Functional analysis of *Escherichia coli* efflux pumps and their cognate pumps in *Mycobacterium tuberculosis*

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The high prevalence of Multidrug Resistant (MDR) bacterial strains has been considered a major concern. Therefore, new antimicrobials have been constantly investigated. The tuberculosis control is known to be a global challenge to public health. Recent studies suggested *Mycobacterium tuberculosis* MDR strains emergence has been directly associated with Efflux pumps systems, e.g., members of the MFS (major facilitator superfamily) and ABC superfamily (ATP-binding cassette). Herein we addressed the role of Efflux pumps on intrinsic resistance to *M. tuberculosis* antimicrobials by employing a genomics approach. Comparisons among highest phenotypic identity of *Escherichia coli* and *M. tuberculosis* efflux pumps on their respective genomes have established novel targets. Based on previous studies in *M. tuberculosis,* novel compounds derived from furoxanes, such as PJ5, PJ10 and PJ21 were developed as antimicobacterial agents, and have shown antimicrobial activity against MDR *M. tuberculosis* strains. The k12 *E. coli* KEIO library (GE Dharmacon) was employed to directly address the role of Efflux pumps on resistance to the same antimicrobial compounds. The library was used to direct identify the mechanism of inhibition to specific efflux pumps targets such as YjiO drug MFS and YdcT ABC transporter. The antimicrobial activity was assayed against *E. coli* mutants to the *yjiO* and *ydcT* genes. The minimum inhibitory concentration (MIC) tests were performed using 0.125-16.0µg/mL of rifampicin (RFP) and 0.48-62.5µg/mL of each compound tested. Next, their synergy of these antimicrobials compounds was assayed by checkerboard test (CB) with RFP. Our preliminary results have shown a 4.0µg/mL RFP MIC to both our WT strain and mutants. So far, the compounds tested have not shown any significant statistical difference when compared to the wild type, Δ*yjiO,* and Δ*ydcT* mutants. Accordingly, the CB assays have shown similar results, showing non-synergy among these compounds. Our *E. coli* data is interesting as these compounds are intended to tuberculosis therapy, i.e., it would not present any disturbance to the intestinal microbiota, whereas *E. coli* is a major member. Our initial data presented here have not shown functional correlation between *Escherichia coli* and *M. tuberculosis* efflux pumps, however these data did open new perspectives on treatments. Other compounds as new targets are currently under investigation.

Key-words: E. coli, efflux pumps, multidrug resistance, M. tuberculosis

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