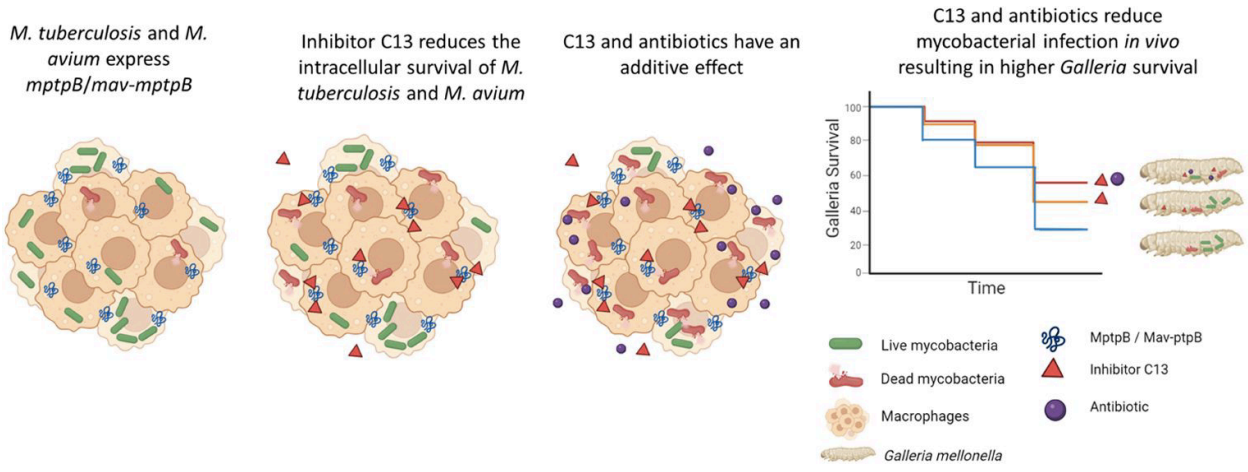
MptpB inhibitors increase the efficacy of antibiotics reducing intracellular burden for Mycobacterium tuberculosis and non-tuberculous Mycobacterium avium

Pablo Rodríguez-Fernández[1], Fraser J. Scott[2], Jennifer S. Cavet[1,3] and **Lydia Tabernero[1,3*]**

[1]School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK. [2] Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow, UK. [3]Lydia Becker Institute for Immunology and Inflammation, University of Manchester, UK.
* Lydia.tabernero@manchester.ac.uk

Abstract

Treatment of *Mycobacterium tuberculosis* and *Mycobacterium avium* chronic infections requires multiple drugs for long periods of time. Mycobacterium protein-tyrosine-phosphatase B (MptpB) is a key *M. tuberculosis* virulence factor that subverts host antimicrobial activity to promote intracellular survival. Inhibition of MptpB reduces infection burden *in vivo* and offers new opportunities to improve current treatments. Recently, we have demonstrated that *M. avium* produces an MptpB orthologue and that the MptpB inhibitor C13 reduces *M. avium* infection burden in macrophages. Combining C13 with the antibiotics rifampicin or bedaquiline showed additive effect reducing intracellular infection of both *M. tuberculosis* and *M. avium* by 50%, compared to monotherapy with antibiotics alone. This additive effect was not observed with pretomanid. Combining C13 with the minor-groove-binding compounds S-MGB-362 and S-MGB-363 also reduced *M. tuberculosis* intracellular burden. Similar additive effects of C13 and antibiotics were confirmed *in vivo* using *Galleria mellonella* infections. We also demonstrated that the reduced mycobacterial burden in macrophages observed with C13 treatments is due to increased trafficking to lysosomes, where bacteria are destroyed.



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