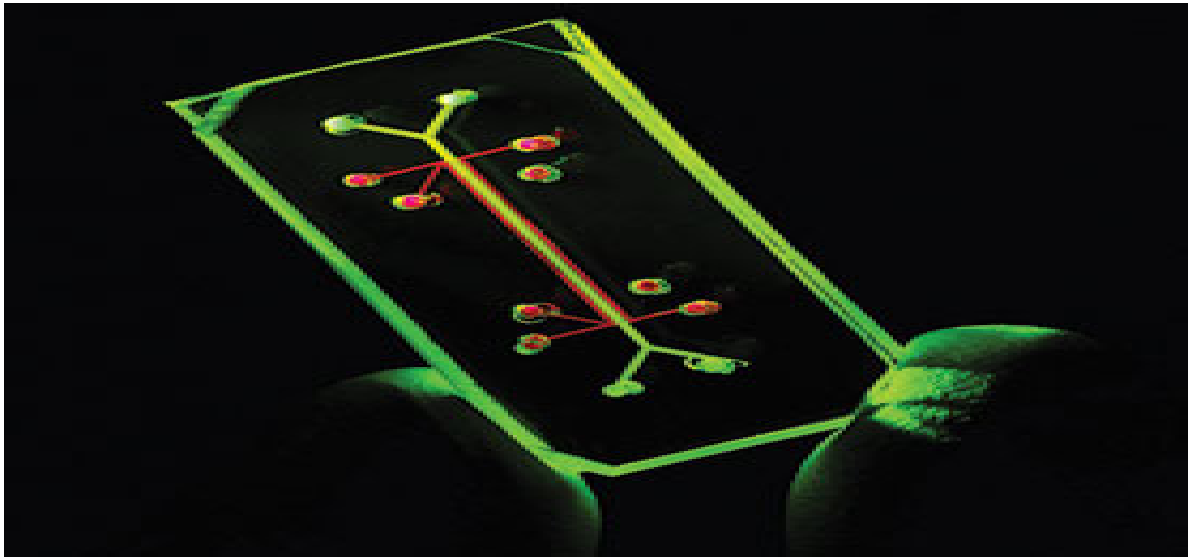
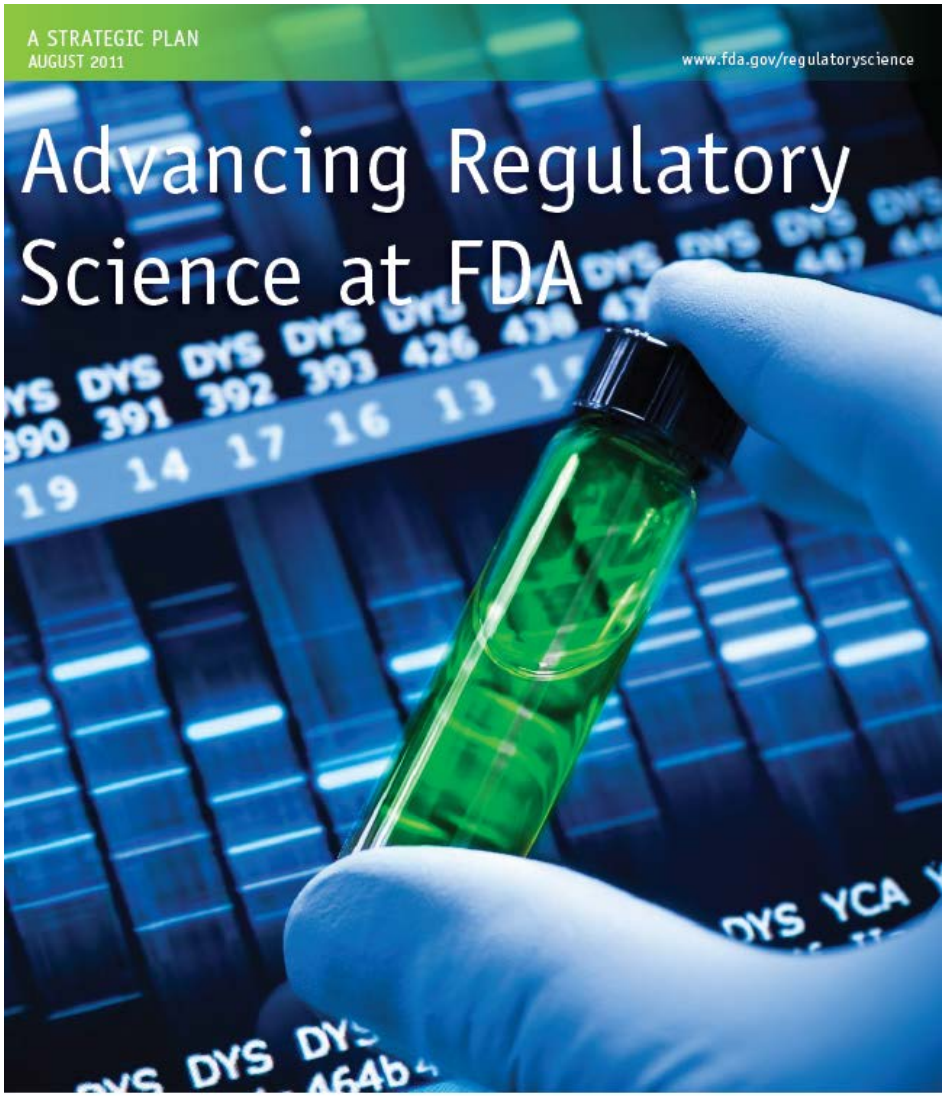
Determining the predicative ability of in *vitro* microphysiological systems to answer critical regulatory questions

Suzanne Fitzpatrick, PhD, DABT, ERT
US Food and Drug Administration

EMA Workshop
October 5, 2017





"FDA will advance regulatory science to speed innovation, improve regulatory decision-making, and get safe and effective products to people in need. 21st Century regulatory science will be a driving force as FDA works with diverse partners to protect and promote the health of our nation and the global community."

https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM268225.pdf

Need for New More Predictive Models

- FDA recognizes that alternative test platforms like organs on a chip can give regulators new tools that are more predictive.
- However. for these new alternative methods to be acceptable for regulatory use -confidence is needed that the questions can be answered by these new methods as with traditional testing

FDA Predictive Toxicology Roadmap

Goal of the Roadmap is to highlight the FDA's commitment to promote the development and evaluation of emerging toxicological methods and new technologies and to incorporate such methods and technologies into regulatory review as applicable.

- Organization
- Training
- Continued Communication
- Collaborations
- Research
- Oversight

Partnerships are Important for Accepting New Technologies

- Fostering collaborations between government researchers and regulators and between government regulators, industry , stakeholders and academia to ensure the most promising technologies are identified, developed validated and integrated into regulatory risk assessment.

FDA-DARPA-NIH Microphysiological Systems Program

- 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)

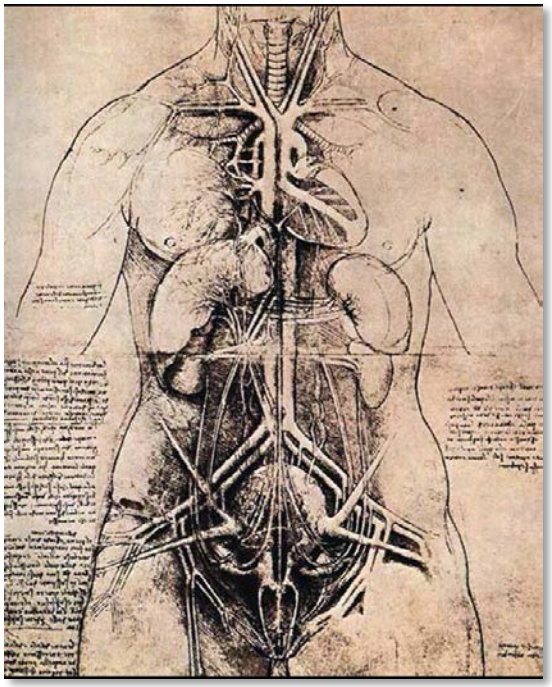
Underlying biology/pathology and mechanistic understanding (RFA-RM-12-001 and RFA RM-11-022)

Advise on regulatory requirements, validation and qualification

This was a unique partnership because it involved regulatory scientists at the very beginning- was able to address identified gaps in knowledge need to regulate FDA products

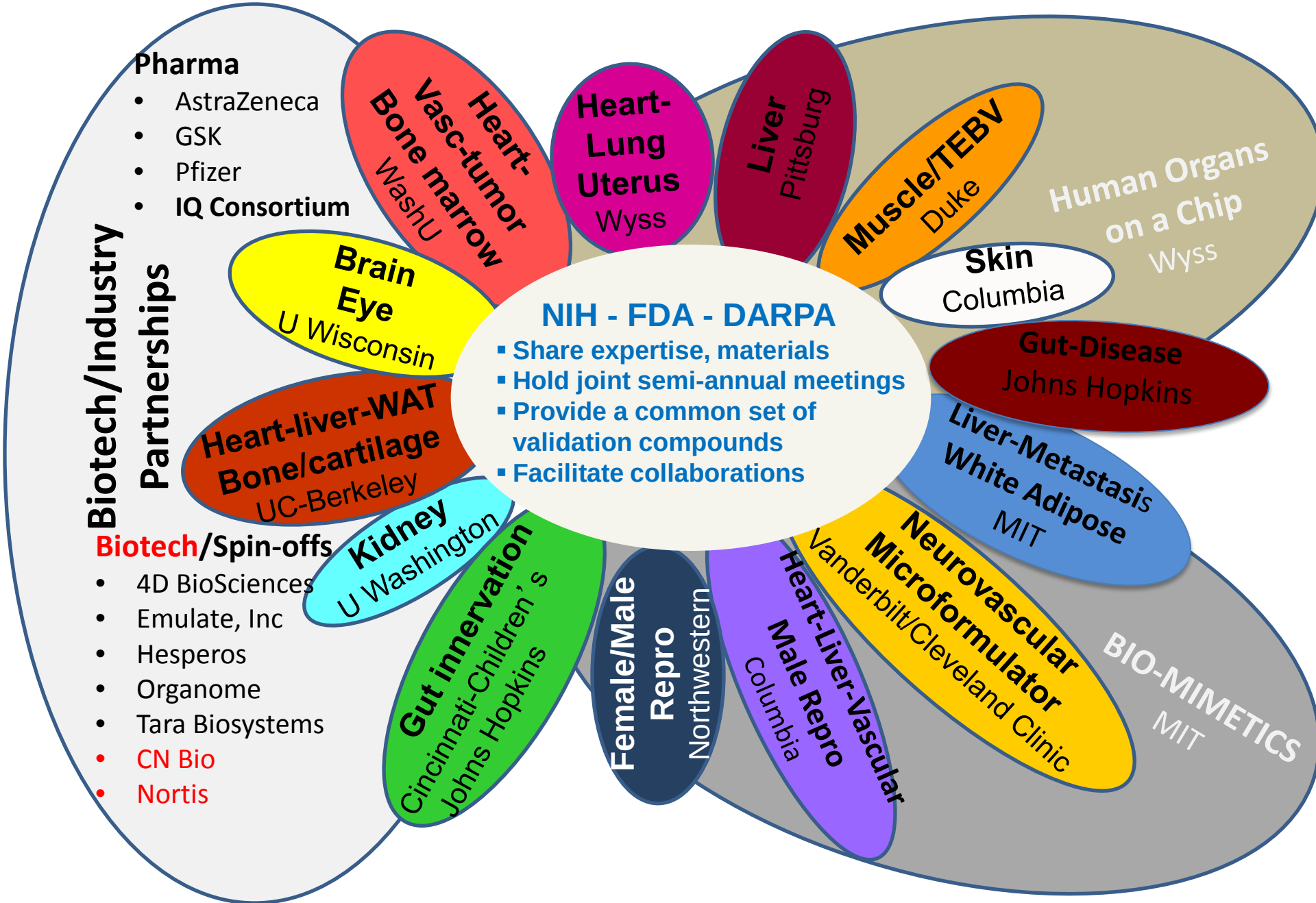
Microphysiological Systems Program "Tissue Chips"

GOAL: Develop an *in vitro* platform that uses <u>human</u> tissues to evaluate the efficacy, safety and toxicity of promising therapies.



- All ten 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.

Microphysiological Systems Consortium



The Tissue Chip Program

GOAL: Develop an *in vitro* platform that uses <u>human</u> tissues to evaluate the efficacy, safety and toxicity of promising therapies.

NIH
National Institutes of Health

Phase 1: Development

Phase 2: Cell incorporation & organ integration

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

Liver

DARPA

DARPA base periods: Organ integration

FDA

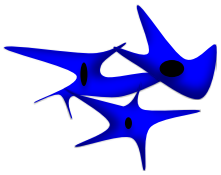
**FDA provides insight and expertise throughout the program

Current Goals:

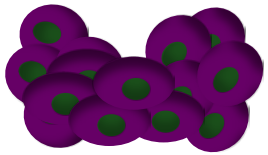
- **Integration**
- **Compound testing**
- **Validation**
- **Partnerships**
- **Adoptions of the tech to the community**

NCATS Future Directions in Tissue-on-chips Technology

Human Fibroblasts



Genetic reproramming



iPSC's

Differentiation/maturation into all major organs

Druggable Genome

- Gene Editing on isogenic background for physiological differences among diverse populations:
- Genetic variation
- Examine various demographics
- Gender or age variation

FY16 **Tissue Chips Testing Centers**

FY16 **Rare disease research and therapeutics**

FY17 **Disease Modeling**

- Disease pathogenesis
- Dissecting mutations in isogenic background

FY17 **Tissue Chips in Space**

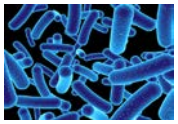
Human-on-a-Chip

Precision Medicine (you-on-chip)

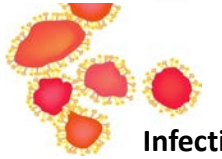
- Drug response in individuals
- Individualized medicine and therapeutics

Clinical Trials on Chips

Microbiome



Environmental Toxins



Infectious disease

Countermeasure Agents

Tissue Chip Testing Centers: Validating Microphysiological Systems

- RFA-TR-16-006
- Resource Centers (U24)
- GOAL: Independent validation of tissue chip platforms
- Partnerships between NCATS, FDA and IQ Consortium
- NCATS support: $12 M over two years; awarded 9/28/16
- FDA and IQ provides expert guidance on reference set of validation compounds, assays, biomarkers
- Testing Centers:
  - MIT (Murat Cirit and Alan Grudzinsky)
  - TAMU (Ivan Rusyn)
- MPS Database:
  - U Pittsburgh (Mark Schurdak)

Tissue-on-chips Disease Models for Efficacy Testing

- RFA-TR-16-017
- GOAL: Develop models for a wide range of human diseases for efficacy testing, assessment of candidate therapies and establishing the pre-clinical foundation that will inform clinical trial design
  - NCATS joined by NCI, NEI, NHLBI, NIAMS, NIBIB, NICHD, NIDCR, NIDDK, NIEHS, NINDS, ORWH
  - NIH support: approximately $ 80 M over five years
  - Bi-phasic:
    - Develop and characterize models of diseases
    - Testing for efficacy of candidate therapeutics

NIH-CASIS Coordinated Program in Tissue Chip Systems Translational Research in Space

- RFA-TR-16-019
- Partnership between NCATS, NASA and CASIS (Center for Advancement of Science in Space)
  - GOAL: Utilize tissue-on-chips technology towards biomedical research at the International Space Station that will lead to a better understanding of the molecular basis of human disease and effectiveness of diagnostic markers and therapeutic interventions
  - Potential impact: Understanding of the effects of microgravity on human organ systems. It could provide better insight into the molecular basis, including epigenome changes for many human conditions in space and provide information for novel drug targets for use on Earth
  - NCATS support: approximately $12 M over four years
  - NASA support: $ 3 M over four years; CASIS: $ 8 M in-kind support
  - http://www.casistissuechip.blogspot.com

FDA CRADA Press Release

Official Press Release
April 11, 2017

FDA Signs Collaborative Agreement with Emulate, Inc. to Use Organs-on-Chips Technology as a Toxicology Testing Platform for Understanding How Products Affect Human Health and Safety

Cooperative Research and Development Agreement (CRADA) to advance and qualify 'Human Emulation System' to meet regulatory evaluation criteria for product testing

Link to Official Press Release
https://emulatebio.com/press/fda-collab-agreement-emulate/

Blog from FDA Voice

'Organs-on-Chips' Technology: FDA Testing Groundbreaking Science

By: Suzanne Fitzpatrick, Ph.D.

On April 11, 2017, FDA announced a multi-year research and development agreement with a company called Emulate Inc. to evaluate the company's "Organs-on-Chips" technology in laboratories at the agency's Center for Food Safety and Applied Nutrition

Link to FDA Blog
https://blogs.fda.gov/fdavoice/index.php/2017/04/organs-on-chips-technology-fda-testing-groundbreaking-science/

NATURE | NEWS

Miniature liver on a chip could boost US food safety

- CFSAN Researchers will be evaluating the effectiveness of this technology to better understand the effects of medicines, disease-causing bacteria in foods, chemicals, and other potentially harmful materials on the human body

CRADA Between EMULATE and FDA- Goals

- Begin with the Liver on a Chip
- Beta Test the Emulate System
- Look at concordance of chip data with in vivo, in silico and other in vitro (2-D) data on same compounds
- Begin to develop performance standards for organs on a chip-applicable to chips
- Resource for FDA regulators and researchers

U.S. FOOD & DRUG ADMINISTRATION

Questions?

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