Trypanosomatid parasites are agents of life-threatening human diseases such as leishmaniasis (caused by *Leishmania*), Chagas' disease (*Trypanosoma cruzi*) and sleeping sickness (*Trypanosoma brucei*). These parasites are transmitted by blood-feeding insects to human hosts and are widespread mostly in tropical and subtropical countries. However, cases of leishmaniasis also happen in southern parts of Europe, and global warming will probably increase incidence of these diseases in European countries. There are many problems with the existing treatments, which include: (*i*) toxicity, (*ii*) development of parasite resistance, (*iii*) limited availability due to, for instance, high cost. **Since the development of the new anti-trypanosomatid drugs is relatively unprofitable for pharmaceutical companies, government-funded research is necessary to encourage progress in this field.**

In principle, targeting the folate pathway is one interesting strategy to kill various pathogens. Both human and parasite cells need folate for growth, and blocking the folate pathway is mechanism of action of some anti-cancer drugs, for instance – methotrexate. One convenient strategy for blocking the folate pathway in parasites is repurposing these existing anti-cancer drugs. However, trypanosomatid parasites differ from humans since they have a specific protein, pteridine reductase 1 (PTR1), that causes resistance to methotrexate. Several attempts have been recently reported to design inhibitors of this enzyme, but they are hindered partly due to the limited knowledge about structural characteristics of this protein. In particular, the dynamical properties of this enzyme are barely known. On the other hand, there are many studies showing that the enzyme dynamics are crucial for its function. **Therefore, in the current project, we decided to investigate the PTR1 dynamics in the context of its interactions with substrates and inhibitors. Such information would be very helpful in the design of compounds targeting PTR1 and thus killing trypanosomatid parasites.**

Investigating biomolecule dynamics by experimental methods is costly and partly limited, since from experiments we usually obtain either average structures (e.g., crystallography), ensembles thereof (e.g., nuclear magnetic resonance) or time scales of certain movements (e.g., fluorescence anisotropy). Therefore, we decided to employ computational methodology, in particular – molecular dynamics and related techniques. These methods allow for simulating molecular movements in real time. **Molecular dynamics methods may reveal important functional motions of the PTR1 protein, and how they are related to its enzymatic activity and inhibitor binding. From the dynamical studies we can also derive knowledge about the most important factors determining protein–inhibitor complex formation. Furthermore, we will compare dynamical properties of the PTR1 protein variants from different parasitic species.** Such studies will result in better understanding of the protein target and will be useful for the future design of PTR1 inhibitors.