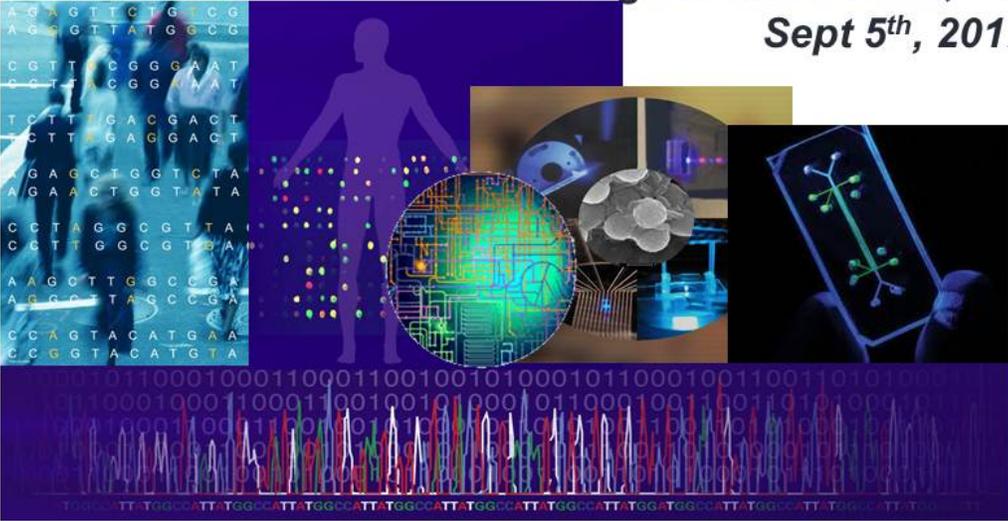


# NIH Microphysiological Systems Program

Margaret Sutherland, PhD

Sept 5<sup>th</sup>, 2012

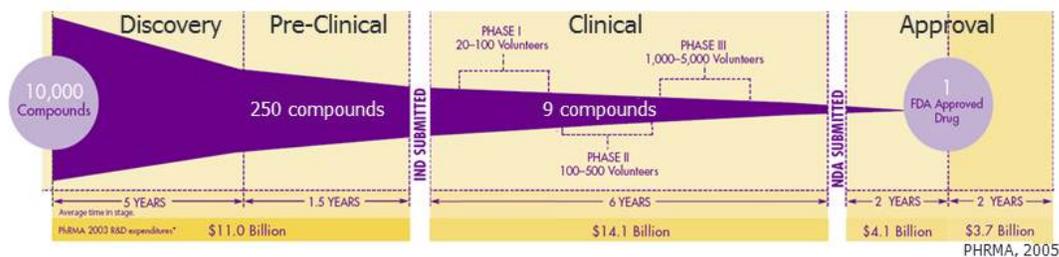


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# Advancing Regulatory Science

The current system for drug and vaccine development is characterized by high attrition of drug candidates at every stage:

- This adds significant time and expense to the overall enterprise.



One problem is that pre-clinical testing is slow and inaccurate:

- On average, requires 1.5 years.
- Correctly predicts human efficacy and toxicity only 11% of the time.
- In some cases, animal models are all we have.

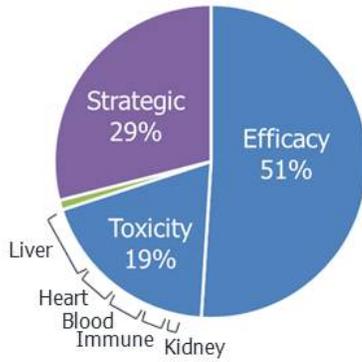


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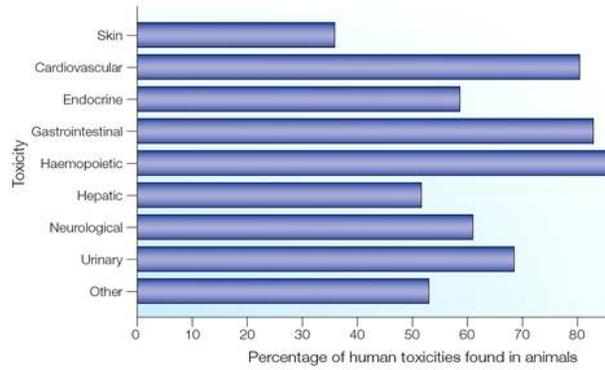
# Advancing Regulatory Science

## Drug Failure Modes

Why drugs fail human trials



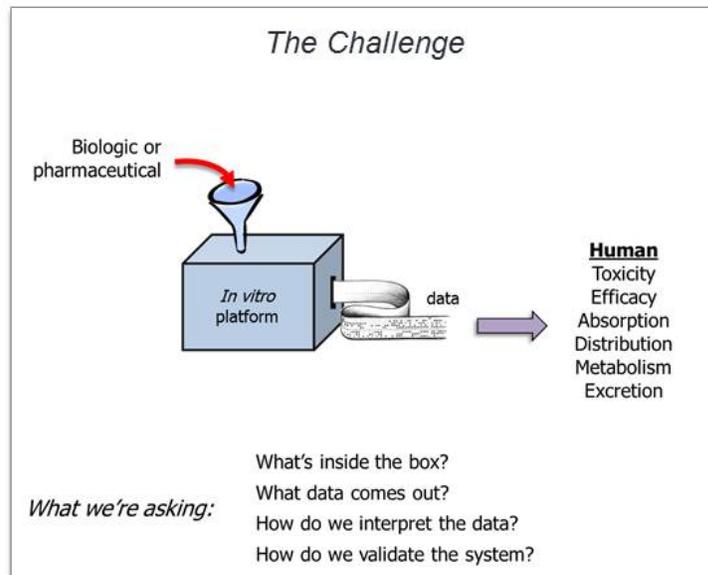
Human toxicities found in animals



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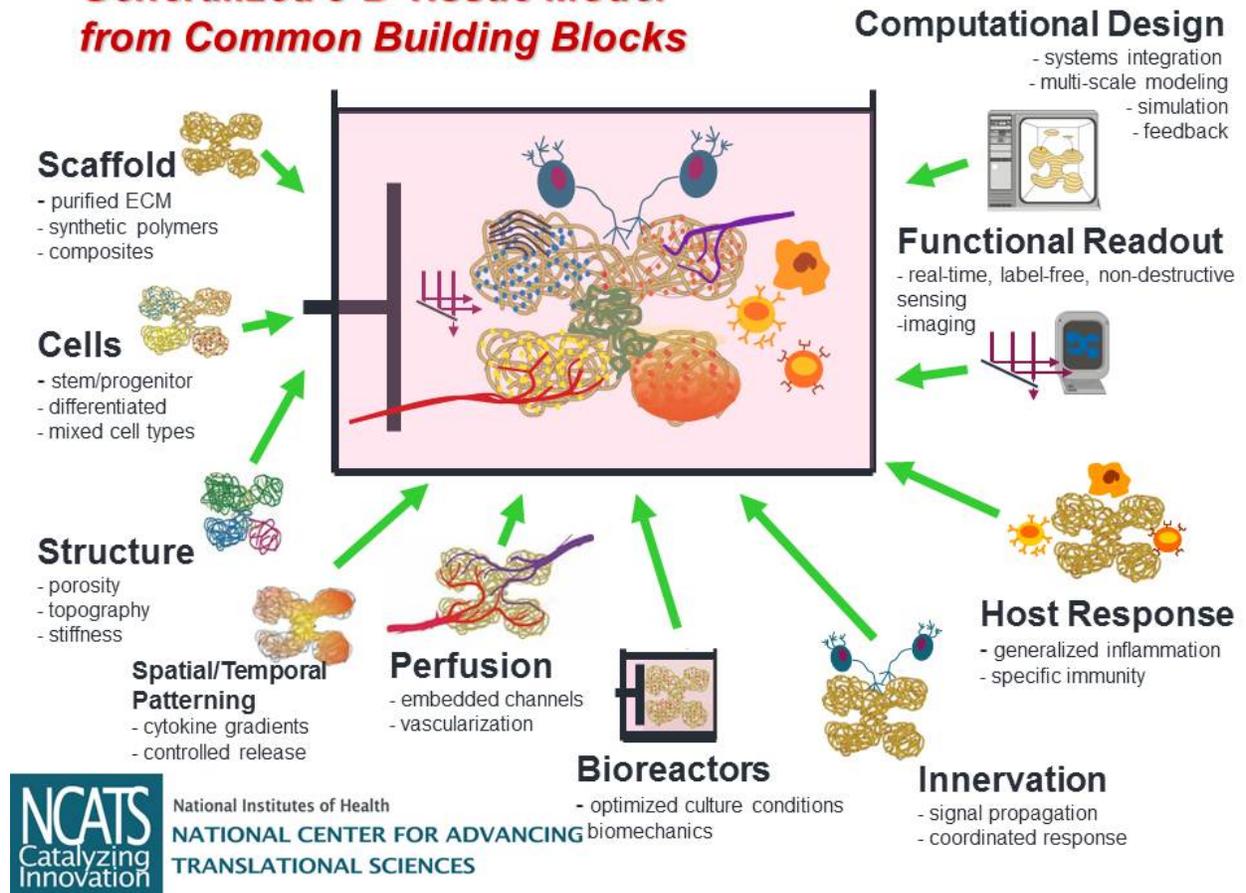
# Advancing Regulatory Science

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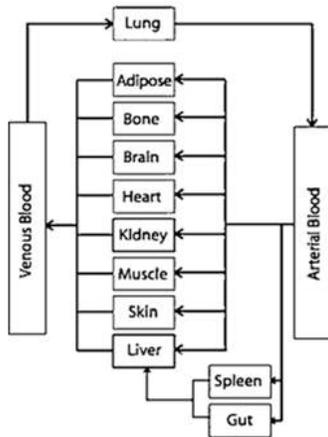
# Generalized 3-D Tissue Model from Common Building Blocks



# Advancing Regulatory Science



Goal: Develop an *in vitro* platform that uses human tissues to evaluate the efficacy and toxicity of medical countermeasures.



## Platform features

- All human physiological systems will be functionally represented by human tissue constructs:
  - Circulatory
  - Endocrine
  - Gastrointestinal
  - Immune
  - Integumentary
- Physiological interactions within and among human tissues.
- Modular, reconfigurable platform.
- Allows any data collection and analysis.
- Tissue viability for at least 4 weeks.



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# Advancing Regulatory Science

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- FDA-NIH Joint Leadership Council formed in 2010
- Issued RFA for Advancing Regulatory Science through Novel Research & Science-Based Technologies Program (\$7M, 4 awards):
  - Accelerating Drug & Device Evaluation through Innovative Clinical Trial Design
  - Replacement Ocular Battery
  - **Heart-Lung Micromachine for Safety and Efficacy Testing (Don Ingber)**
  - Characterization/Bioinformatics-modeling of Nanoparticle: Complement Interactions



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# DARPA-FDA-NIH Microphysiological Systems Program

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- Started in 2011 to support the development of human microsystems, or organ “chips,” to screen for safe and effective drugs swiftly and efficiently (before human testing)
- Collaboration through coordination of independent programs



Engineering platforms and biological proof-of-concept (DARPA-BAA-11-73: Microphysiological Systems)



Underlying biology/pathology and mechanistic understanding (RFA-RM-12-001 and RFA RM-11-022)



Advise on regulatory requirements, validation and qualification



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# DARPA and FDA Partnerships with NIH

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## Memorandum of Understanding (MOU)

- NIH and DARPA will independently manage and fund separate programs that will be highly coordinated across the two agencies
- FDA provides regulatory and toxicology expertise
- Program coordination
  - Sharing of scientific expertise, materials, resources
  - Jointly held semi-annual meetings
  - Development of a common set of validation compounds
  - Facilitation of collaborations



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# NIH Tissue Chip Team

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## *Division of Program Coordination, Planning, & Strategic Initiatives*

James Anderson & Elizabeth Wilder

## *Team Co-leads (National Institute of Neurological Disorders & Stroke)*

Margaret Sutherland & Danilo Tagle

## *15 NIH Institutes and Centers*

NIDA	NIGMS	NCI
NIDDK	NIAID	NIAMS
NIEHS	NCRR	NINR
NIDCD	NHLBI	NICHD
NIDCR	NEI	NIBIB



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## NIH Investment - \$70M/5 years

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*Goal: Develop microsystems with deeper complexity:*

- *Physiologically accurate*
- *Genetically diverse*
- *Pathologically representative*

**RFA RM-11-022:** Integrated Microphysiological Systems for Drug Efficacy and Toxicity Testing in Human Health and Disease (UH2/UH3)

**RFA RM-12-001:** Stem/Progenitor Cell-Derived Human Micro-organs and -tissues (U18)



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## Integrated Microphysiological Systems for Drug Efficacy and Toxicity Testing (UH2/UH3)

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- **GOAL:** Develop *in vitro* microphysiological systems representative of major organs/tissues in the human body, that will facilitate the assessment of biomarkers, bioavailability, efficacy, and toxicity of therapeutic agents prior to clinical trials.
- **SCOPE/ACTIVITIES:**
  - Multicellular architecture representative of the tissue of origin
  - Functional representation of normal human biology
  - Reproducible and viable operation under physiological conditions maintained up to 4 weeks in culture
  - Capacity for representation of normal and disease phenotypes,
  - Capacity for representation of population diversity
  - Amenable to high content screening for repeated dose efficacy testing, and for toxicology, and safety screening



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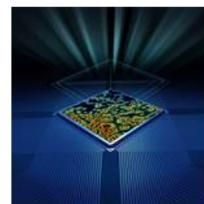
## Integrated Microphysiological Systems for Drug Efficacy and Toxicity Testing (UH2/UH3) *(cont.)*

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- **UH2/Phase I (2 years)**
  - Research undertaken in support of developing physiologically relevant microsystems
- **UH3/Phase II (3 years)**
  - Research directed towards integration of developed microsystem modules from the UH2 phase
  - Successful achievement of the defined milestones for the Phase I period necessary
  - Synergistic interactions among NIH and/or DARPA funded investigators
  - Availability of funds



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## Stem/Progenitor Cell-Derived Human Micro-organs and -tissues (U18)

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- **GOAL:** Develop stem- and progenitor-derived cell resources to seed circulatory, endocrine, gastrointestinal, immune, integumentary, musculoskeletal, nervous (including eye), reproductive, respiratory and urinary microsystems.
- **SCOPE/ACTIVITIES:**
  - Improvements in differentiation efficiencies towards cell-type diversity, genetic complexity, population diversity, and disease modeling
  - Development of 3D culturing approaches to enhance cellular microenvironments



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# Additional Requirements

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- Intellectual Property (IP) Management Plan
- Resource Sharing Plan
- Milestones Funding Plan
- Additional performance requirements:
  - Participate in coordinated NIH and DARPA program, e.g. implement guidelines and procedures developed by the NIH Scientific Steering Committee
  - Participate in bi-annual workshops and quarterly conference calls with the NIH



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## UH2/UH3 Award Recipients (10)

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- **Cornell University:** Microphysiological systems and low-cost microfluidic platform with analytics; PIs: Michael L. Shuler, Cornell University, James Hickman, University of Central Florida
- **Duke University:** Circulatory system and integrated muscle tissue for drug and tissue toxicity; PI: George Truskey
- **Harvard University:** Human cardio-pulmonary system on a chip; PI: Kevin Parker
- **Massachusetts Institute of Technology:** All-human microphysical model of metastasis and therapy; PI: Linda Griffith
- **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; PI: James A. Thomson
- **University of California-Berkeley:** Disease-specific integrated microphysiological human tissue models; PIs: Kevin Healy, Luke Lee
- **University of California-Irvine:** An integrated in vitro model of perfused tumor and cardiac tissue; PI: Steven George
- **University of Pittsburgh:** A 3-D biomimetic liver sinusoid construct for predicting physiology and toxicity; PIs: Lansing Taylor, University of Pittsburgh, Martin Yarmush, Rutgers University
- **University of Washington:** A tissue-engineered human kidney microphysiological system; PI: Jonathan Himmelfarb.
- **Vanderbilt University:** Neurovascular unit on a chip: Chemical communication, drug and toxin responses; PIs: John Wikswo, Vanderbilt University, Damir Janigro, Cleveland Clinic, Donna Webb, Vanderbilt University, Kevin Niswender, Vanderbilt University



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## U18 Awards

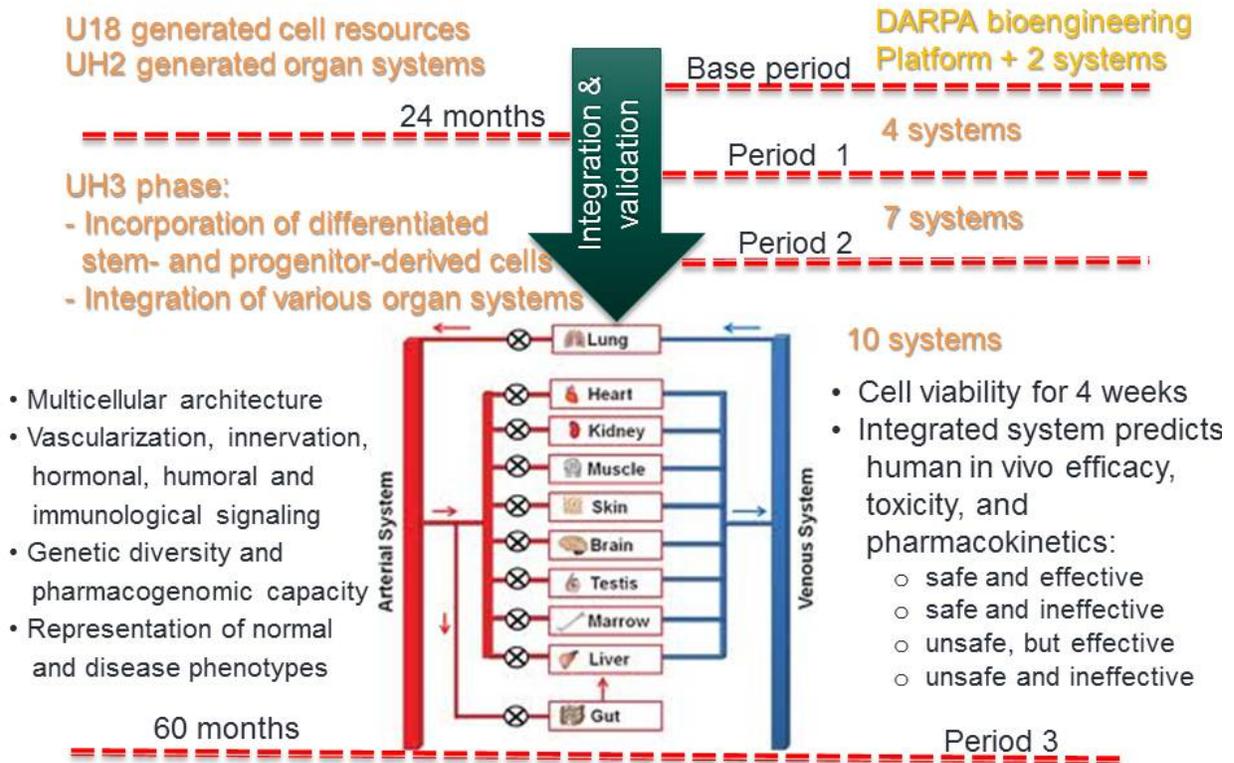
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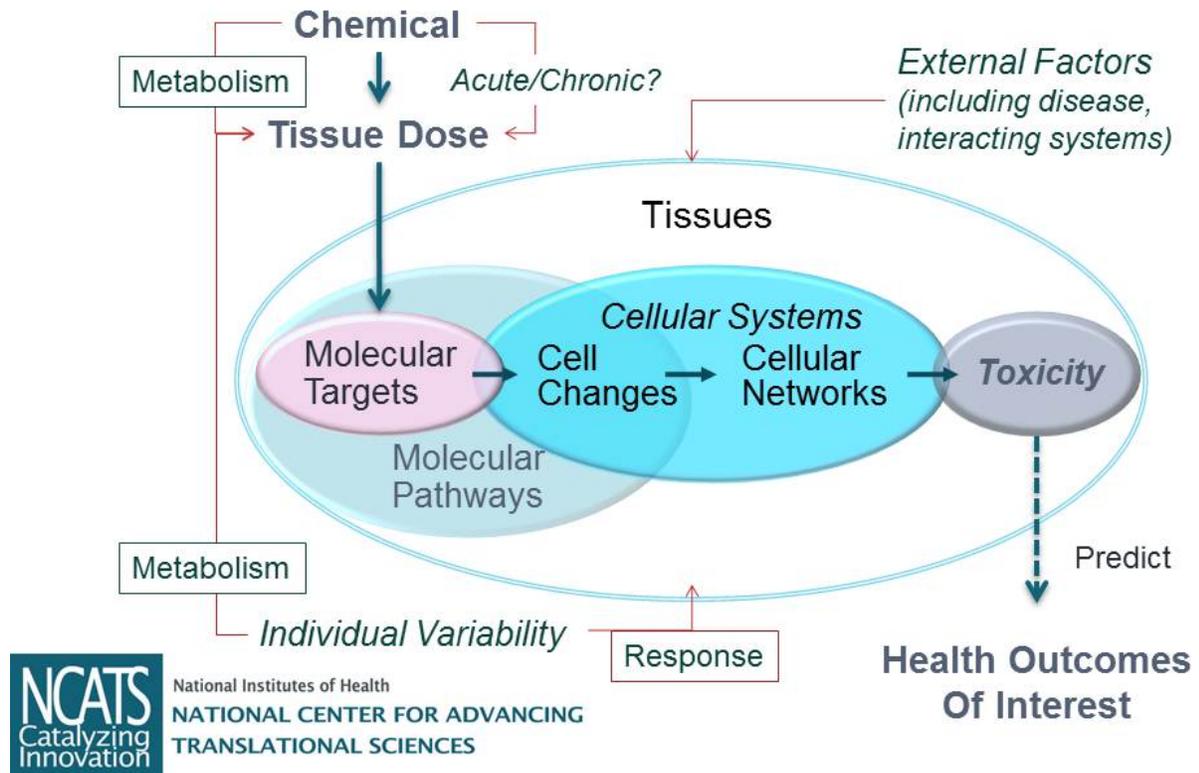
- **Cincinnati Children's Hospital Medical Center:** Generating human intestinal organoids with an enteric nervous system; PI: James Wells
- **Columbia University Health Sciences:** Modeling complex disease using induced pluripotent stem cell-derived skin constructs; PI: Angela Christiano
- **Johns Hopkins University:** Human intestinal organoids: Pre-clinical models of non-inflammatory diarrhea, PI: Mark Donowitz
- **Johns Hopkins University:** A 3-D model of human brain development for studying gene/environment interactions; PI: Thomas Hartung
- **University of Pennsylvania:** Modeling oxidative stress and DNA damage using a gastrointestinal organotypic culture system; PI: John Lynch
- **University of Pittsburgh:** Three-dimensional osteochondral micro-tissue to model pathogenesis of osteoarthritis; PI: Rocky Tuan,
- **The University of Texas Medical Branch at Galveston:** Three-dimensional human lung model to study lung disease and formation of fibrosis; PI: Joan Nichols



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# Tissue Chip Program Overview





# Advancing Regulatory Science

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## Criteria for Selecting Test Compounds

- Do individual organ models respond to test compounds with the expected organ-specific effects?
- Do linked organ system models respond to test compounds with the expected systemic effects?
- Selection of test compounds should consider:
  - Individual organ function → linked organ functions
  - Direct organ toxicities → dependent organ toxicities
  - Study read-outs? → health outcomes of interest?



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# Advancing Regulatory Science

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## Drugs Producing Toxicity

- Organ-specific toxicities:
  - Liver: hepatocyte injury, functional deficits (including metabolic changes, failure)
  - Heart: contractile failure, remodeling, lesions
  - Kidney: diuresis, proximal/distal tubular necrosis, failure
  - Pulmonary: obstruction, necrosis, edema
- System-dependent organ toxicities
  - Adverse systemic effects downstream from tissue with the drug receptor
  - Drugs for which metabolism is important
  - Drugs that induce a cytokine storm



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