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Review

New tuberculosis drug leads from naturally occurring compounds

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SUMMARY

Tuberculosis (TB) continues to be a significant cause of mortality and morbidity worldwide. An estimated 2 billion individuals are infected with *Mycobacterium tuberculosis* and annually there are approximately 10 million new cases of clinical TB and 1.5 million deaths. Currently available drugs and vaccines have had no significant impact on TB control. In addition, the emergence of drug resistant TB is considered a public health crisis, with some strains now resistant to all available drugs. Unfortunately, the growing burden of antibiotic resistance is coupled with decreased effort in the development of new antibiotics. Natural sources are attractive starting points in the search for anti-tubercular drugs because they are extremely rich in chemical diversity and have privileged antimicrobial activity. This review will discuss recent advances in the development of TB drug leads from natural products, with a particular focus on anti-mycobacterial compounds in late-stage preclinical and clinical development.

Contents

Emergent drug-resistant tuberculosis

The spread of drug resistant TB is a major threat to global TB control. These strains are now entrenched in most countries and are spreading at an alarming rate. Multi-drug resistant (MDR) TB isolates are resistant to isoniazid (INH) and rifampicin, the two frontline drugs for TB treatment, and have been detected in every country surveyed. In 2015 there were an estimated 480,000 new cases of MDR-TB, however only 50% of patients on MDR-TB treatment were successfully treated.[1] This means hundreds of thousands of people worldwide are going untreated

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and continuing to spread drug resistant forms of the disease. Extensively drug-resistant (XDR) TB strains, first detected in 2006, are resistant to front-line and second-line anti-tubercular antibiotics. XDR-TB is now present in over 100 countries and represents approximately 10% of MDR-TB cases.[1] Delayed diagnosis and inappropriate treatment leads to multiplication of resistance; this is best highlighted by the alarming emergence of totally drug resistant (TDR) TB, which is essentially untreatable using current drugs.[2] In addition, TB treatment is long; standard treatment for drug sensitive strains is 6 to 12 months, while patients with drug resistant TB must endure a longer course of treatment (24 months or longer) with harsh side effects, high cost and a low chance of cure. The combination of long treatment and side effects results in poor compliance, which is a major contributor to the development of resistance. Thus it is evident that current methods of treatment and control for TB are not sustainable in the face of highly drug resistant TB; there is an obvious and urgent need for the development of new TB drugs that are effective against drug resistant *M. tuberculosis* strains, as well as strategies to reduce duration of treatment regimens.

Natural products as new treatments for TB

The search for new anti-TB agents has been slow; the last major anti-TB drug to be licensed for human use was rifampicin in 1963. Since that time a handful of compounds have entered human trials, and encouragingly two compounds, bedaquiline and delamanid, have recently received fast-tracked approval for use against MDR-TB.[3] However both drugs are associated with side-effects and are only recommended for those without other treatment options. Considering the restrictions on bedaquiline use, and the fact that XDR and TDR strains cannot be adequately treated with currently available antibiotics, many more compounds must enter the TB drug development 'pipeline' in order to adequately combat the TB problem. New anti-TB compounds must overcome the issues with current treatments (Table 1). The ideal anti-TB drug must display high potency, particularly against drug-resistant strains, and possess an adequate safety profile. In addition drugs should be active against latent and replicating forms of *M. tuberculosis* and have limited drug/drug interactions, particularly with anti-retroviral agents.

In recent years the field of drug discovery has focused on target-based and genetics-driven approaches to identify new antibiotics. However, this strategy has not been overly successful, as inhibition of enzyme activity often does not correlate with killing of whole bacteria.[4] Large high-throughput (HTS) screening programs have also been employed with a view to rapidly elucidate 'hit' molecules. However, these studies have been typically performed using small molecule 'corporate' chemical libraries that are relatively limited in diversity. Furthermore, antibacterials that are successful in the clinic do not generally follow Lipinski's 'rule of five' for drug likeness, while most corporate compound collections are heavily biased towards such compounds.[4] A review of HTS campaigns by Novartis revealed that natural products were the most diverse compound class tested, with significantly higher hit rates compared to the compounds sourced from synthetic and combinatorial libraries.[5] Indeed, in recent years there has been renewed interest in the use of natural products, due to the wide range of pharmacophores and a high degree of stereochemistry, and therefore three-dimensionality that natural products possess.[6] Identification of bioactive molecules from natural sources involves a defined series of steps to characterize/synthesize the products of interest (Figure 1). In addition, natural products are often bioactive molecules that may display high degrees of bioavailability, thus increasing their capacity to access their site of action within target cells.

The remainder of this review focuses on recent advances in the identification of natural products as anti-mycobacterial agents and potential TB drug leads. We will focus predominately on natural products, their derivatives and 'nature-inspired' compounds that have entered lead optimization and pre-clinical development stages, as well as products that have entered clinical trials (Figure 2). We have kept the definition of natural products relatively broad in order to include the major TB drug candidates in development, with a focus on 5 major compound classes.

Phenazines

Phenazines are a diverse class of aromatic compounds produced both synthetically in the dye industry as well as biosynthetically by many species of the *Actinobacteria* phylum.[7] As biological molecules, phenazines are involved in redox reactions as well as competitive and symbiotic interactions.[8,9] The role of phenazines as inhibitory molecules translates to broad-spectrum antibiotic activity against bacteria and fungi. Antifungal phenazines were first isolated from *Pseudomonas fluorescens*[10] and since then, novel phenazines have been synthesised as potential antitumour drugs[11] as well as antibiotics.[12] **Riminophenazines** are currently under re-investigation as lead compounds for TB treatment. Historically derived from lichens, riminophenazines were developed decades ago as potential TB drugs.[13] Recent years have revived interest in this class of compounds due to the antitubercular activity of clofazimine. Several chemical series of novel riminophenazine derivatives have been synthesised and evaluated for lead development, aiming to improve activity and reduce lipophilicity.[14]

Clofazimine is a riminophenazine originally discovered in 1954 through structural modifications of diploicin, extracted from *Buellia canescens*.[15] While development of clofazimine for TB treatment was delayed by studies showing inactivity in guinea pig and monkey models,[16] it is currently used as a WHO group five drug for MDR-TB.[17] This is due to a reassessment of clofazimine as a TB drug, which discovered that when used in combination with gatifloxacin, ethambutol, pyrazinamide, prothionamide, kanamycin and high-dose isoniazid for 9 months, clofazimine was able to

Table 1
Desired properties of new anti-TB drugs.

Problem with existing therapy	Desired characteristics of new drugs
Lengthy treatment	Increased capacity to inhibit bacterial growth and shorten treatment time (e.g. <4 month).
High pill burden	Lower the number of pills and frequency of doses by using highly potent and bioavailable drugs. Also aim for intermittent treatment.
Expensive	Cheap to make and easily available to the developing world.
Side effects	Less toxic drugs. Intermittent treatment.
Interaction with other drug	Minimal drug-drug interaction with anti-virals, diabetes and non-TB drugs.
Drug resistant *M. tuberculosis* strains	Novel drugs with new mechanism of action.
Lack of efficacy against latent TB	Active against non-replicating bacteria and work effectively in hypoxic conditions. Drugs that can penetrate granulomas.

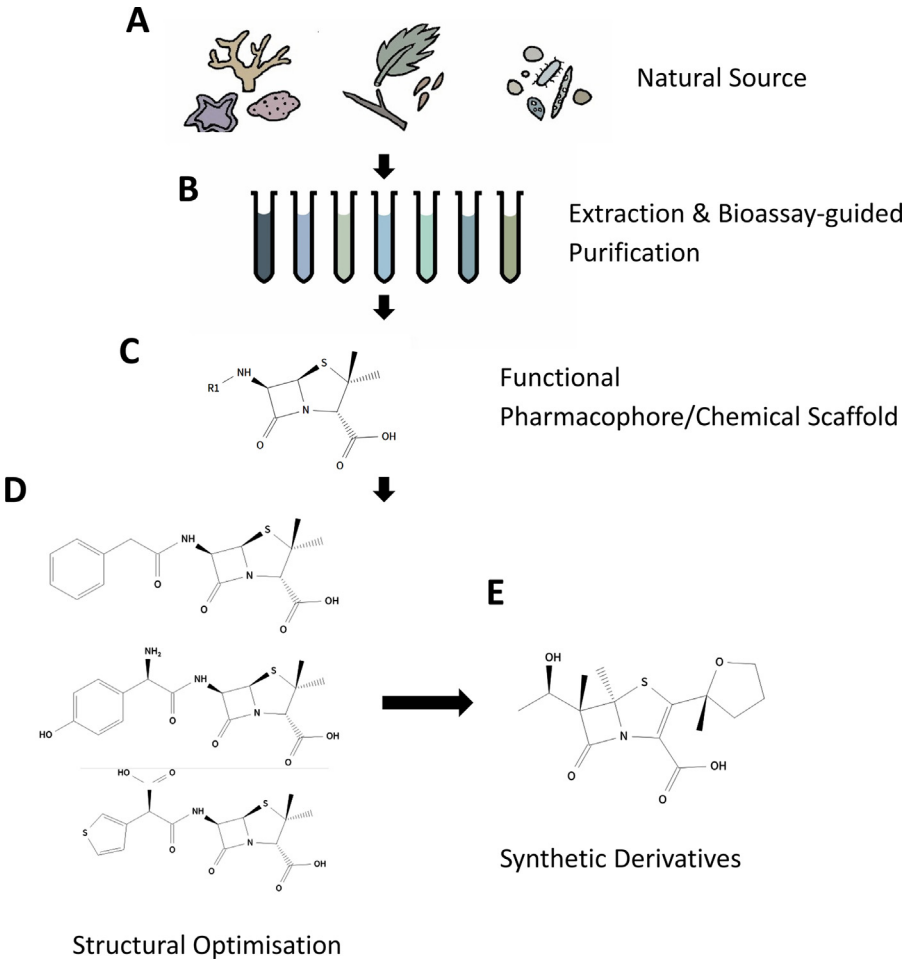

Figure 1. Identification of new drugs from natural sources. **A.** Prominent natural sources of bioactive molecules include *Actinomycetes* spp, terrestrial plants and marine species. Sessile organisms produce many secondary metabolites in competition for space and resources which can be exploited for drug development. **B.** Whole organisms or components of interest are subjected to sequential fractioning to identify pure, active samples from which the molecule of interest can be identified. **C.** Bioactive chemical scaffold are identified which can be subject to structure activity relationship studies in order to identify a functional pharmacophore. **D.** Modifications around the functional pharmacophore generate a series of chemical analogues which can be tested for activity and drug-likeness. **E.** As structure optimisation proceeds, derivative products can lead to novel chemical classes and several generations of antibiotics.

treat 88% of MDR-TB patients studied.[18] As a result of this research, investigation of clofazimine's potential to shorten treatment for drug-susceptible TB commenced. Results in mouse models of *M. tuberculosis* infection indicated greater early bactericidal activity and earlier lung. culture conversion (3 months compared to 5 months) in clofazimine-containing first-line treatment.[19] Clofazimine accumulates within cells[20] and tissues to high concentrations[21], leading to undesirable side-effects which researchers seek to minimise.

TBI-166 is a preclinical candidate for TB drug development identified from a series of clofazimine analogues. Initial investigation found TBI-166 to have potent *in vitro* activity against *M. tuberculosis* H37Rv in culture and within macrophages with low cytotoxicity. TBI-166 was effective against drug-resistant clinical isolates of *M. tuberculosis* but not against non-replicating *M. tuberculosis in vitro*. At a dose of 20 mg/kg in *M. tuberculosis* H37Rv-infected mice, TBI-166 resulted in greater than one $\log_{10}$ CFU/mL reduction than the clofazimine control.[22] Pharmacokinetic studies in rats and beagle dogs have also been completed, showing TBI-166 to be stable but eliminated slowly from the body. [23,24] At this stage it is unclear whether TBI-166 is able to improve upon clofazimine's long half-life and accumulation in body tissues, which leads to one major side-effect of clofazimine treatment, skin discolouration.

Piperidines

Piperidines are a class of heterocycline amines commonly used as scaffolds for the synthesis of pharmaceutical compounds. They are a derivative of piperine, the alkaloid responsible for the heat in black pepper. When piperine is extracted from pepper fruits and hydrolysed, piperidine is formed.[25,26] Piperidines can also be extracted from black pepper and have been also found in other plants.[27] This class of molecules includes a wide range of drugs such as vasodilators, antipsychotics, neuroleptics and opioids. Of particular interest for the subject of this review are the subclass of dipiperidines, which have been investigated as potential TB drug leads as a result of their identification in high-throughput screening programs.[28,29] **SQ609** is a preclinical dipiperidine identified by Sequella from a screening program using a library of dipiperidines.[30] SQ609 is an adamantine-containing hydroxydipiperidine with potent *in vitro* activity against *M. tuberculosis* H37Rv. Testing in mice indicated that SQ609 had prolonged therapeutic effects and was able to prevent TB-induced weight loss after treatment ceased. SQ609 is believed to target cell wall synthesis and has good oral bioavailability.[31]

BTZ043 is a piperidine-containing benzothiazinone currently undergoing GLP toxicity testing before entering Phase I trials.

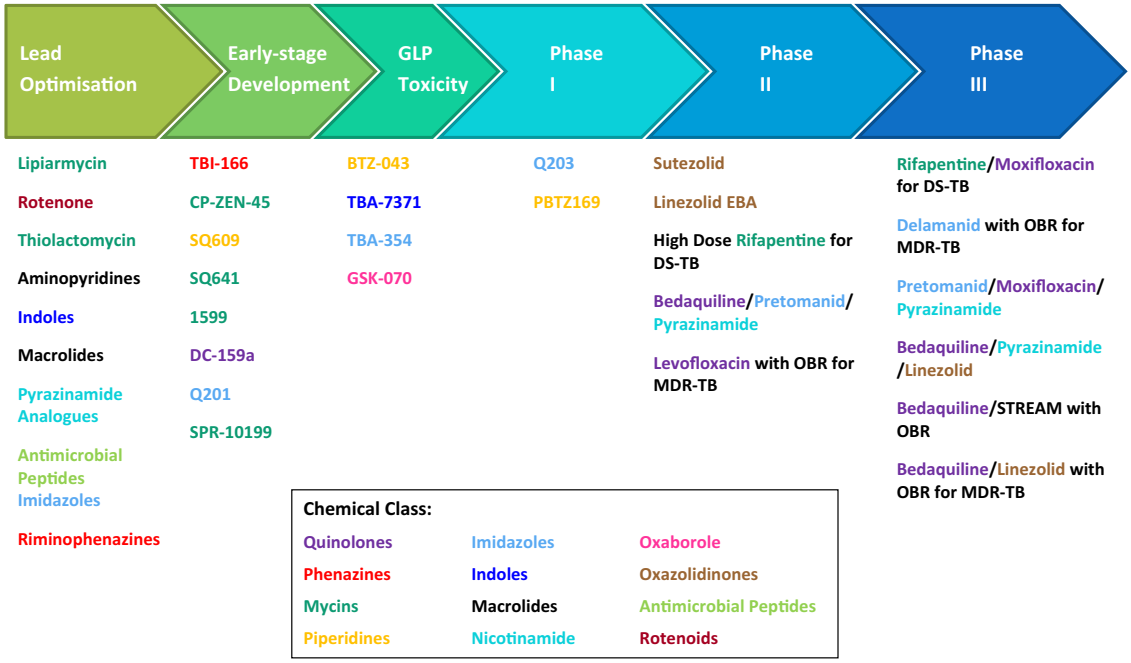

Figure 2. Lead compounds currently in development for the treatment of TB are shown with chemical classes. Adapted from WHO Global Tuberculosis Report 2016. DS-TB: drug-sensitive tuberculosis; MDR-TB: multi-drug resistant tuberculosis; OBR: Optimized Background Regimen; STREAM: Standardized Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB.

Discovered through a screen of sulfur-containing heterocycles against *M. smegmatis*,*M. aurum*, *M. vaccae* and *M. fortuitum in vitro*,[32] BTZ403 has been found to be active against all tested clinical isolates of *M. tuberculosis* including MDR and XDR strains.[33] BTZ043 inhibits DprE1, a key enzyme in the arabinogalactan and arabinomannan synthesis pathway.[34] It has been found to work synergistically with bedaquiline, pretomanid, moxifloxacin, meropenem and SQ-109 *in vitro* to inhibit *M. tuberculosis* H37Rv.[34] **PBTZ169** is a derivative of BTZ043 developed by iM4TB and undergoing Phase I clinical trials in Russia. PBTZ169 interacts with the same active site residues in DprE1 as BTZ403. However, in comparison to BTZ403, PBTZ169 has improved potency, safety and efficacy in mouse models of TB. Combination treatment with PBTZ169, bedaquiline and pyrazinamide was found to be more effective than standard isoniazid, rifampicin and pyrazinamide treatment for two months in mice.[32] PBTZ169 has also been found to work in synergy with clofazimine against replicating and non-replicating *M. tuberculosis* H37Rv *in vitro*, as well as in a mouse model of chronic TB.[35] As such, PBTZ169 is a promising candidate for novel TB treatment regimes.

Mycins

Throughout history, mycin antibiotics have formed the foundation of treatment for infectious diseases. Largely sourced from *Actinobacteria* spp., mycins are produced as secondary metabolites, which perform many functions in bacteria and fungi, such as competition, transport and chemical signalling. They fall under several broad categories including beta-lactams, tetracylines and aminoglycosides. Since the discovery of streptomycin 70 years ago as the first drug with proven activity against TB,[36] several new-generation mycin compounds have entered the pipeline for TB drug development. **SQ641** is an analogue of capuramycin, a nucleoside antibiotic originally sourced from *Streptococcus griseus*.[37] Like capuramycin, SQ641 is a translocase I inhibitor and was developed as a series of capuramycin derivatives and found to display activity against drug-susceptible and drug-resistant strains of *M. tuberculosis*.[38,39] In a mouse model of chronic *M. tuberculosis* infection, SQ641 was able to reduce bacterial lung burden by 1.0–1.5 $\log_{10}$ CFU.[40] However, its lipophilicity and low water solubility has led to studies with delivery vehicles[41] as well as further chemical modifications to improve intracellular activity.[42] A capuramycin analogue, **UT-01320**, inhibits bacterial RNA polymerases and has been shown to work in synergy with SQ641 to inhibit *M. tuberculosis* H37Rv growth to a greater extent than each molecule alone.[43] **CPZEN-45** is a caprazamycin derivative that inhibits WecA, a transferase involved in arabinogalactan biosynthesis[44] and has potent activity *in vitro* against *M. tuberculosis* H37Rv but limited activity against gram-positive and negative strains such as *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella pneumoniae*.[45] CPZEN-45 had no acute cytotoxic effects at concentrations up to 3 mg/ml and cell permeability assays revealed good solubility.[46] As a lead compound, it is in early-stage development.

Thiolactomycin is an inhibitor of bacterial fatty acid biosynthesis.[47] Originally isolated from a previously unknown *Nocardia* spp. in 1982, thiolactomycin is a broad-spectrum antibiotic with weak toxicity when tested in mice.[48,49] Thiolactomycin was evaluated for anti-mycobacterial activity in the search for new TB drugs and found to block mycolic acid synthesis along with fatty acid synthesis through inhibition of FAS-II, but not FAS-I. Thiolactomycin is also active against a clinical isolate of XDR-TB but loses efficacy against *M. tuberculosis* strains with KasA G269S mutations.[50] As a result of these findings, several derivatives of thiolactomycin have been synthesised and evaluated as lead candidates for TB drug discovery.[51–53]

Lipiarmycin A3 was originally discovered as a 3:1 mixture of lipiarmycin A3 and lipiarmycin A4 isolated from *Actinoplanes deccanensis*[54] until structure elucidation studies were completed.[55,56] Lipiarmycin A3 is a bacterial RNA polymerase inhibitor also known as tiacumicin B and fidaxomicin, a drug approved by the Food and Drug Administration (FDA) in 2011 for treatment of *Clostridium difficile* infection.[57] To date, rifampicin and lipiarmycin A3 are the only RNA polymerase inhibitors to gain FDA approval

and be used clinically. Lipiarmycin A3 is effective against *M. tuberculosis* H37Rv *in vitro* and has potent activity against clinical isolates of MDR-TB. No cross-resistance with rifampicin is observed for lipiarmycin A3 as the compound binds to a separate region of RNA polymerase.[58] Issues with developing lipiarmycin A3 as a TB drug involve the compound's physical properties such as a high molecular weight (MW >1000 Da), low solubility in water and low systemic absorption after oral administration.[59] If these hurdles can be overcome, lipiarmycin A3 has significant potential as the starting point for a drug candidate.

Rifapentine is a derivative of the rifamycin family, which includes rifampicin or rifampin, rifabutin and rifalazil. Rifamycin B was first isolated from *Amycolatopsis rifamycinica*[60] but was poorly active and thus modified to produce the more effective, but intravenous rifamycin SV. Extensive structure optimisation then led to the synthesis of rifampin.[61] In attempts to improve upon TB treatment regimes, rifampin has been subject to many structure-optimisation studies. In 1965, rifapentine was developed by Sanofi-aventis and it was approved by the FDA in 1998. Rifapentine has similar activity to rifampin, but persists in the blood at therapeutic levels for longer (72 h post-antibiotic effect)[62] and is better able to treat atypical mycobacterial infections such as those arising from the *M. avium* complex.[63] Rifapentine also better accumulates in macrophages and thus has more activity against intracellular bacilli.[64] Currently, high-dose rifapentine in combination with other drugs is undergoing Phase II clinical trials for the treatment of drug-susceptible TB. Results showed that a 6 month regimen that included weekly administration of high-dose rifapentine and moxifloxacin was as effective as the control regimen (2 months daily isoniazid/rifampin/pyrazinamide/ethambutol (HRZE) followed by 4 months daily isoniazid/rifampicin). However, the 4-month regimen was not noninferior to the control regimen.[65]

Quinolones

The quinolones are a broad class of compounds, many of which occur naturally in *Pseudomonas spp.*[66,67], *Escherichia spp.*[68] and many other bacterial species as cell-signalling molecules.[69] Nalidixic acid was the first discovered quinolone and was originally derived from quinolone itself, a by-product of quinine distillation.[70] Four generations of quinolone antibiotics have since been developed, including the fluoroquinolones and diarylquinolones which are of particular interest to TB drug development, especially given that molecules in this class are already used in the clinic as second-line TB drugs. **DC-159a** is a novel 8-methoxy fluoroquinolone and a preclinical candidate for Phase I clinical trials, scheduled to begin in 2011 but currently on hold.[71] As a broad-spectrum antibacterial, DC-159a exhibits activity against *Streptococcus* spp., *Staphylococcus* spp.[72] and several other clinically relevant bacteria,[73] as well as having potent activity against fluoroquinolone-resistant strains of bacteria including *M. tuberculosis* H37Rv.[74,75] In a mouse model of *M. tuberculosis* infection, DC-159a was found to be more effective than moxifloxacin at bacterial clearance during initial and extended treatment. This effectiveness was dose-dependent and the early bactericidal activity of DC-159a indicated that it may be a candidate for shortening TB treatment.[76]

Bedaquiline (marketed as Sirturo) is a novel diarylquinolone that is the first new TB drug approved for use in over 40 years. Unlike the fluoroquinolones, bedaquiline is a narrow-spectrum antibiotic and exhibits little activity beyond the mycobacterial species. Bedaquiline targets ATP synthase by inhibiting the proton pumping mechanism[77] and has bactericidal effects on both active and non-replicating bacilli.[78] Early clinical trials showed bedaquiline to be safe and effective in increasing sputum culture conversion and reducing the treatment time required for sputum-negative conversion,[79,80] which led to the fast track approval of the drug by the FDA for use only in cases of MDR-TB. Bedaquiline has a black-box warning for potential induction of long QT syndrome, which can lead to abnormal and potentially fatal heart rhythm. A Phase II 14-day bactericidal activity study of a bedaquiline/pretomanid/pyrazinamide regimen (BPaZ) in treatment-naive, sputum smear-positive patients with pulmonary TB showed BPaZ to have the highest activity compared to other combinations.[81] A similar treatment combination of bedaquiline/pretomanid/linezolid is in advanced Phase II clinical trials to assess treatment for MDR-TB and XDR-TB (NiX-TB). Current Phase III trials of bedaquiline in combination therapy include a comparison of a 6 and 9 month bedaquiline-containing regimen against the WHO and Bangladesh regimen (STREAM Stage 2) and an open label RCT of a 6-9 month injection free regimen containing bedaquiline, linezolid, levofloxacin, ethionamide/high dose isoniazid, and pyrazinamide (NeXT).

Moxifloxacin is a repurposed 8-methoxy fluoroquinolone currently undergoing Phase III clinical trials as part of combination therapy. First used as a broad-spectrum antibiotic for the treatment of various respiratory and enteric infections, moxifloxacin exhibits favourable pharmacokinetics[82] and penetration through human peripheral cavities.[83] In the search for new TB treatments amongst novel and existing drugs, moxifloxacin was found to have activity against *M. tuberculosis* in mouse[84] and human[85] studies. Early clinical trials showed that replacing isoniazid or ethambutol with moxifloxacin in a standard 4-month HRZE treatment regimen resulted a shorter time to sputum-negative conversion but a lower proportion of favourable outcomes in patients.[85]Nevertheless, the safety of daily oral moxifloxacin over four months was confirmed by this study and the potential for moxifloxacin to reduce treatment time warrants further investigation. Incorporating moxifloxacin into standard treatment regimens with a 4 or 6 month treatment schedule found that the 6-month treatment was as effective as standard treatment but the 4 month treatment did not demonstrate noninferiority to standard treatment.[65] Investigation continues as to the feasibility of reducing treatment time. An ongoing Phase III trial aims to assess a combination of pretomanid/moxifloxacin/pyrazinamide (PaMZ) for 4 to 6 months in patients with drug-susceptible TB in comparison to standard HRZE treatment. The 14-day early bactericidal activity of PaMZ was comparable with that of HRZE and higher than bedaquiline treatment, bedaquiline/pyrazinamide and bedaquiline/pretomanid, but lower than pretomanid/pyrazinamide.[86] As an oral regimen which can be administered at a fixed dose, PaMZ has the potential to simplify treatment for drug-susceptible and MDR-TB.

Levofloxacin is another repurposed fluoroquinolone normally used in the treatment of sinusitis, bronchitis and urinary tract infection patients with no alternative treatment options.[87] Levofloxacin was found to be active against all tested drug-resistant strains of *M. tuberculosis in vitro* and treatment of four patients with a second-line treatment regime which included levofloxacin showed that it was well-tolerated and resulted in clinical improvement.[88] As such, further investigation as to the rate of major adverse events associated with levofloxacin treatment compared to standard treatment of TB patients was carried out, with results indicating no significant difference between the two groups.[89] Population pharmacokinetic studies comparing levofloxacin, gatifloxacin and moxifloxacin found levofloxacin to have the highest maximum plasma concentrations, largest volume of distribution, and longest elimination half-life.[90] A comparison of moxifloxacin and lexifloxacin for the treatment of MDR-TB in patients found no significant difference between sputum culture conversion at 3 months for the two groups.[91]

Antimicrobial peptides

Antimicrobial peptides (AMPs) are a family of polypeptides produced by living organisms as a host defence mechanism. These are amphipathic molecules, which inhibit the growth of viruses, bacteria, fungi and protozoa.[92,93] Some AMPs derived from bacteria are potent against *M. tuberculosis* and have been well characterised.[94] They are still classified within the 'lead optimization' phase of anti-TB drug development, but considering their potential they will be discussed in detail here.

AMPs- Inhibition of cell wall biosynthesis

Teixobactin is a recently discovered AMP, which interferes with bacterial cell wall synthesis.[95] Ling et al. used iChip to isolate and cultivate previously uncultured soil bacteria and through screening against *Staphylococcus aureus* identified teixobactin produced by *Eleftheria terrae* as a potent antimicrobial, including activity against *M. tuberculosis* H37Rv. The mechanism of action was identified as inhibition of peptidoglycan synthesis, however interestingly teixobactin-resistant strains of *S. aureus* or *M. tuberculosis* could not be generated.[95] Recently texiobactin has been synthesised with the synthetic natural product displaying inhibitory activity against *M. tuberculosis* H37Rv, although this activity was reduced compared to natural teixobactin.[96]

Sansanmycins are members of the uridylpeptide family, another antibiotic involved in inhibition of cell wall biosynthesis.[97,98] Uridylpeptide antibiotics have been shown to inhibit translocase I (MraY) involved in peptidoglycan synthesis and the target is predicted to be the same in *M. tuberculosis*.[97,99] These peptides were isolated from *Streptomyces* sp and sansanmycin A and B were activity against drug susceptible and MDR strains of *M. tuberculosis*.[98,100] Simple semi-synthetic and biosynthetic modifications to the sansanmycin natural product has resulted in derivatives with greater activity against virulent *M. tuberculosis*, including MDR and XDR strains.[101]

AMPs-Inhibition of proteolysis

Cyclomarin A is a cyclic peptide from marine *Streptomyces* CN3-982.[102] It is active against *M. tuberculosis* both in culture and intracellularly.[103] Its target is caseinolytic protease C1 (ClpC1), which is essential for mycobacterial survival.[103,104] Total synthesis of Cyclomarin A resulted in derivatives with activity against *M. tuberculosis* and also against *Plasmodium falciparum,* highlighting the broad-spectrum activity of certain AMPs.[105] **Lassomycin** is an AMP produced by the soil bacterium *Lentzea kentuckyensis sp.* and was discovered through screening of extracts from soil actinomycetes against *M. tuberculosis*, and displays activity against MDR and XDR strains.[106] Generation of a lassomycin resistant strain of *M. tuberculosis* led to the discovery of its target ClpC1.[106] ClpC1 in complex with ClpP1P2 is responsible for protein degradation and maintaining cellular homeostasis.[107,108] Interestingly, lassomycin increases the ATPase activity of ClpC1, this may result in decoupling of the ATPase and proteolysis activity of ClpC1 and ClpP1P2 complex.[106] Recent attempts at synthesising lassomycin proved to be challenging with loss of activity against *M. tuberculosis* as a result of incorrect conformation.[109] However, with advances in synthesis, lassomycin's novel mode of action together with high specificity against *M. tuberculosis* may result in drug lead for *in vivo* studies.

Another cyclic peptide inhibitor of proteolysis in mycobacteria which has advanced to *in vivo* studies in mice is **ecumicin.**[110] Ecumicin also targetes ClpC1 and increases the activity of this ATPase similar to lassomycin.[110] Ecumicin was discovered by a high throughput screen of *Actinomycete* extracts against *M. tuberculosis* H37Rv and displayed good activity against drug-susceptible, MDR, XDR and non-replicating *M. tuberculosis*.[110] When delivered in polymeric micelle formulation, ecumicin could reduce *M. tuberculosis* bacterial load in the lungs of infected mice.[110] Ecumicin however was not as effective as rifampicin *in vivo*, suggesting more work is needed to improve its pharmacokinetics properties.

AMPs- Inhibiting DNA replication pathway

Griselimycin, produced by two strains of Streptomyces, is a cyclic peptide antibiotic discovered in the 1960s. The natural peptide has poor solubility, but more stable analogues of grislimycin, particularly Cyclohexylgriselimycin, are active against intracellular *M. tuberculosis* and drug-resistant strains.[111] In both an acute and chronic murine model of TB, treatment with cyclohexylgriselimycin significantly reduced bacterial loads compared to untreated mice.[111] Griselimycin binds to DnaN, which is the sliding clamp of DNA polymerase.[111] This binding block the interaction of DnaN with DNA polymerase and other elements involved in DNA repair result in killing of mycobacteria.[111]

Other AMPs

Lariatins are a group of novel anti-mycobacterial peptides originally isolated from *Rhodococcus jostii* K01-B0171. The topology of the lariatins forms a threaded loop resembling a lasso and this structure, along with post-translational modifications prevent protease degradation of these peptides. Lariatin A is the most promising lead currently in early-stage development (*M. tuberculosis* MIC = 0.39 μg/mL *in vitro*).[112] A recent mutational study of lariatin A found that amino acids Tyr6, Gly11, and Asn14 were essential for anti-mycobacterial activity, while mutation of Val15, Iso16 and Pro18 enhanced activity.[113] Finally **Trichoderins** are a new class of aminolipopeptides sourced from the fungal strain *Trichoderma sp.* 05FI48, isolated from an unidentified marine sponge. They were found to be highly active against *M. smegmatis*, *M. bovis* and *M. tuberculosis in vitro*, with trichoderin A being most promising (MIC = 0.1, 0.02 and 0.12 μg/mL respectively).[114] One interesting property of the trichoderins is that their potency under hypoxic conditions remains unchanged.[114] These peptides appear to work through inhibiting ATP synthesis, although further work needs to be done to confirm this.[115] Trichoderins are in early stage development as potential drug leads for TB.

Conclusions

Current control strategies have had little impact on TB control and new therapies are urgently needed. Some strains of *M. tuberculosis* are resistant to all existing antibiotics used for TB treatment, highlighting the requirement for new drugs with novel modes of action. The high rates of target-based molecule discovery and high-throughput screening using synthetic compound libraries has renewed interest in natural products as a source of diverse bioactive molecules with anti-bacterial activity. As detailed in this review, a number of natural products and 'nature-inspired' molecules show particular promise as anti-mycobacterial agents with clinical potential. While natural products are a rich and underutilised source of novel chemical scaffolds, the process of isolating and purifying active compounds is labour-intensive and time-consuming. Natural product screens rely on bioassay-guided fractionation and require intensive structure-determination, unlike screening of chemical compound libraries, which begins with pure compounds of known structure.[116] One other problem lies with intellectual property rights, which are more difficult to enforce and protect when the source of a novel drug grows freely in the environment.[117] Despite these issues, natural products remain the most productive source of drug leads to this day, and no doubt will continue to benefit researchers in drug discovery.[6] The ability to identify anti-bacterial compounds from previously uncultured species of soil bacteria,[95] metagenomic approaches to explore

microbial diversity[118] and the successful clinical application of marine natural products provides hope that nature will deliver the required starting points to control the TB epidemic.

Conflict of interest statement

none to declare.

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