



# 4th BioCHIP Berlin International Forum on Biochips & Microfabrication

28-29 May 2024

# Catalog

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DEMACH

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# Editor's Statement

This is not yet the final version.  
We'll keep posting updates until  
the event day.

Please check back to find out the  
latest release.

Thank you.  
DEMACH Team

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## SPEAKER

- ATLANT 3D / DENMARK
- BIELEFELD UNIVERSITY / GERMANY
- BIOASTER / FRANCE
- CNR NANOTEC - INSTITUTE OF NANOTECHNOLOGY, LECCE (ITALY) / ITALY
- CNR NANOTEC / ITALY
- FEDERAL INSTITUTE FOR MATERIALS RESEARCH AND TESTING (BAM) / GERMANY
- IFOM / ITALY
- INESC TEC / PORTUGAL
- INSTITUT FÜR BIOPROZESS- UND ANALYSENMESSTECHNIK E.V. IBA / GERMANY
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- MAX PLANCK INSTITUTE FOR MOLECULAR CELL BIOLOGY AND GENETICS / GERMANY
- SHIBAURA INSTITUTE OF TECHNOLOGY / JAPAN
- TU BERLIN, CHAIR OF MICRO AND PRECISION DEVICES, BERLIN, GERMANY;  
TISSUSE GMBH, BERLIN, GERMANY/ GERMANY
- UNIVERSITY OF PALERMO / ITALY
- VITAL3D TECHNOLOGIES / LITHUANIA
- 
- 

Last updated: April 19, 2024

# PRIMO

## CREATE SMARTER CELL CULTURE MODELS



The flexibility to set and optimize the *in vitro* cell microenvironment of your experiments on demand:



Design 2D and 3D cell cultures,



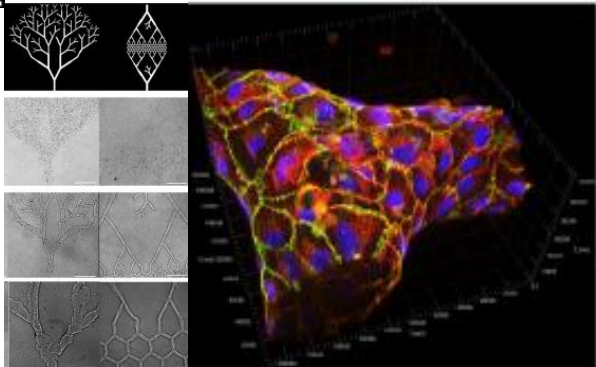
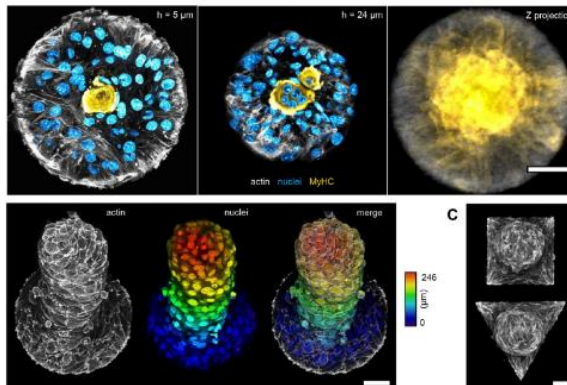
Shape organoids and spheroid arrays,



Create organ-on-chips and microfluidic chips.

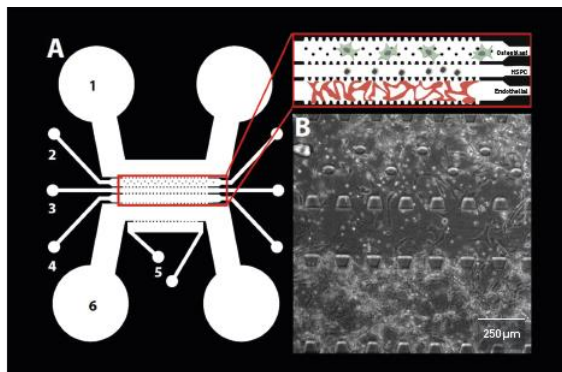
The PRIMO bioengineering platform relies on a contactless UV projection module and a dedicated software (LEONARDO) to tune the biochemistry & topography of your cellular models.

P. Guillamat et al., Nature Materials, 2022



E. Mazarin-Arghiri et al., Biomaterials, 2023

B. Souquet et al., Methods in Molecular Biology, 2021





Atlant 3D introduces Direct Atomic Layer Processing (DALP) technology, a pivotal innovation in the realm of 3D microfabrication. This cutting-edge approach, essential for applications in thin film fabrication, microfluidics, and Lab-on-a-chip devices, overcomes the limitations of traditional microfabrication methods. Our DALP technology, featuring spatial atomic layer deposition (ALD), enables unprecedented precision in creating thin films with enhanced detail, miniaturization, and material compatibility.

A key feature of DALP technology is its exceptional control over the patterning, surface properties, and thickness of the fabricated thin films. Our technology stands out for its ability to deposit materials on a diverse range of substrates (including Si, glass, and polymers) and on complex surfaces such as trenches and pores. Importantly, this is achieved without the need for vacuum or inert gas chambers.

We will showcase examples of devices fabricated using this method, demonstrating the versatility of DALP in creating various microfluidic sensors, such as pressure, temperature, and electrochemical sensors. Additionally, the technology has been applied to develop advanced transistors and non-contact displacement sensors.

Atlant 3D's DALP represents a transformative advancement in 3D microfabrication, enhancing the efficiency and scope of prototyping, development, and integration of new technologies in the microfluidic field.

# Advanced Additive Manufacturing Solutions

Boston Micro Fabrication is the world leader in advanced additive manufacturing solutions based on Projection Micro Stereolithography (PμSL) technology. Many leading companies worldwide are adopting PμSL to 3D print true microstructures with ultra-high printing resolution ( $2\mu\text{m}$ ~ $50\mu\text{m}$ ) and printing tolerance ( $\pm 10\mu\text{m}$  ~  $\pm 25\mu\text{m}$ ).



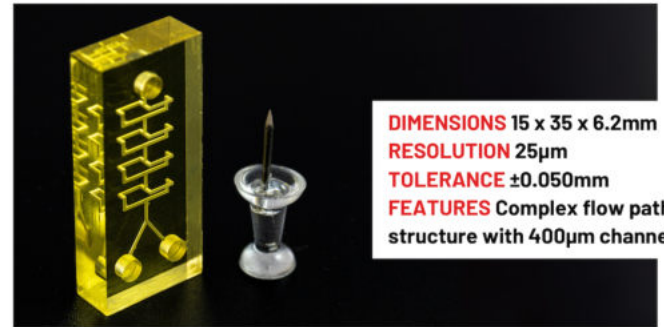
## Microfluidic Devices

### Manetco Microfluidic Chip

**DIMENSIONS** 43.4 x 15 x 2.4mm  
**RESOLUTION**  $10\mu\text{m}$   
**TOLERANCE**  $\pm 0.05\text{mm}$   
**FEATURES** 200 $\mu\text{m}$  channels



### Microfluidic Chip



**DIMENSIONS** 15 x 35 x 6.2mm  
**RESOLUTION**  $25\mu\text{m}$   
**TOLERANCE**  $\pm 0.050\text{mm}$   
**FEATURES** Complex flow path structure with 400 $\mu\text{m}$  channels

### Microfluidic Chip with Luer Lock Connector



**DIMENSIONS** 19 x 10 x 10.5mm  
**RESOLUTION**  $10\mu\text{m}$   
**TOLERANCE**  $\pm 25\text{mm}$   
**FEATURES** 0.217mm square 3D microfluidic channels with built-in luer lock connector for easy leak-free fluid flow.

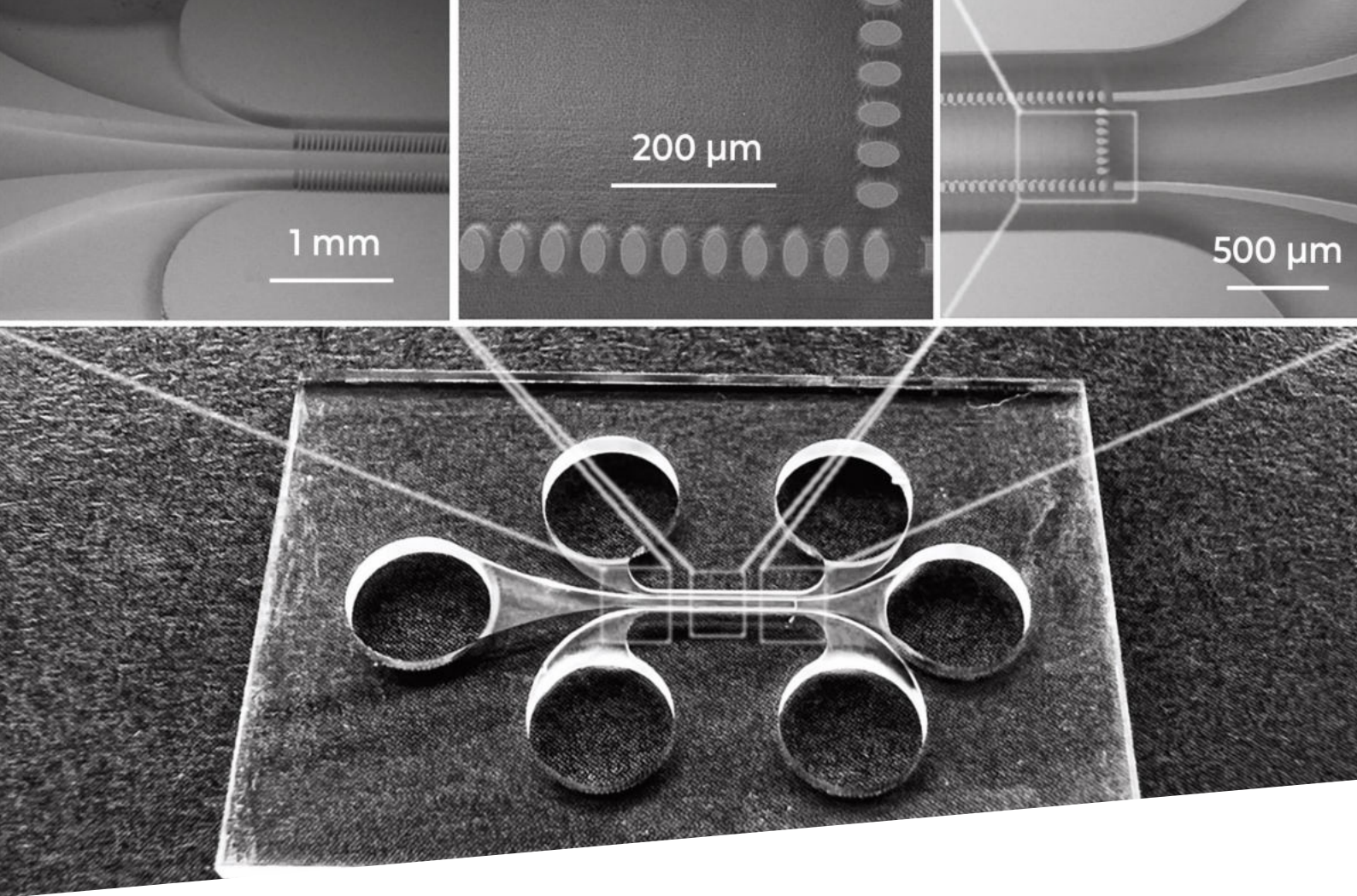
### Microfluidic Chip



**DIMENSIONS** 14.6mm x 8.6mm x 2.8mm  
**RESOLUTION**  $10\mu\text{m}$   
**TOLERANCE**  $\pm 0.025\text{mm}$   
**FEATURES** 400 $\mu\text{m}$  square channels and five 2.2 mm circular wells

Today, building a microfluidic device by hand requires several hours of intensive labor and researchers want to reduce the time it takes to produce these devices. Fortunately, BMF's projection micro stereolithography (PμSL) technology enhances design freedom and complexity, rapidly photopolymerizing entire layers of resin with UV light for quicker processing. It allows the printing of detailed 3D channels down to 100 microns and supports high-precision micro-tooling for materials like PDMS, commonly used in soft lithography.





## **Femtosecond laser based prototyping of 3D glass microfluidics**

Microfluidics is an emerging topic nowadays, as it is seen as a prospective tool in bioresearch, drug testing, gas flow engineering, and many other fields. Various applications require distinct fabrication approaches and different materials. Femtosecond laser-based microfabrication techniques allow for the processing of a vast variety of materials, as well as the application of different fabrication techniques even within the same chip. In this presentation, we will showcase various microfluidic structures fabricated by combining distinct femtosecond laser-based processing techniques, as well as microfluidics fabricated from different materials.



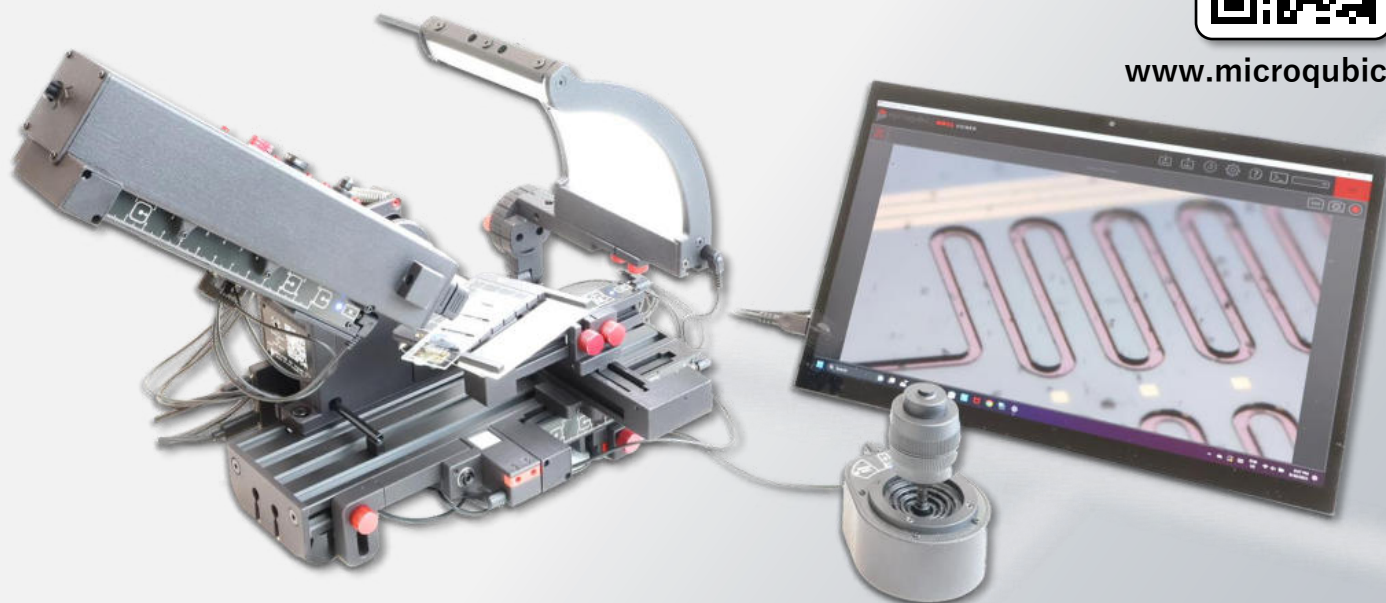


# The most versatile 2D/3D microscopy systems

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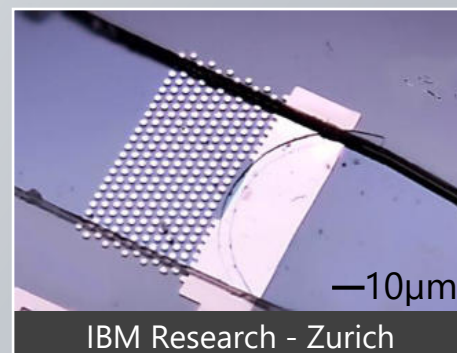
- 4K imaging from almost any angle
- Focus stacking and HDR
- Live measurements and scale bar down to micrometer precision



Polytechnique Montréal



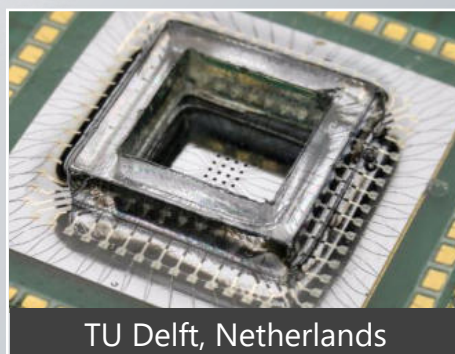
microfluidic ChipShop, Germany



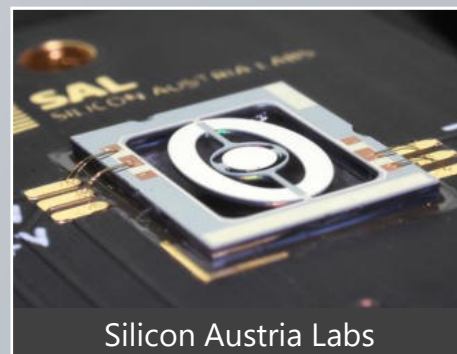
IBM Research - Zurich



Microbritt, UK



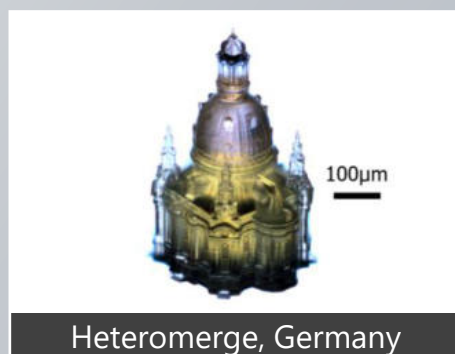
TU Delft, Netherlands



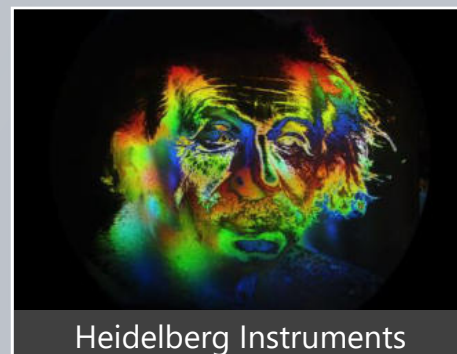
Silicon Austria Labs



KLOE, France



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Heidelberg Instruments

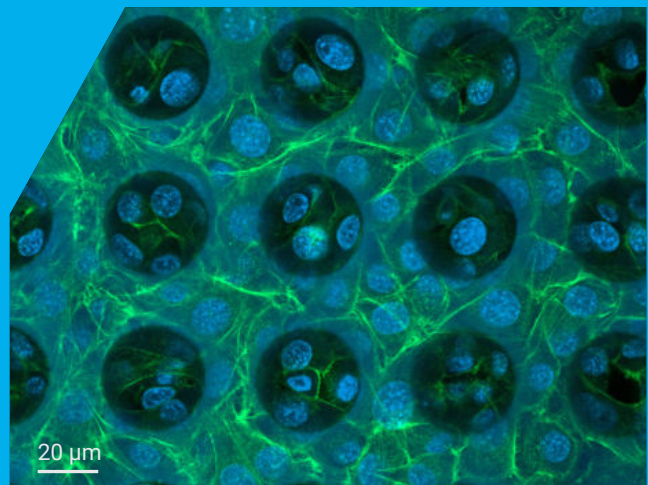
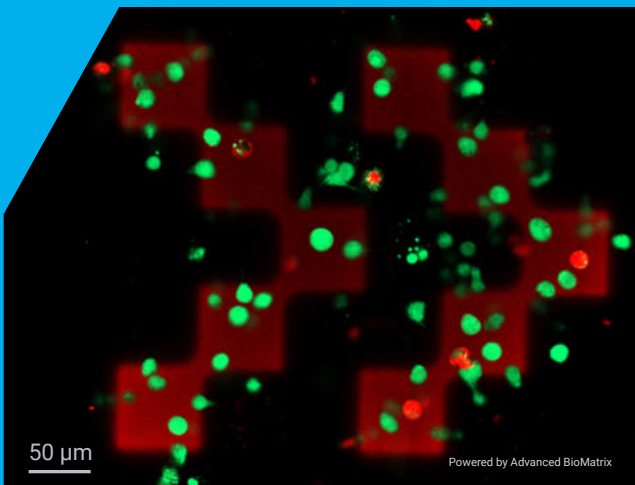
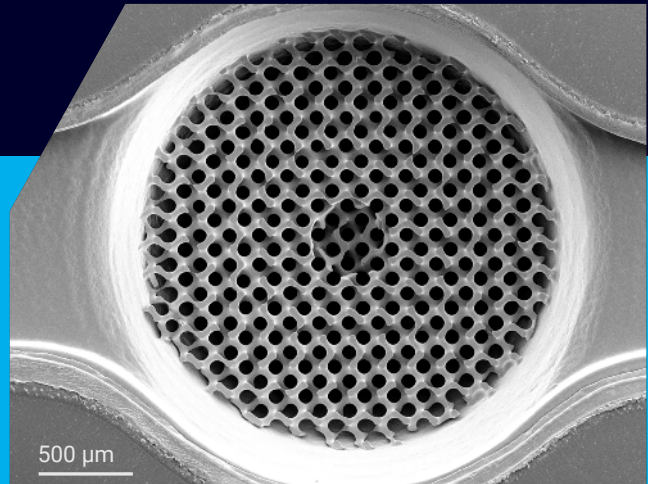
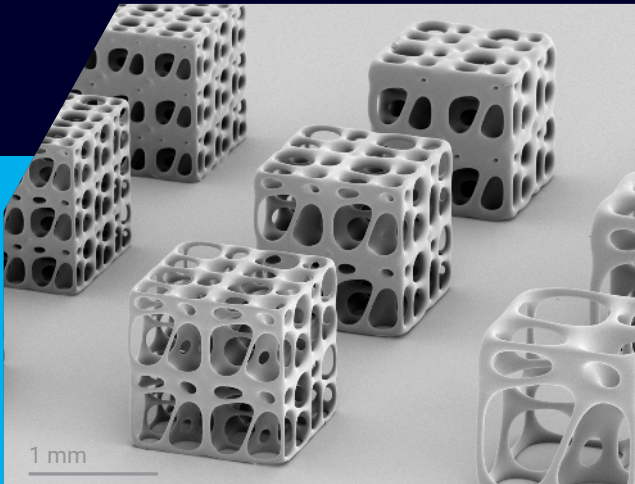
PCT patent  
pending

Designed and manufactured  
in SWITZERLAND



Microqubic AG  
Feldpark 29, 6300 Zug  
Switzerland

# Think big. Print nano.



## Biomedical engineering

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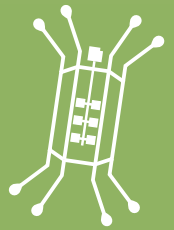
[nanoscribe.com](https://nanoscribe.com)



# BiProMicro - Single-cell cultivation under dynamic environmental conditions for bioprocess scalability predictions.

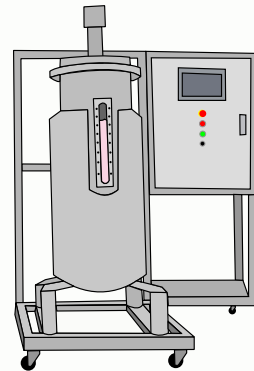
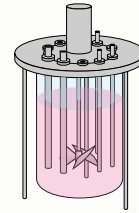
Luisa Blöbaum, Julian Schmitz

Multiscale Bioengineering, Bielefeld University, Universitätsstraße 25, 33615 Bielefeld



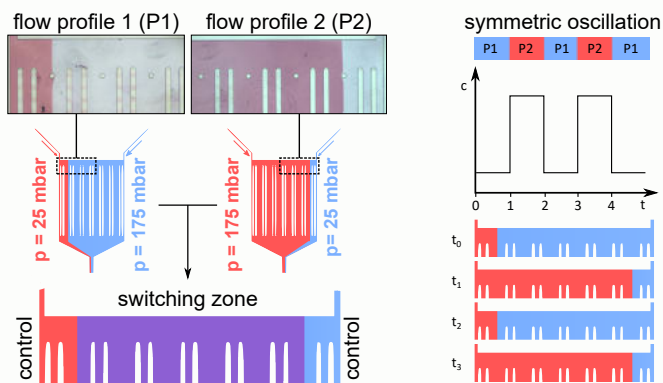
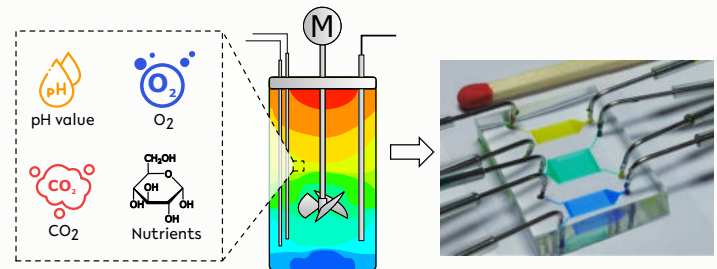
## The Problem: Cultivation conditions differ between development and production

The development of new bioprocesses for the manufacturing of biotechnological products is done in small-scale vessels like microtiter plates or shake flasks (mL). However, the final industrial process is performed in large-scale bioreactors (m<sup>3</sup>) to produce a sufficient amount of product. Therefore, the bioprocess finally has to be scaled up from lab scale to production scale. As a result of the differences in dimension between these two scales, cultivation conditions vary immensely in terms of oxygen availability, CO<sub>2</sub> concentration, nutrient supply, pH value, and other bioprocess relevant parameters [1]. Additionally, in contrast to lab-scale cultivation devices large-scale bioreactors come with environmental gradients that applied cells have to cope with. Consequently, a bioprocess that is performing outstanding in lab scale does not necessarily work in large scale [2]. To date, no technology is available that allows the development of a novel bioprocess in lab scale already under the cultivation conditions of its final scale. Consequently, bioprocess scale-up becomes a laborious and high-risk undertaking [3].



## Our Approach: Emulating large-scale bioreactors on-chip

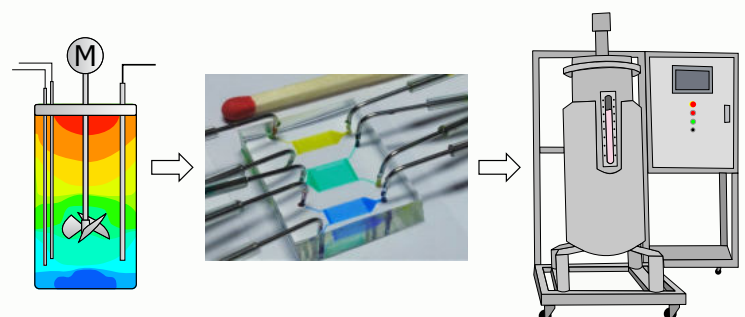
To overcome these obstacles in bioprocess scale-up we developed a microfluidic device to mimic bioprocess relevant conditions on-chip during single-cell cultivation [4]. Based on computational fluid dynamics (CFD) simulation, we identify the most influential environmental parameters and gradients from large-scale bioreactors and emulate them on our microfluidic cultivation device [5]. This way, cells can be cultivated and analyzed under bioprocess relevant conditions without the need to operate a large-scale bioreactor.



Emulating large-scale bioreactors is done by operating a multi-inlet chip with pressure driven pumps. By changing between certain inlet pressure settings different pumping profiles can be generated and environmental conditions on-chip can be oscillated [6]. Hence, cells that are trapped in the switching zone experience dynamic cultivation conditions, while cells in the control zone are cultivated under constant conditions. Corresponding to the previously identified bioprocess relevant conditions flow profiles can be established and cellular behavior is monitored by live cell imaging. This enables the emulation of a large-scale bioreactor on-chip.

## Our Vision: Predicting scalability of bioprocesses

Using our dynamic microfluidic single-cell cultivation device we aim at simplifying bioprocess scale-up by making laborious testing in bigger scales obsolete. This way expenses of scaling up bioprocesses can be reduced massively. In the future we want to establish our technology as an essential element in modern bioprocess development workflows. After cell line and strain development supplies multiple candidates for the final industrial bioprocess, we screen them for their scalability and identify unsuitable cells already in the development stage of a novel bioprocess.



- References:**
- [1] Lara et al. 2006. Mol. Biotechnol. 34 (3), 355–382.
  - [2] Nadal-Rey et al. 2020. Biotechnol. Adv. 107660.
  - [3] Crater and Lievense 2018. FEMS Microbiol. Lett. 365 (13).

- [4] Täuber et al. 2022. Biotechnol. Bioeng. 119(11): 3194-3209.
- [5] Blöbaum et al. 2023. Biotechnol. Adv. 62, 108071.
- [6] Blöbaum et al. 2023. STAR Protocols 4(3): 102436.

Contact us  
on LinkedIn:



## **TITLE: RESOLVE Project: an innovative platform to characterize EVs for liquid biopsy**

**Authors:** Francesco Ferrara<sup>1</sup>, Alessia Foscarini<sup>1</sup>, Alessandro Romano<sup>2</sup>, Valentina Marassi<sup>3</sup>, Maria Serena Chiriaco\*<sup>1</sup>

**Presenting author:** Maria Serena Chiriaco

**Corresponding author:** [mariaserena.chiriaco@nanotec.cnr.it](mailto:mariaserena.chiriaco@nanotec.cnr.it)

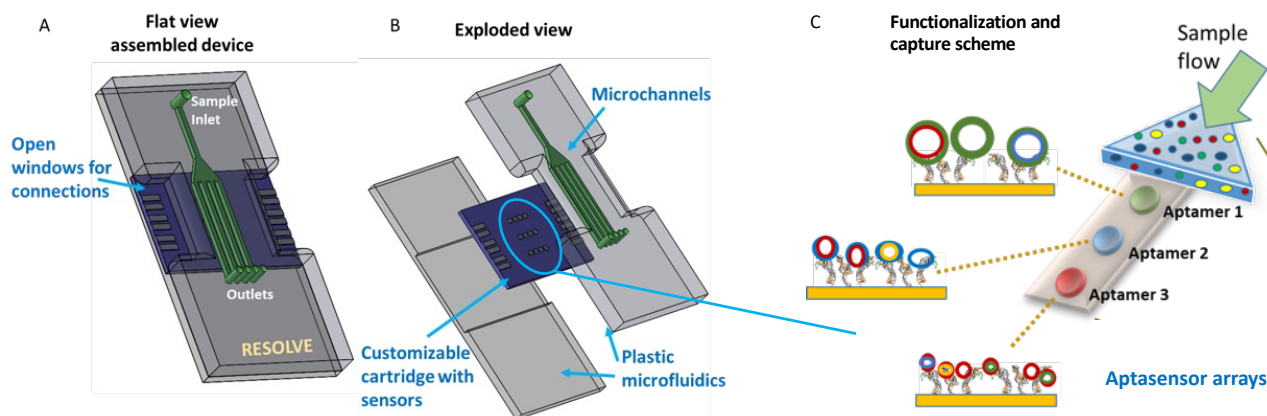
<sup>1</sup> CNR NANOTEC – Institute of Nanotechnology, via per Monteroni, 73100, Lecce, Italy

<sup>2</sup> Division of Neuroscience, Institute of Experimental Neurology, San Raffaele Scientific Institute, Via Olgettina, 60, 20132, Milan, Italy

<sup>3</sup> Department of Chemistry “Giacomo Ciamician”, University of Bologna, 40126 Bologna, Italy

Precision medicine allow to tailor the clinical approach, depending on the makeup of patients' DNA and expression issues. Liquid biopsy and the chance to use selected biomarkers from biological fluids, could strongly contribute to the improvement of an increasingly patient-oriented method. Among the most important effectors of cellular interplay, Extracellular Vesicles (EVs) are on the rise for their multiple roles, encompassing physiological functions, cancer progression and invasiveness modulation, neurodegeneration.

RESOLVE platform by means of the integration of electrochemical sensing and microfluidic tools for the characterization of subpopulation of EVs will provide researchers and clinicians a new approach with features of ease-of-use, plug-n-play, sample-in/answer-out operation mode. Finally, RESOLVE will enable non-invasive liquid biopsy through a cost-effective, disposable and customizable system.



## Title: TITAN Project: microfluidic and sensing tools for immunotherapy

Authors: Maria Serena Chiriaco<sup>\*1</sup>, Elisabetta Primiceri<sup>1</sup>, Antonio Turco<sup>1</sup>, Valeria Garzarelli<sup>1,2</sup>, Giulia Siciliano<sup>1</sup>, Alessia Foscari<sup>1</sup>, Marco de Tullio<sup>1,3</sup> and Francesco Ferrara<sup>\*1</sup>

<sup>1</sup> CNR NANOTEC – Institute of Nanotechnology, via per Monteroni, 73100, Lecce, Italy

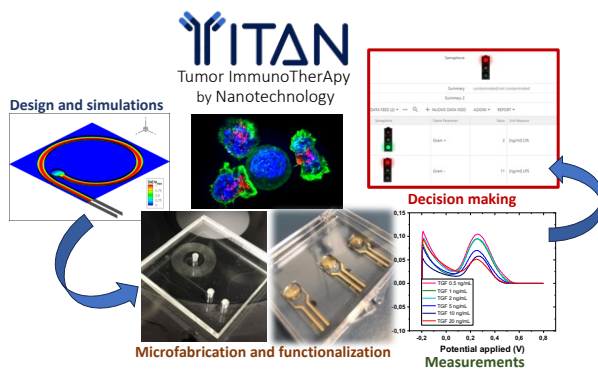
<sup>2</sup> University of Salento, Dept. of Mathematics & Physics E. de Giorgi, Via Arnesano, 73100, Lecce, Italy

<sup>3</sup> Department of Mechanics, Mathematics and Management (DMMM), Polytechnic University of Bari, Via Re David 200, Bari, 70125, Italy

\* Correspondence: [francesco.ferrara@nanotec.cnr.it](mailto:francesco.ferrara@nanotec.cnr.it)

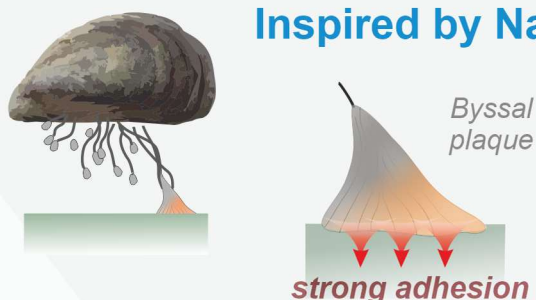
Presenting author: Francesco Ferrara

Immunotherapy with genetically engineered T cells has achieved some spectacular success in clinical trials addressing tumors. A key need is the widespread availability of small-scale bioreactors providing in-process monitoring. TITAN platform aims to the continuous sampling of critical quality attributes, to quickly recognize deviations from the desired range and take appropriated corrective actions. Parameters to verify and related tools include: bacterial contamination; counting cells by microfluidic and electrical detection; ratio live/dead cells on a capacitive sensor; cytokines production identified by electrochemical methods; T-cell function tests through the production of spheroids into droplet microfluidic devices. The integration of sensors, microfluidics and control system has been achieved through the development of TITAN platform using microcontroller and Labview interface as user-friendly management.



# Micropatterning of Mussel-Inspired Materials: Empower selective functionality

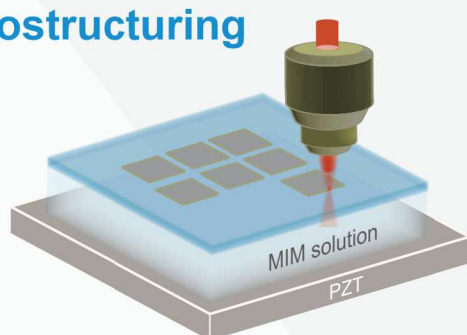
## Inspired by Nature



The development of universally applicable **surface-modification platforms** is crucial

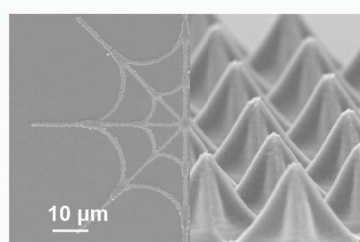
**Mussel-inspired materials (MIMs)** shows strong adhesive properties and great reactivity for chemical functionalization

## Microstructuring



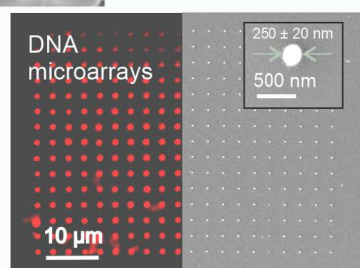
Our micropatterning technique based on **multiphoton lithography** of MIMs does not require photomasks, stamps, or multistep procedures

## Freedom of Design



It enables MIM patterns with **micrometer resolution** and full freedom of design

## Functionality



This invention paves the way for **innovative applications** of MIMs in various multifunctional systems and microdevices



Topolniak et al. Adv. Mater. 2022 Tavasolyzadeh et al. Small 2023



## Development of 3D microfluidics integrated with photonics by fs-laser micromachining

João M. Maia<sup>a,\*</sup>, Carolina Cameira<sup>a,b</sup>, and P. V. S. Marques<sup>a,b</sup>

<sup>a</sup>CAP – Centre for Applied Photonics, INESC TEC, Porto 4150-179, Portugal

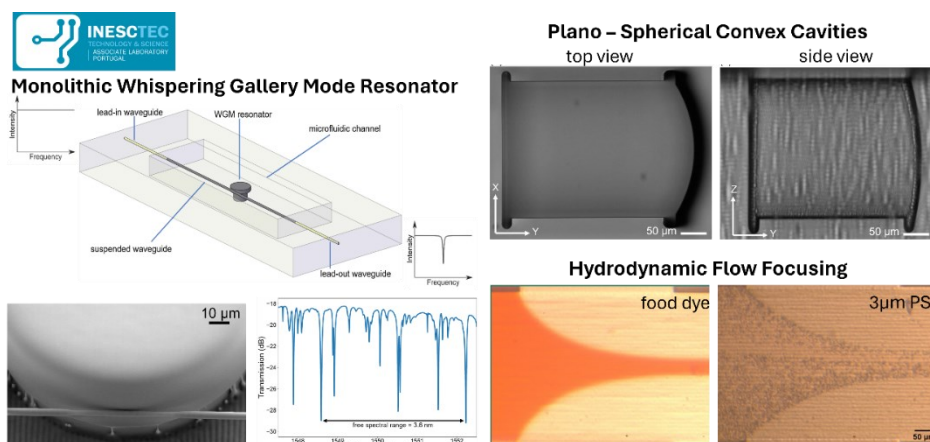
<sup>b</sup>Department of Physics and Astronomy, Faculty of Sciences, University of Porto, Porto 4169-007, Portugal

[joao.m.maia@inesctec.pt](mailto:joao.m.maia@inesctec.pt)

Ultrafast laser machining is a versatile microfabrication technique capable of volume processing of glass with sub-micrometric resolution. The technique relies on non linear absorption of the pulsed beam to trigger a material modification that is confined to the focal volume.

A possible pathway for material modification is linked to an increase of the refractive index within the focal volume, which enables the design of optical waveguides in glass by writing the waveguide's core. Propagation losses of 0.1 dB/cm at 1550 nm are obtained in silica waveguides, while low losses spanning from the visible to the near infrared band are achieved in borosilicate waveguides. Besides applications in integrated optics, this modification also enables the design of novel sensing platforms in borosilicate glass based on plasmonics and whispering gallery mode (WGM) resonance by translating the waveguides to the glass substrate.

In fused silica and ULE® glass, fs-laser exposure also turns the laser-modified volume more selective to etching in HF acid. Aided by the 3D capabilities of laser direct writing, this technique can then be exploited to design microstructured microfluidic channels or optical cavities. The inherent high resolution of the process can also be leveraged into producing monolithic optofluidic systems which combine integrated optics with microfluidics. The figure below shows some examples of the work we have conducted on this topic. First, a monolithic silica WGM resonator, consisting of a microdisk coupled to a suspended waveguide made inside a microfluidic channel, is shown. The proposed methodology provides precise control over the dimensions and geometry of the device, with thermal post-processing being done to place both structures tangent to one another and to decrease their surface roughness down to nanometric scale. Then, spherically-shaped interfaces are designed and used to build cavities and lenses for applications in optical sensing and optical tweezers. Lastly, microfluidic channels for 2D and 3D flow focusing are produced and applied in cell sorting.



**Acknowledgements.** This project is co-financed by Component 5 – Capitalization and Business Innovation, integrated in the Resilience Dimension of the Recovery and Resiliency Plan within the scope of the Recovery and Resilience Mechanism (MRR) of the European Union (EU), framed in the Next Generation EU, for the period 2021-2026 within the scope of the HfPT project with reference 41.

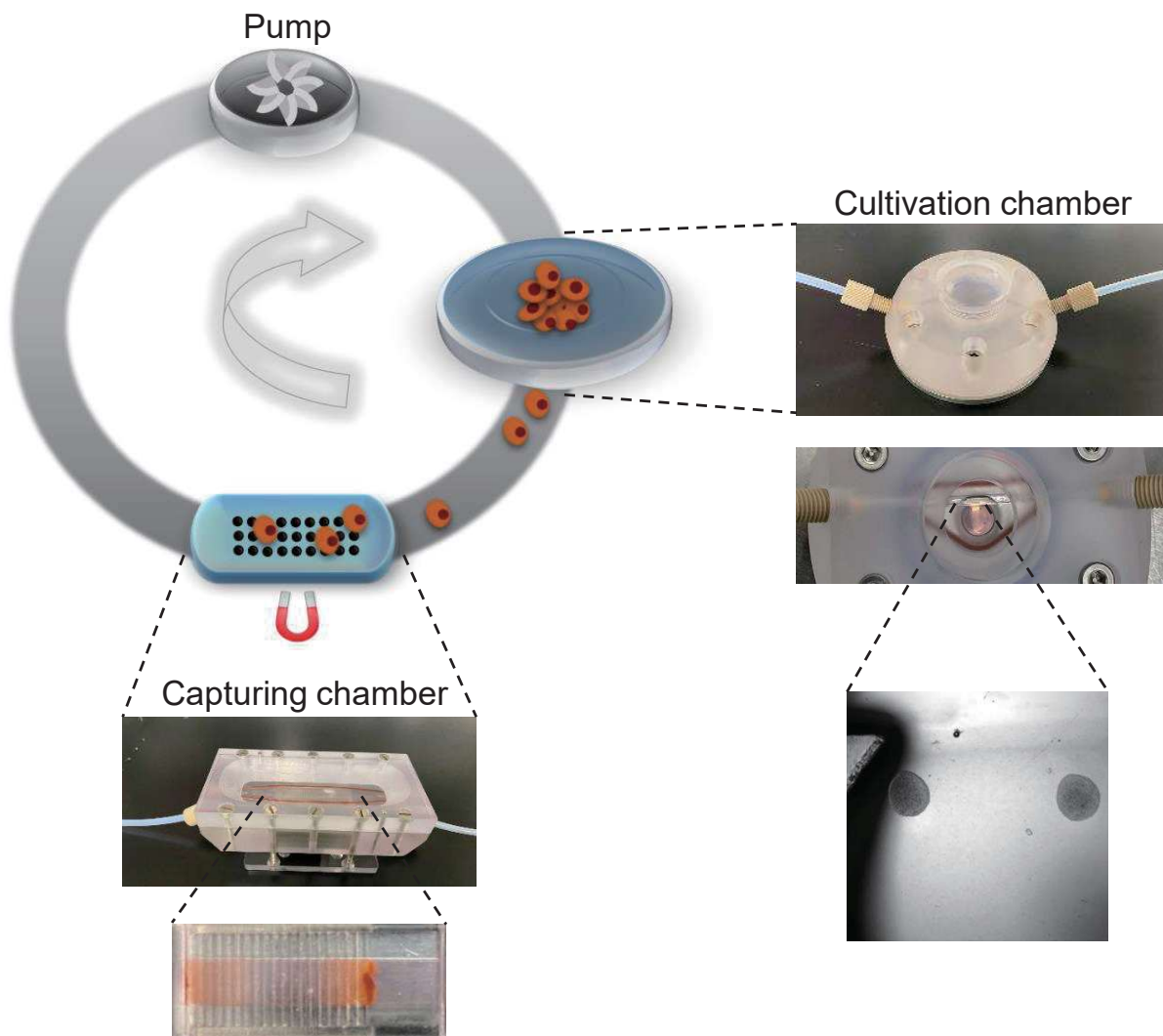


## A microfluidic metastasis-on-chip system using magnetic beads to capture circulating tumor cells

M. Mohamadian Namaqi, Dr. F. Moll, Dr. S. Wiedemeier, Dr. K. Lemke

Institute for Bioprocessing and Analytical Measurement Techniques e.V., Heilbad Heiligenstadt

The research focuses on a dynamic metastasis model containing a cultivation and a capturing chamber. The cultivation chamber was engineered to culture cancer spheroids within an extracellular matrix under controlled flow conditions. The capturing chamber was equipped with a magnet and an engineered magnetic flux concentrator for balancing the magnetic force and spreading out the magnetic beads evenly in the capturing chamber. This integrated setup recreates the metastasis process; invading cells leaving the spheroids and ECM are promptly captured by the EPCAM-Dynabeads™ inside the capturing chamber. Beyond its ability to capture fresh circulating tumor cells for further study, this system holds potential for investigating the efficacy of anticancer drugs on metastatic cells, contributing to advancements in cancer treatment approaches.



### *Microfluidics for automated C. elegans embryo extraction*

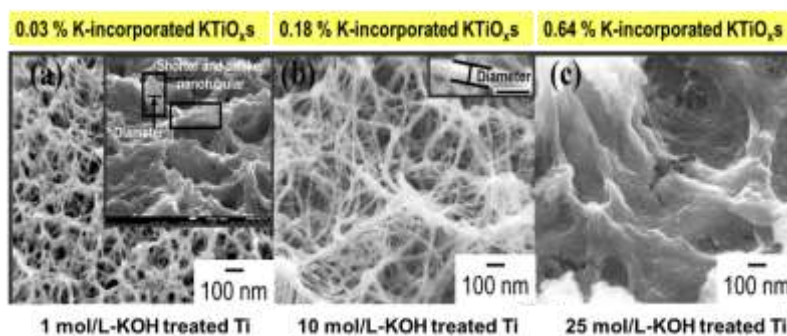
The nematode worm *C. elegans* is a model biological organism used to study numerous biological processes, model diseases, and understand the effects of pharmaceutical drugs. Further, *C. elegans* embryos are foundational to understanding developmental processes in molecular biology. At present, embryos are typically extracted by hand under a dissection microscope, mounted onto a glass slide, and imaged under a fluorescent microscope to visualize molecular phenomenon. This process is both time-consuming and repetitive which means two things: 1. Large-scale studies are technically difficult, and 2. The process is amenable to automation. To this end I have developed a microfluidic system which extracts *C. elegans* embryos in an automated fashion and can be run as a continuous, cyclic process. While neither the embryo extraction process nor the studied molecular phenomenon can be sped up, a high-fidelity process can run continuously without human oversight, drastically increasing the number of embryos that can be extracted in a given day. This high-fidelity automation, along with parallelization would enable previously infeasible large-scale genome-wide biophysics studies. In this talk I will outline the development of this embryo-extracting, automated microfluidic system as well as the types of large-scale studies it will enable.

## Study of facile synthesis of nanostructured potassium incorporated titanium oxide film to fabricate the brand new bioelectrode based on direct electron transfer

Up to date, nanostructured Ti-based materials have attracted attention due to the unique and diverse physico-chemical properties and the potential for photocatalysis, especially water purification because of their large band gap energy, corrosion resistance, mechanical durability, and low costs. One of the major advantages of the Ti-based materials is that it remains stable after the repeated catalytic cycles, whereas other materials for photocatalysis such as CdS or GaP suffer degradation and can even produce toxic endproducts. Therefore, those materials affect harm effect on environment, but Ti-based materials are eco-friendly candidate. Among them, nanostructured potassium incorporated titanium oxide films ( $\text{KTiO}_x\text{s}$ ) represent a promising candidate, in particular due to the possibility to tune the electrical and optical properties by controlling the K content. In order to increase the photocatalytic effect, a high surface area and sensitivity of the surface charge are recommended. Therefore, nanostructured titanium oxide materials with the possibility of tuning of the surface charge are promising candidate for high performance photocatalysis. However, currently, the nanostructure fabrication generally involves complicated process, low reproducibility and/or high cost for chemical modification. Hence, a simple method to synthesize and to tune the desired morphology and property is strongly desirable.

In this contribution, we demonstrate the wet corrosion process (WCP) which is a simple one-step method for nanostructures fabrication involving treatment with KOH

solution. The relation between the nanostructures generated and the function of bioelectrode was systematically investigated as a function of the WCP condition. Pure Ti substrates were used to synthesize on nanostructures fabrication. For WCP, various concentrations of KOH solutions were used.



# Development of an on-chip micropump for the optimized emulation of physiological flow conditions in microfluidic multi-organ-chip platforms

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The on-chip micropump for microfluidic multi-organ-chip (MOC) consists of three PDMS-membranes which are directly integrated in the microfluidic of the MOC platform and pneumatically driven by an external control unit.

## Problem:

- Emulating human physiology – Limited emulation the human blood flow characteristics of microfluidic-based MOC platform
- Vascularization – Lack or absence of vascularization limits the size and complexity of the cultivated organ models
- Use of blood – Demanding use of blood or blood models as a working medium in the microfluidic MOC platforms
- Viscosity – Prediction & controllability of microfluidic flow conditions through the influence of the viscosity of the working medium
- Cross-sectional comparison – No direct transfer between rectangular microchannels & vessels with idealized circular cross-section

## Goal:

- Generate necessary flow conditions in the rectangular microchannel to **enhance endothelialization** in the entire microfluidic system
- Prioritized development and optimization of the on-chip micropump's design, especially concerning **geometric modifications of the PDMS-membranes**
- **Characterization of microfluidic flow conditions** generated by the **new pump design** using standard cell culture media and a blood model to determine the influence of viscosity on microfluidic flow

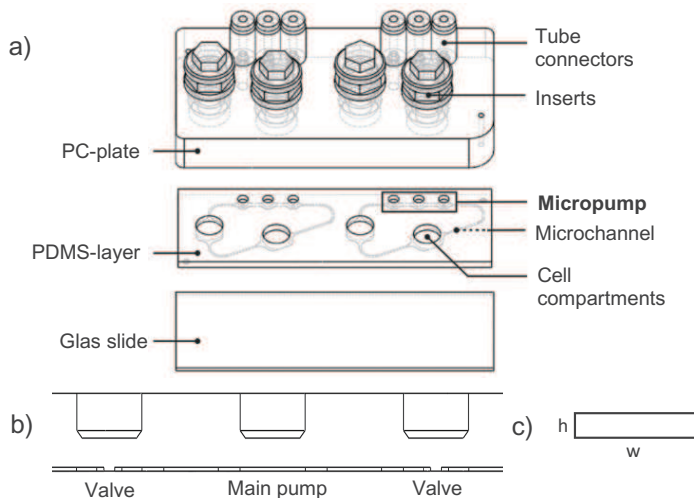


Figure 1: a) Schematic layout of the investigated 2OC and cross-section of b) the micropump and c) the microchannel (100  $\mu\text{m}$  x 500  $\mu\text{m}$ , h x w)

## Approach:

- Rectangular microchannel of the investigated 2OC is assigned to a human vessel type, representing the in-vivo flow characteristics as a physiological reference
- Current microfluidic flow characteristics are compared to defined physiological blood flow - If deviations occur, new pump designs are developed based on geometric PDMS-membrane modifications
- Microfluidic flow characteristics generated by the new pump design are quantitatively and qualitatively evaluated using  $\mu\text{PIV}$
- Developed pump design is characterized using  $\mu\text{PIV}$  with varied serum concentrations in cell culture media and a blood model (HCT 30 %) at CBT (37°C)

## Execution and results:

- Investigated rectangular microchannel is assigned to human **arterioles** based on fluid mechanical principles as well as functional and structural analysis
- Defined **physiological blood flow conditions in human arterioles** (circular, unbranched, straight) considers various determinants: laminar flow type, periodic flow with reduced pulsatility compared to arteries, homogeneously distributed wall shear stress. Challenging determination of apparent viscosity of blood in the due to various influencing factors, ranging approx. from 3 to 5,5 mPa · s
- **Improvement of microfluidic flow** in the rectangular channel, which must be generated by the new pump design in order to **reproduce physiology more realistically**:
  - Pulsatile flow, reduce peak (peak-average-ratio < 60 %)
  - Increase average flow rate (performance) with adjustability of precise volume flows
  - More homogeneous distribution of wall shear stress average of 1,5 Pa, including reduction of maximum values close to pump
  - Reduce backflow (close to pump)
  - Consideration of viscosity of used medium for accurate prediction of the occurring flow conditions
- The **new on-chip micropump design enhances microfluidic flow conditions for endothelial cells** by increasing flow rate and average wall shear stress while reducing backflow using cell culture media at CBT (~ 37°C)

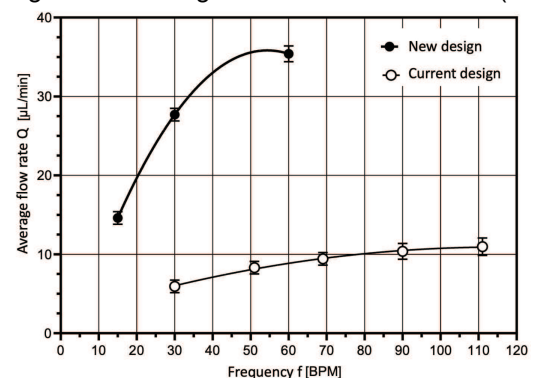


Figure 2: Standard curve of the average flow rate generated by the current and developed pump design depending on frequency

- Using **blood** (models) with physiological HCT still presents **challenges** because of microchannel occlusions, **but concepts** have been **developed** to solve this challenge



# Electrospun nanofiber mats as a platform for the development of microfluidic devices for rare cells capture with diagnostic purposes



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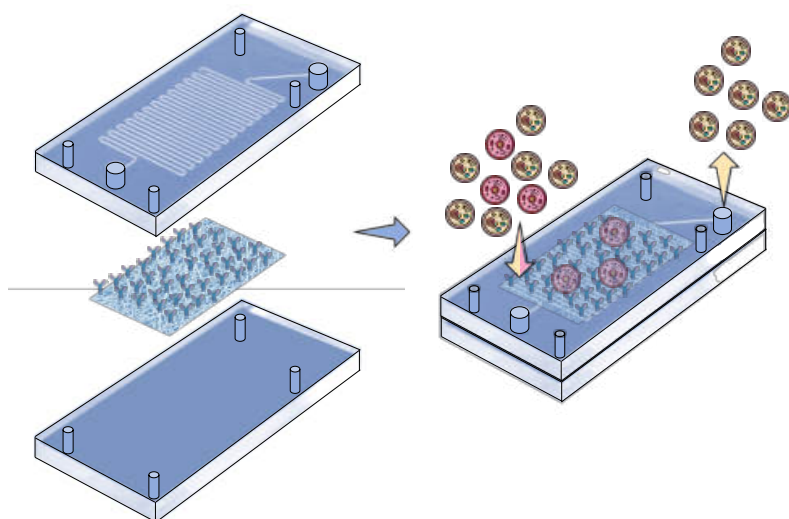
Early detection and effective treatment significantly impact survival rates in disease management. Micromanipulation is a dependable method for manually isolating rare cells from biological fluids for molecular or cytogenetic analysis. While effective, this approach is costly and time-consuming due to the need for skilled personnel and specialized equipment<sup>1</sup>.

This study aims to enhance the efficiency and affordability of diagnosis in hospital settings by developing a device for semi-automated selection of rare cells from biological samples. The device utilizes electrospun nanofiber mats, that offer high surface area to be functionalized with antibodies to selectively capture target cells based on surface antigens, in the optics of being used as a substrate for a microfluidic device (Fig. 1). The advantages of microfluidic systems include the micro-scale features that match that of many biological systems and laminar flow, which enables precision delivery of fluids, in combination with high surface-to-volume ratio that favours mass exchange<sup>2</sup>.

Nanofiber mats were fabricated from Nylon 6.6 and Polyacrylic Acid (PAA) polymers solution. The first phase of the work was devoted to the determination of the operating parameters for electrospinning to optimize the morphology of the mats, their mechanical resistance and handling characteristics. Bioconjugation methods employing EDC/NHS chemistry were developed to impart cell-capture capabilities to the mats. Fluorescently labeled antibodies enabled assessment of conjugation success via fluorimetry and spectrofluorimetry.

Cell capture tests were conducted using mesenchymal stem cells (MSC), as a model, on antibody-decorated mats. Optical

and confocal microscopy were used to evaluate capture efficacy. Subsequent release strategies were also studied. Capture of model cells resulted successful holding the potential of the implementation of this nanotechnology for the development of microfluidic devices with diagnostic purposes.



**Figure 1** Schematic representation of the combination of the nanofibrous mat and the microfluidic device for the isolation of specific cells.

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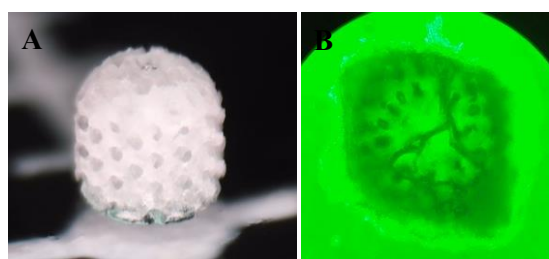


## Advancements in Two-Photon Polymerization Towards Precision Bioprinting and Microfluidic Device Fabrication

Over the past decade, there has been intensive development in lab-on-a-chip biological platforms due to advancements in various emerging technologies, enabling the production of reliable devices with enhanced spatial resolution and 3D configurations. Microfluidic chips provide extensive customization options and exceptional biocompatibility, presenting the potential for finely regulating biological growth on a micro-scale<sup>1</sup>. All these advantages are hampered by the many fabrication challenges and issues that are related to material choice for biocompatibility when producing microfluidic devices. One possible solution to overcome these challenges would be to use 3D printing with biocompatible polymers. 3D printing greatly accelerates the transition from conceptualization to prototype creation. Additionally, it enables the fabrication of intricate geometries, simplifying the generation of molds for PDMS casting. These molds can seamlessly incorporate structures of varying heights within a single 3D printing session.

Two-photon polymerization (2PP) possesses genuine 3D writing capabilities, allowing for fabricating intricately designed constructs with arbitrary geometry. As the demand for precise microstructures grows, two-photon polymerization has evolved into an attractive technique for crafting intricate microstructures with exceptional resolution and accuracy. Within the spheres of bioprinting and biochips, the customization of 2PP presents unprecedented avenues for advancing biomedical devices and platforms. The recent adaptations of 2PP tailored for bioprinting and biochips, unravel their potential in tissue engineering, organ-on-a-chip systems, and biomedical exploration<sup>2,3</sup>. Nevertheless, the hurdles faced in bioprinting using 2PP encompass issues such as material compatibility, cell viability, and scalability. Additionally, there is a focus on examining inventive strategies and methodologies to overcome these challenges<sup>4</sup>. By overcoming these hurdles and continuing to innovate, 2PP holds immense promise in revolutionizing the landscape of tissue engineering and biomedical research, offering new avenues for the development of advanced therapeutic strategies and disease models.

Vital3D Technologies combines stereolithography printer architecture with 2PP printing capabilities to achieve high-precision 3D printing without losing any speed. With our FemtoBrush<sup>TM</sup> technology, we can dynamically adjust the 3D-printing resolution by elongating and rotating the laser beam shape. This is achieved by leveraging the interplay between axial and lateral spatial confinement of the photoreaction within the focal volume of a concentrated laser beam. It allows to creation of more sophisticated 3D structures in detail (Fig.1). Consequently, we use this technology for bioprinting applications and microfluidic device fabrication.



**Figure 1** The spheroidal scaffold made with FemtoBrush<sup>TM</sup> technology. A) The spheroidal scaffold after the development B) After 5 days HeLa cells seedings in DMEM (1x)+ GlutaMAX with FBS and Pen Strep media.

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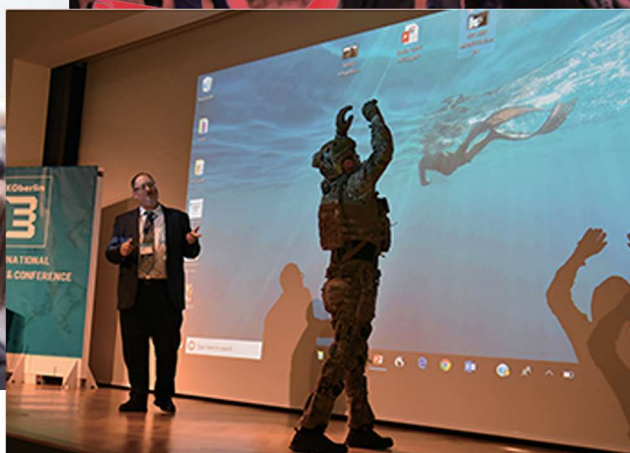
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