Résumé du projet de thèse *(1 page maximum, en anglais)*
Indiquer la participation de chaque co-directeur et structure dans la gestion du projet. Please indicate explicitely the specific contribution of each supervisor to the PhD project.

Placental malaria is characterized by infected erythrocytes accumulation in the placenta, causing adverse birth outcomes. Placental sequestration is mediated through the interaction between VAR2CSA, a member of the PfEMP1 family, expressed on the IEs surface and the chondroitin sulfate A (CSA) in the placenta. VAR2CSA is a prime candidate for the development of an anti-disease vaccine. This project proposes to define targets of protective Immunity to VAR2CSA by developing and using human monoclonal antibodies

Detailed project:

Although malaria vaccine has long been a research priority, little progresses were made over the last decades. One major hurdle that could explain the failure of malaria vaccines to date is that the malaria parasite has an extraordinary ability to evade the Host immune system. Among emerging strategies, anti-disease vaccines are being explored. Placental malaria is linked to the massive accumulation of *Plasmodium falciparum*-infected erythrocytes (IEs) and monocytes in the placental intervillous spaces, leading to maternal as well as fetal and infant mortality. Placental parasites bind to chondroitin sulfate A (CSA) to sequester in the placenta, and women become resistant over successive pregnancies as they acquire antibodies that block IEs adhesion to CSA. The *P. falciparum*-derived protein VAR2CSA has been identified as the main parasite ligand mediating IEs binding to CSA and is the target of antibodies associated to protection. Humoral immunity to VAR2CSA consists mainly of cytophilic antibodies that have two predominant functions: (1) blocking adhesion of IEs to CSA and (2) opsonizing IEs to facilitate phagocytosis/cytotoxicity. Both functions are associated with protection, but their relative importance in multigravida women is still unknown. The VAR2CSA CSA-binding domain has been mapped to the N-terminal region (DBL1-DBL2). Recombinant proteins encompassing this region are leading vaccine candidates. We recently reported the safety and immunogenicity of a VAR2CSA-derived PM vaccine (PRIMVAC) in both malaria naïve and *P. falciparum*-exposed non-pregnant women in a Phase Ia/Ib clinical trial. The recent production of human monoclonal Abs (humAbs) to malaria proteins has expanded our ability to understand the fine specificity of naturally acquired and artificially induced (i.e., through vaccination) protective Abs that can be used to inform the design of next generation malaria vaccines and develop new therapeutics such as passive transfer of protective humAbs.

We hypothesize that high affinity humAbs that recognize strain-transcending VAR2CSA epitopes will block IE binding to CSA and/or recognize epitopes that facilitate opsonic phagocytosis/cytotoxicity and Ab cooperativity. Further, we aim to identify the epitopes recognized by these humAbs by X-ray crystallography and cryo-electron microscopy to design second-generation placental malaria vaccines and therapeutics.

In this project, we aim to I) develop new VAR2CSA vaccine candidates (B. GAMAIN Team) II) isolate humAbs to VAR2CSA from multigravid women residing in a malaria endemic area with naturally acquired immunity to VAR2CSA and from malaria naïve women vaccinated with the PRIMVAC vaccine (DBL1-DBL2 construct containing the CSA binding domain ClinicalTrials.gov, NCT02658253) (B. GAMAIN Team); III) Develop a murine Model for Preclinical Studies of Var2CSA-Mediated Pathology Associated with Malaria in Pregnancy (R. AMINO team) IV) Perform a preclinical evaluation of placental malaria vaccine candidates targeting the var2CSA antigen and of the monoclonal antibodies (B. GAMAIN and R. AMINO Teams).