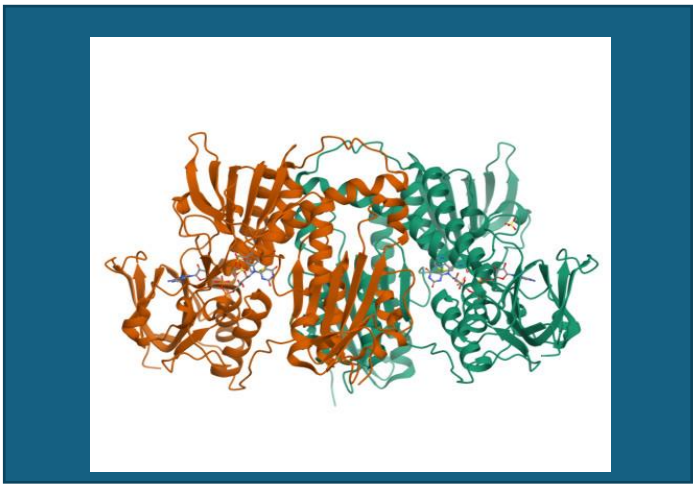
Project title: Tryp4Leish: a One Health approach for the structure-based discovery of anti-leishmania agents interfering with the trypanothione-based defense system in trypanosomatids

Acronym: Tryp4Leish



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Description:

Neglected infectious diseases are responsible for a significant health and socioeconomic burden in large parts of the world, particularly in resource-poor countries. Among them, leishmaniasis is increasingly becoming a concern for Europe too, driven by factors like the climate change and globalization. Despite a significant effort to develop new drugs to treat leishmaniasis over the past years, existing therapies suffer from various shortcomings, therefore development of new, more effective, safe and affordable treatments for leishmaniasis is an urgent need.

Aims:

The Tryp4Leish general objective is the exploitation of two key enzymes involved in the trypanothione-polyamine Leishmania metabolism, namely trypanothione reductase (TR) and ornithine decarboxylase (ODC), as drug targets for the discovery of novel anti-parasitic agents.

Expected results:

The expected results are: 1. establishing auranofin, a TR inhibitor previously identified by members of the Tryp4Leish consortium, as a potential repurposing candidate for the treatment of canine Leishmania infection; 2. optimization of a class of 5-nitrothiophene (5-NTHs) TR inhibitors previously identified by some of the Tryp4Leish members, in order to select 1-2 lead compounds that will undergo in vivo studies in a murine model of the infection; 3. identification of a novel class of TR inhibitors derived from the combination of the pharmacophore of 5-NTHs with that of auranofin; 4. determination of an X-ray crystal structure of LiODC useful for structure-based design and 5. hit identification/optimization of novel ODC inhibitors able to kill L. infantum promastigotes/amastigotes.

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