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Targeting *Trypanosoma brucei* FPPs by fragment- based drug discovery

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Trypanosoma brucei is the causative agent of Human African Trypanosomiasis (HAT), one of the most neglected diseases with only limited medication options for treatment. Therefore, new drugs with a better safety and efficiency profile for the two stages of the disease are highly demanded. Nitrogen-containing bisphosphonates have demonstrated anti-parasite activity. They inhibit farnesyl pyrophosphate synthase (FPPS) and are in clinical use for bone diseases. They are also investigated for a broader application, such as antitumor or antiparasitic agents. However, due to their pharmacokinetic properties, alternative chemotypes are highly desired. Previous efforts at Novartis have identified an allosteric pocket on human FPPS by a fragment based approach, and a similar pocket also exists in *T. brucei* FPPS. The combination of these results laid the foundation of this work. In the first step, *T. brucei* FPPS protein was subjected to an NMR fragment screen using 1H, water-LOGSY and T1rho NMR experiments. Mixtures of eight compounds were screened, and fragments fulfilling hit criteria were followed up in single compound NMR experiments. We further validated fragment hits in protein-observed 2D-NMR experiments and estimated Kd values by NMR. Additionally, we investigated fragment binding on *T. cruzi* and human FPPS to enable selectivity studies and the comparison of results. This approach identified 25 diverse fragment hits for *T. brucei* FPPS, which were subjected to crystallization experiments to identify the exact binding location and binding mode. In summary, we demonstrated the application of a fragment-based approach for the identification of *T. brucei* FPPS binding compounds and further want to drive the drug discovery process from initial fragment hits to tool compounds with high binding affinity that inhibit the FPPS enzyme function selectively and interfere the parasitic growth.

Figure1: *T. brucei FPPS complexed with bisphosphonate (PDB: 2i19)*

Biography

Lena Muenzker is a Marie Curie PhD Fellow in the FragNet program under the supervision of Dr. Wolfgang Jahnke and Dr. Andreas Marzinzik in the Chemical Biology and Therapeutics Department at Novartis Basel, Switzerland, and Prof. Gerhard Klebe at the Philipps-Universität Marburg, Germany. She graduated with a Master's Degree in Biological Chemistry from the University of Vienna in 2015. During her studies, she did a 6-month internship on the synthesis of oligosaccharides at Synphabase, Switzerland, and carried out her Master's Project in Prof. Paul Robert Hansen's lab at the University of Copenhagen focusing on lipidated cyclic and bicyclic antimicrobial peptide synthesis. After her studies, she took the opportunity to join Prof. Nathanael Gray's lab at the Dana Farber Cancer Institute and learned new methods related to protein kinase inhibitors. She will expand her experience in her PhD project, which comprises structural biophysics and FBDD to identify novel inhibitors of *Trypanosoma brucei* FPPS.

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