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PhD position available

Targeting a unique mRNA decapping enzyme for trypanosomatid infectious disease drug discovery, chemical biology and biotechnology applications

We have an open PhD position in the laboratory of Susanne Kramer at Würzburg University. The student will work in an international team that includes the laboratories of Maria Gorna at Warsaw University and of Martin Zoltner, at the Biocev in Prague. The joined project aims to characterise a highly unusual mRNA decapping enzyme of *Trypanosoma brucei* (sleeping sickness); see below for more details. The candidate should be highly motivated, enthousiastic, open minded, and fluent in English language. Knowledge in molecular and cellular biology techniques is of advantage, but can also be aquired during the PhD. If you are interested, please apply via email to **susanne.kramer@uni-wuerzburg.de**.

more information:

Kinetoplastids encode no homologues of canonical mRNA decapping enzymes. We have recently identified the ApaH-like phosphatase ALPH1 acting as the major or only mRNA decapping enzyme in the sleeping sickness causing Trypanosoma brucei and likely in all Kinetoplastids. mRNA decapping by an ApaH like phosphatase is unprecedented in the eukaryotic kingdom. In contrast to canonical decapping enzymes, ALPH1 cleaves its substrate between the beta and gamma Phosphate instead of between the alpha and beta phosphate.

The aim of this proposal is the identification and characterisation of an ALPH1-specific inhibitor for three main reasons: First, we aim to understand this novel mechanism of mRNA decapping in more detail. A specific inhibitor offers the opportunity to study the pathway in all pathogenic Kinetoplastids, including parasites and stages that cannot be genetically manipulated and cultured and is also essential to control in vitro activity studies of the enzyme. Second, the fact that the enzyme is essential in Kinetoplastids combined with the absence of the entire enzyme family of ApaH-like phosphatases from mammalian systems renders ALPH1 attractive for target-based drug discovery to treat African Sleeping sickness, the Leishmaniases, Chagas disease and related animal diseases. Third, an ALPH1 inhibitor is required to employ ALPH1 for biotechnology applications, for example for the production of diphosphorylated mRNAs.

We have assembled an international team combining expertise in trypanosome biology, first stage drug discovery and structural biology of mRNA interacting proteins. We have already purified active enzyme at sufficient amounts and we have developed a robust, high-throughput compatible assay. It is now feasible to identify specific inhibitors of ALPH1 activity by compound library screens followed by assessment of validated hit compounds for potency in cell culture and for decapping inhibition monitored in situ. Structural characterisation of ALPH1 with bound inhibitor will be leveraged for mechanistic insight and exploratory chemistry guiding rational design. Ultimately, we aim to develop these compounds into essential research tools, for biotechnology application (harnessing the unique ALPH1 enzymatic activity) and novel anti-trypanosomatid preclinical candidate drugs.

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https://www.biozentrum.uni-wuerzburg.de/zeb/research/groups/kramer-lab/