PhD defence Eliane Tihon

Study of the genetic diversity of Trypanosoma congolense and its resistance to the drug Isometamidium Chloride

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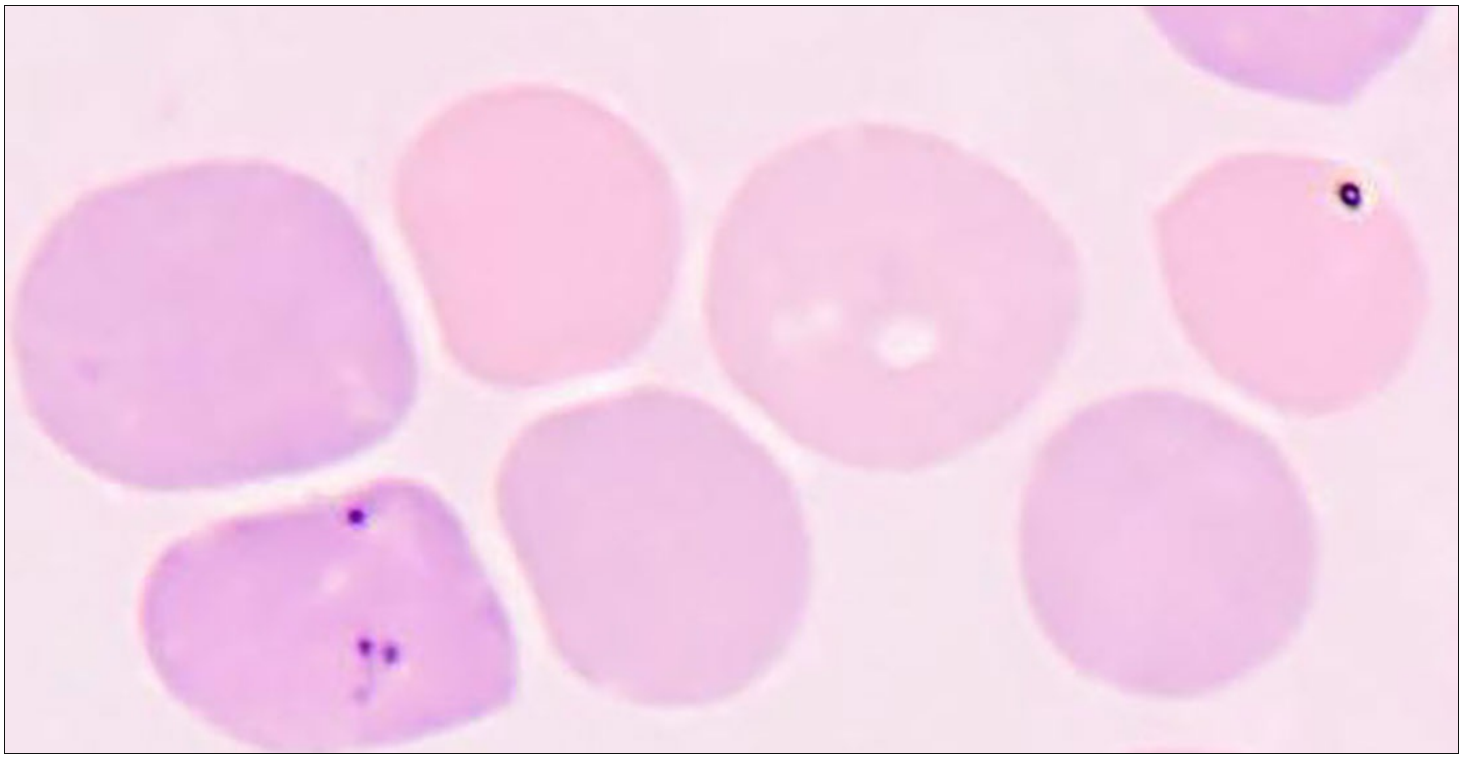

Dit is de omschrijving

Supervisors: Prof. Dr. Jan Van Den Abbeele (ITM), Prof. Dr. Jean-Claude Dujardin (University of Antwerp).

Summary:

Trypanosoma congolense is one of the major pathogens responsible for animal African Trypanosomiasis (AAT), a disease affecting about 10 million km^2 of the sub-Saharan region on the African continent and considered as one of the principal causes of hunger and poverty in this region. Isometamidium Chloride (ISM) is the principal drug used to counteract *T. congolense* infections in livestock. However, numerous cases of ISM resistance in different African regions have been reported, representing a serious problem in the battle against AAT.

To gain a better insight into the genetic and molecular mechanisms underlying ISM resistance in *T. congolense*, we performed a whole genome comparison of a selection of sensitive and resistant field isolates sampled between 1971 and 2014 in 10 countries where the disease is endemic. Sequencing analyses revealed evidence for recombination and complex genetic exchanges among *T. congolense* parasites, and highlighted a geographically asymmetric distribution of genetic diversity across Africa: parasites collected within a short period of time in Zambia showed a much higher genetic diversity compared with the strains sampled over a period of 30 years in the other countries. The factors resulting in this asymmetric diversity remain speculative but we suggest that the close proximity to wildlife observed in this region as well as the presence of specific tsetse fly vector played a key role. However, we did not observe any clear genetic patterns in *T. congolense* field isolates that could explain drug sensitivity.

To further investigate the genomic changes potentially associated with the development of ISM resistance in *T. congolense*, we conducted an ISM resistance induction experiment in the murine host to generate three independent ISM resistant cell lines starting from the same sensitive field isolate. The *in vivo* induction of ISM resistance could only be achieved in immune-deficient hosts. Then, Whole Genome Sequencing analysis comparing the *in vivo*-induced ISM resistant lines to the sensitive line identified point mutations in genes coding for different transporters and transmembrane products. In line with this, we identified a decreased uptake of ISM by the resistant parasites and observed a potential involvement of endocytosis as drug delivery mechanism. The exact mechanisms leading to ISM resistance in *T. congolense* remain to be further elucidated, but our findings suggest that modifications in drug transport may be the underlying basis for acquisition of drug resistance. Moreover, the development of full resistance is strongly enhanced when the host immune response is compromised.