

Current status in the development of the new anti-tuberculosis drugs

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Tuberculosis (TB) is still the greatest single infectious cause of mortality worldwide. However, powerful new anti-TB drugs with new mechanisms of action have not been developed in the last over thirty years.

It is expected that development of the new effective anti-TB drug will bring us various outcomes such as shortening the total duration treatment, improvement of the treatment completion ratio, prevention and treatment of the multiple drug resistant tuberculosis (MDR-TB) and reducing the total medical expenditure.

A new anti-TB drug needs to show the well pharmacokinetic distribution and permeation into lung tissue and cells. Furthermore, it is also desired that the novel candidate exhibits the potent bactericidal activity both against exponential and stable phase of *M. tuberculosis in vivo*. In addition, it is ideal that the novel agent possesses narrow anti-microbial spectrum specialized only against Mycobacterial species.

Nitroimidazopyran is the center of attention in the world today as a most potent novel drug candidate for TB. Its leading compound PA-824 is being developed at the stage of the first clinical trial phase I. PA-824 possesses two types of mechanism; inhibitions of the biosynthesis of protein and cell wall lipid of *M. tuberculosis*. PA-824 exhibits bactericidal activity against both replicating and static *M. tuberculosis*. It also shows potent bactericidal activity against MDR-*M. tuberculosis*.

Among the new rifamycin derivatives, rifalazil (KRM-1648) is the most promising drug candidate. The development of rifalazil is in progress at the stage of the clinical trial phase II. Rifalazil demonstrates potent long-acting oral activity against *M. tuberculosis* both in animal models and in humans.

Gatifloxacin (GFLX) and moxifloxacin (MXFX) are the 8-methoxy-fluoroquinolone representatives. They show bactericidal activity against

replicating *M. tuberculosis* both *in vitro* and in murine tuberculosis models.

ABT-773 and HMR-3647 are the ketolide compound representatives; they possess a potential bactericidal activity against *M. avium-intracellulare* complex (MAC) *in vitro*, but these ketolide compounds are ineffective against macrolide resistant MAC strains.

Caprazamycin-B (CPZ-B) is the promising novel antibiotic recently developed in Japan, which was isolated from *Streptomyces* species. In contrast to current anti-TB drugs, CPZ-B with a novel chemical structure possesses specific bactericidal activity only against Mycobacterial species especially *M. tuberculosis* including MDR strains and MAC isolates. CPZ-B inhibits the biosynthesis of the cell wall of Mycobacteria, and exhibits moderate therapeutic efficacy that is dose size dependent in pulmonary tuberculosis model induced in mice. Any cyto-toxicity is not observed in the preceding animal experiments.

“The Global Alliance for TB Drug Development (GATB)”, recently formed organization under WHO initiative started funding pharmaceutical companies to develop the novel agents for TB. GATB has recently set up a new project called “Aerosolized new drug in DDS”. It has a potentially promising scope for developing new ant-TB drugs and the management of chemotherapy as well.