Marco Pieroni et al., J AIDS Clin Res 2014, 5:11
http://dx.doi.org/10.4172/2155-6113.S1.009

OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference on
HIV/AIDS, STDs, & STIs
October 27-29, 2014 Embassy Suites Las Vegas, USA

Novel approaches toward the eradication of resistant and persistent *M. tuberculosis* strains

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Tuberculosis (TB), caused by *M. tuberculosis* (*Mtb*) is one of deadliest diseases that the human kind have faced throughout the centuries, and the toll of deaths caused by this disease is still remarkable. TB is thought to represent a concern only in the developing countries, where extreme life conditions boost the spread of the disease. However, global warming, business travels and the steadily increasing migration flows from countries where TB is endemic, pose a real threat to contract TB also in the developed countries; and the whole scenario becomes almost intolerable when resistant strains such as multi-drug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) take over. Two main hurdles characterize TB infection: drug-resistance and the presence of persistent strains that extend the duration of the therapy and make it more difficult to eradicate. Although hundreds of compounds are often disclosed, that have *in vitro* activity against drug-resistant and drug-susceptible *Mtb*, a different idea is needed to face the disease at 360 degrees. Efflux pumps are known to be important means to modulate antibiotic resistance for many bacteria and for *Mtb* in particular. As it is true that the main mechanism by which *Mtb* eludes chemotherapy is represented by mutations at the target binding sites of the most common drugs, it is as well true that: 1) efflux systems are effectors of the innate drug-resistance machinery; 2)their contribution is crucialin conferring high-level of resistance; 3) they contribute to lower the concentration of the drug inside the mycobacterial cell, enabling the emergence of resistance; 4) it has been demonstrated that efflux pump inhibitors are able to restore the activity of old drugs toward which the bacteria had become resistant. As such, inhibition of efflux pumps may help in preventing the raise of resistances, in containing its spread, and in re-establish obsolete therapeutic options. Moreover, thioridazine (TZ), by virtue of its capability to affect the efflux systems of the macrophage, not only acts as an inhibitor of bacterial efflux pumps, but has also shown to cure resistant TB when administered in combination with other antituberculars on compassionate basis. However, TZ, indicated for the treatment of schizophrenia, shows general toxicity at the anti-TB therapeutic doses. All of these findings prompted us to prepare analogues of thioridazine as inhibitors of the mycobacterial efflux pumps. Taking *M. smegmatis* as *Mtb* surrogate for the preliminary investigation, these compounds were tested for their ability to inhibit the efflux of ethidium bromide (EtBr) and,in a combination assay, to enhance the potency of known antimycobacterials and mycobacterial efflux substrates (rifampin, claritromycin, ofloxacin, ciprofloxacin and ethidium bromide), when administered at only ¼ of their MICs. We were pleased to notice that while UPAR 223 was an inhibitor of EtB reflux slightly better than TZ and Verapamil, UPAR 174 was able to enhance up to 128 times the activity of RIF in the combination assay. As such, we strongly believe that these compounds may serve as effective tools for an innovative antituberculosis regimen.

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