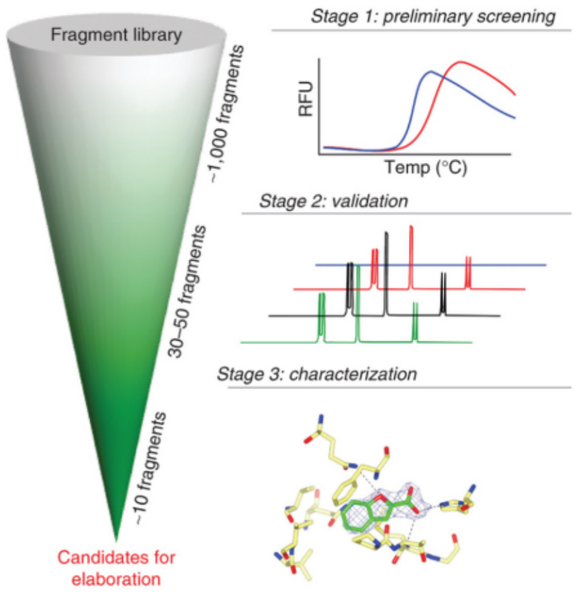
Fragment-based approaches for the discovery of inhibitors of key targets in *Mycobacterium tuberculosis*

Abell Group Research

UNIVERSITY OF CAMBRIDGE

Introduction to fragment based drug discovery and tuberculosis



• Fragment-based screening offers an efficient approach to lead discovery since:

i. A larger portion of chemical space can be sampled with fewer compounds.
ii. Hit compounds are more efficient binders with a high proportion of atoms forming favourable contacts.

• Screening is typically performed using a range of biophysical techniques, with hit compounds validated in secondary screens.

• Aided by knowledge of the binding mode, fragments are elaborated into more potent ligands through fragment linking, merging or growing.

• Tuberculosis is a major disease with about one third of the world population infected.

•The emergence of multidrug resistant strains of *M. tuberculosis* has highlighted the importance of developing new therapies.

References: E H Mashalidis *et al*, *Nature Protocols* **2013**, *8*, 2309-2324; Y L Janin, *Bioorg Med Chem* **2007**, 15, 2479–2513

Development of direct inhibitors of InhA

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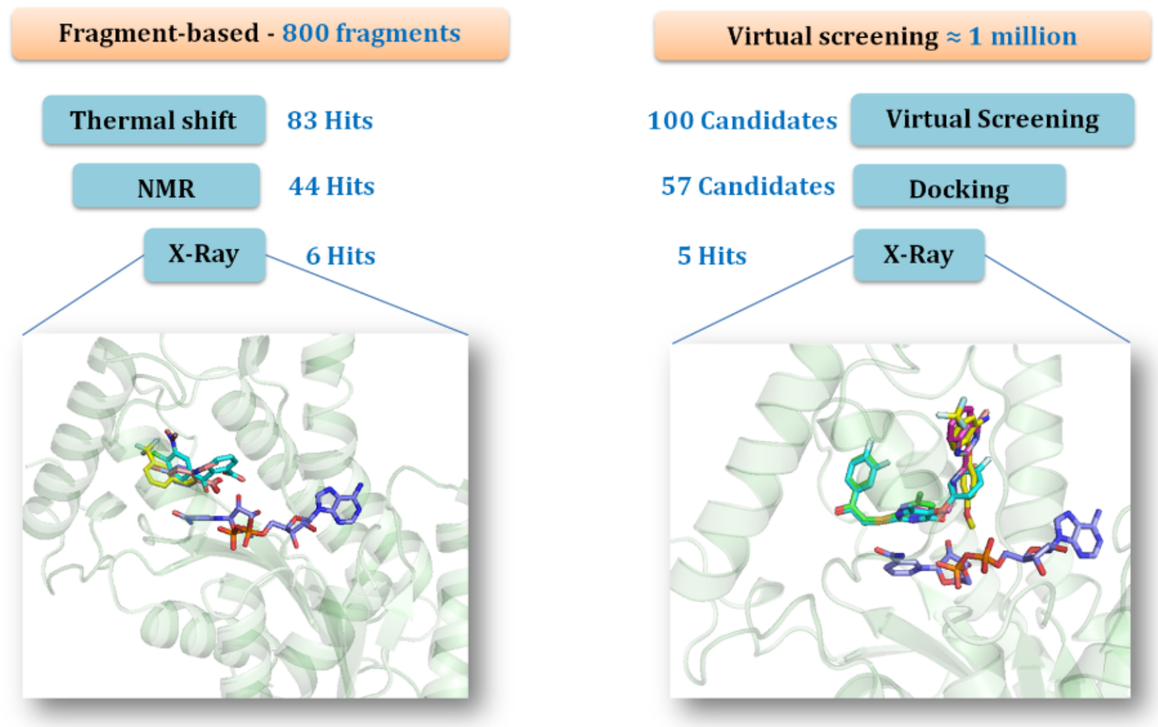

Targeting Coenzyme A biosynthesis

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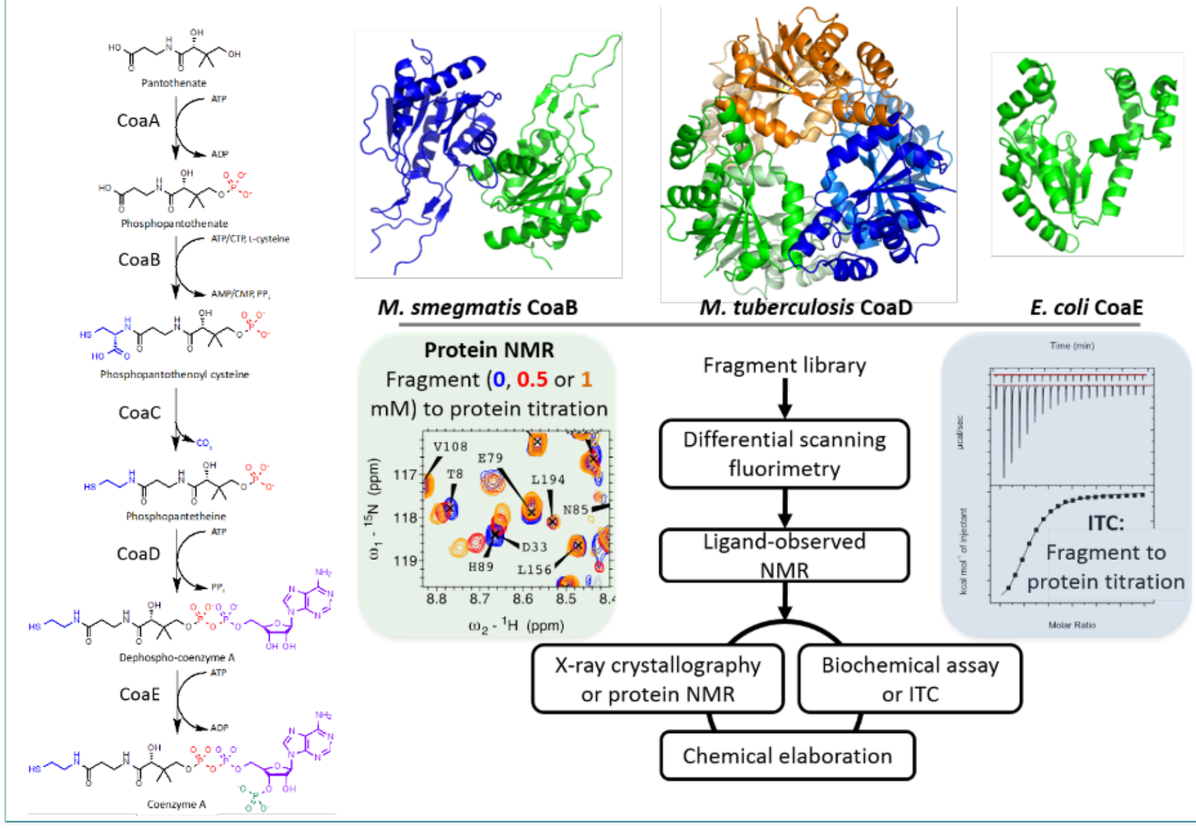

Development of EthR inhibitors for use as Ethionamide boosters

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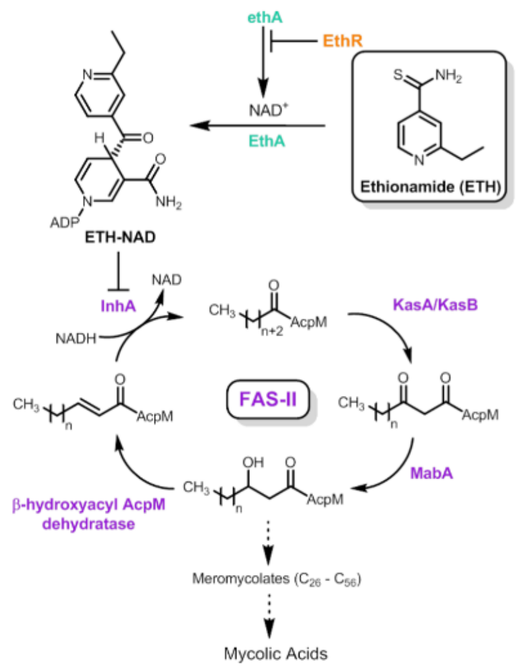
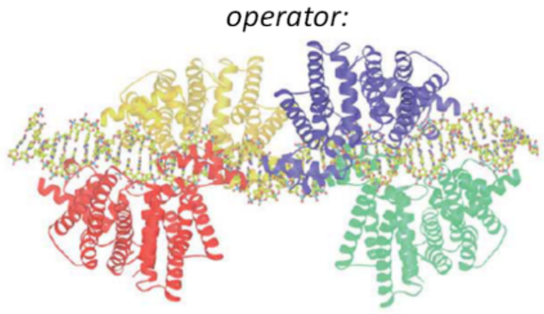
Mechanism of ethionamide action:



Model of EthR octamerising on its DNA operator:



- High therapeutic dose of ethionamide leads to toxicity and poor patient compliance
- EthR binds to ethA promoterregion as a homooctamer
- EthR ligands inhibit DNA binding allosterically and enhance EthA expression
- Development of EthR inhibitors as ethionamide boosters

References: N Willand *et al*, *Nature Med.* **2009**, *15*, 537-544

Cytochrome P450 enzymes as novel drug targets

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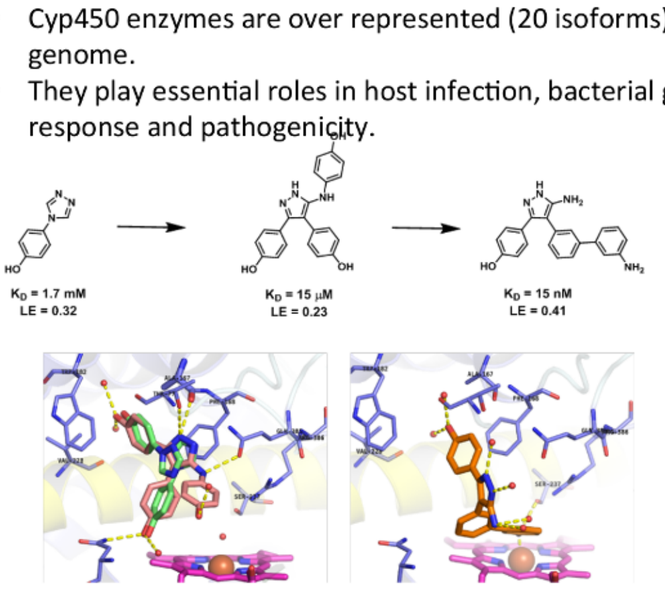
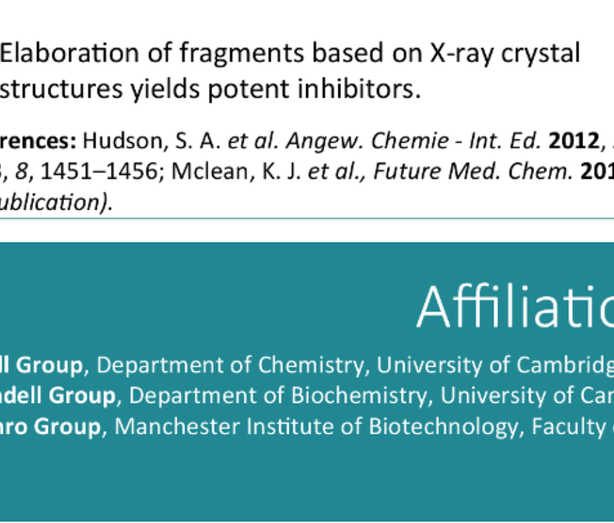
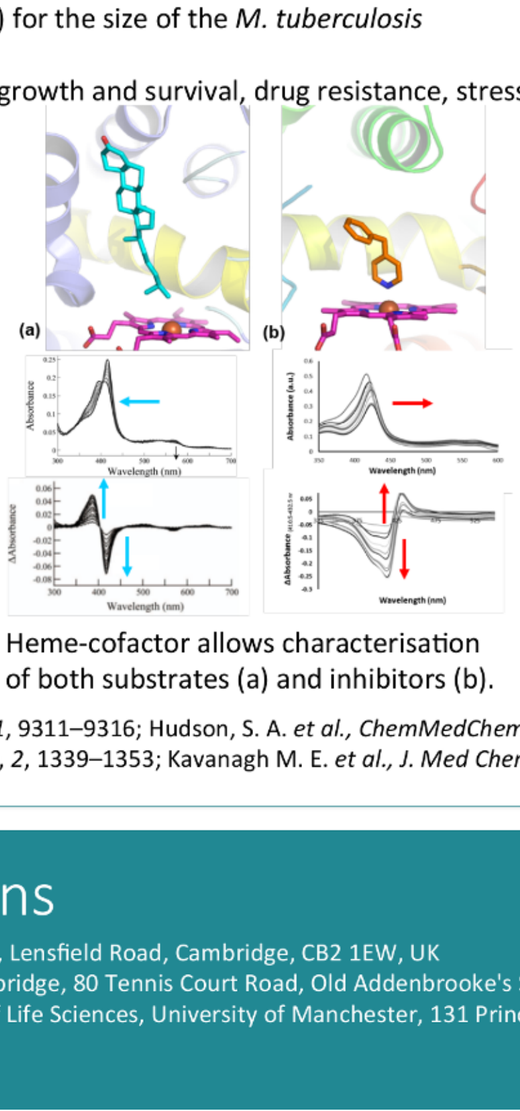
- Cyp450 enzymes are over represented (20 isoforms) for the size of the *M. tuberculosis* genome.
- They play essential roles in host infection, bacterial growth and survival, drug resistance, stress response and pathogenicity.







- Elaboration of fragments based on X-ray crystal structures yields potent inhibitors.
- Heme-cofactor allows characterisation of both substrates (a) and inhibitors (b).

References: Hudson, S. A. *et al. Angew. Chemie - Int. Ed.* **2012**, *51*, 9311–9316; Hudson, S. A. *et al., ChemMedChem* **2013**, *8*, 1451–1456; Mclean, K. J. *et al., Future Med. Chem.* **2010**, *2*, 1339–1353; Kavanagh M. E. *et al., J. Med Chem (in publication).*

Mass spectrometry techniques to study protein structure and protein-ligand interactions

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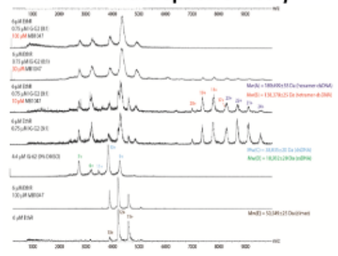
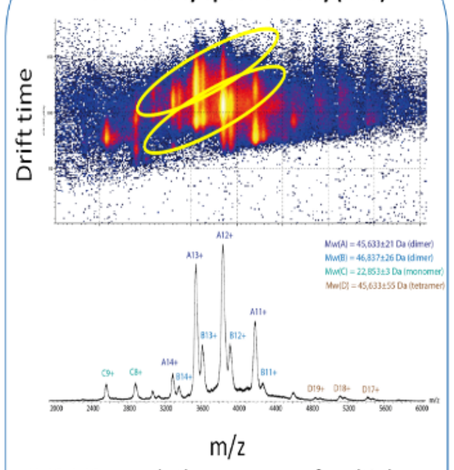
Native mass spectrometry



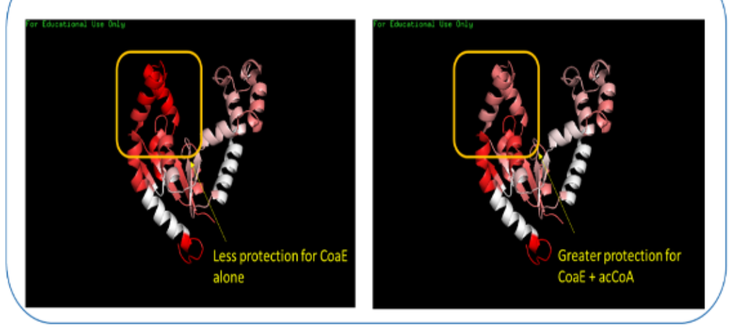
Native MS reveals that fragment molecules disrupt the interaction between EthR and its DNA operator.

Ion-mobility spectrometry (IMS)



IMS-MS reveals the presence of multiple conformers of EthR under high activation conditions

Hydrogen-deuterium exchange (HDX)-MS



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