Linda G Griffith
- Selected products: LiverChip®, LiverChip® 36

**DRAPER**
- Scientific founders: Joseph Charest
- Selected products: Microphysiological Systems

### Parenchymal tissue on-a-Chip

**TARA**
- Scientific founders: Milica Radisic, Gordana Vunjak-Novakovic
- Selected products: Cardiac Biowire™, II AngloChip™

**μOrgano**
- Scientific founders: Kevin Healy, Thomas Eschenhagen
- Selected products: Engineered Heart Tissue (EHT), 3D Cardiac Systems, Nerve-on-a-Chip™

### Hepatic tissue on-a-Chip

**organovo**
- Scientific founders: Gabor Forgacs, Keith Murphy
- Selected products: ExVive3D™ Liver, ExVive3D™ Kidney

**Aspect Biosystems**
- Scientific founders: Tamer Mohamed, Konrad Walus, Sam Wadsworth, Simon Beyer
- Selected products: Lab-on-a-Printer™, 3DBioRing™ Airway

**insphere**
- Scientific founders: Jan Lichtenberg, Jens M. Kelm, Wolfgang Moritz
- Selected products: 3D Insight™ Liver, 3D Insight™ Islet, 3D Insight™ Tumor

**3D Biomatix**
- Scientific founders: Nicholas Kotov
- Selected products: PERFECTA3D™, HANGING DROP PLATES

**Hurel Corporation**
- Scientific founders: Greg Baxter, Robert Freedman
- Selected products: Humanhuman™, HumanBx™, HurelTox™, HurelFlow™

**Hurel Corporation**
- Scientific founders: Matthew R. Gevaert
- Selected products: 3DKUBE™

**Kiyatec**
- Scientific founders: William L. Warren
- Selected products: MemMlad® Technology

**VaxDesign**
- Scientific founders: Michael Moore
- Selected products: Standard / Triple Chamber Neuron Device

**AxoSim**
- Scientific founders: Bernadette Bung
- Selected products: Neuro Device

**Xona Biologics**
- Scientific founders: Margaret Magdesian
- Selected products: Neuronal Diode

**myriamed**
- Scientific founders: Noo Li Jeon, Carl W. Cotman, Anne Taylor
- Selected products: Standard / Triple Chamber Neuron Device
Working with Pharma:
IQ Microphysiological Systems Affiliate

<table>
<thead>
<tr>
<th>AbbVie</th>
<th>BMS</th>
<th>GSK</th>
<th>Novartis</th>
<th>Theravance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amgen</td>
<td>Celgene</td>
<td>Jansen</td>
<td>Pfizer</td>
<td>Vertex</td>
</tr>
<tr>
<td>Astellas</td>
<td>Eisai</td>
<td>Merck</td>
<td>Sanofi</td>
<td></td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Eli Lilly</td>
<td>Merck KgA</td>
<td>Seattle Genetics</td>
<td></td>
</tr>
<tr>
<td>Biogen</td>
<td>Genentech</td>
<td>Mitsubishi Tanabe</td>
<td>Takeda</td>
<td></td>
</tr>
</tbody>
</table>

Goals of IQ MPS Affiliate:

- To serve as a thought leader for both MPS developers and stakeholder organizations in the industry implementation and qualification of MPS models
- To provide a venue and supporting legal oversight for cross-pharma collaboration and data sharing that facilitates expeditious uptake and impact of MPS
- To create focused engagement with regulatory agencies on the current status and evolving field of MPS in an industry setting
- To develop external partnerships and collaborations to help advance industry priorities
Building Confidence: Tissue Chip Validation Framework

**3) Industrial**
- Use by industry and regulatory agencies
- Proprietary set of compounds?
- CRO-type environment

**2) Analytical**
- Independent: testing for robustness, reproducibility, reliability, relevance
- Validation set of compounds, biomarkers, assays
- TC Testing Centers

**1) Physiological**
- Organ function and structure
- Training set of reference compounds
- TC 1.0 developers

**Publications:** (as of Oct 2017)
A total of 506 original and review articles (cited over 5600 times) published in top tier journals, including *Nature Medicine, Nature Communications, Nature Materials, PNAS, Science, Science Translational Medicine,* etc.

**Path to Adoption and Commercialization**

- **Javelin Biotech**
  - Murat Cirit
- **Texas A&M Tissue Chip Testing Consortium**
  - Ivan Rusyn
- **MPS Database:** [https://mps.csb.pitt.edu/](https://mps.csb.pitt.edu/)
  - U Pittsburgh (Mark Schurdak)

- **Tissue Chip Testing Centers:**
  - MIT (Murat Cirit and Alan Grodzinsky)
  - TAMU (Ivan Rusyn)
- **MPS Database:** [https://mps.csb.pitt.edu/](https://mps.csb.pitt.edu/)
  - U Pittsburgh (Mark Schurdak)
Tissue Chip Testing Centers: Validating Microphysiological Systems

- Resource Centers (U24)
- **GOAL:** Independent analytical validation of tissue chip platforms
  - Portability, reproducibility, sensitivity, specificity, dosing paradigm, cellular vs. organ toxicity, toxicity readouts, etc.
  - Reference set of validation compounds, assays, biomarkers with input from IQ consortium and FDA based on technical specifications of each platform from MPS developers
- Partnerships among NCATS, FDA and IQ Consortium; adherence to OECD guidelines
- NCATS support: Initially awarded in 2016 for two years and renewed in 2018 for two more years
- FDA and IQ Consortium provide expert guidance on reference set of validation compounds, assays, biomarkers
- **Testing Centers:**
  - MIT (Murat Cirit and Alan Grodzinsky)
  - TAMU (Ivan Rusyn)
- **MPS Database:** [https://mps.csb.pitt.edu/](https://mps.csb.pitt.edu/)
  - U Pittsburgh (Mark Schurdak)
- **Platforms tested during first two years:**
  - Kidney on chip
  - BBB on chip
  - Brain on chip
  - Bone/tumor on chip
  - Heart on chip
  - Gut on chip
  - Skeletal muscle on chip
  - Microvasculature on chip
  - White adipose tissue on chip
  - Liver on chip
  - Skin on chip

First TCTC publication: Nature Scientific Reports (2018) 8:14882
NextGen Testing Centers 2018-2020

MIT transitioning to Javelin Biosciences

- CNBio Liver
- CNBio Liver-Tumor
- Nortis Kidney
- TissUse Bone marrow
- TissUse Pancreas-Liver
- Stemonix microBrain
- Stemonix microHeart
- Mimetas CNS
- Mimetas Liver

Texas A & M TC Testing Consortium

- Duke Arteriole blood vessel (Truskey)
- UC-Irvine Vascular malformations – Hereditary Hemorrhagic Telangiectasia, Port Wine disease and Sturge-Weber syndrome (Hughes)
- UC-Berkeley Vasculature with flow, Skeletal Muscle, Pancreatic islet (Healy)
- U-Pitt Vascularized Liver Acinus (Taylor)
- U-Pitt Osteochondrial unit and joint chip (Tuan)
- U-Washington iPSC-derived kidney organoids, vascularized kidney MPS (Himmelfarb)
- Columbia Cardiomyocyte, Liver, Integrated Heart-Liver-Skin-Bone-Tumor chip (Vunjak-Novakovic)
- U-Penn Airway and Bone Marrow (Huh)
- U-Rochester Salivary gland (Benoit)
- Harvard Stem cell-derived renal organoids (Bonventre)
- UC-Davis Atria on a chip (George)
Why send Tissue Chips to the ISS National Laboratory?

• The Chips in Space initiative seeks to better understand the role of microgravity on human health and disease and to translate that understanding to improved human health on Earth.

• Many of the changes in the human body caused by spaceflight resemble the onset and progression of diseases associated with aging on Earth, such as bone loss, muscle wasting, and immune dysfunction. But the space-related changes occur much faster. This means that scientists may be able to use tissue chips in space to model changes that might take months, years or decades to happen on Earth.

• The automation and miniaturization required for spaceflight has contributed to the commercialization opportunities of tissue chip technology, which advances validation and allows broader adoption of the technology on Earth.
Future NIH Initiatives for Tissue Chips

• Co-culture of many differentiated iPSC-derived cell types per tissue architecture and composition
• Integration of different tissue chips to form human body on chip
• Genome editing to introduce various polymorphisms on isogenic iPSC lines
• Developmental/pediatric response to drugs/toxins
• Rare diseases

Clinical Trials-on-chips for Precision Medicine (You-on-chip) coming soon

Nociception-on-chip RFA-TR-19-003
Immune system-on chip PAR-19-138
ADRD on chip RFA-NS-19-027
Thank you!

boyeon.lee@nih.gov