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

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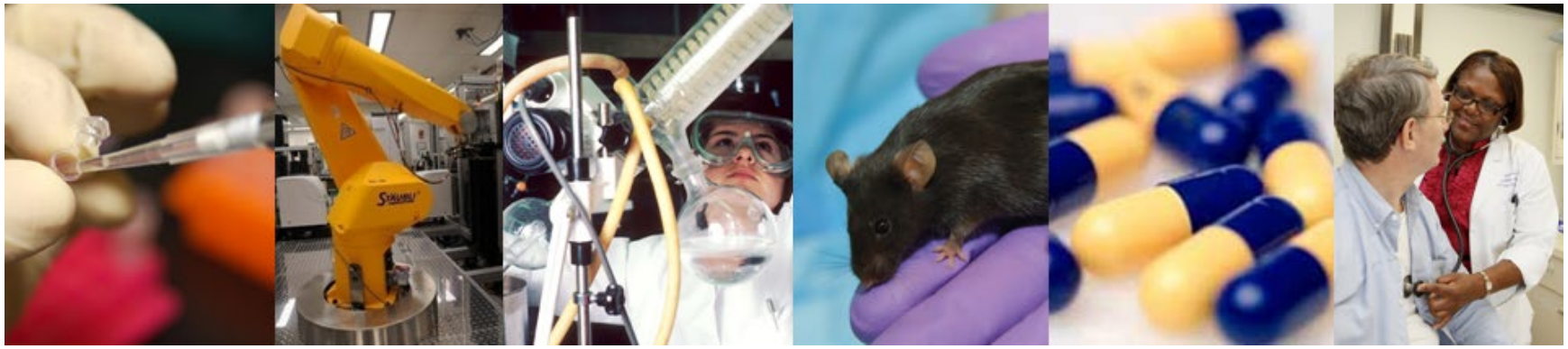


Mission: To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.

- NCATS focuses on the scientific and organizational problems in translation

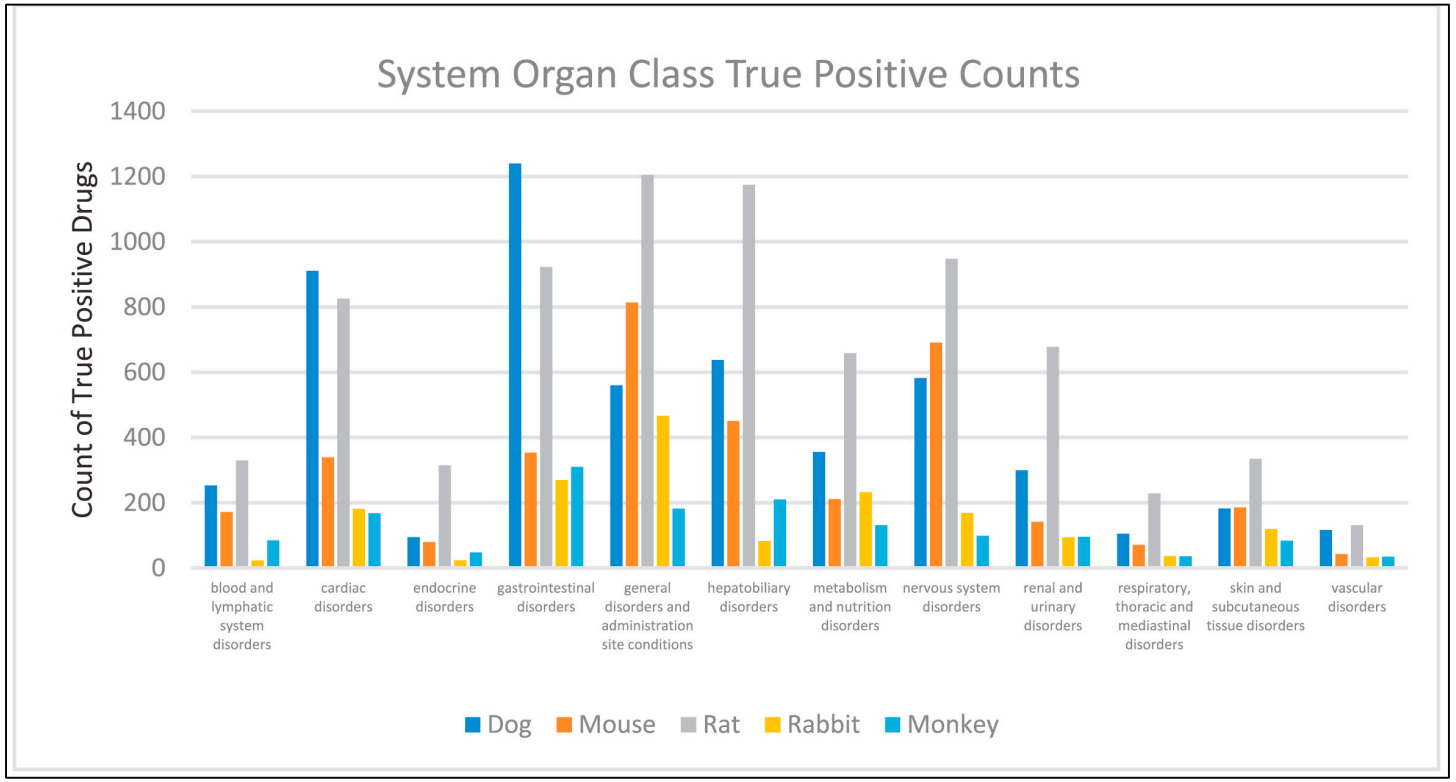
NCATS is all about getting more treatments to more patients more quickly.

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)

3,290 approved drugs
1,637,449 adverse events
70 years

Most animal models are poor predictors of human response

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Microphysiological Systems Program: Tissue Chips for Drug Screening

GOAL: Develop an *in vitro* platform that uses <u>human</u> 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**

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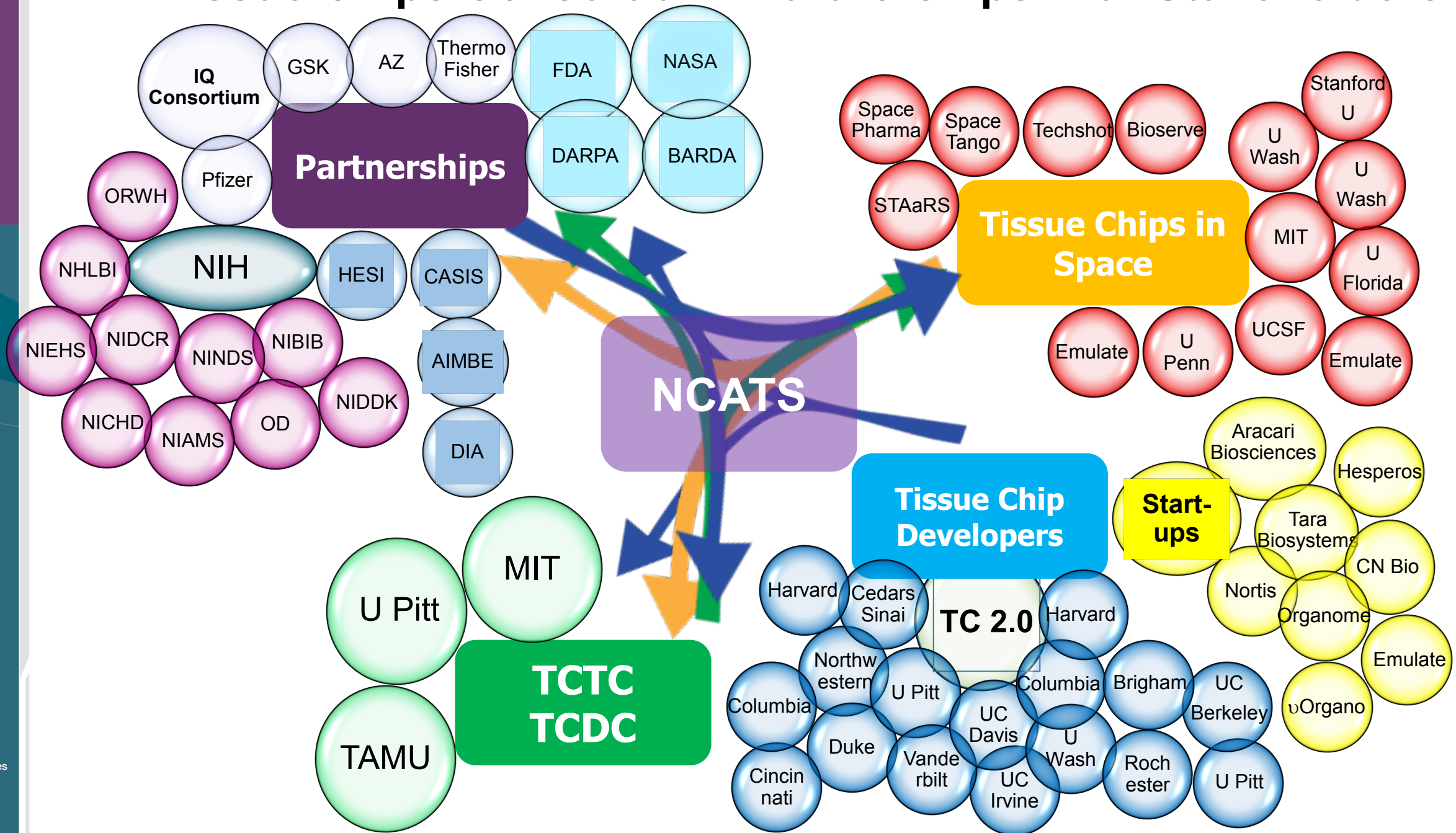
NIH Tissue Chips Consortium- Partnerships with Stakeholders



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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

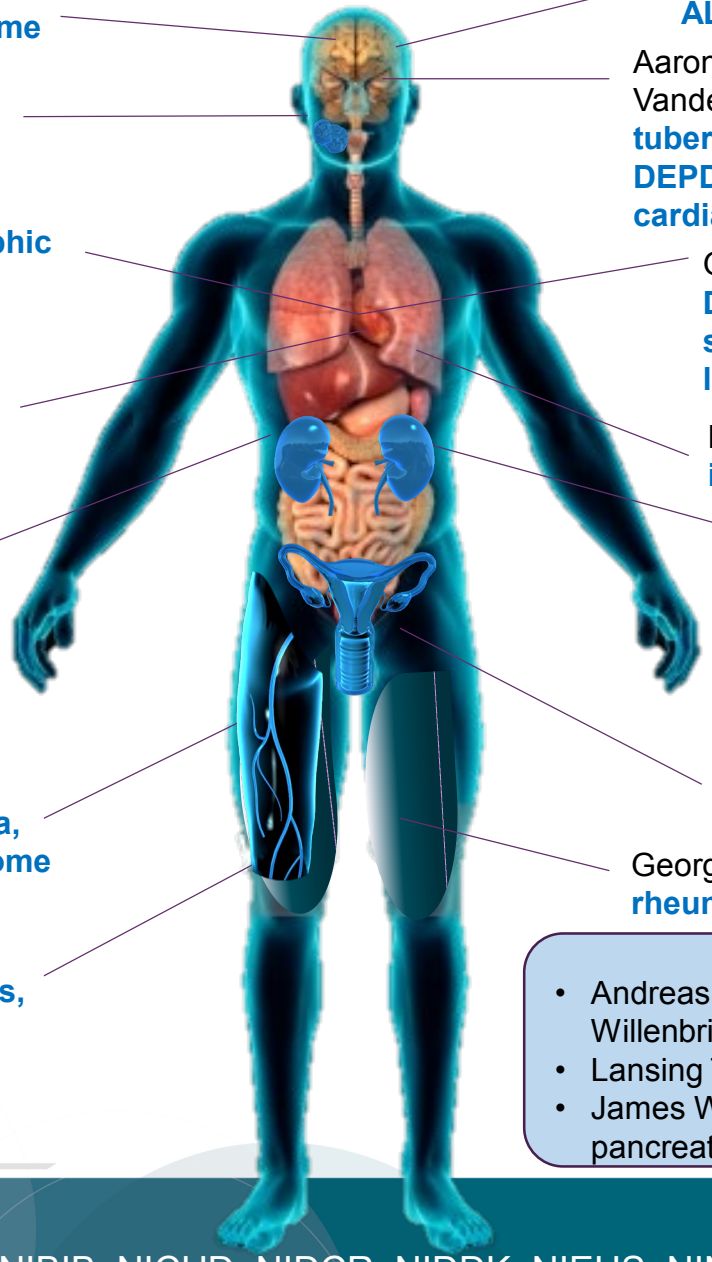
Kevin Kit Parker, William Pu, Harvard U
Barth syndrome, catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic cardiomyopathy

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

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

George Truskey, Duke U
rheumatoid arthritis, atherosclerosis

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

NCATS, NHLBI, NIAMS, NIBIB, NICHD, NIDCR, NIDDK, NIEHS, NINDS, ORWH

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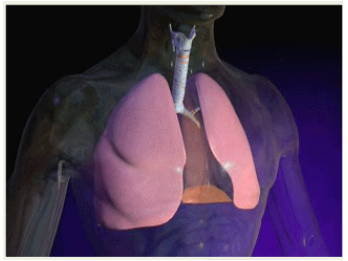
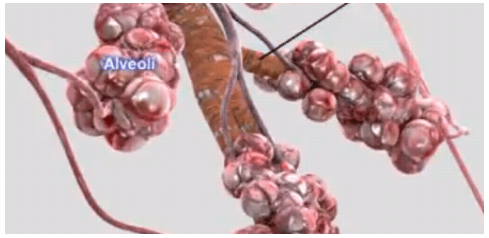
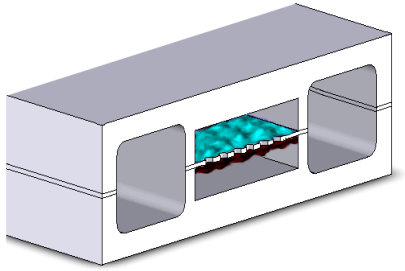
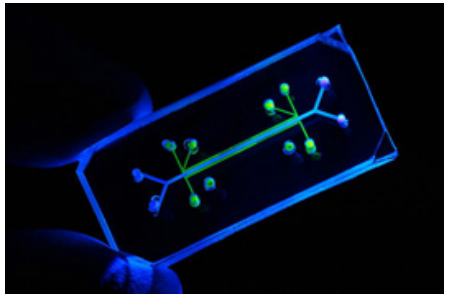
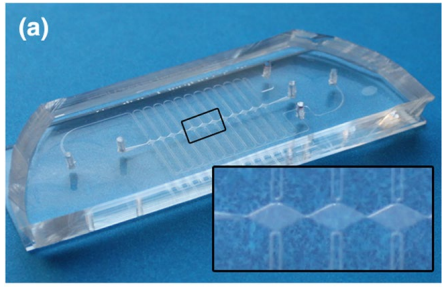
Microphysiological Systems: *In Vitro* Mimics of Human Organ Function

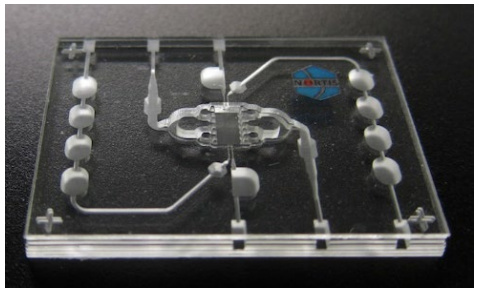


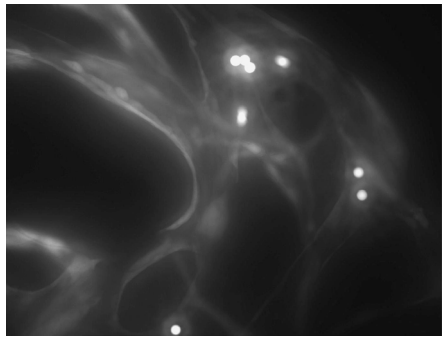


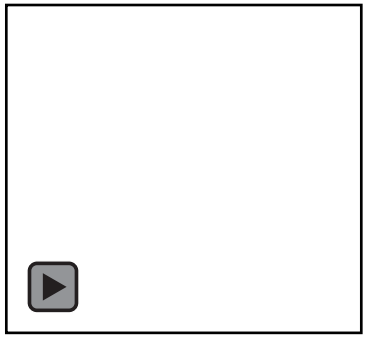


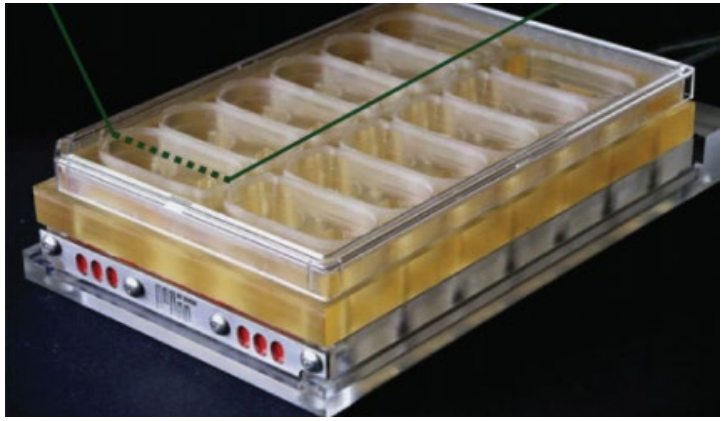


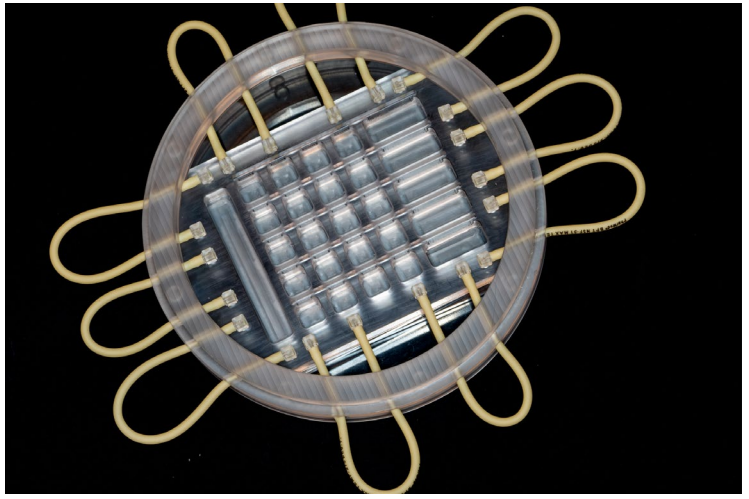


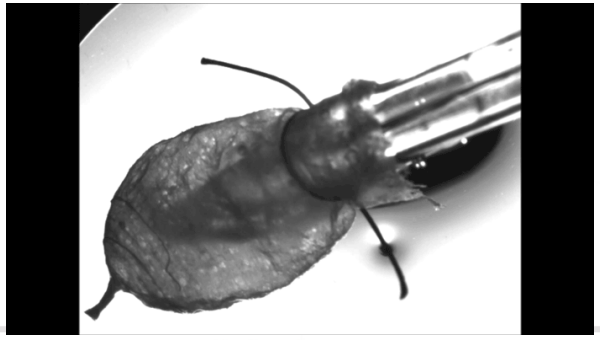




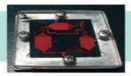
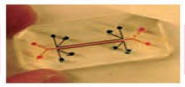
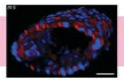
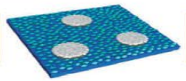
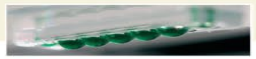
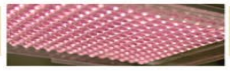
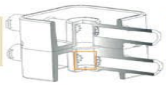


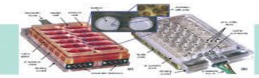
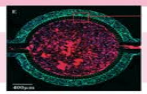
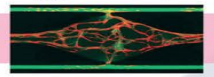
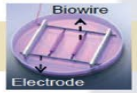
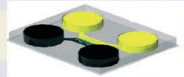
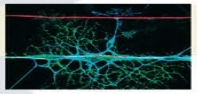






Commercial Activities around Organ-on-chip Technologies

		Scientific founders	Selected products
Body on-a-Chip			
Hesperos®		Michael Shuler James Hickman	Multi-Organ Chip (2, 4 organs) (5-10 organs)*
TISSUSE Emulating Human Biology		Uwe Marx	2-Organ-Chip (2-OC) 4-Organ-Chip (4-OC) Human-on-a-Chip (HoC)*
Tissue interface on-a-Chip			
emulate		Donald Ingber	Lung on-a-Chip Airway on-a-Chip Gut on-a-Chip Kidney on-a-Chip Bone Marrow on-a-Chip
AlveoliX In-vitro models inspired by nature		Olivier Guenat	Lung-on-a-chip array
NORTIS		Thomas Neumann	Kidney on-a-Chip Vessel on-a-Chip
Quorum		Axel Guenther	Artery on-a-Chip
Parenchymal tissue on-a-Chip			
Hepregen		Sangeeta Bhatia	HepatoPac® HepatoMune™
organovo™		Gabor Forgacs Keith Murphy	ExVive3D™ Liver ExVive3D™ Kidney*
Aspect biosystems		Tamer Mohamed Konrad Walus Sam Wadsworth Simon Beyer	Lab-on-a-Printer™ 3DBioRing™ Airway
insphero		Jan Lichtenberg Jens M. Kelm Wolfgang Moritz	3D Insight™ Liver 3D Insight™ Islet 3D Insight™ Tumor
3D Biomatrix™ Three-Dimensional Cell Culture		Nicholas Kotov	PERFECTA3D® HANGING DROP PLATES
HµREL CORPORATION		Greg Baxter Robert Freedman	HµRELhuman™ HµRELflux™ HµRELTox™ HµRELflow™
KIYATEC®		Matthew R. Gevaert	3DKUBE™
VAXDESIGN		William L. Warren	MIMIC® Technology

		Scientific founders	Selected products
CNBio innovations		Linda G Griffith	LiverChip® LiverChip® 36
DRAPER		Joseph Charest	Microphysiological Systems
MIMETAS the organ-on-a-chip company		Jos Joore Paul Vulto Thomas Hankemeier	OrganoPlates®
SYNVIVO		Kapil Pant B. Prabhakar Pandian	SynTumor SynBBB SynRAM SynTox
4DBio 4DESIGN BIOSCIENCES		G. Wesley Hatfield Christopher Hughes Steven George Abraham Lee	Vascularized micro-organ (VMO) platform
AIM BIOTECH		Roger Kamm	3D cell culture chips
TARA		Milica Radisic Gordana Vunjak-Novakovic	Cardiac Biowire™ II AngioChip*
µOrgano		Kevin Healy	µOrgano
EHT Technologies		Thomas Eschenhagen	Engineered Heart Tissue (EHT)
myriamed		Wolfram-Hubertus Zimmermann	3D Cardiac Systems
AxoSim		Michael Moore	Nerve-on-a-Chip™
xona MICROFLUIDICS		Noo Li Jeon Carl W. Cotman Anne Taylor	Standard / Triple Chamber Neuron Device
MicroBrain BT		Bernadette Bung	Neuronal Diode
ananda		Margaret Magdesian	Neuro Device

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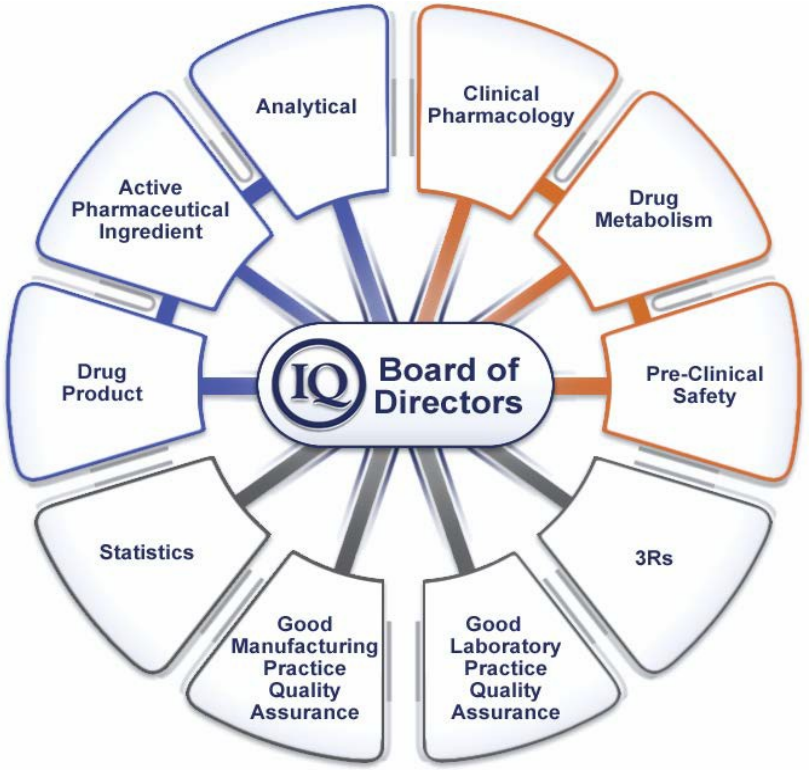
Working with Pharma:
IQ Microphysiological Systems Affiliate

AbbVie	BMS	GSK	Novartis	Theravance
Amgen	Celgene	Jansen	Pfizer	Vertex
Astellas	Eisai	Merck	Sanofi	
AstraZeneca	Eli Lilly	Merck KgA	Seattle Genetics	
Biogen	Genentech	Mitsubishi Tanabe	Takeda	



Goals of IQ MPS Affliate:

- 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

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Building Confidence: Tissue Chip Validation Framework

Comput Struct Biotechnol J.(2016) 14: 207–210.

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

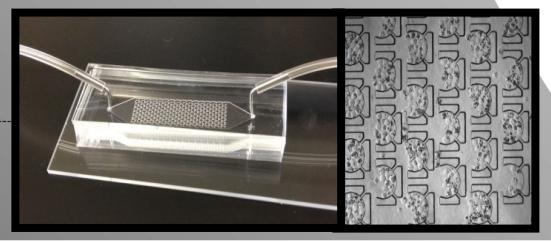
1) Physiological

- Organ function and structure
- Training set of reference compounds
- TC 1.0 developers

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/
  - U Pittsburgh (Mark Schurdak)

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



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.*

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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/
  - 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

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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)

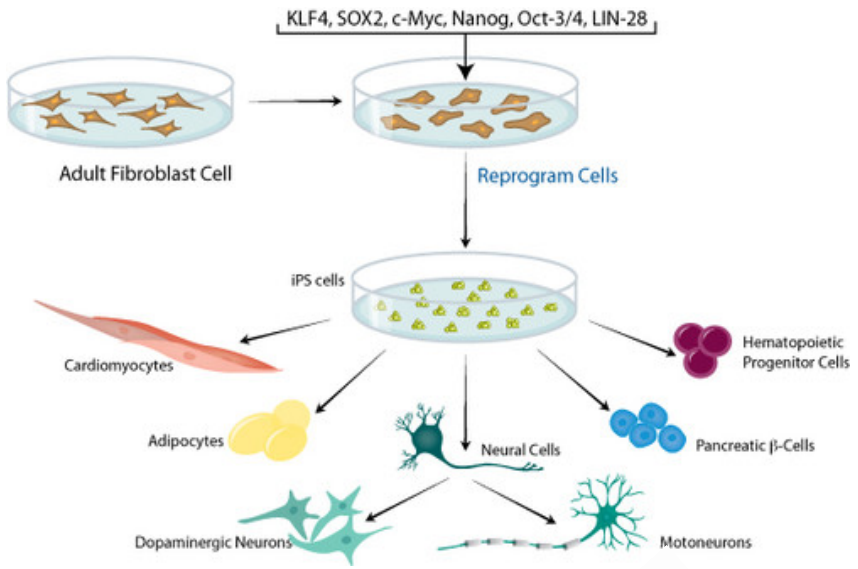
Why send Tissue Chips to the ISS National Laboratory?

- 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



Human body on Chip

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

- 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

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NCATS Improving Health Through Smarter Science

- **Website:** https://ncats.nih.gov/tissuechip
- **Facebook:** facebook.com/ncats.nih.gov
- **Twitter:** twitter.com/ncats_nih_gov
- **YouTube:** youtube.com/user/ncatsmedia
- **E-Newsletter:** https://ncats.nih.gov/enews
- **Announce Listserv:** https://bit.ly/1sdOI5w

Thank you!

boyeon.lee@nih.gov

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