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Current Development and Future Prospects in Chemotherapy of Tuberculosis

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Abstract

Although treatment of drug-susceptible tuberculosis (TB) under ideal conditions may be successful in ≥95% of cases, cure rates in the field are often significantly lower due to the logistical challenges of administering and properly supervising the intake of combination chemotherapy for 6–9 months. Success rates are far worse for multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB cases. There is general agreement that new anti-TB drugs are needed to shorten or otherwise simplify treatment for drug-susceptible and MDR/XDR-TB, including TB associated with HIV infection. For the first time in over 40 years, a nascent pipeline of new anti-TB drug candidates has been assembled. Eleven candidates from 7 classes are currently being evaluated in clinical trials. They include novel chemical entities belonging to entirely new classes of antibacterials, agents approved for use against infections other than TB, and an agent already approved for limited use against TB. In this article, we review the current state of TB treatment and its limitations and provide updates on the status of new drugs in clinical trials. In the conclusion, we briefly highlight ongoing efforts to discover new compounds and recent advances in alternative drug delivery systems.

Keywords

tuberculosis; anti-tubercular agents; drug therapy; multidrug-resistant tuberculosis; investigational drugs

CURRENT TREATMENT OF TUBERCULOSIS AND ITS LIMITATIONS

Chemotherapy for tuberculosis (TB) was possible only after the discovery of streptomycin in 1944. The introduction of isoniazid constituted the basis of primary anti-TB chemotherapy in the 1950s to 1960s. At that time, the anti-tuberculosis drug regimen generally comprised streptomycin, isoniazid and para-aminosalicylic acid in the initial

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months, followed by isoniazid and para-aminosalicylic acid in subsequent months, requiring a total duration of administration of 18 months. In 1965, rifampicin was discovered. In the 1970s, short-course treatment for TB was commenced. The important drug components for a short-course regimen are shown in Table 1 as Category A drugs. Properly administered short-course chemotherapy for TB confers bactericidal and sterilizing actions against *Mycobacterium tuberculosis* and prevents emergence of drug resistance.

Drug-susceptible tuberculosis

The Directly Observed Treatment, Short-course (DOTS) strategy, when properly implemented with the necessary infrastructure, produces high TB cure rates and curtails the development of acquired drug-resistant TB. Although treatment of drug-susceptible TB under ideal conditions by DOTS may be successful in ≥95% of cases,[1] cure rates in the field are often significantly lower.[2] Indeed, in practice, the DOTS strategy has proven difficult for many national TB control programmes to sustain adequately over long periods of time. In particular, the failure to ensure patient adherence to the recommended chemotherapeutic regimen not only lowers cure rates, but leads to the development of drug-resistant TB, inclusive of the formidable scenarios of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB), which are escalating worldwide.[3,4] MDR-TB denotes drug-resistant TB with bacillary resistance to at least isoniazid and rifampicin. XDR-TB denotes MDR-TB with additional bacillary resistance to fluoroquinolones and one or more of the 3 second-line injectables – amikacin, kanamycin and capreomycin. Without a means to rapidly identify MDR- and XDR-TB at the point of care, the DOTS strategy alone is inadequate for treating new cases of TB in settings with a high prevalence of initial drug resistance.

Currently, the standard regimen for treating drug-susceptible pulmonary TB comprises the use of rifampicin, isoniazid and pyrazinamide in combination with either ethambutol or streptomycin for 2 months, followed by continuation of rifampicin and isoniazid for another 4 months – totally 6 months. This is the drug regimen recommended by the World Health Organization (WHO) for the treatment of smear-positive pulmonary TB in newly diagnosed patients.[5] On the whole, daily administration of anti-TB medications in smear-positive TB, especially with cavitation, is associated with lower relapse rate,[6] and thus it should generally be advocated during the first 2 months, followed by three-times weekly administration in the subsequent 4 months. The presence of initial cavitation on chest radiograph and 2-month culture positivity would generally favour prolongation of the continuation phase to 7 months for a total of 9 months of treatment to minimize relapse of TB.[7]

Thus, the current therapy of drug-susceptible TB appears complex and lasts at least 6 months. Furthermore, the drug components of the current regimens (which include rifamycins) have the additional disadvantage of drug-drug interaction with antiretroviral agents,[8] primarily protease inhibitors and non-nucleoside reverse transcriptase inhibitors (at the cytochrome P-450 level), which may produce a significant problem given the high incidence and prevalence of HIV/*M. tuberculosis* co-infection in some parts of the world.

Drug resistance in *M. tuberculosis* arises from man-made selection of mutants that result from spontaneous chromosomal alterations. Selective amplification of drug-resistant

mutants is facilitated by patient non-adherence as well as inappropriately prescribed regimens, poor drug quality, and erratic drug supply, oftentimes reflecting failure in the implementation of TB control programmes.[9]

While DOTS is highly effective in the treatment of drug-susceptible TB, it is generally regarded as insufficient for controlling established MDR-TB.[10] Alternative specific chemotherapy is required using second-line drugs (See Table 1). Among these agents, the fluoroquinolones and the aminoglycosides (and the allied injectable peptide antibiotics) are the most potent.[9,11]

Multidrug-resistant tuberculosis

The treatment regimen for MDR-TB should typically include 5–6 drugs, with either certain or almost certain efficacy based on drug susceptibility testing results and/or previous treatment history. For example, a combination of an aminoglycoside, a fluoroquinolone, ethambutol, pyrazinamide, and ethionamide or prothionamide can be used for MDR-TB with dual bacillary resistance to isoniazid and rifampicin only, but recourse to a regimen of an aminoglycoside, fluoroquinolone, para-aminosalicylic acid, cycloserine, and ethionamide or prothionamide is required for disease with bacillary resistance to isoniazid, rifampicin, ethambutol and pyrazinamide.[9] There are basically 2 treatment approaches. The standardized regimens are designed on the basis of representative drug-resistance surveillance data of specific treatment categories. The individualized regimens are designed on the basis of previous history of anti-TB treatment and results of individual drug susceptibility testing. The delivery of the regimens must be made on a programmatic basis,[12] with the 5 key components as shown in Figure 1.

The WHO recommends treatment for at least 18 months after smear conversion to negativity, even in HIV-negative patients. However, some limited experience has also suggested that, with an intensive combination of active drugs, and the inclusion of fluoroquinolones to which the bacilli are still susceptible, the total treatment duration for some patients may be shortened to 12 – 15 months or one year after sputum culture conversion.[13] Nevertheless, this preliminary impression needs further delineation. For patients with diabetes mellitus, silicosis, slow sputum culture conversion, extensive drug resistance or extensive radiographic disease, a longer duration of therapy is generally required. The prolonged administration of the more “toxic” second-line drugs poses concerns for safety, tolerability and cost. It appears that the time is now right for conducting randomized controlled studies on treatment of MDR-TB.[14] Figure 2 serves to summarize the pertinent issues.

CURRENT TREATMENT OF LATENT TUBERCULOSIS INFECTION AND ITS LIMITATIONS

It is estimated that about 2 billion people in the world are infected with *M. tuberculosis*.[2] While the reader is referred to the recent article by LoBue and Menzies[15] for a more comprehensive review of latent TB infection (LTBI), several aspects related to treatment of this condition are reviewed here. Currently recommended treatment of LTBI to prevent

endogenous reactivation consists of 6–12 months of isoniazid.[16–18] Due to the long duration of therapy and potential for hepatic toxicity, nonadherence to the regimen remains a significant problem. Operational barriers to implementing such treatment regimens on a widespread scale also exist. Shorter and more intermittent rifamycin-containing regimens have been investigated.[19,20] Rifampicin for 4 months is an alternative in the United States and Canada.[17,18,21,22] In the United Kingdom, a 3-mo regimen of rifampicin plus isoniazid is used with success.[20,23] After clinical trials proved its efficacy among HIV-infected individuals with LTBI,[24,25] a 2-month rifampicin-pyrazinamide regimen was briefly in clinical use before being abandoned due to hepatotoxicity concerns.[22] Finally, a 3-month once-weekly regimen combining isoniazid and rifapentine, a rifamycin with a half-life 5 times longer than that of rifampicin, has shown promising efficacy in humans.[26] However, regimens containing rifamycins might still pose difficulties for administration in HIV-positive subjects taking antiretroviral medications.[17] Furthermore, as the prevalence of MDR-TB and XDR-TB increases, so does the prevalence of drug-resistant latent TB infections, creating an increasing need for LTBI regimens based on novel drugs. At the moment, the used combination of pyrazinamide and a fluoroquinolone proves trying due to the associated toxic effects, especially on the liver and joints.[27]

THE NEED FOR NEW ANTI-TUBERCULOSIS DRUGS AND REGIMENS

Thus, there exists a clear and pressing need to develop new anti-TB drugs. They are needed to (i) shorten and simplify treatment of drug-susceptible TB, (ii) provide shorter, safer, more effective and cheaper treatment alternatives for MDR-TB (and XDR-TB), (iii) abolish obstacles to effective treatment of TB in HIV-positive individuals, and (iv) shorten treatment of LTBI.

The desired attributes of a new anti-TB drug are evident from the preceding discussion. In order to shorten the duration of treatment in a meaningful way, the new drug should have “sterilizing” activity, that is bactericidal activity against the small sub-population(s) of drug-tolerant bacilli which persist in a viable state despite exposures to existing drugs that are lethal for the bacterial population at-large, for these microbial “persisters” provide the genesis for relapse after treatment of inadequate duration.[28,29] One or more new drugs capable of shortening the duration of treatment of both drug-susceptible and MDR/XDR-TB are highly desirable. However, given the substantial sterilizing activity of the first-line regimen and the poor sterilizing activity of second- and third-line regimens, it is possible that a new drug be capable of shortening the duration of treatment of MDR/XDR-TB without improving the treatment of drug-susceptible TB.

Certain pharmacological attributes are desirable in order to facilitate use of the new drug in the field, including oral bioavailability and pharmacokinetic/pharmacodynamic (PK/PD) properties enabling once daily (or less frequent) administration. However, where the need is greatest, as in treating XDR-TB, the requirement for such desirable features may be waived. Moreover, advances in drug delivery technology may someday enable alternative routes of administration and improved pharmacokinetic profiles for drug candidates which have unfavorable bioavailability, rapid clearance or other adverse attributes.[30]

Due to the requirement for combination chemotherapy in the treatment of active TB and the common necessity of treating TB and HIV simultaneously, the problem of potential drug-drug interactions is extremely important in the development of new anti-TB drugs.[8] This issue is highlighted in perhaps the most important present class of anti-TB drugs, the rifamycins. Drug-drug interactions have plagued the use of rifampicin for TB. As a potent inducer of cytochrome P450 enzymes (especially CYP3A4), it accelerates the metabolism of HIV protease inhibitors resulting in sub-therapeutic drug concentrations. Rifampicin also induces the activity of efflux transporters such as p-glycoprotein and of Phase II enzymes such as glucuronosyltransferase and sulfotransferase. These drug-drug interactions affect new anti-TB drugs as well. For example, co-administration of TMC207 and rifampicin reduces the TMC207 AUC by approximately 50%.[31] Co-administration of moxifloxacin and rifampicin reduces the moxifloxacin AUC by 27%.[32] Rifapentine induces the cytochrome P450 enzymes at approximately 85% of rifampicin's effect and appears to have a lesser effect on the Phase II enzymes as well, but such interactions remain problematic.[33,34] Rifabutin has a lower inductive effect than either rifampicin or rifapentine and is the rifamycin of choice for co-administration with HIV protease inhibitors.[8] But dosing recommendations are not always evidence based and rifabutin has its share of adverse effects which limit dose increases.

THE CURRENT CLINICAL PIPELINE

New chemotherapeutic advances may arise from optimizing the use of existing anti-TB drugs, re-purposing existing antibiotics for use as anti-TB drugs, or the discovery and development of new chemical entities. Among the drugs currently in clinical trials for TB are examples from each category (Table 2). The progress of the new drugs in the registration process is illustrated in Figure 3.

Rifamycins

Recent renewed interest in high-dose rifamycins, including daily rifapentine therapy, provides a compelling example of the importance of integrating PK/PD principles into TB drug development. Since the introduction of rifampicin four decades ago, the rifamycins have been cornerstone agents in the modern short-course regimen due to their relatively strong sterilizing activity.[28,35] The widely recommended 10 mg/kg dose of rifampicin was established early on as the minimum effective dose capable of producing treatment-shortening effects while keeping the drug acquisition costs as low as possible in order to facilitate global distribution of what was then an expensive new drug. However, despite the critical importance of rifampicin and its relatively low cost today, dosing recommendations have not been seriously re-examined. Fear of an influenza-like syndrome associated with twice- and once-weekly administration of higher rifampicin doses has contributed to the inertia despite the absence of evidence that the syndrome is more frequent when higher doses are administered daily.[36,37] In fact, the prevailing theory of rifampicin antibodies and immune complex-mediated hypersensitivity suggests that daily drug administration should reduce the risk of this adverse reaction.[37,38]

Data from *in vitro* systems and animal models provide compelling evidence that rifampicin's activity against *M. tuberculosis* is concentration-dependent and correlates best

with the quotient of the area under the concentration-time curve and the minimum inhibitory concentration (AUC/MIC).[39,40] According to a study in mice, the 10 mg/kg dose of rifampicin in humans falls at the low end of a steep and tall dose-response curve,[40] indicating that increasing doses may produce log linear increases in bactericidal activity. This premise is supported by existing data from trials examining the early bactericidal activity of rifampicin.[41,42] Limited data from treatment of other infectious diseases with rifampicin suggest that daily doses as high as 1200 mg may be well tolerated.[43,44] Whether such dose increases have the potential to increase the sterilizing activity of rifampicin-containing regimens and thereby shorten treatment remains an important question, although long-term studies in the murine model suggest they would.[45] Taken together, the existing data on the pharmacodynamics of rifampicin strongly support a series of sequential clinical trials to establish the highest well tolerated dose of rifampicin and investigate its treatment-shortening potential.

Rifapentine is a congener with more potent *in vitro* activity (MIC 0.06 vs. 0.25 μg/ml)[46] and a longer serum half-life (11–18 hr vs. 2–4 hr)[47,48] compared to rifampicin. Its development as an anti-TB drug was limited solely to providing an option for once-weekly supervision of therapy during the continuation phase. Although a rifapentine dose of 600 mg is effective in this regard, it has seen little clinical use because it is less effective than conventional rifampicin-based regimens, especially in patients at higher risk of relapse or acquired rifamycin monoresistance.[7,49–52] Encouraged by the concentration-dependent activity of rifamycins and data suggesting higher and/or more frequent doses of rifapentine may be well tolerated in humans,[47,51,53,54] a series of long-term murine model experiments established that some regimens containing rifapentine, pyrazinamide and either isoniazid or moxifloxacin were significantly more effective than the standard daily 1st-line regimen of rifampicin, pyrazinamide and isoniazid.[55–57] Use of rifapentine at 7.5 or 10 mg/kg (corresponding to typical human doses of 450 or 600 mg) in daily regimens or 15 mg/kg (corresponding to typical human doses of 900 mg) in a thrice weekly regimen in combination with isoniazid and pyrazinamide shortened the treatment duration needed to prevent relapse by ≥ 50%.[56] Higher rifapentine doses were even more effective.[45,56] Similar results have been observed with daily rifapentine-containing regimens in a murine model of LTBI.[58] Based on these results, four Phase II and III trials are now underway to evaluate various daily and intermittent rifapentine-based treatment regimens.

The lone Phase III trial involving rifapentine, the RIFAQUIN trial, includes two experimental arms in which the initial phase treatment is with rifampicin (10 mg/kg), moxifloxacin (400 mg), pyrazinamide and ethambutol and the continuation phase treatment is either twice weekly rifapentine (15 mg/kg) and moxifloxacin for 2 months or once weekly rifapentine (20 mg/kg) and moxifloxacin for 4 months. Three Phase II trials will evaluate daily rifapentine-based regimens. A randomized, double blind trial conducted by the U.S. Centers for the Disease Control and Prevention TB Trials Consortium (TBTC) will evaluate the safety, tolerability and efficacy of replacing rifampicin 10 mg/kg with rifapentine 10 mg/kg administered 5 days per week during the first 8 weeks of daily treatment (ClinicalTrials.gov identifier: NCT00694629). Enrollment is expected to be completed in the second quarter of 2010 (S. Dorman, personal communication). In a second trial

conducted in South Africa, investigators from Johns Hopkins University and Cape Town University will evaluate the dose-response of two daily rifapentine doses (7.5 and 10 mg/kg) administered 7 days per week in place of rifampicin during the first 8 weeks of treatment (ClinicalTrials.gov identifier: NCT00814671). In a third trial, investigators from Johns Hopkins University and the Federal University of Rio de Janeiro will evaluate the efficacy of a daily regimen of rifapentine 7.5 mg/kg combined with moxifloxacin, pyrazinamide and ethambutol administered 7 days per week for the first 8 weeks of treatment in a trial conducted in Brazil (ClinicalTrials.gov identifier: NCT00728507).

Fluoroquinolones

The fluoroquinolones are broad-spectrum anti-bacterial drugs that are currently marketed for a variety of infectious indications other than TB. Due to their excellent oral bioavailability, bactericidal activity against *M. tuberculosis*, lack of cross-resistance with existing anti-TB drugs and favourable safety and tolerability profile, they have been employed off-label against MDR-TB and are now regarded as cornerstone agents for this disease.[9,12,21] Newer generation fluoroquinolones such as moxifloxacin and gatifloxacin have potent bactericidal activity which rivals that of isoniazid in animal models[59–61] as well as EBA studies.[62–64] At a dose of 1000 mg, levofloxacin has an EBA at least as strong as that of the 400 mg dose of moxifloxacin or gatifloxacin,[63] which is the highest recommended dose of the latter 2 drugs. These results and additional animal model and human observational data establish these three fluoroquinolones as the preferred agents for treatment of MDR-TB.[13,65–67]

Their favourable profiles have also made the fluoroquinolones the first new antibiotic class to be considered for 1st-line usage against TB since the introduction of rifampicin in 1968. Long-term murine model studies suggest that replacement of ethambutol or isoniazid with moxifloxacin or gatifloxacin in the 1st-line regimen has the potential to improve treatment.[68,69] Replacement of ethambutol with moxifloxacin or gatifloxacin, each at 400 mg, is further supported by the results of three recent Phase II trials. The first study published was TBTC Study 27 in which substitution of moxifloxacin for ethambutol resulted in a higher rate of sputum culture conversion at 4 and 6 weeks but not at 8 weeks.[70] A trial with the same treatment groups conducted by investigators from Johns Hopkins University in Rio de Janeiro found that the moxifloxacin group experienced a higher rate of sputum culture conversion beginning at week 2 and persisting to week 8.[71] The OFLOTUB study evaluated the replacement of ethambutol by ofloxacin 800 mg, moxifloxacin 400 mg or gatifloxacin 400 mg using a new microbiologic outcome measure of serial sputum colony counting.[72] Whereas replacement of ethambutol with ofloxacin resulted in no measureable improvement, use of moxifloxacin or gatifloxacin was associated with more rapid clearance of bacteria from the sputum. In the case of replacing isoniazid with moxifloxacin, which was the substitution associated with the greatest benefit in the murine model,[68] the lone corresponding Phase II trial demonstrated a statistically insignificant 5.5% increase in the 2-month sputum conversion rate in the moxifloxacin arm.[73] The fluoroquinolones have been safe and well-tolerated in these studies. Although it is well known that moxifloxacin produces a small mean increase in the QTc interval, no clinically significant adverse events or arrhythmias have been reported among subjects receiving moxifloxacin-containing regimens. Careful consideration of the potential for additive effects on the QTc interval will

be required before moxifloxacin is combined with new agents which may also prolong the QTc interval (e.g., TMC207). Rifamycins induce the metabolism of moxifloxacin but the clinical significance of the rather modest reductions in AUC is uncertain.[32,34]

Two independent Phase III trials are ongoing to determine whether use of moxifloxacin or gatifloxacin in combination with first-line drugs enables shortening the duration of treatment to 4 months without sacrificing efficacy. The OFLOTUB consortium is evaluating a 4-month regimen based on 2 months of rifampicin-isoniazid-pyrazinamide-gatifloxacin followed by 2 months of rifampicin-isoniazid-gatifloxacin (ClinicalTrials.gov identifier: NCT00216385). The REMoxTB trial is evaluating two 4-month regimens: 2 months of rifampicin-isoniazid-pyrazinamide-moxifloxacin followed by 2 months of rifampicin-isoniazid-moxifloxacin or 2 months of rifampicin-moxifloxacin-pyrazinamide-ethambutol followed by 2 months of rifampicin-moxifloxacin (ClinicalTrials.gov identifier: NCT00864383).

TMC207

TMC207 was the first truly novel chemical entity to enter Phase II clinical trials for a TB indication in 40 years. This diarylquinoline has potent anti-TB activity *in vitro* (MIC, 0.03–0.12 μg/ml) exerted through a novel mechanism: inhibition of the mycobacterial F1F0 proton ATP synthase, an essential enzyme responsible for ATP synthesis.[74,75] This activity is selective for mycobacteria.[74] Resistant mutants selected *in vitro* harbor mutations in *atpE*, which encodes part of the F0 subunit and appear at a frequency of 5×10^{-8} but other resistance mechanisms exist.[74,76] To date, cross-resistance between TMC207 commonly used first- or second-line anti-TB drugs has not been described,[74] making TMC207 potentially useful in both drug-susceptible and drug-resistant TB. That TMC207 is active against non-replicating persisters under anaerobic conditions suggest TMC207 may have valuable sterilizing activity as well.[77,78]

Studies in animal models have demonstrated potent bactericidal activity at drug exposures that appear achievable in humans.[74,79,80] For example, daily treatment with TMC207 alone at 25 mg/kg has a greater bactericidal effect than treatment with the standard first-line regimen of rifampicin, isoniazid and pyrazinamide over the first 2 months of treatment.[74] Moreover, an impressive synergisitic bactericidal effect has been observed when TMC207 is combined with pyrazinamide.[81] Long-term mouse model studies using relapse after treatment as the measure of sterilizing activity have demonstrated that combinations of TMC207 and pyrazinamide with rifampicin, isoniazid or moxifloxacin may be capable of shortening the duration of treatment to less than 6 months.[82,83] Combinations with pyrazinamide and rifapentine may be even more effective. The sterilizing potential of TMC207 in combinations that do not contain pyrazinamide has yet to be evaluated and remains an important question given the unreliability and common omission of pyrazinamide susceptibility testing as well as the high frequency of pyrazinamide resistance reported among MDR *M. tuberculosis* isolates in some hot spots.[67,84,85]

Phase I pharmacokinetic and safety studies in healthy volunteers revealed the drug to be well tolerated with dose-proportional pharmacokinetic parameters over the dose range and time intervals studied.[74] In the single ascending dose study, TMC207 was given in a dose

range of 10 to 700 mg. In the multiple ascending dose study (once daily doses of 50, 150 and 400 mg per day for 14 days), accumulation was observed with a doubling of the area under the time-concentration curve (AUC) by the 14th day.

An open-label randomized trial has been conducted to study the dose-ranging early bactericidal activity (EBA) of TMC207.[80] Newly diagnosed patients with smear-positive pulmonary TB were randomized (15 per arm) to receive daily therapy with isoniazid 300 mg, rifampicin 600 mg, or TMC207 at 25, 100 or 400 mg for 7 days before receiving standard combination therapy. Although TMC207 at 25 and 100 mg had no measurable effect on sputum CFU counts, a bactericidal effect was observed for the 400 mg dose beginning around the fourth day of treatment. The overall reduction in CFU counts with TMC207 was considerably smaller than that produced by isoniazid or rifampicin but several caveats must be considered in the interpretation of these data. First, TMC207 concentrations did not achieve steady state during this trial, so its maximal effect was probably not observed. Second, TMC207 has consistently demonstrated time-dependent bactericidal effects *in vitro*[74] and in mice[31] so it should not be surprising that the same would be observed in the EBA study. Future evaluations of novel TMC207-containing regimens should be extended over a minimum of 14 days to capture this drug's time-dependent activity. A 14-day EBA trial is currently being planned to better understand the dose-response curve for this compound (M. Spigelman, personal communication).

Interim results of a randomized, double blind, placebo-controlled Phase IIb study of TMC207 in newly diagnosed MDR-TB patients have recently been reported.[79] In Stage I of this trial, all patients received an optimized background regimen (typically kanamycin, ofloxacin, ethionamide, pyrazinamide and ethambutol, cycloserine or terizidone) plus either placebo or TMC207 at 400 mg daily for 2 weeks followed by 200 mg thrice weekly for 6 weeks. TMC207 appeared to be well tolerated, although nausea was more common among patients in the TMC207 group. In addition, there was some prolongation of the QT interval noted in the group receiving TMC207; this was of unclear clinical significance. The primary efficacy outcome of time to sputum culture conversion was significantly shorter among patients receiving TMC207. Using liquid culture in the MGIT system, 10 (48%) of 21 evaluable patients receiving TMC207 converted their sputum cultures to negative by 8 weeks compared to 2 (9%) of 23 evaluable patients receiving placebo. These results raise hopes that TMC207-containing regimens may significantly improve the treatment of MDR/XDR-TB. Stage 2 of this trial will evaluate the same treatment arms after 6 months of treatment (ClinicalTrials.gov identifier: NCT00449644). A second open label trial is evaluating the safety and efficacy of the same dose of TMC207 administered for 6 months as part of an individualized regimen for patients with MDR/XDR-TB not responding to current therapy (ClinicalTrials.gov identifier: NCT00910871).

A development program to evaluate the potential of TMC207 in combination with first-line drugs is being pursued in parallel with the development program in MDR-TB. One significant obstacle is the induction of TMC207 metabolism by rifampicin resulting in a 50% reduction in TMC207 AUC, likely through the induction of CYP3A4.[31] Results from murine model experiments suggest that combining rifampicin and TMC207 would still have a net additive effect despite the drug-drug interaction.[31] Additional measures to improve the

activity of the combination could include using other rifamycins with weaker induction of CYP3A4, such as rifabutin and, to a lesser extent, rifapentine. Once-weekly combinations containing TMC207, pyrazinamide and rifapentine have significant bactericidal activity in mice suggesting their potential for widely spaced intermittent ultra-short course regimens but their sterilizing activity and ability to prevent the selection of drug-resistant mutants have not been evaluated.[86,87]

Nitroimidazole derivatives (OPC-67683, PA-824)

The activity of nitroimidazole derivatives against *M. tuberculosis* was first reported over 15 years ago.[88] Two members of this class are currently in Phase II clinical trials for a TB indication and seem devoid of the mutagenicity that plagued many compounds in the class.[89,90]

OPC-67683 is a nitroimidazo-oxazole developed after members of the class were identified in a screen for mycolic acid synthesis inhibitors. Like the related nitroimidazo-oxazine, PA-824, it appears to undergo nitroreductive activation[91] and inhibits ketomycolic acid synthesis as at least one of its mechanisms of action.[89] Cross-resistance to both drugs occurs through mutations in *ddn*, the enzyme responsible for activation.[92] Whether cross-resistance occurs with mutations in *fgd* and *fbiA*, *fbiB*, or *fbiC* which confer resistance to PA-824, has not been reported. OPC-67683 is more potent than PA-824 *in vitro* and *in vivo* with an MIC range of 0.006–0.024 μg/ml and minimum bactericidal dose (MBD), resulting in a 2 $\log_{10}$ reduction in CFU, of 2.5 mg/kg in mice (compared to 50 mg/kg for PA-824 in a similar model [E. Nuermberger, unpublished observations]).[89] As with PA-824, combination of OPC-67683 at the MBD with rifampicin and pyrazinamide resulted in more rapid attainment of negative cultures in the lungs of mice.[89]

In Phase I multi-dose studies with 2 different formulations, OPC-67683 was administered in doses up to 400 mg. A 14-day extended EBA trial has been performed with the newer formulation of OPC-67683 but the results have not been reported in detail. A Phase IIb trial is currently underway in MDR-TB patients randomized to receive an optimized background regimen with either OPC-67683 at 100 or 200 mg twice daily or placebo (ClinicalTrials.gov identifier: NCT00685360).

PA-824 was selected from a library of newly synthesized nitroimidazo-oxazines (also described as nitroimidazopyrans) as the compound having the most potent activity in a murine model.[90] Its MIC ranges from ≤ 0.015 to 0.25 μg/ml against susceptible strains, as well as strains resistant to the commonly used first- and second-line drugs.[90] Activity is limited to members of the *M. tuberculosis* complex, with the exception of *Helicobacter pylori* and some anaerobic bacteria. PA-824 is a pro-drug which is activated by a bacterial deazaflavin (F420)-dependent nitroreductase named Ddn (Rv3547).[91,93] Mutations in the genes encoding the F420 biosynthetic enzymes (*fbiA*, *fbiB* and *fbiC*), the F420-dependent glucose-6-phosphate dehydrogenase responsible for reducing F420 (*fgd*) as well as the activating enzyme itself (*ddn*) confer resistance to PA-824.[90,93–95] The reactive intermediate(s) of PA-824 likely exert anti-TB activity through one or more novel mechanisms including inhibition of ketomycolic acid (cell wall) synthesis, inhibition of protein synthesis and, under certain conditions, generation of intracellular nitric oxide.[90,91]

Like TMC207, PA-824 is active against non-replicating persisters in the *in vitro* Wayne model[90,96] and those selected by treatment of 100-day-old cultures with or without high concentrations of rifampicin,[97] indicating it may have significant sterilizing activity.

PA-824 demonstrates dose-dependent bactericidal and sterilizing activity in a murine model of TB.[96,98] At a daily dose of 100 mg/kg in mice, it has bactericidal activity which approaches that of isoniazid and sterilizing activity comparable to that of rifampicin. Combination of PA-824 with rifampicin and pyrazinamide results in more rapid lung culture conversion than the standard first-line regimen of isoniazid, rifampicin and pyrazinamide.[99,100] The combination of PA-824 with moxifloxacin and pyrazinamide cures mice more rapidly than the first-line regimen.[101] These data suggest PA-824 may be capable of shortening the duration of treatment of drug-susceptible as well as MDR/XDR-TB.

Phase I studies demonstrated less-than-dose proportional increases in PA-824 exposure which, in the multi-dose study, reached a plateau at the 600 mg dose.[102] Maximal serum concentrations were 3.8 μg/ml and the elimination half-life was 16–20 hours.

A randomized partially blinded Phase IIa extended EBA trial has been conducted in South Africa to evaluate the dose-response of PA-824 in newly diagnosed patients with smear-positive pulmonary TB.[103] Subjects received PA-824 in doses of 200, 600, 1000 and 1200 mg or the 4-drug combination of rifampicin, isoniazid, pyrazinamide and ethambutol (Rifafour®) for 14 days. All were blinded as to the dose of PA-824, but no blinding was employed to mask which patients received standard therapy. While not as active as Rifafour over the first 2 days, PA-824 had considerable bactericidal activity, resulting in an average reduction of 0.1 $\log_{10}$ CFU/ml of sputum per day which was sustained over the entire 14 day period. Remarkably, there was no dose-response observed over the range of doses tested. While the lack of dose-response between the 600–1200 mg doses may be explained by the above-mentioned plateau in drug exposure, the lack of dose effect over the 200–600 mg dose range is surprising. However, it may be reconciled with the dose-dependent activity observed in the murine model if the principal pharmacodynamic index correlating with the bactericidal effect is the proportion of the dosing interval in which active drug concentrations exceed the MIC, as recently demonstrated in mice.[104] A second 14-day dose-ranging EBA trial evaluating PA-824 doses of 50, 100, 150 and 200 mg will be completed in the first quarter of 2010 (ClinicalTrials.gov identifier: NCT00944021).

SQ109

SQ109 is an ethylenediamine identified by screening a library of ethambutol derivatives.[105] It has an MIC of 0.16–0.64 μg/ml which does not appear to be affected by resistance to ethambutol.[105,106] The mechanism of action of SQ109 remains to be fully elucidated. Inhibition of cell wall synthesis is implicated by the induction of Rv0341 but, in addition to the lack of evidence of cross-resistance, gene expression analysis suggests it may not be the same as that of ethambutol.[105,106] A remarkable synergistic effect is evident when sub-MIC concentrations of SQ109 and rifampicin are combined[106] and a synergistic effect of combining SQ109 and TMC207 has also been described recently.[107]

In animal models, SQ109 shows extensive tissue distribution and concentration which may explain how the drug maintains activity in mice even when serum concentrations do not exceed the MIC.[105,108] SQ109 in daily doses ranging from 1 to 25 mg/kg is similar in activity to ethambutol at the presumed human-equivalent dose of 100 mg/kg in mice, but combination studies suggest replacement of ethambutol with SQ109 at 10 mg/kg increases the bactericidal activity of the first-line regimen of rifampicin, isoniazid and pyrazinamide.[105,109]

In a Phase I study, SQ109 was safe and well tolerated in single doses up to 300 mg (http://www.sequella.com/docs/Sequella_1sheet09v2_SQ109.pdf, accessed January 2, 2010). The long half-life of 61 hours suggests the potential for widely spaced intermittent therapy. A multi-dose dose escalation study is currently recruiting subjects (ClinicalTrials.gov identifier: NCT00866190). *In vitro* metabolism studies using recombinant cDNA-expressed human CYPs in conjunction with specific CYP inhibitors indicated that CYP2D6 andCYP2C19 were the predominant CYPs involved in SQ109 metabolism, with little effect of CYP3A4.[110]

Oxazolidinones

The oxazolidinones exert their anti-TB activity by inhibiting protein synthesis through a novel mechanism by blocking formation of the ribosomal initiation complex. The only currently marketed oxazolidinone, linezolid, has an MIC range of 0.125–1 μg/ml, with a MIC_{50} of 0.5 μg/ml and an MIC_{90} of 1 μg/ml.[111–113] As a result, it has been used outside of labeled indications in difficult-to treat cases of MDR- and XDR-TB.[114–122] While there is evidence linezolid may contribute to sputum culture conversion in such cases, its individual activity in TB patients and its precise contribution to combination regimens remain unclear. These studies also demonstrate that the duration of linezolid administration is commonly limited by hematologic and neurologic toxicity that can occur with long-term administration.[114,115,117–119] Dosage reductions appear to reduce the incidence of hematologic but perhaps not the neuropathic side effects[116,117,120,121] and the effect on drug efficacy is uncertain.[123,124] In an EBA study comparing linezolid with isoniazid, once and twice daily administration of linezolid 600 mg resulted in a modest bactericidal effect of 0.18 and 0.26 $\log_{10}$ CFU/ml sputum/day (compared to 0.67 for isoniazid) over the first 2 days of treatment, but more limited effects of 0.04–0.09 over the next 5 days.[125] A double blind randomized controlled trial is underway to evaluate low-dose linezolid (e.g., 600 mg daily) vs. placebo added to an optimized background regimen in South African patients with MDR/XDR-TB (ClinicalTrials.gov identifier: NCT00664313). A second open label randomized trial is evaluating linezolid in South Korean patients with XDR-TB (ClinicalTrials.gov identifier: NCT00727844). Nevertheless, new oxazolidinones with more potent *in vivo* activity against *M. tuberculosis* and/or lower risk of toxicity with prolonged administration are desirable.

Oxazolidinones with more potent activity against *M. tuberculosis* have been described. [126–128] The anti-TB activity of PNU-100480 was first reported in 1996.[126] Recent experiments in the murine model show it to be more active than linezolid even when serum concentrations are considerably lower.[129] A long-term experiment demonstrated that

the addition of PNU-100480 at 160 mg/kg shortened the duration of treatment necessary to prevent relapse, suggesting that PNU-100480 has sterilizing activity that could improve the treatment of drug-susceptible as well as drug-resistant TB.[130]

PNU-100480 is currently in Phase I, where single doses of 600 and 1000 mg were well tolerated and bactericidal drug concentrations were maintained in whole blood samples for 12 and 24 hours post-dose, respectively.[131] A multi-dose study of PK, safety, tolerability and whole blood bactericidal activity is currently underway (ClinicalTrials.gov identifier: NCT00990990).

Another oxazolidinone, AZD5847, has entered Phase I with an ascending dose study of the PK, safety and tolerability of the compound (ClinicalTrials.gov identifier: NCT01037725). No information from the pre-clinical evaluation of the compound is publicly available.

Carbapenems

The β-lactams are among the most successful antibiotic classes in clinical use on the basis of their bactericidal activity and favorable safety and tolerability profile. Yet this class has demonstrated little utility against *M. tuberculosis*, primarily because of resistance mediated by BlaC, a bacterial β-lactamase capable of hydrolyzing penicillins, cephalosporins and carbapenems.[132–134] For penicillins and cephalosporins, MICs against *M. tuberculosis* typically exceed the range of clinically achievable drug concentrations.[135,136] Amoxicillin MICs, for example, are typically >16 μg/ml.[135,137] But amoxicillin MICs are lower in the presence of clavulanate, which irreversibly inhibits BlaC.[134,135,137] Clinical experience with this combination in TB patients has been mixed. While anecdotal successes have been reported[138,139] and one extended EBA study demonstrated activity at an oral dose of 1000 mg/250 mg thrice daily,[140] a second study found no EBA with a single daily dose of 3000 mg/750mg.[141] These results may indicate that the principal pharmacodynamic parameter correlating with activity against *M. tuberculosis* is time above MIC ($T_{>MIC}$), as it is for β-lactams against other pathogens and that multiple daily doses are required for activity. An additional finding in the former study was that the EBA over the first 2 days of treatment (0.34 $\log_{10}$ CFU/ml sputum/day) was comparable to that of ofloxacin 600 mg daily but the EBA over the subsequent 5 days (0.02 $\log_{10}$ CFU/ml sputum/day) was very limited, which may indicate limited “sterilizing” activity against more slowly multiplying or non-multiplying organisms.

The carbapenems may hold more promise as anti-TB drugs. In general, they are not as susceptible to hydrolysis as the penicillins and cephalosporins.[134] For example, imipenem MICs are 1.25 to 10 and this drug has activity in a murine model of TB.[136,142,142,143] A small case series suggested that imipenem at a dose of 1 g intravenously every 12 hours contributed activity to combination chemotherapy of MDR-TB patients but the study design did not permit measurement of its individual contribution.[142] Meropenem may be more effective than imipenem. It is hydrolyzed by BlaC so slowly that it functions almost like a β-lactamase inhibitor rather than a substrate.[21,134,136] Against the limited number of strains studied, meropenem was more consistently active than imipenem in the presence of clavulanate (MIC_{90} 0.94 μg/ml for meropenem vs. 10 μg/ml for imipenem).[136] Data from a pulmonary PK study in healthy volunteers suggest that, at a dose of 1 g IV every 8 hours,

meropenem would attain $T_{>MIC}$ values in plasma and alveolar epithelial lining fluid of 64–100% and 38–100% against organisms with MIC values of 2–0.12 μg/ml, respectively, where 40% is the $T_{>MIC}$ target associated with maximal bactericidal activity against bacterial pathogens other than *M. tuberculosis*.[144,145] Efforts are reportedly underway to launch a trial to evaluate the efficacy of meropenem/clavulanate in patients with MDR/XDR-TB.[146]

The principal drawbacks to clinical usage of meropenem and imipenem for TB are the need for intravenous access and, likely, multiple daily doses for maximal efficacy. These are major disadvantages for use in the field. Ertapenem is a marketed carbapenem approved for intramuscular administration. It also has a half-life of 4 hrs (vs. 1 hr for meropenem), which makes it suitable for once daily administration. However, the susceptibility of *M. tuberculosis* to ertapenem has not been described. Oral carbapenems have been developed. Faropenem advanced to Phase II trials against bacterial respiratory tract infections but was not advanced beyond this stage. An oral pro-drug of sulopenem is currently being evaluated in Phase II trials for community-acquired pneumonia (ClinicalTrials.gov identifier: NCT00797108), but its activity against *M. tuberculosis* has not been described.

LL-3858

The anti-TB activity of the pyrrole class was first described in 1998.[147] The discovery of LL-3858 was reported in 2004.[148] While the mechanism of action remains unknown, early reports described an MIC range of 0.06–0.5 μg/ml that was not affected by resistance to isoniazid and rifampicin.[148] Additive activity in combination with first-line drugs in the murine model was also described.[148] To date however, the data remain unpublished and few other details about this compound have been made publicly available. It has reportedly completed Phase I clinical testing and is awaiting regulatory approval to enter Phase II.

DISCOVERY PIPELINE

Although the current clinical pipeline for potential new anti-TB drugs is more robust than ever, given the expected attrition rate in clinical drug development, there is a need for many more candidate compounds. The discovery pipeline for new anti-TB drugs has also grown considerably, especially over the past five years with over 30 discovery and preclinical projects presently being pursued. Although beyond the scope of this review to describe these discovery projects in detail, they derive primarily from two sources, phenotypic screening and pursuit of specific molecular targets.

Phenotypic screening, that is screening general or specific compound libraries to see which compounds will kill *M. tuberculosis in vitro*, has been employed widely to derive “hits” that can be used as starting points in the search for new drug candidate molecules. The advantage of the phenotypic screening approach is that the hits will have already demonstrated the ability to kill the mycobacterium. Literally millions of compounds have been screened over the past 5 to 10 years against *M. tuberculosis*. One of the present rate-limiting steps in this approach is the relative lack of sophisticated medicinal chemistry capability to modify the hits, an expensive and time-consuming step usually necessary for incorporating good drug-like qualities into a candidate molecule.

Pursuing specific targets within *M. tuberculosis* is another commonly used approach in the search for new anti-TB drugs. At present, there are a variety of targets being pursued. These include various cell wall synthetic enzymes, *M. tuberculosis*-specific kinases, proteases, energy metabolism intermediaries, and what are felt to be persistence-specific enzymes that are used by *M. tuberculosis* to maintain dormancy. One advantage of target-specific discovery programs is that it is relatively easy to make sure the compounds that are being synthesized continue to hit the desired target and one has a better understanding of the mechanism of cell death.

Of note, there have been relatively few discovery efforts that seek to improve TB therapy through immunomodulatory effects on the host. Such agents would primarily act by influencing the patient's immune system to kill *M. tuberculosis* or prevent reactivation from latency.

NOVEL APPROACHES TO DRUG DELIVERY

Other approaches to improving drug therapy of TB involve optimizing the delivery systems for drug administration, be they for use with novel or existing therapeutics. Various techniques are under investigation oftentimes with two new methods being used simultaneously.[149]

One of the most promising approaches is the use of nanoparticles.[30,150,151] These are drug carriers that may have the following desirable attributes: high stability, high capacity, feasibility of incorporation of both hydrophilic and hydrophobic substances, and feasibility of oral and inhalational administration in addition to parenteral. As nanoparticles can be designed to yield a sustained release from the matrix, they also have the possibility to reduce dosing frequency. Although liposomal formulations have also been considered for similarly novel delivery systems of TB drugs, the potential flexibility with nanoparticles appears much greater than for liposome-encapsulated drugs.

Nanoparticles may also be useful for targeted therapies aiming to deliver drugs selectively to intracellular sites, such as those within monocytes, macrophages or the reticuloendothelial system. The rationale for this approach is that the persistent organisms responsible for lengthy treatment periods may be intracellular.[152–154] However, this assumption has never been well validated.[155]

Inhalational approaches for TB treatment are also being tested.[156,157] One of the presently used parenterally administered second-line drugs, capreomycin, is being tested in human volunteers in a Phase I study as an inhalational product. The formulation being used with capreomycin is large porous particles.[158] Many of the other commonly used first-line drugs, as well as some investigational agents, have also been formulated and tested in an inhalational delivery system. Inhalational approaches deliver much higher doses of drug to the lung, but the exact histological localization of increased delivery is not clear.

One overriding aspect of novel delivery systems that always needs to be taken into consideration is cost of goods. Because of the limited resources available in virtually all TB endemic countries and because of the presently very inexpensive cost of goods for first-line

drugs, all new delivery systems, as well as new compounds, are subject to cost considerations. This can be a limiting factor for the feasibility of using some of the novel delivery approaches.

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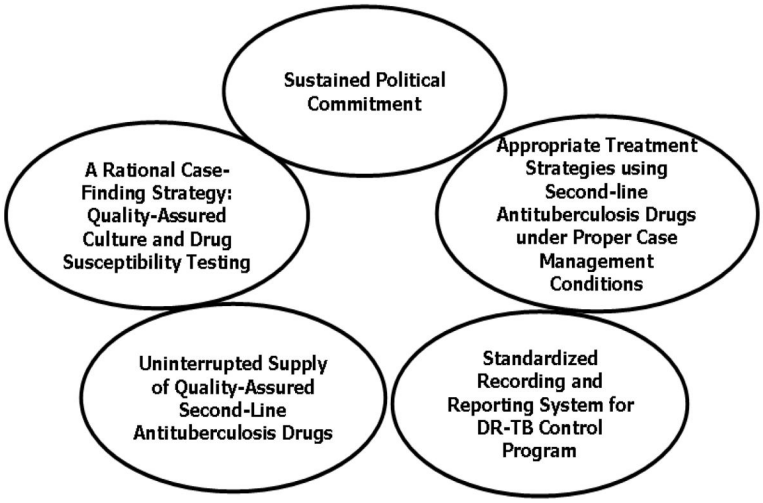


Figure 1.
DOTS Framework Applied to the Management of Drug-Resistant TB

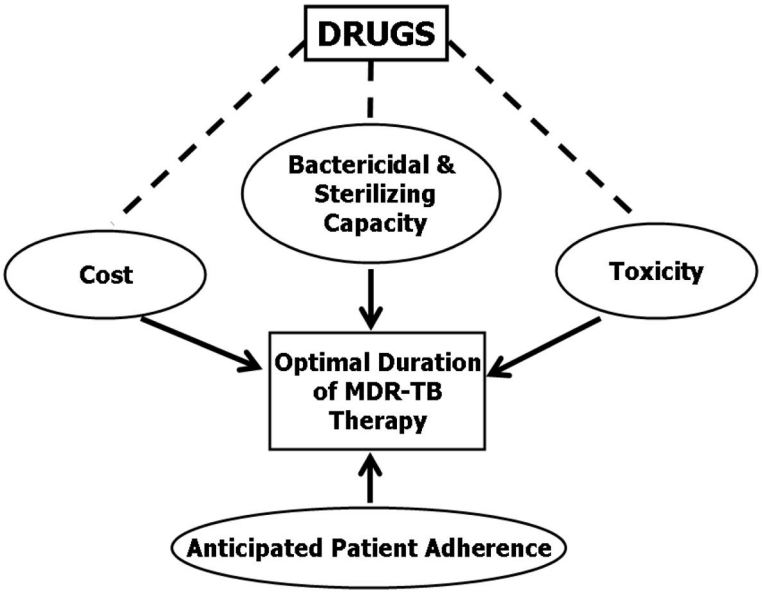


Figure 2.
Major Determinants of Optimal Treatment for Multidrug-Resistant TB

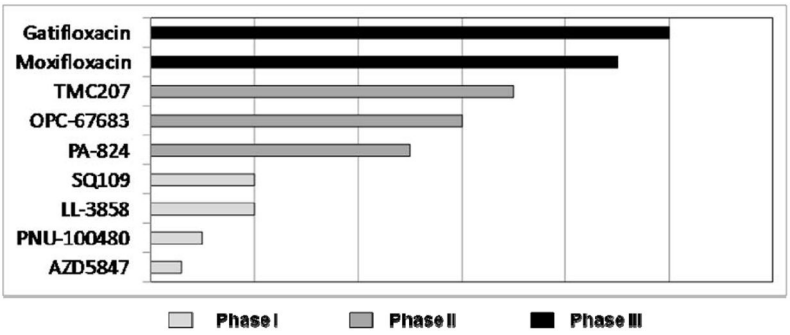


Figure 3.
The global clinical portfolio: New anti-TB drugs in registration programs

Table 1

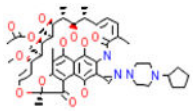
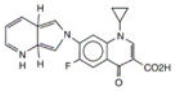
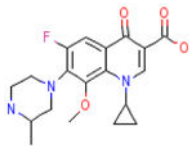
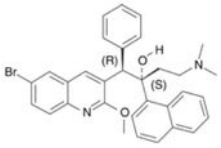
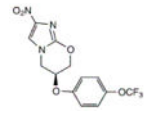
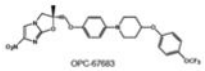
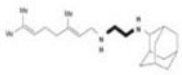
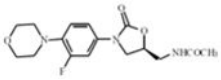
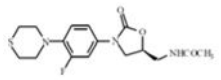
Categories of Anti-TB Drugs

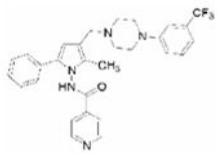
Category A: first-line oral drugs
Isoniazid
Rifampicin
Ethambutol
Pyrazinamide
Category B: injectable agents
Streptomycin (*)
Amikacin
Kanamycin
Capreomycin
Category C: fluoroquinolones
Ofloxacin
Levofloxacin
Moxifloxacin
Category D: oral bacteriostatic second-line agents
Ethionamide
Prothionamide
Cycloserine
Terizidone
Para-aminosalicylic acid
Category E: agents with efficacy that is not totally clear/certain
Clofazimine
Amoxicillin clavulanate
Thiacetazone
Linezolid
Imipenem/cilastatin
Clarithromycin

* first-line drug

Table 2

New anti-TB drug candidates in clinical development

Molecular structure	Drug	Class	Mechanism(s) of action	Target
	rifapentine	rifamycin	Inhibition of RNA synthesis	DNA-dependent RNA polymerase
	moxifloxacin	fluoroquinolone	Inhibition of DNA synthesis	DNA gyrase
	gatifloxacin	fluoroquinolone	Inhibition of DNA synthesis	DNA gyrase
	TMC207	diarylquinoline	Inhibition of ATP synthesis	F1F0 proton ATP synthase
	PA-824	nitroimidazo-oxazine	Inhibition of cell wall lipid synthesis, inhibition of protein synthesis, indirect effects of nitric oxide generation (?)	unknown
	OPC-67683	nitroimidazo-oxazole	Inhibition of cell wall lipid synthesis, inhibition of protein synthesis, indirect effects of nitric oxide generation (?)	unknown
	SQ109	diethylamine	Inhibition of cell wall synthesis	unknown
	linezolid	oxazolidinone	Inhibition of protein synthesis	ribosomal initiation complex
	PNU-100480	oxazolidinone	Inhibition of protein synthesis	ribosomal initiation complex
Not available	AZD5847	oxazolidinone	Inhibition of protein synthesis	ribosomal initiation complex

Molecular structure	Drug	Class	Mechanism(s) of action	Target
	LL-3858	pyrrole	unknown	unknown