# Novel collaborative R&D networks for NTDs in endemic areas: the case of DND*i* Lead Optimization Latin America

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## BACKGROUND

Neglected tropical diseases (NTDs) are a diverse group of communicable diseases that prevail in tropical and subtropical conditions and affect more than one billion people. Highly debilitating and potentially lethal diseases, the NTDs not only have direct health impact in the patients, but generate a tremendous social and economic impact. The pharmacotherapy available for NTDs is unsatisfactory. Lack of efficacy, toxicity, long course treatments, emergence of resistant strains, and high cost are some of the associated problems. The Lead Optimization Latin America (**LOLA**) consortium (Figure 1), based in Brazil, is an innovative and collaborative network focused on the early stages of drug discovery. It is DND*i*'s youngest lead optimization network, follows the precepts of open innovation, and represents a step towards capacity building objectives in endemic areas. All three consortia focus on providing high quality chemical leads that could ultimately be developed into short-course oral treatments for Chagas disease and leishmaniasis, aligned with DND*i*'s target product profile.

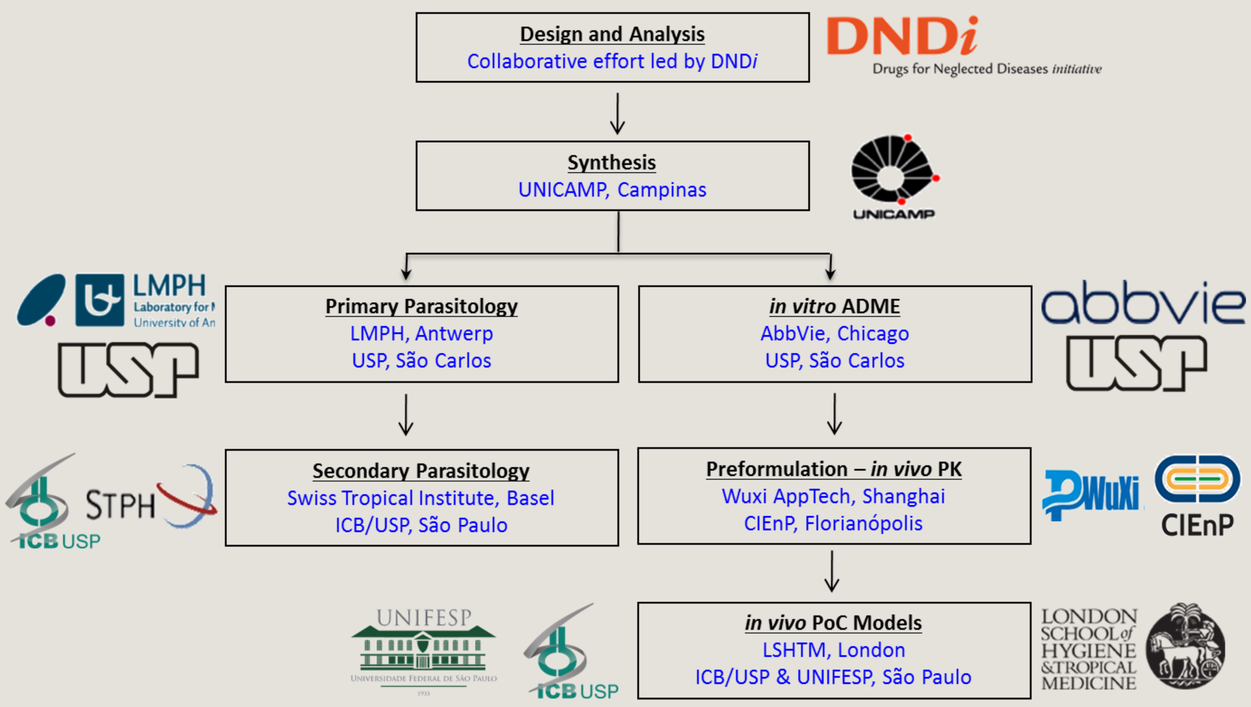


Figure 1. Organizational structure of the Lead Optimization Latin America (LOLA) Consortium

## MATERIALS & METHODS

LOLA gathers academic and non-academic partners from the region under the same goal of identifying and optimizing new chemical entities for leishmaniasis and Chagas disease. Initial hits are identified via large screening campaigns, validated via multicentre confirmatory assays, and prioritized according to chemical diversity and possible mode of action. After the initial step, new chemical series enter hit-to-lead (H2L) phase, where they are submitted to iterative design-synthesis-trial-analysis cycles, aiming at improving pharmacodynamics, pharmacokinetics, and selectivity. Assays employing the intracellular forms of the parasites are used in parallel in multiple *in vitro* ADME assays to support hit optimization (Figure 2). The criteria defined in the target candidate profile (TCP) (Table 1) guide the optimization cycles until a pre-clinical candidate with acceptable characteristics is found, or the chemical series is abandoned.

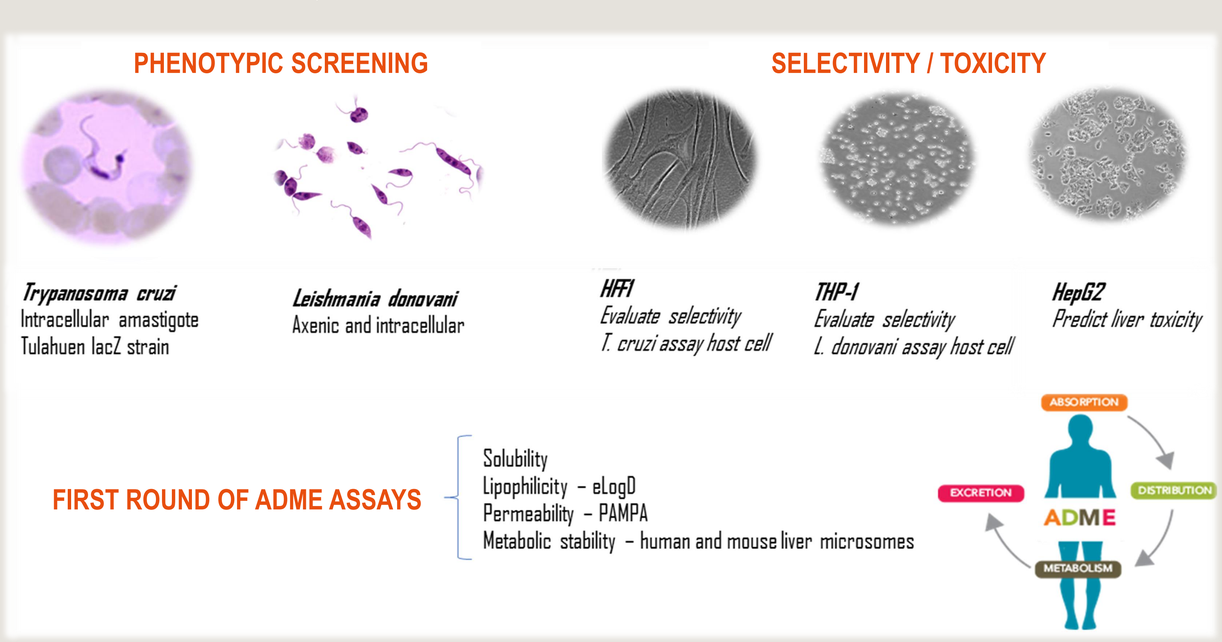


Figure 2. First-tier assays used for parallel multiparameter optimization of compounds

## RESULTS & DISCUSSION

Chemical synthesis activities are concentrated in Brazil (UNICAMP), and screening activities have been conducted at USP and in collaboration with several international partners (mainly LMPH, Wuxi, and AbbVie). Recently, new partners have been integrated into the consortium, opening the possibility to conduct *in vivo* pharmacokinetics and toxicology studies, as well as animal models of Chagas disease and leishmaniasis.

Table 1. Target candidate profile for new chemical entities for treatment of visceral leishmaniasis

| | Acceptable (functional cure) | Ideal (sterile cure) |
|---|---|---|
| Efficacy *In vivo* | >95% reduction in parasitaemia in liver & spleen in mouse or hamster model with *L. donovani* | 100% reduction in liver & spleen in mouse or hamster model - *L. donovani* & *L. infantum* |
| Efficacy *In vitro* | Consistent activity within 10 fold vs. a panel of drug-sensitive and drug-resistant strains and isolates from India and E. Africa<br>*In vitro*: $E_{max}$ >99% | Consistent activity within 10 fold vs. a panel of drug-sensitive and drug-resistant strains and isolates from India and E. Africa<br>*In vitro*: $E_{max}$ >99%, Cidal mechanism of action |
| Safety *In vitro* | No *in vitro* signals preventing development | No *in vitro* signals preventing development |
| Safety *In vivo* TI | (AUC at NOAEL)/(AUC at $MED_{95}$ ) > 3 | (AUC at NOAEL)/(AUC at $MED_{100}$) > 3 |
| CMC | Synthesis and formulation acceptable to enable PO or IV dosing for 1-10 days in humans | Synthesis and formulation acceptable to enable PO or IV dosing for 1-10 days in humans |
| DMPK | Human dose prediction < 30mg/kg/day given QD or BID | Human dose prediction < 30mg/kg/day given QD or BID |

To date, about 600 compounds, covering seven different chemical series, have been synthesized and screened within the LOLA network. The most advanced series is the benzimidazoles series, with a dual activity profile against *T. cruzi* and *Leishmania spp*. Several analogs were optimized and present better balance between potency, selectivity, and metabolic stability (Figure 3) when compared to the initial hits. A front runner was well tolerated in mice and showed moderate oral exposure, and is currently being tested in proof-of-concept studies.

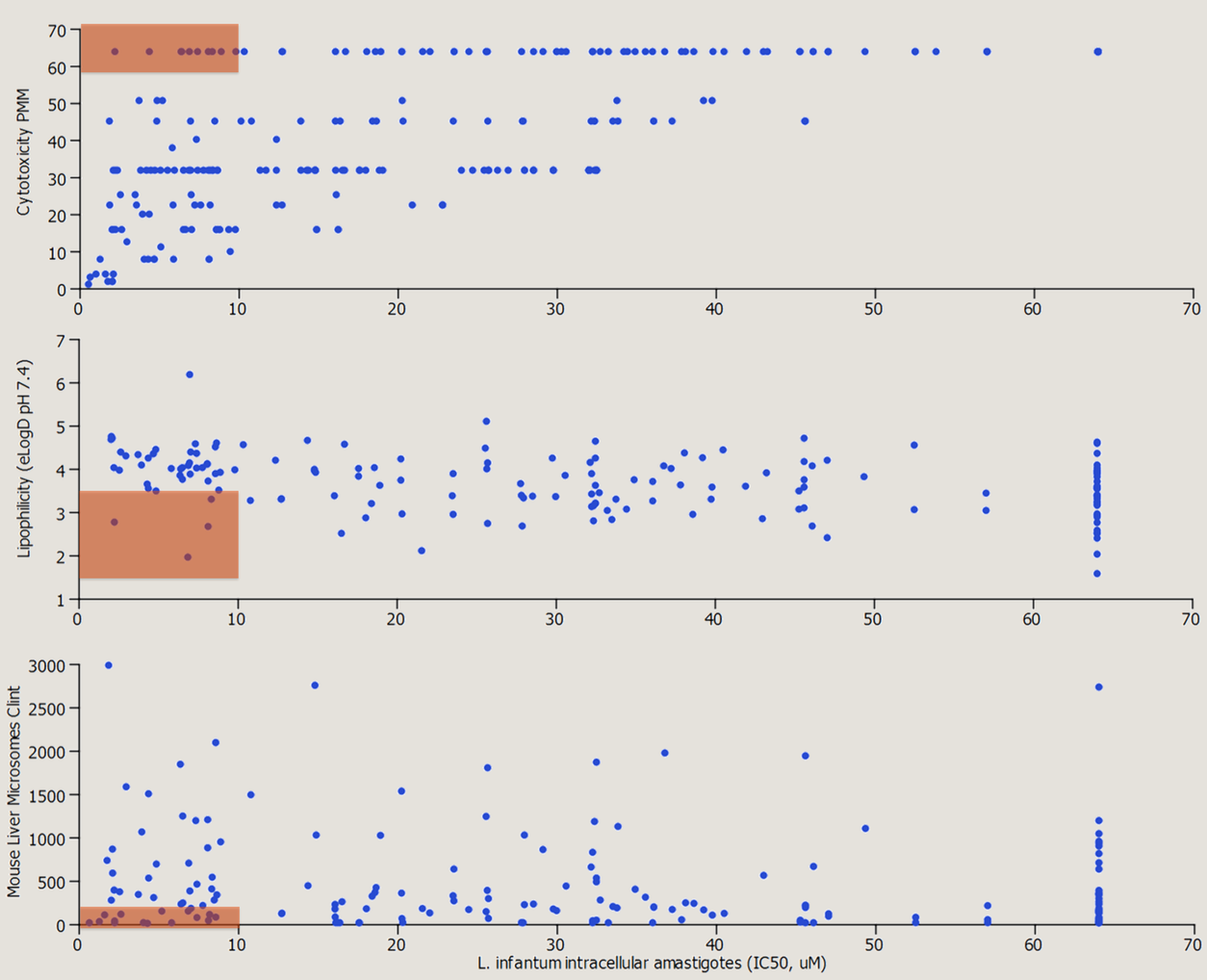


Figure 3. Distribution of multiple properties vs. *in vitro* activity against *L. infantum* intracellular amastigotes for the benzimidazoles series (the most promising analogs are highlighted in orange)

## CONCLUSIONS & PERSPECTIVES

Drug discovery activities conducted in Latin America represented important learning ground for all local teams involved. Relevant structure-activity/properties relationships were established and guided the design of improved analogs that are currently progressing into *in vivo* models. Supporting the development of R&D initiatives in endemic areas will increase the delivery of high quality compounds in the long term that, it is hoped, will progress in the pipeline of novel drugs for NTDs.

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