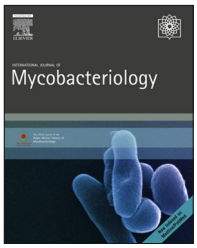
Asian · African society Of Mycobacteriology

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/IJMYCO



Drug development: The cell wall as a drug target

Jonathan A.G. Cox

School of Life & Health Sciences, Aston University, Birmingham, UK

The complex and essential cell wall of *Mycobacterium tuberculosis* represents a plethora of new and old drug targets that collectively form an apparent mycobacterial "Achilles' heel". The mycolic acids are long-chain α-alkyl-β-hydroxy fatty acids ($C_{70–90}$), which are unique to mycobacterial species, forming an integral component of the mycolyl–arabinogalactan–peptidoglycan complex. Their apparent uniqueness to the *M. tuberculosis* complex has rendered components of mycolic acid biosynthesis as powerful drug targets for specific tuberculosis (TB) chemotherapy. Here, I will discuss a contribution to TB drug discovery by deconvolution of the inhibitory mechanisms of a number of antitubercular compounds targeting mycolic acid biosynthesis. I will begin with the early days, elucidating the mode of action of ethionamide [1] and thiolactomycin [2], each targeting two separate components of the fatty acid synthase II (FAS-II) pathway. I will further discuss the recently discovered tetrahydropyrazo[1,5-*a*]pyrimidine-3-carboxamide compounds [3] which selectively target the essential, catalytically silent *M. tuberculosis* EchA6, providing a crucial lipid shunt between β-oxidation and FAS-II and supplying lipid precursors for essential mycolate biosynthesis. Finally, I will discuss the recent discovery of the mode of action of the indazole sulfonamides [4], inhibiting *M. tuberculosis* KasA by, a completely novel inhibitory mechanism.

Conflict of interest

The author declared that there is no conflict of interest.

REFERENCES

[1] L.G. Dover et al., EthA, a common activator of thiocarbamide-containing drugs acting on different mycobacterial targets, Antimicrob. Agents Chemother. 51 (3) (2007) 1055–1063.

[2] L. Kremer et al., Thiolactomycin and related analogues as novel anti-mycobacterial agents targeting KasA and KasB condensing enzymes in Mycobacterium tuberculosis, J. Biol. Chem. 275 (22) (2000) 16857–16864.

[3] J.A. Cox et al., THPP target assignment reveals EchA6 as an essential fatty acid shuttle in mycobacteria, Nat. Microbiol. 1 (2016) 15006, http://dx.doi.org/10.1038/nmicrobiol.2015.6.

[4] K.A. Abrahams et al., Identification of KasA as the cellular target of an anti-tubercular scaffold, Nat. Commun. 7 (2016) 12581, http://dx.doi.org/10.1038/ncomms12581.

E-mail address: j.a.g.cox@aston.ac.uk

Peer review under responsibility of Asian African Society for Mycobacteriology.
http://dx.doi.org/10.1016/j.ijmyco.2016.09.012