Development of a physiological microsystem, from a blood-brain barrier-on-chip to a vascularized glioblastoma-on-chip.

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The blood-brain barrier (BBB) limits the transport of drugs and nanocarriers, and hampers the development of innovative therapeutic solutions against neurological disorders. The fight against most common and aggressive brain tumor, the glioblastoma multiforme (GBM), faces too many therapeutic failures, with a survival after diagnosis of 12 to 18 months only. The preclinical screening of innovative drug candidates relies on conventional 2D *in vitro* models which may be too simplistic, and animal experimentation with ethical issues and interspecies differences. Poor translational results in clinical assays are unfortunately the norm. Tissue engineering and physiological microsystems, as organ-on-chips, promise alternative models that mimic a complex microenvironment in healthy or pathological contexts: the 3D organization of different human cell types, the extracellular matrix, and the chemical gradients and mechanical constraints of the blood flow.

Firstly, a self-organized 3D model of BBB micro-vasculature was optimized in a fibrin and collagen type I hydrogel. Human brain microvascular endothelial cells arranged into capillaries, supported by pericytes and astrocytes, and expressed specific tight-junction proteins membrane transporters and carriers (*1*–*3*). A second phase of the project has started, with the design of microchip prototypes as a scaffold for the hydrogel enabling nutritive medium to be flown into a central venule. Assays with GBM cells (U87-MG) are carried out, aiming at understanding the impact of cell-cell communication (including through microvesicles) on the stability of the extracellular matrix and on the BBB. This project will question the possible EPR (enhanced permeability and retention) effect in the glioblastoma. The study will focus on the detection of the transport of, first standardized molecules and nanoparticles to test the BBB within the GBM context, then nanocarriers and drug candidates. Their efficiency and specificity will be assessed by imaging and biomolecular techniques, but also via the instrumentation of the GBM-on-chip with biosensors.

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