US interagency OOC development program: from funding to qualification for regulatory acceptance

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

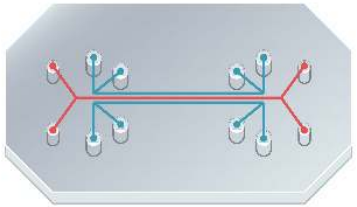
Organ chip and Tissue Chip, from development to regulatory adaptation Meeting
March 5, 2021

FDA Encourages the Use of New Testing Methodologies

- FDA and regulators worldwide will incorporate new testing methodologies into regulatory standards if certain standards are met
- Important to ensure regulator's familiarity with techniques before they see it in a regulatory submission
- Any technology considered for regulatory use has to be proven to be reliable, robust, reproducible, fit the context of use, etc.
- FDA does not fund the development of MPS for regulatory use in the support of new products

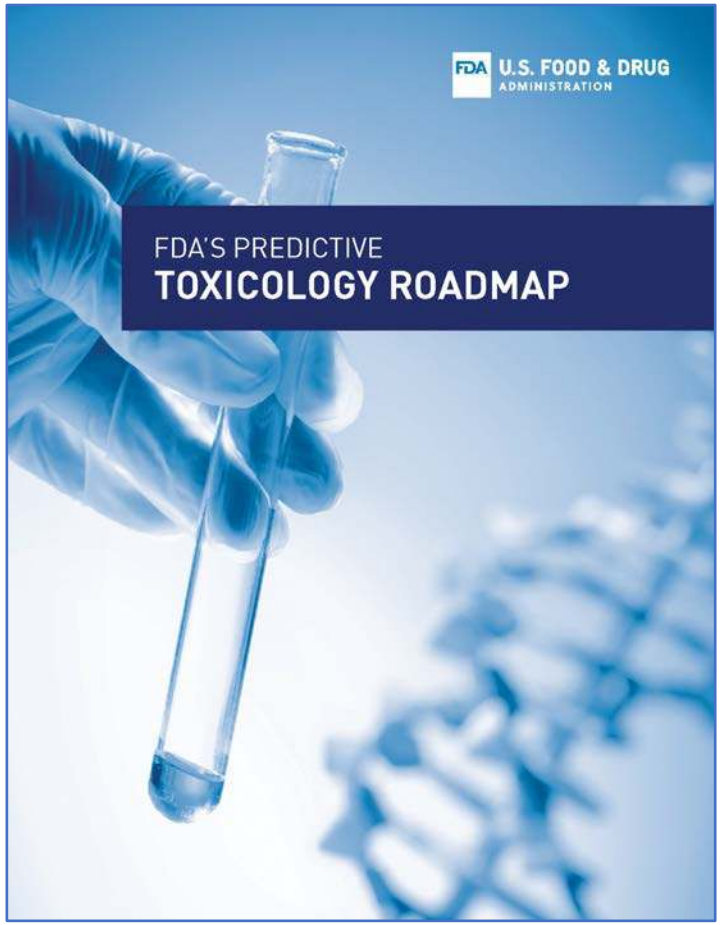
History of FDA's Involvement with MPS

- 2010: FDA and NIH Common Fund awarded grant money to Wyss to develop a heart-lung micromachine
- 2011: DARPA approached FDA's Office of the Chief Scientist requesting to work together to develop a human body on a chip for medical countermeasures. DARPA funded MPS research and involved the FDA from the beginning of the MPS program to help ensure that regulatory challenges of reviewing drug safety and efficacy are considered during development of the MPS platform
- 2012: NCATS funded the Tissue Chip Development Program. FDA has been a partner throughout the program
- And the rest is MPS history!
- **IMPORTANT LESSON-Critical to have regulators at the table beginning if aim is to use method for regulatory use**



FDA Predictive Toxicology Roadmap

- https://blogs.fda.gov/fdavoice/index.php/2017/12/fda-launches-predictive-toxicology-roadmap-to-enable-advances-in-toxicity-testing/



Alternative Methods Working Group (AMWG)

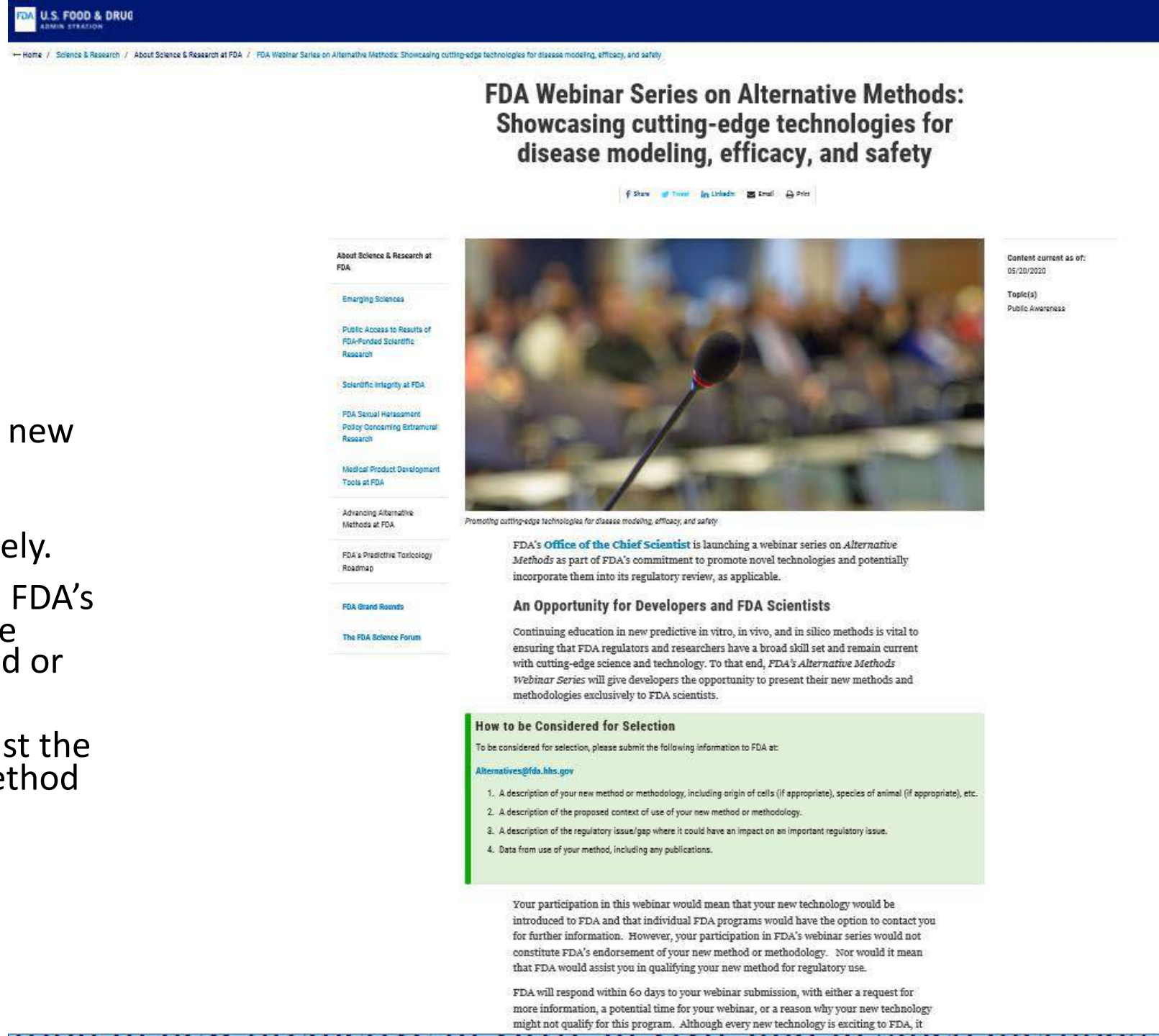
- Under Office of Chief Scientist (OCS), Office of Commissioner; members from each Center and OCS
- Discuss alternative activities across FDA for use in toxicity and efficacy assessment
- Interact with U.S. federal and global partners to facilitate discussion, development, and acceptance of regulatory performance criteria for such assays
- Updates are on FDA Alternatives website (https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda)
- Comments to FDA at alternatives@fda.hhs.gov

Objectives of FDA's Alternative Methods Working Group

- Discuss FDA-wide new in vitro, in vivo, and in silico methods, including research, training, and communication.
- Interact with U.S. Federal partners and other global stakeholders to facilitate discussion and development of draft performance criteria for such assays.
- Establish a dialogue and develop partnerships with FDA stakeholders to explore regulatory science applications for such technologies.
- Identify the performance criteria of microphysiological systems by engaging with FDA experts and FDA stakeholders through public-private partnerships.

FDA Office of the Chief Scientist Webinar Series on Alternative Methods

- Opportunity for developers to present new methods and methodologies to FDA.
- Webinars will be held monthly and advertised to all FDA scientists exclusively.
- If selected, developers' participation in FDA's webinar series would not constitute the agency's endorsement of a new method or methodology.
- Nor would it mean that FDA would assist the developer in qualifying his/her new method for regulatory use.



U.S. FOOD & DRUG ADMINISTRATION

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FDA Webinar Series on Alternative Methods: Showcasing cutting-edge technologies for disease modeling, efficacy, and safety

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- FDA Sexual Harassment Policy Concerning Extramural Research
- Medical Product Development Tools at FDA
- Advancing Alternative Methods at FDA
- FDA's Predictive Toxicology Roadmap
- FDA Grand Rounds
- The FDA Science Forum

Content current as of: 05/20/2020

Topic(s)
Public Awareness

Promoting cutting-edge technologies for disease modeling, efficacy, and safety

FDA's **Office of the Chief Scientist** is launching a webinar series on *Alternative Methods* as part of FDA's commitment to promote novel technologies and potentially incorporate them into its regulatory review, as applicable.

An Opportunity for Developers and FDA Scientists

Continuing education in new predictive in vitro, in vivo, and in silico methods is vital to ensuring that FDA regulators and researchers have a broad skill set and remain current with cutting-edge science and technology. To that end, *FDA's Alternative Methods Webinar Series* will give developers the opportunity to present their new methods and methodologies exclusively to FDA scientists.

How to be Considered for Selection

To be considered for selection, please submit the following information to FDA at:

Alternatives@fda.hhs.gov

1. A description of your new method or methodology, including origin of cells (if appropriate), species of animal (if appropriate), etc.
2. A description of the proposed context of use of your new method or methodology.
3. A description of the regulatory issue/gap where it could have an impact on an important regulatory issue.
4. Data from use of your method, including any publications.

Your participation in this webinar would mean that your new technology would be introduced to FDA and that individual FDA programs would have the option to contact you for further information. However, your participation in FDA's webinar series would not constitute FDA's endorsement of your new method or methodology. Nor would it mean that FDA would assist you in qualifying your new method for regulatory use.

FDA will respond within 60 days to your webinar submission, with either a request for more information, a potential time for your webinar, or a reason why your new technology might not qualify for this program. Although every new technology is exciting to FDA, it

FDA Office of the Chief Scientist Webinar Series on Alternative Methods

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Advancing Alternative Methods at FDA Webpage

Publications

An FDA/CDER perspective on nonclinical testing strategies: Classical toxicology approaches and new approach methodologies (NAMs)

Opportunities for use of one species for longer-term toxicology testing during drug development: A cross-industry evaluation

Strategies for Rapid Risk Assessment of Color Additives Used in Medical Devices

An In Vitro Blood Flow Loop System for Evaluating the Thrombogenicity of Medical Devices and Biomaterials

Simultaneous UHPLC-MS/MS Method of Estradiol Metabolites to Support the Evaluation of Phase-2 Metabolic Activity of Induced Pluripotent Stem Cell Derived Hepatocytes

Liver Microphysiological Systems for Predicting and Evaluating Drug Effects

Considerations for an In Vitro, Cell-Based Testing Platform for Detection of Drug-Induced Inotropic Effects in Early Drug Development. Part 2: Designing and Fabricating Microsystems for Assaying Cardiac Contractility With Physiological Relevance Using Human iPSC-Cardiomyocytes

Use of high-throughput enzyme-based assay with xenobiotic metabolic capability to evaluate the inhibition of acetylcholinesterase activity by organophosphorous pesticides

Assessment of Intestinal absorption of 3-MCPD by Caco-2 cells

Biology-inspired microphysiological systems to advance patient benefit and animal welfare in drug development

Quantifying drug-induced structural toxicity in hepatocytes and cardiomyocytes derived from hiPSCs using a deep learning method

FDA's Alternative Report

Released January 5, 2021

AMWG First Case Study – *In vitro* Micro physiological Systems

- Define agreed-upon terminology for MPS and research/regulatory gaps for which MPS may be useful.
- Identify partnerships to advance MPS technology.
- Develop draft performance criteria for MPS and discuss internally and then with stakeholders
- Develop mechanisms to request information from MPS developers and end users

FDA Draft Definitions

Microphysiological System (MPS): A microphysiological system is an in vitro platform composed of cells; explants derived from tissues/organs; and/or organoid cell formations of human or animal origin in a micro-environment that provides and supports biochemical/electrical/mechanical responses to model a set of specific properties that define organ or tissue function.

Organ-on-a-chip: Organ-on-a-chip is a miniaturized physiological environment engineered to yield and/or analyze functional tissue units capable of modeling specified/targeted organ-level responses.

Feedback welcome: **Alternatives@fda.hhs.gov**

FDA Encourages Stakeholder Dialogue

- FDA Stakeholders are encouraged to discuss with FDA the potential use of MPS and other new predictive methodologies for toxicity and efficacy of FDA-regulated products. Venues include:
  - AMWG webinars-see FDA Alternatives Webpage
  - Meetings such as this NASEM Meeting
  - Other Joint Meetings on MPS
  - By email –alternatives@fda.hhs.gov
  - Pre-IND/IDE meetings/written responses with FDA regulators
  - Critical Path Innovation Meetings – outside of a regulatory application

FDA Internal Research- FDA User Group

FDA scientists are developing in-house MPS and collaborating with several external partners

FDA signs collaborative agreement with CN Bio Innovations to use Organs-on-Chips to improve drug development and evaluation

POSTED OCT 2017

London, UK, October 26 2017: CN Bio Innovations Limited announced today that it has entered into a Research Collaboration Agreement with the US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research.

FDA Center for Drug Evaluation and Research

TISSUSE Emulating Human Biology

FDA National Center for Toxicological Research

Original Report

Adaptation of a Simple Microfluidic Platform for High-Dimensional Quantitative Morphological Analysis of Human Mesenchymal Stromal Cells on Polystyrene-Based Substrates

Johnny Lam[1], Ross A. Marklein[1], Jose A. Jimenez-Torres[2], David J. Beebe[2], Steven R. Bauer[1], and Kyung E. Sung[1]

SLAS Technology
2017, Vol. 22(6) 646–661

DOI: 10.1177/2472630317726050
journals.sagepub.com/home/jla
SAGE

FDA Center for Biologics Evaluation and Research

Human iPSC-based Cardiac Microphysiological System For Drug Screening Applications

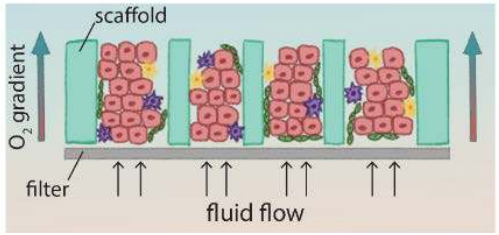
Anurag Mathur[1,2], Peter Loskill[1,2], Kaifeng Shao[1], Nathaniel Huebsch[4,5], SoonGweon Hong[1], Sivan G. Marcus[1], Natalie Marks[1], Mohammad Mandegar[4,5], Bruce R. Conklin[4,5], Luke P. Lee[1,3] & Kevin E. Healy[1,2]

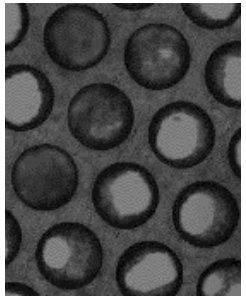
FDA Center for Food Safety and Applied Nutrition

FDA and Emulate sign a Collaborative Agreement
October 29, 2020

Cardiac and hepatic systems being evaluated in the Division of Applied Regulatory Science

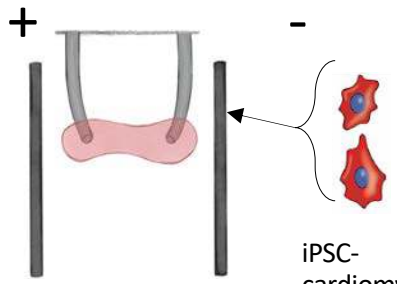
1. CN Bio Innovations LiverChip

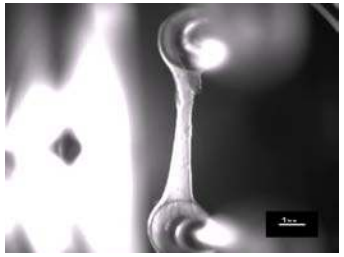




Outputs:
- Cell death
- Metabolism
- Biomarkers
- Gene expression

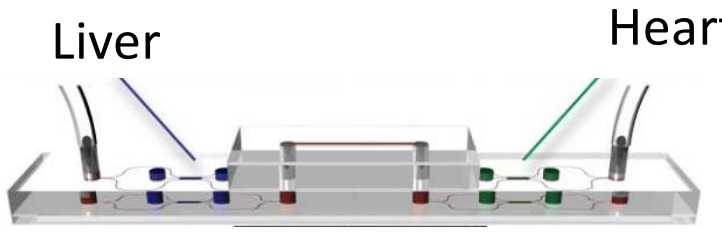
2. Engineered Heart Tissue (EHT)





Outputs:
- Contractility
- Calcium cycling
- Length of contractions

3. Berkeley Heart-Liver system

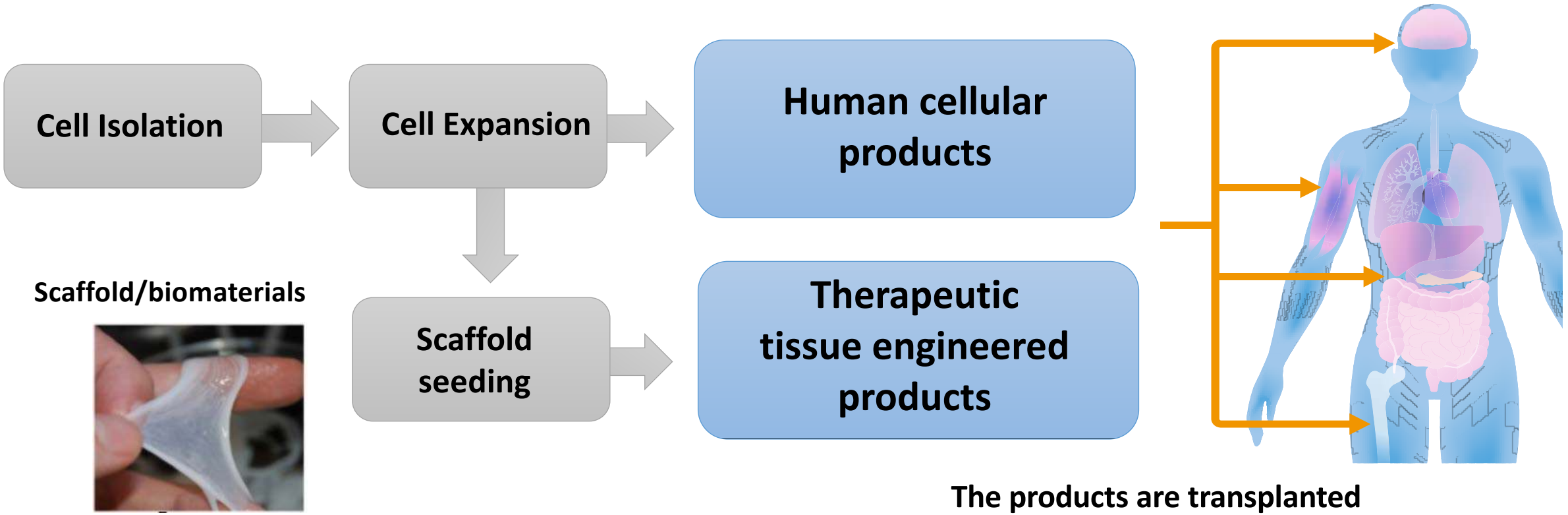


Combined system designed to use iPSC-derived cells

CBER: Regenerative Medicine Cellular Therapies

Slides courtesy of Kyung Sung

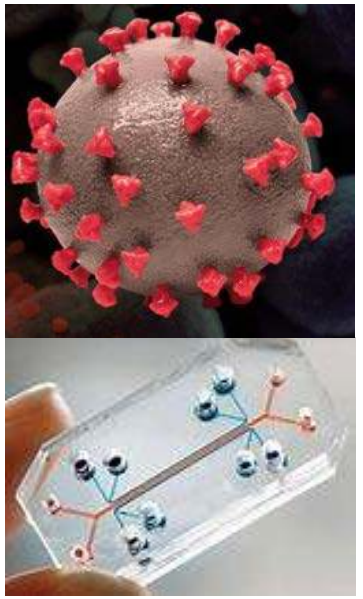
Regenerative medicine is the process of replacing or regenerating human cells, tissues or organs to restore or establish normal function.



COVID-19 Organ-on-Chip Models: Extramural

Slide courtesy Tracy MacGill, Office of Counterterrorism and Emerging Threats

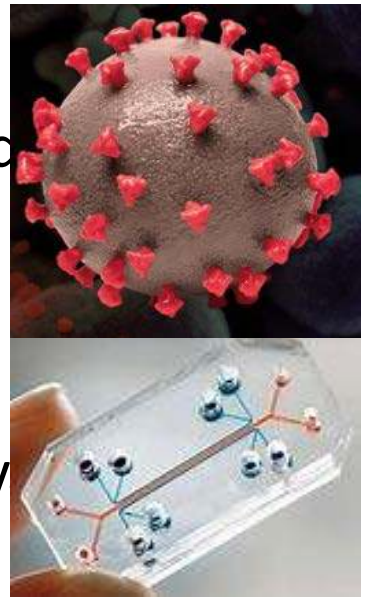
- FDA and NIH/NIAID awarded a $5.4 M contract to the University of Liverpool and global partners to understand coronavirus (including SARS-CoV-2) disease severity through analysis of non-clinical and clinical samples.
- The project includes development of *in vitro* coronavirus models to inform medical countermeasure (MCM) development and evaluation
  - COVID-19 organ-on-chip models led by Public Health England
  - Initial focus is lung-chip model development and MCM testing with additional model(s) to follow
  - Transcriptomics and imaging (mass cytometry, CODEX) will support comparison of *in vitro* (cell culture, organ chips) and *in vivo* responses



COVID-19 Organ Chip Models: Intramural

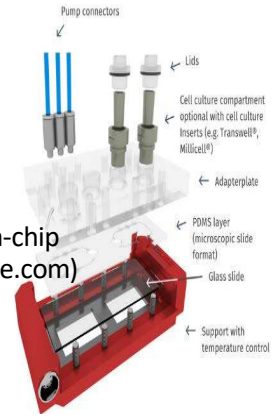
- CBER project (Dr. Tony Wang): Understanding the protective immunity against SARS-CoV-2 and Testing vaccine safety and efficacy using Lung-chip

- Highlights:
  - The study will infect the Lung-Chip with multiple strains of SARS-CoV-2 and delineate the initial innate immune response toward the virus to explore susceptibility to SARS-CoV-2 infection.
  - The study will examine the antibody response in the Lung-Chip generated by human plasma samples containing high titer neutralizing antibodies against SARS-CoV-2, showing how these antibodies may protect human lung cells from viral infection and enable cellular immunity from SARS-CoV-2.
  - Knowledge obtained from the study will provide insights into antibody-dependent enhancement (ADE), which is relevant to evaluating the safety of vaccines for COVID-19.



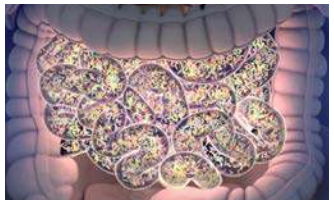
NCTR: Development of Two-Organ MPS Models for Reproductive Toxicity Assessment

- Conventional tests are time intensive and require large numbers of rodents
- NCTR in partnership with TissUse will develop a MPS containing organoids
- for two tissues linked by a microfluidic circuit for drug toxicity testing
- Initial efforts will develop rat *in vitro* MPS models that approximate *in vivo* hepatic drug metabolism and spermatogenesis
- Future efforts will extend to
  - Rat-to-human extrapolation
  - Characterization and qualification of the MPS models for regulatory use



Two organ-on-a-chip platform (tissuse.com)

CVM's MPS Initiative



- Focus: Gut-on-a-Chip
- Short term goal
  - Develop a gut-on-a-chip model for determining the impact of antimicrobial drug residues on the human intestinal microbiome, including the development of antimicrobial resistance.
- Long term goal
  - Develop performance standards for qualification of the model to fill a gap in tools needed to support the evaluation of antimicrobial drug products intended for use in food-producing animals.

Context of Use Qualification

- Beyond analytical validation, what steps need to be taken to enable regulatory use, without proving utility each time?

- FDA developed concept of “qualification:” a conclusion that the results of an assessment using the model or assay can be relied upon to have a specific interpretation and application in product development and regulatory decision-making

- Inextricable to qualification is concept of “context of use:” a clearly articulated description delineating the manner and purpose of use for a particular approach

Start with a Regulatory Question-Context of use

- What question needs to be answered and for what purpose?
  - How much “validation/qualification” is needed for a particular assay will depend on the particular context of use.

  - Helps define acceptable applicability domain and limitations
  - Context could be expanded over time
  - Reference compounds are determined by context of us

Moving toward regulatory use

- Does an assay provide data that can be used to answer fundamental drug development questions?
- Is the assay mature enough?
  - Stable platform, cells
- What endpoints are being measured?
  - Are they predictive of in vivo effects?
  - Translatable to human?
- Has scientific validity been shown?
  - Is it reproducible?
  - What test compounds have been assessed?
    - Need compounds with in vivo data
    - Positives and negatives
- Applicability domain
  - Define compounds the assay can assess and not assess
- Criteria for success
  - What are sensitivity and specificity?

Remember-Change Takes Time- But It will Happen If We All Work Together

Questions

Plese contact me

Suzanne Fitzpatrick, PhD, DABT, ERT

Email-Suzanne.Fitzpatrick@fda.hhs.gov