ABSTRACT

Trypanosomiasis is one of the major parasitic disease for which control is still far from reality. The classical vaccination approaches by using dominant surface proteins, has not been successful, mainly due to antigenic variation of the parasite surface coat. On the other hand, the chemotherapeutic drugs in current use for the treatment of this disease are toxic and problems of resistance are increasing. Therefore, alternative approaches in both treatment and vaccination against trypanosomiasis were evaluated in this study.

Human trypanolytic factor, APOL1, has been exploited as an alternative approach for the treatment of human African trypanosomiasis (HAT). APOL1 lyses trypanosomes except the ones which are causing HAT. In case of *T. rhodesiense* the resistance to the trypanolytic capacity of APOL-1 is due to the expression of serum resistance associated (SRA) protein which neutralizes APOL1 through the interaction with the C-terminal of this lipoprotein. Deletion of the SRA interacting domain of APOL1 resulted in Tr-APOL1 that is lytic to both NHS-sensitive as well as resistant *T. rhodesiense*. Hence, Tr-APOL1 represents a possible drug against all *T. rhodesiense* parasites provided specific targeting is guaranteed. Hence, the Tr-APOL1 was conjugated with a single domain camel VHH or nanobody that targets the oligo-mannose moiety of VSG or the trypanosomal transferrin receptor (pESAG6). Our results showed that treatment with NbAn33 conjugated Tr-APOL1 cured mice infected with either NHS-resistant *T. rhodesiense* or NHS-sensitive *T. brucei*. Our results thus suggest that Tr-APOL1 could be developed as an alternative drug for treatment of HAT.

Trypanosomiasis is mainly considered as a disease of Africa. However, *Trypanosoma evansi* infections are not limited to Africa, and occur also in South America and Asia. Surprisingly, information on the immunobiological aspects of this infection are scarce. Hence, one part of this PhD work focused on the study of experimental *T. evansi* infection in different immunological settings. When the role of antibodies was evaluated in *T. evansi* infection model, the results showed that IgM antibodies are crucial for both parasitemia control and survival the infected host. On the other hand, although *T. evansi* causes the induction of TNF, INFγ and Nitric Oxide (NO) in the early stage of infection, none of these molecules are crucial for parasitemia control and survival of the infected animal.
Finally, as an alternative strategy of vaccination, GPI-anchor of VSG has been evaluated. Using liposomes as slow delivery system, GPI administered prior to infection resulted in better control of parasitemia and pathological conditions and thus longer lifespan of infected mice. These results related to the fact that the treatment oriented the classically activated inflammatory macrophages, to more counter-inflammatory alternatively activated macrophages. Therefore, this strategy is actually an anti-disease approach rather an anti-parasitic strategy since the animals are not cleared from their parasites due to this treatment.

In conclusion, in this study we have been able to develop alternative strategies for treatment of human African trypanosomiasis by using nanobodies conjugated truncated APOL1 and a GPI-based anti-disease treatment as an alternative strategy for trypanosomiasis control.