SDD-41 (ID 101)

Novel potential drug scaffold against visceral Leishmaniasis discovered using a drug repurposing approach

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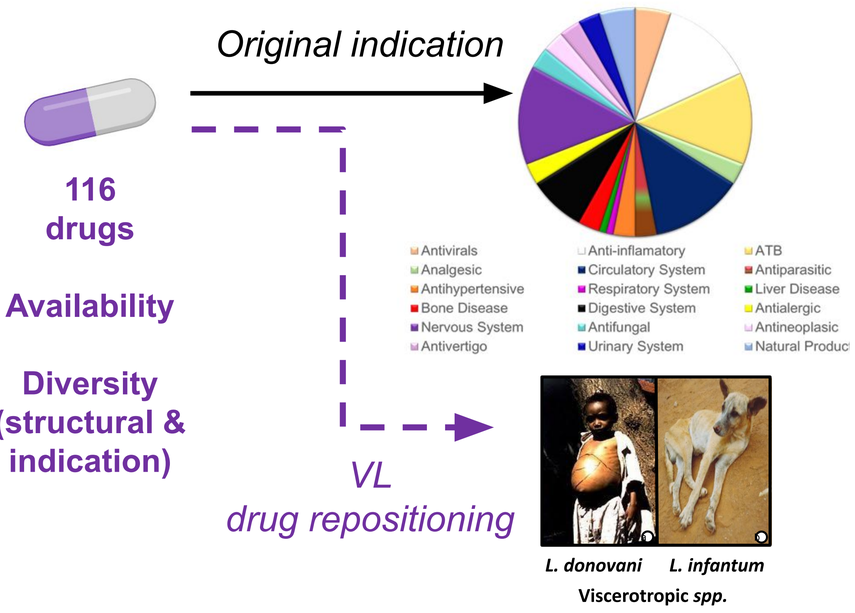
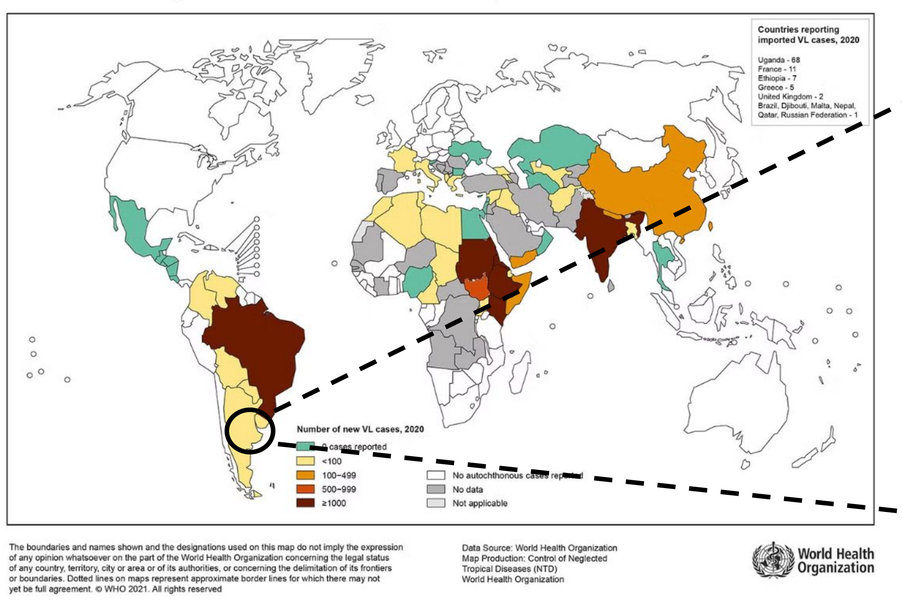
INTRODUCTION

STRATEGY



WORLD



URUGUAY

2010
vector
Lutzomyia longipalpis

2015
Autochthonous dogs infection

2018
Human infection

METHODOLOGY & RESULTS

Phenotypic screening

Promastigote (insect)

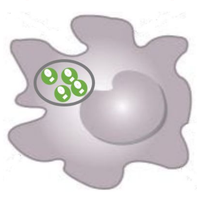
Primary[1]
116 drugs tested at 100 µM.

Cut-off viability ≤ 60%

Secondary[2]
THP-1 human-derived macrophages
***21 drugs** tested at 20 µM*

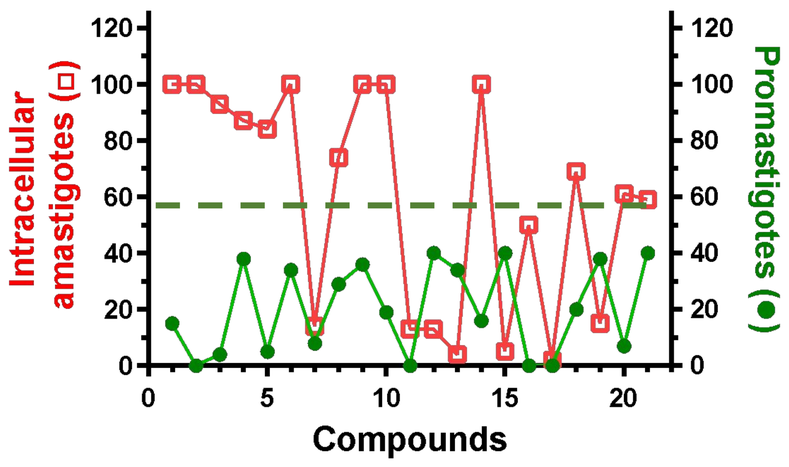
8 drugs showed viability ≤ 60%

Amastigote (mammals)



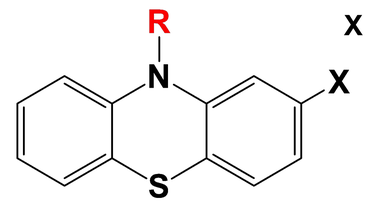
Tertiary[2]
murine macrophages (BMDM)
***5 drugs** without background against physio-pathological models of VL*
***(neither ex vivo nor in vivo studies)** were tested at 20 µM*

Parasite viability (%)

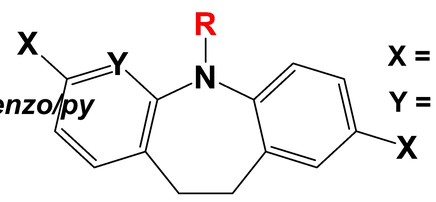


R = Alkyl or cyclic chains with secondary or tertiary amines

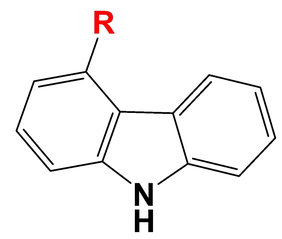
Phenothiazine



Benzo-cyclohepta-benzo/pyridine



9H-carbazole



EC_{50} ~ 1 - 7.5 µM (S.I > 2 to > 12.5)
Miltefosine ~ 5 µM (S.I. > 4)

DISCUSSION & CONCLUSIONS

The phenotypic screening *versus* both parasite stages showed different potency. This stresses the importance of performing the **studies in the clinical and relevant stage of the pathology (amastigote)**.
We have identified 8 new drugs that impair the viability of intracellular amastigotes, **five of these drugs proved active against *L. infantum* amastigotes infecting primary cultures of murine macrophages.** Interestingly, these compounds showed a similar or better bioactivity profile than the antileishmanial drug Miltefosine. Most of the chemical entities have a tricyclic scaffold that was originally developed for central nervous system (CNS) disorders. The structural features of these compounds include basic amine moieties and varying degrees of lipophilicity, which likely contribute to compounds' permeability, phagolysosome accumulation[3], and interaction with the parasite's molecular target(s).
These findings support the potential of **repurposing CNS drugs or related scaffolds** for the development of new anti-VL agents.
Based on potency and pharmacokinetic data, we will carry out **therapeutic efficacy studies** with the most promising drug/s in murine model of VL.

REFERENCES

[1] Romero, A.H.; Aguilera, E.; Gotopo, L.; Cabrera, G.; Dávila, B.; Cerecetto, H. *RSC Med Chem.* **2023**, *14*, 1992-2006.

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[3] Trapp, S.; Rosania, G.R.; Horobin, R.W.; Kornhuber, J. *Eur Biophys J*. **2008**, *37*, 1317-1328.

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