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TEACHING OLD DRUGS NEW TRICKS: REPROGRAMMING THIOAMIDE'S BIOACTIVATION TO FIGHT MULTIDRUG RESISTANT MYCOBACTERIUM TUBERCULOSIS

Nicolas Willand[1], Marc Gitzinger[2], Benoit Deprez[1] and Alain Baulard[1]

[1]P Lille University, France
[2]BioVersys AG, Switzerland

Antimicrobial resistance (AMR) is a growing public health problem worldwide and tuberculosis is the bacterial infection most affected by AMR. The estimated global burden of multi-drug resistant tuberculosis is 450,000 each year. The most alarming figure is that extensively drug resistant *Mycobacterium tuberculosis* (*M. tuberculosis*) (XDR-Mtb) has already been reported in more than 92 countries, which forces us to develop innovative approaches to revert resistance. The originality of our approach arises from the peculiar observation that a significant number of anti-TB antibiotics are prodrugs, meaning that they become active inside of the mycobacteria thanks to specific mycobacterial enzymatic bioactivations, tightly controlled by transcriptional regulators. Ethionamide (*ETH*), for instance, requires intracellular activation by a monooxygenase called *EthA*. *EthR*, a transcriptional repressor (TR), controls the expression of *EthA* and thus limits *ETH* conversion into its active form. Use of *EthR* inhibitors in combination with *ETH* showed a strong effect in boosting *EthA* production and thus sensitivity to the prodrug. Using a combination of phenotypic and molecular assays, we have discovered and optimized a new type of compounds called SMARt (Small Molecule Aborting Resistance) that are now able to wake-up cryptic bio-activation pathways of ethionamide, and consequently revert resistance to the prodrug. Treatment of a large panel of clinical isolates highly resistant to *ETH* with the combination of SMARt-420 and *ETH*, allowed inhibiting growth with MIC below the resistant threshold of 0.5 µg/mL. In this experiment, SMARt-420 did not only increase the basal sensitivity of *M. tuberculosis* to ethionamide but also fully reversed ethionamide acquired resistance. Finally, mice infected with an ethionamide-resistant mycobacterial strain were also successfully treated orally with the combination of ETH and SMARt-420 (50 mpk) and a 4.6 log reduction of the bacterial load in the lun≈gs was observed. From our last generation of SMARt molecules, we have now been able to select a preclinical candidate.

nicolas.willand@univ-lille2.fr