SELECTIVE TARGETING OF *T. CRUZI* AND *T. BRUCEI* CYSTEINE PROTEASES

Birgit J. Waldner\(^1\), Rafaela S. Ferreira\(^2\), Viviane Corrêa\(^2\), Klaus R. Liedl\(^1\)

\(^1\)Institute of General, Inorganic and Theoretical Chemistry, Department of Theoretical Chemistry, University of Innsbruck, Innsbruck, Austria; \(^2\)Instituto de Ciências Biológicas, Departamento de Bioquímica e Imunologia, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

*Trypanosoma cruzi* and *Trypanosoma brucei* are parasites that cause Chagas' disease and African sleeping sickness. Both parasites require the essential cysteine proteases Cruzain (*T. cruzi*) and Rhodesain (*T. brucei*) for survival. While current treatments lack efficiency in late-stage disease, cause a number of undesirable side-effects and drug resistancies have emerged, investigation of cysteine protease inhibitor efficacy has led to therapeutic agents already in clinical trials for *T. cruzi*.

To find new effective treatments against both Chagas' disease and African sleeping sickness, the development of potent and selective inhibitors against Cruzain and Rhodesain is of crucial importance. To minimize side-effects, selectivity against the human analogue cysteine proteases Cathepsin B and L has to be achieved. In this work, we present molecular dynamics (MD) studies of Cruzain, Rhodesain, Cathepsin B and L to investigate differences in binding site flexibility between parasitic and human cysteine proteases. In addition we used chemometric approaches to uncover binding site similarities and differences that can be exploited for selective targeting of cysteine proteases. Through the use of an ensemble of conformations obtained through MD simulations for chemometric analysis, we considered the influence of binding site conformational variability on binding site characteristics.

We determined key drivers of selectivity and specificity in the investigated cysteine proteases. The results are complementary to existing studies and can directly be used for the design of new virtual screening and (ensemble) docking experiments for the discovery of new inhibitors as well as for the optimization of known inhibitor structures.

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