PhD defence Marlene Jara-Portocarrero

Functional characterization of Leishmania throughout in vitro biological cycle: the quest for a quiescent stage among amastigotes

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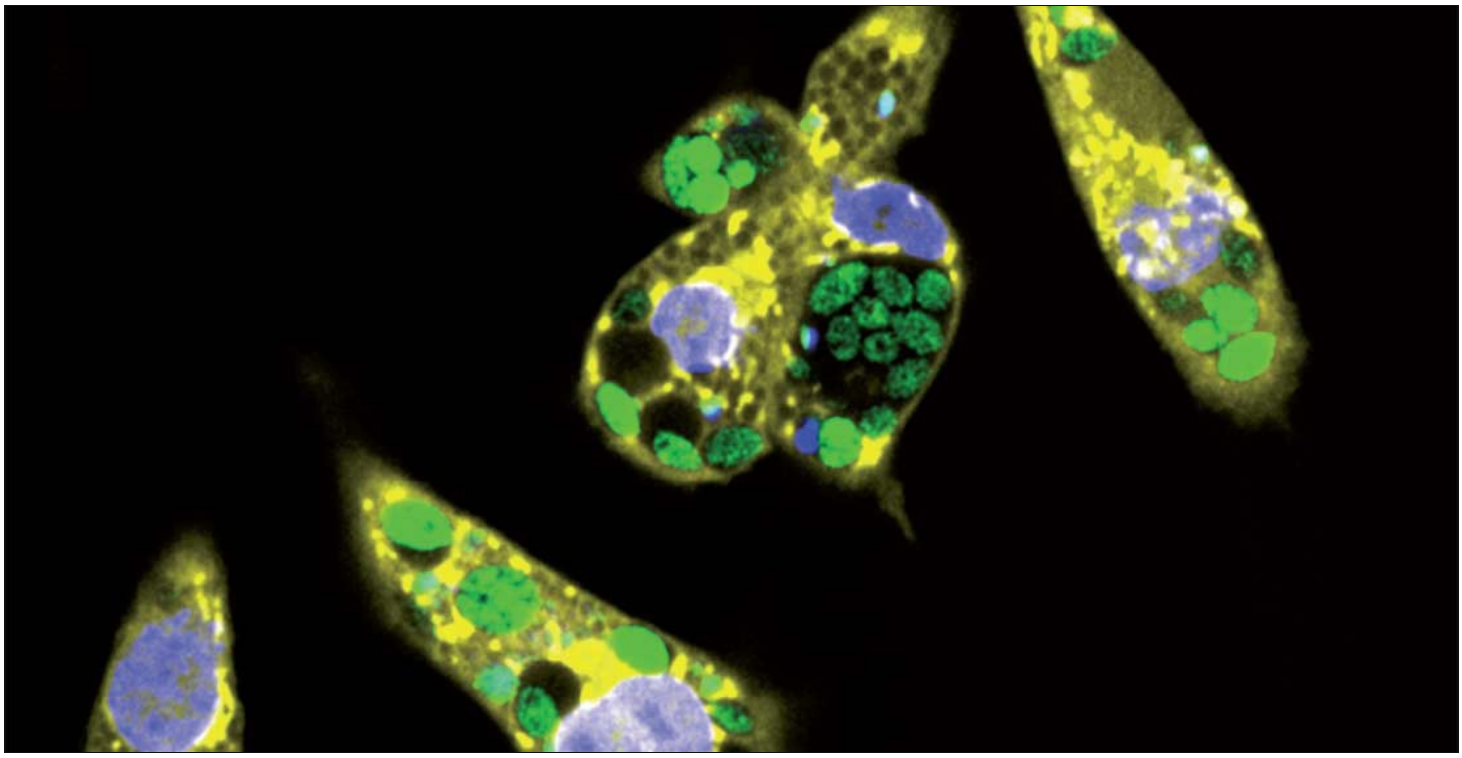

Dit is de omschrijving

Supervisors:

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- Prof. Dr. Paul Cos (University of Antwerp)

Abstract:

Leishmaniasis encompasses mild to fatal diseases caused by the infection with protists of the genera *Leishmania*. Parasitological evidence suggests that *Leishmania* amastigotes can remain in tissues of infected individuals as subclinical infections. These latent infections represent a threat as the onset or recrudescence of the disease is unpredictable. Latent infection in other microorganisms are associated with a downregulated physiological stage called quiescence. Although quiescence is a known process for bacteria it has been scarcely studied among protists.

The goal of this thesis was to unravel if *Leishmania* amastigotes can be quiescent. Our first hypothesis was that *Leishmania* infection can produce long term persistent but subclinical infections after the chemotherapy and clinical cure of mucosal leishmaniasis. Accordingly, we found that 41.2 % of the patients had subclinical persistence of a low number of parasites on their healed mucosa 6 to 18 months after treatment. The results highlight that *Leishmania* overcome the host immune system and chemotherapy to remain in their host. These subclinical infections resemble the well-known latent infections of Mycobacterium tuberculosis characterized by quiescent stages.

Secondly, we hypothesized that *Leishmania* amastigotes should share common parasitological and molecular features of others quiescent microorganism. We found that the steady infection index of amastigotes *in vitro* was associated with downregulation in the content of proteins, kDNA minicircle and with a dramatic drop in rDNA expression. Metabolomics showed amastigotes are characterized by a downregulation in the levels of biosynthetic molecules as amino acids and polyamines. Altogether, these results showed that amastigotes are endowed with molecular features of quiescence.

Thirdly, we hypothesized that the expression of GFP within the rDNA locus (rGFP expression) could be a biosensor to monitor the potential diversity of quiescent stages among amastigotes at single cell level. We found a positive and stage specific relation between rGFP expression and the proliferative condition of *Leishmania*. Moreover, rGFP expression showed that among amastigotes different quiescent stages may coexist; the population could include shallow and deep quiescent stages that may be sorted by their levels rGFP expression.

In summary this work supports the occurrence of quiescence among *Leishmania* amastigotes and offers the use of rGFP expression as a tool for further molecular and metabolic characterization of quiescent subpopulations. This may contribute to the understanding of the mechanisms that drive the maintenance of this clinically and epidemiologically relevant stage.