Various Aspects of Laboratory Diagnosis of Tuberculosis on Multidrug Resistant Tuberculosis

Preeti Sharma[1#], Jinendra Singh Chauhan[2], Birjesh Singh[3]
[1#]AISECT University, Bhopal, M.P., India,
[2]Govt. BLP PG College, MHOW, Indore, M.P., India,
[3]AISECT University, Bhopal, M.P., India.

Abstract: - The latest WHO report estimates about 1.6 million global deaths annually from TB, which is further exacerbated by drugresistant (DR) TB and comorbidities with diabetes and HIV. Exiguous dosing, incomplete treatment course, and the ability of the tuberculosis bacilli to tolerate and survive current first-line and second-line anti-TB drugs, in either their latent state or active state, has resulted in an increased prevalence of multidrug-resistant (MDR), extensively drug-resistant (XDR), and totally drugresistant TB (TDR-TB). Although a better understanding of the TB microanatomy, genome, transcriptome, proteome, and metabolome, has resulted in the discovery of a few novel promising anti-TB drug targets and diagnostic biomarkers of late, no new anti-TB drug candidates have been approved for routine therapy in over 50 years, with only bedaquiline, delamanid, and pretomanid recently receiving tentative regulatory approval. Considering this, alternative approaches for identifying possible new anti-TB drug candidates, for effectively eradicating both replicating and non-replicating Mycobacterium tuberculosis, are still urgently required. Subsequently, several antibiotic and non-antibiotic drugs with known treatment indications (TB targeted and non-TB targeted) are now being repurposed and/or derivatized as novel antibiotics for possible use in TB therapy.

Keywords: - Adjunct drugs, Drug resistance, Monotherapy, Mycobacterium tuberculosis.

I. INTRODUCTION

Tuberculosis (TB), caused by the organism Mycobacterium tuberculosis, is considered to be the most prevalent cause of death in humans from a single infectious agent. The latest WHO report estimates 10.0 million people globally with active TB, resulting in 1.6 million deaths (300,000 of which are co-infected with HIV) (WHO 2018). This high incidence of TB is ascribed to several factors including (1) the difficulties/ complications in totally eradicating M. tuberculosis (Mtb) from its diseased host, due to the physiological competence (persistence) of the infectious agent (Cambier et al. 2014; Mishra and Surolia 2018), (2) its tolerance to current anti TB drugs/antibiotics (Antonova et al. 2018; Lee et al. 2019; Liu et al. 2016), and (3) the compromised immune status of the infected host (Bonds and Sampson 2018; Campanico et al. 2018). This is further exacerbated by the increased prevalence of drug-resistant (DR), multi-drug-resistant (MDR), extensively drug-resistant (XDR), and totally drug-resistant (TDR) TB causing strains, in many populations (Jansen and Rhee 2017; Kolyva and Karakousis 2012).

Even though TB is generally considered to be a curable disease (for most drug-sensitive clinical TB cases), the current first-line anti-TB drugs (isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB)) given as part of the Directly Observed Therapy Short Course (DOTS), are inadequate for totally eradicating TB (Chetty et al. 2017; Evans and Mizrahi 2018). This is also partially because other socioeconomic and demographic factors like poor hygiene, income constraints, malnutrition, overcrowding and poor ventilation, lack of social support, and stigmatization also significantly contribute to the continued communicability and persistence of TB (Creswell et al. 2011; Duarte et al. 2018; Ivanovs et al. 2016; Lönnroth et al. 2010). Although an improved understanding of TB and the Mtb biosystem, using a variety of omics research strategies, has to date resulted in the discovery of various novel and promising anti-TB drug targets over the years (Gibson et al. 2018; Haas et al. 2016; Loots 2016; Luies et al. 2017; Swanepoel and Loots 2014), new treatment strategies are still urgently needed to alleviate the TB burden, and especially so considering the recent rise in DR-strains of Mtb, and subsequently the need for faster treatment strategies, and better patient compliance to such agents (Dong et al. 2017; Lin et al. 2018; Mori et al. 2017). New anti-TB drug discovery, is now more than ever, focused on finding new anti-TB agents, which exhibit lower toxicity, improved efficacy, and prevent or even cures MDRTB (Castelo-Branco et al. 2018).

Over these past 4 decades, there has been little in terms of novel anti-TB drug discoveries, which is most likely attributed to extremely high costs typically required for developing and testing such, exacerbated by the low-profit margins when such eventually reaches the market (Tacconelli et al. 2018). According to recent reports, the cost of developing totally novel drugs has escalated to about $2.6 billion per drug and to the duration of development up to 15 years, before a potential novel drug is eventually commercialized (Ramón-García et al. 2016). Subsequently, big-pharma and other academic or commercial research groups no longer find this approach to drug discovery an attractive business option (Deshpande et al. 2017). Besides, there is now also the requirement, as part of the drug development pipeline, to determine synergistic efficacy and safety, with other therapeutic agents, and this further hampers new drug discovery in terms of development time and costs (Evans and Mizrahi 2018). For these reasons, repurposing existing drugs has also become a more popular option in recent years (RamónGarcía et al. 2016; Savoia 2016).

As newer information on the derivatives of old TB (antibiotic and non-antibiotic) drugs and previously repurposed (successful and unsuccessful; antibiotic and nonantibiotic) TB drugs are becoming available, this review encapsulates the most recent reports (including review articles) on investigational compounds (associated with old therapeutic agents) and drugs with repositioning potential for anti-TB therapy accumulated over the last 6 years. The review articles were included because of insights provided by the authors as regards the topic of discussion. Currently, information on newly synthesized compounds either related to old therapeutic agents (or non-related) and those non-related to repurposed drugs in any way is numerous and inexhaustible. This paper, therefore, only provides a quick go-to for readers interested in anti-TB drug discovery and development, relative to both old therapeutic agents and drugs with repositioning potentials (antibiotic and non-antibiotic).

II. INVESTIGATIONAL COMPOUNDS WITH PROMISING ANTI-TB POTENTIAL

At present, the WHO anti-tuberculosis essential medications list include EMB, INH, RIF, PZA, rifabutin, amikacin, amoxicillin-clavulanic acid (AMC), BDQ, clofazimine (CFZ), cycloserine, DLM, ethionamide (ETH), levofloxacin (LFX), linezolid (LZD), meropenem,moxifloxacin (MFX), paminosalicylic acid (PAS), streptomycin, and rifapentine (RPT) (WHO 2015, 2019). The 3 recently approved (BDQ, DLM, and PMD) medications have adverse side effects even when co-administered and are only administered under stringent conditions where treatment options are limited.New anti-TB drugs are still insufficient and the numbers of investigational compounds undergoing human clinical trials are limited.

Therefore, the need for continuous discovery of anti-TB compounds with new action mechanism and reduced treatment duration, lower toxicity and higher potency (including latent TB stages), low production and purchase cost, easy accessibility, improved drug-drug interaction, and their subsequent inclusion in TB therapy cannot be overemphasized. In this regard, we will discuss a few of the investigational compounds (related to old antimicrobial agents) recently reported to show promising anti-TB potential.

Decoquinate derivatives

The multi-therapeutic efficacy of decoquinate, an anticoccidial drug used in poultry and livestock farming, was evaluated by Beteck et al. (2018). In their study, the authors converted DQ via divergent chemistry, into several analogs of N-alkylated quinolone amides, three of which showed remarkable activity against Mtb. Furthermore, due to DQ's lipophilic decyl side chain, active DQ analogs will most likely diffuse passively over the Mtb mycolic acid cell wall. This characteristic should allow excellent intracellular penetration and enhanced activities against Mtb encapsulated in macrophages and granulomatous lesions, and possibly shorten treatment duration remarkably (Aljayyoussi et al. 2017). This observation is corroborated by the Rosenthal et al. (2012) investigation, whereby upon exposure of BALB/c mice to an INHPZA- RIF regimen instead of INH-PZA-RPT, approximately 50% reduction in TB treatment duration was recorded. The reduction was attributed to the increased daily dose of RPT instead of rifampin (10 mg/kg of RIF was replaced with 7.5–10 mg/kg of RPT) which resulted in greater exposure of the mice to the former.

Additionally, the N-alkylated amide DQs expressed anti- Mtb MIC_{90} of 1.25–3.64 μM, caused by possible cell wall homeostatic disruptions (Beteck et al. 2018). A follow-up in vitro and murine (C57BL/6 male mice) study by Tanner et al. (2019) evaluating multiple parameters (e.g., in vitro microsomal stability, kinetic solubility, lipophilicity, and pharmacokinetic parameters) of these DQs further showed promising anti-TB drug profiles. The addition of the DQ analogs in TB therapy will, however, require further anti-Mtb murine investigations and clinical trials to ascertain its pharmacokinetics/pharmacodynamics relative to humans.

Primaquine derivatives

The 2012 approval of the anti-TB compound BDQ (a diarylquinoline derivative; MIC = 0.05–0.22 μM) (Andries et al. 2005), and its characteristic non-cross-resistance to MDR and XDR-Mtb strains (Kaur et al. 2015), recently led to investigating the use of various quinolone derivatives, such as the antimalarial drug primaquine, for use as explorative scaffolds for the synthesis of similar compounds with anti-TB action. Pavić et al. (2018) reported the anti-Mtb activity of both urea 2 m and bis-urea 4u, 2 primaquine derivatives as (MIC = 4.29 μM). The 2 PQ analogs, from "4 series of PQ derivatives" (amides 1a-k; ureas 2a-s; semicarbazides 3a-c; and bis-ureas 4a-u), displayed favorably low cytotoxicity (2 m (321.88 μM) and 4u (128.30 μM)), while also exhibiting a better anti-Mtb activity than the reference drug ciprofloxacin in the study.

Coumarin derivatives

Report on the antimicrobial activity of coumarin-based compounds has been increasing over the years. Coumarins possess a variety of biological properties that includes Mtb inhibition (Abdizadeh et al. 2017; Basanagouda et al. 2014; Jeyachandran et al. 2012; Kawate et al. 2013; Niu et al. 2017), and based on the parent compound's (coumarin: 1,2- benzopyrone) structural versatility and scaffolding ability (Bansal et al. 2013; Kapp et al. 2017), newer derivatives having potential anti-TB activity have been synthesized and investigated in vitro Reddy (Reddy et al. 2015a; Reddy et al. 2015b). Recently, Mangasuli et al. (2018) and Reddy et al. (2018) reported the synthesis of 2 specific coumarin derivatives, (1) a coumarin-theophylline hybrid (3a) and (2) a coumarin-oxime ether derivative (1 h), which both exhibited excellent anti-TB activity of MIC 0.32 μM and 0.12 μM respectively—MIC ranges close to the first-line anti-TB drug INH. Additionally, the majority of the derivatives in the study of Reddy et al. (2018) exhibited MICs in the range of 0.12– 16.51 μM—while also projecting good cytotoxicity profiles against Vero cells and excellent DNA cleaving properties (depicting nuclease activity). According to Mangasuli et al. (2018), 3a also showed good binding interactions with the Mtb 4DQU enzyme and possible broad-spectrum antimicrobial properties (inhibiting Candida albicans, Escherichia coli, Staphylococcus aureus, and Salmonella typhi). Possible anti-TB MOA exhibited by coumarin derivatives includes disruption of cytochrome synthesis; inhibition of cell proliferation; activation of macrophages; kinase inhibitor. The inclusion of other compound moieties (of interest to TB drug development) (e.g., oxime and heterocyclic moieties) in the coumarin nucleus could provide avenues for synthesizing potential new anti-TB lead drugs.

III. QUANTITATIVE ANALYSIS

A typical quantitative analysis involves the sequence of step shown in the diagram given below (Figure 1). In some instances, one or more of these steps can be omitted. For e.g. if the sample is already in liquid state, the dissolution steps can be avoided [3].

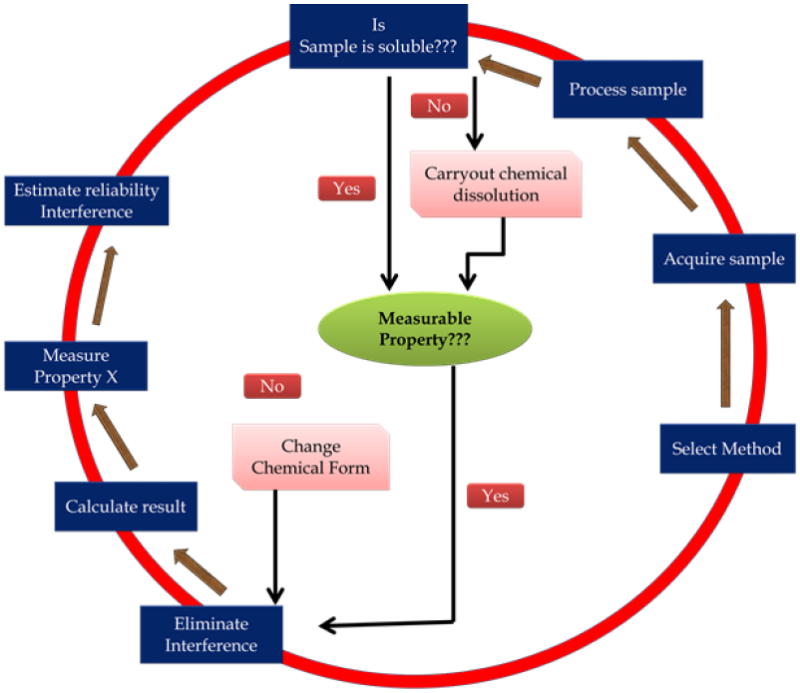

Figure 1: Steps of Quantitative Analysis

The methods of analysis in analytical chemistry may be broadly classified into two group i.e. classical methods and instrumental methods of analysis. The major drawback with the classical methods of analysis is that the methods employed are not very sensitive, the amount of sample required is quite high as well as since some of the chemical properties of the analyte are being exploited therefore the analyte loses its identity. So, when the analyte is present in low concentration or the amount of sample is very low then the classical methods of analysis will be utilized to carry out the analysis.

In order to overcome the above-mentioned problems in the analysis of these low concentration compounds, instrumental methods of analysis started to emerge. Unlike, the classical method of analysis, where some chemical properties of analyte is exploited, in instrumental methods of analysis some physical property of analyte is exploited.

Chromatography

Separation of chemical components in a mixture is vital in any type of chemical analysis. When trying to identify an unknown substance, firstly the sample must be simplified as much as possible into its constituent compounds. Then, an unknown analyte can be characterized easily. Techniques related to chromatography have been used for centuries to separate substance such as dyes extracted from plants. It was a Russian chemist and botanist Michael Tswett who in 1906 first used the term chromatography to describe his work on the separation of coloured plant pigments into bands on a column filled with chalk. The significance of his work was not realized until 1930's when Lederer and others described their work on separation of plant pigments, including carotenoids and xanthophylls. Paper and thin layer chromatography had been developed rapidly during this period with many applications being published. In 1940s the development of ion exchange, partition, column chromatography and the initial study on gas chromatography has been reported by the researchers. During the year of development, three chromatographers namely Tiselius (Sweden), Martin and Synge (UK) received Nobel Prize for their work in the field of chromatography [4]. The 1940's saw a rapid expansion in the use of chromatographic methods in the laboratory but the introduction and development of gas-liquid chromatography in 1950's represented a significant milestone, ushering in the era of instrumental methods of separation which spawned many variations of modern chromatography in use today [5]. Developments in engineering techniques, microelectronics, microcomputers and new materials have enabled manufacturers to produce reliable automated instruments that achieve reproducible chromatography.

Ever since its discovery, chromatography has evolved as a powerful tool in the laboratory for the separation and identification of different compounds in a mixture. In this overview, the main focus is to know, what are the important developments in the field of chromatography which have been reported and how they evolved in the past years.

IV. FUNDAMENTALS

The mobile phases which are used in MLC have surfactants at concentrations above the CMC. The unique nature of MLC is the use of the aqueous surfactant solutions. Surfactant belongs to the class of compounds known as amphiphiles, or molecules having both a hydrophobic and hydrophilic component [19]. The hydrophobic component is generally referred as the tail group and hydrophilic group is known as the head. The term surfactant comes from a contraction of ―surface active agent‖ and is defined as a material which when present at low concentrations, adsorb onto the interface, or surface of the system and thereby alters the interfacial free energies of the interface [20]. Surfactants are generally classified by the charge of the hydrophobic head group i.e. anionic, cationic, nonionic, and amphoteric or zwitterionic [Table 1]. The most commonly used household and industrial surfactants are anionic. The anionic surfactant dissociates in aqueous solutions to give a negatively charged surface active portion and an inactive cation, commonly Na+ or K+. In MLC, the most commonly used anionic surfactant is the alkyl sulfate, sodium dodecyl sulfate (SDS).

Figure 2: Sodium dodecyl sulphate

Table 1: Most Commonly used Surfactants in MLC and their Characteristics

Type	Compound	Name	CMC*	A.N#
Anionic	$C_{12}H_{25}SO_4Na$	Sodium dodecyl sulfate	8.1	62
Cationic	$C_{16}H_{33}N(CH3)_3Br$	Cetyl trimethyl ammonium bromide	0.83	90
Zwitter ionic	$C_{32}H_{58}N_2SO_7$	3-[(3-cholamidopropyl) dimethylammonio]-1-propanesulfonate	8	10
	$C_{32}H_{58}N_2O_8S$	3-[(3-Cholamidopropyl) dimethylammonio]-2-hydroxy-1-propanesulfonate	8	11
Non ionic	$C_{12}H_{25}(C_2H_4O)_{23}OH$	Polyoxyethylene 23 dodecyl ether	0.06	41
	$C_{14}H_{22}O(C_2H_4O)_{9.5}$	p-Octylbenzene polyoxyethylene 9.5 alcohol	0.3	140

*Critical Micelles Concentration
#Aggregation Number

The ―colloidal ions‖ later became known as micelles after the term was borrowed from biology and popularized by G. S. Hartley in his book ―Aqueous Solutions of Paraffin-Chain Salts, A Study in Micelle Formation‖ in 1937 [24]. When surfactant concentrations exceed the CMC, the surface tension and free energy has lowered by formation of molecular aggregates known as micelles. Micelles remain in solution and in dynamic equilibrium with the monomers in solution. Micelles are generally formed with their hydrophobic tail group oriented inward, and the hydrophilic head group oriented outward. This is because when the surfactant is dissolved in polar solvent (water) hydrophobic tails get aggregate inwardly and the hydrophobic head aggregate at outwardly (Figure 3). Here, these normal micelles solubilize the nonpolar solute into a polar solvent. At the concentrations close to the CMC, most surfactants form spherical micelles, however, as the concentration of ionic surfactant increases, other micelle shapes are formed in the sequence of spherical, cylindrical, hexagonal, and laminar as shown in figure.

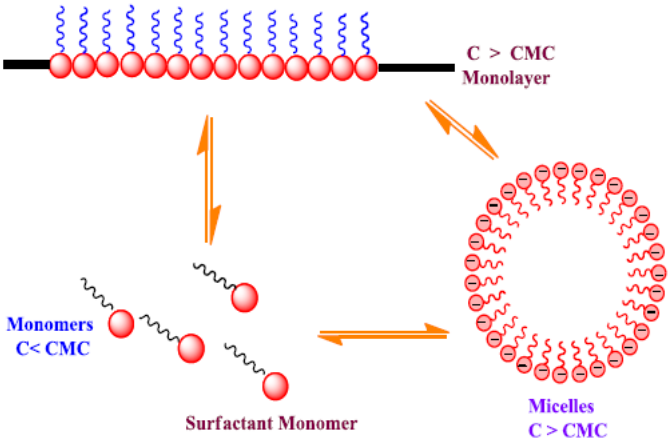

Figure 3: Shows that Surfactant can Exist in Different Shapes Depending upon their Concentration in the Sample

V. CONCLUSION

Several factors can hinder the advancement of research involving drug repurposing—including legislative, organizational, regulatory, and technical factors that cannot be overlooked (Pushpakom et al. 2019). The success of drug repositioning leverages on the facts that (1) common biomolecular pathways are associated with different diseases mechanisms and that (2) previously approved drugs for other diseases are an important consideration for treating such since they have already been determined to have favorable human pharmacokinetic properties, the latter of which often helps circumvent the early phase clinical trials, and subsequently reduces the costs and time to bring such drugs to market. Selecting such, however, requires a thorough search of the literature housed in the drug repositories and databases (e.g., Therapeutic Target Database (TTD), Pubchem, Pathway Interaction Database (PID) and Search Tool for Retrieval of Interacting Genes/Proteins (STRING), Clinical trials and Adverse Effect data and

Side Effect Resource (SIDER)), as well as an in-depth understanding of a particular disease and the mechanisms by which successful drug candidates already function in alleviating such disease, to predict which other compounds, already available for the treatment of other diseases, may be investigated for treating these.

REFERENCES

[1] Alsaad N, Dijkstra JA, Akkerman OW, de Lange WCM, van Soolingen D, Kosterink JGW, van der Werf TS, Alffenaar JWC (2016) Pharmacokinetic evaluation of sulfamethoxazole at 800 milligrams once daily in the treatment of tuberculosis. Antimicrob Agents Chemother 60:3942–3947

[2] Ammerman NC, Swanson RV, Bautista EM, Almeida DV, Saini V, Omansen TF, Guo H, Chang YS, Li S-Y, Tapley A, Tasneen R, Tyagi S, Betoudji F, Moodley C, Ngcobo B, Pillay L, Bester LA, Singh SD, Chaisson RE, Nuermberger E, Grosset JH (2018) Impact of clofazimine dosing on treatment shortening of the first-line regimen in a mouse model of tuberculosis. Antimicrob Agents Chemother 62:e00636–e00618

[3] Andries K, Verhasselt P, Guillemont J, Göhlmann HWH, Neefs J-M, Winkler H, Van Gestel J, Timmerman P, Zhu M, Lee E, Williams P, de Chaffoy D, Huitric E, Hoffner S, Cambau E, Truffot-Pernot C, Lounis N, Jarlier V (2005)

[4] A diarylquinoline drug active on the ATP Synthase of Mycobacterium tuberculosis. Sci 307:223–227 Antonova AV, Gryadunov DA, Zimenkov DV (2018) Molecular mechanisms of drug tolerance in mycobacterium tuberculosis. Mol Biol 52:372–384

[5] Arab HH, Salama SA, Omar HA, Arafa E-SA, Maghrabi IA (2015) Diosmin protects against ethanol-induced gastric injury in rats: Novel anti-ulcer actions. PLoS One 10:e0122417

[6] Arnold A, Cooke GS, Kon OM, Dedicoat M, Lipman M, Loyse A, Chis Ster I, Harrison TS (2017) Adverse effects and choice between the injectable agents amikacin and capreomycin in multidrug-resistant tuberculosis. Antimicrob Agents Chemother 61:e02586–e02516

[7] Bansal Y, Sethi P, Bansal G (2013) Coumarin: a potential nucleus for antiinflammatory molecules. Med Chem Res 22:3049–3060

[8] Basanagouda M, Jambagi VB, Barigidad NN, Laxmeshwar SS, Devaru V (2014) Synthesis, structure–activity relationship of iodinated-4- aryloxymethyl-coumarins as potential anti-cancer and antimycobacterial agents. Eur J Med Chem 74:225–233

[9] Bax HI, de Steenwinkel JE, ten Kate MT, van der Meijden A, Verbon A, Bakker-Woudenberg IA (2015) Colistin as a potentiator of anti-TB drug activity against Mycobacterium tuberculosis. J Antimicrob Chemother 70:2828–2837

[10] Chien J-Y, Yu C-J, Hsueh P-R (2017) High incidence of fluoroquinolone resistance and effect of efflux pump inhibitors on moxifloxacin resistance among Mycobacterium tuberculosis isolates causing urinary tract infection in Taiwan. Int J Antimicrob Agents 50:491–495

[11] Cleghorn LAT, Ray PC, Odingo J, Kumar A, Wescott H, Korkegian A, Masquelin T, Lopez Moure A, Wilson C, Davis S, Huggett M, Turner P, Smith A, Epemolu O, Zuccotto F, Riley J, Scullion P, Shishikura Y, Ferguson L, Rullas J, Guijarro L, Read KD, Green SR, Hipskind P, Parish T, Wyatt PG (2018) Identification of morpholino thiophenes as novel Mycobacterium tuberculosis inhibitors, targeting QcrB. J Med Chem 61:6592–6608

[12] Coelho TS, Silva RSF, Pinto AV, Pinto MCFR, Scaini CJ, Moura KCG, Almeida da Silva P (2010) Activity of β-lapachone derivatives against rifampicin-susceptible and -resistant strains of Mycobacterium tuberculosis. Tuberculosis 90:293–297

[13] Gupta S, Tyagi S, Bishai WR (2015) Verapamil increases the bactericidal activity of bedaquiline against Mycobacterium tuberculosis in a mouse model. Antimicrob Agents Chemother 59:673–676

[14] Gurumurthy M, Verma R, Naftalin CM, Hee KH, Lu Q, Tan KH, Issac S, Lin W, Tan A, Seng K-Y, Lee LS-U, Paton NI (2017) Activity of faropenem with and without rifampicin against Mycobacterium tuberculosis: evaluation in a whole-blood bactericidal activity trial. J Antimicrob Chemother 72:2012–2019

[15] Haas CT, Roe JK, Pollara G, Mehta M, Noursadeghi M (2016) Diagnostic 'omics' for active tuberculosis. BMC Med 14:37

[16] Halicki PB, Ferrreira LA, de Moura KCG, Carneiro PF, Del Rio KP, Carvalho TSC, Pinto MCFR, Silva PA, Ramos DF (2018) Naphthoquinone derivatives as scaffold to develop new drugs for tuberculosis treatment. Front Microbiol 9:673

[17] Keri RS, Pandule SS, Budagumpi S, Nagaraja BM (2018) Quinoxaline and quinoxaline-1, 4-di-N-oxides: An emerging class of antimycobacterials. Arch Pharm 351:1700325

[18] Kling A, Lukat P, Almeida DV, Bauer A, Fontaine E, Sordello S, Zaburannyi N, Herrmann J, Wenzel SC, König C (2015) Targeting DnaN for tuberculosis therapy using novel griselimycins. Sci 348: 1106–1112 Koen N, van Breda SV, Loots DT (2018a) Elucidating the antimicrobial mechanisms of colistin sulfate on Mycobacterium tuberculosis using metabolomics. Tuberculosis 111:14–19

[19] Lan Q-Y, Liu Q-L, Cai J, Liu A-W (2015) 3-cinnamoyl-4-hydroxy-6- methyl-2H-pyran-2-one (CHP) inhibits human ovarian cell proliferation by inducing apoptosis. Int J Clin Exp Pathol 8:155–163

[20] Lange C, Chesov D, Heyckendorf J (2019) Clofazimine for the treatment of multidrug-resistant tuberculosis. Clin Microbiol Infect 25:128– 130

[21] Lechartier B, Cole ST (2015) Mode of action of clofazimine and combination therapy with benzothiazinones against Mycobacterium tuberculosis. Antimicrob Agents Chemother 59:4457–4463

[22] Molina-Torres CA, Barba-Marines A, Valles-Guerra O, OcampoCandiani J, Cavazos-Rocha N, Pucci MJ, Castro-Garza J, VeraCabrera L (2014) Intracellular activity of tedizolid phosphate and ACH-702 versus Mycobacterium tuberculosis infected macrophages. Ann Clin Microbiol Antimicrob 13:13

[23] Mori G, Chiarelli LR, Riccardi G, Pasca MR (2017) New prodrugs against tuberculosis. Drug Discov Today 22:519–525

[24] Naftalin CM, Verma R, Gurumurthy M, Hee KH, Lu Q, Yeo BCM, Tan KH, Lin W, Yu B, Seng KY (2018) Adjunctive use of celecoxib with anti-tuberculosis drugs: evaluation in a whole-blood bactericidal activity model. Sci Rep 8:13491

[25] Ramón-García S, González del Río R, Villarejo AS, Sweet GD, Cunningham F, Barros D, Ballell L, Mendoza-Losana A, FerrerBazaga S, Thompson CJ (2016) Repurposing clinically approved cephalosporins for tuberculosis therapy. Sci Rep 6:34293

[26] Ran K, Gao C, Deng H, Lei Q, You X, Wang N, Shi Y, Liu Z, Wei W, Peng C, Xiong L, Xiao K, Yu L (2016) Identification of novel 2- aminothiazole conjugated nitrofuran as antitubercular and antibacterial agents. Bioorg Med Chem Lett 26:3669–3674

[27] Rayasam GV, Balganesh TS (2015) Exploring the potential of adjunct therapy in tuberculosis. Trends Pharmacol Sci 36:506–513

[28] Reddy DS, Hosamani KM, Devarajegowda HC (2015a) Design, synthesis of benzocoumarin-pyrimidine hybrids as novel class of antitubercular agents, their DNA cleavage and X-ray studies. Eur J Med Chem 101:705–715

[29] Tseng C-H (2018) Metformin decreases risk of tuberculosis infection in type 2 diabetes patients. J Clin Med 7:264

[30] Tyagi S, Ammerman NC, Li S-Y, Adamson J, Converse PJ, Swanson RV, Almeida DV, Grosset JH (2015) Clofazimine shortens the duration of the first-line treatment regimen for experimental chemotherapy of tuberculosis. Proc Natl Acad Sci 112:869–874