Emerging Drugs for Active Tuberculosis

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ABSTRACT

Tuberculosis (TB) drug research and development lay largely fallow from the 1960s to the turn of the century. A realization that current treatments for this major public health epidemic are proving inadequate to control the disease and prevent development and spread of drug resistance has stimulated renewed activity during the past 5 to 10 years. As a result, there are now seven drugs in clinical development for TB and many groups working on discovery-stage projects. This article summarizes the published information available on the seven clinical candidates and describes some of the challenges faced by those pursuing research and development of novel TB therapies.

KEYWORDS: Tuberculosis, treatment, clinical development, drug resistance

Physicians are using the same first-line treatment regimen for active tuberculosis (TB) today as they have since the 1980s.1 This multidrug regimen is highly efficacious when delivered and taken appropriately, but it is lengthy, complex, and has the potential for significant side effects, and therefore challenges patients' adherence to the recommended treatment. The basic regimen recommended by the World Health Organization (WHO), American Thoracic Society, U.S. Centers for Disease Control and Prevention, and Infectious Disease Society of America2 includes 2 months of intensive, directly observed therapy with isoniazid, rifampicin, pyrazinamide, and ethambutol (the 'intensive phase') followed by a minimum of 4 months of isoniazid and rifampicin, with treatment administered daily or at least three times a week (the “continuation phase”). This regimen is highly efficacious when administered under trial conditions, demonstrating cure rates of 95% or higher, with relapse rates of less than 5% in the first 1 to 2 years following treatment completion.3 However, widespread promotion of this treatment regimen through WHO, national TB treatment programs, and other TB control organizations has provided only limited success in global TB control. The WHO 2008 Global Report on TB4 reports that in 2006 there were 9.2 million new cases of active TB worldwide and 1.7 million deaths, including 200,000 individuals who died from HIV-associated TB. These figures represent a slowing of progress in control of TB relative to the WHO-reported data for the previous 5 years.4

The complexity and duration of current TB treatment regimens are major factors in limiting progress in TB control. Successful use of these regimens in the field requires a labor-intensive strategy known as directly observed treatment, short-course (DOTS)5 to ensure high rates of patient treatment adherence and completion, which has proven difficult for many national TB control programs to sustain adequately over long periods.4 Failure to achieve patient adherence to the recommended treatment regimen not only lowers cure rates, raising both transmission and mortality rates, but leads to the development of drug resistant strains of Mycobacterium tuberculosis. Multidrug-resistant TB (MDR-TB), including its most highly resistant forms, extensively drug resistant TB (XDR-TB),6 is increasing in incidence and spreading globally.7 Currently available, second-line drugs for treatment of drug resistant TB are inherently inadequate; they have limited efficacy and...
significant associated toxicities, are more difficult to administer than the first-line drugs, and are far more costly.8,9 Despite a clear need for more field-effective TB treatments (i.e., drug regimens that could be easily administered and adhered to), while demonstrating high levels of safety and efficacy against both drug sensitive and drug resistant strains of M. tuberculosis, the last new class of TB drugs discovered was the rifamycins discovered in the late 1950s10 and first used to treat TB in the early 1960s. In the past 10 years or so, this lack of activity has finally begun to change, with efforts in both the public and private sectors (and frequently involving collaborations between these two sectors) under way to discover and develop improved TB therapies. This article summarizes many of these efforts, with a particular emphasis on the most advanced compounds, which are currently in clinical development.

**THE DRUG RESEARCH AND DEVELOPMENT PROCESS**

The process followed throughout the pharmaceutical industry to discover and develop new drugs has been reviewed many times11,12 and will not be described in detail here. Suffice it to say that for TB drug discovery the research process most often begins either via phenotypic screening of compound libraries against M. tuberculosis or a surrogate organism, such as M. smegmatis or bacille Calmette-Guérin (BCG) growing in vitro culture under one or more of a variety of conditions (such as aerobic, low oxygen, or nitrogen starvation, or in infected macrophages) or compound libraries are screened against a “target” of interest. The target has typically been a mycobacterial protein believed important for bacterial survival in the host. In some cases, investigators have screened against whole pathways (such as transcription/translation or more recently, electron transport). Once a set of compounds is identified with activity against the pathogen or target (“hits”), they must be winnowed down to identify “lead” compounds (i.e., compounds that have druglike properties and the potential to fulfill the ideal “product profile” as discussed in the following section). Lead compounds are then optimized, primarily by medicinal chemists, working with biologists to identify key structure–activity and structure–toxicity relationships. One or more optimized lead compounds are then selected for intensive preclinical testing before selection of a compound to enter human testing (“clinical development”; divided into phases I to III,13 leading to registration). Throughout the research and development process, compounds are evaluated in a series of assays and tests to compare them to a predefined, ideal or “target product profile.” Compounds that continue to demonstrate the potential to fulfill the criteria described in this product profile are advanced, whereas those that fail to meet key milestones are typically terminated from further development.

**TARGET PRODUCT PROFILES**

In the search for improved drugs to treat drug sensitive, active tuberculosis, the target product profile might include (1) the ability to shorten treatment duration to 2 months or less (typically defined as potency greater than the best current drug, rifampin, 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 goods.

For MDR– and XDR-TB, the target product profile might pose a somewhat lower “bar” because the currently available drugs are less effective, have more associated adverse effects, and are significantly more expensive.14 For this therapeutic indication, then, the desired characteristics of a new drug might include (1) novel mechanism of action (to ensure activity against a maximum number of strains resistant to the current drugs); (2) safety profile at least as good and preferably better than the current second-line TB drugs; (3) ability to shorten treatment duration and/or improve cure rates when given in combination with other second-line TB drugs; (4) orally bioavailable; (5) pharmacokinetic–pharmacodynamic profile consistent with once daily or less frequent dosing; (6) minimal or no interactions with hepatic cytochrome P450 enzymes; and (7) low cost of goods relative to current second-line TB drugs.

**EMERGING DRUGS FOR TB: CANDIDATES IN CLINICAL DEVELOPMENT**

Seven candidate TB drugs representing five different chemical classes are currently known to be undergoing clinical evaluation. These will be described by chemical class, in order according to stage of clinical development.

**Fluoroquinolones: Gatifloxacin and Moxifloxacin**

The furthest advanced of these seven are two drugs belonging to the family of C8-methoxy fluoroquinolones:
gatifloxacin and moxifloxacin. Both gatifloxacin and moxifloxacin are approved drugs for other indications (gatifloxacin from Bristol-Myers Squibb in the United States and moxifloxacin from Bayer Healthcare Pharmaceuticals). Both are now in phase III clinical evaluation for treatment of newly diagnosed, drug sensitive, adult, pulmonary TB. The gatifloxacin phase III trial is approximately two thirds enrolled at the time of this writing (target enrollment: 2070 patients); the pivotal, phase III moxifloxacin trial began recruiting patients in January 2008.

The fluoroquinolones exert their action against *M. tuberculosis* by inhibiting the activity of DNA gyrase (topoisomerase II), thereby interfering with bacterial DNA replication, transcription, and repair. The in vitro potency of gatifloxacin and moxifloxacin against *M. tuberculosis* has been well characterized, and their potential for treatment-shortening demonstrated in the mouse model of TB. Evaluation of moxifloxacin in combination with the four first-line TB drugs in a set of systematic evaluations in the mouse TB infection model indicated that substitution for isoniazid should have the greatest effect on treatment shortening. Similar systematic preclinical evaluation of gatifloxacin in a TB infection model before initiation of phase III development for TB has not been published, and gatifloxacin is being evaluated only in place of ethambutol in the standard drug combination.

Both drugs have pharmacokinetic properties consistent with once daily or less frequent, oral dosing (the half-life of gatifloxacin is reported to be 8 hours and that of moxifloxacin 12 hours with oral dosing). Neither drug has significant interactions with cytochrome P450 enzymes.

The safety profile of both fluoroquinolones includes potential for cardiac QTc interval prolongation, which limits the acceptable dose of these compounds. Gatifloxacin also causes rare dysglycemic episodes, particularly in diabetic and/or elderly patients, a finding that led to stronger warnings and a contraindication for use in diabetics being incorporated into the drug's label in 2006. Also of note, fluoroquinolones as a class have been associated with an increased risk for specific arthropathies, although these are generally reversible upon cessation of treatment and with rare, severe hepatotoxicity.

Human testing has demonstrated significant early bactericidal activity (EBA) for both moxifloxacin and gatifloxacin against *M. tuberculosis* relative to first-line TB drugs. As shown by Gosling et al, over the first 5 days of treatment, moxifloxacin demonstrated an EBA similar to that of isoniazid and greater than that of rifampicin. In a study by Johnson and colleagues, over days 2 to 7 of treatment, moxifloxacin and gatifloxacin demonstrated similar EBAs—both greater than that of isoniazid during the same period. A recent phase II study that substituted gatifloxacin, moxifloxacin, or ofloxacin for ethambutol in the first 2 months of TB treatment and measured effects on serial sputum *M. tuberculosis* colony counts demonstrated that moxifloxacin substitution caused a greater fall in colony counts relative to ethambutol, ofloxacin, or gatifloxacin during the early phase of a biexponential decrease. During the late phase of this biexponential decrease, gatifloxacin and moxifloxacin substitution caused similar decreases in colony counts, significantly greater than ethambutol did, whereas ofloxacin substitution had an effect no different than ethambutol's. There were no significant differences among treatment arms in 2-month sputum conversion rates in this study.

Three phase II studies have been conducted recently exploring the effect of moxifloxacin substitution for either ethambutol or isoniazid during the first 2 months of treatment for newly diagnosed adult, pulmonary TB. In the first of these, a study conducted by the U.S. CDC TB Trials Consortium and known as TBTC Study 27, moxifloxacin substitution for ethambutol resulted in no apparent effect on 2-month sputum conversion rates to negativity, but did show a faster median time to sputum conversion. In a similarly designed study in Brazil, sponsored by Johns Hopkins University, moxifloxacin substituted for ethambutol increased the 2-month sputum conversion rate by 17% (*p* = 0.02). The third phase II study, CDC TBTC Study 28, was recently completed; a preliminary data analysis suggested that moxifloxacin substituted for isoniazid during the first 2 months of TB treatment had no statistically significant effect on 2-month sputum conversion rates. Taken together, the results of these phase II trials of gatifloxacin and moxifloxacin suggest that substitution of either fluoroquinolone for ethambutol or isoniazid during the first 2 months of therapy is no less efficacious than standard intensive phase therapy and may confer some advantage in more rapidly clearing the lungs of bacilli. Therefore, each drug has been advanced into late-stage development to evaluate its ability as part of a first-line regimen to shorten treatment duration.

The phase III trials currently being conducted, one evaluating the substitution of gatifloxacin for ethambutol and the other evaluating moxifloxacin substituted for either ethambutol or isoniazid in standard TB treatment, are designed to determine whether either

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*Sponsored by University College London and conducted with its partners: the Bayer Healthcare/TB Alliance partnership, the British Medical Research Council, and clinical trial sites in several high-burden countries.*
or both of these fluoroquinolones, substituted into first-line therapy in either of the ways described and administered for a total of 4 months, has the potential to shorten drug-sensitive TB treatment from 6 months to 4 months. The major advantages of a safe and efficacious 4-month regimen would be to decrease the public health system’s burden in delivering TB treatment and improve treatment-completion rates, thereby reducing development of drug resistance.

**Diarylquinoline—TMC207**

This novel compound, also referred to in the literature as R207910, is a diarylquinoline, owned by Johnson & Johnson and being developed by its subsidiary, Tibotec. It was originally discovered by whole-cell phenotypic screening and acts by inhibiting the *M. tuberculosis* adenosine triphosphate (ATP) synthase. The mechanism of action was identified by genomic sequencing of resistant mutants followed by complementation experiments in the surrogate host, *Mycobacterium smegmatis*. Subsequent experiments confirmed the compound’s ability to bind to and inhibit the ATP synthase subunit c.

TMC207 demonstrates significant in vitro potency against *M. tuberculosis*—both drug sensitive (*M. tuberculosis* H37Rv, MIC 0.03 to 0.12 mg/ml) and multidrug-resistant strains, and has a narrow spectrum of activity, being largely specific for mycobacteria. In both acute and chronic infection models in the mouse, TMC207 demonstrated potent activity against *M. tuberculosis*, showing greater bacterial activity early after infection than isoniazid, the most bacterialidal of the current first-line TB drugs early in treatment, and greater bactericidal activity late in infection than rifampicin, alone. It demonstrated equivalent activity to the combination of rifampicin, isoniazid, and pyrazinamide when dosed five times a week at 25 mg/kg starting 4 weeks after infection. TMC207 also increased bactericidal activity in the mouse model when added to amikacin, moxifloxacin, ethionamide, and pyrazinamide, drugs commonly used to treat MDR-TB. Together these results suggest that TMC207 has significant potential to shorten treatment duration for both drug-sensitive and MDR-TB.

TMC207 is currently in phase II of clinical development, being evaluated for safety and its ability to improve efficacy of MDR-TB treatment when added to an optimized regimen of second-line drugs. The investigational new drug application (IND) was filed in November 2006. Phase I studies included single ascending dose (25 to 700 mg) and multiple ascending dose (25 to 400 mg per day for 14 days) studies in healthy volunteers, and drug–drug interaction studies with ketocnazole, isoniazid, rifampicin, and pyrazinamide. These studies showed that the compound demonstrates linear pharmacokinetics, with a Tmax of ~5.5 hours and a long terminal elimination half-life; it does not reach steady state with 14 days of dosing. TMC207 is metabolized by cytochrome P450 3A4, leading to ~50% reductions in its plasma levels when coadministered with rifampicin at standard TB doses. Therefore, Tibotec and Johnson & Johnson made the strategic decision to evaluate TMC 207 in MDR-TB patients, a setting felt to provide the best opportunity to assess safety and efficacy of long-term administration of this novel compound while maximizing its risk:benefit profile. As of this writing, ~50 MDR-TB patients have received 2 months of TMC207 (400 mg daily for 2 weeks followed by 200 mg three times a week for a total of 2 months) or placebo in addition to a standardized MDR-TB treatment regimen consisting of kanamycin, pyrazinamide, ethionamide, ofloxacin, and terizidone/cycloserine. Results of this first stage of the phase II trial are pending. The second stage of this phase II/III trial is planned to involve a total of 150 additional subjects treated for 6 months with the standardized MDR-TB treatment regimen plus TMC207 or placebo, and evaluated for safety, tolerability, pharmacokinetics, and efficacy of TMC207 (as measured primarily by sputum conversion rates). Patients are to be followed for 2 years following completion of the experimental phase for safety.

**Nitroimidazoles—PA-824 and OPC-67683**

The nitroimidazoles represent a novel class of drugs for TB treatment. Two members of this chemical class are presently in phase II of clinical development: PA-824, a nitroimidazo-oxazine, being evaluated currently for drug sensitive TB, and OPC-67683, a nitroimidazo-oxazol, currently being studied in MDR-TB patients. PA-824 was first identified and its anti-*M. tuberculosis* activity characterized in the mid-1990s by Pathogensis, a small biotechnology company, 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 them for TB. Since then the TB Alliance has brought PA-824 through preclinical development, filed an IND in April 2005, conducted phase I clinical evaluations, and is now evaluating the compound’s safety, tolerability, pharmacokinetic properties, and efficacy in drug-sensitive, sputum-smear-positive, adult, pulmonary TB patients.

OPC-67683, a structurally related compound, was discovered and is being developed for TB by Otsuka Pharmaceutical. Each compound’s activity appears to be specific for the *M. tuberculosis* complex and to work by the same or similar novel mechanisms of action. The mechanism of action of these drugs is not yet completely delineated, but both are prodrugs whose activation generates radicals with toxic effects on mycobacterial mycolic acid and protein biosynthesis.
PA-824’s in vitro potency against *M. tuberculosis* H37Rv has been reported to be 0.13 μg/ml and 0.15 to 0.3 μg/mL. Importantly, PA-824 has similar potency against MDR-TB strains. It also shows significant bactericidal activity against nonreplicating mycobacteria, suggesting it may have potential to shorten treatment duration because of the “persistent” bacilli in a treated host are also believed to be non-replicating or slowly replicating organisms.

In the mouse model, PA-824 has demonstrated bactericidal efficacy early in infection (during the intensive phase) equivalent to that of isoniazid and to have activity in the continuation phase of treatment similar to that of rifampicin plus isoniazid, consistent with the hypothesis that PA-824 is effective against “persistent” mycobacteria and should have the ability to shorten treatment duration. More recent data from the mouse infection model demonstrated that PA-824 in combination with moxifloxacin and pyrazinamide cleared lungs of bacilli more rapidly than the standard regimen of isoniazid, rifampin, and pyrazinamide. This result suggests this isoniazid- and rifampicin-sparring regimen should be evaluated further for safety and efficacy as a potential novel regimen for MDR-TB treatment and for treatment of HIV-positive TB patients on antiretroviral therapy (because it would avoid rifampicin-based drug–drug interactions with antiretroviral agents metabolized by CYP3A4, such as some protease inhibitors).

OPC-67683 is a markedly potent compound in vitro against *M. tuberculosis*. Its MIC against strain H37Rv is 0.012 μg/mL and its activity is reported to be similar against a range of MDR-TB strains. In a mouse model, OPC-67683 was demonstrated to increase the efficacy of combination treatment with standard drugs and estimated to have potential to shorten the standard 6-month treatment duration by approximately 2 months.

Neither PA-824 nor OPC-67683 appears to have significant interactions with the cytochrome P450 enzyme system. Both compounds are orally bioavailable and have pharmacokinetic properties consistent with once daily or less frequent dosing.

OPC-67683 is currently in phase II clinical testing in MDR-TB patients. The TB Alliance recently completed a phase IIa, proof of concept study with PA-824 in drug-sensitive, smear-positive, adult pulmonary TB patients in South Africa, demonstrating a clinically significant extended EBA for this drug over a 14-day dosing period, when administered orally at 200–1200 mg per day.

**Ethylenediamine—SQ109**

SQ109 is a novel 1,2-ethylenediamine. It was originally identified as part of a collaboration between the biotech company Sequella, Inc., and the National Institute of Allergy and Infectious Diseases of the U.S. National Institutes of Health to synthesize via combinatorial chemistry and screen ethambutol analogs for killing *M. tuberculosis* in vitro under aerobic conditions using a high-throughput bioluminescence-based assay. Its mechanism of action appears to involve inhibition of cell wall synthesis but seems to differ from that of ethambutol because it has bactericidal activity in vitro against ethambutol-resistant strains of *M. tuberculosis* and has different effects than ethambutol on gene expression in microarray studies.

The MIC of SQ109 on a variety of drug sensitive and drug resistant strains of *M. tuberculosis* grown under aerobic conditions in vitro is reported to range from 0.16 to 0.63 μg/mL. In mice, SQ109 at 1 and 10 mg/kg demonstrated activity similar to ethambutol at 100 mg/kg, but less activity than isoniazid at 25 mg/kg. The compound is metabolized by CYP2D6 and CYP2C19 in human liver microsome assays. Human absorption, distribution, metabolism, and excretion data (ADME) have not yet been published for this compound, but interspecies pharmacokinetics suggest a very large volume of distribution.

Based on in vitro data, SQ109 was reported to be synergistic in its bactericidal activity with rifampicin and isoniazid. In liquid culture (BACTEC 460), SQ109 at half its MIC demonstrated a synergy quotient of 0.45 with isoniazid at half its MIC and of 0.38 with rifampicin at one tenth its MIC, in inhibiting *M. tuberculosis* growth. In a mouse chronic infection model, isoniazid, rifampicin, and SQ109 (SQ109 at 10 mg/kg) cleared lungs of bacilli faster than isoniazid, rifampicin, and ethambutol during the first 8 weeks of treatment.

To date, SQ109 has been tested in a single phase I study, a single ascending dose trial (5 to 300 mg). Cmax and AUC increased in a dose-related manner; the half-life increased with dose in a nonlinear fashion, being substantially longer at the higher doses. It was reported to be 61.1 hours following a single 300 mg dose, consistent with a large volume of distribution also measured at the higher doses. Sequella plans to initiate a phase I, multiple ascending dose study of SQ109 by the end of 2008.

**Pyrrole—LL-3858**

LL-3858 is a pyrrole derivative being developed by Lupin, Ltd. Little published information is available about this compound. Its mechanism of action is unknown. Its MIC in vitro against *M. tuberculosis* has been reported to be 0.12 to 0.25 μg/mL, and it demonstrated synergistic activity with rifampicin in vitro. As of the last public report, this compound is in phase I of clinical development in India.
EMERGING DRUGS FOR TB: DISCOVERY UPDATE

Given the relatively minimal amount of effort that was expended on TB drug research after the discovery of the rifamycins in the late 1950s through the end of the twentieth century, it is not surprising that there are only five classes of compounds currently in clinical development for a TB indication. The more recent reawakening of this field has, however, begun to populate the discovery pipeline more robustly. The Stop TB Working Group on New Drugs recently reported that research groups from academia, large and small pharmaceutical companies, government, and not-for-profit public–private partnerships are exploring several dozen targets and chemical classes for their potential to contribute to improving TB therapy.62

Current TB drugs target bacterial functions crucial to survival of replicating M. tuberculosis: the cell wall (e.g., isoniazid, ethambutol), transcription (e.g., rifamycins), and energy metabolism (e.g., pyrazinamide). To be effective against circulating MDR- and XDR-TB strains new TB drugs will need to have novel mechanisms of action. Additionally, to contribute substantially to the efficacy of the front-line combination regimen by shortening treatment duration, new drugs will likely need to target populations of slowly replicating or nonreplicating bacilli. To date, discovery projects have typically taken one of two major approaches: either whole cell phenotypic screening against replicating M. tuberculosis (or a surrogate mycobacterium) or target-based drug discovery, focusing on targets essential in replicating mycobacteria in vitro. The former has been the far more successful, leading to the discovery, for example, of TM207, PA-824 and OPC-67683, and SQ109. To date, no novel anti-TB compounds discovered by target-based screening have reached clinical development. Target-based drug discovery has not yet proven to be productive for anti-infective discovery in general.63 However, the strong intellectual appeal of this approach means many groups continue to pursue it. Recently, investigators have begun to focus on identifying essential targets within nonreplicating mycobacteria with the goal of killing the population of bacilli that persist in hosts even in the face of ultimately efficacious drug treatment,64,65 and with the expectation that selective killing of nonreplicating, persistent bacilli will shorten the required treatment duration.

Challenges for TB Drug Research and Development

The ability of genetically drug sensitive M. tuberculosis to persist for long periods of time in a host being treated with appropriate doses of effective drugs renders TB treatment durations exceptionally long and TB drug discovery particularly challenging. Efforts to meet this challenge would be greatly facilitated by a far better understanding of the biological mechanisms responsible for this persistence. Several investigators are devoting considerable effort to elucidating this biology.55–67

An additional challenge for TB drug discovery and development is the need to identify and develop effective, ideally synergistic, drug combinations rather than single drugs, to prevent development of drug resistance. The need to discover and identify combination regimens poses many hurdles, including (1) an extra layer of testing and triage in the preclinical phase to identify optimized candidate drug combinations, (2) complicated development challenges posed by the potential for drug–drug interactions, (3) the necessity of defining the safety and efficacy of the individual components of the combination regimen in addition to the safety and efficacy of the regimen as a whole, (4) formulation challenges to ensure the final regimen can be easily administered to patients, preferably as a fixed dose combination to prevent misuse of the individual drugs as monotherapy, and (5) additional regulatory hurdles beyond those faced for novel, individual drugs.

TB drug clinical development is further hampered by the exceptionally long duration of human studies, particularly pivotal, phase III trials, required by a minimum of 6-month treatment duration in control arms, long-term follow-up of 6 months to 2 years posttreatment to accurately assess relapse rates, and a lack of validated biomarkers to shorten these trial timelines. It has been proposed that initial pursuit of an MDR-TB indication may prove a faster route to regulatory approval than drug sensitive disease—an approach that has been successful in other infectious disease indications.14,68 Whether clinical evaluation occurs in drug resistant or drug sensitive patients, a relative lack of experienced TB drug clinical trial sites in high-burden settings further slows the pace of clinical development.69,70 55

Despite these significant challenges, 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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