PhD defence Franck Dumetz

Role of the gene dosage in the acquisition of antimony resistance in Leishmania donovani: experimental evidence

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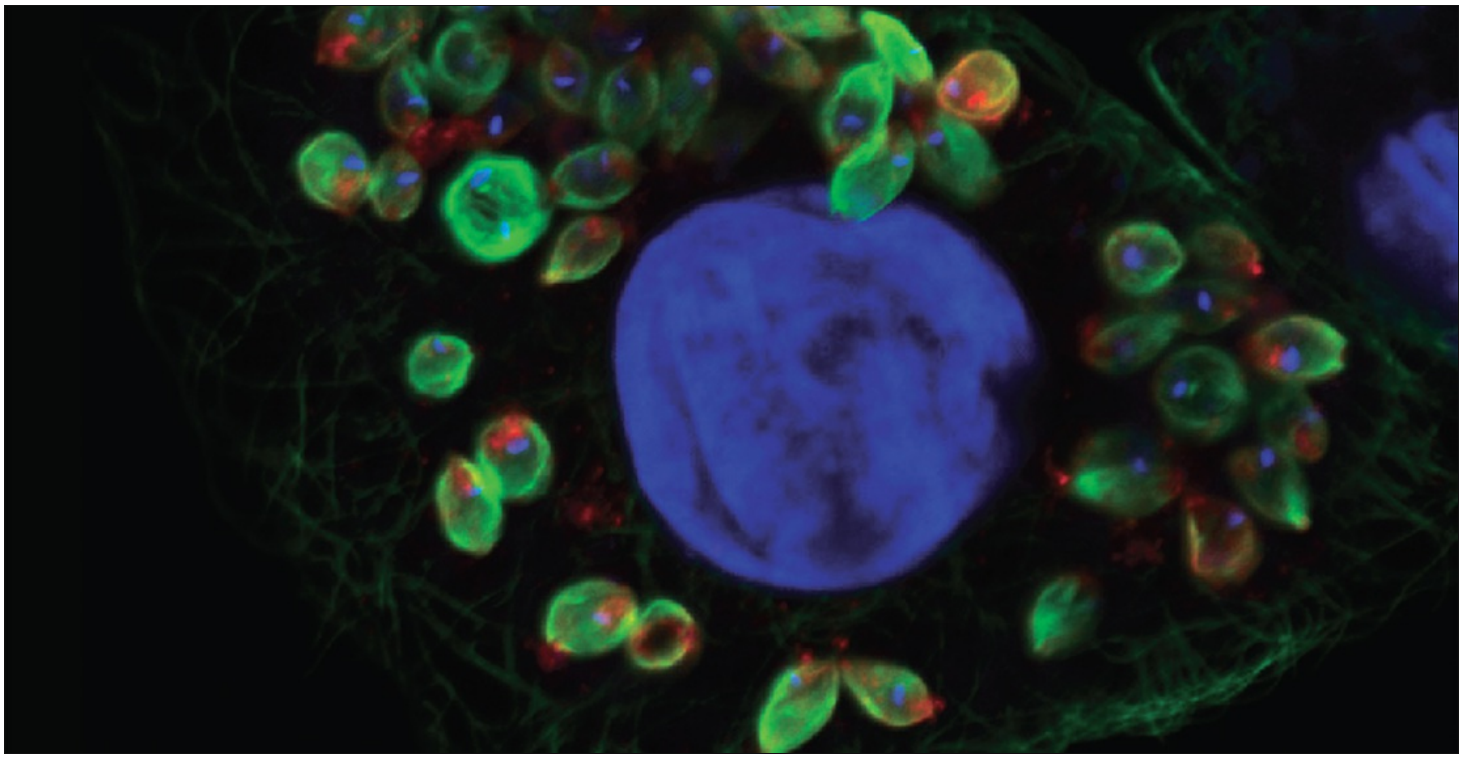
University of Antwerp - Antwerpen
Booking recommended



Dit is de omschrijving

Supervisors

- Prof. Dr. Jean-Claude Dujardin (ITM/University of Antwerp)
- Dr. Géraldine De Muylder (ITM)

Summary

Leishmania donovani is the etiological agent of visceral leishmaniasis in the Indian sub-continent (ISC). Leishmania are protozoa alternating between two life forms: the extracellular promastigotes in the insect vector and the intracellular amastigotes in the mammalian host. Pentavalent antimony was the first line drug in the ISC from 1923 to 2005 when it was abandoned because of treatment failure and drug resistance.

In a previous phylogenomic study, we were able to show the circulation of two genetically different *L. donovani* in the ISC (i) the Core Group (CG) endemic in the Gangetic plains and (ii) another population called ISC1 found in the Nepalese high-lands. Interestingly, 100% of the CG isolates showed a unique ancestral character, the intra-chromosomal amplification (ICA) of the H- and M-loci. However, the link between the genomic features and drug resistance was not clear. The main hypothesis of this PhD was that gene dosage would play a major role in the development of antimonial resistance in the ISC.

My overall goal was to analyse in experimental conditions the emergence of antimonial resistance upon in vitro selection.

Firstly, I characterized the stability of the parasite genome during the life cycle. The genome and transcriptome of *Leishmania* strains were compared in vitro, in the sand fly *Phlebotomus argentipes*, and in golden Syrian hamsters. While the genome sequence itself was stable, a drastic and strain- specific modulation of parasite's karyotype was observed inside the mammalian host. This was highly correlated with transcription levels, supporting the adaptive function of gene dosage.

Secondly, I analysed the molecular adaptations developed by ISC1 and CG strains during in vitro selection of resistance to trivalent antimonials (SbIII). The ISC1 strain required more time and molecular adaptations (genomics and metabolomics) to become resistant than the CG ones. We hypothesised that CG strains were pre-adapted to SbIII resistance, which we demonstrated by exposing different strains directly to a maximal concentration of SbIII: all the ISC1 isolates died while all the CG ones survived. Dissecting the mechanism by overexpressing the H-locus, we identified one gene has being the main driver, MRPA, responsible for SbIII sequestration. Naturally amplified in the CG strains, it was amplified in the selected SbIII-resistant ISC1 strain by duplication of a whole arm of chromosome 23, bearing MRPA.

Gene dosage is thus a very important mechanism for the acquisition of antimony resistance and MRPA amplification is the first one emerging in natural and experimental conditions.

Registration

If you plan to attend this public PhD defence, please send an e-mail to fdumetz@itg.be .