Courtesy of NMI Natural and Medical Sciences Institute at the University of Tübingen. Beatriz Molina-Martínez et al 2022 Biofabrication 14 025004.

CASE STUDY

3D BRAIN-ON-A-CHIP

BOOSTING RESEARCH IN NEURODEGENERATIVE DISEASES

The innovative FEMTOPRINT® micromanufacturing technology enabled the realization of a 3D Human Brain-on-a-Chip to better recapitulate functional and structural neuronal networks.

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THE GOAL

In collaboration with the Medical Sciences Institute at the University of Tübingen (NMI, Germany), FEMTOprint realized a novel glass 3D Brain-on-a-Chip allowing the growth of 3D culture models that can better mimic the structure and the functionality of neural tissue than conventional 2D monolayer cultures, reducing the gap from in vitro to in vivo studies.

THE KEY INNOVATION

The 3D glass chip was engineered for modelling a microphysiological system designed to investigate human neuronal physiology and diseases, with high-throughput.

It represents a major step towards improved predictive in vitro models which will facilitate the development of more efficacius treatment for neurodegenerative pathologies.

PRODUCT ADVANTAGES

- Monolithic, 3D geometry (Fig. a)
- Integration of electrical sensing (add-on: Optical sensing) (Fig. b)
- Micrometric features
- Biocompatibility and sterilizability
- Optical transparency

Fig. a

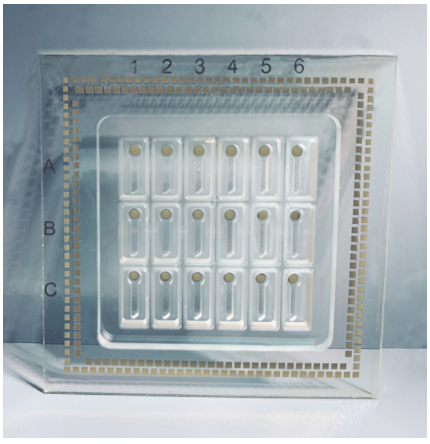

Fig. b

A 3D BRAIN-ON-A-CHIP TO CLOSE THE GAP FROM IN VITRO TO IN VIVO STUDIES IN NEURODEGENERATIVE DISEASES

Despite recent progress in treating diseases, many brain disorders are largely lacking therapeutic treatment. Failures of prospective drugs in clinical trials reflect the challenging complexity of the nervous system, and also may stem from partially inadequate preclinical models.

Well-established two-dimensional (2D) cultures of adherent cells reliably mimic certain aspects of neuronal dysfunctions with high throughput. Yet their results are not entirely predictive of clinical efficacy.

UNMET NEEDS IN NEURODEGENERATIVE DISEASE RESEARCH

Engineered three-dimensional (3D) culture models better mimic the structure of neural tissue and present one path towards levelling the translational gap from in vitro to in vivo studies. To generate in vitro models that better recapitulate important features of neuronal networks, recent approaches combine microfluidics and 3D culture techniques.

This is particularly important for induced pluripotent stem cell (iPSCs) culture, where the 3D microenvironment was shown to have a major impact in iPSC derivation, maintenance, neuron differentiation and maturation. Moreover, 3D cultures of iPSC-derived neurons were shown to recapitulate pathological features related to neurodegenerative diseases that were not reproducible in monolayer cultures, such as amyloid beta-aggregation in Alzheimer's disease or dopaminergic neuron cell death in Parkinson's disease.

However, their compact 3D architecture challenges functional detection, with most approaches relying on either optical techniques or planar microelectrodes.

FEMTOPRINT®
3D PRINTING FOR GLASS MICRODEVICES

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CASE STUDY
3D BRAIN-ON-A-CHIP:

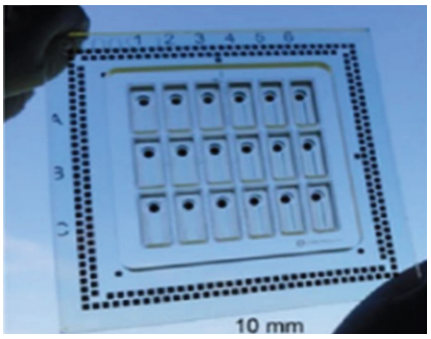

Fig. c

A 3D BRAIN-ON-A-CHIP

FEMTOprint SA (Muzzano, Switzerland) developed a 3D neuro-microphysiological system (nMPS) in a collaboration with The Medical Sciences Institute at the University of Tübingen (NMI,Germany). This system is based on microelectrode arrays (MEA) and glass microfluidics (fig.c), capable of electrophysiological readout of 3D human neuronal circuits in a microplate compatible format [1].

A core innovation is the addition of insulating caps on substrate-integrated microe- lectrodes (capped microelectrodes, CME), inspired by tunnels which enable neurite recordings from adherent neurons. The system enables 3D cell co-culture in a hydrogel scaffold (fig. d) with unguided extension of neurites into the CME (fig.e).

Neurons, astrocytes and microglia form a complex neuronal network with axons, dendrites, and synaptic structures dispersed in the 3D space (fig. f-g).

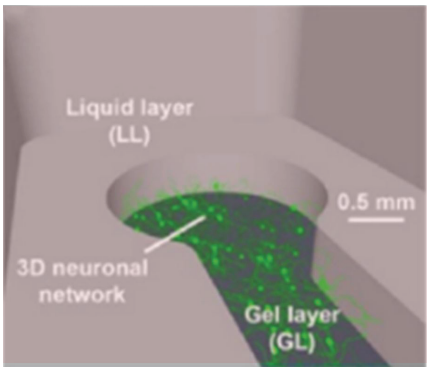

Fig. d

FABRICATION METHOD

The microfluidic device needs to support simultaneous morphological and functional assessment, by means of multiple independent wells, and enable long-term culture lasting at least several weeks, without any external perfusion systems.

Functionality of the CME requires precise microfabrication at the micron scale, transparent materials with sufficient thermal stability (170 °C), compatibility with organic solvents, and biocompatibility. Thus, glass was selected over thermoplastics or siloxanes, as it also provided the benefit of reusability.

In this context, FEMTOprint's highly sophisiticated technology platform proved to be a reliable, fast, and cost-effective fabrication method. Furthermore, it allowed precise, 3D micron-sized structures to be etched into the multi-well microfluidics. The microplate is also compatible with automated handling and high-content analysis for improved throughput of human induced pluripotent stem cell derived neurons.

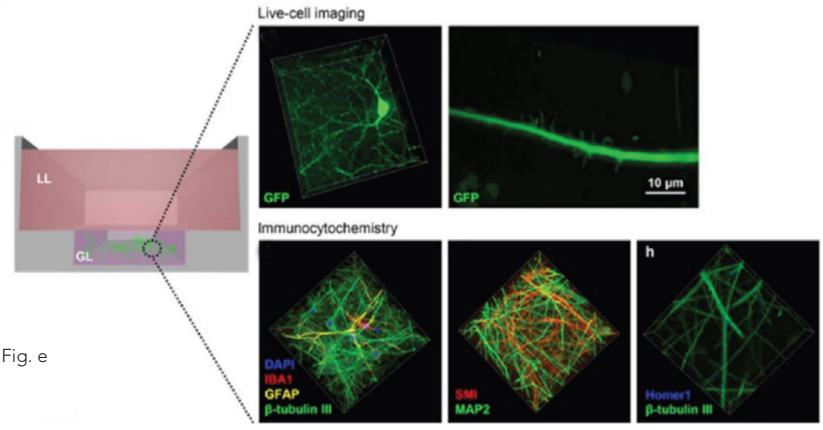

Fig. e

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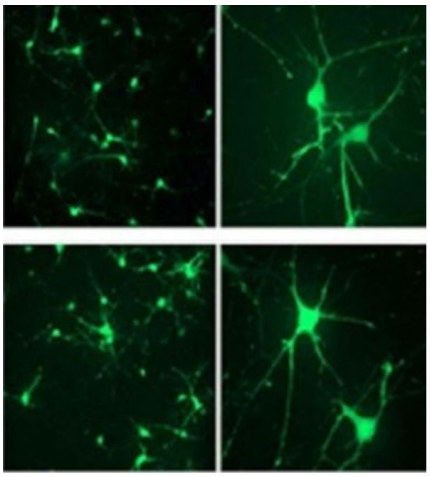


Fig. f

Fig. g

MEASURING 3D NEURONAL ACTIVITY WITH CME

Recreating and understanding 3D cell-to-cell interactions and morphology in vitro creates new opportunities to model cognitive, sensory, and motor functions, and, thus, brain disorders. Neurons cultured in a 3D hydrogel extend neurites in all directions. When neurons fire action potentials, the electrical signals travel into the caps.

The restricted spread of transmembrane currents generates extracellular action potentials of up to hundreds of microvolts. Measurements are parallelized with microscopy-based readouts, such as calcium imaging and optogenetic stimulation.

CONCLUSION

Thanks to this work, the ultrafast, laser-based FEMTOPRINT(R) technology platform has achieved a new level of complexity and precision to meet the needs of this particular application, which would not have been possible with conventional micro-fabrication techniques.

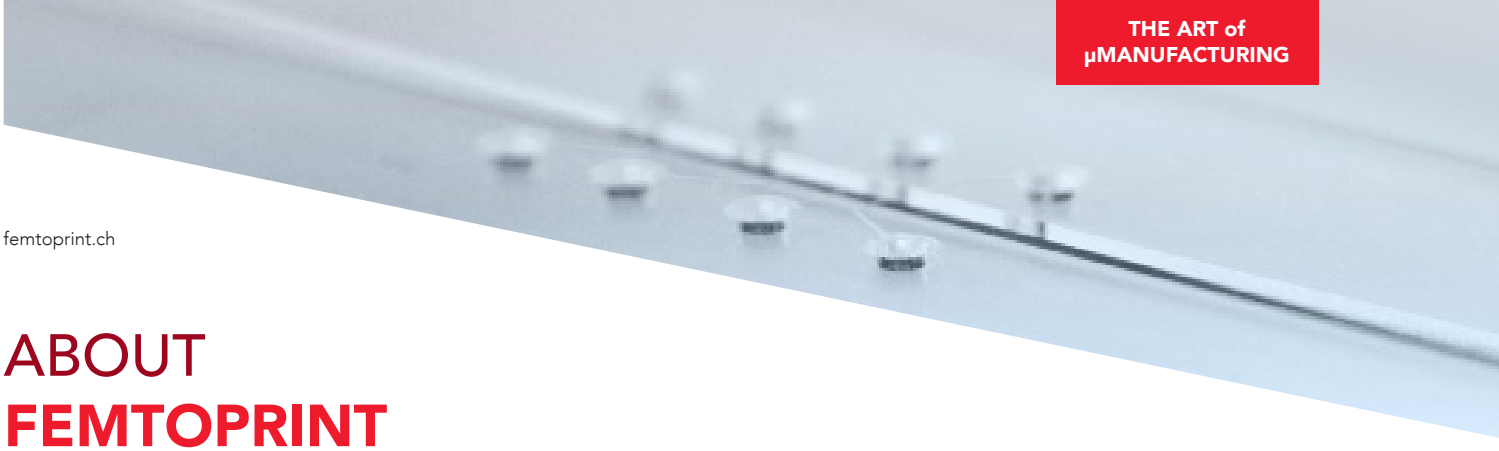
No less important for the Organ-on-a-Chip functionality was the material of choice. Glass allowed robust thermal stability, compatibility with organic solvents, and biocompatibility, in addition to the benefit of reusability and, consequently, cost-savings. One lesson learned is that, the FEMTOPRINT® technology can indeed contribute to expand the possibilities of the next generation of Organ-on-a-chip technology by integrating diffe- rent features within the single device using a monolithic fabrication, avoiding daunting and costly assembly and alignment steps.

On top of this, the functionalization of the glass surface through post treatments, such as hydrophobic or hydrophilic coatings, and the ability to integrate electronic and optical biosensors further expands the potential research progress given by these powerful, next generation devices in the field of neurodegenerative diseases.

[1] Beatriz Molina-Martínez et al 2022 Biofabrication 14 025004.

The FEMTOPRINT® technology could indeed contribute to expand the possibilities of the next generation Organ-on-a-Chip by integrating different features.

FEMTOPRINT®
3D PRINTING FOR GLASS MICRODEVICES



ABOUT FEMTOPRINT

COMPETENCIES

- Design for manufacturing
- Product engineering and development
- Excellent skills in material sciences, physics, optics, photonics and microfabrication
- Rapid prototyping
- Pilot & volume manufacturing
- Structural & functional characterization
- Quality control

PERFORMANCES

- Free-form geometries
- Process resolution ~ 1 µm
- Standard roughness Sa ≤ 100 nm
- After post-process treatment Sa < 10 nm
- Aspect ratio: > 1:500
- Substrate thickness: up to 30 mm
- Working area: up to 12″

WHY FEMTOprint

- Trusted partner from product development to wafer-scale volumes manufacturing
- Excellence in delivering superior quality, Swiss Made
- One-stop glass manufacturing foundry, vertically integrated
- Free-form design at the µm scale
- Fast tunaround time in prototyping

FEMTOprint is a Swiss high-tech Contract Development and Manufacturing Organization (CDMO) specialized in high-precision 3D microfabrication in glass. With the ground-breaking FEMTOPRINT® microfabrication platform we serve leading industrial Customers with feasibility, rapid prototyping, and pilot- and industrial series manufacturing at the wafer-level.

FEMTOprint's manufacturing plant operates out of Muzzano, Switzerland . In 2022, a subsidiary in Neuchâtel, Switzerland, has been opened to focus on the development of optical & photonic applications. The company is ISO certified 9001 and 13485:2016.

INDUSTRIES

Life Sciences & Diagnostics | Medical | Optics & Photonics | Watchmaking I Aerospace Quantum | Semiconductors | Industrial Machinery | VR & AR | Automotive | Energy

APPLICATIONS

Microfluidics | Micro-optics | Photonics | Microelectronics | Micromechanics | MEMS | Packaging | Mastering | Or the combination of some of them!

The core FEMTOPRINT® micro manufacturing platform relies on ultrafast, laser based and etching methods, creating novel, three-dimensional glass microdevices with micrometric resolution. The platform is completed with additional capabilities, but not limited to: Laser welding, three-dimensional waveguide inscription, dicing and surface treatments fused silica, borosilicate, ULE, boroaluminosilicate or alkali-free glass. A large variety of transparent substrates can be employed as raw material to create complex 3D structures, such as but not limited to: while the maximum working area is currently 300 mm in diameter and 30 mm in thickness.

ADVANTAGES

- Free-form microfabrication technlogy with micro-metric accuracy
- High surface quality and outstanding process repeatability, suitable for wafer-scale
- production
- Glass offers numerous functional advantages over for example plastics, ceramics
- and metals.
- Integration of optical, fluidic, and mechanical functionalities
- Wafer-scale production for series volumes
- Engineering expertise to support product development
- Full control over proprietary processes and systems

We want to be part of your success, contact us:

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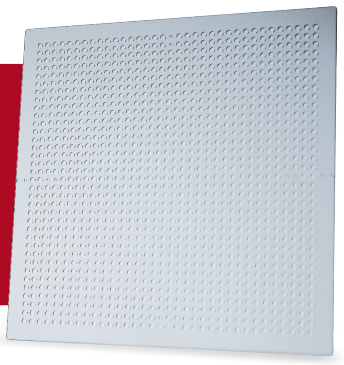

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