Automated and high-volume wafer-scale microfabrication of organ-on-chip (OoC) polymer structures and components

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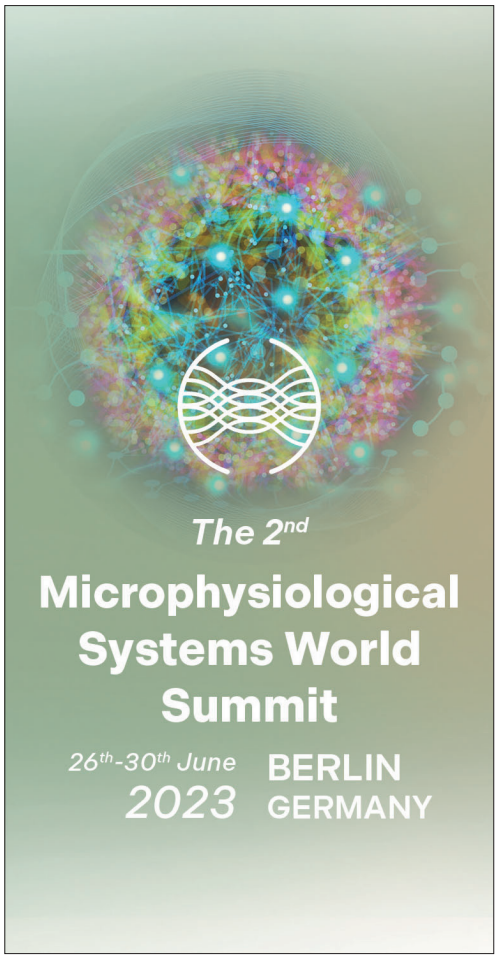
Welcome



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Track 4:
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compounds, demonstrating its potential to predict safety-related issues before entering the animal testing phase.

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Quantitative fluid dynamic characterization of an organ-on-chip model using phase resolved Doppler OCT

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Organ-on-chip (OoC) systems are novel microfluidic microsystems that combine the advantages of well-characterised human cells with the benefits of engineered, physiological-like microenvironments manufactured in the system. The extracellular matrix (ECM) is the natural microenvironment of cells in the human body responsible for providing the appropriate stimuli to cells to control cell processes such as proliferation, migration, and apoptosis. OoCs can mimic the ECM, via channels and porous membranes, by providing the cells with physiological-like mechanical stimuli governed by the fluid dynamics in the system [1]. Understanding the fluid dynamics in OOC can aid in fine-tuning the stimuli sensed by the cultured cells, understanding cell behavior and cell fate. The current state of the art methods for characterizing fluid dynamics in the OoC systems are simulations, theoretical calculations, and empirical observations, therefore a quantitative characterization technique is lacking. Optical coherence tomography (OCT) has been used in previous studies to measure omnidirectional flow velocities in flow systems [2].

In this study, we measured the flow in a cuvette using a Thorlabs GANYMEDE II HR series (high axial resolution of 3 mm in air) spectral domain OCT system. We made quantitative 2D flow measurements using the phase-resolved Doppler method. This work was then extended to extract flow dynamics, in the Bi/ond inCHIPit using titania scattering nanoparticles, which would be a novel way of flow characterization in the field of OOC. The results are compared to the theoretical Hagen-Poiseuille equations and COMSOL simulations and found to be in good agreement. The results of the study were further extended to determine the shear stress experienced by the cells in the culture well of the OoC.

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Automated and high-volume wafer-scale microfabrication of organ-on-chip (OoC) polymer structures and components

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Organ-on-chip (OoC) technology is a promising improvement within *in vitro* cell culture, better mimicking functional units of human organs compared to conventional techniques. Current fabrication of three-Dimensional (3D) components in OoC, such as thin membranes and microfluidic structures, is often achieved via soft lithography, bonding, and punching of access holes of polymers, such as polymethylsiloxane (PDMS). However, these methods often suffer from the need of manual fabrication steps, drastically increasing production time and reducing yield due to handling errors and manual alignment of the layers. Consequently, the scalability is limited, which is a crucial aspect for a more widespread adaptation of OoC technology. In this work, we present a reproducible and scalable process for the direct patterning of various 3D polymer structures. The investigated process employs commercially available systems from IC packaging to mould pillars, membranes, and microfluidic channels with varying dimensions and thicknesses. Our process simultaneously improves the control over the thickness and dimensions of these structures in comparison to conventional fabrication techniques. Furthermore, proof of functionality is presented by adapting this technology to an existing OoC platform which incorporates integrated electrodes used for electrophysiological recording, stimulation, and TEER measurements. We demonstrate a complete process for wafer-scale microfabrication of OoCs, enabling low-cost, high-volume automated production. This is an important next step to large-scale manufacturing of

OoCs, enabling more biologists and scientists to integrate OoCs into their workflow.

References
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3D chip model to study cellular interplay in cancer cell invasion through Notch signaling

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The mechanoregulated Notch pathway controls cell fate decisions through juxtacrine signaling between neighboring cells and paracrine signaling via environmental cues. In the tumor microenvironment (TME), the role of Notch varies from tumor suppressor to oncogene, depending on the cancer cell type. Notch activation in the TME is influenced by factors such as extracellular matrix (ECM), hypoxia, inflammatory cytokines, and binding of ligands [1]. The complexity of TME makes it difficult to recapitulate the physiological and pathological aspects of the disease in a classical 2D cell culture. In contrast, 3D models may include molecular, chemical, and biomechanical components of the TME facilitating the study of tumor progression, invasion, and immune evasion in a relevant environment [2]. Current organ-on-chip models are great research tools to co-culture up to 4 cell types (cancer cells, cancer associated fibroblasts, endothelial cells, and immune cells) in 3D, and to incorporate fluid dynamics to simulate from blood flow to interstitial flow, among other aspects [3].

In this research, we benefit from the one-ligand-one-receptor fidelity of Notch signaling to study the cellular crosstalk in the TME. We use our in-house, easy-to-fabricate platform to investigate the role of the Notch ligand Jagged1 in highly metastatic triple negative breast cancer cells. Our device is made of PDMS bound to high-resolution imaging compatible glass, which allows *in vitro* observation of the cancer invasion in real-time. The design includes nine sets of two well compartments connected by a channel of 1 mm x 4 mm x 2 mm (LxWxH). The formation of an ECM filled channel allows the isolation and collection of cells and media from different compartments for biochemical analyses. Through our device, we aim to reveal the mechanistic insights of tumor and TME interactions, highly relevant for the advancement of future drug development and treatment.

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Unified organoid system for modeling heart and kidney interaction on-a-chip

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Heart and kidney diseases cause high morbidity and mortality. Both organs have vital functions in the human body and reciprocally influence each other's behavior: pathological changes in one can damage the other. There are already multiple independent *in vitro* (human) models of heart and kidney, but none have so far captured their dynamic crosstalk [1]. Our aim is to develop a microfluidic system which can be used to study heart and kidney interaction *in vitro*. The validation of a unified organoid system will enable the investigation of diseases involving the two organs and their potential treatments.

The commercially available Ibidi µ-Slide III 3D perfusion chip was used for developing the combined culture of heart and kidney tissue on-a-chip. Cardiac microtissues (cMTs) [2] and kidney organoids (kOs) [3] derived from human induced pluripotent stem cells (hiPSCs) were loaded after 21 days from their formation in static culture onto two separated communicating chambers. We applied a unidirectional flow with a rate of 100 µl/min and the dynamic culture conditions were maintained for 72 hours. Tissue viability in the system was monitored and assessed by the beating of cMTs and the quality/presence of sarcomeres and nephron structures in cMTs and kOs, respectively. The tissues were then collected for downstream analyses. Functional characterization was performed through MuscleMotion to evaluate the contraction properties of cMTs and the uptake of albumin in kOs.

We expect this system will enable us to study the cardiac and kidney interaction with a high level of control and, where unidi-