[MS5-P41] Fragment-Based Approaches for Anti-Tuberculosis Drug Discovery. Ali Ryan,[a,b] Olga Eleftheriadou,[a] Alice Halman,[a] Christian Sieg,[a] Sebastian Keany,[b] Alessio Ciulli,[c] Chris Abell,[c] Edward D. Lowe,[d] Edith Sim,[a,b]

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Mycobacterium tuberculosis (*Mtb*) remains the main cause of mortality worldwide by bacterial infection. Cholesterol metabolism is essential for mycobacterial infection and long-term survival inside of host macrophages. Crucial for this pathway and *Mtb* survival inside of macrophages is 2-hydroxy-6-oxo-6-phenylhexa-2.4-dienoate hydrolase (HsaD) which catalyses the hydrolysis of carbon-carbon bonds via a serine protease-like catalytic triad [1]. The enzyme has a large active site cavity and readily forms crystals [2]. Its high thermal stability makes HsaD an ideal target for fragment-based drug discovery. To investigate novel inhibitors of HsaD a fragment library consisting of 1,258 compounds was screened via differential scanning fluorimetry (DSF) and hits were further checked by NMR. Inhibition efficiency of hits was characterized via a colorimetric assay using 2-hydroxy-6-oxo-6-phenylhexa-2.4-dienoic acid (HOPDA), an artificial, coloured substrate [1]. Two initial compounds referred to here as A and B were identified. A structure-activity relationship (SAR) study was performed using analogues of compounds A and B via DSF analysis and IC_{50} determination by colorimetric assay. The crystal structures of HsaD with the best analogues of A and B are presented showing that the compounds interact with different areas of the active site cavity. The data collectively provide information for growing of each of these fragments to improve binding

[1]Lack, N.A., Yam, K.C., Lowe, E.D., Horsman, G.P., Owen, R.L., Sim, E. & Eltis, L.D. (2010). *Journal of Biological Chemistry* **285**, 434-443.
[2]Lack, N., Lowe, E.D., Liu, J., Eltis, L.D. Noble, M.E., Sim, E. & Westwood, I.M. (2008). Acta Crystallographica Section F Structural Biology and Crystallization Communications **64**, 2-7.

Keywords: Mycobacterium tuberculosis; fragment-based drug discovery; HsaD