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Extended Abstract

Searching for Selective Scaffolds against *Plasmodium falciparum* Glucose-6-Phosphate Dehydrogenase 6-Phosphogluconolactonase †

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Malaria is a parasitic disease caused by *Plasmodium* spp., being one of the major causes of death worldwide with two-hundred million new infections and hundreds of thousands of deaths in 2015. Despite the important advances in its prevention and treatment, its resistance to current drug therapies is still a serious risk in its eradication.

There is urgency in finding novel targets and drugs operating by novel mechanisms, avoiding cross-resistance to classical antimalarials. In this context, the bifunctional enzyme Glucose-6-phosphate dehydrogenase 6-phosphogluconolactonase appears to be a promising therapeutic target due to its crucial role in regulating the PPP pathway (pentose phosphate pathway), which is the major source of redox potential in *Plasmodium falciparum*.

In the last few years, our group detected a specific mutation between the human and the *Plasmodium falciparum* form in the binding site of Glucose-6-phosphate (G6P), the endogenous ligand of Glucose-6-phosphate dehydrogenase (G6PD). This mutation involves the substitution of an Arginine (human) by an Aspartate (parasite), which allowed us to create a validated in-house homology model of *Pf*G6PD.

Based on this result, the group has focused their efforts, through different molecular modelling techniques, in the discovery of selective scaffolds against *Pf*G6PD. Current efforts address the development of a complete structural model of the bifunctional enzyme, which may offer novel opportunities to develop molecules capable of inhibiting this relevant enzyme.