PhD defence Aya Hefnawy

Incorporating drug resistance studies in the quest for novel antileishmanial agents.

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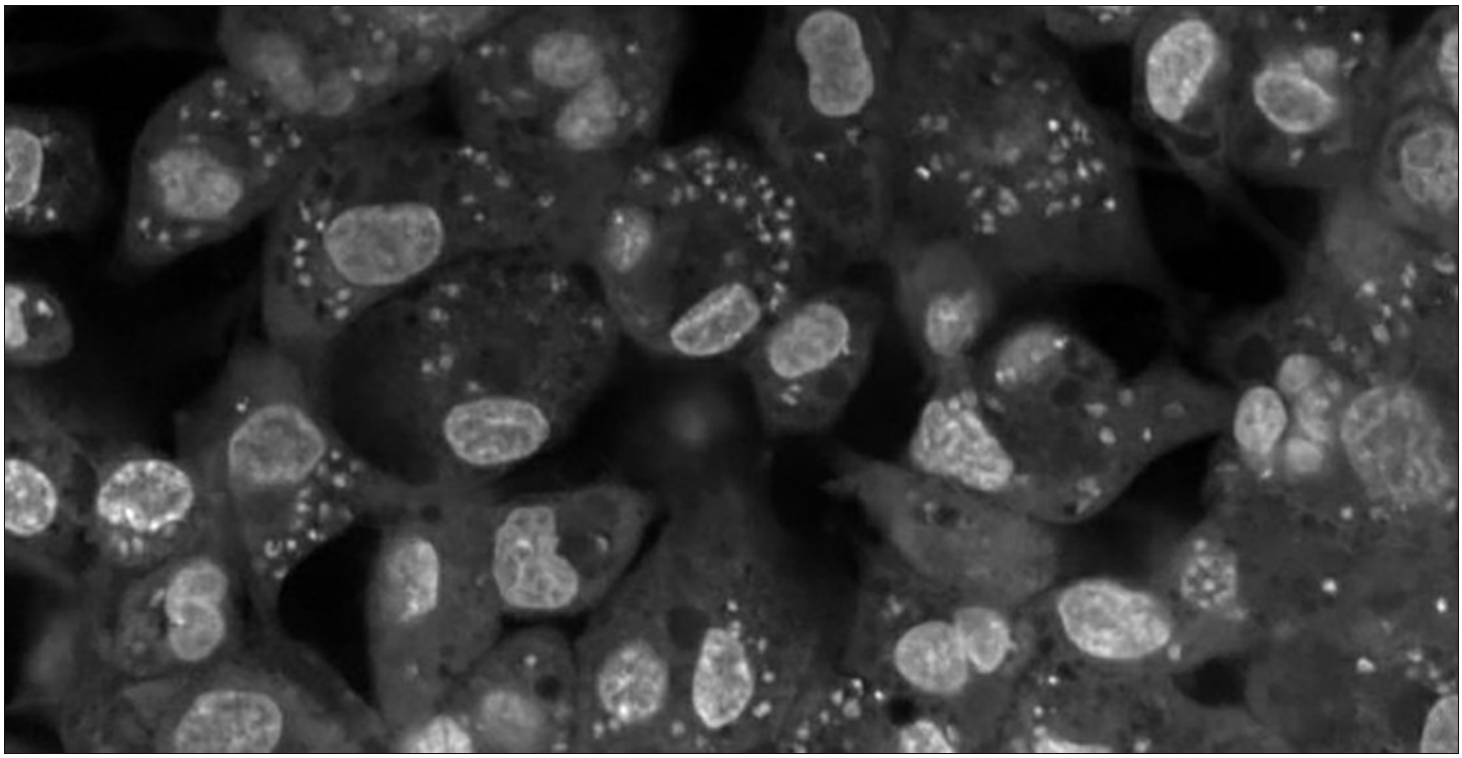
University of Antwerp - Antwerpen



Dit is de omschrijving

Supervisors

- Prof. Dr. Jean-Claude Dujardin (ITM, University of Antwerp)
- Prof. Dr. Dirk Valkenborg (University of Antwerp)

Abstract

Visceral leishmaniasis (VL) is a neglected tropical disease that is lethal if left untreated. Drug resistance (DR) is a major problem for VL in the Indian sub continent (ISC). New chemotherapeutic agents are needed and there is no implementation of DR studies into the industrial R&D pipeline. In this study we reviewed the utility of DR studies for two compounds, antimonials (SSG) and miltefosine (MIL), both of which are no longer used as first line treatment options for VL in the ISC. We investigated how implementation of DR studies could have extended their use. Based on that we recommended the implementation of DR studies in an early stage of the R&D process through two approaches.

(A) Testing the efficacy of the newly discovered compounds on clinically isolated resistant strains.

(B) Utilizing DR studies to understand mechanisms of resistance to new compounds and possibly identify their mode of action. These two recommendations were tested in this PhD thesis**.** In collaboration with GSK, newly identified compounds from the Leishbox were tested on recently isolated ISC strains including an SSG-Resistant one**.** Only 45 percent of the compounds showed panactivity. This finding shows the importance of validation of the results of High-Throughput Screens (HTS) with a panel of recent clinical isolates of different geographical origin and isolates with demonstrated resistance to currently used compounds. For approach B one of the panactive compounds of the Leishbox with a promising profile was chosen (further-called compound X).

Resistance to X was selected in a stepwise manner in promastigotes. The time to develop resistance to compound X was found to be longer than developing resistance to MIL or SSG. X-Resistance was stable in the absence of drug pressure and amastigotes were also found to be resistant to X. Genomic and metabolomic characterization was performed to understand molecular adaptations of X-resistant parasites. In contrast to vast metabolic variations between X-resistant and X-sensitive parasites, only few genomic changes have been identified including a SNP in the gene encoding dynamin-1 like protein. Both these genomic and metabolic adaptations could give cues to the mechanism of resistance to X.

This work highlights the importance of academic and industrial collaboration. DR in *Leishmania* is an inevitable threat to any new drug candidate so implementing DR studies is the next logical step in the industrial drug discovery pipeline.