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Future target-based drug discovery for tuberculosis?

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SUMMARY

New drugs that retain potency against multidrug/extensively drug-resistant strains of *Mycobacterium tuberculosis*, with the additional benefit of a shortened treatment duration and ease of administration, are urgently needed by tuberculosis (TB) control programs. Efforts to develop this new generation of treatment interventions have been plagued with numerous problems, the most significant being our insufficient understanding of mycobacterial metabolism during disease. This, combined with limited chemical diversity and poor entry of small molecules into the cell, has limited the number of new bioactive agents that result from drug screening efforts. The biochemical, target-driven approach to drug development has been largely abandoned in the TB field, to be replaced by whole-cell or target-based whole-cell screening approaches. In this context, the properties of a good drug target are unclear, since these are directly determined by the ability to find compounds, using current screening algorithms, which are able to kill *M. tuberculosis*. In this review, we discuss issues related to the identification and validation of drug targets and highlight some key properties for promising targets. Some of these include essentiality for growth, vulnerability, druggability, reduced propensity to evolve drug resistance and target location to facilitate ready access to drugs during chemotherapy. We present these in the context of recent drugs that have emerged through various approaches with the aim of consolidating the knowledge gained from these experiences to inform future efforts.

1. Background

Tuberculosis (TB), caused by infection with the slow-growing actinomycete *Mycobacterium tuberculosis*, currently causes 1.4 million deaths every year and 8–10 million new infections [1,2]. TB is treated with a complex treatment regimen, consisting of multiple antibiotics that target diverse cellular processes [3]. Furthermore, TB eradication efforts have included use of the most widely administered vaccine in human history, *Mycobacterium bovis* BCG. Despite this, TB continues to remain a constant source of human suffering, representing a failure on multiple levels in disease prevention, treatment, and health policy implementation. The protracted treatment period currently used for management of active TB disease is logistically complicated in resource-limited settings, which, together with other factors, has resulted in the rapid emergence of progressive drug-resistant TB [4]. There is an urgent medical need to develop new anti-tubercular agents with rapid sterilizing activity and novel modes of action to create a simplified, shorter treatment algorithm that is less onerous on the control programs of endemic countries [5–7].

Current drug development efforts have led to a few new candidate compounds/compound classes, as well as repurposed antibiotics that are in various stages of clinical development [3] (Figure 1). These recent successes provide an opportunity to reflect on current gaps in TB drug development and critical features required for new candidate compounds and their cellular targets. Currently, there is poor consensus on the key properties that constitute the ideal drug target for eliminating *M. tuberculosis*. Moreover, an insufficient understanding of host–pathogen interactions has limited the identification of targets for host-adjunctive therapy [8,9]. In this review, we discuss the recent successes in TB drug development and attempt to highlight some key properties of the targets that have emerged in an attempt to

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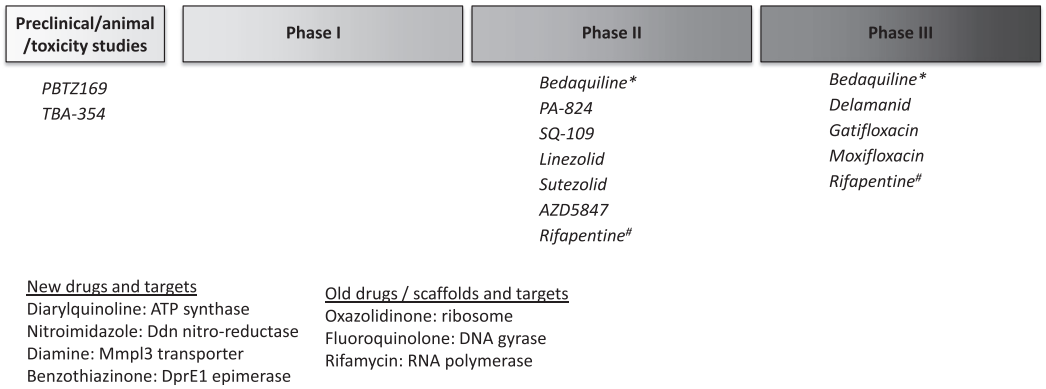

Figure 1. Tuberculosis drug development pipeline. Shown are the drugs in various stages of preclinical and clinical development with their corresponding drug targets. Information provided courtesy of the Working Group on New TB Drugs (www.newtbdrugs.org, updated June 2014). *Bedaquiline is currently in Phase III for MDR-TB and Phase II for drug susceptible TB. #Rifapentine Phase II for drug susceptible TB and Phase III for LTBI.

inform further efforts. An emerging approach to target-based drug discovery is the use of strains depleted for essential or conditionally essential targets. These and related concepts will be discussed herein along with issues that emerged from the workshop entitled "Targets for Tomorrow" organized by the Biology/Targets Subgroup of the Stop TB Working Group on New Drugs, held at the Gordon Research Conference for Tuberculosis Drug Development in Lucca, Italy in July 2013.

2. Out with the old – in with the new

The traditional, target-based approaches that utilize biochemical assays, three-dimensional structural information, and demonstrated biological function have worked well in drug discovery for various communicable (in particular viral) and non-communicable diseases. However, these approaches have had no substantive success against bacterial infectious diseases, including TB [10]. Consequently, current screening modalities are dominated by whole-cell screens for bactericidal activity on pathogenic and non-pathogenic mycobacteria. Target identification and validation of vulnerability only occurs once biological potency has been demonstrated. As such, the useful (or detrimental) properties of any target are not considered during early screening design. The use of hypomorphs in vulnerable metabolic pathways that are essential provides a convenient marriage of the two methods. However, this method is fraught with problems of achieving sufficient gene repression and downstream polar effects in the case of polycistronic genes.

3. New TB drugs

Among the recent successes in TB drug development is the identification of bedaquiline, which kills *M. tuberculosis* by inhibition of the membrane-bound F_1F_o ATP synthase complex, resulting in depletion of cellular ATP levels and eventual death of the organism [11]. This drug displayed notable bactericidal activity in early bactericidal activity studies and is approved for use under the trade name of Sirturo for treatment of patients with drug-resistant TB [12,13]. Another promising group of compounds is the nitro-dihydro-imidazooxazole derivatives, such as OPC-67683 (delamanid), which kills *M. tuberculosis* by inhibition of mycolic acid biosynthesis [14–17]. The related bicyclic nitroimidazole, PA-824, has demonstrated promise as a new TB drug with the ability to kill both replicating and non-replicating *M. tuberculosis* bacteria through a multi-faceted mechanism that involves inhibition of mycolic acid biosynthesis and respiratory poisoning through intracellular release of nitric oxide [18–22]. The identification of the benzothiazinones, a new class of candidate compounds that inhibit decaprenyl-phosphoribose epimerase (DprE1) and thereby interrupt the final steps of arabinogalactan biosynthesis, represents another class of antibiotics that target cell wall biogenesis through a distinct, novel mechanism [23,24]. More recent efforts have yielded another novel class of imidazopyridine amide compounds (the lead compound being Q203) that prevent proliferation of *M. tuberculosis* by inhibition of the cytochrome bc_1 complex in the mycobacterial respiratory chain [25–28]. Finally, the diamine SQ109, which is currently in Phase II studies, was shown to target the transporter MmpL3, involved in cell wall biosynthesis and other targets [29].

A striking feature of the abovementioned novel drugs/drug candidates is their ability to either inhibit energy metabolism or cell wall biosynthesis and, in some cases, both of these processes. This would suggest that perhaps these, and related processes represent highly vulnerable areas of mycobacterial metabolism. However, this hypothesis is dependent on the success of Q203 and the benzothiazinones in the clinical setting. Furthermore, the limited diversity in chemistry currently available may preclude the development of drugs that target other processes.

3.1. Repurposed drugs

In addition to novel compounds, there are various clinically validated classes of compounds that have been investigated for biological potency against *M. tuberculosis*. Among these are the oxazolidinones, such as linezolid [30] and, more recently, PNU-100480 (sutezolid), which is more potent than linezolid and synergizes with moxifloxacin and pyrazinamide in the murine model of TB infection [31,32]. Despite this difference in efficacy, the recent demonstration of linezolid's curative activity in patients with XDR-TB validates this class of compounds for further development [30]. The promising activity displayed by the analogue AZD5847 [33], which is currently in phase IIA trials, is further evidence of this. Clofazimine, a hydrophobic rhiminophenazine used traditionally for treatment of leprosy also features prominently among the repurposed TB drugs for treatment of drug-resistant TB [34]. This drug is postulated to undergo reduction by the mycobacterial type II NADH dehydrogenase and, upon subsequent oxidation, leads to the formation of reactive oxygen species [35]. Clofazimine accumulates inside host macrophages/tissues and is able to crystallize in pulmonary macrophages [36]. Whilst these are undesirable effects in any drug, they may contribute to the efficacy of this compound in treating leprosy and TB. The promising activity of clofazimine in the murine model of TB infection has led to the search for new analogs, where these side effects have been reduced [37].

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