BioISI - Biosystems & Integrative Sciences Institute

Development of a new hybrid therapeutic agent against malaria by targeting the Aquaglyceroporin from *plasmodium spp*

Place of work/: BioISI, Chemistry for Biological Systems Group, Computational Laboratory, 8.5.55D

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Malaria is one of the current global public health problems. Besides the significant progress made on this disease, it is still responsible for thousands of deaths each year [1]. Continued resistance to currently available antimalarial drugs enforces the need for new therapies. Existing drugs are limited to only a few parasite targets, most of which are restricted to the asexual blood stage that causes the clinical symptoms. However, in order to efficiently fight malaria, agents against all states of the parasite's life cycle should be developed.

The *Plasmodium spp* aquaglyceroporin (PfAQP) is a constitutive water and glycerol protein channel in the parasite membrane [2]. During the blood stage, the fast reproduction of the Plasmodium in the host red blood cells requires massive biogenesis, which includes the synthesis of lipids for new membranes. To successfully achieve this task, the parasite incorporates glycerol into the lipids of the new synthesized parasite membranes by obtaining it from the host pool and translocating it through PfAQP [3]. As glycerol is crucial for the replication of the parasite, PfAQP is expected to have a central role in the metabolomic pathway and is consequently a promising target for the development of new antimalarial therapies [4].

Recent reports showed that different polyalcohols with similar chemical properties as glycerol are able to block and consequently inhibit PfAQP permeation function [5,6]. Therefore, in this master thesis project, the objective is to structurally characterize PfAQP and evaluate the efficiency of different polyalcohols (1,3-propanediol, ribitol, xylitol, erythritol D-arabinol) in inhibiting the permeation function. The most promising polyalcohols will afterwards be coupled with current available antimalarial drugs through a chemical linker, enabling the development of new hybrid molecules that can block PfAQP proteins, and at the same time, use them as carriers of antimalarial drugs that after chemical cleavage, release the antimalarial payload. To achieve these goals, we will use several computationally-based methodologies such as Molecular Dynamics (MD), Steered MD simulations, and Potential of Mean Force calculations. In the end, the results will be used not only for writing the Thesis but also a scientific paper.

Bibliography

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