Organs-on-Chip Facility (OOCF)
Annual Report 2023

University of Bern

A Core Facility of the ARTORG Center for Biomedical Engineering Research

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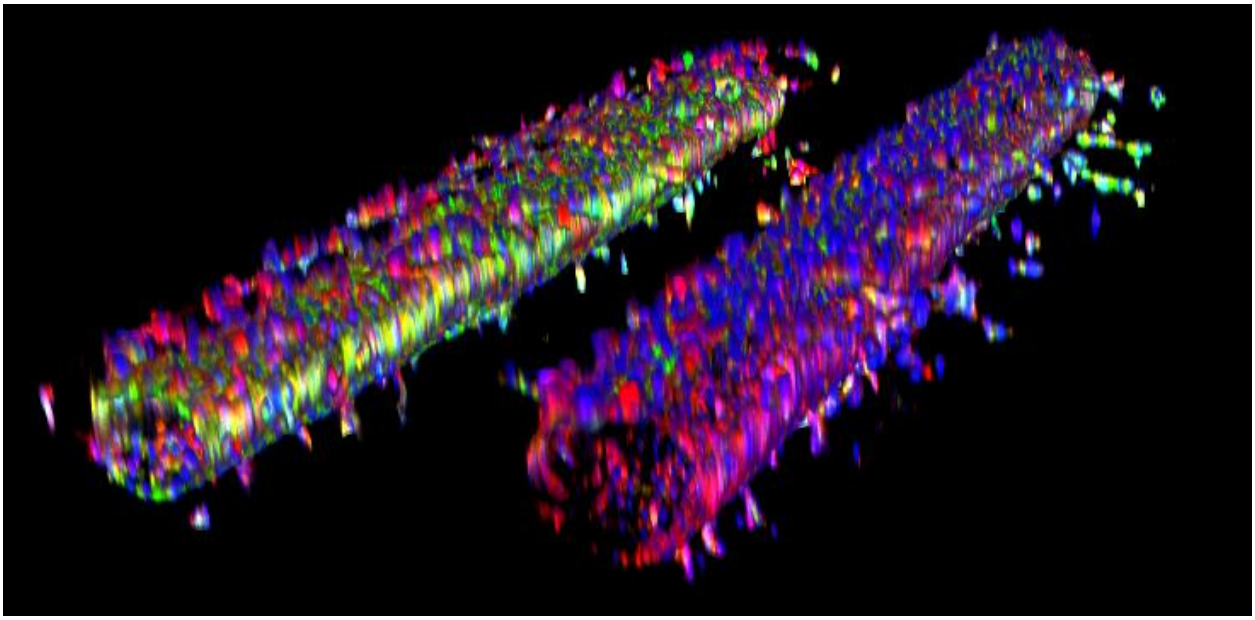
Table of content:



Rendering of two 200um in diameter endothelial vessels with angiogenic sprouting. Ref: Ferrari et al., iScience. 2023 Feb 13;26(3):106198 [CC-BY 4.0; https://creativecommons.org/licenses/by/4.0/]

1. The Organs-on-Chip Facility at UniBE

The Organs-on-Chip Facility (OOCF) of the ARTORG Centre at the University of Bern (UniBE) aims to provide researchers at UniBE and beyond with a state-of-the-art infrastructure for the design, fabrication, and testing of microfluidic chips used as organs-on-chip models. This facility aims to advance biomedical research in preclinical and clinical fields, push the boundaries of OOC technology for precision medicine, identifying personalized treatment strategies and contributing to broader innovations in biomedical research. As such, the facility serves to advance the principles of the 3Rs (Replacement, Reduction and Refinement) in animal testing.

The OOCF is located at the ARTORG Center and is part of the Organs-on-Chip Technologies (OOC) Lab, headed by Prof. Olivier Guenat. In 2023, the OOCF was used by around 40 researchers from ten different research groups of the University of Bern and beyond. The OOCF staff run a laboratory for microfabrication (BioMEMS) and an OOC cell culture laboratory (OOC Culture Lab). They offer users of the OOCF an introduction to the laboratory-specific equipment, safety procedures and support in the development of customized microfluidic chips. The use of the OOCF is based on user fees. An annual user fee is charged to all users to cover part of the OOCF costs. Since 2022, the OOCF user fees are reimbursed by the Swiss National Science Foundation, which means that OOCF user fees can be budgeted in SNSF projects.

2. OOCF News

In 2023, we replaced several aging pieces of equipment and expanded our overall inventory. All CO_2 incubators that had reached the end of their service life, as well as -80° and -150°C freezers, had to be replaced. In addition, we were able to acquire a rheometer, an instrument we have been anticipating for a long time, to determine the stiffness of hydrogels to be used in OOCs. All of this new equipment is available to OOCF users.

2.1. OOCF Staff

OOCF staff (state 2.7.2024):

- OOC cell culture lab manager: Sabine Schneider (sabine.schneider@unibe.ch)
- BioMEMS lab manager: Denise Ackermann (denise.ackermann@unibe.ch)
- EVOS microscope responsible: Karin Schmid-Rechberger (karin.rechberger@unibe.ch)
- Zeiss microscope responsible: Tobias Weber (tobias.weber@unibe.ch), (from July 2024: Johannes Fehr (johannes.fehr@unibe.ch)

There were several changes in 2023 in the OOCF staff team. Sabine Schneider took over responsibility as manager of the OOC cell culture laboratory and Denise Ackermann took over responsibility for the BioMEMS laboratory. We would like to thank Severin Müller for his work as the former manager of the BioMEMS laboratory.

Laboratory managers: Sabine Schneider (left), lab manager of the OOC cell culture lab, Denise Ackermann (middle), lab manager of the BioMEMS lab, and Severin Müller (right), former manager of the BioMEMS lab.

Regarding microscopy, Karin Schmid-Rechberger remained responsible for the EVOS microscope, while Tobias Weber (responsible for the Zeiss microscope) will hand over his responsibilities to Johannes Fehr in August 2024. Many thanks to Tobias for his help in ensuring that the Axio was up and running.

Microscopes responsible: Karin Schmid-Rechberger (left), Tobias Weber (middle, until the end of July 2024) & Johannes Fehr (from August 2024).

2.2. BioMEMS Laboratory

A new Anton Paar MCR102e rheometer has been acquired, enabling precise measurement of the stiffness of various hydrogels. Hydrogels are essential components in organs-on-chip systems because they mimic the extracellular matrix (ECM), replicating key properties such as mechanical stiffness and density, as well as chemical composition. This advanced rheometer enhances our ability to characterize these properties, thereby improving the fidelity and functionality of organ-on-chip models. The following illustration (Fig. 1) shows a graph obtained with the rheometer while measuring fibrin gel. This graph illustrates the relationship between stress and strain, providing detailed insights into the mechanical properties of the fibrin gel, such as its stiffness and viscoelastic behavior.

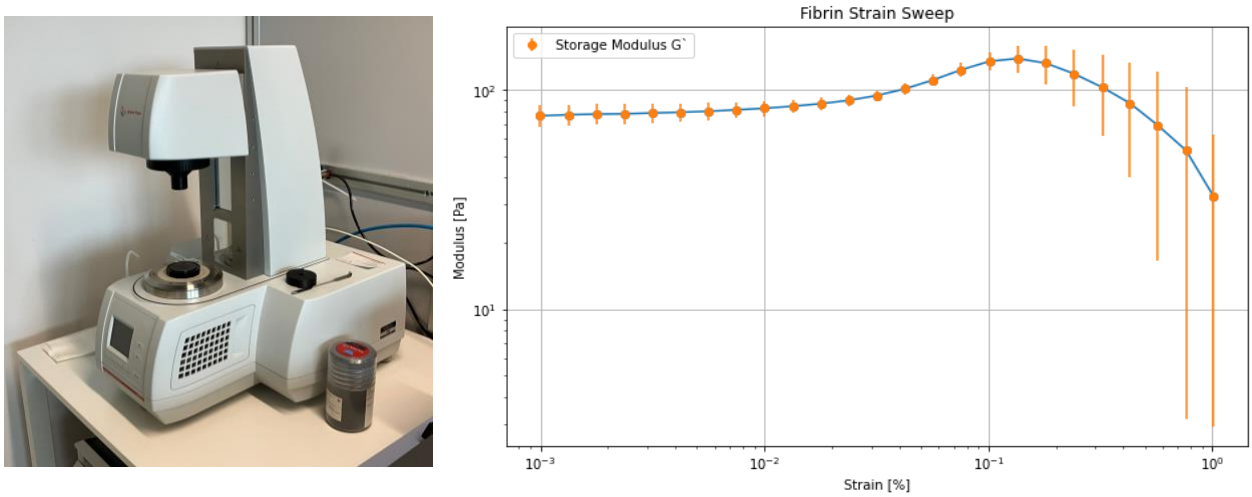


Fig. 1. The new Anton Paar MCR102e being tested, and a typical strain sweep curve of a fibrin hydrogel used in OOC systems.

2.3. Organs-on-Chip Culture Laboratory

In the organ-on-chip culture lab, we had to replace all incubators and the -20°C, -80°C, and -150°C freezers as they were at the end of their life. Upgrading these critical pieces of equipment ensures that we maintain the precise environmental conditions necessary for our experiments, thereby enhancing the reliability and reproducibility of our research. Another important update is that the OOC culture lab will move from the U1 floor to the E-floor in June 2024, while this report is being written. This relocation will provide upgraded facilities and more space, enhancing our ability to conduct cutting-edge research in organ-on-chip systems.

2.4. Organs-on-Chip Microscopy

The OOCF has several microscopes suitable for organs-on-chip, with long focal distance objectives, environmentally controlled boxes (CO_2, humidity) and space for pumping systems and sensors. They are all part of the Microscopy Group (MIC) of the University of Bern. The 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. The Thermo Fischer EVOS M7000 is also available, it is an automated microscope for time-lapse imaging under CO_2 and humidity-controlled environment. Finally, a Nikon spinning-disk microscope with environmental chamber is also available. It is managed by the LIF facility. All microscopes can be reserved via OpenIris.

3. Adding an Immune Component in OOCs

OOC models increasingly enable the recapitulation of complex biological processes. Here, we provide a recent example of introducing immune components into a flow-driven organ-on-chip. Lisette van Os, former PhD student of the OOC lab, succeeded to develop a lung infection-on-chip model. This innovative system enables real-time visualization of peripheral blood mononuclear cells (PBMCs) responding to a biochemical gradient mimicking infection (Fig. 2, 3). Key features of this model include a co-culture of endothelial and lung epithelial cells within a three-channel design fabricated through soft lithography.

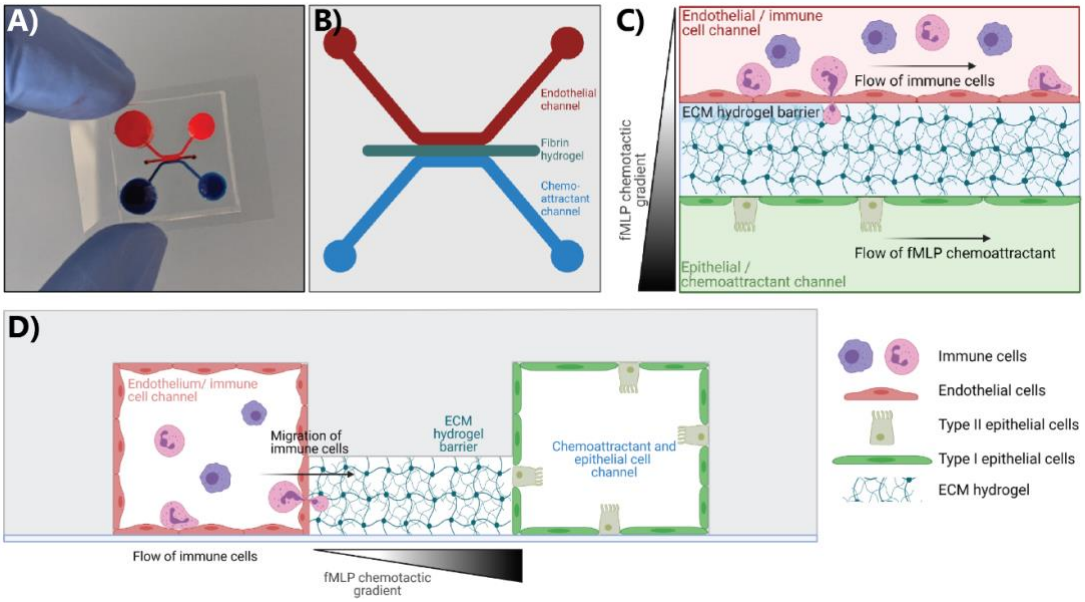


Fig. 2. Picture of the microfluidic chip with three channels filled with dyes. B) Schematic design of the whole chip, C) Detailed view of the three fluidic channels, with endothelial cells, the hydrogel and the epithelial cells. D) cross-section perspective of the model. Ref: Van Os et al. Eur J Pharm Sci. 2023 Aug 1;187:106485. [CC-BY 4.0; https://creativecommons.org/licenses/by/4.0/].

The central channel, filled with ECM hydrogels, is flanked by channels simulating endothelial and epithelial barriers. A chemotactic gradient across the hydrogel barrier induces immune cell migration through the endothelial channel.

She observed that in the absence of other cell types, immune cells migrated towards the chemotactic gradient but not into the hydrogel, suggesting that immune cells were able to recognize the chemoattractant within the system. After adding an endothelial barrier, immune cells extravasated into the hydrogel (Fig. 3). Lung epithelial cells were cultured on the opposite side of the endothelial-hydrogel barrier to model immune cell migration in ARDS. The lung epithelial cells reacted to fMLP stimulation by increasing immune cell migration. She also discovered that extravasation was notably delayed when endothelial cells were subjected to bi-directional flow, compared to the uni-directional flow induced by piston pumps typical in tilters, which are often used in the OOC community for basic cell perfusion. However, this non-physiological flow profile adversely affects endothelial cell functions. These findings are crucial for the OOC community, given the widespread use of tilter-based solutions that eliminate the need for tubing.

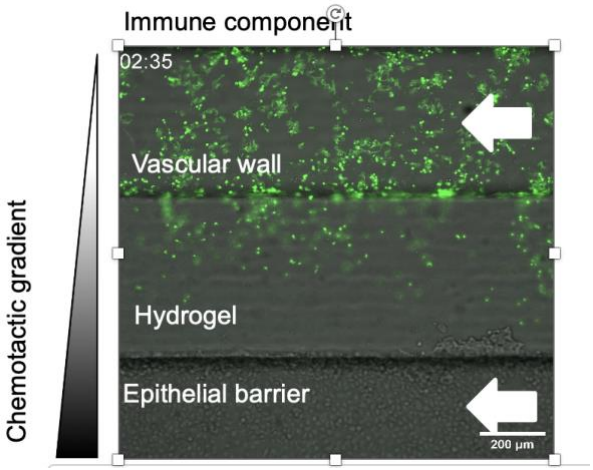


Fig. 3. PBMC migration across the endothelium, the ECM, towards the epithelium as a response to a chemotactic gradient. Ref: Van Os et al. Eur J Pharm Sci. 2023 Aug 1;187:106485 [CC-BY 4.0; https://creativecommons.org/licenses/by/4.0/].

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 3 users/group) that uses the OOCF. The user fees are unchanged from last year. The fees aim at covering parts of the running costs of the OOCF. 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, ideally as part of a collaboration within a funded project. Please contact us early so we can help shape your needs and plan accordingly. 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 (typically 3 users/group)	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.-
Rheometer	Introduction and use[5)]	On demand	On demand
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) until July 2024, from August 2024, Johannes Fehr (Johannes.fehr@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) please contact Denise Ackermann (denise.ackermann@unibe.ch)

5. Acknowledgments

The OOCF is grateful for and acknowledges the important support of the ARTORG Center, the Resource Committee of the Medical Faculty of the University of Bern and the MSc in Biomedical Engineering program, without which the acquisition of new equipment and the replacement of old equipment would not have been possible.

Bern, July 2024
Prof. Dr. Olivier Guenat – Director ARTORG Organs-on-Chip Facility