Regulating microglia reactivity to protect the developing brain: a role for oxytocicnergic neurons

Every year, 30 million infants worldwide are delivered after intra-uterine growth restriction (IUGR) and 15 million are born preterm. These two conditions are the leading causes of ante/perinatal stress and brain injury responsible for neurocognitive and behavioral disorders in more than 9 million children each year. Most pharmacological candidates to prevent perinatal brain damage have failed to demonstrate substantial benefits. In contrast, environmental enrichment based on developmental care, skin-to-skin contact and vocal/music exposure appear to confer positive effects on brain structure and function. However, mechanisms underlying these effects remain unknown. There is strong evidence that an adverse environment during pregnancy and the neonatal period can influence hormonal responses of the newborn with long-lasting neurobehavioral consequences in infancy and adulthood. In particular, excessive cortisol release in response to perinatal stress associated with prematurity or IUGR is recognized to induce brain-programming effects and neuroinflammation, a key predictor of subsequent neurological impairments. These deleterious effects are known to be balanced by Oxytocin (OT), a neuropeptide released by the hypothalamus, and plays a role during the perinatal period and in social behavior. In addition, preclinical studies suggest that OT is able to regulate the central inflammatory response to injury in the adult brain. Using a rodent model of IUGR associated with developing white matter damage, we recently reported that Carbetocin, a brain permeable OT receptor (OTR) agonist, induced a significant reduction of activated microglia, the primary immune cells of the brain. Moreover this reduced microglia reactivity was associated with long-term neuroprotection. These findings make OT a promising candidate for neonatal neuroprotection through neuroinflammation regulation. However, the mechanisms linking endogenous OT and central inflammation response to injury have not yet been established.

We hypothesize that endogenous OT, which responds to developmental care interventions, is able to prevent inflammatory-induced injury in the developing brain through direct or indirect effects on microglial activation. Using in vitro and in vivo cellular and molecular readouts in loss- and gain-of-function paradigms, structural advanced brain imaging, functional connectivity tools, and behavioral phenotyping, we propose to:

- Aim #1: Investigate the effect of the OT neuron activity on neuroinflammation and microglial functions.
- Aim #2: Elucidate the role of OT neuron activity on developing white matter vulnerability towards systemic inflammation
- Aim #3: Explore putative mechanisms underlying the anti-inflammatory effect of OT in the developing brain.

The overarching goal of this project is to assess the protective role of OT in the developing brain through modulation of microglial activation, a key feature of brain injury observed in infants born preterm or growth-restricted, by using novel research strategies in a translational perspective. This project is therefore expected to have several impacts not only restricted basic insights into microglial cell physiology and reactivity and its consequences on brain development, but also to design clinical trials testing interventions associated with endogenous OT release as a relevant strategy to alleviate neuroinflammation in neonates.

Required profile: Background in molecular biology and data analysis, immunohistochemistry, primary cells culture, animal model, transgenic mice colony management, behavioural testing.

Duration of the research internship: 3 years for each position

Activity rate: PhD 80%, Post-Doc 70%

Start of the internship: January 2021

Application procedure: Please send your Curriculum Vitae and a statement of motivation to Jerome Mairesse (Jerome.Mairesse@unige.ch) and Olivier Baud (Olivier.baud@unige.ch). (You can also use these contacts for any further questions and information).

Deadline for application: 15th Dec 2020