# A vascularized glioblastoma multiforme within a 3D perfused microphysiological system:

## combining a self-organized microvasculature and a central venule in a hydrogel.

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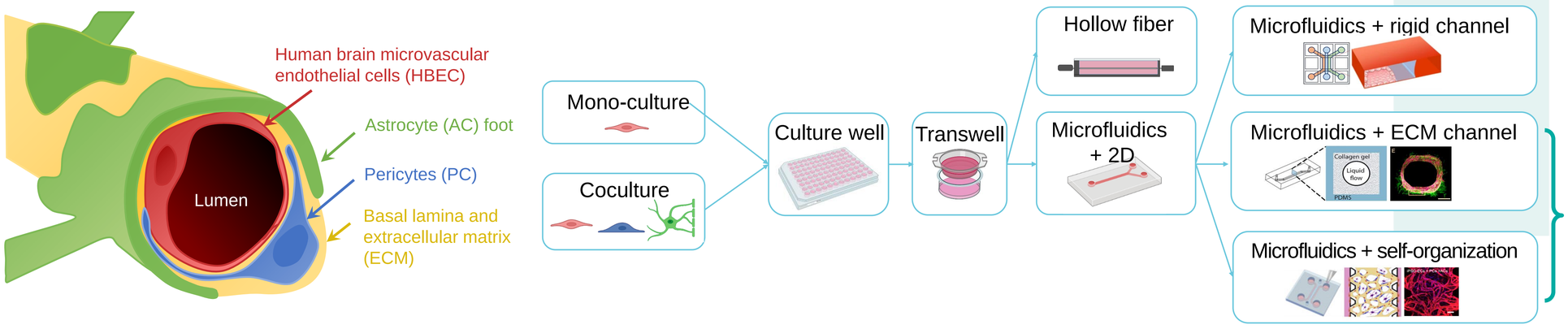
## Introduction

The most frequent and aggressive brain tumor is the glioblastoma multiforme (GBM). After diagnostic, the median patient survival is only of 15 months after diagnosis. There is a crucial need in unlocking the development of innovative drug treatments.

The blood-brain barrier (BBB):
- inhibits > 98% drugs to reach brain tissues
- hampers the development of new chemotherapy against GBM.

The clinical failure rate could be lowered with:
- drug nano-vectorization
- screening on pertinent preclinical models.

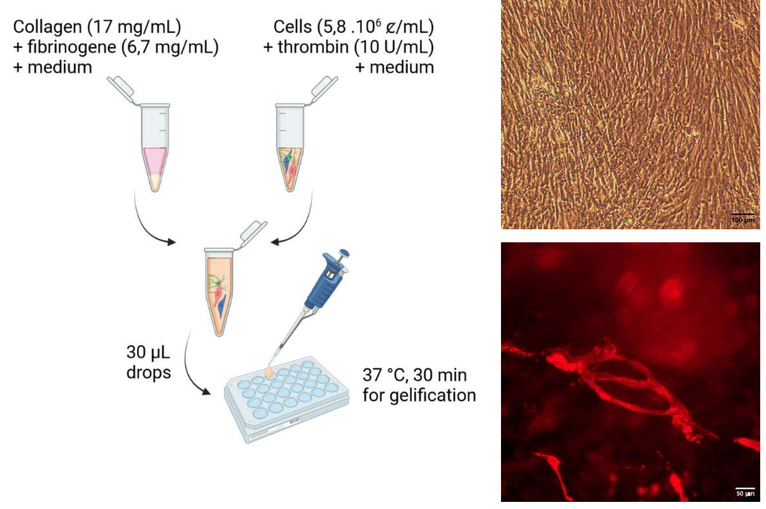



### The 3D-Glimpse project

- Development of a BBB and GBM-on-chip
- Dynamic culture under perfusion to mimic the blood flow
- Instrumentation with biosensors for an integrated detection of nanocarriers transport.
- Validation as an alternative to animal testing for drug screening

## Development of the BBB-on-chip.

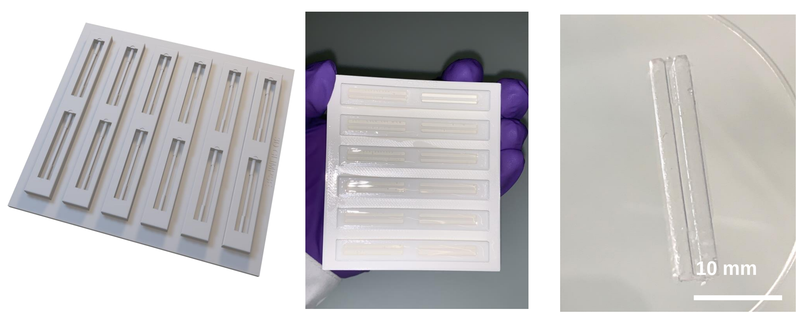
3D coculture of human brain cells (HBEC:AC:PC at 1:0.5:2 ratio) in an ECM hydrogel (collagen I + fibrin) enabled their self-organization as a vascularized tissue. Optimized as free drops, the hydrogel was then poured in the polydimethylsiloxane (PDMS) microchip prototype over a needle, to create a central venule. The first perfusion assays of this venule confirmed the microchip design but induced as yet some degradation of the hydrogel.



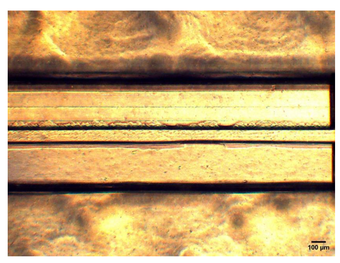


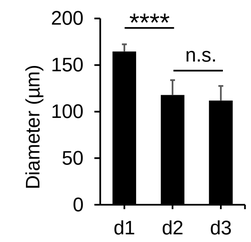

Hydrogel after 1 week of static culture under bright field and fluorescent microscope. Tight junctions (CD31) of endothelial cells were immunostained and showed the self-organized microarchitecture as a capillary network.

After software-assisted design, molds were 3D printed in polylactic acid to cast PDMS microchips.

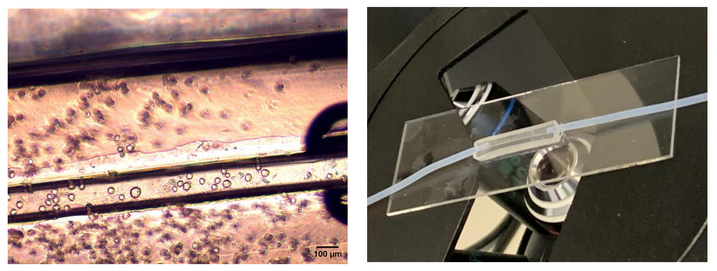



Similarly, a guide was designed for the reproductive and controlled needle insertion.



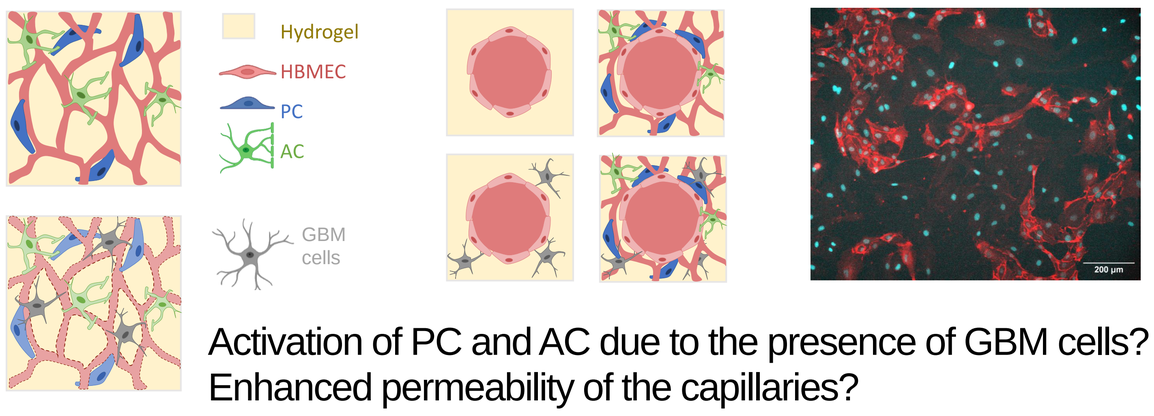

The central venule carved into the collagen-fibrin hydrogel retracted in the first 24 h then remained stable over time.



Preliminary results have been obtained for endothelial cells seeding and perfusion.

## BBB-on-chip in a healthy versus tumoral context.

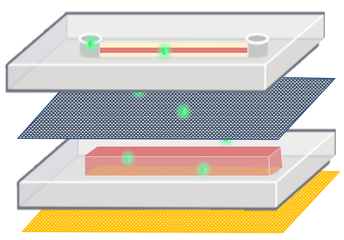
The microchip will be adapted to fit the microenvironment of a vascularized brain tumor, with adjunction of GBM cells (U87) to create a GBM-on-chip.

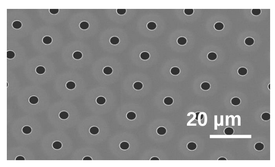



Activation of PC and AC due to the presence of GBM cells?
Enhanced permeability of the capillaries?

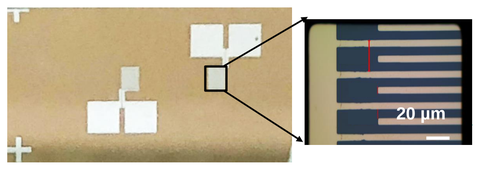
## Instrumentation of the BBB and GBM-on-chip.

Functionalized piezo-electrical substrates will be used as biosensors to detect the transport of nano-vectorized drugs through the BBB in healthy and pathological conditions.






A micro-processed porous membrane was developed for a controlled separation of the microchip chambers.




A lithium niobate acoustic sensor was elaborated for specific biodetection.

## **Perspectives:** transport and therapeutic efficiency screening.

Besides the transport, nanocarriers will be screened for their delivery specificity, and their toxicity towards targeted and off-target cells. The goal is to guide their dosage adjustment to prevent the strong side-effects of those chemotherapeutic treatments.

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