New drugs to treat difficult tuberculous and non-tuberculous mycobacterial pulmonary disease

Simon F K Lee[1], Barbara Laughon[2], Timothy D McHugh[3], Marc Lipman[4, *]

Affiliations:

1 HIV Medicine, Chelsea & Westminster Hospital, London

2 Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

3 UCL Centre for Clinical Microbiology, Department of Infection, University College, Royal Free Campus, Rowland Hill Street, London NW3 2PF, UK

4 UCL Respiratory, Division of Medicine, Royal Free Campus, Rowland Hill Street, London, NW3 2PF, UK

* Corresponding author:

Mailing address: Respiratory Medicine, Royal Free London NHS Foundation Trust, Pond Street, London NW3 2QG, UK

Telephone: +44 207 317 7560

Email: marclipman@nhs.net

Abstract

Purpose of review:

Treatment of drug-sensitive tuberculosis (DS-TB) is effective, whereas that of multi-drug resistant (MDR-) and extensively drug resistant tuberculosis (XDR-TB) as well as non-tuberculous mycobacterial (NTM) disease are less so. Therapy in general requires good adherence to potentially toxic drug regimens over prolonged periods. Poor adherence is associated with resistance development and poor outcome. This review will present promising new treatments, both new drugs and regimens, for difficult mycobacterial pulmonary infections.

Recent findings:

A number of new and repurposed drugs including bedaquiline, delamanid, pretomanid, linezolid and clofazimine, and drug regimens, such as the STREAM trial regimens, are currently progressing from basic research through clinical trials.

Summary:

1. The role of bedaquiline and delamanid in TB and NTM treatment is still not clearly defined
2. New and repurposed drugs such as pretomanid, linezolid and clofazimine have the potential to advance TB and NTM treatment. Inhaled liposomal amikacin shows promise in pulmonary NTM disease
3. Patients with MDR-TB, XDR-TB and NTM disease should be offered the choice to participate in drug trials that may shorten or otherwise improve their experience of treatment
4. The use of an effective regimen based on appropriate NTM-specific drug susceptibility testing should be a cornerstone of treatment for NTM as much as it is for *Mycobacterium tuberculosis* (Mtb) treatment
5. All new drugs identified for Mtb should also be tested for activity against NTM, though robust tools for NTM drug susceptibility testing are required

Keywords: Tuberculosis, NTM, non-tuberculous, MDR-TB, mycobacteria, regimen

Introduction

Current treatment for drug sensitive (DS-TB) tuberculosis (Mtb) dates from the MRC trials of the 1970s, after introduction of TB drugs in the 1940s (1). Treatment of TB unresponsive to initial protocol-led treatment is based on sensitivity results. Although effective, treatment needs to be prolonged and can have significant adverse effects (2,3).

Treatment for NTM is dependent on combinations of rifamycin and macrolide antibiotics, largely extrapolated from Mtb studies, in the absence of much needed clinical trial or pharmacokinetic data as NTM studies have lagged behind TB research (4–6). However, NTMs in general, and the rapid-growing mycobacteria such as *M. abscessus* in particular, have significantly more intrinsic and inducible resistance than Mtb (7–10). NTM research disease *in vivo* is further limited by a lack of animal models (11–13). Current NTM guidelines are therefore based on no more than a handful of randomised controlled trials and observational studies in NTM disease and often use poorly-effective and badly tolerated drug combinations (4,5). Regimen efficacy, if not patient acceptability, has recently been improved by the addition of drugs such as tigecycline, clofazimine, linezolid, telithromycin, moxifloxacin and carbapenems.

Multi-drug resistant (MDR-), extensively drug resistant (XDR-), totally-drug resistant tuberculosis (TDR-TB) and pulmonary NTM disease, most frequently due to *Mycobacterium avium* complex (MAC, which includes *M. intracellulare* and *M. chimaera*), *M. kansasii, M. abscessus* and M. *fortuitum,* are increasingly common. This plus less than satisfactory outcomes for NTM disease mean that now more than ever we need new solutions for TB and NTM disease (6,7,14) The Stop TB Partnership's (http://stoptb.org/) Working Group on New TB Drugs plays a major role in raising awareness of MDR-TB and co-ordinating information about preclinical data and trials. They maintain an up-to-date list of potential new drugs for DS-TB and MDR-TB (www.newtbdrugs.org). The state of the current drug development pipeline for tuberculosis has been recently reviewed (15).

In this current article, we will discuss new and recently repurposed drugs for use in the treatment of difficult mycobacterial infection including novel drug regimens. Here, difficult mycobacterial infection is taken to mean active complex pulmonary DS-TB with single-agent resistance or toxicity, MDR-/XDR-TB or NTM disease. Adjunct therapies will not be reviewed.

Novel Drugs in Mycobacterial infection

For the first time in many years, antituberculosis drug development is an active area of research (16) (Figure 1). Delamanid and bedaquiline are the first drugs to obtain a license as treatment for Mtb in nearly 50 years. Both have now entered clinical practice and are major components of many on-going clinical trials. In addition, there are studies optimising the dose of currently used therapies including high-dose rifampicin or isoniazid and fluoroquinolones (TBTC 32/NIAID OPTI-Q).

Rifampicin is the most important drug for treatment of DS-TB, and increasing the dose up to three times is well tolerated and associated with improved bacteriological although not clinical outcome (17–23). The related rifamycin, rifapentine, is non-inferior to rifampicin in the standard regimen or when ethambutol is replaced by moxifloxacin (24–29). Rifapentine-containing regimens are being evaluated in TBTC 31, a registration trial for US FDA licensing. Such studies may have an influence on how we best treat difficult pulmonary TB and NTM disease dependent on the resistance profile.

Bedaquiline and related compounds

Bedaquiline is a novel oral agent that inhibits Mycobacterial ATP synthase, increasing culture conversion rate and improving outcomes in MDR-TB (30–32). Although a very promising drug with bactericidal activity in Mtb infection, it is bacteriostatic and lacks *in vivo* activity against

Mycobacterium avium (33,34). Despite this, anecdotal evidence suggests that bedaquiline may be useful in pulmonary NTM disease (35).

Bedaquiline pioneered a novel and productive line of research investigating respiratory chain targets in mycobacteria. TBAJ-587 and -876 are related molecules identified by high-throughput screening of novel members of the diarylquinoline family for greater anti-tubercular activity with an improved safety profile. They are undergoing preclinical evaluation (36–38).

Telacebec/Q203

Like bedaquiline, Q203, acts on the respiratory chain. It is bacteriostatic *in vitro* although its activity can be increased by inhibition of parallel pathways (39–41). Current research is aimed at making the molecule less lipophilic (42,43) and at determining its synergism with other antimycobacterial agents. Early bactericidal activity (EBA) phase 2 studies in humans started in 2018.

An interesting possibility is targeting different parts of the mycobacterial terminal respiratory chain with different agents and achieving synthetic lethality. Oxidative phosphorylation is essential to both actively dividing and persister mycobacteria and such an approach would, therefore, potentially target the different mycobacterial states with the same agents (41,44–46).

Delamanid

Delamanid inhibits cell wall synthesis and improves culture conversion rates in MDR-TB patients when added to an optimised background regimen (47,48). Several trials of optimised background regimen plus or minus delamanid in MDR-TB, including a trial involving people living with HIV (PLHIV) on antiretroviral therapy (ART), are due to report in the near future (NCT01424670)

(49,50). Delamanid has some activity *in vitro* against *M. kansasii* but not *M. avium* or *M. intracellulare* and there is no current *in vivo* data (11).

Neither bedaquiline nor delamanid were initially tested in children, however, there are several recently completed trials (NCT01859923 and NCT01856634) of delamanid in paediatric MDR-TB plus anecdotal reports of the safety and efficacy of both agents in paediatric MDR-TB cohorts (51,52).

Initially there were concerns when combining delamanid and bedaquiline due to overlapping cardiac toxicity. However, clinical practice has shown that this is safe with careful monitoring, and that the effects on the electrocardiographic QT interval are neither additive nor synergistic (50). A trial is currently assessing this combination together with an optimised background regimen for MDR-TB (ACTG5343).

Pretomanid/PA-824

Pretomanid is a pro-drug structurally related to delamanid. In addition to effects on mycolic acid synthesis, it is a respiratory chain poison by acting as a nitrous oxide donor, with effects, therefore, on both dividing and non-replicating, anaerobic, persistent mycobacteria (53–55). It has activity against *M. tuberculosis* and *M. kansasii* but not against *M. avium, M. chelonae* or *M. fortuitum* (11,53,55). It has been evaluated for EBA with bedaquiline and pyrazinamide (56–58) as well as with moxifloxacin and pyrazinamide - and the latter combination is now in a phase 2 study for DS and MDR-TB (SimpliciTB) (58).

Linezolid and related oxazolidinones

Linezolid is effective in the treatment of MDR-TB but prolonged use is associated with myelosuppression and neuropathies (59,60). Sutezolid, AZD5847/posizolid, contezolid and

delpazolid are currently in clinical phases of development that appear to have similar activity to linezolid against Mtb, although may not share resistance mechanisms (61–66). Delpazolid, in particular, has activity against *Mycobacterium* abscessus (67) and is in phase 2 trials against DS-TB (NCT02836483). Finally, TBI-223 has reduced activity against mammalian mitochondrial protein synthesis, which predicts less myelosuppression and neuropathy (68).

Carbapenems

Meropenem-clavulanate is a combination of commonly-used antimicrobials with good safety profiles. It shows efficacy in Mtb sputum conversion, albeit with the caveats that it requires intravenous administration and has only been proven in combination with linezolid (69). Other carbapenems, especially once-daily ertapenem, are also of interest (70).

Clofazimine

The antileprotic agent, clofazimine, has recently been repurposed as a useful part of MDR-TB treatment (71) and included as one of the key drugs in the 2018 WHO revised MDR-TB guidelines with linezolid, bedaquiline and the fluoroquinolones (72). However the efficacy, optimal dose and duration of clofazimine remain to be determined. It has no activity in the 14 day extended EBA, suggesting it primarily has a sterilising effect (57).

Clofazimine has a low minimum inhibitory concentration (MIC) against most NTM species, synergises with amikacin and clarithromycin and has been successfully used in a number of cohort studies (73–77). *M. abscessus* can aquire resistance through an identified mechanism, potentially allowing rapid genotypic resistance testing (78). *C*lofazimine has few drug-drug interactions and has been used successfully in solid organ transplant patients with MAC infection (79). However, it has a number of adverse effects; and the clofazimine analogue, TBI-166, is currently in phase 1 trials as a drug with potentially less toxicity (80,81).

Gycylcyclines

The first in class antibiotic, tigecycline, has potent anti-NTM activity (82). The addition of tigecycline is beneficial in infections caused by fast-growers such as *M. chelonae* and *M. abscessus* but it has no activity against slow-growing Mycobacteria including *M. tuberculosis* (82–85).

Co-trimoxazole

Co-trimoxazole has shown activity in observational studies but requires proof of efficacy in controlled trials (86).

SQ109

SQ109 has several distinct mechanisms of action. synergises with first-line and novel agents, improves culture conversion rates in MDR-TB and is approaching phase 3 studies (87–91). However, some *in vivo* studies showed no EBA and a large trial closed the SQ109 arm early when no activity was demonstrated (22,92).

Benzothiazinones

BTZ-043 and macozinone function by inhibition of cell wall synthesis. Both have significant anti-tubercular activity though no activity against slow-growing NTMs (93,94). They are undergoing optimisation studies (95–97). Macozinone (PBTZ-169) has good activity against M. tuberculosis in vitro and in animal models and has recently entered Phase 1 and 2 clinical trials (NCT03036163/ 03423030/ 0333473) (98).

Spectinamides

A number of semisynthetic spectinomycin analogues have been developed with narrow-spectrum anti-tubercular activity (99,100). The current lead candidate, Lee-1810, has a good safety profile

and is active in several mouse models of MDR- and XDR-TB. In addition it synergises with rifampicin and pyrazinamide (101). There is no reported evidence of any effect on NTMs.

Others

GSK-286 is a member of a new antimicrobial class active against intracellular Mtb via effects on cholesterol catabolism. First in human studies are expected in 2019.

Glaxo-Smithkline is developing a range of oral leucyl-tRNA synthetase inhibitors for use against Mtb infection (102–104). GSK-656 is the current lead compound and is completing first in human dose-ranging and early antimicrobial activity studies (NCT03075410) (105).

OPC-167832 is a novel antimycobacterial agent that inhibits cell wall synthesis. It is being developed in combination with delamanid and has begun a phase 2 clinical trial (106,107).

TBA-7371 inhibits PDE6 as well as DprE1, the same target as the benzothiazinones. It is being evaluated in phase I trials, and preclinical properties have been published (NCT03199339) (108).

Auranofin is an oral gold preparation used in Rheumatic conditions. Auranofin is active against replicating and non-replicating Mtb via inhibition of mycobacterial thioredoxin (109). Its role in Mtb treatment is being investigated (NCT20968927).

Nitazoxanide, the anti-helminthic agent, is currently being assessed for EBA in a study in Haiti (NCT02684240) (110,111).

The novel fluoroquinolone DC-159a has some activity against DS-TB, quinolone-resistant MDR-TB, *M. kansasii* and *M. leprae* but only limited effect on other NTMs, and no *in vivo* data are available (11,112,113).

The capuramycin analogue SQ-641 targets mycobacterial translocase 1, which is essential for cell wall synthesis. *In vitro,* SQ641 is a potent agent with strong bactericidal activity when compared to standard treatments for DS-TB, MDR-TB and NTMs. It has synergistic activity with ethambutol, rifamycins and aminoglycosides where these are used. However there are little current *in vivo* data (11,114–116).

The fluorocycline antibiotic TP-271 has activity against *M. fortuitum* and *M. abscessus* but there are no *in vivo* data (117).

The benzimidazole SPR720 is the orally available prodrug of SPR719 and is active against a range of NTM species *in vitro (118).*

The caprazamycin derivative CPZEN-45 targets cell wall synthesis. It has the potential to be used in aerosol therapy. It has activity both against MDR-TB strains and against MAC (11,119,120).

Trials of new drug regimens for TB

Novel regimens for tuberculosis use new or repurposed agents to shorten the standard WHO treatment regimens or to reduce their inherent toxicity (Figure 2). There is also the interesting possibility that a single regimen for DS- and MDR-TB may be developed, simplifying practice. TB drug trials now often adopt the multi-arm design previously seen in oncology studies to more rapidly compare several multiple-agent regimens in parallel (121).

Modifications to WHO standard regimens

The current role, dose and duration of isoniazid and rifampicin in standard DS-TB treatment are reasonably well-established, although isoniazid can be effectively substituted by moxifloxacin (29). Several studies have sought to shorten the WHO standard DS-TB regimen by adding or substituting additional sterilising agents such as high dose rifampicin, linezolid, bedaquiline, rifapentine, fluoroquinolones or delamanid to standard therapy. Many of these regimens would also be useful for difficult pulmonary TB including MDR-TB as they do not rely solely on first-line drugs for efficacy. However, adding fluoroquinolones to standard regimens does not allow them to be shortened despite the fluoroquinolone-containing regimens having a higher initial bactericidal activity (122–124). In fact, none of the modified regimens has yet been shown to be non-inferior to standard therapy (TRUNCATE-TB ;CDC TBTC study 31, RIFASHORT) (25–28).

Trial evidence suggests that not all DS-TB patients need the currently-recommended 6 month course of treatment, and that some are therefore over-treated for the benefit of those who require at least 6 months of therapy (1,125). The TRUNCATE-TB trial suggests a new paradigm where those who do not achieve success with an initial 2 month rapid treatment will go on to receive the standard 6 month course. The new or repurposed drugs used include combinations of high-dose rifampicin or rifapentine, linezolid, levofloxacin, clofazimine and bedaquiline.

Similarly, several studies set out to define populations (SHINE-TB; PredictTB (NCT02821832), NexGen EBA(NCT02371681)) who require different durations of therapy, and thereby allow the personalisation of treatment, using host and mycobacterial markers such as CT-PET scanning, site of disease, bacterial load, specific resistance patterns and biomarkers (126,127).

An important, recent development in treatment of MDR-TB, the “Bangladesh regimen,” demonstrated good clinical outcomes for MDR-TB with 9 rather than 20-24 months treatment

(75,128,129). It is unclear how it will function in areas where there is a higher level of resistance to key components (130). Early results from STREAM stage 1, comparing the Bangladesh regimen head-to-head with the WHO standard regimen, did not show non-inferiority of the 9-month regimen to the standard 20-24 month treatment. However, the fully enrolled study continues to monitor patient outcomes. Stage 2 (NCT02409290) assesses additional shortened regimens, including at least one that would be the first completely oral regimen for MDR-TB (131,132).

Regimens using new agents

A number of novel regimens are being assessed where rifampicin and isoniazid are replaced by bedaquiline or delamanid. These regimens would also function well in MDR-TB, allowing a single therapeutic combination to be used for both major forms of the disease (75,128,129). Such regimens lack rifampicin's drug-drug interactions, for example with antiretroviral medication, an important factor given the high HIV-TB co-infection rate in many parts of the world.

In EBA, regimens such as 2 months moxifloxacin, pyrazinamide and pretomanid are equivalent or superior to standard DS-TB treatment in terms of culture conversion (STAND trial) (56–58). This regimen is improved by the addition of bedaquiline (SimpliciTB trial NCT03338621/ NCT02193776). Preliminary results presented at CROI 2017 was positive with good sputum conversion and safety profile data (133). Similarly, pretomanid and bedaquiline, in combination with varying doses and durations of linezolid, are being assessed in patients (50% of whom will be PLHIV) with DS- and XDR-TB or who have not responded to, or been intolerant of, treatment for MDR-TB (Nix-TB/ZeNix-TB trials).

Many important studies are due to report over the next few years. These include novel partnerships between NGOs, the WHO, academic and private partners. TB-PRACTECAL (NCT02589782) is investigating regimens for MDR-TB including bedaquiline and pretomanid. endTB is looking at

MDR-TB regimens including bedaquiline and/or delamanid. NexT is looking at 9 months treatment of MDR-TB with a combination of bedaquiline and traditional drugs.

Important trials in NTM infections

Reflecting the inevitable focus on TB, there are few current clinical trials evaluating new drugs or regimens in NTM infection. A contemporary workshop suggested a road-map for NTM research (134). Recent phase II and III RCTs of liposomal inhalational amikacin show some benefit when it is added to a multi-drug regimen (135,136). There is also interest in the potentially synergistic combination of clofazimine and amikacin against several species of NTM (74,76). The only currently-recruiting studies involving NTM involve the use of inhaled nitrous oxide in NTM infection (NCT03473314).

Conclusion

The Mtb drug pipeline is in better health than it has been for several years with a number of interesting compounds in or approaching clinical trials. Similarly, the licensing of the first two new drugs for Mtb infection in 50 years, delamanid and bedaquiline, has resulted in a flurry of novel regimens against both DS- and MDR-TB undergoing evaluation. In contrast, many of these new drugs have barely been tested on NTM. With the increasing incidence of NTM disease in resource-rich countries and the recognition that this is likely to be significantly underestimated in TB-endemic areas, it is surely only a matter of time before priorities shift to encompass the need for focussed research developing drug therapies to treat NTM. This must be in parallel with the production of robust tools that can accurately determine NTM drug susceptibility.

Key points

1. Bedaquiline and delamanid are new effective drugs against *Mycobacterium tuberculosis* that are forming the core of novel regimens for drug sensitive and resistant tuberculosis.

2. New regimens have the potential to significantly reduce the length and toxicity of treatment for drug sensitive and resistant tuberculosis

3. Research on non-tuberculous mycobacteria is at a much earlier stage than research on *Mycobacterium tuberculosis*

4. Several promising novel drugs are in development that possess activity against *Mycobacterium tuberculosis* and may have activity against non-tuberculous mycobacteria

5. Research into non-tuberculous mycobacteria needs to be prioritised due to its increasing frequency and poor outcomes

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Figure Legends:

Figure 1: New and repurposed anti-mycobacterial drugs in the Global TB Drug Development pipeline (Updated Oct 2018)

Figure 2: Drug regimens to treat tuberculosis currently in trials and studies (Updated Oct 2018)

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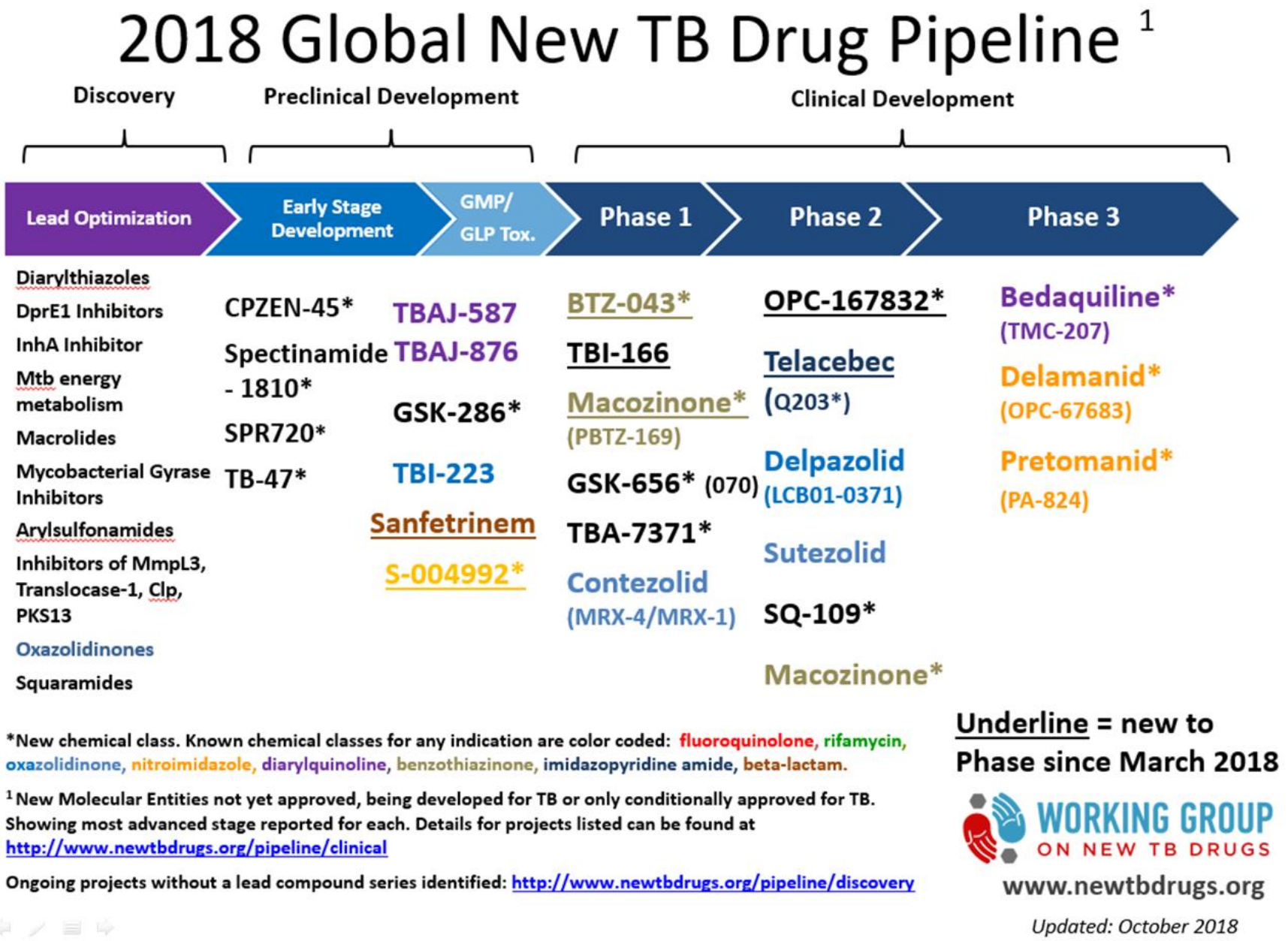

Figure 1: New and repurposed anti-mycobacterial drugs in the Global TB Drug Development pipeline (Updated Oct 2018)

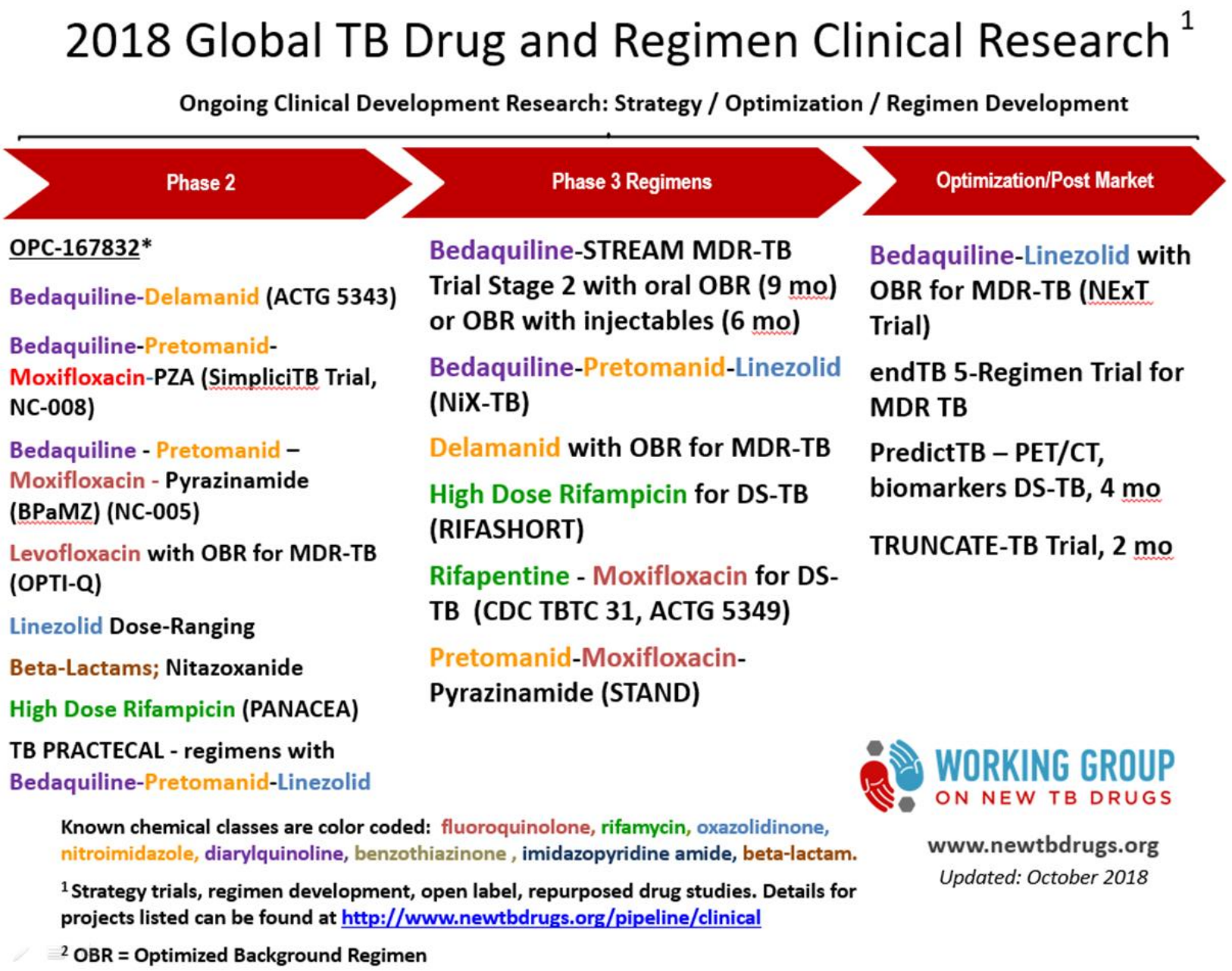

Figure 2: Drug regimens to treat tuberculosis currently in trials and studies (Updated Oct 2018)