**Title: SYNERGY AMONG EFFLUX AND CANONIC MUTATIONS TO DETERMINE DRUG RESISTANCE IN *Mycobacterium tuberculosis***

**Authors** Coelho, T.S.[1,2,3], Machado, D.[4], Halicki, P.C.B.[3]; Couto, I.[4], Maschmann, R.[1,2], Ramos, D.[3], von Groll, A.[3], Rossetti, M.L.R.[1,2], Viveiros, M.[4], Silva, P.E.A.[3]

**Institution** [1]Programa de Pós-Graduação em Biologia Celular e Molecular - Centro de Biotecnologia, Universidade Federal do Rio Grande do Sul (Av. Bento Gonçalves 9500, Campus do Vale - Porto Alegre - RS – Brazil);
[2]FEPPS - Fundação Estadual de Produção e Pesquisa em Saúde, Centro de Desenvolvimento Científico e Tecnológico (CDCT) (Avenida Ipiranga, 5400 – Jardim Botânico - Porto Alegre, RS, Brazil);
[3]Núcleo de Pesquisa em Microbiologia Médica (NUPEMM), Faculdade de Medicina, Universidade Federal do Rio Grande (Rua General Osório s/n, Centro - Rio Grande, RS, Brazil);
[4]Grupo de Micobactérias, Unidade de Microbiologia Médica, Instituto de Higiene e Medicina Tropical, Universidade Nova de Lisboa (Rua da Junqueira, 100 - Lisboa, Portugal).

**Abstract:**

Antimicrobial resistance in *Mycobacterium tuberculosis* has become one of the major limitations for the effective treatment of tuberculosis. The increase of incidence of tuberculosis with drug-resistant *M. tuberculosis* strains has threatened the TB control strategies. Several mutations in specific loci of the *M. tuberculosis* have been reported as main basis for drug resistance, however, additional mechanisms, such as efflux may contribute to bacterial survival in presence of antibiotics. In the present study, we evaluate the contribution of efflux in drug resistance in five MDR strains (three resistant to INH and RIF, all with mutations in *kat*G S315T and *rpo*B S531L; one resistant to INH, RIF and AMK with mutations in *kat*G D735A, *rpo*B S531L and *rrs* A>G 1401) and one strain mono resistant to OFX with mutation in gyrA D94N, all with high-level resistance. We used BACTEC$^{TM}$ MGIT$^{TM}$ 960 system and the Epicenter V5.53A equipped with the TB eXiST software through relationship between time to detection (TTD) of bacterial growth in presence and absence of efflux pump inhibitor (EPIs): verapamil, chlorpromazine and thioridazine. The result showed that, in general, the classical EPIs increased the TTD when combined with INH, RIF and OFX, except in combination with AMK in Pre-XDR and H37Rv strains. Furthermore, in most of the combinations among antibiotic plus EPIs there was inhibition of >99% bacterial growth, indicating a susceptibility profile. These results suggest that despite of presence of the canonic mutations correlated to a high-level resistance, the efflux can act synergistically, reducing the biological cost as well as increasing the probability of bacteria to survive at high drug concentrations. Thus, the use of EIP efflux pump as part of therapy to TB should more deeply evaluated.

**Key-words:** Resistance, time to detection, tuberculosis

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