Review

Development of New Anti-tuberculosis Drug Candidates

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\textit{Mycobacterium tuberculosis}, the causative agent of tuberculosis, is a tenacious and remarkably successful pathogen that has latently infected a third of the world’s population. Each year there are eight million new cases of TB, two million deaths, and moreover, the rapid spread of the human immunodeficiency virus (HIV) has exacerbated the TB epidemic (Wright et al. 2009). Although TB can be cured with chemotherapy, the treatment is exceedingly lengthy, taking 6~9 months. Apart from significant toxicity, the lengthy therapy also results in poor patient compliance, which is the main reason for the emergence of drug-resistant, and often deadly multidrug-resistant, TB (MDR-TB) bacteria. Currently, TB chemotherapy includes a cocktail of first-line drugs: isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB) or streptomycin (SM), given for six months (Shi et al. 2007). 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-aminosalicyclic acid (PAS), kanamycin, fluoroquinolones, capreomycin, ethionamide and cycloserine, which are generally less effective or more toxic with serious side effects. Treatment is made 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 (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 \textit{M. tuberculosis} growing under aerobic conditions, and/or potency greater than the best current drug, rifampin, under conditions where \textit{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 the duration of treatment); (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) a 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. Seven candidate TB drugs representing five different chemical classes are currently known to be undergoing clinical evaluation. This review provides a brief update on the most recent developments in efforts to discover new anti-TB drugs.

**Nitroimidazo-oxazine (PA-824)**

A series of bicyclic nitroimidazofuran originally investigated as radiosensitizers in cancer chemotherapy,
A series of 328 3-substituted nitroimidazo-pyran (NAPs) were synthesized on the basis of the structure of CGI-17341. One NAP compound, the nitroimidazo-oxazine PA-824 (Fig. 1), exhibited a low MIC (0.015 to 0.025 µg/ml) against M. tuberculosis and became a leading compound. PA-824 was identified first, and its anti-M. tuberculosis activity characterized (Stover et al. 2000) in the mid-1990s by Pathogenesis. 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 them for treatment of TB. Since then, the TB Alliance has brought PA-824 through preclinical development, filed an Investigational New Drug Application (IND) in April 2005, and conducted Phase I clinical evaluations of its safety, tolerability, pharmacokinetic properties, and efficacy in drug-sensitive, sputum smear-positive, adult patients with pulmonary TB. PA-824 is currently undergoing Phase II clinical trials (Global Alliance for TB Drug Development, 2009).

In vitro studies showed that the MICs of PA-824 against fully susceptible and MDR strains ranged from 0.015 to 0.25 µg/ml, and that PA-824 activity was concentration-dependent. The bactericidal activity of PA-824 (25 to 50 mg/kg) was comparable to that of isoniazid (25 mg/kg) in mice and guinea pigs (Stover et al. 2000; Lenaerts et al. 2005; Tyagi et al. 2005) and to those after intravenous (20 mg/kg) and oral (40 mg/kg) delivery of the drug. Animals dosed via the pulmonary route showed drug loads that remained locally in the lungs for up to 32 h 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.

Recently Ginsberg et al. (2009a) evaluated the safety, tolerability, and pharmacokinetics of PA-824 in two escalating-dose clinical studies, one a single-dose study (50, 250, 500, 750, 1000, 1250, 1500 mg) and the other a multiple-dose study (200, 600, 1000, 1400 mg, 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 (1500-mg dose) in the single-dose study and 3.8 µg/ml (600-mg dose) in the multiple dose study. 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 administration once daily for up to 7 days, and the pharmacokinetic param-
eters 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 upon coadministration of RIF, INH, PZA in various combinations (Nuerberger et al. 2006; Ginsberg et al. 2009a), justify investigation of this novel compound for the treatment of tuberculosis. Since multiple doses of 1000 mg were associated with a moderate, reversible increase in creatinine, Ginsberg et al. (2009b) made a further assessment of the effects of PA-824 on renal function in healthy subjects. The results suggested that PA-824 causes the creatinine level to rise by inhibiting renal tubular creatinine secretion, an effect considered to be clinically benign, since it has been described for several marketed drugs.

Barry and colleagues (Stover et al. 2000; Manjunatha et al. 2006a) found that PA-824 is a prodrug that requires mycobacterial glucose-6-phosphate dehydrogenase (FDG1) or its cofactor, coenzyme F420, for transformation into an active form. Activated PA-824 inhibits the synthesis of proteins and cell wall lipids. PA-824 activity is limited to *M. tuberculosis* complex (Manjunatha et al. 2006) and is active in susceptible and resistant *M. tuberculosis* strains. No cross-resistance with standard anti-TB drugs has been observed (Stover et al. 2000). Mutations in the *Rv3547* gene have been described in PA-824-resistant strains. Complementing these mutants with intact *Rv3547* fully restored their ability to metabolize PA-824 (Manjunatha et al. 2006). A further study (Singh et al. 2008) revealed that *Rv3547* was a deazoflavin-dependent nitroreductase (Ddn) that converts PA-824 into three primary metabolites, the major one being 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*. Des-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. Singh et al. (2008) therefore concluded that PA-824 might act as an intracellular NO donor and augment the 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. This would make it a very promising drug for treatment of latent TB together with second-line or new anti-tuberculosis drugs, and shorten the duration of treatment.

**Nitro-dihydro-imidazooxazole (OPC-67683)**

OPC-67683, a novel nitro-dihydro-imidazooxazole (Fig. 2) active against *M. tuberculosis*, is structurally related to PA-824, and was discovered, and is being developed for treatment of TB (Table 1). OPC-67683 is a mycolic acid biosynthesis inhibitor (Sasaki et al. 2006). It exerts 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 (Matsumoto et al. 2006; Sasaki et al. 2006). Studies of the post-antibiotic effect of OPC-67683 on intracellular *M. tuberculosis* have show the agent to be highly and dose-dependently active against intracellular *M. tuberculosis* H37Rv after a 4-h pulsed exposure. 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 resulted in markedly 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 that it might be applicable 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 400 mg OPC-67683 in patients with pulmonary TB was low during the first 4 days. However, from day 4 onwards, a significant decrease in CFU was seen (Van den Boogaard et al. 2009; Kaiser Family Foundation 2009). OPC-67683 in multiple doses up to 400 mg was tolerated well by healthy volunteers, and no serious adverse events were reported. 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 undergoing Phase II clinical testing in MDR-TB patients, and is expected to be a powerful therapeutic.

![OPC-67683](image-url)
Diaryl quinoline (TMC 207)

The discovery of diarylquinoline (Fig. 3) as a promising TB drug that can shorten therapy (Andries et al. 2005) has generated much excitement. Andries and colleagues identified diarylquinoline compounds that are 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, Fig. 2) as the most active agent, with a MIC of 0.003 µg/ml for *M. smegmatis* and 0.030 µg/ml for *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* were able to 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 subunit C encoded by the 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 are responsible for resistance to diarylquinoline. The target for diarylquinoline was proposed to be the mycobacterial F1F0 proton ATP synthase (Andries et al. 2005), which is a new target for drugs in mycobacteria. Indeed, TMC207 is also active against MDR-TB strains, and at a low dose it has a bactericidal effect against *Mycobacterium leprae* in mice (Gelber et al. 2009). Transposon mutagenesis analysis has suggested that F1F0 ATP synthase is an essential enzyme in *M. tuberculosis*, although it is not essential for *E. coli*; mutants of F1F0 were viable, but grew at a reduced rate and showed attenuated virulence in mice (Zhang et al. 2006). TMC207 was more active than INH and RIF in a mouse model (Andries et al. 2005) and was able to shorten TB therapy from four months to two in mice with established infection (Andries et al. 2005). Of particular interest is the synergy between diarylquinoline and PZA, which seems to be the most effective drug combination for sterilizing infected spleens and lungs (Andries et al. 2005). Combinations including TMC207 but not PZA (TMC207-INH-RFP and TMC207-MXF-RFP) were less active than TMC207-PZA-containing regimens administered either alone or with the addition of INH, RFP, or MXF (Ibrahim et al. 2007). These results demonstrate a synergistic interaction between TMC207 and PZA. Veziris and colleagues (Veziris et al. 2009; Nuerberger et al. 2009) have reported the activity of once-weekly regimens containing TMC207 in a murine model. In their first experiment, TMC207 alone had similar activity when given at the same total dose either 5 days per week, twice weekly, or once weekly. In the second experiment, TMC207 was more active than rifapentine, both given once weekly, and its activity was not enhanced by addition of rifapentenine or moxifloxacin. In the third experiment, addition of rifapentine to the once-weekly TMC207 regimen again had little...
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Effect. However, addition of pyrazinamide to the TMC207/rifapentine combination yielded significantly greater bactericidal activity and culture-negative organs in 9 of the 10 mice after 2 months of treatment. These results suggest that TMC207 and rifapentine kill much the same persisting bacterial populations, while pyrazinamide is unique among antituberculosis drugs in showing greater bactericidal activity as metabolic activity decreases and therefore kills the most persistent residual mycobacteria. 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 (Andries et al. 2005) could be explained in the same way as the synergy of DCCD with PZA (Andries et al. 2005). TMC207 had excellent early and late bacterial activity, good pharmacokinetic and pharmacodynamic properties with a long half-life, and absence of significant toxicity in mouse and preliminary human safety testing, raising the hope that diarylquinoline might be applicable for shortening TB therapy in humans (Andries et al. 2005, Ibrahim et al. 2009).

There are several unusual features of TM207 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 in comparison with *M. tuberculosis* (Zhang et al. 2006). However, in this case, diarylquinolines are even more active against fast-growing *M. smegmatis* than against *M. tuberculosis* (Andries et al. 2005), which is quite unusual. Second, the high early and late bactericidal activity in mice is notable 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. Fourth, 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. 2008a) was conducted with human patients who were treated for 7 days with TMC207 at 25 mg, 100 mg, and 400 mg per day. Patients treated with either 600 mg per day Rif or 300 mg per day INH were used as controls. This study showed that TMC207 at 400 mg per day significantly decreased the CFU counts in the sputum of treated patients in comparison with the pretreatment levels (Rustomjee et al. 2008b). A drug-drug interaction study was conducted with 16 healthy volunteers who received a single dose of 300 mg TMC207 alone and seven daily doses of 10 mg/kg body weight 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 of when it was administered alone, indicating that metabolism of TMC207 is induced by coadministration with Rif (Rustomjee et al. 2008b). 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 25 mg/kg of body weight or 12.5 mg/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 (Lounis et al. 2008). The minimum bactericidal dose of TMC207 when it was tested as part of the combination was identical to that when it was tested as monotherapy. Because of drug-drug interaction in humans, the activity of TMC207 might 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 increased in the following 3 weeks, while the bactericidal activity of isoniazid was limited to the first week of treatment (Lounis et al. 2008).

In the first of two stages of a phase 2 randomized controlled trial (Diacon et al. 2009), 47 patients with newly diagnosed multidrug-resistant pulmonary tuberculosis were assigned to receive either TMC207 (400 mg daily for 2 weeks, followed by 200 mg three times a week for 6 weeks; 23 patients) or placebo (24 patients) in combination with a standard five-drug, second-line antituberculosis regimen. The results revealed that the addition of TMC207 reduced the time for conversion to a negative sputum culture. Most adverse events were mild to moderate, and only nausea occurred significantly more frequently. This mild adverse event was found to be related to high selectivity: human mitochondrial ATP synthase (50% inhibitory concentration [IC50] > 200 µM) displayed more than 20,000-fold lower sensitivity for TMC207 in comparison with mycobacterial ATP synthase (IC50 10 nM) (Haagsma et al. 2009). With regard to the mechanism of resistance, a recent in vitro study (Huitric et al. 2010) has sequenced the atpE gene, which encodes a transmembrane and oligomeric C subunit of ATP synthase, and which was previously shown to be involved in resistance. Among 53 TMC207-resistant strains, 15 were found to have five different point mutations resulting in five different amino acid substitutions, while in 38 strains no atpE mutations were found, and sequencing of the complete F0 ATP synthase operon (atpB, atpE and atpF genes) and the F1 ATP synthase operon (atpH, atpA, atpG, atpD and atpC genes) from three resistant strains revealed no mutations, indicating the presence of other alternative resistance mechanisms. Competition assays showed no measurable reduction in the fitness of the mutants in comparison with the isogenic wild types.

Overall, because of its potent activity against M. tuberculosis, its distinct mechanism of action, and its impressive activity at what appear to be human-equivalent dosages in the murine model, TMC207 is a particularly promising new drug candidate.

**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 intracellular mycobacteria (Paramasivan et al. 2005). Moxifloxacin and gatifloxacin (Fig. 4) are candidates for shortening the period of TB treatment, since they have the lowest MICs and greatest bactericidal activity, as expressed in the rate of fall in CFU count (Shandil et al. 2007).

Moxifloxacin is a broad-spectrum 8-methoxy fluoroquinolone (Fig. 4) with activity against both gram-positive and 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 and 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 (Shi et al. 2007). No cross-resistance with 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 have demonstrated MICs of 0.25 to 0.5 mg/l (Shandil et al. 2007). In vitro studies and studies in mice have shown enhanced bactericidal activity when moxifloxacin and isoniazid are coadministered (Yoshimatsu et al. 2002). Efficacy of moxifloxacin has also been shown in humans. Early bactericidal activity (EBA) studies conducted on newly diagnosed pulmonary TB patients showed comparable activity of moxifloxacin (400 mg) and isoniazid (300 mg or 6 mg/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 comparing the standard regimen with a regimen of 2RHZM/2RHM and a regimen of 2RMZE/2RM has recently been started (Rosenthal et al. 2006). Moxifloxacin could be of

**Moxifloxacin**

**Gatifloxacin**

Fig. 4. Chemical structures of moxifloxacin and gatifloxacin.
use in the treatment of latent TB. The combination of 3 months of once-weekly moxifloxacin and rifapentine was as effective as 6 months of isoniazid monotherapy in a mouse model of latent TB (Nuernberger et al. 2005). A single dose of moxifloxacin of up to 800 mg 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 associated with moxifloxacin require extended evaluation (Van den Boogaard et al. 2009).

Gatifloxacin and moxifloxacin show cross-resistance. The MICs of gatifloxacin against M. tuberculosis range from 0.2 to 0.5 mg/l (Rodríguez et al. 2002). In vitro studies and studies in mice showed improved activity of rifampin and isoniazid when gatifloxacin was added, and even more efficacy was noted when the regimen also included pyrazinamide (Kubendiran et al. 2006). A multicenter trial is currently enrolling patients at five locations in Africa (Umubeyi et al. 2007). It is intended to compare 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 (Kaiser Family Foundation 2009). 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 development of mycobacterial resistance and the recently found association between gatifloxacin and dysglycemic events are concerns.

Ethambutol derivative (SQ109)

SQ109 (Fig. 5) 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 diaminopyrimidines, and studies to date suggest that SQ109 should not necessarily be considered a second-generation EMB analogue. Although its mechanism of action involves inhibition of cell wall formation, 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 (Chen et al. 2006). It inhibits growth of M. tuberculosis in macrophages to a similar extent as INH and to a greater extent than EMB (Jia et al. 2005; Protopopova 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 25 mg/kg SQ109 and 100 mg/kg 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 order to improve its bioavailability, based on an esterase-sensitive carbamate prodrug strategy, a novel series of prodrugs of SQ109 has been reported (Meng et al. 2009), and some carbamate prodrugs of SQ109 also appear promising. 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 properties different to and more favorable than those of ethambutol, suggesting that it should be regarded as a truly new diamine, and not just an ethambutol analogue. SQ109 could be included in regimens containing RIF and INH, since synergism with both drugs has been demonstrated. Clinical trials are ongoing to establish its future role in TB treatment.

Pyrrrole derivative (LL3858)

Pyrrrole derivatives have demonstrated activity against M. tuberculosis in vitro (Protopopova et al. 2007). Recently, a substituted pyrrrole derivative, LL3858 (Fig. 5), 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 news about this compound is eagerly awaited.

Oxazolidinone (Linezolid)

The oxazolidinones are a new class of synthetic antibiotics exerting broad activity against gram-positive bacteria and mycobacteria through a unique mechanism involving inhibition of ribosomal protein synthesis. Other positive attributes include high oral bioavailability and lack of cross-resistance with existing antibiotics. Linezolid (Fig. 5) is the first oxazolidinone to be used clinically, although it is not approved for use in patients with TB. Its MIC for M. tuberculosis is 0.125-1 µg/ml (Alcala et al. 2003). It has been reported that 100 mg/kg once daily appeared to be bacteriostatic or weakly bactericidal, causing an approximately 1~1.5 log reduction in bacterial counts over 28 days, and that 600 mg linezolid orally twice daily in salvage regimens for MDR-TB was 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 (Fortun et al. 2005; Von der
Liposomal linezolid acts as an inhibitor of bacterial ribosomal protein synthesis. In vitro-selected linezolid-resistant *M. tuberculosis* (MIC 4–32 µg/ml) was reported to harbor 23S rRNA gene mutation (Hilleman et al. 2008), but Richter et al. (Richter et al. 2007) claimed that they had found the first linezolid-resistant clinical isolates of *M. tuberculosis* (MIC 8 µg/ml) harboring no such kind of mutation, suggesting different mechanisms of resistance.

**Concluding Remarks**

For the first time in 40 years, several new drug candidates with promising attributes have entered the clinical development pipeline for the treatment of TB. With luck, 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 TB, MDR-TB and even XDR-TB. Additional drug candidates are percolating up through discovery and preclinical development programs. Although many challenges must be overcome before any of these new drugs contributes meaningfully to TB control, 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.

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