Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Microbiology

New tuberculosis drugs on the horizon

Stewart T Cole[1] and Giovanna Riccardi[2]

Tuberculosis (TB) remains a major global health concern whose control has been exacerbated by HIV and the emergence of multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains of *Mycobacterium tuberculosis*. The demand for new and faster acting TB drugs is thus greater than ever. In the past decade intensive efforts have been made to discover new leads for TB drug development using both target-based and cell-based approaches. Here, we describe the most promising anti-tubercular drug candidates that are in clinical development and introduce some nitro-aromatic compounds that inhibit a new target, DprE1, an essential enzyme involved in a crucial step in mycobacterial cell wall biosynthesis.

Addresses
[1] Global Health Institute, Ecole Polytechnique Fédérale de Lausanne, CH-1015 Lausanne, Switzerland
[2] Dipartimento di Genetica e Microbiologia, Università degli Studi di Pavia, 27100 Pavia, Italy

Corresponding author: Riccardi, Giovanna (giovanna.riccardi@unipv.it)

Current Opinion in Microbiology 2011, **14**:570–576

This review comes from a themed issue on
Antimicrobials
Edited by James Collins and Stefano Donadio

Available online 5th August 2011

1369-5274/$ – see front matter

DOI 10.1016/j.mib.2011.07.022

Introduction

Tuberculosis (TB) is a chronic and complex disease resulting from infection with the slow-growing pathogen, *Mycobacterium tuberculosis*, which may be present in intracellular and extracellular forms; these display widely different metabolic states, ranging from exponential growth to latency, in various lesions within the same patient [1,2••]. Presently, TB accounts for the annual loss of two million lives as a result of poverty, homelessness, synergy with the HIV/AIDS pandemic and the spread of multidrug-resistant (MDR) and extensively-drug resistant (XDR) strains of *M. tuberculosis* [1,3–4]. While most of the 9 million new cases each year occur in the developing world, the industrialized nations are also at increasing risk owing to the inexorable spread of drug-resistant disease, global travel and immigration [5].

Standard TB chemotherapy, recommended by the WHO, includes two months of intensive, directly observed therapy with four first-line drugs (isoniazid, rifampicin, pyrazinamide and ethambutol), followed by a minimum of 4 months of isoniazid and rifampicin treatment. MDR-TB, owing to strains resistant to both isoniazid and rifampicin, requires a further two years of treatment with second-line drugs such as fluoroquinolones (FQs), aminoglycosides, ethionamide, D-cycloserine and basic peptides [6]. XDR-TB arose from MDR-strains with acquired resistance to aminoglycosides and FQs and, more recently, new forms of resistant bacilli have appeared that are totally drug-resistant or super-XDR [4,7•].

TB treatment is confounded by the relative inefficacy of the drugs available and the variety of physiological states in which *M. tuberculosis* can exist. In particular, non-replicating or latent bacilli constitute a challenge to therapy because of their phenotypic drug resistance. Any anti-TB compounds in development must cope with this reservoir of bacilli in order to eliminate the disease and this is a tall order given that a third of the world's population is latently infected with *M. tuberculosis*. Furthermore, since many TB patients are also co-infected with HIV, new TB drugs must be compatible with anti-retroviral therapy [8].

Approaches and obstacles to drug discovery

In the recent past, the pharmaceutical industry has favoured a target-based approach to drug discovery in all therapeutic areas. Here, an essential function, generally an enzyme, is used in high throughput screening to identify inhibitors present in vast chemical libraries of synthetic compounds. Medicinal chemistry is then employed to progress hits, meeting predefined criteria, through to leads and ultimately to candidate drug (CD) status. After passing preclinical toxicological evaluation, the CD enters clinical trials. While successful in some cases, the HTS approach has failed miserably in the antibacterial discovery area as documented candidly by GlaxoSmithKline [9] and reviewed extensively by other experts [10].

In our own experience, target-based screens generate hits but these usually fail to show useful minimum inhibitory concentrations (MIC) against *M. tuberculosis*. The reasons for this collective failure remain unclear but may include the inability of many synthetic compounds to enter bacteria and find their target, highly active efflux systems or other innate resistance mechanisms. It is also conceivable that the physico-chemical properties of compounds developed for cancer or metabolic diseases, which constitute a large part of current chemical libraries, are more suited to eukaryotic than to prokaryotic cells. In the field of TB, all of the drug candidates currently in

development or in clinical trials were discovered on the basis of their whole cell activity [11].

New TB molecules in clinical development

Currently, there are more drugs in progress for tuberculosis treatment than at any period in the past 50 years. Indeed, for the first time several molecules appear on the horizon of which ten compounds are in clinical development: four of them are existing drugs redeveloped or repurposed for TB while six are new chemical compounds specifically developed for tuberculosis [12••]. This topic has been reviewed recently by several authors and their articles should be consulted for more details than can be given here [12••,13•,14••,15•,16••,17••].

Fluoroquinolones (FQs)

FQs (Table 1) are broad spectrum antibiotics targeting DNA gyrase and DNA topoisomerases. FQs became the most important second-line drugs for treating MDR-TB. They are effective against extracellular multiplying bacteria as well as intracellular latent bacteria [18]. Use of FQs in MDR-TB has been helpful in treating the infection [14••].

The recently developed *gatifloxacin* and *moxifloxacin* are in phase III clinical trials to investigate whether treatment of drug-susceptible TB can be shortened to 4 months by substituting gatifloxacin for ethambutol (ETH), or moxifloxacin for ETH or isoniazid [12••]. There is concern about the development of acquired FQ resistance in undiagnosed TB patients owing to the widespread use of these drugs for other infectious diseases or when FQ is the only active drug in a failing TB regimen [13•].

Diarylquinoline TMC-207

TMC207 (Table 1 and Figure 1, also known as R207910) is a diarylquinoline that inhibits the *c* subunit of ATP synthase and causes a decrease of cellular ATP levels. It was discovered by screening more than 70,000 compounds for activity against the saprophytic *Mycobacterium smegmatis* [19]. The mode of action was identified through the isolation of drug-resistant spontaneous mutants harbouring alterations in the *atpE* gene, coding for the ATP synthase *c* subunit; particularly, changes at D32V and A63P were associated with resistance [20]. Human mitochondrial ATP synthase displays more than 20,000-fold lower sensitivity for TMC207 compared to mycobacterial ATP synthase, thus suggesting that TMC207 may not elicit ATP synthesis-related toxicity in mammalian cells [21].

A study of nearly 100 spontaneous TMC-207-resistant mutants, obtained from seven different clinical isolates, found that mutation of *atpE* only partially accounted for the resistance observed. In 38 of these isolates no mutations were found in the ATP synthase operon, suggesting that TMC-207 has additional, as yet unknown, targets or resistance mechanisms [17••,22].

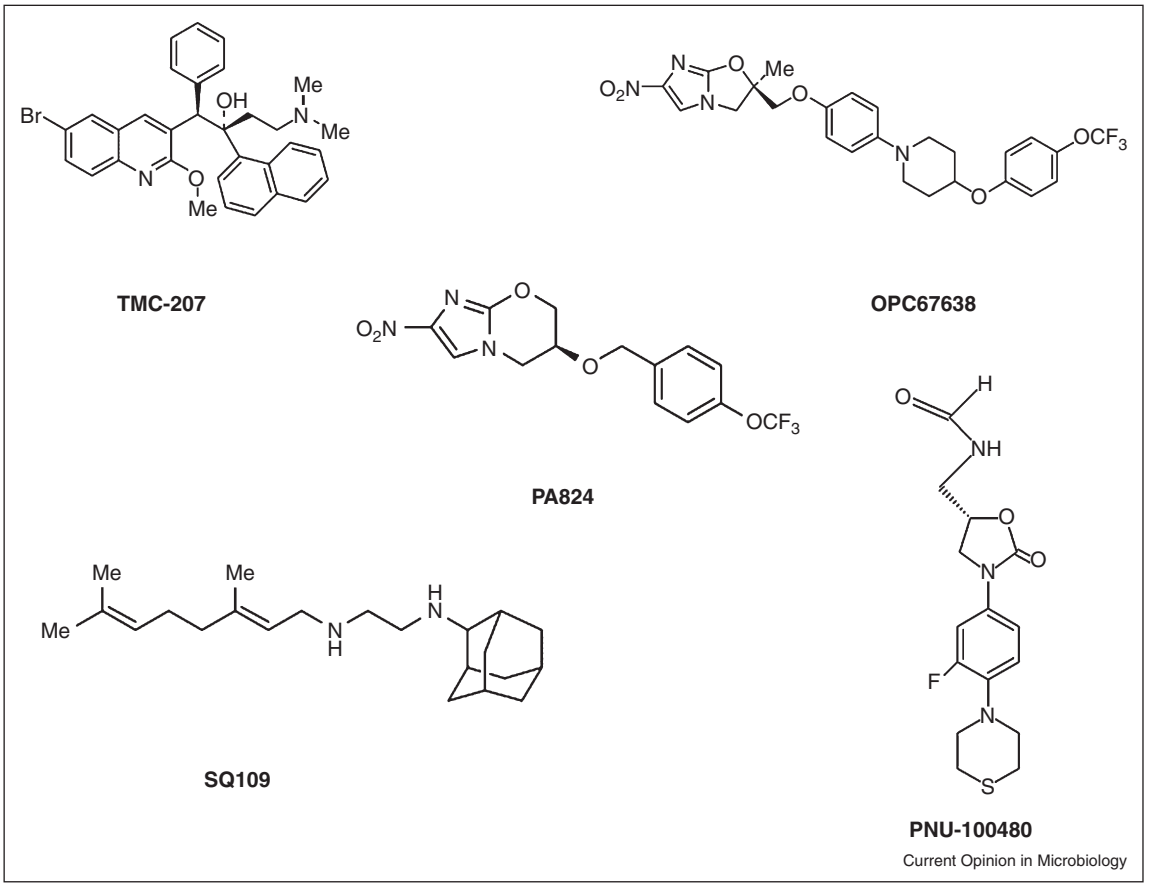
Recently, Rao *et al.* [23] have shown that *de novo* ATP synthesis is essential for the viability of nonreplicating mycobacteria (NRM) and demonstrated a high bactericidal activity of TMC-207 against the NRM. This unique dual bactericidal activity, with equal potency on replicating and dormant bacilli, distinguishes diarylquinolines from all the currently used antituberculosis drugs, such as isoniazid and rifampicin [24]. TMC-207 is very potent against both drug-susceptible and drug-resistant *M. tuberculosis* strains exhibiting MIC equal to or lower than isoniazid and rifampicin, and is now in phase II clinical trials. The drug is metabolized by the cytochrome P450 isoenzyme CYP3A4, making coadministration difficult with drugs that induce CYP3A4, such as rifampicin [19]. Current and future studies will define the role of

Table 1

Compounds described in this work

Compound	Year of discovery	Chemical class	Target	Development stage	Developing organization
Fluoroquinolones	1970s	Fluoroquinolones	DNA gyrase and DNA topoisomerases	phase III clinical trials	Various
TMC-207	2005	Diarylquinolines	*c* subunit of ATP synthase	phase II clinical trials	J&J/Tibotec and TB Alliance
PA824	2000	Nitroimidazoles	mycolic acid biosynthesis	phase II clinical trials	TB Alliance
OPC67683	2006	Nitroimidazoles	mycolic acid biosynthesis	phase II clinical trials	Otsuka
SQ109	2004	Ethylenediamine	Not completely defined	phase I/II clinical trials	Sequella, supported by NIH
Rifamycins	1959	Rifamycins	RNA polymerase	phase III clinical trials	CDC TBTC, JHU, & Sanofi-Aventis
Linezolid	2005	Oxazolidinones	50S ribosomal subunit	phase II clinical trials	Pfizer
PNU-100480	2010	Oxazolidinones	50S ribosomal subunit	phase I clinical trials	Pfizer
AZD5847	2009	Oxazolidinones	50S ribosomal subunit	phase I clinical trials	AstraZeneca
Benzothiazinone	2009	Benzothiazinones	DprE1 epimerase	Pre-clinical	Alere
Dinitrobenzamide	2009	Dinitrobenzamides	DprE1 epimerase	Pre-clinical	None
VI-9376	2010	Nitro-bromoquinoxaline	DprE1 epimerase	Pre-clinical	Vichem

Figure 1



Chemical structures of new TB molecules in clinical development.

this molecule in a shortened treatment regimen for tuberculosis treatment.

Nitroimidazoles (PA-824 and OPC67683)

One peculiarity of nitroimidazoles is that they are active against replicating and non-replicating bacteria with metronidazole being best known for its activity against anaerobes. Two nitroimidazoles are now in clinical development.

PA-824 (Table 1 and Figure 1) is a prodrug that requires intracellular activation for its biological function. Rv3547 from *M. tuberculosis*, a deazaflavin-dependent nitroreductase (Ddn), transforms PA-824 into three primary metabolites. The main metabolite is the corresponding *des*-nitroimidazole. *Des*-nitro metabolite formation generated reactive nitrogen species, including nitric oxide (NO), which are the major effectors of the anaerobic activity of these compounds [25]. PA-824 has no effect on the viability of *M. leprae*, consistent with the loss of the *ddn* gene from the genome [26]. Microarray analysis of the mode of action of PA-824 showed a puzzling mixed effect on genes responsive to both cell wall inhibition and respiratory chain poison [13•]. The aerobic killing mechanisms of this drug seems to inhibit mycolic acid biosynthesis via an unknown mechanism while the anaerobic killing is believed to work through inhibition of cytochrome *c* oxidase by nitric oxide, effectively poisoning cell respiration [27,14••].

OPC67683 (Table 1 and Figure 1) is a nitro-dihydroimidazooxazole that is active against *M. tuberculosis in vitro* and in mice and inhibits mycolic acid biosynthesis. Like PA-824, it requires metabolic activation and Ddn has been suggested as the key enzyme involved in this process [28]. Both PA-824 and OPC67683 drugs are currently in phase II clinical trials for the treatment of MDR-TB.

Recently, it has been demonstrated that PA-824 exhibits time-dependent activity in a murine model of tuberculosis and similar time-dependent pharmacodynamic parameters are likely to be observed for OPC-67683 [29]. Pharmacodynamic studies should be performed for new anti-TB drugs in development to aid compound and dose selection for clinical trials [29].

Finally, more data are needed to clarify the mechanism by which these molecules exert their bactericidal effect.

Ethylenediamine (SQ109)

ETH is perceived as the weakest component of directly observed therapy and thus most in need of improvement. Attempts have been made to synthesize more potent derivatives using combinatorial chemistry. SQ109 is a novel 1,2-ethylenediamine-based ETH analogue that was identified from a library of over 60,000 combinatorial compounds (Table 1 and Figure 1). No data on the mode of action are available and the target remains elusive as no effect on EmbA or EmbB, the targets of ETH, was seen with a proteomic approach comparing the effects of 24-h treatment on *M. tuberculosis* H37Rv [30]. The combination of SQ109 with TMC207 improved an already excellent TMC207 MIC for *M. tuberculosis* H37Rv by 4–8-fold as well as the rate of killing of bacteria over that of each drug singly [31]. SQ109 is in phase I/II clinical trials.

Rifamycins

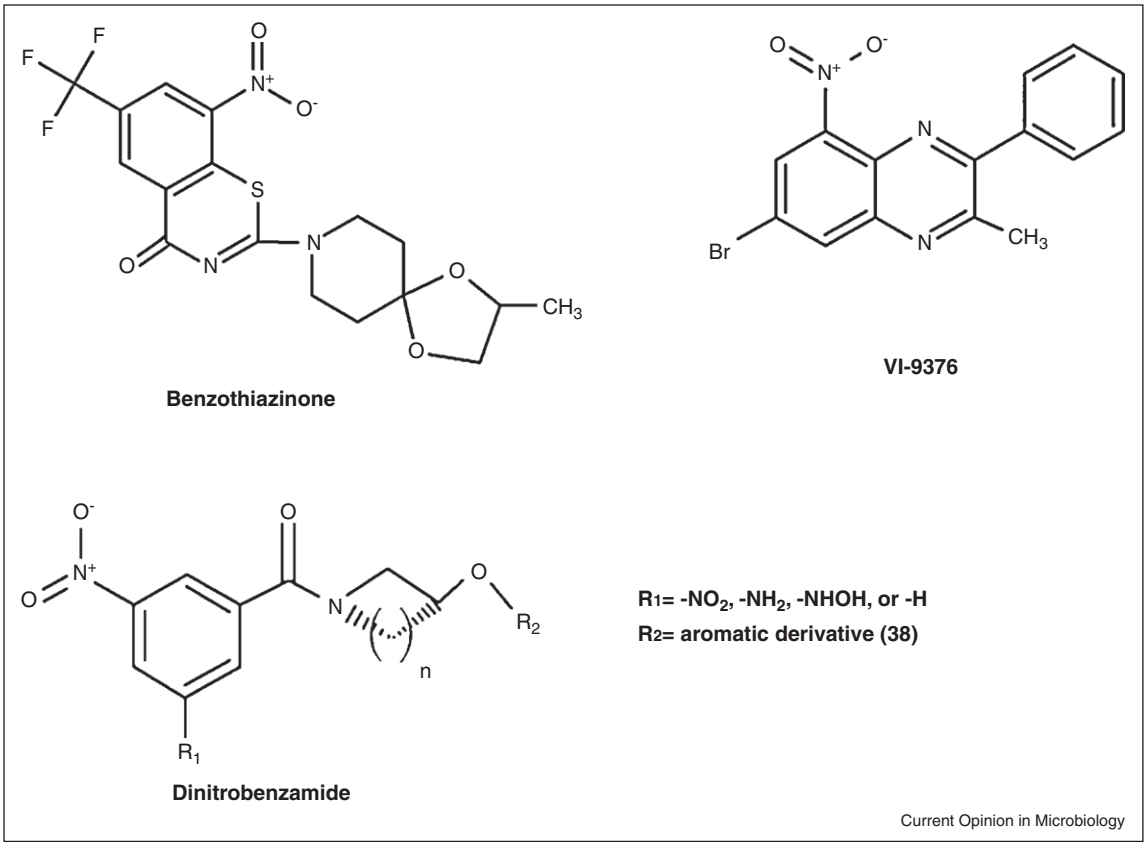
Rifamycins (Table 1) are potent inhibitors of RNA polymerase. Three semisynthetic rifamycins (rifampicin, rifapentine, rifabutine) have been utilized for the treatment of various microbial infections. Among these, rifampicin is the cornerstone for first-line TB treatment.

Rifapentine, a more potent analogue with a longer half-life than rifampicin, is an interesting candidate for shortening TB treatment [32]. However, like rifampicin, rifapentine induces the expression of P450 enzymes. Phase II B clinical trials are in progress to assess the effects of high doses of rifapentine, given with moxifloxacin, once or twice per week, and daily rifapentine in the first line regimen to shorten treatment [12••].

Oxazolidinones (Linezolid, PNU-100480, AZD5847)

Oxazolidinones, such as linezolid (Table 1), inhibit protein synthesis by binding to the 50S ribosomal subunit and share no cross-resistance with other protein synthesis inhibitors. However, rare cases of oxazolidinone resistance have been associated with 23S rRNA alterations during treatment [33,34]. It is noteworthy that after prolonged treatment, toxicity was observed with this molecule [35]. Linezolid has been used off-label in combination regimens to treat MDR-TB patients [36] but its contribution to such combinations is still unclear [12••].

Figure 2



Chemical structures of new molecules in preclinical development.

PNU-100480 is a linezolid analogue that has shown strong bactericidal activity in the murine model [37,38] and AZD5847, a next-generation oxazolidinone, is highly tuberculocidal (Table 1 and Figure 1) and appears safer than linezolid. Both compounds are now in phase I trials.

A combination therapy with PNU-100480, moxifloxacin, and pyrazinamide was more efficient than the standard treatment of rifampicin, isoniazid, and pyrazinamide. These data suggest that PNU-100480 has the potential to shorten treatment of tuberculosis [39].

In preclinical development: Benzothiazinones, magic molecules for a magic target?

Recently, two different series of nitro-aromatic compounds, the benzothiazinone, BTZ043, (Table 1, Figure 1) and the dinitrobenzamide (DNB, Table 1, Figure 2), were found to be highly active against *M. tuberculosis*, including MDR-TB and XDR-TB strains. Interestingly, both compounds have the same target, the heterodimeric enzyme, decaprenylphosphoryl-β-D-ribose 2′-epimerase, encoded by the *dprE1* and *dprE2* genes [40••,41]. In a third whole cell screen, DprE1 was found to be the target of VI-9376 (Table 1), a molecule structurally related to BTZ (Figure 2) [42]. DprE1 and DprE2 are involved in the biosynthesis of D-arabinose and, in particular, are essential for transformation of decaprenylphosphoryl-D-ribose (DPR) to decaprenylphosphoryl-D-arabinose (DPA), a precursor for the synthesis of the mycobacterial cell-envelope polysaccharides, arabinogalactan and liporabinomannan [43,44]. Arabinogalactan is a fundamental component of the mycobacterial cell wall, which covalently binds the outer layer of mycolic acids to peptidoglycan; without DPA a complete mycobacterial cell wall cannot be produced.

BTZ display low nanomolar activity and covalently modify DprE1 thereby ablating its function [45••]. The lead compound, BTZ043, is currently in late preclinical development. To monitor the potential development of BTZ-resistance, a total of 240 sensitive and MDR clinical isolates from four European hospitals were surveyed for the presence of mutations in the *dprE1* gene and for BTZ susceptibility. All 240 strains were susceptible, thus establishing the baseline before the introduction of BTZ043 in clinical trials [46].

Conclusions

There are grounds for cautious optimism in the field of TB drug development since 10 candidates, from five different chemical classes, are now at various stages of clinical development. Nonetheless, we should remember that there is a high attrition rate during clinical trials before a candidate is approved for human use and resistance to new compounds will eventually arise, so drug discovery efforts should be intensified. The target-to-drug approach has been both unsuccessful and disappointing in the field of anti-infective agent discovery leading investigators to revisit phenotypic screening of libraries of synthetic compounds or natural products as a means of hit-generation and target finding. The value of this approach was beautifully illustrated by the discovery and development of TMC-207, followed by PA-824 and BTZ043. The latter compound was a most powerful tool for finding and pharmacologically validating an unknown yet highly vulnerable drug target, decaprenyl-phosphoribose 2′-epimerase. This enzyme can now be exploited in target-based approaches including structure-assisted drug design, fluorescence polarization assays or other enzymatic screens in attempts to find new pharmacophores or sites for inhibition, which, hopefully, could result in 'magic' for TB treatment [47].

Acknowledgements

We thank the European Commission for support (VI Framework, contract N. LSHP-CT-2005-018923 and VII Framework, contract N. 260872).

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Glaziou P, Floyd K, Raviglione M: **Global burden and epidemiology of tuberculosis**. *Clin Chest Med* 2009, **30**:621-636.

2. •• Chao MC, Rubin EJ: **Letting sleeping dos lie: does dormancy play a role in tuberculosis?** *Annu Rev Microbiol* 2010, **64**:293-311.
Evaluates the results of several *in vitro* models of dormancy and considers the applicability of various animal models for studying aspects of human latency and resistance to killing by antibiotics.

3. Harrington M: **From HIV to tuberculosis and back again: a tale of activism in 2 pandemics**. *Clin Infect Dis* 2010, **50(Suppl. 3)**:S260-S266.

4. Cegielski JP: **Extensively drug-resistant tuberculosis: there must be some kind of way out of here**. *Clin Infect Dis* 2010, **50(Suppl. 3)**:S195-S200.

5. Carvalho AC, Migliori GB, Cirillo DM: **Tuberculosis in Europe: a problem of drug resistance or much more?** *Expert Rev Respir Med* 2010, **4**:189-200.

6. Fu LM: **The potential of human neutrophil peptides in tuberculosis therapy**. *Int J Tuberc Lung Dis* 2003, **7**:1027-1032.

7. • Velayati AA, Masjedi MR, Farnia P, Tabarsi P, Ghanavi J, Ziazarifi AH, Hoffner SE: **Emergence of new forms of totally drug-resistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug-resistant strains in Iran**. *Chest* 2009, **136**:420-425.
The first description of tuberculosis caused by totally drug resistant strains.

8. Harries AD, Zachariah R, Corbett EL, Lawn SD, Santos-Filho ET, Chimzizi R, Harrington M, Maher D, Williams BG, De Cock KM: **The HIV-associated tuberculosis epidemic – when will we act?** *Lancet* 2010, **375**:1906-1919.

9. Payne DJ, Gwynn MN, Holmes DJ, Pompliano DL: **Drugs for bad bugs: confronting the challenges of antibacterial discovery**. *Nat Rev Drug Discov* 2007, **6**:29-40.

10. Fischbach MA, Walsh CT: **Antibiotics for emerging pathogens**. *Science* 2009, **25**:1089-1093.

11. Riccardi G, Pasca MR, Buroni S: ***Mycobacterium tuberculosis*: drug resistance and future perspectives**. *Future Microbiol* 2009, **4**:597-614.

12. Ma Z, Lienhardt C, McIlleron H, Nunn AJ, Wang X: **Global**
•• **tuberculosis drug development pipeline: the need and the reality**. *Lancet* 2010, **375**:2100-2109.
A detailed and clear report of new TB drugs. A few suggestions to achieve the goal of TB elimination are indicated.

13. Lalloo UG, Ambaram A: **New antituberculous drugs in**
• **development**. *Curr HIV/AIDS Rep* 2010, **7**:143-151.
Updated overview of new antitubercular drugs.

14. Leibert E, Rom WN: **New drugs and regimens for treatment of**
•• **TB**. *Expert Rev Anti Infect Ther* 2010, **8**:801-813.
A survey on the new TB drugs focused on clinical achievements.

15. Shi R, Sugawara I: **Development of new anti-tuberculosis drug**
• **candidates**. *Tohoku J Exp Med* 2010, **221**:97-106.
A detailed report of new TB drugs.

16. Burman WJ: **Rip Van Winkle wakes up: development of**
•• **tuberculosis treatment in the 21st century**. *Clin Infect Dis* 2010, **50(Suppl. 3)**:S165-S172.
A detailed report of new TB drugs as well as the kind of studies that are part of TB drug development.

17. Barry CE 3rd, Blanchard JS: **The chemical biology of new drugs**
•• **in the development for tuberculosis**. *Curr Opin Chem Biol* 2010, **14**:456-466.
Describes the most promising new drugs in late-stage development and the important role that chemical biology has played in this field.

18. García-Tapia A, Rodríguez JC, Ruiz M, Royo G: **Action of fluoroquinolones and Linezolid on logarithmic- and stationary-phase culture of *Mycobacterium tuberculosis***. *Chemotherapy* 2004, **50**:211-213.

19. Matteelli A, Carvalho AC, Dooley KE, Kritski A: **TMC207: the first compound of a new class of potent anti-tuberculosis drugs**. *Future Microbiol* 2010, **5**:849-858.

20. Andries K, Verhasselt P, Guillemont J, Göhlmann HW, Neefs JM, Winkler H, Van Gestel J, Timmerman P, Zhu M, Lee E *et al.*: **A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis***. *Science* 2005, **307**:223-227.

21. Haagsma AC, Abdillahi-Ibrahim R, Wagner MJ, Krab K, Vergauwen K, Guillemont J, Andries K, Lill H, Koul A, Bald D: **Selectivity of TMC207 towards mycobacterial ATP synthase compared with that towards the eukaryotic homologue**. *Antimicrob Agents Chemother* 2009, **53**:1290-1292.

22. Huitric E, Verhasselt P, Koul A, Andries K, Hoffner S, Andersson DI: **Rates and mechanisms of resistance development in *Mycobacterium tuberculosis* to a novel diarylquinoline ATP synthase inhibitor**. *Antimicrob Agents Chemother* 2010, **54**:1022-1028.

23. Rao SP, Alonso S, Rand L, Dick T, Pethe K: **The protonmotive force is required for maintaining ATP homeostasis and viability of hypoxic, nonreplicating *Mycobacterium tuberculosis***. *Proc Natl Acad Sci USA* 2008, **105**:11945-11950.

24. Bald D, Koul A: **Respiratory ATP synthesis: the new generation of mycobacterial drug targets?** *FEMS Microbiol Lett* 2010, **308**:1-7.

25. Singh R, Manjunatha U, Boshoff HI, Ha YH, Niyomrattanakit P, Ledwidge R, Dowd CS, Lee IY, Kim P, Zhang L *et al.*: **PA-824 kills nonreplicating *Mycobacterium tuberculosis* by intracellular NO release**. *Science* 2008, **322**:392-395.

26. Manjunatha UH, Lahiri R, Randhawa B, Dowd CS, Krahenbuhl JL, Barry CE 3rd: ***Mycobacterium leprae* is naturally resistant to PA-824**. *Antimicrob Agents Chemother* 2006, **50**:350-354.

27. Manjunatha U, Boshoff HI, Barry CE: **The mechanism of action of PA-824: Novel insights from transcriptional profiling**. *Commun Integr Biol* 2009, **2**:215-218.

28. Matsumoto M, Hashizume H, Tomishige T, Kawasaki M, Tsubouchi H, Sasaki H, Shimokawa Y, Komatsu M: **OPC-67683 a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis *in vitro* and in mice**. *PLoS Med* 2006, **3**:e466.

29. Ahmad Z, Peloquin CA, Singh RP, Derendorf H, Tyagi S, Ginsberg A, Grosset JH, Nuermberger EL: **PA-824 exhibits time-dependent activity in a murine model of tuberculosis**. *Antimicrob Agents Chemother* 2011, **55**:239-245.

30. Boshoff HI, Myers TG, Copp BR, McNeil MR, Wilson MA, Barry CE 3rd: **The transcriptional responses of *Mycobacterium tuberculosis* to inhibitors of metabolism: novel insights into drug mechanisms of action**. *J Biol Chem* 2004, **279**:40174-40184.

31. Reddy VM, Einck L, Andries K, Nacy CA: **In vitro interactions between new antitubercular drug candidates SQ109 and TMC207**. *Antimicrob Agents Chemother* 2010, **54**:2840-2846.

32. Rosenthal IM, Zhang M, Williams KN, Peloquin CA, Tyagi S, Vernon AA, Bishai WR, Chaisson RE, Grosset JH, Nuermberger EL: **Daily dosing of rifapentine cures tuberculosis in three months or less in the murine model**. *PLoS Med* 2007, **4**:e344.

33. Bobkova EV, Yan YP, Jordan DB, Kurilla MG, Pompliano DL: **Catalytic properties of mutant 23 S ribosomes resistant to oxazolidinones**. *J Biol Chem* 2003, **278**:9802-9807.

34. Bozdogan B, Appelbaum PC: **Oxazolidinones: activity, mode of action, and mechanism of resistance**. *Int J Antimicrob Agents* 2004, **23**:113-119.

35. De Bus L, Depuydt P, Libbrecht L, Vandekerckhove L, Nollet J, Benoit D, Vogelaers D, Van Vlierberghe H: **Severe drug-induced liver injury associated with prolonged use of linezolid**. *J Med Toxicol* 2010, **6**:322-326.

36. Fortun J, Martin-Davila P, Navas E, Perez-Elias MJ, Cobo J, Tato M, De la Pedrosa EG, Gomez-Mampaso E, Moreno S: **Linezolid for the treatment of multidrug-resistant tuberculosis**. *J Antimicrob Chemother* 2005, **56**:180-185.

37. Wallis RS, Jakubiec WM, Kumar V, Silvia AM, Paige D, Dimitrova D, Li X, Ladutko L, Campbell S, Friedland G *et al.*: **Pharmacokinetics and whole-blood bactericidal activity against *Mycobacterium tuberculosis* of single doses of PNU-100480 in healthy volunteers**. *J Infect Dis* 2010, **202**:745-751.

38. Wallis RS, Jakubiec W, Kumar V, Bedarida G, Silvia A, Paige D, Zhu T, Mitton-Fry M, Ladutko L, Campbell S *et al.*: **Biomarker-assisted dose selection for safety and efficacy in early development of PNU-100480 for tuberculosis**. *Antimicrob Agents Chemother* 2011, **55**:567-574.

39. Williams KN, Brickner SJ, Stover CK, Zhu T, Ogden A, Tasneen R, Tyagi S, Grosset JH, Nuermberger EL: **Addition of PNU-100480 to first-line drugs shortens the time needed to cure murine tuberculosis**. *Am J Respir Crit Care Med* 2009, **180**:371-376.

40. Makarov V, Manina G, Mikusova K, Möllmann U, Ryabova O,
•• Saint-Joanis B, Dhar N, Pasca MR, Buroni S, Lucarelli AP *et al.*: **Benzothiazinones kill *Mycobacterium tuberculosis* by blocking arabinan synthesis**. *Science* 2009, **324**:801-804.
Describes a very promising new antitubercular drug as well as an unknown yet highly vulnerable drug target.

41. Christophe T, Jackson M, Jeon HK, Fenistein D, Contreras-Dominguez M, Kim J, Genovesio A, Carralot JP, Ewann F, Kim EH *et al.*: **High content screening identifies decaprenyl-phosphoribose 2′ epimerase as a target for intracellular antimycobacterial inhibitors**. *PLoS Pathog* 2009, **5**:e1000645.

42. Magnet S, Hartkoorn RC, Székely R, Pató J, Triccas JA, Schneider P, Szántai-Kis C, Orfi L, Chambon M, Banfi D *et al.*: **Leads for antitubercular compounds from kinase inhibitor library screens**. *Tuberculosis (Edinb)* 2010, **90**:354-360.

43. Mikusová K, Huang H, Yagi T, Holsters M, Vereecke D, D'Haeze W, Scherman MS, Brennan PJ, McNeil MR, Crick DC: **Decaprenylphosphoryl arabinofuranose, the donor of the D-arabinofuranosyl residues of mycobacterial arabinan, is formed via a two-step epimerization of decaprenylphosphoryl ribose**. *J Bacteriol* 2005, **187**:8020-8025.

44. Wolucka BA: **Biosynthesis of D-arabinose in mycobacteria – a novel bacterial pathway with implications for antimycobacterial therapy**. *FEBS J* 2008, **275**:2691-2711.

45. Trefzer C, Rengifo-Gonzalez M, Hinner MJ, Schneider P,
•• Makarov V, Cole ST, Johnsson K: **Benzothiazinones: prodrugs**

that covalently modify the decaprenylphosphoryl-beta-D-ribose 2′-epimerase DprE1 of *Mycobacterium tuberculosis*. *J Am Chem Soc* 2010, **132**:13663-13665.
Convincing demonstration of the mechanism of action of benzothiazinones through identification of the covalently modified target.

46. Pasca MR, Degiacomi G, Ribeiro AL, Zara F, De Mori P, Heym B, Mirrione M, Brerra R, Pagani L, Pucillo L *et al.*: **Clinical isolates of *Mycobacterium tuberculosis* in four European hospitals are uniformly susceptible to benzothiazinones**. *Antimicrob Agents Chemother* 2010, **54**:1616-1618.

47. Manina G, Pasca MR, Buroni S, De Rossi E, Reccardi G: **Decaprenylphosphoryl-β-D-ribose 2′-epimerase from *Mycobacterium tuberculosis* is a magic drug target**. *Curr Med Chem* 2010, **17**:3099-3108.