Malaria infection is a global health concern caused by different *Plasmodium* species out of which the *Plasmodium falciparum* is the most lethal. Cerebral malaria is a severe clinical manifestation resulting from this infection and is characterized by the destruction of the blood brain barrier formed principally by cerebral microvascular endothelial cells (CMVECs). Also, during the blood stage of this infection, malaria parasite-infected red blood cell derived extracellular vesicles (MiRBC-EVs) are released into the systemic circulation following the bursting of infected red blood cells. The exact mechanism of cerebral malaria has not yet been clarified as it has been attributed to be multifactorial, involving vascular and inflammatory mechanisms. The composition and activities of MiRBC-EVs with various body cells are currently gaining attention but little is known about its interactions with brain immune cells such as microglia.

Therefore, this thesis was designed to characterize the mechanisms involved in the pathogenesis of cerebral malaria by investigating i) the characteristics of adult human cerebral microcirculation by investigating the expression profiles of brain endothelial markers (CD31 and von Willebrand Factor (vWF)) in the brain and its implication in the pathogenesis of cerebral malaria, ii) the small RNA content of the MiREVs, and iii) the interaction between human microglia generated from human peripheral blood mononuclear cells (monocytes) and the MiRBC-EVs.

Taken together, the results contained in this thesis show that the regional variation of CMVECs phenotypic expression profiles imply variations in structure and function of endothelial cells of the cerebral microcirculation and this could influence the pathological outcomes in cerebral malaria. Secondly, MiRBC-EVs contain small regulatory molecules in addition to parasite and host RNAs which can influence the regulatory functions of the MiRBC-EVs during malaria. Lastly, human microglia responds to MiRBC-EVs and this interaction may possibly result in neuroinflammation which could contribute to the pathogenesis of cerebral malaria.

Giving these findings, we can say that this thesis has succeeded in providing relevant information beneficial to the body of knowledge for the understanding of the mechanisms that could be involved in the pathogenesis of cerebral malaria.

Jury:
Prof. Luis Filgueira (Thesis supervisor)
Dr. Pierre-Yves Mantel, (Thesis co-supervisor)
Prof em. Giampietro Corradin, (External examiner)
Prof. Hans-Peter Beck (External examiner)
Prof. Michael Walch (Internal examiner)
Prof Jens Stein (President of the Jury)