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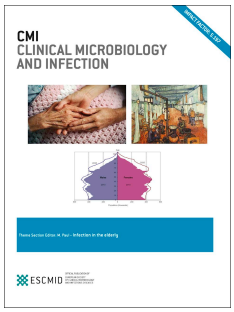

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Candidate anti-tuberculosis medicines and regimens under clinical evaluation

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Abstract

Background: Tuberculosis (TB) is the leading cause of mortality by an infectious disease world-wide. Despite national and international efforts, the world is not on track to end TB by 2030. Antibiotic treatment of TB is longer than for most infectious diseases and complicated by frequent adverse events. To counter emerging *Mycobacterium tuberculosis* drug resistance and provide effective, safe drug treatments of shorter duration, novel anti-TB medicines and treatment regimens are needed. Through a joint global effort, more candidate medicines are in the clinical phases of drug development than ever before.

Objectives: To review anti-TB medicines and treatment regimens under clinical evaluation for the future treatment of drug-susceptible and drug-resistant TB.

Sources: Pre-clinical and clinical studies on novel anti-TB drugs.

Content: Description of novel protein synthesis inhibitors (oxazolidinones and oxaboroles), respiratory chain inhibitors (diarylquinolines and cytochrome bc1 complex inhibitor), cell wall inhibitors (DprE1 inhibitors, thioamides and carbapenems) and cholesterol metabolism inhibitor currently evaluated in clinical trials and novel clinical trial platforms for the evaluation of treatment regimens, rather than single entities.

Implications: A large number of potential anti-TB candidate medicines and innovations in clinical trial design for the evaluation of regimens, rather than single medicines, provide hope for improvements in the treatment of TB.

Introduction

After years of sluggish decline, the estimated incidence of tuberculosis (TB) rose to 10.6 million cases and deaths increased to 1.3 million in 2022 due to the COVID-19 pandemic [1]. Among the estimated 10.6 million incident cases, 3.1 million cases are not notified or given appropriate treatment, further contributing to the ongoing transmission of *Mycobacterium tuberculosis* [1].

Most pulmonary TB cases are "drug-susceptible" (DS-TB) and treatable with the 6-month rifampicin-based standard regimen developed 50 years ago. The World Health Organization (WHO) also now recommends a 4 month-rifapentine-based regimen for the treatment of pulmonary TB under certain conditions [2]. Overall successful outcomes in TB have remained in the range of 83% to 86% for several years [1]. More recently it has been demonstrated that high treatment success can be achieved for DS-TB patients by a treatment strategy, including bedaquiline, linezolid, isoniazid, pyrazinamide, and ethambutol over 8 weeks and retreatment in case of relapse [3].

The duration, complexity and toxicities of the standard regimen frequently result in nonadherence, leading to suboptimal outcomes and emergence of resistance.

In 2022, the incidence of TB caused by strains of *M. tuberculosis* resistant to rifampicin and isoniazid (multidrug-resistant; MDR) or just to rifampicin (rifampicin resistant; RR) was estimated to be 410,000 [1]. Successful treatment outcomes for MDR/RR-TB are reported in 63% of individuals, substantially lower than for DS-TB. More than 70% of MDR/RR-TB cases worldwide are the result of primary transmission of drug-resistant *M. tuberculosis* [4].

During the 2010's, important breakthroughs were made in MDR-TB and extensively-drug-resistant (XDR)-TB treatment, first with demonstrating the potency of oxazolidinones (linezolid) essentially as monotherapy among highly resistant patients in a Korea-based clinical trial [5, 6], then with registration of the first diarylquinoline (bedaquiline) and the nitroimidazoles (delamanid and pretomanid) for MDR/RR-TB treatment [7-9]. Though the reduction in median time to sputum culture conversion (SCC) over 6 months was not significant in the primary analysis of the Phase 3 trial of delamanid (51 days

versus 57 days), overall SCC at 2 months (58.4% and 53.5%) and 6 months (87.6% and 86.1%) was higher than previous reports from controlled trials assessing MDR-TB treatment, suggesting broader improvements in MDR-TB diagnosis and treatment over time [10].

The subsequent bedaquiline, pretomanid, and linezolid regimen resulted in substantial reduction of MDR/RR-TB treatment durations to 6 months of therapy with approximately 90% of treatment success [9, 11]

The World Health Organization (WHO) has recommended combination regimens with bedaquiline, pretomanid, linezolid with or without moxifloxacin (BPaLM) as front-line treatment [10]. Though greatly improving outcomes and reducing treatment duration, these regimens are still fraught with toxicities requiring close clinical monitoring, challenging many treatment programs [7]

Emerging resistance to bedaquiline [11-13], threatens the TB medicine most integral to MDR/RR-TB treatment. The need to develop new transformative regimens of shorter duration, more favourable safety profile, with limited to no pre-existing resistance has never been greater.

In response to these challenges and building from the success of several initiatives linking activities of academia, industry, government agencies, non-governmental organizations and donors including the Cape Town Declaration of the Working Alliance for TB Drug Development [14] in 2000, the TB Drug Accelerator [15] (established in 2012 as a TB drug discovery and development mechanism), and recent successes in treatment shortening for drug-susceptible TB [3, 16], two large TB regimen development partnerships – UNITE4TB [17], and the Project to Accelerate New Treatments for Tuberculosis (PAN-TB) [18], have been launched to further advance regimen development. Both are closely coordinated and share the aim to develop transformative regimens of shorter duration (< 4 months) with limited to no pre-existing *M. tuberculosis* drug resistance.

TB Drug Pipeline

The TB pipeline with recently approved drugs, a robust pipeline of new agents and classes present an unprecedented opportunity to identify transformative new TB regimens (see **Figure 1** [19], for a description and **Figure 2** for mechanisms of action).

The following summary highlights a list of promising agents based on target and class according to stage of clinical development:

Protein Synthesis Inhibitors

Oxazolidinones inhibit protein synthesis; linezolid (LZD) has been very effective in treating highly drug resistant tuberculosis [5, 6]. In the first controlled clinical trial assessing linezolid's use in treatment of refractory MDR-TB and XDR-TB, a high proportion of patients [27/38 (71%)] achieved cure, while "only" 4/38 (11%) acquired resistance [6], consistent with the infrequent emergence of resistance observed in vitro [5, 6, 20]. However, longer-term treatment with linezolid results in substantial side-effects, including myelosuppression and neuropathy requiring dose reduction or treatment interruption in a high proportion of patients [7]. Toxicity is mediated through inhibition of host mitochondrial protein synthesis and associated with higher drug levels at the end of the dosing interval [6]. Two clinical trials – ZeNiX and PRACTECAL - demonstrated that use of 600mg (1200mg was used previously), given for 9 or 26 weeks, lead to reduced toxicity, sustained high cure rate, and subsequently recommended in the recent WHO treatment guidelines [21]. Now candidate agents from the class with anticipated similar efficacy but possibly improved safety have been identified, including sutezolid, depazolid, TBI-223 and tedizolid (table 1). Oxaboroles are a new class of protein synthesis inhibitors showing promising safety and efficacy results in an early bacterial efficacy trial with the component Ganfeborole (GSK3036656) (table 1).

Respiratory chain inhibitors

As *M. tuberculosis* cannot utilize substrate-level phosphorylation, oxidative phosphorylation represents their only source of energy. Inhibition of the mycobacterial respiratory chain, generating adenosine 5'-triphosphate (ATP), represent targets divergent from most currently used TB drugs. This dependency applies to non-replicating organisms as well, highlighting the potential for treatment-shortening.

Bedaquiline specifically inhibits mycobacterial ATP synthase by binding to subunit c of the enzyme essential for energy generation in *Mycobacterium tuberculosis*. First approved by US Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2012 and 2014, respectively, is indicated as part of combination therapy for the treatment of pulmonary MDR-TB in adults and, children (5 years and older and weighing ≥ 15 kg). Bedaquiline is listed by WHO as a group A drug for inclusion in all MDR/RR-TB regimens, making it integral to new regimens. Novel respiratory chain inhibitors are the diarylquinolines TBAJ-876 and TBAJ-587 and sudapyridine, and the the cytochrom bc1 complex inhibitor telacebec (Q203) (table 2).

Mycobacterial cell wall synthesis disruption

Delamanid, a dihydro-nitroimidazooxazole derivative, acts by inhibiting the synthesis of mycobacterial cell wall components, methoxy mycolic acid and ketomycolic acid [22]. It is currently included as a group C drug in WHO guidelines. In a systematic review and meta-analysis Nasiri et.al. [23] concluded the overall pooled treatment success of delamanid containing regimen was 80.9% and 72.5% in observational and experimental studies respectively. In its 2022 guidelines, WHO has conditionally recommended including delamanid in the treatment of MDR/RR-TB in children of any age on the longer regimen. Pretomanid (PA-824) was first identified in 2000, in a series of nitroimidazopyran derivatives synthesized and tested for anti-TB activity. It has activity against static *M. tuberculosis* isolates that survive under anaerobic conditions. It was developed by TB Alliance for the treatment of tuberculosis in combination with bedaquiline and linezolid (BPaL) and was first approved in 2019. Whether

pretomanid can be substituted with delamanid as results from preclinical studies [24] needs to be evaluated in clinical studies.

DprE1 (decaprenylphosphoryl-β-d-ribose 2'-epimerase) is a critical enzyme in the production of lipoarabinomannan and arabinogalactan, both essential components of mycobacterium cell wall [25]. Inhibition of DprE1 leads to cell lysis and bacterial death [26]. Currently, four DprE1 inhibitors, in three chemical classes are in clinical development. The two benzothiazinones (BTZ-043 and PBTZ-169), a carbostyril derivative (quabodepistat previously known as OPC-167832) and an azaindole (TBA-7371). Phase 2a trials for all four compounds have completed and both quabodepistat and BTZ-043 have advanced to phase 2b/c trials (figure 3, table 3).

Novel compounds with alternative activities to those mentioned above are the ethionamide/ prothionamide booster alpibectir (BVL-GSK098), a new ß-lactam named sanfetrinem cilexetil and GSK2556286, an inhibitor of the mycobacterial cholesterol mechanism (table 4).

Regimens in clinical development

Bedaquiline received accelerated (US)/conditional (EU) approval in 2012 and 2014, respectively, and delamanid received conditional (EU) approval in 2014, based on trials that showed benefit on sputum culture conversion when added to an optimized background regimen for MDR-TB treatment. These agents were licensed without specific combination agents. The paucity of agents for constructing new effective regimens at the time of approval amplified the risk for the emergence of resistance to them.

Pretomanid was the first drug licensed for use as part of a specific regimen (2019 in the US), building on the previous successful evaluation of linezolid[6] and bedaquiline[27]. As the available recommended treatment for highly drug-resistant TB had poor outcomes at the time, FDA approved the combination on the basis of robust efficacy (90% favourable outcome after 6 months) in a single arm clinical trial of 109 XDR-TB and treatment-intolerant or non-responsive MDR-TB patients. However frequent side effects including peripheral neuropathy (81%) and myelosuppression (48%), attributable

to linezolid dosing at 1200 mg daily, made this treatment less feasible for a broader range of patients with less severe disease [7]. Subsequent studies [9, 21] that included MDR/RR-TB patients, and that used a more tolerable 600 mg daily dose of linezolid, led the WHO [2] to recommend BPaLM for MDR/RR-TB and BPaL for MDR/RR and FQ-R TB (pre-XDR, 2021 definition). As WHO revised the definitions and provided novel treatment guidelines for drug-resistant TB a situation resulted where regulatory agency approvals of pretomanid as part of the BPaL regimen are restricted to patients with XDR-TB while WHO recommends the BPaL(M) regimen for the treatment of MDR/RR-TB and pre-XDR-TB but not for XDR-TB. This situation must be solved urgently.

The desired profile that new TB regimens could efficiently treat all forms of TB regardless of resistance patterns might be feasible. Treatment response for MDR-TB and DS-TB were closely comparable in the NC005 and SimpliciTB trials [28, 29] and now an all oral 6-month regimen is available for MDR TB. While WHO has developed updated target regimen profiles for TB treatment the rich pipeline of drugs in advanced stages of development, opens the possibility for a pan-TB regimen that could treat both DS-TB and DR-TB.

As experience has shown, shorter, less toxic and affordable regimens cannot be designed at the drawing table. Human safety and drug-drug-interactions cannot be reliably predicted preclinically as the recent example of the BPaMZ regimen demonstrates. Withdrawal due to adverse events (mostly hepatic) in 10% (28 of 277) of patients in both investigational arms showed the limitations of this combination [29].

Consequently, a new dawn of regimen development is emerging, as evidenced by the development pathways of the new drugs quabodepistat, ganfeborole, BTZ-043 and sutezolid (**Figure 3**). In general, a candidate drug will usually be evaluated in a 14-day early bactericidal (EBA) monotherapy trial to show its anti-TB effect and generate some information on PK-PD and dose selection. With quabodepistat and BTZ-043, for efficiency in development, phase 1b multiple dosing was first evaluated in TB patients to generate efficacy information for phase 2 dose selection. Next, these agents are each undergoing evaluation in 4-month dose-finding combination studies. TBAJ-876, after completing Phase

1 studies in healthy subjects, is being evaluated for anti-TB activity in a dose-ranging study in combination with pretomanid and linezolid, for an initial 8-week period, followed by HR continuation. These efforts aim to generate data for PK-PD modelling and will inform on efficacy over a longer treatment duration, but also on toxicities that occur late in treatment, and their relation to exposure, following the example of two oxazolidinone studies – PanACEA-SUDOCU and DECODE – planned for this purpose.

As outlined, selection of the most promising partner drugs for combination requires human trials, before a pivotal phase 3 trial is launched, since time, financial and logistical challenges prohibit multiple regimens from being evaluated in parallel in phase 3 trials. Innovative regimen selection trials will perform an adaptive selection step to choose an effective and safe combination, currently using a sputum bacteriological endpoint for this interim decision (phase 2b). The final primary endpoint will then focus on sterilizing activity across a range of disease severity, specifically the power of a regimen to prevent relapse, for confirming regimen efficacy [30]; this will include an exploration of the optimal length of treatment with a duration-randomization assessment (phase 2c). Optionally, de-risking phase 2 designs, if successful, with exceptionally promising arms might not require any adaptation, potentially allowing for a seamless transition into a phase 3 trial. As such, a large platform trial like PARADIGM4TB may evolve into a phase 3 platform that may generate pivotal licensing data on more than one regimen, whilst simultaneously containing a phase 2b regimen selection phase.

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S.T. is an employee and shareholder in GSK.

D.B.A. is an employee of, and shareholder in, GSK, and reports patents planned, issued or pending.

M.D. is an employee of Otsuka Novel Products GmbH

E.S is an employee of TB Alliance.

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Contribution: M.H. and C.W. designed the structure of the review. M.H. D.B-A., M.D., N.H., M.K., E.S., S.T. and C.W. wrote the first draft. M.H. D.B-A., M.D., N.H., M.K., E.S., C.L., C.W. and S.T. revised the manuscript. All authors approved the manuscript for submission and publication.

References:

[1] World Health Organization, Global tuberculosis report 2023, in: W.H. Organization (Ed.) Geneva, 2023.
[2] World Health Organization, WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-susceptible tuberculosis treatment., Geneva, Switzerland, 2022.
[3] N.I. Paton, C. Cousins, C. Suresh, E. Burhan, K.L. Chew, V.B. Dalay, Q. Lu, T. Kusmiati, V.M. Balanag, S.L. Lee, R. Ruslami, Y. Pokharkar, I. Djaharuddin, J.J.R. Sugiri, R.S. Veto, C. Sekaggya-Wiltshire, A. Avihingsanon, R. Sarin, P. Papineni, A.J. Nunn, A.M. Crook, T.-T.T. Team, Treatment Strategy for Rifampin-Susceptible Tuberculosis, N Engl J Med 388(10) (2023) 873-887.
[4] E.A. Kendall, M.O. Fofana, D.W. Dowdy, Burden of transmitted multidrug resistance in epidemics of tuberculosis: a transmission modelling analysis, The Lancet. Respiratory medicine 3(12) (2015) 963-72.
[5] M. Lee, S.N. Cho, C.E. Barry, 3rd, T. Song, Y. Kim, I. Jeong, Linezolid for XDR-TB--Final Study Outcomes, N Engl J Med 373(3) (2015) 290-1.
[6] M. Lee, J. Lee, M.W. Carroll, H. Choi, S. Min, T. Song, L.E. Via, L.C. Goldfeder, E. Kang, B. Jin, H. Park, H. Kwak, H. Kim, H.S. Jeon, I. Jeong, J.S. Joh, R.Y. Chen, K.N. Olivier, P.A. Shaw, D. Follmann, S.D. Song, J.K. Lee, D. Lee, C.T. Kim, V. Dartois, S.K. Park, S.N. Cho, C.E. Barry, 3rd, Linezolid for treatment of chronic extensively drug-resistant tuberculosis, N Engl J Med 367(16) (2012) 1508-18.
[7] F. Conradie, A.H. Diacon, N. Ngubane, P. Howell, D. Everitt, A.M. Crook, C.M. Mendel, E. Egizi, J. Moreira, J. Timm, T.D. McHugh, G.H. Wills, A. Bateson, R. Hunt, C. Van Niekerk, M. Li, M. Olugbosi, M. Spigelman, T.B.T.T. Nix, Treatment of Highly Drug-Resistant Pulmonary Tuberculosis, N Engl J Med 382(10) (2020) 893-902.
[8] M.T. Gler, V. Skripconoka, E. Sanchez-Garavito, H. Xiao, J.L. Cabrera-Rivero, D.E. Vargas-Vasquez, M. Gao, M. Awad, S.K. Park, T.S. Shim, G.Y. Suh, M. Danilovits, H. Ogata, A. Kurve, J. Chang, K. Suzuki, T. Tupasi, W.J. Koh, B. Seaworth, L.J. Geiter, C.D. Wells, Delamanid for multidrug-resistant pulmonary tuberculosis, N Engl J Med 366(23) (2012) 2151-60.
[9] B.T. Nyang'wa, C. Berry, E. Kazounis, I. Motta, N. Parpieva, Z. Tigay, V. Solodovnikova, I. Liverko, R. Moodliar, M. Dodd, N. Ngubane, M. Rassool, T.D. McHugh, M. Spigelman, D.A.J. Moore, K. Ritmeijer, P. du Cros, K. Fielding, T.-P.S. Collaborators, A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis, N Engl J Med 387(25) (2022) 2331-2343.
[10] World Health Organization, WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update, World Health Organization, Geneva, 2022.
[11] E. Chesov, D. Chesov, F.P. Maurer, S. Andres, C. Utpatel, I. Barilar, A. Donica, M. Reimann, S. Niemann, C. Lange, V. Crudu, J. Heyckendorf, M. Merker, Emergence of bedaquiline resistance in a high tuberculosis burden country, Eur Respir J 59(3) (2022).
[12] B. Derendinger, A. Dippenaar, M. de Vos, S. Huo, R. Alberts, R. Tadokera, J. Limberis, F. Sirgel, T. Dolby, C. Spies, A. Reuter, M. Folkerts, C. Allender, D. Lemmer, A. Van Rie, S. Gagneux, L. Rigouts, J. Te Riele, K. Dheda, D.M. Engelthaler, R. Warren, J. Metcalfe, H. Cox, G. Theron, Bedaquiline resistance in patients with drug-resistant tuberculosis in Cape Town, South Africa: a retrospective longitudinal cohort study, Lancet Microbe 4(12) (2023) e972-e982.
[13] C. Lange, A. Vasiliu, A.M. Mandalakas, Emerging bedaquiline-resistant tuberculosis, Lancet Microbe 4(12) (2023) e964-e965.
[14] Cape Town Declaration of the Working Alliance for TB Drug Development (https://www.tballiance.org/downloads/publications/CapeTownDeclaration.pdf), 2000.
[15] B.B. Aldridge, D. Barros-Aguirre, C.E. Barry, 3rd, R.H. Bates, S.J. Berthel, H.I. Boshoff, K. Chibale, X.J. Chu, C.B. Cooper, V. Dartois, K. Duncan, N. Fotouhi, F. Gusovsky, P.A. Hipskind, D.J. Kempf, J. Lelievre, A.J. Lenaerts, C.W. McNamara, V. Mizrahi, C. Nathan, D.B. Olsen, T. Parish, H.M. Petrassi, A. Pym, K.Y. Rhee, G.T. Robertson, J.M. Rock, E.J. Rubin, B. Russell, D.G. Russell, J.C. Sacchettini, D. Schnappinger, M. Schrimpf, A.M. Upton, P. Warner, P.G. Wyatt, Y. Yuan, The Tuberculosis Drug Accelerator at year 10: what have we learned?, Nat Med 27(8) (2021) 1333-1337.

[16] S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, R.E. Chaisson, A.C.T. Group, C. Tuberculosis Trials, Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis, N Engl J Med 384(18) (2021) 1705-1718.
[17] M.J. Boeree, C. Lange, G. Thwaites, N. Paton, R. de Vrueh, D. Barros, M. Hoelscher, UNITE4TB: a new consortium for clinical drug and regimen development for TB, Int J Tuberc Lung Dis 25(11) (2021) 886-889.
[18] PAN-TB Project to Accelerate New Treatments for Tuberculosis.).
[19] Drug Pipeline I Working group for new TB drugs. 2023).
[20] D. Hillemann, S. Rusch-Gerdes, E. Richter, In vitro-selected linezolid-resistant Mycobacterium tuberculosis mutants, Antimicrob Agents Chemother 52(2) (2008) 800-1.
[21] F. Conradie, T.R. Bagdasaryan, S. Borisov, P. Howell, L. Mikiashvili, N. Ngubane, A. Samoilova, S. Skornykova, E. Tudor, E. Variava, P. Yablonskiy, D. Everitt, G.H. Wills, E. Sun, M. Olugbosi, E. Egizi, M. Li, A. Holsta, J. Timm, A. Bateson, A.M. Crook, S.M. Fabiane, R. Hunt, T.D. McHugh, C.D. Tweed, S. Foraida, C.M. Mendel, M. Spigelman, T. ZeNix Trial, Bedaquiline-Pretomanid-Linezolid Regimens for Drug-Resistant Tuberculosis, N Engl J Med 387(9) (2022) 810-823.
[22] M. Matsumoto, H. Hashizume, T. Tomishige, M. Kawasaki, H. Tsubouchi, H. Sasaki, Y. Shimokawa, M. Komatsu, OPC-67683, a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis in vitro and in mice, PLoS Med 3(11) (2006) e466.
[23] M.J. Nasiri, M. Zangiabadian, E. Arabpour, S. Amini, F. Khalili, R. Centis, L. D'Ambrosio, J.T. Denholm, H.S. Schaaf, M. van den Boom, X. Kurhasani, M.P. Dalcolmo, S. Al-Abri, J. Chakaya, J.W. Alffenaar, O. Akkerman, D.R. Silva, M. Munoz-Torrico, B. Seaworth, E. Pontali, L. Saderi, S. Tiberi, A. Zumla, G.B. Migliori, G. Sotgiu, Delamanid-containing regimens and multidrug-resistant tuberculosis: A systematic review and meta-analysis, Int J Infect Dis 124 Suppl 1(Suppl 1) (2022) S90-S103.
[24] S.E. Mudde, A.M. Upton, A. Lenaerts, H.I. Bax, J.E.M. De Steenwinkel, Delamanid or pretomanid? A Solomonic judgement!, J Antimicrob Chemother 77(4) (2022) 880-902.
[25] M. Jankute, S. Grover, A.K. Rana, G.S. Besra, Arabinogalactan and lipoarabinomannan biosynthesis: structure, biogenesis and their potential as drug targets, Future Microbiol 7(1) (2012) 129-47.
[26] G.S. Kolly, F. Boldrin, C. Sala, N. Dhar, R.C. Hartkoorn, M. Ventura, A. Serafini, J.D. McKinney, R. Manganelli, S.T. Cole, Assessing the essentiality of the decaprenyl-phospho-d-arabinofuranose pathway in Mycobacterium tuberculosis using conditional mutants, Mol Microbiol 92(1) (2014) 194-211.
[27] A.H. Diacon, A. Pym, M.P. Grobusch, J.M. de los Rios, E. Gotuzzo, I. Vasilyeva, V. Leimane, K. Andries, N. Bakare, T. De Marez, M. Haxaire-Theeuwes, N. Lounis, P. Meyvisch, E. De Paepe, R.P. van Heeswijk, B. Dannemann, T.C.S. Group, Multidrug-resistant tuberculosis and culture conversion with bedaquiline, N Engl J Med 371(8) (2014) 723-32.
[28] C.D. Tweed, R. Dawson, D.A. Burger, A. Conradie, A.M. Crook, C.M. Mendel, F. Conradie, A.H. Diacon, N.E. Ntinginya, D.E. Everitt, F. Haraka, M. Li, C.H. van Niekerk, A. Okwera, M.S. Rassool, K. Reither, M.A. Sebe, S. Staples, E. Variava, M. Spigelman, Bedaquiline, moxifloxacin, pretomanid, and pyrazinamide during the first 8 weeks of treatment of patients with drug-susceptible or drug-resistant pulmonary tuberculosis: a multicentre, open-label, partially randomised, phase 2b trial, The Lancet. Respiratory medicine 7(12) (2019) 1048-1058.
[29] M. Eristavi, E. Variava, F. Haraka, M.P. Dalcolmo, H. Mayanja-Kizza, M. Olugbosi, M. Li, L. Lombard, M. Cevik, L. Thompson, D. Sloan, M. Spigelman, J. Nedelman, M. Beumont, E. Sun, SimpliciTB results and Hepatic Safety of Pretomanid Regimens +/- Pyrazinamide, Conference of Retroviruses and Opportunistic Infections, Seattle, WA, 2023.
[30] P.P. Phillips, K.E. Dooley, S.H. Gillespie, N. Heinrich, J.E. Stout, P. Nahid, A.H. Diacon, R.E. Aarnoutse, G.S. Kibiki, M.J. Boeree, M. Hoelscher, A new trial design to accelerate tuberculosis drug development: the Phase IIC Selection Trial with Extended Post-treatment follow-up (STEP), BMC Med 14(1) (2016) 51.

[31] R. Tasneen, F. Betoudji, S. Tyagi, S.Y. Li, K. Williams, P.J. Converse, V. Dartois, T. Yang, C.M. Mendel, K.E. Mdluli, E.L. Nuermberger, Contribution of Oxazolidinones to the Efficacy of Novel Regimens Containing Bedaquiline and Pretomanid in a Mouse Model of Tuberculosis, Antimicrob Agents Chemother 60(1) (2015) 270-7.
[32] R.S. Wallis, R. Dawson, S.O. Friedrich, A. Venter, D. Paige, T. Zhu, A. Silvia, J. Gobey, C. Ellery, Y. Zhang, K. Eisenach, P. Miller, A.H. Diacon, Mycobactericidal activity of sutezolid (PNU-100480) in sputum (EBA) and blood (WBA) of patients with pulmonary tuberculosis, PLoS One 9(4) (2014) e94462.
[33] N. Heinrich, C. Manyama, E. Ntinginya, S. Mpagama, A. Liyoyo, F. Mhimbira, B. Mbeya, M.A. Sebe, R. Wallis, P. Phillips, L. Wildner, R. Aarnoutse, L. Hoffmann, M. Hoelscher, S. Svenson, PanACEA SUDOCU combination dose-finding trial shows sutezolid is a safe oxazolidinone, Conference on Retroviruses and Opportunistic Infections, Seattle, WA, 2023.
[34] J.S. Kim, Y.H. Kim, S.H. Lee, Y.H. Kim, J.W. Kim, J.Y. Kang, S.K. Kim, S.J. Kim, Y.S. Kang, T.H. Kim, J. Mok, M.K. Byun, H.J. Park, J.S. Joh, Y.B. Park, H.S. Lim, H. Choi, S.H. Lee, H. Kim, J. Yang, H. Kim, X. Shen, A. Alsultan, I. Cho, L. Geiter, T.S. Shim, Early Bactericidal Activity of Delpazolid (LCB01-0371) in Patients with Pulmonary Tuberculosis, Antimicrob Agents Chemother 66(2) (2022) e0168421.
[35] Z. Zong, W. Jing, J. Shi, S. Wen, T. Zhang, F. Huo, Y. Shang, Q. Liang, H. Huang, Y. Pang, Comparison of In Vitro Activity and MIC Distributions between the Novel Oxazolidinone Delpazolid and Linezolid against Multidrug-Resistant and Extensively Drug-Resistant Mycobacterium tuberculosis in China, Antimicrob Agents Chemother 62(8) (2018).
[36] A. Dierig, M. Hoelscher, S. Schultz, L. Hoffmann, A. Jarchow-MacDOnald, E. Svenson, L.H. Te Brake, R. Aarnoutse, M. Boeree, T. McHugh, L. Wildner, X. Gong, P. Phillips, L. Minja, E. Ntinginya, S. Mpagama, A. Liyoyo, R. Wallis, M.A. Sebe, F. Mhimbira, B. Mbeya, M. Rassool, L. Geiter, Y. Cho, N. Heinrich, A Phase IIb, Open-Label, Randomized Controlled Dose Ranging Multi-Center Trial to Evaluate the Safety, Tolerability, Pharmacokinetics and Exposure-Response Relationship of different doses of Delpazolid in combination with Bedaquiline, Delamanid Moxifloxacin in Adult Subjects with Newly Diagnosed, Uncomplicated, Smear-Positive, Drug-sensitive Pulmonary Tuberculosis, Trials in press (2023).
[37] D.A. Negatu, J.J.J. Liu, M. Zimmerman, F. Kaya, V. Dartois, C.C. Aldrich, M. Gengenbacher, T. Dick, Whole-Cell Screen of Fragment Library Identifies Gut Microbiota Metabolite Indole Propionic Acid as Antitubercular, Antimicrob Agents Chemother 62(3) (2018).
[38] D. Tenero, G. Derimanov, A. Carlton, J. Tonkyn, M. Davies, S. Cozens, S. Gresham, A. Gaudion, A. Puri, M. Muliaditan, J. Rullas-Trincado, A. Mendoza-Losana, A. Skingsley, D. Barros-Aguirre, First-Time-in-Human Study and Prediction of Early Bactericidal Activity for GSK3036656, a Potent Leucyl-tRNA Synthetase Inhibitor for Tuberculosis Treatment, Antimicrob Agents Chemother 63(8) (2019).
[39] A.H. Diacon, C.E. Barry, 3rd, A. Carlton, R.Y. Chen, M. Davies, V. de Jager, K. Fletcher, G. Koh, I. Kontsevaya, J. Heyckendorf, C. Lange, M. Reimann, S.L. Penman, R. Scott, G. Maher-Edwards, S. Tiberi, G. Vlasakakis, C.M. Upton, D.B. Aguirre, A first-in-class leucyl-tRNA synthetase inhibitor, ganfeborole, for rifampicin-susceptible tuberculosis: a phase 2a open-label, randomized trial, Nat Med 30(3) (2024) 896-904.
[40] T.A. Black, U.K. Buchwald, The pipeline of new molecules and regimens against drug-resistant tuberculosis, J Clin Tuberc Other Mycobact Dis 25 (2021) 100285.
[41] K. Pethe, P. Bifani, J. Jang, S. Kang, S. Park, S. Ahn, J. Jiricek, J. Jung, H.K. Jeon, J. Cechetto, T. Christophe, H. Lee, M. Kempf, M. Jackson, A.J. Lenaerts, H. Pham, V. Jones, M.J. Seo, Y.M. Kim, M. Seo, J.J. Seo, D. Park, Y. Ko, I. Choi, R. Kim, S.Y. Kim, S. Lim, S.A. Yim, J. Nam, H. Kang, H. Kwon, C.T. Oh, Y. Cho, Y. Jang, J. Kim, A. Chua, B.H. Tan, M.B. Nanjundappa, S.P. Rao, W.S. Barnes, R. Wintjens, J.R. Walker, S. Alonso, S. Lee, S. Oh, T. Oh, U. Nehrbass, S.J. Han, Z. No, J. Lee, P. Brodin, S.N. Cho, K. Nam, Discovery of Q203, a potent clinical candidate for the treatment of tuberculosis, Nat Med 19(9) (2013) 1157-60.
[42] V.R. de Jager, R. Dawson, C. van Niekerk, J. Hutchings, J. Kim, N. Vanker, L. van der Merwe, J. Choi, K. Nam, A.H. Diacon, Telacebec (Q203), a New Antituberculosis Agent, N Engl J Med 382(13) (2020) 1280-1281.

[43] V. Makarov, G. Manina, K. Mikusova, U. Mollmann, O. Ryabova, B. Saint-Joanis, N. Dhar, M.R. Pasca, S. Buroni, A.P. Lucarelli, A. Milano, E. De Rossi, M. Belanova, A. Bobovska, P. Dianiskova, J. Kordulakova, C. Sala, E. Fullam, P. Schneider, J.D. McKinney, P. Brodin, T. Christophe, S. Waddell, P. Butcher, J. Albrethsen, I. Rosenkrands, R. Brosch, V. Nandi, S. Bharath, S. Gaonkar, R.K. Shandil, V. Balasubramanian, T. Balganesh, S. Tyagi, J. Grosset, G. Riccardi, S.T. Cole, Benzothiazinones kill Mycobacterium tuberculosis by blocking arabinan synthesis, Science 324(5928) (2009) 801-4.
[44] A. Treu, C. Hölscher, J. Kokesch-Himmelreich, F. Marwitz, J. Dreisbach, P.J. Converse, S. Tyagi, S. Gerbach, L. Gyr, A. Lemm, J. Volz, A. Hölscher, N. Heinrich, F. Kloss, E. Nuermberger, D. Schwudke, M. Hoelscher, A. Römpp, K. Walter, The clinical-stage drug BTZ-043 accumulates in tuberculosis lesions and efficiently acts against Mycobacterium tuberculosis, Research Square (https://doi.org/10.21203/rs.3.rs-2615777/v1) (28 February 2023, PREPRINT (Version 1)).
[45] M.E. Ramey, F. Kaya, A.A. Bauman, L.M. Massoudi, J.P. Sarathy, M.D. Zimmerman, D.W.L. Scott, A.M. Job, J.A. Miller-Dawson, B.K. Podell, M.A. Lyons, V. Dartois, A.J. Lenaerts, G.T. Robertson, Drug distribution and efficacy of the DprE1 inhibitor BTZ-043 in the C3HeB/FeJ mouse tuberculosis model, Antimicrob Agents Chemother (2023) e0059723.
[46] clinicaltrials.gov:, BTZ-043 - Multiple Ascending Dose (MAD) to Evaluate Safety, Tolerability and Early Bactericidal Activity (EBA) (NCT04044001), https://clinicaltrials.gov/ct2/show/NCT04044001?term=BTZ-043&draw=2&rank=2, 2019.
[47] clinicaltrials.gov:, A Single Ascending Dose Study of BTZ043 (NCT03590600), https://clinicaltrials.gov/ct2/show/NCT03590600?term=BTZ-043&draw=2&rank=3, 2018.
[48] N. Heinrich, V. De Jager, J. Dreisbach, P. Gross-Demel, S. Schultz, S. Gerbach, F. Kloss, R. Dawson, K. Narunsky, L. Matt, L. Wildner, T. McHugh, U. Fuhr, C. Mouhdad, L.H. te Brake, M. Boeree, R. Aarnoutse, E.M. Svensson, X. Gong, P. Phillips, A. Diacon, M. Hoelscher, BTZ-043 Shows Good Safety and Strong Bactericidal Activity in a Combined Phase1b/2a Study in Tuberculosis Patients, Lancet Preprint Server (2023).
[49] G.T. Robertson, M.E. Ramey, L.M. Massoudi, C.L. Carter, M. Zimmerman, F. Kaya, B.G. Graham, V. Gruppo, C. Hastings, L.K. Woolhiser, D.W.L. Scott, B.C. Asay, F. Eshun-Wilson, E. Maidj, B.K. Podell, J.J. Vasquez, M.A. Lyons, V. Dartois, A.J. Lenaerts, Comparative Analysis of Pharmacodynamics in the C3HeB/FeJ Mouse Tuberculosis Model for DprE1 Inhibitors TBA-7371, PBTZ169, and OPC-167832, Antimicrob Agents Chemother 65(11) (2021) e0058321.
[50] clinicaltrials.gov:, Study to Evaluate the Safety, Tolerability and Pharmacokinetics of PBTZ169 in Multiple Dosing (NCT03776500), https://clinicaltrials.gov/ct2/show/NCT03776500?term=PBTZ-169&draw=2&rank=1, 2018.
[51] clinicaltrials.gov:, Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Ex-vivo Antitubercular Activity of PBTZ169 Formulation (NCT03423030), https://clinicaltrials.gov/ct2/show/NCT03423030?term=PBTZ-169&draw=2&rank=3, 2018.
[52] clinicaltrials.gov:, Phase 2a Study of PBTZ169 (NCT03334734), https://clinicaltrials.gov/ct2/show/NCT03334734?term=PBTZ-169&draw=2&rank=2, 2020.
[53] N. Hariguchi, X. Chen, Y. Hayashi, Y. Kawano, M. Fujiwara, M. Matsuba, H. Shimizu, Y. Ohba, I. Nakamura, R. Kitamoto, T. Shinohara, Y. Uematsu, S. Ishikawa, M. Itotani, Y. Haraguchi, I. Takemura, M. Matsumoto, OPC-167832, a Novel Carbostyril Derivative with Potent Antituberculosis Activity as a DprE1 Inhibitor, Antimicrob Agents Chemother 64(6) (2020).
[54] R. Tasneen, A. Garcia, P.J. Converse, M.D. Zimmerman, V. Dartois, E. Kurbatova, A.A. Vernon, W. Carr, J.E. Stout, K.E. Dooley, E.L. Nuermberger, Novel Regimens of Bedaquiline-Pyrazinamide Combined with Moxifloxacin, Rifabutin, Delamanid and/or OPC-167832 in Murine Tuberculosis Models, Antimicrob Agents Chemother 66(4) (2022) e0239821.
[55] R. Dawson, A.H. Diacon, K. Narunsky, V.R. De Jager, K.W. Stinson, X. Zhang, Y. Liu, J. Hafkin, Phase I Single Ascending Dose and Food Effect Study in Healthy Adults and Phase I/IIa Multiple Ascending Dose Study in Patients with Pulmonary Tuberculosis to Assess Pharmacokinetics, Bactericidal Activity, Tolerability, and Safety of OPC-167832, Antimicrob Agents Chemother (2023) e0147722.
[56] clinicaltrials.gov:, Early Bactericidal Activity of TBA-7371 in Pulmonary Tuberculosis (NCT04176250), https://clinicaltrials.gov/ct2/show/NCT04176250?term=TBA-7371&draw=2&rank=2, 2019.

[57] M. Flipo, R. Frita, M. Bourotte, M.S. Martinez-Martinez, M. Boesche, G.W. Boyle, G. Derimanov, G. Drewes, P. Gamallo, S. Ghidelli-Disse, S. Gresham, E. Jimenez, J. de Mercado, E. Perez-Herran, E. Porras-De Francisco, J. Rullas, P. Casado, F. Leroux, C. Piveteau, M. Kiass, V. Mathys, K. Soetaert, V. Megalizzi, A. Tanina, R. Wintjens, R. Antoine, P. Brodin, V. Delorme, M. Moune, K. Djaout, S. Slupek, C. Kemmer, M. Gitzinger, L. Ballell, A. Mendoza-Losana, S. Lociuro, B. Deprez, D. Barros-Aguirre, M.J. Remuinan, N. Willand, A.R. Baulard, The small-molecule SMARt751 reverses Mycobacterium tuberculosis resistance to ethionamide in acute and chronic mouse models of tuberculosis, Sci Transl Med 14(643) (2022) eaaz6280.
[58] clinicaltrials.gov:, A Phase 2 Trial to Evaluate the EBA, Safety and Tolerability of Eto Alone and in Combination with BVL-GSK098 (BETO) (NCT05473195), https://clinicaltrials.gov/ct2/show/NCT05473195?term=BVL-GSK098&draw=2&rank=2, 2022.
[59] G.V. Doern, G. Pierce, A.B. Brueggemann, In vitro activity of sanfetrinem (GV104326), a new trinem antimicrobial agent, versus Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis, Diagn Microbiol Infect Dis 26(1) (1996) 39-42.
[60] clinicaltrials.gov:, EBA, Safety and Tolerability of Sanfetrinem Cilexetil (NCT05388448), https://clinicaltrials.gov/ct2/show/NCT05388448?term=Sanfetrinem+cilexetil&draw=2&rank=1, 2022.
[61] K.L. Brown, K.M. Wilburn, C.R. Montague, J.C. Grigg, O. Sanz, E. Perez-Herran, D. Barros, L. Ballell, B.C. VanderVen, L.D. Eltis, Cyclic AMP-Mediated Inhibition of Cholesterol Catabolism in Mycobacterium tuberculosis by the Novel Drug Candidate GSK2556286, Antimicrob Agents Chemother 67(1) (2023) e0129422.
[62] E.L. Nuermberger, M.S. Martinez-Martinez, O. Sanz, B. Urones, J. Esquivias, H. Soni, R. Tasneen, S. Tyagi, S.Y. Li, P.J. Converse, H.I. Boshoff, G.T. Robertson, G.S. Besra, K.A. Abrahams, A.M. Upton, K. Mdluli, G.W. Boyle, S. Turner, N. Fotouhi, N.C. Cammack, J.M. Siles, M. Alonso, J. Escribano, J. Lelievre, J. Rullas-Trincado, E. Perez-Herran, R.H. Bates, G. Maher-Edwards, D. Barros, L. Ballell, E. Jimenez, GSK2556286 Is a Novel Antitubercular Drug Candidate Effective In Vivo with the Potential To Shorten Tuberculosis Treatment, Antimicrob Agents Chemother 66(6) (2022) e0013222.
[63] clinicaltrials.gov:, A Study to Evaluate Safety, Tolerability and Pharmacokinetics of GSK2556286 in Healthy Adult Participants, https://clinicaltrials.gov/ct2/show/NCT04472897?term=GSK2556286&draw=2&rank=1, 2020.

Figure 1. 2023 Global TB Drug Pipeline [19]

Figure 2. TB Drug targets and agents/class

Figure 3. Graphical display of the drug development plan for quabodepistat, ganfeborole, BTZ-043 and sutezolid .

Tables

Table 1. Protein synthesis inhibitors

Compounds	Description
Oxazolidinones	
Sutezolid (PNU-100480)	Compared to linezolid: • Thiomorpholine analogue with potential to avert toxicity through better specificity for bacterial ribosomes • Showed higher potency in mouse model, with similar potential to shorten treatment [31]. In clinical evaluation • Demonstrated early bactericidal activity (EBA) of 0.088 log10CFU/ml*d (95% CI -0.112 to -0.065) when 600mg twice daily administered as 14-day monotherapy [32] • In 12-week 75-participant PanACEA-SUDOCU trial (in combination with bedaquiline, delamanid and moxifloxacin), no neuropathy or myelosuppression demonstrated; nor added efficacy on primary endpoint of quantitative bacterial load [33]. • Despite 1 case of drug-induced hepatotoxicity, no further hepatic safety signals stemming from Phase 2A trial observed. • Additional Phase 2 investigation planned in EDCTP -funded PanTB -HM trial, by PAN-TB collaboration, and by ACTG.
Delpazolid (LCB01-037)	• Depazolid appears to have lower C_{min} mainly through a more rapid elimination and therefore may have less toxicity [34]. • In 13 clinical isolates of linezolid resistant TB from China, 7 were delpazolid-susceptible, raising possibility for incomplete cross-resistance [35]. • Currently under evaluation in 16-week dose-finding study; results expected in 2nd half of 2024 [36].
TBI-223	Compared to linezolid: • In mitochondrial protein synthesis, inhibition 14-fold lower [37]. • In murine studies, efficacy appears equivalent. • In development by TB Alliance; currently in phase I human trials • Further testing planned by ACTG.
Tedizolid	Tedizolid is another repurposed oxazolidinone currently evaluated in a phase 2A study.
Oxaboroles	
Ganfeborole (GSK3036656)	• First in class oxaborole boron-containing Leucyl-tRNA synthetase inhibitor; interferes with protein synthesis/translation and shown to target *M. tuberculosis* in vitro and in vivo [38]. • Low dose compound recently completed 14-day phase 2a EBA trial in rifampicin-susceptible pulmonary TB patients: o Daily treatment with Ganfeborole at 5, 15 and 30 mg associated with EBA, measured by rate of change in log_{10} colony forming units and time to positivity of *M. tuberculosis* cultures over 14 days; 30 mg dose displayed highest EBA [39]. o Further phase 2a trial with Ganfeborole in combination with bedaquiline or delamanid or BTZ-043 is currently underway.

Table 2. Respiratory chain inhibitors

Compounds	Description
Diarylquinolines	

TBAJ-876
and
TBAJ-587
	• TBAJ-876 and TBAJ-587 are dialkoxypyridine analogues of bedaquiline resulting from next-generation diarylquinoline lead optimization efforts.
	• Compared with bedaquiline (and its metabolites):
	  ○ Both compounds selected based on improved potency and reduced potential for QT prolongation as demonstrated by in vitro cardiac ion channel current inhibition screening studies and dog studies [40].
	  ○ Minimal inhibitory concentrations (MIC) of TBAJ-876 and TBAJ-587 approximately 8- to 10-fold lower against laboratory and clinical strains.
	  ○ Similarly, N-des-methyl metabolites of TBAJ-876 and TBAJ-587 have lower MIC.
	  ○ *In vivo*, lower doses of TBAJ-876 and TBAJ-587 produced similar efficacy.
	  ○ At similar doses, more rapid bactericidal and sterilizing activity observed, including against rv0678 strains.
	  ○ Although shared mechanism of action (vulnerable to same resistance mutations), greater potency could provide efficacy against rv0678 while maintaining higher barrier to resistance.
	  ○ Mutations in *Rv0678,* as most common mechanism leading to resistance by activation of transcription of an efflux transporter (MmpL5-MmpS5); clofazimine resistance also associated with mutations in *Rv0678* through same mechanism [13].
	• Phase 1 trials completed for both compounds, demonstrating generally well-tolerated safety profile.
	• Phase 2 trial of TBAJ-876 underway in patients with drug-susceptible TB, with range of doses being evaluated in combination with pretomanid and linezolid.

Sudapyridine	• Sudapyridine - bedaquiline derivative developed in China; currently undergoing phase 3 evaluation there.
Cytochrom bc1 complex inhibition	
Telacebec (Q203)	• First-in-class, orally active imidazopyridine carboxamide inhibitor of the QcrB subunit of the cytochrome bc1 complex, causing depletion of ATP synthesis [41]. • MIC_{50} of 2.7 nM in broth culture medium and MIC_{50} of 0.28 nM against *M. tuberculosis* H37Rv, infected macrophages. • Following single- and multiple-dose Phase 1 studies, 14-day monotherapy trial in drug-sensitive TB patients demonstrated dose-dependent EBA [42]. • Highly active against two other mycobacterial species, *M. leprae* and *M.* ulcerans - causative agents of leprosy and Buruli ulcer, respectively.

Table 3. Mycobacterial cell wall synthesis disruption

Compounds	Description
DprE1 inhibitors	
BTZ-043	• First molecule discovered in 2009 with inhibitory activity against DprE1 enzyme. • Very low in vitro inhibitory activity at nanomolar concentrations [43]. • Accumulates within rim of necrotic lesions and within 8 hours after administration, penetrates whole granuloma of C3HeJ/FeB 9 mice that display a human-like pathology [44]. • Shown 2.5 log reduction of log_{10}CFU/lung at 200mg/kg after 8 weeks of dosing in C3HeJ/FeB 9mice [45]. • To date, 96 individuals exposed to BTZ-043 doses between 250 and 1750 mg in three phase 1-2 studies [46, 47]; when taken with food, bioavailability markedly increases. • In phase 2a EBA trial BTZ-043 (given as monotherapy), strong bactericidal effect over 14 days, similar to rifampicin [48] and did not show any significant safety concern.
Macozinone PBTZ-169	• Derivative of BTZ-043 but incorporates piperazine component. • In vitro, has demonstrated efficacy against MDR/RR strains of *M. tuberculosis;* reduction in log10CFU/Lung of around 0.5 over 8 weeks of treatment in C3HHeJ mice [49]. • From 2018 to 2020, two phase 1 trials conducted to investigate the effects of different formulations [50, 51]. • In 2017, phase 2a EBA trial conducted in Russia and Belarus assessing three doses [52].
Quabodepistat OPC-167832	• Novel carbostyril derivative proved to have low MICs against *Mycobacterium tuberculosis* (ranging from 0.24 ng/ml to 2 ng/ml), with bactericidal activity against both growing and intracellular bacilli. • Did not show antagonistic effects with other anti-TB medicines tested, both in vitro and in vivo studies. • In mouse models of chronic TB, showed potent bactericidal activities with a 2-log reduction in log_{10}CFU/lung over 8 weeks at 20mg/kg OD • Treatment regimen containing agent showed efficacy in preventing relapse compared to standard treatment regimen for drug susceptible TB [53, 54]. • In phase 1b/2a study, all tested doses (3, 10, 30 and 90 mg) appeared to have significant bactericidal activity and did not show any significant safety concern [55].
TBA-7371	• Non-covalent azaindole inhibitor of DprE1. • Demonstrates potent in vitro bactericidal activity against M tuberculosis with minimum bactericidal concentration similar to its MIC against replicating M. tuberculosis. • MIC_{90} of TBA-7371 is 0.64 µg/mL and MIC range is 0.04 to 5.12 µg/mL. • Demonstrated dose-responsive bacteriostatic and bactericidal *in vivo* efficacy against acute and chronic murine (Kramnik) TB; with a 1-log reduction in log_{10}CFU/lung over 8 weeks at 100mg/kg BID [49].

	• Single- and multiple-dose Phase 1 studies have been completed, and a phase 2 dose-ranging and dose fractionation study has been recently completed, showing highest activity with thrice daily dosing regimen [56].

Table 4. Compounds with other modes of action

Compounds	Description
Thioamides	
Alpibectir BVL-GSK098	Alpibectir an amido-piperidine, acts as a booster by activating *mymA* allowing for >3-fold lower doses of ethionamide while re-establishing sensitivity in ethionamide resistant TB strains and potentiating it's activity [57]. It is currently in phase 2a development [58].
Penicillin binding proteins and transpeptidases	
Sanfetrinem cilexetil	Sanfetrinem cilexetil is a first in class oral tricyclic carbapenem, previously developed to treat otitis media in children 3 decades ago. Recently repurposed for TB after being identified as the most active against intracellular TB in a screen of 2,000 β-lactam compounds and is very stable against β-lactamases[59]. A phase 2a 14-day EBA study in pulmonary TB patients is ongoing [60].
Cholesterol Metabolism	
GSK2556286	GSK2556286 is a Rv1625 agonist leading to increased cAMP and reduced cholesterol metabolism [61]. In vivo it demonstrates intracellular activity, and possibly sterilising and treatment shortening qualities [62]. A phase 1 double-blind, randomized, sequential, parallel-dose cohort study in healthy adult participants is currently recruiting [63].

2024 Global New TB Drug Pipeline[1]

Discovery	Preclinical Development		Clinical Development			Regulatory Market Approvals
Lead Optimization	Early Stage Development	GMP / GLP Tox.	Phase 1	Phase 2	Phase 3	
Indazole sulfonamides	FIM-253	GSK-839*	TBD09 (MK-7762)	Telacebec* (Q203)	Sudapyridine (WX-081)	
Diarylthiazoles	TBD10 (MK-3854)	OTB-658	GSK-286*	Alpibectir (BVL-GSK098)*		
DprE1 Inhibitors	CLB-073*		TBAJ-587	TBAJ-876		Bedaquiline*
Direct InhA Inhibitors	SPR720*		TBI-223	Sanfetrinem		Delamanid*
Mtb energy metabolism	MPL-447*		Macozinone* (PBTZ-169)	Delpazolid, Sutezolid, Tedizolid		Pretomanid*
Gyrase Inhibitors	JSF-3285*			BTZ-043*		
Arylsulfonamides	CPZEN-45*			TBA-7371*		
Inhibitors of MmpL3, Translocase-1, ClpC1, ClpP1P2, PKS13, F-ATP synthase, RNAP	NTB-3119*			Quabodepistat (OPC-167832*)		
Oxazolidinones	MBX-4888A (1810)*			Ganfeborole (GSK-656*/070)		
DnaE1 / Nargenicin analogs	FNDR-20364*			Pyrifazimine (TBI-166) SQ-109*		

*New chemical class. Known chemical classes for any indication are color coded: rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound identified: http://www.newtbdrugs.org/pipeline/discovery

Underline = updates since November 2022

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: March 2024

DNA Gyrase
- Fluoroquinolones - GyrA
- SPR-720 - GyrB

Folic Acid Metabolism
- p-Aminosalicylic Acid (PAS)

RNA Polymerase
- Rifamycins – Rifampin/Rifapentine

Cell Wall Synthesis (Mycolic Acids)
- Isoniazid
- Ethionamide
- Alpibectir (Ethionamide booster)

Ribosome (50S)
- Oxazolidinones
  - Linezolid, Sutezolid, TBI-223, MK-7762, Delpazolid, Tedizolid
- Macrolides/Ketolides

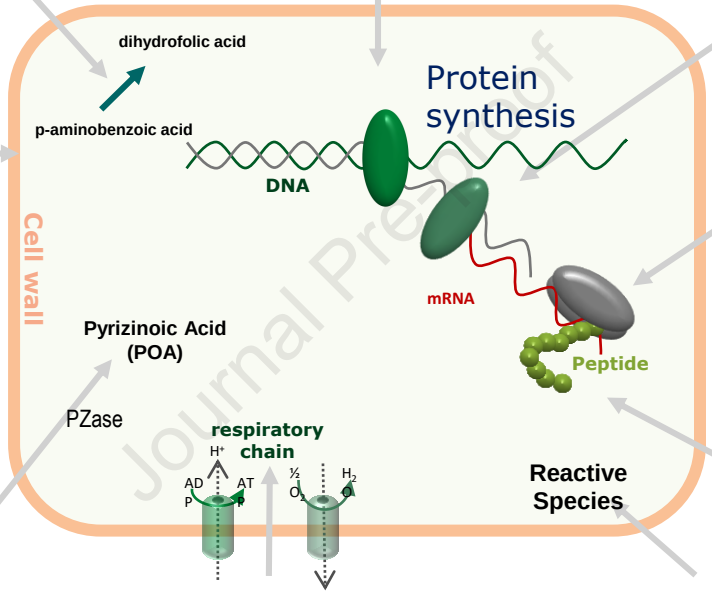
Cell Wall Synthesis (Peptidoglycan)
- Cycloserine
- Beta-lactams, Carbapenems
- Sanfetrinem

Ribosome (30S)
- Aminoglycosides
- Streptomycin
- Capreomycin
- Viomycin

Cell Wall Synthesis (Arabinogalactan)
- Ethambutol
- DprE1 Inhibitors
  - TBA-7371
  - Quabodepistat (OPC-167832)
  - BTZ-043 / PBTZ169

Amino acyl tRNA Synthetases
- Ganfeborole – LeuRS

Protein Degredation
- ClpP/ClpC



Proton Motive Force
- Pyrazinamide

Multiple Targets
- Nitroimidazoles
  - Pretomanid
  - Delamanid

Other Mechanisms
- GSK-286 - Cholesterol metabolism
- MmpL3
- Iron acquisition
- Fatty Acid Biosynthesis

ATP Synthesis
- Diarylquinolines - ATP Synthase
  - Bedaquiline
  - TBAJ-587
  - TBAJ-876
  - Sudapyridine
- Q203 – Cytochrome bc
- Pyrifazimine
- Clofazimine – NADH Dehydrogenase

Q =Quabodepistat, G =Ganfeborole, T =BTZ-043, B =Bedaquiline, D =Delamanid, Pa =Pretomanid, M =Moxifloxacin, L =Linezolid, Z =Pyrazinamide, H =Isoniazid, R =Rifampicin, E =Ethambutol