The accumulation of infected erythrocytes (IE) in the placenta is a key feature of pregnancy-associated malaria (PAM). The first receptor molecule shown to be responsible for cytoadhesion in the syncytiotrophoblast lining of the placenta is chondroitin sulfate A (CSA). When a woman is infected during pregnancy, she develops anti-adhesion antibodies that are strain-independent of the infecting IE, indicating that a conserved parasite ligand is in effect mediating the binding to CSA. The first putative parasite ligand proposed in the host-parasite interaction was a domain present on the protein PfEMP-1, a major variant surface antigen encoded by the multicopy *var* gene family. The ligand in play was the DBL-γ domain, first identified from two *var* genes, the FCR3*var*CSA gene and CS2*var* gene.

The first part of this thesis concerns the study of four different DBL-γ protein domains (482, 498, 701 and 732 DBL-γ domains), named after the numbers given to each of the placental isolates from which they originate. These domains, collectively called *var*PAM DBL-γ were previously demonstrated to bind CSA. As an extension of this study, my work here showed that immune recognition of 482 and 732 DBL-γ domains by plasma samples from a pregnant women cohort is pregnancy-specific. Pregnant women who have higher antibody reactivities to these two domains appear to be less vulnerable to placental infections. Based on these findings, it is postulated that 482 and 732 DBL-γ domains contain some important epitopes for CSA-binding, that are probably also the target of protective maternal antibodies. So far, evidence has also accumulated to show that other PfEMP-1 domains like CIDR-α and DBL-X can interact with CSA. This supports the notion that CSA-binding motifs are probably structurally very similar to each other, differing only in their primary amino acid sequences. Studying the physico-

chemical behaviour of these domains, eventually leading to an elucidation of their crystal structures, will help to unfold basic structural requirements for CSA binding.

The different domains from the full-length 732*var* gene, which comprises four DBL domains and one CIDR domain was characterized in the second part of this thesis. Interestingly, two of these domains, CIDR-1α and DBL-3γ, were shown to bind CD36 and CSA receptors, respectively. Given that the majority of placental parasites are generally known to bind CSA only, the observed CD36 recognition was an unexpected finding. The molecular mechanism that suppresses the adhesive characteristic of CIDR-1α within a CSA-binding PfEMP-1 molecule is unknown. Therefore, future work could be directed at understanding this mechanism responsible for the dichotomy in adhesion.

When analyzed for their reactivities with pregnant women sera in ELISA, the two domains showed differential antibody recognition. Specifically, the level of antibodies to recombinant 732 DBL-3γ correlated with a decrease of parasite density in the placenta. In contrast, anti-CIDR-1α antibody titres increased with placental parasite density. From this result, it is tempting to conclude that antibodies to DBL-3γ may play a role in protecting a woman from placental infections. However, what remains a riddle is the immunological significance of the presence of antibodies to CIDR-1α in PAM

In summary, results presented in this thesis provide a basis for further understanding molecular mechanisms of CSA-cytoadhesion and development of immunity in pregnant women, and may have important implications in the search for a PAM vaccine. .