

Targeting Drug Resistance Mechanisms in *Mycobacterium tuberculosis*

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An Ancient Disease Returns

Historically, tuberculosis (TB) has left a scar as mankind's greatest infectious killer. With evidence of TB infection dating back nine millennia to a Neolithic Eastern Mediterranean settlement [1], this ancient disease meant almost certain death to those infected, a phenomenon spanning pre-antibiotic eras from the time of the Roman empire all the way to the beginning of the 20th century. But with the advent of antibiotics starting around 80 years ago, TB then became a curable disease. It had no longer the deadly effectiveness as it did for ancient Roman and Victorian populations. As an effect, *Mycobacterium tuberculosis*, the causative agent of TB discovered by Robert Koch in 1882, finally faded out of the limelight.

However, in the 1980s, with the epidemic of acquired immune deficiency syndrome (AIDS), TB has returned as one of the most dangerous infectious diseases of the modern times. Remarkably, the TB that we face today is not exactly the same disease of the past. Decades of widespread clinical application of antibiotics has resulted in the emergence of drug resistant strains of *M. tuberculosis* [2]. The accumulation of resistance mutations has given rise to the rapid evolution of *M. tuberculosis* strains that are multidrug resistant (MDR), extensively drug resistant (XDR), or more recently, totally drug resistant (TDR) [3,4]. Treatment of TB cases caused by these drug resistant *M. tuberculosis* strains has become more difficult, even impossible [5,6]. More alarmingly, studies suggest that these drug resistant *M. tuberculosis* strains might further evolve to regain fitness and thus able to spread out to HIV-negative populations [7].

Fighting TB in the Era of Drug Resistance

To tackle the growing epidemic of drug resistant TB, multiple approaches will need to be implemented simultaneously, combining the efforts of government, academic and industrial entities. These approaches include increased funding for research in antibiotic resistance and drug development for TB, development of methods for protecting the efficacy of existing drugs, and prioritization for making use of current non-TB drugs for TB treatment. Studies of pharmacodynamic and pharmacokinetics may help to improve the current regimens, namely shortening treatment courses and preventing collapses.

The development of innovative, effective drug combinations should also be encouraged to diversify therapeutic choices, especially those for drug resistant TB cases. It is important to note that studies involved in the development of new drugs continue to play a key role in strengthening the current asset for TB chemotherapy. Emphasis, however, should be placed on compounds that attack non-traditional targets, as to lower the risk for acquired drug resistance mechanisms.

Drug development is yet a time-consuming and costly process. It takes on average 12-15 years and half a billion U.S. dollars to bring an active compound from the laboratory to the market [8], while resistant bacteria typically appear within less than 2 years after a new drug is introduced to the clinic [9]. Therefore, methods for efficacy protection should be prepared even before a new drug is approved and brought into practice.

One of these methods is by the inhibition of the molecular mechanisms responsible for drug resistance. In this method, a specific inhibitor of the resistance mechanism is added to a regimen to allow the compromised antibiotic to regain its activity in the face of the resistance determinant [10]. A typical example demonstrating the effectiveness of this method is the use of β -lactamase inhibitors to inhibit β -lactamases, which inactivate β -lactam antibiotics, thereby regaining activity for β -lactams [11,12]. The combination of meropenem and the β -lactamase inhibitor clavulanate effectively kills drug resistant *M. tuberculosis* strains as well as the tubercle bacillus growing in anaerobic conditions [12]. This suggests that the aforementioned drug combination may also be useful for treatment of latent TB. For β -lactam/ β -lactamase inhibitor combinations become viable TB treatment options, the question of whether or not the *M. tuberculosis* β -lactamase BlaC will evolve to resist against clavulanate and other β -lactamase inhibitors [13] needs to be answered.

Targeting resistance mechanisms can also be used to boost the anti-TB activity of TB and non-TB drugs. For example, ethionamide has been used as a second-line TB antibiotic to treat *M. tuberculosis* strains that are resistant to first-line drugs such as isoniazid or rifampicin. The clinical use of ethionamide, nevertheless, is restricted because of its cytotoxicity to host cells [14-16]. Ethionamide is a pro drug that requires enzymatic activation in the cytoplasm of *M. tuberculosis* by EthA, an intrinsic monooxygenase that converts ethionamide to toxic nicotinamide adenine dinucleotide adducts. Unfortunately, the expression of EthA is repressed by a transcription regulator, EthR, thus limiting the anti-TB activity of ethionamide [14-16]. Recent studies demonstrate that the expression of EthA and hence the activation of ethionamide could be chemically boosted by specific inhibitors of EthR [14,15]. These inhibitors thereby potentiate the anti-TB activity of ethionamide against both drug sensitive and resistant strains of *M. tuberculosis*. By enhancing the anti-TB activity of ethionamide, this method may help lower usage doses and consequently reduce the toxicity of this important drug.

Future Perspectives

It has been widely established that TB is associated with poverty, overpopulation, and inadequate hygiene. With the current population trends (rapid growth in underdeveloped and aging in developed regions), the increased prevalence of poverty, the lack of access to clean water and sanitation, and the continued epidemic of AIDS, TB will continue to be one of the most important infectious agents in the near

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future. Besides efforts to find new drugs, both development of novel alternative therapeutics and improvement of the current therapies will be required for the successful fight against the spreading epidemic of drug resistant TB. Methods for pharmaceutical inhibition of resistance mechanisms may play an important role in this new era of antibiotic development. This approach would not only help to protect the efficacy of the current TB drugs but also boost the anti-TB activity of the existing TB- and non-TB drugs, ultimately broadening the therapeutic options for TB treatment.

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