Homology modelling of *Trypanosoma brucei* major surface proteases and molecular docking of variant surface glycoproteins and inhibitor ligands for drug design

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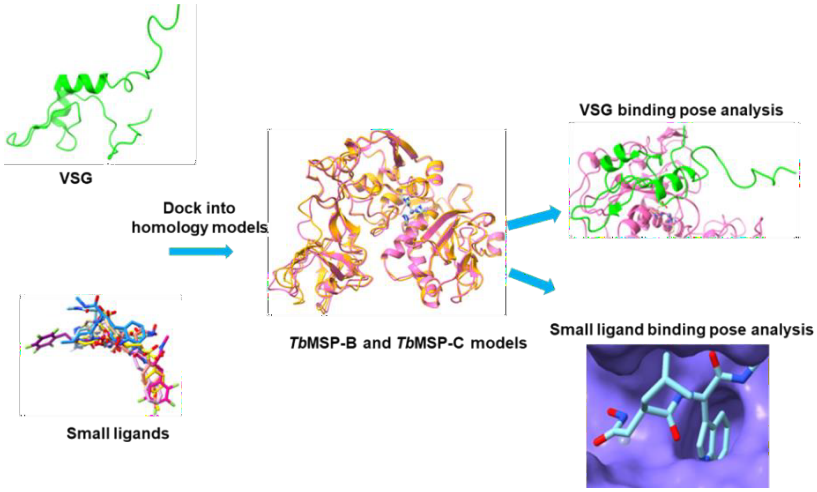

Docking of VSG molecules and inhibitor ligands into trypanosome major surface proteases

Introduction: The current chemotherapeutics for animal African trypanosomiasis (AAT), a trypanosome-caused disease, which hampers livestock production in sub-Saharan Africa are now of low efficacy. Major surface proteases (MSPs) of trypanosomes are also possible drug targets. A *Trypanosoma brucei* MSP-B (*Tb*MSP-B) mediates parasite antigenic variation via cleavage of the protective variant surface glycoprotein (VSG) molecules for replacement with a new variable type. Whilst *Tb*MSP-A has no apparent role in VSG cleavage; it is not known if *Tb*MSP-C is involved in VSG cleavage.

Methodology: The study aimed to address a role of *Tb*MSP-C in VSG cleavage, and to select ligands with a possible inhibitory effect on the MSPs as well as to determine the depth of the substrate binding pockets of *Tb*MSP-B and *Tb*MSP-C. Two VSG molecules and several small ligand molecules were docked into the three-dimensional structures of *Tb*MSP-A, *Tb*MSP-B and *Tb*MSP-C.

Results: *Tb*MSP-C showed an affinity for similar VSG sites as *Tb*MSP-B, but these sites differed from those recognised by *Tb*MSP-A. Docking small inhibitor ligands enabled identification of ligands with potential anti-trypanosomal activity and revealed the depth of the S_1' pockets of *Tb*MSP-B and *Tb*MSP-C, which is influential in ligand and substrate binding.

Discussion and conclusion: This study is the first that predicted that *Tb*MSP-C cleaves VSG molecules. The study also identified hit ligands that can be tested *in vitro* for anti-trypanosomal activity. It also identified the depth of the S_1' pockets of *Tb*MSP-B and *Tb*MSP-C, which should be targeted in drug design.

References:
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