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A New Hope in TB Treatment: The Development of the Newest Drugs

Ruiru Shi² and Isamu Sugawara¹

¹Department of Tuberculosis, Shanghai Pulmonary Hospital,
Tongji University School of Medicine, Shanghai,

²Sino-US Tuberculosis Research Center, Henan Provincial Chest Hospital,
Zhengzhou, Henan,
China

1. Introduction

TB chemotherapy is made up of a cocktail of first-line drugs: isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB) or streptomycin (SM), given for six months. If the treatment fails as a result of bacterial drug resistance, or intolerance to one or more drugs, second-line drugs are used, such as para-aminosalicylate (PAS), kanamycin, fluoroquinolones, capreomycin, ethionamide and cycloserine, that are generally either less effective or more toxic with serious side effects. Treatment becomes quite difficult by the presence of metabolically silent, persistent or dormant bacteria within host lesions, which are not susceptible to the antimycobacterial drugs that usually kill growing bacteria, but not persistent bacteria (Zhang, 2004). Therefore, in the search for improved drugs to treat drug sensitive, active tuberculosis, the target product profile might include (Zhang, 2006; Ginsberg, 2008): (1) the ability to shorten treatment duration to 2 months or less (typically defined as potency greater than the most active first-line drug, isoniazid, against *M. tuberculosis* growing under aerobic conditions, and/or potency greater than the best current drug, rifampin, under conditions where *M. tuberculosis* is slowly replicating; the latter serves as a model of the “drug-persistent” state and therefore as a marker of a compound's potential to shorten treatment-duration); (2) safety at least as good as that of current first-line TB drugs; (3) a novel mechanism of action for TB treatment; (4) oral bioavailability; (5) pharmacokinetic-pharmacodynamic profile consistent with once-daily or less frequent dosing; (6) minimal or no interactions with hepatic cytochrome P450 enzymes (and therefore minimal potential for drug-drug interactions, especially with antiretroviral therapy); and (7) low cost of drugs. Seven candidate TB drugs representing five different chemical classes are currently known to be undergoing clinical evaluation (Ginsberg, 2010). This review will provide a brief update on the latest developments in current TB drug discovery efforts.

2. PA-824

A series of bicyclic nitroimidazofurans originally investigated as radio sensitizers in cancer chemotherapy, were found to possess activity against replicating *M. tuberculosis in vitro* and

had also significant *in vivo* activity in a murine infection model. The nitroimidazo-oxazine PA-824, exhibited a low MIC (0.015 to 0.025 µg/ml) against *M. tuberculosis* and became a leading compound. PA-824 was first identified and its anti-*M. tuberculosis* activity characterized (Stover et al., 2000) in the mid-1990s by Pathogenesis Corporation, later purchased by Chiron (now Novartis). In 2002, Chiron out-licensed this compound and its analogs to the Global Alliance for TB Drug Development (TB Alliance), granting it a worldwide exclusive license to develop it for TB. Since then the TB Alliance has brought PA-824 through preclinical development, filed an Investigational New Drug Application (IND) in April 2005, conducted Phase I clinical evaluations, its safety, tolerability, pharmacokinetic properties, and efficacy in drug-sensitive, sputum smear-positive, adult pulmonary TB patients. PA-824 is currently undergoing Phase II clinical trials (Ginsberg, 2010).

In vitro studies showed MICs of PA-824 against fully susceptible and MDR strains ranging from 0.015 to 0.25 µg/ml. PA-824 activity is concentration dependent (Stover et al., 2000; Lenaerts et al., 2005; Tyagi et al., 2005). The bactericidal activity of PA-824 (25 to 50 mg/kg) was comparable to that of isoniazid (25mg/kg) in mice and guinea pigs (Stover et al., 2000; Lenaerts et al., 2005; Tyagi et al., 2005) and to those of rifampin (20mg/kg) and moxifloxacin (100mg/kg) in mice. PA-824 showed greater activity than isoniazid and moxifloxacin *in vitro* and in mice and comparable activity to combination therapy with rifampin and isoniazid (Lenaerts et al., 2005; Tyagi et al., 2005; Hu et al., 2008)). PA-824 (100mg/kg) has been incorporated in the standard regimen in mice to evaluate its potential to shorten treatment duration. Only the regimen in which isoniazid was replaced with PA-824 achieved faster lung culture conversion and a lower CFU count after 2 months of treatment than the standard regimen. However, relapse rates were similar in these regimens (Nuernberger et al., 2006). The sterilizing activity of a regimen containing PA-824 (100mg/kg), moxifloxacin (100 mg/kg), and pyrazinamide (150 mg/kg) was recently found to be better than that of rifampin (10 mg/kg), isoniazid (25 mg/kg), and pyrazinamide (150 mg/kg) in mice, indicating that PA-824 could be incorporated in a rifampin-free regimen to treat MDR-TB (Nuernberger et al., 2008). PA-824 (100 mg/kg) was highly active in a mouse model for latent TB when combined with moxifloxacin (100 mg/kg) (Nuernberger et al., 2005). PA-824 was spray-dried into porous particles containing a high drug load and possessing desirable aerosol properties for efficient deposition in the lungs (Sung et al., 2009). Pharmacokinetic parameters were determined in guinea pigs after the pulmonary administration of the PA-824 powder formulation of three doses (20, 40 and 60 mg/kg of body weight) and compared to those after the intravenous (20 mg/kg) and oral (40 mg/kg) delivery of the drug. Animals dosed by the pulmonary route showed drug loads that remained locally in the lungs for 32h after exposure, whereas those given the drug orally cleared the drug more rapidly. Therefore, pulmonary delivery may achieve the same efficacy as oral delivery at the same body dose, with a potential improvement in effectiveness related to pulmonary infection.

Ginsberg et al. (Ginsberg et al., 2009a) evaluated the safety, tolerability, and pharmacokinetics of PA-824 in two escalating-dose clinical studies, one being a single-dose study (50, 250, 500, 750, 1000, 1250, 1500mg) and the other being a multiple-dose study (200, 600, 1000, 1400mg, up to 7 days of daily dosing). In 58 healthy subjects dosed with PA-824 across these studies, PA-824 was well tolerated with no significant or serious adverse events. In both studies, following oral administration, PA-824 reached maximal plasma levels in 4 to

5 hours, independent of dose. Maximal blood levels averaged approximately 3 µg/ml (1500mg dose) in the single-dose study and 3.8 µg/ml (600mg dose) in the multiple dose study. The steady state was achieved after 5 to 6 days of daily dosing, with an accumulation ratio of approximately 2. The elimination half-life averaged 16 to 20 hours. Overall, PA-824 was well tolerated following oral doses once daily for up to 7 days, and pharmacokinetic parameters were consistent with a once-a-day regimen. The results of these studies, combined with the demonstrated activity of PA-824 against drug-sensitive and multidrug-resistant *M. tuberculosis* with no influence of serum concentration by coadministration of RIF, INH, PZA in various combinations (Nuermberger et al., 2006; Ginsberg et al., 2009a), support investigation of this novel compound for the treatment of tuberculosis. Since multiple doses of 1000mg were associated with a moderate, reversible increase in creatinine, Ginsberg et al. made a further assessment (Ginsberg et al., 2009b) of the effects of PA-824 on renal function in healthy subjects. The results suggests that PA-824 causes creatinine level to rise by inhibiting renal tubular creatinine secretion and such an effect is considered clinically benign since it has been described for several marketed drugs.

Recently, Ahmad (Ahmad et al., 2011) found that PA-824 exhibited time-dependent activity in a murine model of tuberculosis. Diacon (Diacon et al., 2010) concluded that PA-824 demonstrated bactericidal activity over the dose range of 200 to 1200mg daily over 14 days by evaluation of its early bactericidal activity and pharmacokinetics in smear-positive tuberculosis patients. Garcia-Contreras et al. (Garcia-Contreras et al., 2010) evaluated the effects of PA-824 therapeutic aerosols on the extent of TB infection in the low-inoculum aerosol infection guinea pig model. Four weeks after infection by the pulmonary route, animals received daily treatment for 4 weeks of either a high or a low dose of PA-824 dry powder aerosol. The lungs and spleens of animals receiving the high dose of inhaled PA-824 particles exhibited a lower degree of inflammation, bacterial burden, and tissue damage than those of untreated or placebo animals. Their studies indicate the potential use of PA-824 dry powder aerosols in the treatment of TB.

It has been found that PA-824 is a prodrug that needs the mycobacterial glucose-6-phosphate dehydrogenase (FDG1) or its cofactor, coenzyme F420, to be transformed into an active form (Stover et al., 2000; Manjunatha et al., 2006a; Singh et al., 2008). Activated PA-824 inhibits the synthesis of proteins and cell wall lipids. PA-824 activity is limited to *M. tuberculosis* complex (Manjunatha et al., 2006b) and is active in susceptible and resistant *M. tuberculosis* strains. No cross-resistance with standard anti-TB drugs has been observed. Mutations in the Rv3547 gene have been described in PA-824 resistant strains. Complementing these mutants with intact Rv3547 fully restored the ability of the mutants to metabolize PA-824 (Manjunatha et al., 2006a). In a further study by Barry et al. (Singh et al., 2008) revealed that Rv3547 was a deazaflavin-dependent nitroreductase (Ddn) that converted PA-824 into three primary metabolites; the major one is the corresponding des-nitroimidazole (des-nitro). When derivatives of PA-824 were used, the amount of des-nitro metabolite formed was highly correlated with anaerobic killing of *M. tuberculosis*. Dea-nitro metabolite formation generated reactive nitrogen species, including nitric oxide (NO), which are the major effectors of the anaerobic activity of these compounds. Furthermore, NO scavengers protected the bacilli from the lethal effects of the drug. Thus Barry et al. (Singh et al., 2008) concluded that PA-824 might act as intracellular NO donors and could augment a killing mechanism intrinsic to the innate immune system.

In summary, PA-824 has three key characteristics: (1) a unique mechanism of action, (2) a narrow spectrum of activity and (3) no cross-resistance with current antituberculosis drugs. Thus, PA-824 seems a most promising drug to treat latent TB together with second-line or new anti-tuberculosis drugs and shorten treatment duration.

3. OPC-67683

OPC-67683, a novel nitro-dihydro-imidazo[4,5-c]oxazole active against *M. tuberculosis*, is structurally related to PA-824 and discovered and being developed for TB by Otsuka Pharmaceutical Co. OPC-67683 is a mycolic acid biosynthesis inhibitor (Sasaki et al., 2006). It possesses highly potent activity against TB, including MDR-TB, as shown by its exceptionally low minimum inhibitory concentration (MIC) range of 0.006~0.024 µg/ml *in vitro* and highly effective therapeutic activity at low doses *in vivo* (Sasaki et al., 2006; Matsumoto et al., 2006). Additionally, the results of the post-antibiotic effect of OPC-67683 on intracellular *M. tuberculosis* showed the agent to be highly and dose-dependently active also against intracellular *M. tuberculosis* H37Rv after a 4h-pulsed exposure, and this activity at a concentration of 0.1 µg/ml was similar to that of the first-line drug rifampicin at a concentration of 3 µg/ml. The combination of OPC-67683 with rifampin and pyrazinamide exhibited a remarkably quicker eradication (by at least 2 months) of viable TB bacilli in the lung in comparison with the standard regimen consisting of rifampicin, isoniazid, ethambutol and pyrazinamide (Matsumoto et al., 2006). Furthermore, OPC-67683 did not affect, nor was affected by, the activity of liver microsome enzymes, suggesting the possibility for OPC-67683 to be used in combination with drugs, including anti-retrovirals, that induce or are metabolized by cytochrome P450 enzymes (Matsumoto et al., 2006). The early bactericidal activity of 400mg OPC-67683 in patients with pulmonary TB was low during the first 4 days. From day 4 onwards, a significant decrease in CFU was seen (Kaiser Family Foundation, 2009; Boogaard et al., 2009). OPC-67683 in multiple doses up to 400mg was tolerated well by healthy volunteers. No serious adverse events were reported (Kaiser Family Foundation, 2009; Boogaard et al., 2009). In summary, OPC-67683 is a promising new anti-TB drug with bactericidal and sterilizing activity *in vitro* and in mice. This drug is currently in Phase II clinical testing in MDR-TB patients and expected to be a powerful therapeutic.

4. TMC 207

The discovery of diarylquinoline as a promising TB drug that can shorten therapy (Andries et al., 2005) has generated much excitement. Andries et al. identified diarylquinoline compounds that were highly active against mycobacteria in *in vitro* drug screening using fast-growing *Mycobacterium smegmatis*. Modification of the diarylquinolines led to the identification of diarylquinoline TMC207 (R207910, J compound), as the most active agent, with minimum inhibitory concentration (MIC) of 0.003 µg/ml for *M. smegmatis* and 0.030 µg/ml *M. tuberculosis*. TMC207 is much less active against other bacterial species, such as *E. coli* and *S. aureus* (MIC>32 µg/ml). *M. tuberculosis* and *M. smegmatis* could develop resistance to diarylquinoline at a frequency of 1×10^{-7} to 1×10^{-8} . Diarylquinoline-resistant *M. smegmatis* and *M. tuberculosis* strains were found to harbor mutations in the subunit C encoded by *atpE* gene (D32V for *M. smegmatis* and A63P for *M. tuberculosis*) in the FO moiety of mycobacterial F1F0 proton ATP synthase, which is a key enzyme for ATP synthesis and

membrane-potential generation. Complementation studies confirmed that the mutations in *atpE* were responsible for resistance to diarylquinoline. The target for diarylquinoline was proposed to be the mycobacterial F1F0 proton ATP synthase, which was a new drug target in mycobacteria. In fact, TMC207 is also active against MDR-TB strains. Based on transposon mutagenesis analysis, F1F0 ATP synthase seems to be an essential enzyme in *M. tuberculosis* although the enzyme is not essential for *E. coli* because mutants of F1F0 were viable but grew at a reduced rate and were attenuated for virulence in mice (Zhang, 2003). TMC207 was more active than INH and RIF in the mouse model (Andries et al., 2005) and could shorten TB therapy from four months to two months in mice with an established infection model. Of particular interest is the synergy between diarylquinoline and PZA, which seems to be the most effective drug combination in sterilizing infected spleens and lungs. This finding is consistent with the previous observation that N,N'-dicyclohexylcarbodiimide (DCCD) -- which also inhibits the same C chain of the FO moiety of F1F0 ATPase as diarylquinoline -- has synergy with PZA against *M. tuberculosis* (Zhang, 2003). Thus, the observed synergy of diarylquinoline with PZA [24] could be explained the same way as the synergy of DCCD with PZA. TMC207 had excellent early and late bacterial activity, good pharmacokinetic and pharmacodynamic properties with a long half life, absence of significant toxicity in mouse and preliminary human safety testing, raising the hope that diarylquinoline might be used for shortening TB therapy in humans (Andries et al., 2005).

There are several unusual features of TMC207 that require further explanation. First, antimycobacterial drugs usually do not show the same degree of activity against fast and slow growing mycobacteria. Drugs like INH, RIF, and PZA are more active against slow growing *M. tuberculosis* but less active against fast growers like *M. smegmatis*, which has higher efflux activity and is better able to maintain its energy status compared with *M. tuberculosis*. However, in this case, diarylquinolines are even more active against fast growing *M. smegmatis* than against *M. tuberculosis*, which is quite unusual. Second, the high early and late bactericidal activity in mice is unusual because other TB drugs show either early or late sterilizing activity but not both. Third, the selective activity of diarylquinolines against the mycobacterial enzyme F1F0 ATPase (present in all mycobacteria, but also in host cell mitochondria) without apparent toxicity is quite remarkable. Finally, mycobacteria would be expected to have alternative means, such as the electron transport chain, to produce energy or ATP without F1F0 ATPase, and thus the inhibition of F1F0 ATPase by diarylquinoline would not be lethal unless TMC207 also interferes with other drug targets in the mycobacteria.

An extended early bactericidal assay (Rustomjee et al., 2008ab) was conducted with human patients who were treated for 7 days with TMC207 given at 25mg, 100mg, and 400mg per day. Patients treated with either 600mg per day of RIF or 300mg per day of INH were used as controls. This study showed that TMC207 given at 400mg per day revealed a significant decrease in CFU counts in the sputum of treated patients in comparison with the pretreatment levels. A drug-drug interaction study was conducted in 16 healthy volunteers who received a single dose of 300mg of TMC207 alone and seven daily doses of 10mg/kg of body weight of RIF. The area under the concentration-time curve (AUC) from time zero to 336 h for TMC207 after its coadministration with RIF was about half that when it was dosed alone, indicating that the metabolism of TMC207 is induced by coadministration with RIF. Lounis et al. (Lounis et al., 2008) assessed the impact of reducing the dose of TMC207 on its

efficiency when TMC207 was combined with a background regimen of INH, RIF and PZA. Addition of 25mg/kg of body weight or 12.5mg/kg TMC207 to the background regimen resulted in faster bacterial clearance and culture negativity. The difference in efficacy between the two doses was not statistically significant. The minimal bactericidal dose of TMC207 when it was tested as a part of the combination was identical to that when it was tested as monotherapy. Because of the drug-drug interaction in human, the activity of TMC207 in human could be less than that expected from studies with mice. Data from the mouse model demonstrate that TMC207 has significant activity, even when its exposure is reduced by 50% and when it is added to a strong background regimen of INH, RFP, and PZA (Lounis et al., 2008). In killing kinetic studies, the bactericidal effect of TMC207 in mice was modest during the first week of treatment, but it increased in the following 3 weeks, while the bactericidal activity of isoniazid was limited to the first week of treatment.

Because of its potent activity against *M. tuberculosis*, its distinct mechanism of action, and its impressive activity at what appear to be human-equipotent dosages in the murine model, TMC207 is a particularly promising new drug candidate. Recently, Zhang (Zhang et al., 2011) used an established experimental model of latent TB infection chemotherapy in which mice are aerosol-immunized with a recombinant BCG vaccine prior to low-dose aerosol infection with *Mycobacterium tuberculosis*, the efficacy of TMC207 alone and in combination with rifapentine was compared to currently recommended control regimens as well as once-weekly rifapentine + isoniazid and daily rifapentine +/- isoniazid. Parameters used were monthly lung CFU counts and relapse rates. Lung CFU counts were stable around 3.75 log₁₀ for up to 7.5 months post-infection in untreated mice. Rifamycin-containing regimens were superior to isoniazid monotherapy. TMC207 exhibited sterilizing activity at least as strong as that of rifampin alone and similar to that of rifampin + isoniazid, but daily rifapentine +/- isoniazid was superior to TMC207. Addition of TMC207 to rifapentine did not improve rifapentine's sterilizing activity in this model. That signifies that TMC207 has substantial sterilizing activity and may enable treatment of DR-LTBI (drug-resistant latent tuberculosis infection) in 3-4 months.

5. Moxifloxacin and gatifloxacin

The fluoroquinolones are a promising class of drugs for the treatment of TB. In particular, they are distributed broadly throughout the body, including within cells, which explains their efficacy against mycobacteria. Moxifloxacin and gatifloxacin are candidates for shortening TB treatment, since they have the lowest MICs and greatest bactericidal activity, as expressed in the rate of fall in CFU count (Paramasivan et al., 2005; Shandil et al., 2007).

Moxifloxacin is a broad-spectrum 8-methoxy fluoroquinolone with activity against both gram-positive and gram-negative bacteria. The fluoroquinolones are a promising class of drugs for the treatment of TB. In particular, they are distributed broadly throughout the body, including within cells, which explains their efficacy against intracellular mycobacteria. Moxifloxacin and gatifloxacin are active against gram-negative bacteria, including anaerobes. It inhibits bacterial DNA gyrase, an enzyme that is essential for the maintenance of DNA supercoils, which are necessary for chromosomal replication (Shindikar & Viswanathan, 2005). The development of mycobacterial resistance to fluoroquinolones has been described in MDR strains and in strains from HIV-infected TB patients with a low CD4 count (Shandil et al., 2007). Fluoroquinolone resistance is due to stepwise mutations in the quinolone resistance-

determining region of the mycobacterial *gyrA* and *gyrB* genes (Ginsberg, 2008). No cross-resistance with the first-line anti-TB drugs has been shown (Hu et al., 2003). Moxifloxacin is metabolized by glucuronidation and sulfation (Phase II metabolism) rather than by CYP450-mediated (Phase I) metabolism (Nijland et al., 2007). *In vitro* studies with moxifloxacin show MICs of 0.25 to 0.5mg/l (Shandil et al., 2007). *In vitro* studies and studies in mice showed enhanced bactericidal activity of moxifloxacin and isoniazid when coadministered (Yoshimatsu et al., 2002). Moxifloxacin efficacy has also been shown in humans. Early bactericidal activity (EBA) studies in newly diagnosed pulmonary TB patients showed comparable activity of moxifloxacin (400mg) and isoniazid (300mg or 6mg/kg) (Pletz et al., 2004). The regimen with moxifloxacin caused the fastest decrease in CFU during the early phase of a biexponential fall (in a nonlinear model that differentiates between quickly and slowly eliminated bacilli) (Rustomjee et al., 2008b). A multicenter three-armed trial in which the standard regimen is compared to a regimen of 2RHZM/2RHM and a regimen of 2RMZE/2RM has recently started (Rosenthal et al., 2006). Moxifloxacin could be of use in the treatment of latent TB (Hu et al., 2008). The combination of 3 months of once-weekly moxifloxacin and rifapentine was as effective as 6 months of isoniazid monotherapy in a mouse model for latent TB (Ginsberg et al., 2009b). A single dose moxifloxacin of up to 800mg was tolerated well but little is known about the long-term tolerability in TB patients. In February 2008, Bayer distributed a "Dear Doctor" letter warning physicians about rare but severe hepatological and dermatological adverse events associated with moxifloxacin. Therefore, the adverse events of moxifloxacin require extended evaluation (Boogaard et al., 2009).

Gatifloxacin and moxifloxacin show cross-resistance. The MICs of gatifloxacin against *M. tuberculosis* range from 0.2 to 0.5mg/l (Rodriguez et al., 2002). *In vitro* studies and studies in mice showed improved activity of rifampin and isoniazid when gatifloxacin was added and even more when the regimen also included pyrazinamide (Kubendiran et al., 2006). A multicenter trial is enrolling patients at five African sites. It compares the efficacy and tolerability of a 4-month regimen of 2 months of rifampin plus isoniazid plus pyrazinamide plus gatifloxacin followed by 2 months of rifampin plus isoniazid plus gatifloxacin (2RHZG/2RHG) to the standard 2RHZE/4RH regimen. An increased risk of dysglycemia was described in elderly patients using gatifloxacin for a variety of bacterial infections (Chen et al., 2006). Elderly patients with hypoglycemia or hyperglycemia were 4 or 17 times more likely to have used gatifloxacin than controls. Therefore, the risk of mycobacterial resistance development and the recently found association between gatifloxacin and dysglycemic events are concerns. If the phase III trials demonstrate safety and efficacy, a 4-month, fluoroquinolone-based treatment for DS-TB could be registered for use by 2015 (Ginsberg, 2010).

6. SQ109

SQ109 is an investigational new drug candidate that was identified from a library of over 60,000 combinatorial compounds, based on a 1,2-ethylenediamine pharmacophore from ethambutol (Kaiser Family Foundation, 2009). However, only the diamine nucleus remains and studies to date suggest that SQ109 should not necessarily be considered a second-generation EMB analogue. Although its mechanism of action involves cell wall inhibition, the specific target of SQ109 remains unknown. *In vitro*, it has an MIC range of 0.11-0.64

µg/ml against *M. tuberculosis*, including strains resistant to INH, RIF or EMB [41]. It inhibits growth of *M. tuberculosis* in macrophages to a similar extent as INH and to a greater extent than EMB (Protopopova et al., 2005; Jia et al., 2005). *In vitro*, at sub-MIC concentrations, SQ109 demonstrates synergy with RIF and INH and additive activity with streptomycin, but neutral effects with EMB and PZA. Some synergy between SQ109 and RIF is also evident against RIF-resistant strains (Chen et al., 2006). SQ109 has demonstrated activity in murine models, where it is at least four times as potent as EMB, as 25mg/kg of SQ109 and 100mg/kg of EMB have similar effects (Protopopova et al., 2005). Substitution of SQ109 for EMB enhances the activity of the standard four-drug 2-month initial regimen of HREZ (Nikonenko et al., 2007). The activity of SQ109 in the mouse is particularly remarkable, given the low serum concentrations. This is presumably because the drug has a rapid tissue distribution that results in sustained concentrations in lungs and spleen that exceed the MIC (Jia et al., 2005). In summary, SQ109 is a potential anti-TB drug that has entered Phase I / II clinical trials. It has low MICs against both susceptible and resistant *M. tuberculosis*. SQ109 has different and more favorable properties than ethambutol, suggesting that it should be regarded as a truly new diamine, and not just as an ethambutol analogue. SQ109 could be included in regimens containing RIF and INH, since synergism with both drugs has been shown. Clinical trials are ongoing to establish its future role in TB treatment.

The combination of SQ109 with TMC207 improved an already excellent TMC207 MIC for *M. tuberculosis* H37Rv by 4- to 8-fold and enhanced the drug postantibiotic effect by 4 h (Reddy et al., 2010). Thus, SQ109 can be used as combination of other anti-TB drugs in the near future.

7. LL3858

Pyrrole derivatives have demonstrated activity against *M. tuberculosis in vitro* (Protopopova et al., 2007). Recently, a substituted pyrrole derivative, LL3858 has advanced to Phase I testing for TB. Preliminary data suggest that LL3858 has potent *in vitro* activity, with an MIC range of 0.06-0.5 µg/ml against *M. tuberculosis*, including MDR strains (Arora, 2004). Monotherapy in a murine model of TB yielded bactericidal activity at doses well below the toxic threshold. Moreover, addition of LL3858 significantly enhanced the sterilizing activity of the standard HRZ regimen (Arora, 2004). Further information on this compound is eagerly awaited.

8. Linezolid

The oxazolidinones are a new class of synthetic antibiotics with broad activity against gram-positive bacteria and mycobacteria through a unique mechanism of ribosomal protein synthesis inhibition. Other positive attributes include high oral bioavailability and lack of cross-resistance with existing antibiotics. Linezolid is the first oxazolidinone to be used clinically, although it is not approved for use in TB. Its MIC for *M. tuberculosis* is 0.125-1µg/ml (Alcala et al., 2003). It is reported that 100mg/kg once daily appeared to be bacteriostatic or weakly bactericidal, causing approximately 1~1.5 log reduction in bacterial counts over 28 days and that 600mg of linezolid orally twice daily in salvage regimens for MDR-TB has been associated with sputum culture conversion and cure, albeit with frequent dose- or treatment-limiting side effects such as anaemia, thrombocytopenia, and peripheral

or optic neuropathy (Fortum et al., 2005; Von der Lippe et al., 2006). Linezolid acts as an inhibitor of bacterial ribosomal protein synthesis. *In vitro*-selected linezolid-resistant *M. tuberculosis* (MIC 4~32 µg/ml) were reported to harbor 23S rRNA gene mutation (Hillemann et al., 2008), but Richter et al. claimed that they had found the first linezolid-resistant clinical isolates of *M. tuberculosis* (MIC 8 µg/ml) with no such kind of mutation, suggesting different mechanisms of resistance (Richter et al., 2007).

When interaction between linezolid and *M. tuberculosis* was examined using an experimental *in vitro* model, linezolid seems an alternative as far as generation of resistance is concerned in the treatment of multi-resistant tuberculosis (Cremades et al., 2011).

Drug	Class	Sponsor(s) ^a	Mechanism of action	Target	Mechanism of resistance	Development of stage
PA-824	Nitroimidazo-oxazine	GATB	Inhibition of protein and cell wall lipid synthesis, while anaerobic activity by the generating reactive nitrogen species, including nitric oxide	F420-dependent nitroreductase	Rv0407, Rv3547, Rv3261, Rv3262 gene mutations	Phase II
OPC-67683	Nitroimidazo-oxazine	Otsuka	Inhibition of cell wall lipid synthesis, inhibition of mycolic acid biosynthesis	a nitroreductase	Rv3547 gene mutations	Phase II
TMC207	Diarylquinoline	Tibotec	Inhibition of ATP synthesis and membrane potential	F1F0 proton ATP synthase	atpE gene mutation	Phase II
Moxifloxacin	Fluoroquinolone	Bayer, GATB	Inhibition of DNA synthesis CDC, NIH, FDA	DNA gyrase	gyrA gene mutation	Phase III
Gatifloxacin	Fluoroquinolone	OFLOTUB, NIH	Inhibition of DNA synthesis consortium ^b	DNA gyrase	gyrA gene mutation	Phase III
SQ109	Diethylamine	Sequella	Inhibition of cell wall synthesis	unknown	unknown	Phase I/II
LL3858	Pyrrole	Lupin	unknown	unknown	unknown	Phase I
Linezolid	Oxazolidinone	NIH, Pfizer	Inhibition of protein synthesis	Ribosomal inhibition	23S rRNA mutation	lead optimization

^aGATB, Global Alliance for TB Drug Development; CDC, US Centers for Disease Control and Prevention TB Trials Consortium; NIH, US National Institutes of Health; FDA, US Food and Drug Administration.
^bLupin Ltd, NIH National Institute of Allergy and Infectious Diseases TB Research Unit, TB Research Center (Chennai), World Health Organization Special Programme for Research and Training in Tropical Diseases.

Table 1. Promising new drug candidates and their drug targets

9. Conclusion and future prospective

A number of potential candidate drugs with novel modes of action have entered clinical trials in recent years, and these are likely to be effective against resistant strains. This review summarizes, first, how to identify *M. tuberculosis* among many acid-fast bacilli and second,

how to evaluate drug resistance against isolated *M. tuberculosis*. Lastly the latest information about these candidate drugs, including PA-824, OPC-67683, TMC207, moxifloxacin, gatifloxacin, SQ109, LL3858 and linezolid, and describes their activity, pharmacokinetics, mechanisms of action, and development of resistance against them. Promising new anti-TB drug candidates and their drug targets are summarized in Table 1.

For the first time in 40 years, several new drugs with promising attributes have entered the clinical development pipeline for the treatment of TB. With good fortune, one or more of these agents will fulfill or exceed its potential demonstrated in animal models and provide a new cornerstone for the treatment of drug-sensitive and drug-resistant TB. Additional candidates are percolating up through discovery and preclinical development programs. In spite that many challenges must be overcome before any of these new drugs contributes meaningfully to control of TB, TB drug research and development today is in a stronger position to successfully meet the urgent public health need for improved TB therapies than it has been for half a century due to renewed interest, scientific and technological advances, and the combined efforts of the public and private sectors. These efforts must be further enhanced to ensure ultimate success in discovering, developing and delivering radically improved therapies for TB patients.

PNU100480 (Pfizer) and AZD5847 (AstraZeneca) are being repurposed for TB (Ginsberg, 2010). Addition of PNU100480 to first-line drugs shortened the time needed to cure murine tuberculosis significantly. They are now in phase I testing of multiple dose safety, tolerability and pharmacokinetics when administered as an oral suspension over 14 days in healthy volunteers. The results are not yet available at the time of writing this chapter.

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11. References

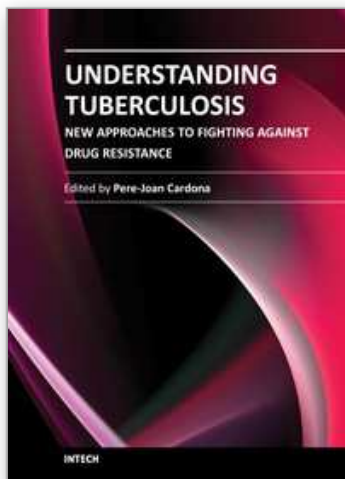
- Ahmad, Z.; Peloquin, C. A.; Singh, R. P.; Derendorf, H.; Tyagi, S.; Ginsberg, A.; Grosset, J. H. & Nuernberger, E. L. (2011). PA-824 exhibits time-dependent activity in a murine model of tuberculosis. *Antimicrob. Agents Chemother.*, 55, 239-245, ISSN 0066-4804
- Alcala, L.; Ruiz-Serrano, M.J.; Turegano, C.P.; Viedma, D.G.; Diaz-Infantes, M.; Marin-Arriaza, M. &
- Bouza, E. (2003) *In vitro* activities of linezolid against clinical isolates of *Mycobacterium tuberculosis* that are susceptible or resistant to first-line antituberculous drugs. *Antimicrob. Agents Chemother.*, 47, 416-417, ISSN 0066-4804
- Andries, K.; Verhasselt, P.; Guillemont, J.; Gohlmann, H.W.H.; Neefs, J.M.; Winkler, H.; Gestel, J.V.; Timmerman, P.; Zhu, M.; Lee, E.; Williams, P.; DeChaffoy, D.; Huitric, E.; Hoffner, S.; Cambau, E.; Truffot-Pernot, C.; Lounis, N. & Jarlier, V. (2005) R207910, a diarylquinoline active on ATP synthase of *Mycobacterium tuberculosis*. *Science*, 307, 223-227, ISSN 1095-9203
- Arora, S. (2004) Eradication of *Mycobacterium tuberculosis* infection in 2 months with LL3858: a preclinical study. *Int. J. Tuberc. Lung Dis.*, 8 (Supl.1), S29, ISSN 1027-3719

- Boogaard, J.V.D.; Kibiki, G.S.; Kisanga, E.R.; Boeree, M.J. & Aarnoutse, R.E. (2009) New drugs against tuberculosis: problems, progress, and evaluation of agents in clinical development. *Antimicrob. Agents Chemother.*, 53, 849-862, ISSN 0066-4804
- Chen, P.; Gearhart, J.; Protopopova, M.; Einck, L. & Nacy, C.A. (2006) Synergistic interactions of SQ109, a new ethylene diamine, with front-line antitubercular drugs *in vitro*. *J. Antimicrob. Chemother.*, 58, 332-337, ISSN 0305-7453
- Cremades, R.+ Rodriguez, J. C.; Garcia-Pachon, E.; Galiana, A.; Ruiz-Garcia, M.; Lopez, P. & Royo, G. (2011). *APMIS*, 119, 304-308, ISSN 1600-0463
- Diacon, A.H.; Pym, A.; Grobusch, M.; Patientia, R.; Rustomjee, R.; Page-Shipp, L.; Beule, K.; Andries, K. & McNeeley, D.F. (2009) The diarylquinoline TMC207 for multidrug-resistant tuberculosis. *N. Engl. J. Med.*, 23: 2397-2405, ISSN 0028-4793
- Diacon, A. H.; Dawson, R.; Hanekom, M.; Narunsky, K.; Maritz, S. J.; Venter, A.; Donald, P. R.; Whitney, K.; Ginsberg, A. M. & Spigelman, M. K. (2010). Early bactericidal activity and pharmacokinetics of PA-824 in smear-positive tuberculosis patients. *Antimicrob. Agents Chemother.*, 54, 3402-3407, ISSN 0066-4804
- Fortum, J.; Martin-Davila, P. & Navas, E. (2005) Linezolid for the treatment of multidrug-resistant tuberculosis. *J. Antimicrob. Chemother.*, 56, 180-185, ISSN 0305-7453
- Garcia-Contreras, L.; Sung, J. C.; Muttill, P.; Padilla, D.; Elbert, K. J.; Hickey, A. J. & Edwards, D. A. (2010). Dry powder PA-824 aerosols for treatment of tuberculosis in guinea pigs. *Antimicrob. Agents Chemother.*, 54, 1436-1442, ISSN 0066-4804
- Ginsberg, A.M. (2008) Emerging drugs for active tuberculosis. *Semin. Respir. Crit. Care Med.*, 29, 552-559, ISSN 1069-3424
- Ginsberg, A.M.; Laurenzi, M.W.; Rouse, D.J.; Whitney, K.D. & Spigelman, M.K. (2009a) Safety, tolerability and pharmacokinetics of PA-824 in healthy subjects. *Antimicrob. Agents Chemother.*, 53, 3720-3725, ISSN 0066-4804
- Ginsberg, A.M.; Laurenzi, M.W.; Rouse, D.; Whitney, K.D. & Spigelman, M.K. (2009b) Assessment of the effects of the nitroimidazo-oxazine, PA-824, on renal function in healthy subjects. *Antimicrob. Agents Chemother.*, 53, 3726-3733, ISSN 0066-4804
- Ginsberg, A. M. (2010). Drugs in development for tuberculosis. *Drugs*, 70, 2201-2214, ISSN 0012-6667
- Hillemann, D.; Rusch-Gerdes, S. & Richter, E. (2008) *In vitro*-selected linezolid-resistant *Mycobacterium tuberculosis*. *Antimicrob. Agents Chemother.*, 52, 800-801, ISSN 0066-4804
- Hu, Y.; Coates, A.R.M. & Mitchison, D.A. (2003) Sterilizing activities of fluoroquinolones against rifampin-tolerant populations of *Mycobacterium tuberculosis*. *Antimicrob. Agents Chemother.*, 47, 653-657, ISSN 0066-4804
- Hu, Y.; Coats, A. R. & Mitchison, D. A. (2008). Comparison of the sterilizing activities of the nitroimidazopyran PA-824 and moxifloxacin against persisting *Mycobacterium tuberculosis*. *Int. J. Tuberc. Lung Dis.*, 12, 69-73, ISSN 1027-3719
- Jia, L.; Tomaszewski, J.E.; Hanrahan, C.; Coward, L.; Noker, P.; Gorman, G.; Nikonenko, B. & Protopopova, M. (2005) Pharmacodynamics and pharmacokinetics of SQ109, a new diamine-based antitubercular drug. *Br. J. Pharmacol.*, 144, 80-87, ISSN 1476-5381
- Kaiser Family Foundation. Open Forum on Key Issues in TB Drug Development, London, United Kingdom. HYPERLINK "http://www.kaisernetwork.org/health_cast

- Accessed 22 Nov 2009" http://www.kaisernetwork.org/health_cast. Accessed 22 Nov 2009.
- Kubendiran, G.; Paramasivan, C.N.; Sulochana, S. & Mitchison, D.A. (2006) Moxifloxacin and gatifloxacin in an acid model of persistent *Mycobacterium tuberculosis*. *J. Chemother.*, 18, 617-623, ISSN 1120-009X
- Lenaerts, A.J.; Gruppo, V.; Marietta, K.S.; Johnson, C.M.; Driscoll, D.K.; Tompkins, N.M.; Rose, J.D.; Reynolds, R.C. & Orme, I.M. (2005) Preclinical testing of the nitroimidazopyran PA-824 for activity against *Mycobacterium tuberculosis* in a series of in vitro and in vivo models. *Antimicrob. Agents Chemother.*, 49, 2294-2301, ISSN 0066-4804
- Lounis, N.; Gevers, T.; Berg, J.V.D. & Andries, K. (2008) Impact of the interaction of R207910 with rifampin on the treatment of tuberculosis studied in the mouse model. *Antimicrob. Agents Chemother.*, 52, 3568-3572, ISSN 0066-4804
- Manjunatha, U.H.; Boshoff, H.; Dowd, C.S.; Zhang, L.; Albert, T.J.; Norton, J.E.; Daniels, L.; Dick, T.; Pang, S.S. & Barry, C.E. (2006a) Identification of a nitroimidazo-oxazine-specific protein involved in PA-824 resistance in *Mycobacterium tuberculosis*. *Proc. Natl. Acad. Sci. USA*, 103, 431-436, ISSN 0027-8424
- Manjunatha, U.H.; Lahiri, R.; Randhawa, B.; Dowd, C.S.; Krahenbuhl, J.L. & Barry, C.E. (2006b) *Mycobacterium leprae* is naturally resistant to PA-824. *Antimicrob. Agents Chemother.*, 50, 3350-3354, ISSN 0066-4804
- Matsumoto, M.; Hashizume, H.; Tomoshige, T.; Kawasaki, M.; Tsubouchi, H.; Sasaki, H.; Shimokawa, Y. & Komatsu, M. (2006) OPC-67683, a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis in vitro and in mice. *Plos Med.*, 3:e466, ISSN 1549-1277
- Nijland, H.M.; Ruslami, R.; Suroto, A.J.; Burger, D.M.; Alisjahbana, B.; van Crevel, R. & Aarnoutse, R.E. (2007) Rifampicin reduces plasma concentrations of moxifloxacin in patients with tuberculosis. *Clin. Infect. Dis.*, 45, 1001-1007, ISSN 1058-4838
- Nikonenko, B.V.; Protopopova, M.; Samala, R.; Einck, L. & Nacy, C.A. (2007) Drug therapy of experimental tuberculosis (TB): improved outcome by combining SQ109, a new diamine antibiotic, with existing TB drugs. *Antimicrob. Agents Chemother.*, 51, 1563-1565, ISSN 0066-4804
- Nuermberger, E.; Tyagi, S.; William, K.N.; Rosenthal, I.; Bishai, W.R. & Grosset, J.H. (2005) Rifapentine, moxifloxacin, or DNA vaccine improves treatment of latent tuberculosis in a mouse model. *Am. J. Respir. Crit. Care Med.*, 172, 1452-1456, ISSN 1073-449X
- Nuermberger, E.; Rosenthal, I.; Tyagi, S.; Williams, K.N.; Almeida, D.; Peloquin, C.A.; Bishai, W.R. & Grosset, J.H. (2006) Combination chemotherapy with the nitroimidazopyran PA-824 and first-line drugs in a murine model of tuberculosis. *Antimicrob. Agents Chemother.*, 50, 2621-2625, ISSN 0066-4804
- Nuermberger, E.; Tyagi, S.; Tasneen, R.; Williams, K.N.; Almeida, D.; Rosenthal, I. & Grosset, J.H. (2008) Powerful bactericidal and sterilizing activity of a regimen containing PA-824, moxifloxacin, and pyrazinamide in a murine model of tuberculosis. *Antimicrob. Agents Chemother.*, 52, 1522-1524, ISSN 0066-4804
- Paramasivan, C.N.; Sulochana, S.; Kubendiran, G.; Venkatesan, P. & Mitchison, D.A. (2005) Bactericidal action of gatifloxacin, rifampin, and isoniazid on logarithmic- and

- stationary-phase cultures of *Mycobacterium tuberculosis*. *Antimicrob. Agents Chemother.*, 49, 627-631, ISSN 0066-4804
- Pletz, M.W.R.; De Roux, A.; Roth, A.; Neumann, K.H.; Mauch, H. & Lode, H. (2004) Early bactericidal activity of moxifloxacin in treatment of pulmonary tuberculosis: a prospective, randomized study. *Antimicrob. Agents Chemother.*, 48, 780-782, ISSN 0066-4804
- Protopopova, M.; Hanrahan, C. & Nikonenko, B. (2005) Identification of a new antitubercular drug candidate, SQ109, from a combinatorial library of 1,2-ethylenediamines. *J. Antimicrob. Chemother.*, 56, 968-974, ISSN 0305-7453
- Protopopova, M.; Bogatcheva, E.; Nikonenko, B.; Hundert, S.; Einck, L. & Nacy, C.A. (2007) In search of new cures for tuberculosis. *Med. Chem.*, 3, 301-316, ISSN 0929-8673
- Reddy, V. M.; Einck, L.; Andries, K. & Nacy, C. A. (2010). In vitro interactions between new antitubercular drug candidates SQ109 and TMC207. *Antimicrob. Agents Chemother.*, 54, 2840-2846, ISSN 0066-4804
- Richter, E.; Rusch-Gerdes, S. & Hillemann, D. (2007) First linezolid-resistant clinical isolates of *Mycobacterium tuberculosis*. *Antimicrob. Agents Chemother.*, 51, 1534-1536, ISSN 0066-4804
- Rodriguez, J.C.; Ruiz, M.; Lopez, M. & Royo, G. (2002) In vitro activity of moxifloxacin, levofloxacin, gatifloxacin and linezolid against *Mycobacterium tuberculosis*. *Int. J. Antimicrob. Agents*, 20, 464-467, ISSN 0924-8579
- Rosenthal, I.M.; Williams, K.; Tyagi, S.; Peloquin, A.; Vernon, A.; Bishai, W.R.; Grosset, J.H. & Nuermberger, E.L. (2006) Potent twice-weekly rifapentine-containing regimens in murine tuberculosis. *Am. J. Respir. Crit. Care Med.*, 174, 94-101, ISSN 1073-449X
- Rustomjee, R.; Lienhardt, C.; Kanyok, T.; Davies, G.R.; Levin, J.; Mthiyane, T.; Reddy, C.; Sturm, A.W.; Sirgel, F.A.; Allen, J.; Coleman, D.J.; Fourie, B. & Mitchison, D.A. (2008a) A phase study of the sterilizing activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *Int. J. Tuberc. Lung Dis.*, 12, 128-138, ISSN 1027-3719
- Rustomjee, R.; Diacon, A.; Allen, J.; Venter, A.; Reddy, C.; Patienta, R.F.; Mthiyane, T.C.; De Marez, T.; Van Heeswijk, R.; Kerstens, R.; Koul, A.; De Beule, K.; Donald, P. R. & McNeeley, D.F. (2008b) Early bactericidal activity and pharmacokinetics of the investigational diarylquinoline TMC207 in treatment of pulmonary tuberculosis. *Antimicrob. Agents Chemother.*, 52, 2831-2835, ISSN 0066-4804
- Sasaki, H.; Haraguchi, Y.; Itotani, M.; Kuroda, H.; Hashizume, H.; Tomishige, T.; Kawasaki, M.; Matsumoto, M.; Komatsu, M. & Tsubouchi, H. (2006) Synthesis and antituberculosis activity of a novel series of optically active 6-nitro-2,3-dihydroimidazo [2,1-b] oxazoles. *J. Med. Chem.*, 49, 7854-7860, ISSN 1520-4804
- Shandil, R.K.; Jayaram, R.; Kaur, P.; Gaonkar, S.; Suresh, B.L.; Mahesh, B.N.; Jayashree, R.; Nandi, V.; Bharath, S. & Balasubramanian, V. (2007) Moxifloxacin, ofloxacin, sparfloxacin, and ciprofloxacin against *Mycobacterium tuberculosis*: evaluation of in vitro and pharmacodynamic indices that best predict in vivo efficacy. *Antimicrob. Agents Chemother.*, 51, 576-582, ISSN 0066-4804
- Shindikar, A.V. & Viswanathan, C.L. (2005) Novel fluoroquinolones: design, synthesis, and in vivo activity in mice against *Mycobacterium tuberculosis* H37Rv. *Bioorg. Med. Chem. Lett.*, 15, 1803-1806, ISSN 0960-894X

- Singh, R.; Manjunatha, U.; Boshoff, H.I.M.; Hwan, H. Y.; Niyomrattanakit, P.; Ledwidge, R.; Dowd, C.S.; Lee, I.Y.; Kim, P.; Zhang, L.; Kang, S.; Keller, T.H.; Jiricek, J. & Barry, C.E. (2008) PA-824 kills nonreplicating *Mycobacterium tuberculosis* by intracellular NO release. *Science*, 322, 1392-1395, ISSN 1095-9203
- Stover, C.K., Warrenner, P., VanDevanter, D.R.; Sherman, D.R.; Arain, T.M.; Langhorne, M.H.; Anderson, S.W.; Towell, J.A.; Yuan, Y.; McMurray, D.N.; Kreiswirth, B.N.; Barry, C.E. & Baker, W.R. (2000) A small molecule nitroimidazopyran drug candidate for the treatment of tuberculosis. *Nature*, 405, 962-966, ISSN 0028-0836
- Sung, J.C.; Garcia-Contreras, L.; VerBerkmoes, J.L.; Peloquin, C.A.; Elbert, K.J.; Hickey, A.J. & Edwards, D.A. (2009) Dry powder nitroimidazopyran antibiotic PA-824 aerosol for inhalation. *Antimicrob. Agents Chemother.*, 53, 1338-1343, ISSN 0066-4804
- Tyagi, S.; Nuermberger, E.; Yoshimatsu, T., Williams, K.; Rosenthal, I.; Lounis, N.; Bishai, W. & Grosset, J. (2005) Bactericidal activity of the nitroimidazopyran PA-824 in a murine model of tuberculosis. *Antimicrob. Agents Chemother.*, 49, 2289-2293, ISSN 0066-4804
- Umubyeyi, A.N.; Rigouts, L.; Shamputa, I.C.; Fissette, K.; Elkrin, Y.; de Rijk, P.W.; Struelens, M.J. & Portaels, F. (2007) Limited fluoroquinolone resistance from Rwanda: results of a national surgery. *J. Antimicrob. Chemother.*, 59, 1031-1033, ISSN 0305-7453
- Von der Lippe, B.; Sandven, P. & Brubakk, O. (2006) Efficacy and safety of linezolid in multidrug resistant tuberculosis (MDR-TB)—a report of ten cases. *J. Infect.*, 52, 92-96, ISSN 0163-4453
- Yoshimatsu, T.E.; Nuermberger, E.; Tyagi, S.; Chaisson, R.; Bishai, W. & Grosset, J. (2002) Bactericidal activity of increasing daily and weekly doses of moxifloxacin in murine tuberculosis. *Antimicrob. Agents Chemother.*, 46, 1875-1879, ISSN 0066-4804
- Zhang, T.; Li, S. Y.; Williams, K. N.; Andries, K. & Nuermberger, E.L. (2011). Short-course chemotherapy with TMC-207 and rifapentine in a murine model of latent tuberculosis infection. *Am. J. Respir. Crit. Care Med.*, 2011 (Epub ahead of print), ISSN 1073-449X
- Zhang, Y. (2003) Mode of action of pyrazinamide: disruption of membrane potential and transport by pyrazinamide. *J. Antimicrob. Chemother.*, 52, 790-795, 0305-7453
- Zhang, Y. (2004) Persistent and dormant tubercle bacilli and latent tuberculosis. *Front. Biosci.*, 9, 1136-1156, ISSN 1093-9946
- Zhang, Y.; Post-Martens, K. & Denkins, S. (2006) New drug candidates and therapeutic targets for tuberculosis therapy. *Drug Discovery Today*, 11, 21-27, ISSN 1359-6446



Understanding Tuberculosis - New Approaches to Fighting Against Drug Resistance

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In 1957, a Streptomyces strain, the ME/83 (S.mediterranei), was isolated in the Lepetit Research Laboratories from a soil sample collected at a pine arboretum near Saint Raphael, France. This drug was the base for the chemotherapy with Streptomycin. The euphoria generated by the success of this regimen led to the idea that TB eradication would be possible by the year 2000. Thus, any further drug development against TB was stopped. Unfortunately, the lack of an accurate administration of these drugs originated the irruption of the drug resistance in Mycobacterium tuberculosis. Once the global emergency was declared in 1993, seeking out new drugs became urgent. In this book, diverse authors focus on the development and the activity of the new drug families.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
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Phone: +86-21-62489820
Fax: +86-21-62489821

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