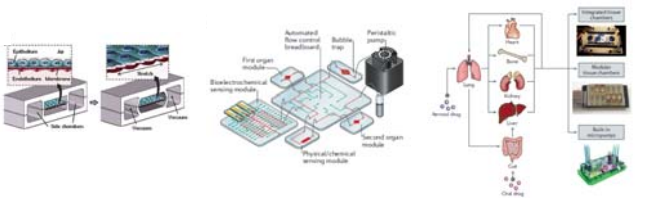
Introduction to BioMEMS & Medical Microdevices

Organ-on-a-Chip (OOCs)

Prof. Steven S. Saliterman, http://saliterman.umn.edu/



FDA Modernization Act of 2021

- A bill to amend the *Federal Food, Drug, and Cosmetic Act* to allow manufacturers and sponsors of a drug to use "alternative testing methods to animal testing" to investigate the "safety and effectiveness of a drug," and for other purposes.
- Broadening the scope of "acceptable preclinical models" for drug development.
- Enabling researchers to test a drug's safety and efficacy using more advanced and humane methods in "place of animals" whenever possible.

Applause applause!

- The Act strikes "animal" and inserts "nonclinical tests or studies."
- The bill defines "nonclinical tests or studies" as a test or study that is most likely to predict human response based on scientific evidence and occurs before or during the clinical trial phase of the investigation of the safety and effectiveness of a drug.
- Such test or study may include the following:
  - Cell-based assays
  - Organ chips and microphysiological systems
  - Sophisticated computer modeling
  - Other human biology-based test methods

H. R. 2565

Cost of Drug Development 2000-2019

JAMA Network | Open.

Original Investigation | Statistics and Research Methods

Costs of Drug Development and Research and Development Intensity in the US, 2000 - 2019

Aylin Sertkaya, PhD; Trinidad Beleche, PhD; Amber Jessup, PhD; Benjamin D. Sommers, MD, PhD

RESULTS The estimated mean cost of developing a new drug was approximately $172.7 million (2018 dollars) (range, $72.5 million for genitourinary to $297.2 million for pain and anesthesia), inclusive of postmarketing studies. The cost increased to $515.8 million when cost of failures was included. When the costs of failures and capital were included, the mean expected capitalized cost of drug development increased to $879.3 million (range, $378.7 million for anti-infectives to $1756.2 million for pain and anesthesia); results varied widely by therapeutic class. The pharmaceutical industry as a whole experienced a decline of 15.6% in sales but increased R&D intensity from 11.9% to 17.7% from 2008 to 2019. By contrast, R&D intensity of large pharmaceutical companies increased from 16.6% to 19.3%, whereas sales increased by 10.0% (from $380.0 to $418.0 billion) over the same 2008 to 2019 period, even though the cost of drug development remained relatively stable or may have even decreased.

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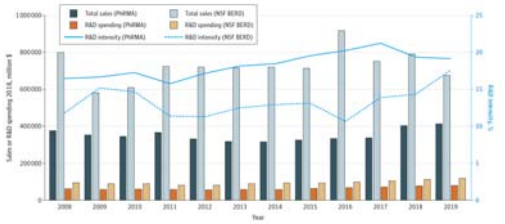
Sertkaya A, Beleche T, Jessup A, Sommers BD. Costs of Drug Development and Research and Development Intensity in the US, 2000-2018. *JAMA Network Open*. 2024;7(6):e2415445-e2415445. doi:10.1001/jamanetworkopen.2024.15445

Sales, R & D, R & D Intensity…

Figure 2. Sales, Research and Development (R&D) Spending, and R&D Intensity, 2008-2019



Data are from the National Science Foundation (NSF) **Business Enterprise Research and Development Survey (BERD)** and the **Pharmaceutical Research and Manufacturers of America (PhRMA)**. Data are adjusted to real 2018 US dollars using the Medical Care Consumer Price Index.

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Sertkaya A, Beleche T, Jessup A, Sommers BD. Costs of Drug Development and Research and Development Intensity in the US, 2000-2018. *JAMA Network Open*. 2024;7(6):e2415445-e2415445. doi:10.1001/jamanetworkopen.2024.15445

Organ-on-a-Chip Research

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https://youtu.be/5l0QVeFbS0c

Why Organ-on-a-Chip Technology?

- Drug discovery and cancer modeling – need for advanced, preclinical models.
  - Traditionally animals have been used.
    - Ethical and species differences concerns.
    - Errant pharmacokinetic predictions.
    - Regulations may prohibit testing – ie. cosmetics testing in EU since 2013.
  - Cell-based assays using human derived cells have been an alternative approach, but....
    - Cells often do not retain their original organ function and morphology.
    - Difficult to predict drug efficacy, toxicity and organ interactions.

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Kimura H, Sakai Y, Fujii T. Organ/body-on-a-chip based on microfluidic technology for drug discovery. *Drug Metabolism and Pharmacokinetics.* 2018;33(1):43-48.
Zhang B, Korolj A, Lai BFL, Radisic M. Advances in organ-on-a-chip engineering. *Nature Reviews Materials.* 2018;3(8):257-278.

Why OOC?

- Better replication of the pathophysiology of human disease.
- Better understanding of drug sensitivities for specific subsets of patients.
- ECM engineering for mimicking healthy and disease states.
- Assessment of environmental chemical teratogenic effects.

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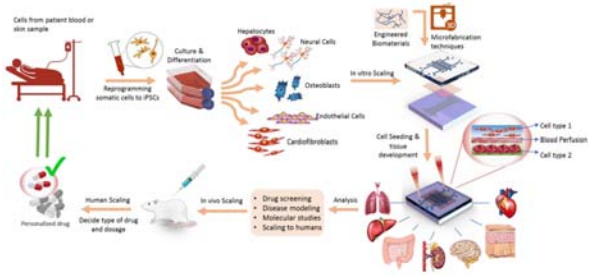
Cell Cycle for Personalized Medicine…



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Jodat YA, Kang MG, Kiaee K, et al. Human-Derived Organ-on-a-Chip for Personalized Drug Development. *Current pharmaceutical design.* 2018;24(45):5471-5486. doi:10.2174/1381612825666190308150055

- Schematic of the cycle used in OOCs for personalized medicine.
  - The cells are derived from patient and cultured and reprogrammed to different cell types.
  - The device is fabricated using various microfabrication and 3D printing techniques.
  - Next, the printed cells are seeded and cultured on the device. The target drug candidates are tested and analyzed using the OOC model followed by *in vivo* test.
  - Next, the drug dosage and type are decided based on the responses received from the *in vivo* and OOC device and are later scaled to achieve the personalized drug for the patient.

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Jodat YA, Kang MG, Kiaee K, et al. Human-Derived Organ-on-a-Chip for Personalized Drug Development. *Current pharmaceutical design*. 2018;24(45):5471-5486. doi:10.2174/1381612825666190308150055

What's Required for Organ-Specific Structures?

- The predictive value of a model is improved the more the species-specific biology is mimicked, including the tissue microenvironment and architecture.
  - Epithelial Barriers
    - For lung, airway, gut, kidney proximal tubules and glomeruli, and placenta.
  - Vascular and Lymphatic Barriers
    - For blood-brain and blood-retina barriers, microvasculature, artery, and lymphatic vessels
  - Parenchymal Tissues
    - For myocardium, skeletal muscles, liver, tumors, adipose tissue and peripheral nerves.
- Consideration for Interaction of multiple organs (ie. drug absorption, distribution, metabolism, and elimination).

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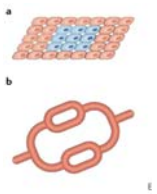
Zhang B, Korolj A, Lai BFL, Radisic M. Advances in organ-on-a-chip engineering. *Nature Reviews Materials*. 2018;3(8):257-278.

Four Components of an Organ-on-a-Chip…

1. Geometric confinement and patterning:
   - Spatially defined multicellular co-culture.
   - Phenotypical change may be induced by physical confinement.
2. Control of flow:
   - Fluid inlets and outlets.
   - Physiological cell to liquid ratio.



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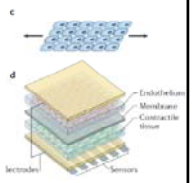
Maoz, B. M. et al. Organs- on-Chips with combined multi- electrode array and transepithelial electrical resistance measurement capabilities. Lab. Chip 17, 2294–2302 (2017).

3. Environmental control (c).
   - Mechanical stimulation and actuation.
   - Electrical stimulation.
   - Environmental control of O_2, CO_2, pH, nutrients and growth factors.
   - On demand presence of drugs or toxins.
4. Sensor and physiologic readouts.
   - Built-in electrodes.
   - Optical readouts.
   - Online sensors for biochemical readouts.



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Methods

- 3D printing and microfabrication.
- Incorporating multiple cell types.
- Guided spacial confinement of cells.
- Use of sensors and microfluidic channels.
- Contrast this to an *organoid approach* which relies on the spontaneous self-assembly of cells to achieve complex tissue and organ-level organization and function.

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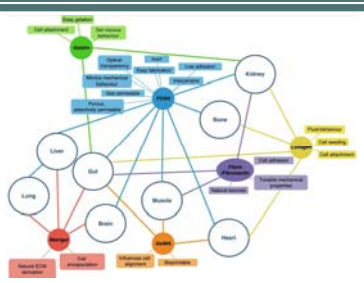
Zhang B, Korolj A, Lai BFL, Radisic M. Advances in organ-on-a-chip engineering. *Nature Reviews Materials.* 2018;3(8):257-278.

OOC Systems, Biomaterials & Properties



Various OOC systems with their commonly used biomaterials (coloured circles) and associated properties. (coloured squares).

Biomaterial:
- **Gelatin**
- **PDMS**
- **Collagen**
- **Fibrin/Fibronectin**
- **GelMA**
- **Matrigel**

Terms sound foreign? AI search each one.

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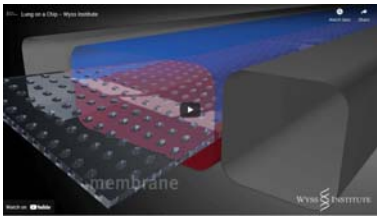
Cao UMN, Zhang YL, Chen JL, Sayson D, Pillai S, Tran SD. Microfluidic Organ-on-A-chip: A Guide to Biomaterial Choice and Fabrication. Review. *Int J Mol Sci.* Feb 2023;24(4):22. 3232. doi:10.3390/ijms24043232

Lung-on-a-Chip…



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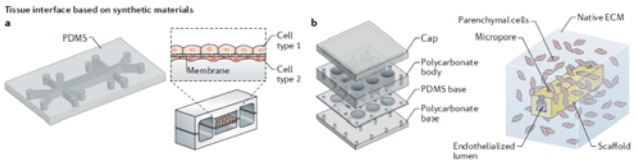
https://youtu.be/52lL9gemyDw

Reproducing the Tissue Barrier Function…



PDMS membranes. (e.g., Lung)

Perfusion bioreactor and synthetic microfabricated scaffold. (Scaffold with Vasculature)

See Huh & Zang articles:

a) Huh, D. et al. Reconstituting organ- level lung functions n a chip. Science 328, 1662–1668 (2010).
b) Zhang, B. et al. Biodegradable scaffold with built- in vasculature for organ- on-a- chip engineering and direct surgical anastomosis. Nat. Mater. 15, 669–678 (2016).

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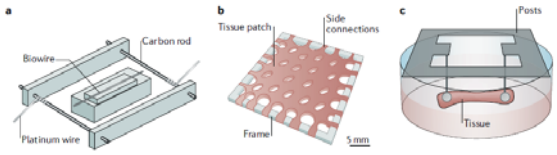
Reproducing Elongated Parenchymal Tissues…

Cardiomyocytes…



Tissue compact along wires.

Posts can anchor a tissue network.

Tissues can hang upside down on pillars.

a) Sun, X. & Nunes, S. S. Biowire platform for maturation of human pluripotent stem cell- derived cardiomyocytes Methods 101, 21–26 (2016).
b) Bian, W., Badie, N., Himel IV, H. D. & Bursac, N Robust T- tubulation and maturation of cardiomyocytes using tissue- engineered epicardial mimetics. Biomaterials 35, 3819–3826 (2014).
c) Stoehr, A. et al. Spontaneous formation of extensive vessel- like structures in murine engineered heart tissue. Tissue Eng. Part A 22, 326–335 (2016).

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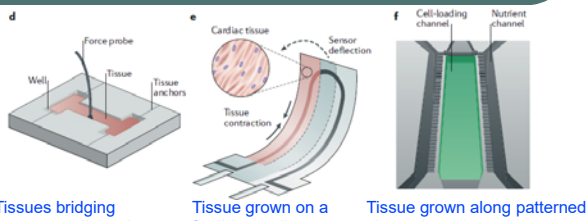


Tissues bridging across parallel rods.

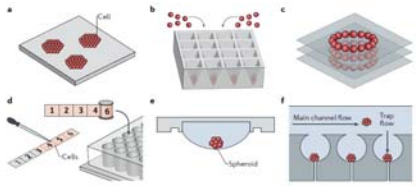
Tissue grown on a flexible cantilever.

Tissue grown along patterned channels and grooves.

d) Schroer, A. K., Shotwell, M. S., Sidorov, V. Y. Wikswo, J. P. & Merryman, W. D. I- Wire Heart- on-a- Chip II: biomechanical analysis of contractile, three- dimensional cardiomyocyte tissue constructs. Acta Biomaterialia 48, 79–87 (2017).
e) Lind, J. U. et al. Instrumented cardiac microphysiological devices via multimaterial three- dimensional printing. Nat. Mater. 16, 303–308 (2016).
f) Mathur, A. et al. Human iPSC- based cardiac microphysiological system for drug screening applications. Sci. Rep. 5, 8883 (2015).

Reproducing Spherical Parenchymal Tissues…

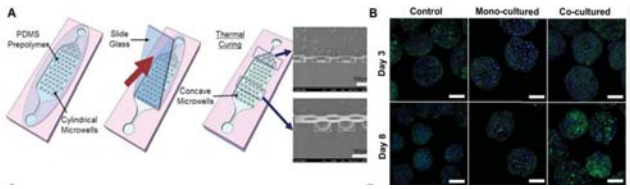
Micro-patterned Clusters | Inverted Pyramidal Wells | 3D Multilayer Printing



Rolled-up Scaffolds | Hanging Droplets | Microfluidic Cell Trapping

a) Khetani, S. R. & Bhatia, S. N. at. Biotechnol. 26, 120–126 (2008).
b) Stevens, K. R. et al. Transl Med. 9, eaah5505 (2017).
c) Marga, F. et al. Biofabrication 4, 022001 (2012).
d) Rodenhizer, D. et al. Nat. Mater. 15, 227–234 (2016).
e) Frey, O., Misun, P. M., Fluri, D. A., Hengstler, J. G. & Hierlemann, A. Nat. Commun. 5, 4250 (2014).
f) Lai, B. F. L. et al. Adv. Funct. Mater. https://doi.org/10.1002/adfm.201703524 (2017).

Example: Liver-on-a-Chip…



Microwell array PDMS plate based liver-on-a-chip device.

Generated 3D spheroids on day 3 and 8.

Kostrzewski T, Cornforth T, Snow SA, Ouro-Gnao L, Rowe C, Large EM, et al. Three-dimensional perfused human in vitro model of non-alcoholic fatty liver disease. World J Gastroenterol. 2017 1 14;23(2):204–15.

Challenges

- Material selection
- Cellular fidelity
- Multiplexing and fluid handling
- Imaging and Sensing
- Validation and integration with existing drug development platforms.
- Scalable production, cost and market size.

Zhang B, Korolj A, Lai BFL, Radisic M. Advances in organ-on-a-chip engineering. *Nature Reviews Materials.* 2018;3(8):257-278.

Materials…

- PDMS (Silicone)
  - Elastic modulus of ~1-3 Mpa – compliant and deformable.
  - Easily moldable – 2-part mix, vacuum de-bubble and pour.
  - Sections can be plasma or ozone treated and "stacked" together allowing for complex microchannels.
  - Suitable for biomimetic ECM scaffolds.
  - Optically transparent, biocompatible and oxygen permeable.
  - Susceptible to medium evaporation, bubble formation and unwanted absorption of hydrophobic drugs/compounds.

Cellular Fidelity…

- Immortalized cell lines.
  - Serial changes affect genotype and phenotype
- ESCs (embryonic stem cells), and patient specific iPSCs (induced pluripotential cells).
  - More accurate modeling.
  - Differentiation may be accomplished within the device.
  - IPSCs can be expanded into heterogenous cell populations which can self-organize into organoids (fidelity of gene and protein expression, tissue morphology, and metabolic and physiological function.)
- Animal/human samples.
  - Can be a challenge to collect – especially myocardial cells.

Zhang B, Korolj A, Lai BFL, Radisic M. Advances in organ-on-a-chip engineering. *Nature Reviews Materials.* 2018;3(8):257-278.

Fluid Handling…

- External pumping
  - Syringes, vacuum and peristaltic pumps.
- Integrated micropumps
  - e.g. pneumatic, electrostatic, magnetic and piezoelectric
- For control of nutrients, oxygen and waste removal.
- For circulation of signaling, metabolic and angiogenic factors.
- Integration of body-on-a-chip subunits.

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Example Platform – Translational OOC…

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https://youtu.be/jkq0BTILrq0

Body-on-a-Chip

1. Multiorgan systems on a chip.
2. Useful in predicting human response prior to clinical testing of a drug or as augmentation of clinical studies to test underlying mechanisms.
3. Modeling organ physiology allowing better understanding of underlying mechanisms of response to drugs and chemicals.
4. Animal models often do not predict human response effectively increasing the demand for more advanced model platforms.
5. Rate of development of these systems has been exponential.

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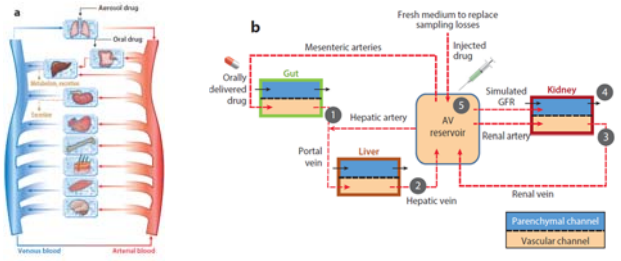
Sung JH, Wang YI, Narasimhan Sriram N, et al. Recent Advances in Body-on-a-Chip Systems. *Anal Chem*. Jan 2 2019;91(1):330-351. doi:10.1021/acs.analchem.8b05293

Body-on-a-Chip Concept…



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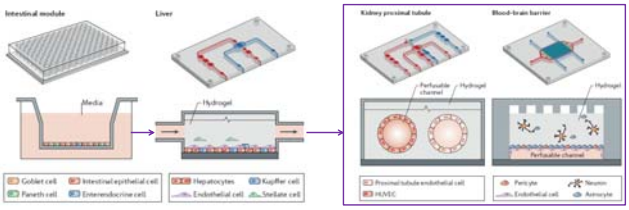
Prantil-Baun R, Novak R, Das D, Somayaji MR, Przekwas A, Ingber DE. Physiologically Based Pharmacokinetic and Pharmacodynamic Analysis Enabled by Microfluidically Linked Organs-on-Chips. In: Insel PA, ed. *Annual Review of Pharmacology and Toxicology*, Vol 58. Vol 58:2018:37-64.

Organ Coupling for Body-on-a-Chip…



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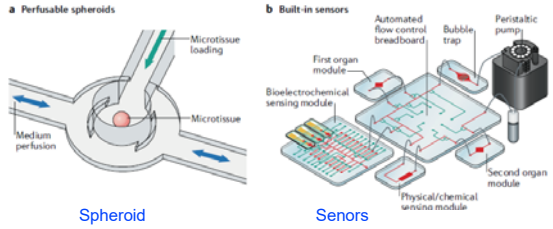
Vernetti, L. et al. Functional coupling of human microphysiology systems: intestine, liver, kidney proximal tubule, blood- brain barrier and skeletal muscle. Sci. Rep. 7, 42296 (2017).

Modeling Multi-Organ Interactions…



Spheroid Senors

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a) Kim, J.-Y. et al. 3D spherical micro-tissues and microfluidic technology for multi- tissue experiments and analysis. J. Biotechnol. 205, 24–35 (2015).
b) Zhang, Y. S. et al. Multisensor- integrated organs-on-chips platform for automated and continual in situ monitoring of organoid behaviors. Proc. Natl Acad. Sci. USA 114, E2293–E2302 (2017).

Imaging and Sensing

- Conventional optical and confocal fluorescence microscopes.
  - Post-printing bioreactors can now be followed in real-time while controlling the external environment.
- Microsensors can be made to monitor oxygen concentration, pH, glucose consumption.
- Antibody and aptamer-based sensing.
- Trans-epithelial electrical resistance (TEER)
  - Correlated with tissue health, drug delivery and tissue diffusion.

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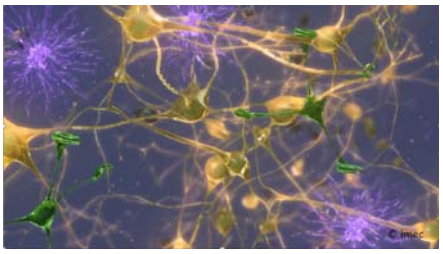
Zhang B, Korolj A, Lai BFL, Radisic M. Advances in organ-on-a-chip engineering. *Nature Reviews Materials.* 2018;3(8):257-278.

High Density Electrode for OOC Sensing…



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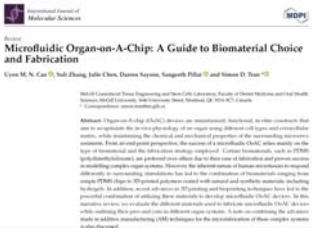
https://youtu.be/FcvDvCXyF4k

Recommended Reading


REVIEWS

Human organs-on-chips for disease modelling, drug development and personalized medicine


Microfluidic Organ-on-A-Chip: A Guide to Biomaterial Choice and Fabrication

Steven S. Saliterman

Ingber DE. Human organs-on-chips for disease modelling, drug development and personalized medicine. *Nature Reviews Genetics.* Aug 2022;23(8):467-491. doi:10.1038/s41576-022-00466-9

Cao UMN, Zhang YL, Chen JL, Sayson D, Pillai S, Tran SD. Microfluidic Organ-on-A-chip: A Guide to Biomaterial Choice and Fabrication. *Int J Mol Sci.* Feb 2023;24(4):3232. doi:10.3390/ijms24043232

bioengineering

MDPI

Review

Tiny Organs, Big Impact: How Microfluidic Organ-on-Chip Technology Is Revolutionizing Mucosal Tissues and Vasculature

Ishita Dasgupta, Durga Prasad Kangineni, Hasan Abdelsaid, Yixiao Ma and Abhinav Bhushan *

Department of Biomedical Engineering, Illinois Institute of Technology, Chicago, IL 60616, USA;

* Correspondence:

Abstract: Organ-on-chip (OOC) technology has gained importance for biomedical studies and drug development. This technology involves microfluidic devices that mimic the structure and function of specific human organs or tissues. OOCs are a promising alternative to traditional cell-based models and animals, as they provide a more representative experimental model of human physiology. By creating a microenvironment that closely resembles in vivo conditions, OOC platforms enable the study of intricate interactions between different cells as well as a better understanding of the underlying mechanisms pertaining to diseases. OOCs can be integrated with other technologies, such as sensors and imaging systems to monitor real-time responses and gather extensive data on tissue behavior. Despite these advances, OOCs for many organs are in their initial stages of development,

Steven S. Saliterman

Dasgupta I, Rangineni DP, Abdelsaid H, Ma YX, Bhushan A. Tiny Organs, Big Impact: How Microfluidic Organ-on-Chip Technology Is Revolutionizing Mucosal Tissues and Vasculature. Review. *Bioengineering-Basel*. May 2024;11(5):20. 476. doi:10.3390/bioengineering1050476

Key Points

- The Federal Food, Drug, and Cosmetic Act to allows manufacturers and sponsors of a drug to use “alternative testing methods to animal testing” to investigate the “safety and effectiveness of a drug,” and for other purposes.
- The bill defines “nonclinical tests or studies” as a test or study that is most likely to predict human response based on scientific evidence and occurs before or during the clinical trial phase of the investigation of the safety and effectiveness of a drug.
- Cost for new drugs, inclusive of failures and capital, is around $879 million.

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Key Points…

- Issues with animals include ethics, species differences, errant pharmacokinetic predictions.
- The “cell cycle for personalized medicine’ includes:
  - Taking cells from the patient.
  - Reprograming somatic cells to iPSCs.
  - Culture and cellular differentiation.
  - Combining with OCC devices with cell seeding and tissue development.
  - Doing analysis for drug screening, disease modeling, molecular studies and scaling to humans.
  - Producing human doses.
- The predictive value of a model is improved the more the species-specific biology is mimicked, including the tissue microenvironment and architecture.

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Key Points…

- The basic 4 components of OOC:
  1. Geometric confinement and patterning.
  2. Control of flow.
  3. Environmental control.
  4. Sensor and physiologic readouts.
- OCC biomaterials include Gelatin, PDMS, Collagen, Fibrin/Fibronectin, GelMA, Matrigel.
- Body-on-a-Chip (BOC) require organ coupling, and modeling multi-organ interactions.
- Imaging and sensing include conventional optical and confocal fluorescence microscopes, and use of post-print bioreactors with real-time monitoring and control of the external environment.

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Appendix

- Evolution of Organ-on-a-Chip Systems
- Drug Evaluation
- Validation
- Scalability
- OOC, Cell type, Condition & Drugs Tested

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Evolution of Organ-on-a-Chip Systems

- Lab-on-a-chip systems emerged in the early 1990s, combining microfluidics technology, micro and nanofabrication methods, novel chemical sensors and analytical chemistries.
- The next step came with incorporating cells in the 2000s.
  - Movement from *in vitro* to *in vivo-like* environments.
  - Recognition of the ECM role in signalling, cell growth, adhesion, mechanical environment, among others.
  - Need to supply nutrients and oxygen, and remove waste products. Desire to move from diffusion only systems to creating *vasculature*.

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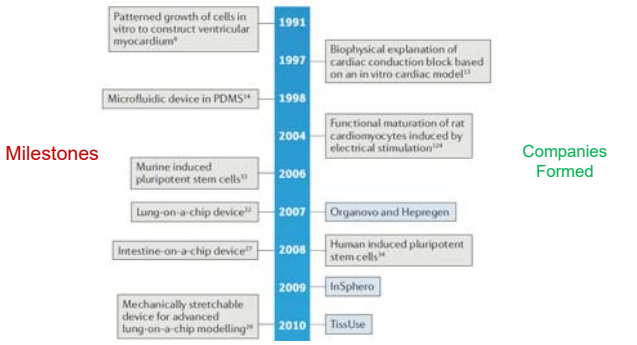
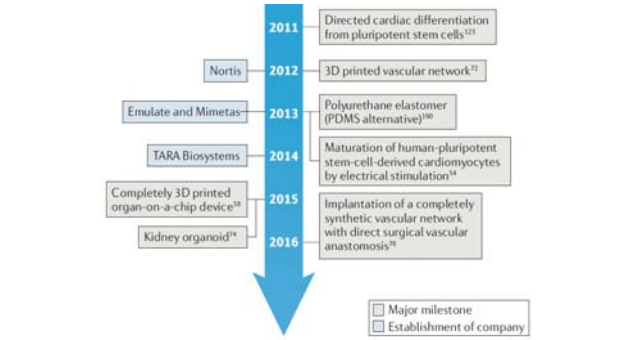
Kimura H, Sakai Y, Fujii T. Organ/body-on-a-chip based on microfluidic technology for drug discovery. *Drug Metabolism and Pharmacokinetics*. 2018;33(1):43-48.



Zhang B, Korolj A, Lai BFL, Radisic M. Advances in organ-on-a-chip engineering. *Nature Reviews Materials*. 2018;3(8):257-278.



Drug Evaluation with Organ Chips

- Microfluidic cell culture devices and vascularized Organ Chips offer a potentially exciting new approach to predict PK/PD properties in vitro.
- Vascularized microfluidic models that reconstitute physiological features and multicellular phenotypes are superior to typical cell lines, plate-based assays, and single-channel microfluidic devices.
- Computational abilities offer the capability to run more physiological experiments and to extrapolate in vivo predictions of drug behaviors in humans from in vitro data obtained with linked vascularized organs-on-a-chip.

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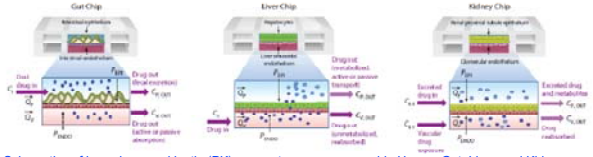
Prantil-Baun R, Novak R, Das D, Somayaji MR, Przekwas A, Ingber DE. Physiologically Based Pharmacokinetic and Pharmacodynamic Analysis Enabled by Microfluidically Linked Organs-on-Chips. In: Insel PA, ed. *Annual Review of Pharmacology and Toxicology, Vol 58*. Vol 58.2018:37-64.

Individual Organs-on-a-Chip…



Schematics of how pharmacokinetic (PK) parameters are measured in Human Gut, Liver, and Kidney Chips. All three chips are lined with organ-specific epithelium(upper channel) and vascular endothelium (lower channel) on opposite sides of a porous, matrix coated membrane in the central two channels of the device.

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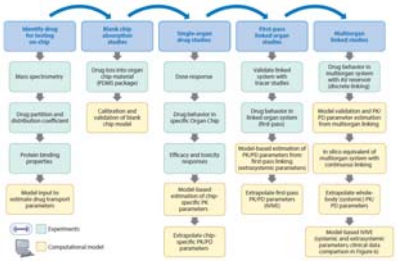
Work Flow to Evaluate a Drug…



Work flow to evaluate a drug in linked organ studies using a Human Body–on–Chips and to extrapolate pharmacokinetic /pharmacodynamic (PK/PD) parameters.

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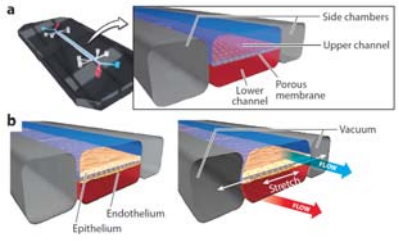
Vascularized Organ-on-a-Chip…



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Validation

- Validation will ensure that the biological functions produced on the chip are representative of the native tissue, with an understanding of any lack of similarity.
- Translational research is dependent on collaboration between researcher and industry.
- FDA and other regulatory collaboration with industry is necessary for standards – and selecting suitable physiological hallmarks, for validation of organ-on-a chip devices.

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Scalability

- Research-oriented soft lithography techniques are slow, expensive, are typically manually completed with multiple process steps and low yield, and lack reproducibility.
  - 3D printing/bioprinting may be useful –especially for complex microarchitectures and embedded sensors.
  - Preservation of printed cell/tissues within devices (device shelf-life) is a challenge.

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OOC, Cell type, Condition & Drugs Tested

OOC	Cell types used	Target disease or condition	Drugs tested	Functionality tested	Ref.
Lung on a chip	Cell line	Lung Cancer (NSCLC)	Tyrosine kinase inhibitor	Mechanical Strain, transformation epithelial endothelial tissue-tissue interface	(122)
Liver on a chip	Primary hepatocytes	Non-alcoholic fatty liver disease (NAFLD)	Pioglitazone, metformin	Oxygen gradient, Cell phenotyping, fat accumulation, metabolic capacity	(59)
	Primary hepatocytes	Potential drug toxic effects	Acetaminophen (APAP)	Configuration, arrangement of capillary layers, inflammatory reaction towards, enhanced cellular stress, expression of genes	(60)
	Primary hepatocytes	Drug-induced liver injury (DILI)	Troglitazone	Efflux, media collection, compatibility for microfluidic coupling, clearance rates for drugs	(123)
	Cell line (HepG2/C3A)	Mitochondrial dysfunction	Troglitazone, rotenone	2D cell aggregates, real-time oxygen measurement, mitochondrial Stress	(61)

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Jodat YA, Kang MG, Kiaee K, et al. Human-Derived Organ-on-a-Chip for Personalized Drug Development. *Current pharmaceutical design*. 2018;24(45):5471-5486. doi:10.2174/1381612825666190308150055

Kidney on a chip	hiPSCs	Albuminuria	Adriamycin	Cyclic mechanical strain, urinary filtrate, regulated vacuum, kidney glomerular capillary wall	(67)
	Primary cell	CysA-induced damage	Cyclosporine A	Renal proximal tubule (PT) composed of a perfusable open lumen that possesses a programmable architecture	(68)
	Primary cell	Chronic kidney disease, urothelial cancer	Aristolochic acid I	Organ-organ interactions	(69)
Gut on a chip	Cell line	Drug absorption	SN-38 (7-ethyl-10-hydroxycamptothecin)	Barrier function, microvilli expression, permeability coefficient	(124)
	Cell line	Gut radiation injury	DMOG (dimethyl(oxalylglycin)	Villus differentiation, paracellular permeability, radio-protective effects of drug	(72)
	hiPSCs	Biologically responsive to exogenous stimuli	Tumor necrosis factor-α, IFN-γ	Epithelial-immune cell interactions, permeability	(125)

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CNS and PNS on a chip	Human neural progenitor cell line	Molecular toxicology	Acetaminophen, 5-fluorouracil, retinoic acid, doxorubicin, pitavastatin	Various cell states, protein expression	(75)
	hiPSC-derived neurons	Familial Alzheimer's disease	β-secretase inhibitor	Fluidic isolation, separation of axons from the soma	(76)
	Primary cell, hiPSC	Motor neuron disease	Motor neuron progenitor	Effect of microvascular network perfusion on neural activity	(126)

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