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The pain-killer carprofen elicits pleiotropic mechanisms of bactericidal action with potential to reverse antimicrobial drug resistance in tuberculosis

The alarming rise of antimicrobial drug resistance in *Mycobacterium tuberculosis* coupled with the shortage of new antibiotics has elevated tuberculosis (TB) control to a major global health challenge. Repurposing drugs with known clinical properties and safety profiles offers a direct route to clinical trials. Our earlier studies using a whole-cell, high throughput phenotypic assay (HT-SPOTi) revealed that carpofen, a non-steroidal anti-inflammatory drug (NSAID), selectively inhibited the growth of replicating, non-replicating and multi-drug-resistant clinical isolates of *M. tuberculosis* [1-6]. The antibacterial activity of NSAIDs has been confirmed independently as in the case of aspirin and ibuprofen reducing mycobacterial loads in murine models. NSAIDs have also demonstrated sensitisation of mycobacteria to other antimicrobials. We have investigated the mechanisms through which NSAIDs eliminate *M. tuberculosis* from the host environment. Integrative molecular and microbiological approaches showed that carprofen, a bactericidal drug, inhibited bacterial drug efflux mechanisms. Carprofen also restricted mycobacterial biofilm-like growth, highlighting the requirement of efflux-mediated communicative systems for the formation of biofilms. Transcriptome profiling revealed that carprofen likely acts by targeting respiration through the disruption of membrane potential, which may explain why spontaneous drug-resistant mutants could not be isolated in practice due to the pleiotropic nature of carprofen's anti-tubercular action. This repurposed mycobactericidal and immunomodulatory drug has the potential to reverse TB antimicrobial drug resistance, offering a swift path to clinical trials of novel TB drug combinations.

Biography

Sanjib Bhakta is a reader in Molecular Microbiology and Director of Mycobacteria Research Lab at ISMB, Birkbeck, University of London & UCL. His specialties are : Microbiology, Molecular Biology & Biochemistry, Drug Discovery, Target Identification and validation in *Mycobacterium tuberculosis*, Model & Method development (*in vitro & ex vivo*) for whole cell (phenotypic) screening of inhibitors, drug susceptibility testing, repurposing drugs

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