Organ on a Chip Standardization and Research

Darwin R. Reyes, Ph.D.

May 20th, 2024 – ICCVAM Public Forum

NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY
U.S. DEPARTMENT OF COMMERCE

MPS Standardization Efforts in the USA

- **OTEES* Working Group**
- The 3Rs Collaborative (formerly The North American 3Rs Collaborative)
- Standards Coordinating Body (SCB): Regenerative Medicine
- Center for Alternative to Animal Testing (CAAT), Johns Hopkins University

*__OTEES WG__ = Organ/Tissue on a Chip Engineering & Efficacy Standards Working Group

OTEES* Working Group Mission

- To build up the basis for publications regarding guidelines as well as important engineering aspects of OoC/ToC, which can serve as the first step towards standardization of these systems.

- Mapping out as many aspects of standardization as possible will ultimately provide us with a roadmap for OoC/ToC standardization - In progress

*__OTEES WG__ = Organ/Tissue on a Chip Engineering & Efficacy Standards Working Group

Overview of Standardization

July 2021

Co-chairs initiated conversations to create the working group

(Darwin Reyes, **NIST**; Nureddin Ashammakhi, **MSU**)

September 2021

First meeting of the working group with members from: NIST, FDA, ATCC, Emulate, Hesperos, Kiyatec, Michigan State University, and Synvivo

December 2021

Templates for guidelines were created for three organ models

(Heart, Kidney and Liver)

May 2022

Website was created (sponsored by NIST)

April 2023

First workshop of the OTEES Working Group

(Co-sponsored by NIST and Michigan State University)

February 2024

First publication in ***Lab on a Chip***

From animal testing to in vitro systems: advancing standardization in microphysiological systems, 2024

Online presence: website ...

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Organ-on-a-Chip/Tissue-on-a-Chip Engineering and Efficacy Standardization Working Group

Upcoming Event

Workshop on Standards for Microphysiological Systems/Organ-Tissue on a Chip 2023, April 27 & 28, 2023

BACKGROUND

Advances in microfluidic technologies have led to innovative lab-on-a-chip, organ-on-a-chip (OoC)/tissue-on-a-chip (ToC), and other advanced *in vitro* three-dimensional (3D) modeling systems. These *in vitro* platforms have been increasingly used to study cell cultures/tissues under normal and disease states, thus helping develop drugs and theranostics. In addition to the advantages they may offer over conventional *in vitro* cell culture and animal experiments, these technologies have their specific properties and limitations. While many of these approaches use the same biomaterials and microfabrication techniques, and some have already become commercially available products, there are still biomaterials, cells-related and process-based risks that must be reasonably determined, addressed, and reduced to an acceptable level.

There are notable examples of microfluidic devices and on-chip products in different countries, with early adoption in various research and development level projects. The ultimate promise for many of these devices is the potential to be used as an accepted drug testing platform, which, when validated and standardized, can largely reduce animal testing and limit the problems seen in drug candidate attrition due to inadequacy of the two-dimensional (2D) cell culture models. Thus, a validated and standardized platform will, in turn, reflect on industrial advancements of biomedical products well beyond the current limits.

To achieve this potential and advance the use of microfluidics-based technologies, standardization is required, which, once in place, will also help regulatory bodies and industry to get approvals and achieve better technology penetration and acceptance in the scientific community, industry, and clinics. Stakeholders in other areas of microfluidic technologies such as flow control, interconnections, and others have already started international standardization efforts in these areas. Bringing together a working group with interdisciplinary expertise that covers a wide range of stakeholders to develop guidelines and standards for OOC is required and timely.

MISSION

This working group has the mission to build up the basis for publications regarding guidelines as well as important engineering aspects of OoC/ToC, which can serve as the first step towards standardization of these systems. Mapping out as many aspects of standardization as possible will ultimately provide us with a roadmap for OoC/ToC standardization.

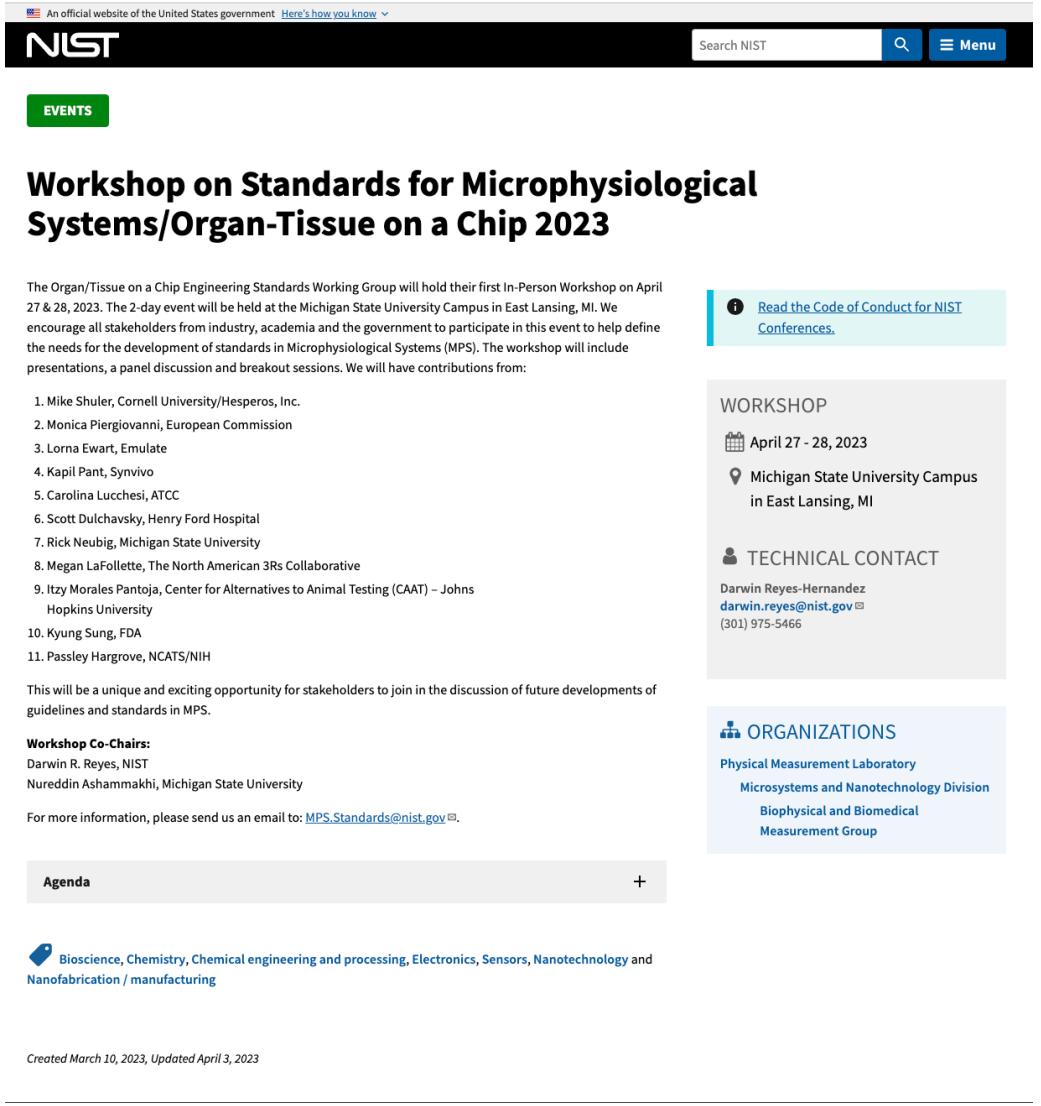
CURRENT CONTRIBUTORS/ STAKEHOLDERS (IN ALPHABETICAL ORDER)

ATCC
Emulate
Hesperos, Inc.
FDA
Kiyatec, Inc.
Michigan State University
NIST
Synvivo
Xona Microfluidics

WORKING GROUP COORDINATORS

Darwin R. Reyes, Ph.D. (NIST)
Nureddin Ashammakhi, M.D., Ph.D. (Michigan State University)

Bioscience, Chemistry, Chemical engineering and processing, Electronics, Sensors, Nanotechnology and Nanofabrication / manufacturing



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EVENTS

Workshop on Standards for Microphysiological Systems/Organ-Tissue on a Chip 2023

The Organ/Tissue on a Chip Engineering Standards Working Group will hold their first In-Person Workshop on April 27 & 28, 2023. The 2-day event will be held at the Michigan State University Campus in East Lansing, MI. We encourage all stakeholders from industry, academia and the government to participate in this event to help define the needs for the development of standards in Microphysiological Systems (MPS). The workshop will include presentations, a panel discussion and breakout sessions. We will have contributions from:

1. Mike Shuler, Cornell University/Hesperos, Inc.
2. Monica Piergiovanni, European Commission
3. Lorna Ewart, Emulate
4. Kapil Pant, Synvivo
5. Carolina Lucchesi, ATCC
6. Scott Dulchavsky, Henry Ford Hospital
7. Rick Neubig, Michigan State University
8. Megan LaFollette, The North American 3Rs Collaborative
9. Itzy Morales Pantoja, Center for Alternatives to Animal Testing (CAAT) – Johns Hopkins University
10. Kyung Sung, FDA
11. Passley Hargrove, NCATS/NIH

This will be a unique and exciting opportunity for stakeholders to join in the discussion of future developments of guidelines and standards in MPS.

Workshop Co-Chairs:
Darwin R. Reyes, NIST
Nureddin Ashammakhi, Michigan State University

For more information, please send us an email to: MPS.Standards@nist.gov.

Agenda +

Bioscience, Chemistry, Chemical engineering and processing, Electronics, Sensors, Nanotechnology and Nanofabrication / manufacturing

Created March 10, 2023, Updated April 3, 2023

Read the Code of Conduct for NIST Conferences.

WORKSHOP

April 27 - 28, 2023

Michigan State University Campus in East Lansing, MI

TECHNICAL CONTACT

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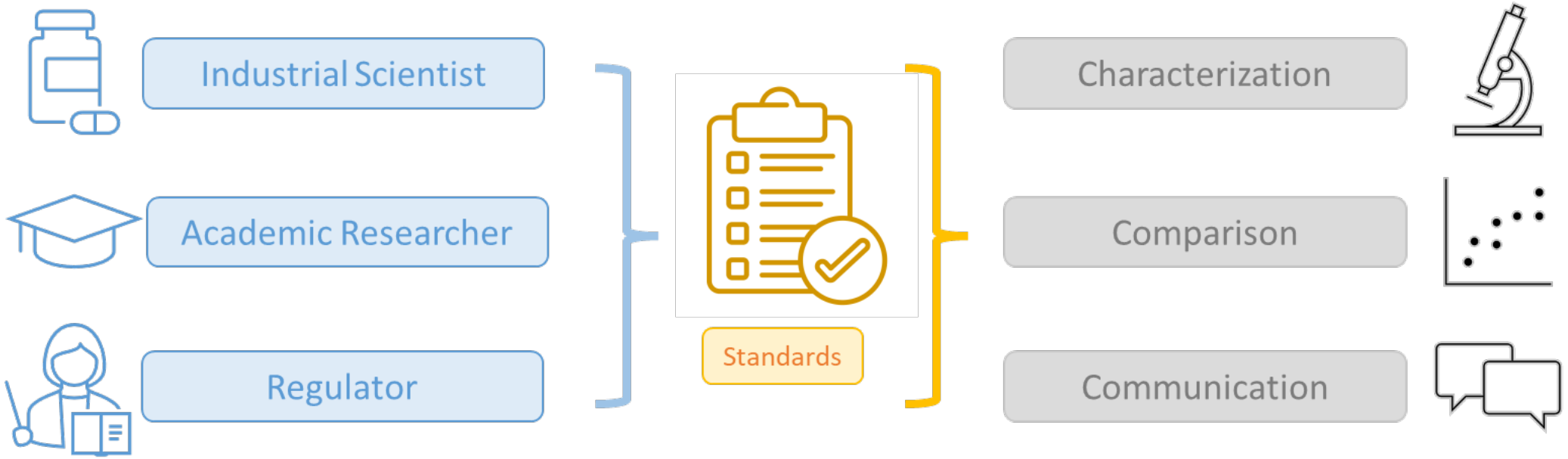
(301) 975-5466

ORGANIZATIONS

Physical Measurement Laboratory
Microsystems and Nanotechnology Division
Biophysical and Biomedical Measurement Group

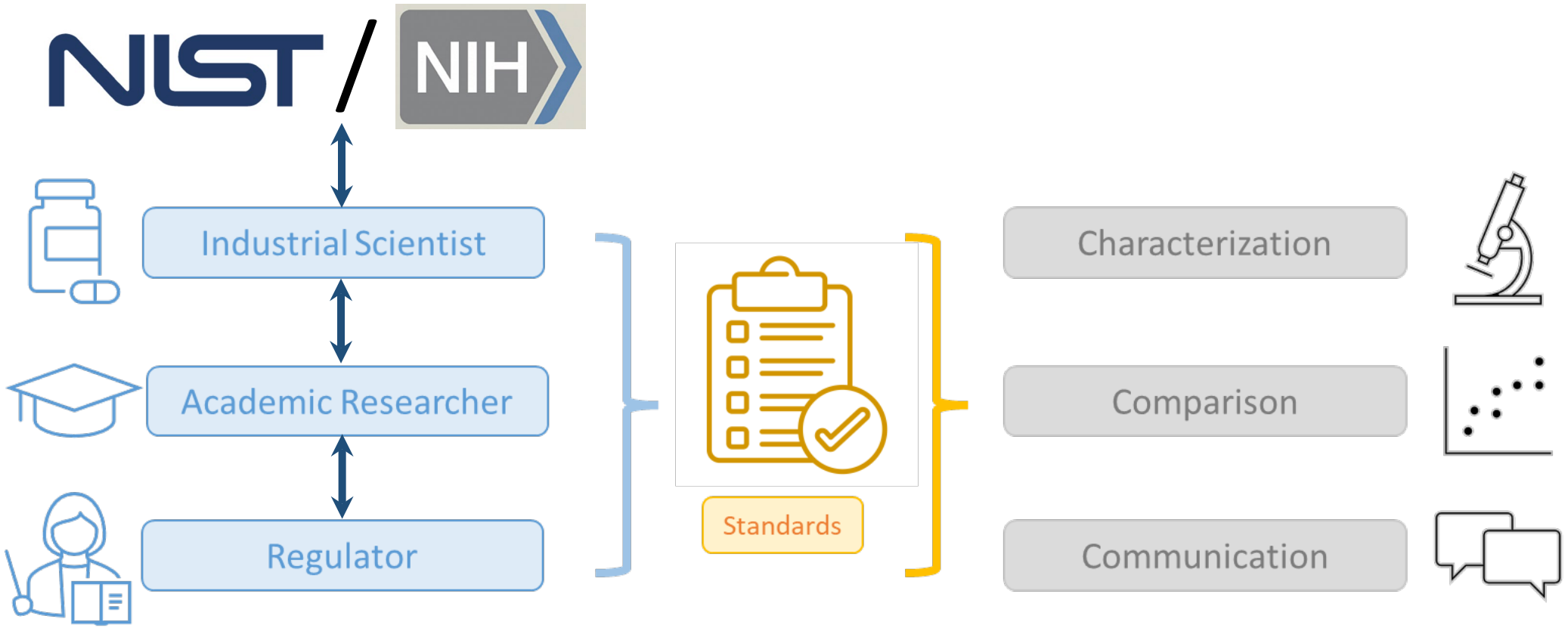
Standards development process



Standards are developed as a result of the work of different collaborating stakeholders. Standards will help with characterizing and comparing different microphysiological systems, and with communication between stakeholders.

Reyes *et al*. *Lab Chip,* **2024**, *24*, 1076

Standards development process



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Reyes *et al*. *Lab Chip,* **2024**, *24*, 1076

Ecosystem in MPS Standardization

NIST

USA

OTEES WG
(OoC/ToC Engineering and Efficacy Standardization Working Group)
(Darwin Reyes, Co-Chair)

The 3Rs Collaborative

SCB
(Standards Coordinating Body)

CAAT
(Center for Alternatives to Animal Testing, JHU)

International

IQ MPS
(International Consortium for Innovation and Quality in Drug Development)

IMPS Society: Standardization Interest Group
(International Microphysiological Systems Society)
(Darwin Reyes, Co-Chair)

European Commission

EUROoCS
(European Organ-on-Chip Society)

Europe Specific Countries Standard Organizations
(e.g., NEN, The Netherlands)

JMAC
(Japan bio Measurement & Analysis Consortium)

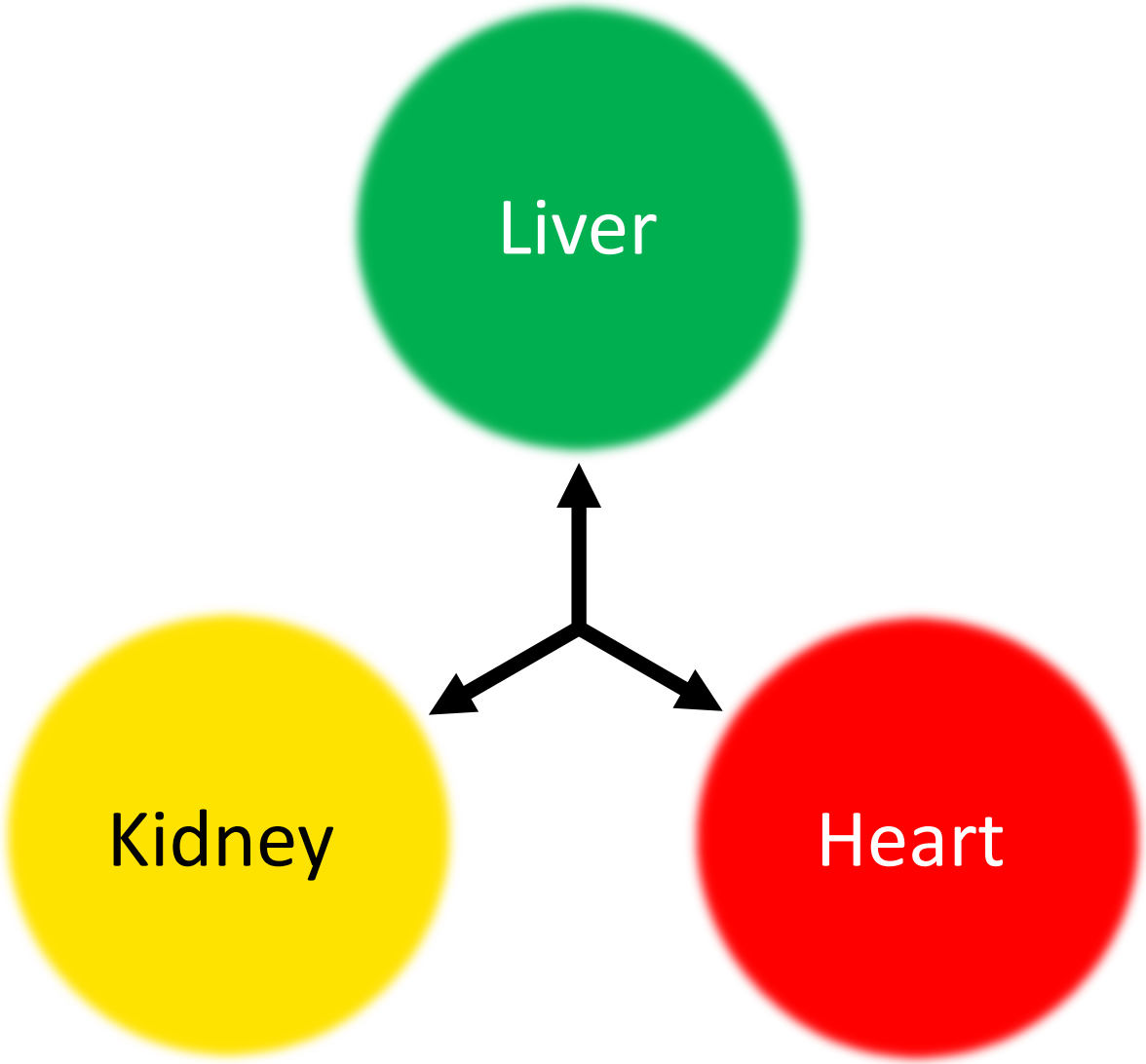
KoCVAM
(Korea Alternative Animal Test Method Verification Center)

International Standards:

ISO

ASTM International

OTEES Working Group



Organ/Tissue on a Chip Engineering and Efficacy Working Group

Tables of functional units of three (3) organ models to provide the basis for future guidelines. The Working Group decided on the creation of these tables with inputs to the organ model with known outputs (based on in vivo results from the literature) as a way of functionality assessments of organ/tissue models from different providers in a standardized form.

First version: December 15, 2021, Second version: January 2022

Model Organs: Perturbations (inputs) and range of physiological responses (outputs)

Model organ	Heart		
Perturbation (input) *specific for the organ*	1) doxorubicin	2) cell maturity	3)
Physiological responses (output or measurand)			
Physical/Engineering parameters			
Method of analysis			

ange of physiological responses (outputs)

Kidney		
mal (and Convoluted) Tubule		
for oxicity (in ased solutions)	2) Cis-platin	3)
	5)	6)

Model organ	Liver Sinusoid		
Perturbation (input) *specific for the organ*	1) Chemicals Pharmaceuticals: (acetaminophen, halothane, etc) Non-Biological: (list?) Environmental: (pesticides, aflatoxins, etc)	2) Biol... (Peptides, Proteins, etc.)	3) Lifestyle (alcohol, Fat)
Physiological Responses (output/measure)	1) chemical composition Functional: (albumin, urea) Biological: (glutathione)	2) CYP activity (1A2, 2C9/19, 2D6, 2E1, 3A4)[1] Alternatives (2C8, 2A6, 2D6, 2B6, 3A5)	3) Transporters (LIST)
	4) Genomics		
Pathophysiological Responses	1) Viability /Senescence	2) Stress Makers (ROS, RNS, ALT, AST, ALP)	3) Morphology
	4) Proteomics		
Physical/Engineering Parameters	1) Shear/Flow	2) Oxygen Tension (zonation)	3) Chip Material
Method of analysis	1) Elisa/Colormetric	2) Imaging (BF, TEM, SEM, fluorescence, etc.)	3) RNAseq, Mass Spectrometry

Work in Progress

- Development of a Roadmap for OTEES (USA)
- Vocabulary of terms for a possible ASTM International or ISO standard (Kidney)

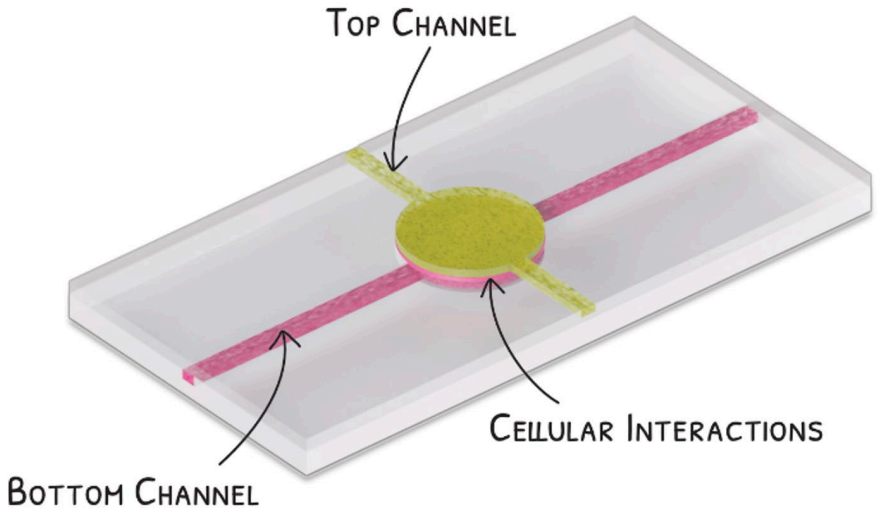
- Workshop at the MPS World Summit 2024
  - Speakers from the USA, Europe and Asia
- Plans for an annual (USA) meeting of industry stakeholders, government agencies, and academia
  - Possible venues: NIST, FDA, …

Work in Progress

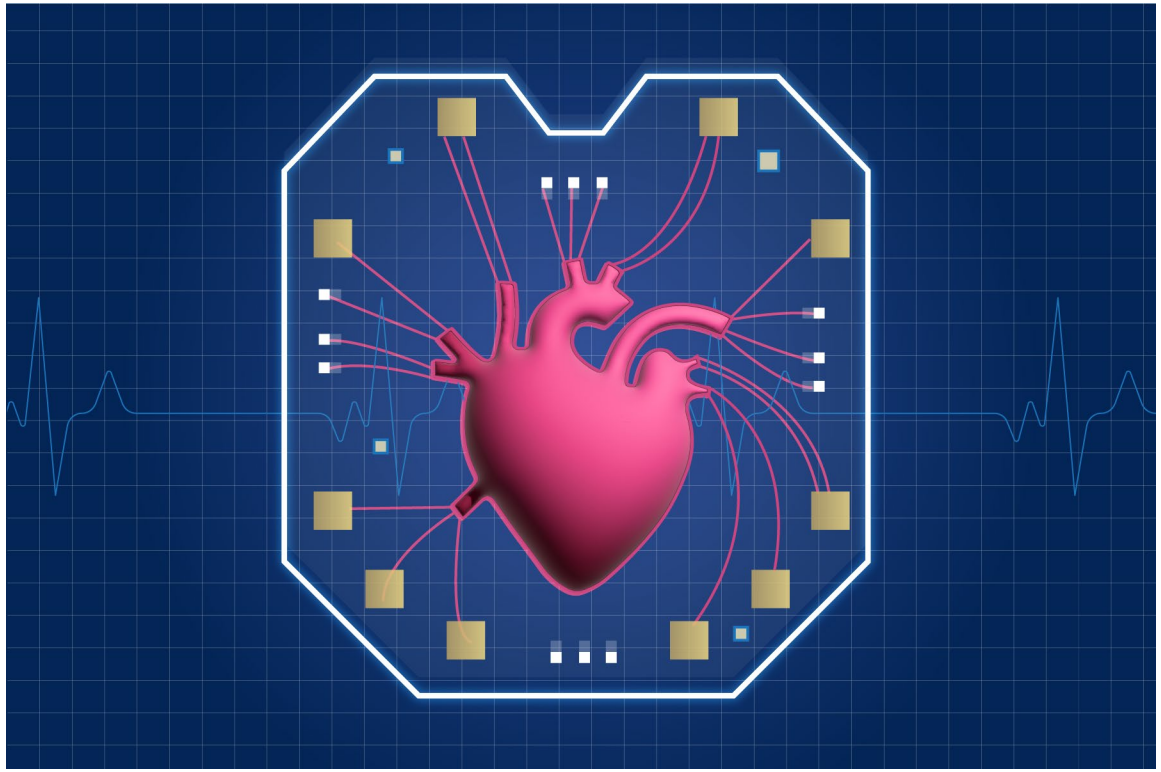
Interactions with other government agencies

- MOU with NCATS/NIH
  - Will allow for:
    - **Develop opportunities**, such as **workshops**, that would bring together stakeholders **to discuss** the progress of the MPS translational programs and generate **new ways to advance the standardization of MPS and New Approach Methodologies (NAMs**)
    - Developing programs that **advance translation and adoption of MPS**
    - Engaging in additional activities, where appropriate, to **promote the adoption of MPS as NAMs**"
- FDA (through OTEES and others)
- Future collaborations with other NIH institutes

Organ on a Chip Platforms with Integrated Electronics

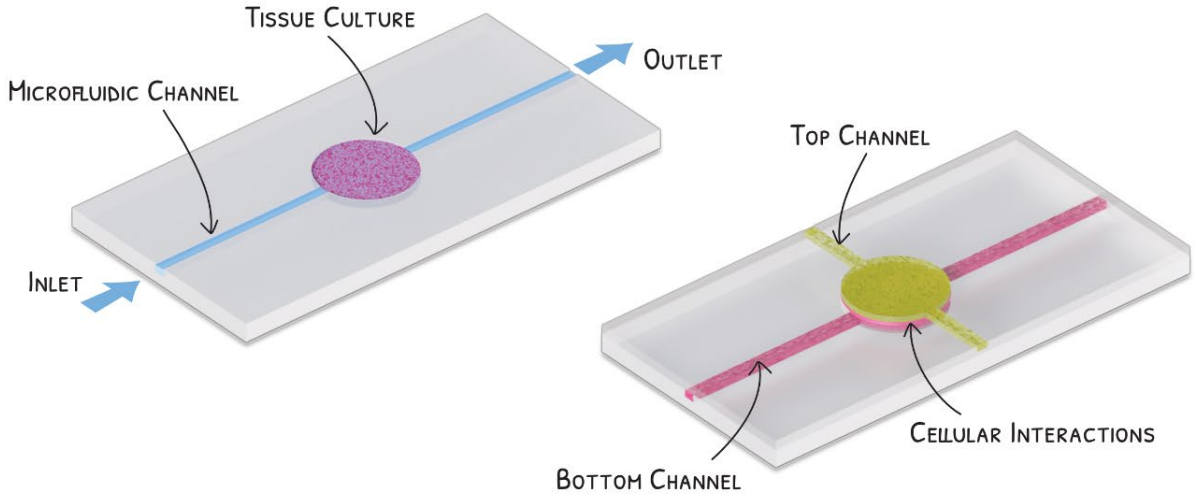


Organ on a Chip systems for cancer cell migration assays and cell-cell interactions between cancer and neighboring cells

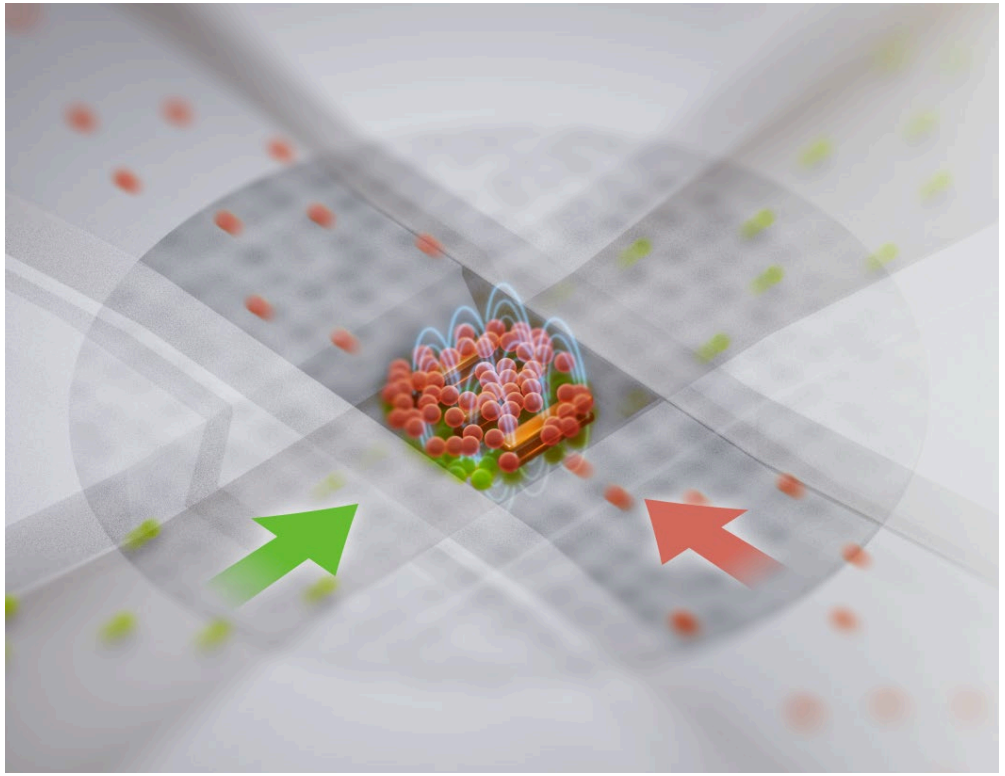


Heart on a Chip

Organ on a Chip Platform with Integrated Electronics



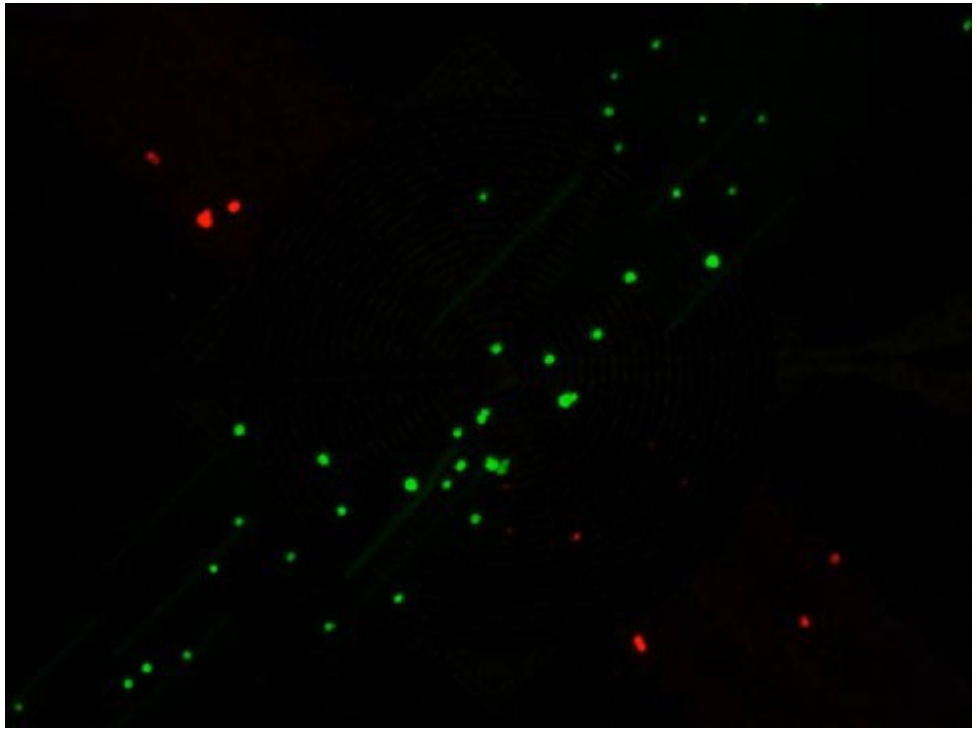
Organ-on-a-chip devices use microchannels to bring small, controlled amounts of fluid into contact with tissue cultures.



Rendering of an organ-on-a-chip device showing two overlapping channels with a thin semi-permeable membrane between them. Electrodes, on the membrane, are used to trap cells in each channel.

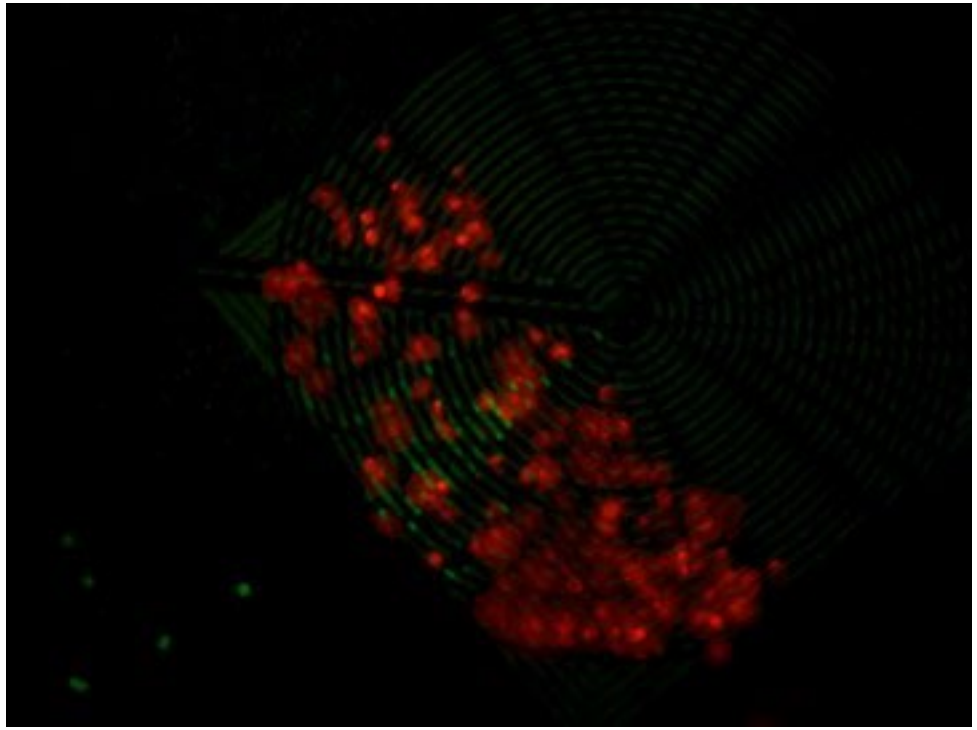
Simultaneous dielectrophoretic (DEP) trapping

Simultaneous DEP Trapping



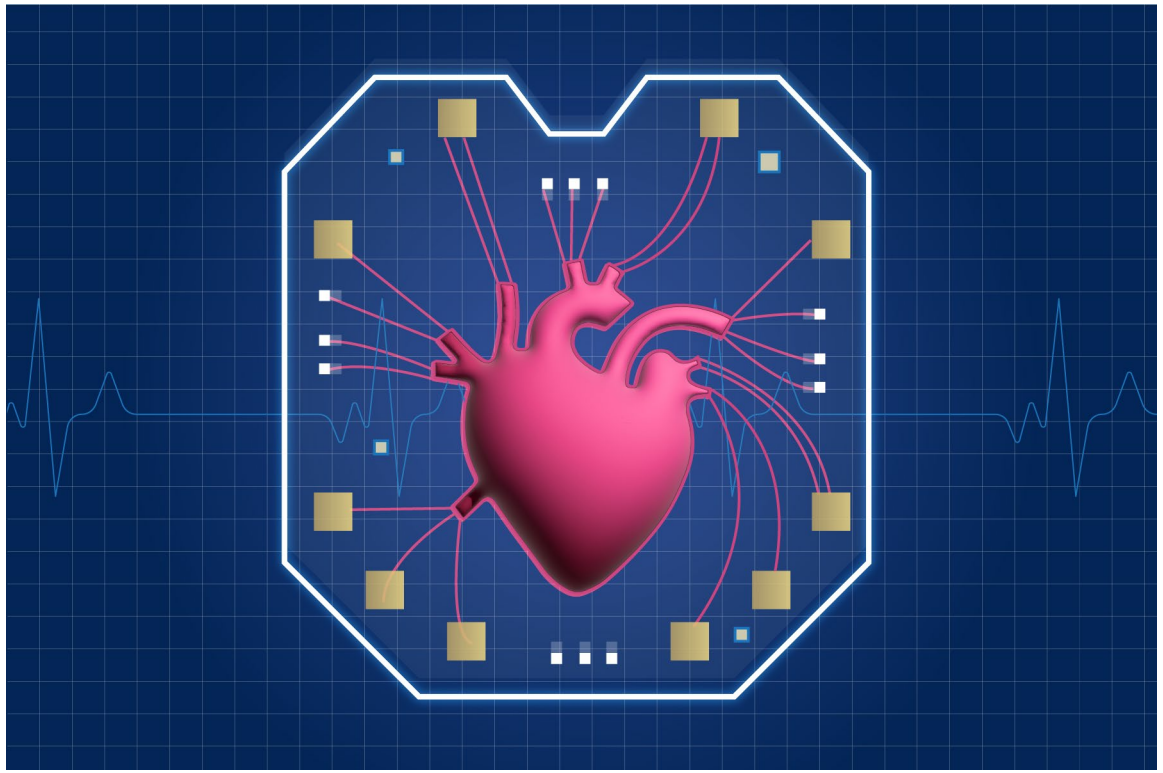
Liver (Red, top) and Endothelial cells (Green, bottom), < 2 $V_{p\text{-}p}$, 10 MHz

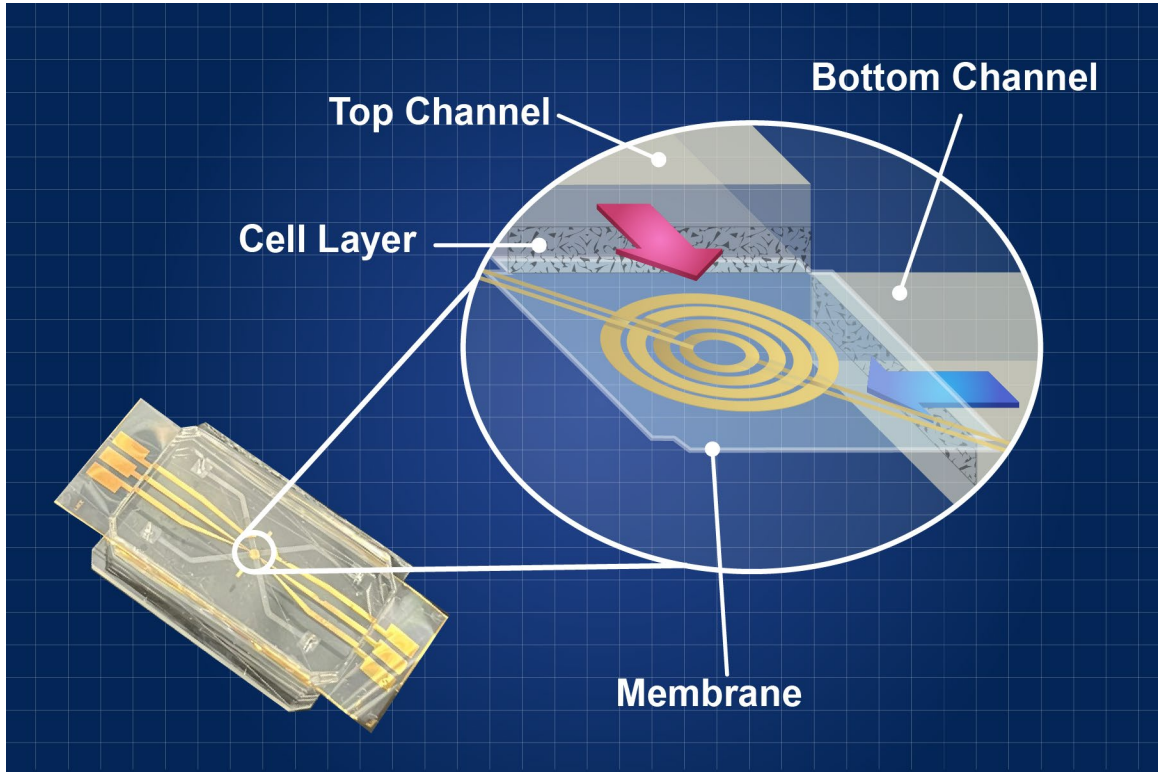
Cell-cell interactions



Liver (Green, top) and Endothelial cells (Red, bottom)

Bioelectronic Sensors for Heart on a Chip

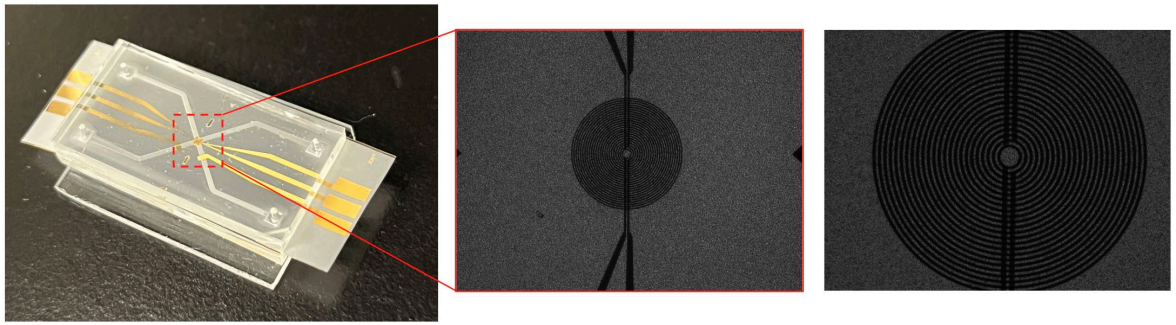




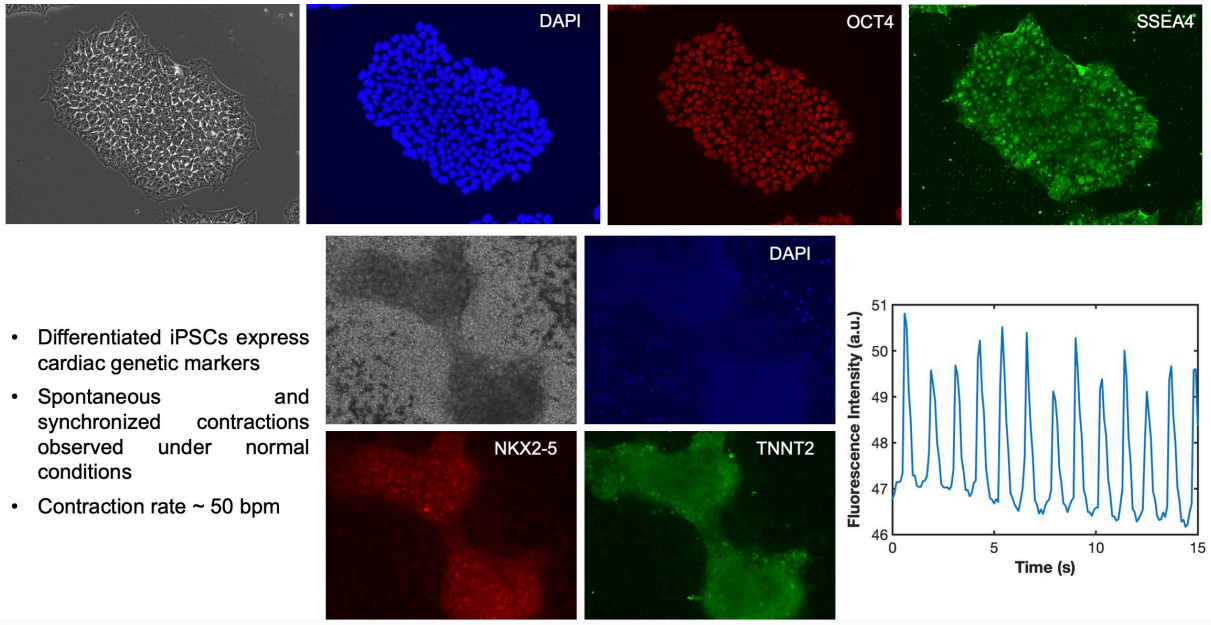
Bioelectronic Sensors for Heart on a Chip

NIST

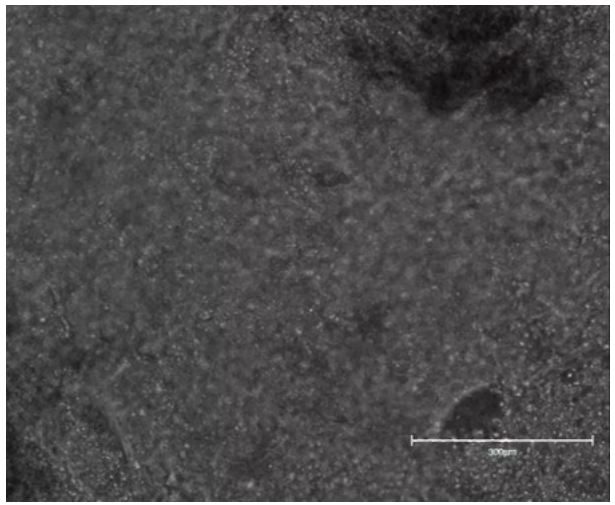
Device Design, Fabrication, and Assembly



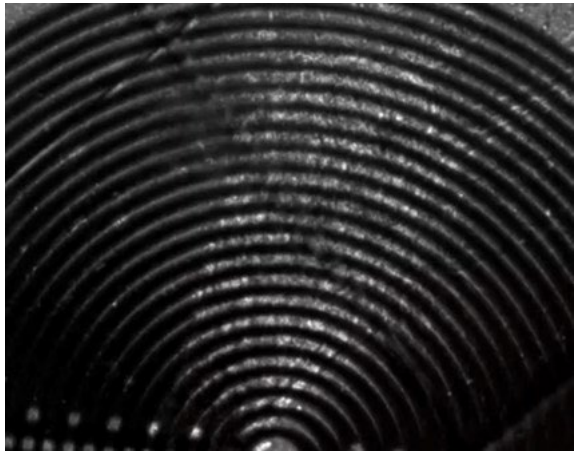
Characterization of iPSCs & iPSC-Derived Cardiomyocytes



- Differentiated iPSCs express cardiac genetic markers
- Spontaneous and synchronized contractions observed under normal conditions
- Contraction rate ~ 50 bpm



Well-plate



MPS/Organ on a Chip Device

iPSC-derived cardiomyocytes – Optical observation of functional capabilities

Acknowledgements

Thanks!