The NIH Microphysiological Systems Program: Tissue Chips for Drug Safety and Efficacy Studies

Scientific Advisory Committee on Alternative Toxicological Methods Meeting
Sept 20th 2019

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Office of the Director, NCATS, NIH

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Outline:

- National Center for Advancing Translational Sciences (NCATS), NIH
- Microphysiological Systems/Tissue Chips
- NIH Tissue Chips Consortium
- Building confidence and evolving MPS technology
- Building Partnerships
- Future Initiatives and Summary

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, e.g. tools for predictive safety and efficacy

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

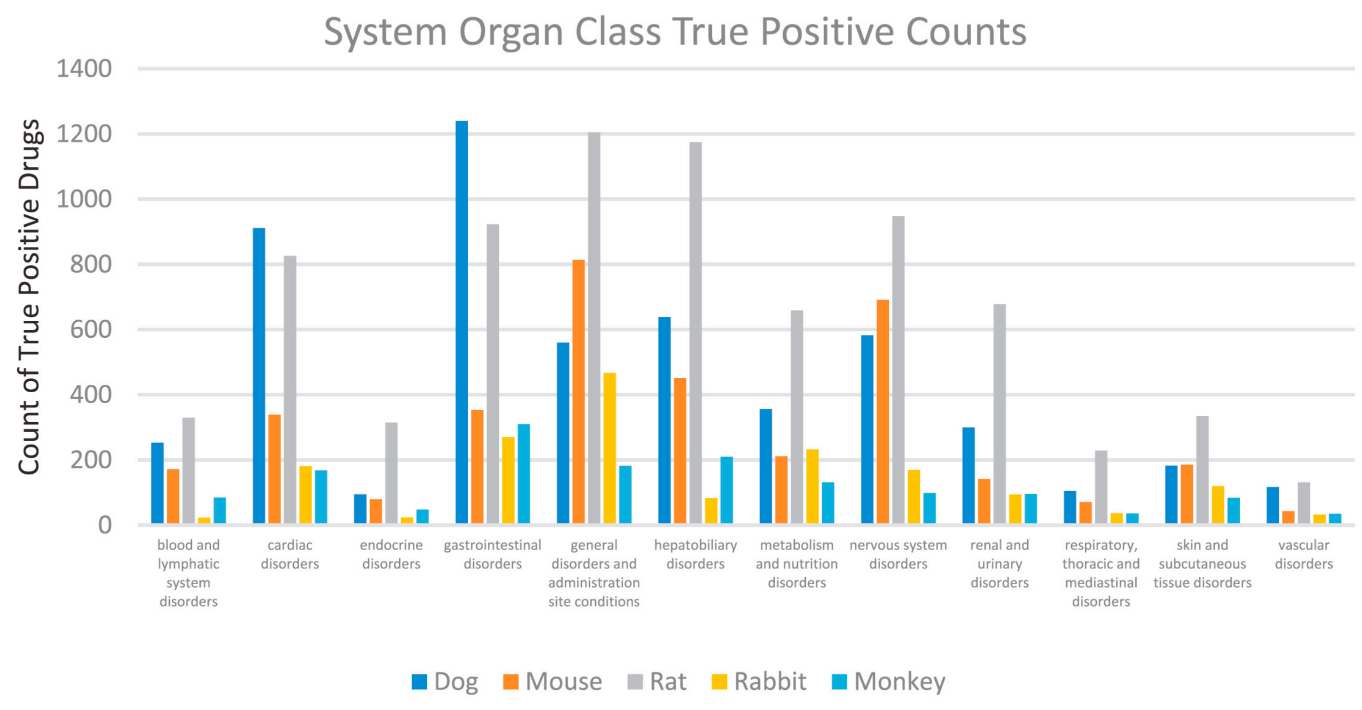
  (***phRMA***, *Biopharmaceutical Research Industry Profile, 2016)*

- ❑ The current drug discovery paradigm has a failure rate of 90%:

  - 55% due to lack of efficacy
  - 28% due to toxic effects in humans

- ❑ Clinical trials of homogenous and small sample sizes are used to predict the outcomes on diverse populations

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



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

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

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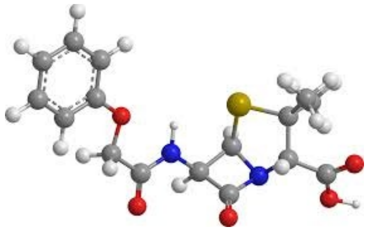
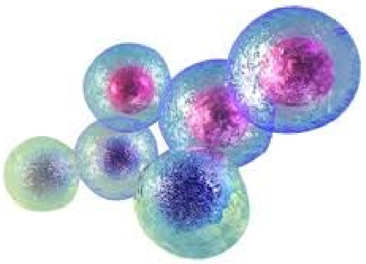
Therapeutic Modalities are Increasingly Human-specific and Personalized

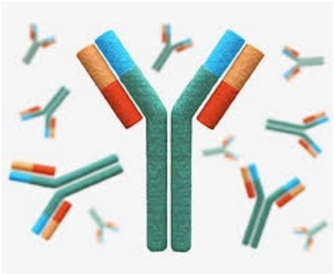
SMALL MOLECULES



CELL THERAPIES



ANTIBODIES



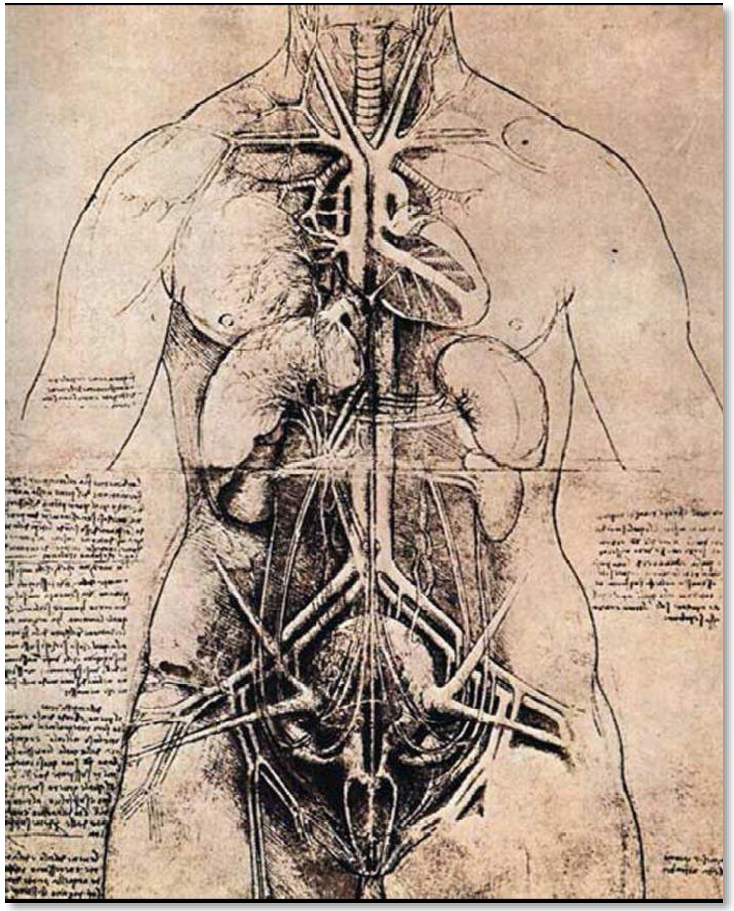
GENE THERAPIES

PROTEIN THERAPIES

ANTISENSE

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 and other stakeholders**

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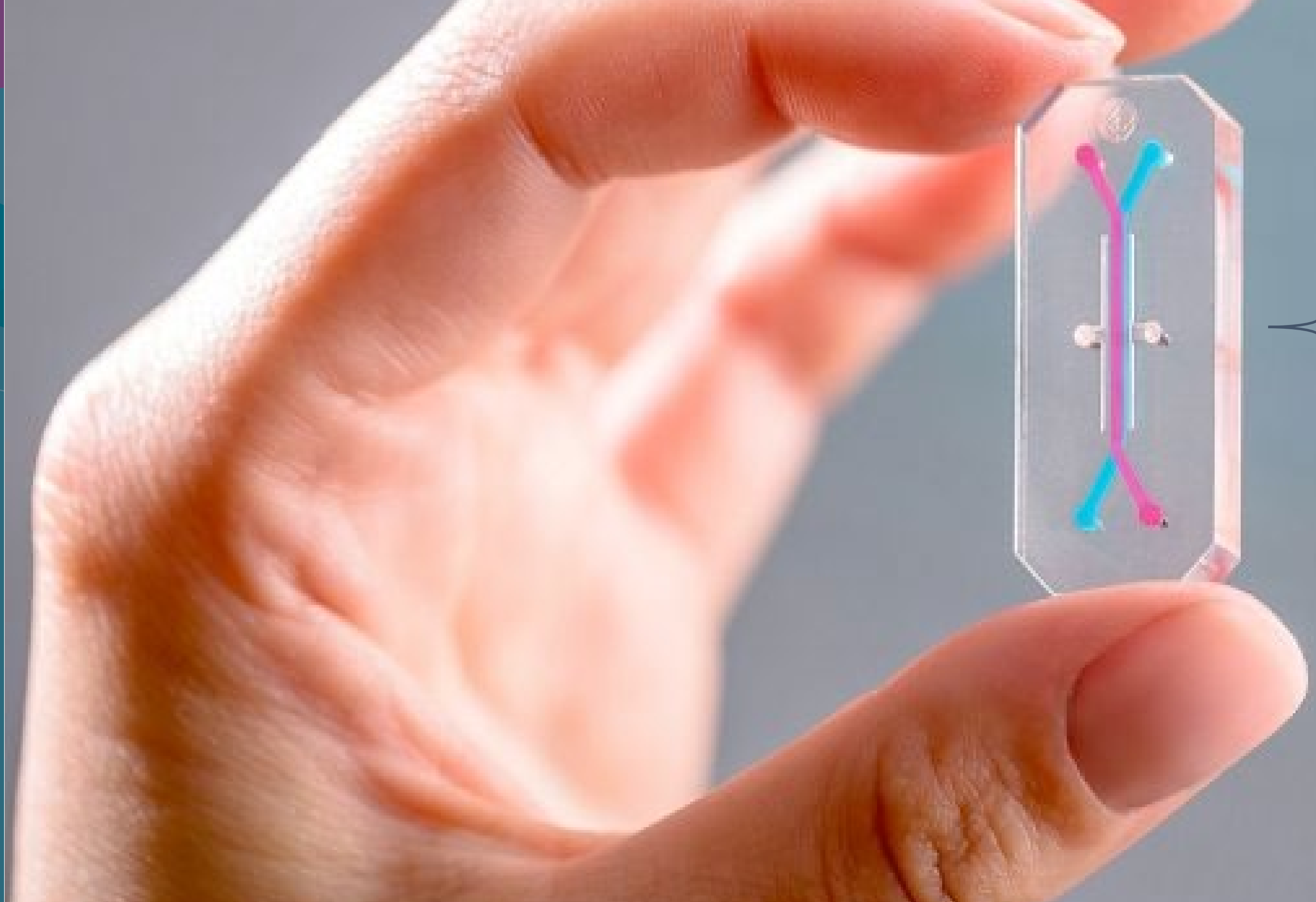
Tissue Chips

- a multi-channel 3-D microfluidic cell culture chip that simulates the activities, mechanics and physiological response of entire organs and organ systems



Scaffold	• purified ECM , synthetic polymers, composites
Cells	• human-derived primary or iPSCs;
Structure	• porosity, topography, stiffness
Spatial and Temporal Patterning	• controlled release of cytokine and hormone gradients
Perfusion	• microfluidic cell culture devices, vasculature
Bioreactor	• biomechanical properties
Innervation	• signal propagation, coordinated response
Host Response	• generalized inflammation, specific immunity
Functional Readout	• real-time, label-free, non-destructive sensing, imaging
Computational Design	• systems integration multi-scale modeling

Representing relevant biology on bioengineered chips

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Microphysiological Systems Program: Tissue Chips 1.0 for Safety and Toxicity Testing

AstraZeneca

Pfizer

gsk GlaxoSmithKline

NIH National Institutes of Health

Platform and cell resources development

Physiological Validation, training set of compounds, multi-organ integration

2012-13 | 2013-14 | 2014-15 | 2015-16 | 2016-17

NIH National Institutes of Health

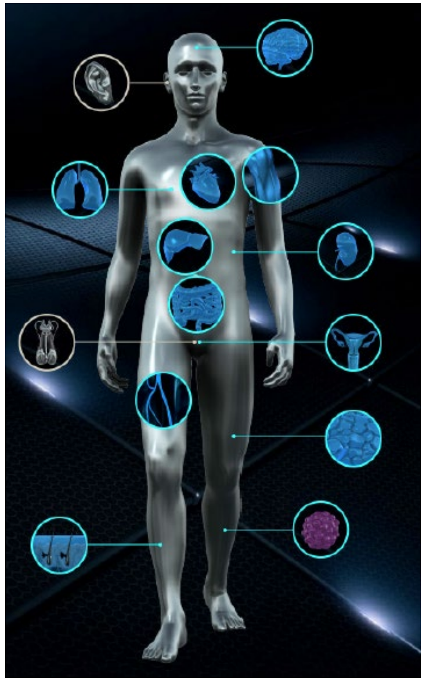
$75 M over 5 years – cell source, platform development, validation and integration (NCATS, CF, NIBIB, NIEHS, NICHD, ORWH, NCI)

DARPA

$75 M over 5 years - development of 10-organ platforms

FDA

****FDA provides insight and expertise throughout the program**

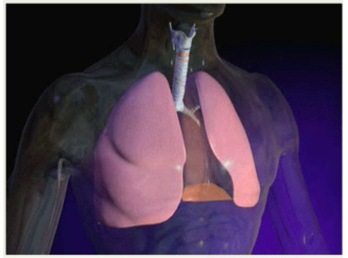
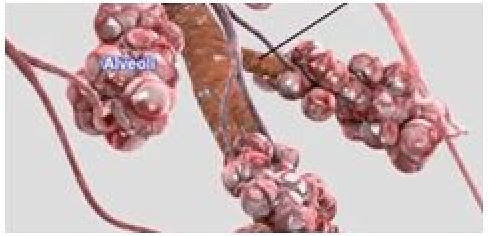


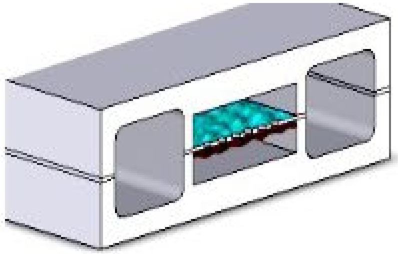
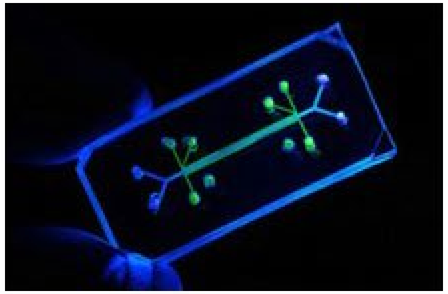
GOALS:

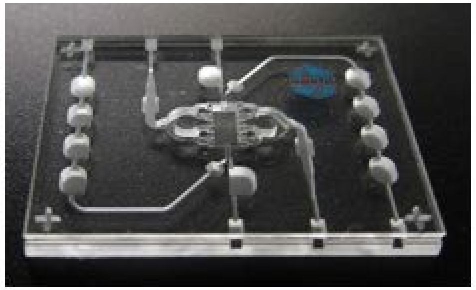
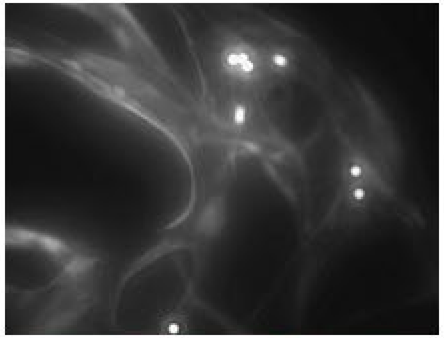
- Develop single organ and Multi-organ chips
- Functional and physiological validation
- Compound testing
- Partnerships

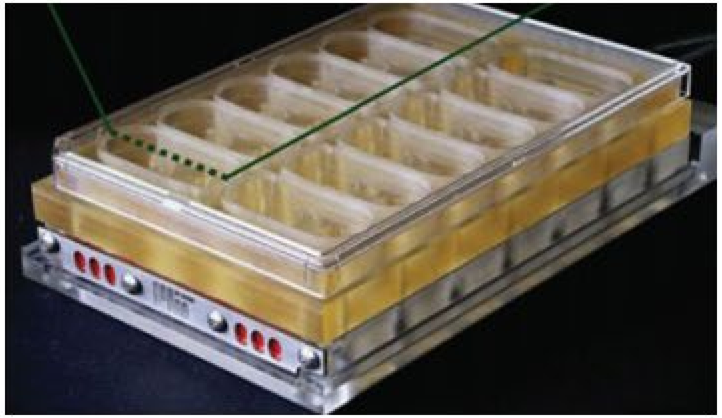
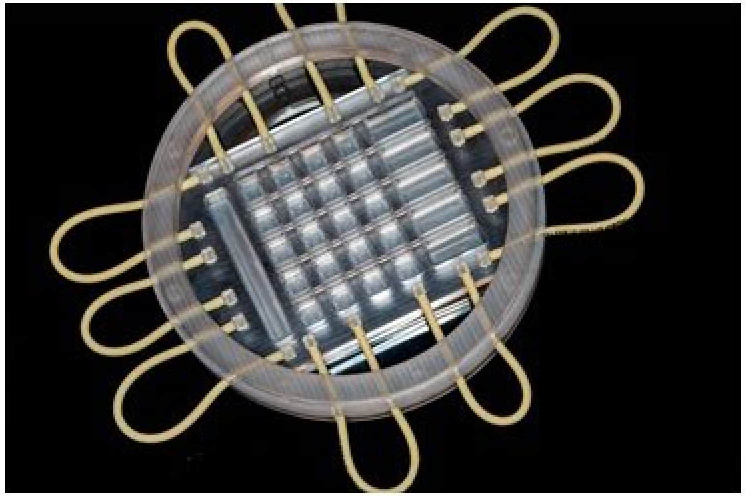
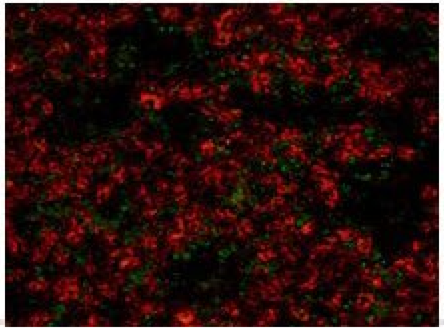
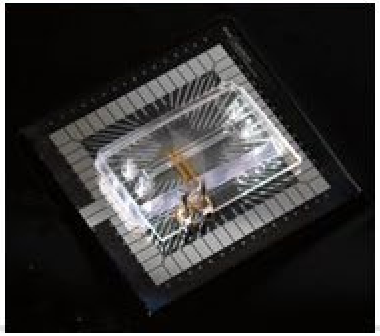
Phased award and milestone-driven

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

Diversity of Bioengineered Platforms

Tissue Chips 1.0 to Predict Drug Safety (2012-2017)

- James A. Thomson; Morgridge Institute for Research at the University of Wisconsin-Madison
Human induced pluripotent stem cell and embryonic stem cell-based models for predictive neural toxicity and teratogenicity

- John P. Wikswo; Vanderbilt University
Neurovascular unit on a chip: Chemical communication, drug and toxin responses

- Steven C. George; University of California, Irvine
An integrated in vitro model of perfused tumor and cardiac tissue

- D. Lansing Taylor; University of Pittsburgh
A 3-D biomimetic liver sinusoid construct for predicting physiology and toxicity

- James M. Wells; Cincinnati Children's Hospital Medical Center
Generating human intestinal organoids with an enteric nervous system

- John P. Lynch; University of Pennsylvania
Modeling oxidative stress and DNA damage using a gastrointestinal organotypic culture system

- George A. Truskey; Duke University
Circulatory system and integrated muscle tissue for drug and tissue toxicity

- Rocky S. Tuan; University of Pittsburgh
Three-dimensional osteochondral micro-tissue to model pathogenesis of osteoarthritis

- Linda Griffith; Massachusetts Institute of Technology
All-human microphysical model of metastasis and therapy

- Thomas Hartung; Johns Hopkins University
A 3-D model of human brain development for studying gene/environment interactions

- Kevin K. Parker; Harvard University
Human cardio-pulmonary system on a chip

- Joan E. Nichols; The University of Texas Medical Branch at Galveston
Three-dimensional human lung model to study lung disease and formation of fibrosis

- Mark Donowitz; Johns Hopkins University, Baltimore
Human intestinal organoids: Pre-clinical models of non-inflammatory diarrhea

- **Teresa Woodruff; Northwestern University**
Ex Vivo Female Reproductive Tract Integration in a 3-D Microphysiologic

- Jonathan Himmelfarb; University of Washington, Seattle
A tissue-engineered human kidney microphysiological system

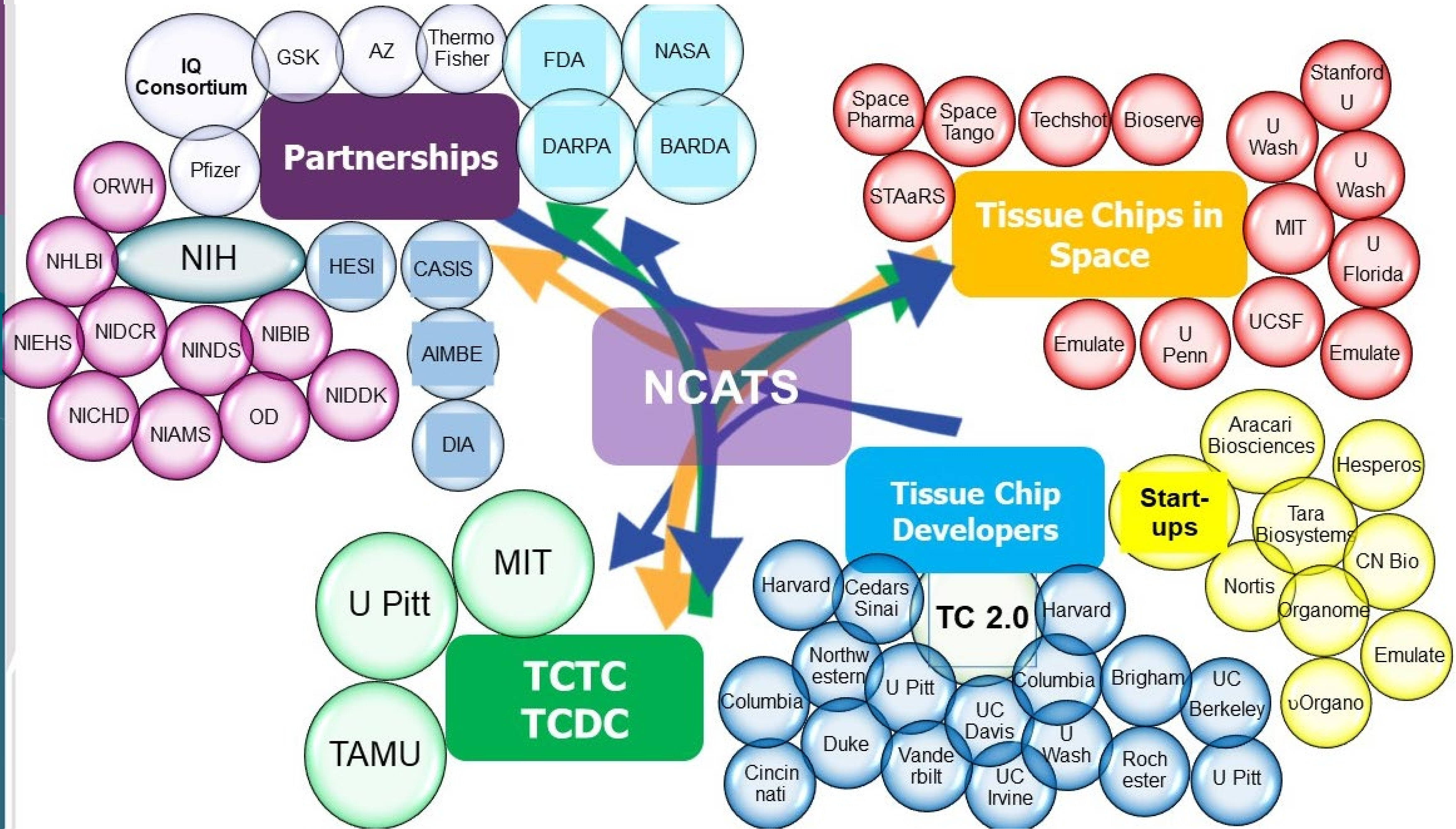
- Gordana Vunjak-Novakovic; Columbia University Health Sciences
Integrated Heart-Liver-Vascular Systems for Drug Testing in Human Health and Disease

- Angela Christiano; Columbia University Health Sciences
Modeling complex disease using induced pluripotent stem cell-derived skin constructs

- **Kevin E. Healy; University of California, Berkeley**
Disease-specific integrated microphysiological human tissue models

- Michael L. Shuler; Cornell University
Microphysiological systems and low cost microfluidic platform with analytics

NIH Tissue Chips Consortium- Partnerships with Stakeholders



Commercial Activities around Organ-on-chip Technologies

Body on-a-Chip

Company	Scientific founders	Selected products
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)*
CN Bio innovations	Linda G Griffith	LiverChip®, LiverChip® 36
Draper	Joseph Charest	Microphysiological Systems

Tissue interface on-a-Chip

Company	Scientific founders	Selected products
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
Mimetas (the organ-on-a-chip company)	Jos Joore, Paul Vulto, Thomas Hankemeier	OrganoPlates®
SynVivo	Kapil Pant, B. Prabhakar Pandian	SynTumor, SynBBB, SynRAM, SynTox
4D Bio (4Design Biosciences)	G. Wesley Hatfield, Christopher Hughes, Steven George, Abraham Lee	Vascularized micro-organ (VMO) platform
AIM Biotech	Roger Kamm	3D cell culture chips

Parenchymal tissue on-a-Chip

Company	Scientific founders	Selected products
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	HµREL*human*™, HµREL*flux*™, HµREL*Tox*™, HµREL*flow*™
KIYATEC	Matthew R. Gevaert	3DKUBE™
VaxDesign	William L. Warren	MIMIC® Technology
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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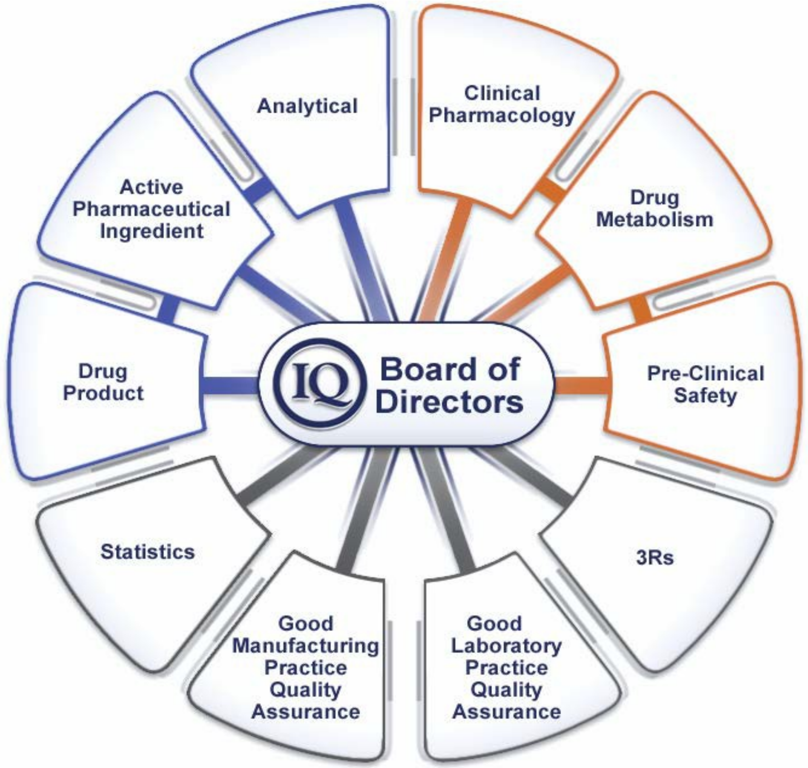
Working with Pharma: IQ Microphysiological Systems Affiliate

Mission To serve as a unified voice, advisory body and thought leader for both developers and stakeholder organizations in industry implementation and qualification of MPS models

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	



- Multi-disciplinary team of pharmaceutical scientists representing expertise and interests in drug metabolism and distribution, safety, and the 3Rs of animal use for research
- Ability to leverage existing legal framework and data sharing agreements between IQ member companies
- Provide a venue for cross-pharma collaboration and data sharing that facilitates expeditious uptake and impact of MPS
- Provide a focus of engagement with government (regulatory and non-regulatory) and academic stakeholders with interests and investment in MPS

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Building Confidence: Tissue Chip Validation Framework

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

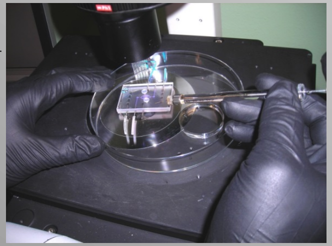
3) Industrial
- Use by industry and regulatory agencies
- Proprietary set of compounds?
- CRO-type environment

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/
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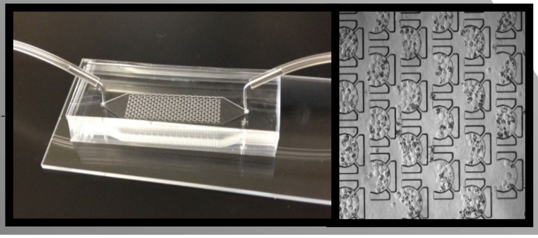

Publications: (as of Oct 2017)
A total of 506 original and review articles (cited over 5600 times) published in top tier journals, including *Nature Medicine, Nature Communications, Nature Materials, PNAS, Science, Science Translational Medicine, etc.*

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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

Publications thus far:

- Kidney on chip
  - Nature *Scientific Reports* (2018) 8:14882
  - CPT Pharmacometrics Syst. Pharmacol. 2019, 8:316
- Brain on chip
  - Front. Big Data 2019, doi: 10.3389/fdata.2019.00023.

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NextGen Testing Centers and Business Models for Self-Sustainability

MIT transitioned to **Javelin Biotech**

- 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)

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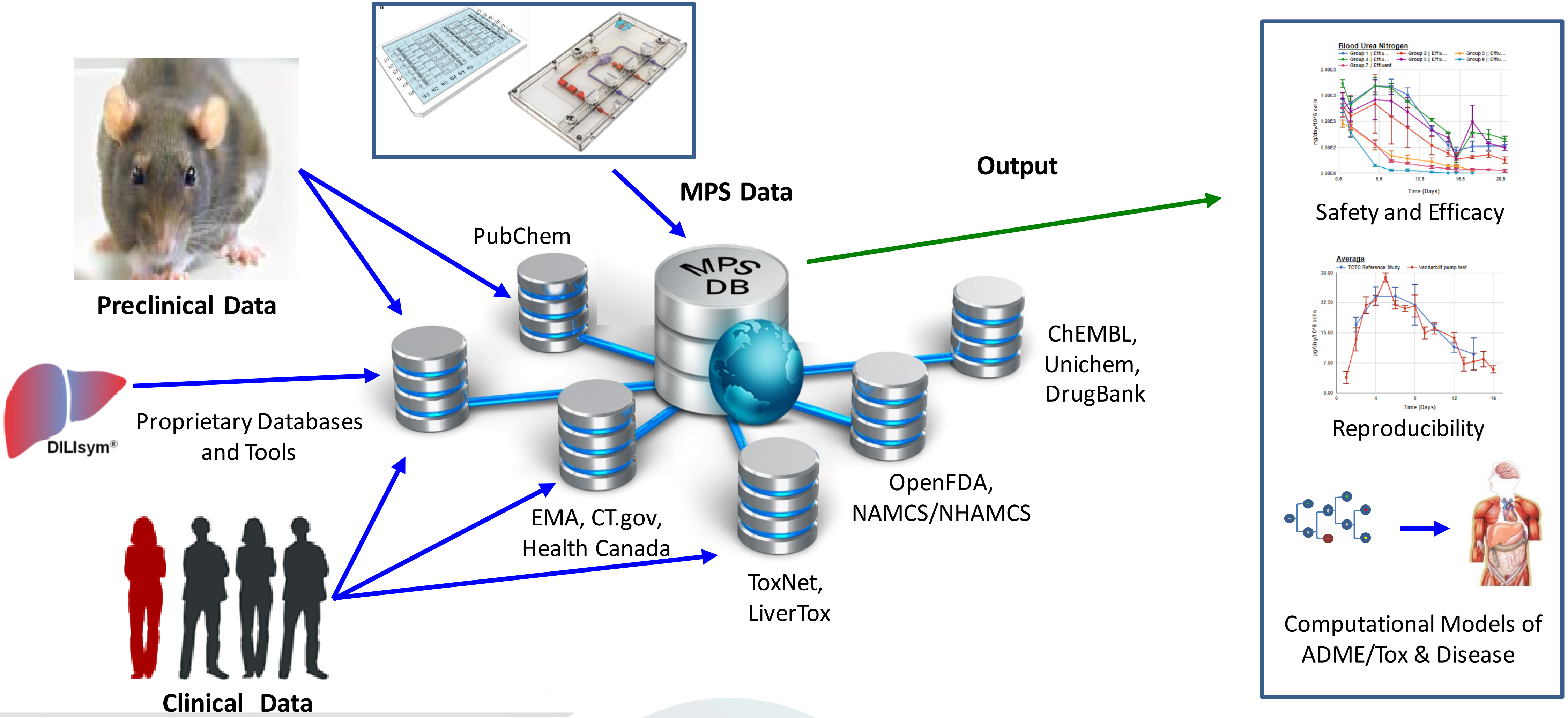
The MPS DB Center is Key to Analyze and Model MPS Data Relative to Experimental Animal and Human Data



Mark Schurdak, Director of Operations and **Bert Gough**, Associate Professor
University of Pittsburgh Drug Discovery Institute

MPS DB Center Content and Tiered Review for Public Access

Current MPS-Db Content

MPS Experimental Models

- **58** models
- Covering **11** organs
- Developed at **14** Centers

Data

- **171** studies
- **133,675** data points
- **10,516** images
- **2,981** videos
- From **8** data providers

Data Release Progress	Studies	Data Points	Images	Videos
0. Data provider review	81	74,824	7,754	2,981
1. Tissue Chip Developer review	28	16,462	230	0
2. NCATS, FDA, IQ Consortium access	43	29,864	1,254	0
3. Public Access	19	12,525	1,278	0
Total	**171**	**133,675**	**10,516**	**2,981**

Mark Schurdak, Director of Operations and **Bert Gough**, Associate Professor
University of Pittsburgh Drug Discovery Institute

NIH Tissue Chips 2.0 for Disease Modeling and Efficacy Testing 2018 to 2022)

Kam Leong, Columbia U
Proteus Syndrome and DiGeorge Syndrome

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

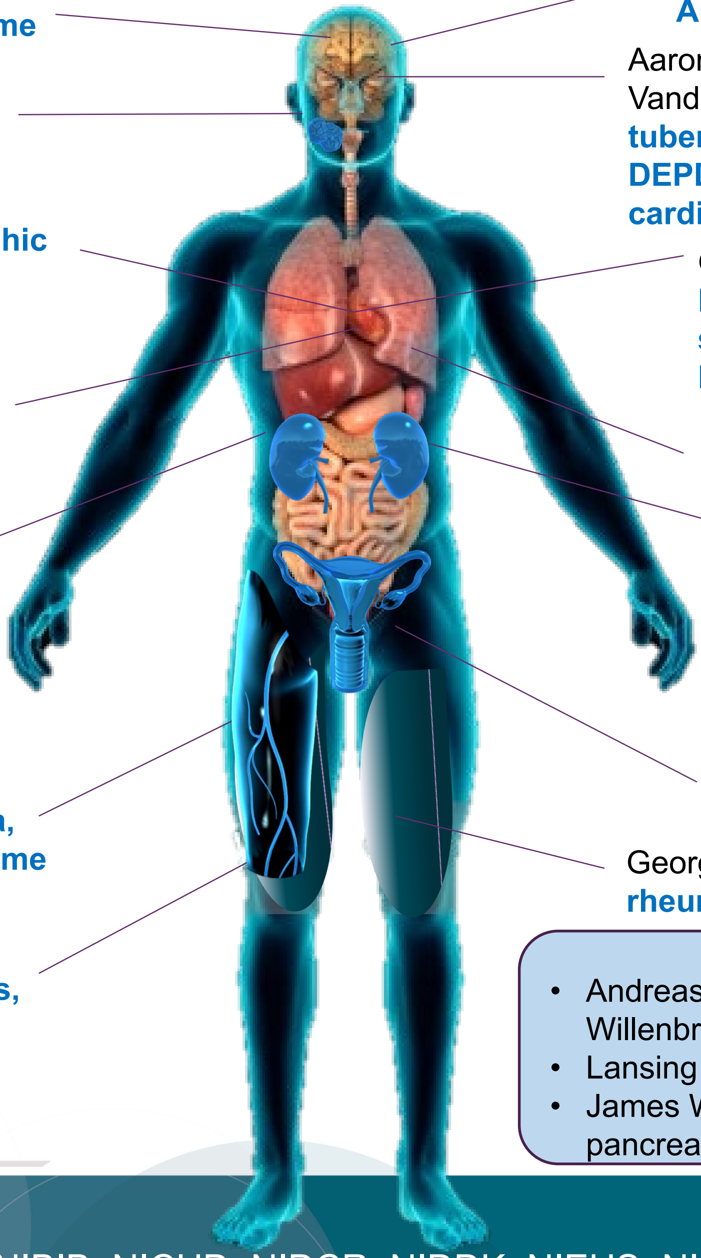
Kevin Kit Parker, William Pu, Harvard U
Barth syndrome, catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic cardiomyopathy

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

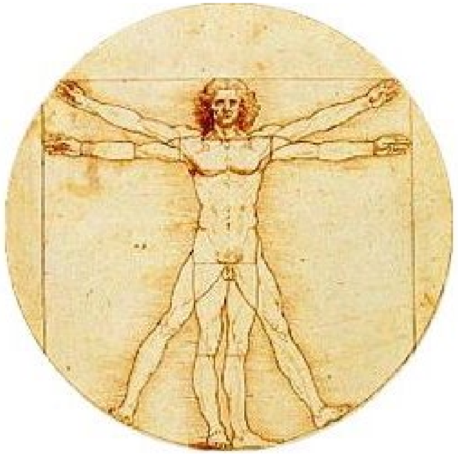
Type-2 Diabetes Mellitus

- 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

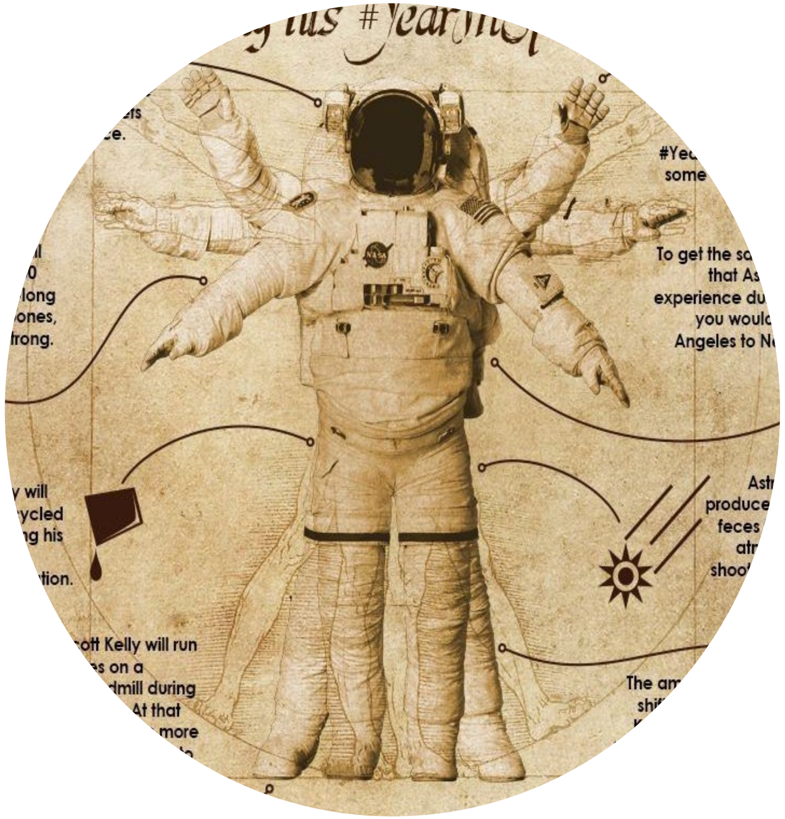
NIH National Center for Advancing Translational Sciences

Physiological Changes under Prolonged Microgravity



- **Early response (<3 weeks)**
  - **Upper body fluid shift**
  - **Neurovestibular disturbances**
  - **Sleep disturbances**
  - **Bone demineralization**

- **Intermediate (3 weeks to 6 months)**
  - **Bone resorption**
  - **Muscle atrophy**
  - **Cardiovascular deconditioning**
  - **GI disturbances**
  - **Hematological changes**



Long Duration (greater than 6 months)
  - **Muscle atrophy**
  - **Cardiovascular deconditioning**
  - **GI disturbances**
  - **Hematological changes**
  - **Declining immunity**
  - **Renal stone formation**

- **Reverts to normal on return to Earth**

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.

NIH and ISS-NL Coordinated Program in Tissue Chip Systems Translational Research in Space

Immunosenescence

UCSF
BioServe Space Technologies

PI: Sonja Schrepfer

Post-traumatic osteoarthritis

MIT
techshot

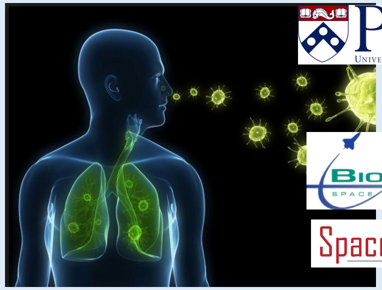
PI: Al Grodzinsky

Drugs across blood-brain barrier

emulate
Space Tango

PI: Christopher Hinojosa

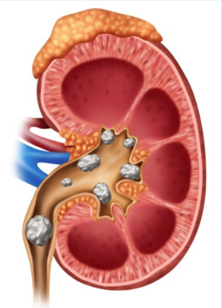
Lung infection



Penn University of Pennsylvania
BioServe Space Technologies
Space Tango

PI: Scott Worthen

Proteinuria and kidney stones formation



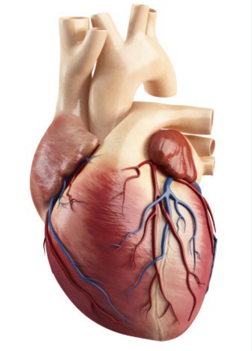
W School of Pharmacy University of Washington
BioServe Space Technologies

PI: Jonathan Himmelfarb

Cardiac dysfunction & engineered heart tissues

W University of Washington
The Ohio State University
BioServe Space Technologies

PI: Deok-Ho Kim



Stanford University
UCSB
BioServe Space Technologies

PI: Joseph Wu

Muscle wasting (sarcopenia)

UF University of Florida
Space Tango

PI: Siobhan Malany

Gut inflammation

emulate
Space Tango

PI: Christopher Hinojosa

Improved biology: study human biology that otherwise would be difficult or take longer on earth

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- **Technological improvements:** Organs on chip control systems are more complex than the chips – need for robust, automated, reduced footprint, turnkey (“astronaut/fighter pilot proof”); standardization, minimize variability

48 ft^{3}n lab

ISS U.S. NATIONAL LABORATORY

NASA CASIS POWERED THROUGH PARTNERSHIP

2 ft^3 for launch

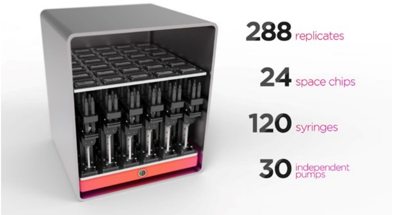
techshot

Space Tango

BioServe Space Technologies

SPACEX

1.6 ft^3 for on orbit



Ground requirements for 24 Chips

- 72 samples preparations
- 8 syringe pumps
- 4 incubators (48 cubic feet)
- 216 small petri dishes for effluent
- 24 large petri dishes or 72 smaller for triplex chips
- 216 syringes for media and fixative
- ~216 feet of tubing

On-orbit operational requirements

- Support up to 10 days of automated perfusion
- 72 individual media or fixative channels and 72 effluent bags
- Downlink telemetry ISS to monitor operation while on orbit
- Payload development - Fit within **compact volumes**
  - **Stowage Locker – Launch**: (17.34”w x 20.32”L x 9.97” H) – 4 syringe pumps, one power module
  - **SABL – on orbit:** (11.1”w x 16.66”L x 7.75”H) – 2 syringe pumps, 2 SABLs

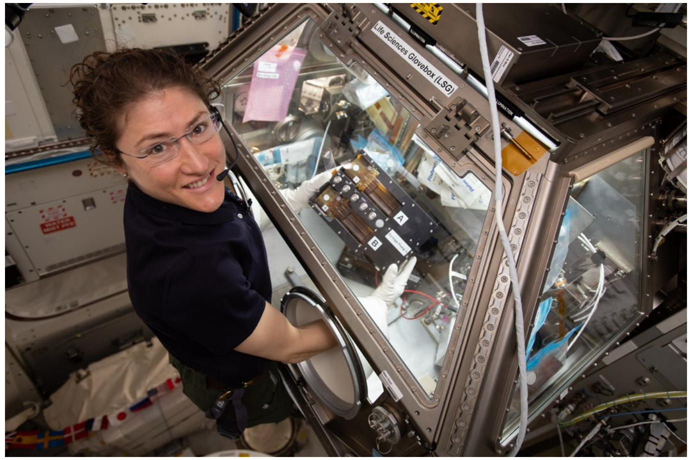
Improved Tissue Chip Techology: Automation and miniaturization of control systems

- SpaceX CRS-16 Launch
  - Kennedy Space Center - December 5, 2018
    1:16 pm
  - Payload included Immunosenescence on chip project

- SpaceX CRS-17 Launch
  - Kennedy Space Center – May 4, 2019
    2:48 am
  - Payload included tissue chip projects:
    - Lung infection/bone marrow
    - Proteinuria and kidney stone formation
    - Osteoarthritis
    - BBB permeability

“NIH to rocket 3-D tissue chips into space to study diseases in microgravity”

- May 6, 2019 7:04 a.m. EDT, ISS crew members captured the Dragon spacecraft
- Berthed to the Harmony module on May 6, 2019 9:33 a.m. EDT
- Dragon capsule returned to Earth June 3, 2019 after approximately four-week stay at the ISS.



NASA astronaut Christina Koch works inside the
Life Sciences Glovebox conducting tissue chips research

- Samples being analyzed
    - Biological – omics marker analysis (transcriptomics, metabolomics, epigenetic), histological, immunohistochemical
    - Technological – structural soundness of chips platform and instrumentation; experimental automation
- Testing of compounds on re-flight

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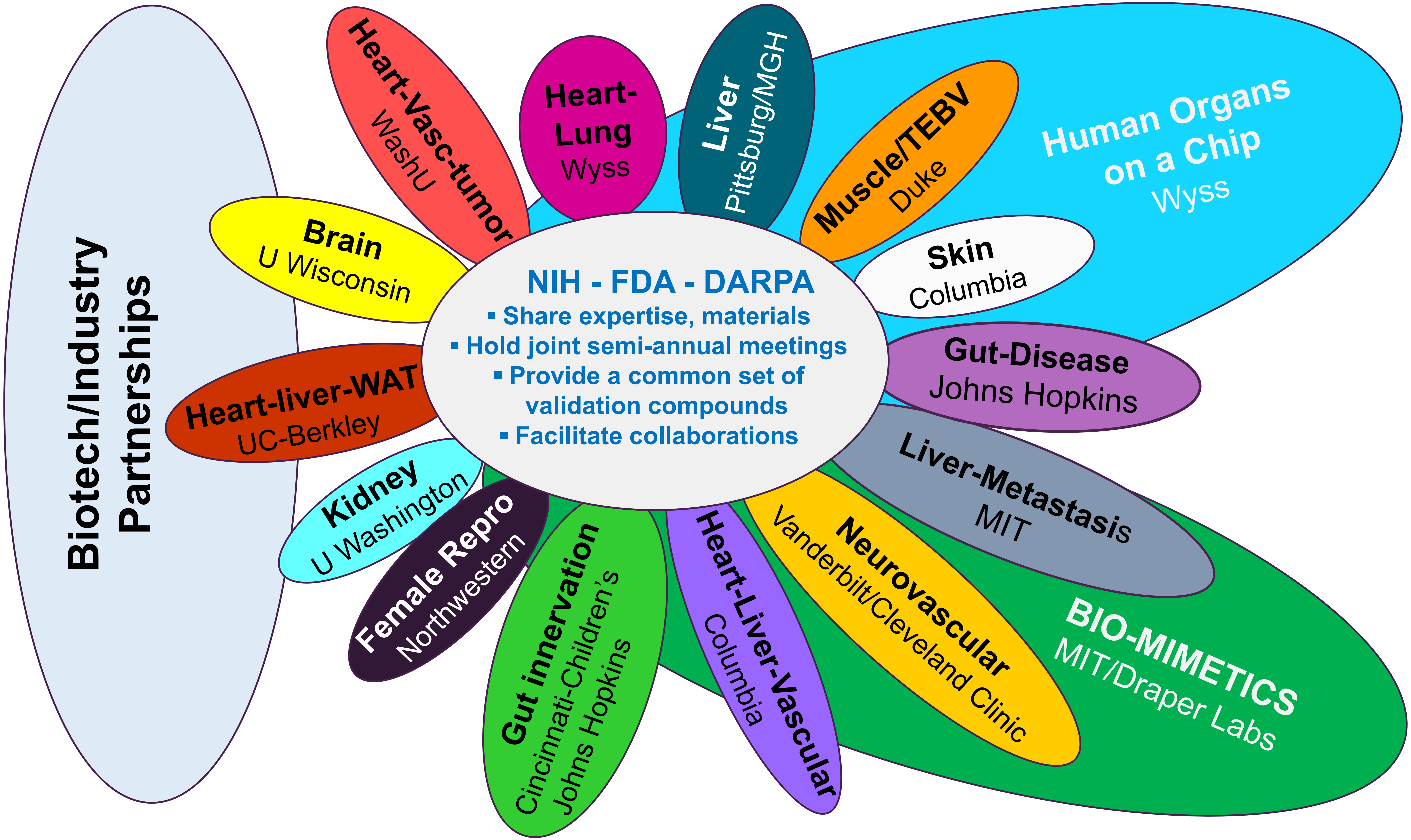
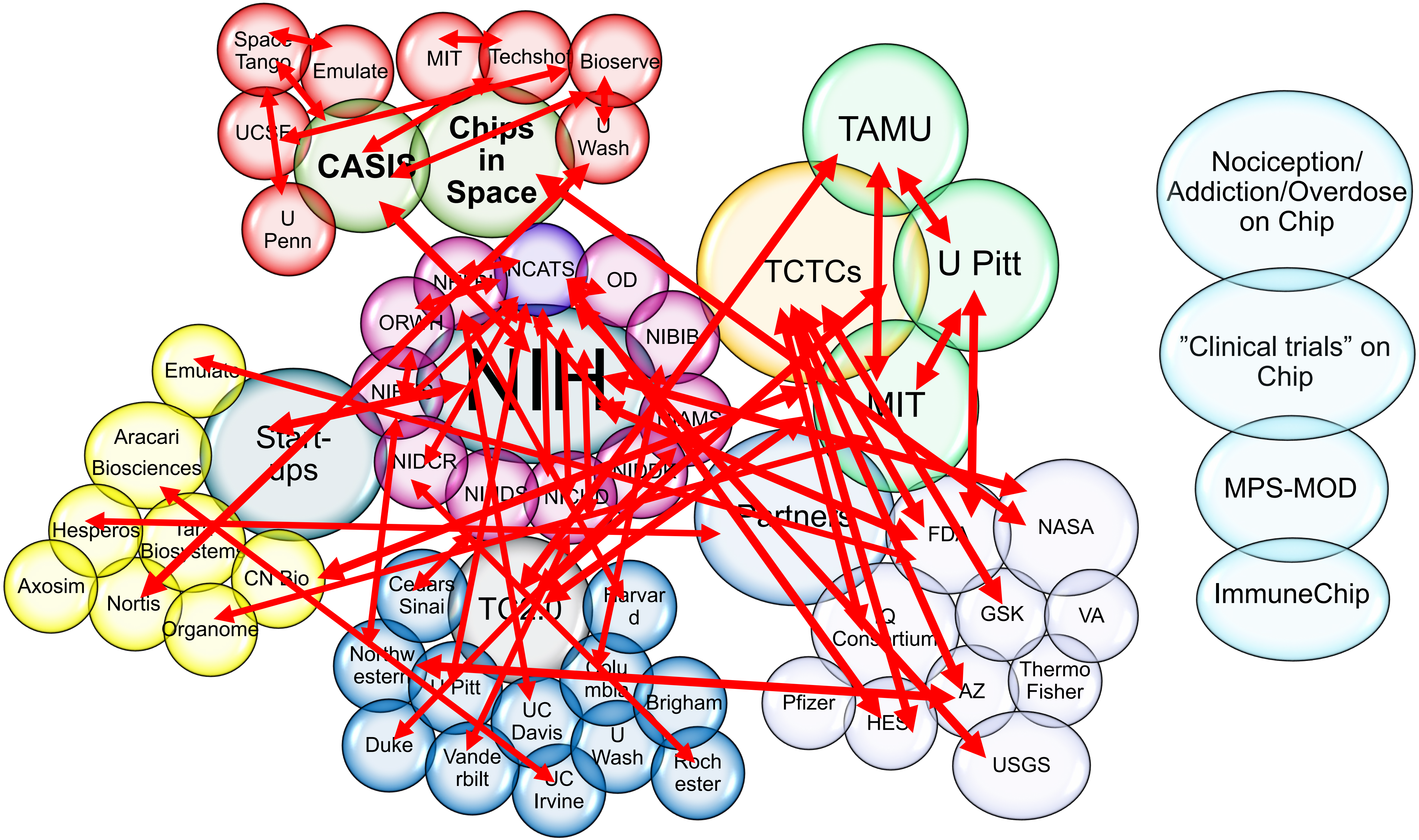
Tissue Chip Consortium 2012-2017



Microphysiological Systems Consortium 2018 -



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"Fundamental learnings from program evolution"
Brian Berridge

- Clearly identify gaps and opportunities
  - Create established supporting partnerships (e.g. government agencies)
  - Involvement of end-users from the start (e.g. FDA, pharma)
- Give researchers what they need to succeed
  - Establish a precompetitive environment
    - Supplemental funding
    - Consortium meetings for updates, group troubleshooting, and networking
    - Access to proprietary resources and/or information
  - Programmatic support and guidance
- Expect setbacks and failures
  - Build in procedures to avoid e.g. milestone-driven phased awards
  - Invite feedback to help guide progress


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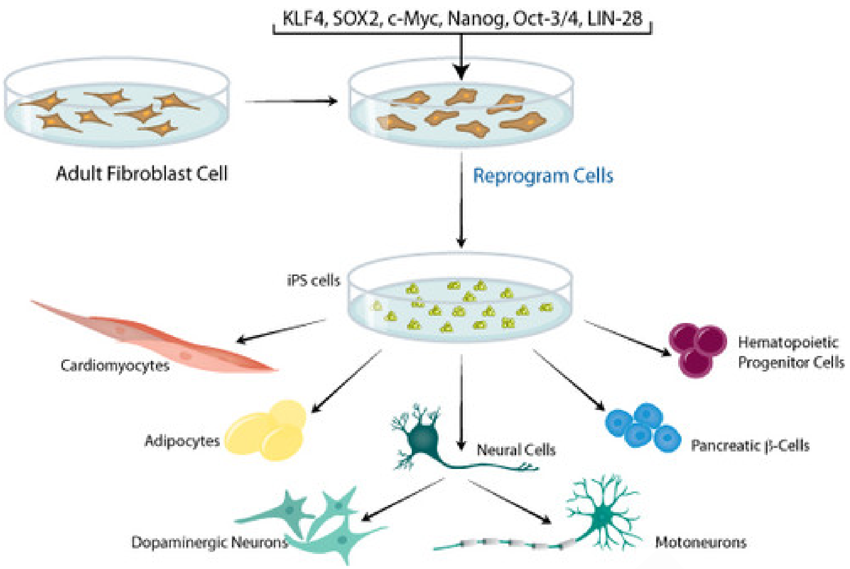
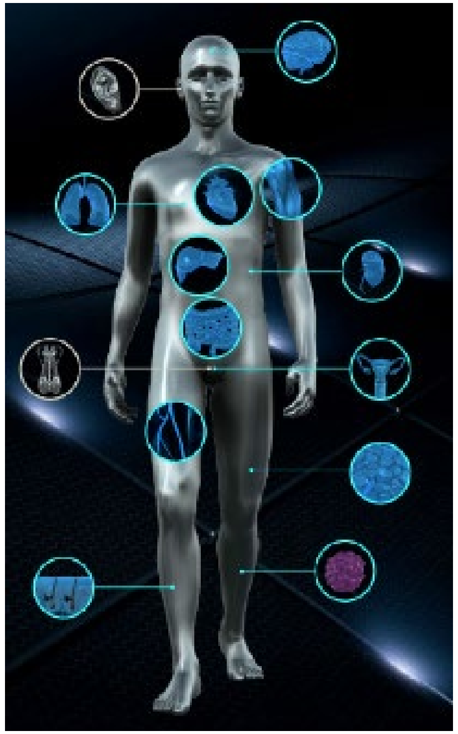
Current NIH Initiatives for Tissue Chips



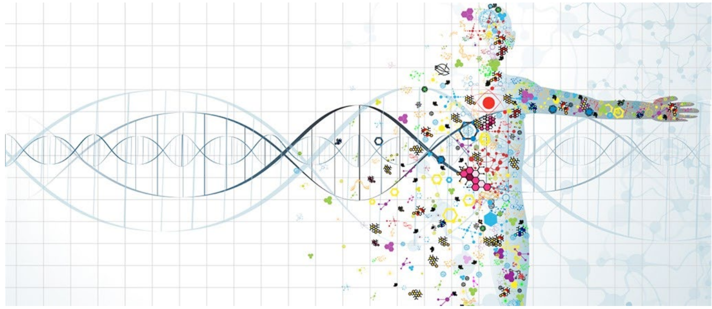


Human body on Chip

- **Clinical Trials-on-chips for Precision Medicine (You-on-chip)** **RFA-TR-19-014** *(October 9, 2019)*
- **BBB/interface on chip RFA-HL-20-21** *(December 2, 2019; October 19, 2020)*

To be awarded:

- **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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RFA-TR-19-014 "Clinical Trials" on a Chip: Tissue Chips to Inform Clinical Trial Design and Implementation in Precision Medicine

- **RFA Goal:** To demonstrate the utility of tissue chips in informing clinical trial framework and for precision medicine through trial design, establishing recruitment criteria and stratification of patient populations towards identifying the best responders to candidate therapeutics
- **Participating NIH ICs:** NCATS, NCI, NIAMS, NICHD, NIDCR, NINDS
- **Areas of interests:**
  - Use of tissue chip models that have the potential to substantially impact clinical trial design in terms of anticipated key outcomes (e.g., assessment of clinical benefit and risk, safety and tolerability profile, dosing regimen, population stratification to include the best responders, identification of surrogate clinical trial endpoints
  - Studies on mission-relevant diseases and disorders for the participating ICs
- **Application receipt date:** October 9, 2019

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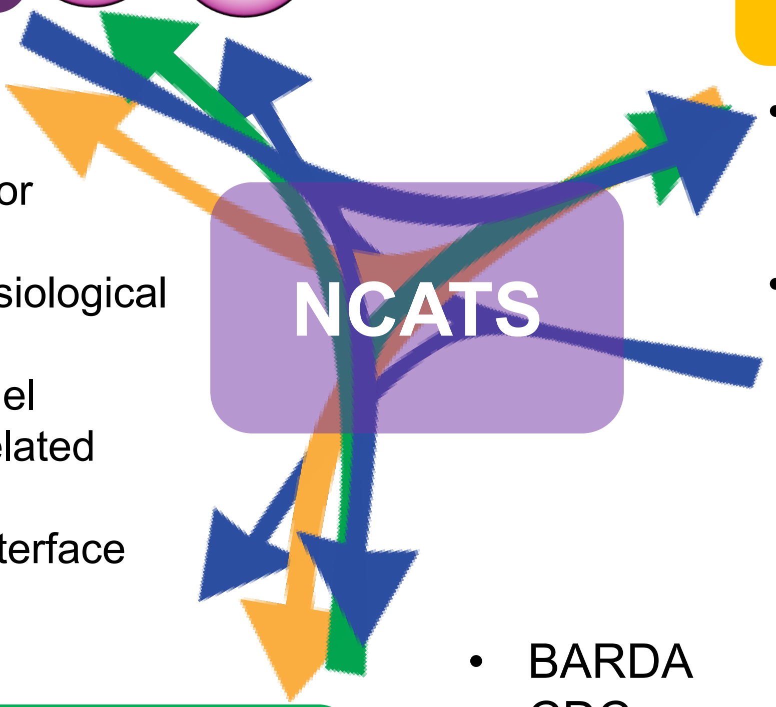
Growing Partnerships and Investments in MPS beyond NCATS

Other NIH ICs

NCI, ORWH, NHLBI, NIDCR, NINDS, NIBIB, NIEHS, NIAMS, NIDDK, NICHD, OD

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



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
- CDC
- Translational Research Institute for Space Health
- NASA Human Research Program
- EPA
- USGS

Other Countries

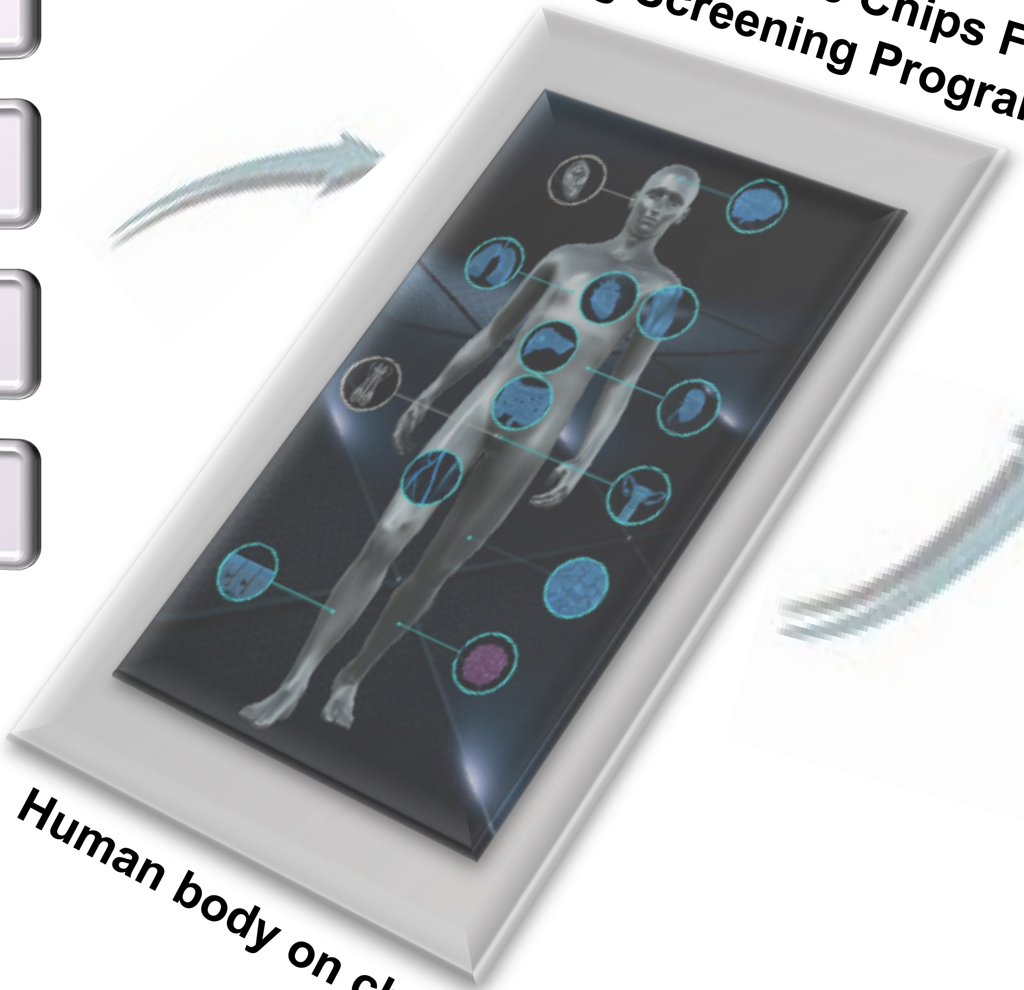
Asia, Europe, Australia

Summary and Future Directions

Partnerships with NCATS

Other NIH Institutes and Centers	• NHLBI, NIAMS, NIBIB, NICHD, NCI, NIDSCR, NIDDK, NIEHS, NINDS, ORWH
Government agencies	• DARPA, FDA • NASA
Pharma	• AstraZeneca • GSK • Pfizer
Non-profits	• IQ MPS Affiliate • CASIS/ISS NL

NCATS Tissue Chips For Drug Screening Program



Human body on chip

- Predictive toxicology
- Disease models and efficacy studies
- Microgravity and space radiation effects
- Tools for clinical trials
- Personalized chips and precision medicine
- Microbiome
- Environmental toxins and contaminants
- Infectious agents
- Countermeasures

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Tissue Chips Consortium Partners – Lead: Danilo A. Tagle

Program Manager: **Lucie Low, Ph.D.**

Trans-NIH Microphysiological Systems Working Group

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- Steven Becker (NEI)
- Lisa Begg (OD)
- Bonnie Burgess-Beusse (NIDDK)
- Warren Casey (NIEHS)
- Preethi Chander (NIDCR)
- Ricardo Cibotti (NIAMS)
- Ki-Cha Flash (NCATS)
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- Daniel Gossett (NIDDK)
- Halonna Kelly (NIAID)
- Anthony Kirilusha (NIAMS)
- Lillian Kuo (NIAID)
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- Jennie Larkin (NIDDK)
- Sara Lin (NHLBI)
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- Mary Perry (OD)
- Leslie Reinlib (NIEHS)
- Dobrila Rudnicki (NCATS)
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- Seila Selimovic (NIBIB)
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- Lillian Shum (NIDCR)
- Kentner Singleton (NIAID)
- Christine Sizemore (NIAID)
- Brian Sorg (NCI)
- Denise Stredrick (OD)
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- Katerina Tsilou (NICHD)
- Dawn Walker (NCATS)
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- David Weinberg (NICHD)
- Vicky Whittemore (NINDS)
- Bradley Wise (NIA)
- Da-Yu Wu (NIDA)
- Nastaran Zahir (NCI)

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  - Paul Brown, Ph.D., CDER
  - Tracy Chen, Ph.D., DABT, OC
  - Karen Davis-Bruno, Ph.D., CDER
  - Suzanne Fitzpatrick, Ph.D., CFSAN
  - Timothy McGovern, Ph.D., CDER
  - Donna Mendrick, Ph.D., NCTR
  - Thomas Papoian, Ph.D., DABT, CDER
  - Alexandre Ribeiro, Ph.D., CBER
  - James Weaver, Ph.D., CDER
- **ISS-NL (CASIS)**
  - Michael Roberts, Ph.D.
  - Marc Giulianotti, Ph.D.
  - Bill McLamb, Ph.D.
  - Melissa Rhodes, Ph.D.
- **IQ MPS Affiliate**
  - IQ MPS Executive Committee (EC): IQ MPS Chair (Will Proctor, Genentech), Vice Chair (Monicah Otieno, Janssen) and Vice Chair-Elect (Terry van Vleet, AbbVie); IQ-NCATS engagement workstream POC (Jason Ekert GSK)
  - Szczepan Baran, Ph.D., Novartis
  - Ananthsrinivas Chakilam, Ph.D., Vertex
  - Yvonne Dragan, Ph.D., Takeda
  - David Duignan, Ph.D., AbbVie
  - Jeetendra Eswaraka, DVM, Ph.D., Amgen
  - Jason Ekert, Ph.D., GSK
  - Lorna Ewart, Ph.D., AstraZeneca
  - Jinping Gan, Ph.D., BMS
  - Peggy Guzzie-Peck, Ph.D., DABT, J & J
  - Claire Jeong, Ph.D., GSK
  - Douglas Keller, Ph.D., Sanofi
  - Jonathan Phillips; Ph.D., Boehringer Ingelheim
  - William Proctor, Ph.D., DABT, Genentech
  - Terry Van Vleet, Ph.D., DABT, AbbVie
  - Rahda Sura, Ph.D., AbbVie
  - Matthew Wagoner, Ph.D., Takeda
  - David Watson, Ph.D., Eli Lilly
  - Yvonne Will, Ph.D., Pfizer

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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!

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