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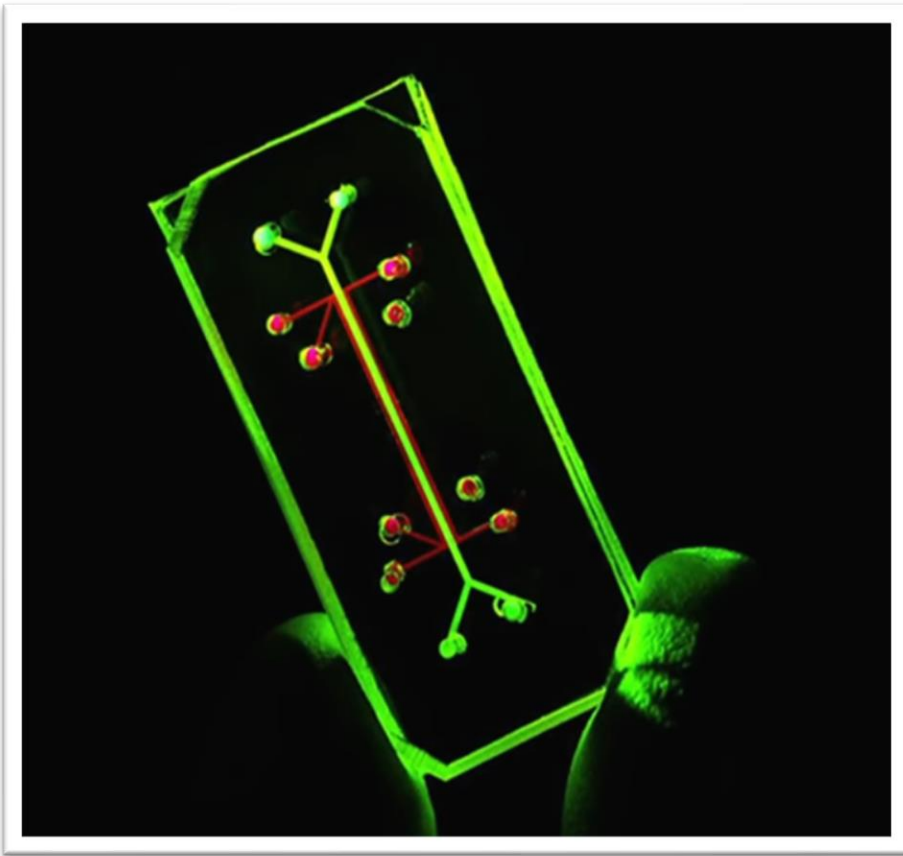
Cell architects:
a home away from
home for the cells

Organs-on-a-Chip: A Fast Track for Engineered Human Tissues in Drug Development

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Organs-on-a-chip (OOCs) are miniature tissues and organs grown *in vitro* that enable modeling of human physiology and disease. The technology has emerged from converging advances in tissue engineering, semi-conductor fabrication, and human cell sourcing. Encompassing innovations in human stem cell technology, OOCs offer a promising approach to emulate human patho/physiology *in vitro*, and address limitations of current cell and animal models. Here, we review the design considerations for single and multi-organ OOCs, discuss remaining challenges, and highlight the potential impact of OOCs as a fast-track opportunity for tissue engineering to advance drug development and precision medicine.

Organ-On-A-Chip Platforms: A Convergence of Advanced Materials, Cells, and Microscale Technologies

*Samad Ahadian, Robert Civitarese, Dawn Bannerman, Mohammad Hossein Mohammadi, Rick Lu, Erika Wang, Locke Davenport-Huyer, Ben Lai, Boyang Zhang, Yimu Zhao, Serena Mandla, Anastasia Korolj, and Milica Radisic**

Significant advances in biomaterials, stem cell biology, and microscale technologies have enabled the fabrication of biologically relevant tissues and organs. Such tissues and organs, referred to as organ-on-a-chip (OOC) platforms, have emerged as a powerful tool in tissue analysis and disease modeling for biological and pharmacological applications. A variety of biomaterials are used in tissue fabrication providing multiple biological, structural, and mechanical cues in the regulation of cell behavior and tissue morphogenesis. Cells derived from humans enable the fabrication of personalized OOC platforms. Microscale technologies are specifically helpful in providing physiological microenvironments for tissues and organs. In this review, biomaterials, cells, and microscale technologies are described as essential components to construct OOC platforms. The latest developments in OOC platforms (e.g., liver, skeletal muscle, cardiac, cancer, lung, skin, bone, and brain) are then discussed as functional tools in simulating human physiology and metabolism. Future perspectives and major challenges in the development of OOC platforms toward accelerating clinical studies of drug discovery are finally highlighted.

promise at suppressing irregular cardiac pacing in preclinical trials in 1980,[2] whereas a subsequent cardiac arrhythmia suppression trial in 1991 proved that the risk of a fatal cardiac event was 2.5 times higher for patients taking encainide and flecainide.[3] Research and development costs in drug development still continue to increase with the total cost up to $2.5 billion for every drug approval.[4] However, despite this increasing investment in drug development and discovery, the number of drugs approved by the Food and Drug Administration (FDA) has decreased over the last couple of decades.[5]

One of the main reasons for high cost and low efficiency of conventional drug development process is the lack of physiologically relevant preclinical models capable of predicting human responses to new drugs.[6] Animal models have been provided a living system with possible assessment of drug efficacy on target site and nontarget organ toxicity. However, the use of animal models is associated

1. Introduction

Incredible functionality

For instance, into the lung on a chip, designated the model of the year, bacteria or human white cells can be added, where the latter coming through the blood stream, makes its way through the cell layers and engulfs the bacteria

https://www.youtube.com/watch?v=CpkXmtJOH84&t=104s
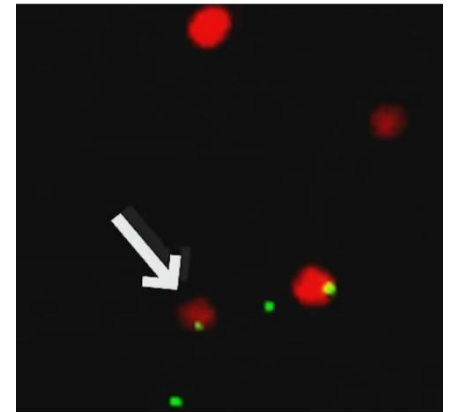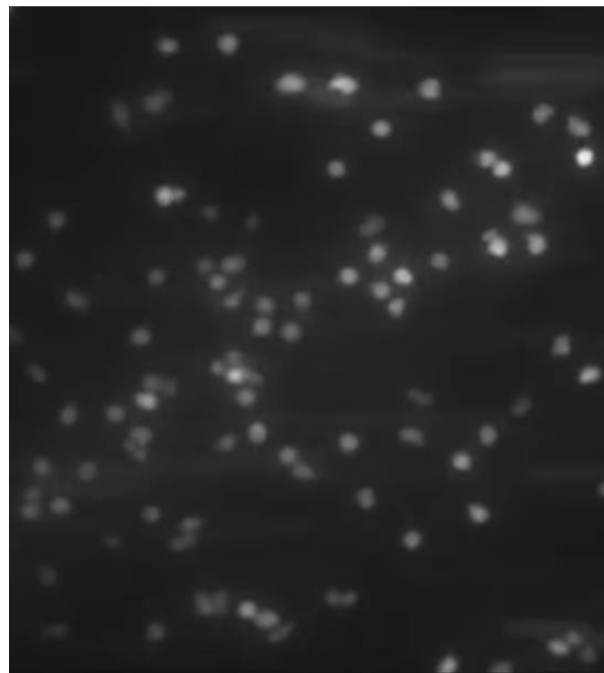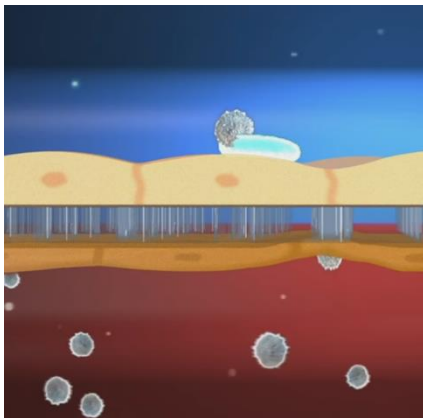
A Human Breathing Lung-on-a-Chip

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Abstract

Here we describe a microphysiological system that replicates the functional unit of the living human lung. This human "breathing lung-on-a-chip" microdevice provides unique capabilities to reconstitute three-dimensional microarchitecture, dynamic mechanical activity, and integrated physiological function of the alveolar–capillary interface. We demonstrate the potential of this microengineered biomimetic model for screening environmental particulates and modeling complex human disease processes.

Keywords: organ-on-a-chip; microfluidics; lung; lung-on-a-chip

https://www.jove.com/video/2651/procedure-for-lung-engineering

Researchers from Wyss Institute have also built bone marrow-on-a-chip, got it to act like whole living marrow and manufacture blood cells in 2014.

In 2015 researchers at the National Institute of Health developed a placenta on-a-chip to better understand the work that the temporary organ plays in pregnancy.

Lab-on-a-chip: catching molecular messages sent by tumors | Yong Zeng | TEDxLawrence
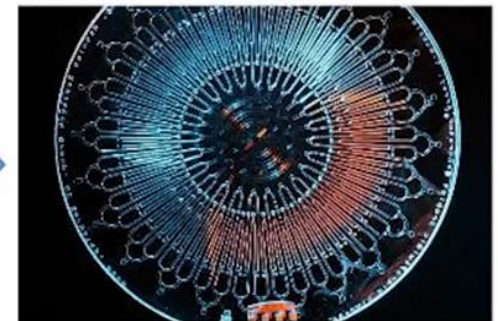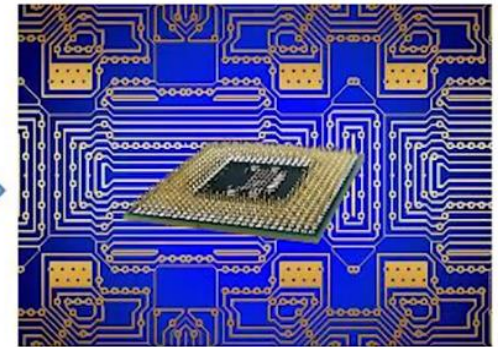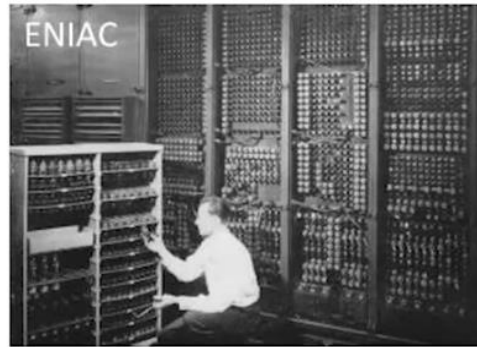
ORGANS-ON-CHIPS: EXPLORING THE UTILITY OF BIOSYNTHESISED ORGAN TISSUE TO IMPROVE EFFICIENCY OF THE DRUG DEVELOPMENT PROCESS

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Professor Dr. D.F. Stamatialis

AUGUST
2015

UNIVERSITY OF TWENTE.

Advantage:

Replacement of animals
        Failing animals
        Costs animals
Toxicity screening
Personalized medicine
Efficacy
Whole body response
Costs
Higher sensitivity to external stimuli
Replacement/reducing human trials
Better identification of target organs/drugs
Predict human drug toxicity
Length
PK/PD
        ADME
Hit Rate (predictability of new drug)
Preclinical
Drug side effect
Safety
Drug-dose response
Better understanding of target
Repurposing of drugs

Disadvantage:

Possible interaction between drug vector and microfluidic system
Interaction between drug and PDMS poly(dimethylsiloxane)
Only subset of cells (no connecting tissues)
Difficult to monitor genomic levels of cells
Models fail to fully mimic organ-specific functions
Unclear if models fully mimics functions
Not developed enough
3D system difficult to sustain long-term
PDMS (often used as a membrane) much thicker than normal
Difficult to obtain human organ specific cells with both proliferative capacity and full differentiation capability
More expensive than well plates
Phenotypic mismatch between cell lines and in vivo situation

RESULTS: According to stakeholders, organ-on-a-chip may be most promising in the basic research stage (90%) or the preclinical stage (88%) of drug development. Simple models can be used for target identification (70%) while complex models could lead to replacement of animals (78%). However, head-to-head studies are needed to change regulations, leaving organ-on-a-chip as an additional test in drug development for now. There are significant differences between stakeholders' opinions about advantages. Most promising organ-on-chip developments should target organs like Liver (20%), heart (18%) and kidney (17%).
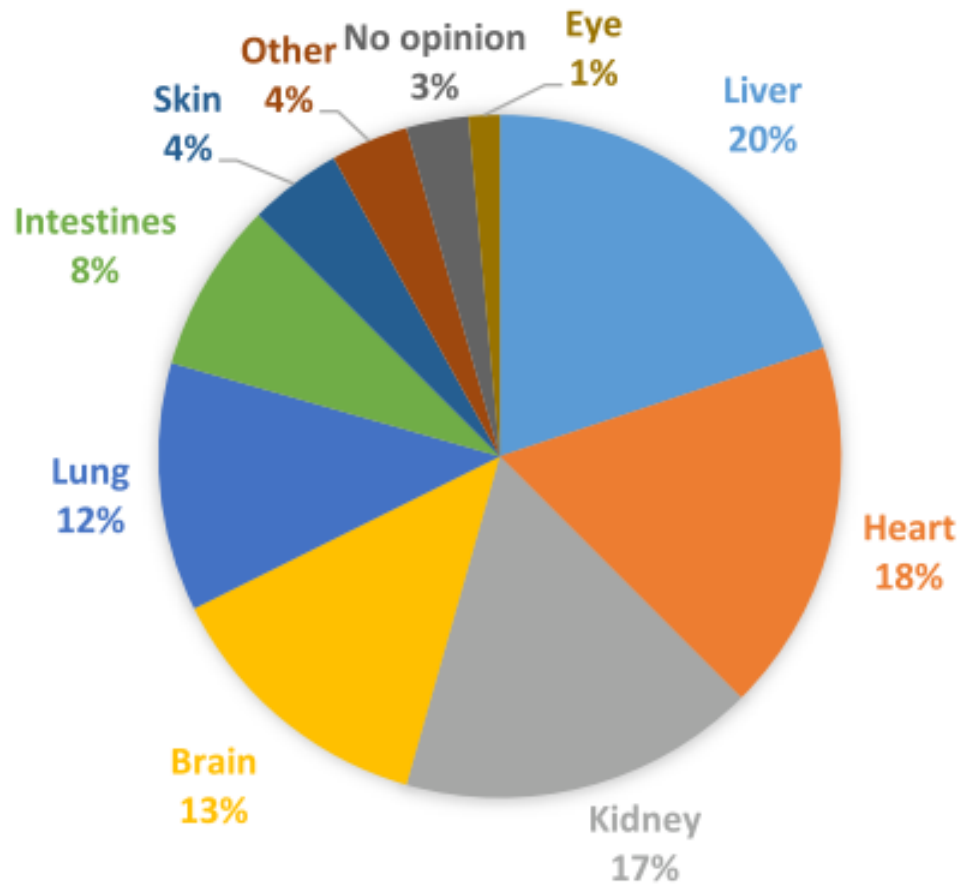
Figure 3Which organs should be developed first as an OOC model according to stakeholders?

Microfluidic organs-on-chip

Sangeeta N Bhatia[1,2] & Donald E Ingber[3–5]

An organ-on-a-chip is a microfluidic cell culture device created with microchip manufacturing methods that contains continuously perfused chambers inhabited by living cells arranged to simulate tissue- and organ-level physiology. By recapitulating the multicellular architectures, tissue-tissue interfaces, physicochemical microenvironments and vascular perfusion of the body, these devices produce levels of tissue and organ functionality not possible with conventional 2D or 3D culture systems. They also enable high-resolution, real-time imaging and in vitro analysis of biochemical, genetic and metabolic activities of living cells in a functional tissue and organ context. This technology has great potential to advance the study of tissue development, organ physiology and disease etiology. In the context of drug discovery and development, it should be especially valuable for the study of molecular mechanisms of action, prioritization of lead candidates, toxicity testing and biomarker identification.
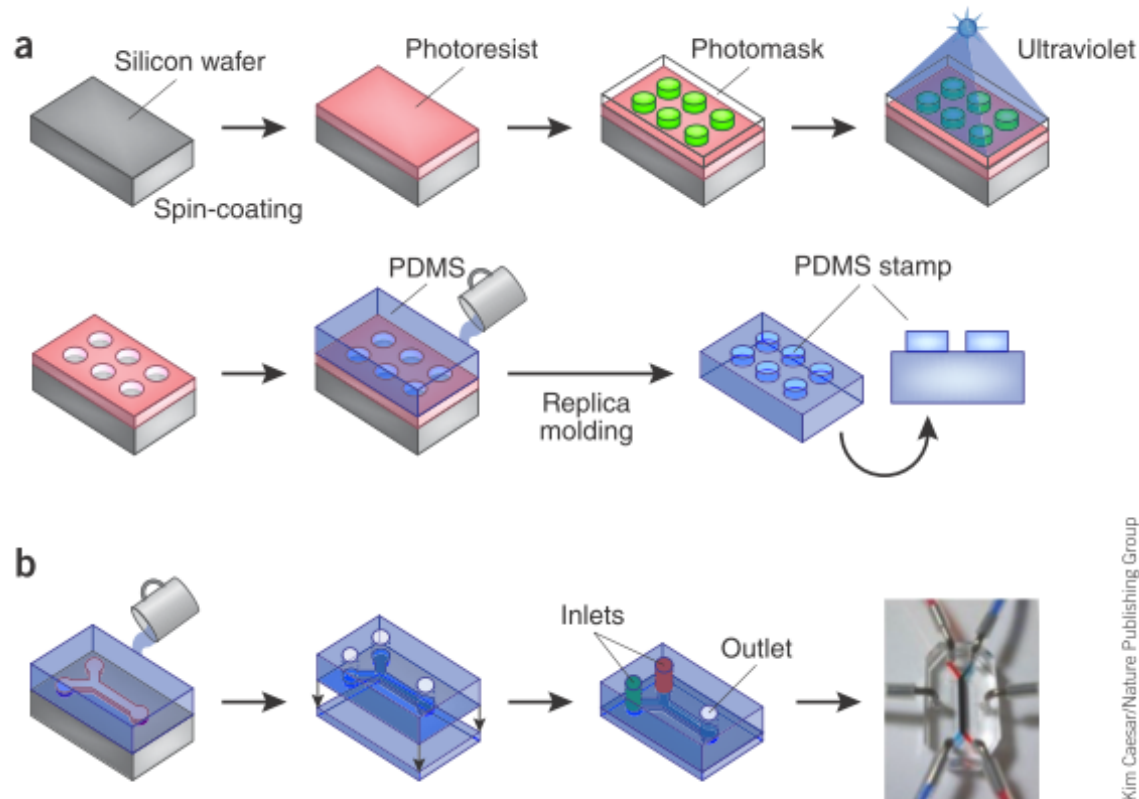
Figure 1 Fabrication methods for microfluidic chips. (**a**) Replica molding[10] creates stamps with shapes complementary to patterns etched in silicon chips by photolithography. A thin uniform film of a photosensitive material (photoresist) is spin-coated on a silicon chip, which is then overlaid with a photomask (e.g., a transparent glass plate patterned with opaque chrome layers) bearing a microscale pattern generated with computer-assisted design software. The photomask protects some regions of the photoresist and exposes others during exposure to high-intensity ultraviolet (UV) light. The UV-exposed material dissolves in a developer solution, leaving the microscale pattern etched into the photoresist. Elastomeric stamps with a surface topography complementary to the etched surface are created by a replica-molding technique in which liquid prepolymer of PDMS is cast on top of the etched photoresist pattern, polymerized and peeled off. The PDMS stamp can be used for microcontact printing of ECM molecules on any substrate, including those within microfluidic devices (not shown). (**b**) A single-channel microfluidic device is fabricated by making a PDMS stamp with two inlets, a single main channel and one outlet and conformally sealing it to a flat glass substrate. A photograph of a two-chamber microfluidic culture device, with red and blue dye are perfused through upper and lower channels, is shown at the right. The clear side channels are used to apply cyclic suction to rhythmically distort the flexible central membrane and adherent cells.
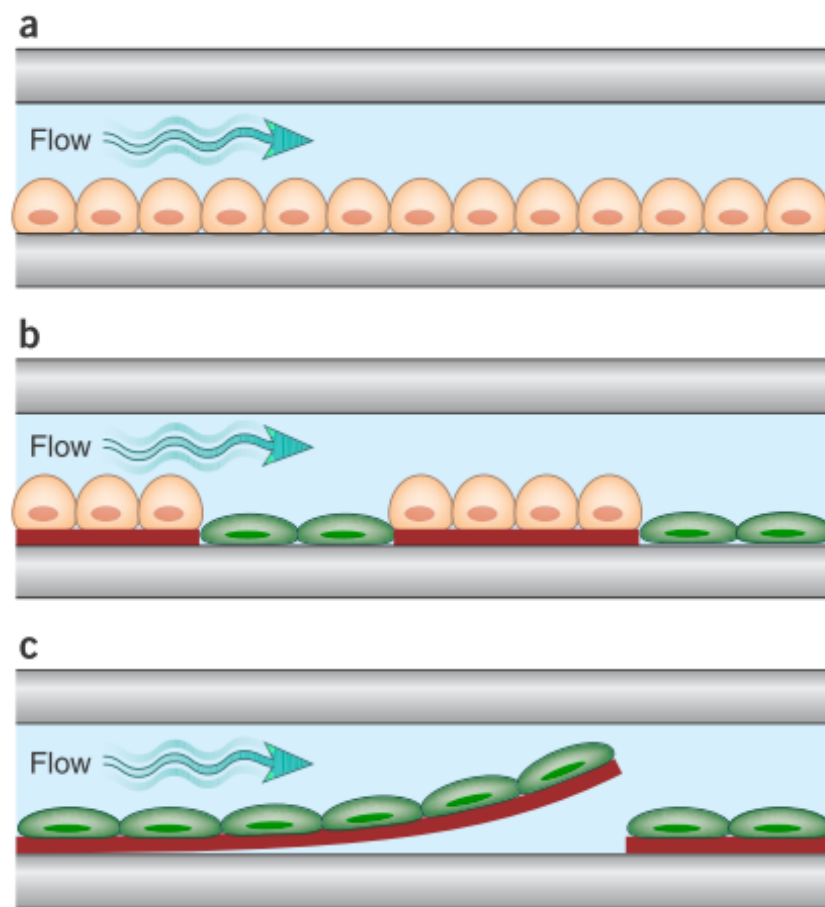
Figure 2 Examples of increasingly complex single-channel, organ-on-chip designs. (**a**) Cells of a single type are cultured as a monolayer on a planar rigid (e.g., glass) or flexible (e.g., PDMS) substrate on one side of a microfluidic channel through which medium is perfused. (**b**) Cells of two types are cultured in direct juxtaposition by micropatterning ECM adhesive islands within the microfluidic chamber that preferentially support one cell population (e.g., hepatocyte). These cells are delivered first, and the empty spaces are then filled with the second cell population (e.g., fibroblast). (**c**) Cells in a tissue construct engineered with ECM are cultured in a microfluidic channel. In this example, microcontact printing of ECM in a linear pattern on a thin PDMS layer coated over the substrate is used to orient muscle cells to create an anisotropic muscle tissue layer. When parts of the PDMS film are released from the substrate, they bend up when the cells contract, allowing measurement of cell contraction forces under flow[35].
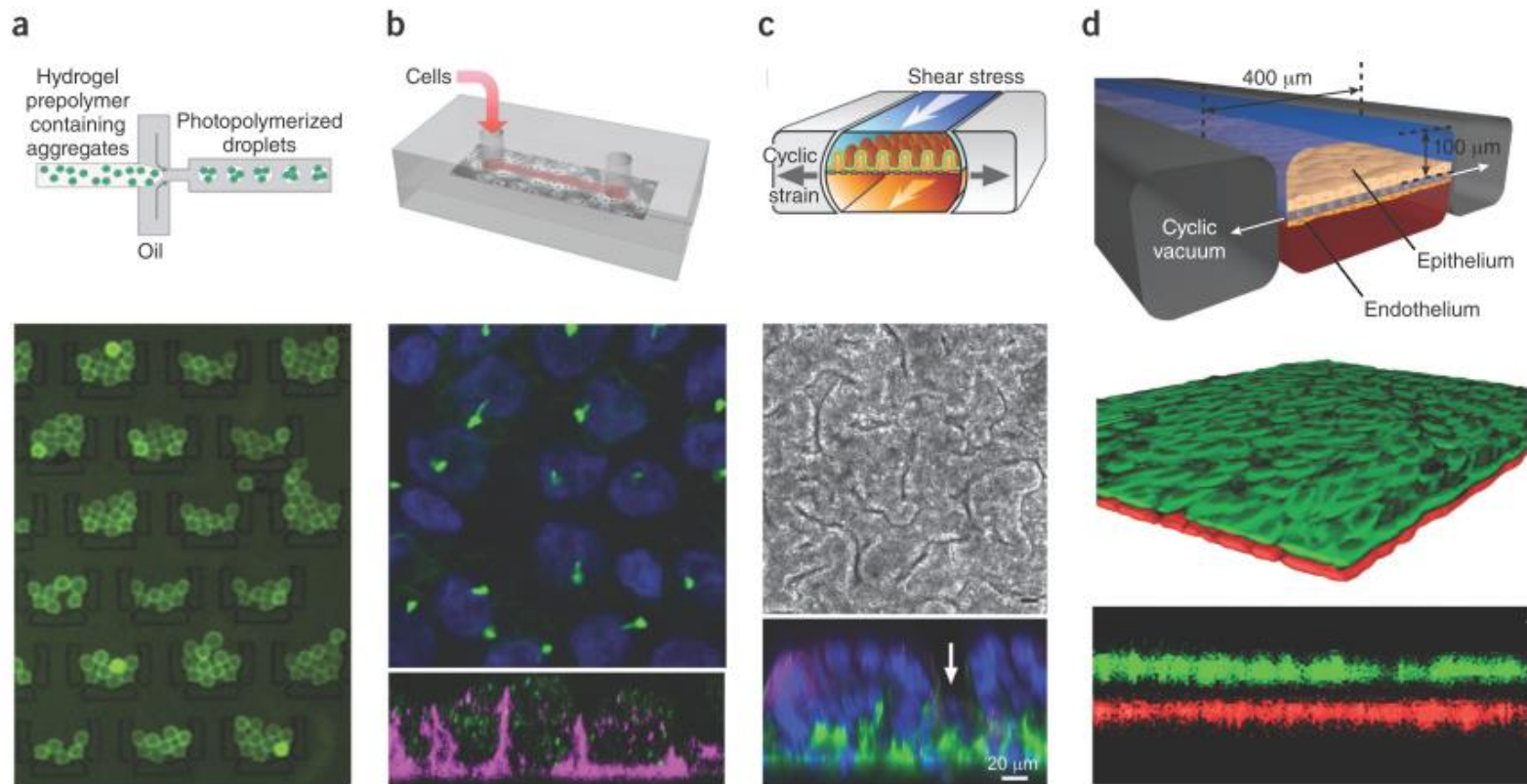
Figure 4 Examples of increasingly complex organ-on-chip designs. (**a**) A liver-on-a-chip in which hepatic microtissues composed of microscale hydrogels containing hepatocytes and fibroblasts are microengineered in one microfluidic system (top) and then used to populate another chip for culture and real-time multiplexed analysis (bottom)[104]. (**b**) A kidney-on-a-chip in which human kidney proximal tubular epithelial cells are cultured on the top of a porous membrane separating two channels, enabling analysis of transcellular transport, uptake and secretion (top)[73]. The upper fluorescence image of the epithelium shows enhanced formation of primary cilia (green) on the apical cell surfaces; the lower fluorescence cross-sectional view shows repolarization of Na+K+ ATPase (magenta) to the basal side. Fluorescence images reprinted from ref. 73 with permission of The Royal Society of Chemistry. (**c**) A gut-on-a-chip in which human Caco-2 intestinal epithelial cells are cultured on top of an ECM-coated, porous PDMS membrane separating two channels. Application of cyclic suction to side chambers mimics peristalsis (top)[48,49]. The phase-contrast micrograph shows a large region of the culture with undulating structures reminiscent of intestinal villi; the bottom fluorescence view shows a cross-section of this crenulated epithelial monolayer confirming the presence of crypts (arrow) separating adjacent villi. Fluorescence image reprinted from ref. 48 with permission of The Royal Society of Chemistry. (**d**) A 'breathing' lung-on-a-chip that recapitulates the alveolar-capillary interface. Human alveolar epithelial cells are cultured on top of a flexible, porous, ECM-coated membrane and human capillary endothelial cells on the bottom. Air is passed through the upper channel to create an air-liquid interface with the alveolar epithelium, and culture medium is flowed through the vascular channel, with or without human immune cells (top)[44,45]. Breathing motions are mimicked by applying cyclic suction to full-height side chambers that rhythmically distort and relax the flexible PDMS side walls and attached porous membrane. The fluorescence confocal 3D reconstruction at the bottom and the cross-sectional view shown at higher magnification in the inset show the tissue-tissue interface formed between the alveolar epithelium (green) and the endothelium (red). Fluorescence images reprinted from ref. 44 with permission of AAAS.
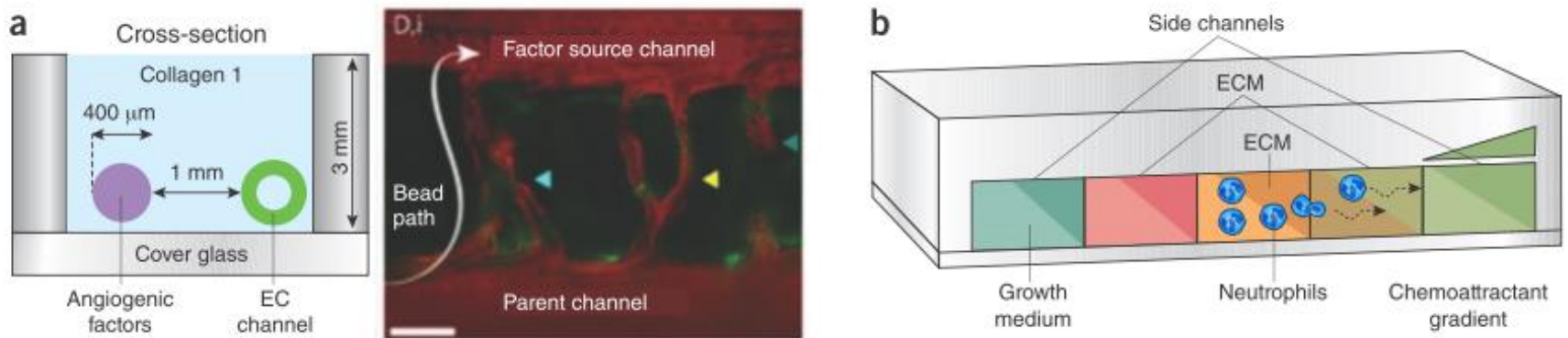
Figure 3 Microfluidic chip models of angiogenesis and immune cell invasion that incorporate ECM gels. (**a**) Sacrificial materials are deposited in linear patterns in an ECM gel and later removed to create two channels (left). One is populated with vascular endothelial (EC) cells[38], and the other is used to deliver angiogenic factors. Angiogenic stimuli induce the endothelial cells to undergo sprouting angiogenesis and then functionally link to the source channel, forming new microvessels that support fluid flow (right). Red indicates microparticles flowing in the medium. Fluorescence image reprinted from ref. 38 with permission. (**b**) A gradient-generating microfluidic culture device for analyzing immune cell migration through ECM gels when stimulated with a chemotactic gradient[39].
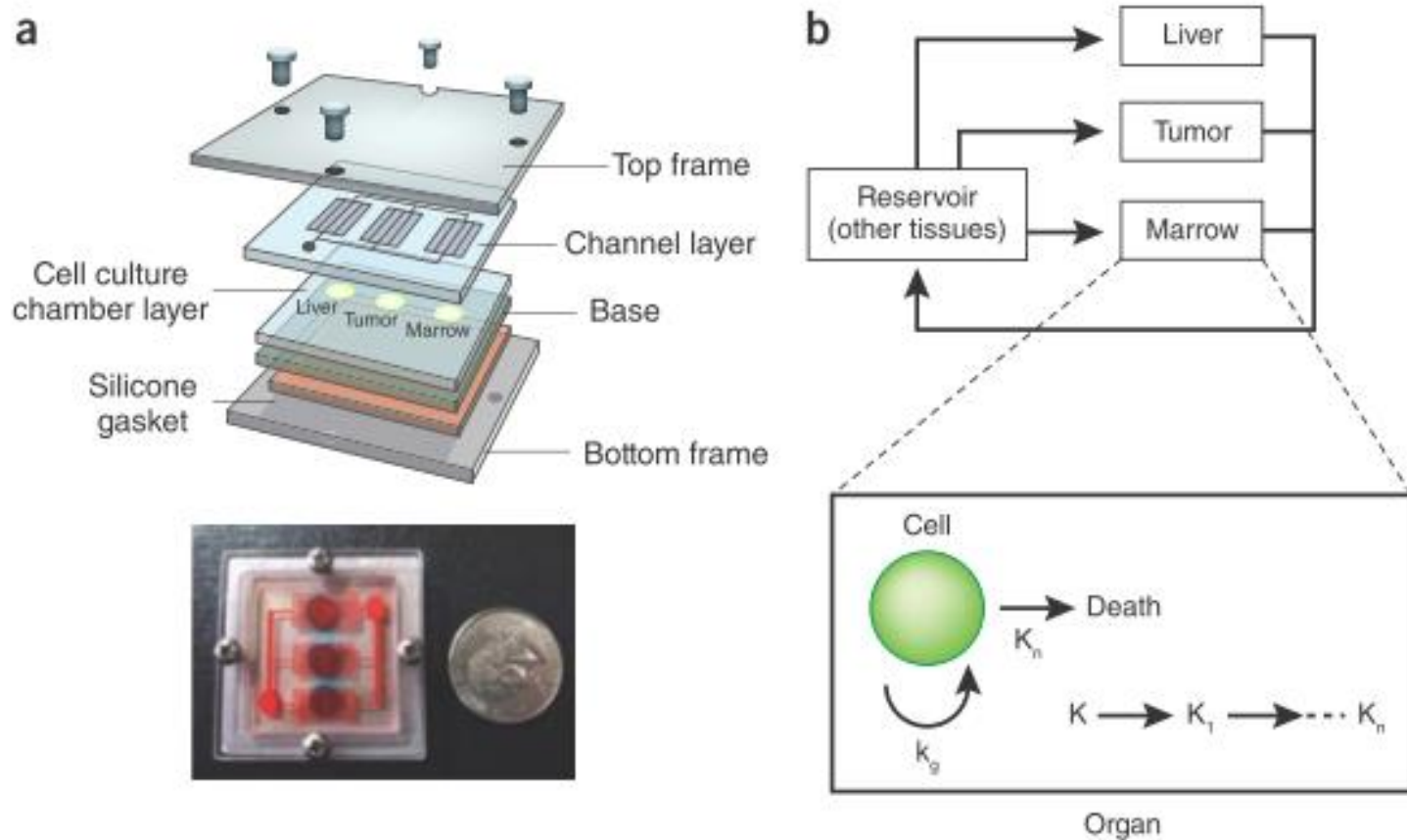
Figure 5 A multi-organ microfluidic framework used for PK/PD modeling. (**a**) Schematic diagram (top) and photograph (bottom) of a three-chamber chip used for PK modeling by flowing medium through liver, tumor and marrow cells cultured as monolayers in separate chambers and linked fluidically. (**b**) A flow diagram of the connections between the liver, tumor and marrow compartments in the chip shown in **a** (top), and a pharmacodynamics model for cell death in each compartment (bottom). Reprinted from ref. 156 with permission of The Royal Society of Chemistry.

Microfabrication of human organs-on-chips

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'Organs-on-chips' are microengineered biomimetic systems containing microfluidic channels lined by living human cells, which replicate key functional units of living organs to reconstitute integrated human organ-level pathophysiology *in vitro*. These microdevices can be used to test efficacy and toxicity of drugs and chemicals, and to create *in vitro* models of human disease. Thus, they potentially represent low-cost alternatives to conventional animal models for pharmaceutical, chemical and environmental applications. Here we describe a protocol for the fabrication, microengineering and operation of these microfluidic organ-on-chip systems. First, microengineering is used to fabricate a multilayered microfluidic device that contains two parallel elastomeric microchannels separated by a thin porous flexible membrane, along with two full-height, hollow vacuum chambers on either side; this requires ~3.5 d to complete. To create a 'breathing' lung-on-a-chip that mimics the mechanically active alveolar-capillary interface of the living human lung, human alveolar epithelial cells and microvascular endothelial cells are cultured in the microdevice with physiological flow and cyclic suction applied to the side chambers to reproduce rhythmic breathing movements. We describe how this protocol can be easily adapted to develop other human organ chips, such as a gut-on-a-chip lined by human intestinal epithelial cells that experiences peristalsis-like motions and trickling fluid flow. Also, we discuss experimental techniques that can be used to analyze the cells in these organ-on-chip devices.

Box 1 | Fabrication of the gut-on-a-chip ● TIMING 8.5–18.5 d

First, fabricate the SU-8 silicon master and prepare PDMS as described in Steps 1–23 of the PROCEDURE before proceeding to the following steps specific to gut-on-a-chip.

Fabrication of the upper and lower microchannels ● TIMING 5.5 h

1. Perform Step 24 of the PROCEDURE to clean the silicon master.
2. Pour 3 g of 15:1 (wt/wt) PDMS mixture onto the bottom surface of a Petri dish, and spread it uniformly.
3. Place the cleaned master on the spread PDMS with SU-8 features facing up and wait for 10 min on a level surface.
4. Pour 15:1 (wt/wt) PDMS mixture onto the silicon master and degas it in a vacuum desiccator for 30 min.
▲ CRITICAL STEP Use 15 g and 3 g of PDMS for the fabrication of the upper and lower microchannel slabs, respectively.
5. Fully cure PDMS in an oven maintained at 60 °C for at least 4 h.
6. Peel the cured PDMS off of the master, and cut it into a 2-cm-wide × 3-cm-long rectangular block using a scalpel.
▲ CRITICAL STEP Be careful when you are using a scalpel, in order to avoid injuries and fracture of fragile silicon masters.
7. Punch holes through the upper channel layer by using a biopsy punch with a diameter of 2 mm.

Fabrication of porous PDMS membranes ● TIMING 1 d

8. Pour degassed 15:1 (wt/wt) PDMS mixture into an empty Petri dish to generate a 1-cm-thick flat PDMS slab.
9. Cure PDMS in a leveled dry oven at 60 °C for 4 h.
10. Use a scalpel to cut the fully cured PDMS along the edge of the Petri dish, and remove it from the dish by using tweezers.
11. Rinse the removed PDMS slab with 100% ethanol, and dry it completely using compressed nitrogen or air.
12. Treat the PDMS block with oxygen plasma for 1.5 min, and silanize it in a vacuum desiccator overnight according to PROCEDURE Steps 52–54.
13. Place a silicon master containing an array of microfabricated circular pillars (10 μm in diameter and 30 μm in height) with a center-to-center spacing of 25 μm at the center of the bottom surface of a clean Petri dish.
14. Pour 3 g of degassed 15:1 (wt/wt) PDMS mixture onto the wafer, and spread it evenly.
▲ CRITICAL STEP Avoid the formation of air bubbles.
15. Gently put a silanized PDMS slab from step 12 (in this box) on the surface of the silicon master covered with uncured PDMS.
▲ CRITICAL STEP Release the slab very slowly to prevent formation of air bubbles.
16. Place a frosted glass slide on the silanized PDMS block, and place 3 kg weight on the glass slide.
17. Wait for 30 min to allow for intimate contact between the PDMS slab and microfabricated master surface.
▲ CRITICAL STEP Perform this step on a level surface.
18. Move the entire assembly to a dry oven at 60 °C, and incubate it overnight.
19. Remove the sample from the oven, take off the weight, and cool the assembly to room temperature over 30 min.
20. Use a scalpel to lift up a corner of the slab, and slowly peel it from the wafer.
▲ CRITICAL STEP Apply 100% ethanol to the gap between the PDMS surface and the silicon wafer during this step to facilitate the detachment of the PDMS layer.

Alignment and assembly of the microdevice ● TIMING 1.5 d

21. Clean the upper PDMS layer (**Fig. 5a**) and the porous PDMS membrane with packaging tape.
▲ CRITICAL STEP Do not apply excessive pressure when you are cleaning the membrane surface, in order to avoid unwanted damage of the device and delamination.
22. Treat the membrane surface and the channel side of the upper PDMS layer with plasma by using a corona generator for 3 s and 1 min, respectively (**Fig. 5b**).
▲ CRITICAL STEP Use sweeping motions to achieve uniform treatment, and keep the tip of the electrode of the corona generator ~5 mm away from the sample surface for best results.
23. Overlay the upper microchannel layer on the PDMS membrane, and bring them in contact.
▲ CRITICAL STEP Press the PDMS slabs to permit intimate contact between layers and to remove trapped air.
24. Incubate the assembled layers in a dry oven at 80 °C for at least 12 h.
25. Remove the sample from the oven, and cool it down to room temperature for 1 h.
26. Cut along the edges of the upper PDMS channel layer bonded to the membrane by using a scalpel, and gently peel the silanized flat PDMS slab from the assembly.
▲ CRITICAL STEP Put a few drops of 100% ethanol between the layers for easier detachment.
27. Tear off the portions of a porous membrane located over the lateral vacuum chambers using fine-tip tweezers under a stereoscope (**Fig. 5c**).
28. Expose the membrane surface and the channel side of the lower PDMS layer to the corona for 1 min (**Fig. 5d**).
29. Perform Steps 84 and 86 from the PROCEDURE to align and bond the device (**Fig. 5e**).
▲ CRITICAL STEP After completion of this step, attempt to pull apart the upper and lower PDMS slabs to qualitatively determine the success of device bonding. Incomplete or unsuccessful bonding results in peeling off and separation of the PDMS slabs.
30. Bend the tips of six 18-gauge blunt needles by 90° by using pliers, and break off the needle at a point near the syringe entry port.
31. Insert the needles into the access ports of the central cell culture channels and side vacuum chambers.
32. Cut six pieces of 4-cm-long silicone tubing, and connect them to the free ends of the needles.

(continued)

Box 1 | (continued)

33. Perform Steps 100–103 of the PROCEDURE to complete the fabrication of the device (**Fig. 5f**).
▲ CRITICAL STEP To examine the quality and performance of the device, connect the device to the vacuum pump and test vacuum-assisted membrane stretching after the completion of this step. Leakage of vacuum from the side chamber owing to unsuccessful PDMS bonding results in little or no stretching of the membrane. Alternatively, fill the central cell culture channels with deionized water, and check for the leakage of water into the side chambers when vacuum is applied. Incomplete removal of the membrane in the side vacuum channels leads to varying degrees of membrane stretching along the channel length. These undesirable events can be visually detected by using a microscope.
34. For sterilization, flow 70% ethanol through the channels, dry the device in an oven at 60 °C for 2 h and perform Steps 104 and 105 of the PROCEDURE.

Microfluidic cell culture: 5–15 d

35. Introduce 500 μl of the ECM coating solution (see Reagent Setup) into both the upper and lower central microfluidic channels, and pinch off tubing to prevent coating solution from leaking out of the device.
▲ CRITICAL STEP Ensure that the entire microchannels are filled with the ECM solution without any trapped air bubbles.
? TROUBLESHOOTING
36. Place the microdevice in a humidified 37 °C incubator for over 2 h.
37. Flow culture medium through the channels to remove residual coating solution flow culture medium at 30 μl h^{-1} overnight without mechanical stretching.
38. Aspirate the culture medium from a T75 flask containing ~90% confluent Caco-2 cells, and wash the cells with Ca^{2+}- and Mg^{2+}-free PBS twice.
39. Incubate the cells with 1 ml of prewarmed trypsin/EDTA solution (0.05% (wt/vol)) in a humidified incubator (37 °C, 5% CO$_2$) for 10 min.
40. Resuspend the trypsinized cells with 10 ml of culture medium containing 20% (vol/vol) FBS and antibiotics, transfer the sample to a 15-ml sterile conical tube, and centrifuge the cells at 500g for 5 min.
41. Remove the supernatant and resuspend the cells with culture medium to yield a seeding density of ~5 × 10^5 cells cm^{-2}.
42. Load a 1-ml syringe with the cell suspension solution and attach a 25G 5/8 needle to the syringe.
43. Inject the cells into the microchannel through the tubing connected to the outlet of the upper central microchannel. During this step, the inlet and outlet of the lower microchannel remain closed. After seeding, clamp both ends of the upper channel.
▲ CRITICAL STEP Injection of the cell suspension solution should be performed very slowly and carefully in order to prevent introduction of air bubbles. Make sure that the needle attached to the syringe containing cell suspension is tightly fit into the outlet tubing.
44. Incubate the device in a humidified incubator for ~1.5 h to allow the seeded cells to adhere on the ECM-coated membrane surface.
45. After cell attachment, gently aspirate the culture medium from the upper and lower microchannels to remove unbound cells and cell debris.
46. Connect the inlet tubing to a syringe pump, and perfuse the upper microchannel at 30 μl h^{-1} in a humidified incubator for 24–36 h to allow the cells to grow to confluence. Close the tubing connected to the lower microchannel by using clamps during this step.
47. Once the cells form a confluent monolayer, flow the culture medium in both the upper and lower microchannels at 30 μl h^{-1}.
48. For coculture with microbes, switch the cell culture medium to antibiotic-free DMEM, and perfuse the device for at least 12 h before seeding the microbial cells. During this perfusion, proceed with the next step.
49. Grow the microbial cells (e.g., *Lactobacillus rhamnosus* GG) in autoclaved MRS broth medium without shaking in a humidified incubator (37 °C, 5% CO$_2$) for 12 h.
! CAUTION Use a separate incubator for microbial cultures to prevent cross-contamination.
50. Take 1 ml of microbial culture broth and spin it down at 12,000g at room temperature for 5 min.
51. Aspirate the supernatant and add antibiotic-free culture medium to obtain a final cell density of ~1.0 × 10^7 c.f.u. ml^{-1}.
? TROUBLESHOOTING
52. In a microbial culture hood, seed the microbial cells into the upper microchannel by using the method described above, and incubate the mixture in a humidified incubator for ~1.5 h to allow the microbes to attach to the apical surface of the intestinal epithelial cells.
! CAUTION Use a separate incubator for the coculture devices in order to prevent cross-contamination.
53. Open the outlet tubing connected to microchannels, remove unbound microbial cells by aspirating culture medium, and perfuse both the upper and lower channels with antibiotic-free culture medium at 40 μl h^{-1}.
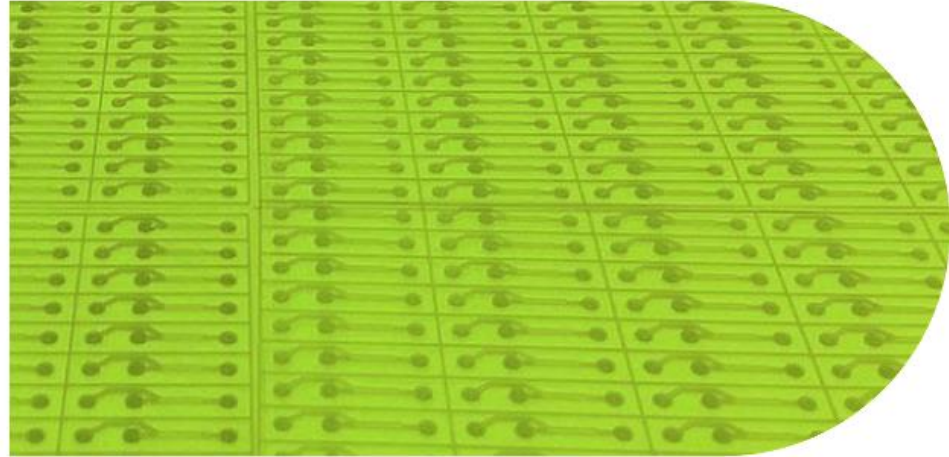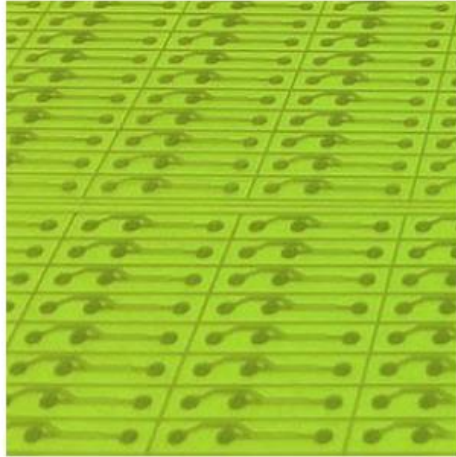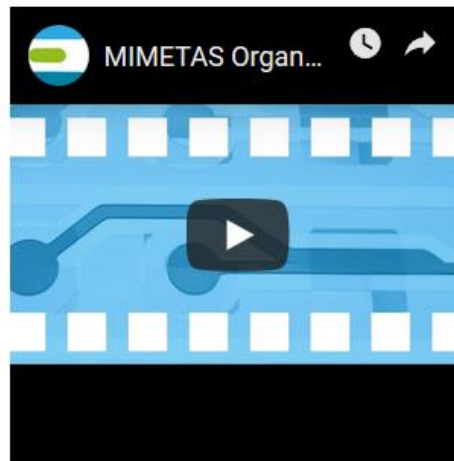
Technology

This is how the OrganoPlate® works

The OrganoPlate® is a microfluidic 3D cell culture plate, supporting up to 96 tissue models on a single plate. Phaseguides™ enable precise, barrier-free definition of culture matrices and cells in 3D, supporting cell-cell interactions and unprecedented imaging and quantification.

This video demonstrates the working principles of the OrganoPlate®

MIMETAS Organ...

Technology
Model design in OrganoPlates
Assays
Biomimetic
Compatible
Easy-to-use
Publications

Continuous perfusion without pumps and

Brain

In 2014, IBM announced the creation of TrueNorth, a chip that's the size of a postage stamp, yet contains one million neurons.

In 2016 Ian Johnston for the Independent UK reports a tiny implant the size of a grain of sand has been created that can connect computers to the human body without the need for wires or batteries, opening up a host of futuristic possibilities.

Regarding this in 2018 scientists from New Brain announced recording the bionic brain chips with human brain memory cells, popped to make humans super intelligent and cure memory loss.

Microfluidic chip for plasma separation from undiluted human whole blood samples using low voltage contactless dielectrophoresis and capillary force

Chia-Chern Chen,[a] Po-Hsiu Lin[b] and Chen-Kuei Chung*[b]

⊕ Author affiliations

Abstract

A plasma separating biochip is demonstrated using a capillary-driven contactless dielectrophoresis method with low voltage (~1 V) and high frequency induced electrostatics between red blood cells. The polarized red blood cells were aggregated and separated from plasma with a 69.8% volume separation and an 89.4% removal rate of red blood cells.
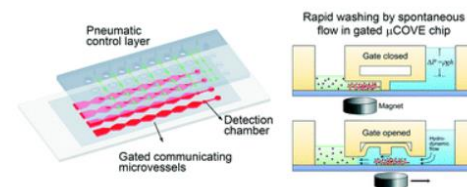
2014
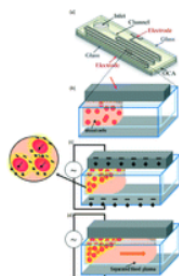
Paper

Microfluidic communicating vessel chip for expedited and automated immunomagnetic assays

Yang Yang and Yong Zeng

A simple device exploits hydrostatic pressure-driven flow to simplify and expedite the immunoassay workflow.

Download PDF Article HTML

2018

Lab on a Chip is a MEDLINE indexed journal with IF=5.995, published by the Royal Society of Chemistry

The In Silico Lab-On-A-Chip uDeviceX performs Dissipative Particle Dynamics simulations of blood and cancer cell separation in complex microfluidic channels with subcellular resolution. The software emulates the conditions and the geometric complexity of microfluidic experiments. These simulations provide sub-micron resolution while accessing time scales relevant to engineering designs.

This is a Free software, which comes with the GNU GPL v2.0 license. This forces you to share your improvements too.

This work, including the development of the software, started at the CSE Laboratory of ETH Zurich, headed by Prof. Petros Koumoutsakos. The team included researchers from ETH Zurich, Brown University, Universita da Svizzera Italiana (USI) and Consiglio Nazionale delle Ricerche (CNR).

https://udevicex.github.io/uDeviceX/
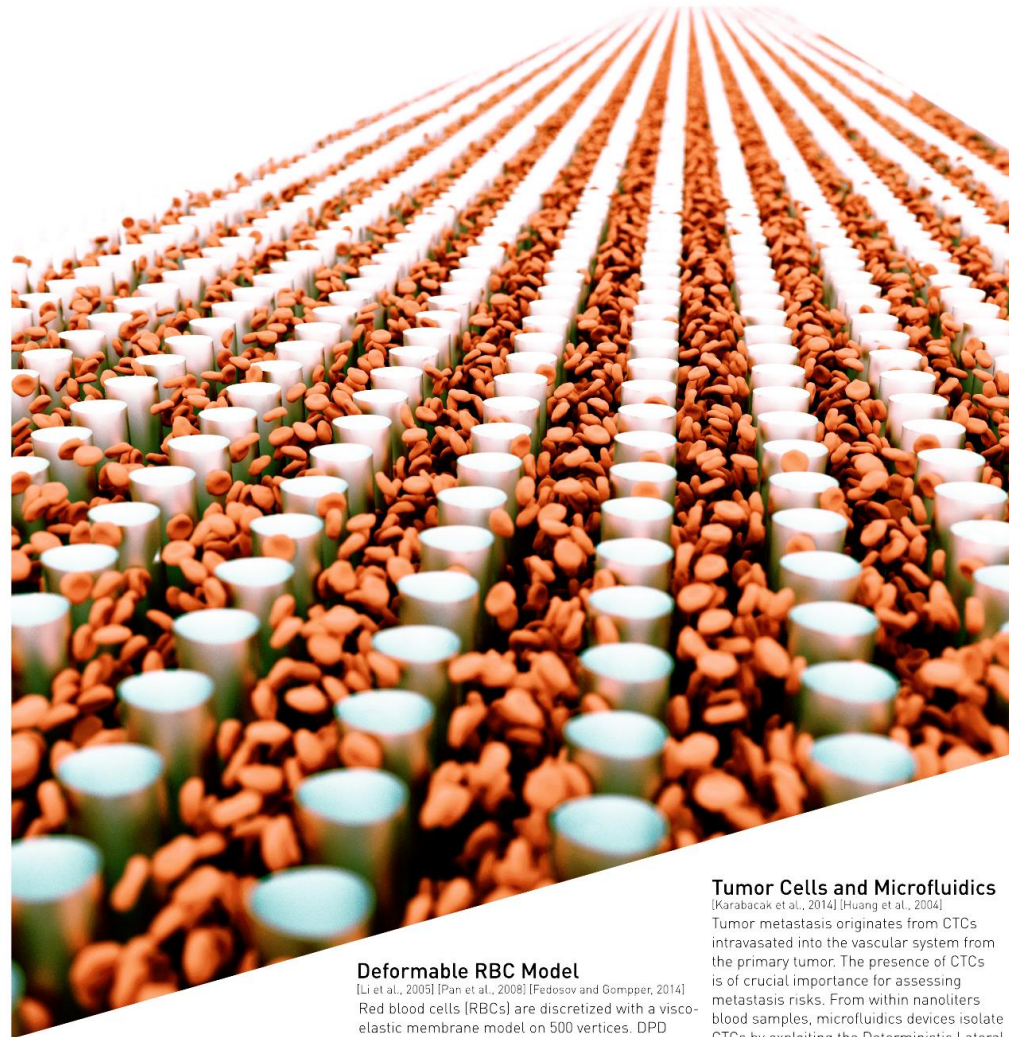
Dissipative Particle Dynamics
[Hoogerbrugge and Koelman, 1992] [Groot and Warren, 1997]

Dissipative Particle Dynamics (DPD) is an N-body algorithm in which discrete particles interact through pairwise forces.

The force acting on the particle i is computed as:

$$\mathbf{F}_i = \sum_{j \neq i}^{N} (\mathbf{F}_{ij}^C + \mathbf{F}_{ij}^D + \mathbf{F}_{ij}^R) \, , \; i = 1, ..., N$$

Conservative Dissipative Random

Dissipative and random force are related through the fluctuation-dissipation theorem. [Espanol, 1995]

Particles trajectories are then integrated with a Velocity-Verlet time-stepping scheme.

Deformable RBC Model
[Li et al., 2005] [Pan et al., 2008] [Fedosov and Gompper, 2014]

Red blood cells (RBCs) are discretized with a visco-elastic membrane model on 500 vertices. DPD provides a unified framework for capturing the complex interactions between the solvent, the microchannel geometry, Circulating Tumor Cells (CTCs) and RBCs, at submicron resolution.
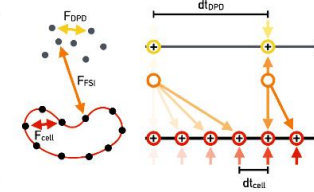
The separation of the temporal scales between the flow and cell dynamics can be effectively exploited in order to decrease time-to-solution.

Tumor Cells and Microfluidics
[Karabacak et al., 2014] [Huang et al., 2004]

Tumor metastasis originates from CTCs intravasated into the vascular system from the primary tumor. The presence of CTCs is of crucial importance for assessing metastasis risks. From within nanoliters blood samples, microfluidics devices isolate CTCs by exploiting the Deterministic Lateral Displacement effect in the microchannel flow.

Our simulation software enables us to assess the performance of several microfluidic devices in terms of cell-sorting throughput **at unprecedented scales**.

The simulation software effectively harnesses the compute power offered by the Piz Daint and Titan supercomputers. Features:

- 12X - **45X faster than LAMMPS** DPD
- 3.9 - **4.5X faster than HOOMD-Blue** DPD
- **65% of the nominal peak performance, 35% overall**
- Domain sizes up to 58 mm³
- Up to 1.43 billion deforming RBCs
- Weak-scaling efficiency of 99+%
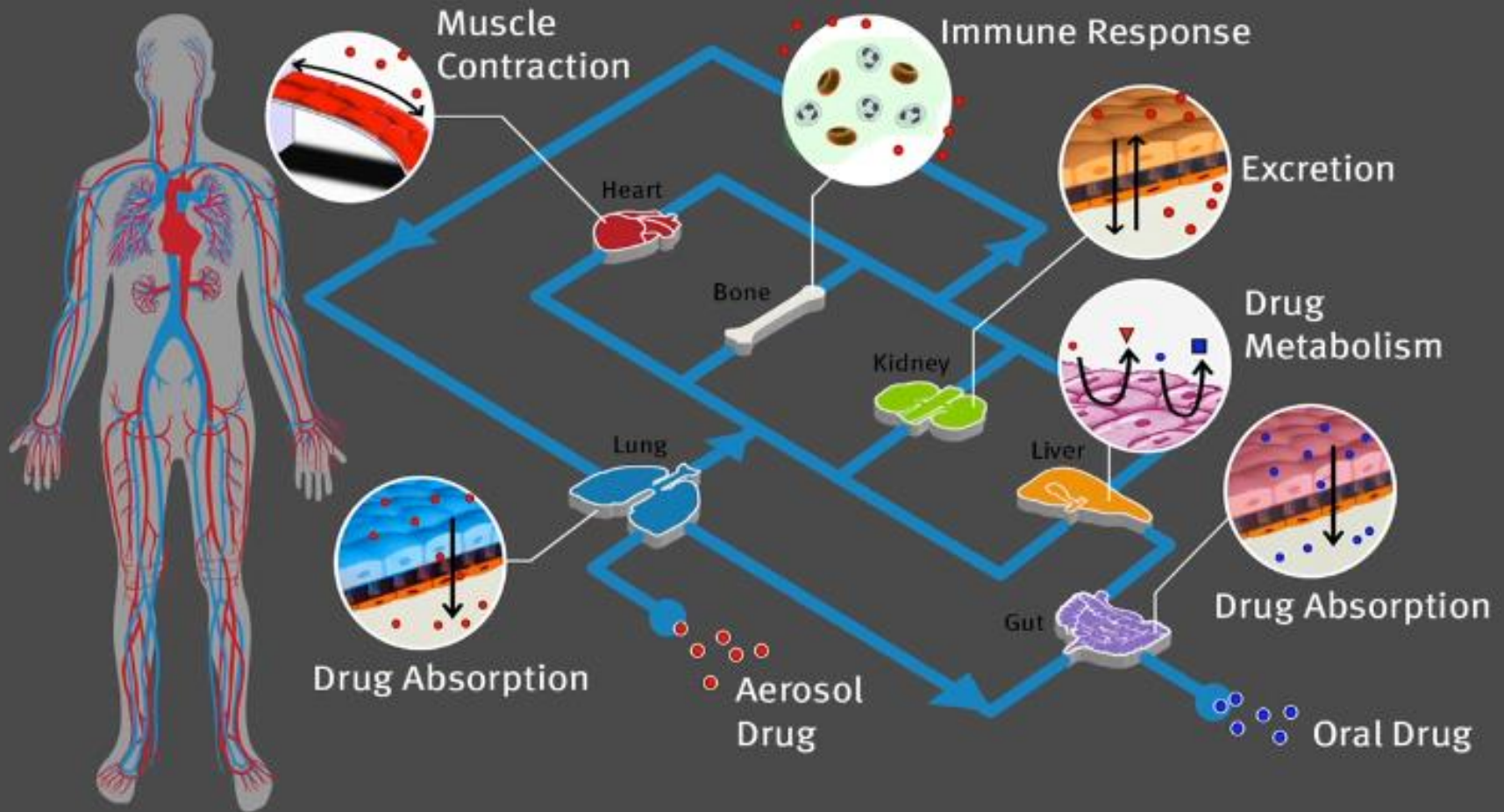
Defense Advanced Research Project Agency (DARPA) funded 7 way platform, developed at MIT, means 7 tissues on a platform, which interact because of the flowing growth medium, which is driven by the pneumatically actuated micropumps to emaluate the human circulatory system, providing nutrients and oxygen to the cells.
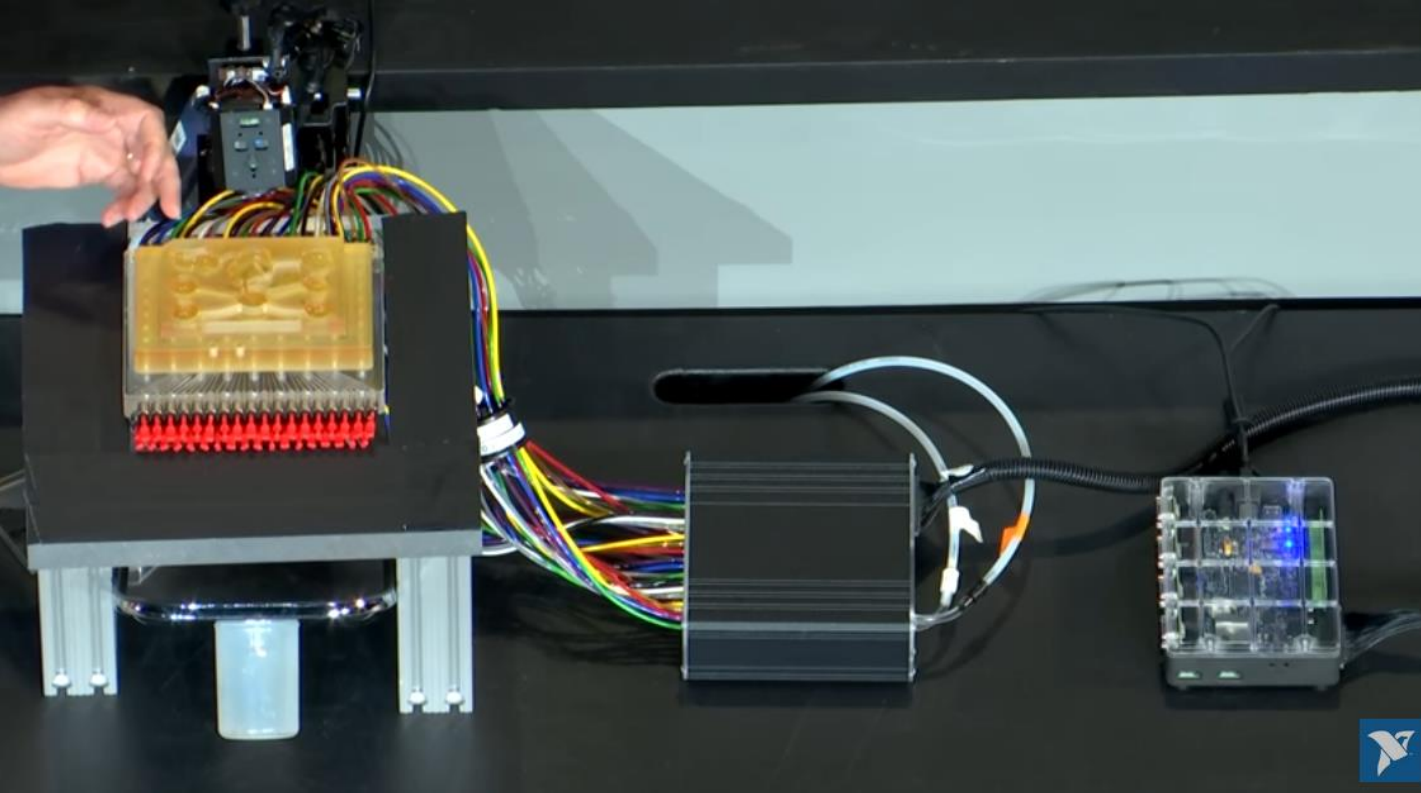
Those micropumps are driven by a valve box, which was designed by Continium (innovation design company, which partnered on that project) and programmed in LabView.

Will help to study multiple organs interaction in diseases like diabetes or autoimmune disorders, where a given person may respond differently to a standard therapy and will assist in understanding what types of toxic effects drugs have on a human. In March 2018, MIT developed a 10 artificial organs platform.

In 2017, researchers at Ohio State University have developed new technology that allows the body to generate any type of cell to help heal injuries. According to a university press release, the technique, called tissue nanotransfection, uses a fingernail-sized nanochip, which is placed over a patient's skin or tissue.

A droplet containing genetic material is placed on top of the chip, and then zapped with an electrical current. The DNA is delivered through channels created by the current, and it reprograms skin cells to turn into specific cell types that can then be used in other parts of the body.

When tested on a mouse with a damaged leg, researchers found vascular cells converted from skin cells formed new blood vessels that allowed the leg to heal in two weeks.

The non-invasive technology was also able to generate nerve cells in the legs of brain-damaged mice. Once the cells were harvested, they were injected into the brain to help with stroke recovery. The nanochip also tested effectively in pigs and is expected to be approved for human trials within a year.

Organoids & Organ-on-a-Chip Asia 2021
Date: 15 - 16 November 2021
Location: Tokyo, Japan

Lab-on-a-Chip and Microfluidics Europe 2022
Date: 21 - 22 June 2022
Location: Rotterdam, The Netherlands

https://www.organonachip.org.uk/events/
Including Organ-on-a-Chip e-Symposium
Date: 17 November 2021!

NNT 2021, the 20th International Conference on
Nanoimprint and Nanoprint Technologies
Date: 16 - 17 November 2021
Online, free of charge!

annual meeting

2ND WORKSHOP ON NEXT GEN ORGAN-ON-CHIP & ORGANOIDS

CSEM is delighted to invite you to the 2nd networking workshop on Next Gen Organ-on-Chip & Organoids. Register now!

NEXT GEN ORGAN-ON-CHIP & ORGANOIDS
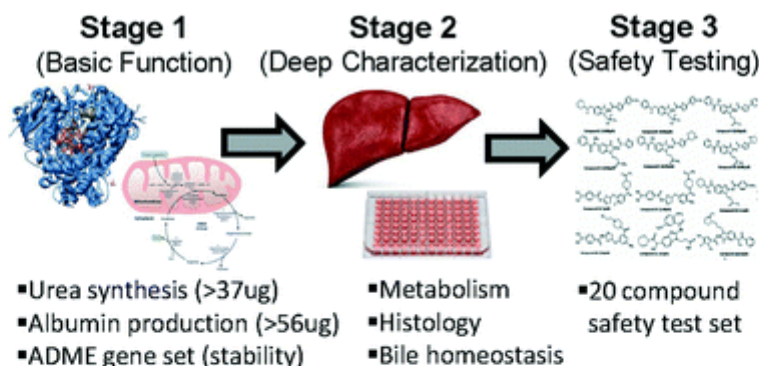26 - 27 JAN 2022 GENEVA

INTERNATIONAL FORUM
ON BIOCHIPS & BIOCHIP SOLUTIONS

Date: 10 - 11 May 2022
Location: Berlin, Germany

4 – 8 SEPT. 2022 BORDEAUX FRANCE
ESB 2022
32TH ANNUAL CONFERENCE OF THE EUROPEAN SOCIETY FOR BIOMATERIALS

Liver microphysiological systems development guidelines for safety risk assessment in the pharmaceutical industry

Andreas R. Baudy, Monicah A. Otieno, Philip Hewitt, Jinping Gan, Adrian Roth, Douglas Keller, Radhakrishna Sura, Terry R. Van Vleet and William R. Proctor

This pharmaceutical industry guidance based on a 3-staged benchmarking strategy aims to help MPS developers and end users identify what could be the most valuable models for safety risk assessment, as well as provide an overview of contexts of use.

Stage 1 (Basic Function)
- Urea synthesis (>37ug)
- Albumin production (>56ug)
- ADME gene set (stability)

Stage 2 (Deep Characterization)
- Metabolism
- Histology
- Bile homeostasis

Stage 3 (Safety Testing)
- 20 compound safety test set

From the themed collection: Microphysiological systems in pharmaceutical safety and ADME applications

An *in vitro* vascularized micro-tumor model of human colorectal cancer recapitulates *in vivo* responses to standard-of-care therapy

Stephanie J. Hachey, Silva Movsesyan, Quy H. Nguyen, Giselle Burton-Sojo, Ani Tankazyan, Jie Wu, Tuyen Hoang, Da Zhao, Shuxiong Wang, Michaela M. Hatch, Elizabeth Celaya, Samantha Gomez, George T. Chen, Ryan T. Davis, Kevin Nee, Nicholas Pervolarakis, Devon A. Lawson, Kai Kessenbrock, Abraham P. Lee, John Lowengrub, Marian L. Waterman and Christopher C. W. Hughes

VMTs recapitulate *in vivo* drug responses and also reconstitute the cellular diversity of tumors.
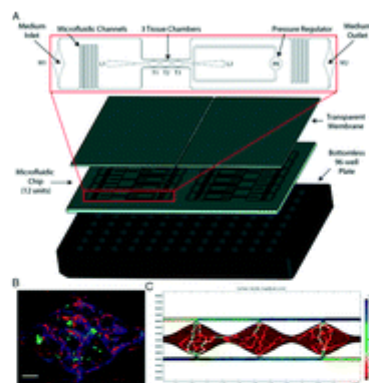
From the themed collection: organ-on-a-chip systems: translating concept into practice

Paper

A microphysiological early metastatic niche on a chip reveals how heterotypic cell interactions and inhibition of integrin subunit β₃ impact breast cancer cell extravasation

Martina Crippa, Simone Bersini, Mara Gilardi, Chiara Arrigoni, Sara Gamba, Anna Falanga, Christian Candrian, Gabriele Dubini, Marco Vanoni and Matteo Moretti

Our microfluidic model of early metastatic niche reproduced the extravasation of breast cancer cells in presence of immune blood cells and allowed us to test the effect of an already approved inhibitor of integrin β₃ on cancer cell extravasation.
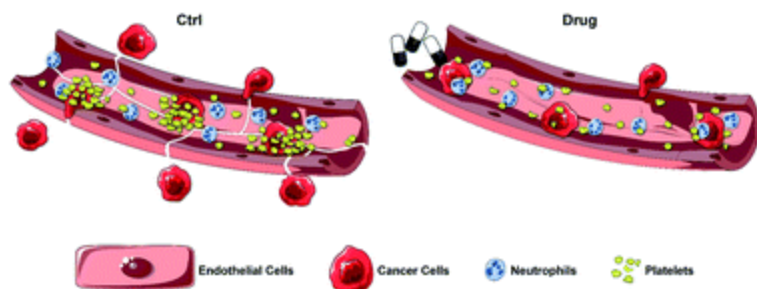
Ctrl   Drug

Endothelial Cells   Cancer Cells   Neutrophils   Platelets

From the themed collection: organ-on-a-chip systems: translating concept into practice

Organotypic primary blood vessel models of clear cell renal cell carcinoma for single-patient clinical trials

María Virumbrales-Muñoz, Jiong Chen, Jose Ayuso, Moonhee Lee, E. Jason Abel and David J. Beebe

Identification and testing of personalized anti-angiogenic treatments for clear cell renal cell carcinoma using patient-derived microfluidic models of normal and tumor-associated blood vessels.
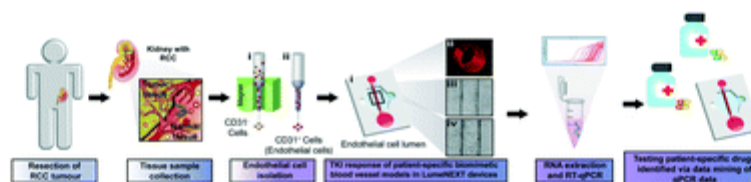
From the themed collection: organ-on-a-chip systems: translating concept into practice

Table 1 Standardisation in OoC – gap analysis

	Current scenario	Future needs	Priority
Definition	No uniform definition of MPS/OoC and related vocabulary	A consensus on terminology is necessary to start the qualification process	+++
Classification	Some categories can be identified (OoC focusing on barrier, parenchyma, multi organs) but there is no consensus	Identification of categories will facilitate the qualification process	+++
Functional requirements	Functional requirements are not uniformly agreed upon. Many developers perform an internal technical validation, but it is usually only partial and not fully reported	Identification of requirements and performance indicators (relevant parameters, units, measurement method, acceptability range...)	+++
Device material	There is a wide use of PDMS but also other plastics. The issue of molecule absorption is not uniformly addressed	Identify suitable test methods for molecule adsorption quantification	+++
Production process	Low TRL[a] devices are produced with soft lithography and rapid prototyping, no standardisation is usually needed	Standards for plastic materials can be used for high TRL[a] devices	++
Compatibility	Standardisation effort to create common interfaces among different OoCs and with laboratory equipment	Promote the development of standards for OoC integration	++
Sterilization and packaging	Low TRL[a] devices are sterilized with non-standard methods (UV light under biological hood or autoclave)	Standards for sterilization and packaging can be used for high TRL[a] devices	+
Quality	Some developers of commercialized OoC already perform quality control	Promote the use of GMP	+
Ancillary devices	Many standards are applicable in this field. Many products offered by major companies are already CE marked	Monitoring and updating of existing standards	+
Assays/endpoints	Relevant endpoints are organ-specific and application-specific	Standardized lists for specific context of uses have to be agreed upon and used as a basis for qualification	+++
Test compounds/drugs	Building lists of reference compounds is a widely accepted validation method in regulatory sciences	Standardized lists have to be agreed upon and used as a basis for qualification	+++
Cell source	Primary cells, iPSC and cell lines are all widely used. Standardisation in the field is rather poor	Promote the standardisation of protocols for cell culture and maintenance, sharing of best practices	++
Practical use	GLP, GIVIMP and GCCP are applicable	Disseminate and increase the use of best practices among developers	++
Other material	Some standards exist for materials used as matrixes or scaffold. Issue of molecule absorption is not uniformly addressed	Identify test methods for molecule adsorption on matrixes (measurement methods, units, ranges)	+

[a] TRL = Technology Readiness Level.

To read:

https://www.frontiersin.org/articles/10.3389/fbioe.2021.721843/full;
https://www.hindawi.com/journals/sci/2021/6621806/;
https://core.ac.uk/download/pdf/79498508.pdf;
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