Refreshing the antileishmanial pipeline: Hybrid molecules as potential drugs against leishmaniasis

Project Background Information/Introduction:

The leishmaniases are a complex group of devastating diseases with a wide clinical spectrum that annually affects more than 1 million people throughout 98 countries, leading to approximately 20,000 deaths per year in its most severe form, the visceral leishmaniasis. Additionally, most endemic regions comprise communities living under substandard conditions, with low income and social-economic standards.[1,2] There are three major manifestations: cutaneous leishmaniasis, known for skin lesions that are either localised or spread all over the body; mucocutaneous leishmaniasis, a late progression of other cutaneous leishmaniasis variants, which is characterised by destructive mucosal lesions, mostly in the nasal septum, palate and lips; and visceral leishmaniasis, a manifestation that affects liver, spleen and bone marrow causing an important immunosuppression, which can lead to death if untreated. The chronic dermatological lesions open room to other opportunistic infections that might be lethal, also affecting the individual's mental health as the disfiguring aspect of the disease leads to strong social stigma that isolate them from society.[1] The range of drugs available to treat leishmaniasis are far from ideal: they induce serious side effects, leading to several disorders ranging from nephro-hepatotoxicity to teratogenicity, according to the drug used. The route of administration is also a concern, considering that most drugs are parenterally administered, requiring special infrastructure in endemic regions. Moreover, some of the available drugs have shown a decrease on responsiveness to treatment – which together with their expensive costs and undesired shortcomings, makes the discovery of new alternative treatments an urgent matter.[1] In the last decade, tamoxifen, a known anti-breast cancer drug, was shown to be active against some species of Leishmania.[3–6] In addition, previous work from our group has shown that clemastine fumarate, an anti-histaminic drug used for the treatment of allergic rhinitis, displays potent anti-leishmanial activity (data unpublished). Both molecules have been proposed to target the same enzyme, inositol phosphorylceramide synthase (IPCS), which is found in the parasite but not in the host. This enzyme has been investigated in the past years as a potential drug target in pathogenic fungi.

Research Aim/Objectives/Questions/Hypotheses:

In this project, we aim to design and synthesise tamoxifen/clemastine hybrid molecules to better understand these molecules' activity, validate IPCS as the drug target and improve their activity.

Data/Methods/Analysis:

Current work is focused on developing hybrid molecules derived from both tamoxifen and clemastine that can be used to fully elucidate the molecular target in the parasite. With this known we will be in a better place to develop new more effective and safe therapies. By overlapping models of the parental drugs (tamoxifen and clemastine), we have identified a new scaffold for the hybrids, that can also be used as a light activated labelling tool to enable the identification and isolation of the protein targets and hence better understand the mechanism of action. The first generation of hybrid molecules have been synthesised with their activity against Leishmania major promastigotes assessed in vitro. This is achieved using the colorimetric AlamarBlue assay – with which we can calculate if a molecule is active or not against that species. Excitingly, these simply hybrids show activity comparable to Tamoxifen. A second generation of hybrid molecule synthesis is in progress based on the most active molecule from the first series. Once optimised, the probe will be used as a biochemical tool to identify and validate the parasite protein targets.

Contributions to the SDGs:

This research provides insights on promising drug targets in leishmaniasis treatment, which directly represents a contribution to **SDG 3: Good Health and Well-being**. As it is common in all neglected tropical diseases (NTD), leishmaniases has predominant impact on communities living in poverty living on less than $1.25 a day (the costs of a treatment are many times this). If not fatal, the disease has long term impact with an estimated 40M suffering from mental health and other social stigma, leading to patient isolation from society, which brings an extra need on efficient treatments that stop the disease before it affects the whole life of a person and their surroundings. Thus, when researching about leishmaniasis and new potential treatments for leishmaniasis, it is impossible not to mention poverty and the need for better living settings – in some cases, for example, people die from the treatment rather than the disease or become more susceptible to other diseases. The disease has knock on effects of loss of income and consequent increase in malnourishment, loss of opportunity and education and an increase in social stratification (**SDG 1: No Poverty, SDG 2: Zero Hunger and SDG 10: Reduced Inequalities**). Even though this research does not directly address these other social impacts of the disease, it is important to mention that efficient, safe and affordable treatments might change entire communities in ways that were not primarily predicted by scientists, because the final goal is to improve human lives that are undeniably complex.

Lessons learnt and key takes/reflections:

This research project, together with all the other projects from the Durham GCRF-CDT cohort have shown that collaborative multidisciplinary research is extremely positive when bringing together people from different places and fields and putting they together to work towards one

goal. The different backgrounds and mindsets that are present in this research have taught me many skills whilst a PhD candidate that I will have within me for the rest of my life. Leishmaniasis is a very intriguing topic of research due its complexity, and because it affects so many people worldwide, it brings up important reflections on what is our role while scientists and how important it is to give it back to society.

Project Information:

- Supervisors and Partners:
  - Prof. Patrick G. Steel
  - Dr. Paul W. Denny
  - Dr. Silvia R. B. Uliana
- Project Duration: 3 Years
- Project Resources (funded by): Durham University, Durham Global Challenges Centre for Doctoral Training – GCRF-CDT
- Author: Victor de Sousa Agostino (victor.de-sousa-agostino@durham.ac.uk)

References:

1. Burza, S., Croft, S. L. & Boelaert, M. Leishmaniasis. Lancet 392, 951–970 (2018).

2. WHO. World Health Organizatio. Status of endemicity of cutaneous leishmanisis worldwide, 2016. (2016).

3. Miguel, D. C., Yokoyama-Yasunaka, J. K. U., Andreoli, W. K., Mortara, R. A. & Uliana, S. R. B. Tamoxifen is effective against Leishmania and induces a rapid alkalinization of parasitophorous vacuoles harbouring Leishmania (Leishmania) amazonensis amastigotes. J. Antimicrob. Chemother. 60, 526–534 (2007).

4. Miguel, D. C., Yokoyama-Yasunaka, J. K. U. & Uliana, S. R. B. Tamoxifen is effective in the treatment of Leishmania amazonensis infections in mice. PLoS Negl. Trop. Dis. 2, (2008).

5. Trinconi, C. T. et al. Tamoxifen inhibits the biosynthesis of inositolphosphorylceramide in Leishmania. Int. J. Parasitol. Drugs Drug Resist. 8, 475–487 (2018).

6. Miguel, D. C. et al. Tamoxifen as a potential antileishmanial agent: Efficacy in the treatment of Leishmania braziliensis and Leishmania chagasi infections. J. Antimicrob. Chemother. 63, 365–368 (2009).

7. Trinconi, C. T. et al. Topical tamoxifen in the therapy of cutaneous leishmaniasis. Parasitology 145, 490–496 (2018).