Chapter

Drug Repurposing for Tuberculosis

Nicole C. Cardoso, Carel B. Oosthuizen, Nashied Peton and Vinayak Singh

Abstract

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is a major global health concern given the increase in multiple forms of drug-resistant TB. This underscores the importance of a continuous pipeline of new anti-TB agents. From recent studies, it is evident that the increase in drug efficacy is being achieved through re-engineering old TB-drug families and repurposing known drugs. This approach has led to producing a newer class of compounds which not only saves time and investment in developing newer drugs but is also effective in identifying drug candidates with novel mechanisms to treat multi-drug resistant strains. The repurposed drugs moxifloxacin, linezolid, and clofazimine are used to treat extensively drug-resistant TB when first- and/or second-line drugs fail. The chapter covers a detailed background on the current status of the repurposed drugs in the TB drug-discovery pipeline and discusses a potential way forward.

Keywords: tuberculosis, repurposed drugs, drug discovery pipe-line, *Mycobacterium tuberculosis*

1. Introduction

Highlights

- Within TB drug discovery, drug repurposing is a growing field and has established several viable candidates from 'old' drugs for further investigation.
- Drug repurposing for TB could improve therapeutic interventions in low to middle income countries and is an ideal approach due to the saving of time, effort, and most importantly, money.
- The use of computational techniques, including virtual screening of known drugs, have been shown to accelerate the process.
- This approach has the potential to lead to the identification of novel drug targets in *M. tuberculosis*, which could initiate new target-based discovery programs.

Tuberculosis (TB) has been, and continues to be a global health threat, and remains the leading cause of death due to a single infectious agent (*M. tuberculosis*), having claimed ~1.4 million lives in 2019 alone [1]. In the past 2 years, the Covid-19 pandemic has further exacerbated the threat of TB mainly due to a decrease in TB case detection, with trajectories predicting an increase of ~1 million additional

new cases per year from 2020 to 2025 [1]. Furthermore, considering the increasing prevalence of drug resistant (DR) (Rif resistant-RR, multidrug resistant-MDR, and extensively drug resistant- XDR) forms of TB infections, the need for more effective treatment strategies has not been direr. The current standard treatment regimen for drug-susceptible (DS) TB has been in use for decades and includes a combination of four drugs: isoniazid (Inh), rifampicin (Rif), ethambutol (Emb) and pyrazinamide (Pza) for 2 months and a further 4 months of only Inh and Rif (**Figure 1** [2, 3]). The treatment of DR-TB is more complicated and can take up to 18 months, depending on the resistance profile of the infection. Although available, several challenges are faced during the treatment of TB disease. Most notable is the duration and complexity of treatment, toxicity and in the case of HIV-TB coinfection, the possible adverse interactions between anti-TB drugs and antiretrovirals. Despite these challenges, treatment success rates of 85% and 57% have been reported for DS- and DR-TB respectively in 2019 [1]; however, these will not be sufficient to meet the milestones setup as part of the End TB Strategy which include a 90% reduction in incidence rates and 95% reduction in mortality by 2035 compared to 2015 [4]. Optimization and implementation of innovative tools including new drug and treatment regimens are predicted to significantly improve this outlook.

The past 20 years have seen considerable progress in the TB drug discovery arena, with 13 new compounds currently in clinical trials (https://www.newtbdrugs.org/pipeline/clinical). The highlights of TB drug discovery include Bedaquiline (Bdq), Delamanid and, most recently, Pretomanid (PA-824). Within the last 9 years, these were the first three new drugs to be approved for the treatment of TB since the discovery of Rif in the 1960's. Although currently only approved for the treatment of

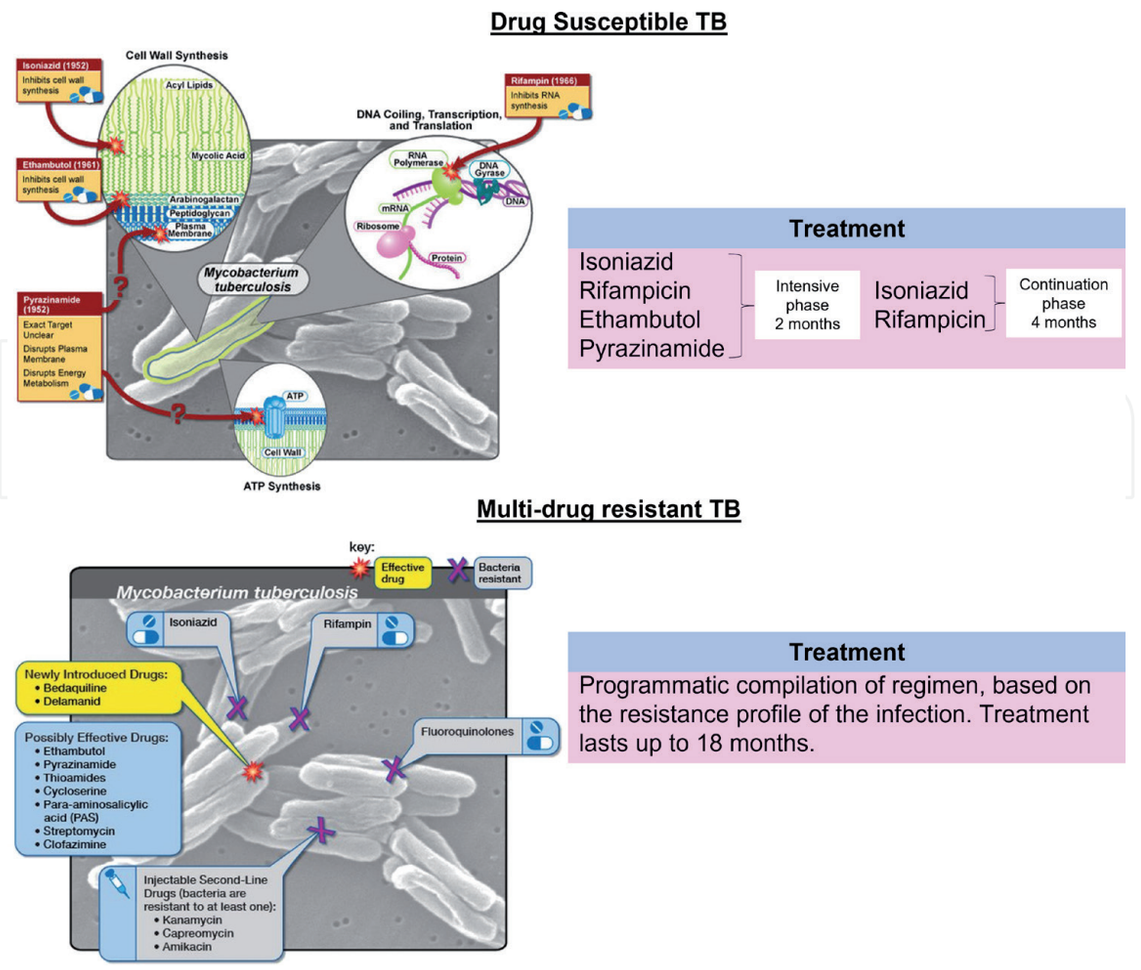

Figure 1.
Current drugs used for the treatment of TB. Adapted from [2, 3] (CC BY 2.0).

DR-TB, both Bdq and PA-824 are being tested as part of novel combination regimens for the treatment of DS-TB. Further highlighting the progress of the TB drug discovery field, the pre-clinical pipeline is also rich in new compounds.

The current scope of the drug discovery and development pipeline is promising; however, the development of a novel drug is a complicated, laborious, and expensive endeavour. From initial screening to clinical usage, the development of a new compound can take up to 15 years and cost more than $1 billion (**Figure 2**) [5, 6]. In addition, there is a high attrition rate of hit compounds during the discovery cascade and clinical trials, further adding to the difficulty of getting novel antimicrobials into the clinic [5–7]. To overcome some of the challenges faced during conventional drug discovery programs, a strategy that has been gaining more interest in recent years is "Drug Repurposing".

Drug repurposing is the process of identifying novel uses of existing drugs for the treatment of disease outside of the scope of the original medical indication. It is also referred to as drug repositioning, redirecting, re-tasking, reprofiling or recycling [8, 9]. This strategy offers several advantages over a conventional drug discovery approach, including (i) reduced risk of failure, (ii) quicker development times, (iii) less investment and lower average costs, and (iv) the possibility of identifying new targets and/or pathways for further investigation (**Figure 2**) [8–10]. Drug repurposing has been successfully applied to several diseases and conditions including HIV, cancer and arthritis [9]. While offering notable advantages over a conventional approach, candidate compounds discovered via drug repurposing are still subject to regulatory requirements prior to therapeutic implementation. These requirements include compound acquisition and licencing, development/optimization for the new application via clinical trials and registration with the relevant regulatory bodies (**Figure 2**).

Repurposing is not new to the treatment of TB. The backbone of the current regimen, Rif, belongs to the rifamycin group of antibiotics [11]. Rifamycins were originally developed for broad-spectrum antibacterial activity and through structure–activity relationship studies, was shown to have the greatest growth inhibitory effect against mycobacteria [11, 12]. The mechanism of action (MoA) of rifamycins involves the inhibition of DNA-dependent RNA polymerase, thus interfering with

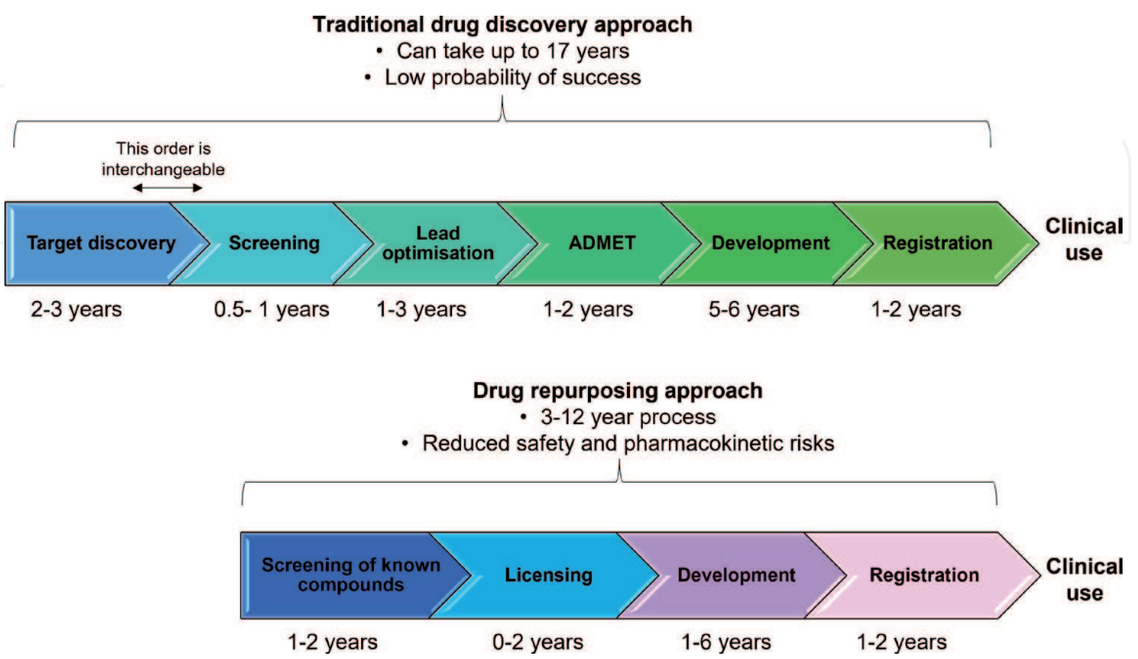

Figure 2.
A comparison of the time taken to get into the clinic when using a traditional drug discovery approach versus a drug repurposing approach. ADMET: Absorption, distribution, metabolism, excretion and toxicity. Adapted from [5].

transcription. While the main application is for DS-TB, Rif has also been used for other bacterial infections e.g. treatment of staphylococcal endocarditis, eradication of group A beta-hemolytic streptococci from pharyngeal carriages and as prophylaxis for close contacts of paediatric patients with *Haemophilus influenzae* or *Neisseria meningitidis* infections [13]. In recent years, drug repurposing has once again gained traction for novel TB treatments, evidenced by 6 different repurposed drugs currently being evaluated in Phase II or III clinical trials [1]. Following an analysis of the published literature related to drug repurposing for TB, the repurposed drugs that are currently in the pre-clinical and clinical pipeline, their molecular mechanisms and therapeutic applications will be discussed further.

2. State of the art

In order to assess what the current scientific field entails, a network analysis was conducted from the Web of Science database (All Databases) using the search terms: repurpose* (repurposed, repurposing), tuberculosis and drug* (drugs). A total of 424 publications were identified within the search criteria and it is evident from **Figure 3** that there has been an increase in research involved with the repurposing of old drugs in the fight against TB. In 2020, 77 manuscripts were published related to this topic, and this is expected to further increase in 2021. Additionally, VOS viewer, was used to assess specific keywords within the total number of publications (https://www.vosviewer.com/). The co-occurrences of all keywords were counted using a full counting method. The minimum keyword occurrence was set to three and out of the 416 identified keywords, 35 met the selection criteria. The third most occurring keyword, after "*M. tuberculosis*" and "Tuberculosis", was "*in vitro*", which indicates that this field of enquiry is still at an early stage (**Figure 4**). This is reiterated by the increase in publications on repurposing in recent years (**Figure 3**) as well as the identification of "drug repositioning" in **Figure 5**. Interestingly, the only drug that satisfied the selection criteria was thioridazine, an antipsychotic drug. It would be expected that additional repurposed drugs will occupy this space as more data becomes available and clinical trials are completed.

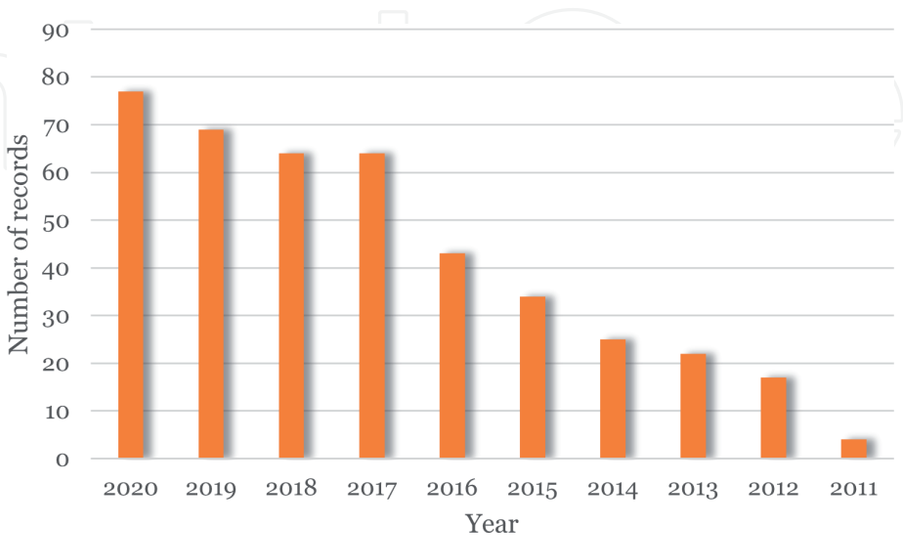

Figure 3.
A steady incline in recent years of the number of scientific articles, related to the search topic "repurposing drugs for tuberculosis". The bars represent the number of published articles according to year. The year 2020 accounts for 18.2% of the published articles related to this topic. (web of science (https://www.webofknowledge.com)).

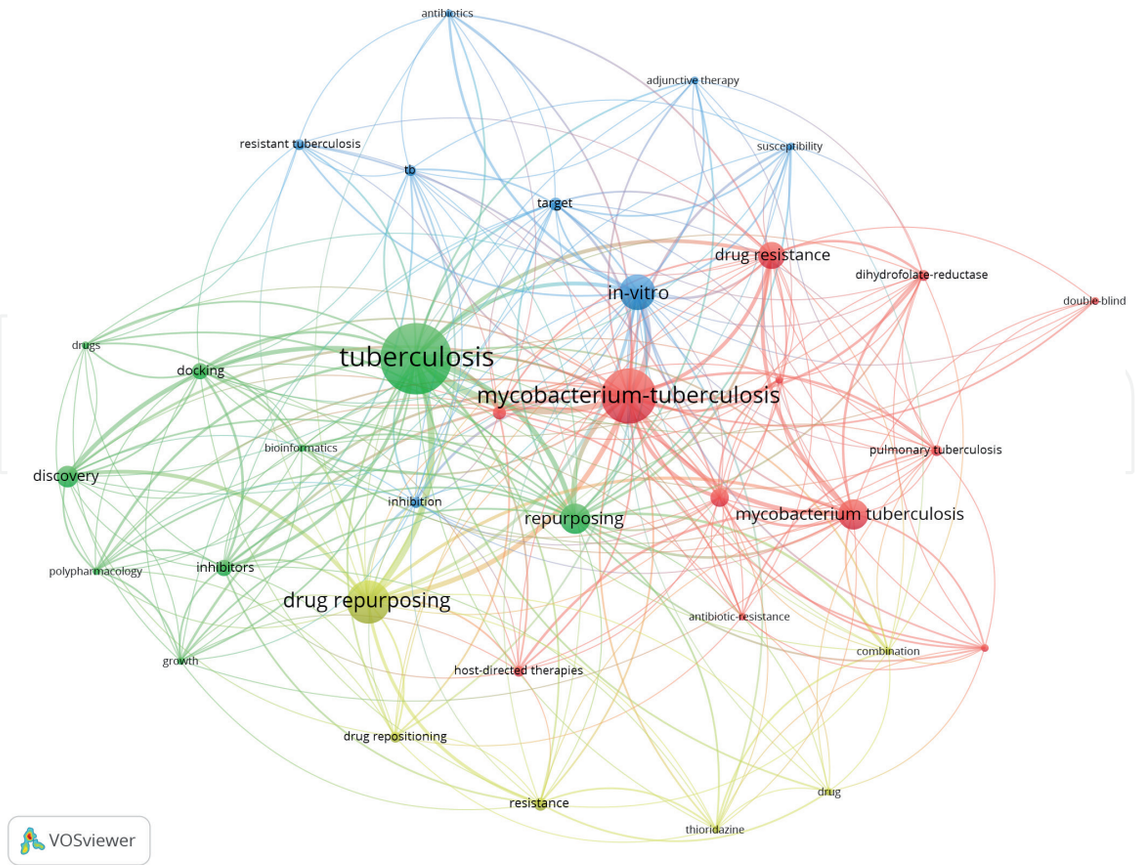

Figure 4.
Bibliographic network analysis of the keywords in published scientific articles, using the search terms "repurposing drugs for tuberculosis" (web of science – All databases). The circles indicate 35 of the most re-occurring keywords, while the size of the circles represents the importance of the keyword. The lines represent the interconnectivity of the keywords (www.vosviewer.com).

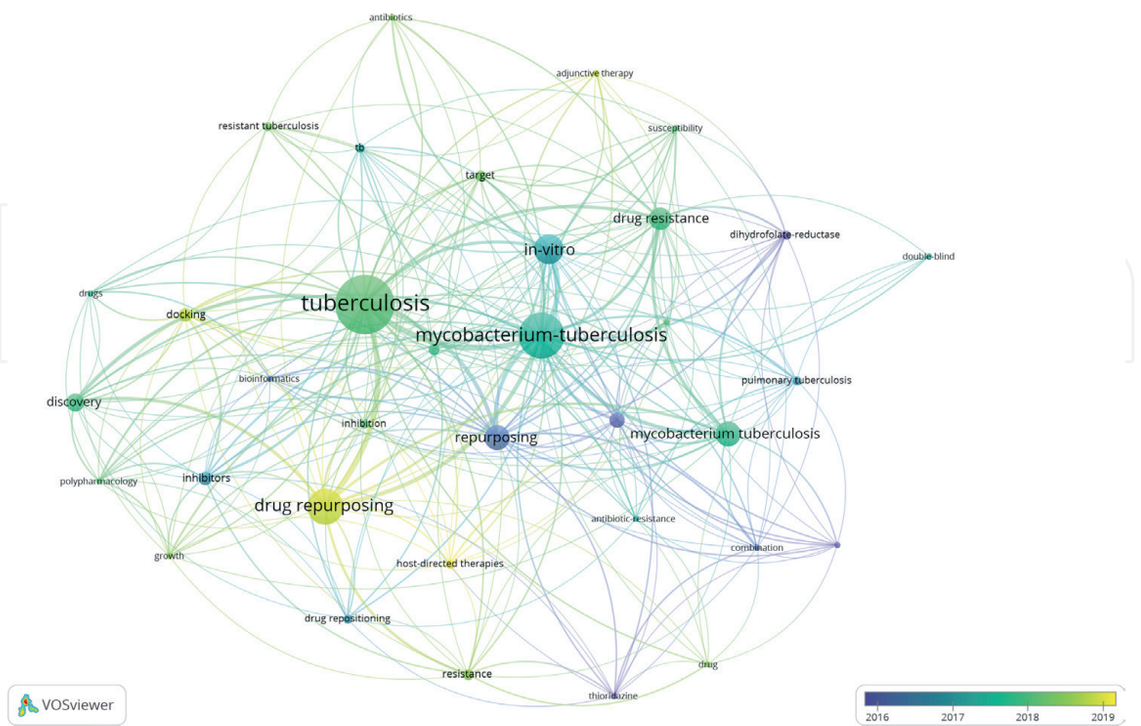

Figure 5.
A time-correlation analysis of the published material related to the search terms. An increase in articles mentioning "drug repurposing", "host-directed therapies" and "adjunctive therapy" can be seen. A trend towards computational approaches, including "docking" is also evident (www.vosviewer.com).

3. Repurposed drugs in the clinical development pipeline

There are approximately thirty chemical compounds currently being investigated in the global TB drug pipeline, of which 15 are classified as repurposed and will be discussed further.

3.1 Linezolid, Sutezolid, Delpazolid and TBI-223

Linezolid, also known as Zyvox, is a first-generation oxazolidinones which are a class of antibiotics that inhibits bacterial protein synthesis. Linezolid works by binding to a site on the bacterial ribosome thereby preventing the formation of a functional 70S ribosomal unit which is an essential component of the bacterial translation process [14–17]. Linezolid was initially approved for the treatment of infections originating from Gram-positive bacteria and used primarily in the treatment of complicated skin infections such as methicillin-resistant *Staphylococcus aureus* (MRSA). Although linezolid exhibits good antimycobacterial properties, its use is limited to DR-TB as its long term toxicity profile have been associated with neurological disorders resulting from nerve damage as well as immunosuppression resulting from decreased production of vital immune cells required for host defence [16, 17]. Analogues of Linezolid namely Sutezolid, Delpazolid, Posizolid, Contezolid and TBI-223 are second-generation oxazolidinones that are showing promising potential as antimycobacterial agents. This is due to enhanced safety profiles and reduced toxicity compared to Linezolid as well as more potent activity against mycobacteria *in vitro*. Studies and clinical trials for these analogues are ongoing with the hopes that they may also be effective in shortening current TB treatment regimens [16, 18, 19].

3.2 Moxifloxacin, Gatifloxacin, levofloxacin and DC-159a

Moxifloxacin and Gatifloxacin are fourth-generation broad-spectrum antibiotics belonging to the family of fluoroquinolone drugs. The main function of this class of antimicrobials is to inhibit the bacterial enzymes DNA gyrase and topoisomerase IV which are crucial for DNA duplication events such as transcription, recombination and cell replication [16, 18, 19]. They were initially approved for the treatment of a number of bacterial infections of the skin, stomach and lungs and along with levofloxacin has also shown promise as an effective and safe candidate for inclusion in the current TB treatment regimen [16, 20]. This is mainly because of their potent antimycobacterial activity as studies have shown that they can significantly improve sputum culture conversion rate and clinical outcome of TB treatment as well as reduce TB resurgence after treatment [17, 21]. These antimicrobials are currently being evaluated as a possible replacement for Isoniazid or Ethambutol in patients with poor tolerability as they were shown to exhibit potent antimycobacterial activity *in vitro* [16]. Moxifloxacin, Gatifloxacin and Levofloxacin are the most commonly prescribed fluoroquinolone drugs used to treat patients with MDR-TB. Despite these analogues displaying enhanced antimycobacterial activity *in vitro* and *in vivo*, levofloxacin was shown to be more cost-effective, and therefore more accessible in resource-limited high burden settings [18]. In comparison to moxifloxacin, gatifloxacin and levofloxacin, DC-159a, a relatively new fluoroquinolone analogue was shown to exhibit enhanced bactericidal activity against MDR-TB both *in vitro* and *in vivo* and may therefore be a promising new therapeutic candidate for reducing treatment time for both MDR- and drug-sensitive (DS)-TB [22, 23].

3.3 Clofazimine and TBI-166

Clofazimine is an antibiotic belonging to the class of Riminophenazines that is currently approved for the treatment of leprosy [19, 24]. Clofazimine possesses both antimicrobial and anti-inflammatory properties and although its mechanism of action is still unclear, the outer membrane of bacteria appears to be the primary target of this inhibitor [19]. Although Clofazimine has shown good activity against MDR- and XDR-TB, its efficacy in humans is still under investigation specifically concerning long term use and its major adverse effect of causing skin discoloration [25]. Clofazimine is mainly utilised in combination with other drugs in the second-line treatment of drug-resistant TB and has been classified as a Group 5 medicine by the WHO [24]. TBI-166 a new generation analogue of Clofazimine was demonstrated to exhibit superior antimycobacterial activity in comparison to its predecessor as well as reduced skin discoloration and is currently in a Phase 1 clinical trial [25, 26].

3.4 Sanfetrinem (Trinem beta-lactam)

Sanfetrinem cilexetil is an orally available tricyclic beta-lactam developed by Glaxo Smith Kline (GSK) in the early 1990's with broad antibacterial activity on both Gram-negative and Gram-positive bacteria. The development of this drug was halted after phase 2 clinical trials. However, it has recently been identified as a potential beta-lactam against *M. tuberculosis*, with an MIC of 1.5 μg/mL against H37Rv and an intracellular MIC of 0.5 μg/mL in THP1 monocytes. Furthermore, it has been reported that the drug showed potent activity against a range of susceptible and resistant clinical isolates with an MIC90 of 1–4 μg/mL. In an *in vivo* investigation, sanfetrinem cilexetil was comparable to meropenem and amoxicillin/clavulanate [27]. Similar to other carbapenems, it targets the cell wall by inhibiting the formation of peptidoglycan [28]. This drug is currently under pre-clinical investigation with a planned phase 1 clinical trial.

3.5 Spectinamide 1810 (Spectinamide)

Spectinamides are semisynthetic derivatives of spectinomycin with a narrow spectrum activity against *M. tuberculosis* and present its activity through selective inhibition of the bacterial S16 ribosomal subunit. One factor that contributes to their potent antitubercular activity is the evasion of efflux through the Rv1258c efflux pump. This feature makes spectinamides promising candidates against MDR TB, which have been shown to upregulate efflux pumps [29]. Two derivatives, 1599 and 1810 were investigated for their combinational effect in an infected mice model co-currently administering different combinations of the derivatives with Bdq, Emb, Inh, levofloxacin, linezolid, moxifloxacin, PA-824, Pza, and Rif. The researchers showed that spectinamide 1599 showed synergistic activity in combination with rifampicin and pyrazinamide [30]. Spectinamide 1810 is currently in pre-clinical investigation and being developed by Microbiotix, Inc.

3.6 Meropenem, Faropenem (Carbapenem Beta-lactam)

Meropenem is a carbapenem-type beta-lactam antibiotic which has shown bactericidal activity against susceptible and resistant *M. tuberculosis* strains. In combination with clavulanate, it was able to sterilise cultures within 14 days [31]. Meropenem is used in the treatment of a variety of bacterial infections. One phase

2 clinical trial on newly diagnosed TB has been completed, and an additional two trials are currently recruiting suitable candidates.

3.7 Thioridazine (phenothiazine)

Thioridazine was a drug used in the treatment of anxiety disorders and schizophrenia. Manufactured by Novartis, it was removed from the market in 2005 due to associated cardiac arrhythmias and other adverse effects. The removal of this drug had a devastating effect on patients being treated for schizophrenia, and a study in Finland indicated a doubling of hospital admitted relapsed patients after the withdrawal of the drug [32]. Thioridazine was coincidentally the only drug that appeared in the network analysis on the topic of repurposing drugs for TB (**Figures 2** and **3**). It has shown *in vitro* bactericidal activity against susceptible and resistant strains of *M. tuberculosis* as well as intracellular activity on human macrophages with limited cellular toxicity [33, 34]. A retrospective study on a trial conducted in Argentina on 17 XDR-TB patients revealed the potential use of this drug in a last-resort treatment. Thioridazine was combined with linezolid and moxifloxacin. Although clinically relevant adverse effects (neurotoxicity and haematological disorders) were observed, and two patients had to have the treatment halted, the combination was able to achieve negative cultures in 15 patients and status of "cured" in 11 patients. The authors have recommended the use of this combination for compassionate use [35].

4. Repurposed drugs in discovery

Numerous ongoing projects are in pre-clinical development across the globe, with collaborative research groups spanning across both industry and academia. Many of these groups form part of the Tuberculosis Drug Accelerator (TBDA) program. Selected repurposed drugs that are currently in pre-clinical development, and which have been assessed *in vitro* or *in vivo* will be discussed further. It is worth noting that several computational screening programs of approved drugs are also ongoing against known targets in *M. tuberculosis.*

4.1 Carprofen and Oxyphenbutazone

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of drugs that are generally used to relieve pain and reduce inflammation, mainly functioning by inhibiting the activity of cyclooxygenase enzymes involved in the regulation of inflammation and blood clotting [19]. In mouse models of TB, the common NSAIDs namely aspirin and ibuprofen were shown to decrease both the size and number of lung lesions and bacillary load as well as improve survival rates [36]. Studies have revealed that analogues in this family namely Carprofen and Oxyphenbutazone were found to exhibit bactericidal activity against mycobacteria through inhibition of mycobacterial drug efflux mechanisms and biofilm growth [19, 36]. Both their antimicrobial and anti-inflammatory properties combined with their low likelihood of adverse effects following administration make them very strong candidates for repurposing as TB treatment.

4.2 Disulfiram

Disulfiram is a nontoxic drug belonging to the family of Carbamates. It is primarily used to treat chronic alcohol addiction, but has demonstrated potent antimycobacterial activity against clinical isolates, MDR and XDR strains [19, 37].

Moreover, it was demonstrated that the bactericidal activity of Disulfiram is synergistically enhanced in the presence of the metal ion copper, with the mechanism of action of this compound still under investigation [37].

4.3 Metformin (Biguanides)

Metformin, a biguanide drug approved for glycaemic control in patients suffering from Type II diabetes mellitus, falls within the group of host-directed therapies against TB. Multiple adjunctive activities have been investigated. *In vitro* studies have shown a potentiation of the standard TB drugs, an increased immune response and mediation of phagosome-lysosome fusion. The phagolysosome fusion leading to the inhibition of bacterial growth is due to the expression of AMP-activated protein kinase, which in turn increases the production of mitochondrial reactive oxygen species (mROS) [38, 39]. The adjunctive properties and potential in TB treatment have been captured in two reviews [40, 41]. A phase II clinical trial investigating the safety and tolerability of metformin in TB/HIV patients is yet to start, and the investigation is planned to be completed in 2024.

4.4 Metronidazole (Nitroimidazole)

Metronidazole is a broad-spectrum antibiotic used in the treatment of gastrointestinal infections. Some parasitic infections including amebiasis, giardiasis and trichomoniasis are also treated by this drug [42]. The exact mechanism of this drug has not been fully elucidated, but it has been hypothesised that the drug renders its action through the blocking of nucleic acid synthesis via an intermediate of metronidazole and through the production of a toxic metabolite in anaerobic bacteria through the reduction of the nitro group by the redox potential of the electron transport chain [43]. It has been shown that metronidazole was able to inhibit the growth of mycobacterial bacilli under anaerobic non-replicating conditions but showed no activity under aerobic conditions [44]. *In vivo* studies in macaques (a non-human primate model), showed similar efficacy of inhibiting reactivation of latent TB, as compared to a combination of isoniazid and rifampicin [45]. In a phase 2 clinical trial investigating the effect of metronidazole vs. placebo on pulmonary MDR-TB, some efficacy was observed in sputum smears after 1 month of treatment, but the benefit was not sustained past 2 months of treatment. The study was ultimately halted due to the occurrence of peripheral neuropathies within the test subject group [46]. Although metronidazole is associated with several adverse effects, other and newer nitroimidazoles are extremely important within the clinical pipeline against TB. These include pretomanid and delamanid which are both part of multiple phase 2 and 3 clinical trials.

4.5 Tolcapone, Entacapone (catechol-O-methyltransferase (COMT) inhibitor)

Entacapone and tolcapone are two catechol-O-methyltransferase inhibitors used as an adjunct in the treatment of Parkinson's disease. Both have shown some activity against *M. tuberculosis* with a relatively high minimum inhibitory concentration (MIC) of 260 μM observed for entacapone, which was significantly lower than the cytotoxic concentration [47]. Their proposed mechanism against TB is what makes these molecules an interesting class to investigate. The mechanism is similar to isoniazid; however, they do not need enzymatic activation to bind to the enoyl–acyl carrier protein reductase (InhA) target. Furthermore, it has been proposed that it might be a possible treatment in MDR-TB, as it could evade the KatG activation associated with isoniazid resistance in many resistant strains [19, 47].

5. Target-based repurposing

An additional benefit of drug repurposing is the potential to identify or validate vulnerable targets and/or pathways that can be exploited for further drug development [8–10]. Bortezomib is the first human proteasome inhibitor approved for the treatment of multiple myeloma and mantle cell lymphoma [48]. Using a target mechanism-based whole-cell screen, bortezomib was identified as an inhibitor of the mycobacterial caseinolytic protease (ClpP1P2), with growth inhibitory activity, thus validating it as a druggable target [49]. Further investigations have focused on structural modifications of bortezomib to increase selectivity for the mycobacterial ClpP1P2 complex over the human proteasome while maintaining antimycobacterial activity [49–51]. The *M. tuberculosis* DosRST two-component regulatory system is important for survival under non-replicating conditions which is thought to contribute to the required prolonged therapy for TB, and is therefore considered a promising target for drug development [52]. Artemisinin is used for the treatment of Malaria and was identified as an inhibitor of *M. tuberculosis* DosRST during a whole-cell phenotypic high throughput screen and is currently in the hit-to-lead phase of drug development [52, 53]. In addition to the identification of promising repurposed drugs by whole-cell screening, recent efforts have focused on computational modelling and virtual screening of known drugs against targets of interest. Using this approach two drugs were identified as inhibitors of *M. tuberculosis* DNA gyrase (GyrB): echinacoside which has been investigated for the treatment of Parkinsons and Alzheimers, and epirubicin which is a treatment for breast cancer [54–56]. Virtual screening has also identified Sulfadoxine, Pyrimethamine, Lifitegrast and Silfenadil as inhibitors of *M. tuberculosis* MurB or MurE, enzymes involved in peptidoglycan synthesis [57].

6. Conclusion and future prospects

The need for novel treatment strategies for TB is becoming more urgent if the goal of a TB-free world is to be realised. While the current treatment regimens have a success rate of 85% for DS-TB, there is, unfortunately, an increase in the incidence of DR-TB, which only has a treatment success rate of 57% and harsh side-effects for patients [1]. The drug discovery pipeline is relatively rich with new material; however, the conventional screening and development strategies have led to the identification of multiple chemical scaffolds that inhibit the same targets, referred to as promiscuous targets e.g. DprE1, MmpL3 and QcrB [58]. Furthermore, the global economic climate has significantly reduced the available funding for scientific research and due to the low return on investment, several pharmaceutical companies no longer support in-house drug discovery programs for infectious diseases [6], further hampering the quest for new drugs with novel targets. To this end, drug repurposing provides an appealing strategy with several advantages as outlined above. The success of Rif, Linezolid and the fluoroquinolones provides strong support for drug repurposing for the treatment of TB. The high number of repurposed drugs in the discovery phase of compound development and in advanced clinical trials suggests that this strategy is becoming more widely accepted in the TB research community and has good potential for success. Furthermore, with the continual advances in computational biology and open sharing of compound data across disease areas, it is not unreasonable to expect a boost in drug repurposing research in the future. This could possibly further reduce the time and cost to develop repurposed TB drugs, and aid in trying to meet the global goals of eradicating TB.

Acknowledgements

V. S. acknowledges the support from the South African Medical Research Council (SAMRC).

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