



Contribution ID: 59

Type: **Poster Presentation**

## New crystal structure of MSHB from *Mycobacterium tuberculosis* shows insight into the catalytic mechanism

Wednesday, 10 July 2013 17:40 (1 hour)

### Abstract content <br> &nbsp; (Max 300 words)

The enzymes of the pathway leading to the synthesis of mycothiol (MSH) and those enzymes involved in its recycling are potential drug targets, since mycothiol, that is used by Actinomycetes for defense against electrophilic toxins and oxidative stress, is not found in humans.

The structure of MshB was first described by Maynes et al. (PDB code 1q74). The pentacoordinate zinc(II) in the active site was found to be liganded to His13, Asp16, His147 and two water molecules. A mechanism was proposed in which the tetrahedral transition state, formed during amide hydrolysis, would be stabilized by the positively charged  $Zn^{2+}$  and the imidazolium side chain of His144. The structure of MshB was determined almost simultaneously by McCarthy et al. (PDB code 1q7t), who crystallized the enzyme in the presence of  $\beta$ -octylglucoside (BOG), which was found to occupy a location near the catalytic zinc. Hydrogen bonding to the glucopyranoside ring of BOG was interpreted as being analogous to that occurring with the natural substrate. In particular, three conserved residues, Arg68, Asp95 and His144 were hydrogen bonded via their sidechains to the 3-OH, 4-OH and 6-OH hydroxyl groups of BOG respectively.

Huang and Hernick have recently explored the kinetics of MshB and suggested that Tyr142, a residue that was not previously implicated in the mechanism, plays a major role in the catalysis. They modelled the predicted position of Tyr142 based on their observations.

This work, in which acetate (one of the normal reaction products) is visualized in the active site, provides necessary structural evidence for the proposal that Tyr142 is indeed located in the predicted position. This structure also rules out the possibility of His144 acting as a component of the oxyanion hole. Furthermore, the geometry we observe in the active site strongly suggests that the protonated form of Asp15 fulfils the role of general acid as originally suggested by Maynes et al. and rules out the proposal of Huang and Hernick that the general acid is His144. Furthermore, the structure reported here enables a detailed analysis of the binding of the natural substrate via hydrogen bonding to Arg68, Asp95 and His144, and identifies a change in the conformation of the side chain of Asp95 that stabilizes the substrate binding loop in the absence of substrate.

### Apply to be<br> considered for a student <br> &nbsp; award (Yes / No)?

yes

### Level for award<br>&nbsp;(Hons, MSc, <br> &nbsp; PhD)?

PhD

**Main supervisor (name and email)<br>and his / her institution**

Prof BT Sewell trevor.sewell@uct.ac.za  
University of Cape Town

**Would you like to <br> submit a short paper <br> for the Conference <br> Proceedings (Yes / No)?**

no

**Primary author:** Mr BROADLEY, Simon (Electron Microscope Unit)

**Presenter:** Mr BROADLEY, Simon (Electron Microscope Unit)

**Session Classification:** Poster2

**Track Classification:** Track F - Applied Physics