Oral presentation

Structure-based drug design for new therapies for Leishmaniasis and Chagas disease

E. Pohl[1], A.M. Silber[2], S. Freitag-Pohl[1], K Sowerby[1]

[1]Department of Chemistry, Durham University, Durham DH13 LE, UK
[2]Department of Parasitology, University of São Paulo, São Paulo, Brazil
ehmke.pohl@durham.ac.uk

The World Health Organisation has identified a diverse range of diseases which share a set of common features as neglected tropical diseases (NTDs). NTDs mainly occur in the (sub-)tropics, they afflict mainly the poorest part of the society and often lead to chronic, debilitating and stigmatising diseases. Among the NTDs, Leishmaniasis and Chagas disease are due to infections by protozoan parasites of *Leishmania spp*. and *Trypanosoma cruzi*, respectively. Current therapies for both types show limited and in many cases diminishing efficacy due to rising resistance with severe, sometimes lethal side effects. There is a clear and recognized need to identify and characterise new drug targets towards novel therapies [1].

It has been long recognized that the thiol-based redox system plays a crucial role in the survival of a range of protozoan parasites in the mammalian host. The sulfur-containing amino acid cysteine represents the key molecule in any thiol metabolism. Although it is assumed that the parasites can scavenge cysteine from the hosts, trypanosomatids, including *Leishmania spp* and *T. cruzi*, possess the necessary enzymes for *de-novo* biosynthesis and there is mounting evidence that these proteins represent potential new drug targets [2].

In this project we focused on the first two steps where serine in acetylated to O-acetyl serine by serine-O-acetyltransferase (SAT) and coveted into cysteine by the PLP-dependent cysteine synthase (CS). We have expressed, purified and characterised both enzymes from different parasites. High-resolution crystal structures of CS from *T. cruzi*, *Leishmania infantum* and T. *theileri* reveal different states in the catalytic cycle (Figure 1). This allowed us to begin the fragment-based drug discovery campaign supported docking and molecular modelling studies.

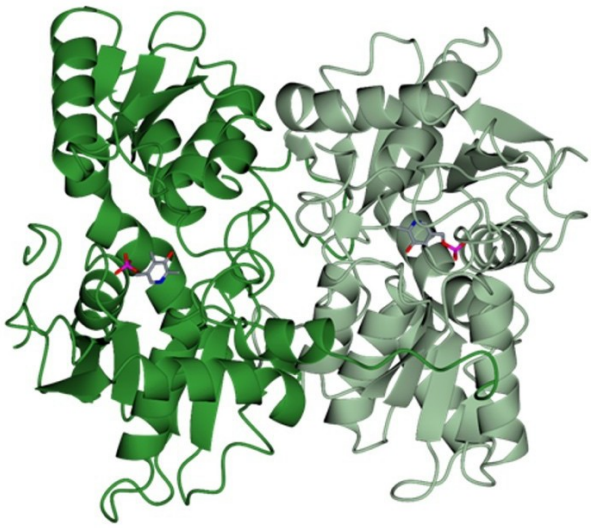

Figure 1. Crystal structure of homodimeric cysteine synthase from *T. cruzi* determined at 1.8 Å Bragg spacing[3]

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[2] Williams, R. A.; Westrop, G. D.; Coombs, G. H. Two pathways for cysteine biosynthesis in Leishmania major. Biochemical Journal. *Biochemical J.* **2009**, *420* (3), 451– 462,; Romero, I.; Téllez, J.; Romanha, A. J.; Steindel, M.; Grisard, E. C.. *Antimicrob. Agents Chemother.* **2015**, *59* (8), 4770–478.

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