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Progress in utilization of *Mycobacterium tuberculosis* cytochrome P450 monooxygenases as novel drug targets

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Mycobacterium tuberculosis

- **Lung pathogen – causes Tuberculosis (TB)**
- **Leading cause of death world wide**
- **One third of the worlds population affected by TB**
- **Leading killer of people living with HIV/AIDS**
- **Drug resistance (MDR, XDR & TDR)**
- **Novel drugs and drug targets**

Gandhi et al., 2006; Migliori et al., 2012; Raviglione et al., 2012; WHO fact sheet, 2013

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M. tuberculosis: Cytochrome P450 monooxygenases

- 20 P450s
- Heme-thiolate enzymes
- Stereo- and regio-specific activity
- CYP121, CYP125 and CYP128 – essential
- *M. tuberculosis* P450s : novel drug targets
- What's the problem ??

Hydrocarbon hydroxylation
Alkene epoxidation
Alkyne oxygenation
Arene epoxidation
Aromatic hydroxylation
N-Dealkylation
S- Dealkylation
O- Dealkylation
N-Hydroxylation
N-Oxidation
S-Oxidation
Oxidative deamination
Oxidative dehalogenation
Alcohol and aldehyde oxidations
Dehydrogenation
Dehydratations
Reductive dehalogenation
N-Oxide reduction
Epoxide reduction
Reductive β-scission of alkyl peroxides
NO reduction
Isomerizations
Oxidative C-C bond cleavage

Reactions catalyzed by P450s (*Sono et al., 1996*)

Hudson et al. 2012;Ouellet et al., 2013

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M. tuberculosis P450 research: Major problems

- **Essential P450s – biased**
- **Expression of *M. tuberculosis* P450s**
- **P450 inhibitors**
- **P450 family specific targeting**

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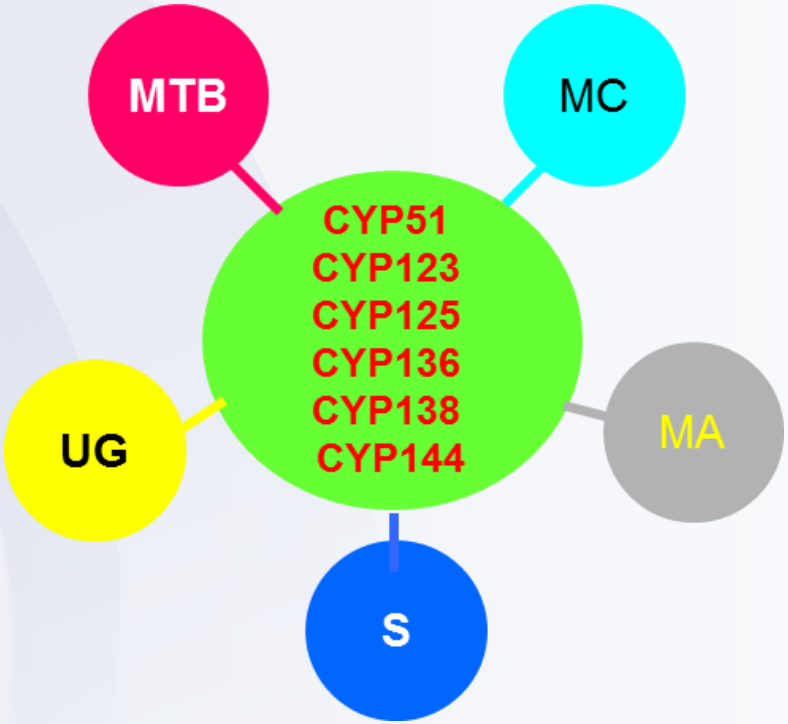
M. tuberculosis P450 research: Potential new P450 candidates



Syed et al. unpublished data

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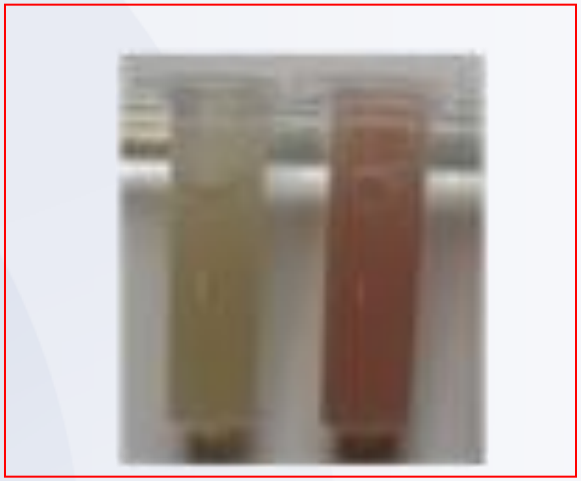
M. tuberculosis P450 research: Expression



P450 expression library

Syed et al. unpublished data

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M. tuberculosis P450 research: P450 inhibitors

CYP121A1 & CYP125A1 | **CYP123A1, CYP128A1 & CYP135A1**

↓ ↓

Crystal structures | **3d-models**

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Active site mapping

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Virtual screening of chemical libraries

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Potential P450 inhibitors

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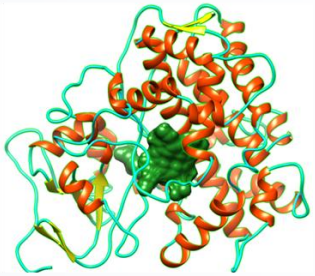
***In vitro* validation (in progress)**

CYP123A1

CYP128A1



CYP135A1

Syed et al. unpublished data

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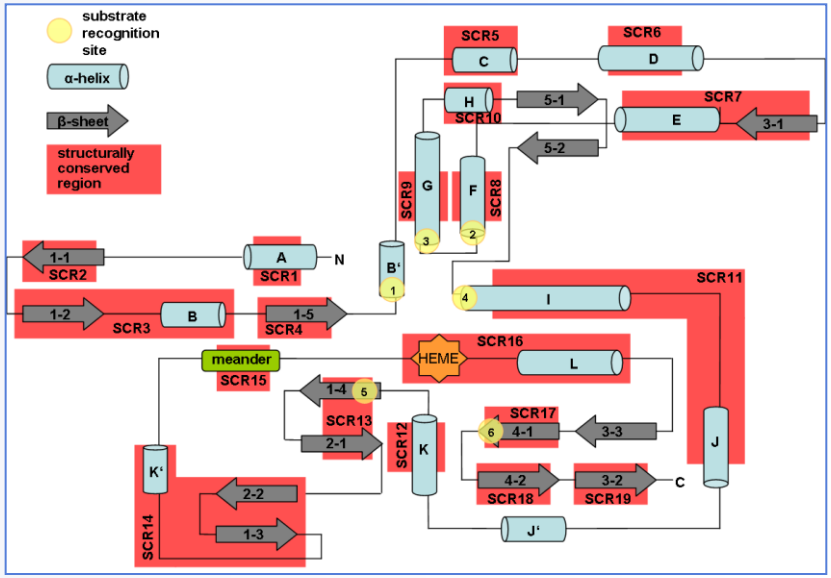
P450 family specific targeting: Major problems

- Primary sequence – diversity
- Similar three dimensional fold
- Classification based on homology
- >40%- family & >55%- subfamily
- What makes each P450 family unique?
- Characteristics of P450 family?



A topological overview of the conserved CYP structure (*Sirim et al., 2012*)

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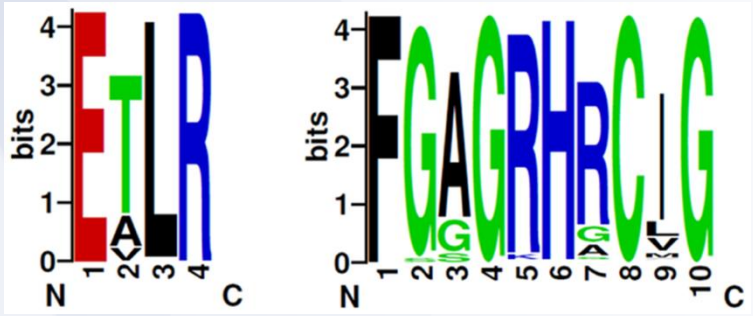
P450 family specific signatures

- 67 P450 families across biological kingdoms
- EXXR and CXG motif based signatures



CYP51 family EXXR and CXG motifs (407 P450s)

- P450 family specific amino acids
- P450 family specific active site cavity amino acid conservation – *in progress*

Syed and Mashele 2014

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M. tuberculosis P450 Research: Progress

- New *M. tuberculosis* P450s : Potential drug candidates
- Expression of *M. tuberculosis* P450s - achieved
- Identified potential *M. tuberculosis* P450 inhibitors
- P450 family specific drug targeting - *possible*

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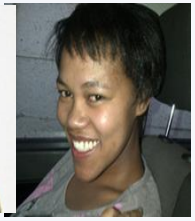
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Mr Que


Mr Richie


Mr Seiso

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Thank you

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