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Repurposing—a ray of hope in tackling extensively drug resistance in tuberculosis

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SUMMARY

Tuberculosis (TB) remains a serious concern more than two decades on from when the World Health Organization declared it a global health emergency. The alarming rise of antibiotic resistance in *Mycobacterium tuberculosis*, the etiological agent of TB, has made it exceedingly difficult to control the disease with the existing portfolio of anti-TB chemotherapy. The development of effective drugs with novel mechanism(s) of action is thus of paramount importance to tackle drug resistance. The development of novel chemical entities requires more than 10 years of research, requiring high-risk investment to become commercially available. Repurposing pre-existing drugs offers a solution to circumvent this mammoth investment in time and funds. In this context, several drugs with known safety and toxicity profiles have been evaluated against the TB pathogen and found to be efficacious against its different physiological states. As the endogenous targets of these drugs in the TB bacillus are most likely to be novel, there is minimal chance of cross-resistance with front-line anti-TB drugs. Also, reports that some of these drugs may potentially have multiple targets means that the possibility of the development of resistance against them is minimal. Thus repurposing existing molecules offers immense promise to tackle extensively drug-resistant TB infections.

1. Introduction

The global resurgence of tuberculosis (TB) has been fuelled by its synergy with the AIDS pandemic,[1] and the transmission of drug-resistant strains of the causative agent, *Mycobacterium tuberculosis*.[2,3] Diabetes, smoking, alcoholism, and other lifestyle-related factors have boosted the rise in TB in wealthy nations, while its stronghold remains in the poorer countries struggling to cope with the effects of population explosions, overcrowding, pollution, poverty, and malnutrition.[4]

Through partnerships between pharmaceutical companies and research-led institutes, drug discovery and development has accelerated considerably in recent times, leading to a handful of successful novel lead chemical entities aimed at the drug-resistant forms of TB. However, we should refrain from being over-enthusiastic about these wonderful drugs and focus on strengthening the growing arsenal of anti-TB therapeutic agents to outpace the pathogen's evolving resistance.[5] The development of resistance mainly involves genetic evolution of the pathogen to overcome the deleterious effects of the drug and is hastened by inappropriate prescription/administration and patient non-compliance. Thus, it is not unlikely that resistance towards novel agents will arise in the organism, making it more important to work towards increasing the available treatment options that target diverse metabolic pathways in the pathogen.

The major problem in the elimination of *M. tuberculosis* from an infected individual is its resilience and coping mechanisms, which enable it to face varied hostile environments.[6] Under inhospitable conditions, the bacilli enter into physiological stagnation, becoming viable but non-culturable, commonly referred to as dormant. A third of the global population harbours the TB bacillus in its dormant state, causing a latent TB infection. Ten percent of these infected individuals regularly progress to active TB disease. The dormant bacilli are resilient to standard chemotherapy, and as a

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Table 1
Current uses of drugs and progress made towards repurposing them for TB treatment. Drugs marked with an asterisk (*) are probable candidates for inclusion in TB treatment regimens as host-directed adjuvant therapy due to their immune-modulatory activity

Name	Class	Current use	In vitro MIC against $H_{37}Rv$	Stage of repurposing	References
Ivermectin	Avermectin	Anti-helminthic	6.8 μM	Anti-TB property detected by MTT assay	55
Carprofen*	2-Arylpropanoid acid NSAID	Analgesic	146 μM	Anti-TB property detected in vitro by HT-SPOTi	75
Clofazimine	Riminophenazine	Anti-leprosy	1.6 μM	NC003 (phase IIa) – complete; results in 2014. Second-line treatment for TB	48
Chlorpromazine*	Phenothiazine	Anti-psychotic	47 μM	Mouse model studies using MDR-TB strains	69
Disulfiram*	Thiocarbamate	Alcohol withdrawal drug	5.3 μM	Anti-TB property detected by broth dilution tests	71
Entacapone	Nitrocatechol	Anti-Parkinson's drug	205 μM	Anti-TB property predicted by systems biology. In vitro activity detected by broth dilution	62
Gatifloxacin	Fluoroquinolone	Respiratory infections	660 nM	Phase III; enrolment complete	25
Linezolid	Oxazolidinone	Gram-positive bacteria	741 nM	Phase II completed	44
Metronidazole	Nitroimidazole	Broad-spectrum antibiotic	>1.4 mM	Phase II completed	33
Meropenem/ clavulanic acid	β-Lactams	Antibiotic	1.7 μM	In vivo and small-scale human patient studies	39, 42
Moxifloxacin	Fluoroquinolone	Acute bacterial sinusitis	1.1 μM	REMox TB – completed STAND (phase III) – enrolment begins in 2014	26
Nitazoxanide	Nitrothiazole	Anti-protozoal	52 μM	In vitro activity detected	60
Oxyphenbutazone*	Pyrazolidinedione NSAID	Analgesic	200 μM (12.5 μM against non-replicant)	In vitro activity detected	76
Pyrvinium pamoate	Methylquinolinium	Anti-helminthic	310 nM	In vitro activity detected by Alamar blue assay	57
Tebipenem/ clavulanic acid	β-Lactams	Antibiotic	2.9 μM	Enzyme inhibition studies	36, 37
Thioridazine	Phenothiazine	Anti-psychotic	27 μM	Anti-TB property detected in vitro by BACTEC 460-TB	64, 69
Tolcapone	Nitrocatechol	Anti-Parkinson's drug	457 μM	Anti-TB property predicted by systems biology	62

TB, tuberculosis; MIC, minimum inhibitory concentration; NSAID, non-steroidal anti-inflammatory drug; MDR, multidrug-resistant.

consequence, there is a biphasic pattern of elimination of the pathogen from the infected host, necessitating a lengthy duration of drug treatment.[7] An effective means to control the spread of the disease would be to eliminate the dormant bacilli; however, there are almost no effective treatments to remove this subset of pathogens from the primary host.[8]

Formulating a commercial drug usually begins from a modest laboratory bench and is a lengthy and expensive process, requiring highly skilled experimental researchers and state-of-the-art facilities. Furthermore, out of the thousands of potential molecules, only a handful are finally identified as druggable hits. Although there is wide debate on the reasons for the high attrition rates seen in clinical trial pipelines, there is no conflict over the fact that success rates in drug development are very low.[9] A thorough investigation of 835 drug developers revealed that 10% of all entities in phase I trials were finally approved by the US Food and Drug Administration.[10] As a result, there is an unbalanced risk–benefit assessment biased more towards the risk element and higher regulatory hurdles and complexity of clinical trials, leading to commercial and financial decisions driving project termination.

The most common roadblocks faced by novel chemical or molecular entities result from inappropriate compound selection, leading to poor biological efficacy, a lack of equivalence between in vitro models, animal models, and the human disease, and finally poor study design. Advances in genome sequencing announced firmly the one compound–one target paradigm of drug discovery, which in the light of growing resistance needs to be re-evaluated. There is a pressing need for new treatments; hence the repurposing or repositioning of drugs to treat TB is progressively gaining favour. It is a powerful strategy that complements novel drug design, thereby populating the clinical trials pipeline. Regulators often require long-term data including a number of study arms with a variety of patient age and risk groups, necessitating the recruitment of a large number of patients. Repurposing benefits from the knowledge obtained from prior, long-term administration of the drug to a wide phenotypically distinct human population. These molecules are thoroughly characterized with regards to metabolism and safety and thus this strategy can be instrumental in saving valuable time and funds.

2. Repurposing is an attractive strategy

Both the terms 'repurposing' and 'repositioning' have the same broader meaning, however other terms such as drug reprofiling, drug retasking, or therapeutic switching have also been employed.[11]

Drugs originally developed to treat a certain condition may interact with unrelated targets exhibiting a secondary biological effect, thereby offering positive therapeutic windows for a variety of different applications, as seems to be the case for thalidomide.[12] These drugs do not necessarily require toxicity profiling, target validation, hit-to-lead optimization, and/or in vivo metabolic studies. The most notable example of a successfully repurposed drug is sildenafil (Pfizer); this was developed as an antihypertensive drug and turned out to be a selective inhibitor of the human phosphodiesterase 5,[13] and thus provided a solution to erectile dysfunction. It is now being considered as an adjuvant host-directed therapy to shorten treatment times for TB and has shown promise in mouse model studies.[14]

As alluded to above, thalidomide is another example of a drug with various applications. Made infamous due to its teratogenic effect on unborn children, it is now regularly used in the treatment of leprosy[15] and has shown great promise in relieving TB meningitis symptoms in children.[16] With increasing numbers falling prey to drug-resistant TB and treatment options gradually decreasing, we aim to discuss the drugs that show promise in TB treatment, to enable deliberations on their inclusion in TB treatment trials.