The unicellular parasites from the order Trypanosomatida include *Trypanosoma brucei*, *Trypanosoma cruzi* and *Leishmania* spp. which cause infectious diseases African Trypanosomiasis (HAT), Chagas disease and the Leishmaniases, respectively; all are classified by the WHO as neglected tropical diseases. All remain a persistent global problem, in particular in rural areas with high poverty rates. Chagas disease affects about 8-10 million people and is responsible for 14,000 annual deaths; the costs of treatment and lost productivity are estimated to amount to 7 billion US$ per year. The leishmaniases constitute a spectrum of diseases ranging from the usually self-healing but potentially disfiguring cutaneous leishmaniasis, over the highly disfiguring mucocutaneous, to the visceral leishmaniasis (VL), which is invariably fatal if left untreated. An estimated 600 million people are at risk of VL according to the WHO and there are 50,000-90,000 new cases per year, giving rise to 26,000 to 65,000 deaths annually. Currently available treatments have serious limitations ranging from adverse toxicity over complex administration to emerging resistance. HAT treatment, until recently, relied on only few old-fashioned and highly toxic drugs. The situation has improved with the recent development of new treatment regimens and new drugs fed into the development pipeline, such as the recently approved fexinidazole against *T. brucei gambiense*. Still, fexinidazole and other nitroimidazole drugs are prone to future resistance formation by the parasite. Importantly, drugs for effective, non-toxic and easy-to-administer treatment of the leishmaniases and Chagas disease are clearly lacking: there is an urgent need for new drugs. To date, all approved drugs against Trypanosomatida-caused diseases were discovered by phenotypic screening and the vast majority are repurposed drugs (previously developed for alternative indications). The disadvantage of these approaches is that the mode of action remains often fully or partially unknown and drugs can thus not be improved or adapted to mutations that may cause drug resistance. The alternative approach for drug discovery, target-based drug design, has been hampered by the lack of a sufficient number of good drug targets.

We propose that the unique decapping enzyme of Trypanosomatida, ALPH1, is an attractive target for drug development against trypanosomiasis for several reasons. (1) ALPH1 is essential for trypanosomes. mRNA decapping is the second crucial step in the 5´ to 3´ mRNA decay pathway, preceded by the removal of the poly(A) tail and followed by 5´ to 3´ exoribonucleolytic degradation. Since the canonical decapping enzyme DCP2 is absent in Trypanosomes, decapping by ALPH1 is the only option trypanosomes have to degrade mRNAs via the 5´ to 3´decay pathway, which is the major pathway of mRNA decay in the parasites. (2) The entire family of enzymes similar to ALPH1 is absent from mammals. This lowers the chances that drugs targeting ALPH1 would cause toxic side effects by affecting human proteins. (3) ALPH1 is already characterized in great detail, both biochemically and in the cellular context. ALPH1 can be produced recombinantly in bacteria as an active and soluble protein. Thus, ALPH1 can be used in purified protein form and in parasites to test activity of potential drug candidates.

In this project we will undertake the systematic search for and characterisation of inhibitors of the Trypanosomatida ALPH1 with three major aims: (i) to provide an essential research tool to study function and mechanism of this unique mRNA decapping pathway; (ii) to provide a drug candidate for treatment of Trypanosomatida-caused diseases and (iii) to employ the unusual enzyme activity of ALPH1 for biotechnology applications such as modification of RNA.