Glioblastoma multiforme – on a chip

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Research Focus
Our research group focus is the development of novel *in vitro* neural models and hybrid bioelectrical systems. We aim towards a better understanding of the interactions among cell populations of the neurovascular unit (NVU). We combine human pluripotent stem cell (hPSC) - derived cells and microfluidics to mimic the human physiology and reinforce our brain-on-chip models in health and disease. This will be a joint project with the Neuro-oncology group of Michael Andäng at Uppsala University in order to expand our studies in Cancer Stem Cells (CSCs).

Background
Human glioblastoma multiforme (GBM) is the most aggressive brain cancer with a very low life expectancy after diagnosis. Even with a combinatorial treatment (surgery, chemotherapy and radiation therapy) the average prognosis remains less than 1.5 years [1,2]. GBM is characterized by a highly heterogeneous cell population; among those reside the glioma-initiating cells (GICs) which can give rise to the glioma tumor and share common characteristics with stem cells at the gene expression level. These cells reinforce the tumor via self-renewal or differentiation and they are highly resistant to therapy. Therefore, a better understanding of their biology could lead to more effective targeted therapies. Data from the Andäng lab has recently shown that ion channel blockers selectively impaired the viability of GICs and increased survival in a mouse model of human GBM. These novel and exciting finding is underlined by impaired nutrient transport and specifically upregulated glutamate transporters in GICs [3].

One of the key elements for disease progression and therapeutic resistance in the case of glioblastoma is the tumor microenvironment (TME). TME consists of a variety of cell types including stromal, endothelial and immune cells, which interact and influence the phenotype of GICs and possibly guide the tumor initiation. In addition, the blood brain barrier (BBB) acts as an insulator between the brain microenvironment and the blood. As a result, drug and nutrient supply from the blood to the brain tissue is hindered. Thus, GBM is highly resistant to chemotherapy. In our lab we use established protocols for derivation of brain microvascular endothelial cells (BMECs) from hPSCs to model the BBB function *in vitro*[4].

Aim
The aim of the project is to investigate novel metabolic functions of GICs and their interactions with the BBB. Nutrient transport and the glutamate-glutamine cycle will be addressed for cancerous and non-cancerous cell types. Similarities of cancer stem cells and stem cells with relevance to metabolism will be investigated.

Methods
Cell Culture (hiPSCs cultures and differentiation, GBM patient-derived primary cell lines), Immunocytochemistry (ICC), Microscopy (Widefield, Confocal and Live Cell Imaging), RNA isolation - cDNA synthesis and qPCR, RNA sequencing, Ionizing Radiation Imaging (Scintillation)

Requirements
Basic knowledge of sterile cell culture techniques is recommendable
Duration of the project: at least 6 months

References

1 Ostrom, Q. T. *et al.* CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. *Neuro-oncology* **17 Suppl 4**, iv1-iv62, doi:10.1093/neuonc/nov189 (2015).
2 Nguyen, H. S., Awad, A. J., Shabani, S. & Doan, N. Molecular Targeting of Acid Ceramidase in Glioblastoma: A Review of Its Role, Potential Treatment, and Challenges. *Pharmaceutics* **10**, doi:10.3390/pharmaceutics10020045 (2018).
3 Niklasson, M. *et al.* Membrane-Depolarizing Channel Blockers Induce Selective Glioma Cell Death by Impairing Nutrient Transport and Unfolded Protein/Amino Acid Responses. *Cancer Res* **77**, 1741-1752, doi:10.1158/0008-5472.CAN-16-2274 (2017).
4 Stebbins, M. J. *et al.* Differentiation and characterization of human pluripotent stem cell-derived brain microvascular endothelial cells. *Methods* **101**, 93-102, doi:10.1016/j.ymeth.2015.10.016 (2016).