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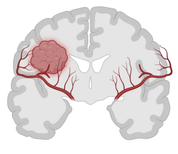
Development of an instrumented physiological microdevice to study the impact of the vascular microarchitecture and tumoral context on the brain angiogenesis and blood-brain barrier

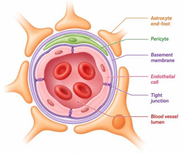
Thomas Sivier*, Emilie Mouric, Souhayb Bulaich, Thérèse Leblois , Agathe Figarol

Université Marie et Louis Pasteur, CNRS, institut FEMTO-ST, F-25000 Besançon, France

Introduction



Glioblastoma (GBM)
Most aggressive brain tumor
12-18 months median survival

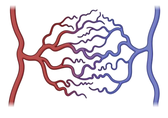


Blood-brain-barrier (BBB)
- Protects the brain from most external agressions
- Allows the passage of nutrients, oxygen and metabolic waste

KNOWLEDGE GAP

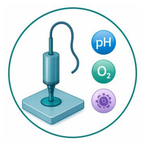
SIBorG project
A vascularized GBM-on-chip model

New engineered tool using organ-on-chip technology



Functional vascularization:
- ❖ Complex and perfused microvascular architecture
- ❖ Dynamic conditions to mimic the blood flow
- ❖ **GBM cells to recreate GBM microenvironment**

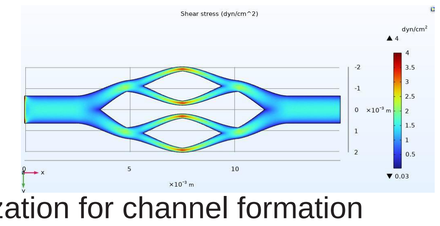
Relevant alternative
- ❖ Bioengineering tool for drug nano-vectorization
- ❖ Alternative to animal testing

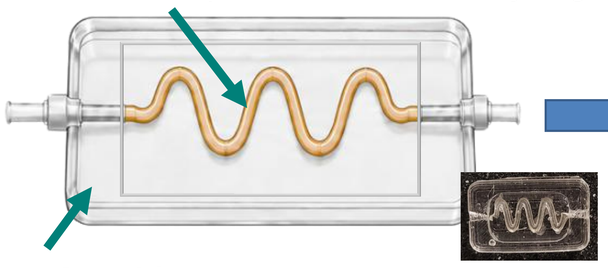


Integrated monitoring
- ❖ Real-time detection of nanocarriers transport, pH, O_2
- ❖ BBB integrity, therapeutic delivery and hypoxia

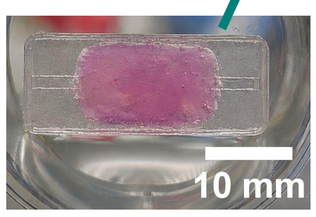
BBB-on-chip device

First complex design as vascular architecture
- Ongoing COMSOL Multiphysics® simulation to determine the optimal vascular design
- Sacrificial template, dissolved after hydrogel polymerization for channel formation



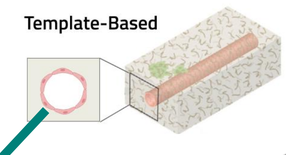


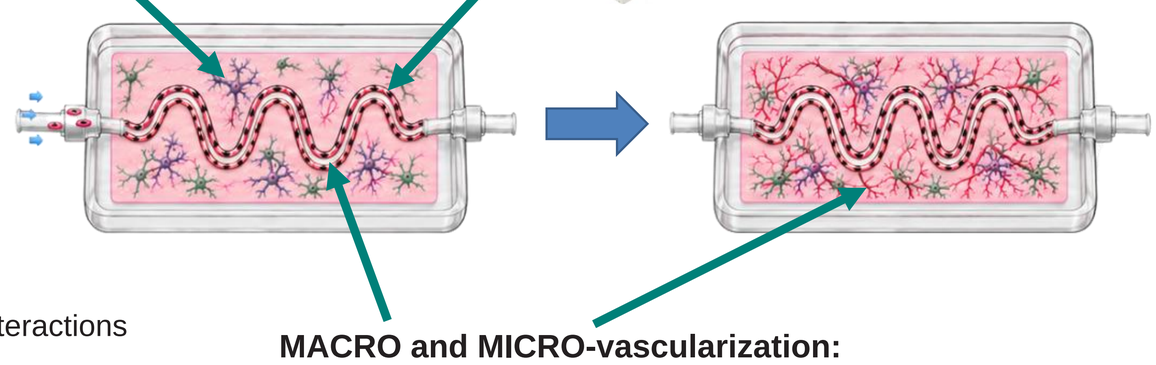
PDMS mold:
- Cast inside central compartment around the sacrifical template



Hydrogel as 3D scaffold
- 3D cell organization and interactions
- Extracellular matrix protein
- Pooled inside central compartment around sacrifical template

3D cell culture:
- Endothelial brain cells (HBMEC)
- Human astrocytes (HA)
- Human pericytes (HP)





MACRO and MICRO-vascularization:
- Gelatin-based arteriole template used as a sacrificial material
- Self-assembled capillaries through angiogenesis

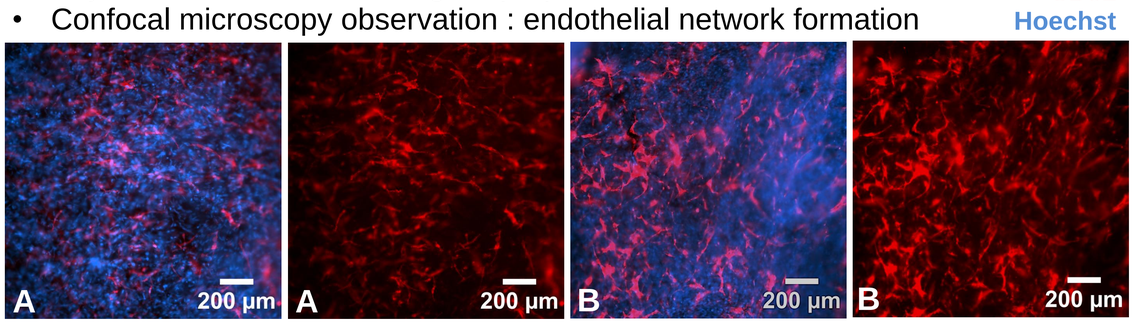
Device optimization

1 **Hydrogel composition :** thrombin, fibrinogen and collagen-I

Tests:
- 8 different concentrations, hyaluronic acid addition
- Physicochemical and rheological properties
- Confocal microscopy observation : endothelial network formation

Hydrogel after 7 days

CD31
Hoechst



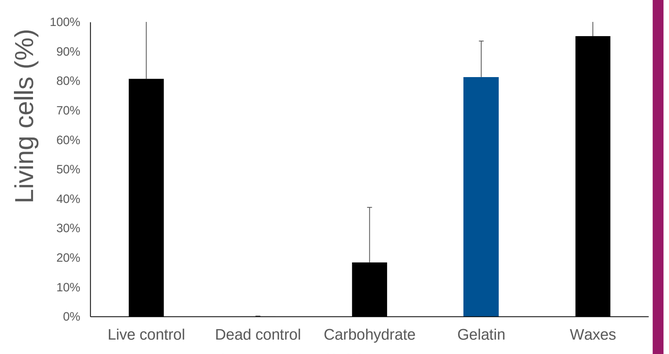
Endothelial cells after 7 days (**Hoechst**) and endothelial network formation (**CD31**) with 2.5 mg/mL (A) or 5 mg/mL (B) hyaluronic acid

→ **final optimal hydrogel: thrombin (1 U/mL), collagen-I (2.5 mg/mL), fibrinogen (5 mg/mL) and hyaluronic acid (2.5 mg/mL)**

2 **Sacrificial material:**
3 materials evaluated: carbohydrate glass, gelatin and paraffin/polyester wax
- ✓ Physicochemical properties
- ✓ Biocompatibility on cells (live dead protocol)

	Synthesis	Molding demolding in PDMS	Dissolution at 37°C
Carbohydrate glass	✓	✗	✓
Gelatin	✓	✓	✓
Waxes	✓	✓	✗

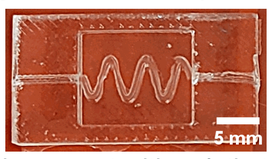
Physicochemical properties



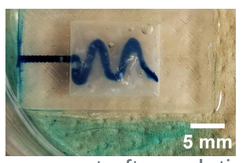
Biocompatibility on HBMEC

→ **validation of gelatin as optimal sacrificial material**

Channel formation:
- Insertion of a gelatin template into the PDMS microchip
- ongoing assays with 3D bio-printing to obtain well-defined template

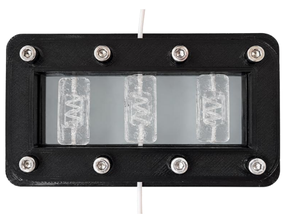


Microchip support with gelatin template

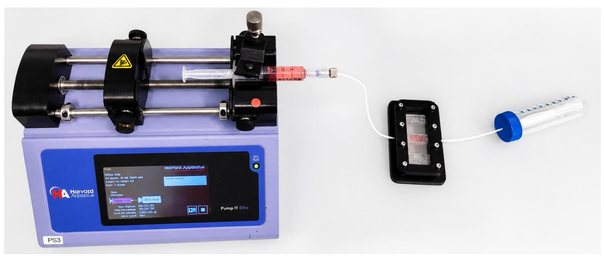


Microchip support after gelatin dissolution

3 **Culture under perfusion**:
- ✓ Initial perfusion experiments are ongoing
- ✓ The chip must be closed during culture for a stable flow
- ✓ Reversible support system ‘’Lock and Play’’ (using CAD and 3D printing) to ensure closure



Lock and Play device



Dynamic culture setup

Perspectives:
- ✓ Ongoing work to determine the optimal vascular architecture regarding shear stress
- ✓ Integration of sensors for real-time monitoring of O_2 and pH
- ✓ Validation of the model with integrity and permeability assays, detection of nanocarriers
- ✓ Incorporation of GBM cells to establish a GBM-on-chip model

Conclusion

- ➢ Gelatin is an ideal sacrificial material for complexifying vascular architecture of the BBB-on-chip device due to its favorable physicochemical and biocompatible properties
- ➢ Ongoing COMSOL Multiphysics® simulations aim to determine the optimal design taking into account shear stress constraints
- ➢ O_2 and pH sensors will allow real-time metabolic monitoring, while BBB integrity and permeability will be evaluated
- ➢ Incorporating U87 cells will establish a GBM-on-chip model

Our model provides a promising platform to investigate nanocarrier transport and evaluate drug delivery strategies in a physiologically relevant microenvironment

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Contacts
SIVIER Thomas
+33 3 08 66 61 62
thomas.sivier@femto-st.fr

Besançon
www.femto-st.fr

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