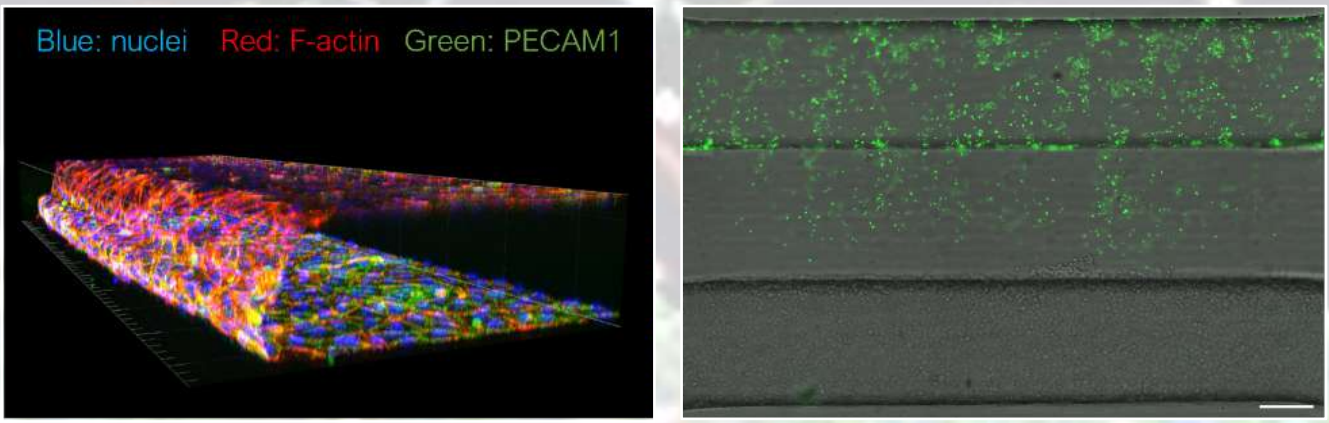
UNIVERSITÄT BERN

# ARTORG Center Organs-on-Chip Facility

## Annual Report 2022




Left: Endothelial vessel on chip, Right: Immune cells extravasating across an endothelial barrier and migrating through a hydrogel barrier in response to a chemotactic gradient (L. van Os et al., *Eur. J. Pharm. Sci.*, 187, 2023). Background picture: Twin vessels with angiogenic sprouting (D. Ferrari et al., iScience 2023).

October 2023

# OOCF Annual Report 2022

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## 1. Introduction

The ARTORG Center's Organs-on-Chip Facilities (OOCF) serves researchers at UniBE and beyond, offering state of the art infrastructure for the design, fabrication, and testing of Organs-on-Chip systems. It is located at the Murtenstrasse 50 and is part of the ARTORG Organs-on-Chip Technologies (OOC) laboratory, led by Prof. Olivier Guenat. In 2022, the OOCF was used by about 40 researchers from ten different research groups on the University of Bern campus and beyond. The OOCF staff oversees a microfabrication lab (BioMEMS), where microfluidic chips can be designed, fabricated, and tested, and an OOC cell culture lab (OOC Culture Lab). They provide OOCF users with an introduction to the laboratory specific equipment and assistance in developing custom microfluidic chips. To keep administrative costs as low as possible, an annual user fee is charged to all users, to cover a small portion of OOCF staff salaries and maintenance costs. Importantly, OOCF user fees have recently become reimbursable by the Swiss National Science Foundation, if users have such a grant. New equipment could be purchased in 2022 to replace outdated equipment.

## 2. OOCF News

### 2.1. OOCF Staff

In 2022/3, there were important personnel changes at the OOCF. Sonja Gempeler, who headed the OOC culture lab left her position as well as Rrahim Gashi, who had completed his MSc degree in biomedical engineering and was responsible for the BioMEMS lab. We thank them wholeheartedly for their outstanding contributions, it was always a real pleasure to work with them. We sincerely wish them all the best for their future endeavors.

We had the pleasure to welcome Severin Müller, who has assumed the role of BioMEMS Lab manager since January 2022. He will remain in this role until the end of 2023 and then focus on his MSc thesis project. At that time, Denise Ackermann will take over the position of the new BioMEMS lab manager. A warm welcome to her as well! Additionally, we were delighted to welcome Sabine Schneider as our new OOC Culture Lab manager. She joined us in January 2023. She comes from the Institute of Physiology (Bern) and brings many years of cell culture and molecular biology expertise.

*Left: Sabine Schneider, the new OOC culture lab manager, and Severin Müller (middle), the OOCF BioMEMS lab manager, and Denise Ackermann (right).*

## 2.2. BioMEMS Laboratory

A new Henniker HPT 200 plasma reactor (Fig. 1A) with a Pfeiffer Vacuum pump, were purchased to complement the first plasma reactor acquired in 2010. The new plasma reactor has a more powerful and variable output (0-200 W) than the old one (30 W) and allows to reduce the utilization rate of the old one, which was currently used beyond its capacity limit (daily operation, including some weekends, without possibility of maintenance). Together with the plasma reactor, we acquired two laminar flow hoods (Fig. 1B) allowing to protect microfluidic chips during their production, after plasma exposure from dust particles.

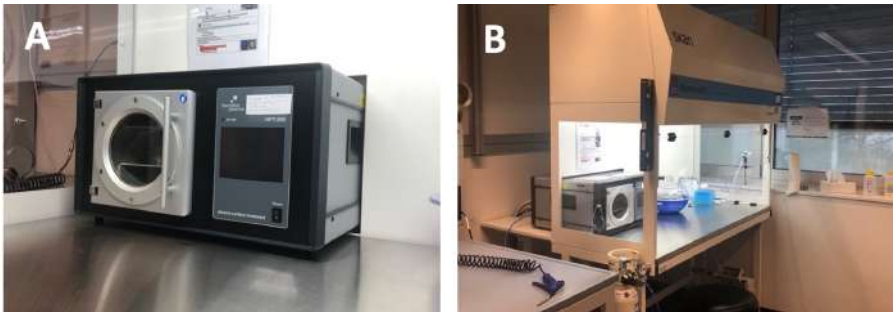


*Fig. 1. A) New plasma cleaner set-up in a new laminar flow hood (B) allowing to protect microfluidic devices from dust particles during their fabrication.*

## 2.3. Organs-on-Chip Culture Laboratory

After the DBMR moved out of Murtenstrasse 50, we had to purchase some important equipment that was no longer available: an Eppendorf refrigerated centrifuge, a NanoDrop One photometer, a PCR thermocycler and a Nikon cell culture microscope.

## 2.4. Organs-on-Chip Microscopy

The OOCF has several microscopes suitable for organs-on-chip, in particular with long focal distance objectives, environmentally controlled boxes ($CO_2$, humidity) and rooms for perfusion, etc. They are all part of the Microscopy Group (MIC) of the University of Bern.

A Zeiss Axio Imager is an upright microscope with an environmental chamber ($CO_2$, humidity controlled). It can be used for material sciences as well as life sciences applications. Tobias Weber is responsible for the microscope. A Thermo Fischer EVOS M7000 is also available, it is an automated microscope for time-lapse imaging under $CO_2$ and humidity-controlled environment. Karin Schmid is responsible for the microscope. Finally, a Nikon spinning-disk microscope with environmental chamber is also available. It is managed by the LIF facility. Tobias Weber (tobias.weber@unibe.ch) and Karin Schmid (Karin.rechberger@unibe.ch) are responsible for the Zeiss and the EVOS microscopes, respectively.

*Left: Karin Schmid-Rechberger, right: Tobias Weber.*

## 3. Microvasculature-on-Chip: A Success Story

One of the widely adopted microfluidic chips created at the OOCF is designed to establish a network of perfusable microvessels. It has already been used in several research projects, and several research partners from around the world are presently using it. These vessels are created within a hydrogel chamber, that is the result of a self-assembly process of endothelial cells and fibroblasts or pericytes. Functional, perfusable microvasculature with vessel sizes between 10 and 100um are created. Various types of endothelial cells from various organs, including the lung, the umbilical cord,

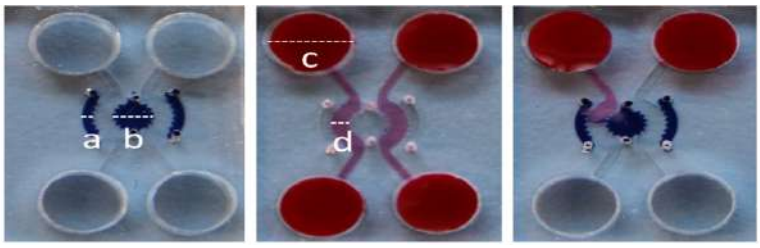


*Fig. 2. Microfluidic chip with three compartments filled with hydrogel (in blue), allowing for the culture of three cultures fluidically connected to each other by microfluidic channels filled with cell culture medium (in red). (Bichsel et al., Tissue Eng. A, 2015).*

and the liver, have been conducted in the lab.

### 3.1. Effects of the pericytes on the microvasculature functions

By employing the microvasculature-on-chip, we assessed the crucial functions of lung pericytes. These specialized cells line the self-assembled endothelial lumen, enabling them to remain open and perfusable. Pericytes play a pivotal role in controlling the size of microvessels, resulting in a denser network with smaller diameters compared to microvessels composed solely of endothelial cells. Moreover, this innovative setup allows for the observation of pericytes' ability to contract the microvessels upon exposure to vasoconstrictors like phenylephrine (Fig. 3), shedding light on their dynamic role in regulating blood flow (Bichsel et al., Tissue Eng. A, 2015).

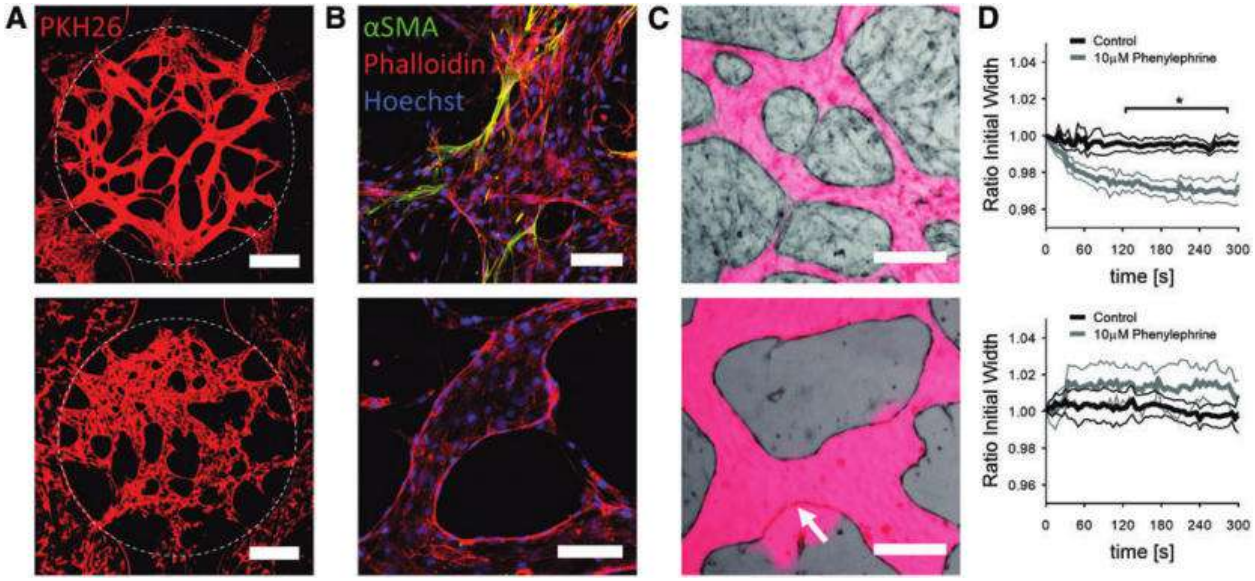


*Fig. 3. The presence of pericytes affects vessel morphology, permeability and vasoactive response to phenylephrine (top row: co-culture of endothelial cells with pericytes, bottom row: endothelial cells only). A) view of the central chamber scale bar 500um; B) detailed view showing some a-SMA positive pericytes lining the endothelium, scale bar: 200um; C) vessels with pericytes were smaller and less leaky than those without pericytes, scale bar: 100um; D) Vessels with pericytes contract upon exposure to phenylephrine (Ref. Bichsel et al., Tissue Eng. 2025).*

### 3.2. Testing the effects of Nintedanib a triple kinase inhibitor

We used the microfluidic vasculature-on-chip to study the effects of nintedanib, a triple kinase inhibitor, on the process of vascular remodeling. This in vitro model was created using primary endothelial cells and primary lung fibroblasts, which allowed us to simulate perfusable microvessels. Using this innovative microvessel model, we comprehensively analyzed how nintedanib affects factors such as permeability, vascularized area and cell-cell interactions. Nintedanib showed a significant antivasculogenic effect already at minimal concentrations of 10 nM, leading to increased vascular permeability. In addition, nintedanib led to a reduction in microvessel density and diameter and affected the organization of fibroblasts around endothelial microvessels. These results emphasize the ability of nintedanib to modulate endothelial network formation and interactions with perivascular elements.

Overall, our study demonstrates that advanced in vitro microvasculature models have the potential to elucidate the mechanisms of action of antifibrotic drugs on microvascular remodeling in a three-dimensional context. This may refine our understanding of these drugs beyond traditional animal studies (Zeinali et al., Angiogenesis, 2018, 21:861-871)

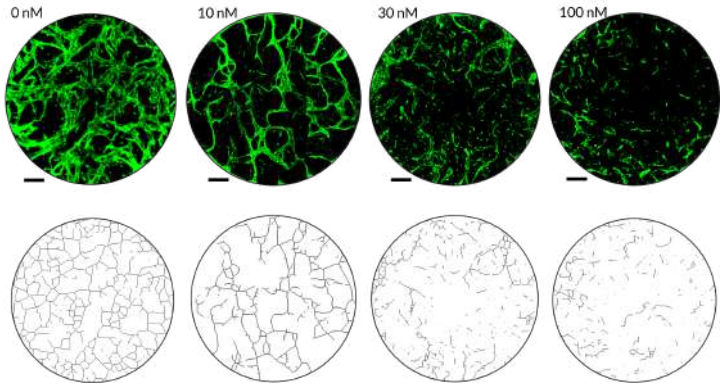


*Fig. 4. Nintedanib's anti-neovasculogenic effect. The density of the vessels is reduced with increasing concentration (Zeinali et al., Angiogenesis, 2018).*

## 4. OOCF User Fees

To keep the administrative costs as low as possible, an affordable yearly user fee is requested to each research group (typically 2-3 users/group) that uses the OOCF. The user fees are unchanged from last year. The user fees for the OOC culture lab were redefined in function of the frequency of the lab use. The fees aim at covering parts of the running costs of the laboratories (repair costs, replacement of equipment), the costs of the consumables, and a small part of the salary of the OOCF staff. If you need large volumes of consumables (PDMS, medium, etc.), please inform the respective lab manager, so that we don't run out of stock (the additional costs will be billed separately). The microscope user fees are aligned with those defined by the MIC group of the University of Bern.
**Important, we encourage each PIs to add OOCF user fees in their SNF research proposals.**

The OOCF also offers to design customized organs-on-chip. This can range from helping to create basic soft lithography molds (CAD) to the complete design of complex organs-on-chip. To assess your needs, contact: olivier.guenat@unibe.ch

**Table: OOCF User Fees (prices in CHF)**

| Services | What | Users Uni Bern | External Users |
|---|---|---|---|
| **BioMEMS-Lab** | Introduction [1)] | 30.- | 50.- |
| | Year | 1500.- | On demand |
| **Organ-on-Chip Culture Lab** | Introduction [1)] | 30.- | 50.- |
| | Year – occasional users (5-10x/yr) | 1500.- | On demand |
| | Year – regular users (10-20x/yr) | 3000.- | NA |
| | Year – frequent users (>20x/yr - weekly) | 6000.- | NA |
| **Zeiss Axio-Imager M2** | Instructions [2)] | 50.- | 100.- |
| | Use (per hour) [3)] | 25.- | 50.- |
| **EVOS Thermo** | Instructions [2)] | 50.- | 100.- |
| | Use (per hour) [4)] | On demand | On demand |
| **Spin-Coater** | Instructions | 50.- | 100.- |
| **Plasma-Cleaner** | Instructions | 50.- | 100.- |
| **OOC design** | Design customized organ-on-chip | On demand | On demand |

[1)] The general introduction must be completed regardless of whether the lab is used only once or on a regular basis, Contact the responsible lab manager.
[2)] please contact Tobias Weber (tobias.weber@unibe.ch)
[3)] If extra support is required by the lab technician, an additional 100.- per hour will be charged
4) please contact Karin Schmid (karin.rechberger@unibe.ch)

## 5. Acknowledgments

The OOCF is deeply grateful for the support of the Resource Committee ("Ressourcenauschuss") of the Medical Faculty of the University of Bern, and the University of Bern Stiftung for their generous support.

Bern, October 2023
Olivier Guenat - ARTORG Organs-on-Chip Facility