**Studying astrogliosis during brain development in preterm infants with intraventricular haemorrhage.**

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**Doctoral thesis theme**

Preterm infants are at high risk of haemorrhage into their brain- called intraventricular haemorrhage (IVH)- within the 48h after birth [1] and it is thought to arise from damage to the fragile blood vessels of germinal matrix (GM) [2]. GM is the area adjacent to the lateral ventricles in the developing brain and this is a hugely important area for neurogenesis, as formed by neural stem cells (NSCs) that proliferate and migrate to form neurons and glia throughout the brain [3]. Due to this, IVH crucially affects development in all domains from infancy to adulthood. Data from the Neonatal Research Network indicates that 40% of infants under 1000g at birth will develop IVH and 10% of them will develop hydrocephalus necessitating implantation of a ventriculo-peritoneal shunt to prevent CSF build-up[4]. 40% of these infants will develop cerebral palsy, 25% with multiple disabilities, with significant consequences for the individual, family, and society as a whole.

Pilot research has been undertaken to prove the potential for this project. Initial work assessing the effect of cerebrospinal fluid (CSF) from infants with IVH on primary human fetal cortical NSCs has demonstrated that IVH-CSF induces a premature neuroglial switch. Astrogliosis is a known consequence of brain injury in these infants and could account for some of downstream developmental problems seen in IVH.

Building on CSF biomarker research previously performed by Prof Heep [5-7] we have analysed inflammatory markers (IL-1beta, IL-6, MCP1), and IGF-1 in serial CSF samples from several patients. In addition to this we have profiled the micro-RNA content of extracellular vesicles found in the CSF which is novel for this patient group [8]

**Brief Survey of the project**

***Hypothesis:*** We hypothesize that the NSCs and their environment specifically interact in response to development and to the damage following IVH. Detailed knowledge of these changes (growth factors, inflammatory markers, involved signaling pathways) will support planning of therapies to improve endogenous repair mechanisms during development.

***Methods and work program:*** For addressing this hypothesis, we will apply multiple molecular techniques and neural stem cell culture, to characterize IVH-CSF and how this affects human fetal NSCs differentiation. We also aim to translate these results into a preclinical model of IVH injury

***Primary Objectives:*** With this project we aim to investigate the effects of intraventricular haemorrhage in brain development and to plan therapeutic strategies which will improve endogenous repair mechanisms.

***Secondary Objective:*** We also aim to build up a collaborative network between the Department of Human Medicine at the University of Oldenburg (Germany), the Bristol Medical School at the University of Bristol (UK) and Department of Clinical Science at the University of Lund (Sweden).