

LEISHDRUG consortium

Title:

Targeting the Leishmania kinome for the development of novel anti-parasitic strategies

Abstract:

Visceral leishmaniasis is caused by the protozoan parasites *Leishmania donovani* and *Leishmania infantum* and is a potentially fatal disease in endemic areas around the world. During the infectious cycle, *Leishmania* alternate between the insect promastigote stage and the vertebrate aflagellate amastigote stage that proliferates inside infected host macrophages provoking the pathology of the disease. This consortium uses a highly interdisciplinary approach to reveal *Leishmania* signaling molecules associated with amastigote virulence, with the major aim to exploit parasite-specific pathways for anti-leishmanial drug development.

We use innovative drug screening concepts not applied previously on parasitic systems. We will utilize visual high-content screening to discover compounds capable to kill intracellular *Leishmania* amastigotes without deteriorating the host cell. This phenotype-based strategy relies on fluorescent parasites and macrophages as read-outs and will allow simultaneous assessment of anti-leishmanial activity and host cell toxicity under physiological conditions. We will apply a target-based strategy utilizing recombinant *Leishmania* protein kinases for inhibitor identification and structure-guided drug design.

The identification of appropriate target kinases, with only limited homology to their mammalian counterparts will rely on (i) *in silico* analysis by applying novel bioinformatic tools developed by consortium members, and (ii) *in vitro* assay based on their phospho-transferase activity towards recombinant *Leishmania* phospho-proteins.

The major objectives of this proposal are (i) to screen small molecule and peptide libraries for hit compounds with leishmanicidal activity using phenotype- and target-based strategies, (ii) to identify anti-parasitic lead compounds and assess their pharmacokinetic profiles using cell-culture and experimental infection models for leishmaniasis, and (iii) to initiate lead optimization by structure-based drug design.