## ANR Program: NEUROCM

# Identification of host and parasite causative and remedial factors of neuroinflammation in the context of cerebral malaria

In most tropical areas where malaria is endemic, young children are most prone to develop severe malaria, and eventually to die. Despite a recent decrease in malaria mortality due to extensive malaria control through insecticide impregnated bednets and increased use of artemisinin derivatives, 275,000 African children still die every year from malaria. Cerebral malaria is the most severe form of malaria, a neuropathology that may lead to death or neurological sequelae. Pathophysiology of cerebral malaria is complex and multifactorial. *Plasmodium falciparum*-infected erythrocytes adhere to vascular endothelium and other erythrocytes in brain, cause microvascular obstruction, elicit a local inflammation, blood brain barrier impairment and a range of immune cellular host responses aiming to resolve this process of neuroinflammation. Thus, cerebral malaria cure depends on both parasite neutralization and brain inflammation resolution. The NEUROCM project will study both aspects.

It is currently believed that cerebral malaria is caused by dedicated parasite variants that specifically localize in brain through interaction between parasite proteins expressed on the surface of infected red blood cells and brain endothelium. The NEUROCM project aims to identify these parasite proteins. To achieve this, parasite variants originating from two clinical groups of patients (uncomplicated and cerebral malaria) will be compared using a proteogenomic approach. Identified proteins will then be functionally characterized by a cellular and molecular biology approach.

Parasite sequestration and interaction with brain endothelium lead to host immune response resulting in neuroinflammation. The mechanical obstruction of brain blood flow leads to hypoxia and local inflammatory state. This important dysregulation triggers two critical mechanisms: activation of microglia (the brain resident macrophages) and influx of myeloid immune cells to the brain. NEUROCM will focus on both mechanisms to identify molecular targets of the cellular host immune response to infection useful to promote the resolution of neuroinflammation. In order to reach this objective, our project will initially include experimental work before validation in humans. The human study will include the same two groups of malaria patients (uncomplicated and cerebral malaria), and an additional group of non-malarial coma. Our experimental murine models will allow the formulation of new scientific hypothesis while proof of concept will be achieved through the correlation of our proposed targets with patient morbidity and mortality parameters.

In addition, the diagnosis of cerebral malaria is always difficult, and a coma in the presence of malaria parasites in the peripheral blood is often considered as cerebral malaria in endemic countries. NEUROCM will allow to differentiate the different etiologies by extensive blood biochemistry and molecular diagnosis in CSF of microbial infections. Thus, NEUROCM will provide, for the first time, an accurate differential diagnosis of cerebral malaria, as well as the identification of the causes of coma in the African child.

The final products of NEUROCM are expected to feed the pipeline of new therapeutic (immune intervention) and preventive (vaccine) strategies that will improve cerebral malaria outcome, as well as other diseases involving neuroinflammation.

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