Poster

Targeting the sphingolipid biosynthesis pathway of protozoan parasites as drug targets

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The protozoa are a large group of single-cell eukaryotes which include important human pathogens such as Toxoplasma gondii (the causative agent of Toxoplasmosis) and Plasmodium falciparum (which causes malaria). Often, these parasitic infections are asymptomatic, however, they become life threatening in critical conditions, such as pregnancy, or in immunocompromised patients. In fact, it is estimated that up to 50% of the world's population is chronically but asymptomatically infected with Toxoplasma. Other members of the protozoa kingdom are considered genuine pathogens, such as Plasmodium [1].

Recent research has identified several enzymes involved in the biosynthesis of sphingolipids as attractive drug targets, as these take part in a plethora of cellular functions such cellular membrane stability, and important signalling pathways, including cell differentiation and apoptosis [2].

This project aims to investigate the structure and function of the enzymes involved in the biosynthesis of sphingolipids, with primary focus on Serine Palmitoyltransferase (SPT), which catalyses the first, rate-limiting step in the de-novo synthesis of sphingolipids. To achieve this, a vastly multidisciplinary approach will be undertaken, starting with the use of novel, state-of-the-art bioinformatic tools, such as AlphaFold2 [3], which will be used for the rational design of protein constructs, with the aim to optimise the protein production, purification, and crystallization processes.

So far, recombinant protein has only been characterised by Bio-SAXS [4]. The newly designed constructs, along with homologous parasite constructs will also be characterised by Bio-SAXS, and crystallisation experiments will be conducted. Following the attainment of crystal structures, novel ligand and fragment screening methods will be employed, and successful leads will be optimised with a rational approach, to maximize efficacy across pathogens and minimize detriment to human health.

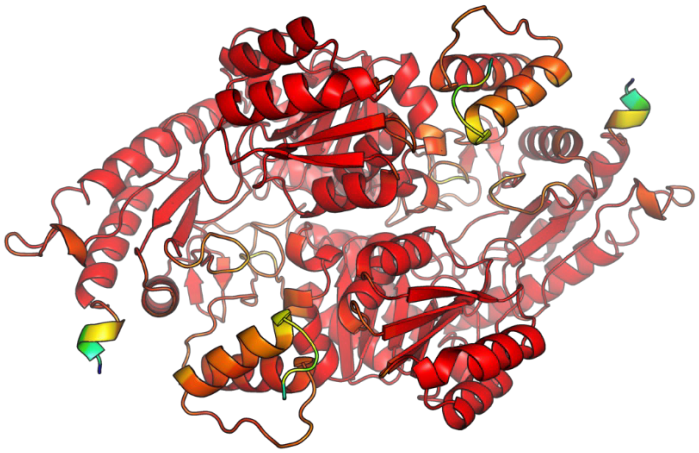

Figure 1. AlphaFold2 Model of the predicted *Toxoplasma gondii* Serine Palmitoyltransferase dimer coloured by model confidence.

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