Antimony resistance in *Leishmania donovani*: an integrated omics study on the promastigote lifestage

Maya Berg[1], Manu Vanaerschot[1], Andris Jankevics[2,3], Hideo Imamura[1] and Jean-Claude Dujardin[1,4]

[1] Unit of Molecular Parasitology, Department of Biomedical Sciences, Institute of Tropical Medicine, Antwerp, Belgium; [2] Institute of Molecular, Cell and Systems Biology, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, U.K; [3] Groningen Bioinformatics Centre, Groningen Biomolecular Sciences and Biotechnology Institute, University of Groningen, Groningen, The Netherlands; [4] Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium.

Background: Thanks to significant improvements in LC-MS technology, metabolomics is increasingly used as a tool to discriminate organisms' responses to various stimuli or drugs [1]. In this study, we implemented an untargeted LC-MS metabolomics approach to gain insights in metabolic differences between clinical antimonial-(SSG)-sensitive and SSG–resistant *Leishmania donovani* isolates [2].

Methods & Results: In a first stage, we compared the metabolic profile of three strains with a different antimony susceptibility profile in two different growth stages: the logarithmic growth stage and the stationary growth stage. This showed that the majority of metabolic changes related to SSG-resistance occurs only in the stationary growth stage, which is in accordance with the hypothesis that during this life stage the parasite will prepare to encounter the host where it can be exposed to the drug. Interestingly, we disclosed several complete metabolic pathways which are upregulated in two SSG-resistant strains such as the cysteine pathway and the ureum cycle, both contributing to the production of thiols. In a second stage we also studied the metabolic effect of Sb^{III} drug pressure on one of these SSG-resistant lines. Exposure to this drug further affected the thiol levels, showing how this resistant parasite deals with the encountered oxidative stress imposed by Sb^{III}. Full genome sequencing of these *L. donovani* strains has been executed in parallel to allow integration of both 'omic datasets.

Conclusion: With a targeted approach we will try to link the functional importance of sequence diversity (SNP) and gene dosage (ploidy, copy number variation) with the intensity levels of differential metabolites in resistant lines. In this way, we hope to enhance our insight into the interactions between the different components of biological systems and how these interactions give rise to a specific phenotype such as drug resistance.

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