NCATS

COLLABORATE. INNOVATE. ACCELERATE.

NCATS Microphysiological Systems (MPS) aka Tissue Chips for Drug Screening Program

ICCVAM Communities of Practice: Evolution of Complex In Vitro Models
July 21, 2025

Danilo A.Tagle, PhD, MS
Director, Office of Special Initiatives
National Center for Advancing Translational Sciences

No Conflicts of Interest

National Center for Advancing Translational Sciences

The Public Health Challenge

10,000

Diseases

and only

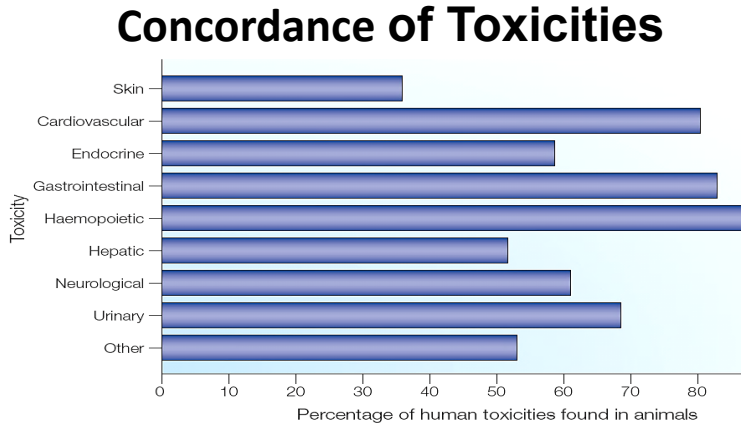
5%

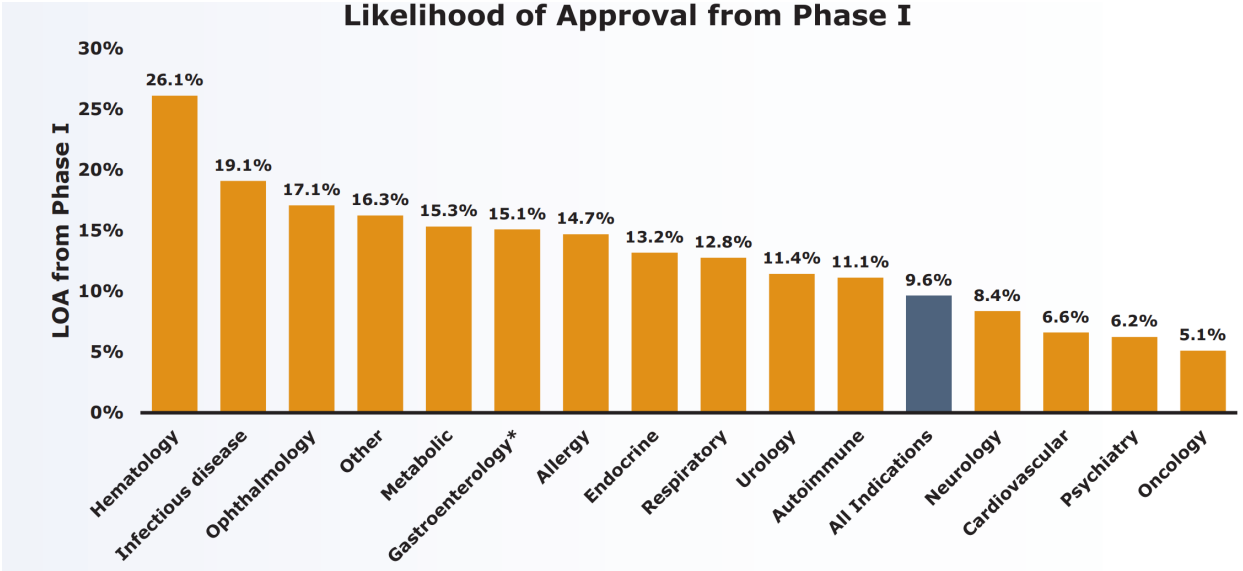
Have Treatments or Cures

Time from early development to the medicine cabinet takes 10-15 years at a cost of $2.6 billion per drug ($6.16 billion in the past 20 years)

9 out of 10

HIGH ATTRITION RATE -
Promising therapeutic candidates fail in clinical trials





Need for human-relevant model systems that can reliably predict health outcomes that can vary due to sex, age, genetics, population variability and interindividual differences

Arrowsmith and Miller, Nature Reviews Drug Discovery, 2013,, 12: 569 ;Cook et al., Nature Reviews Drug Discovery, 2014,13,: 19 ; Wong et al. Biostatistics, 2019, 20: 273-286

National Center for Advancing Translational Sciences

Video: NCATS Tissue Chip for Drug Screening Program

Video originally placed here can be viewed at
https://www.youtube.com/watch?v=4FWmstqT_gk
6 minutes into video

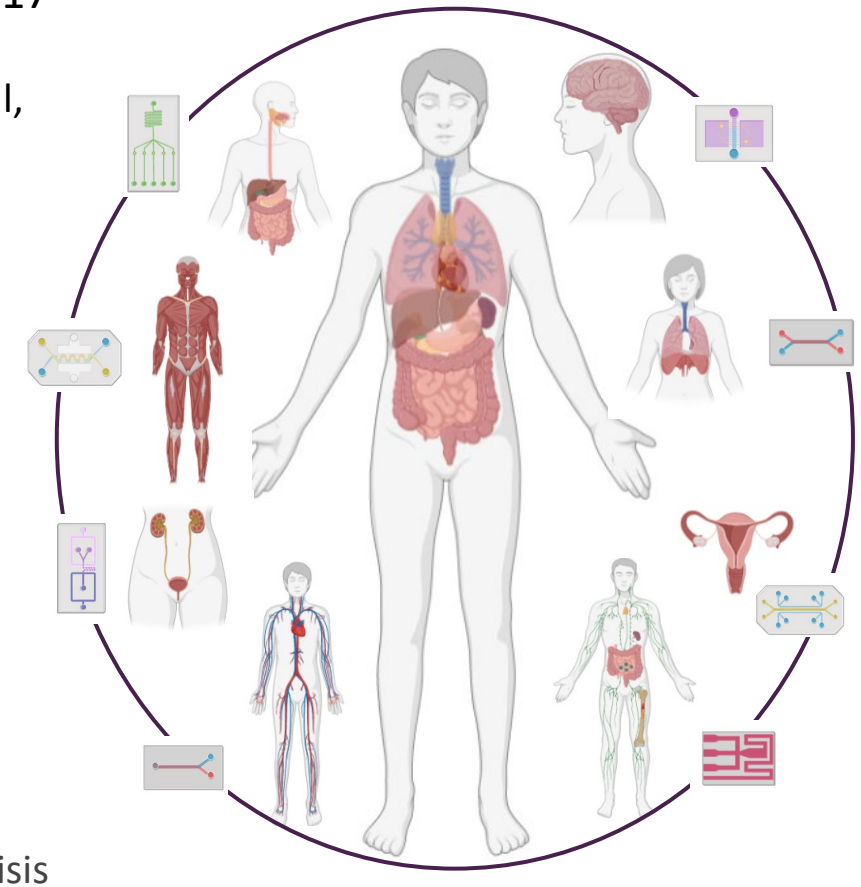
NIH Tissue Chips Program At A Glance

Safety Pharmacology 2012-2017

- Human relevant models especially for hepatic, neuronal, renal, CV, GI and immune toxicities
- Assessing toxicity where no physiologically and pharmacologically relevant models are available

Disease Models and Efficacy 2017-2023

- Capture the pathophysiology, mutation spectrum and phenotypic diversity of human diseases and conditions
- Response to National Health Emergencies, such as opioid crisis **(HEAL) and SARS-Cov2 pandemic**
- Accelerated aging through **Tissue Chips in Space** program
- Alzheimer's disease and related dementias (NINDS)
- Type 2 diabetes (NIDDK)



Partners

- 18 ICs at NIH
- FDA, NASA, DARPA, BARDA, DTRA, VA, EPA
- IQ MPS Affiliate (26 pharma companies)

Clinical Trials on Chips and Precision Medicine 2021-2025

- Inform clinical trial design and execution
- Establish recruitment criteria
- Patient stratification
- Develop clinically relevant surrogate biomarkers
- Represent population and patient diversity

Building Confidence 2016-2022

- Tissue Chips Testing Centers
- MPS Database

Building Community 2022-2024

- MPS World Summit
- International MPS Society

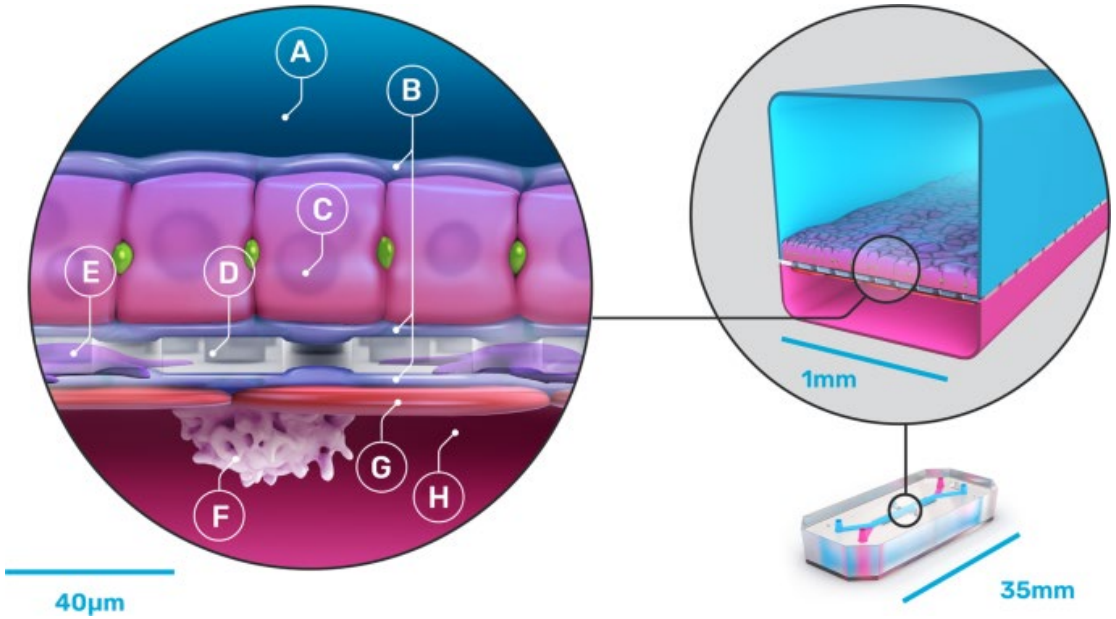
Regulatory Acceptance 2024-2028

- Botulinum Toxin Potency Assay
- Translational Centers for MPS

National Center for Advancing Translational Sciences

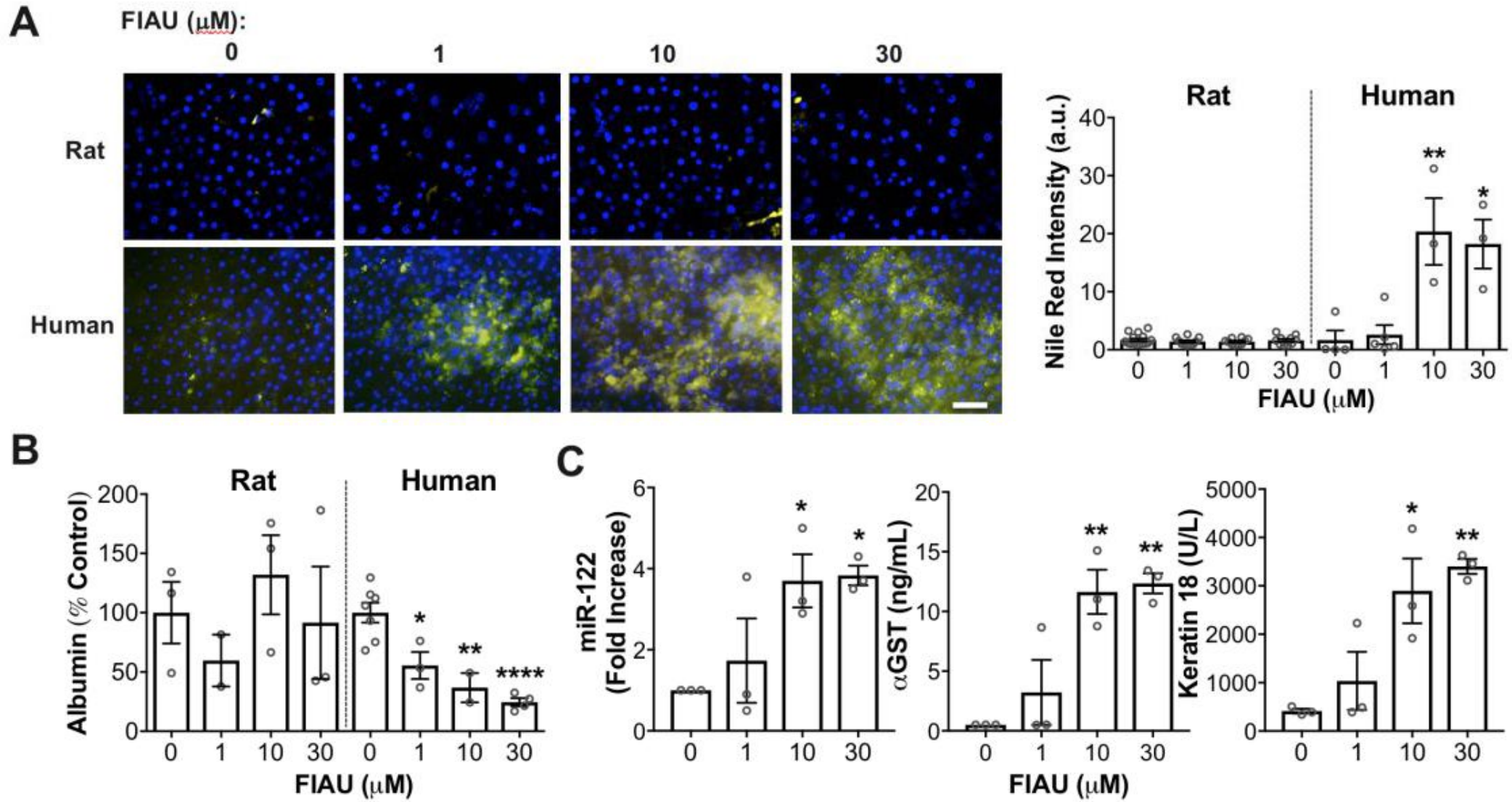
Are Tissue Chips Better Predictors of Human Physiological Response?

- Liver is responsible for concentrating and metabolizing a majority of medications
- Drug-induced liver injury (DILI) is the most common cause of acute liver failure (15-20 per 100,000)
- Adverse drug reactions are an important cause of liver injury that may require discontinuation of the drug, hospitalization, or even liver transplantation



- A - parenchymal channel
- B - extracellular matrix
- C - human hepatocytes
- D - porous PDMS membrane
- E – stellate cells
- F - Kupffer cells
- G - endothelial cells
- H - vascular channel

Differences in Steatosis (Fat Deposits) in Rat and Human Liver Chips following Fialuridine (FIAU) Treatment



Science Translational Medicine, 11: 2019

Follow up blinded study on liver chip to predict DILI

- A group of 22 reference compounds which were subsequently determined to be hepatotoxic
- Was advanced to human use based on previous preclinical data but was withdrawn due to toxicities which collectively are responsible for more than 200 patient deaths and 10 liver transplants
- Controlled with 5 non-hepatotoxic compounds
- Human liver chips showed an 87% sensitivity and 100% specificity in predicting drug toxicity, far outperforming liver spheroids (a common preclinical model) which showed a sensitivity of only 47%.

Nature Commun Med 2022: 2; 154- 170.

https://doi.org/10.1038/s43856-022-00209-1 OPEN

Performance assessment and economic analysis of a human Liver-Chip for predictive toxicology

Lorna Ewart[1✉], Athanasia Apostolou[1], Skyler A. Briggs[1], Christopher V. Carman[1], Jake T. Chaff[1], Anthony R. Heng[1], Sushma Jadalannagari[1], Jeshina Janardhanan[1], Kyung-Jin Jang[1], Sannidhi R. Joshipura[1], Mahika M. Kadam[1], Marianne Kanellias[1], Ville J. Kujala[1], Gauri Kulkarni[1], Christopher Y. Le[1], Carolina Lucchesi[1], Dimitris V. Manatakis[1], Kairav K. Maniar[1], Meaghan E. Quinn[1], Joseph S. Ravan[1], Ann Catherine Rizos[1], John F. K. Sauld[1], Josiah D. Sliz[1], William Tien-Street[1], Dennis Ramos Trinidad[1], James Velez[1], Max Wendell[1], Onyi Irrechukwu[2], Prathap Kumar Mahalingaiah[3], Donald E. Ingber[4,5,6], Jack W. Scannell[7] & Daniel Levner[1]

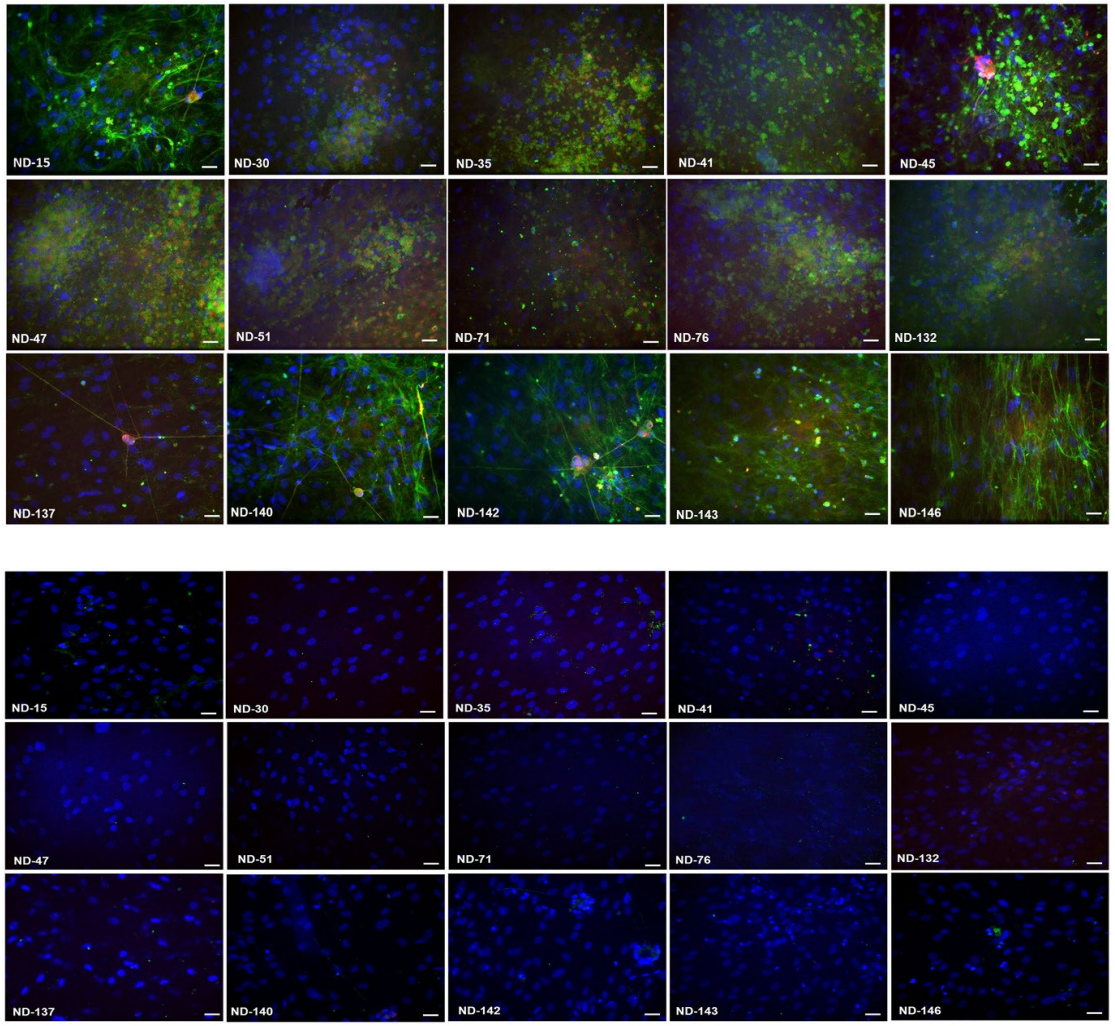
Table 1 Small-molecule drugs used in the Liver-Chip evaluation.

Drug	IQ MPS list	Tested in spheroid	Spheroid false negative	Garside DILI rank
Ambrisentan	Yes, matched with Sitaxsentan	Yes	No	5
Asunaprevir	Yes, no matched pair	No	No	2
Benoxaprofen	No	Yes	Yes	1
Beta-Estradiol	No	Yes	Yes	3
Buspirone	Yes, matched with Nefazodone	Yes	No	4
Chlorpheniramine	No	Yes	Yes	3
Clozapine	Yes, matched with Olanzapine	Yes	No	2
Diclofenac	Yes, no matched pair	Yes	No	2
Entacapone	Yes, matched with Tolcapone	Yes	No	4
Fialuridine	Yes, matched with FIRU	Yes	No	1
FIRU	Yes, matched with Fialuridine	No	No	5
Labetalol	No	Yes	Yes	1
Levofloxacin	Yes, matched with Trovafloxacin	Yes	Yes	2
Lomitapide	No, Mipomersen substitute	No	No	3
Nefazodone	Yes, matched with Buspirone	Yes	No	1
	Yes, matched with Clozapine	No	No	5
Pioglitazone	Yes, matched with Troglitazone	Yes	Yes	3
Simvastatin	No	Yes	Yes	2
Sitaxsentan	Yes, matched with Ambrisentan	Yes	No	1
Stavudine	No	Yes	Yes	1
Tacrine	No	Yes	Yes	2
Telithromycin	Yes, no matched pair	No	No	1
Tolcapone	Yes, matched with Entacapone	Yes	No	1
Troglitazone	Yes, matched with Pioglitazone	Yes	No	1
Trovafloxacin	Yes, matched with Levofloxacin	Yes	No	1
Ximelagatran	No	Yes	Yes	1
Zileuton	Yes, no matched pair	Yes	Yes	2

The 27 small-molecule drugs are listed according to the IQ MPS affiliate classification and their ranking in the Garside DILI severity category, where 1 corresponds to drugs with severe clinical DILI and 5 to those with no DILI[31,50]. Structurally related toxic and non-toxic pairs are indicated as well using bold, italic text.

Efficacy Study: Tissue Chips Model of Rare Autoimmune Demyelinating Neuropathies

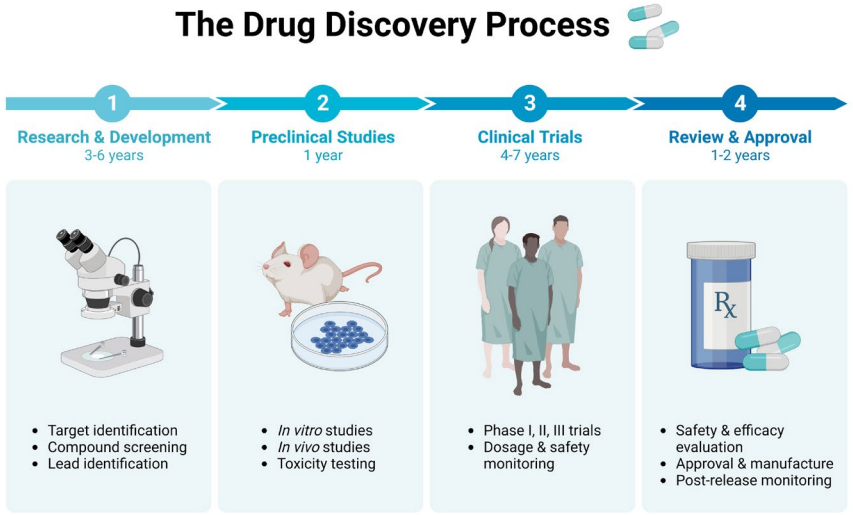
- Chronic autoimmune demyelinating neuropathies are a group of rare neuromuscular disorders including **chronic inflammatory demyelinating polyneuropathy (CIDP)** and **multifocal motor neuropathy (MMN)**
- Tissue chip model consisting of co-culture of human primary Schwann cells (SC) and induced pluripotent stem cell-derived motoneurons (MNs)
- CIDP and MMN patient sera contains anti-GM1 IgM and IgG antibodies which is sufficient to activate the classical complement pathway in SC-MN tissue chips, resulting in detection of C3b and C5b-9
- Efficacy of **TNT005**, a monoclonal antibody that **inhibits C1s protease** rescued the serum-induced complement deposition and functional deficits while treatment with an isotype control antibody has no rescue effect
- **Efficacy data included in an investigational new drug application**



Advanced Therapeutics, Volume: 5, Issue: 6,
First published: 05 April 2022, DOI: (10.1002/adtp.202200030)

National Center for Advancing Translational Sciences

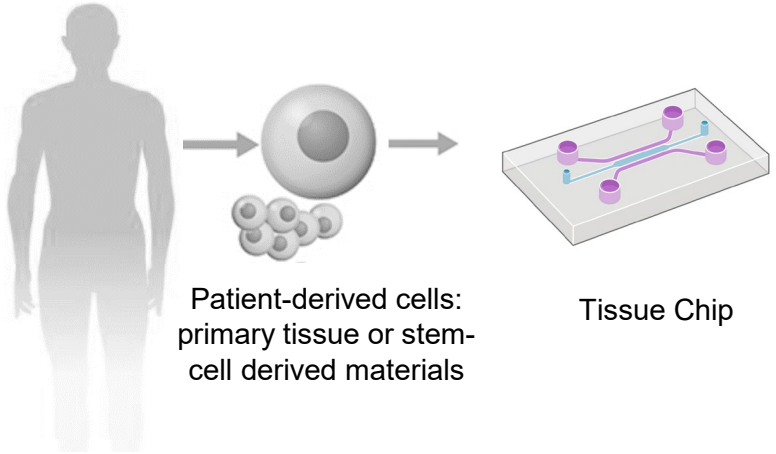
Clinical Trials" on a Chip: Tissue Chips to Inform Clinical Trial Design and Implementation in Precision Medicine



Goal of tissue chips → Inform clinical trial design and execution

1. **Establish recruitment criteria**
2. **Patient stratification**
3. **Develop clinically relevant biomarkers and reliable clinical trial endpoints**

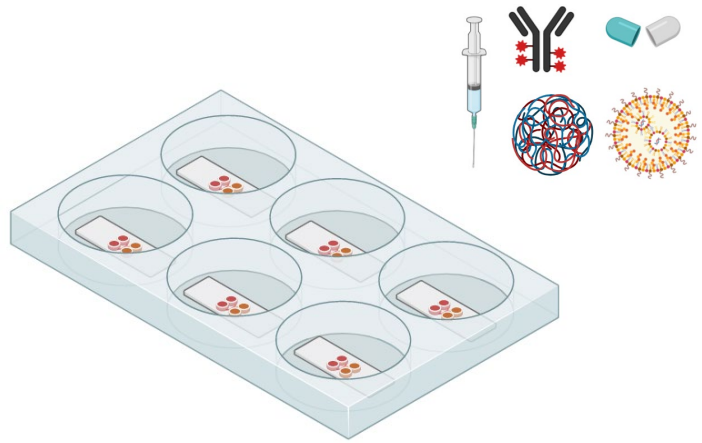
Phase I: Development and validation of disease models containing patient-derived cells



Patient-derived cells: primary tissue or stem-cell derived materials

Tissue Chip

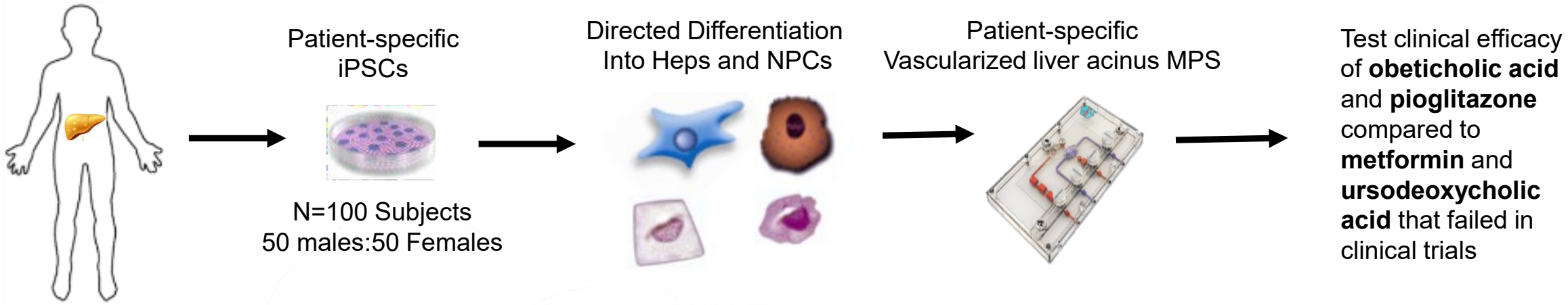
Phase II: Test potential drugs for efficacy and safety assessments in clinical trials



Created with BioRender

Patient-Specific Drug Response in Non-Alcoholic Fatty Liver Disease (NAFLD)

- NAFLD is progressively becoming the most common chronic liver condition worldwide due to close association with obesity and diabetes mellitus
- NAFLD encompasses a spectrum of liver diseases ranging from simple hepatic steatosis (fatty liver) to steatohepatitis (NASH) to cirrhosis and hepatocellular carcinoma (HCC)
- Estimated global prevalence of NAFLD is 25% of the general population
- In the US, the Hispanic population have the highest NAFLD prevalence and poorer outcomes with males associated with a higher likelihood; linked to the frequency of a polymorphism in the PNPLA3 gene in the Hispanic population



Building Confidence Towards Technology Adoption: Tissue Chip Validation Framework

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

3) Industrial (2019…)

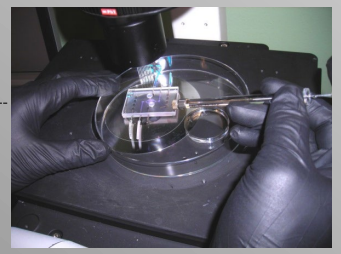
- Use by industry and regulatory agencies
- Proprietary set of compounds
- CRO-type environment

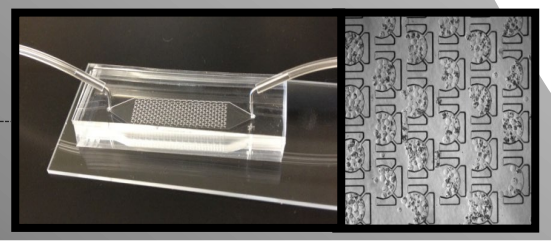
2) Analytical (2017…)

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

1) Physiological (2012…)

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





Path to Adoption and Commercialization

- **Javelin Biotech** (spin off from MIT)
  - CRO business model
- **TEX-VAL Consortium**
  - Play for pay model with academia, government and industry
- **EveAnalytics (formerly BioSystics Analytic)**
  - Quris AI

- **Tissue Chip Testing Centers:**
  - Massachusetts Institute of Technology
  - Texas A&M University
- **MPS Database:** https://mps.csb.pitt.edu/
  - University of Pittsburgh

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.*

National Center for Advancing Translational Sciences

Qualification of MPS as DDTs to Accelerate the Regulatory Acceptance of Innovative Drug Treatments

Who?

Key stakeholders: Patients, Pharma Companies, Regulators, Patient-Advocacy Organizations, Academics, Government Agencies

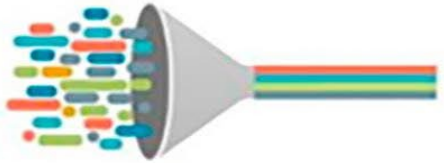
Why? / What?

- To understand disease progression rates and responses to treatments, as these can vary significantly across different patients
- Advance Drug Development Tools

How?

Integrate anonymized patient-level data from past clinical trials and longitudinal observational studies

Data standardization and integration



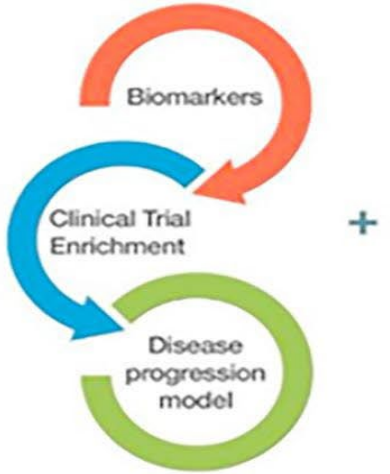
CDISC Data Standards

Development of models relating key covariates over time

IMPACT

- **Actionable data/models to inform optimal trial design**
- **Improved trial efficiency, and accelerated delivery of innovative treatments to the right patients**

Information from model



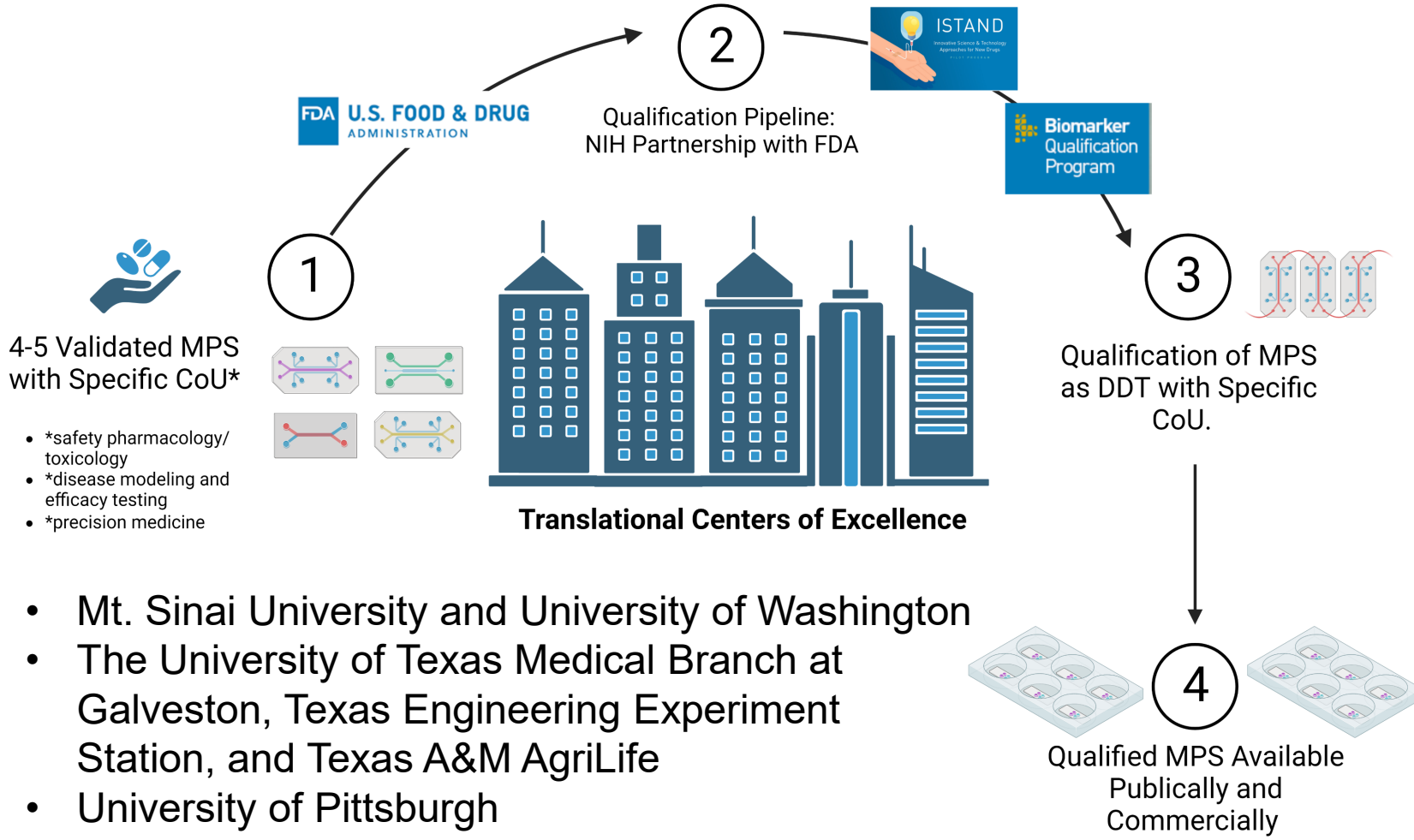
Regulatory agencies

Results in

National Center for Advancing Translational Sciences

Translational Centers for Microphysiological Systems (TraCe MPS)

- To accelerate the translational use of MPS in drug development through **regulatory acceptance and adoption for industrial use**
- Letter of Agreement between NCATS and FDA (Critical Path Institute)
- Qualifying MPS as DDT that are **fit-for-purpose for industry needs** and have **specific context of use (CoU) that will meet regulatory qualification**

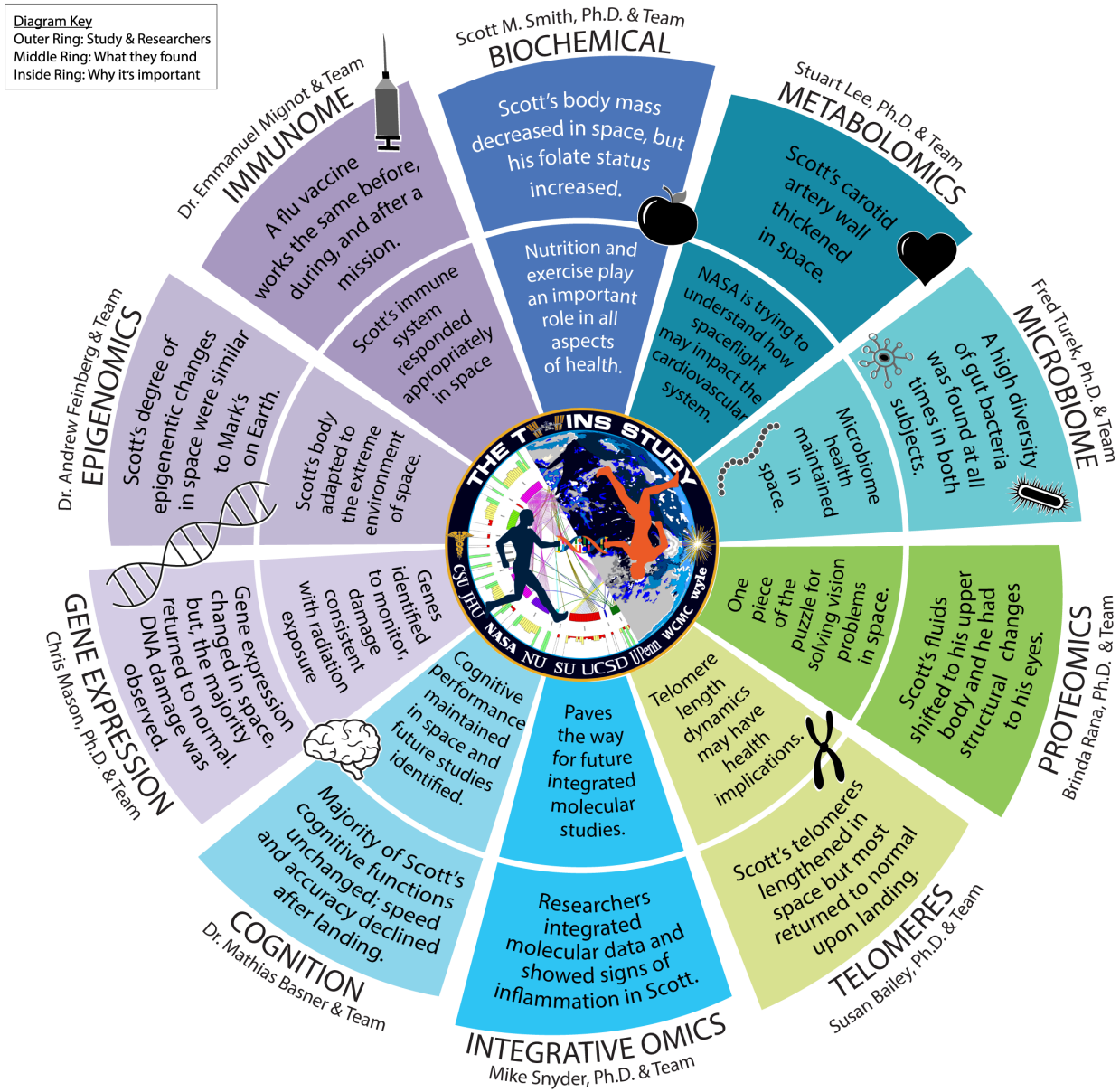


- Mt. Sinai University and University of Washington
- The University of Texas Medical Branch at Galveston, Texas Engineering Experiment Station, and Texas A&M AgriLife
- University of Pittsburgh
- University of Rochester and Duke University

National Center for Advancing Translational Sciences

NASA
Twins Study in Space

Photo and image courtesy of NASA



NASA's Twins Study revealed interesting and assuring data on how a human adapted to space.

The Twins Study team, which included several NIH-funded researchers, detailed many thousands of differences between the Kelley twins at the molecular, cellular, and physiological levels during the 340-day observation period.

National Center for Advancing Translational Sciences

Tissue Chips in Space Projects

- SpaceX 16: December 5, 2018
  - Immunosenescence
- SpaceX 17: May 4, 2019
  - Lung infection/bone marrow; kidney stone formation; osteoarthritis; BBB permeability
- SpaceX 20: March 6, 2020
  - Cardiomyopathy; gut inflammation
- SpaceX 21: Dec 5, 2020
  - Cardiomyopathy; osteoarthritis; muscle wasting
- SpaceX 22: June 3, 2021
  - Kidney stone formation
- SpaceX 24 December 21, 2021
  - Blood-brain barrier
- SpaceX 25 July 15, 2022
  - Immunosenescence; muscle wasting
- SpaceX 26 November 22, 2022
  - Muscle wasting
- SpaceX 27 March 14, 2023
  - Cardiomyopathy

Photo Credit: NASA


Photo Credit: NASA

Photo Credit: Dan Tagle

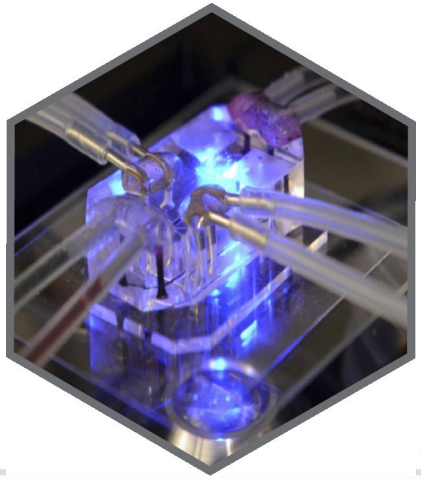
Video: Biomedical Research in Space

Video originally placed here can be viewed at
https://www.youtube.com/watch?v=4FWmstqT_gk
25 minutes into video

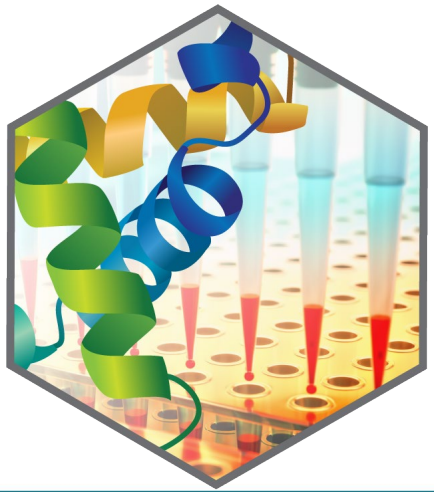
New Program: Compliment-ARIE – Integrate MPS with in silico, in chemico and other NAMs (1)

Digital Twin Models
Digital Twins for treatment of cancers and neuropsychiatric diseases, host-gut microbiome studies

In Silico Models
In silico and ML/AI models for neurodegenerative disease, wound healing, learning/behavior, SARS-CoV-2 propagation, many other diseases



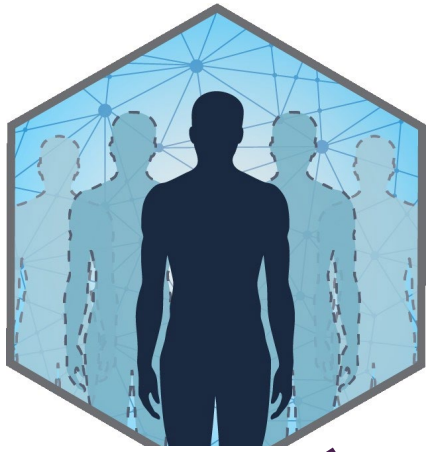
Complex In Vitro Systems
MPS and 3D organoid models for multiple tissues, organs and disease conditions



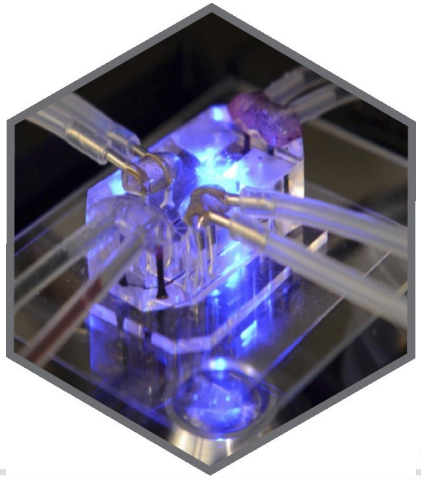
In Chemico Screening
Tox21 high-throughput studies, biochemical assays for skin irritation, ocular toxicity

New Program: Compliment-ARIE – Integrate MPS with in silico, in chemico and other NAMs (2)

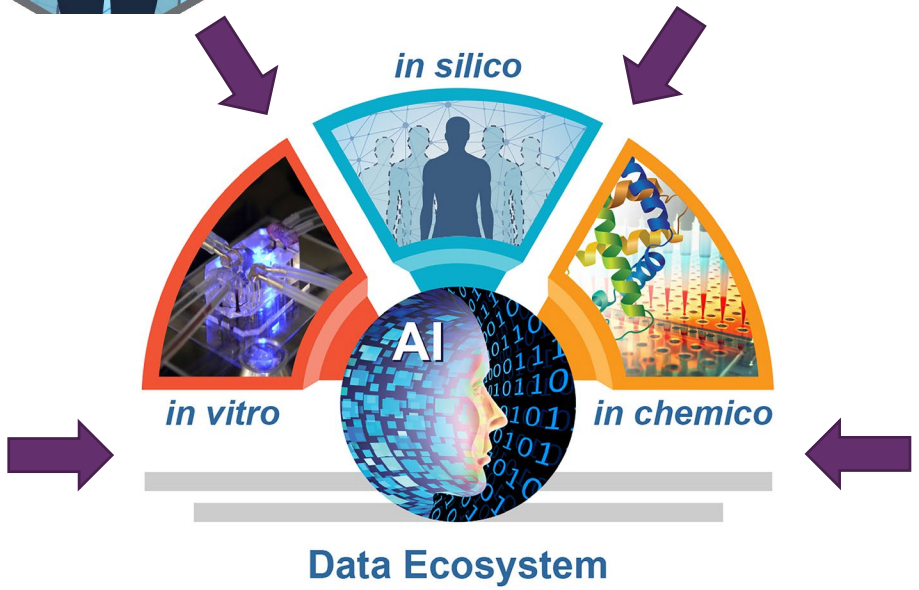
Digital Twin Models
Digital Twins for treatment of cancers and neuropsychiatric diseases, host-gut microbiome studies



In Silico Models
In silico and ML/AI models for neurodegenerative disease, wound healing, learning/behavior, SARS-CoV-2 propagation, many other diseases



Complex In
MPS and 3D
for multiple t
and disease



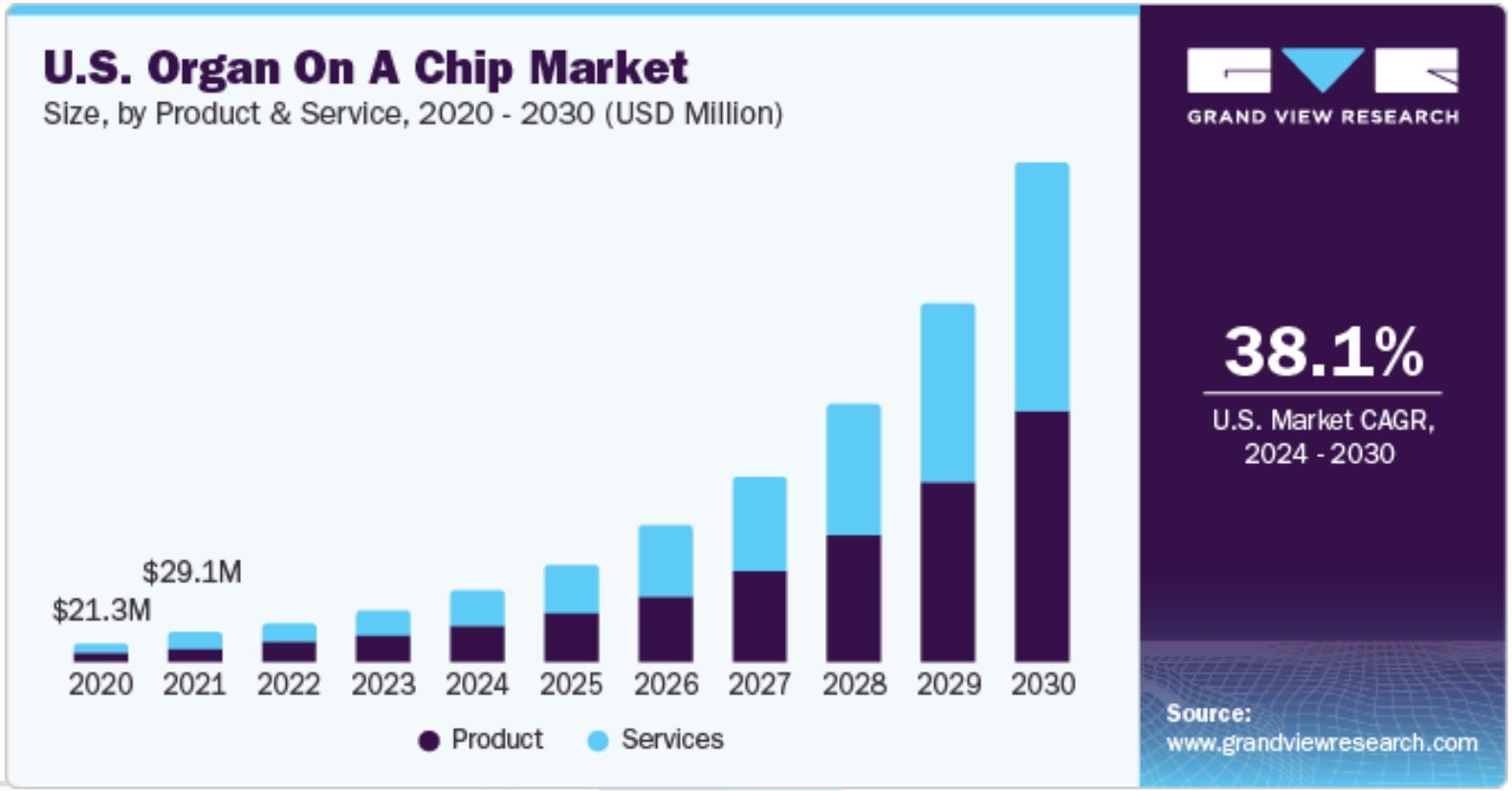
In Chemico Screening
Tox21 high-throughput studies, biochemical assays for skin irritation, ocular toxicity

Compliment-ARIE https://commonfund.nih.gov/complementarie

National Center for Advancing Translational Sciences

Global Market for Tissue Chips

- Global for tissue chips market was valued at USD $117.1 million in 2020
- Projected to reach > $1.6 billion by 2030, growing at a CAGR of 35.1% from 2024 to 2030



Recent Announcements on MPS & other NAMs

FDA NEWS RELEASE

FDA Announces Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs

For Immediate Release: April 10, 2025

Today, the U.S. Food and Drug Administration is taking a groundbreaking step to advance public health by replacing animal testing in the development of monoclonal antibody therapies and other drugs with more effective, human-relevant methods. The new approach is designed to improve drug safety and accelerate the evaluation process, while reducing animal experimentation, lowering research and development (R&D) costs, and ultimately, drug prices.

Zeldin to pursue new ban on animal testing at EPA

Administrator Lee Zeldin plans to revive a ban on animal testing at the Environmental Protection Agency, The Washington Times has learned.

The EPA had pursued a phaseout of animal testing during the first Trump administration, but the Biden administration erased the deadlines, effectively neutering the policy.

Now, Mr. Zeldin plans to put it back in place.

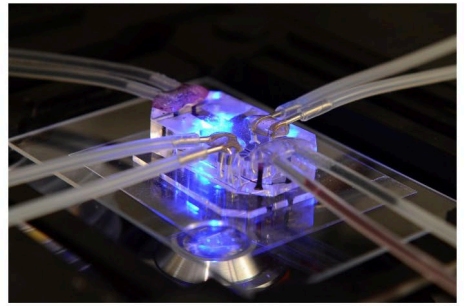
The Washington Times - Thursday, April 10, 2025

Tuesday, April 29, 2025

NIH to prioritize human-based research technologies

New initiative aims to reduce use of animals in NIH-funded research.

The National Institutes of Health (NIH) is adopting a new initiative to expand innovative, human-based science while reducing animal use in research. Developing and using cutting-edge alternative nonanimal research models aligns with the U.S. Food and Drug Administration's (FDA) recent initiative to reduce testing in animals. While traditional animal models continue to be vital to advancing scientific knowledge, using new and emerging technologies can offer unique strengths that, when utilized correctly or in combination, can expand the toolbox for researchers to answer previously difficult or unanswerable biomedical research questions.



NIH, FDA Announce New Joint Venture in Nutrition

The Food and Drug Administration (FDA) and NIH have announced a new research collaboration.

MPS for Chemical Risk Assessments in Food

NIH RECORD

June 6, 2025
Vol. LXXVII, No. 12

NIH National Center for Advancing Translational Sciences

Join us for the 5th MPS WS

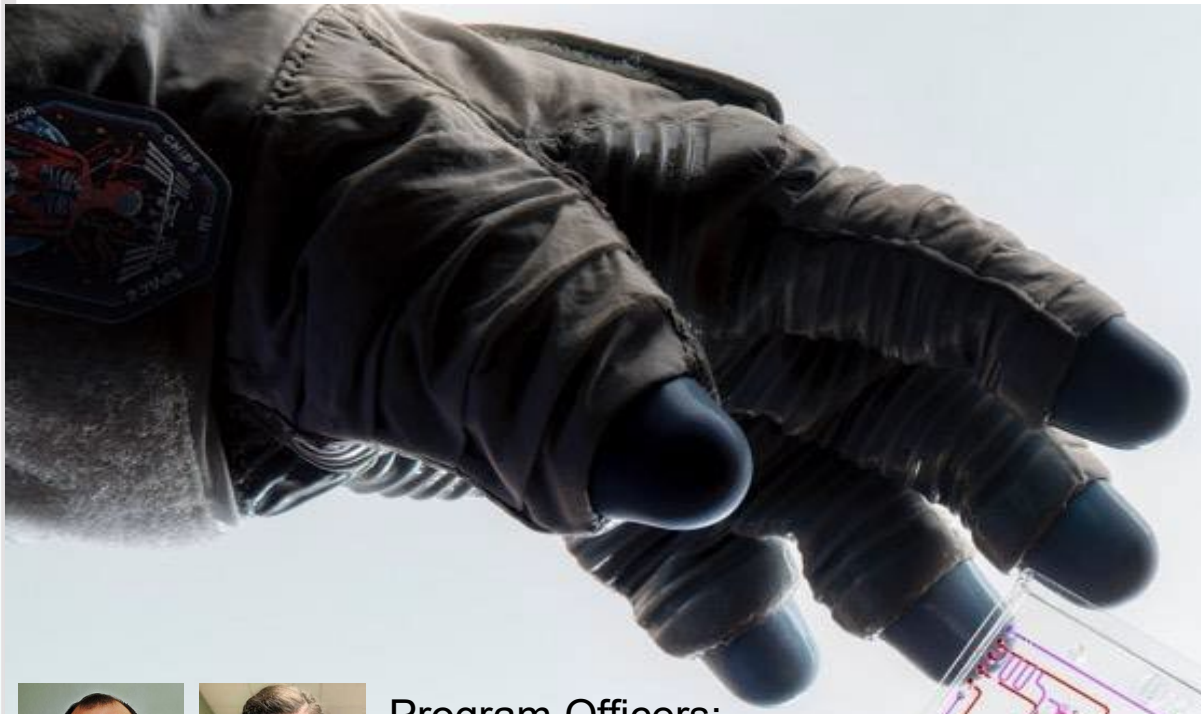
In Washington, D.C.

At the Walter E. Washington Convention Center

May 26-29, 2026

2022 New Orleans, LA
2023 Berlin, Germany
2024 Seattle, WA
2025 Brussels, Belgium

National Center for Advancing Translational Sciences



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

Program Officers:
Passley Hargrove-Grimes
Dmitriy Krepkiy

Program Analyst:
Kris Sunderic

Trans-NIH MPS Working Group:
>55 Program Officers from NCATS, NCI, NHLBI, NIA, NIAID, NIAMS, NIBIB, NICHD, NIDA, NIDCR, NIDCD, NIDDK, NEI, NIEHS, NIMH, NINDS, ORWH/OD

National Center for Advancing Translational Sciences

NCATS
COLLABORATE. INNOVATE. ACCELERATE.

ISS NATIONAL LABORATORY

CASIS
Center for the Advancement of SCIENCE IN SPACE