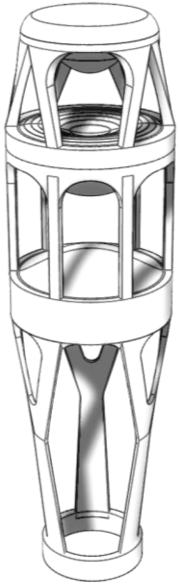
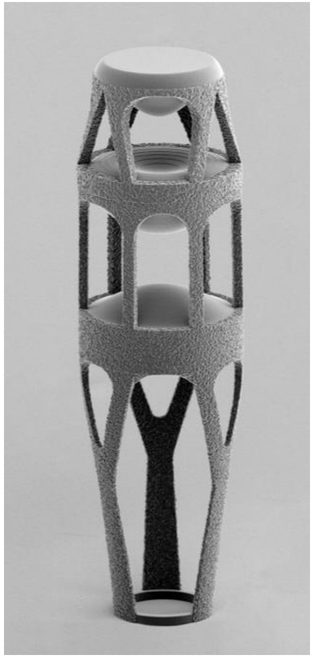
3D microfabrication by Two-Photon Polymerization for biomedical applications

Dr. Jochen Zimmer, Sales Manager, Nanoscribe GmbH & Co. KG

43. Chemnitzer Seminar, Sensor Systems for One Health

We are Nanoscribe
We make microfabrication systems





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35 % **+** R&D intensity

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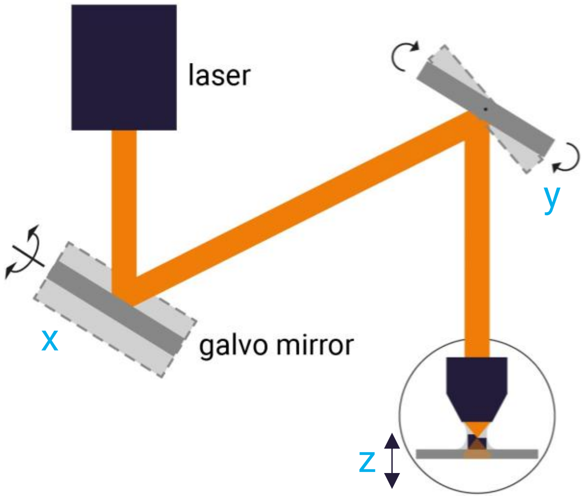
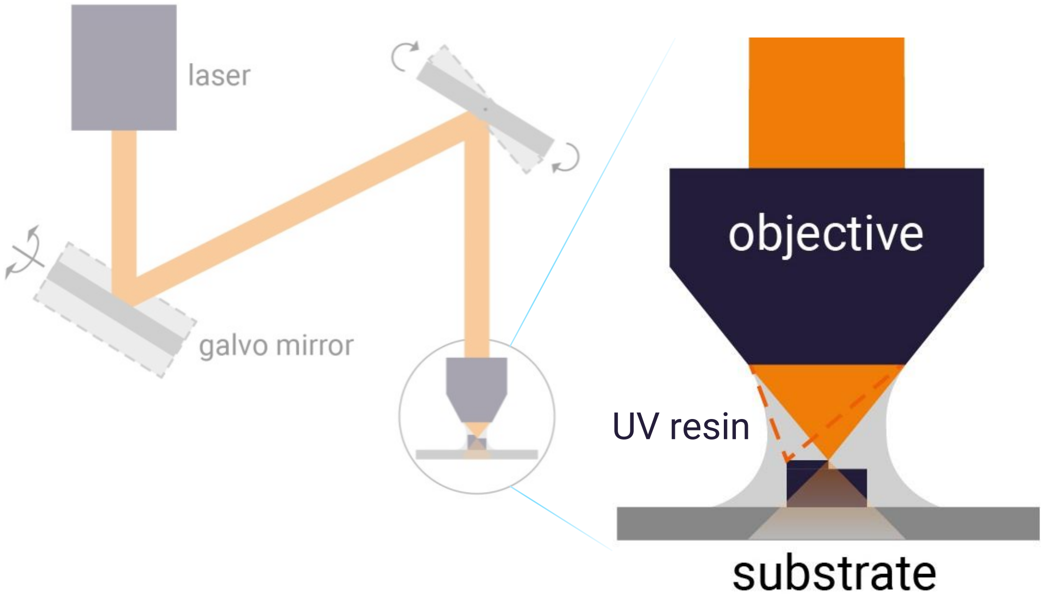
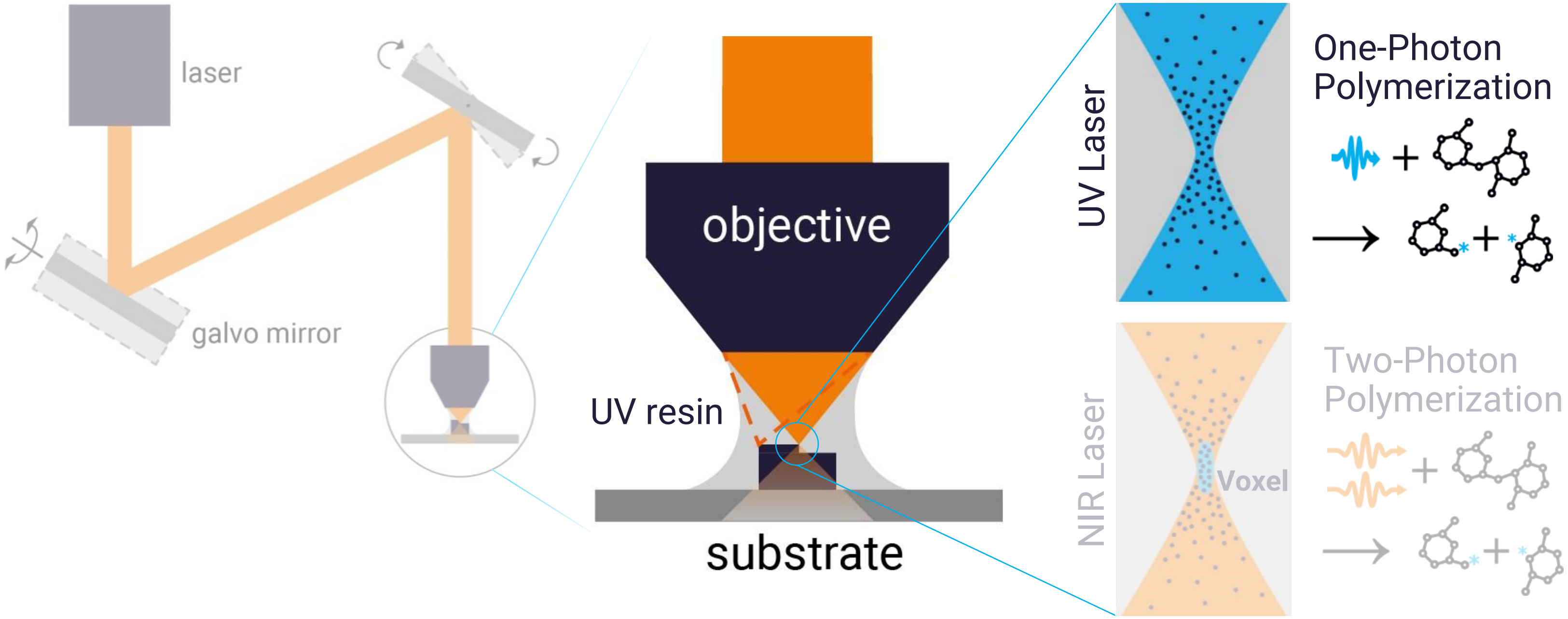
Technology basics
Galvo scanners for highest print speed



Technology basics
Dip-in Laser Lithography (DiLL)

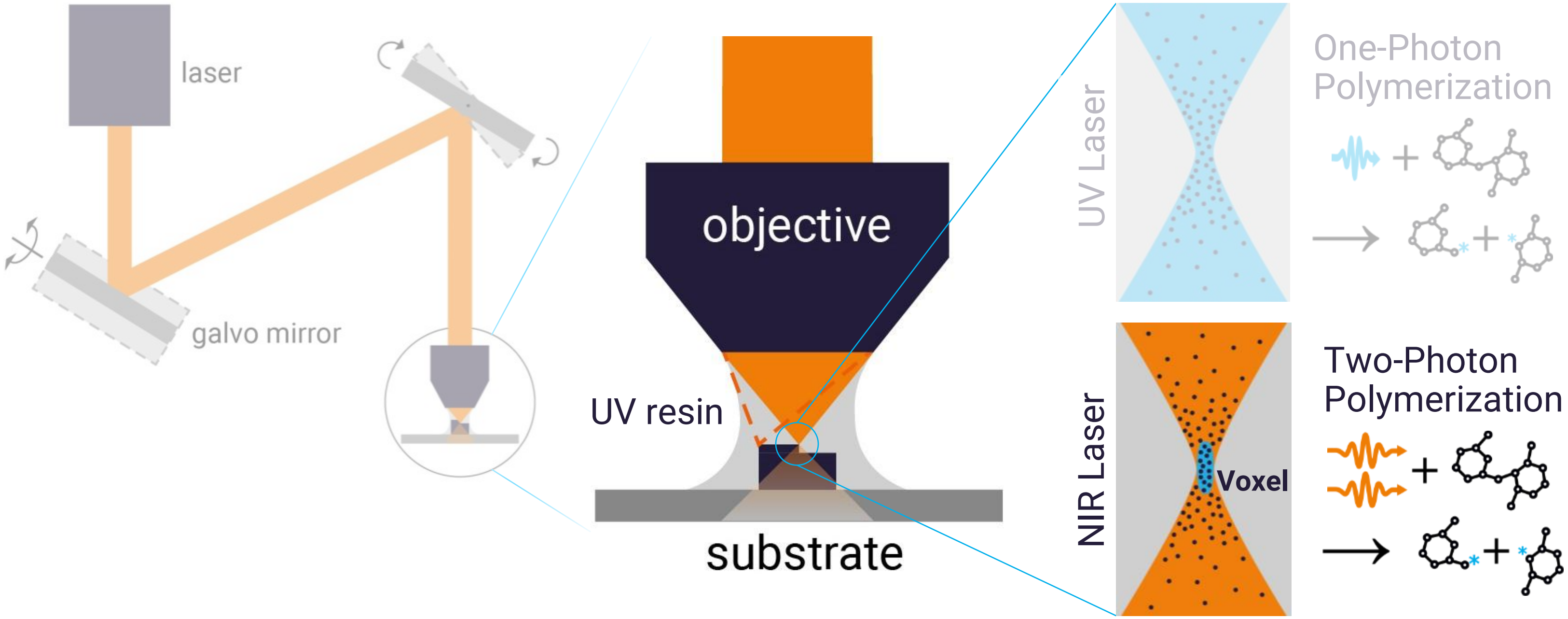


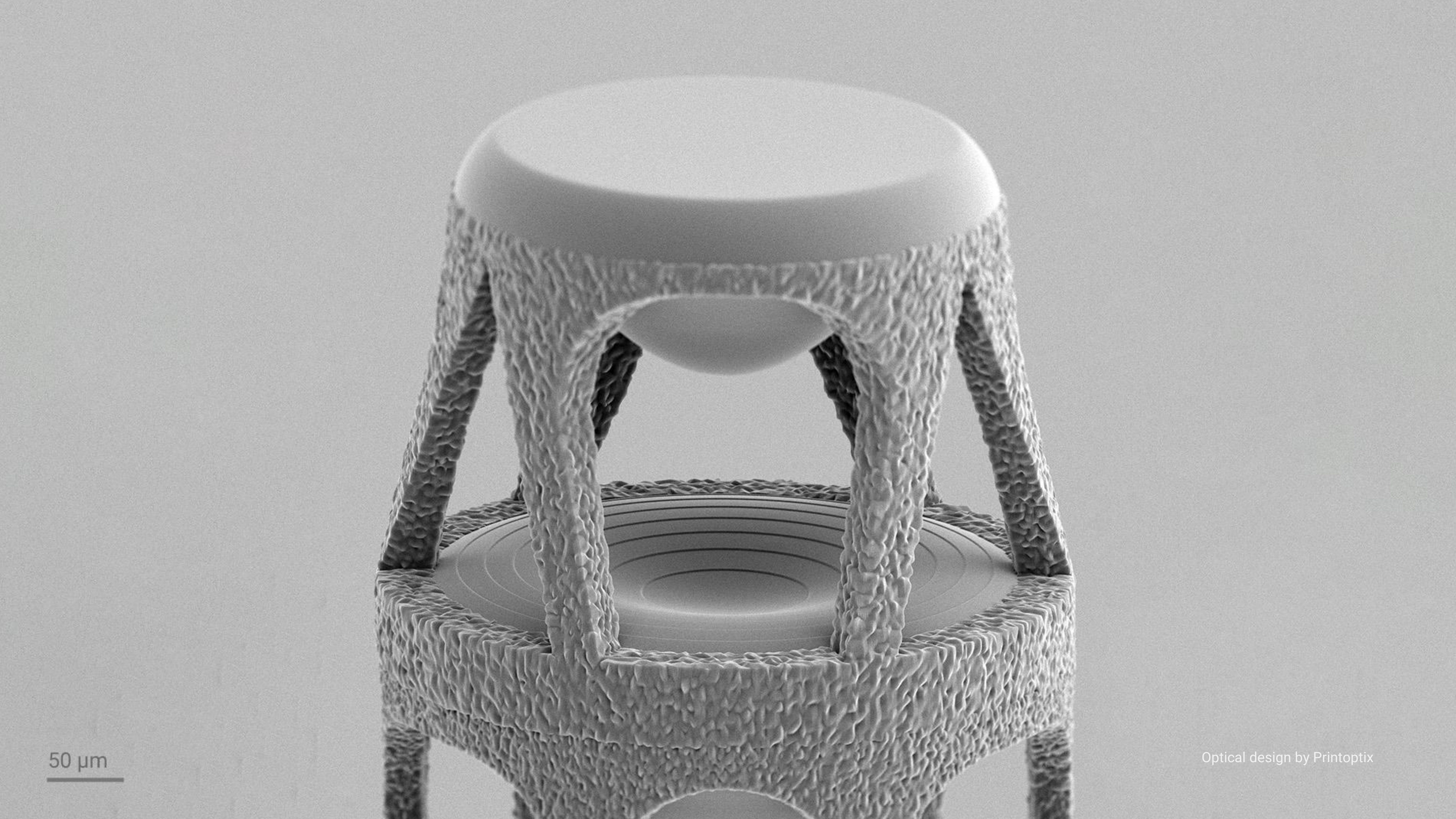
Technology basics
Two-Photon Polymerization (2PP)



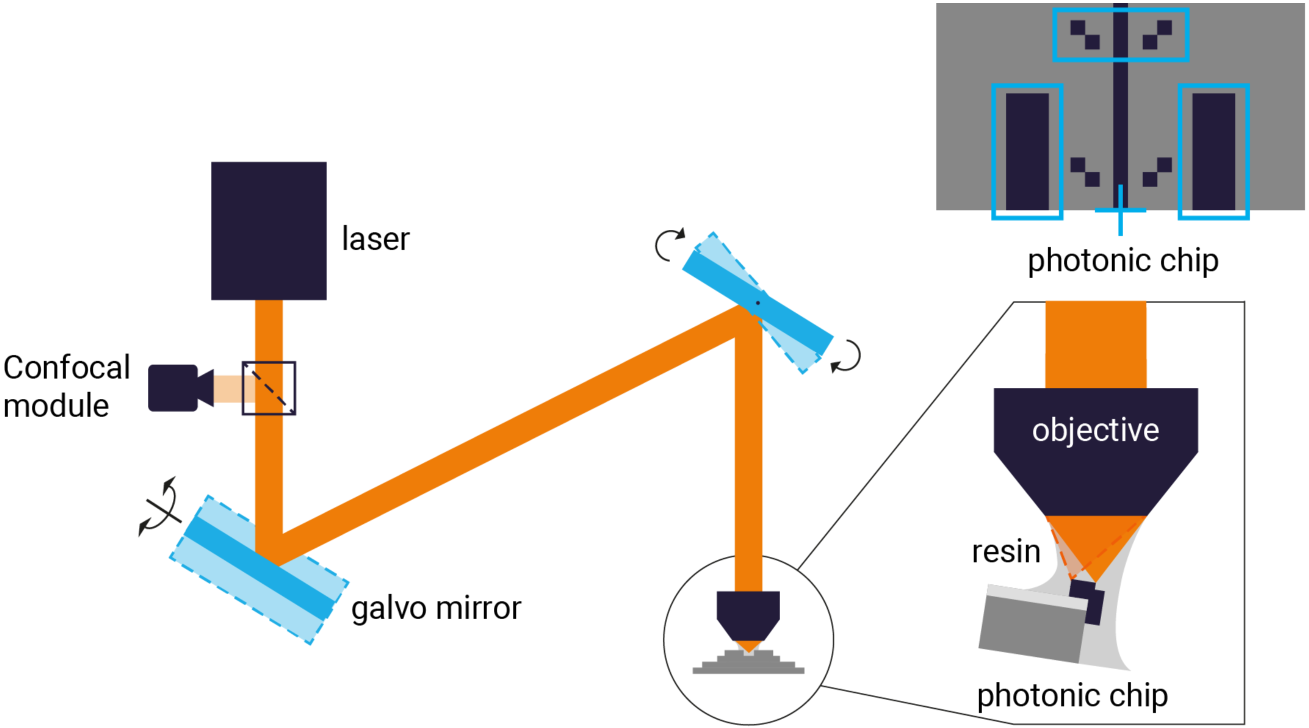
Technology basics

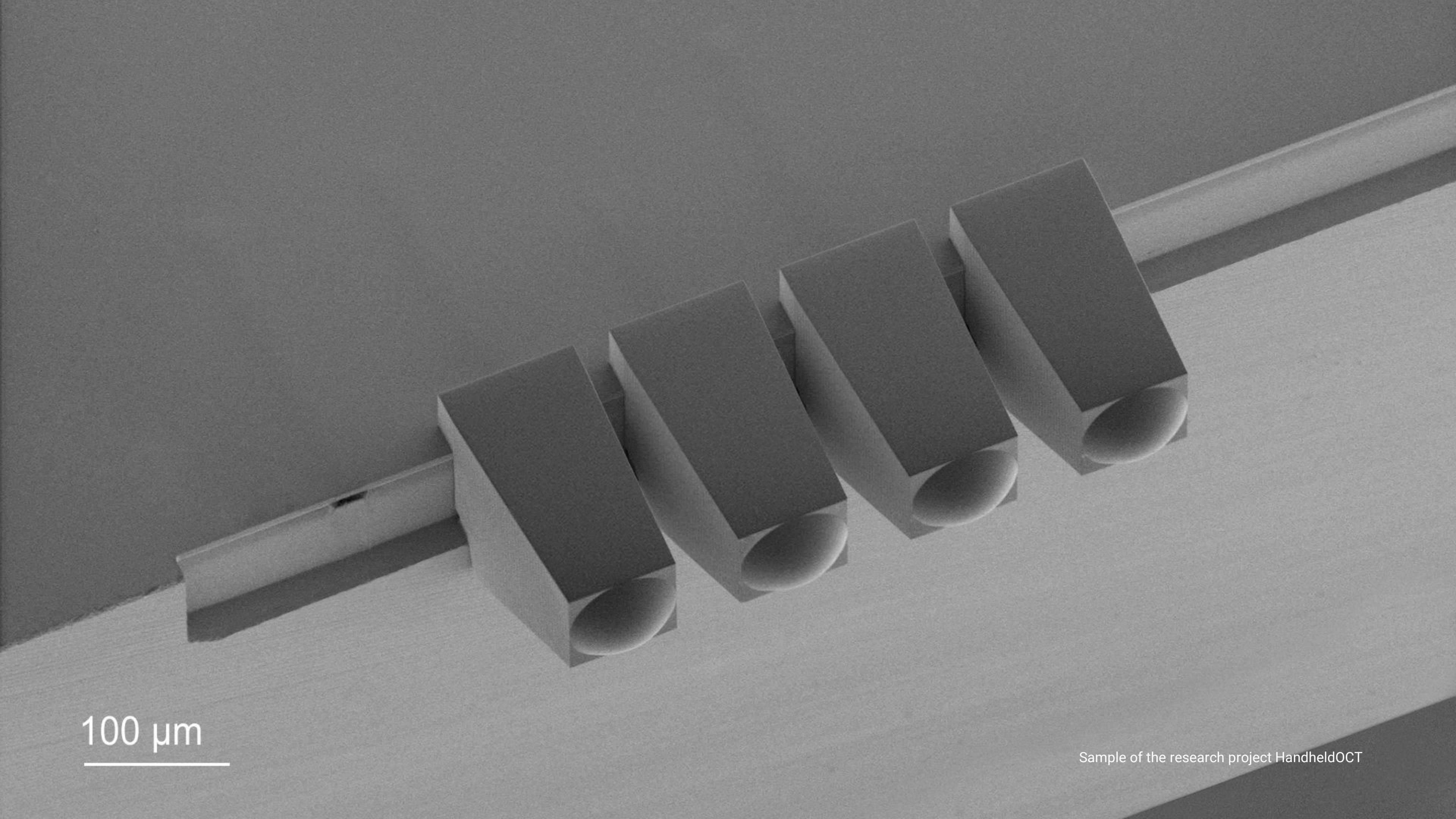
Two-Photon Polymerization (2PP)




50 µm
Optical design by Printoptix

Quantum X align: chip alignment



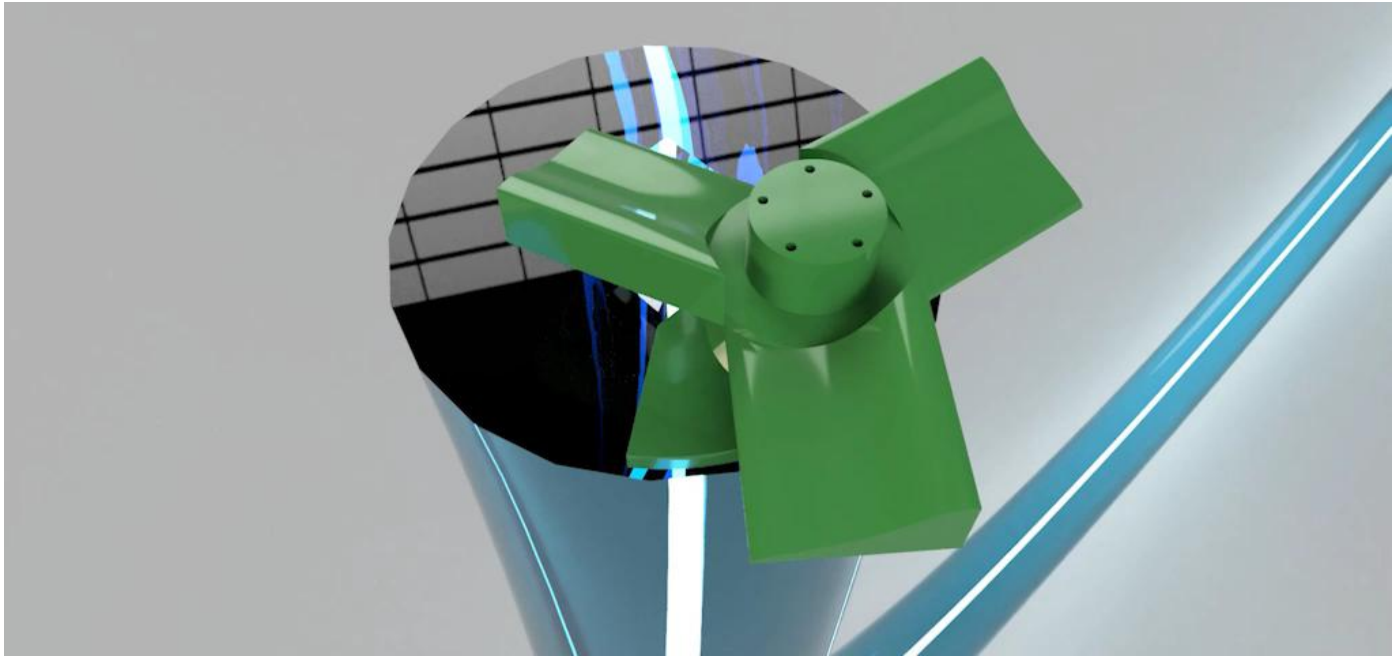

100 µm
Sample of the research project HandheldOCT

Micro-optical sensors

Photonic chip on fiber tip

See:
K. Markiewicz and P. Wasylczyk, "Photonic-chip-on-tip: compound photonic devices fabricated on optical fibers," Opt. Express **27**, 8440-8445 (2019).
https://doi.org/10.1364/OE.27.008440

3D-printed fiber sensors with complex moving parts

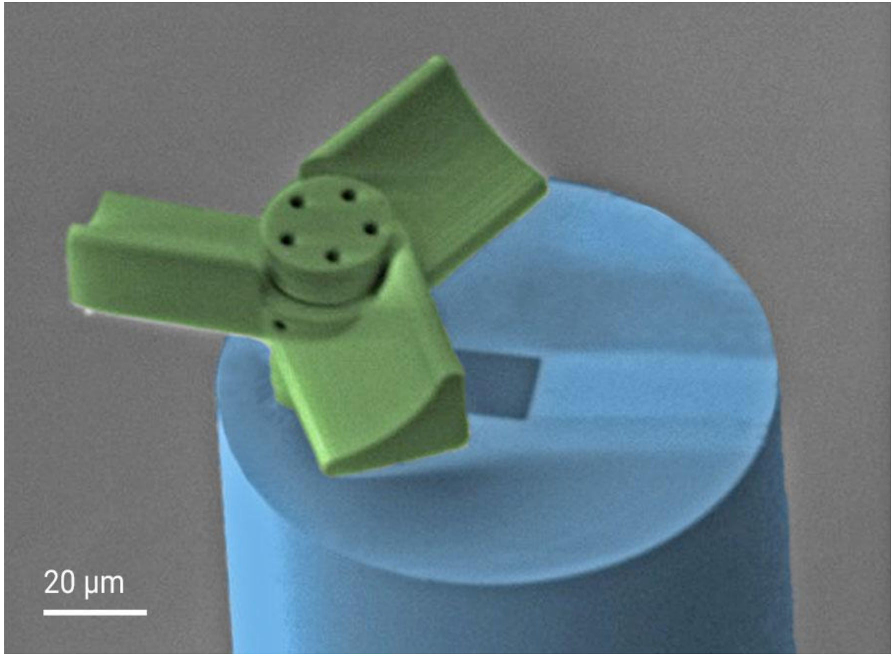


Air Force Institute of Technology - Dayton

Williams, J. C., Chandrahalim, H., Suelzer, J. S. & Usechak, N. G. Multiphoton Nanosculpting of Optical Resonant and Nonresonant Microsensors on Fiber Tips. *ACS Appl. Mater. Interfaces* **14**, 19988–19999 (2022). https://doi.org/10.1021/acsami.2c01033

3D-printed fiber sensors with complex moving parts

- SEM image of the flow sensor 3D-printed on an optical fiber
- The signal is generated by reflected light through the fiber core



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3D-Printed Micro Lens-in-Lens for In Vivo Multimodal Microendoscopy

“many pathological changes are poorly characterized by a single modality and require additional imaging modalities for accurate diagnosis”

Goal: a miniaturized endoscope that can measure structure (OCT) and chemical properties (fluorescence measurements) at the same time

Challenge: high sensitivity fluorescence needs high NA, OCT needs large depth of focus (-> low NA)

J. Li et al. 3D-Printed Micro Lens-in-Lens for In Vivo Multimodal Microendoscopy. Small 18, 2107032 (2022).
https://doi.org/10.1002/smll.202107032

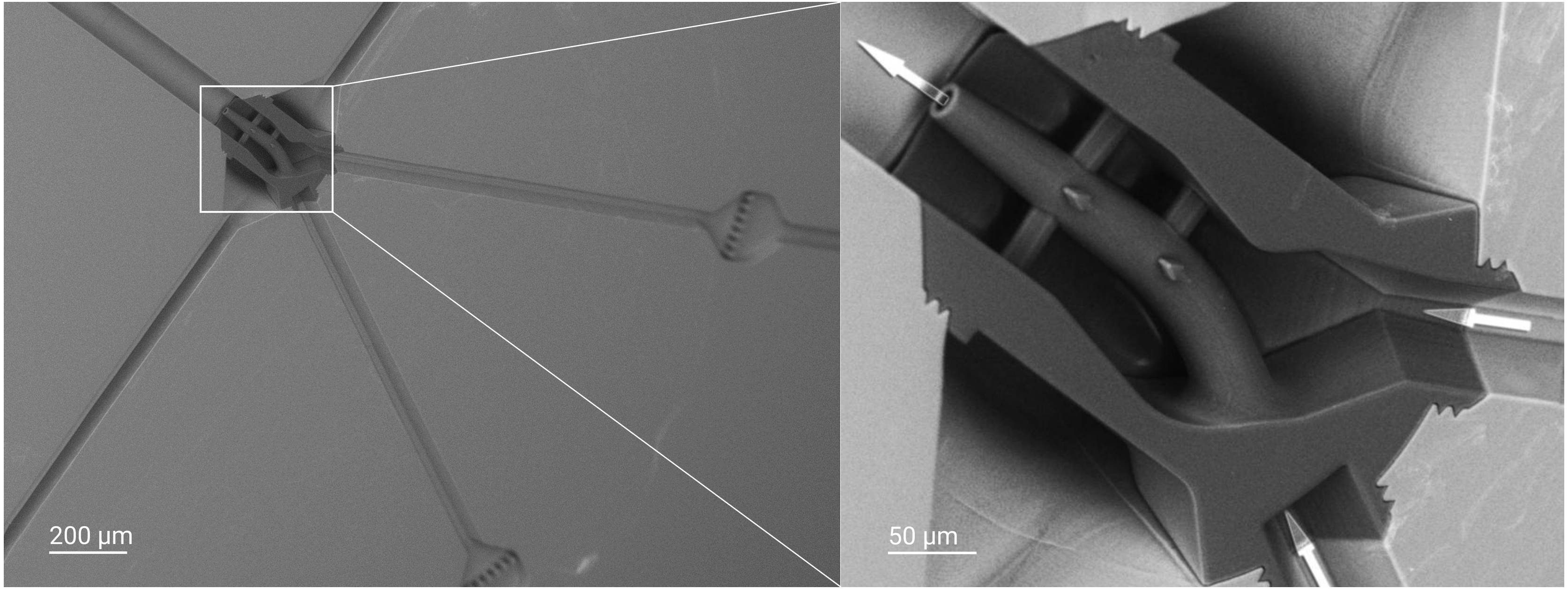
3D-Printed Micro Lens-in-Lens for In Vivo Multimodal Microendoscopy

- Using a double-clad fiber, the core can be used for OCT imaging, and the inner cladding can be used to carry the fluorescence signal
- A 3D microlens is printed onto the fiber with two distinct sections:
  - the center has a low NA (0.08) and is used for OCT imaging
  - the outer section (NA 0.8) is used to capture the fluorescence signal
- The device is autoclavable

J. Li et al. 3D-Printed Micro Lens-in-Lens for In Vivo Multimodal Microendoscopy. Small 18, 2107032 (2022).
https://doi.org/10.1002/smll.202107032

Microfluidics

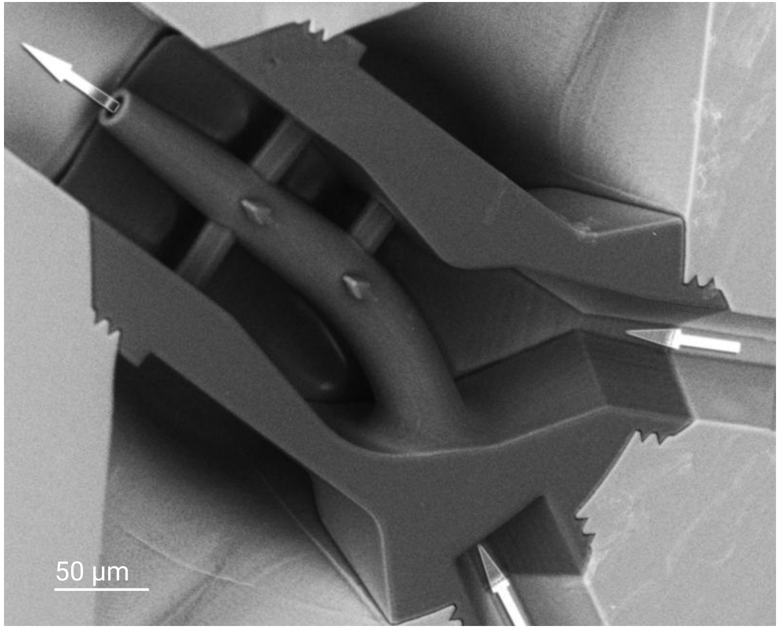
In-chip fabrication of spider-inspired 3D nozzle



J. Lölsberg et alet al. "3D nanofabrication inside rapid prototyped microfluidic channels showcased by wet-spinning of single micrometre fibres." Lab on a Chip 18.9 (2018): 1341-1348.

In-chip fabrication of spider-inspired 3D nozzle

- 3D Microfabrication is used for printing a positive mold of the microfluidic chip for soft lithography
- And direct fabrication of the 3D spinneret inside a replicated chip
- The spinneret has a complex nozzle geometry and is tightly sealed
- High-spatial resolution improves the geometry and thus flow control inside the chip



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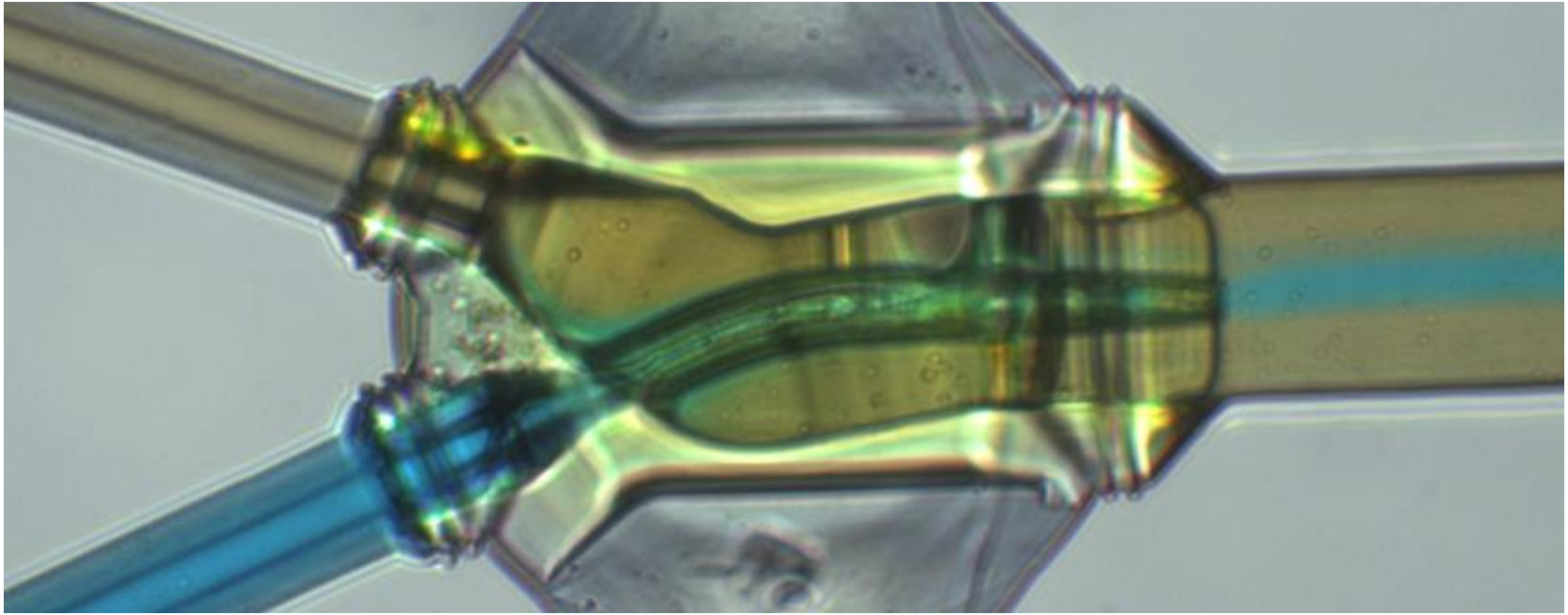

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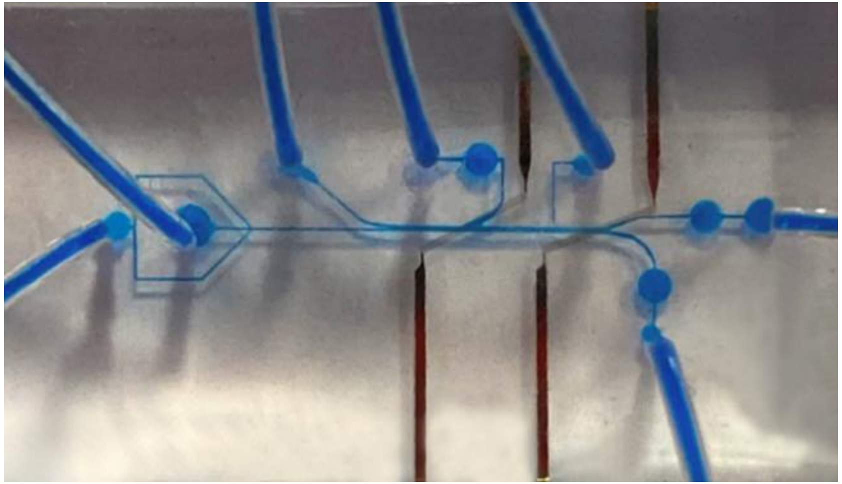
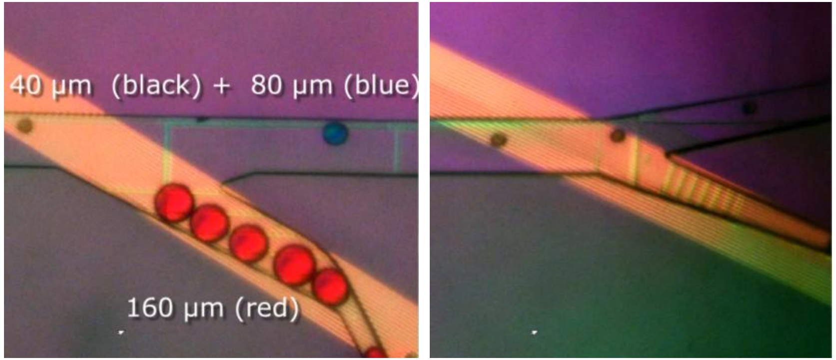
Microdroplet Quality Control Devices



Zhang, Han, et al. "FIDELITY: A quality control system for droplet microfluidics." *Science advances* 8.27 (2022): eabc9108.

- Highly efficient droplet separation with a bandpass filter
- 3D converging (X, Y, Z) channels
- The sloping height (Z) correlates to the desired droplet size to increase sorting efficiency
- The 3D-printed master mold is used to create a PDMS microfluidic system that is later aligned over electrode patterns

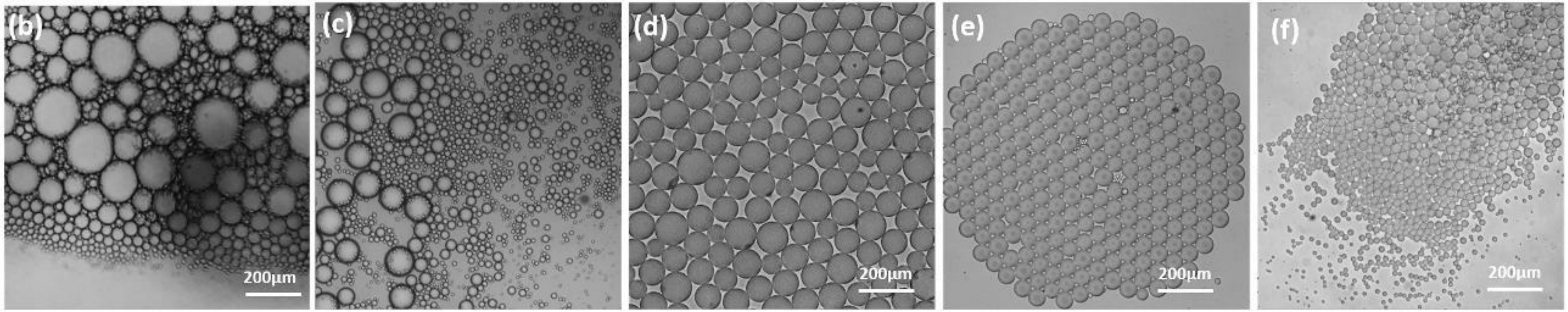
Microdroplet Quality Control Devices



- The device was able to sort particles from 160 to 40 µm in diameter
- Sorting efficiency >99%
- Sorting throughput of 100 droplets/s
- 10X increase compared to other sorting devices

Zhang, Han, et al. "FIDELITY: A quality control system for droplet microfluidics." *Science advances* 8.27 (2022): eabc9108.

Microdroplet Quality Control Devices



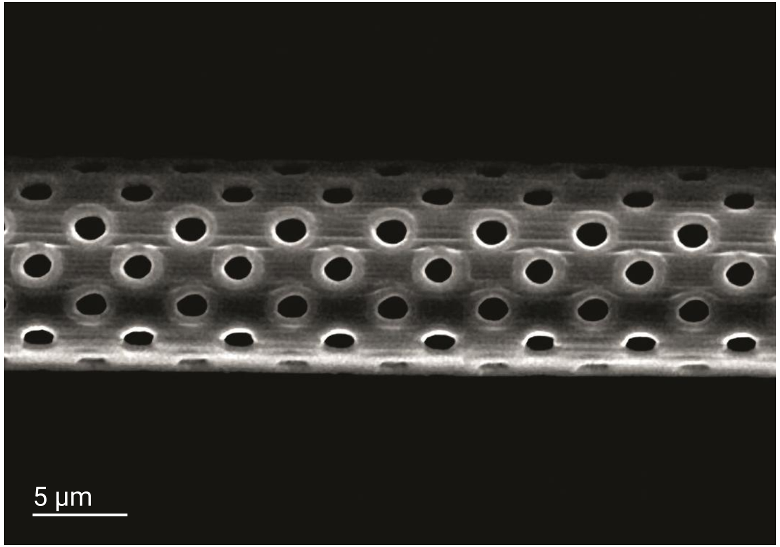
After sonication | Reinjection | Outlet 1 collection | Outlet 2 collection | Outlet 3 collection

Zhang, Han, et al. "FIDELITY: A quality control system for droplet microfluidics."
Science advances 8.27 (2022): eabc9108.

Organ-on-a-chip

Blood-brain barrier model

- 3D Microfabrication allows to fabricate a real-scale biohybrid model
- The freedom in design allows a millimeter-long system of 3D printed porous microchannels
- Tubular structures of 10 µm diameter and pores diameter of 1 µm
- Endothelial cells on the scaffold build a biological barrier



A. Marino, et al. "A 3D Real-Scale, Biomimetic, and Biohybrid Model of the Blood-Brain Barrier Fabricated through Two-Photon Lithography." Small 14.6 (2018): 1702959.

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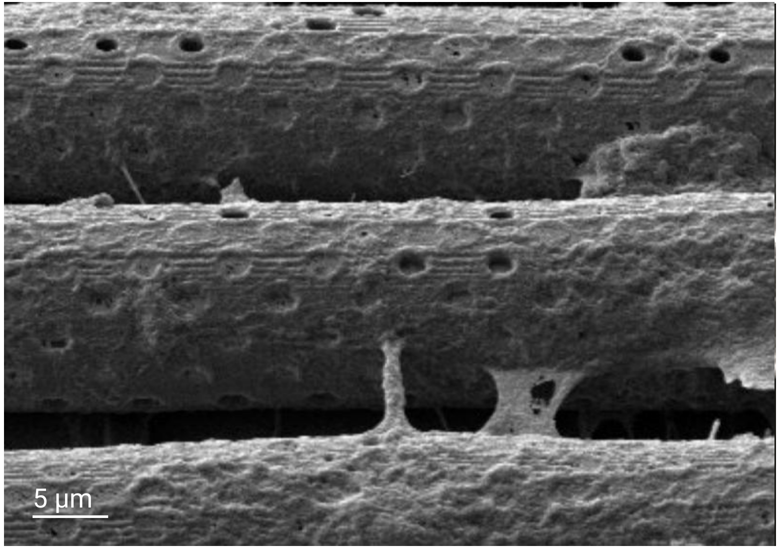

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3D-printed heart-on-a-chip for driving research on cardiac diseases and drug delivery

- Cross-section of the circular cell seeding
- Three tailor-made microcages that function as cell adhesion sites for the 3D freestanding cardiac microtissue
- Surrounding microfluidic channel for contraction force stimulation

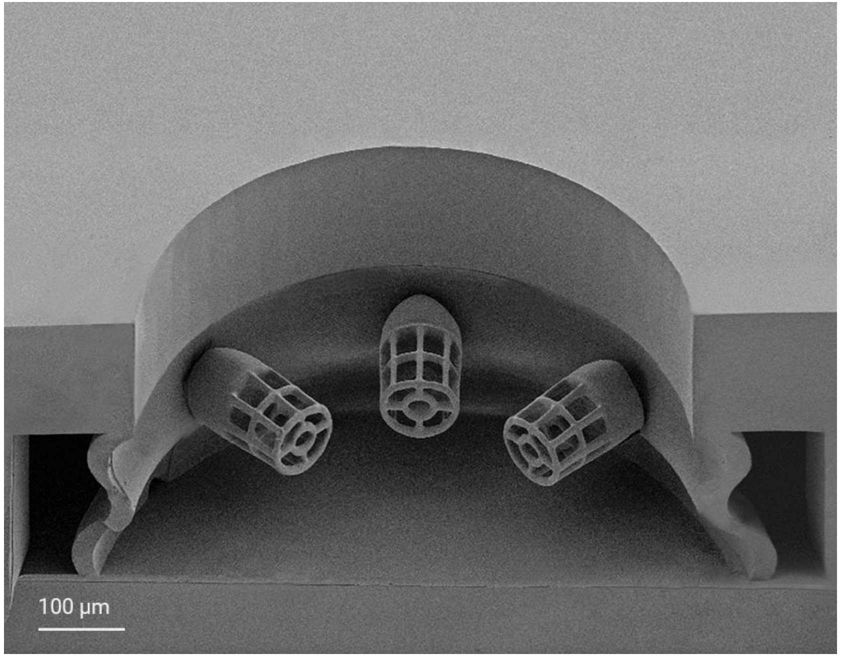

Image: M. Çağatay Karakan,, Boston University Department of Mechanical Engineering

Jayne, R. K. *et al.* Direct laser writing for cardiac tissue engineering: a microfluidic heart on a chip with integrated transducers. *Lab Chip* **21**, 1724–1737 (2021). https://doi.org/10.1039/D0LC01078B

3D-printed heart-on-a-chip for driving research on cardiac diseases and drug delivery

- Fabrication scheme of the heart-on-a-fiber platform:
  - (i - iii) Soft lithography of the seeding well from a negative master template

Jayne, R. K. *et al.* Direct laser writing for cardiac tissue engineering: a microfluidic heart on a chip with integrated transducers. *Lab Chip* **21**, 1724–1737 (2021). https://doi.org/10.1039/D0LC01078B

3D-printed heart-on-a-chip for driving research on cardiac diseases and drug delivery

- Fabrication scheme of the heart-on-a-fiber platform:
  - (iv) Soft lithography of the seeding well from a negative master template
  - (v) Direct writing of the cell attachment sites on the vertical wall of the PDMS seeding well
  - (vi) Bonding the PDMS-based platform on an electrode-patterned glass slab

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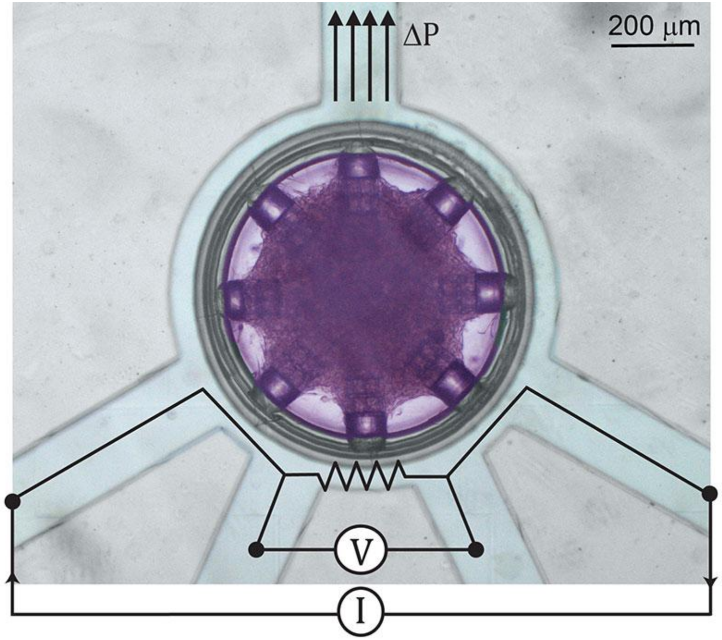
3D-printed heart-on-a-chip for driving research on cardiac diseases and drug delivery

- Microscopic top view of the heart-on-a-chip platform
- 8 cell attachment sites loaded with cardiac tissue
- The tissue aligns with the printed microstructures



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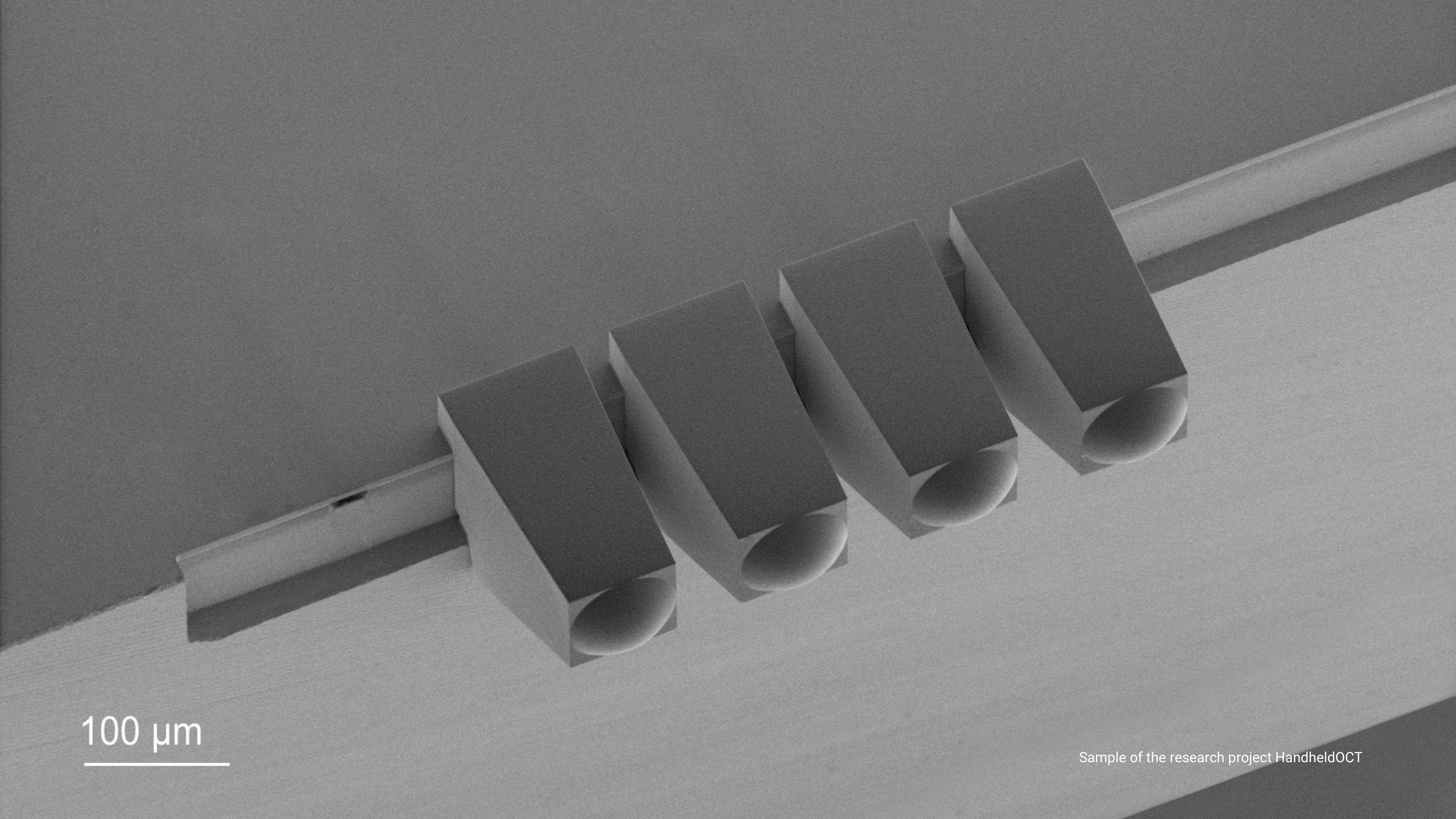
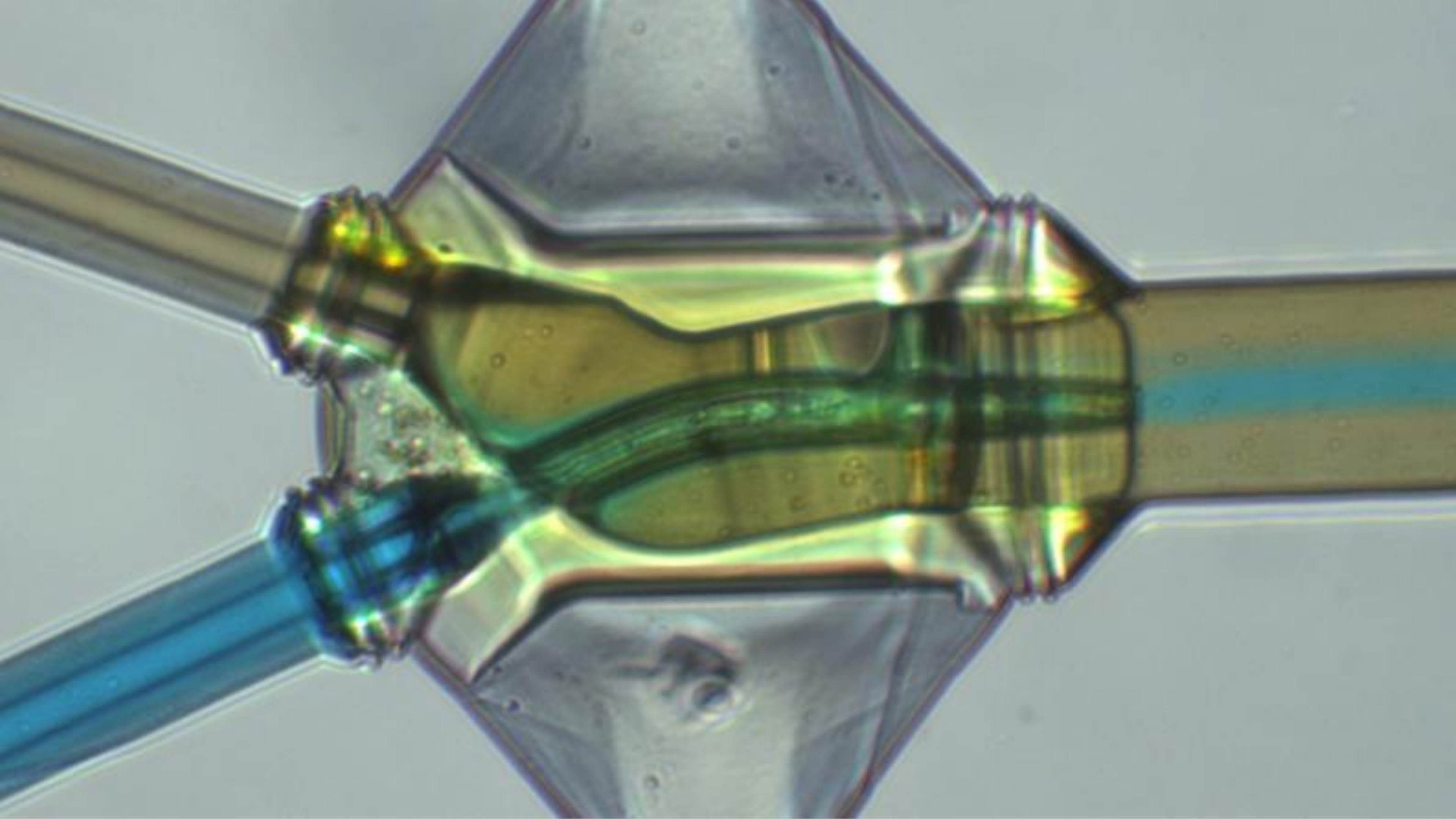
Large-scale perfused tissues via synthetic 3D soft microfluidics

See:
S. Grebenyuk et al. Nat Commun 14, 193 (2023).
https://doi.org/10.1038/s41467-022-35619-1



Sample of the research project HandheldOCT



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