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EC MICROBIOLOGY
Editorial

Tuberculosis - Current Advances in Development of New Drugs against Multidrug-Resistant Strains

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Received: February 17, 2017; **Published:** February 21, 2017

RecTuberculosis (TB), an infection disease caused mainly by the Mycobacterium tuberculosis, still remains a serious public health problem at the global level [1]. In 2015, for example, it was reported 10 million of new cases and 1.3 million of deaths worldwide [2]. Currently, the increased number of multidrug-resistant (MDR-TB) and extensive-drug resistance (XDR-TB) cases raised the concerns about this disease [2]. MDR-TB and XDR-TB have low cure rates and high mortality levels due to difficulties related to the treatment. In addition, cases of totally drug resistant tuberculosis (TDR-TB) have been reported making this scenario more alarming [3,4]. The last survey conducted by World Health Organization (WHO) have reported 480.000 new cases of MDR-TB and approximately 190.000 deaths worldwide [2]. Paradoxically, the numbers of new drugs for TB did not increase proportionally to the emergence of resistance.

Over the past few years, it has been possible to note some advances in the development of drug candidates that may act against TB, however, we are still far from an ideal condition [5]. After a gap of more than 50 years without new TB drugs, the U.S. Food and Drug Administration (FDA) approved bedaquiline (Sirturo®, Janssen Therapeutics) in 2012 for the treatment of MDR-TB. Nevertheless, strains resistant to this new molecule have been reported [6,7].

The current anti-tuberculosis drug pipeline shows six drugs in clinical trial at phase 2 or 3 for MDR-TB treatment. Bedaquiline and delamanid remains in trial phase 3; despite of its approval in several countries justified by the emergence situation caused by MDR-TB. Sutezolid and pretomanid, two others new drug candidates are in trial phase 2 and the repurposed drugs clofazimine and levofloxacin are in phase 3 and 2, respectively [8].

Bedaquiline, a diarylquinoline derivative was discovered through a phenotypic screening and it acts by inhibition of the proton pump of mycobacterial ATP synthase, specifically binding to subunit-c of this enzyme thereby decreasing intracellular ATP levels in *M. tuberculosis* [9,10]. Delamanid (Deltyba®, Otsuka Pharmaceutical) was approved for MDR-TB treatment in 2014 in Europe, Japan, and South Korea. This nitroimidazole derivative acts as a prodrug requiring activation by the mycobacterial enzyme deazaflavin dependent nitroreductase (Ddn). Upon activation, a reactive intermediate metabolite is considered to play a vital role in the inhibition of mycolic acid biosynthesis necessary to mycobacterial cell wall [11,12]. Likewise, pretomanid (also known as PA-824) is a nitroimidazole derivative with potent activity against both replicating and non-replicating *M. tuberculosis*. Like delamanid, this derivative needs to undergo activation by the mycobacterial Ddn enzyme [13] in order to release a metabolite that inhibits the cell wall synthesis. Microarray analysis revealed that pretomanid appears to act as a nitric oxide donor within mycobacterial cells and thus interfering with energy metabolism [14]. Sutezolid is the thiomorpholinyl analog of the drug linezolid. This oxazolidinone derivative inhibits the microbial protein synthesis by binding to the ribosome and block the formation of the initiation complex [15]. Clofazimine belongs to the class of rifamycins and it was originally described in 1962 as an antileprosy drug. Interestingly, it was recently repurposed for MDR-TB due to a series of meta-analysis of studies

that reveals potential of this drug to act against MDR-TB [16]. Clofazimine act as a prodrug being reduced by the mycobacterial enzyme NADH dehydrogenase (NDH-2), and thereby releasing reactive oxygen species [17]. The exact mechanism of action of its active metabolite remains unclear, however, the outer membrane appears to be the main site of action [18]. Levofloxacin is a second-generation fluoroquinolone that act by inhibiting the DNA gyrase and topoisomerase IV, two type II topoisomerase enzymes [19]. These enzymes are essential for microbial DNA replication and therefore levofloxacin acts as a bactericidal drug. Currently, studies are been conducted in order to refine the optimal dose of this fluoroquinolone against MDR-TB [8]. In conclusion, the major challenges involved in drug discovery for TB must consider as promising those drugs active against MDR-TB and XRD-TB. Currently, six drugs are being evaluated in clinical trials, some of them, such as quinolones and clofazimine were repurposed in the therapy. Moreover, the discovery of new validate targets for drugs in MTB is essential to accelerate the development of new drugs.

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Volume 6 Issue 3 February 2017