Ethionamide boosters : comment faire du neuf avec du vieux pour traiter la tuberculose

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Tuberculosis remains a major cause of mortality and morbidity killing each year more than two million people. The emergence of multidrug-resistant strains of Mycobacterium tuberculosis, stresses the need for alternative therapies. Ethionamide (ETH), a second-line antibiotic, is used to treat multidrug-resistant tuberculosis. ETH is a prodrug and needs to be activated by the mycobacterial enzyme EthA in order to inhibit InhA, the enoyl-acyl ACP reductase involved in mycolic acid biosynthesis. We demonstrated that the limited effectiveness of ethionamide is due to the transcriptionnal repression of ethA by the bacterial regulator EthR.

Using SPR screening, crystallography, click-chemistry in situ and rational design, we have identified EthR drug-like inhibitors that increase the efficacy of ethionamide by at least 25-fold in vitro and 3-fold in vivo. Efforts are now continued to develop a clinical candidate. This work is to our knowledge the first strategy to fight tuberculosis by boosting existing drugs.

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